The Burden of Progressive Familial Intrahepatic Cholestasis (PFIC)

What is PFIC?

PFIC is a rare group of inherited pediatric liver diseases resulting from mutations in genes that impact bile acid homeostasis[1]

Clinical features of PFIC may include elevated serum bile acids, severe pruritus, fat-soluble vitamin deficiency, growth impairments, gallstones, increased risk of hepatocellular carcinoma, and progressive liver damage[2,3]

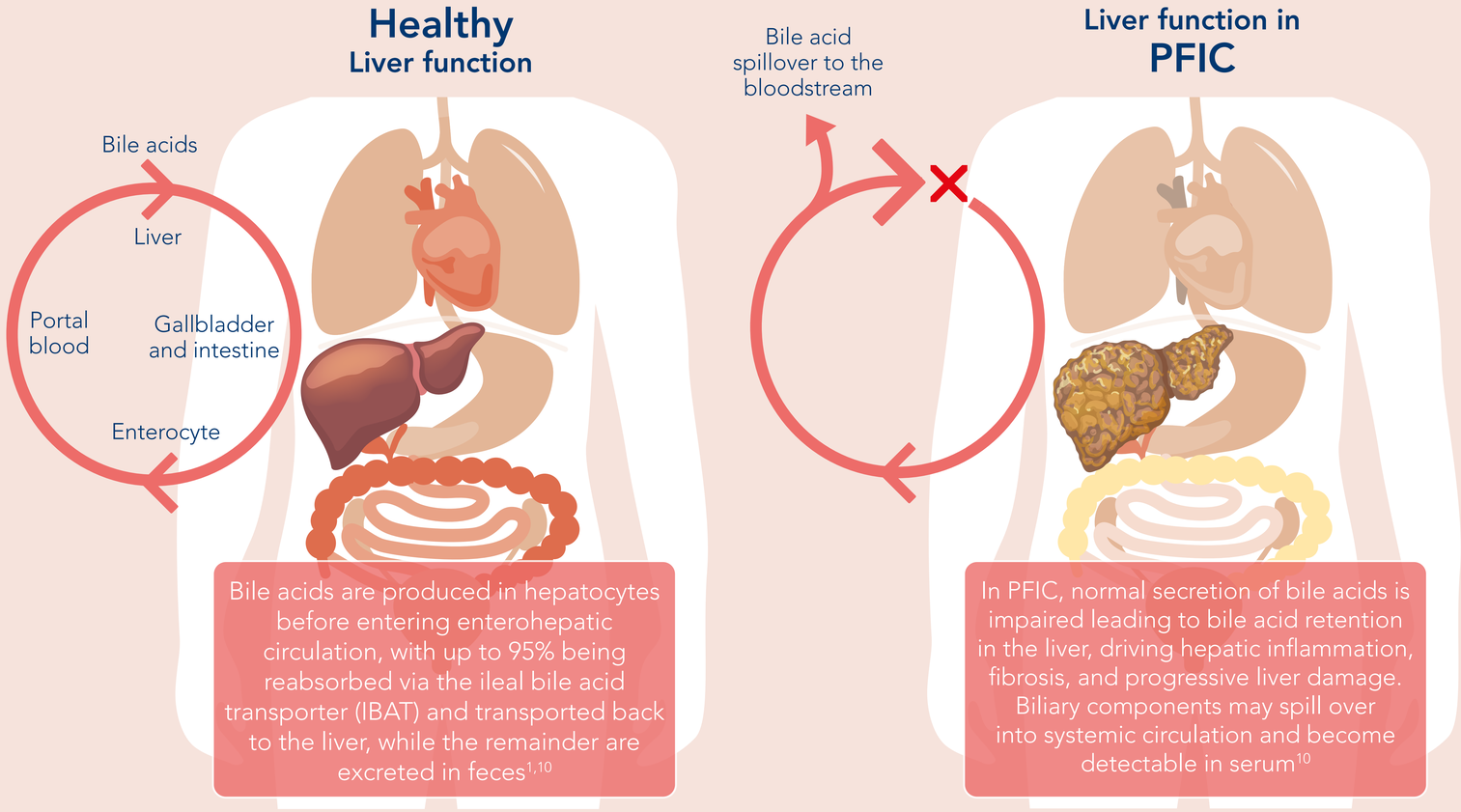
PFIC affects one in 50,000 to 100,000 children[4]

Types of PFIC reflect deficiencies in specific genes including:[1,5,6]

- PFIC1 (*ATP8B1*)
- PFIC2 (*ABCB11*)
- PFIC3 (*ABCB4*)
- PFIC4 (*TJP2*)
- PFIC5 (*NR1H4*)
- PFIC6 (*MYO5B*)
- PFIC7 (*USP53*)
- PFIC8 (*KIF12*)

- Potential mutations in other genetic loci have also been identified[1]
- While PFIC is often considered the most severe presentation of a spectrum of genetic diseases, confirmation by genetic testing may not be conclusive[1,2]
- Symptoms vary by PFIC type, but most include symptoms of cholestasis and/or pruritus[7–9]

Liver function

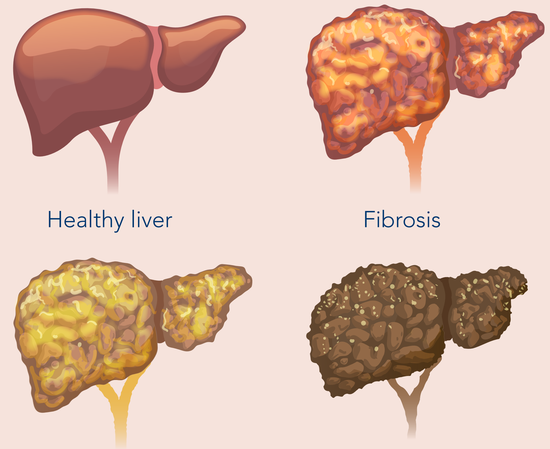


Bile acids are produced in hepatocytes before entering enterohepatic circulation, with up to 95% being reabsorbed via the ileal bile acid transporter (IBAT) and transported back to the liver, while the remainder are excreted in feces[1,10]

In PFIC, normal secretion of bile acids is impaired leading to bile acid retention in the liver, driving hepatic inflammation, fibrosis, and progressive liver damage. Biliary components may spill over into systemic circulation and become detectable in serum[10]

Disease progression and burden

Disease progression often depends on the type of PFIC, but hepatic signs and symptoms may include inflammation, fibrosis, cirrhosis, or end-stage liver disease (ESLD)[2]



Pruritus is one of the most debilitating symptoms of PFIC, and patients may experience intense scratching that leads to bleeding and scarring, considerable sleep disruption impacting daily activities, and reduced quality of life[3]

Higher levels of serum bile acids following surgical biliary diversion have been associated with:

- An increased likelihood of pruritus[11]
- Decreased native liver survival[11]

Caregivers also experience significant burden and may have mental and physical health problems, disruptions in personal relationships, sleep disturbances, and difficulty accomplishing daily activities[12]

Management of pruritus in PFIC, as well as reducing serum bile acids, is critical to reducing the immediate impact of symptoms, preserving the native liver, and improving long-term prognosis[11,13]

1. Goldberg A, Mack CL. *Clin Liver Dis (Hoboken).* 2020;15(3):105–9; 2. Bull LN, Thompson RJ. *Clin Liver Dis.* 2018;22(4):657–69; 3. Baker A, et al. *Clin Res Hepatol Gastroenterol.* 2019;43(1):20–36; 4. Davit-Spraul A, et al. *Orphanet J Rare Dis.* 2009;4:1; 5. # 619658 Cholestasis, progressive familial intrahepatic, 7, with or without hearing loss; PFIC7. 2021. Available at: https://omim.org/entry/619658?search=%22progressive%20familial%20intrahepatic%22&highlight=%22progressive%20familial%20intrahepatic%22. Accessed: January, 2022; 6. # 619662 Cholestasis, progressive familial intrahepatic, 8; PFIC8. 2021. Available at: https://omim.org/entry/619662?search=%22progressive%20familial%20intrahepatic%22&highlight=%22progressive%20familial%20intrahepatic%22. Accessed: January, 2022; 7. Amirneni S, et al. *World J Gastroenterol.* 2020;26(47):7470–84; 8. Bull LN, et al. *J Pediatr Gastroenterol Nutr.* 2021;72(5):667–73; 9. Stalke A, et al. *J Pediatr.* 2022;240:284–91.e9; 10. Karpen SJ, et al. *Hepatol Int.* 2020;14(5):677–89; 11. van Wessel DBE, et al. *Hepatology (Baltimore, MD)* 2021;74(2):892–906; 12. Mighiu C, et al. *Orphanet J Rare Dis.* 2022;17(1):32; 13. Kamath BM, et al. *Liver International* 2020;40:1812–1822.

ALLSC-US-001319
July 2024