# Inborn Errors of Bile Acid Metabolism

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**KEYWORDS**

• Neonatal cholestasis • Cirrhosis • Liver • Zellweger spectrum disorder

**KEY POINTS**

- Inborn errors of bile acid metabolism are rare causes of neonatal cholestasis and liver disease in older children and adults.
- Diagnosis of inborn errors of bile acid metabolism requires a high index of suspicion with low serum bile acids in the presence of hyperbilirubinemia or advanced liver disease.
- Diagnosis is based on either genetic testing using available panels of genes associated with neonatal cholestasis and/or urine liquid secondary ionization mass spectrometry (LCIMS).
- Therapy for single enzyme defects with cholic acid is very effective for most inborn errors of bile acid metabolism except conjugation defects or oxysterol-7$\alpha$-hydroxylase deficiency.

## INTRODUCTION

Bile acids are synthesized by the liver from cholesterol through a complex series of reactions involving at least 15 enzymatic steps. Failure to perform any of these reactions will block bile acid production with failure to produce normal bile acids and, instead, the accumulation of unusual bile acids and intermediary metabolites. Failure to synthesize bile acids leads to reduced bile flow and decreased intraluminal solubilization of fat and fat-soluble vitamins. The intermediates created because of blockade in the bile acid biosynthetic pathway may be toxic to hepatocytes. Multiple recognized inborn errors of bile acid metabolism have been identified and caused by enzyme deficiencies and impaired bile acid synthesis in infants, children, and adults. Patients may present with neonatal cholestasis, neurologic disease, advanced liver disease,

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or fat and fat-soluble vitamin malabsorption. If untreated, progressive liver disease may develop or reduced intestinal bile acid concentrations may lead to serious morbidity or mortality. This review focuses on a description of the disorders of bile acid synthesis that are directly related to defects in the metabolic pathway and their proposed pathogenesis, treatment, and prognosis.

## CHEMISTRY AND PHYSIOLOGY

The bile acids belong to the steroid class classified as acidic sterols. In humans, the principal bile acids synthesized by the liver have hydroxyl groups substituted in the nucleus at the carbon positions C-3, C-7, and C-12.[1,2] During early development, alternative pathways for bile acid synthesis and metabolism become quantitatively important, as is evident from the findings of relatively high proportions of bile acids hydroxylated at the C-1, C-2, C-4, and C-6 positions of the nucleus.[3,4] The two principal bile acids synthesized by the liver and referred to as the primary bile acids are cholic acid (3α,7α,12α-trihydroxy-5ß-cholanoic acid [CA]) and chenodeoxycholic acid (3α,7α-dihydroxy-5ß-cholanoic acid [CDCA]). These bile acids are almost extensively conjugated to the amino acids glycine and taurine.[5] The biosynthetic pathway for bile acids is depicted in **Fig. 1**.

Bile acids perform several important functions. Bile acids are the major catabolic pathways for the elimination of cholesterol from the body.[1,6] Bile acids provide the primary driving force for the secretion of bile and are essential to the development of the

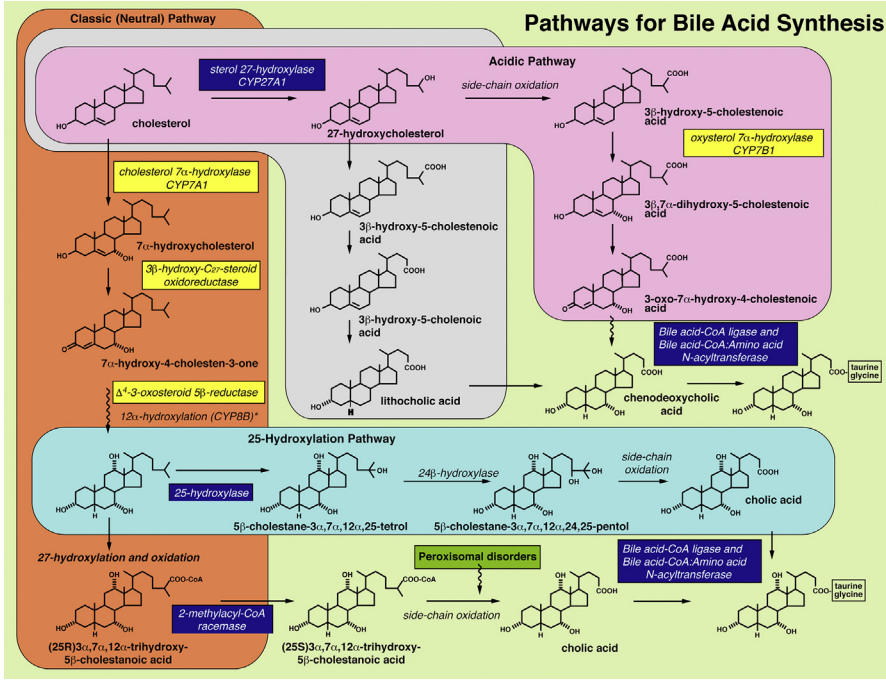


**Fig. 1.** Metabolic pathway for the biosynthesis of the primary bile acids in the classic or neutral pathway and the alternative or acidic pathway. Recognized inborn errors are shown in boxes in the pathways. (*From* Bove KE, Daugherty CC, Tyson W, et al. Bile acid synthetic defects and liver disease. Pediatr Dev Pathol 2000;3(1):1–16; with permission.)