Consequences of Cholestasis and Elevated Serum Bile Acids

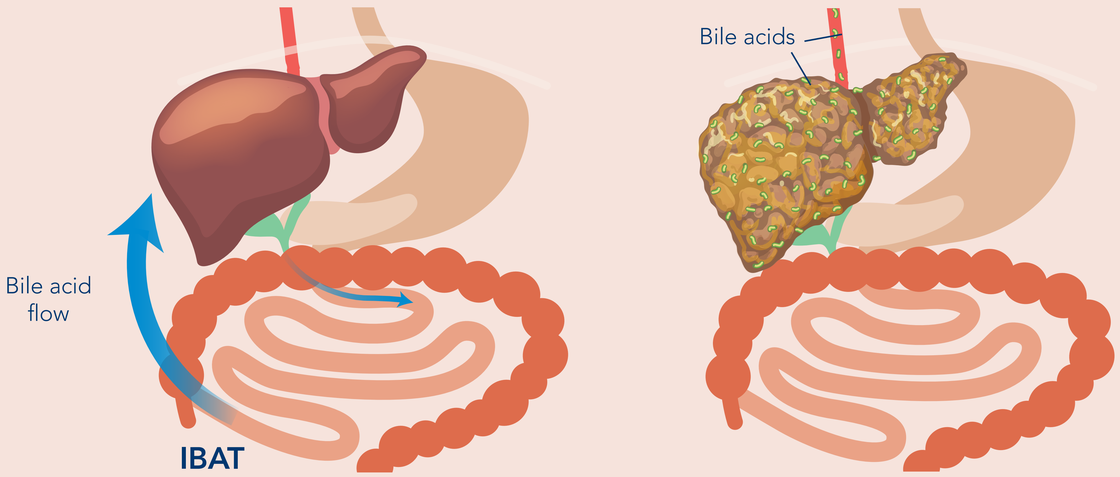
Enterohepatic circulation

Healthy liver function:

- In enterohepatic circulation, bile acids flow from the liver to the small intestine before returning to the liver[1]
- After leaving the liver, bile acids are stored in the gallbladder and released into the intestine to aid in digestion[1]
- Up to 95% of bile acids are resorbed by the ileal bile acid transporter (IBAT) and transported back to the liver[1]

Liver function during cholestasis:

- In cholestasis, secretion of bile acids from the liver is impaired[1,2]
- Cholestasis may result from genetic defects in hepatocytes or cholangiocytes, or from other functional issues in the hepatobiliary system[2]
- Consequent accumulation of bile acids and other biliary components in the liver may cause hepatic inflammation, fibrosis, and progressive liver damage; bile acids and other biliary components may also spill over into systemic circulation



Pruritus as a symptom of cholestasis

Elevated serum bile acids may contribute to pruritus in patients with cholestasis[3]

Pruritus is a hugely debilitating symptom of chronic cholestasis[4]

Patients may experience severe itching so intense that they experience scarring, considerable sleep disruption, and/or mood disturbances[4,5]

Pruritus and other symptoms of cholestasis may contribute to reduced quality of life in patients, impacting aspects of school, social, mental, and physical functioning[6–9]

Caregivers may also experience significant burden and may have mental and physical health problems, disruptions in professional and personal relationships, and increased stress and worry[7,10,11]

Consequences of cholestasis in three pediatric cholestatic liver diseases

Progressive familial intrahepatic cholestasis (PFIC), Alagille syndrome (ALGS), and biliary atresia are three cholestatic liver diseases that can present in pediatrics[12]

Clinical features vary by disease but overlapping signs and symptoms include jaundice, elevated serum bile acids, severe pruritus, portal hypertension, fat-soluble vitamin deficiency, and impaired growth; some patients also have increased risk of hepatocellular carcinoma[2]

PFIC

Patients with PFIC may have elevated serum bile acids and severe pruritus[8,13,14]

- Interventions such as surgical biliary diversion (SBD) that lower serum bile acids may help reduce pruritus and improve native liver survival[13,14]
  - For example, in patients with PFIC2, lower serum bile acid levels post-SBD (<102 µmol/L or decreased ≥75%) predict improved native liver survival[13]
- However, intractable pruritus may necessitate liver transplantation[3]

ALGS

Approximately 80% of patients with ALGS have cholestasis, resulting in elevated serum bile acids, total bilirubin, and cholesterol[15,16]

- SBD can lower serum bile acids in patients with ALGS[17–21]
- Additionally, up to 40% of patients with ALGS and cholestasis exhibit xanthomas, and up to 80% experience pruritus;[22] both can be indications for liver transplantation in absence of end-stage liver disease[23]
- In the GALA study, 1433 patients with ALGS-related neonatal cholestasis had 10- and 18-year native liver survival rates of 54.4% and 40.3%, respectively[24]

Biliary atresia

Patients with biliary atresia have hepatobiliary deterioration that rapidly advances to severe cholestasis

- Kasai portoenterostomy (KPE), the standard of care, may help improve bile flow, resulting in lower total bilirubin and serum bile acid levels which may correlate with improved native liver survival[12,25]
- However, ongoing cholestasis results in pruritus in approximately 40% of patients with an intact native liver after KPE; portal hypertension may occur in approximately 95% of these patients[26]
- Additionally, KPE may fail to correct bile flow and continued disease progression may warrant liver transplantation in approximately 40% of patients by 2 years of age, which rises to more than 70% by 15 years of age[27]

Management of pruritus, 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[14]

ALGS, Alagille syndrome; **IBAT**, ill bile acid transporter; **KPS**, Kasai portoenterostomy; **PFIC**, progressive familial intrahepatic cholestasis; **SBD**, surgical biliary diversion.

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