Journal of Renal and Hepatic Disorders
jrenhep.com
TROIKA PUBLISHER

REVIEW

Liver biopsies in pediatric patients—a histopathological review of common entities

Maria Kamal[1], Zhongxin Yu[2], Neha Varshney[3,*]

[1]Heartland Pathology Laboratory, Wichita, KS 67226, USA
[2]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA
[3]Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

Abstract

With the advent of sophisticated non-invasive assays and advanced radiologic techniques, there has been a significant evolution in the role of liver biopsy in the evaluation and management of hepatic diseases. Liver biopsy has a vital role in establishing the diagnosis, staging and prognostic evaluation of various pediatric liver diseases. It is an essential tool in deciding therapeutic management and treatment response. Liver biopsy when used in combination with clinical findings and other diagnostic modalities is useful in guiding treatment and predicting prognosis in the pediatric population. Here we discuss the indications of liver biopsy in various common pediatric liver diseases.

Keywords: Biopsy; Indications; Liver; Management; Pediatric

Submitted: 05 July, 2024; *Accepted:* 21 February, 2025; *Published:* 20 June, 2025

Author for correspondence: neha.varshney@nm.org (Neha Varshney)

How to cite: Maria Kamal, Zhongxin Yu, Neha Varshney. Liver biopsies in Pediatric patients—a histopathological review of common entities. Journal of Renal and Hepatic Disorders. 2025; 9(1): 1-11. doi: 10.63268/jrenhp.v9i1.198.

Doi: 10.63268/jrenhp.v9i1.198

Introduction

The sophisticated non-invasive assays and advanced radiologic techniques have led to a significant evolution in the role of liver biopsy (LB) in the evaluation and management of liver diseases. LB has a vital role in influencing the diagnosis, staging, management and prognostic evaluation of various pediatric liver diseases [1]. The introduction of ultrasound-guided biopsy and safe sedation in the pediatric population has made it a routine procedure [1]. Neonatal LB is challenging and requires collaboration between a trained pathologist and the clinician. Liver microanatomy in neonates is different from older children and adults. Premature or very young infants have smaller interlobular bile ducts; the presence of copper-associated protein and iron till 4 months of age and persistence of hemopoietic elements until 6 months is normal. Multinucleated hepatocytes can be seen in numerous insults and is a non-specific finding [2]. These pitfalls in LB should be considered while reaching a diagnostic conclusion.

Types of liver biopsy

Percutaneous liver biopsy

Being less invasive and less expensive, the percutaneous approach is the most common method of liver biopsy. It can be performed with or without image guidance. The blind method is performed by locating the biopsy site by percussion of the right upper quadrant of the abdomen, in the midaxillary area. This method is useful for diffuse liver conditions. The image-guided technique uses ultrasound or computed tomography (CT) imaging to find the site of the lesion inside the liver. This approach provides a superior tissue yield. It is associated with reduced complications compared to the blind approach [1].

Trans-jugular liver biopsy

Trans-jugular approach is reserved for high-risk patients with conditions where percutaneous approach is contraindicated like severe liver pathologies, ascites, or hematological disorders [3]. The biopsy specimen obtained through this approach may be more fragmented and smaller in terms of length and the number of complete portal tracts [4].

Laparotomy or laparoscopic liver biopsy

Laparotomy permits direct visualization of the liver, however, the wedge peripheral biopsy obtained is less illustrative of the lesional liver, especially for fibrosis staging. The laparoscopic modality may be considered in special circumstances that include greater risk of hemorrhage, assessment of abdominal lump, ascites of unknown etiology, failed prior percutaneous biopsy attempt, and cases where a large biopsy sample is required [2]. Its advantages include larger specimen yield, better control of procedure-related hemorrhage, and direct visualization and selection of the site prior to biopsy [1, 5]. Table 1 summarizes the advantages and disadvantages of each biopsy modality.

Indications for liver biopsy

It can broadly be classified as diagnostic, prognostic and for assessment of treatment response (Table 2).

Common hepatic conditions in pediatric patients

Neonatal cholestasis

Neonatal cholestasis is defined as conjugated hyperbilirubinemia that results from reduced bile formation and/or excretion, and manifests at birth or early infancy. Neonatal cholestasis has a wide variety of etiologies, some of which can be identified by biochemical assays and imaging. However, liver biopsy is still considered the gold standard test for diagnosis [6]. Common causes of neonatal cholestasis with their histologic features are listed in Table 3.

Extrahepatic biliary atresia is the major causes of neonatal cholestasis representing 25–45% of reported cases [7].

Extrahepatic biliary atresia

Extrahepatic biliary atresia is one of the etiologies that require liver biopsy where response to therapy depends on early diagnosis and treatment [8]. It is especially crucial when imaging methods fail to yield a clear diagnosis, particularly in younger infants with neonatal cholestasis [8, 9]. Histopathologic evaluation of extrahepatic biliary atresia shows a conspicuous ductular reaction, cholestasis, portal tract edema, infiltrating neutrophils, and fibrosis (Fig. 1) [8].

A striking bile duct proliferation is an important feature distinguishing biliary atresia from neonatal hepatitis. Early biopsy before 4 to 6 weeks of age can miss the typical findings [10–12]. LB culture following portoenterostomy may reveal antibiotic-resistant cholangitis.

Idiopathic neonatal hepatitis

Idiopathic neonatal hepatitis (INH) is characterized by persistent cholestasis of infancy which has no identifiable cause, despite exhaustive work-up [13]. The liver biopsy shows giant multinucleated hepatocytes, variable hepatocyte swelling and necrosis, cholestasis, and variable portal and lobular inflammation [14]. Hepatocyte swelling and necrosis may disrupt the reticulin framework [14]. Differentiating extrahepatic biliary atresia and idiopathic neonatal hepatitis is difficult on clinical or laboratory findings. Liver biopsy can help distinguish the two entities. Multinucleated hepatocytes and disrupted reticulin framework are more pronounced in neonatal hepatitis whereas prominent ductular reaction and cholestasis is more evident in biliary atresia [14, 15].

Total parenteral nutrition-associated cholestasis

Cholestasis is an established complication of prolonged total parenteral nutrition (TPN) which could cause significant hepatic injury [16]. Several studies found an association between

Table 1. Advantages and disadvantages of different biopsy methods.

Type of Biopsy	Advantages	Disadvantages
Percutaneous Liver Biopsy		
Blind approach	● Least costly ● Less fragmentation reported	● Not suitable for sampling focal lesions ● Higher rates of complications such as intrahepatic hematoma over image-guided liver biopsy
Image-guided	● Image guidance provides a more accurate sampling of focal lesions	● Increases cost by requiring trained personnel
Trans-jugular Liver Biopsy	● Safer in patients with low platelet, coagulopathies, ascites	● Requires more expertise ● Smaller biopsy size and tissue fragmentation
Laparotomy or Laparoscopic Liver Biopsy	● Useful in patients with increased risk of bleeding, evaluation of abdominal mass, ascites and failure of previous percutaneous liver biopsy ● It provides larger specimen yield, better control of procedure related hemorrhage, and direct visualization and selection of biopsy site	● Most invasive and expensive method ● Longest post-procedure hospitalization

Table 2. Indications of liver biopsy in children.

Indications of liver biopsy		
Diagnostic	Prognostic	Management/Therapeutic
● Neonatal cholestasis and biliary atresia ● Non-alcoholic fatty liver disease ● Neoplasms ● Cryptogenic hypertransaminasaemia	● Non-alcoholic fatty liver disease ● Hepatitis C ● Autoimmune hepatitis ● Neoplasms	● Withdrawal of immunotherapy in Autoimmune hepatitis ● Prior to starting therapy for Hepatitis B to assess necroinflammation and staging of fibrosis to decide if anti-viral and interferon therapy is required ● Hepatitis C ● Neoplasms ● Withdrawal of immunosuppressive therapy in liver transplant recipients

Table 3. Common causes of neonatal cholestasis.

Etiology	Histopathologic findings
Extrahepatic Biliary atresia	Bile plugs, bile ductular proliferation, portal edema, potal inflammation and fibrosis
Paucity of intrahepatic bile ducts	Bile duct loss, Periportal and canalicular cholestasis, minimal portal fibrosis and no or minimal ductular proliferation
Parenteral nutrition-associated cholestasis	Ductular reaction followed by portal fibrosis and cirrhosis
Neonatal hepatitis	Cholestasis, multinucleated hepatocytes, portal and lobular inflammation, hepatocyte necrosis
Metabolic and storage diseases	Steatosis, portal inflammation, fibrosis or cirrhosis, disease specific findings
Infections	Portal and lobular inflammation and fibrosis, viral inclusions

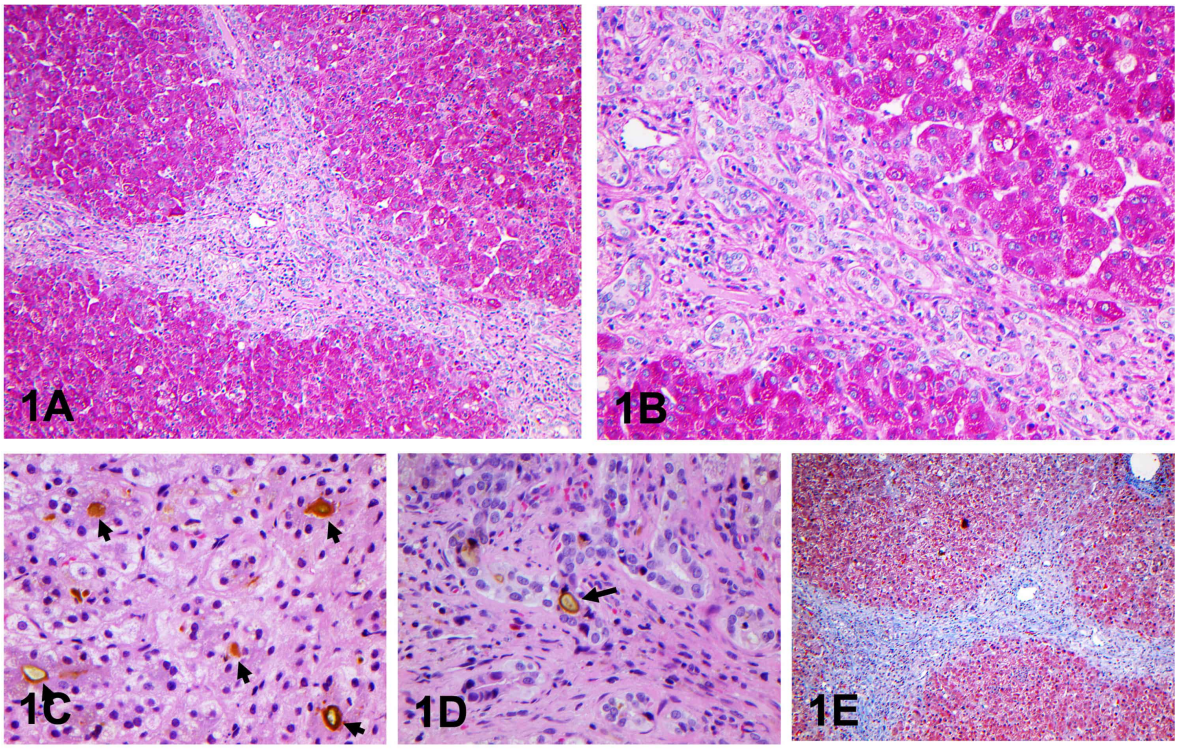

Figure 1. Biliary atresia. (A,B) Low and high-power views demonstrate prominent portal expansion by ductal and ductular proliferation (PAS stain, 200× and 400×, respectively). (C,D) There is prominent canalicular cholestasis (C, indicated by arrows, 400×) and intraductal bile plugs (D, indicated by arrow, 400×). (E) Portal-portal bridging fibrosis (Trichrome stain, 400×).

the severity of the liver disease and the length of TPN therapy [17]. Histopathologically, cholestasis is the major finding in infants and young children along with hepatocellular injury, steatosis, portal inflammation, ductular reaction, ductopenia, perivenular and portal fibrosis, and, sometimes, cirrhosis [18].

Genetic and metabolic disorders

Progressive familial intrahepatic cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a cluster of autosomal recessive cholestatic conditions that presents in infancy and childhood. PFICs are sub-grouped into three types based on clinical presentation, biochemical assays, genetic defect, and liver histopathology (Table 4).

PFIC 1 is an outcome of a defect in gene, ATPase phospholipid transporting 8B1 (*ATP8B1*), PFIC 2 shows a defect in gene *ABCB11*, and PFIC 3 results from a defect in the *MDR3* gene [19]. All these genetic defects lead to faulty bile transport from hepatocytes to canaliculi. Liver biopsy reveals canalicular cholestasis in PFIC 1 and PFIC 2, with fibrosis and a giant cell response more pronounced in PFIC 2 subtype (Fig. 2) while PFIC 3 shows bile duct proliferation and fibrosis [19].

The immunohistochemical staining for faulty bile salt export pump protein (BSEP) in PFIC 2 and the multidrug resistance three protein (MDR3) in PFIC 3 can aid in the diagnosis [20, 21]. Absent or decreased immunoexpression of these antibodies in hepatic canaliculi may be diagnostic for PFIC 2 and PFIC 3 [19, 22]. However, no standardized antibodies are known to help diagnose PFIC 1 [23]. PFIC 1 may show small-sized hepatocytes [24]. Fibrosis presents late in the disease course that can proceed to cirrhosis [23]. Partial biliary diversion (PBD) can alleviate symptoms in cases of ursodeoxycholic acid treatment failure. In cirrhotic patients, symptom relief with PBD becomes less probable [25]. Thus, LB is crucial in deciding management [26, 27].

Alagille syndrome

Alagille syndrome (AGS) is a multisystem disease that is hard to differentiate from biliary atresia in early infancy. It has an autosomal dominant inheritance. Although mostly diagnosed on clinical and extrahepatic criteria, AGS shows a paucity of interlobular bile ducts, an essential feature seen in late infancy or childhood that can only be demonstrated histologically. Prominent canalicular cholestasis may be seen (Fig. 3).

The ductular reaction is usually absent, however, rare cases in early infancy may show a ductular reaction. LB timing in AGS is critical as the paucity of interlobular bile ducts may not be seen in early infancy [28].

α1-antitrypsin deficiency disease

Alpha 1-antitrypsin (A1AT) deficiency is a hereditary metabolic disease that results from a deficiency of alpha 1-antitrypsin enzyme. The diagnosis can be made by isoelectric protein focusing or mutation analysis. Liver biopsy is not essential for diagnosis [2]. Histopathologic evaluation reveals periodic acid-schiff (PAS) positive, diastase-resistant globules in the hepatocytic endoplasmic reticulum (Fig. 4).

These globules may not be evident on microscopic examination in early infancy and may require a1-antitrypsin immunostaining to show them [23]. Severe fibrosis, ductular reaction, and bridging septa at presentation are suggestive of disease progression and may require liver transplantation [29].

Gaucher's disease

Gaucher's disease (GD) is a multisystem lysosomal storage disease caused by defective glucocerebrosidase enzyme activity resulting in glucocerebroside collection in the cells of macrophage-monocyte system of reticuloendothelial system (liver, spleen, bone marrow). Liver involvement is common in GD. Liver biopsy is usually not needed except in cases with questionable diagnosis or cases where the patient's management is dependent on a liver biopsy [30]. Histologic examination shows enlarged Kupffer cells and portal macrophages with a finely stippled cytoplasm caused by deposition of cerebrosides. These cells show PAS positive diastase resistant cytoplasmic granules that compress hepatocytes and hepatic sinusoids that may result in portal hypertension. Pericellular fibrosis is common [14].

Niemann-pick disease

Niemann-Pick disease is a storage disorder caused by lysosomal acid sphingomyelinase deficiency with resultant accumulation of sphingomyelin in macrophages throughout the body especially in liver, spleen, bone marrow and lungs [31]. Liver biopsy typically shows accumulation of sphingomyelin in liver cells and macrophages. Macrophages are enlarged, vacuolated and positive for lipid stains and negative for PAS stain [32].

Wilson disease

Wilson disease (WD) is a disorder of impaired copper metabolism with resultant copper deposition in various organs. Liver is the earliest organ to be involved by WD [2]. Liver biopsy in WD shows microvesicular and macrovesicular steatosis, periportal glycogenated nuclei, and focal necrosis of hepatocytes. The disease may progress to fibrosis, and subsequently cirrhosis [33]. Liver biopsy is not diagnostic for Wilson disease; however, the liver copper content is a part of diagnostic scoring and LB is usually indicated [34]. Increased amount of copper in liver is not diagnostic and only suggestive of WD [35]. The gold standard method for diagnosing elevated copper levels in the liver is atomic spectrophotometry performed on a liver biopsy specimen.

Cystic fibrosis

Cystic fibrosis (CF) is a multisystem disorder with autosomal recessive inheritance generally affecting Caucasians. It is characterized by abnormally viscous secretions caused by an impaired chloride transport because of a mutation in *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene. It mainly affects the airways, digestive system, reproductive system, and the skin [36]. CFTR dysfunction may result in alteration in the bile composition leading to biliary epithelium damage and resulting hepatobiliary complications. Microscopic features of cystic fibrosis associated liver injury may include cholestasis, hepatic steatosis, bile duct proliferation with plugs of PAS positive material, portal inflammation, and variable fibrosis [37]. There are reports of paucity of intrahep-

Table 4. Classification of Progressive familial intrahepatic cholestasis.

	Age	Gene/Transport defect	Histology
PFIC 1	Early infancy	● *ATP8B1/FIC1* ● ATP-dependent aminophospholipid flippase	Intracanalicular cholestasis, bile duct proliferation at the late phase
PFIC 2	Early infancy	● *ABCB11/BSEP* ● ATP-dependent bile acid transport in bile	Bile duct proliferation at the late phase, lobular and portal fibrosis
PFIC 3	Late childhood or young adulthood	● *ABCB4/MDR3* ● ATP-dependent phosphatidylcholine flippase	Extensive bile duct proliferation and periportal fibrosis

Abbreviations: ATP8B1, ATPase phospholipid transporting 8B1; ABCB11, ATP Binding Cassette Subfamily B Member 11; ABCB4, ATP binding cassette subfamily B member 4; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis; MDR3, multidrug resistance Class III.

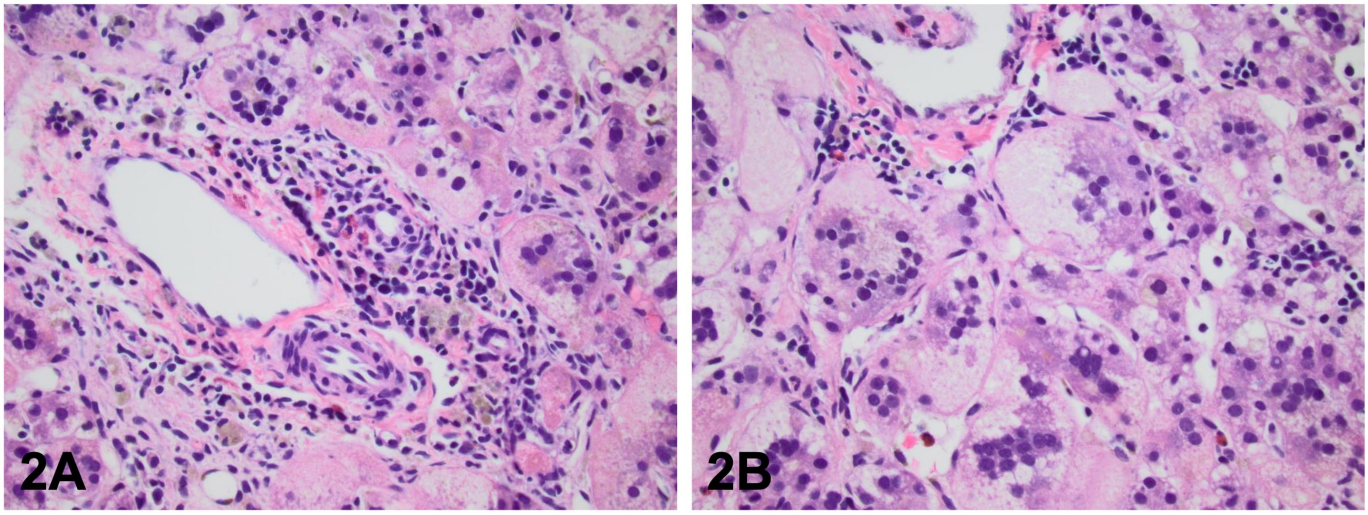

Figure 2. Progressive familial intrahepatic cholestasis 2. (A) Relatively normal portal tract with normal profile of duct and vessels. There is no ductal or ductular proliferation (H&E, 400×). (B) Prominent giant cell transformation (H&E, 400×).

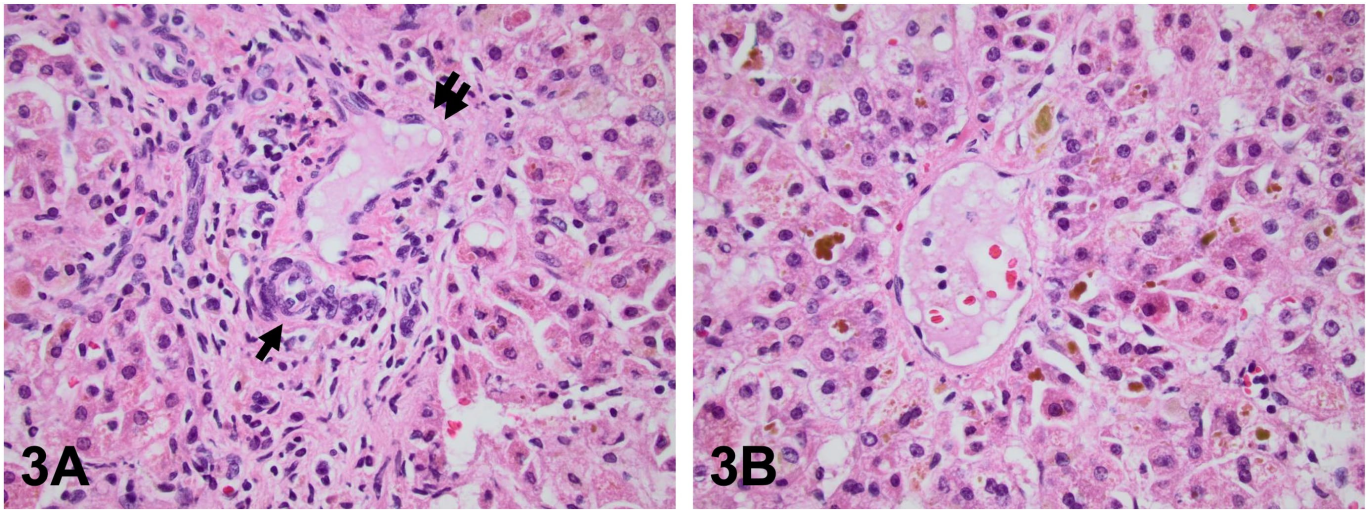

Figure 3. Alagille syndrome/paucity of interlobular bile duct. (A) The portal tract contains an arteriole (indicated by single arrow) and a portal vein (indicated by double arrows) but lacks bile duct (H&E, 400×). (B) The central vein is generally normal. There is usually prominent canalicular cholestasis (H&E, 400×).

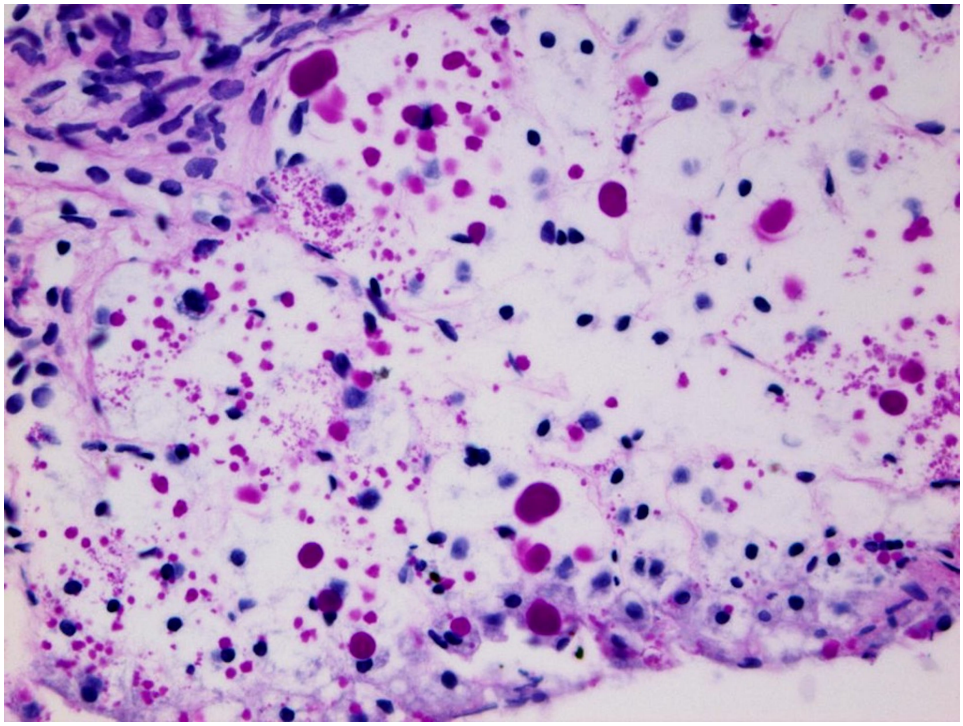

Figure 4. α1-Antitrypsin deficiency disease. A1AT intracytoplasmic inclusions are diastase-resistant and can be demonstrated by Periodic Acid-Schiff (PAS) stain after the tissue being pretreated by diastase (PAS-diastase stain, 400×).

atic bile duct as well [14].

Focal biliary cirrhosis is a common finding in pediatric patients with cystic fibrosis. Liver pathology, however, is not as frequent in adults [37] The disease may evolve to secondary biliary cirrhosis [14].

Reye's syndrome

Reye's syndrome is a fatal disease characterized by encephalopathy and visceral fatty degeneration seen in children and adolescents. Etiopathogenesis is still unclear, however, an association with viral infections, salicylate administration and metabolic disorders have been noticed. Liver biopsy plays an important diagnostic role. Grossly the biopsy specimen appears pale. Microscopic examination reveals a panlobular microvesicular hepatosteatosis positive for fat stains with mild or absent inflammation and necrosis [14]. Enlarged mitochondria with reduced dense bodies are identified on electron microscopic examination of liver tissue [14].

Acute liver failure

Etiologies remain unknown in about half of pediatric acute liver failure (ALF) patients who require liver transplantation [38–40]. Significant coagulopathy in many ALF patients makes percutaneous LB risky, and general anesthesia is required for the trans jugular (TJ) approach in children. Liver biopsy may be helpful in furnishing a diagnosis whenever possible, thus influencing the management [23, 41, 42]. However, sampling error is possible as necrosis and regeneration is frequently patchy [2].

Cryptogenic hypertransaminasemia

LB remains the gold standard in diagnosing cryptogenic hypertransaminasemia since it permits grading inflammation and staging fibrosis that influence management and prognosis. LB is required to diagnose some disease entities (noncirrhotic portal hypertension, nodular regenerative hyperplasia and hepatoportal sclerosis) [2].

Metabolic dysfunction-associated steatotic liver disease/nonalcoholic fatty liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) previously called as nonalcoholic fatty liver disease (NAFLD) comprises a spectrum of diseases that range from steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis [43]. By definition MASLD/NAFLD should have steatosis in ≥5% hepatocytes with no evidence of hepatocellular injury, and NASH should have steatosis in ≥5% hepatocytes along with inflammation and hepatocyte injury with or without fibrosis [44]. Diagnosis of NAFLD requires LB, however, not suggested for screening. Although no unified guidelines exist, all agree that MASLD can be confirmed through biopsy, which is recommended for unclear diagnoses, suspected comorbidities, or persistent alanine transaminase (ALT) elevation [45, 46]. The NASPGHAN guideline recommends liver biopsy in children at risk of NASH or fibrosis (*e.g.*, ALT >80 U/L, Aspartate aminotransferase (AST)/ALT ratio >1). While it aids in diagnosing NAFLD and ruling out other conditions, its accuracy is limited by uneven disease distribution. Adequate sampling (≥2 cm) reduces misclassification risks [47]. Liver biopsy can reliably differentiate NAFLD and NASH. It helps to determine the severity of hepatocytic injury, inflammation and fibrosis which

cannot be determined by normal liver function tests. Liver biopsy can also detect any coexisting diseases. Microscopic examination of NASH on liver biopsy shows macrovesicular steatosis, mixed lobular inflammation, hepatocytic ballooning and fibrosis. Other less common findings include Mallory-Denk bodies, enlarged mitochondria, and glycogenated nuclei. LB is recommended to rule out other diseases before initiating therapy, or any clinical trials [14, 43].

Autoimmune hepatitis

Liver biopsy is an essential requirement to diagnose Autoimmune hepatitis (AIH). AIH is diagnosed based on criteria outlined by the International Autoimmune Hepatitis Group [48, 49]. Histologic evaluation reveals chronic inflammatory infiltrates including lymphocytes and plasma cells in the portal areas, parenchymal collapse, interface hepatitis, and regeneration of hepatocytes with rosette formation (Fig. 5) [23, 50].

Many guidelines on AIH recommend a liver biopsy before treatment withdrawal; however, the European Association for the Study of the Liver (EASL) Clinical Practice Guideline considers it optional [51].

Sclerosing cholangitis

Primary Sclerosing Cholangitis (PSC) is usually diagnosed on a cholangiogram, and the role of liver biopsy remains controversial [52]. Patchy and focal involvement of the liver by PSC makes liver biopsy findings nonspecific. Histopathologic findings include "onion-skin" fibrosis, copper deposits, ductular reaction, edema and fibrosis of the portal tract (Fig. 6) [53, 54].

LB is essential in establishing the diagnosis of overlap syndromes (concomitant AIH and sclerosing cholangitis) and, in case of chronic changes, LB can be helpful in predicting the outcome [2, 55]. Thus, liver biopsy is not useful to diagnose PSC, except in overlap syndrome (PSC coexistent with autoimmune hepatitis). The correct diagnosis is important as the overlap syndrome may respond to immunosuppressive therapy [55, 56].

Infections

Hepatitis B infection

LB may be helpful in guiding therapy for chronic hepatitis B infection. The presence of moderate to marked inflammation or portal fibrosis may benefit from antiviral treatment [57, 58]. LB is essential to exclude cirrhosis before initiating interferon (IFN) therapy in children as it may result in decompensation of liver function [59].

Hepatitis C

LB is not diagnostic for chronic hepatitis C, however, considered the gold standard test to establish the grade of inflammation and fibrosis. Besides, a liver biopsy provides useful information in cases with raised autoimmune markers (like liver-kidney microsomal type 1 (LKM1) autoantibodies), steatosis, and other viral co-infections, that may affect the disease prognosis and the management [59, 60]. It may also exclude cirrhosis before initiating antiviral therapy.

Epstein-Barr virus infection and cytomegalovirus infection

LB can help in diagnosing Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) infections in liver transplant patients. Lobular hepatitis is common in both infections, however, characteristic owl's-eye cytopathic effects of CMV are rare [61, 62]. Immunostaining can be used to support the diagnosis (Figs. 7,8) [63].

LB may occasionally be helpful in diagnosing EBV-associated post-transplant lymphoproliferative disorders [64].

Congenital hyperbilirubinemia

Congenital hyperbilirubinemias can be divided into unconjugated and conjugated hyperbilirubinemias. Gilbert's syndrome is the most common congenital hyperbilirubinemia with an autosomal dominant inheritance. Gilbert's syndrome is a consequence of a mutation in the *UDP-Glucuronosyltransferase 1A1* (*UGT1A1*) gene that encodes uridine diphosphate glucuronosyltransferase (UDP-glucuronosyltransferase) enzyme, that results in bilirubin glucuronidation. Hence, unconjugated hyperbilirubinemia is seen in Gilbert's syndrome. Liver biopsy is essentially normal except for small amounts of iron in hepatocytes. Dubin-Johnson syndrome is an autosomal recessive congenital hyperbilirubinemia which is characterized by impaired excretion of conjugated bilirubin from hepatocytes. It results in non-cholestatic conjugated hyperbilirubinemia. Histologic examination of liver biopsy reveals an accumulation of dark brown pigment in hepatocytes beginning in the perivenular region and spreads to involve the remaining lobule giving liver a dark appearance on gross examination. The pigment resembles lipofuscin pigment, however, it is more abundant, darker, larger and variable in size. On electron microscopy the Dubin-Johnson pigment shows strands of electron-dense material in a background of electron-lucent material. Electron microscopy may be helpful to distinguish the pigment from lipofuscin in difficult cases [14].

Liver tumors

Liver tumors are infrequent in the pediatric population. Accurate diagnosis is essential for proper treatment. Hepatoblastoma is the most frequent malignant liver neoplasm in the pediatric population. Histopathology is often necessary for diagnosis as well as prognosis as small cell undifferentiated variant of hepatoblastoma have worse prognosis [65]. Hepatocellular carcinoma (HCC) is the next most frequent pediatric hepatic malignant tumor. Since biopsy could lead to needle track seeding it should be considered only when imaging cannot reveal the diagnosis [23].

Liver transplantation

Evaluation of post-transplant liver by biopsy is an important part of management in the pediatric population. It is essential to diagnose graft rejection, bile duct injury/obstruction, infections, original disease recurrence, and drug-induced liver injury [23]. It may also guide the withdrawal of immunosuppressive therapy. Protocol LB (performed every 5 or 10 years after transplantation even without a suspect) can provide

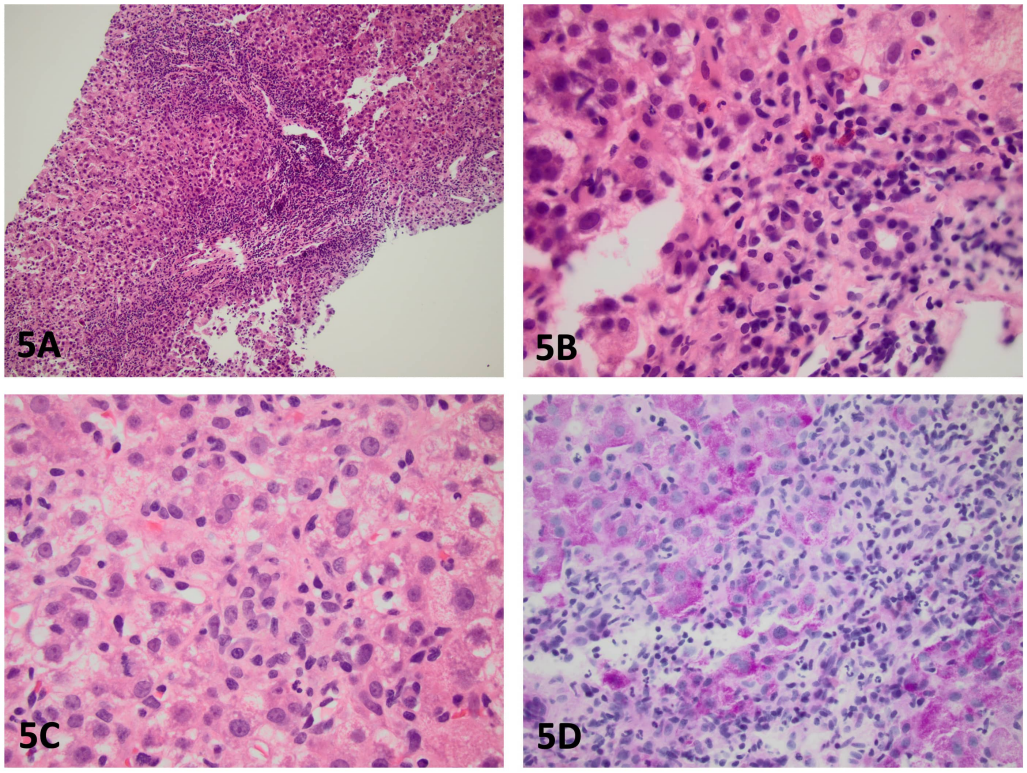

Figure 5. Autoimmune Hepatitis. (A) Lower power view shows severe portal inflammation that extends into periportal and nearby lobules (H&E, 200×). (B,C) The infiltrates are composed predominately of lymphocytes and many plasma cells. (B) highlights plasma cells in the portal/periportal infiltrates and (C) highlights plasma cells in the lobular inflammation (H&E, 400×). (D) PAS stain highlights interface inflammation and hepatocyte necrosis with loss of hepatocytes (PAS stain, 400×).

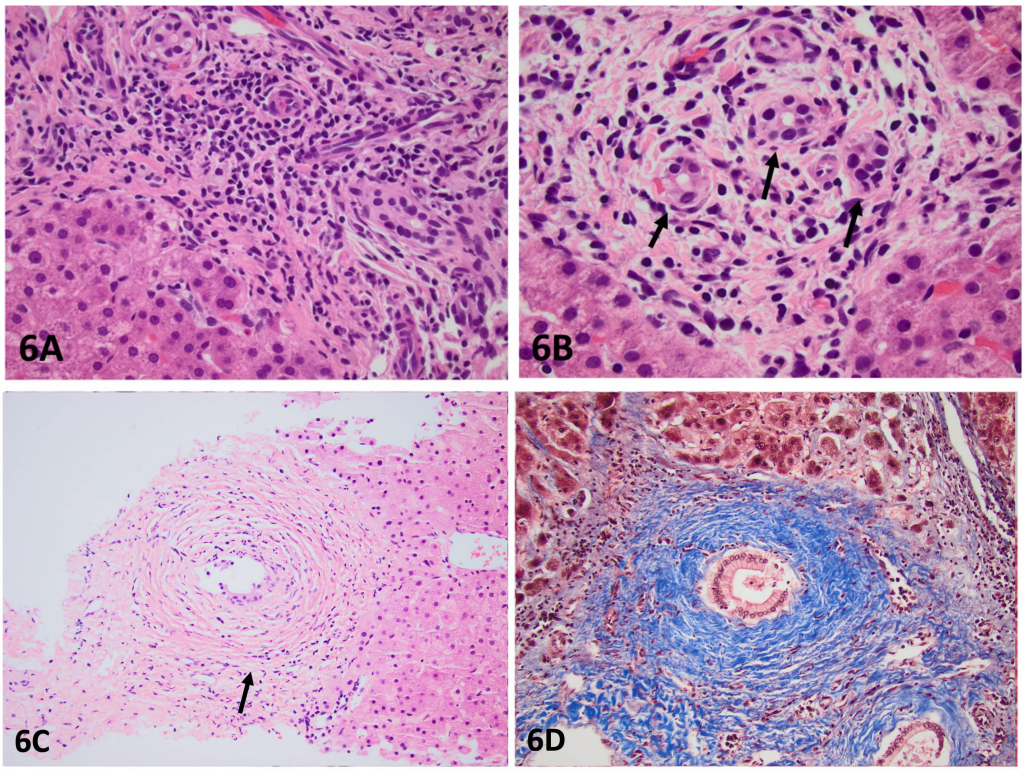

Figure 6. Primary sclerosing cholangitis. (A) Mild portal inflammation with plasma cells (H&E, 400×). (B,C) Mild ductal proliferation with early (B) and late (C) concentric periductal fibrosis (onion skin appearance, indicated by arrows) (H&E, 400×). (D) Trichrome stain highlights concentric periductal fibrosis (Trichrome stain, 400×).

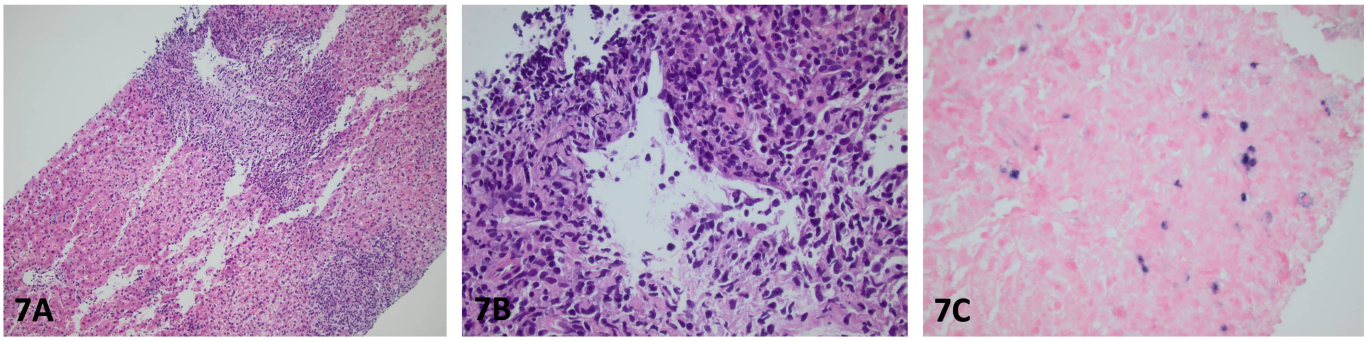

Figure 7. Acute EBV hepatitis. (A,B) Low and high-power views show marked portal expansion by predominately lymphocytic infiltrates. There is interface hepatitis (A) and endothelialitis (B) (H&E stain, 200× and 400× respectively). (C) Epstein-Barr encoding region *in situ* hybridization (EBER ISH) shows EBV infection in the hepatocytes (400×).

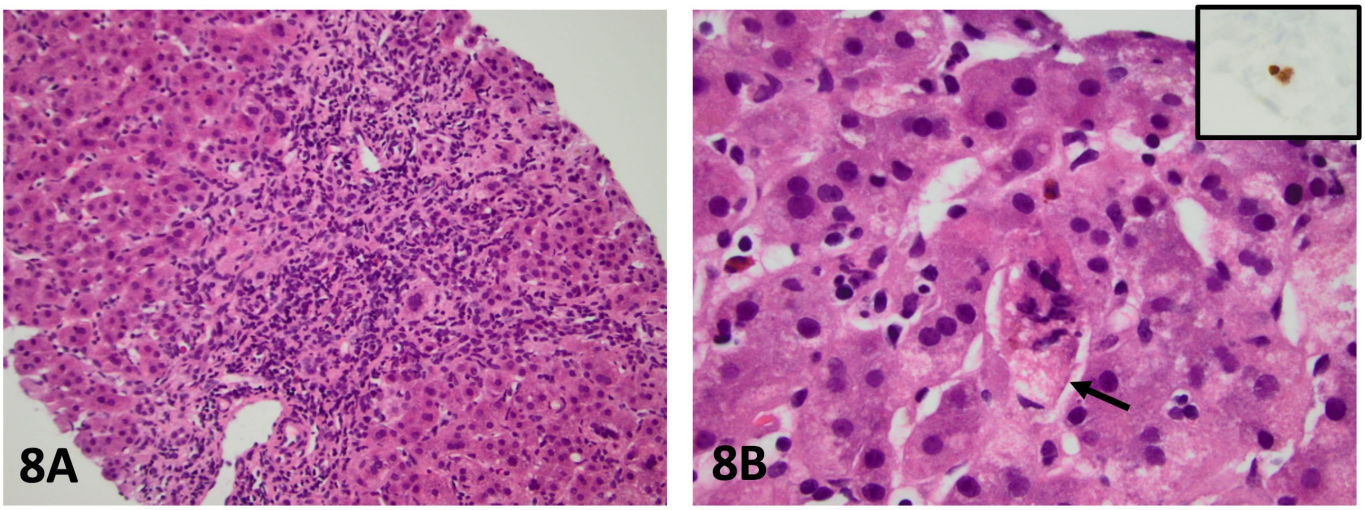

Figure 8. Neonatal CMV hepatitis. (A) Low power view shows mild to moderate portal inflammatory infiltrates composed predominately of lymphocytes. The hepatocytes show diffuse giant cell transformation (H&E, 200×). (B) There is focal hepatocyte necrosis (arrow) (H&E, 400×). Immunohistochemical stain is positive for cytomegalovirus infection (inset).

helpful information regarding inflammation or fibrosis that may have a bearing over post-transplant immunosuppressive therapy for better long-term graft survival [66–68]. However, risk-benefit ratio of protocol LB must be weighed carefully.

Complications of liver biopsy

Liver biopsy is rarely associated with complications. Minor complications include temporary pain at the biopsy site and transient hypotension. Severe pain unresponsive to analgesic therapy or vital sign instability prompt an evaluation for potential bleeding. Mortality related to a liver biopsy is extremely rare and is mostly due to hemorrhage. Other uncommon complications include pneumothorax, hemothorax, arteriovenous fistula, bile peritonitis, hemobilia, organ perforation, infection, and neuralgia [2, 5, 23].

Contraindications to liver biopsy

Liver biopsy has an increased risk of hemorrhage if International Normalized Ratio (INR) >1.5 and platelet count is <60,000/mL. A transjugular liver biopsy is preferred in cases of ascites. Echinococcal cysts may lead to fatal anaphylaxis, hence a contraindication to liver biopsy. Other less common contraindications include vascular lesions, bacterial cholangitis, and extrahepatic biliary obstruction. Premature birth may be a contraindication to liver biopsy if the size of the patient is not adequate [1, 2, 23].

Conclusion

Liver biopsy is imperative in the diagnosis, management, and prognostic evaluation of certain pediatric diseases where other diagnostic modalities are not enough as a diagnostic and prognostic tool. However, being invasive it should be used judiciously. Many pediatric liver diseases show an overlapping morphology and require correlation with clinical and another diagnostic workup. Hence, liver biopsy when used in combination with clinical findings and other diagnostic modalities is useful in guiding treatment and predicting prognosis in pediatric population.

Availability of data and materials

Not applicable.

Author contributions

NV—designed and edited the manuscript. MK and ZXY—drafted the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

No IRB is needed as this is a review article; pictures are blinded (no patient information is shared) and archival slides are used.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

1. Rabbani T, Ascher Bartlett JM, Mittal N. Liver biopsy in children. Indian Pediatrics. 2020; 57: 734–740.
2. Dezsőfi A, Baumann U, Dhawan A, Durmaz O, Fischler B, Hadzic N, *et al*. Liver biopsy in children. Journal of Pediatric Gastroenterology and Nutrition. 2015; 60: 408–420.
3. García-Compean D, Cortés C. Transjugular liver biopsy. An update. Annals of Hepatology. 2004; 3: 100–103.
4. Srivastava A, Prasad D, Panda I, Yadav R, Jain M, Sarma MS, *et al*. Transjugular versus percutaneous liver biopsy in children: indication, success, yield, and complications. Journal of Pediatric Gastroenterology and Nutrition. 2020; 70: 417–422.
5. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. Hepatology. 2009; 49: 1017–1044.
6. Ranucci G, Della Corte C, Alberti D, Bondioni MP, Boroni G, Calvo PL, *et al*. Diagnostic approach to neonatal and infantile cholestasis: a position paper by the SIGENP liver disease working group. Digestive and Liver Disease. 2022; 54: 40–53.
7. Feldman AG, Sokol RJ. Recent developments in diagnostics and treatment of neonatal cholestasis. Seminars in Pediatric Surgery. 2020; 29: 150945.
8. Antala S, Taylor SA. Biliary atresia in children: update on disease mechanism, therapies, and patient outcomes. Clinics in Liver Disease. 2022; 26: 341–354.
9. Nayak NC, Vasdev N. Neonatal cholestasis syndrome: identifying the disease from liver biopsy. Indian Pediatrics. 2002; 39: 421–425.
10. Russo P, Magee JC, Boitnott J, Bove KE, Raghunathan T, Finegold M, *et al*.; Biliary Atresia Research Consortium. Design and validation of the biliary atresia research consortium histologic assessment system for cholestasis in infancy. Clinical Gastroenterology and Hepatology. 2011; 9: 357–362.e2.
11. Patel KR. Biliary atresia and its mimics. Diagnostic Histopathology. 2023; 29: 52–66.
12. Azar G, Beneck D, Lane B, Markowitz J, Daum F, Kahn E. Atypical morphologic presentation of biliary atresia and value of serial liver biopsies. Journal of Pediatric Gastroenterology and Nutrition. 2002; 34: 212–215.
13. Ahmed ABM, Fagih MA, Bashir MS, Al-Hussaini AA. Role of percutaneous liver biopsy in infantile cholestasis: cohort from Arabs. BMC Gastroenterology. 2021; 21: 118.
14. Lefkowitch JH. Childhood liver disease and metabolic disorders. Scheuer's Liver Biopsy Interpretation. 2021; 19: 288–322.
15. Giriyan S, Marathe A. Idiopathic neonatal hepatitis—a case report. Global Journal for Research Analysis. 2015; 4: 13–14.
16. Buonpane CL, Ares GJ, Englert EG, Helenowski I, Cohran VC, Hunter CJ. Utility of liver biopsy in the evaluation of pediatric total parenteral nutrition cholestasis. The American Journal of Surgery. 2018; 216: 672–677.
17. Feldman AG, Sokol RJ. Neonatal cholestasis: updates on diagnostics, therapeutics, and prevention. NeoReviews. 2021; 22: e819–e836.
18. Naini BV, Lassman CR. Total parenteral nutrition therapy and liver injury: a histopathologic study with clinical correlation. Human Pathology. 2012; 43: 826–833.
19. Gunaydin M, Bozkurter Cil AT. Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. Hepatic Medicine. 2018; 10: 95–104.
20. Clayton RJ, Iber FL, Ruebner BH, Mckusick VA. Byler disease. Fatal familial intrahepatic cholestasis in an Amish kindred. American Journal of Diseases of Children. 1969; 117: 112–124.
21. Srivastava A. Progressive familial intrahepatic cholestasis. Journal of Clinical and Experimental Hepatology. 2014; 4: 25–36.
22. Evason K, Bove KE, Finegold MJ, Knisely AS, Rhee S, Rosenthal P, *et al*. Morphologic findings in progressive familial intrahepatic cholestasis 2 (PFIC2): correlation with genetic and immunohistochemical studies. The American Journal of Surgical Pathology. 2011; 35: 687–696.
23. Ovchinsky N, Moreira RK, Lefkowitch JH, Lavine JE. Liver biopsy in modern clinical practice: a pediatric point-of-view. Advances in Anatomic Pathology. 2012; 19: 250–262.
24. Alissa FT, Jaffe R, Shneider BL. Update on progressive familial intrahepatic cholestasis. Journal of Pediatric Gastroenterology and Nutrition. 2008; 46: 241–252.
25. Emerick KM, Elias MS, Melin-Aldana H, Strautnieks S, Thompson RJ, Bull LN, *et al*. Bile composition in Alagille Syndrome and PFIC patients having partial external biliary diversion. BMC Gastroenterology. 2008; 8: 47.
26. Melter M, Rodeck B, Kardorff R, Hoyer PF, Petersen C, Ballauff A, *et al*. Progressive familial intrahepatic cholestasis: partial biliary diversion normalizes serum lipids and improves growth in noncirrhotic patients. The American Journal of Gastroenterology. 2000; 95: 3522–3528.
27. Kaliciński PJ, Ismail H, Jankowska I, Kamiński A, Pawłowska J, Drewniak T, *et al*. Surgical treatment of progressive familial intrahepatic cholestasis: comparison of partial external biliary diversion and ileal bypass. European Journal of Pediatric Surgery. 2003; 13: 307–311.
28. Subramaniam P, Knisely A, Portmann B, Qureshi SA, Aclimandos WA, Karani JB, *et al*. Diagnosis of Alagille syndrome—25 years of experience at King's College Hospital. Journal of Pediatric Gastroenterology and Nutrition. 2011; 52: 84–89.
29. Francavilla R, Castellaneta SP, Hadzic N, Chambers SM, Portmann B, Tung J, *et al*. Prognosis of alpha-1-antitrypsin deficiency-related liver disease in the era of paediatric liver transplantation. Journal of Hepatology. 2000; 32: 986–992.
30. Adar T, Ilan Y, Elstein D, Zimran A. Liver involvement in Gaucher disease—Review and clinical approach. Blood Cells, Molecules & Diseases. 2018; 68: 66–73.
31. Thurberg BL, Wasserstein MP, Schiano T, O'Brien F, Richards S, Cox GF, *et al*. Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann-Pick disease type B). The American Journal of Surgical Pathology. 2012; 36: 1234–1246.
32. Vélez Pinos PJ, Saavedra Palacios MS, Colina Arteaga PA, Arevalo Cordova TD. Niemann-pick disease: a case report and literature review. Cureus. 2023; 15: e33534.
33. Cope-Yokoyama S, Finegold MJ, Sturniolo GC, Kim K, Mescoli C, Rugge M, *et al*. Wilson disease: histopathological correlations with treatment on follow-up liver biopsies. World Journal of Gastroenterology. 2010; 16: 1487–1494.
34. Ferenci P, Caca K, Loudianos G, Mieli-Vergani G, Tanner S, Sternlieb I, *et al*. Diagnosis and phenotypic classification of Wilson disease. Liver International. 2003; 23: 139–142.
35. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised

King's score for liver transplantation. Liver Transplantation. 2005; 11: 441–448.
36. Boëlle PY, Debray D, Guillot L, Clement A, Corvol H; French CF Modifier Gene Study Investigators. Cystic fibrosis liver disease: outcomes and risk factors in a large cohort of French patients. Hepatology. 2019; 69: 1648–1656.
37. Betapudi B, Aleem A, Kothadia JP. Cystic fibrosis and liver disease. StatPearls Publishing: Treasure Island (FL). 2025.
38. Squires RH III, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, *et al*. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. The Journal of Pediatrics. 2006; 148: 652–658.
39. Lee WM, Squires RH III, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. Hepatology. 2008; 47: 1401–1415.
40. Di Giorgio A, Gamba S, Sansotta N, Nicastro E, Colledan M, D'Antiga L. Identifying the aetiology of acute liver failure is crucial to impact positively on outcome. Children. 2023; 10: 473.
41. Miraglia R, Luca A, Gruttadauria S, Minervini MI, Vizzini G, Arcadipane A, *et al*. Contribution of transjugular liver biopsy in patients with the clinical presentation of acute liver failure. Cardiovascular and Interventional Radiology. 2006; 29: 1008–1010.
42. Habdank K, Restrepo R, Ng V, Connolly BL, Temple MJ, Amaral J, *et al*. Combined sonographic and fluoroscopic guidance during transjugular hepatic biopsies performed in children: a retrospective study of 74 biopsies. American Journal of Roentgenology. 2003; 180: 1393–1398.
43. Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, *et al*. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. Journal of Pediatric Gastroenterology and Nutrition. 2012; 54: 700–713.
44. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, *et al*. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018; 67: 328–357.
45. Hunter AK, Lin HC. Review of clinical guidelines in the diagnosis of pediatric nonalcoholic fatty liver disease. Clinical Liver Disease. 2021; 18: 40–44.
46. Lubrecht JW, van Giesen GHJ, Jańczyk W, Zavhorodnia O, Zavhorodnia N, Socha P, *et al*.; ESPGHAN Fatty Liver Special Interest Group. Pediatricians' practices and knowledge of metabolic dysfunction-associated steatotic liver disease: an international survey. Journal of Pediatric Gastroenterology and Nutrition. 2024; 78: 524–533.
47. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, *et al*. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). Journal of Pediatric Gastroenterology and Nutrition. 2017; 64: 319–334.
48. Sakhuja P, Goyal S. Autoimmune hepatitis: from evolution to current status—a pathologist's perspective. Diagnostics. 2024; 14: 210.
49. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, *et al*. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. Journal of Hepatology. 1999; 31: 929–938.
50. Nastasio S, Mosca A, Alterio T, Sciveres M, Maggiore G. Juvenile autoimmune hepatitis: recent advances in diagnosis, management and long-term outcome. Diagnostics. 2023; 13: 2753.
51. Lohse AW, Sebode M, Jørgensen MH, Ytting H, Karlsen TH, Kelly D, *et al*.; European Reference Network on Hepatological Diseases (ERN RARE-LIVER); International Autoimmune Hepatitis Group (IAIHG). Second-line and third-line therapy for autoimmune hepatitis: a position statement from the European Reference Network on Hepatological Diseases and the International Autoimmune Hepatitis Group. Journal of Hepatology. 2020; 73: 1496–1506.
52. Dave M, Elmunzer BJ, Dwamena BA, Higgins PD. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. Radiology. 2010; 256: 387–396.
53. Harrison RF, Hubscher SG. The spectrum of bile duct lesions in end-stage primary sclerosing cholangitis. Histopathology. 1991; 19: 321–327.
54. Fuchs Y, Valentino PL. Natural history and prognosis of pediatric PSC with updates on management. Clinical Liver Disease. 2023; 21: 47–51.
55. Rabiee A, Silveira MG. Primary sclerosing cholangitis. Translational Gastroenterology and Hepatology. 2021; 6: 29.
56. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, *et al*. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology. 2001; 33: 544–553.
57. Jonas MM, Mizerski J, Badia IB, Areias JA, Schwarz KB, Little NR, *et al*.; International Pediatric Lamivudine Investigator Group. Clinical trial of lamivudine in children with chronic hepatitis B. The New England Journal of Medicine. 2002; 346: 1706–1713.
58. Jara P, Bortolotti F. Interferon-alpha treatment of chronic hepatitis B in childhood: a consensus advice based on experience in European children. Journal of Pediatric Gastroenterology and Nutrition. 1999; 29: 163–170.
59. Guido M, Bortolotti F. Chronic viral hepatitis in children: any role for the pathologist? Gut. 2008; 57: 873–877.
60. Chowdhury AB, Mehta KJ. Liver biopsy for assessment of chronic liver diseases: a synopsis. Clinical and Experimental Medicine. 2023; 23: 273–285.
61. Paya CV, Holley KE, Wiesner RH, Balasubramaniam K, Smith TF, Espy MJ, *et al*. Early diagnosis of cytomegalovirus hepatitis in liver transplant recipients: role of immunostaining, DNA hybridization and culture of hepatic tissue. Hepatology. 1990; 12: 119–126.
62. Koch DG, Christiansen L, Lazarchick J, Stuart R, Willner IR, Reuben A. Posttransplantation lymphoproliferative disorder–the great mimic in liver transplantation: appraisal of the clinicopathologic spectrum and the role of Epstein-Barr virus. Liver Transplantation. 2007; 13: 904–912.
63. Barkholt L, Reinholt FP, Teramoto N, Enbom M, Dahl H, Linde A. Polymerase chain reaction and *in situ* hybridization of Epstein-Barr virus in liver biopsy specimens facilitate the diagnosis of EBV hepatitis after liver transplantation. Transplant International. 1998; 11: 336–344.
64. Nuckols JD, Baron PW, Stenzel TT, Olatidoye BA, Tuttle-Newhall JE, Clavien PA, *et al*. The pathology of liver-localized post-transplant lymphoproliferative disease: a report of three cases and a review of the literature. The American Journal of Surgical Pathology. 2000; 24: 733–741.
65. Jeong SU, Kang HJ. Recent updates on the classification of hepatoblastoma according to the International Pediatric Liver Tumors Consensus. Journal of Liver Cancer. 2022; 22: 23–29.
66. Karbaum E, Weidemann S, Grabhorn E, Fischer L, Herden U, Oh J, *et al*. Protocol biopsies in pediatric liver transplantation recipients improve graft histology and personalize immunosuppression. Journal of Pediatric Gastroenterology and Nutrition. 2023; 76: 627–633.
67. Rocque B, Zaldana A, Weaver C, Huang J, Barbetta A, Shakhin V, *et al*. Clinical value of surveillance biopsies in pediatric liver transplantation. Liver Transplantation. 2022; 28: 843–854.
68. Ekong UD. The long-term liver graft and protocol biopsy: do we want to look? What will we find? Current Opinion in Organ Transplantation. 2011; 16: 505–508.