Differential Diagnosis of Pediatric Cholestatic Liver Diseases

What is cholestasis?

- In cholestasis, normal secretion of bile acids from the liver is impaired[1]
  - Cholestasis may result in accumulation of bile acids and other biliary components in the liver, causing hepatic inflammation, fibrosis, and progressive liver damage; bile acids and other biliary components may also spill over into systemic circulation[2,3]
  - Cholestasis can lead to severe pruritus and is a leading cause of liver transplantation in children[2,4]

Distinguishing between key pediatric cholestatic liver diseases

- Pediatric cholestatic liver diseases may have overlapping signs and symptoms, such as jaundice, severe pruritus, and elevated serum bile acids, which can make diagnosis challenging[5,6]
- Diagnostic approaches to distinguish these diseases include collecting health history, examination to identify physical findings, and laboratory evaluations that include genetic testing, other noninvasive tests, or surgical and invasive procedures[1]

In patients with PFIC, genetic testing supports clinical diagnosis in approximately 40% to 60% of patients;[7,8] however, in the remainder of patients who have a clinical diagnosis of PFIC, pathogenic mutations cannot be confirmed molecularly[7,8]

- Genetic testing supports clinical diagnosis in more than 97% of patients with ALGS[9]

Health History[3,10,11]

Medical history

Recurrent cholestasis and pruritus → Consider episodic forms of disease known as **BRIC**

Family history

Maternal ICP → Consider **PFIC**

Consanguinity → Consider **PFIC**

Liver disease in relatives → Consider **ALGS**[a]

Other Noninvasive Tests[3,5,12–15]
(HIDA, ultrasound)

Absence of radiotracer clearance from liver → Consider **biliary atresia**

Presence of gallstones → Consider **PFIC**

May be observed prenatally in some cases

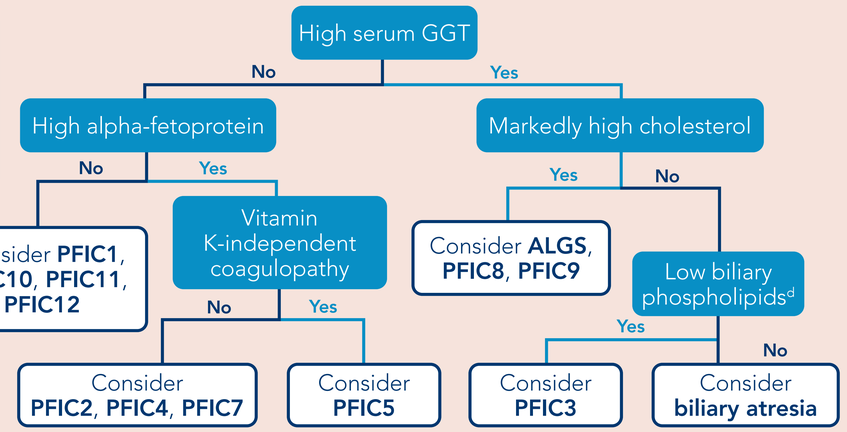
Triangular cord sign, gallbladder abnormalities → Consider **biliary atresia**

Butterfly vertebrae, cardiac changes → Consider **ALGS**

Laboratory Evaluations[3,5,12,16,17–24]

Diagnostic laboratory assessments may include:
- sBAs, ALT, AST, GGT
- Total and/or direct bilirubin
- Alkaline phosphatase
- Prothrombin time, INR

Genetic testing (TGPs, WES, WGS) may supplement diagnosis[c]



Physical Findings[3,16,25,26]

Progressive sensorineural hearing loss[b] → Consider **PFIC1**

Respiratory and neurologic symptoms → Consider **PFIC4**, **PFIC7**, **PFIC10**

Multiorgan involvement (heart murmur, dysmorphic facial features, posterior embryotoxon, neurological symptoms, and/or xanthomas) → Consider **ALGS**

Surgical and Invasive Procedures[3,5,10,12]
(liver biopsy, histological evaluation, cholangiogram)

Ductular reaction; bile duct plugs or obstruction → Consider **biliary atresia**

Bile duct paucity → Consider **ALGS**

Abnormal staining of proteins critical to bile acid transport → Consider **PFIC**

[a]ALGS can also arise from *de novo* mutations; [b]Some patients with mutations in TJP2 experience hearing loss; [c]Genetic confirmation may be required in some countries; [d]Sample obtained by duodenal aspiration or gallbladder puncture.
ALGS, Alagille syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BRIC, benign recurrent intrahepatic cholestasis; GGT, gamma-glutamyl transferase; HIDA, hepatobiliary iminodiacetic acid scan; ICP, intrahepatic cholestasis of pregnancy; INR, international normalized ratio; PFIC, progressive familial intrahepatic cholestasis; sBAs, serum bile acids; TGP, targeted gene panel; WES, whole exome sequencing; WGS, whole genome sequencing.

1. Fawaz R, et al. J Pediatr Gastroenterol Nutr. 2017;64(1):154–68; 2. Karpen SJ, et al. Hepatol Int. 2020;14(5):677–89; 3. Ayoub MD, Kamath BM. Diagnostics (Basel, Switzerland). 2020;10(11):907; 4. Squires RH, et al. Hepatology. 2014;60(1):362–98; 5. Ranucci G, et al. Dig Liver Dis. 2022;54(1):40–53; 6. Kremer AE, et al. Clin Res Hepatol Gastroenterol. 2011;35(2):89–97; 7. Bakır A, et al. Annals of Human Genetics. 2021;Dec 28 Online Ahead of Print; 8. Chen HL, et al. J Pediatr. 2019;205:153–9. e6; 9. Rajagopalan R, et al. Genet Med. 2021;23(2):323-30; 10. Feldman AG, Sokol RJ. Nat Rev Gastroenterol Hepatol. 2019;16(6):346–60; 11. Reichert MC, et al. Biochim Biophys Acta Mol Basis Dis. 2018;1864(4 Pt B):1484–90; 12. Bull LN, Thompson RJ. Clinics in Liver Disease. 2018;22(4):657–69; 13. Brahee DD, Lampl BS. Pediatric Radiology. 2021; 14. Napolitano M, et al. Pediatric Radiology. 2021;51(2):314–31; 15. Saleh M, et al. Appl Clin Genet. 2016;9:75–82; 16. Amirneni S, et al. World J Gastroenterol. 2020;26(47):7470–84; 17. Jung C, et al. J Pediatr Gastroenterol Nutr. 2007;44(4):453–8; 18. Srivastava A. J Clin Exp Hepatol. 2014;4(1):25–36; 19. Aksu AU, et al. Hepatology Communications. 2019;3:471–477; 20. Mandato et al. Orphanet J Rare Dis. 2021;16:179; 21. Qiu Y-L, et al. Human Mutation. 2019;1–11; 22. Gao E, et al. Hepatology. 2020;71: 1879–1882; 23. Vitale G, et al. Cancers. 2022; 14:3421; 24. Gezdirici A, et al. Mol Syndromol 2022;13:471–484; 25. Wei CS, et al. World J Gastroenterol. 2020;26(5):550-61; 26. Vinayagamoorthy V, et al. World J Hepatol. 2021;13: 2024–2038.

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