APPROACHES TO DIAGNOSIS & MANAGEMENT OF

Cholestatic Liver Diseases Across the Pediatric Age Spectrum

November 8, 2024
Hollywood, FL, USA

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Speakers

Niviann M. Blondet, MD

University of Washington and
Seattle Children's Hospital
Seattle, WA

Sara Hassan, MD

Dallas, TX

Amber Hildreth, DO, FAAP

University of California San Diego
and Rady Children's Hospital
San Diego, CA

Learning objectives

- Recognize signs and symptoms of cholestatic liver disease in pediatric patients
- Understand the specific needs of children with different cholestatic liver diseases
- Explore individualized management of cholestatic liver disease in children across the age spectrum, from infancy to adolescence

Agenda

7:00–7:05 AM	Welcome and introductions **Niviann M. Blondet, MD**
7:05–7:20 AM	Case profile: Evaluating a neonate presenting with cholestasis **Niviann M. Blondet, MD**
7:20–7:35 AM	Evolution of pruritus symptoms in a toddler with cholestatic liver disease **Sara Hassan, MD**
7:35–7:50 AM	Diagnosis of an adolescent with new-onset cholestatic liver disease **Amber Hildreth, DO, FAAP**
7:50–8:00 AM	Q&A **All speakers**

CASE PROFILE:

Evaluating a neonate presenting with cholestasis

Niviann M. Blondet, MD

Cholestasis background[1,2]

Cholestasis is defined as an **impairment in the excretion of bile**

- The physical manifestations and biochemical features of cholestasis reflect the **accumulation of components of bile in the serum**
  - Elevated **conjugated bilirubin** is the predominant characteristic in most etiologies

- **Cholestatic jaundice is likely pathologic** and indicative of hepatobiliary dysfunction
- Jaundiced patients benefit from being **diagnosed quickly**, with institution of appropriate therapy as needed

- Cholestasis can be categorized as either **biliary or hepatocellular**, and etiologies can vary substantially by age

1. Fawaz R, et al. *JPGN* 2017;64(1):154-168. **2**. Khalaf R, et al. *Pediatr Gastroenterol Hepatol Nutr* 2016;19(1):1-11.

Case profile

8-week-old male patient

Birth
- Delivered at term (SVD)
- No complications during pregnancy or delivery
- Baby was breastfed

24 hours
- Jaundice observed
- Transcutaneous bilirubin, 8 mg/dL
- Parents advised to follow up with PCP for routine check-up

2-week well-child check
- Jaundice again noted
  - Family was informed this was normal and likely related to breast-feeding
- Because of poor weight gain, PCP recommended formula supplementation and follow-up in 1–2 weeks
  - Family preferred exclusive breast-feeding and did not attend follow-up appointment as baby was doing well

PCP, primary care physician; SVD, spontaneous vaginal delivery.

Polling question

> In patients presenting at 4 weeks with similar symptoms, which of the following would you do next?

1. Full abdominal ultrasound to evaluate for syndromic biliary atresias
2. Fractionation of bilirubin; work-up if conjugated bilirubin >1
3. Intraoperative cholangiography
4. A1AT and TSH assessment
5. HIDA scan
6. Liver biopsy

Please scan QR code to respond

A1AT, alpha-1 antitrypsin; HIDA, hepatobiliary iminodiacetic acid; TSH, thyroid-stimulating hormone.

Case profile (cont'd)

8-week-old male patient

2-month well-child check
- PCP noted scleral icterus, abdominal fullness
- Parents had noticed yellow stools
- Patient referred to ER for urgent evaluation due to persistent cholestasis

ER evaluations

Laboratory values
- ALT, 91 U/L
- AST, 128 U/L
- GGT, 671 U/L
- Direct bilirubin, 3.2 mg/dL

Other assessments
- Common bile duct not visible on US
- Yellow stools

1-day post-ER visit
- Intraoperative cholangiogram confirmed biliary atresia
- Kasai procedure performed
- Liver biopsy identified bile ductular proliferation with bile duct plugs, cholestasis, and extensive bridging fibrosis

Patient eventually discharged
- On combination of fortified breast milk, multivitamins, ursodiol, and antibiotics
- Cholestatic at discharge

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ER, emergency room; GGT, gamma-glutamyl transferase. PCP, primary care physician; US, ultrasound.

Initial work-up of neonates with cholestasis

> Biliary atresia needs to be ruled out as soon as possible[1]

Initial work-up[2,3]

- Aimed at **excluding other causes** of neonatal cholestasis
- Typically includes **physical examination**, collection of **laboratory data**, and **noninvasive imaging**
- However, most **initial investigations cannot accurately distinguish** biliary atresia from other causes of conjugated hyperbilirubinemia

The diagnostic work-up generally starts with examination of the eyes, stool, and first bilirubin value[4,5]

Considerations

Because no single test or procedure in the initial work-up can establish a positive diagnosis of biliary atresia, typically **several related clinical observations are needed** to form a well-founded suspicion of a **biliary atresia diagnosis**, which may be definitively ascertained via an intraoperative cholangiography[2]

1. Robie DK, et al. *Am Surg*. 2014;80(9):827-831. **2.** Ranucci G, et al. *Dig Liver Dis*. 2022;54(1):40-53. **3.** Moreira RK, et al. *Arch Pathol Lab Med*. 2012;136(7):746-760. **4.** Hartley JL, et al. *Lancet*. 2009;374(9702):1704-1713. **5.** Biliary Atresia. NIDDK website. https://www.niddk.nih.gov/health-information/liver-disease/biliary-atresia. Accessed November 7, 2024.

Diagnostic challenges and differential diagnosis

The signs and symptoms of biliary atresia can overlap with other forms of neonatal cholestasis

Condition	Features shared with biliary atresia	Features distinct from biliary atresia
Alagille syndrome[1-3]	• Jaundice • Early ductular proliferation possible	• Extrahepatic manifestations (eg, butterfly vertebra, characteristic facial features, cardiac anomalies) • Genetics (variations in *JAG1* or *NOTCH2*)
A1AT deficiency[1,2,4,5]	• Jaundice • Ductular proliferation	• Low serum A1AT • Genetics (variations in *SERPINA1*)
MDR3 deficiency[2,6]	• Jaundice • Portal fibrosis with ductular proliferation	• Genetics (variations in *ABCB4*) • Typically presents in older infants
Choledochal cysts[1,7,8]	• Cysts • Jaundice • Ductal dilation	• Larger in size than in cystic-type biliary atresia • Intrahepatic duct dilation present • Normal gallbladder
Neonatal sclerosing cholangitis[1,2,9]	• Biliary fibrosis	• Extrahepatic manifestations (eg, ichthyosis, alopecia) • Normal gallbladder

The timing and accuracy of the diagnostic work-up are essential so patients receive the correct treatment as soon as possible[10]

A1AT, alpha-1 antitrypsin; MDR3, multidrug resistance protein 3. **1.** Brahee DD, Lampl BS. *Pediatr Radiol*. 2022;52(4):685-692. **2.** Vij M, Rela M. *Future Sci OA*. 2020;6(5):FSO466. **3.** Ayoub MD, Kamath BM. *Clin Liver Dis.* 2022;26(3):355-370. **4.** Townsend SA, et al. *Aliment Pharmacol Ther*. 2018;47(7):877-885. **5.** Mitchell EL, Khan Z. *Curr Pathobiol Rep*. 2017;5(3):243-252. **6.** Sticova E, Jirsa M. *Ann Hepatol*. 2020;19(2):126-133. **7.** Schooler GR, Mavis A. *Radiol Case Rep*. 2018;13(2):415-418. **8.** Brown ZJ, et al. *HPB (Oxford)*. 2023;25:14-25. **9.** Grama A, et al. *Front Immunol*. 2023;14:1206025. **10.** Ranucci G, et al. *Dig Liver Dis.* 2022;54(1):40-53.

A closer look at diagnostics for patients presenting with neonatal cholestasis

Category	Examples	Supportive findings
Physical examination[1-3]	• Presence of syndromic facies • Audible murmur • Direct observation of stool color	• Jaundice lasting >14 days (>21 days if infant is preterm) • Dark urine and pale stool
Laboratory testing[1,2]	• Abnormal hepatic profile	• Conjugated hyperbilirubinemia • Elevated GGT
Imaging[1,4,5]	• Ultrasound • Radioisotope studies (eg, TEBIDA, HIDA) • ERCP • MRCP • Percutaneous cholangiography	• Enlarged liver • Gallbladder abnormalities (eg, absent or small) • Triangular cord sign • Nonvisualization of the common or extrahepatic bile duct • Absent/reduced excretion of tracer into bowel within 24 hours
Liver biopsy[1,2]	• Histology	• Portal tract expansion and fibrosis • Ductular proliferation • Bile plugs and portal edema
Other[1]	• Duodenal tube test	• Clear intestinal secretions without bile

Operative cholangiography is the gold standard for diagnosing biliary atresia[1]

ERCP, endoscopic retrograde cholangiopancreatography; GGT, gamma-glutamyl transferase; HIDA, hepatobiliary iminodiacetic acid; MRCP, magnetic resonance retrograde cholangiopancreatography; TEBIDA, N-tert-butyliminodiacetic acid.
1. Hartley JL, et al. *Lancet*. 2009;374(9702):1704-1713. **2.** Moreira RK, et al. *Arch Pathol Lab Med*. 2012;136(7):746-760. **3.** Kamath BM, et al. *J Pediatr Gastroenterol Nutr*. 2018;67(2):148-156. **4.** Brahee DD, Lampl BS. *Pediatr Radiol*. 2022;52(4):685-692. **5.** Parra DA, et al. *BMC Pediatr*. 2023;23:22.

Genetic testing in patients with cholestatic liver diseases

- **Genetic testing for cholestatic liver disease without a clear cause is recommended early** in the diagnostic process in infants and children and after excluding other causes for cholestatic liver disease in adults[1]
- In recent years, genetic testing approaches for cholestatic liver diseases have shifted from direct sequencing of individual genes to more advanced approaches, including **targeted gene panels, WES,** and **WGS**[2,3]

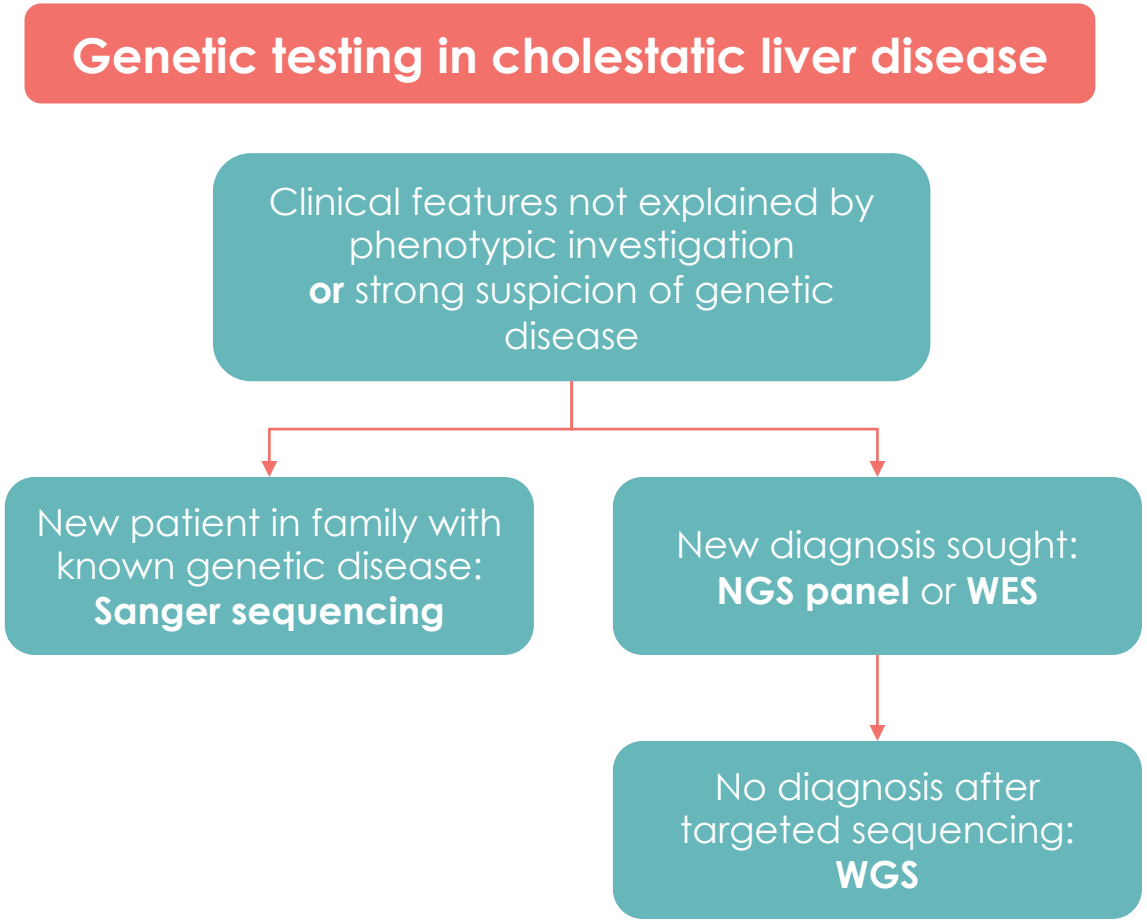


Figure from European Association for the Study of the Liver. *J Hepatol.* 2024;81(2):303-325.

NGS, next-generation sequencing; WES, whole-exome sequencing; WGS, whole-genome sequencing.

1. European Association for the Study of the Liver. *J Hepatol*. 2024;81(2):303-325. **2.** Vitale G, et al. *Cancers (Basel)*. 2022;14(14):3421. **3.** McKiernan P, et al. *JHEP Rep*. 2023;6(1):100949.

Interpreting genetic testing results

Considerations for cholestatic liver disease

Genetic variations can be classified, according to the **American College of Medical Genetics and Genomics** guidelines, into 5 tiers based on evidence including population data and computational data[1]:

- **Pathogenic**
- **Likely pathogenic**
- **Uncertain significance (ie, VOUS)**
- **Likely benign**
- **Benign**

Various methods may help clarify whether a variant should be **classified as pathogenic or likely pathogenic**, including[2]:

- In silico prediction tools
- Family testing (affected and unaffected members)
- Functional testing methods (eg, immunohistochemistry, in vitro experimental analysis)
- Emerging data from other families

Disagreement about the classification of variants is **not infrequent**:

- Inconsistencies in variant classification are seen across different laboratories, clinicians, and ClinVar entries[3,4]
- The rate of intralaboratory interpretation differences ranges from 10–40%[5]
- Second opinions, consultation with experts, and counseling for patients regarding diagnostic uncertainty are recommended[3,6]

Genetic testing results should be interpreted by an expert in the disease process[1]

VOUS, variant of uncertain significance. **1.** Richards S, et al. *Genet Med.* 2015;17:405-425. **2.** European Association for the Study of the Liver. *J Hepatol.* 2024;81(2):303-325. **3.** Bland A, et al. *Genet Med*. 2018;20(3):369-373. **4.** SoRelle JA, et al. *JAMA Netw Open.* 2020;3(4):e203812. **5.** Lin L, et al. *Hum Mutat*. 2023;2023:1-11. **6.** Berrios C, et al. *Genet Med*. 2021;23:2289-2299.

Considerations for genetic testing in cholestatic liver diseases

- Despite advancements in technology, **challenges** around **interpretation of genetic tests** in patients with cholestatic liver diseases remain[1]
- **Results** from genetic testing **may not be definitive** (eg, a large deletion in a patient with ALGS might not be detected)[2]
- Genetic testing results should be **interpreted by an expert** in the **disease process**[3]
- In the absence of genetic confirmation, information obtained using clinical, biological, and histopathologic features, including probing the patient's **family history, may support a clinical diagnosis**[1,4]

ALGS, Alagille syndrome. **1.** McKiernan P, et al. *JHEP Rep*. 2023;6(1):100949. **2.** Spinner NB, et al. Alagille Syndrome. 2000 [updated 2024] In: Adam MP, et al, eds. *GeneReviews®* Seattle: University of Washington; 1993-2024. **3.** Richards S, et al. *Genet Med*. 2015;17:405-425. **4.** European Association for the Study of the Liver. *J Hepatol*. 2009;51(2):237-267.

Evolution of pruritus symptoms in a toddler with cholestatic liver disease

Sara Hassan, MD

Case profile

6-year-old female patient; father has ALGS

Surgical history
- Attempted intraoperative cholangiogram and Kasai procedure as a newborn for neonatal cholestasis

Medical history
- Jaundice
- Pruritus
- Xanthomas
- Fat-soluble vitamin deficiencies

Referring specialist
- Primary care physician

ALGS, Alagille syndrome.

Case profile (cont'd)

6-year-old female patient; father has ALGS

Physical examination
- Jaundice
- Scleral icterus
- Hepatomegaly
- Xanthomas: face, ears, knuckles, fingers, elbows, toes, feet
- No developmental delay
- Stable vital signs
- Normal BMI
- No growth failure

Laboratory values/genetics
- Total/direct bilirubin: 13/7 mg/dL
- Serum bile acids >100 µmol/L
- *JAG1* variant

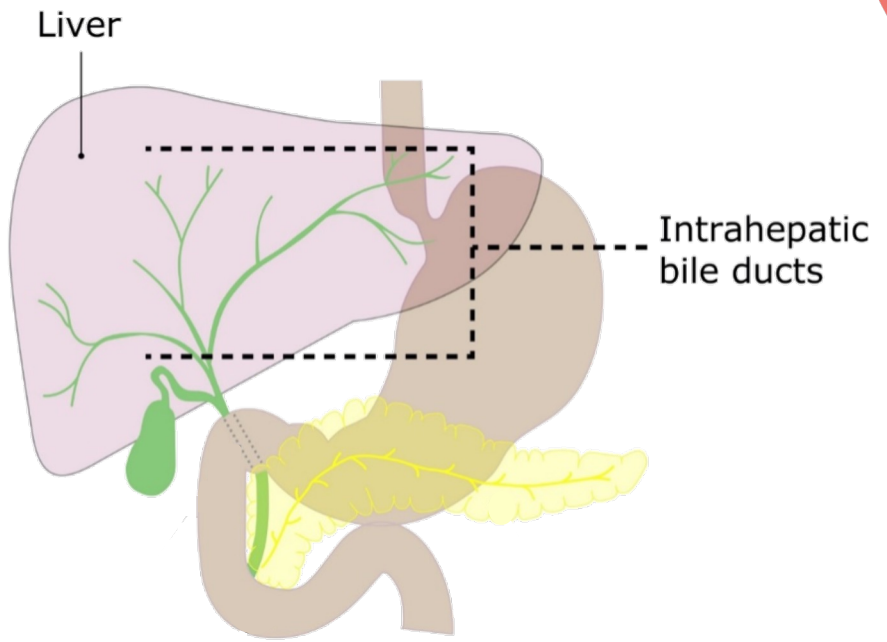
Interventions
- Fat-soluble vitamin supplementation
- Focus on nutrition
- Medication management for itching

Future considerations
- Evaluation for liver transplantation

ALGS, Alagille syndrome; BMI, body mass index; IBAT, ileal bile acid transporter.

Clinical features of ALGS

- **Hepatic features** of ALGS may include bile duct abnormalities or progressive liver disease that result in secondary clinical manifestations[1,2]
- **Liver disease burden** in ALGS is substantial: **95%** have liver involvement at any age; **85%** have neonatal cholestasis[3]
- **Intrahepatic bile duct paucity** is among the most prominent features, occurring in **75%–100%** of patients[1,2]
- Bile duct paucity results in **cholestasis** (ie, impaired bile flow from the liver)[4]
- Only **24%–40%** of patients with ALGS and neonatal cholestasis reach adulthood with their **native liver**[3,5]
  - Median age of liver transplantation: **2.8 years**[3]
  - **72%** of transplantations occur in patients aged ≤5 years[3]
- ALGS is caused by pathogenic alterations in *JAG1* (**~94%** of cases) or *NOTCH2* (**2%–4%** of cases)[5,6]

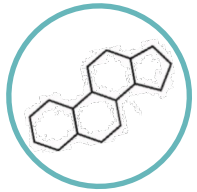


Released as part of an open knowledge project by Cancer Research UK (http://www.cancerresearchuk.org); Cancer Research UK / Wikimedia Common.

ALGS, Alagille syndrome. **1.** Kamath BM, et al. *J Pediatr Gastroenterol Nutr*. 2018;67(2):148-156. **2.** Ayoub MD, Kamath BM. *Clin Liver Dis*. 2022;26(3):355-370. **3.** Vandriel SM, et al. *Hepatology*. 2023;77(2):512-529. **4.** Kamath BM, et al. *Liver Int*. 2020;40(8):1812-1822. **5.** Kamath BM, et al. *Hepatol Commun*. 2020;4(3):387-398. **6.** Gilbert MA, et al. *Hum Mutat*. 2019;40(12):2197-2220.

Clinical features of ALGS: Consequences of cholestasis

Liver disease in ALGS typically manifests as **elevated serum bile acids, bilirubin,** and **cholesterol**[1]



Accumulation of **bile acids** in the liver is associated with:

- **Damage to hepatocytes and cholangiocytes** due to the solubilizing properties of bile acids at high concentrations[2,3]
- Spillover into systemic circulation that may contribute to **pruritus**, which occurs in up to **88%** of patients. [4,5] The **primary indications for LT** are **complications of persistent cholestasis** (intractable pruritus, growth failure, xanthomas, metabolic bone disease, and/or fat-soluble vitamin deficiency)[6]

Cholestatic jaundice occurs in **66%–87%** of patients[5,7]

Xanthomas occur in **25%–42%** of patients and result from hypercholesterolemia,[1,5] which is primarily due to accumulation of **lipoprotein X** in the serum[8]

ALGS, Alagille syndrome. **1.** Ayoub MD, Kamath BM. *Clin Liver Dis*. 2022;26(3):355-370. **2.** Hofmann AF. *Arch Intern Med*. 1999;159(22):2647-2658. **3.** Karpen SJ, et al. *Hepatol Int*. 2020;14(5):677-689. **4.** Kamath BM, et al. *Liver Int*. 2020;40(8):1812-1822. **5.** Kamath BM, et al. *J Pediatr Gastroenterol Nutr*. 2018;67(2):148-156. **6.** Vandriel SM, et al. *Hepatology*. 2023;77(2):512-529. **7.** Turnpenny PD, Ellard S. *Eur J Hum Genet*. 2012;20(3):251-257. **8.** Kohut TJ, et al. *Semin Liver Dis*. 2021;41(4):525-537.

Clinical features of ALGS: Consequences of cholestasis (cont'd)

> **Other complications of chronic cholestasis** can include[1-2]:

- Hepatomegaly (in 71%–93% of patients), cirrhosis (in 26%–95% of patients)
- Splenomegaly (in 35%–70% of patients), portal hypertension (69% of patients)

> Patients may also have **fat-soluble vitamin deficiency** that can lead to **bleeding**, **risk of fractures**, and **impaired growth**[3]

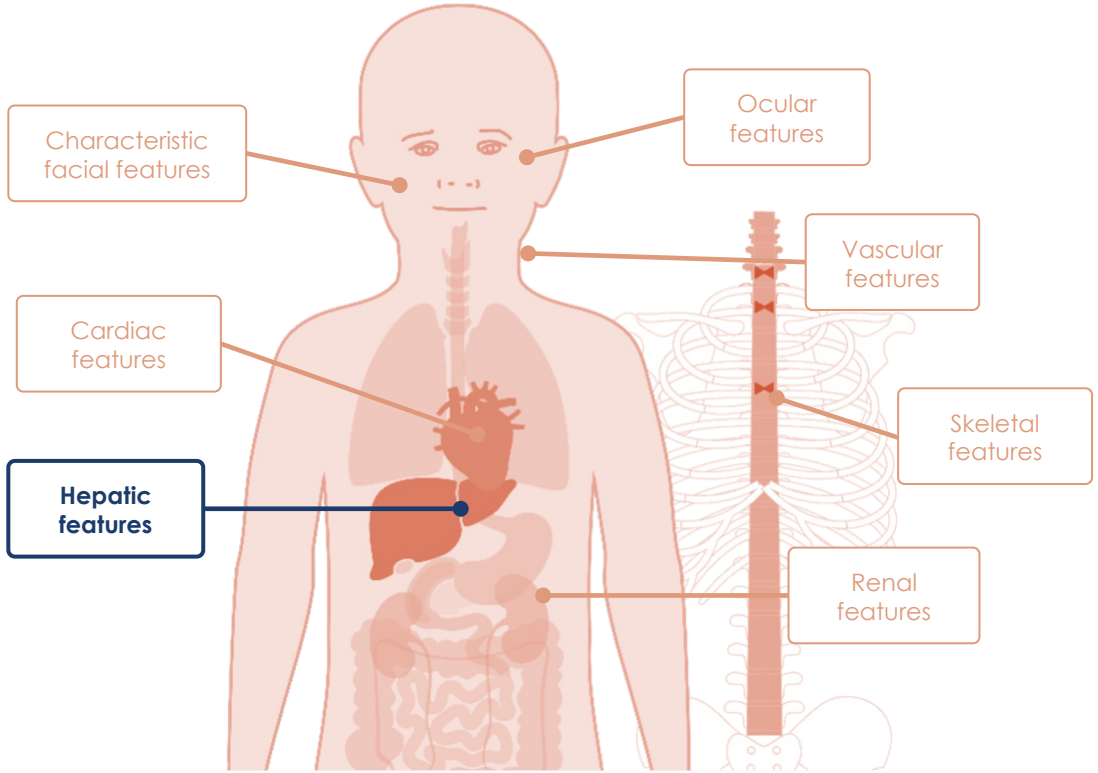
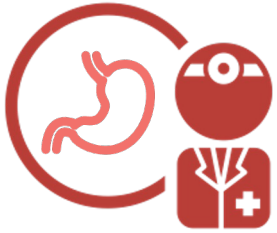


Figure adapted from Mašek J, Andersson ER. *Development*. 2017;144(10):1743-1763.

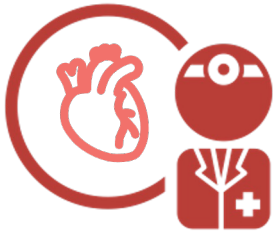
ALGS, Alagille syndrome. **1.** Kamath BM, et al. *J Pediatr Gastroenterol Nutr*. 2018;67(2):148-156. **2.** Vandriel SM, et al. *Hepatology*. 2023;77(2):512-529. **3.** Ayoub MD, Kamath BM. *Diagnostics (Basel)*. 2020;10(11):907.

Multidisciplinary care team for patients with ALGS

A variety of different specialists may be involved in the care of patients with ALGS[1,2]

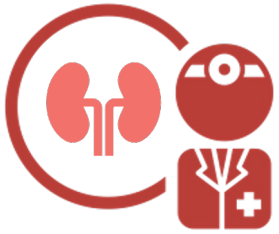


Gastroenterologists



Cardiologists

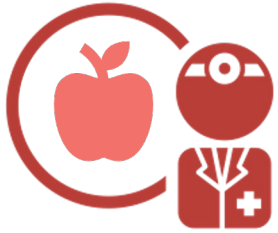
Surgeons



Nephrologists

Medical geneticists

Hepatologists



Nutritionists

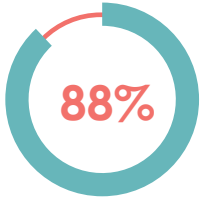
Ophthalmologists

Orthopedists

ALGS, Alagille syndrome. **1.** Saleh M, et al. *Appl Clin Genet*. 2016;9:75-82. **2.** Hall M, et al. *JBJS Case Connect*. 2019;9:e0063.

Burden of disease in ALGS

ALGS is a lifelong disease that can impact patients and caregivers



Persistent pruritus is present in up to **88%** of patients[1,2]

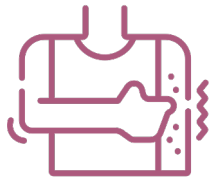
Patients with ALGS have substantially **reduced health-related QoL** compared with healthy peers and children with other forms of chronic disease (eg, A1ATD, PFIC)[3-5]

Caregivers of children with ALGS report significant limitations on their time, as well as **increased stress**, **worry**, and **interruption of family activities**[3]

A1ATD, alpha-1 antitrypsin deficiency; ALGS, Alagille syndrome; PFIC, progressive familial intrahepatic cholestasis; QoL, quality of life. **1.** Kamath BM, et al. *J Pediatr Gastroenterol Nutr*. 2018;67(2):148-156. **2.** Vandriel SM, et al. *Hepatology*. 2023;77(2):512-529. **3.** Elisofon SA, et al. *J Pediatr Gastroenterol Nutr*. 2010;51(6):759-765. **4.** Kamath BM, et al. *J Pediatr*. 2015;167(2):390-396.e3. **5.** Lind RC, et al. *J Pediatr Gastroenterol Nutr*. 2010;50(suppl 2):E155.

Burden of pruritus in patients with ALGS and their caregivers

Patients consider pruritus to be the **most distressing** symptom in ALGS[1,2]



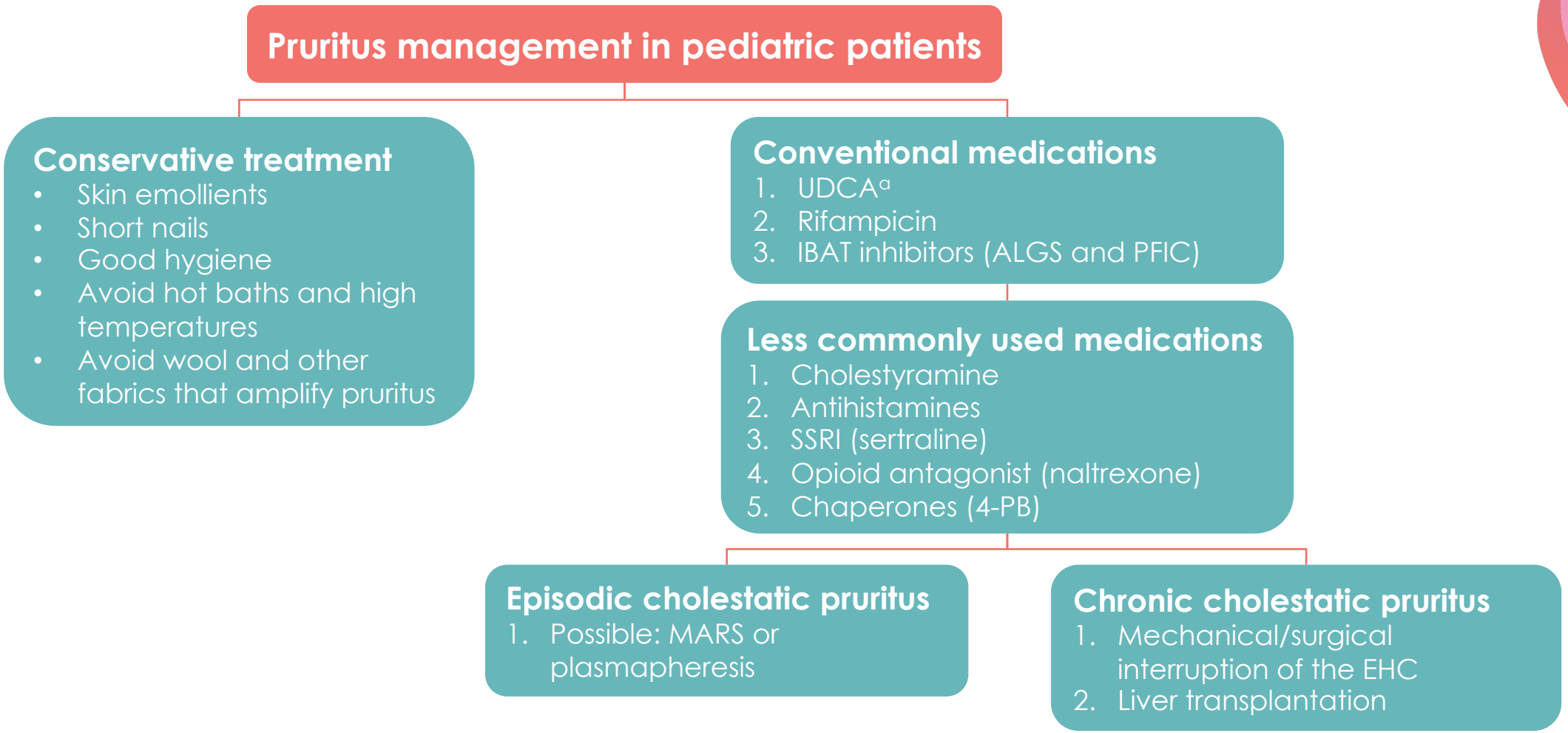
Refractory pruritus in patients with cholestatic disease is associated with **scratching**, **bleeding**, and **scarring**[1]

In children, severe pruritus can be associated with **sleep deprivation**, **mood disturbances**, decreased **school** performance, and **suicidal ideation**[3,4]

More severe pruritus in a child with ALGS is correlated with increased **parental fatigue** and decreased parental **physical**, **emotional**, and **social functioning**[5]

ALGS, Alagille syndrome. **1.** Kamath BM, et al. *J Pediatr Gastroenterol Nutr*. 2018;67(2):148-156. **2.** Rodrigo M, et al. *Biology*. 2023;12(5):756. **3.** Langedijk JAGM, et al. *Front Med*. 2021;8:639674. **4.** Pedersen MR, Mayo MJ. *Clin Liver Dis*. 2020;15(3):120-124. **5.** Kamath BM, et al. *Hepatol Commun*. 2020;4(7):1012-1018.

Management of cholestatic pruritus in pediatric patients



[a]UDCA is not generally considered a first-line treatment due to lack of evidence; however, because of its low risk profile, it is often tried as one of the first options in the management of cholestatic pruritus. 4-PB, 4-phenylbutyric acid; ALGS, Alagille syndrome; EHC, enterohepatic circulation; IBAT, ileal bile acid inhibitor; MARS, molecular adsorbent recirculating system; PFIC, progressive familial intrahepatic cholestasis; SSRI, selective serotonin reuptake inhibitor; UDCA, ursodeoxycholic acid. European Association for the Study of the Liver. *J Hepatol.* 2024;81(2):303-25.

Temporal evolution of pruritus in patients with ALGS

> Data from the LOGIC natural history study

Study description

A longitudinal, observational, multicenter, North American study characterizing the burden and natural history of childhood cholestatic liver diseases, including ALGS

Patients with ALGS

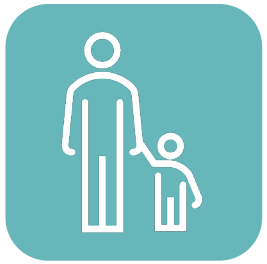
293 patients with ALGS (defined by clinical criteria and/or genetic testing); all patients were aged <25 years with evidence of cholestasis and no history of liver transplantation at enrollment

Key pruritus[a] results

- Prevalence of pruritus decreased over time in patients with ALGS and cholestasis who had their native livers
- Percentages of patients with pruritus peaked at age 2 years and were generally lower for older patients

[a]Measured by the Clinician Scratch Scale. ALGS, Alagille syndrome; LOGIC, Longitudinal Study of Genetic Causes of Intrahepatic Cholestasis. Kamath BM, et al. *Hepatol Commun*. 2020;4(3):387-398.

Pruritus severity assessment in young children



Physical and behavioral evidence[1,2]

- Signs of scratching (blood on sheets, rubbing on furniture, etc)
- Behavior at school/teacher viewpoint
- Parent/caregiver feedback
- Patient input

Validated scales for cholestatic pruritus

- PRUCISION: Captures severity of pruritus and sleep disturbance as reported by patients and caregivers[3]
- ItchRO: Assesses itching behavior as reported by pediatric patients and caregivers[4]

ItchRO, Itch Reported Outcome. **1**. Alagille Syndrome Alliance. Family stories. https://alagille.org/isaiahs-algs-story/. Accessed October 16, 2024. **2**. Building Your Alagille Syndrome (ALGS) Support System. https://www.alagillesyndrome.com/pdfs/Support_System_Guide_US-2100089.pdf. Accessed October 16, 2024. **3.** Gwaltney C, et al. *Adv Ther*. 2022;39:5105-5125. **4.** Kamath BM, et al. *Patient*. 2018;11:69-82.

Polling question

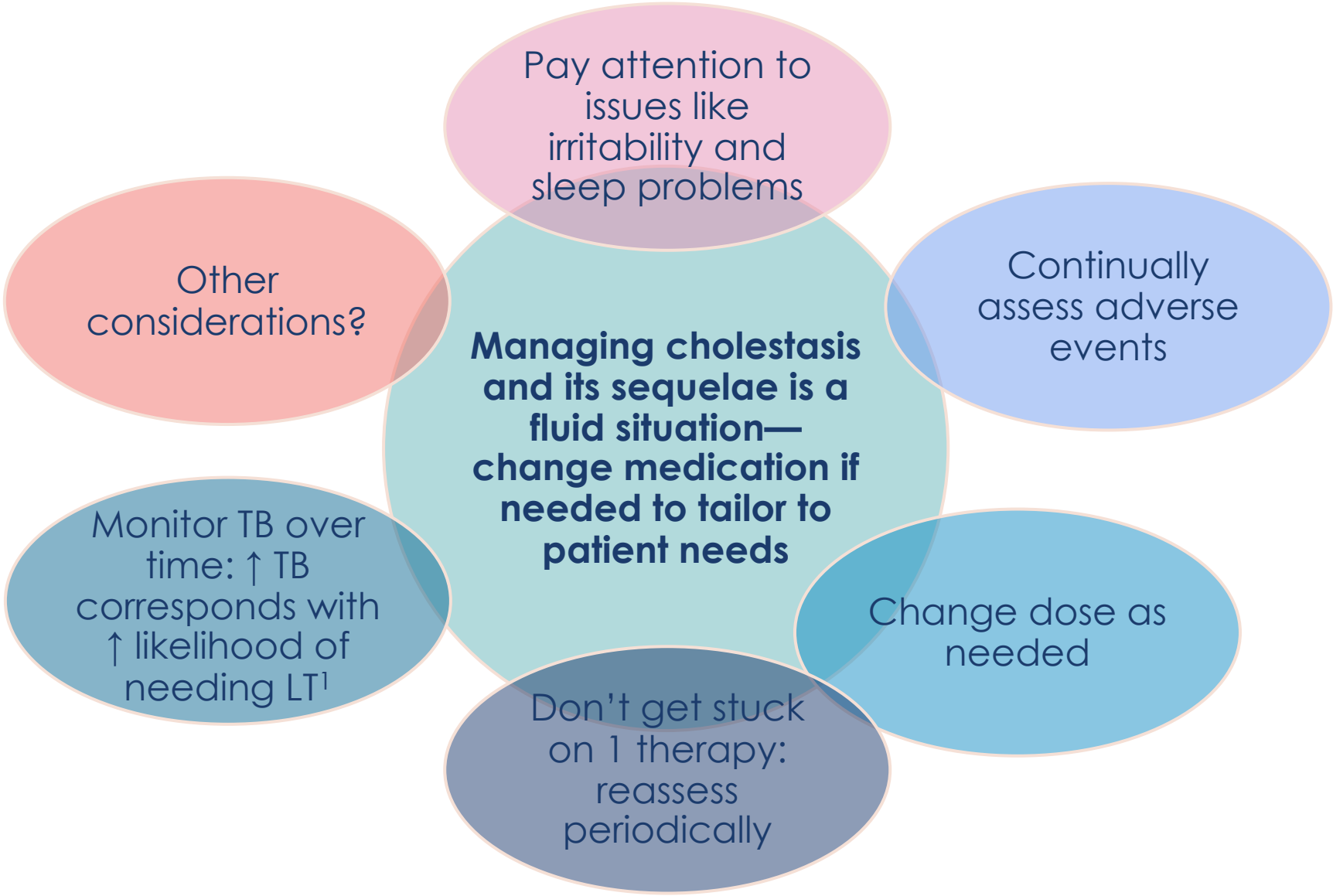
> What approaches do you preferentially use to assess pruritus in school-aged children with cholestasis?

1. Formal assessment (eg, PRUCISION, ItchRO, other instrument)
2. Physician clinical assessment
3. Patient report
4. Caregiver report

Please scan QR code to respond

ItchRO, Itch Reported Outcome.

Key considerations for managing cholestatic pruritus in children



LT, liver transplant; TB, total bilirubin. **1**. Vandriel SM, et al. *Hepatology*. 2023;77(2):512-529..

Diagnosis of an adolescent with new-onset cholestatic liver disease

Amber Hildreth, DO, FAAP

Case profile

17-year-old female patient; no family history of cholestasis

Surgical history
- None

Medical history
- Anxiety
- Oral contraception

Referring specialist
- Emergency department

Physical examination
- Jaundice

Laboratory values
- Total bilirubin: 35 mg/dL
- Direct bilirubin: 28 mg/dL
- AST: 42 U/L
- ALT: 86 U/L
- INR: 1.3
- GGT: 43 U/L

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, internalized normalized ratio.

Case profile (cont'd)

17-year-old female patient; no family history of cholestasis

Genetics
- Heterozygous pathogenic *ABCB11* variant

Liver biopsy results
- Severe canalicular cholestasis
- Stage 1 pericentral and periportal fibrosis
- Mixed inflammation
- Bile duct loss
- Absent BSEP staining

Interventions
- Discontinued oral contraception
- Steroids

Future considerations
- Risk of cholestasis with hormonal contraception and pregnancy
- Vanishing bile duct syndrome

BSEP, bile salt export pump.

Overview of PFIC

- **PFIC** is a group of **rare**, **inherited liver diseases** resulting in progressive, potentially fatal, liver disease[1,2]
- PFIC **classically** presents in **infancy** or **early childhood**[1,2]
- Diagnosis of PFIC is generally based on a combination of **clinical assessments**, **laboratory or biochemical approaches**, and **genetic testing**[2]

Although PFIC represents a heterogenous spectrum of disease, **common signs and symptoms** include:[2]

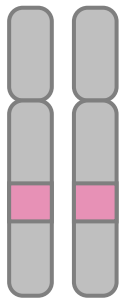
- Jaundice
- Pruritus
- FSV deficiency
- Poor growth
- Elevated serum bile acids
- Abnormal liver function tests
- Enlarged liver and/or spleen
- Diarrhea and pale or discolored stools

FSV, fat-soluble vitamin; PFIC, progressive familial intrahepatic cholestasis. **1.** Srivastava A. *J Clin Exp Hepatol*. 2014;4(1):25-36. **2.** Baker A, et al. *Clin Res Hepatol Gastroenterol.* 2019;43(1):20-36.

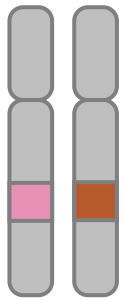
Genetics: Classic presentation of PFIC

- Historically, PFIC has been described as an **autosomal recessive** disorder (ie, caused by **variants in both copies of a PFIC-associated gene**)[1-3]
- The classic presentation of PFIC refers to cases where patients have the **clinical signs** and symptoms of PFIC **AND** either **homozygous** variants or **compound heterozygous** variants[1]

Types of variants[4]



Homozygous
Patients with homozygous variants have identical variants on both copies of a PFIC-associated gene



Compound heterozygous
Patients with compound heterozygous variants have a different variant on each copy of a PFIC-associated gene

PFIC, progressive familial intrahepatic cholestasis. **1.** Armineni S, et al. *World J Gastroenterol*. 2020;26(47):7470-7484. **2.** Baker A, et al. *Clin Res Hepatol Gastroenterol*. 2019;43(1):20-36. **3.** National Human Genome Research Institute. Autosomal Recessive Disorder. https://www.genome.gov/genetics-glossary/Autosomal-Recessive-Disorder. Accessed October 29, 2024. **4.** Morris-Rosendahl DJ. *Dialogues Clin Neurosci*. 2010;12(1):116-120.

Subtypes of PFIC

- Several types of PFIC reflecting deficiencies in specific genes are currently described,[1] including:

PFIC1 (*ATP8B1*)
PFIC2 (*ABCB11*)
PFIC3 (*ABCB4*)
PFIC4 (*TJP2*)
PFIC5 (*NR1H4*)
PFIC6 (*SLC51A*)
PFIC7 (*USP53*)
PFIC8 (*KIF12*)
PFIC9 (*ZFYVE19*)
PFIC10 (*MYO5B*)[a]
PFIC11 (*SEMA7A*)
PFIC12 (*VPS33B*)
PFIC13 (*PSKH1*)

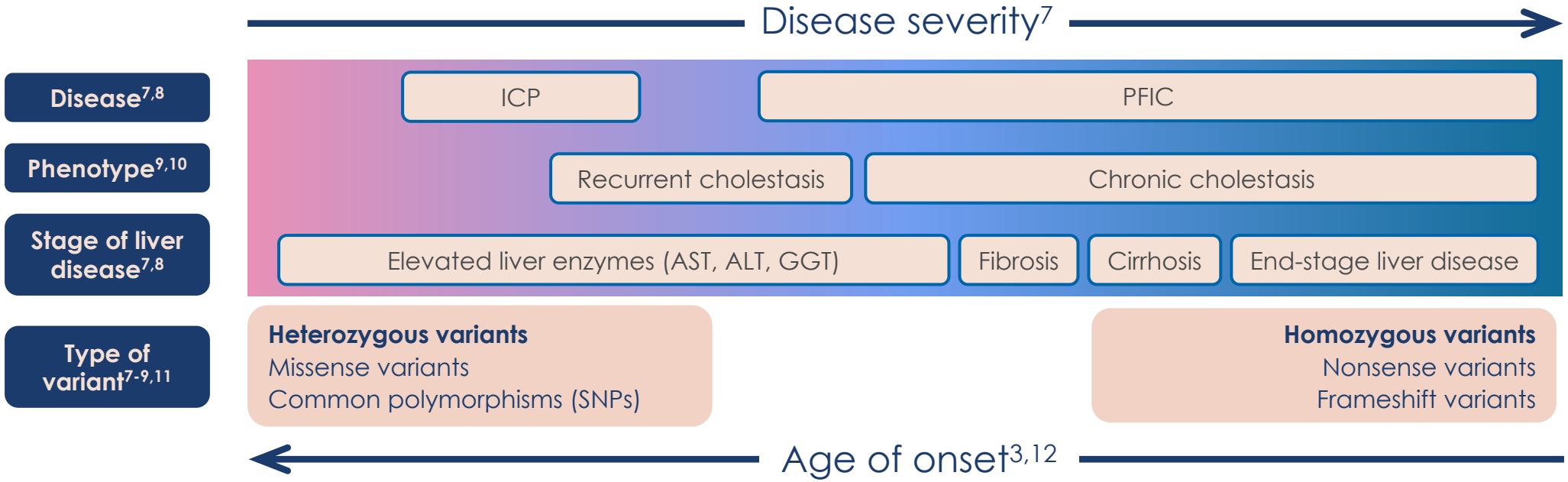
- PFIC1, PFIC2, and PFIC3 are the best known and most studied types of PFIC[2]
- Potential variants in other genetic loci have also been identified (eg, *AP1S1*, *SCYL1*, *VIPAS39*, *ABCC12*, *LSR*, and *WDR83OS*)[3,4]

[a]PFIC10 (MYO5B deficiency) was previously known as PFIC6 and may be referred to by that nomenclature in some existing publications. According to the Online Mendelian Inheritance in Man database, MYO5B deficiency is formally classified as PFIC10. PFIC, progressive familial intrahepatic cholestasis.

1. Online Mendelian Inheritance in Man. https://www.omim.org/clinicalSynopsis/table?mimNumber=601847,619484,619658,602347,615878,619662,617049,619849,619874,620010,619868,211600,620962. Accessed October 29, 2024. **2.** Vinayagamoorthy V, et al. *World J Hepatol*. 2021;13(12):2024-2038. **3.** Pfister ED, et al. *Liver Int*. 2022;42(5):1084-1096. **4.** Maddirevula S, et al. *Genet Med*. 2019;21(5):1164-1172.

PFIC: A spectrum of disease

- Variants in PFIC-associated genes may contribute to a spectrum of liver disease that ranges from mild to severe[1-7]
- Increasing evidence suggests that patients with late-onset PFIC may present with a range of cholestatic phenotypes[1-6]



ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ICP, intrahepatic cholestasis of pregnancy; PFIC, progressive familial intrahepatic cholestasis; SNP, single-nucleotide polymorphism.
1. Ibrahim SH, et al. *Hepatology*. 2022;75(6):1627-1646. **2.** Miller GC, Clouston AD. *Hum Pathol*. 2020;96:2-7. **3.** Nayagam JS, et al. *Hepatol Commun*. 2022;6(10):2654-2664. **4.** Dröge C, et al. *J Hepatol*. 2017;67(6):1253-1264. **5.** Aamann L, et al. *Scand J Gastroenterol*. 2018;53(3):305-311. **6.** Vitale G, et al. *J Gastroenterol*. 2018;53(8):945-958. **7.** Reichert MC, Lammert F. *Semin Liver Dis*. 2018;38(4):299-307. **8.** Stattermayer AF, et al. *J Hepatol*. 2020;73(3):651-663. **9.** Gunaydin M, Cil ATB. *Hepat Med*. 2018;10:95-104. **10.** van Ooteghem, NAM, et al. *J Hepatol*. 2002;36:439-443. **11.** Jüngst C, et al. *Dig Dis*. 2022;40(4):489-496. **12.** Schatz SB, et al. *Hepatol Commun*. 2018;2(5):504-514.

Could it be late-onset PFIC?

Certain presentations of cholestasis may share signs and symptoms with PFIC and **may benefit from reassessment** for potential PFIC[1,2]

Idiopathic cholestasis

Patients with signs of cholestasis manifesting without apparent cause[3-5]

Cholestasis with pruritus or unusual presentation

Patients who are receiving care for another liver disease but who have unusual symptoms, including

- Small-duct PSC[6-8]
- AMA-negative PBC[1,9]
- MASLD with pruritus[10,a]

Secondary cholestasis triggered by liver issue

Patients with symptoms of cholestatic pruritus who have recently experienced liver issues, including

- History of ICP[2,6,11]
- Drug-induced cholestasis[2,6]
- Hormone-induced cholestasis triggered by birth control, menopause, etc[12]

History of complicated gallstones

Patients with a complicated history of gallstones, including

- Gallstones present in bile ducts[6,13]
- Very strong family history of gallstones and incident at a young age[14,15]
- LPAC leading to stones in the gallbladder or liver[16]

[a]A multi-society Delphi consensus proposed a change to steatotic liver disease nomenclature, with MASLD chosen to replace NAFLD.[17] AMA, antimitochondrial antibody; ICP, intrahepatic cholestasis of pregnancy; LPAC, low phospholipid-associated cholelithiasis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis.

1. Nalbantoglu I, Jain D. *Semin Diagn Pathol*. 2019;36(6):389-394. **2.** Chan AP, Venick RS. *J Clin Gastroenterol*. 2023;57(7):686-693. **3.** Vitale G, et al. *J Gastroenterol*. 2018;53(8):945-958. **4.** Aamann L, et al. *Scand J Gastroenterol*. 2018;53(3):305-311. **5.** Jüngst C, et al. *Dig Dis*. 2022;40(4):489-496. **6.** Hilscher MB, et al. *Mayo Clin Proc*. 2020;95(10):2263-2279. **7.** Oliveira HM, et al. *Eur J Case Rep Intern Med*. 2017;4(2):000537. **8.** European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. **9.** Chascsa DM, Lindor KD. *Clin Liver Dis*. 2018;22(3):589-601. **10.** Boehlig A, et al. *Biomedicines*. 2022;10(2):451. **11.** Tan YW, et al. *World J Gastroenterol*. 2018;24(41):4716-4720. **12.** Zu Y, et al. *Front Pharmacol*. 2021;12:761255. **13.** Dröge C et al. *Explor Dig Dis*. 2023;2:34-43. **14.** Sarin SK, et al. *Hepatology*. 1995;22(1):138-141. **15.** Hsing AW, et al. *Int J Cancer*. 2007;121(4):832-838. **16.** Goubault P, et al. *J Visc Surg*. 2019;156(4):319-328. **17.** Rinella ME, et al. *J Hepatol*. 2023;79:1542-1556.

Approach for differential diagnosis[1,2]

Recent recommendations suggest pursuing genetic testing during the clinical work-up for diagnosis of cholestatic liver disease[3]

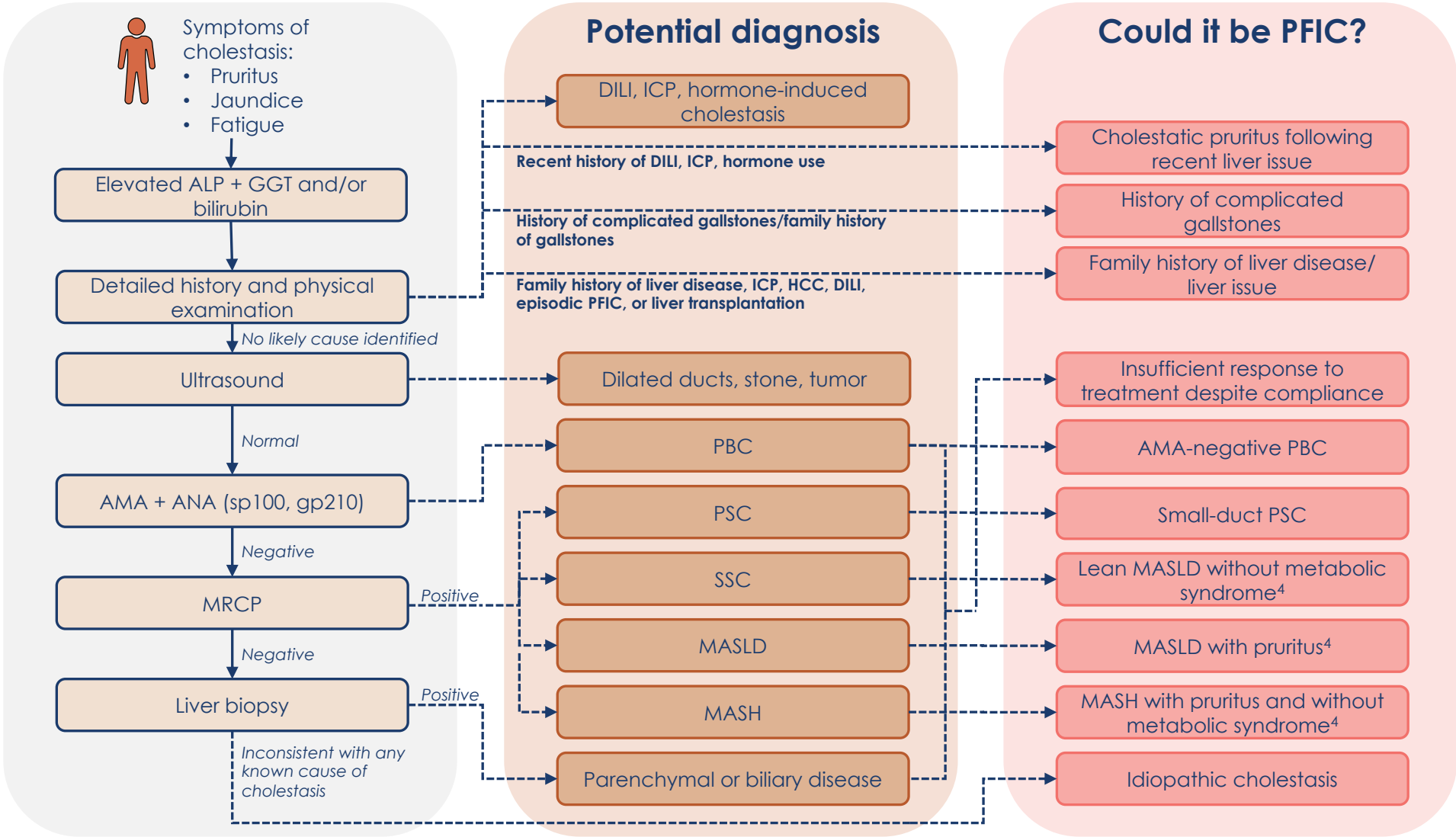


Figure adapted from references 1 and 2. ALP, alkaline phosphatase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; DILI, drug-induced liver injury; GGT, gamma-glutamyl transferase; gp210; glycoprotein 210; HCC, hepatocellular carcinoma; ICP, idiopathic cholestasis of pregnancy; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRCP, magnetic resonance cholangiopancreatography; PBC, primary biliary cholangitis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; sp100, speckled protein 100; SSC, secondary sclerosing cholangitis. **1.** Dröge C, et al. *Explor Dig Dis.* 2023;2:34–43. **2.** European Association for the Study of the Liver. *J Hepatol.* 2009;51:237–267. **3.** European Association for the Study of the Liver. *J Hepatol*. 2024;81(2):303-325. **4.** Boehlig A, et al. *Biomedicines.* 2022;10:451.

Polling question

> When do you utilize genetic testing in your diagnostic work-up of adolescent patients with suspected cholestatic liver disease or in patients with late-onset cholestatic liver disease?

1. Following clinical assessment (eg, symptoms, laboratory values, ultrasound)
2. In parallel to clinical assessment
3. After liver biopsy
4. Genetic testing is not available to my practice

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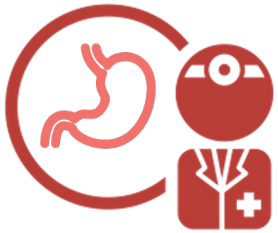
Multidisciplinary care team for adolescents with PFIC

A variety of different specialists may be involved in the care of patients with PFIC[1,2]

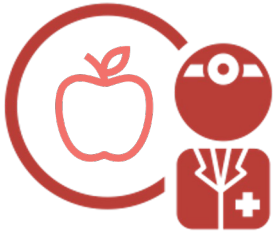


Gastroenterologists

Hepatologists (adult and pediatric)

Medical geneticists

Obstetricians/ gynecologists



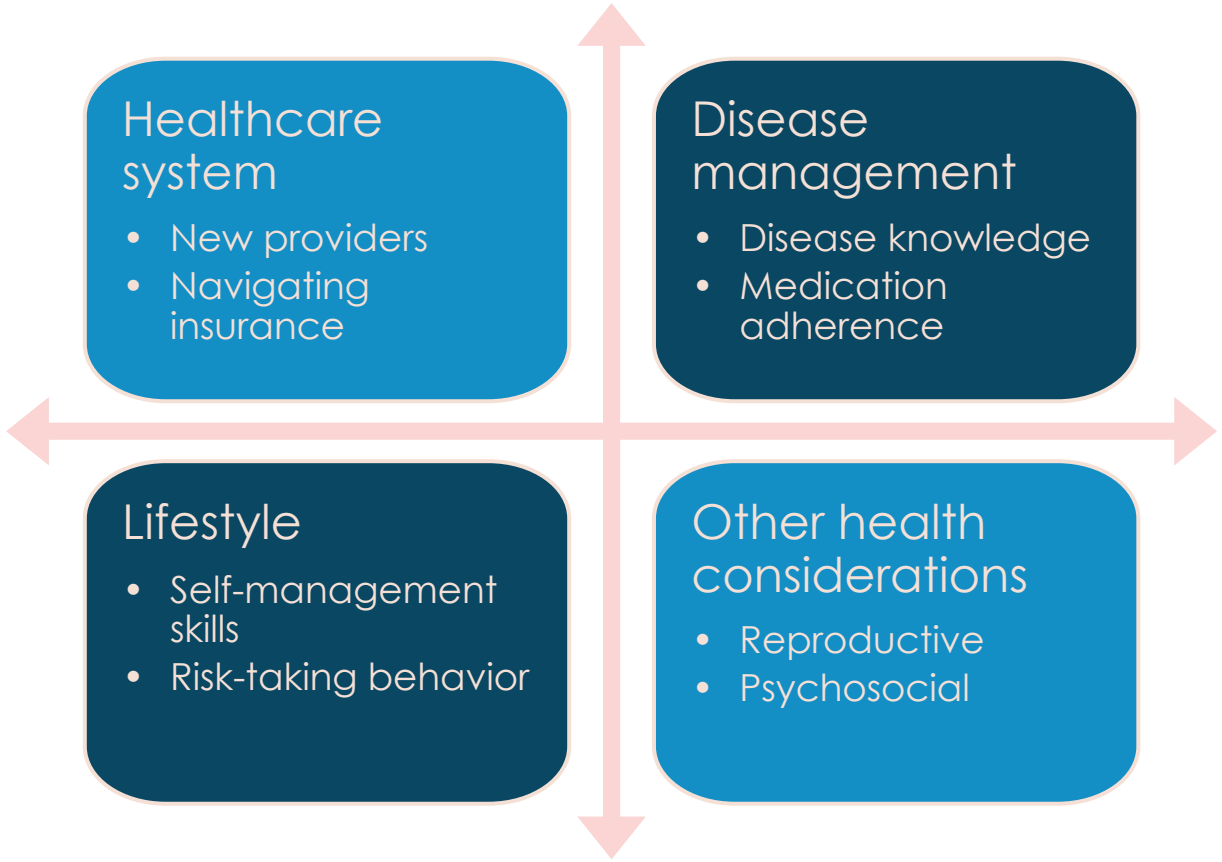
Dieticians/ nutritionists

PFIC, progressive familial intrahepatic cholestasis. **1.** Pillarisetty LS, Sharma A. StatPearls. 2024. https://www.ncbi.nlm.nih.gov/books/NBK551503/?report=printable. Accessed October 28, 2024.
2. Cheng K, Rosenthal P. *Hepatol Commun*. 2023;7(12):e0314.

Considerations for adolescent patients with cholestatic liver disease

- There can be **increased risk for complications and morbidities for adolescent patients** with cholestatic liver diseases as patients move from a child/family-centered model of care to a patient-centered model of care[1]
- **Barriers during** such a **healthcare transition** may be **multifaceted** and include individual, family, and system-wide factors[1]
- A **multidisciplinary approach and partnership between pediatric and adult providers** can support a successful transition of care for adolescent patients[1,2]

Potential factors that may impact adolescent patients as they move into adulthood



1. Vittorio J, et al. *J Pediatr Gastroenterol Nutr.* 2023;76(1):84-101. **2.** Selvakumar PKC, et al. *Cleve Clin J Med*. 2019;86(7):454-464.

Q & A

Thank you!

Scan to view speaker bios, presentation slides and recording, and post-symposium evaluation