Management of neonatal cholestasis

Cholestasis is a frequent occurrence in newborns, affecting one in every 2500 infants. Immaturity of hepatic metabolic and excretory functions contributes to decreased bile production and transport. The potential causes of neonatal cholestasis are extensive, but most cases fall into a few categories, including anatomic, metabolic and infectious. Pruritus and malabsorption are common manifestations of neonatal cholestasis, regardless of etiology. Medical management of cholestasis is largely supportive, treating the complications of cholestasis rather than the underlying mechanism. Medications for pruritus have variable efficacy and include ursodeoxycholic acid, cholestyramine and rifampin. Fat-soluble vitamin supplementation is often required secondary to fat malabsorption. Enteral absorption of long-chain triglycerides is also decreased, necessitating formulas high in medium-chain triglycerides. Infants may require 125% of the recommended daily allowance of calories for adequate growth and supplementation with enteral feeding tubes may be required.

KEYWORDS: bile, cholestasis, cholestyramine, fat-soluble vitamin, malabsorption, neonatal, phenobarbital, pruritus, rifampin, ursodeoxycholic acid, vitamin A, vitamin D, vitamin E, vitamin K

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Cholestasis is defined as impaired canalicular flow of bile, resulting in accumulation of biliary components, such as bilirubin, bile acids and cholesterol, in blood and tissues. Neonatal cholestasis is estimated to affect one in every 2500 infants [1]. There are multiple causes of neonatal cholestasis, often related to either the response of the newborn liver to endogenous agents or to specific pathological conditions. The list of potential causes of neonatal cholestasis is exhaustive (**Box 1**), although most cases fall into a few discrete categories [2]. These include anatomic causes (e.g., biliary atresia), metabolic causes (e.g., α-1-antitrypsin deficiency or total parenteral nutrition [TPN] [3,4]) and infectious causes (e.g., sepsis). After a brief review of the pathophysiology of neonatal cholestasis, this review will focus on the medical management of cholestasis.

Pathophysiology

Bile secretion is an essential function of the liver by which bile acids are delivered to the intestine for lipid solubilization and adsorption and metabolic products (e.g., cholesterol, bilirubin, porphyrins and xenobiotics) are excreted. Bile acids are formed via multiple, complex steps in the degradation of cholesterol. Two key steps in bile production involve the uptake of bile acids from the blood by hepatocytes and their excretion into the biliary canaliculus. The two principle bile acids synthesized in the liver are cholic acid and chenodeoxycholic acid, and extensive conjugation with primarily glycine and taurine occurs within the hepatocyte. The active transport of solutes across the canalicular membrane is the rate-limiting step in bile formation [2,5].

When compared with the adult liver, the liver of the term infant is immature in both metabolic and excretory functions. Bile flow can be divided into bile acid-dependent and bile acid-independent flow, with the former providing the primary force of generating bile flow early in life. As a consequence of the immaturity of the hepatic metabolic and excretory functions, TPN induces liver changes that could be directly related to the kind of artificial nutrition and, in part, to the way the nutrients are administered. As described previously [3], these changes can be divided into three types: direct, adaptive and pathologic.

Pruritus

Pruritus can be a troublesome manifestation of cholestasis. Cholestatic pruritus is uncommon in the neonatal period, with the exception of diseases including paucity of bile ducts, such as Allagile syndrome, and the progressive familial intrahepatic cholestasis syndromes. The prevalence of pruritus in liver disease is more common in older infants, children and adults. Pruritus

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Box 1. Differential diagnosis of neonatal cholestasis.

Idiopathic neonatal
- Hepatitis

Infections: viral
- Cytomegalovirus
- Rubella
- Reovirus 3
- Adenovirus
- Coxsackie virus
- Human herpes virus 6
- Varicella zoster
- Herpes simplex
- Parvovirus
- Hepatitis B and C
- HIV

Infections: bacterial
- Sepsis
- Urinary tract infection
- Syphilis
- Listeriosis
- Tuberculosis

Infections: parasitic
- Toxoplasmosis
- Malaria

Bile duct anomalies
- Biliary atresia
- Choledochal cyst
- Alagille syndrome
- Nonsyndromic bile duct paucity
- Inspissated bile syndrome
- Caroli syndrome
- Choledocholithiasis
- Neonatal sclerosing cholangitis
- Spontaneous common bile duct perforation

Metabolic disorders
- α_1-antitrypsin deficiency
- Galactosemia
- Glycogen storage disorder type IV
- Cystic fibrosis
- Hemochromatosis
- Tyrosinemia
- Arginase deficiency
- Zellweger's syndrome
- Dubin–Johnson syndrome
- Rotor syndrome
- Hereditary fructosemia
- Niemann Pick disease, type C
- Gaucher's disease
- Bile acid synthetic disorders
- Progressive familial intrahepatic cholestasis
- North American Indian familial cholestasis
- Aagenaes syndrome
- X-linked adreno-leukodystrophy

Endocrinopathies
- Hypothyroidism
- Hypopituitarism (septo-optic dysplasia)

Data obtained from [1].

Box 1. Differential diagnosis of neonatal cholestasis.

Chromosomal disorders
- Turner's syndrome
- Trisomy 18
- Trisomy 21
- Trisomy 13
- Cat-eye syndrome
- Donohue's syndrome (leprechaunism)

Toxic
- Parenteral nutrition
- Fetal alcohol syndrome
- Drugs

Vascular
- Budd–Chiari syndrome
- Neonatal asphyxia
- Congestive heart failure

Neoplastic
- Neonatal leukemia
- Histiocytosis X
- Neuroblastoma
- Hepatoblastoma
- Erythrophagocytic lymphohistiocytosis

Miscellaneous
- Neonatal lupus erythematosus
- 'Le foie vide' (infantile hepatic non regenerative disorder)
- Indian childhood cirrhosis

Data obtained from [1].

can be persistent or intermittent, and may be generalized or localized to specific areas, such as the palms and soles. Physical and psychological processes can exacerbate the pruritus and management is often difficult.

The exact cause of pruritus has yet to be determined but most researchers agree that more than one factor is involved in the pathogenesis of pruritus in cholestatic infants. Traditionally, it has been assumed that pruritus arises secondary to the accumulation of pruritogenic substances in the bile. Bile acids have been the most studied of such substances, with varied conclusions [6–8]. Inconsistencies in the bile salt–pruritus interaction have prompted the hypothesis that bile salts may act directly on the liver, causing the release of a pruritogenic compound.

More recently, the focus has shifted to a theory implicating endogenous opioids as central mediators of pruritus, as the occurrence of pruritus with opioid mediation is well known [9]. The role of the serotonin neurotransmitter systems have also been studied regarding their potential role in causing cholestasis-induced pruritus. Serotonin has been shown to be involved with cholestasis-induced fatigue, but less is known regarding its role in cholestasis-induced pruritus [10,11].

Malabsorption

Solubilization of fat-soluble vitamins by bile salts is necessary for their absorption across the brush border of the small intestine. Micelles are critically important in the absorption of fats, particularly long-chain triglycerides (LCTs), and require a critical micellar concentration of bile salts.

One of the major complications of cholestasis is fat malabsorption. Failure to secrete bile salts secondary to cholestasis results in a deficiency of bile salts in the intestine. Intraluminal bile acid concentration falls below the critical micellar concentration and micelles are not formed correctly, leading to malabsorption [12].

Failure to thrive can be a significant consequence of fat malabsorption and monitoring of growth parameters is essential, with nutritional supplementation when indicated. Although medium-chain triglycerides are absorbed more readily by the intestinal mucosa than LCTs, they cannot be used alone since essential fatty acid deficiency can result. Signs of fatty acid deficiency include flaky, dry skin, poor hair growth, thrombocytopenia and poor wound healing [2].

The fat-soluble vitamins A, D, E and K require solubilization by bile acids into micelles in order to be absorbed across the intestine. Cholestatic infants are particularly susceptible to fat-soluble vitamin deficiency as a consequence of malabsorption. Vitamin A deficiency was estimated to occur in 43% of cholestatic infants in one study [13]. Xerophthalmia, or 'dry eye', is the most recognized manifestation of vitamin A deficiency which, if left untreated, can progress to corneal ulceration. Vitamin D deficiency in cholestatic infants predisposes them to metabolic bone disease. Of note, some patients may have bone disease that persists despite normal levels of serum 25-hydroxyvitamin D, suggesting that other hormonal or nutritional parameters may be important in the development of bone disease in infants with cholestasis [14]. Addressing chronic vitamin E deficiency is of particular importance as it can lead to a progressive neuromuscular syndrome characterized by areflexia, peripheral neuropathy and posterior column dysfunction. Anemia can also be a manifestation of vitamin E deficiency. Vitamin K deficiency may be a presentation of cholestasis and intracranial hemorrhage secondary to vitamin K deficiency, and continues to be a frequent cause of death in infants with cholestasis [2]. Vitamin K is required for some coagulation proteins, such as factors II and VII, with deficiency leading to an increased propensity to bleeding [15].

Intestinal absorption of calcium and phosphorus is decreased in malabsorption secondary to cholestasis due to the formation of insoluble soaps. Such deficiency can contribute to bone disease that is unresponsive to vitamin D supplementation, and enteral supplements may be required to reverse bone disease.

Micronutrients can also be affected by cholestasis. Zinc is an essential trace element, present in over 100 metalloenzymes, and low plasma zinc is common in cholestasis. Plasma zinc concentrations do not correlate well with total body zinc status, making diagnosis of zinc deficiency difficult [16]. Selenium functions as an antioxidant, catalyzing the reduction of hydrogen peroxide and lipid hydroperoxidases. Selenium deficiency has been reported in 13–33% of children with cholestasis [17]. Mild deficiency is defined as a plasma selenium level less than 40 µg/l and severe deficiency as a level less than 10 µg/l.

Management of cholestasis

The medical management of cholestasis is largely supportive. Management is often related to the treatment of the complications of chronic cholestasis rather than the underlying mechanism. These complications include pruritus, malabsorption and nutritional deficiencies.

Pruritus

Cholestatic pruritus is probably a result of multiple mechanisms. Utilizing combination therapy with agents with varying mechanisms of action may be beneficial (see TABLE 1).

Ursodeoxycholic acid (UDCA) is a hydrophilic choleretic agent that increases bile flow and reduces membrane toxicity by hydrophobic bile acids [18]. Studies regarding the efficacy of UDCA in the treatment of cholestatic disease have shown conflicting results. In a 2.5-year, open-label, crossover study to determine the effects of UDCA on the clinical symptoms and biochemical test results of 13 patients with intrahepatic cholestasis, Narkewicz *et al.*, found that all patients with pruritus experienced symptomatic improvement with treatment as well as improvement in biochemical parameters [19]. UDCA is generally safe, although diarrhea is an uncommon side effect in the pediatric population. The dosage of UDCA is 10–30 mg/kg/day in divided doses.

Cholestyramine is a nonabsorbable, nonspecific anion exchange resin that binds bile acids, decreasing enterohepatic circulation by preventing their reabsorption in the terminal ileum [2].

Table 1. Medical management.

Medication	Dose	Side effects	Notes
Ursodeoxycholic acid	10–30 mg/kg/day in divided doses	Diarrhea	First-line therapy, choleretic agent and replaces hydrophobic bile acids
Cholestyramine	240 mg/kg orally, divided in three doses	Constipation, abdominal discomfort, anorexia, fat malabsorption and interference with the absorption of several drugs	A nonspecific anion exchange resin that binds bile acids
Phenobarbital	5–10 mg/kg/day	Sedation	Microsomal enzyme inducer
Rifampin	10 mg/kg/day	Hepatotoxicity, multiple drug interactions	Microsomal enzyme inducer

There has been no randomized study to assess the efficacy of cholestyramine but it has been shown to improve pruritus in the majority of patients within the first 2 weeks of treatment, although response may be transient. Recommended dosing of cholestyramine is 240 mg/kg orally in three divided doses, with the initial dose limited to 1 g daily. Dosing can be adjusted to a recommended maximum dosage of 4 g daily in children who are 10 years of age and younger and 8 g for those older than 10 years [20]. As the greatest amount of bile acids available for binding are thought to be in the gallbladder in the morning, cholestyramine administration is recommended 30 min prior to both breakfast and lunch, as well as 30 min after lunch [21]. In addition to a difficult dosing regimen, cholestyramine has a poor palatability making it difficult to give to children. Other side effects, although mild, include constipation, abdominal discomfort, anorexia and fat malabsorption. Hypoproteinemic hemorrhage and hyperchloremic metabolic acidosis after cholestyramine have been described in case reports [22]. Cholestyramine also interferes with the absorption of several drugs, including UDCA, thyroxin and oral contraceptive pills, and it is recommended that no other medications should be taken within 4 h of cholestyramine ingestion when feasible.

Phenobarbital is a microsomal enzyme inducer that can stimulate bile acid-independent flow and decrease bile acid-pool size [2]. Phenobarbital is used less frequently owing to its sedating side effect. The therapeutic dose of phenobarbital is 5–10 mg/kg/day.

Rifampin, another microsomal enzyme inducer, also enhances bile acid detoxification, and bilirubin conjugation and excretion [23]. In a non-placebo-controlled open trial of 24 children with cholestatic pruritus, unresponsive to other treatments, Yerushalmi *et al.* found that rifampin dosed at 10 mg/kg/day resulted in complete or partial response in 90% of the patients [24].

UV phototherapy is used to treat a variety of pruritic conditions. In a study of eight patients with cholestatic liver disease and pruritus, phototherapy did not result in significant improvement in pruritus [25].

If medical treatment fails and pruritus is severe, partial biliary diversion (biliary drainage through a stoma) or partial ileal bypass may be successful in relieving cholestatic pruritus [26]. By decreasing the load of bile acids to the ileum, the sole site of bile acid transport, enterohepatic circulation is lessened. Such diversion has been shown to provide relief from pruritus and, perhaps, reversal of liver disease in patients with progressive familial intrahepatic cholestasis with a low or normal γ-glutamyl transferase level [27]. In addition, biliary diversion should be considered in patients with arteriohepatic dysplasia (Allagile syndrome) who have symptoms refractory to medical therapy [28].

Malabsorption & nutritional deficiencies

As discussed earlier, UDCA is a choleretic agent that may decrease the degree of cholestasis in some settings. One function of UDCA is to increase the rate of transport of intracellular bile acids across the canalicular membrane [1]. Besides cholestasis-induced pruritus, UDCA is often used as first-line therapy for TPN-induced cholestasis and biliary atresia.

The ratio of serum vitamin E (mg/dl) to total serum lipids (g/dl) has been described as the most reliable index of vitamin E deficiency. This is due to the fact that cholestasis results in elevated serum lipids into which vitamin E can partition, causing an artificial elevation in the serum vitamin E concentration. A ratio less than 0.6 mg/g in infants and children aged less than 12 years or a ratio less than 0.8 mg/g in those older than 12 years indicates vitamin E deficiency [2]. For vitamin E deficiency, if cholestatic infants do not correct with traditional vitamin E

supplementation (Aquasol E), the water soluble form, d-α-tocopherol polyethylene glycol 1000 succinate (TPGS), should be attempted. The dosing range is 15–25 IU/kg/day while monitoring the vitamin E to total lipid ratio every 3 months and adjusting the dose to maintain adequate levels [29]. TPGS offers the advantage of being free from toxicity and obviating the need for intramuscular administration. TPGS can also be used as a vehicle for co-administering other fat-soluble vitamins.

Supplementation with vitamin A should begin after documenting vitamin A deficiency using either serum retinol or relative dose–response testing. Serum retinol testing has been estimated to have a sensitivity of 90% in detecting vitamin A deficiency and a specificity of only 78%, limiting testing for screening purposes. An additional test for vitamin A deficiency, the relative dose response (RDR), is a functional test of vitamin A reserves and has been found to be an accurate, noninvasive test to determine actual vitamin A status in patients with chronic liver disease. Feranchak *et al.* developed an oral version of the typical intramuscular RDR. After a small oral dose of vitamin A (1500 IU Aquasol A combined with 25 IU/KG TPGS) is given, the plasma retinol increases markedly if hepatic vitamin A stores are low [13]. Oral vitamin A supplementation for cholestatic infants is recommended with Aquasol A and doses range between 3000 and 25,000 IU/day.

Supplementation of vitamin D should begin after documenting a serum 25-hydroxyvitamin D below 15 ng/ml. As with other fat-soluble vitamin supplementation, absorption of vitamin D by the gastrointestinal tract can be enhanced by co-administration with TPGS [30]. If the vitamin D level is above 15 ng/ml, periodic 25-hydroxyvitamin D level testing is continued. Supplementation is recommended with vitamin D2 (Drisdol) at 3–10× RDA for age using at least 400 IU or 25-hydroxyvitamin D (Calderol), using a dose of 3–5 µg/kg/day [17].

Supplementation of vitamin K should begin after documentation of deficiency. Prolongation of the prothrombin time (PT)/International Normalized Ratio in comparison with the partial thromboplastin time suggests a vitamin K deficiency. Response of the PT to intramuscular injection of vitamin K is the most accurate mode of assessing vitamin K deficiency [17]. Supplementation of vitamin K is recommended with Mephyton®, using a dosing range between 2.5 mg biweekly and 5.0 mg/day.

For water-soluble vitamin supplementation in infants with cholestasis, most believe that it is prudent to supplement with a multivitamin at one- to two-times the RDA. Deficiencies

Table 2. Vitamin supplementation.

Supplement	Oral dose	Parental dose	Deficiency
Vitamin A	Aquasol A: 3000–25,000 IU/day	50,000 IU/month every 2 months	Serum retinol <20 µg/dl (screening) Oral RDR; rise in retinol >20% at 10 h
Vitamin D	Drisdol® (vitamin D2): 3–10× RDA Calderol 3–5 µg/kg/day		25-OH-D <15 ng/ml
Vitamin E	TPGS 15–25 IU/kg/day		Vitamin E to total lipid ratio (g/dl) <0.6 mg/g (<12 yo) and <0.8 mg/g (>12 yo)
Vitamin K	Mephyton® 2.5 mg biweekly to 5.0 mg/day	AquaMephyton 2–5 mg im. every 4 weeks	Prolonged prothrombin time
Multivitamin	1–2 times RDA		
Calcium	Elemental calcium 25–100 mg/kg/day		Serum ionized calcium low despite normal vitamin D levels
Phosphorus	Elemental phosphorus 25–50 mg/kg/day		Serum phosphorus
Magnesium	Magnesium oxide 1–2 mEQ/kg/day p.o.		
Zinc	Zinc sulfate 1 mg/kg/day		Serum concentration <60 µg/dl
Selenium	Sodium selenite 1–2 µg/kg/day p.o.		Plasma level <40 µg/l

p.o.: Orally; RDA: Recommended daily allowance; RDR: Relative dose response; yo: Years old.

of vitamins B_1, B_6 and C and folic acid have been described in patients with chronic liver disease [17].

Enteral supplementation with elemental calcium and phosphorus should commence after documentation of low serum concentration of calcium and/or phosphorus [31]. Magnesium deficiency should be documented with a low serum level and treated with magnesium oxide to minimize decreased bone mineral density secondary to cholestasis [32]. It has been recommended that in infants who are growing poorly with inadequate oral intake or low plasma zinc concentration (60 µg/dl), supplementation for 2–3 months as a therapeutic trial should be instituted [17].

Supplementation with selenium is recommended at 1–2 µg/kg per day for deficiency and 1 µg/kg per day for those on total TPN for maintenance. Nutrient levels should be monitored periodically during treatment. TABLE 2 provides a summary of medications used to treat nutritional deficiencies in neonates with cholestasis.

Future perspective

Research will further increase knowledge regarding the transport of bile acids and specific molecular defects that lead to clinical disease. Such knowledge will allow specific therapies to be developed that target individual diseases, or specific cellular processes, leading to improved treatment efficacy. In addition, increased knowledge regarding molecular defects associated with cholestatic liver disease will allow the number of disorders classified as idiopathic neonatal cholestasis to decrease as specific diagnoses are made.

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Executive summary

Pathophysiology

- Cholestasis is defined as impaired canalicular bile flow.
- Most causes can be categorized as anatomic, metabolic and infectious.
- Hepatic metabolic and excretory function is immature in the newborn.
- Active transport of solutes across the canalicular membrane is the rate-limiting step in bile formation.
- Bile flow can be divided into bile acid-dependent flow and bile acid-independent flow with the former most important early in life.

Pruritus

- Pruritus is more common in intrahepatic bile duct paucity and progressive familial intrahepatic cholestasis.
- Mechanisms may involve accumulation of pruritogenic substances in the bile, endogenous opioids and the serotonin neurotransmitter systems.

Malabsorption

- Failure to secrete bile salts impairs absorption of fats and fat-soluble vitamins.
- Micelles are required for absorption fats, particularly long-chain fatty acids.

Management of pruritus

- Medical management of cholestasis is largely supportive.
- Ursodeoxycholic acid is a choleretic agent that alters the bile acid pool and increases the rate of canalicular bile acid transport.
- Cholestyramine is a nonabsorbable nonspecific anion exchange resin that binds bile acids, decreasing enterohepatic circulation.
- Phenobarbital and rifampin are microsomal enzyme inducers that can stimulate bile acid-independent flow.
- Efficacy of phototherapy for cholestatic pruritus has not been proven.
- Biliary diversion may be beneficial in those with severe pruritus not controlled with medical therapy.

Management of malabsorption

- Medium-chain triglycerides are absorbed more readily by the intestinal mucosa than long-chain fats.
- Supplementation with fat-soluble vitamins A, D, E and K is frequently needed.
- Chronic vitamin E deficiency can lead to a progressive neuromuscular syndrome.
- Use of oral d-α-tocopherol polyethylene glycol 1000 succinate can aid in the absorption of other fat soluble vitamins.
- Supplementation with a multivitamin at once or twice RDA may be prudent.
- Serum levels of calcium, phosphorus, magnesium, selenium, and zinc should be monitored and appropriate supplementation instituted after documenting deficiency.

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