

The Liver in Pediatric Gastrointestinal Disease

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ABSTRACT

Hepatic involvement is often encountered in gastrointestinal (GI) diseases, in part because of the close anatomic and physiologic relations between the liver and GI tract. Drainage of the mesenteric blood supply to the portal vein permits absorbed and/or translocated nutrients, toxins, bacterial elements, cytokines, and immunocytes to gain hepatic access. Liver problems in digestive disorders may range from nonspecific hepatocellular enzyme elevations to significant pathologic processes that may progress to end-stage liver disease. Hepatobiliary manifestations of primary GI diseases in childhood and adolescence are not uncommon and include several well-described associations, such as sclerosing cholangitis with inflammatory bowel disease. Liver damage may also result from the effects of drugs used to treat GI diseases, for example, the hepatotoxicity of immunomodulatory therapies. This review highlights the important features of the hepatic and biliary abnormalities associated with 3 common pediatric GI conditions: inflammatory bowel disease, celiac disease, and cystic fibrosis.

Key Words: biliary tract disorders, celiac disease, cystic fibrosis, hepatotoxicity, inflammatory bowel disease, liver disorders, pediatrics

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Disorders of the hepatobiliary system are relatively common manifestations of gastrointestinal (GI) diseases, in part because of the close anatomic and physiologic relations between the gut and the liver. The liver is the recipient of first-pass drainage of the mesentery via portal venous channels, allowing hepatic uptake of absorbed, translocated, and endogenously synthesized nutrients, toxins, bacterial antigens, immunocytes, cytokines, and chemokines. Hepatobiliary involvement in GI disorders represents part of a disease spectrum with a common pathogenesis in many clinical situations, such as the autoimmune phenomena seen in primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) (1). Hepatic abnormalities also arise as a consequence of drug treatment. A wide range of medication-related disorders have been described, from nonspecific transaminase elevations to

well-known clinicopathologic associations. This monograph highlights important aspects of the pathogenesis, diagnosis, and present management of hepatobiliary abnormalities associated with 3 common GI disorders in the pediatric population: IBD, celiac disease, and cystic fibrosis (CF). Less frequently encountered hepatobiliary manifestations of infectious and autoimmune GI disorders are listed in Table 1, but are beyond the scope of this review.

HEPATIC MANIFESTATIONS OF IBD

IBD encompasses a group of chronic inflammatory diseases of the GI tract that includes Crohn disease (CD), ulcerative colitis (UC), and indeterminate colitis. Hepatic and biliary tract abnormalities (Table 2) may represent part of the overall disease process in these disorders, or may occur as a consequence of medical therapy. Published data on the prevalence of liver disease in IBD are limited and hampered by a variety of definitions (eg, transient liver function test abnormalities, persistent transaminase elevations to chronic cholestasis to cirrhosis), different diagnostic criteria, and assessment methods (2,3).

In a comprehensive study of 555 patients with childhood IBD, alanine aminotransferase elevations persisted >6 months in only 3% of patients (4). This finding contrasts markedly with the observation of transient transaminase increases in up to 60% of pediatric subjects with IBD (5). Aside from isolated enzyme elevations, adult studies indicate a 5% to 10% prevalence rate for clearly defined IBD-related liver diseases (3,6–10). The most commonly documented associations, in descending order of frequency, are PSC, nonalcoholic fatty liver disease (NAFLD), cholelithiasis, autoimmune hepatitis (AIH), and primary biliary cirrhosis (PBC) (3,6–10).

PSC

PSC is a chronic cholestatic liver disease of unknown etiology, characterized by inflammation and fibrosis of the intra- and/or extrahepatic bile ducts, leading to progressive hepatic fibrosis, biliary cirrhosis, and end-stage liver disease (11). PSC should be suspected in patients with IBD when routine liver function tests demonstrate both elevated transaminase and γ -glutamyltransferase (GGT) levels, with or without symptoms related to cholestasis or chronic liver disease.

Epidemiology

PSC occurs at any age, exhibits a 2:1 male-to-female predominance, and is more common in white individuals. The overall prevalence varies widely with age, ranging from up to 8.5/100,000 adults in Scandinavia (12,13) to 0.23/100,000 in a Canadian population-based pediatric study (14). IBD (most commonly UC) accompanies a diagnosis of PSC in up to 80% of adult and pediatric patients (12,15–27). Conversely, PSC previously was reported in only 1% to 5% of children with IBD (4,5,27–29). A recent study identified PSC-type lesions by magnetic resonance cholangiopancreatography (MRCP) in 15% of 73 pediatric IBD cases, suggesting

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TABLE 1. Hepatic and biliary tract disorders in “non-IBD” pediatric gastrointestinal diseases

Gastrointestinal disease	Hepatic disorder	Biliary tract disorder
Celiac disease	Cryptogenic transaminase elevations AIH NAFLD (steatosis) Acute hepatic failure (rare case reports)	PBC PSC
Cystic fibrosis	Transaminase elevations NAFLD (steatosis) Congestive hepatopathy Portal hypertension	Focal biliary cirrhosis Multilobular biliary cirrhosis Microgallbladder Cholelithiasis Neonatal cholestasis Biliary stricture Sclerosing cholangitis (rare) CCA (rare)
Autoimmune polyglandular syndrome	AIH	
Autoimmune enteropathy	AIH	
Behcet disease	Budd-Chiari syndrome	
Intestinal infection and infestation	Hepatic abscess (<i>Salmonella</i> , <i>Shigella</i> , <i>Amoeba</i>); portal hypertension (schistosomiasis)	Cholelithiasis (<i>Salmonella</i> , chronic carrier); biliary obstruction, cholangitis (<i>Ascaris</i> , liver flukes, <i>Cryptosporidium</i>)

AIH = autoimmune hepatitis; CCA = cholangiocarcinoma; IBD = inflammatory bowel disease; NAFLD = nonalcoholic fatty liver disease; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis.

a higher IBD-associated PSC prevalence than previously estimated (30).

Pathogenesis/Genetics

The most widely accepted theory of PSC pathogenesis invokes an immune-mediated progressive attack on the intra- and extrahepatic bile ducts, leading to chronic cholestasis and fibrosis (11,31). Bile duct injury may be triggered by exposure to enteric infectious agents, to bacterial toxins, or by ischemic injury. A genetic PSC predisposition is demonstrated by a 100-fold disease risk in siblings of affected individuals (32). To date, 6 different major histocompatibility complex haplotypes have been identified in relation to PSC, 3 associated with increased and 3 with decreased risk (33). Because major histocompatibility complex alleles are unlikely to be solely responsible for determining risk, other genetic determinants have been examined. Proposed risk factors for PSC (reviewed in 27) involve gene mutations linked to either IBD or biliary excretory dysfunction, including CARD1, CARD15, BSEP, MDR3, and CFTR.

TABLE 2. Hepatic and biliary tract disorders in IBD

Hepatic disorders	Biliary tract disorders
Transaminase elevations	PSC
Drug-induced hepatotoxicity	PSC-AIH overlap syndrome
AIH	Pericholangitis (small duct PSC)
PSC-AIH overlap syndrome	PBC
NAFLD	Cholelithiasis
Venous thrombosis (hepatic, portal)	Cholangiocarcinoma
Granulomatous hepatitis	
Hepatic abscess	
Budd-Chiari syndrome	
Hepatic amyloidosis	

AIH = autoimmune hepatitis; IBD = inflammatory bowel disease; NAFLD = nonalcoholic fatty liver disease; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis.

Clinical Features

PSC often develops insidiously, with little clinical sequelae despite significant histopathologic injury (16,23,24). Approximately 10% of patients with IBD and PSC manifest hepatic involvement before experiencing any GI symptoms (18). Although IBD-related PSC predominantly accompanies a UC diagnosis, up to 15% of cases have been identified in patients with CD (15,20, 34–36). The colitis in this setting is often extensive in distribution but relatively mild in severity (15,20). This may represent a distinct clinical phenotype, additionally characterized by backwash ileitis and relative rectal sparing (15,18,37–39). Adults with PSC also exhibit a higher cumulative risk of colorectal malignancy, compared with patients with IBD without PSC (15,37,38).

Diagnosis

A combination of factors leads to a PSC diagnosis, which include biochemical evidence of bile duct injury (elevated GGT), characteristic histopathologic findings (bile duct inflammation, periductal fibrosis), and typical radiographic appearance (strictures and dilatations of the intra- and/or extrahepatic biliary system). Children show a higher frequency of autoimmune features than adults, with liver biopsies demonstrating an increased prevalence of PSC-AIH overlap syndrome (20–22,40). This syndrome is characterized by elevated immunoglobulin G levels, positive autoimmune markers, and interface hepatitis (piecemeal necrosis) on liver biopsy. Patients are female predominant and manifest symptoms at a younger age than do those with IBD and PSC alone (22,41). In the absence of liver histopathology, a PSC-AIH overlap syndrome diagnosis may be confounded by several laboratory variables. For example, auto-antibodies (anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody) are frequently detected in PSC, although with low specificity and varying frequency (42). Atypical peripheral anti-neutrophil cytoplasmic antibodies are found in up to 90% of patients with both IBD-associated PSC and PSC-AIH overlap syndrome (42,43).

Endoscopic retrograde cholangiopancreatography is the standard technique to confirm PSC (44). The typical beaded appearance of the biliary tree results from multifocal strictures involving the intra- and/or extrahepatic bile ducts, with intervening segments of apparently normal or minimally dilated ducts. Children demonstrate involvement of both intra- and extrahepatic bile ducts (40%–67%) more commonly than either isolated intrahepatic duct stricturing (12%) or isolated extrahepatic duct disease (0%–10%) (20–22,26). MRCP is an attractive diagnostic alternative in children because of its noninvasive nature and minimal procedure-associated complications. A meta-analysis comprising 456 patients indicated that MRCP showed good sensitivity (86%) and specificity (94%) for diagnosing PSC (45). Accordingly, MRCP can be recommended as a first-choice diagnostic test. Endoscopic retrograde cholangiopancreatography is indicated when therapeutic intervention is planned (eg, stenting of a dominant stricture), and it should be considered in children with a strong clinical suspicion of PSC and a negative MRCP.

Percutaneous liver biopsy generally is not required to confirm PSC alone. In 1 small group of pediatric patients with known disease, characteristic findings of periductal concentric fibrosis of small interlobular bile ducts (onion skinning) were reported in only 25% (19); however, biopsy is an essential tool for diagnosing a PSC-AIH overlap syndrome. It also may be helpful in assessing small duct disease and staging the degree of hepatic involvement.

Management

Unfortunately, no consistently effective medical therapy for PSC has been demonstrated. Treatment with ursodeoxycholic acid (UDCA) has been the most extensively studied. A daily dose of 13 to 15 mg · kg⁻¹ · day⁻¹ resulted in significant decreases in transaminase and GGT levels and reduced pruritus in adults (46,47); however, at higher doses (28–30 mg · kg⁻¹ · day⁻¹), a recent study reported an increase in severe adverse events, including increased liver transplant and mortality rates, when compared with placebo (48). A Cochrane meta-analysis of adult PSC investigations did not demonstrate sufficient evidence to support UDCA's beneficial effect on disease progression, on survival free of transplantation, and on liver histology (49). The effects of UDCA on long-term outcomes in children are unclear, and present data do not justify this therapy in patients with subclinical disease. A multicenter trial assessing the effects of UDCA on liver injury and inflammation in pediatric PSC is under way.

Enteric flora by-products have been implicated in the pathogenesis of PSC, and several trials of antibacterial agents have been conducted. In 14 children with PSC-IBD given long-term (4–56 months) oral vancomycin, significant improvement was shown in symptoms and transaminase and GGT levels (50). Liver enzymes increased when therapy was discontinued, and retreatment normalized these tests (50). Antimicrobial agents also have been evaluated in adults. A randomized trial found a significant decrease in serum alkaline phosphatase in patients receiving vancomycin for 12 weeks (51). In the same study, patients treated with metronidazole did not achieve this primary endpoint and experienced a higher frequency of adverse events (51). Other antimicrobials, including metronidazole in combination with UDCA, minocycline, and azithromycin, have shown some degrees of efficacy (52–54). Larger and longer-term studies are still needed to evaluate antibiotics as safe and effective therapy. Children with autoimmune sclerosing cholangitis or PSC-AIH overlap syndrome usually respond to corticosteroids (44). Other immunomodulators, often used as part of IBD management, have

little influence on the clinical course of PSC in adult studies, and these agents are not recommended (31,55–58).

Orthotopic liver transplantation (OLT) is the sole therapeutic option for patients with PSC with end-stage liver disease, although reported OLT rates range widely (59–61). In 2 large pediatric PSC studies, 20% required OLT at a median of 6.7 to 12 years after diagnosis (20,21). PSC accounted for 3% of 3723 children listed for OLT in the Studies of Pediatric Liver Transplantation (SPLIT) between 1995 and 2008 (61). Posttransplant outcome is excellent and not different from patients transplanted for other causes, with 1- and 5-year survival rates of 98.7% and 86.6%, respectively (61). Nevertheless, recurrent PSC following OLT was reported in 10% of a large pediatric cohort (61). Patients with IBD-associated PSC who require OLT often manifest less severe intestinal disease when compared with patients not requiring transplant (62,63); however, in one-third of cases, preexisting UC worsens after OLT and is associated with a higher rate of neoplasia (64–68). IBD may also develop *de novo* after OLT for PSC, despite immunosuppressive therapy (65,68). Further evidence linking these intestinal and hepatic disorders is suggested by the observation that the PSC recurrence rate post-OLT is lower in patients with UC who undergo colectomy (for dysplasia or refractory disease) before or concurrently with transplant, compared with subjects whose colons remain *in situ* (68,69).

Risk of Malignancy and Cancer Screening

In addition to the known risk factors for colorectal cancer (CRC) in UC (extent and duration of disease, earlier age at onset, and presence of colorectal dysplasia; 64), a 4-fold increased CRC risk is seen in conjunction with PSC (70). In these cases, CRC is frequently located in the right colon and tends to be advanced (71,72). Surveillance colonoscopy at 1- to 2-year intervals from the time of PSC diagnosis, therefore, is recommended for patients ≥16 years of age with PSC-UC (44). Ongoing surveillance recommendations have not been established for patients <16 years (44). CRC also has been reported in up to 7% of patients with PSC-UC following OLT, and posttransplant management should include an annual screening colonoscopy (64). Because intestinal disease in patients with PSC with IBD often exhibits a relatively low degree of endoscopic activity, a prudent approach during all screening examinations is to obtain multiple biopsies in all regions of the colon, despite a benign endoscopic appearance. For all of the children with a primary PSC diagnosis, a colonoscopy should be performed regardless of GI symptoms, considering the high prevalence of IBD in this setting. If the colonoscopy is normal in the asymptomatic patient, it should be repeated if GI symptoms occur (73).

The coexistence of IBD with PSC is also a risk factor for biliary tract malignancy, including cholangiocarcinoma (CCA) and gallbladder carcinoma (17). CCA carries a poor prognosis, with a median survival of <12 months (64). OLT is not an effective therapy, owing to high tumor recurrence and poor long-term survival rates (59,64). CCA is, fortunately, rare in children, with the youngest reported case in a 14-year-old patient with PSC-UC (74). The diagnosis is challenging, in part because CCA's cholangiographic appearance may mimic that of a benign, dominant stricture of PSC. Adult studies have examined a variety of diagnostic and screening modalities (44,75). These include serum tumor markers, liver imaging, and biliary cytopathologic testing (44,75). The latter can be improved by incorporating molecular techniques such as fluorescent *in situ* hybridization (76). Carbohydrate antigen 19-9 (CA 19-9) has been extensively evaluated as a predictive serum tumor marker. In 1 adult study, a CA 19-9 cutoff value of

129 U/mL showed a sensitivity of 79% and a specificity of 98% for CCA (77). The positive predictive value, however, was only 57% and only advanced cases were detected (77). Of note, the diagnostic utility of CA 19-9 was examined only in patients with PSC with suspected CCA, and no study has confirmed a specific screening cutoff value in asymptomatic patients (44). Despite the relative absence of evidence-based screening recommendations, a serum CA 19-9 (using a 20-U/mL cutoff) and abdominal ultrasound at 12-month intervals have been proposed for CCA surveillance in adults with PSC (11,44,75). Routine surveillance in children presently is not recommended (44).

IBD and Other Hepatobiliary Disorders

AIH is an immune-mediated progressive inflammation of the liver, characterized by elevated immunoglobulin G levels, positive serum autoimmune markers, and the presence of periportal inflammation and interface hepatitis on liver biopsy. AIH was found in <1% of 555 pediatric patients with IBD (4), whereas prevalence rates as high as 16% have been reported in adults (78). AIH in UC may be less responsive to standard treatment and progress to cirrhosis more frequently than AIH without colitis (78). Because PSC-AIH overlap is more commonly diagnosed in children and young adults, an MRCP should be performed in the child with AIH-IBD who exhibits signs of cholestasis, who demonstrates cholangitis on liver biopsy, or who experiences an incomplete response to medical therapy (3,11).

In terms of other IBD-associated liver diseases, PBC also has been reported, but occurs much less frequently than PSC (79). NAFLD is generally related to nutritional status, medication use, or comorbid factors such as diabetes (79). Other less frequently encountered associations are listed in Table 2.

IBD Drug-Induced Liver Injury

Drugs prescribed for IBD treatment may be the cause of rare but serious hepatic complications (Table 3). Therefore, routine care includes screening for these problems and rapid modification of therapy as indicated.

Thiopurines

The thiopurines, azathioprine (AZA) and 6-mercaptopurine (6-MP), are effective agents for both inducing and maintaining remission in IBD (80). In adults, 6-thioguanine (6-TG) also was shown to be effective in patients with IBD not responsive to or intolerant of AZA/6-MP. This hematopoietically active 6-MP metabolite was, however, subsequently withdrawn because of its association with hepatic nodular regenerative hyperplasia (NRH) (81). The mean prevalence of thiopurine-induced hepatotoxicity in patients with IBD has been reported at 3%, in a review comprising 3485 pediatric and adult patients (82). When evaluating only studies with specifically indicated follow-up periods, the incidence of liver injury in patients with IBD was estimated at 1.4% per patient-year of thiopurine treatment (82).

Thiopurine-induced liver toxicity can be divided into 3 subtypes: hypersensitivity reaction, idiosyncratic cholestasis, and endothelial cell injury. The latter may result in veno-occlusive disease, peliosis hepatis, sinusoidal dilatation, and perisinusoidal fibrosis (82,83). Histopathologic changes during therapy include acute hepatocellular hepatitis, cholestatic hepatitis, and NRH (83,84). Hepatotoxicity also may present with a serum sickness picture; however, toxicity is most frequently manifested by asymptomatic transaminase elevations, which usually return to normal levels following dose reduction or drug withdrawal.

TABLE 3. Hepatotoxicity of common medications used in IBD in children

Medication	Hepatotoxic effect	Outcome/management
5-Aminosalicylates	<ol style="list-style-type: none"> 1. Transaminase elevations 2. Idiosyncratic hepatocellular injury, cholestasis, or mixed picture 3. Granulomatous hepatitis 	<ol style="list-style-type: none"> 1. Self-limiting, often resolve upon drug withdrawal 2. Can be fatal if acute liver failure; requires prompt drug withdrawal 3. Associated with chronic use; requires drug withdrawal
Thiopurines	<ol style="list-style-type: none"> 1. Transaminase elevations 2. Idiosyncratic cholestasis, acute hepatocellular necrosis, or mixed 3. Endothelial cell injury: <ol style="list-style-type: none"> A. Veno-occlusive disease, peliosis hepatic, sinusoidal dilatation, perisinusoidal fibrosis B. Noncirrhotic nodular regenerative hyperplasia 	<ol style="list-style-type: none"> 1. Mild, self-limiting, may require dose reduction or drug discontinuation 2. Regular liver function test monitoring, more frequent within the first months of treatment; thiopurine metabolite monitoring may be useful; often improves upon drug withdrawal; may progress and can be fatal if severe cholestasis 3. Prompt intervention to avoid clinical deterioration; may improve after drug withdrawal; symptomatic, supportive treatment; control of portal hypertension and its related complications
MTX	<ol style="list-style-type: none"> 1. Transaminase elevations 2. Macrovesicular steatosis, hepatocellular necrosis 3. Hepatic fibrosis, cirrhosis (rare) 4. Hepatitis B reactivation (rare) 	<ol style="list-style-type: none"> 1. Usually mild, self-limiting, but may require dose reduction or withdrawal 2. Regular liver function test monitoring; routine liver biopsy in patients with IBD on chronic use is controversial (see text) 3. Often asymptomatic and nonprogressive; control of portal hypertension and its complications if symptomatic 4. Routine screening for HBsAg, anti-HBc before treatment; if positive, oral antiviral prophylaxis, or careful monitoring of HBV DNA levels
Infliximab	<ol style="list-style-type: none"> 1. Transaminase elevations 2. Hepatocellular injury with autoimmune markers 3. Cholestasis (rare) 4. Hepatitis B reactivation 	<ol style="list-style-type: none"> 1. Transient, asymptomatic, may require drug discontinuation if persistent 2. Usually improves after drug withdrawal and/or corticosteroid treatment; can be severe; regular liver function test monitoring 3. Self-limiting, reversible with supportive treatment 4. Can be severe; routine screening for HBsAg, anti-HBc before treatment; oral antiviral prophylaxis if positive

HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IBD = inflammatory bowel disease; MTX = methotrexate.

Liver injury commonly occurs within the first 5 months after thiopurine initiation (85–87), but some cases may be detected after a longer treatment period. Hepatotoxicity has been associated with increased levels of the thiopurine metabolite 6-methylmercaptopyurine (6-MMP) (88). One study of 173 adults with IBD reported a mean 6-MMP concentration of $\sim 10,500$ pmol per 8×10^8 erythrocytes in the hepatotoxicity group (enzymes >2 times the upper limit of normal [ULN] or cholestasis), versus ~ 3400 pmol per 8×10^8 erythrocytes in the nonhepatotoxicity group (89). In a pediatric IBD cohort, liver injury was associated with 6-MMP levels in excess of 5700 pmol per 8×10^8 erythrocytes (88). Transaminase elevations also have been reported with normal metabolite concentrations (83,89); therefore, liver chemistries should be monitored closely during the first few months of therapy or when increasing drug dosage. Thiopurines should be discontinued promptly if jaundice develops (with or without signs of portal hypertension), because this finding may herald hepatic veno-occlusive disease (90).

NRH is a rare but important adverse effect of thiopurines, most commonly seen with 6-TG (81) and less frequently with AZA (84). It is characterized by diffuse transformation of normal hepatic parenchyma into small, regenerative nodules with little to no fibrosis, leading to noncirrhotic portal hypertension (91). Patients may manifest only liver enzyme abnormalities, or the diagnosis first may be suspected in the setting of profound portal hypertension. Imaging modalities such as magnetic resonance imaging or contrast-enhanced computed tomography are helpful in suspected cases, but liver biopsy with reticulin staining is required to establish a diagnosis (91). Between 1994 and 2005, 37 cases (age range 10–54 years) of AZA-associated NRH therapy were identified in 11 centers, with a median span of 48 months from therapy commencement to diagnosis (83). NRH of varying degrees also was reported in 53% of 37 biopsies from patients with IBD (age range 9–67 years) who received 6-TG for 1 to 3 years (92). Additional NRH risk factors include stricturing intestinal disease, ileal resection, and male sex (83). The natural history is not clear, and the mainstay of treatment remains control of portal hypertension and its related complications. One report described a patient with CD in whom NRH regressed after AZA withdrawal, suggesting that early diagnosis may be essential for preventing portal hypertension (93).

Methotrexate

Methotrexate (MTX), a folic acid antagonist, has been used in IBD refractory to conventional treatment, and it also is effective for inducing and maintaining remission in CD (94–96). The incidence of MTX-induced liver enzyme abnormalities ranges from 3% to 33%, depending on the duration of treatment (96–102). A meta-analysis of hepatotoxicity in IBD reported a pooled incidence rate for transaminase increases >2 -fold above the ULN of 0.9/100 person-months (103). This is comparable with the toxicity rate associated with thiopurines (103). Liver injury is more common in those patients with baseline transaminase elevations, underlying liver disease, and concurrent use of other hepatotoxic drugs (97).

The effects of MTX are related to cumulative dose, and include macrovesicular steatosis, inflammation, cellular necrosis, hepatic fibrosis, and cirrhosis (104). These findings may remain clinically and biochemically silent for years. Furthermore, elevated liver enzymes during MTX treatment neither correlate with nor are predictive of abnormal histology (97,105). In non-IBD clinical settings, guidelines for liver biopsy assessment have been developed for patients on long-term therapy. The 2009 National Psoriasis Foundation Consensus recommends that patients with no additional risk factors for liver injury should have liver function tests monitored monthly for the first 6 months of MTX treatment, then every

1 to 2 months thereafter (106). A liver biopsy should be performed if 5 of 9 serum aspartate aminotransferase (AST) levels are elevated for a 12-month period, or if the serum albumin declines below the normal range in a patient with normal nutritional status (106). Biopsy also should be considered at a cumulative dose of 3000 to 4000 mg (106). Despite these guidelines, studies in patients with IBD have yielded no consensus regarding the need for biopsy. In 1 series of adult patients with IBD who received cumulative MTX doses >1500 mg (the previously recommended “threshold” level), 15 of 17 biopsies either were normal or showed only mild inflammation (97). In addition, no significant changes in the incidence of liver function test abnormalities were noted when cumulative doses exceeded 3000 mg (97). Fortunately, the majority of liver enzyme abnormalities appear to be transient and normalize either spontaneously or with dose reduction (97,103). Persistent transaminase elevations requiring drug withdrawal have been reported in only 5% of patients (97).

Tumor Necrosis Factor- α Antagonists

Infliximab, a chimeric monoclonal antibody that binds to tumor necrosis factor- α (TNF- α), is an effective pediatric IBD treatment (107,108). In the ACCENT (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen) I trial evaluating maintenance infliximab therapy in CD, liver enzyme abnormalities were observed in 42% of patients (7,107). Hepatocellular injury with autoimmune markers has been reported with infliximab use, and often improves after stopping the drug and, in some cases, after adding corticosteroids (109). A case of cholestatic liver injury was reported in an adult patient with CD immediately following an infliximab infusion (110), and other cases of infliximab-associated acute hepatitis were documented in patients with rheumatoid polyarthritis and psoriatic rheumatism (111). As fatal cases of reactivation of chronic hepatitis B have occurred (112,113), present recommendations include hepatitis B screening before starting treatment with any biologic agent. If positive, antiviral therapy should be offered (113). In addition to this transient elevation of liver enzymes during treatment, liver toxicity has not been documented for other commonly used TNF- α antagonists, including adalimumab and certolizumab (114–116).

T-cell non-Hodgkin lymphoma has been reported with anti-TNF- α therapy, and the lymphoma risk is significantly increased with the addition of thiopurines (117). Hepatosplenic T-cell lymphoma subtype, a rare but fatal disease, has been diagnosed in patients with IBD receiving thiopurines alone or, more commonly, in conjunction with infliximab (117–119). Cases occurred predominantly in young male patients (119). Most patients had CD for 5 to 21 years, had been treated with thiopurines for 2 to 6 years, and had received 1 to 24 infusions of infliximab (7). Because both anti-TNF- α biologics and thiopurines increase the risk of serious and opportunistic infections and malignancy, and because the risks appear greater when these agents are prescribed in combination, concurrent use should be carefully considered. When such therapy is used, every attempt must be made to optimize both efficacy and safety. Recommended approaches for evaluating and monitoring patients undergoing treatment have been published (120–122).

Other Drugs Used in IBD

Other than steatosis and hepatomegaly, no overt liver injury has been reported with corticosteroids (104). Although sulfasalazine-related hepatotoxicity is uncommon (123), fatal cases of fulminant hepatic failure have been reported (124–127). This idiosyncratic liver injury is marked by a systemic hypersensitivity

reaction (exanthema, fever, eosinophilia, adenopathy, arthralgias), followed by evidence of cholestatic and/or hepatocellular injury (jaundice, overt signs of acute liver failure) (90). Once recognized, the drug should be discontinued promptly. Most cases resolve within weeks, unless cholestasis is severe (90). Chronic sulfasalazine use can also cause mild, transient transaminase elevations, and the drug has been associated with granulomatous hepatitis (128).

Sustained-released mesalamine (5-aminosalicylic acid [5-ASA]) has fewer adverse effects than sulfasalazine, but rarely may cause transient subclinical liver enzyme elevations (7,90). A case of mesalamine-induced granulomatous hepatitis developed in a patient with UC, 2 weeks after starting therapy (129). All aminosalicylate derivatives (eg, sulfasalazine, mesalamine, olsalazine) may influence thiopurine metabolism by inhibiting the enzyme thiopurine S-methyltransferase (TPMT) (130–132). Concomitant use of 5-ASA and thiopurines has, in fact, been shown to increase serum total 6-TG and, in 1 study, reduce 6-MMP levels (133). Thus, the combination of a thiopurine and a 5-ASA drug may enhance the risk for bone marrow suppression, while also reducing the likelihood of thiopurine-induced hepatotoxicity (133).

HEPATIC MANIFESTATIONS OF CELIAC DISEASE

Celiac disease (gluten-sensitive enteropathy) is characterized by an immune-mediated reaction to dietary gluten (in wheat, barley, and rye) that primarily affects the small intestine in genetically susceptible individuals. The resulting losses of absorptive surface area and digestive hydrolases lead to impaired nutrient absorption (134). A wide spectrum of hepatic manifestations (Table 2) range from asymptomatic liver enzyme elevations to nonspecific reactive hepatitis, NAFLD, AIH, and cholestatic liver disease (135). These can be classified into 2 primary categories: cryptogenic and autoimmune (136).

Epidemiology

In the absence of other causes, asymptomatic (silent) celiac disease accounts for 6% to 9% of patients with unexplained liver enzyme elevations (137–140). Adherence to a strict gluten-free diet (GFD) often leads to normalization of aminotransferases and disappearance of autoantibodies (136,141,142). Cryptogenic liver damage (defined as mild elevation of transaminases) is found in about half of untreated pediatric patients (135,140,143). Liver biopsies, when performed, may demonstrate a nonspecific reactive hepatitis with mild periportal inflammation (135,136,144,145). As in silent celiac disease, transaminase elevations in symptomatic patients are reversible on a strict GFD in 75% to 100% of cases (141,142,144,146,147).

In rare celiac cases, liver injury can be progressive, characterized by severe inflammation and fibrosis, occasionally progressing to cirrhosis (144,145). Persistent transaminase elevations may represent a primary, autoimmune disorder sharing a common immunopathogenesis (148). An association with autoimmune liver disorders is well described (135,149,150). Celiac disease has been reported in adults with PBC (135,145,151), AIH (135,145,152), and PSC (135,145,153). Data from pediatric studies demonstrate a wide prevalence range for AIH among celiac patients. This variance may be related to sizes of the studied cohorts, to the frequency of liver function monitoring, and to the diagnostic approach to transaminase elevations (154–157). Cases of autoimmune cholangitis and severe liver failure have been reported both in pediatric (158–160) and in adult patients (144,159,161–163). Acute hepatic failure was described in 4 toddlers at 1 to 24 months after the diagnosis of celiac disease, and 2 required liver transplantation (164).

Pathogenesis

The pathogenesis underlying gluten-mediated liver injury is poorly understood. Hepatic damage may be a consequence of increased intestinal permeability, facilitating translocation of bacterial toxins and other antigens to the liver via the portal circulation (135,147). Cytokines released by chronically inflamed intestinal mucosa also may mediate hepatic inflammation, as postulated for liver involvement in IBD (135). A possible genetic link between celiac disease and AIH is not surprising because both disorders express selected combinations of genes coding for class II human leukocyte antigen (HLA) molecules on chromosome 6: HLA-DQ2 or HLA-DQ8 haplotype for celiac disease; HLA-DR3, HLA-DR4, or HLA-DR52 for AIH (165). NAFLD in patients with celiac disease likely results from the effects of malnutrition leading to abnormal hepatic fat deposition (148).

Diagnosis

Because celiac disease is strongly associated with autoimmune liver disorders, hepatic function tests should be performed at the time of diagnosis (135,136,145,162). In patients with persistently elevated transaminases despite a strict GFD, other, “non-autoimmune” causes of liver injury (eg, viral hepatitis) should be excluded (162). Conversely, screening patients with autoimmune liver disease for specific antibodies to human tissue transglutaminase also is recommended (136,166).

Management

Early diagnosis and dietary management may prevent celiac-related liver damage and even reverse hepatic decompensation (159,167). Unlike cryptogenic transaminase elevations, celiac-associated autoimmune liver disease requires pharmacotherapy in addition to diet alone (137,145,150,154,168,169). A GFD is essential, however, to augment the effect of immunosuppressive treatment by normalizing intestinal permeability, by improving absorption of medications, and by decreasing exposure to triggers of autoimmunity (163,170). In a group of children with celiac disease with AIH, corticosteroid treatment as well as a GFD led to a remission rate of 100%. Of this group, 86% were able to maintain a sustained clinical and biochemical remission, without immunosuppressive therapy, during a 20-month follow-up (170).

The approach to liver involvement in celiac disease should be based on the pattern and extent of abnormal biochemistries, and clinical history and physical findings (162). In a newly diagnosed patient with a normal physical examination, increased transaminase levels <5 times ULN and an aspartate aminotransferase:alanine aminotransferase ratio <1, 1 review suggests rechecking liver enzymes after 6 to 12 months of a strict GFD (162). If transaminases normalize, yearly follow-up studies are indicated (162). We further recommend an AIH evaluation for any patient with laboratory findings consistent with autoimmune liver disease (ie, hypergammaglobulinemia, elevated total gammaglobulin:albumin ratio). Finally, celiac screening should be considered as part of the workup for unexplained elevations of liver enzymes, regardless of GI symptoms (135,166).

HEPATIC MANIFESTATIONS OF CF

CF, a multisystem disease caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, is the most common life-limiting, autosomal recessive disorder among white individuals, with an average incidence of 1 in 3000 live births (171). With improved care and increased life expectancy, CF-related liver

disease (CFLD; Table 2) has increasingly been reported, and is now the most important nonpulmonary cause of death in the CF population (172). Thus, early identification of liver involvement and prompt therapeutic intervention are of great importance.

Epidemiology

The true prevalence of CFLD is difficult to determine, because no definition for this condition is universally accepted and clinically insignificant liver enzyme elevations are common (173,174). Nonspecific transaminase increases have been documented in more than 50% of infants, often resolve by 2 to 3 years of age, and do not appear to affect the future development of CFLD (175). By contrast, patients with CF who develop significant liver disease and cirrhosis may have normal or only slightly elevated liver enzymes (172,175). The incidence of CFLD has been estimated at 2.5/100 patient-years during the first 10 years of life, declining sharply during the second decade (173). Long-term follow-up studies have found the prevalence of abnormal hepatic histopathology in CF to range from 27% to 41% (173,175,176). Focal biliary cirrhosis is considered the most common CFLD, with a frequency of 20% to 30% (172,177). Approximately 5% to 10% of children with CF develop cirrhosis before or during puberty (173,175,176). Most of these patients eventually progress to portal hypertension and present with related complications during the second decade (172,178–181).

Pathogenesis

The *CFTR* is expressed on apical membranes of cholangiocytes and gallbladder epithelial cells, where it plays a critical role in chloride and water secretion to support normal bile formation and flow (182). Viscous, inspissated bile in CF causes ductular obstruction leading to hepatotoxicity from retained bile components, to fibrosis, and ultimately to cirrhosis (182). Approximately one-third of patients with overt signs of biliary obstruction develop progressive liver disease, whereas others exhibit only minimal changes. Several important risk factors for biliary tract involvement have been hypothesized, including male sex (173,175,183), history of meconium ileus (173,176,183), pancreatic insufficiency (176,183,184), and severe CF genotype (173,184). The role these factors play in the development of CFLD is, however, controversial. Some reports correlate meconium ileus or its equivalent (ie, distal intestinal obstruction syndrome) with increased liver disease prevalence (173,176,183), yet others fail to support this finding (175,184,185). No specific *CFTR* mutations are associated with the presence and/or severity of CFLD, and the same *CFTR* mutation yields variable liver phenotypes (183,184).

Because the pathogenesis of CFLD appears multifactorial, the importance of gene modifiers has been investigated. Among candidate genes studied to date, only the *SERPINA1* Z allele is significantly associated with CFLD and portal hypertension (186). The *SERPINA1* protein, also known as α -1-antitrypsin, is expressed mainly in hepatocytes. Unlike the normal protein encoded by the M allele, the protein encoded by the Z allele is misfolded and accumulates in the endoplasmic reticulum, leading to apoptosis, fibrosis, and cirrhosis (187). *SERPINA1* Z effects in CF may be mediated by hepatic stellate cells activated by *CFTR*-deficient cholangiocytes, or may result from direct hepatocellular injury by the misfolded protein (186). Individuals who express this polymorphism (2.2% of patients with CF are carriers), are at increased risk for severe liver disease and portal hypertension (186). Because *SERPINA1* appears to be an important CFLD modifier, it may be a candidate for risk factor screening.

Clinical Manifestations

Neonatal cholestasis, which can mimic extrahepatic biliary atresia, often is the initial CF hepatobiliary manifestation and usually resolves spontaneously within the first few months of life (178,188). Infants with a history of meconium ileus may be at a greater risk (176). In older patients, focal biliary cirrhosis may lead to biliary obstruction, progressive periportal fibrosis, multilobular biliary cirrhosis, portal hypertension, and related complications (172). Clinically, apparent liver involvement often develops before or during puberty and slowly progresses to portal hypertension or end-stage liver disease in later adolescence and adulthood (172,175,176,179,181). The most common presentation is an incidental finding of hepatomegaly, with or without associated liver function test abnormalities. Other *CFTR*-related hepatobiliary manifestations include multilobular biliary cirrhosis, microgallbladder, cholelithiasis, and, rarely, sclerosing cholangitis (172, 175,177,188–190).

Diagnosis

CFLD should be considered in any patient with CF with hepatomegaly, splenomegaly, jaundice, biliary colic, or abnormal liver enzymes. A CFLD diagnosis is invoked only after excluding other causes of chronic liver disease (172). Liver biopsy may identify the predominant type of hepatic lesion, as well as determine the severity and extent of fibrosis or cirrhosis (172). Ultrasound with Doppler is helpful in assessing liver parenchyma and evaluating for portal hypertension. Although MRCP is not routinely performed in all patients, it is useful for early detection of extra- and intrahepatic biliary duct abnormalities, which may be seen in the absence of symptomatic liver disease (172,191).

The pathognomonic CF hepatic lesion of focal biliary cirrhosis involves scattered areas of portal fibrosis, cholestasis, bile duct proliferation, and plugging of bile ductules by eosinophilic material (182). The most prevalent liver histopathologic finding is, however, steatosis, noted in up to 60% of subjects (172,175). Steatosis does not appear to be directly related to the CF gene defect, but rather is attributed to overall malnutrition and other, specific CF nutritional deficiencies (eg, essential fatty acids, carnitine, choline) (175,188).

Management

UDCA, normally produced in small quantities by the liver, is presently the only available treatment that may prevent or halt the progression of liver disease in CF. Endogenous UDCA exerts a protective role against liver injury in children without hepatobiliary manifestations (192). Although UDCA improves bile flow and normalizes both liver tests and histopathologic abnormalities (193–195), it does not appear to exert a significant positive effect either on patient survival or on progression of hepatic fibrosis (196). A dose-response relation in CFLD has been reported, with a maximal effect at $20 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ (197,198). UDCA is generally well tolerated, without any significant adverse effects. Early treatment may be beneficial in patients at risk for liver disease, such as in those with a history of meconium ileus (199). Although UDCA may be useful for preventing intrahepatic sludge and stones, it has no role in the management of documented gallstones. Calcium bilirubinate is the main component of biliary calculi in patients with CF, and these concretions are insensitive to dissolution by bile acid therapy. Therefore, cholecystectomy is the treatment of choice in patients with symptomatic cholelithiasis (182).

Cirrhosis and liver failure can adversely affect lung function in CF. OLT should be considered in patients with decompensated cirrhosis, growth failure or portal hypertension (181), before deterioration of pulmonary function (181,200). The Child-Turcotte-Pugh score has been used to determine prognosis in cirrhotic subjects. This scoring system (which includes serum albumin as a determinant) may, however, overstate the degree of hepatic involvement, because albumin levels may be reduced for reasons other than liver disease (eg, malnutrition, recurrent pulmonary infections) (181). Despite concerns of immunosuppressive therapy effects on pulmonary infections, OLT has been shown to improve lung function in CF (200,201). Both graft and patient survivals are similar in children with CF as in patients receiving transplants for other indications (202,203). One- and 5-year survival rates after OLT have been reported at 75% to 100% and 75% to 81.4%, respectively (200,202–204), with late mortality generally being related to the progression of pulmonary disease (202). Aggressive treatment of lung infections, based on preoperative colonization and surveillance cultures, should be continued during the postoperative period. Nutritional support also should be provided pretransplant, because height and weight below the fifth percentile at the time of transplant are associated with greater mortality (203). Combined lung-liver or heart-lung-liver transplantation has also been performed in patients with CF, with the overall 1- and 5-year survival rates reported at 69% to 91.6% and 49% to 75%, respectively (205,206).

SUMMARY

Liver involvement in GI diseases is being increasingly recognized in the pediatric population. Problems range widely from nonspecific elevation of liver enzymes to life-threatening clinicopathologic associations. Although nonspecific liver function test abnormalities are relatively common in IBD, pediatric gastroenterologists must be aware that specific disorders, such as PSC, have a substantially increased prevalence. Because a diagnosis of PSC may precede the onset of IBD-related symptoms, a screening colonoscopy for all children with PSC is advisable at the time of diagnosis, even in asymptomatic patients. Common drugs used to treat IBD may induce rare but serious hepatic disease, and appropriate surveillance should be part of routine patient care. Although up to 50% of patients with celiac disease manifest cryptogenic elevations of transaminases that are often reversible on a strict GFD, persistent liver test abnormalities may be related to specific autoimmune hepatobiliary disorders. As the prevalence of celiac disease is higher in patients with autoimmune liver disease than in the general population, the practitioner should be aware of several well-described associations to enable early detection of celiac disease in these patients. Finally, CFLD is relatively common in patients with CF and may affect patients' quality of life. Early diagnosis and prompt treatment of CFLD and its related complications will improve long-term outcomes.

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