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Treatment of Cholestasis in Infants and Young Children

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Abstract

Purpose of Review Cholestasis is characterized by a conjugated hyperbilirubinemia secondary to impaired bile synthesis, transport, or excretion from the liver. It is always pathologic and can be indicative of an underlying hepatobiliary, genetic, or metabolic disorder, several of which require timely diagnosis to ensure proper management and optimal outcomes. This review provides an overview of the evaluation of cholestasis with a focus on current and emerging treatment strategies.

Recent Findings Increased accessibility of next generation sequencing (NGS) allows for utilization of genetic testing early in the diagnostic process. This may alter the clinical algorithm for diagnosis of cholestatic disorders. An enhanced understanding of the underlying pathophysiology may help guide future development of targeted therapies, such as ileal bile acid transporter (IBAT) inhibitors. These were recently approved for treatment of cholestatic pruritus in patients with Alagille syndrome and Progressive Familial Intrahepatic Cholestasis.

Summary Current management of cholestasis is aimed at the biochemical consequences of impaired bile flow, including malnutrition, pruritus, and progressive fibrosis. NGS has led to an enhanced understanding of biliary pathology and may guide development of future treatment modalities based on specific gene mutations. Rapid discernment of the underlying etiology is essential as new treatment modalities emerge.

Keywords Neonatal cholestasis · Biliary atresia · Alagille syndrome · Cholestatic pruritus · IBAT inhibitors · Next generation sequencing

Introduction

Cholestasis is defined as a decrease or absence of bile flow from the liver to the small intestine. This can be caused by defects in bile production, transmembrane transport, or a mechanical obstruction to bile flow. Neonatal cholestasis affects roughly 1 in 2500 term births and early identification is critical as this may impact treatment outcomes [1, 2]. Practice guidelines endorsed by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) in 2017 can help guide evaluation of the pediatric patient with cholestasis. Any infant presenting with jaundice beyond two to three weeks of life should undergo evaluation. An elevated serum conjugated or direct bilirubin level > 1.0 mg/dL warrants further diagnostic evaluation. A threshold of 2.0 may be appropriate in infants with intestinal failure-associated liver disease [1]. Recent reports have also suggested that a lower conjugated/direct bilirubin level of > 0.3–0.5 mg/dL and > 10% of the total bilirubin in the first few days of life should also trigger suspicion for cholestasis and consideration for further investigation [3–5].

The diagnostic algorithm for neonatal cholestasis has evolved in recent years with the advent of next generation sequencing (NGS) enabling rapid identification of disorders that cannot be directly diagnosed from routine serologic tests or liver biopsy. Genetic sequencing is being utilized earlier in the diagnostic pathway in concert with evaluation for biliary atresia and other treatable disorders.

The biochemical features of cholestasis reflect the retention of bile components in the serum, namely bilirubin, bile acids and cholesterol. These may lead to clinical manifestations of jaundice, pruritus, xanthomas, and malnutrition. Damage to the liver parenchyma can also lead to progressive fibrosis and cirrhosis with resultant portal hypertension

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and loss of hepatic synthetic function over time. The pattern and severity of each of these abnormalities varies with the underlying disorder. This review presents an overview of cholestasis in infants and children with a focus on current and emerging treatment strategies.

Clinical Presentation

Infants with cholestatic jaundice often present with scleral icterus and may also have symptoms of acholic stool, dark urine, and increased irritability secondary to pruritus, which may be helpful in distinguishing cholestasis from physiologic jaundice. Family history of liver disease, especially in siblings, suggests an underlying genetic abnormality, early emphysema in family members raises suspicion for alpha-1 antitrypsin (A1AT) deficiency, and history of consanguinity increases the likelihood of an autosomal recessive pathology [6].

If there is progression of the underlying liver disease, physical exam may also reveal hepatosplenomegaly, ascites, and signs of malnutrition and frailty with low muscle mass, temporal wasting, and delayed growth. Physical exam findings that may provide additional diagnostic clues include hypotonia (mitochondrial or peroxisomal disorder), heart murmur (Alagille syndrome or biliary atresia), dysmorphic facies (Alagille syndrome or underlying chromosomal abnormality), cataracts, chorioretinitis, and microcephaly (congenital infection).

Diagnostic Evaluation

The first step in evaluating for cholestasis is to fractionate the total bilirubin level. Cholestatic jaundice is defined as a serum conjugated bilirubin concentration greater than 1.0 mg/dL. Once established, further evaluation should be performed in a stepwise approach with a focus on rapid identification of treatable disorders (Fig. 1). Conditions such as sepsis/infection, hypothyroidism, inborn errors of metabolism (i.e., galactosemia), and panhypopituitarism must be diagnosed and treated promptly to avoid progression of systemic illness. Biliary obstruction, as seen with choledochal cysts, may be identified with ultrasound [7].

Biliary atresia (BA) must also be identified promptly as early surgical intervention has been associated with better long-term outcomes. The work-up often includes a series of laboratory tests, imaging, and liver histology to exclude other causes of cholestasis. Definitive diagnosis is made with cholangiogram. Hepatoportoenterostomy (HPE) or Kasai procedure, is a surgical attempt to restore bile flow from the liver to the intestine. During this procedure, a Roux-en-Y loop of bowel is created and directly anastomosed to the hilum of the liver, following excision of the biliary remnant and portal fibrous plate. Younger age at the time of HPE, specifically when performed before 45 days of age, is associated with improved outcomes. Native liver survival declines when HPE is performed beyond 60 days

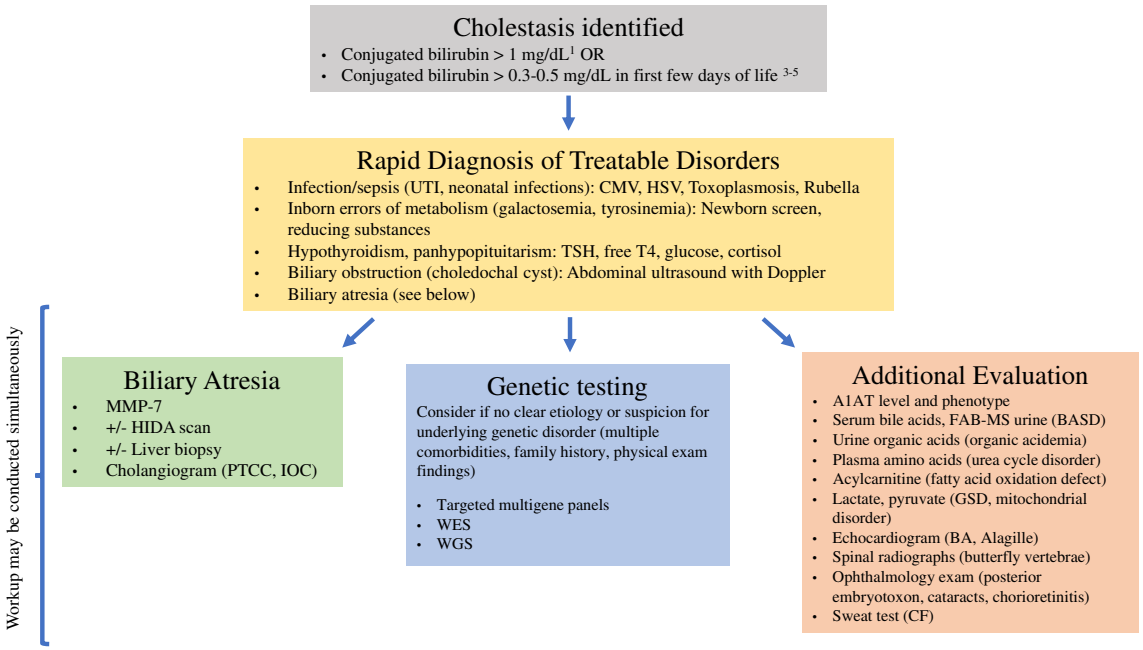

Fig. 1 Diagnostic Approach to Evaluation of Cholestasis in Neonates and Young Infants

of life thereby emphasizing the importance of timely diagnosis [8–10].

Serum measurement of matrix metalloproteinase-7 (MMP-7) has recently been explored as a potential biomarker of BA that may help to guide decisions regarding the pursuit of more invasive studies. MMP-7 is highly expressed in the intrahepatic bile ducts and an elevated serum MMP-7 has been noted around 1–2 months of age in patients with BA, with positive and negative predictive values exceeding 90 and 95% respectively [11, 12]. Further validation is needed to clarify the role of MMP-7 in the diagnostic algorithm of neonatal cholestasis.

The remainder of the workup for cholestasis is guided by the overall clinical presentation of the patient. Hospitalized infants with complex comorbidities may also have multifactorial cholestasis in the setting of infection, cardiac dysfunction, delays in enteral stimulation, and use of parenteral nutrition. Family and maternal history along with physical exam findings can help guide next steps in patients without a clear etiology to cholestasis (Table 1) [13–21].

Role of Next-Generation Sequencing

Genetic disorders account for more than 25–50% of all cases of neonatal cholestasis [22••, 23]. Identification of the precise etiology can be challenging due to the extensive overlap of clinical presentations. Routine serologic and other diagnostic assessments are often insufficient to distinguish between these disorders. Historically, genetic testing was limited to analysis of a single gene based on clinical observation and initial evaluation; however, given the large number of potential genetic causes of cholestasis, single-gene testing has become impractical, and moreover, may result in delays in timely diagnosis. Next-generation sequencing (NGS), including multigene panels, whole exome sequencing (WES), and whole genome sequencing (WGS), now enables rapid testing of multiple genes simultaneously, with available results within days to weeks. This allows for the utilization of genetic testing early in the diagnostic process. A recent study using a 66 gene panel in 716 infants and older children with cholestasis or liver disease of unknown etiology reported a positive or likely positive molecular diagnosis in 11.7% and a single pathogenic or likely pathogenic variant in another 12.7% of patients [22••]. The analysis of multiple genes in a single panel reduces the time to identify, or perhaps exclude, specific genes as a cause of cholestasis. While the increased accessibility and affordability of NGS has allowed for rapid evaluation of these patients, wide-spread testing also presents the need for additional considerations. The ongoing discovery of new gene variants, single mutations in known pathogenic genes, unclear pathogenicity and variable phenotypes have made interpretation of these results challenging at times. The use of NGS without selection may give rise to unnecessary or uninterpretable information which may complicate rather than clarify the diagnosis [23] With continued implementation, multigene panels may alter the clinical algorithm for diagnosis of cholestatic disorders, including the necessity of liver biopsy.

Common Causes of Cholestasis (Table 1)

A brief overview of common causes of neonatal cholestasis is presented here. A more detailed review and approach to evaluation are presented in Table 1.

Biliary Atresia

Biliary atresia (BA) is a progressive, idiopathic, fibro-obliteration of the bile ducts which can lead to progressive fibrosis, cirrhosis, and eventually end-stage liver disease. It is universally fatal if not treated and is the most common identifiable cause of neonatal cholestasis and the leading indication for pediatric liver transplant. The etiology of BA remains elusive and is likely multifactorial in origin with contributing factors including exposure to viral or toxic pathogens in utero, immunologic mechanisms and possible predisposing genetic factors [24]. Biliary atresia may occur in isolation (70%), with laterality malformations (10% to 15%) also known as biliary atresia splenic malformation syndrome (BASM), or with other congenital anomalies (10% to 15%). Those with laterality malformations often have a worse prognosis. HPE outcomes vary widely between institutions and geographically, and many patients will ultimately require liver transplantation. The most important prognostic factors impacting long-term outcomes include younger age at the time of HPE (< 60 days), the experience of the surgeon and health-care center at which the procedure is performed, and the decrease in total bilirubin level in the months following HPE. Patients with a total bilirubin > 2 mg/dL at 3 months following HPE should be consider for liver transplant evaluation [25].

Medical care following HPE consists of choleretic medications, antibiotics for cholangitis prophylaxis, fat-soluble vitamin (FSV) and nutritional supplementation. Those with BA require life-long care for the evaluation and management of complications including progressive liver disease with portal hypertension, recurrent cholangitis, and hepatocellular carcinoma (HCC).

Alagille Syndrome

Alagille syndrome is an autosomal dominant disorder characterized by a paucity of intrahepatic bile ducts. Mutations in the *JAG1* gene account for approximately 90% of patients; a smaller percentage of patients have mutations in *NOTCH2*

Table 1 Common causes of cholestasis in infants and young children

Diagnosis	*Associated gene*	*Unique clinical features*	*Targeted diagnostic testing*	*Disease-specific therapies*	*References*
Anatomic Obstruction					
Biliary Atresia		Splenic malformations, situs inversus, cardiac malformations, interrupted IVC	Cholangiogram, liver biopsy	Hepatoportoenterostomy (Kasai procedure)	[7]
Choledochal cyst			US, MRCP	Surgical excision, choledochoenterostomy	[7]
Inspissated bile syndrome			US, MRCP	Biliary tract irrigation	[7]
Genetic Etiologies					
Alagille syndrome	JAG1 (95%), NOTCH2 (2.5%)	Cardiac defects, butterfly vertebrae, distinctive triangular facies (prominent forehead, pointed chin), posterior embryotoxon, vascular anomalies, renal dysplasia, renal tubular acidosis	Genetic testing, liver biopsy (bile duct paucity), ophthalmologic exam (evaluate for posterior embryotoxon), spinal radiographs, echocardiogram	IBAT inhibitors	[7, 13]
Cystic fibrosis	CFTR	Lung disease, pancreatic insufficiency	Genetic testing, sweat test	CFTR modulators	[7]
A1AT deficiency	SERPINA1	Lung disease, panniculitis, vasculitis	Genetic testing, A1AT phenotype	None	[7, 13, 14]
Niemann-Pick Disease Type C	NPC1, NPC2	Neurologic (hypotonia, ataxia, seizures, dysarthria)	Genetic testing	Miglustat	[15]
Bile acid synthesis defects	HSD3B7, AKR1D1, CYP7B1, AMACR, ABCD 3, ACOX2	Variable age (neonatal up to school-age children), acholic stools, fat soluble vitamin deficiencies, low serum bile acids	Genetic testing, serum bile acids	Cholic acid supplementation	[16]

Table 1 (continued)

Diagnosis	*Associated gene*	*Unique clinical features*	*Targeted diagnostic testing*	*Disease-specific therapies*	*References*
Bile acid transport defects					
PFIC 1	ATP8B1	Poor growth, pancreatic insufficiency, hearing impairment, diarrhea	Genetic testing	IBAT inhibitors	[17, 18]
PFIC 2	ABCB11	Poor growth, skin excoriations, ↑ risk HCC	Genetic testing		[17, 18]
PFIC 3	ABCB4	↑ Risk intrahepatic stone formation	Genetic testing		[17, 18]
PFIC 4	TJP2	Neurologic and respiratory disorders	Genetic testing		[17–19]
PFIC 5	NR1H4	Coagulopathy Rapid progression to ESLD	Genetic testing		[17, 19, 20]
PFIC 6	MYO5B	Diarrhea (microvillous inclusion disease)	Genetic testing		[17]
Inborn errors of metabolism					
Galactosemia	GALT	Cataracts, sepsis	Newborn screening, serum galactose-1-phosphate level	Lactose free diet	[7]
Tyrosinemia Type 1	FAH	Renal and neurologic manifestations	Newborn screening, urine succinylacetone	Low protein diet, nitisinone (2- nitro-4-trifluoromethylbenzol)-1,3-cyclohexanedione)	[7, 21]
Endocrinopathies					
Hypothyroidism		Lethargy, failure to thrive, myxedema, hypotonia, macroglossia, dry skin	Newborn screen, serum free T4 and TSH	Thyroid hormone supplement	[1]
Hypopituitarism		Shock, hypoglycemia	TSH, free and total T4, morning cortisol, brain MRI	Thyroid hormone, growth hormone, cortisol replacement	[1]

IVC = inferior vena cava; US = ultrasound; MRCP = magnetic resonance cholangiopancreatography; IBAT = ileal bile acid transporter; A1AT = alpha-1 antitrypsin; PFIC = progressive familial intrahepatic cholestasis; HCC = hepatocellular carcinoma; ESLD = end-stage liver disease

(2.5%). The incidence of disease is likely underestimated given the incomplete penetrance and variable phenotypic presentation.

This is a multisystemic disorder which may also involve cardiac, skeletal, renal, (neuro)vascular, and ocular abnormalities as well as characteristic dysmorphic facies (Table 1). Bile duct paucity is seen on liver histology which can result in chronic cholestasis, the accumulation of bile acids and subsequent liver injury. Treatment is generally aimed at the consequences of cholestasis, namely pruritus, xanthomas, and nutritional deficiencies. Liver transplantation is reserved for those with end stage liver disease or debilitating pruritus significantly impacting quality of life [26].

A recent large, international cohort study of Alagille patients revealed that only 40.3% of patients survived to adulthood with their native liver. A total bilirubin level < 5.0 mg/dL between 6 and 12 months of age appears to be associated with improved hepatic outcomes. [27••]

Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis (PFIC) disorders consist of a growing selection of autosomal recessive conditions characterized by bile acid transport defects with varying underlying genetic mutations (see Table 1). These disorders typically present during infancy and childhood. Intractable pruritus is a dominant feature, especially in PFIC 1 and 2.

Patients with PFIC 1 and 2 present during infancy with low-gamma-glutamyl transpeptidase (ggt) cholestasis, whereas those with PFIC 3 often present later in childhood and have an elevation in ggt. Individuals with PFIC 1 secondary to FIC1 deficiency and mutations in *ATP8B1* often have extrahepatic manifestations such as diarrhea, hearing loss, pancreatic insufficiency, and ocular abnormalities. Liver transplantation does not address these additional manifestations and patients with PFIC 1 may develop graft steatosis and worsening diarrhea following transplant. Patients with PFIC 2 or severe BSEP deficiency secondary to mutations in *ABCB11*, have an increased risk for the development of hepatocellular carcinoma (HCC).

PFIC 3 involves mutations in the ABCB4 gene also known as multidrug resistance protein-3 P-glycoprotein (MDR3). As previously stated, these patients tend to present later in childhood or even adulthood and have an elevation in ggt. Many patients are predisposed to cholesterol precipitation and gallstone formation. PFICs 4–6 are more recently discovered, rare cholestatic disorders with broad extrahepatic systemic manifestations likely related to complexity in the expression of their underlying genetic mutations [28, 29].

Complications of Cholestasis: Monitoring and Treatment Strategies

The management of cholestasis is often aimed at the biochemical consequences of impaired bile flow. These include malnutrition, pruritus, xanthoma formation, and progressive fibrosis. Together, these complications can significantly impact the quality of life of both patients and caretakers. Monitoring recommendations and disease specific therapies are outlined in Table 2.

Malnutrition and Fat-soluble Vitamin (FSV) Deficiencies

The nutritional evaluation should include a detailed investigation of dietary intake, nutritional supplementation, and ongoing assessments to help guide long-term management. In children with chronic cholestatic and/or end-stage liver disease, nutritional deficiencies should be identified without delay to permit early interventions aimed at the optimization of infant development and the prevention of further complications.

Routine assessment of anthropometrics is a critical component of the nutritional assessment. An adequately measured length (< 2 years) or height (≥ 2 years) may be a more accurate reflection of nutritional status than weight, especially in the context of ascites and/or organomegaly. Mid upper arm circumference (MUAC) and triceps skin fold (TSF) are also useful in the assessment of malnutrition as they are less likely to be influenced by fluid overload. They have also been shown to be a more accurate reflection of short-term changes in nutritional status and can provide important information regarding body composition. MUAC measures both muscle mass and adipose tissue, whereas TSF reflects adiposity. These anthropometric measures are helpful predictors of growth in infants and children with chronic liver diseases [30, 31]. The frequency at which these measurements should be performed is variable and depends largely on the degree of malnutrition, ranging from every 2 weeks to 3 months [31].

Impaired bile salt excretion can adversely affect nutrition, resulting in fat malabsorption and FSV deficiencies. These include vitamins A, D, E and K. For lipids and FSV to be absorbed they must be emulsified and incorporated into micelles which are directly absorbed across enterocytes through passive diffusion or specific transporters. They are then reorganized into chylomicrons and released into the lymphatic system for later use or storage. Cholestasis leads to an insufficient concentration of intraluminal bile acids being excreted from the liver which are necessary for micelle formation. Additionally, enteropathy

Table 2 Recommendations for Monitoring and Management of Cholestasis

COMPLICATION			
Malnutrition	Assessment	Treatment Strategies	Monitoring Frequency
	Length MUAC TSF	• Provide > 130% caloric requirement • ↑ kcal/oz • MCT formula • NG feeds • Parental nutrition	Every 2 weeks to 3 months
FSV Deficiency	Assessment	Recommended Dose	Preparation
Vitamin A	Retinol: RBP > 0.8	• Orally 5000 IU/day up to maximum of 25–50,000 IU/day • Monthly IM 50,000 IU	Vitamin A capsules Vitamin A parenteral
Vitamin D	25-OH Vitamin D < 20 ng/mL	• 800–8000 IU/day of Vitamin D2 or D3 • Calcitriol 0.05–0.2 µg/kg per day	Oral D2, D3 capsule/solution 1,25-OH vitamin D capsule/solution 1,25-OH vitamin D injection
Vitamin E	α-tocopherol: lipid ≤12 yr > 0.6 mg/g > 12 yr > 0.8 mg/g	• 25–50 IU/kg/day as TPGS up to 100 IU/kg/day	Alpha-tocopherol (Aqua-E) Liqui-E (TPGS-D-alpha tocopheryl polyethylene glycol 1000 succinate)
Vitamin K	INR ≥1.2	• 2.5–5 mg/day 3 × per week • 1-10mg IV	Mephyton tablets (PO) AquaMephyton (Subq, IM, IV)
Pruritus			
Pharmacologic Therapies	Medications	Recommended Dose	Adverse Effects
Choleretic Agents	Ursodeoxycholic acid	15–30 mg/kg/day	Diarrhea, abdominal pain, vomiting
Bile acid sequestrants	Cholestyramine	240 mg/kg/day (max dose 8g/day)	Poor palatability, abdominal pain, constipation, worsening FSVD
Pregnane X receptor (PXR) agonist	Rifampin	5–10 mg/kg/day (max dose 600mg/day)	Hepatitis, idiosyncratic hypersensitivity reaction, red discoloration of secretions
Opioid antagonists	Naltrexone	0.25–0.5 mg/kg/day (max dose 50 mg/day)	Nausea, diarrhea, irritability
SSRIs	Sertraline	1–4 mg/kg/day	GI upset, agitation, drug eruption
IBAT inhibitors	Maralixibat Odevixibat	ALGS: 380 mcg/kg/day PFIC: 40–120 mcg/kg/day (max dose 6 mg/day) ALGS: 120 mcg/kg/day	Abdominal pain, diarrhea, LFT abnormalities, FSV deficiencies
Surgical Intervention	Considerations		

Table 2 (continued)

COMPLICATION		
Partial external biliary diversion	Need for ostomy Worsening FSV deficiencies	
Ileal exclusion	Symptom recurrence	
Orthotopic liver transplantation	Need for immunosuppression	
Advanced Fibrosis/Cirrhosis Portal HTN	Assessment	Monitoring Frequency
	• Physical exam • Abdominal ultrasound • Surveillance endoscopy • Liver stiffness (i.e., Elastography) • Histology	6 -12 months
Hepatocellular Carcinoma	Initial Assessment	Monitoring Frequency
	• AFP • Abdominal Ultrasound	6 months

MUAC = Mid-Upper Arm Circumference; TSF = triceps skin fold; MCT = medium chain triglyceride; NG = nasogastric; FSV = fat soluble vitamin; RBP = retinol binding protein; IU = international units; IM = intramuscular; TPGS = tocopheryl polyethylene glycol succinate; INR = international normalized ratio; SSRI = selective serotonin reuptake inhibitor; IBAT = ileal bile acid transporter; ALGS = Alagille syndrome; PFIC = progressive familial intrahepatic cholestasis; LFT = liver function tests; HTN = hypertension; AFP = alpha fetal protein

secondary to underlying liver disease with portal hypertension, decreased intake, endocrine dysfunction, and increased energy needs in these infants further complicate nutritional needs [31]. Malnutrition and vitamin deficiencies can impact long-term outcomes. The goals of treatment are to correct the underlying deficiencies thereby reducing morbidity and preventing further complications. This is particularly important in patients with end-stage liver disease necessitating transplantation. Optimization of nutritional status prior to surgery may help to hasten post-transplant recovery and decrease the rate of complications.

Infants with chronic cholestasis often require 130–150% of the daily caloric requirements due to increased metabolic demands compounding concerns for fat malabsorption. Formulas enriched in medium-chain triglycerides (MCTs) are often utilized as a lipid supplement in cholestatic infants and young children. Although MCTs have a lower energy content than long-chain triglycerides (LCTs) their shorter chains allow for passive diffusion through the gastrointestinal tract and thereby directly into the portal circulation. Unlike LCTs, MCTs do not require micellar solubilization because they bypass the lymphatic system, with approximately 95% bioavailability, even in the setting of severe cholestasis [31]. The optimal proportion of total lipids as MCTs for nutritional management is between 30 and 50%. MCT content in the diet in excess of 80% may result in essential fatty acid deficiency and should be avoided. If unable to achieve adequate weight gain and growth despite caloric fortification with MCT-enriched formulas, supplemental nasogastric tube feeds or parental nutrition should be considered [31].

FSV deficiencies can lead to complications such as rickets and bone fractures, coagulopathy with hemorrhage, cerebellar ataxia, and impaired vision [32]. The prevalence of these deficiencies increases with the severity of cholestasis. Vitamin levels are inversely correlated with total bilirubin [32]. Initial supplementation is provided through water-soluble ADEK multivitamin preparations. These aqueous formulations, such as DEKAs Essential, are specifically designed for cholestasis and can be transported directly into the portal circulation independent of bile salts. They contain amounts of Vitamins A, D, E and K in significant excess of typical recommended daily values. Depending on the severity of cholestasis, additional supplementation of individual FSVs may also be necessary [33].

The chemical modification of a vitamin also helps to promote greater water solubility. The conjugation of α tocopheryl succinate with polyethylene glycol-1000 creates a water-soluble molecule (TPGS). This formulation of tocopherol (or Vitamin E) has excellent intestinal absorption even in the setting of severe cholestasis [32]. When TPGS is co-administered with other FSVs, it helps to enhance the absorption of the unmodified vitamins. Alternatively, periodic intramuscular administration of vitamins can help circumvent poor intestinal absorption. This approach is generally not favored by patients or their families. In the United States, preparations are available for parenteral administration of vitamins A, D, and K, but not for vitamin E. Vitamin levels should be monitored closely until stable levels are achieved, or cholestasis has improved (Table 2).

Pruritus

The impairment of bile flow leads to a buildup of bile acids in the liver which eventually spill over into the bloodstream. Increased serum bile acids are associated with significant pruritus. Cholestatic pruritus often presents as an intense, unrelenting itch and has frequently been described in patients with Alagille syndrome and PFIC. Clinical manifestations may include visible scratch marks, skin excoriations and scaring, as well as poor weight gain, impaired sleep, and growth. Pruritus may have a profound effect on quality life with interruptions in sleep, and irritability leading to difficulties concentrating thereby impacting school performance [34].

The treatment of choice for pruritus associated with cholestasis is correction of the underlying hepatobiliary disease, when possible. If the underlying etiology cannot be corrected, treatment is aimed at the pruritus itself. Pharmacologic agents used in the treatment of cholestatic pruritus include choleretics, bile acid sequestrants, pregnane X receptor (PXR) agonists, opioid antagonists, and selective serotonin reuptake inhibitors (SSRIs) [35, 36]. These are summarized in Table 2.

When pruritus is refractory to medical therapies surgical treatments should be explored. For cholestatic infants without evidence of advanced fibrosis or portal hypertension, a partial external biliary diversion (PEBD), internal diversion or ileal exclusion procedure aimed at interrupting enterohepatic circulation may be considered to help ameliorate symptoms of pruritus and cholestasis [37, 38]. PEBD disrupts the enterohepatic circulation of bile salts by partially diverting bile from the gallbladder through a loop of bowel which connects the gallbladder with the abdominal skin through a stoma. The influx of bile salts into the intestine and their subsequent reuptake are consequently diminished. Long-term efficacy is uncertain, and the burden of a lifelong stoma is also significant [34, 39]. When surgical interruption is ineffective or with advanced liver disease, liver transplantation may be considered to address ongoing consequences of cholestasis including pruritus, xanthomas, growth failure and poor quality of life.

Progressive Liver Disease and Hepatocellular Carcinoma

The accumulation of bile acids in the liver may contribute to ongoing inflammation and liver injury. Damage to the liver parenchyma can also lead to progressive fibrosis and cirrhosis, portal hypertension and loss of hepatic synthetic function over time. Progressive fibrosis and early signs of portal hypertension can be detected by the presence of splenomegaly on physical examination. Thrombocytopenia and confirmation of splenomegaly on abdominal imaging such as ultrasound also help to corroborate physical exam findings. The presence of abdominal ascites and bleeding secondary to esophageal varices signify hepatic decompensation and may be indications for liver transplantation. Noninvasive markers of liver fibrosis have largely replaced the need for invasive procedures such as liver biopsy. Liver stiffness may be evaluated over time by transient elastography (TE), shear wave elastography (SWE), and magnetic resonance elastography (MRE) [40–42].

Hepatocellular carcinoma (HCC) can occur in anyone in whom cirrhosis develops, but persons with BSEP deficiency, tyrosinemia and A1AT deficiency also carry an increased risk. Individuals with advanced fibrosis and cirrhosis require lifelong screening with serum alpha fetal protein (AFP) and abdominal ultrasound [43, 44].

Emerging Treatments

Bile acids are reabsorbed from the ileum via specific transporters. Inhibitors of the apical sodium-dependent bile acid transporter (ASBT), also known as ileal bile acid transporter (IBAT) inhibitors, are novel therapies aimed at blocking entry of bile acids into enterocytes through selective binding of these transporters to ameliorate symptoms of pruritus. These minimally absorbed oral therapies interrupt the enterohepatic circulation of bile acids by increasing fecal excretion and reducing the hepatic uptake of bile acids. This also reduces activation of both the hepatic and ileal farnesoid X receptor (FXR) thereby increasing bile acid synthesis from cholesterol in the liver. Thus, IBAT inhibitors both reduce bile acid reabsorption while increasing bile acid synthesis and secretion in the hepatocytes. In pediatric trials of patients with Alagille syndrome and PFIC, this resulted in the reduction of pruritus, serum bile acids and xanthomas. Clinically meaningful improvements in growth and quality of life were also observed. [45••, 46, 47••]

These therapies have a favorable safety profile and are generally well-tolerated. The most common adverse reactions reported in clinical trials included diarrhea, abdominal pain, vomiting, and liver test abnormalities. Serum bilirubin, alanine and aspartate transaminases, alkaline phosphatase, ggt, and prothrombin time (INR) should be determined before initiation of treatment and intermittently during the course of therapy. Additionally, bile salt depletion can cause malabsorption of fat and fat-soluble vitamins, which may require supplementation.

There are currently two IBAT inhibitors approved for use in children. Odevixibat has been approved for the treatment of cholestatic pruritus in patients with PFIC ≥ 3 months of age and Alagille syndrome ≥ 12 months, while maralixibat has been approved for patients with Alagille syndrome and age ≥ 3 months. Though there is emerging data to suggest that these therapies may delay the progression of liver disease and

prolong transplant-free survival, long-term data and further exploration of these findings are necessary [48••]. At present, investigation of the use of IBAT inhibitors for treatment of other cholestatic liver diseases such as biliary atresia and primary sclerosing cholangitis are ongoing.

Conclusions

Cholestasis in infants and young children requires early recognition and a thoughtful approach to timely diagnosis. Though BA accounts for a majority of these cases, an increasing number of genetic etiologies are being recognized. Current treatment strategies are aimed at addressing the biochemical consequences of cholestasis including pruritus, xanthomas, nutritional deficiencies, and improved quality of life. The increased availability of NGS may help reduce the time to identify and eliminate specific genes thereby reshaping the diagnostic algorithm of cholestasis. The widespread use of rapid multigene testing has also led to newly identified genetic variants and an improved understanding of biliary physiology. This enhanced understanding may help to guide the future development of targeted therapies and new treatment modalities based on specific gene mutations.

Author Contributions J.V. was responsible for the design of the manuscript. Both J.V. and N.H participated in the writing and review of the main manuscript as well as the prepared tables and figures.

Declarations

Conflicts of Interest Nicole Heinz has no conflicts of interest to disclosure.
Jennifer Vittorio is a consultant for Mirum Pharma and Albireo Pharma.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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