Childhood Cholestatic Liver Diseases that Persist Into Adulthood

Lessons for the Adult Gastroenterologist

Alvin P. Chan, MD and Robert S. Venick, MD

Abstract: Children with cholestatic liver diseases are increasingly living into adulthood, thanks to innovations in medical and surgical therapies. The excellent outcomes observed in pediatric liver transplantation for diseases, such as biliary atresia, have transformed the life trajectory of children born with once-fatal liver diseases. The evolution of molecular genetic testing, has helped expedite the diagnosis of other cholestatic disorders, improving the clinical management, disease prognosis, and family planning for inherited disorders, such as progressive familial intrahepatic cholestasis and bile acid synthesis disorders. The expanding list of therapeutics, including bile acids and the newer ileal bile acid transport inhibitors, has also helped slow the progression of disease and improve the quality of life for certain diseases, like Alagille syndrome. More and more children with cholestatic disorders are expected to require care from adult providers familiar with the natural history and potential complications of these childhood diseases. The aim of this review is to bridge the gap between pediatric and adult care in children with cholestatic disorders. The present review addresses the epidemiology, clinical features, diagnostic testing, treatment, prognosis, and transplant outcomes of 4 hallmark childhood cholestatic liver diseases: biliary atresia, Alagille syndrome, progressive familial intrahepatic cholestasis, and bile acid synthesis disorders.

Key Words: biliary atresia, Alagille syndrome, bile acid synthesis disorders, progressive, familial intrahepatic cholestasis

(*J Clin Gastroenterol* 2023;57:686–693)

Cholestatic liver disease is a major cause of morbidity and mortality in infants and children, affecting 1 in 2500 live births in North America.[1] Pediatric cholestasis is often caused by inherited defects of bile metabolism or obstructions of the biliary tract. Many children born with cholestatic liver disease go on to develop chronic liver disease by young adulthood and a significant portion will require liver transplantation (LTx) during their lifetime. Indeed, cholestatic disorders account for nearly one-half of the roughly 600 pediatric LTx performed annually in the United States.[2] With improvements in medical and surgical therapies, children with cholestatic liver diseases are now increasingly living into adulthood. The 15-year to 20-year patient survival rate after pediatric LTx is 75%,[3] and the survival rate with one's native liver into adulthood is 25% to 50% depending on the type of pediatric cholestatic disorder.[4–6] Given the growing number of adults with a history of congenital cholestatic liver disease, it is important for adult providers to have an understanding of the most common pediatric cholestatic disorders and their implications in adulthood. This review article highlights four hallmark causes of pediatric cholestasis—biliary atresia (BA), Alagille syndrome (ALGS), bile acid synthesis disorders (BASDs), and progressive familial intrahepatic cholestasis (PFIC)—which represent the vast majority of pediatric cholestatic disorders and the most likely to persist into adulthood. The aim is to highlight their etiology, diagnostic workup, clinical course, management, and transplant outcomes, while providing pertinent insight to adult gastroenterologists who will eventually care for these patients.

BILIARY ATRESIA

BA is an idiopathic, progressive, fibroinflammatory cholangiopathy of the intra- hepatic and extrahepatic bile ducts. BA is the most common cause of neonatal cholestasis, presenting typically in the first few weeks of life with jaundice and acholic stools. BA affects an estimated 1 in 12,000 live births in the United States, 1 in 5000 in Taiwan, and 1 in 18,000 in Europe, with a slight female preponderance.[7,8] If not recognized and intervened in the first months of life, the disease rapidly progresses to biliary cirrhosis with the need for LTx in infancy.

The etiology of BA is multifactorial, caused by a combination of genetic factors, vascular, infectious, and toxic insults. Viral infections have frequently been implicated. One theory is that certain viruses initiate cholangiocyte apoptosis and release antigens that trigger an exagerrated host inflammatory response against biliary epithelia, resulting in progressive bile duct injury and biliary cirrhosis.[9] The most extensively studied viruses in the development of BA are reovirus type 3, rotavirus type C, and cytomegalovirus. There are animal models showing that viruses can induce BA, yet there is not consistent data to support these viruses as causative of BA in humans.[10–12]

The typical neonate with BA develops jaundice with conjugated hyperbilirubinemia that persists and progresses beyond 2 weeks of age. One of the more common symptoms in infants with BA is the development of progressively acholic stools. If no intervention is performed in the first 3 months of life, other signs manifest, including failure to thrive, muscle wasting, hepatosplenomegaly, ascites, pruritus, coagulopathy, and cirrhosis. 10% to 15% of patients

From the Division of Pediatric Gastroenterology, Department of Pediatrics, Hepatology and Nutrition, David Geffen School of Medicine, UCLA, Los Angeles, CA.

A.P.C. is supported by the National Institute Of Diabetes And Digestive and Kidney Diseases of the National Institutes of Health under Award Number T32DK007180.

The authors declare that they have nothing to disclose.

Address correspondence to: Robert S. Venick, MD, Division of Pediatric Gastroenterology, Department of Pediatrics, Hepatology and Nutrition, David Geffen School of Medicine, UCLA, Mattel Children's Hospital UCLA, Box 951752, Los Angeles 90095-1752, CA (e-mail: Rvenick@mednet.ucla.edu).

DOI: 10.1097/MCG.0000000000001850

with BA have other extrahepatic congenital anomalies including polysplenia or asplenia, intestinal malrotation, abdominal situs inversus, intestinal atresia, annular pancreas, renal anomalies, cardiac defects, and vascular abnormalities, such as preduodenal or absent portal vein, interrupted retrohepatic vena cava, and anomalous hepatic arterial circulation.[13–18]

Serum transaminases are typically mildly elevated in patients with BA, whereas alkaline phosphatase and gamma-glutamyl transpeptidase (GGT) levels are significantly elevated. Ultrasound findings of BA may include an atretic or absent gallbladder, abnormal shape and thickness of the gallbladder, and the triangular cord sign, which is an echogenic fibrous tissue representing a remnant of the extrahepatic bile duct.[19,20]

Technetium 99–labeled hepatoiminodiacetic acid scans can be performed as part of the diagnostic workup.[21] If excretion of the tracer is observed into the intestine, then BA is essentially ruled out. Liver biopsy can be a very sensitive and specific test to delineate BA from other causes of neonatal cholestasis.[22] The procedure is a cornerstone of the diagnostic workup for many cholestatic diseases in infancy, and it can be performed safely and percutaneously with timely results. Liver biopsies in BA clasically reveal an obstructive biliary pattern with hepatocellular and canalicular cholestasis and eventually proliferation of the biliary ductules in the portal tracts. As the unrelieved obstruction progresses, other signs may develop, including focal hepatocyte necrosis, multinucleated giant hepatocytes, portal tract edema, and intralobular fibrosis. If the biopsy findings are consistent with BA, the infant will undergo definitive testing with an intraoperative cholangiogram followed by a Kasai hepatoportoenterostomy. More recently, matrix metallopeptidase-7, a protein involved in fibrosis, liver remodeling, and regeneration, has been shown to be a reliable biomarker for the diagnosis of BA with high sensitivity and specificity.[23]

Medical management of children with BA aims to prevent and treat potential complications of end-stage liver disease, including failure to thrive, fat-soluble vitamin deficiencies, pruritus, ascites, portal hypertension, and cholangitis. Kasai and Suzuki first introduced the hepatoportoenterostomy in 1959, and the procedure gradually gained acceptance as the optimal therapy to restore bile flow in affected infants.[24] The early success of the Kasai procedure is measured clinically by the re-establishment of bile flow into the intestine based on the presence of pigmented stools and the normalization of serum bilirubin levels. A summary of key clinical characteristics, diagnosis, and management is provided (Table 1).

The most common complication after portoenterostomy is ascending cholangitis, which occurs in 30% to 60% of children.[25] Episodes of cholangitis must be recognized promptly and treated aggressively because of the increased risk of accelerated cirrhosis.[25,26] Prophylactic oral antibiotics after a Kasai have demonstrated a benefit in preventing cholangitis.[27] Meanwhile, corticosteroids after portoenterostomy have not been shown to improve successful bile drainage or transplant-free survival after a Kasai procedure.[28]

Most major series have confirmed the relationship between age at the time of hepatoportoenterostomy and resolution of cholestasis. Kasai procedures performed before 60 days of life, ideally between 30 and 45 days of life, seem to produce the best opportunities at reversing cholestasis and

TABLE 1. Summary of Key Characteristics of Pediatric Cholestatic Liver Diseases that Persist Into Adulthood

				Serum laboratory tests				
Disease	**Gene/protein**	**Defect**	**Clinical features**	**ALT**	**GGT**	**Bile acid**	**Diagnosis**	**Treatment**
Biliary atresia	N/A	Biliaryobstruction	Cholangitis, 10% extrahepatic	↑	↑↑	↑	Cholangiogram;biopsy	Kasai, UDCA
ALGS (AD)	*JAG1*/Jagged-1 *NOTCH2*/Notch2	Notch signaling pathway	Pruritis, extrahepatic	↑	↑	↑	Genetic; clinical	UDCA, antipruritics
BASD (AR)	Variable	Bile acid synthesis	No pruritis	↑	↔	↓	Genetic; urine /serum bile acid	Primary bile acid
PFIC-1 (AR)	*ATP8B1*/FIC1	Phospholipid transport	Pruritis, extrahepatic	↑	↔	↑	Genetic	UDCA, antipruritics
PFIC-2 (AR)	*ABCB11*/BSEP	Bile salt export	Pruritis, cancer risk	↑↑	↔	↑	Genetic	UDCA, antipruritics
PFIC-3 (AR)	*ABCB4*/MDR3	Phosphatidylcholine exchange	Pruritis, ICP, gallstones	↑↑	↑	↑	Genetic	UDCA, antipruritics

ALT indicates alanine transaminase; AD, autostomal dominant; ALGS, Alagille syndrome; AR, autosomal recessive; BASD, bile acid synthesis disorder; GGT, gamma-glutamyl transpeptidase; ICP, intrahepatic cholestasis of pregnancy; N/A, not applicable; PFIC, progressive familial intrahepatic cholestasis; UDCA, urosdeoxycholic acid.

achieving transplant-free survival.[29,30] Other significant factors that predict a successful Kasai are the extent of hepatic fibrosis at the time of surgery and the number of postoperative episodes of cholangitis. Even when a hepatoportoenterostomy restores bile drainage, intrahepatic disease often progresses and by early adulthood, roughly 75% of children with BA will have required LTx.[31] Nonetheless, a Kasai procedure allows for the opportunity for continued growth and development, sometimes for several years, before needing LTx. This additional time provides access to more potential donors and lowers the risk of technical complications seen more frequently in infants and toddlers undergoing LTx. Along these lines, the Kasai should be viewed not as a cure for BA, but rather, as a bridge and a means of preventing rapid progression of disease.

LTx is the only option once the liver damage becomes irreversible. The first attempted LTx in humans was performed in 1963 by Dr Thomas Starzl on a 3-year-old child with BA.[32] Today, BA is the leading indication for pediatric LTx accounting for 40% of all pediatric LTx and up to 75% of transplants in children under the age of 2.[33] BA has been responsible for innovations and technical advancements in the field of LTx over the past 60 years.

Signs and symptoms of a failing portoenterostomy should prompt referral for LTx. The specific indications for LTx in children or young adults with BA are persistent cholestasis, failure to thrive, recurrent cholangitis, portal hypertension, hepatopulmonary syndrome, portopulmonary hypertension, hepatorenal syndrome, intractable ascites, hepatocellular carcinoma, and hepatic encephalopathy.

Improvements in surgical techniques, intraoperative management, critical care, and long-term medical management have combined to yield ever-improving results for children with BA who undergo LTx. Specifically, 5-year patient and graft survival for children with BA are 97% and 90%, respectively,[34] and 20-year survival rates are 75%.[3] In a recent analysis of nearly 1500 children with BA undergoing LTx, significant risk factors for patient or graft loss include technical variant graft, re-transplantation, and donor age <6 months.[34]

For the adult provider, BA is an ongoing disease that requires close management throughout life. Even after successful treatment with the Kasai operation in infancy, less than 25% of adult patients survive with their native livers.[4] Biochemical liver function tests should be checked at least every 6 months. Nutritional markers, such as fat-soluble vitamins, iron, calcium, phosphate, and alkaline phosphatase, should be assessed if poor growth or cholestasis are present. BA patients with signs and symptoms of portal hypertension, including splenomegaly and thrombocytopenia, should undergo regular endoscopic surveillance for esophageal varices with potential variceal ligation and treatment with non-selective beta blockers. Given that up to 25% of explants of patients undergoing LTx for BA have demonstrated pre-malignant or malignant nodules, careful surveillance for hepatocellular carcinoma with monitoring of alpha-fetoprotein and either abdominal ultrasound or magnetic resonance imaging with gadoxetic acid (Eovist in the United States) should also be part of routine care.[35,36] Medical management of ascites and hepatic encephalopathy and screening for hepatopulmonary syndrome, and portopulmonary hypertension are also essential parts of long-term care for patients with BA who survive long-term with their native livers. Recommended surveillance and special considerations for adult gastroenterologists are summarized (Table 2).

ALAGILLE SYNDROME

ALGS is an autosomal dominant, multisystem disorder that can manifest with liver, cardiovascular, facial, ocular, skeletal, and renal anomalies (Table 1 and Table 3). The phenotype was first described in 1969 by Daniel Alagille. The incidence of ALGS is estimated between 1 in 30,000 to 50,000 live births.[37] Ninety-five percent of ALGS cases result from heterozygous mutations in *JAG1* on chromosome 20, which encodes the ligand JAGGED1 in the Notch signaling pathway. The remaining 5% of ALGS cases are due to *NOTCH2* mutations on chromosome 1. As signals originating from the NOTCH receptors are involved in the development of multiple organ systems, mutations in these genes yield the pleiotropic manifestations observed in ALGS. Interestingly, the same mutations often have variable expression and different phenotypic characteristics within the same family.

TABLE 2. Surveillance of Adult Patients ($\geq$18 Y Old) With Pediatric Cholestatic Liver Disease

Disease	% Native liver by adulthood	Surveillance	Special considerations
Biliary atresia	23	LFT, GGT, AFP, abdomen US/MRI	High index of suspicion for cholangitis with unexplained fever, abdominal pain, and elevation in liver tests
ALGS	24-40	LFT, GGT, AFP, abdomen US/MRI Echo and/or electrocardiogram as needed (cardiac) Urinalysis, blood pressure, creatinine (renal) Brain/neck MR angiography (cerebrovascular)	Genetic counseling before conception due to AD inheritance; prenatal testing has little clinical utility due to variable penetrance
BASD	?	LFT, GGT, AFP, abdomen US/MRI Urinary bile acids	Bile acid dosing adjusted according to urinary bile acid levels
PFIC-1	44	LFT, GGT, AFP, abdomen US/MRI	Possible prenatal diagnosis
PFIC-2	28	LFT, GGT, AFP, abdomen US/MRI	Possible prenatal diagnosis;high index of suspicion for cancer due to increasd risk
PFIC-3	?	LFT, GGT, AFP, abdomen US/MRI	Possible prenatal diagnosis;high index of suspicion in unexplained adult-onset cholestasis

AD indicates autosomal dominant; AFP, alpha-fetoprotein; ALGS, Alagille syndrome; BASD, bile acid synthesis disorder; GGT, gamma-glutamyl transpeptidase; LFT, liver function tests; MRI, magnetic resonance imaging; PFIC, progressive familial intrahepatic cholestasis; US, ultrasound;

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 3. Prevalence of Clinical Manifestations in Alagille Syndrome

System involved	Proportion of patients (%)
Hepatic	89-95
Cardiac	94
Facial	92
Ocular	80
Skeletal	61
Renal	44
Vascular anomalies	4-38

Approximately 89% to 95% of patients with ALGS have hepatic involvement.[38] ALGS tends to present with neonatal cholestasis with an elevated GGT and direct bilirubin. Histologically, patients with ALGS demonstrate a paucity of bile ducts, with fewer than one-half of the portal tracts containing bile ducts. To accurately make the diagnosis of ALGS, many pathologists prefer to have at least 10 portal tracts present for evaluation. Of note, paucity of intrahepatic bile ducts in infancy is not exclusive to ALGS, as this can be a transient and nonspecific finding associated with other conditions, including prematurity, metabolic liver disease, infection, drug-induced liver injury, and inflammatory disorders. The progression of liver disease in ALGS is variable, with spontaneous resolution of mild cholestasis in some children, but development of cirrhosis and liver failure in others.

Most children who have ALGS and chronic cholestasis will accumulate bile acids systemically, causing intractable pruritus by 6 months of life.[39] Severe cholestatic pruritus can lead to debilitating excoriations, lichenification of the skin, secondary infections, significant sleep deprivation, and reduced health-related quality of life. Medical therapy for cholestatic pruritus in ALGS includes ursodeoxycholic acid (ursodiol), antihistamines (diphenhydramine, hydroxyzine), bile acid-binding resins (cholestyramine), hepatic enzyme inducers (phenobarbital, rifampin), opioid antagonists (naltrexone), selective serotonin reuptake inhibitors (sertraline), and ileal bile acid transport inhibitors (maralixibat). Biliary diversion can also help interrupt enterohepatic circulation of bile acids, although long-term efficacy is uncertain and the burden of a lifelong stoma is less than ideal for many patients and families.[40,41]

Severe refractory pruritus is an accepted indication for LTx and is recognized as a reason for children in the United States with ALGS awaiting LTx to receive PELD exception points. Other leading indications for patients with ALGS needing a LTx include the development of biliary cirrhosis, which can manifest with severe portal hypertension and liver synthetic function failure.[42] Recent reports indicate that up to 30% of children with ALGS will progress to end-stage liver disease requiring LTx by 5 years old, and 60% to 76% by the age of 18.[43–45] Recent Scientific Registry of Transplant Recipients analysis of over 150 children with ALGS who received LTx demonstrated the mean age at LTx was 3 years old, mean weight 14 kg, and mean PELD score 22, with the 1-year and 5-year patient survival at 95% and 94%, respectively.[46]

Extrahepatic manifestations of ALGS consist of abnormal facial features, including triangular facies, which becomes especially evident later in childhood, hypertelorism, and deep-set eyes. Ocular features include posterior embryotoxin, a clinical term referring to displacement and prominence of Schwalbe's line anterior to the limbus in the cornea, without impairment in visual function. Butterfly vertebrae due to a fusion defect of the anterior arches is the most commonly observed skeletal anomaly in ALGS, whereas spina bifida occulta, short ulna, and hypoplastic phalanges may also be seen. Importantly, patients with ALGS are at higher risk of fractures due to chronic cholestasis and impaired vitamin D absorption, higher prevalence of chronic kidney disease, and impairments in the Notch signaling pathway that is important in osteoblast and osteoclast activity. As a result, these patients require close monitoring of vitamin D levels and careful attention to post-LTx steroid dosing to prevent exacerbation of osteopenia.

ALGS is often associated with growth retardation, with over half of patients < 5th percentile for height and weight for their age. The etiology is multifactorial, due to a combination of poor caloric intake, especially in the setting of organomegaly and ascites, malabsorption from cholestasis, and genetics. Although post-LTx catch up growth is observed in ALGS, this is somewhat limited. Cardiac manifestations of ALGS vary in severity and include tetralogy of fallot, double outlet right ventricle, valvular pulmonic stenosis, and most commonly, peripheral pulmonic stenosis. Involvement of colleagues from cardiology and anesthesia in the multidisciplinary LTx selection committee discussion is essential in the peri- LTx and post-LTx care of ALGS patients. Neurological anomalies, including cerebrovascular aneurysms and moyamoya, are not uncommon and can be an important cause of morbidity and mortality in these patients. Magnetic resonance angiography of the brain and neck vessels should be obtained pre-LTx and periodically post-LTx. Colleagues from neurosurgery and interventional radiology may also need to be involved. Other important vascular anomalies to the aorta, renal vessels, celiac artery, and hepatic artery can also be seen in ALGS. Dyslipidemia is another manifestation of ALGS due to cholestasis and cholesterol dysregulation. The cholestatic hypercholesterolemia seen in ALGS leads to the formation of an abnormal lipoprotein, called liproprotein X.[47] Although it is not atherogenic, it is a predisposing factor to xanthomas, which can be cosmetically disfiguring, bothersome to patients and their families, and problematic when they occur over the joints.

NOTCH2 is expressed in renal tubular and glomerular epithelia, whereas *JAG1* is expressed in the endothelium of glomeruli and collecting tubules.[48,49] Thus, patients may present with structural renal disorders, such as renal agenesis/hypoplasia, cysts, hydronephrosis, collecting system anomalies, and renal vascular anomalies. In addition, they may have functional renal disorders, including renal tubular acidosis, nephritis, and diminished glomerular filtration rates, which require long-term renal follow-up and careful attention, particularly in the post-LTx setting due to the routine use of calcineurin inhibitors. A summary of key features in ALGS is listed (Table 3).

For the adult provider, lifelong multidisciplinary follow-up care of ALGS patients is crucial (Table 2). The cardiac manifestations are generally established in childhood, but the renal and vascular anomalies may develop throughout life making periodic surveillance necessary. Other manifestions, such as growth and pruritis, also need to be carefully monitored with adjustment of nutritional supplements and medications. Standard laboratory evaluations should be serially monitored. Given the risk of hepatocellular carcinoma, annual ultrasound and serum alpha-fetoprotein testing is also recommended. Finally, as ALGS is inherited in an autosomal

dominant manner, genetic counseling should be provided before conception to assist with family planning. Prenatal testing can be considered, but the variable clinical phenotype and lack of genotype-phenotype correlation preclude its utility in clinical practice.

BILE ACID SYNTHESIS DISORDERS

BASDs are a heterogeneous group of autosomal recessive disorders caused by defects in bile acid production. Mutations in any of the bile acid synthesis enzymes result in a deficiency in primary bile acids and an overproduction of intermediary bile acids. Accumulation of these atypical bile acid metabolites in the liver causes progressive hepatocyte injury and inflammation. Left untreated, BASDs eventually culminate in cirrhosis and liver failure.

As a group, BASDs are rare. Of the 17 known bile acid synthesis enzymes, only 11 distinct defects have been reported to date.[50] The estimated incidence is 1 per 50,000 to 100,000 in the general population[50] and 1 per 50 in infants and children with unexplained cholestasis.[51,52] However, the incidence is likely to increase given the rise in genetic testing.[53]

The phenotype of BASDs is highly variable, due in large part to the number of enzyme defects and the lack of genotype-phenotype correlation.[54] The age of onset, specific symptoms, and rate of progression can vary from early infancy to adulthood. Most BASDs present as neonatal cholestasis, but milder forms of the disease may not present until adulthood.[55–57] The 2 most frequently reported BASDs are 3β-Hydroxy-Δ5-C27-steroid oxidoreductase (HSD3B7) deficiency and Δ4-3-oxosteroid-5β-reductase (5β-reductase deficiency). HSD3B7deficiency is the most prevalent type, whereas 5β-reductase deficiency is the most lethal form, with a mortality rate as high as 50% if not treated within the first few months of life. Information on other specific bile acid defects is described elsewhere.[50,58]

Regardless of the defect, all BASDs share three clinical features that distinguish them from other cholestatic liver diseases[58] (Table 1). First, pruritis is usually absent in BASDs, but it is often the predominant symptom in other inherited cholestatic disorders, like ALGS and PFIC. Instead, the main clinical manifestations of BASDs are jaundice, failure to thrive, diarrhea, and fat-soluble vitamin deficiency; less common symptoms include rickets, areflexia, and renal cysts.[59,60] Second, the serum GGT, typically elevated with hepatobiliary injury, is characteristically normal or even low-normal in BASDs. Third, the total serum bile acid concentrations are low in BASDs, but high in other cholestatic disorders. The presence of all three features should raise suspicion for a BASD.

The gold standard for diagnosis is mass spectrometry of urine or serum to identify specific bile acid profiles associated with known enzyme defects.[51,61] In general, the intermediary bile acids are high, whereas the primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), are low. The rapid turnaround time for urine fast atom bombardment ionization mass spectrometry (FAB-MS) makes it the preferred initial test when a BASD is suspected—but it is important that ursodeoxycholic acid be stopped for at least 5 days before urine collection to avoid contamination of test results. Newer diagnostic technologies, such as next-generation sequencing with multigene panels or whole-exome sequencing, are proving beneficial for the evaluation of unexplained cholestasis because of the high-throughput analysis for a large number of genes.[53] A typical cholestasis genetic panel, for example, tests ~70 genes, of which, 9 are specific to BASDs (*AKR1D1*, *AMACR*, *BAAT*, *CYP7A1*, *CYP8B1*, *CYP27A1*, *DJCR7*, *HSD3B7*, *SLC27A5*). Unfortunately, high cost and long wait times (up to 4 wk turnaround) limit their widespread usage. However, as the technology and availability of these tests continue to improve, multigene panels can redefine the clinical algorithm for diagnosing not only BASDs but also cholestatic disorders in general. Finally, there is only a limited role for liver biopsy in diagnosing BASDs. The histopathologic features of BASDs, which include periportal inflammation, intralobular cholestasis, and giant cell transformation, are nonspecific.[62] The times when liver biopsy may be helpful are stratification of disease severity and exclusion of other possible etiologies.

When it comes to management, the type of defect in the BASD is less important. Most BASDs are treated with an oral primary bile acid medication to bypass the defect causing the block in bile acid synthesis. Treatment not only restores the missing primary bile acid but also inhibits the synthesis of the hepatotoxic intermediary metabolites by negative feedback regulation. CA is the bile acid of choice because of its excellent safety profile.[63–65] CA is started at a dose of 10 to 15 mg/kg/day and titrated by 10% increments according to the reduction or disappearance of atypical bile acid metabolites in urine on FAB-MS analysis. CDCA is an alternative if CA is unavailable,[66] but contraindicated during pregnancy due to hepatotoxicity risk. Both CA and CDCA therapies are safe, efficacious, and well-tolerated long-term solutions allowing very favorable outcomes into adulthood.[63–66] In the largest follow-up study to date, all 15 patients on prolonged CA therapy (median period of 21.4 y) were alive with their native livers and maintained normal serum liver biochemistry.[64] In the rarer bile acid amidation defects, such as those caused by bile acid-CoA ligase deficiency and bile acid-CoA:N-acyl amino acid transferase deficiency, CA is not an effective therapy because the defects are in the final steps of bile acid synthesis in which primary bile acids are conjugated to glycine or taurine before secretion into bile. In these cases, glycocholic acid is needed.[67] Ursodeoxycholic acid offers little benefit to BASDs; it may stimulate bile flow and temporarily improve liver enzyme levels, but fails to downregulate the synthesis of hepatotoxic bile acid intermediates. If undiagnosed or untreated, LTx will inevitably be required. Although it is curative, published data on the long-term outcomes of transplantation are lacking.

For the adult provider, lifelong oral bile acid replacement therapy should guarantee successful transition into adulthood and excellent quality of life without the need for LTx.[64] Surveillance testing should be performed annually with serum transaminases, alpha-fetoprotein and liver ultrasound for hepatocellular carcinoma screening, and urinary bile acid analysis with FAB-MS for medication optimization (Table 2).

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

PFIC is a rare class of inherited disorders caused by defects in bile canalicular transport that result in abnormal bile formation and progressive liver disease. Twelve subtypes of PFIC have been identified, each with a different genetic defect.[68] The most common subtypes are PFIC-1 (FIC1 deficiency/*ATP8B1* mutation), PFIC-2 (bile salt export pump deficiency/*ABCB11* mutation), and PFIC-3 (multidrug resistance protein-3 deficiency/*ABCB4* mutation). In PFIC-1 and PFIC-2, bile acid secretion is impaired, whereas in

PFIC-3, bile phospholipid secretion is disrupted. PFIC-1 and PFIC-2 account for two-third of PFIC cases, and PFIC-3 one-third of cases.[69] Together, PFIC makes up 10% to 15% of neonatal cholestasis cases.[70–72]

All the PFIC subtypes share many common clinical features, but differ in certain respects[73,74] (Table 1). PFIC-1 and PFIC-2 tend to present in the first months of life, whereas PFIC-3 may arise later, sometimes even during young adulthood. The hallmark signs and symptoms of all forms of PFIC are cholestasis, jaundice, and pruritis. Often, pruritis is the most debilitating part of the disease and thus the primary target of early intervention. PFIC-1 is unique because of its propensity to develop extrahepatic complications because of the multiorgan tissue expression of *ATP8B1*. Extrahepatic symptoms may include diarrhea, pancreatitis, hearing loss, delayed puberty, and short stature.[75,76] Of the 3, PFIC-2 has the most aggressive liver phenotype, with a significant risk for early liver failure and hepatobiliary malignancy (up to 15% with hepatocellular carcinoma or cholangiocarcinoma). Biochemically, they all have elevated serum bile acid levels; but PFIC-3 is differentiated from PFIC-1 and PFIC-2 by persistently high GGT levels, a consequence of biliary epithelium injury from the detergent effects of bile salts in the absence of biliary phospholipids.[77] Histologically, PFIC-2 generally presents with the most severe features, including extensive lobular inflammation, fibrosis, ductular reaction, bile plugs, and giant cell transformation. Both PFIC-1 and PFIC-2 can show bile duct paucity, whereas PFIC-3 is more likely to demonstrate bile duct proliferation.

PFIC is diagnosed only through genetic testing. Next-generation sequencing and cholestasis sequencing panels have led to the identification of novel gene variants associated with PFIC,[53] particularly in adults with late-onset liver disease. In one report, targeted genomic sequencing revealed *ABCB4* variants in up to 50% of adults with unexplained cholestasis or recurrent gallstones.[78] It is expected that the expanding use of genetic testing will continue to uncover new PFIC variants.

PFIC is managed medically and surgically for both definitive therapy and bridge to transplantation.[73] Ursodeoxycholic acid therapy is recommended in all cases to slow the progression of liver damage. In select cases, long-term therapy can even reverse advanced liver fibrosis.[79] Other medical treatments include supplementation of medium-chain triglycerides and fat-soluble vitamins, as well as antipruritic therapies. A combination of different antipruritics is frequently required to target the various mechanisms of pruritis. Recently, the first drug in the class of ileal bile acid transporter inhibitors (Odevixibat, Albireo Pharma, Boston, MA) has been approved in the United States, United Kingdom, and Germany for treatment of pruritis in all subtypes of PFIC.[80] So far, the results are promising. A second drug (Maralixibat, Mirum Pharmaceuticals, Foster City, CA) is now also in clinical trial.[81] These medications decrease serum bile acids by interrupting the enterohepatic circulation.[44]

In medically refractory cases, surgical options should be considered. Biliary diversion procedures may reduce pruritis and decelerate liver injury. However, liver transplantation is the only cure. The primary indications for LTx are refractory cholestatic pruritis and end-stage liver disease. Given the disease's natural course, most PFIC cases require LTx by early adulthood. According to global consortium data, native liver survival at 18 years of age is 44% and 28% for PFIC-1 and PFIC-2, respectively.[5,6]

For the adult provider, the management of PFIC can be divided between LTx patients and those still with their native livers. For LTx recipients, providers should provide the same post-transplant care as they usually would for any other diagnosis, but be privy to 2 issues unique to PFIC.[67] First, extrahepatic complications may persist and even exacerbate after transplantation in PFIC-1 due to the widespread tissue distribution of *ATP8B1* expression. Chronic diarrhea occurs in 93% and liver steatosis in 73% of cases.[71] In one series, 25% required re-transplantation for steatohepatitis.[82] Second, there is a risk for disease recurrence after transplantation in PFIC-2.[83,84] The median time to disease recurrence was 37-month post-transplant, according to 1 report.[83] Recurrent disease develops due to the formation of de novo autoantibodies against the bile salt export pump, a response likely triggered by changes in immunosuppression, infection, and acute rejection. Treatment is targeted against antibody mediated rejection and consists of higher immunosuppression, rituximab, bortezomib, intravenous immunoglobulin, and plasmapheresis to remove the antibodies. Rarely, liver re-transplantation or hematopoietic stem cell transplantation is needed.[85]

For non-transplanted patients, providers should routinely monitor for signs and symptoms of worsening liver disease. They should refer patients for LTx if pruritis becomes unbearable or signs of decompensated liver disease develop. Given the heightened risk for malignancy with chronic liver disease, especially in PFIC-2, providers should also regularly screen for hepatocellular carcinoma with yearly serum alpha-fetoprotein levels and liver ultrasounds.

Finally, for patients with unexplained liver disease, providers should have a high index of suspicion for PFIC. Milder phenotypes of PFIC-3 can be misdiagnosed or overlooked in childhood.[77,86] These may present in adulthood as drug-induced liver injury, intrahepatic cholestasis of pregnancy, and cholesterol choledocholithiasis.[87] Unfortunately, undiagnosed cases can present with portal hypertensive bleeding as the first symptom. Early diagnosis and timely treatment may prevent or delay the progression to end-stage liver disease. Thus, providers should have a low threshold to pursue genetic testing when the cause of cholestasis is unclear (Table 2).

CONCLUSION

Advances in medical and surgical care have substantially improved the prognosis of children with cholestatic liver diseases, particularly BA, ALGS, BASD, and PFIC. As a significant proportion of these children are now surviving into adulthood, adult gastroenterologists should be cognizant of the natural history and long-term outcomes of these diseases. As young adults, they will need smooth transition of care to adult providers familiar with their underlying condition and unique issues that might come up post-transplant. Successful transition of care requires preparation and collaboration between pediatric and adult providers that starts with knowledge about the diseases. Adult gastroenterologists will play pivotal roles in the long-term health of patients with congenital cholestatic liver disease.

REFERENCES

1. Karpen SJ. Pediatric cholestasis: epidemiology, genetics, diagnosis, and current management. *Clin Liver Dis*. 2020;15:115–119.

2. Kwong AJ, Ebel NH, Kim WR, et al. OPTN/SRTR 2020 Annual Data Report: Liver. *Am J Transplant*. 2022;22(suppl 2): 204–309.
3. Kelly DA, Bucuvalas JC, Alonso EM, et al. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl*. 2013;19:798–825.
4. Lykavieris P, Chardot C, Sokhn M, et al. Outcome in adulthood of biliary atresia: a study of 63 patients who survived for over 20 years with their native liver. *Hepatology*. 2005;41: 366–371.
5. van Wessel DBE, Gonzales E, Hansen BE, et al. Defining the natural history of rare genetic liver diseases: Lessons learned from the NAPPED initiative. *Eur J Med Genet*. 2021;64: 104245.
6. van Wessel DBE, Thompson RJ, Gonzales E, et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. *J Hepatol*. 2020;73:84–93.
7. Danks DM, Campbell PE, Jack I, et al. Studies of the aetiology of neonatal hepatitis and biliary atresia. *Arch Dis Child*. 1997;52:360–367.
8. Yoon PW, Bresee JS, Olney RS, et al. Epidemiology of biliary atresia: a population-based study. *Pediatrics*. 1997;99:376–382.
9. Corrado MM, Mack CL. Diagnostic tools for early detection of biliary atresia: is a newborn screen attainable? *Clin Liver Dis*. 2022;19:25–28.
10. Bobo L, Ojeh C, Chir D, et al. Lack of evidence for rotavirus by polymerase chain reaction/enzyme immunoassay of hepatobiliary samples from children with biliary atresia. *Pediatr Res*. 1997;41:229–234.
11. Czech-Schmidt G, Verhagen W, Szavay P, et al. Immunological gap in the infectious animal model for biliary atresia. *J Surg Res*. 2001;101:62–67.
12. Szavay PO, Leonhardt J, Czech-Schmidt G, et al. The role of reovirus type 3 infection in an established murine model for biliary atresia. *Eur J Pediatr Surg*. 2022;12:248–250.
13. Desmet VJ. Congenital diseases of intrahepatic bile ducts: variations on the theme "ductal plate malformation. *Hepatology*. 1992;16:1069–1083.
14. Davenport M, Savage M, Mowat AP, et al. Biliary atresia splenic malformation syndrome: An etiologic and prognostic subgroup. *Surgery*. 1993;113:662–668.
15. Carmi R, Magee CA, Neill CA, et al. Extrahepatic biliary atresia and associated anomalies: Etiologic heterogeneity suggested by distinctive patterns of associations. *Am J Med Genet*. 1993;45:683–693.
16. Vazquez J, Lopez Gutierrez JC, Gomez M, et al. Biliary atresia and the polysplenia syndrome: Its impact on final outcome. *J Pediatr Surg*. 1995;30:485–487.
17. Lilly JR, Chandra RS. Surgical hazards of co-existing anomalies in biliary atresia. *Surg Gynecol Obstet*. 1974;139:49–54.
18. Meyers RL, Book LS, O'Gorman MA, et al. High-dose steroids, ursodeoxycholic acid, and chronic intravenous antibiotics improve bile flow after Kasai procedure in infants with biliary atresia. *J Pediatr Surg*. 2003;38:406–411.
19. Park WH, Choi SO, Lee HJ. Technical innovation for noninvasive and early diagnosis of biliary atresia: The ultrasonographic "triangular cord" sign. *J Hepatobiliary Pancreat Surg*. 2001;8:337–341.
20. Farrant P, Meire HB, Mieli-Vergani G. Improved diagnosis of extraheptic biliary atresia by high frequency ultrasound of the gall bladder. *Br J Radiol*. 2001;74:952–954.
21. Gilmour SM, Hershkop M, Reifen R, et al. Outcome of hepatobiliary scanning in neonatal hepatitis syndrome. *J Nucl Med*. 1997;38:1279–1282.
22. Ridaura Sanz C, Navarro Castilla E. Role of liver biopsy in the diagnosis of prolonged cholestasis in infants. *Rev Invest Clin*. 1992;44:193–202.
23. Lertudomphonwanit C, Mourya R, Fei L, et al. Large-scale proteomics identifies MMP-7 as a sentinel of epithelial injury and of biliary atresia. *Sci Transl Med*. 2017;9:eaan8462.
24. Kasai M, Suzuki S. A new operation for "non-correctable" biliary atresia: Hepatic portoenterostomy. *Shujutsu*. 1959;13: 773–779.
25. Wu ET, Chen HL, Ni YH, et al. Bacterial cholangitis in patients with biliary atresia: Impact on short-term outcome. *Pediatr Surg Int*. 2001;17:390–395.
26. Lunzmann K, Schweizer P. The influence of cholangitis on the prognosis of extrahepatic biliary atresia. *Eur J Pediatr Surg*. 1999;9:19–23.
27. Bu LN, Chen HL, Chang CJ, et al. Prophylactic oral antibiotics in prevention of recurrent cholangitis after the Kasai portoenterostomy. *J Pediatr Surg*. 2003;38:590–593.
28. Bezerra JA, Spino C, Magee JC, et al. Use of corticosteroids after hepatoportoenterostomy for bile drainage in infants with biliary atresia: the START randomized clinical trial. *JAMA*. 2014;311:1750–1759.
29. Fawaz R, Baumann U, Ekong U, et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2017;64:154–168.
30. Fanna M, Masson G, Capito C, et al. Management of biliary atresia in France 1986 to 2015: Long-term results. *J Pediatr Gastroenterol Nutr*. 2019;69:416–424.
31. Sundaram SS, Mack CL, Feldman AG, et al. Biliary atresia: Indications and timing of liver transplantation and optimization of pretransplant care. *Liver Transpl*. 2017;23:96–109.
32. Starzl T, Marchioro TL, Vonkaulla KN, et al. Homotransplantation of the liver in humans. *Surg Gynecol Obstet*. 1963;117:659–676.
33. Venick RS, Farmer DG, Soto JR, et al. One thousand pediatric liver transplants during thirty years: lessons learned. *J Am Coll Surg*. 2018;226:355–366.
34. Taylor SA, Venkat V, Arnon R, et al. Society of pediatric liver transplantation. improved outcomes for liver transplantation in patients with biliary atresia since pediatric end-stage liver disease implementation: Analysis of the Society of Pediatric Liver Transplantation Registry. *J Pediatr*. 2020;219:89–97.
35. Calinescu AM, Rougemont AL, Anooshiravani M, et al. Features of nodules in explants of children undergoing liver transplantation for biliary atresia. *J Clin Med*. 2022;11:1578–1589.
36. Parolini F, Boroni G, Milianti S, et al. Biliary atresia: 20-40-year follow-up with native liver in an Italian centre. *J Pediatr Surg*. 2019;54:1440–1444.
37. Mitchell E, Gilbert M, Loomes KM. Alagille syndrome. *Clin Liver Dis*. 2018;22:625–641.
38. Menon J, Shanmugam N, Vij M, et al. Multidisciplinary management of alagille syndrome. *J Multidiscip Healthc*. 2022;15:353–364.
39. Kamath BM, Baker A, Houwen R, et al. Systematic review: the epidemiology, natural history, and burden of alagille syndrome. *J Pediatr Gastroenterol Nutr*. 2018;67:148–156.
40. Wang KS, Tiao G, Bass LM, et al. Childhood Liver Disease Research Network (ChiLDReN). Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis. *Hepatology*. 2017;65:1645–1654.
41. Lemoine C, Superina R. Surgical diversion of enterohepatic circulation in pediatric cholestasis. *Semin Pediatr Surg*. 2020;29: 150946.
42. Kamath BM, Yin W, Miller H, et al. Studies of Pediatric Liver Transplantation. Outcomes of liver transplantation for patients with Alagille syndrome: the studies of pediatric liver transplantation experience. *Liver Transpl*. 2012;18:940–948.
43. Kamath BM, Schwarz KB, Hadzić N. Alagille syndrome and liver transplantation. *J Pediatr Gastroenterol Nutr*. 2010;50:11–15.
44. Kamath BM, Stein P, Houwen RHJ, et al. Potential of ileal bile acid transporter inhibition as a therapeutic target in Alagille syndrome and progressive familial intrahepatic cholestasis. *Liver Int*. 2020;40:1812–1822.
45. Gonzales E, Hardikar W, Stormon M, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and

cholestatic pruritus (ICONIC): a randomised phase 2 study. *Lancet*. 2021;398:1581–1592.
46. Black K, Ziogas IA, Thurm C, et al. Pediatric liver transplant survival in Alagille syndrome is comparable to biliary atresia- a linked database analysis. *J Pediatr Gastroenterol Nutr*. 2022;75:257–263.
47. Davit-Spraul A, Pourci ML, Atger V, et al. Abnormal lipoprotein pattern in patients with alagille syndrome depends on icterus severity. *Gastroenterology*. 1996;111:1023–1032.
48. Valamparampil JJ, Reddy MS, Shanmugam N, et al. Living donor liver transplantation in Alagille syndrome-Single center experience from South Asia. *Pediatr Transplant*. 2019;23:e13579.
49. Kamath BM, Podkameni G, Hutchinson AL, et al. Renal anomalies in Alagille syndrome: a disease-defining feature. *Am J Med Genet A*. 2012;158A:85–89.
50. Heubi JE, Setchell KDR, Bove KE. Inborn errors of bile acid metabolism. *Clin Liver Dis*. 2018;22:671–687.
51. Setchell KD, Heubi JE. Defects in bile acid biosynthesis–diagnosis and treatment. *J Pediatr Gastroenterol Nutr*. 2006;43 (Suppl 1):S17–S22.
52. Al-Hussaini AA, Setchell KDR, AlSaleem B, et al. Bile acid synthesis disorders in arabs: a 10-year screening study. *J Pediatr Gastroenterol Nutr*. 2017;65:613–620.
53. Karpen SJ, Kamath BM, Alexander JJ, et al. Use of a comprehensive 66-gene cholestasis sequencing panel in 2171 cholestatic infants, children, and young adults. *J Pediatr Gastroenterol Nutr*. 2021;72:654–660.
54. Cheng JB, Jacquemin E, Gerhardt M, et al. Molecular genetics of 3beta-hydroxy-Delta5-C27-steroid oxidoreductase deficiency in 16 patients with loss of bile acid synthesis and liver disease. *J Clin Endocrinol Metab*. 2003;88:1833–1841.
55. Fischler B, Bodin K, Stjernman H, et al. Cholestatic liver disease in adults may be due to an inherited defect in bile acid biosynthesis. *J Intern Med*. 2007;262:254–262.
56. Molho-Pessach V, Rios JJ, Xing C, et al. Homozygosity mapping identifies a bile acid biosynthetic defect in an adult with cirrhosis of unknown etiology. *Hepatology*. 2012;55:1139–1145.
57. Kobayashi M, Koike M, Sakiyama M, et al. 3 beta-hydroxy-Delta(5)-C-27-steroid dehydrogenase/isomerase deficiency in a 23-year-old woman. *Pediatr Int*. 2000;42:685–688.
58. Sundaram S, Bove K, Lovell M, Sokol R. Mechanisms of disease: inborn errors of bile acid synthesis. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5:456–468.
59. Zhao J, Setchell KDR, Gong Y, et al. Genetic spectrum and clinical characteristics of 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase (HSD3B7) deficiency in China. *Orphanet J Rare Dis*. 2021;16:417–431.
60. Zhang Y, Yang C, Wang W, et al. Prognosis and clinical characteristics of patients with 3 beta-hydroxy-Delta 5-C27-steroid dehydrogenase deficiency diagnosed in childhood: a systematic review of the literature. *Medicine (Baltimore)*. 2022;101:e28834.
61. Vaz FM, Ferdinandusse S. Bile acid analysis in human disorders of bile acid biosynthesis. *Mol Aspects Med*. 2017;56:10–24.
62. Bove KE. Liver disease caused by disorders of bile acid synthesis. *Clin Liver Dis*. 2000;4:831–848.
63. Gonzales E, Matarazzo L, Franchi-Abella S, et al. Cholic acid for primary bile acid synthesis defects: a life-saving therapy allowing a favorable outcome in adulthood. *Orphanet J Rare Dis*. 2018;13:190.
64. Gonzales E, Gerhardt MF, Fabre M, et al. Oral cholic acid for hereditary defects of primary bile acid synthesis: a safe and effective long-term therapy. *Gastroenterology*. 2009;137:1310–1320.e1-3.
65. Heubi JE, Setchell KDR. Open-label phase 3 continuation study of cholic acid in patients with inborn errors of bile acid synthesis. *J Pediatr Gastroenterol Nutr*. 2020;70:423–429.
66. Kimura A, Mizuochi T, Takei H, et al. Bile acid synthesis disorders in Japan: long-term outcome and chenodeoxycholic acid treatment. *Dig Dis Sci*. 2021;66:3885–3892.
67. Heubi JE, Setchell KD, Jha P, et al. Treatment of bile acid amidation defects with glycocholic acid. *Hepatology*. 2015;61:268–274.
68. Online Mendelian Inheritance in Man, OMIM®. CHOLESTASIS, PROGRESSIVE FAMILIAL INTRAHEPATIC, 1; PFIC1. Accessed September 8, 2022. https://www.omim.org/entry/211600
69. Davit-Spraul A, Gonzales E, Baussan C, et al. Progressive familial intrahepatic cholestasis. *Orphanet J Rare Dis*. 2009;4:1–12.
70. Jacquemin E. Progressive familial intrahepatic cholestasis. *Clin Res Hepatol Gastroenterol*. 2012;36(suppl 1):26–35.
71. Hori T, Nguyen JH, Uemoto S. Progressive familial intrahepatic cholestasis. *Hepatobiliary Pancreat Dis Int*. 2010;9:570–578.
72. Baker A, Kerkar N, Todorova L, et al. Systematic review of progressive familial intrahepatic cholestasis. *Clin Res Hepatol Gastroenterol*. 2019;43:20–36.
73. Mehl A, Bohorquez H, Serrano MS, et al. Liver transplantation and the management of progressive familial intrahepatic cholestasis in children. *World J Transplant*. 2016;6:278–290.
74. Alam S, Lal BB. Recent updates on progressive familial intrahepatic cholestasis types 1, 2 and 3: Outcome and therapeutic strategies. *World J Hepatol*. 2022;14:98–118.
75. Lykavieris P, van Mil S, Cresteil D, et al. Progressive familial intrahepatic cholestasis type 1 and extrahepatic features: no catch-up of stature growth, exacerbation of diarrhea, and appearance of liver steatosis after liver transplantation. *J Hepatol*. 2003;39:447–452.
76. Pfister ED, Dröge C, Liebe R, et al. Extrahepatic manifestations of progressive familial intrahepatic cholestasis syndromes: presentation of a case series and literature review. *Liver Int*. 2022;42:1084–1096.
77. Jacquemin E. Role of multidrug resistance 3 deficiency in pediatric and adult liver disease: one gene for three diseases. *Semin Liver Dis*. 2001;21:551–562.
78. Avena A, Puggelli S, Morris M, et al. ABCB4 variants in adult patients with cholestatic disease are frequent and underdiagnosed. *Dig Liver Dis*. 2021;53:329–344.
79. Frider B, Castillo A, Gordo-Gilart R, et al. Reversal of advanced fibrosis after long-term ursodeoxycholic acid therapy in a patient with residual expression of MDR3. *Ann Hepatol*. 2015;14:745–751.
80. Thompson RJ, Arnell H, Artan R, et al. Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomised, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2022;7:830–842.
81. Loomes KM, Squires RH, Kelly D, et al. Maralixibat for the treatment of PFIC: long-term, IBAT inhibition in an open-label, Phase 2 study. *Hepatol Commun*. 2022;6:2379–2390.
82. Okamoto T, Sonoda M, Ogawa E, et al. Long-term outcomes of living-donor liver transplantation for progressive familial intrahepatic cholestasis type 1. *J Pediatr Gastroenterol Nutr*. 2021;72:425–429.
83. Stindt J, Kluge S, Dröge C, et al. Bile salt export pump-reactive antibodies form a polyclonal, multi-inhibitory response in antibody-induced bile salt export pump deficiency. *Hepatology*. 2016;63:524–537.
84. Maggiore G, Gonzales E, Sciveres M, et al. Relapsing features of bile salt export pump deficiency after liver transplantation in two patients with progressive familial intrahepatic cholestasis type 2. *J Hepatol*. 2010;53:981–986.
85. Brinkert F, Pukite I, Krebs-Schmitt D, et al. Allogeneic haematopoietic stem cell transplantation eliminates alloreactive inhibitory antibodies after liver transplantation for bile salt export pump deficiency. *J Hepatol*. 2018;69:961–965.
86. Schatz SB, Jüngst C, Keitel-Anselmo V, et al. Phenotypic spectrum and diagnostic pitfalls of ABCB4 deficiency depending on age of onset. *Hepatol Commun*. 2018;2:504–514.
87. Stättermayer AF, Halilbasic E, Wrba F, et al. Variants in ABCB4 (MDR3) across the spectrum of cholestatic liver diseases in adults. *J Hepatol*. 2020;73:651–663.