Clinical and Experimental HEPATOLOGY

Clin Exp HEPATOL 2019; 5, 3: 203–209
DOI: https://doi.org/10.5114/ceh.2019.87632
Received: 26.02.2019, **Accepted:** 31.03.2019, **Published:** 05.09.2019

Review paper

Hepatobiliary manifestations of inflammatory bowel disease in children

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Abstract

Inflammatory bowel disease (IBD) diagnosis and therapy is challenging for every pediatrician, especially when complicated with extraintestinal manifestations. The article reviews current literature on the hepatobiliary manifestations associated with inflammatory bowel disease in the pediatric population.

Key words: children, inflammatory bowel disease, Crohn's disease, ulcerative colitis, hepatobiliary manifestations.

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Introduction

Although numerous studies about hepatobiliary manifestations in inflammatory bowel disease (IBD) in adults have been published, data concerning the pediatric population are still insufficient. The diagnosis of hepatic disorders often starts with abnormal liver enzyme tests, which have been found in up to 40% of pediatric patients with IBD [1-3]. The association between an increased likelihood of IBD-liver disease and elevation of alanine aminotransferase (ALT) and glutamyl transpeptidase (GGT) activities within 90 days' follow-up after the diagnosis of IBD was reported [3]. Valentino *et al.* estimated the probability of developing abnormal liver enzymes at 16.3% after 1 month of IBD diagnosis and even at 58% over 150 months of follow-up [4]. The 3 main groups of causes of hepatobiliary diseases in IBD patients with their supposed mechanisms related to IBD are presented in Table 1 and with reported increased risk of development are included in Table 2 [5-8]. In this review, some of them will be discussed.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic liver disease manifested by multifocal biliary strictures caused by inflammation and fibrosis. PSC's connection with IBD is unquestionable (from 76% to around 90% of PSC patients also have IBD) and often it is diagnosed simultaneously with IBD [9-11]. The latest hypothesis of PSC development in IBD suggested that PSC is likely to have an underlying multifactorial etiology including genetic predisposition, altered gut microbiota and altered bile acid (BA) metabolism and immune-mediated processes (Table 1) [5]. Among IBD pediatric patients, the diagnosis of PSC is noted in 1.5% to 9.8% of cases, more often in ulcerative colitis (UC) [1, 4, 10, 12-14]. Deneau *et al.* reported PSC in 9.9% of UC children and in 0.6% of Crohn disease (CD) patients [10]. Recent reports have revealed that the prevalence of PSC in adults ranges from 0.76% to 5.4% in patients with UC and from 1.2% to 3.4% in CD patients [13-16]. IBD patients with coexistent PSC are more often men than women [11, 12]. There are differences in colonoscopy lesions in PSC-UC compared to UC patients, showing increased pancolitis, rectal sparing and backwash ileitis more commonly found in PSC-UC. Additionally, these patients more often develop colorectal carcinoma (CRC). However, in pediatric UC patients, severe liver disease may be an earlier and more common outcome than colorectal cancer [10, 15]. The data of occurrence of CRC in PSC-IBD children are not sufficient. The long-term

Table 1. Types and mechanisms of hepatobiliary disorders in patients with inflammatory bowel disease (IBD) [5-8]

Type	Mechanism related to IBD
1. Extraintestinal manifestations	
A. Immune mediated	
Primary sclerosing cholangitis	– Gut lymphocyte homing hypothesis – presence of shared chemokines and adhesion molecules by the liver and gut, activated lymphocytes from the inflamed gut enter the enterohepatic circulation and cause hepatic inflammation – The "leaky gut" hypothesis – increased intestinal permeability and translocation of bacterial metabolites from the inflamed gut to the liver; microbiome dysbiosis may contribute to biliary injury – Genetic predisposition – Bile acids (BA)-microbiome interaction – possible altered BA excretion in the colon due to cholestasis; impaired microbiota enzymatic activity may be associated with BA metabolism
Autoimmune hepatitis	Immune mediated
Autoimmune sclerosing cholangitis	Immune mediated
B. Thrombotic disorders	
Portal vein thrombosis	– Multifocal vascular infarcts in the intestinal microcirculation, characterized by chronic vasculitis, with focal arteritis and fibrin deposition – Acquired factors – hypercoagulation related to inflammation, surgery, prolonged immobilization, central venous catheters, fluid depletion, steroid therapy, smoking, elevated number of platelets
Venous thromboembolism	
Hepatic vein thrombosis	
2. Drug-induced liver injury	
Sulfasalazine Thiopurines Glucocorticoids Methotrexate Anti-TNFs	Related to medication toxicity
3. Underlying disorder – not related to IBD	
Cholelithiasis	– Abnormal malabsorption of bile acids that interfere with enterohepatic circulation – Reduced gallbladder motility
Viral hepatitis	Immunosuppressive therapies predispose to viral infection/reinfection
Non-alcoholic fatty liver disease/steatohepatitis	Due to steroid therapy, anti-TNF-α, methotrexate, obesity
IgG4-cholangiopathy	Immune mediated
Hepatic amyloidosis	Amyloid deposition in the vasculatures and sinusoids of almost any organ, including the liver as an effect of inflammation
Granulomatous hepatitis	Secondary to different medications, including sulfasalazine

study of Yoon *et al.* revealed that 15.4% (n = 2) of pediatric patients with PSC-IBD developed CRC in the observational period, but after 18 years of age in all cases [17]. No cholangiocarcinoma was also found in pediatric patients with IBD/PSC in this study [17]. According to American College of Gastroenterology Guidelines annual colon surveillance is recommended in every PSC adult patient with UC beginning at the time of PSC diagnosis [18]. Currently there are no guidelines for colon cancer screening in children with UC and coexisting PSC. In the pediatric population PSC remains one of the important causes of morbidity and mortality in IBD patients [10, 19]. Deneau *et al.* found that a child newly diagnosed with UC had approximately a 5% chance of developing PSC or autoimmune sclerosing cholangitis (ASC) and a 3% chance of liver transplantation or death due to progression to complicated liver disease over the next 5 years [10]. It is worth mentioning that PSC diagnosis may precede IBD and may develop in an IBD patient who has undergone colectomy [20-22].

Small duct phenotype of PSC is presented in patients with normal cholangiograms associated with abnormal liver biopsy result. This subunit is diagnosed in 13% of PSC cases, mainly in younger patients, and has a more favorable prognosis [9, 11].

Autoimmune hepatitis

Autoimmune hepatitis (AIH) manifested by elevated transaminases activities, interface hepatitis in biopsy, high immunoglobulin G (IgG) concentration and

specific serum autoantibodies, coexisting with IBD has been reported. Data showed that the frequency of AIH in IBD ranged from 0.6% to 1.6%, but a population-based study conducted in Utah revealed the frequency of 0.3% [10, 12, 21, 22]. In the Gregorio *et al.* study involving children with autoimmune liver disease, 18% of AIH patients also manifested IBD [23]. Nowadays, the knowledge about AIH is insufficient to determine whether the AIH course differs in individuals with and without IBD and which type of AIH (1 or 2) is more prevalent in IBD [10]. However, Perdigoto *et al.* noted a satisfactory response to therapy in adult patients with colitis and AIH compared to patients with PSC/ASC and IBD [24]. AIH may occur in the setting of medications, mostly tumor necrosis factor α (TNF-α) inhibitors. On the other hand, in the patients most refractory to therapy with PSC/AIH combined with IBD, the effectiveness of anti-TNF-α agents has been reported [25].

Autoimmune sclerosing cholangitis

A clear distinction between AIH and PSC in the course of IBD may be difficult because of the number of overlapping features. ASC shares the diagnostic criteria for both PSC and AIH. In the Deneau *et al.* study, ASC occurred in 2.3% of UC pediatric patients and 0.9% of CD children, similarly to another report by Valentino *et al.* (1.7% only in UC) [4, 10]. However, as many as 44% of children with ASC were also diagnosed with IBD in the Gregorio *et al.* study [23]. Reported data suggested that IBD patients with ASC are at greater risk of refractory disease and escalation of therapy is needed with more aggressive initial treatment [26].

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive accumulation of fat in the liver. In adults, the estimated 8.2% prevalence of NAFLD in the IBD population is lower than 33.6% observed in the general population of the United States [27]. However, according to the systemic review of Gizard *et al.*, the prevalence of NAFLD in IBD patients ranged from 1.5% to 56% compared to 6.3% to 33% in the general population [14]. The widespread increase of obesity among children made NAFLD a common pathology, but currently there are no available data concerning coexistence of IBD with NAFLD in the pediatric population [28]. In the Valentino *et al.* study ultrasound signs of fatty infiltration of the liver were detected in 18 of 129 examined children with IBD and abnormal liver enzymes, but all of them had low body mass index (BMI) [4].

Table 2. The increased risk of hepatobiliary disorders development in Crohn's disease and ulcerative colitis

Hepatobiliary disorder	Crohn's disease	Ulcerative colitis
Primary sclerosing cholangitis	+	+
Autoimmune sclerosing cholangitis	+	+
Steatohepatitis	+	+
Granulomatous hepatitis	+	NA
Hepatic amyloidosis	+	NA
Liver abscess	+	NA
Cholelithiasis	+	NA
Autoimmune hepatitis	+	+
Primary biliary cirrhosis	NA	+
Drug-induced liver injury (DILI)	+	+

NA – not applicable

Cholelithiasis

The association between cholelithiasis and IBD has already been reported [29, 30]. In children with IBD the presence of gallstones was described in 2.3% of patients [22]. In adults, the prevalence rate of cholelithiasis was estimated from 11% to 34% of patients with CD and in UC patients, based on the systemic review, which did not significantly differ from the general population [14]. However, chronic cholecystitis is diagnosed more often in UC and CD patients compared to non-IBD ones [31]. Parente *et al.* suggested that increased risk of cholelithiasis in CD may be caused by ileal resection [7]. Other suggested risk factors of gallstones are parenteral nutrition, changes in bile composition and impaired gallbladder emptying after surgery (Table 1).

Viral hepatitis

The response to HBV vaccination is significantly lower in people with IBD, as shown in the studies conducted on the IBD population of adults and children [32, 33]. It was established that only 56% of children with IBD had immunity to HBV as defined by an anti-HBs level ≥ 10 mIU/ml after the standard vaccination [34]. The absence of immunity was associated with older age, lower serum albumin levels and pancolitis. There is increased concern about reactivation of the HBV, due to chronic treatment of IBD patients with immunosuppressive drugs such as azathioprine (AZA), methotrexate (MTX) or anti-TNF-α agents, which is why the completion of vaccinations for hep-

Table 3. Hepatobiliary manifestations of drug-induced liver disease in inflammatory bowel disease [4]

Medication	Manifestations
5-ASA	– Acute liver failure – Granulomatous hepatitis – Drug-induced autoimmune hepatitis – DRESS syndrome
Thiopurines	– Cholestasis – Peliosis hepatitis – Veno-occlusive disease – Nodular regenerative hyperplasia – Hepatosplenic T-cell lymphoma – Sinusoidal obstructive syndrome
Methotrexate	– Fibrosis/Cirrhosis
Anti-TNF	– Cholestasis – Autoimmune hepatitis – Reactivation of hepatitis B
Glucocorticosteroids	– Reactivation of hepatitis B – Liver steatosis?

5-ASA – aminosalicylis acid, DRESS – drug reaction with eosinophilia and systemic symptoms, TNF – tumor necrosis factor

atitis B is extremely important [35]. For non-responders, a new full vaccination course should be recommended, and during anti-TNF therapy prophylaxis with antiviral drugs (lamivudine, entecavir, tenofovir) should be used for 6-12 months after cessation of anti-TNF agents or until obtaining the therapeutic endpoints in patients with elevated HBV DNA [36, 37]. The percentage of HCV infection among IBD patients is similar to that of the general population. There is no evidence of reactivation of HCV infection during immunosuppressive therapy and HCV treatment does not affect the course of IBD [38]. However, there is a lack of studies assessing the effects of such treatment in children. According to recommendations, all children infected with HCV who receive anti-TNF agents should have regular evaluation of liver enzymes and viral copies (HCV RNA) [39].

Drug-induced liver injury

Drug-induced hepatotoxicity is well known. Valentino *et al.* reported a significant association between the medication (corticosteroids, antibiotics and even exclusive enteral nutrition) used for IBD therapy in children and abnormal liver enzymes. However, the authors suggested that elevated liver enzymes might reflect uncontrolled IBD rather than the medications themselves because of the latest hypotheses which link the intestine disease with liver inflammation (Table 1) [4]. The main manifestations of drug-induced liver diseases are presented in Table 3.

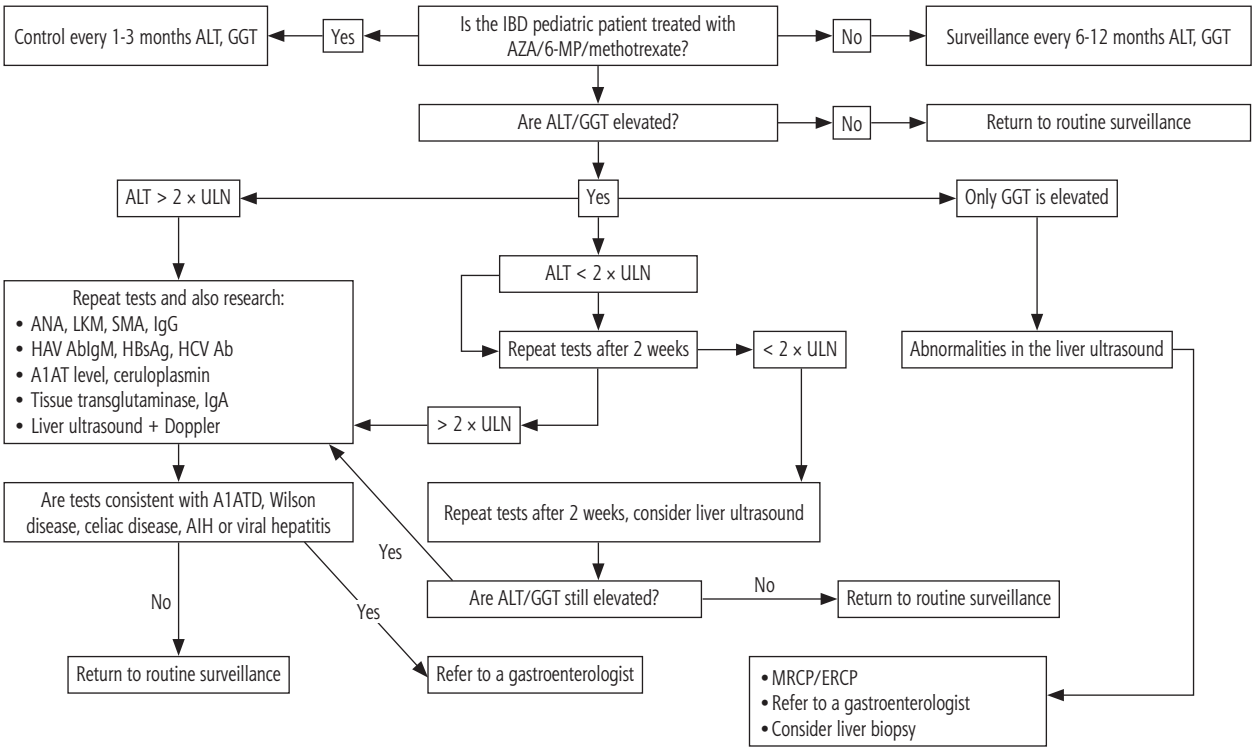
The use of methotrexate (MTX) in children with CD may be associated with elevated liver enzymes and rarely with severe fibrosis and cirrhosis when frequently applied, especially at high doses (like in adults with rheumatoid arthritis). A meta-analysis concerning prevalence of hepatotoxicity caused by MTX in pediatric IBD patients showed abnormal liver parameters in 10.2% of children, with the requirement of dose reduction in 6.4% of cases and discontinuation of therapy in 4.5% [40]. In a multicentre study, elevated liver enzymes were detected at least once in 39% of pediatric CD cases, during the first year of MTX use, and 18% required dose reduction or treatment cessation [41].

Hepatotoxicity after administration of infliximab has been reported in 0.4-6.7% of patients [42]. Among children with CD treated with infliximab, elevated alanine aminotransferase was observed in 24% of cases [43]. The mechanism is thought to be idiosyncratic. In genetically predisposed individuals, the drug reacting with cytokines may trigger the hepatic antigens and after presentation by the immune cells causes an immune reaction [44]. As mentioned above, the use of anti-TNF-α may also be associated with the risk of hepatitis B reactivation, especially when used in combination with other immunomodulatory drugs. That is why screening with serology (HBsAg, HBcAg) and vaccination for those who are seronegative is strongly recommended for all patients who might be considered for anti-TNF therapy.

Sulfasalazine can cause hepatocellular damage and cholestatic injury. It was estimated that liver toxicity affected about 0.4-2.9% of adults receiving that drug and sporadic pediatric patients [45, 46]. Newer, enteric-coated formulations, e.g. mesalamine, were reported as much safer for children [47].

Azathioprine is bio-transformed in the liver and kidneys into 6-mercaptopurine, and then into 6-thioguanine nucleotides, which have been associated with hepatotoxicity. The incidence rate of liver injury varies among studies, mainly due to lack of an opportunity for routine measurement of thiopurine metabolites. Liver injury caused by thiopurine affects about 1.4-7.1% of patients/year of the therapy and about half of the patients experience transient ALT activity elevation, which resolves spontaneously [48]. Cholestasis is rarely observed; however, it is an indication for immediate cessation of the therapy.

Corticosteroids (CCS) are recommended in the severe stage of IBD and have numerous side effects, manifested as dyslipidemia, glucose intolerance, insulin resistance, central adiposity and overt diabetes.



ALT – alanine aminotransferase, GGT – gamma-glutamyl transferase, IBD – inflammatory bowel disease, AZA – azathioprine, 6-MP – 6-mercaptopurine, ULN – upper limit of normal, ANA – antinuclear antibodies, LKM – liver kidney microsome, SMA – smooth muscle antibodies, IgG – immunoglobulin G, HAV – hepatitis A virus, AbIgM – immunoglobulin M antibody, HBsAg – hepatitis B surface antigen, HCV – hepatitis C virus, Ab – antibody, A1AT – alpha-1 antitrypsin, IgA – immunoglobulin A, A1ATD – alpha-1 antitrypsin deficiency, AIH – autoimmune hepatitis, MRCP – magnetic resonance cholangiopancreatography, ERCP – endoscopic retrograde cholangiopancreatography

Fig. 1. Diagnostic algorithm for increased activity in liver enzymes in child with inflammatory bowel disease adapted from Valentino *et al.* [51]

These medications change hepatic lipid metabolism, inducing liver steatosis. In pediatric IBD patients the duration of the CCS therapy usually does not exceed 12 weeks, but some reports suggested an association of CCS use with elevated liver enzymes [4].

Portal vein thrombosis

Portal vein thrombosis (PVT) is a rare complication of IBD, occurring more frequently in the setting of recent abdominal surgery [49]. PVT was found in 45% of patients undergoing restorative proctocolectomy [49]. Overall venous thromboembolism was reported in 0.7% of IBD children [50]. The proposed reasons include the mobilization of the small intestine into the mesentery root, the tension of anastomosis of the capsule and manipulation of mesenteric vessels [49].

Conclusions

An increase in liver enzymes' activity in the course of IBD always necessitates finding the cause of this condition. A diagnostic algorithm for abnormal liver enzymes in children with IBD was proposed by Valentine *et al.* (Fig. 1) [51]. Among hepatobiliary pathologies associated with IBD in pediatric patients, PSC and ASC are the most prevalent and important because of the potential risk of liver transplantation (LT). Abnormal liver enzymes in pediatric IBD without PSC/ASC may reflect the effect of medication hepatotoxicity or uncontrolled inflammation on the liver in IBD. Viral hepatitis screening is recommended in IBD individuals, especially for HBV due to the possible impact of immunosuppressive drugs on reactivation of the disease. Other causes of elevated liver enzymes, such as PVT, AIH and NAFLD, are rarely seen in children. Taking all these aspects into account, good cooperation between IBD clinicians, gastroenterologists and the general practitioners is needed.

Disclosure

The authors report no conflict of interest.

References

1. Pusateri AJ, Kim SC, Dotson JL, et al. Incidence, pattern, and etiology of elevated liver enzymes in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2015; 60: 592-597.

2. Mendes FD, Levy C, Enders FB, et al. Abnormal hepatic biochemistries in patients with inflammatory bowel disease. Am J Gastroenterol 2007; 102: 344-350.
3. Goyal A, Hyams JS, Lerer T, et al. Liver enzyme elevations within 3 months of diagnosis of inflammatory bowel disease and likelihood of liver disease. J Pediatr Gastroenterol Nutr 2014; 59: 321-323.
4. Valentino PL, Feldman BM, Walters TD, et al. Abnormal liver biochemistry is common in pediatric inflammatory bowel disease: prevalence and associations. Inflamm Bowel Dis 2015; 21: 2848-2856.
5. Palmela C, Peerani F, Castaneda D, et al. Inflammatory bowel disease and primary sclerosing cholangitis: a review of the phenotype and associated specific features. Gut Liver 2018; 12: 17-29.
6. Zezos P, Kouklakis G, Saibil F. Inflammatory bowel disease and thromboembolism. World J Gastroenterol 2014; 20: 13863-13878.
7. Parente F, Pastore L, Bargiggia S, et al. Incidence and risk factors for gallstones in patients with inflammatory bowel disease: a large case-control study. Hepatology 2007; 45: 1267-1274.
8. Braun M, Fraser GM, Kunin M, et al. Mesalamine-induced granulomatous hepatitis. Am J Gastroenterol 1999; 94: 1973-1974.
9. Deneau MR, El-Matary W, Valentino PL, et al. The natural history of primary sclerosing cholangitis in 781 children: A multicenter, international collaboration. Hepatology 2017; 66: 518-527.
10. Deneau M, Jensen MK, Holmen J, et al. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: epidemiology and natural history. Hepatology 2013; 58: 1392-1400.
11. Loftus EV, Harewood GC, Loftus CG, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut 2005; 54: 91-96.
12. Dotson JL, Hyams JS, Markowitz J, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. J Pediatr Gastroenterol Nutr 2010; 51: 140-145.
13. Lindberg J, Stenling R, Palmqvist R, Rutegård J. Early onset of ulcerative colitis: long-term follow-up with special reference to colorectal cancer and primary sclerosing cholangitis. J Pediatr Gastroenterol Nutr 2008; 46: 534-538.
14. Gizard E, Ford AC, Bronowicki JP, Peyrin-Biroulet L. Systematic review: The epidemiology of the hepatobiliary manifestations in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2014; 40: 3-15.
15. Soetikno RM, Lin OS, Heidenreich PA, et al. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. Gastrointest Endosc 2002; 56: 48-54.
16. Tsaitas C, Semertzidou A, Sinakos E. Update on inflammatory bowel disease in patients with primary sclerosing cholangitis. World J Hepatol 2014; 6: 178-187.
17. Yoon J, Oh SH, Kim HJ, et al. Primary sclerosing cholangitis with inflammatory bowel disease in korean children. Pediatr Gastroenterol Hepatol Nutr 2015; 18: 268-275.
18. Lindor KD, Kowdley KV, Harrison ME, American College of Gastroenterology. ACG Clinical Guideline: Primary Sclerosing Cholangitis. Am J Gastroenterol 2015; 110: 646-659; quiz 60.
19. Liberal R, Zen Y, Mieli-Vergani G, Vergani D. Liver transplantation and autoimmune liver diseases. Liver Transpl 2013; 19: 1065-1077.
20. Riley TR, Schoen RE, Lee RG, Rakela J. A case series of transplant recipients who despite immunosuppression developed inflammatory bowel disease. Am J Gastroenterol 1997; 92: 279-282.
21. Hyams JS. Extraintestinal manifestations of inflammatory bowel disease in children. J Pediatr Gastroenterol Nutr 1994; 19: 7-21.
22. Jose FA, Garnett EA, Vittinghoff E, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2009; 15: 63-68.
23. Gregorio GV, Portmann B, Karani J, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology 2001; 33: 544-553.
24. Perdigoto R, Carpenter HA, Czaja AJ. Frequency and significance of chronic ulcerative colitis in severe corticosteroid-treated autoimmune hepatitis. J Hepatol 1992; 14: 325-331.
25. Nedelkopoulou N, Vadamalayan B, Vergani D, Mieli-Vergani G. Anti-TNFα treatment in children and adolescents with combined inflammatory bowel disease and autoimmune liver disease. J Pediatr Gastroenterol Nutr 2018; 66: 100-105.
26. Trivedi PJ, Chapman RW. PSC, AIH and overlap syndrome in inflammatory bowel disease. Clin Res Hepatol Gastroenterol 2012; 36: 420-436.
27. Sourianarayanane A, Garg G, Smith TH, et al. Risk factors of non-alcoholic fatty liver disease in patients with inflammatory bowel disease. J Crohns Colitis 2013; 7: e279-285.
28. Welsh JA, Karpen S, Vos MB. Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010. J Pediatr 2013; 162: 496-500.e1.
29. Cohen S, Kpplan M, Gottlieb L, Patterson J. Liver disease and gallstones in regional enteritis. Gastroenterology 1971; 60: 237-245.
30. Bargiggia S, Maconi G, Elli M, et al. Sonographic prevalence of liver steatosis and biliary tract stones in patients with inflammatory bowel disease: study of 511 subjects at a single center. J Clin Gastroenterol 2003; 36: 417-420.
31. Lin J, Shen B, Lee HJ, Goldblum JR. Histopathological characterization of cholecystectomy specimens in patients with inflammatory bowel disease. J Crohns Colitis 2012; 6: 895-899.
32. Belle A, Baumann C, Bigard MA, et al. Impact of immunosuppressive therapy on hepatitis B vaccination in inflammatory bowel diseases. Eur J Gastroenterol Hepatol 2015; 27: 877-881.
33. Urganci N, Kalyoncu D. Immunogenecity of hepatitis A and B vaccination in pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2013; 56: 412-415.
34. Moses J, Alkhouri N, Shannon A, et al. Hepatitis B immunity and response to booster vaccination in children with inflammatory bowel disease treated with infliximab. Am J Gastroenterol 2012; 107: 133-138.
35. Loras C, Gisbert JP, Mínguez M, et al. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. Gut 2010; 59: 1340-1346.
36. Rahier JF, Ben-Horin S, Chowers Y, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 2009; 3: 47-91.
37. Liver EAFTSOT. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012; 57: 167-185.
38. Rojas-Feria M, Castro M, Suárez E, et al. Hepatobiliary manifestations in inflammatory bowel disease: the gut, the drugs and the liver. World J Gastroenterol 2013; 19: 7327-7340.

39. Saubermann LJ, Deneau M, Falcone RA, et al. Hepatic issues and complications associated with inflammatory bowel disease: a clinical report from the NASPGHAN Inflammatory Bowel Disease and Hepatology Committees. J Pediatr Gastroenterol Nutr 2017; 64: 639-652.
40. Valentino PL, Church PC, Shah PS, et al. Hepatotoxicity caused by methotrexate therapy in children with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis 2014; 20: 47-59.
41. Turner D, Doveh E, Cohen A, et al. Efficacy of oral methotrexate in paediatric Crohn's disease: a multicentre propensity score study. Gut 2015; 64: 1898-1904.
42. Ghabril M, Bonkovsky HL, Kum C, et al. Liver injury from tumor necrosis factor-α antagonists: analysis of thirty-four cases. Clin Gastroenterol Hepatol 2013; 11: 558-564.e3.
43. Church PC, Guan J, Walters TD, et al. Infliximab maintains durable response and facilitates catch-up growth in luminal pediatric Crohn's disease. Inflamm Bowel Dis 2014; 20: 1177-1186.
44. Colina F, Molero A, Casís B, Martínez-Montiel P. Infliximab-related hepatitis: a case study and literature review. Dig Dis Sci 2013; 58: 3362-3367.
45. Boyer DL, Li BU, Fyda JN, Friedman RA. Sulfasalazine-induced hepatotoxicity in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1989; 8: 528-532.
46. Amos RS, Pullar T, Bax DE, et al. Sulphasalazine for rheumatoid arthritis: toxicity in 774 patients monitored for one to 11 years. Br Med J (Clin Res Ed) 1986; 293: 420-423.
47. D'agata ID, Vanounou T, Seidman E. Mesalamine in pediatric inflammatory bowel disease: a 10-year experience. Inflamm Bowel Dis 1996; 2: 229-235.
48. Gisbert JP, González-Lama Y, Maté J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. Am J Gastroenterol 2007; 102: 1518-1527.
49. Remzi FH, Fazio VW, Oncel M, et al. Portal vein thrombi after restorative proctocolectomy. Surgery 2002; 132: 655-661; discussion 61-62.
50. Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut 2011; 60: 937-943.
51. Valentino PL. Diagnostic algorithm for increased activity in liver enzymes in child with IBD. In: Mamula P, Markowitz JE, Baldassano RN (eds.). Pediatric inflammatory bowel disease. Springer, New York, NY 2013; 95-107.