Primary bile acid disorders: A largely unknown group of rare genetic diseases in newborns

Abstract
Primary bile acid disorders (BASD) in newborns are rarely found with a prevalence of 1-9/1,000,000 and include 1-2 % of all cases with neonatal cholestasis. Causes are different gene defects, which lead to liver enzyme defects, which play a major role in both cholic acid pathways, the classical with production of cholic acid and the alternative one with chenodeoxycholic acid. They are found in both genders in the same distribution. Early diagnosis is very important to introduce a bile acid replacement therapy as soon as possible as the treatment of choice to date. Diagnosis will be confirmed by molecular trsting, liver biopsy and different forms of mass spectrometry methods. Differential diagnosis includes progressive familial intrahepatic cholestasis, neonatal hepatitis and biliary atresia. Further gene therapy approaches must be developed, like CRISP Cas9 technology, to repair the spontaneous point mutations on DNA of these patients to cure and not to treat them the whole life finally.

Keywords
BASD-children-cholestasis-bile acid

Introduction
Inherited defects in bile acid synthesis are uncommon genetic disorders that can manifest as neonatal cholestasis, neurological problems, or deficiencies in fat-soluble vitamins. There are nine recognized defects in bile acid synthesis, including deficiencies in oxysterol 7α-hydroxylase, Δ4-3-oxosteroid-5ß-reductase, 3ß-hydroxy-Δ5-C27-steroid dehydrogenase, cerebrotendinous xanthomatosis (sterol 27-hydroxylase deficiency), α-methylacyl-CoA racemase, and Zellweger syndrome (cerebrohepatorenal syndrome). These conditions are characterized by the inability to produce normal bile acids and an accumulation of abnormal bile acids and bile acid intermediates. Individuals with inherited defects in bile acid synthesis typically present with the characteristic features of normal or low serum bile acid levels, normal γ-glutamyl transpeptidase levels, and the absence of itching. Failure to diagnose any of these conditions can lead to liver failure or progressive chronic liver disease. If identified early, many patients can have a significant clinical improvement with oral bile acid therapy.Inborn errors of bile acid synthesis are rare genetic disorders that account for up to 1–2% of cases of neonatal cholestasis, a condition characterized by the development of conjugated or direct hyperbilirubinemia within the first few months of life. Most patients with inborn errors of bile acid synthesis respond well to oral bile acid therapy.Cholic acid and chenodeoxycholic acid, the primary bile acids, are produced through a series of enzymatic modifications to cholesterol involving at least 14 enzymes, multiple subcellular compartments, and two complementary chemical pathways. The classic 'neutral' pathway is the main route for bile acid synthesis and produces both cholic acid and chenodeoxycholic acid in roughly equal amounts. The rate-limiting step in this pathway is the modification of the steroid nucleus, which occurs in hepatic microsomes and is catalyzed by cholesterol 7α-hydroxylase, the product of the CYP7A1 gene. The farnesoid X receptor (FXR) plays a crucial role in regulating CYP7A1 through bile acids. FXR is a member of the superfamily of ligand-activated transcription factors that acts on target genes as both a monomer and as a heterodimer with the retinoid X receptor (RXR). Bile acids are natural ligands for FXR, with chenodeoxycholic acid being the most potent activator of human FXR. FXR activation by primary bile acids leads to the upregulation of the atypical nuclear receptor small heterodimer protein (SHP), which interacts with liver receptor homolog 1 (LRH-1) and inhibits LRH-1's ability to activate CYP7A1. LRH-1 is also crucial for SHP gene expression, as the SHP–LRH-1 complex reduces SHP expression, thereby decreasing the negative feedback signal.An alternative 'acidic' pathway has also been identified, in which the initial step is C27-hydroxylation of cholesterol by sterol 27-hydroxylase, followed by C7α-hydroxylation by oxysterol 7α-hydroxylase. This pathway results in the production of primarily chenodeoxycholic acid. In both the classic and alternative pathways, side-chain modification occurs after steroid nucleus modification and is initiated in other organelles: C27-hydroxylation takes place in mitochondria, but further side-chain modification requires functioning peroxisomes. The final step in primary bile acid synthesis is the conjugation of cholic acid and chenodeoxycholic acid to taurine or glycine.In the past 20 years, deficiencies have been found in the genes encoding the multiple enzymes involved in the bile acid synthesis pathways. These defects are thought to cause liver disease in two ways. First, impaired hepatocyte production of primary bile acids reduces canalicular bile acid secretion, thereby hindering bile acid dependent bile flow. Second, potentially hepatotoxic atypical bile acid precursors accumulate in hepatocytes and cause cellular injury. These disruptions most commonly present in infants as cholestasis that can resemble other neonatal liver diseases, including biliary atresia.

Classical and alternative bile acid pathways

Bile acid synthesis occurs through two pathways: the classic 'neutral' pathway and the alternative 'acidic' pathway. In the classic 'neutral' pathway, the rate-limiting step in bile acid formation is the conversion of cholesterol to 7α-hydroxycholesterol by cholesterol 7α-hydroxylase. Multiple sequential steps modify both the steroid nucleus and the side chain to produce cholic acid and chenodeoxycholic acid. The main enzymes involved in this process include cholesterol 7α-hydroxylase, 3β-hydroxy-Δ5-C27-steroid dehydrogenase (encoded by HSD3B7), sterol 12a-hydroxylase, Δ4-3-oxosteroid-5β-reductase (encoded by AKR1D1 [previously known as SRD5B1]), and 3α-hydroxysteroid dehydrogenase. A series of side-chain modifications then occurs to yield cholic and chenodeoxycholic acid. Alternatively, in the alternative 'acidic' pathway, cholesterol is converted to 3β-hydroxy-5-cholestanoic acid by sterol 27-hydroxylase (encoded by CYP27A1). This is followed by conversion to 3β, 7α-dihydroxy-5-cholestenoic acid by oxysterol 7α-hydroxylase (encoded by CYP7B).

Enzyme defect	Gene encoding the affected enzyme (reference)	Urine bile acid profile	serum bile acid profile	Clinical features
Oxysterol 7α-hydroxylase deficiency	*CYP7B*[11]	↑ Sulfate and glycosulfate conjugates of 3β-δ5-monohydroxy bile acids Absence of primary bile acids	Extremely high levels of bile acids, primarily 3β-δ5-monohydroxy bile acids	Neonatal hepatitis (single reported case; unrecognized cases could be due to prenatal or early-postnatal death)
Δ^4-3-oxosteroid-5β-reductase deficiency	*AKR1D1*(*SRD5B1*)	↑ 3-oxo-δ4 bile acids ↑ Allo bile acids ↓ Primary bile acids	↑ 3-oxo-δ4 bile acids ↑ Allo bile acids ↓ Primary bile acids	Neonatal hepatitis with rapid progression to liver failure Neonatal hemochromatosis
3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase deficiency	*HSD3B7*	↑ Dihydroxy & trihydroxy cholenoic acids ↓ Primary bile acids	↓ or absence of primary bile acids	Neonatal hepatitis Late-onset liver disease Malabsorption
Cerebrotendinous xanthomatosis (sterol 27-hydroxylase deficiency)	*CYP27A1*	↑ Plasma cholestanol: cholesterol ratio	↑ Bile alcohol glucuronides	Progressive neurologic dysfunction in 2nd–3rddecade of life Chronic diarrhea Bilateral juvenile cataracts Neonatal cholestasis
Alpha methylacyl-CoA racemase deficiency	*AMACR* gene on chromosome 5p13.2-q11.1[71]	↑ C27 trihydroxycholestanoic and pristanic acid ↓ Primary bile acids	↑ C27 trihydroxycholestanoic and pristanic acid ↓ Primary bile acids Normal long-chain fatty acids and phytanic acid	Adult onset peripheral neuropathy Neonatal cholestasis with considerable fat-soluble-vitamin deficiency
Zellweger syndrome (cerebrohepatorenal syndrome)	12 *PEX* gene mutations; *PEX1* mutations are the most common.	Atypical monohydroxy, dihydroxy and trihydroxy C27 bile acids ↓ Primary bile acids	↑ Long-chain fatty acids ↑ Cholestanoic and pipecolic acid ↑ C29 dicarboxylic acid ↓ Primary bile acids	Craniofacial abnormalities Neuronal migration defects Polycystic kidneys

Table 1

Genetic, biochemical and clinical features of bile acid synthesis defects in the newborn

Discussion

The overall prevalence of BAS defects is unknown, but estimated prevalence may be around 1-9/1,000,000, excluding cerebrotendinous xanthomatosis (1-67). Inborn errors in BAS likely account for 1-2% of cases of unexplained liver disease in infants, children, and adolescents (1-67).The age at diagnosis varies (3,6,7,12,24). Presentation may occur in infancy with liver cholestasis, in childhood with unexplained liver disease, or in adulthood with neurologic disease (1-68). Infants and children may present with complications secondary to fat malabsorption and fat-soluble vitamin deficiency, including rickets, bleeding diathesis, neuroaxonal dystrophy, and night blindness (23,34,50,55).The seven inborn errors of BAS leading to liver cholestasis include: 3-beta-hydroxy-C27-steroid oxidoreductase deficiency (BAS defect type 1), delta4-3-oxosteriod-5-beta reductase deficiency (BAS defect type 2), oxysterol 7alpha-hydroxylase deficiency (BAS defect type 3), 2-methylacyl-CoA racemase deficiency (BAS defect type 4), trihydroxycholestanoic acid (THCA) CoA oxidase deficiency, bile acid CoA ligase deficiency, and defective amidation, and cerebrotendinous xanthomatosis (1-67). Cholesterol 7alpha-hydroxylase deficiency leads to hypercholesterolemia without liver cholestasis. A reported defect in side chain oxidation in the alternate 25-hydroxylation pathway needs further confirmation.Diagnosis is based on serum hepatic enzyme and bilirubin profile, and analysis of urine, serum, and bile using liquid secondary ionization mass spectrometry (LSIMS) and gas chromatography-mass spectrometry (GC-MS)(1-67).The spectrum of differential diagnoses is large and includes neonatal cholestasis, unexplained fat-soluble vitamin deficiency in infancy and childhood, unexplained liver disease in infancy, childhood, and adolescence, and unexplained neurologic disease in adults (1-6, 17,34,48).Most defects can be diagnosed antenatally from embryonic tissue when there has been a previously affected sibling. Urine from suspected cases may be screened by LSIMS in the first neonatal days, and therapy initiated before significant morbidity develops.The clinical presentation, liver histopathology, diagnostic procedures, and response to therapy of each of the nine known bile acid synthesis defects have been characterized. Bile acid synthesis defects share three important clinical features that should raise clinical suspicion for these disorders (34,56,64). First, while other cholestatic liver diseases

are associated with elevated total serum bile acid concentrations, levels are generally normal or low in infants with bile acid synthesis defects. Second, the serum level of γ-glutamyl transpeptidase (GGTP), which is often elevated in patients with other cholestatic liver diseases, is characteristically normal or minimally elevated in those with inborn errors of bile acid synthesis. Third, pruritus, which is a common and distressing feature of chronic cholestasis, is usually absent in infants with bile acid synthesis defects. A high index of suspicion is required to prevent the diagnosis of a bile acid synthesis defect being overlooked, as the clinical presentations of these rare disorders can be similar to those of other causes of neonatal liver failure, neonatal cholestasis, and chronic liver disease. Importantly, many bile acid synthesis defects are readily treatable and therefore have an excellent prognosis if recognized and treated early in life. Moreover, these disorders represent 'accidents of nature' that have led to a more thorough understanding of basic biochemistry and biology, which can be applied to normal liver physiology and the pathophysiology of other diseases. In this Review, the current state of our understanding of bile acid synthesis defects is characterized, with emphasis on the translational and clinical investigations that have led to the emergence of this relatively new field within hepatology. It should be noted that because of the rarity of these diseases, many of the treatment recommendations mentioned are based on expert opinion rather than on firm data.Disorders in bile acid synthesis are a growing group of significant liver problems. These conditions have similar clinical presentations to other causes of neonatal cholestasis and chronic liver disease, so a high level of suspicion is necessary for diagnosis. Early detection is crucial because most of these disorders can be effectively treated with bile acid replacement therapy (1-67). The current gold standard for definitive diagnosis, FAB-MS and GC-MS analyses of serum and urine, is technically challenging and only available in a few specialized referral laboratories (2,3,8,18). Our improved understanding of these disorders demonstrates the success of combining modern biochemical and molecular techniques to uncover the causes of rare liver diseases.

Treatment is based on primary bile acid therapy (1-67). Cholic acid creates a bile acid pool that stimulates bile flow and fat absorption. It does not appear to be effective for type 3. Ursodeoxycholic acid (UDCA) therapy creates a bile acid pool but does not suppress production of toxic intermediates and is not very effective at facilitating fat absorption. Glycocholic acid therapy is the treatment of choice for bile acid CoA ligase deficiency and defective amidation, improving fat absorption and growth (24,54,55,57).Prognosis depends on the type of defect (1-68). In all defects that affect the steroid nucleus of the bile acid molecule, if untreated, progressive liver disease may develop, or reduced intestinal bile acid concentrations may lead to serious morbidity or mortality. Long-term survival and clinical improvement are possible with early treatment. In those defects that affect the side chain, liver disease is milder, and neurological disease may predominate.

References

1. Ichimiya H, et al. Treatment of chronic liver disease caused by 3 beta-hydroxy-delta 5-C27-steroid dehydrogenase deficiency with chenodeoxycholic acid. Arch Dis Child. 1990;65:1121–1124. [PMC free article] [PubMed] [Google Scholar]
2. Setchell KD, et al. Identification of a new inborn error in bile acid synthesis: mutation of the oxysterol 7α-hydroxylase gene causes severe neonatal liver disease. J Clin Invest. 1998;102:1690–1703. [PMC free article] [PubMed] [Google Scholar]
3. Schwarz M, et al. Disruption of cholesterol 7alpha-hydroxylase gene in mice: II. bile acid deficiency is overcome by induction of oxysterol 7alpha-hydroxylase. J Biol Chem. 1996;271:18024–18031. [PMC free article] [PubMed] [Google Scholar]
4. Schwarz M, et al. Identification and characterization of a mouse oxysterol 7alpha-hydroxylase cDNA. J Biol Chem. 1997;272:23995–24001. [PubMed] [Google Scholar]
5. Axelson M, Sjovall J. Potential bile acid precursors in plasma—possible indicators of biosynthetic pathways to cholic and chenodeoxycholic acids in man. J Steroid Biochem. 1990;36:631–640. [PubMed] [Google Scholar]
6.. Shoda J, et al. Formation of 7 alpha- and 7-beta-hydroxylated bile acid precursors from 27-hydroxycholesterol in human liver microsomes and mitochondria. Hepatology. 1993;17:395–403. [PubMed] [Google Scholar]
7.. Ishibashi S, et al. Disruption of cholesterol 7alpha-hydroxylase gene in mice: I. postnatal lethality reversed by bile acid and vitamin supplementation. J Biol Chem. 1996;271:18017–18023. [PubMed] [Google Scholar]
8. Gonzales E, et al. SRD5B1 (AKR1D1) gene analysis in delta(4)-3-oxosteroid 5beta-reductase deficiency: evidence for primary genetic defect. J Hepatol. 2004;40:716–718. [PubMed] [Google Scholar]
9. Lemonde HA, et al. Mutations in SRD5B1 (AKR1D1), the gene encoding delta(4)-3-oxosteroid 5beta-reductase, in hepatitis and liver failure in infancy. Gut. 2003;52:1494–1499. [PMC free article] [PubMed] [Google Scholar]
10. Setchell KD, et al. Delta 4-3-oxosteroid 5 beta-reductase deficiency described in identical twins with neonatal hepatitis: a new inborn error of bile acid synthesis. J Clin Invest. 1988;82:2148–2157. [PMC free article] [PubMed] [Google Scholar]
11. Heubi JE, et al. Inborn errors of bile acid metabolism. Semin Liver Dis. 2007;27:282–294. [PubMed] [Google Scholar]

12. Siafakas CG, et al. Abnormal bile acid metabolism and neonatal hemochromatosis: a subset with poor prognosis. J Pediatr Gastroenterol Nutr. 1997;25:321–326. [PubMed] [Google Scholar]
13. Shneider BL, et al. Delta 4-3-oxosteroid 5 beta-reductase deficiency causing neonatal liver failure and hemochromatosis. J Pediatr. 1994;124:234–238. [PubMed] [Google Scholar]
14. Clayton PT, et al. Delta 4-3-oxosteroid 5 beta-reductase deficiency: failure of ursodeoxycholic acid treatment and response to chenodeoxycholic acid plus cholic acid. Gut. 1996;38:623–628. [PMC free article] [PubMed] [Google Scholar]
15. Levy P, et al. Acute infusions of bile salts increase biliary excretion of iron in iron-loaded rats. Gastroenterology. 1991;101:1673–1679. [PubMed] [Google Scholar]
16. Clayton PT, et al. 3-Oxo-delta 4 bile acids in liver disease. Lancet. 1988;1:1283–1284. [PubMed] [Google Scholar]
17. Sumazaki R, et al. Gene analysis in delta 4-3-oxosteroid 5 beta-reductase deficiency. Lancet. 1997;349:329. [PubMed] [Google Scholar]
18. Bove KE, et al. Bile acid synthetic defects and liver disease. Pediatr Dev Pathol. 2000;3:1–16. [PubMed] [Google Scholar]
19. Daugherty CC, et al. Resolution of liver biopsy alterations in three siblings with bile acid treatment of an inborn error of bile acid metabolism (delta 4-3-oxosteroid 5 beta-reductase deficiency) Hepatology. 1993;18:1096–1101. [PubMed] [Google Scholar]
20. Bazzoli F, et al. Relationship between serum and biliary bile acids as an indicator of chenodeoxycholic and ursodeoxycholic acid-induced hepatotoxicity in the rhesus monkey. Dig Dis Sci. 1982;27:417–424. [PubMed] [Google Scholar]
21. Sarva RP, et al. Comparison of the effects between ursodeoxycholic and chenodeoxycholic acids on liver function and structure and bile acid composition in the Rhesus Monkey. Gastroenterology. 1980;79:629–636. [PubMed] [Google Scholar]
22. Wikvall K. Purification and properties of a 3 beta-hydroxy-delta 5-C27-steroid oxidoreductase from rabbit liver microsomes. J Biol Chem. 1981;256:3376–3380. [PubMed] [Google Scholar]
23. Clayton PT, et al. Familial giant cell hepatitis associated with synthesis of 3 beta, 7 alpha-dihydroxy-and 3 beta,7 alpha, 12 alpha-trihydroxy-5-cholenoic acids. J Clin Invest. 1987;79:1031–1038. [PMC free article] [PubMed] [Google Scholar]
24. Stieger B, et al. Differential interaction of bile acids from patients with inborn errors of bile acid synthesis with hepatocellular bile acid transporters. Eur J Biochem. 1997;244:39–44. [PubMed] [Google Scholar]
25. Buchmann MS, et al. Lack of 3 beta-hydroxy-delta 5-C27-steroid dehydrogenase/isomerase in fibroblasts from a child with urinary excretion of 3 beta-hydroxy-delta 5-bile acids: a new inborn error of metabolism. J Clin Invest. 1990;86:2034–2037. [PMC free article] [PubMed] [Google Scholar]
26. Schwarz M, et al. The bile acid synthetic gene 3beta-hydroxy-delta(5)-C(27)-steroid oxidoreductase is mutated in progressive intrahepatic cholestasis. J Clin Invest. 2000;106:1175–1184. [PMC free article] [PubMed] [Google Scholar]
27. Cheng JB, et al. Molecular genetics of 3beta-hydroxy-delta5-C27-steroid oxidoreductase deficiency in 16 patients with loss of bile acid synthesis and liver disease. J Clin Endocrinol Metab. 2003;88:1833–1841. [PubMed] [Google Scholar]
28. Jacquemin E, et al. A new cause of progressive intrahepatic cholestasis: 3 beta-hydroxy-C27-steroid dehydrogenase/isomerase deficiency. J Pediatr. 1994;125:379–384. [PubMed] [Google Scholar]
29. Horslen SP, et al. 3Beta-hydroxy-delta 5-C27-steroid dehydrogenase deficiency; effect of chenodeoxycholic acid therapy on liver histology. J Inherit Metab Dis. 1992;15:38–46. [PubMed] [Google Scholar]
30. Witzleben CL, et al. A new category of causes of intrahepatic cholestasis. Pediatr Pathol. 1992;12:269–274. [PubMed] [Google Scholar]
31. Yamato Y, et al. 3Beta-hydroxy-delta5-C27-steroid dehydrogenase deficiency: diagnosis and treatment. J Paediatr Child Health. 2001;37:516519. [PubMed] [Google Scholar]
32. Moghadasian MH, et al. Cerebrotendinous xanthomatosis: a rare disease with diverse manifestations. Arch Neurol. 2002;59:527–529. [PubMed] [Google Scholar]
33. Gallus GN, et al. Clinical and molecular diagnosis of cerebrotendinous xanthomatosis with a review of the mutations in the CYP27A1 gene. Neurol Sci. 2006;27:143–149. [PubMed] [Google Scholar]
34. Verrips A, et al. Clinical and molecular genetic characteristics of patients with cerebrotendinous xanthomatosis. Brain. 2000;123:908–919. [PubMed] [Google Scholar]
35. Setchell KDR, Street JM. Inborn errors of bile acid synthesis. Semin Liver Dis. 1987;7:85–99. [PubMed] [Google Scholar]
36. Clayton PT, et al. Familial giant cell hepatitis with low bile acid concentrations and increased urinary excretion of specific bile alcohols: a new inborn error of bile acid synthesis? Pediatr Res. 1995;37:424–431. [PubMed] [Google Scholar]
37. Cruysberg JR, et al. Juvenile cataract associated with chronic diarrhea in pediatric cerebrotendinous xanthomatosis. Am J Ophthal. 1991;112:606–607. [PubMed] [Google Scholar]
38. Wevers RA, et al. Paediatric cerebrotendinous xanthomatosis. J Inherit Metab Dis. 1992;15:374–376. [PubMed] [Google Scholar]

39. Setchell KDR, et al. Disorders of bile acid synthesis and metabolism: a metabolic basis for liver disease. In: Suchy FJ, et al., editors. Liver Disease in Children. New York: Cambridge University Press; 2007. pp. 736–766. [Google Scholar]
40. Bove KE, et al. Bile acid synthetic defects and liver disease: a comprehensive review. Pediatr Dev Pathol. 2004;7:315–334. [PubMed] [Google Scholar]
41. Westin S, et al. FXR, a therapeutic target for bile acid and lipid disorders. Mini Rev Med Chem. 2005;5:719–727. [PubMed] [Google Scholar]
42. Edwards PA, et al. BAREing it all: the adoption of LXR and FXR and their roles in lipid homeostasis. J Lipid Res. 2002;43:2–12. [PubMed] [Google Scholar]
43. Otte K, et al. Identification of farnesoid X receptor beta as a novel mammalian nuclear receptor sensing lanosterol. Mol Cell Biol. 2003;23:864–872. [PMC free article] [PubMed] [Google Scholar]
44. Makishima M, et al. Identification of a nuclear receptor for bile acids. Science. 1999;284:1362–1365. [PubMed] [Google Scholar]
45. Parks DJ, et al. Bile acids: natural ligands for an orphan nuclear receptor. Science. 1999;284:1365–1368. [PubMed] [Google Scholar]
46. Wang H, et al. Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. Mol Cell. 1999;3:543–553. [PubMed] [Google Scholar]
47. Goodwin B, et al. A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol Cell. 2000;6:517–526. [PubMed] [Google Scholar]
48. Kuipers F, et al. The farnesoid X receptor (FXR) as modulator of bile acid metabolism. Rev Endocr Metab Disord. 2004;5:319–326. [PubMed] [Google Scholar]
49. Vlahcevic ZR, et al. Regulation of bile acid biosynthesis. Gastroenterol Clin North Am. 1999;28:1–25. [PubMed] [Google Scholar]
50. Russell DW, et al. Bile acid biosynthesis. Biochemistry. 1992;31:4737–4749. [PubMed] [Google Scholar]
51. Ichimiya H, et al. Bile acids and bile alcohols in a child with hepatic 3 beta-hydroxy-delta 5-C27-steroid dehydrogenase deficiency: effects of chenodeoxycholic acid treatment. J Lipid Res. 1991;32:829–841. [PubMed] [Google Scholar]
52. Chiang JYL, Ferrell JM. Bile acid receptors FXR and TGR5 signaling in fatty liver diseases and therapy. Am J Physiol Gastrointest Liver Physiol. 2020 Mar 1;318(3):G554-G573. doi: 10.1152/ajpgi.00223.2019. Epub 2020 Jan 27. PMID: 31984784; PMCID: PMC7099488.
53. Jiao N, Baker SS, Chapa-Rodriguez A, Liu W, Nugent CA, Tsompana M, Mastrandrea L, Buck MJ, Baker RD, Genco RJ, Zhu R, Zhu L. Suppressed hepatic bile acid signalling despite elevated production of primary and secondary bile acids in NAFLD. Gut. 2018 Oct;67(10):1881-1891. doi: 10.1136/gutjnl-2017-314307. Epub 2017 Aug 3. PMID: 28774887.
54. Chiang JYL, Ferrell JM. Discovery of farnesoid X receptor and its role in bile acid metabolism. Mol Cell Endocrinol. 2022 May 15;548:111618. doi: 10.1016/j.mce.2022.111618. Epub 2022 Mar 11. PMID: 35283218; PMCID: PMC9038687.
55. Chen HL, Wu SH, Hsu SH, Liou BY, Chen HL, Chang MH. Jaundice revisited: recent advances in the diagnosis and treatment of inherited cholestatic liver diseases. J Biomed Sci. 2018 Oct 26;25(1):75. doi: 10.1186/s12929-018-0475-8. PMID: 30367658; PMCID: PMC6203212.
56. Feldman AG, Sokol RJ. Neonatal Cholestasis: Updates on Diagnostics, Therapeutics, and Prevention. Neoreviews. 2021 Dec 1;22(12):e819-e836. doi: 10.1542/neo.22-12-e819. PMID: 34850148; PMCID: PMC10103174.
57. Farooqui N, Elhence A, Shalimar. A Current Understanding of Bile Acids in Chronic Liver Disease. J Clin Exp Hepatol. 2022 Jan-Feb;12(1):155-173. doi: 10.1016/j.jceh.2021.08.017. Epub 2021 Aug 23. PMID: 35068796; PMCID: PMC8766695.
58. Bove KE. Liver disease caused by disorders of bile acid synthesis. Clin Liver Dis. 2000 Nov;4(4):831-48. doi: 10.1016/s1089-3261(05)70144-6. PMID: 11232360.
59. Amendola M, Squires JE. Pediatric Genetic Cholestatic Liver Disease Overview. 2022 Sep 15 [updated 2023 May 25]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2024. PMID: 36108118.
60. Vasavan T, Ferraro E, Ibrahim E, Dixon P, Gorelik J, Williamson C. Heart and bile acids - Clinical consequences of altered bile acid metabolism. Biochim Biophys Acta Mol Basis Dis. 2018 Apr;1864(4 Pt B):1345-1355. doi: 10.1016/j.bbadis.2017.12.039. Epub 2018 Jan 6. PMID: 29317337.
61. Potter CJ. Cholestasis in the Premature Infant. Clin Perinatol. 2020 Jun;47(2):341-354. doi: 10.1016/j.clp.2020.02.009. Epub 2020 Mar 4. PMID: 32439115.
62. Heubi JE, Bove KE, Setchell KDR. Oral Cholic Acid Is Efficacious and Well Tolerated in Patients With Bile Acid Synthesis and Zellweger Spectrum Disorders. J Pediatr Gastroenterol Nutr. 2017 Sep;65(3):321-326. doi: 10.1097/MPG.0000000000001657. PMID: 28644367; PMCID: PMC5559188.
63. Baumann U, Sturm E, Lacaille F, Gonzalès E, Arnell H, Fischler B, Jørgensen MH, Thompson RJ, Mattsson JP, Ekelund M, Lindström E, Gillberg PG, Torfgård K, Soni PN. Effects of odevixibat on pruritus and bile acids in children with cholestatic liver disease: Phase 2 study. Clin Res Hepatol Gastroenterol. 2021 Sep;45(5):101751. doi: 10.1016/j.clinre.2021.101751. Epub 2021 Jun 26. PMID: 34182185.

64. Kriegermeier A, Green R. Pediatric Cholestatic Liver Disease: Review of Bile Acid Metabolism and Discussion of Current and Emerging Therapies. Front Med (Lausanne). 2020 May 5;7:149. doi: 10.3389/fmed.2020.00149. PMID: 32432119; PMCID: PMC7214672.
65. Bedoyan SM, Lovell OT, Horslen SP, Squires JE. Odevixibat: a promising new treatment for progressive familial intrahepatic cholestasis. Expert Opin Pharmacother. 2022 Nov;23(16):1771-1779. doi: 10.1080/14656566.2022.2140040. Epub 2022 Oct 30. PMID: 36278881; PMCID: PMC10074157
66. Fagan EA. Intrahepatic cholestasis of pregnancy. Clin Liver Dis. 1999 Aug;3(3):603-32. doi: 10.1016/s1089-3261(05)70087-8. PMID: 11291241.
67. Heubi JE, Setchell KDR. Open-label Phase 3 Continuation Study of Cholic Acid in Patients With Inborn Errors of Bile Acid Synthesis. J Pediatr Gastroenterol Nutr. 2020 Apr;70(4):423-429. doi: 10.1097/MPG.0000000000002618. PMID: 31899729.