Hepatic Abnormalities in Inflammatory Bowel Disease

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Contents

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Hepatobiliary Complications in Patients With IBD

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Prevalence of Hepatobiliary Complications in Patients With IBD

- Complications of the liver or biliary ducts are common in patients with inflammatory bowel disease (IBD)[1]
  - May occur at any time during the course of IBD, and clinical course is often independent of intestinal inflammation[2,3]
  - Range from benign to serious, progressive, life-threatening diseases[1]
  - May be related to IBD (eg, PSC), distinct process (eg, viral hepatitis), or induced by drugs used to treat IBD[1,2]
- It has been estimated that up to 30% of patients with IBD develop abnormal liver tests[4]

- Abnormal liver enzymes are frequently encountered in patients with IBD, and a thorough evaluation is required to correctly identify the etiology[5]
  - UC is diagnosed in 48% to 68% of patients with PSC, and up to 13% of patients with PSC have CD
- Concomitant IBD and PSC significantly increases the risk for colon cancer, particularly in patients with UC[5]
  - Patients with UC and PSC are almost 5 times more likely to experience development of colon cancer and dysplasia compared to patients with UC alone

CD=Crohn's disease; IBD=inflammatory bowel disease; PSC=primary sclerosing cholangitis; UC=ulcerative colitis.

1. Yarur AJ, et al. *Inflamm Bowel Dis*. 2014;20(9):1655-1667. **2.** Fousekis FS, et al. *Gastroenterol Res*. 2018;11(2):83-94. **3.** Restellini S, et al. *Liver Int*. 2017;37(4):475-489. **4.** Rojas-Feria M, et al. *World J Gastroenterol*. 2013;19(42):7327-7340. **5.** Patel P, Dalal S. *Clin Liver Dis (Hoboken).* 2021;17(4):292-296.

Review of Laboratory Tests to Assess Liver Injury

- The standard comprehensive hepatic panel includes markers of liver damage[1-2,a-b]:

Laboratory Parameters	Normal Adult Ranges[1,3,c]	Function[1,2]
ALT and AST	**ALT:** 29-33 IU/L in men; 19-25 IU/L in women **AST:** 8-48 U/L	• Found in hepatocytes and other tissues • Released into the bloodstream in response to hepatocyte injury or death • ALT is considered more liver specific • AST can be elevated with skeletal muscle injury (eg, myositis), cardiac muscle damage (eg, myocardial infarction), or red blood cell hemolysis (eg, hemolytic anemia)
ALP	40-129 U/L	• Found in hepatocytes as well as in bone, intestines, kidneys, and white blood cells • Elevation may indicate obstruction or damage of the bile ducts (verify hepatic origin with GGT) or infiltrative disease of the liver (eg, sarcoidosis)
GGT	8-61 U/L	• Abundant in the liver and also present in the kidney, intestine, prostate, and pancreas but not in bone; therefore it can be useful in confirming that an elevated ALP is of liver and not bone origin

Note: These results are typical for adult men except for ALT. Normal results vary from laboratory to laboratory. Ranges may differ for women and children and based on other patient characteristics (eg, body mass index).

[a]As defined by the American College of Gastroenterology. [b]Laboratory measurements of liver chemistries are indirect markers of hepatobiliary disease and are not true measures of hepatic function.
[c]Normal laboratory values for liver blood tests are generally defined as the mean value of a healthy population ± 2 standard deviations.[1]
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=γ-glutamyltransferase.

1. Kwo PY, et al. *Am J Gastroenterol*. 2017;112(1):18-35. **2.** Newsome PN, et al. *Gut*. 2018;67(1):6-19. **3.** Mayo Clinic. https://www.mayoclinic.org/tests-procedures/liver-function-tests/about/pac-20394595. Accessed September 20, 2021.

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Considerations When Interpreting ALT

- A recent ACG clinical guideline review, confirmed ALT ranges in “healthy” controls (prospectively studied populations without liver disease)[1]
  - Normal range for ALT confirmed to be 29-33 IU/L for men and 19-25 IU/L for women
  - A borderline ALT and/or AST elevation is defined as <2x ULN, a mild elevation as 2-5x ULN, moderate elevation as 5-15x ULN, severe elevation as >15x ULN, and massive elevation at >10,000 IU/L
- A normal ALT value does not necessarily indicate the absence of inflammation or fibrosis[2]
  - An observational study in patients with NAFLD and normal liver enzymes showed that 35% had NASH, 20% had advanced fibrosis, and 7% had cirrhosis[2]

Note: Participants in this study had histologically confirmed NAFLD as an entry criterion, which implies that clinically significant NAFLD was suspected by managing clinicians, potentially creating a selection bias. No external validation of the findings was performed.

- Clinical judgment remains paramount in interpreting a patient’s liver chemistry

ACG Summary Statements on Liver Chemistry Tests[1]

1. A true healthy normal ALT level in prospectively studied populations without identifiable risk factors for liver disease ranges from 29 to 33 IU/L for males and 19 to 25 IU/L for females, and levels above this should be assessed by physicians.
2. Elevated ALT or AST above the ULN in a population without identifiable risk factors is associated with increased liver-related mortality.
3. There is a linear relationship between ALT level and BMI that should be assessed by physicians.
4. A normal ALT level may not exclude significant liver disease.
5. ALT levels are higher in males than females.
6. AST and ALT ULN ranges can vary between different labs.
7. Clinicians may rely on local lab ULN ranges for alkaline phosphatase and bilirubin.

ACG=American College of Gastroenterology; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis; ULN=upper limit of normal.

1. Kwo P, et al. *Am J Gastroenterol.* 2017;112(1):18-35. **2.** Gawrieh S, et al. *Am J Gastroenterol.* 2019;114(10):1626-1635.

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Laboratory Tests to Assess Liver Function

- Additional laboratory parameters that can be assessed include markers of liver function, which measure hepatic impairment. Markers of liver function can also be impacted by other extrahepatic factors[1]

Laboratory Parameters	Normal Adult Ranges[2,3,a]	Function[1,4]
Albumin	3.5-5 g/dL	• Plasma protein exclusively synthesized by the liver • Many biological functions, including maintenance of oncotic pressure and metabolism of lipids • Reduction (hypoalbuminemia) may indicate hepatocellular injury due to the inability to make albumin
Bilirubin	0.1-1.2 mg/dL	• Secreted by the liver as a by-product of the breakdown of senescent red blood cells • Elevated bilirubin (hyperbilirubinemia) may indicate hepatocellular dysfunction or cholestasis due to impaired conjugation and/or excretion
Prothrombin	9.4-12.5 s	• Prothrombin time measures extrinsic pathway of coagulation (blood clotting tendency) • Elevated prothrombin time may indicate hepatocellular injury (more sensitive than albumin)
INR	<1.1	• Measures impairment in production of clotting factors and coagulopathy • Does not correlate with risk of bleeding in patients with cirrhosis, because patients have abnormal levels of anticoagulants and procoagulants[5]

Note: Most of these results are typical for adult men except for ALT. Normal results vary from laboratory to laboratory. Ranges may differ for women and children and based on other patient characteristics (eg, body mass index).

[a]Normal laboratory values for liver blood tests are generally defined as the mean value of a healthy population ± 2 standard deviations.[1]
ALT=alanine aminotransferase; INR=international normalized ratio.

1. Kwo PY, et al. *Am J Gastroenterol*. 2017;112(1):18-35. **2.** Mayo Clinic. https://www.mayoclinic.org/tests-procedures/liver-function-tests/about/pac-20394595. Accessed September 20, 2021. **3.** Mayo Clinic. https://www.mayoclinic.org/tests-procedures/prothrombin-time/about/pac-20384661. Accessed September 20, 2021. **4.** Newsome PN, et al. *Gut*. 2018;67(1):6-19. **5.** Harrison MF. *West J Emerg Med*. 2018;19(5):863-871.

Differential Diagnoses for Elevated Liver Laboratory Values

- Abnormal liver blood test results are values outside the standard reference interval[1,2]
  - However, they should be interpreted in the context of a patient's medical history, current health status, and other diagnostic measures
  - Consider assessing abnormal laboratory values with repeat measurements separated in time to confirm an "abnormal" result, especially if there is a mild elevation (eg, AST can be transiently elevated unrelated to liver disease)
- Hepatobiliary injury may be characterized as follows[1-3,a]:
  - Hepatocellular injury: disproportionate elevations of AST and ALT compared with ALP (with or without abnormal bilirubin)
  - Cholestatic injury: disproportionate elevation of ALP compared with AST and ALT (abnormal GGT, with or without abnormal bilirubin)

Type	Causes	Differential Diagnoses[4]
Hepatocellular	ALT predominant	Acute or chronic viral hepatitis, steatohepatitis, acute Budd-Chiari syndrome, ischemic hepatitis, autoimmune, hemochromatosis, medications/toxins, α1-antitrypsin deficiency, Wilson disease, celiac disease
	AST predominant	Alcohol related, steatohepatitis, cirrhosis, nonhepatic (hemolysis, myopathy, thyroid disease, exercise)
Cholestatic	Hepatobiliary causes	Bile duct obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, medication induced, infiltrating diseases of the liver (sarcoidosis, amyloidosis, lymphoma, etc), cystic fibrosis, hepatic metastasis, cholestasis
	Nonhepatic causes of elevated ALP	Bone disease, pregnancy, chronic renal failure, lymphoma or other malignancies, congestive heart failure, childhood growth, infection or inflammation

[a]In addition to assessing the extent of liver chemistry abnormality (which is not always a reliable guide to clinical significance), imaging or liver biopsy may be required to confirm diagnosis.[3]
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=γ-glutamyltransferase.

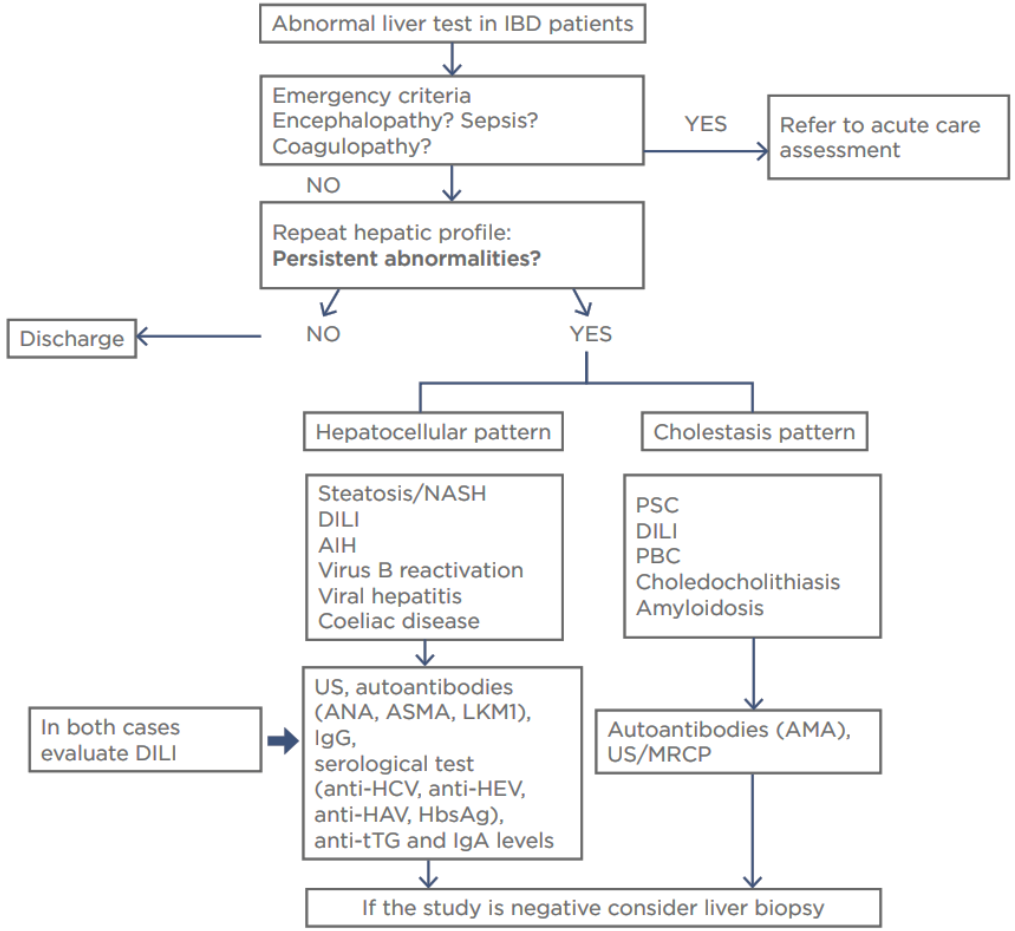
1. Newsome PN, et al. *Gut*. 2018;67(1):6-19. **2.** Kwo PY, et al. *Am J Gastroenterol*. 2017;112(1):18-35. **3.** Crohn's and Colitis Foundation. https://www.crohnscolitisfoundation.org/sites/default/files/legacy/assets/pdfs/liver-disease.pdf. Accessed September 20, 2021. **4.** Lala V, Minter DA. https://www.ncbi.nlm.nih.gov/books/NBK482489/. Accessed September 20, 2021.

Considerations for Diagnosing an Abnormal Liver Test in Patients With IBD

- Approximately 50% of patients with IBD will present with a transient elevation of liver enzymes during long-term follow up[1]
- A retrospective review of clinical records in Italy found DILI to be the most frequent cause of transient LFT alteration (34.1%), possibly linked to an increased and earlier use of immunosuppressants in an attempt to reduce corticosteroid use[2]
  - Fatty liver was found to be the most common cause of persistent abnormal LFTs (65.4%)

Note: The review was limited by a short period of observation, and could be viewed as a potential drawback of results because the percentage of the established diagnosis may have changed as the time passed.

- Although the differential diagnosis should always include DILI, other reasons for liver injury should be considered based on the hepatocellular or cholestatic pattern of disease[1]



AIH=autoimmune hepatitis; AMA=antimitochondrial antibody; ANA=antinuclear antibody; ASMA=anti–smooth muscle antibody; DILI=drug-induced liver injury; HAV=hepatitis A virus; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; IBD=inflammatory bowel disease; IgA=immunoglobulin A; IgG=immunoglobulin G; LFT=liver function test; LKM1=liver kidney microsome antibody; MRCP=magnetic resonance cholangiography; NASH=nonalcoholic steatohepatitis; PBC=primary biliary cholangitis; PSC=primary sclerosing cholangitis; tTg=tissue transglutaminase; US=ultrasound.

1. Klein M, et al. *EMJ Hepatol*. 2020;8(1):26-32. **2.** Cappello M, et al. *Clin Med Insights Gastroenterol.* 2014;7:25-31.

Commonly Occurring Hepatobiliary Manifestations in Patients With IBD

Characterizing Hepatobiliary Injury Associated With IBD

Select Hepatobiliary Manifestations Seen in Patients With IBD[1-4,a]	
Cholestatic	**Primary sclerosing cholangitis (PSC)**
Hepatocellular	**Fatty liver (hepatic steatosis)** • Nonalcoholic fatty liver disease (NAFLD) • Nonalcoholic steatohepatitis (NASH)
	Reactivation of viral hepatitis
Cholestatic or hepatocellular	**Drug-induced hepatotoxicity**

[a]Not a complete list of possible hepatobiliary manifestations.
IBD=inflammatory bowel disease.

1. Fousekis FS, et al. *Gastroenterol Res*. 2018;11(2):83-94. **2.** Glassner K, et al. *Inflamm Bowel Dis*. 2017;23(6):998-1003. **3.** Newsome PN, et al. *Gut*. 2018;67(1):6-19. **4.** Restellini S, et al. *Liver Int*. 2017;37(4):475-489.

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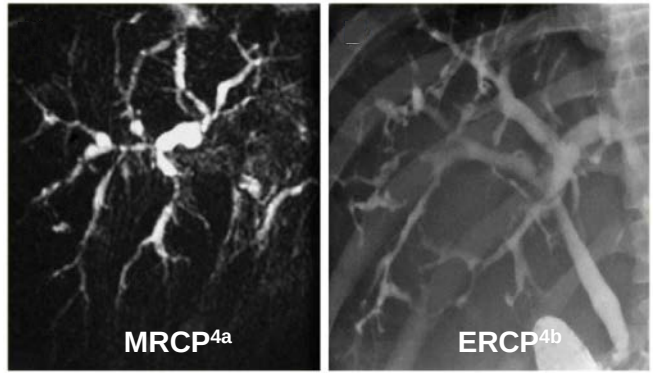
Primary Sclerosing Cholangitis

- Primary sclerosing cholangitis (PSC) is a chronic and progressive cholestatic disease that is characterized by inflammation and fibrosis of intrahepatic and extrahepatic bile ducts[1]
  - About 5% to 10% of patients with IBD experience PSC; conversely, up to 80% of patients with PSC have IBD[2]

- Diagnosis: Assessment of hepatic chemistries (ALP) and cholangiography (multifocal stricturing and dilation of bile ducts with irregular strictures yielding a “beaded” pattern)[1]
  - Large-duct PSC[1,3]
    - MRCP (non-invasive) is the preferred method of diagnosis
    - ERCP is reserved for therapeutic use or for the diagnosis of cholangiocarcinoma
  - Small-duct PSC[1]
    - Requires liver biopsy to confirm as MRCP findings may appear normal
  - Up to 50% of patients with PSC can be asymptomatic at diagnosis. When present, symptoms include pruritus, abdominal pain, jaundice, weight loss, and/or fatigue



- Prognosis: In a Dutch study of data from 44 hospitals, the reported median survival from time of diagnosis until death or liver transplantation was 21.3 years in a population-based cohort vs 13.2 years in the combined transplant centers cohort[5]
  - Historical data reported median survival of 12 years but may be biased by being restricted to specialized centers through tertiary referrals

Note: In the population-based PSC cohort (n=590), 68% of patients had IBD. True population-based figures were difficult to obtain. Not all PSC patients without clinical signs of bowel disease have undergone a screening colonoscopy in the past, which may result in an underestimation of concurrent subclinical IBD.

[a]MRCP with intrahepatic stricturing with alternating normal and dilated segments of bile ducts. [b]ERCP with similar findings.
ALP=alkaline phosphatase; ERCP=endoscopic retrograde cholangiopancreatography; IBD=inflammatory bowel disease; MRCP=magnetic resonance cholangiopancreatography; PSC=primary sclerosing cholangitis.

1. Yarur AJ, et al. *Inflamm Bowel Dis*. 2014;20(9):1655-1667. **2.** Chapman RW. *Clin Liver Dis (Hoboken)*. 2017;9(5):107-110. **3.** Rojas-Feria M, et al. *World J Gastroenterol*. 2013;19(42):7327-7340.
4. Gidwaney NG, et al. *World J Gastroenterol*. 2017;23(14):2459-2469. **5.** Boonstra K, et al. *Hepatology.* 2013;58:2045-2055.

Primary Sclerosing Cholangitis (cont'd)

- Complications include cholangiocarcinoma, cholangitis, gallstones, cholecystitis, gallbladder carcinoma, colorectal cancer, and pouchitis[1]
  - Cholangiocarcinoma: 9% risk after 10 years; for those with dominant strictures, risk is about 26% after 10 years[1,2]
    - Yearly screening for cholangiocarcinoma with abdominal imaging is recommended
  - Colorectal cancer: In an observational longitudinal cohort study, risk was increased 10 times relative to PSC-negative patients with UC[3]

    Note: True population-based figures were difficult to obtain. Not all PSC patients without clinical signs of bowel disease have undergone a screening colonoscopy in the past, which may result in an underestimation of concurrent subclinical IBD.
    - Yearly colonoscopies in patients with colitis (UC or CD) and PSC are recommended[2]
  - Fat-soluble vitamin deficiencies (vitamins A, D, E, K)[4,5]
  - Hepatic osteodystrophy (as assessed by periodic DEXA scans in patients with advanced liver disease)[6]
- Management: No pharmacological therapy has been shown to be effective for PSC; treatment therefore focuses on slowing disease progression and managing complications[4]
  - Liver transplantation yields excellent survival (5-year and 10-year survival rates of 85% and 70%, respectively)
  - PSC can recur in 20% to 25% of cases (depends on diagnostic criteria and time horizon)

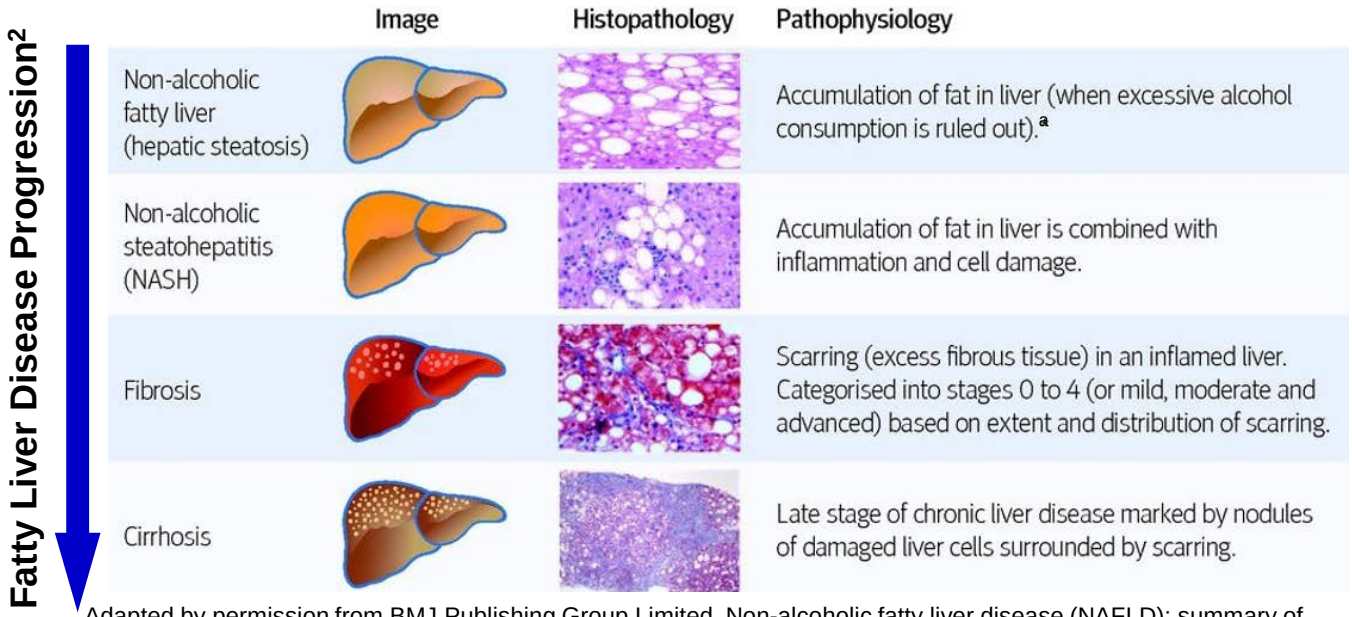
CD=Crohn's disease; DEXA=dual-energy x-ray absorptiometry; IBD=inflammatory bowel disease; PSC=primary sclerosing cholangitis; UC=ulcerative colitis.

1. Fousekis FS, et al. *Gastroenterol Res*. 2018;11(2):83-94. **2.** Yarur AJ, et al. *Inflamm Bowel Dis*. 2014;20(9):1655-1667. **3.** Boonstra K, et al. *Hepatology.* 2013;58(6):2045-2055. **4.** Rojas-Feria M, et al. *World J Gastroenterol*. 2013;19(42):7327-7340. **5.** Albahrani AA, Greaves RF. *Clin Biochem Rev*. 2016;37(1):27-47. **6.** Gatta A, et al. *Clin Cases Miner Bone Metab.* 2014;11(3):185-191.

Fatty Liver

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

- Syndrome with a histological spectrum ranging from benign steatosis to nonalcoholic steatohepatitis (NASH)[1-3]
  - Nonalcoholic fatty liver disease (NAFLD): hepatic steatosis without hepatic injury
  - Nonalcoholic steatohepatitis (NASH): hepatic steatosis with hepatic inflammation
- NAFLD is seen in approximately 10% to 46% of the US population[3]
- Prevalence of NAFLD estimated at 21% to 33% in patients with IBD[4]



Adapted by permission from BMJ Publishing Group Limited. Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance, Glen J, Floros L, Day C, Pryke R, 354, i4428, © 2016.

- Patients with IBD who develop NAFLD may progress to liver cirrhosis
- These patients have an overall 10-year mortality rate of 18.5%[5]

[a]The prevalence in the general population for different stages of NAFLD is uncertain.
IBD=inflammatory bowel disease; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis.

1. Restellini S, et al. *Liver Int*. 2017;37(4):475-489. **2.** Glen J, et al. *BMJ*. 2016;354:i4428. **3.** Glassner K, et al. *Inflamm Bowel Dis*. 2017;23(6):998-1003. **4.** Zou ZY, et al. *Inflamm Bowel Dis.* 2019;25(11):1764-1772. **5.** Bessissow T, et al. *Inflamm Bowel Dis*. 2016;22:1937-1944.

Fatty Liver (cont'd)

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

- Diagnosis:
  - Nonalcoholic fatty liver disease (NAFLD)
    - Largely asymptomatic[1,2]
    - Requires evidence of hepatic steatosis by either imaging (ultrasound, CT, or MRI) or biopsy (gold standard)[1,3,4]
      - Must exclude other conditions, namely excessive alcohol consumption[1]
    - Liver enzymes are nondiagnostic. They can be normal with nonalcoholic steatohepatitis (NASH) and advanced fibrosis or abnormal in the absence of NASH
      - 19% of patients thought to have NAFLD and normal liver enzymes have NASH and stage 2-3 fibrosis[5]
      - 7% of patients thought to have NAFLD and normal liver enzymes have NASH and cirrhosis[5]
  - NASH[3]
    - Requires a biopsy for histologic diagnosis
- Prognosis: NAFLD may be progressive, resulting in complications of cirrhosis such as hepatocellular cancer and liver failure[4]
  - Other complications associated with NAFLD include chronic kidney disease, hypertension, and type 2 diabetes[1]
  - In patients with type 2 diabetes, NAFLD is a risk factor for cardiovascular complications such as atrial fibrillation, myocardial infarction, and ischemic stroke, as well as death from cardiovascular causes[1]
- Management:
  - Lifestyle modification (eg, weight loss, physical activity, diet) is the only evidence-based management for NAFLD/NASH[1]

CT=computed tomography; MRI=magnetic resonance imaging; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis.

1. Glen J, et al. *BMJ*. 2016;354:i4428. **2.** Restellini S, et al. *Liver Int*. 2017;37(4):475-489. **3.** National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/diagnosis. Accessed September 20, 2021. **4.** Nalbantoglu I, Brunt E. *World J Gastroenterol.* 2014;20(27):9026-9037. **5.** Gawrieh S, et al. *Am J Gastroenterol.* 2019;114(10):1626-1635.

Hepatic Complications Related to Treatment of IBD

Hepatobiliary Effects of IBD Therapies

- Most drugs used for the treatment of IBD have potential for hepatotoxicity[1]
  - Mechanism of hepatotoxicity may be **direct** or **indirect** in nature[2]
  - Clinical presentation may be **acute** or **chronic**, and the extent of injury can range from mild liver chemistry abnormalities to symptomatic hepatitis or acute liver failure[1,3]
  - Each drug may **induce one or more types of hepatobiliary manifestations**[2,4]
- Causality may be challenging to establish because patients with IBD often receive multiple drugs or have comorbidities that affect the hepatobiliary system[1]
  - Mechanisms for hepatotoxicity can be immune mediated, metabolic, direct toxic effects, or related to the induction or worsening of intrinsic liver disease[2]

Potential Hepatobiliary Effects of IBD Therapies[2,4]

Direct Effects	Indirect Effects
• Liver chemistry abnormalities • Drug hypersensitivity • Hepatocellular injury • Cholestatic injury • Liver failure	• Worsening of NASH • Reactivation of viral hepatitis B or hepatitis C

IBD=inflammatory bowel disease; NASH=nonalcoholic steatohepatitis.

1. Restellini S, et al. *Liver Int*. 2017;37(4):475-489. **2.** Shah NJ, et al. *Clin Case Rep Rev*. 2017;3(7):1-11. **3.** Koller T, et al. *World J Gastroenterol*. 2017;23(22):4102-4111. **4.** Hirten R, et al. *World J Hepatol*. 2015;7(27):2716-2728.

Viral Hepatitis in IBD

- Hepatitis B and hepatitis C are viral infections that impact the liver and can lead to chronic liver injury and cirrhosis[1-3]
- Prevalence of hepatitis B and hepatitis C is thought to be similar in patients with IBD and the general population[4]
- Diagnosis[2,5]:
  - Majority of patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection are symptom free, with only a minority of patients presenting with nonspecific symptoms (eg, fatigue)
  - Liver blood tests may indicate hepatitis (ALT signifies active inflammation) or even advanced liver disease (elevated bilirubin or INR, or decreased albumin); however, early and definitive diagnosis requires viral serologic testing

Interpreting HBV and HCV Serologies[3,5]

Hepatitis Type	Serology	Indicates
Hepatitis B	Anti-HBs	Immunity (vaccine or prior exposure)
	Anti-HBc	Active or prior history of infection
	Anti-HBc IgM	Acute infection
	HBsAg	Active infection
	HBeAg	Acute or chronic infection
	HBV DNA	Chronic infection
Hepatitis C	Anti-HCV	Active or prior history of infection
	HCV RNA	Active infection

ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HbeAg=hepatitis B e antigen; HbsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; IBD=inflammatory bowel disease; IgM=immunoglobulin M; INR=international normalized ratio.

1. Do A, Reau N. *Hepatol Commun.* 2020;4(3):329-341. **2.** Newsome PN, et al. *Gut*. 2018;67(1):6-19. **3.** Centers for Disease Control and Prevention. https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm. Accessed September 20, 2021. **4.** Restellini S, et al. *Liver Int*. 2017;37(4):475-489. **5.** Kwo PY, et al. *Am J Gastroenterol*. 2017;112(1):18-35.

Considerations for Hepatitis B in IBD

- Viral reactivation risk for patients with IBD depends on the following[1-2,a]:
  - HBV status (highest risk if there is an active infection with detectable HBsAg, or even if anti-HBc is positive)
  - Immunosuppressant status (type, number, duration)
- Prognosis[3]:
  - Reactivation of HBV after immunosuppressive therapy is associated with significant morbidity and mortality, which can be due to hepatic decompensation or acute liver failure
- Management of HBV in patients with IBD:
  - All patients should be screened for HBV at diagnosis of IBD by testing HBsAg, anti-HBc, and anti-HBs[4b]
  - HBV vaccination is recommended in all HBV anti-HBs seronegative patients[4b]
    - Efficacy of HBV vaccination is impaired in patients with IBD; anti-HBs response should be measured after vaccination
  - Patients positive for HBV should receive antiviral treatment for at least 6 months after discontinuation of immunosuppressive therapy[3]
  - Regular monitoring of HBV DNA and ALT may guide treatment to minimize liver injury and improve patient outcomes[2,3,5]

[a]Viral reactivation is defined by an increase of 1 log in viral load or reappearance of the virus after previous clearance. [b]As recommended by the European Crohn's and Colitis Foundation.
ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; DNA=deoxyribonucleic acid; HbsAg=hepatitis B surface antigen; HBV=hepatitis B virus; IBD=inflammatory bowel disease.

1. Restellini S, et al. *Liver Int*. 2017;37(4):475-489. **2.** Axiaris G, et al. *World J Gastroenterol*. 2021;27(25):3762-3779. **3.** Reddy KR, et al. *Gastroenterology*. 2015;148(1):215-219.
4. Rahier JF, et al. *J Crohns Colitis*. 2014;8(6):443-468. **5.** Centers for Disease Control and Prevention. https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm. Accessed September 20, 2021.

Considerations for Hepatitis C in IBD

- Hepatitis C virus (HCV) can be contracted via parenteral exposure, such as blood transfusion (before 1992) and misuse of intranasal or intravenous drugs, tattoos or body piercings, or high-risk sexual contact[1]
- HCV antiviral treatment does not impact IBD, and immunosuppressive therapy for IBD does not reactivate HCV[2]
- Prognosis:
  - If HCV infection is left undiagnosed or untreated, it can progress to cirrhosis and end-stage liver disease[3]
- Management of HCV in patients with IBD:
  - Sustained virologic response with newer HCV antivirals is achievable for most patients with HCV in as little as 8 weeks of treatment[4]
  - Treatment for chronic HCV infection is recommended in all patients, including those with IBD[5]

HCV=hepatitis C virus; IBD=inflammatory bowel disease.

1. Kwo PY, et al. *Am J Gastroenterol*. 2017;112(1):18-35. **2.** Imperatore N, et al. *Front Pharmacol.* 2017;8:867. **3.** Newsome PN, et al. *Gut*. 2018;67(1):6-19. **4.** Mavyret [prescribing information]. North Chicago, IL: AbbVie, Inc; 2021. **5.** Fousekis F, et al. *Gastroenterol Res.* 2018;11(2):83-94.

Hepatobiliary Considerations With Biologic Therapies

- Hepatobiliary complications have been reported in patients treated with biologic therapies for IBD. These include[1,2]:
  - Abnormal liver enzyme levels
  - Drug-induced liver injury
  - Autoimmune hepatitis
  - Cholestatic liver injury
  - Reactivation of viral hepatitis
  - Liver failure
  - Progressive multifocal leukoencephalopathy
- Risk of hepatobiliary complications will vary based on the mechanism of action and which biologic agent is used[1,2]

- Prior to initiating a biologic therapy, baseline liver enzymes should be obtained and patients should be screened for HBV and HCV infection[3]
  - Liver enzymes should be monitored periodically, especially during the first 3 months of treatment
- If ALT elevations are observed during biologic therapy, exclude other causes[3]
  - Minor elevations of ALT (<3 times the upper limit of normal): biologic therapy may be continued with close monitoring until resolution
  - Persistent elevations of ALT (>3 times the upper limit of normal) or presence of alarming clinical symptoms (eg, jaundice): biologic therapy should be discontinued. A liver biopsy or corticosteroid treatment may be considered

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ALT=alanine aminotransferase; HBV=hepatitis B virus; HCV=hepatitis C virus; IBD=inflammatory bowel disease.

1. Hirten R, et al. *World J Hepatol*. 2015;7(27):2716-2728. **2.** Shah NJ, et al. *Clin Case Rep Rev*. 2017;3(7):1-11. **3.** Tran-Minh ML, et al. *World J Hepatol.* 2017;9(13):613-626.

Summary

Up to 30% of patients with IBD may present with abnormal liver chemistries

Several hepatobiliary manifestations may present in patients with IBD, including primary sclerosing cholangitis, fatty liver (hepatic steatosis), and viral hepatitis that warrant further investigation

Liver function tests and accurate medical histories can help differentiate between hepatocellular, cholestatic, and drug-induced injury

Recognizing direct and indirect effects of IBD therapies on the liver will assist with identifying the cause of liver injury, if present, and adjusting treatment if needed

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IBD=Inflammatory bowel disease.

References

References

- Albahrani AA, Greaves RF. Fat-soluble vitamins: clinical indications and current challenges for chromatographic measurement. *Clin Biochem Rev*. 2016;37(1):27-47.
- Axiaris G, Zampeli E, Michopoulos S, Bamias G. Management of hepatitis B virus infection in patients with inflammatory bowel disease under immunosuppressive treatment. *World J Gastroenterol*. 2021;27(25):3762-3779.
- Bessissow T, Le NH, Rollet K, et al. Incidence and predictors of nonalcoholic fatty liver disease by serum biomarkers in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2016;22:1937-1944.
- Boonstra K, Weersma RK, van Erpecum KJ, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology.* 2013;58(6):2045-2055.
- Cappello M, Randazzo C, Bravata I, et al. Liver function test abnormalities in patients with inflammatory bowel diseases: a hospital-based survey. *Clin Med Insights Gastroenterol.* 2014;7:25-31.
- Centers for Disease Control and Prevention. Hepatitis B questions and answers for health professionals. https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm. Accessed September 20, 2021.
- Chapman RW. Update on primary sclerosing cholangitis. *Clin Liver Dis (Hoboken)*. 2017;9(5):107-110.
- Crohn's and Colitis Foundation. Fact sheet: liver complications. https://www.crohnscolitisfoundation.org/sites/default/files/legacy/assets/pdfs/liver-disease.pdf. Accessed September 20, 2021.
- De Vries LCS, Wildenberg ME, De Jonge WJ, D'Haens GR. The future of Janus kinase inhibitors in inflammatory bowel disease. *J Crohns Colitis.* 2017;11(7):885-893.
- Do A, Reau N. Chronic viral hepatitis: current management and future directions. *Hepatol Commun.* 2020;4(3):329-341.
- Fousekis FS, Theopistos VI, Katsanos KH, et al. Hepatobiliary manifestations and complications in inflammatory bowel disease: a review. *Gastroenterol Res*. 2018;11(2):83-94.
- Gatta A, Verardo A, Di Pascoli M, Giannini S, Bolognesi M. Hepatic osteodystrophy. *Clin Cases Miner Bone Metab.* 2014;11(3):185-191.
- Gawrieh S, Wilson LA, Cummings OW, et al. Histologic findings of advanced fibrosis and cirrhosis in patients with nonalcoholic fatty liver disease who have normal aminotransferase levels. *Am J Gastroenterol*. 2019;114(10):1626-1635.
- Gidwaney NG, Pawa S, Das KM. Pathogenesis and clinical spectrum of primary sclerosing cholangitis. *World J Gastroenterol*. 2017;23(14):2459-2469.

References

- Glassner K, Malaty H, Abraham B. Epidemiology and risk factors of nonalcoholic fatty liver disease among patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2017;23(6):998-1003.
- Glen J, Floros L, Day C, Pryke R. Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance. *BMJ*. 2016;354:i4428.
- Harrison MF. The misunderstood coagulopathy of liver disease: a review for the acute setting. *West J Emerg Med.* 2018;19(5):863-871.
- Hirten R, Sultan K, Thomas A, Bernstein DE. Hepatic manifestations of non-steroidal inflammatory bowel disease therapy. *World J Hepatol*. 2015;7(27):2716-2728.
- Imperatore N, Castiglione F, Rispo A, Sessa A, Caporaso N, Morisco F. Timing strategies of direct-acting antivirals and biologics administration in HCV-infected subjects with inflammatory bowel diseases. *Front Pharmacol.* 2017;8:867.
- Klein M, Núñez P, Bay C, Pizarro C, Sedano R, Quera R. Liver disorders in inflammatory bowel disease. *EMJ Hepatol*. 2020;8(1):26-32.
- Koller T, Galambosova M, Filakovska S, et al. Drug-induced liver injury in inflammatory bowel disease: 1-year prospective observational study. *World J Gastroenterol*. 2017;23(22):4102-4111.
- Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. *Am J Gastroenterol*. 2017;112(1):18-35.
- Lala V, Minter DA. Liver function tests. https://www.ncbi.nlm.nih.gov/books/NBK482489/. Accessed September 20, 2021.
- Lichtenstein GR, Loftus EV, Bloom S, et al. Tofacitinib, an oral Janus kinase inhibitor, in the treatment of ulcerative colitis: an interim analysis of an open-label, long-term extension study with up to 4.9 years of treatment. Poster presented at: United European Gastroenterology Week; October 20-24, 2018; Vienna, Austria. Abstract P0368.
- Mavyret [prescribing information]. North Chicago, IL: AbbVie, Inc; 2021.
- Mayo Clinic. Liver function tests. https://www.mayoclinic.org/tests-procedures/liver-function-tests/about/pac-20394595. Accessed September 20, 2021.
- Mayo Clinic. Prothrombin time test. https://www.mayoclinic.org/tests-procedures/prothrombin-time/about/pac-20384661. Accessed September 20, 2021.
- Nalbantoglu I, Brunt E. Role of liver biopsy in nonalcoholic fatty liver disease. *World J Gastroenterol.* 2014;20(27):9026-9037.
- National Institute of Diabetes and Digestive and Kidney Diseases. Diagnosis of NAFLD & NASH. https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/diagnosis. Accessed September 20, 2021.
- Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. *Gut*. 2018;67(1):6-19.

References

- Patel P, Dalal S. Hepatic manifestations of inflammatory bowel disease. *Clin Liver Dis (Hoboken).* 2021;17(4):292-296.
- Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*. 2014;8(6):443-468.
- Reddy KR, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148(1):215-219.
- Restellini S, Chazouilleres O, Frossard JL. Hepatic manifestations of inflammatory bowel diseases. *Liver Int*. 2017;37(4):475-489.
- Rojas-Feria M, Castro M, Suarez E, et al. Hepatobiliary manifestations in inflammatory bowel disease: the gut, the drugs and the liver. *World J Gastroenterol*. 2013;19(42):7327-7340.
- Shah NJ, Gupta NK, Borg BB. A review of liver disorders in inflammatory bowel disease (IBD). *Clin Case Rep Rev*. 2017;3(7):1-11.
- Shamberg L, Vaziri H. Hepatotoxicity of inflammatory bowel disease medications. *J Clin Gastroenterol*. 2018;52(8):674-684.
- Tran-Minh ML, Sousa P, Maillet M, et al. Hepatic complications induced by immunosuppressants and biologics in inflammatory bowel disease. *World J Hepatol.* 2017;9(13):613-626.
- XELJANZ/XELJANZ XR [prescribing information]. New York, NY: Pfizer Inc.; October 2020.
- Yarur AJ, Czul F, Levy C. Hepatobiliary manifestations of inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20(9):1655-1667.
- Zou ZY, Shen B, Fan JG. Systematic review with meta-analysis: epidemiology of nonalcoholic fatty liver disease in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;25(11):1764-1772.