

III. *Clinical Manifestations and Management*

D. The Liver

CHAPTER 49

APPROACH TO NEONATAL CHOLESTASIS

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Cholestasis, defined physiologically as a reduction in canalicular bile flow, is primarily manifested as conjugated hyperbilirubinemia. The major clinical consequences, however, are presumably related to retention of other substances, such as bile acids, which are dependent on bile flow for excretion. The attendant histopathologic features often reflect the nature and degree of the physiologic disturbance and imply the pathophysiologic basis.

There are multiple causes of cholestasis in early life, related either to the response of the neonatal liver to exogenous agents or to specific congenital pathologic conditions. Immature hepatic excretory function creates a milieu wherein infants are susceptible to further impairment of biliary excretion owing to infectious or metabolic insults. Although recognized disorders associated with neonatal cholestasis are numerous, the majority of cases fall into a few discrete and overlapping categories, one of the more frequent ones being the generic “neonatal hepatitis.”

Efforts are being made to alert generalists and specialists worldwide to recognize the neonate with cholestasis at the earliest opportunity. Nevertheless, evaluation of the infant with cholestasis remains a difficult task owing to the diversity of cholestatic syndromes, to their obscure pathogenesis, and to the often nonspecific clinical and pathologic presentation. Prompt identification and diagnostic assessment of the infant with cholestasis are imperative to recognize disorders amenable either to specific medical therapy (eg, galactosemia, sepsis) or to early surgical intervention (eg, biliary atresia) and to institute effective nutritional and medical support to allow optimal growth and development. Although the advent of pediatric liver transplant has saved many, early intervention may avoid the need for organ replacement in some of these patients. For example, in tyrosinemia, a non-transplant option is now readily available and efficacious.

DEVELOPMENTAL PHYSIOLOGY OF HEPATOBILIARY FUNCTION

Although comprehension of liver and biliary development is still at the embryonal stage, it is known that the extrahepatic biliary tree develops from an outgrowth of the ventral foregut, whereas the intrahepatic tree differentiates from the multipotent hepatoblast in a centrifugal fashion.¹ Furthermore, the physiology of bile flow in the adult is well described, and its understanding may assist in the approach of the cholestatic infant and the interpretation of laboratory tests. However, it is paramount to remember that the liver of the term infant is “immature” both in its metabolic and excretory functions. With the increased survival of very premature infants, pediatricians, neonatologists, and gastroenterologists are more likely to be confronted by cholestasis and abnormal liver tests. Thus, a basic understanding of physiology, together with prompt recognition and management, should help improve the outcome of these patients. Our goal is to discuss the expeditious and cost-effective approach to the infant with conjugated hyperbilirubinemia, allowing recognition of those who need specialized care.

Bile flow has traditionally been divided into two components: (1) bile acid–dependent flow, which involves active canalicular transport of bile acids, accompanied by osmotic water flow and diffusion of other solutes, and (2) bile acid–independent flow, which is thought to be mediated by active transport of other anions and cations.² The primary motive force in the generation of bile flow in early life is the hepatocytic secretion of bile acids; there is little contribution of the bile acid–independent component during the neonatal period.³ The hepatobiliary excretory system is both functionally and anatomically underdeveloped at birth, leaving the neonate with a unique propensity toward cholestasis.^{4–6}

Substantial evidence supports the existence of a period of “physiologic cholestasis” associated with immature or altered metabolism and transport of bile acids at birth (Table 49-1). Serum bile acid concentrations, which reflect the net efficiency of intestinal absorption and hepatobiliary function, are maintained at low levels in the fetus by carrier-mediated transplacental transport to the mother.⁷⁻⁹ Postnatally, in the normal infant, both fasting and postprandial serum bile acid concentrations are significantly higher than those found in older children. These levels are similar to those attained in adults with cholestatic disease^{10,11} and persist through the first several months of life. Factors contributing to decreased bile flow and inefficient enterohepatic cycling of bile acids in the neonate include (1) inefficient intestinal and hepatic bile acid uptake owing to the pace of ontogenic expression of bile acid transport proteins, (2) qualitative and quantitative deficiencies of bile acid synthesis, (3) immature hepatic bile acid metabolism, and (4) inefficient hepatocellular secretion.¹²

The suckling rat model has been used extensively in studies of the developing hepatobiliary system.^{13,14} Lower rates of hepatic uptake of bile acids have been demonstrated in experimental systems such as isolated hepatocytes¹⁵ and purified basolateral (sinusoidal) membrane vesicles of developing rats,^{16,17} reflecting immaturity of sodium-coupled bile acid transport. This appears to be secondary to reduced expression of specific transport proteins.¹⁸ In the adult rat, avid extraction of bile acids by periportal hepatocytes results in a decreasing periportal to central lobular gradient for bile acid uptake.^{19,20} Using similar radioautographic techniques, no acinar gradient could be demonstrated in the 14-day-old rat liver,²¹ further supporting the concept of inefficient uptake of bile acids. There is enhanced efflux of taurocholate from suckling rat hepatocytes, which may represent back-diffusion across the sinusoidal membrane; this also contributes to the inefficient hepatic bile acid transport.²² In the ileum, a similar developmental pattern for the transport of bile acids can be demonstrated, with decreased active bile acid uptake during the suckling period.^{23,24} There is significant passive absorption of bile acids in the jejunum of suckling rats, which may combine with decreased hepatic uptake to lead to decreased intraluminal concentrations of some bile acids.²⁵ A recent study in rats looked at the correlation between intestinal resection

length and expression of the apical sodium bile acid transporter. The authors reasoned that there may be an intestinal length “threshold” that determines whether the apical sodium bile acid transporter is up- or down-regulated in response to ileal resection. In parallel, hepatic synthesis of bile acids increases to compensate for decreased absorption up to a certain level, later decreasing when the bile acid pool is severely reduced. These findings are important for two reasons: they illustrate the plasticity of infant bile acid physiology and they offer a hypothesis for the pathogenesis of cholestasis in patients with short bowel.²⁶

Quantitative and qualitative differences in bile acid synthetic pathways are also apparent during early life. Bile acid synthesis begins on day 11 of the 21-day gestation in the rat²⁷ and near week 12 in the human fetus.²⁸ A decreased cholate-to-chenodeoxycholate ratio has been observed in the human fetus compared with that of the adult, indicating immaturity of hepatic α -hydroxylation.²⁹⁻³¹ It is believed that a “threshold” concentration of cholic acid, the primary bile acid, is needed to initiate and maintain bile flow. Cholic acid may be trophic to the developing hepatic excretory system. In the absence of sufficient quantities of cholic acid, there is decreased bile flow.

The immaturity of bile acid synthetic function is also reflected in the presence of “atypical” bile acids found in the fetus and normal neonate.^{30,31} Certain of these atypical bile acids, such as the monohydroxylated compound 3- β -hydroxy-5- Δ -cholenoic acid, which has been detected in amniotic fluid³² and meconium,^{33,34} are thought to directly impair bile acid excretion. Significant amounts of nonsulfated tetrahydroxylated bile acids have been identified in the urine of healthy neonates³⁵ and in the urine of older children and adults with cholestatic liver disease.³³ This polyhydroxylation may increase bile acid solubility, providing a potential alternative pathway for excretion of “toxic” bile acids at a time when transformation and biliary secretion are not fully developed.

Although the mechanisms of intracellular biotransformation of bile acids are not well defined, there is evidence that both the conjugation and sulfation of these organic anions are underdeveloped in early life.^{36,37} Conjugation of bile acids with the amino acids taurine and glycine provides a potential mechanism for detoxification and allows efficient intestinal fat digestion and absorption. In isolated hepatocytes obtained from fetal and suckling rats, the rate of conjugation of a radiolabeled bile acid was shown to increase with postnatal age.³⁷

The development of effective bile acid secretion from the hepatocyte appears to lag behind the onset of bile acid synthesis, as would be expected if cholic acid truly plays a trophic role. This is suggested by studies of the distribution of the bile acid (taurocholate) pool in fetal and newborn rats.³⁸ In the fetus, more than 85% of the bile acid pool is localized in the liver, with only 10% found in the intestinal lumen. By postnatal day 5, this distribution is reversed, with more than 85% of the bile acid pool localized in the intestine. Canalicular excretion of bile acids appears to be the rate-limiting step. Reduced canalicular excretion of bile acids in the fetus appears to be related to an immaturity of the canalicular membrane transport sys-

TABLE 49-1 MANIFESTATIONS OF UNDERDEVELOPED BILE ACID TRANSPORT AND METABOLISM IN EARLY LIFE

Increased serum bile acid levels (physiologic cholestasis)
Decreased hepatic uptake of bile acids from portal blood
Absent lobular gradient
Qualitative and quantitative differences in bile acid synthesis
Decreased conjugation, sulfation, and glucuronidation of bile acids
Enhanced bile acid efflux from hepatocyte
Decreased bile acid secretion rate
Decreased bile acid pool size
Low intraluminal concentrations of bile acids
Decreased ileal active transport of bile acids

tems for bile acids. The potential-dependent transport protein is not detected in rat liver until postnatal day 7, and transport does not occur until day 14.³⁹ The adenosine triphosphate-dependent portion of the transport system, however, appears to be functional in the neonatal period and may play a role in bile acid secretion.⁴⁰ It has been recognized recently that the regulation of bile acid synthesis occurs by a feedback mechanism involving the nuclear receptor farnesoid X.⁴¹ One can speculate that as these feedback loops mature, they may participate in the imbalance between the hepatocellular bile acid pool and canalicular excretory function. Furthermore, the same ontogenic principles apply to other metabolic pathways and transporters localized on hepatocytes and biliary epithelial cells. Thus, metabolism and excretion of xenobiotics (eg, bacterial toxins, maternal drugs) into bile are likely to be both modified by and potentially exacerbate cholestasis by imposing further demand on the immature liver, especially in the sick newborn. Thus, when investigating an infant with cholestasis, especially a preterm infant, one must look beyond the liver because cholestasis is a nonspecific response to a wide variety of insults in the infant.⁴²

During fetal development, canaliculi differentiate from simple intracellular invaginations of two adjacent cell membranes into well-defined structural lumina filled with microvilli.⁴³ Specific changes in the pericanalicular cytoskeleton, which has been implicated in promotion of bile formation, are also noted during development. Compared with adult cells, cultured fetal hepatocytes have a decreased frequency and force of canalicular contractions, which appear to be related to a lack of pericanalicular cytoplasmic actin.⁴⁴ Structural immaturity of both the canaliculi and the pericanalicular cytoskeleton may be significant factors in impaired bile acid secretion during development. Furthermore, studies in both preterm humans and newborn piglets suggest that gallbladder contractility and response to cholecystokinin are also slow to mature, adding an extrahepatic factor to the long list of intrahepatic mechanisms responsible for the increased susceptibility to cholestasis in the infant, in particular the patient dependent on total parenteral nutrition.^{45,46}

Despite abundant data suggesting structural and functional immaturity of hepatic excretory function, the clinical and physiologic implications of “physiologic cholestasis” are unclear. However, a reasonable hypothesis could be advanced: in the presence of lower rates of bile flow, compounds destined for biliary excretion would accumulate in the hepatocyte.¹¹ Certain of these compounds, such as atypical bile acids, are damaging to the membrane or organelle, making hepatic injury likely. Exogenous factors, such as infusion of parenteral nutrition solutions, prolonged fasting, sepsis, or hypoxia, will perturb this already precarious situation and result in the anatomic and clinical manifestations of cholestasis.

DIFFERENTIAL DIAGNOSIS OF CHOLESTASIS

The causes of neonatal cholestasis are diverse (Table 49-2). These include structural anomalies of the biliary tract, both intrahepatic and extrahepatic, which result in

obstruction of bile flow, and infectious, metabolic, hemodynamic, or toxic insults, which cause functional impairment of the hepatic excretory process and bile secretion.

Although the differential diagnosis of cholestasis in the neonate is varied, the clinical presentation is similar, reflecting the underlying decrease in bile flow. Specifically, infants with cholestasis present with variable degrees of jaundice, dark urine, light stools, and hepatomegaly. Synthetic dysfunction and hepatocellular necrosis may be present. In certain patients with rapid progression of hepatocellular disease, fibrosis occurs, with signs of decompensation, such as ascites, appearing early in life. Failure to thrive is not always manifest early in the course; normal development may be falsely reassuring and should not detract the clinician from initiating a workup. Similarly, although premature infants are at increased risk for cholestasis, gestational age and side effects of neonatal intensive care should remain a “default” diagnosis once surgical and medical emergencies have been ruled out. The diagnosis of “transient neonatal cholestasis,” the most frequent form, may be a more limited subset of the generic “idiopathic” neonatal hepatitis.

Jacquemin and colleagues used the term “transient neonatal cholestasis” to describe a group of 92 patients with early-onset neonatal cholestasis, identifiable perinatal complications incriminated in cholestasis, and a spontaneously favorable outcome.⁴⁷ In 85% of the patients, there was a history consistent with acute or chronic perinatal distress. Mean gestational age was 37 weeks, and birth weight was 2,705 g, with one-third of the patients being small for gestational age. Histology was consistent with the previous description of “neonatal hepatitis.” The authors did not identify a correlation between histologic findings and perinatal events. Jaundice resolved in all patients, together with normalization of liver biochemical markers and, importantly, growth. The mean duration of jaundice was 3.5 months, and hepatomegaly resolved at a mean age of 13 months. Most had a biphasic progression of their cholestatic markers, with γ -glutamyl transpeptidase reaching its peak as conjugated bilirubin levels normalized. The importance of this study lies in its description of a subset of patients with early-onset neonatal cholestasis and hepatomegaly, perinatal distress, and a characteristic pattern of biochemical markers, in whom it is appropriate to defer liver biopsy and offer supportive care only. It is all the more important that the population of premature babies is increasing, with numerous perinatal hypoxic and toxic insults. Special attention should be paid to those infants who do not have a clearly identifiable cause of prematurity and develop cholestasis or intrauterine growth retarded infants with cholestasis; together, these problems may be indicative of primary liver disease or of an underlying metabolic defect.

DIAGNOSTIC APPROACH

Because of the severity of many of the conditions leading to neonatal cholestasis, early recognition of cholestasis in an infant and prompt diagnosis of the underlying disorder are imperative to identify disorders that will respond to a specific treatment and to institute general supportive care that

TABLE 49-2 CLASSIFICATION OF DISORDERS ASSOCIATED WITH CHOLESTASIS IN THE NEWBORN

EXTRAHEPATIC DISORDERS	Mitochondrial hepatopathies
Biliary atresia	Other metabolic defects
Bile duct stricture/neonatal sclerosing cholangitis	α_1 -Antitrypsin deficiency
Choledochal cyst	Cystic fibrosis
Anomalies of the pancreaticoduodenal junction	Hypopituitarism
Spontaneous perforation of the bile duct	Hypothyroidism
Inspissated bile	Neonatal iron storage disease
Mass	Infantile copper overload (Menkes syndrome)
Intraductular: stone, rhabdomyosarcoma	Hemophagocytic lymphohistiocytosis
Extraductular: hepatoblastoma, neuroblastoma	Arginase deficiency
INTRAHEPATIC DISORDERS	Toxic
Idiopathic	Total parenteral nutrition-associated cholestasis
“Idiopathic” neonatal hepatitis	Fetal alcohol syndrome
Intrahepatic cholestasis, <i>persistent</i>	Other drugs (maternal or used in neonatal intensive care)
Severe intrahepatic cholestasis with progressive hepatocellular disease (see Chapter 55.6, “Biliary Transport”)	Cholestasis associated with infection
Alagille syndrome (syndromic paucity of the intrahepatic bile ducts, arteriohepatic dysplasia)	Sepsis with possible endotoxemia (urinary tract infection, gastroenteritis)
Nonsyndromic paucity of the intrahepatic bile ducts	Syphilis
Intrahepatic cholestasis, <i>recurrent</i>	Toxoplasmosis
Benign recurrent intrahepatic cholestasis	Listeriosis
Hereditary cholestasis with lymphedema (Aagaens syndrome)	Congenital viral infections
Anatomic	Cytomegalovirus
Congenital hepatic fibrosis or infantile polycystic disease (liver and kidney)	Herpesvirus (herpes simplex and human herpesvirus 6)
Caroli disease	Cocksackievirus
Metabolic or endocrine disorders	Echoviruses
Disorders of amino acid metabolism	Rubella virus
Tyrosinemia	Hepatitis B virus
Disorders of lipid metabolism	Other hepatitis viruses: C? nonA nonB?
Cholesterol ester storage disease (Wolman)	Human immunodeficiency virus (HIV)
Niemann-Pick disease	Parvovirus B19
Gaucher disease	Chromosomal
Disorders of carbohydrate metabolism	Trisomy 18
Galactosemia	Trisomy 21 (Down syndrome)
Fructosemia	Donohue syndrome (leprechaunism)
Glycogen storage disease type IV	Vascular disorders
Disorders of bile acid metabolism, primary	Budd-Chiari syndrome
3β -Hydroxysteroid Δ^5 -C ₂₇ steroid dehydrogenase/isomerase	Perinatal asphyxia
Δ^5 -3-Oxosteroid 5β -reductase (multiple mutations)	Multiple hemangiomata
Disorders of bile acid metabolism, secondary	Cardiac insufficiency
Zellweger syndrome (cerebrohepatorenal syndrome)	Miscellaneous
Peroxisomal enzymopathies	Congenital disorders of glycosylation
Disorders of bile acid transport	Shock, hypoperfusion
Rotor syndrome	Intestinal obstruction
Dubin-Johnson syndrome	Neonatal lupus
	ARC syndrome (arthrogryposis, renal tubular dysfunction, and cholestasis)

may ameliorate the clinical course. The majority of infants with prolonged cholestasis will be found to fall into the diagnostic category of either biliary atresia or “neonatal hepatitis” (Table 49-3); the latter is a “default diagnosis.” As research progresses in pediatric liver disease, the number of cases falling into the “default” category are decreasing. However, at the present time, because of the preponderance of these disorders and the clinical importance of differentiating between them, this chapter focuses on neonatal hepatitis as we know it today; biliary atresia is covered elsewhere in this text. Other specific disorders associated with neonatal cholestasis are discussed in subsequent chapters.

IDIOPATHIC NEONATAL HEPATITIS VERSUS BILIARY ATRESIA

Extensive evaluation of the infant with cholestasis leads to a diagnosis of either idiopathic neonatal hepatitis or biliary

atresia in approximately 40% of infants (see Table 49-3). These terms are descriptive and imply a clinical phenotype rather than an etiology. The precise etiology and mechanism of injury in the majority of cases of neonatal hepatitis and biliary atresia remain obscure. The term “idiopathic obstructive or oblitative cholangiopathy” has been used to include disorders that manifest a range of pathology from predominantly hepatocellular injury to predominantly extrahepatic biliary tract injury.

Several overlapping hypotheses attempt to conceptually unify the pathogenesis of these disorders:

1. The ductal plate malformation theory, proposed initially by Jorgensen,⁴⁸ suggests that altered embryogenesis may be partially responsible for clinically apparent disorders of cholestasis in the neonate. During normal embryogenesis, the earliest form of the bile duct is a cylindrical ductal plate, which is remodeled through an

TABLE 49-3 ESTIMATED FREQUENCY OF VARIOUS CLINICAL FORMS OF NEONATAL CHOLESTASIS

CLINICAL FORM	CUMULATIVE PERCENTAGE
"Idiopathic" neonatal hepatitis	15
Extrahepatic biliary atresia	25–30
α_1 -Antitrypsin deficiency	7–10
Intrahepatic cholestasis syndromes (eg, Alagille, PFIC type 1)	20
Bacterial sepsis	2
Hepatitis	
Cytomegalovirus	3–5
Rubella, herpes	1
Endocrine (hypothyroidism, panhypopituitarism)	1
Galactosemia	1
Inborn errors of bile acid biosynthesis	2–5

PFIC = progressive familial intrahepatic cholestasis.

interaction between the ingrowing mesenchyme and disappearing ductal plate. Defective remodeling or incomplete dissolution, with failure of recanalization, has been postulated to lead to malformation of the ductal plate and subsequent anatomic abnormalities such as biliary atresia or cystic diseases of the hepatobiliary system. Desmet has suggested that ductal plate malformation is a basic morphologic lesion that occurs at different levels of the biliary tree and may be seen in a variety of disorders in addition to biliary atresia, including congenital hepatic fibrosis.¹

On a molecular level, it was recently proposed by Clotman and colleagues that intra- and extrahepatic biliary tract development is regulated in part by a cascade involving hepatocyte nuclear factor (HNF) 6 and HNF1 and that ductal plate malformations are visible in knockout models of these transcription factors.⁴⁹ Similarly, McCright and colleagues created a mouse model of Alagille syndrome, which suggests that Notch-Jagged interactions are necessary for normal intrahepatic biliary development.⁵⁰

2. Landing set forth the concept of infantile obstructive cholangiopathy, suggesting that these cholestatic disorders represent the pathophysiologic continuum of a single, underlying, obliterative process.⁵¹ According to this hypothesis, an initial insult leads to inflammation at various levels of the hepatobiliary tract. The clinical sequelae represent a static or a progressive inflammatory process at the specific site of injury. If the site of injury is predominantly the bile duct epithelium, the resulting cholangitis could lead to progressive sclerosis and obliteration of the bile duct, clinically manifest as biliary atresia. If, on the other hand, the inflammation is primarily hepatocellular, the clinical picture may be one of neonatal hepatitis. The interrelation between these two processes is further supported by evidence of intrahepatic ductal injury in patients with biliary atresia.^{52,53}

Although no specific virus has been consistently identified in patients with "obstructive cholangiopathies," there has been much interest in several

specific potential pathogens in these disorders. The majority of studies dealing with viral etiologies in these conditions are related to biliary atresia and thus are discussed in that section. Inborn errors of bile acid synthesis associated with the clinical picture of neonatal hepatitis have also been identified.^{6,54,55} As our understanding of immune dysregulation and autoimmunity evolves, it appears that in some cases, the primary insult directed against the hepatocyte or cholangiocyte may be (auto)immune,⁵⁶ not unlike diseases found in older subjects (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis). Immunohistochemical analysis of the "giant cell" reveals that these cells likely result from hepatocellular fusion. However, these observations have not shed light on the underlying insult or trigger for this idiosyncratic cellular response.⁵⁷ These studies and others support the contention that the neonatal liver is uniquely susceptible to injury, which, in turn, is manifest in a unique fashion. The initial stereotypic histologic reaction and perpetual injury in infantile obstructive cholangiopathy may result from a wide variety of insults at any level of the hepatobiliary system or beyond in another organ system.

Distinguishing between the intrahepatic, hepatocellular process of neonatal hepatitis and the extrahepatic or mixed injury in biliary atresia is achieved through cholangiography and biopsy and is discussed below.

IDIOPATHIC NEONATAL HEPATITIS

Idiopathic neonatal hepatitis represents the third most common diagnosis in infants with neonatal cholestasis, accounting for 15% overall.^{11,58,59} This relative percentage has steadily decreased since the initial description by Stokes and colleagues.⁶⁰ This shift is attributable to identification of specific disorders (such as α_1 -antitrypsin deficiency and bile acid transport and synthesis defects, which present with a clinical picture of neonatal hepatitis) that were previously included in this category. This diagnosis should be restricted to cases of prolonged neonatal cholestasis in which the classic histologic changes described by Craig and Landing⁶¹ are present on liver biopsy and known infectious or metabolic causes of neonatal hepatocellular disease have been excluded (see Table 49-2). Based on epidemiologic data, two categories of neonatal hepatitis have been proposed: sporadic and familial.¹¹ The increased incidence within certain families suggests that, at least in these cases, hereditary or metabolic factors are operant. In fact, recent studies have suggested that specific forms of intrahepatic cholestasis, previously included in the "idiopathic neonatal hepatitis" category, can be further subdivided based on the observed pathology and presumed pathophysiology (Table 49-4).¹¹ It is from this latter group that future discoveries related to the genetic and molecular basis of bile acid synthesis and transport are likely to be made. As research continues to make progress in these areas, the number of identifiable diseases will increase, and the category of idiopathic neonatal hepatitis will proportionately decrease.

TABLE 49-4 PROPOSED SUBTYPES OF INTRAHEPATIC CHOLESTASIS

Bile duct paucity
Syndromic (Alagille)
Nonsyndromic
Progressive (familial) intrahepatic cholestasis
Disorders of canalicular transport
Bile acid transport
Phospholipid transport
Disorders of bile acid biosynthesis
Undefined

CLINICAL PRESENTATION

“Idiopathic” neonatal hepatitis appears to be associated with low birth weight, but a cause and effect relationship is unclear. The clinical course is highly variable: more than 50% develop jaundice, to a varying degree, within the first week of life. In our experience, the majority appear well; however, as much as one-third have evidence of chronic disease, such as failure to thrive. Acholic stools are uncommon with this disorder but may be present if the cholestasis is severe. The liver (and occasionally the spleen) is firm and enlarged. Biochemical evaluation reveals bilirubin and aminotransferase levels, which are mildly to moderately elevated (2 to 10 times the upper limit of normal). Alkaline phosphatase and γ -glutamyl transpeptidase levels are variably increased (see below). Serum bile acid levels are markedly elevated. A bleeding diathesis, resulting from vitamin K deficiency and/or decreased synthesis of clotting factors, may be present in those with a more fulminant course. Other signs or associated abnormalities such as microcephaly, chorioretinitis, or vascular or skeletal anomalies are unusual and should suggest alternative diagnoses. However, if these signs are absent, the child appears well, and there is a clear history of perinatal distress, “transient” neonatal cholestasis is likely, and the child should be biopsied at the earliest worrisome sign (failure to thrive, acholic stools).

PATHOLOGY

Although several histologic features such as giant cell transformation and extramedullary hematopoiesis are nonspecific and represent a stereotypic response of the neonatal liver to injury, the biopsy can be helpful in excluding other causes of neonatal hepatitis. In biopsy tissue obtained early (ie, within the first 2 months of life), there is disarray of the lobular architecture with hepatocellular swelling (ballooning), focal hepatic necrosis, and multinucleated giant cells (more than four nuclei per cell), representing fusion of adjacent hepatocytes (Figure 49-1). Portal triads may be expanded with inflammatory infiltrate of lymphocytes, neutrophils, and occasional eosinophils. There is extramedullary hematopoiesis, as well as varying degrees of portal fibrosis. Although hepatocellular/canalicular bile stasis in the lobule may be prominent, bile duct proliferation and bile duct plugging in portal triads are usually absent. Interlobular bile ducts/ductules are few in number in certain cases, suggesting paucity. The severity of hepatocellular injury usually correlates with the degree of cholestasis.^{60,62}

MANAGEMENT

Neonatal hepatitis represents a heterogeneous disorder with no specifically delineated causative or perpetuating factors by definition. Management, therefore, is usually directed at nutritional support, vitamin supplementation, and general medical management of the clinical complications of cholestasis, such as pruritus. General medical management of chronic cholestasis is discussed in detail below.

PROGNOSIS

The overall prognosis in idiopathic neonatal hepatitis is difficult to estimate owing to the variability of the clinical course and the generally ill-defined pathogenesis. The factors that allow perpetuation of the cholestatic process and hepatocyte injury are not fully understood. No specific biochemical or histologic correlates with clinical outcome have been identified. A composite of several large series reviewing outcome of patients with idiopathic neonatal hepatitis is presented in Table 49-5.⁶³⁻⁶⁷ From these data, it is clear that sporadic cases (classic giant cell hepatitis) have a more favorable outcome than familial cases. The poor prognosis in a number of familial cases presumably relates to the presence of underlying inborn errors, specifically defects in bile acid metabolism or transport, as have been described in familial cases of clinically defined neonatal hepatitis (eg, progressive familial intrahepatic cholestasis).^{6,54,55} As the underlying causes and pathogenesis of neonatal hepatitis are further defined, more precise prognoses can be established. It is therefore paramount to follow these patients well beyond the normalization of their biochemical markers because neonatal cholestasis may be the harbinger of a metabolic or immune defect manifesting itself later in life. Repeating a liver biopsy for histology, electron microscopy, and metabolic studies (respiratory chain enzymes) is crucial for any child who does not follow a “normal” course, for example, by having a prolonged cholestasis (> 3.5 months), by developing other symptoms such as fasting hypoglycemia, or by presenting with a recurrence of cholestasis.

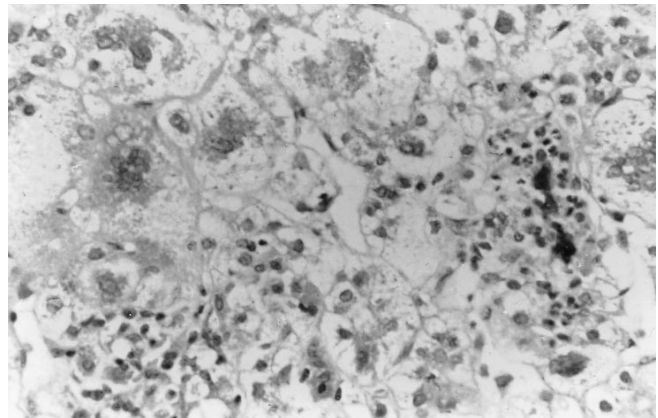


FIGURE 49-1 Liver histology in neonatal hepatitis. This biopsy specimen demonstrates disruption of hepatic lobular architecture with multinucleated giant cells. There are also inflammatory cells within the portal area (hematoxylin and eosin; $\times 400$ original magnification).

TABLE 49-5 STAGED EVALUATION OF NEONATAL CHOLESTASIS

Differentiate cholestasis from physiologic breast milk jaundice and determine severity of disease
Clinical evaluation (history, physical examination, stool color)
Fractionated serum bilirubin (+ serum bile acids)
Tests of hepatocellular and biliary disease (ALT, AST, alkaline phosphatase, GGT)
Tests of hepatic function (serum albumin, prothrombin time, blood glucose, ammonia)
Exclude treatable and other specific disorders
Bacterial cultures (blood, urine)
VDRL test and viral serology as indicated (think HSV)
α_1 -Antitrypsin phenotype
T ₄ and TSH (rule out hypothyroidism)
Metabolic screen: urine-reducing substances (drugs may cause false positives), urine bile acids, serum amino acids, ferritin, urine organic acids
Sweat chloride/mutation analysis
Differentiate extrahepatic biliary obstruction from intrahepatic disorders
Ultrasonography
Hepatobiliary scintigraphy (not always essential)
Liver biopsy

ALT = alanine transaminase; AST = aspartate transaminase; GGT = γ -glutamyl transpeptidase; HSV = herpes simplex virus; T₄ = thyroxine; TSH = thyroid stimulating hormone; VDRL = Venereal Disease Research Laboratory.

EVALUATION OF THE INFANT WITH CHOLESTASIS

Conjugated hyperbilirubinemia in the newborn period always requires further evaluation, which must be prompt and decisive. Fractionation of the bilirubin, which allows identification of patients with cholestatic (as opposed to physiologic or breast milk) jaundice, should be obtained in any infant with prolonged (ie, more than 14 days) hyperbilirubinemia. Cholestasis traditionally is defined as the presence of a conjugated (or direct-acting) fraction of more than 2 mg/dL (35 μ mol/L) or more than 20% of the total bilirubin¹¹; however, we prefer to seriously regard any elevation of conjugated bilirubin. Cost-effectiveness should be considered, and a staged approach should be taken in the evaluation of neonatal cholestasis (see Table 49-5). First, treatable disorders such as sepsis, galactosemia, endocrinopathies, and inborn errors of bile acid synthesis must be identified to initiate appropriate therapy that may prevent further damage to the liver and/or reverse the existing injury. Next, biliary obstruction must be differentiated promptly from intrahepatic cholestatic disorders because early surgical intervention is associated with a better prognosis. Finally, the clinical complications of cholestasis, including coagulopathy owing to hypoprothrombinemia or vitamin K deficiency and the nutritional consequences of fat malabsorption, must be addressed because therapy may improve the ultimate outcome and the general quality of life.

HISTORY AND PHYSICAL EXAMINATION

During the evaluation of the infant with cholestasis, the family history, prenatal and postnatal clinical course, and physical examination on presentation may provide impor-

tant clues. Irritability, poor feeding, and vomiting may indicate a generalized infection or a metabolic disorder such as galactosemia or tyrosinemia or suggest encephalopathy, which is particularly difficult to identify in this age group. Vertebral arch anomalies, posterior embryotoxon, and the murmur of peripheral pulmonic stenosis suggest the diagnosis of Alagille syndrome.⁶⁸ Hepatomegaly is the norm. Splenomegaly should lead to the consideration of a systemic disease, infectious or other. Dysmorphic signs suggest chromosomal abnormalities.

It is important to consider that many cholestatic infants appear well at the onset of their disease: normal weight gain and development do not preclude a condition as severe as biliary atresia. In fact, the hallmark of these children is that, initially, many appear to be prospering in spite of their cholestasis.

In differentiating biliary obstruction from intrahepatic cholestasis, the presence of persistently acholic stools is suggestive but not diagnostic of biliary atresia because they may also be associated with severe intrahepatic cholestatic disease. Conversely, the presence of pigmented stools suggests patency of the biliary system and generally excludes the diagnosis of biliary atresia. Alagille identified four clinical features that, although nonspecific, supported the correct diagnosis of intrahepatic or extrahepatic cholestasis in 82% of the cases.⁶⁹ These clinical variables included stool color within 10 days of admission, birth weight, age at onset of acholic stools, and the features of hepatic involvement, specifically the presence of hepatomegaly and consistency of the liver on palpation. In this study, addition of liver histology to the evaluation increased the diagnostic accuracy by only 3%. In other studies, despite the use of this scoring system, 10% could not be differentiated,⁷⁰⁻⁷² also suggesting that further evaluation is sometimes necessary.

Recently, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published the Neonatal Cholestasis Clinical Practice Guidelines; these are available on-line (<www.naspgn.org/sub/positionpapers.asp>). These guidelines represent the current practice in most tertiary centers in North America and are thought to be the most efficient and cost-effective way to approach the complex problem of neonatal cholestasis.

LABORATORY EVALUATION

There is no pathognomonic or prognostic biochemical feature of neonatal cholestasis. There is no single test consistently reliable in differentiating neonatal hepatitis from biliary atresia. It is not possible to predict either clinically or based on the result of a neonatal screen which infant will develop cholestasis. Nevertheless, several tests may help identify specific causes of cholestasis and assess and monitor the degree of hepatobiliary dysfunction.^{11,70} The laboratory data (see Table 49-5) must be analyzed in the context of the clinical setting. For example, urine-reducing substances may be falsely negative if the infant is not receiving a galactose-containing formula or is vomiting. In these situations, the diagnosis of galactosemia may be

made by measuring the red blood cell galactose-1-phosphate uridyl transferase activity, provided that the infant has received no recent blood transfusions. Elevated serum methionine and tyrosine levels, detected during a metabolic screen, may reflect severe liver disease but not necessarily be diagnostic of an underlying metabolic defect. The diagnosis of tyrosinemia should be confirmed by identification of specific metabolites (succinylacetone, succinylacetoacetate). A phenotype is preferred in the evaluation for α_1 -antitrypsin deficiency because neonates may have low levels of α_1 -antitrypsin despite normal phenotypes, and heterozygotes may have elevated levels in the presence of inflammation. The traditionally requested TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) titers have a low diagnostic yield and should be replaced by a request for specific viral titers or cultures only if there are suspicious features. For example, cytomegalovirus serologies should only be obtained based on maternal history and the clinical setting. It is sometimes difficult to obtain an adequate amount of sweat for a sweat chloride test in a neonate, but this test or more specific testing should be performed if the diagnosis of cystic fibrosis remains in question.

γ -Glutamyl transpeptidase, an enzyme located in the epithelial lining of the biliary tree and canaliculi, is elevated in most cholestatic disorders,⁷³ including biliary atresia, Alagille syndrome, α_1 -antitrypsin deficiency, and idiopathic neonatal hepatitis. Normal levels, however, are seen in progressive familial intrahepatic cholestasis and disorders of bile acid synthesis,^{74–76} where there is an abnormality of bile acid export into the canaliculus—hence, no bile acid-mediated injury of the canalicular membrane.⁷⁷

As recommended in the NASPGHAN consensus guidelines, part of the stepwise workup always involves assessment of synthetic function by obtaining coagulation studies and metabolic function by measuring glucose and ammonia in serum. Although not used routinely in all centers, quantification of serum bile acids can help orient the diagnosis in neonatal cholestasis syndromes. Elevated levels are found in most forms of cholestasis; low serum bile acid concentration in the face of persistently elevated conjugated bilirubin levels should suggest an inborn error of bile acid synthesis. Other third-line investigations are warranted according to the clinical context: transferrin immunoelectrophoresis should be considered when the constellation of signs is consistent with a congenital defect in glycosylation. Serum α -fetoprotein should be measured especially when considering tyrosinemia because of the associated risk of malignancy. This test can be diagnostic and serve as a baseline for subsequent follow-up. In the presence of splenomegaly, Niemann-Pick disease should always be considered and appropriately addressed by performing a bone marrow aspirate. Similarly, neurologic findings should raise the question of mitochondrialopathies and fatty acid oxidation defects. Finally, dysmorphic features, as always in pediatrics, should warrant evaluation. Unfortunately, at the present time, there is no reliable antenatal screening method for most of the conditions leading to neonatal cholestasis.

RADIOLOGIC EVALUATION

ULTRASONOGRAPHY

Real-time ultrasonography is an important adjunct in the diagnosis of neonatal cholestasis.⁷⁸ The study is most helpful in ascertaining the presence of a choledochal cyst, or, rarely, a tumor, which can have a clinical presentation similar to that of biliary atresia. The absence of a gallbladder on a fasting study is suggestive but not diagnostic of biliary atresia. Similarly, the presence of a gallbladder does not exclude this diagnosis. Dilated ducts are usually not present in biliary atresia, reflecting the fibro-obliterative or sclerotic nature of the coincident intrahepatic duct lesion.

In recent years, emphasis has been on trying to find a reliable, noninvasive method of diagnosing biliary atresia. The triangular cord sign, when performed by an experienced sonographer, is a potentially helpful diagnostic tool. In one small study, the characteristic cone-shaped finding cranial to the portal vein bifurcation demonstrated a positive predictive value of 100% when visualized together with an abnormal gallbladder and 88% when the gallbladder was normal.⁷⁹ The main disadvantage is that this ultrasonographic finding is operator dependent.

Recently, pediatric surgeons have also looked at the value of antenatal ultrasonography in the diagnosis and management of hepatobiliary lesions. Indeed, routine ultrasonography at 20 weeks gestation has led obstetricians and radiologists on occasion to find cystic lesions at the hepatic hilum.⁸⁰ Little is known about the natural history of these findings. As more experience is gained in imaging the hepatobiliary system antenatally, this tool may become part of the diagnostic algorithm of neonatal cholestasis.

Finally, a plain chest radiograph should be performed in investigating neonatal cholestasis to look for situs abnormalities, as well as butterfly vertebrae, or rickets, which may help orient the diagnosis.

RADIONUCLIDE IMAGING

Hepatobiliary scintigraphy, using technetium-labeled iminodiacetic acid analogs, may be used to differentiate biliary atresia from nonobstructive causes of cholestasis. The hepatic uptake and secretion into bile of these derivatives of iminodiacetic acid occur by a carrier-mediated organic anion pathway and depend on the structure of the specific analog, the integrity of hepatocellular function, and biliary tract patency.^{81,82} In patients with biliary atresia, particularly early in the disorder, parenchymal function is not compromised; therefore, uptake of the radioisotope is unimpaired, although subsequent excretion into the intestine is absent (Figure 49-2A). Conversely, uptake is usually delayed in infants with neonatal hepatitis owing to hepatocellular dysfunction, but eventually excretion into the bile and intestine occurs (Figure 49-2B). Pretreatment with oral phenobarbital (5 mg/kg/d for 5 days) enhances biliary excretion of the isotope and can increase sensitivity to 94%.^{81,82} There are limitations to this study, however; therefore, the diagnosis should not be made solely on the results of this test. Nonexcretion may be related to severe

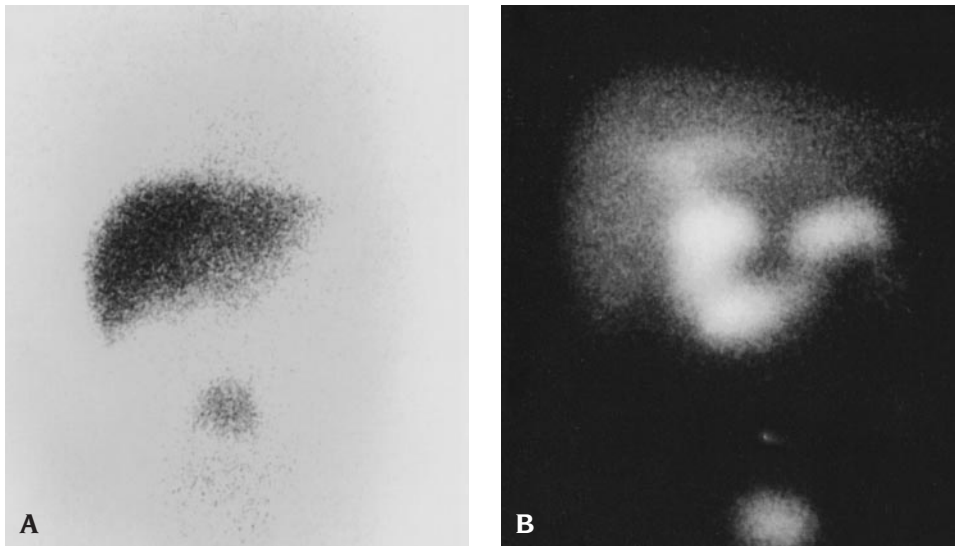


FIGURE 49-2 A, Radioisotope scan in biliary atresia. On a delayed scan, there is good uptake of the isotope by the liver, but there is no evidence of intestinal excretion. B, Radioisotope scan in neonatal hepatitis. Uptake of the isotope by the liver is delayed and decreased; however, excretion into the intestine is noted.

intrahepatic cholestasis rather than extrahepatic obstruction. In a retrospective study, 12 of 21 infants with intrahepatic causes of cholestasis had no excretion in their first study, despite the use of phenobarbital.⁸³ In our experience, one patient with isotopic demonstration of a “patent” biliary system was subsequently diagnosed with biliary atresia. In addition, the 5 days required for phenobarbital administration to optimize diagnostic yield may ultimately affect outcome by delaying surgical intervention. Whereas the passage of the tracer into the gastrointestinal tract is 100% sensitive in excluding biliary atresia, a nonexcreting result is only 60% specific for biliary atresia. This poor specificity, together with the time required to prepare for the study, is progressively excluding hepatobiliary scanning from the diagnostic algorithm.⁷⁷

Although there has been much hope that magnetic resonance imaging would provide a means of exploring the biliary tract, there is no evidence at present to suggest that this method is of benefit in the diagnostic armamentarium when studying small infants.⁸⁴ Other radiographic studies, such as percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography, are not only difficult to perform, but experience has been limited in these infants.^{85–87}

LIVER BIOPSY

In our experience, the liver biopsy remains the most reliable and definitive procedure in the evaluation of the neonate with persistent conjugated hyperbilirubinemia. Tissue may be obtained, in most cases, using a percutaneous technique with local anesthesia.^{11,70,88,89} Careful interpretation by an experienced pathologist yields the correct diagnosis in 90 to 95% of cases. Prompt diagnosis may expedite surgery for biliary atresia and preclude unnecessary surgical exploration. The typical findings in neonatal hepatitis are discussed above. Like the biochemical evaluation, the biopsy needs to be interpreted in the clinical context because the histology of neonatal hepatitis is nonspecific: giant cell transformation and hepatocyte ballooning with lobular disarray represent a nonspecific

response of the newborn liver to an insult. Many of the characteristic histologic findings stem from observational studies in term infants in their first few months of life. Less is known about the histology of the early course of some neonatal cholestasis syndromes or of preterm infants with cholestasis. These conditions are evolving processes, and more information may be gained by performing a repeat biopsy to look for more characteristic findings and to appreciate the evolution.

CONCLUSIONS REGARDING EVALUATION

In evaluating a neonate with cholestasis, both surgical and medical emergencies have to be excluded and attended to in a timely fashion. If galactosemia is suspected, appropriate dietary measures should be taken immediately. If sepsis is the likely cause of the cholestasis, this must be managed urgently. If biliary atresia is suggested, an exploratory laparotomy, often with an intraoperative cholangiogram, is performed to verify the nature and site of the obstruction prior to hepatopertoenterostomy. Finally, if no specific etiology is determined but extrahepatic obstruction is unlikely, the infant is followed and re-evaluated frequently. Empiric therapy may also be instituted to optimize growth and development and ameliorate the consequences of chronic cholestasis (discussed below).

The need to correctly differentiate biliary atresia from intrahepatic disorders is illustrated by a report from Markowitz and colleagues in which four patients who underwent hepatopertoenterostomies on the basis of hepatobiliary scans and intraoperative cholangiograms were subsequently found to have Alagille syndrome on histologic and clinical criteria.⁹⁰ None had adequate drainage postoperatively, two progressed to cirrhosis, and one died from hepatic failure, indicating that the intervening surgery had adversely altered the course of a usually benign disorder. If careful consideration is given to the history, physical examination, and these selected diagnostic tests (see Table 49-5), institution of appropriate surgery may be expedited, unnecessary surgery avoided, and, in many cases, the precise etiology determined.

MEDICAL MANAGEMENT OF CHRONIC CHOLESTASIS

In infants with intrahepatic cholestasis or those with biliary atresia in whom surgical attempts at establishing adequate biliary drainage are unsuccessful, the presence of the clinical consequences of persistent cholestasis directs medical therapy. These complications are related, either directly or indirectly, to diminished bile flow and reflect (1) retention of substances dependent on bile secretion, such as bile acids, bilirubin, and cholesterol; (2) decreased bile acid delivery to the intestine with resultant fat and fat-soluble vitamin malabsorption; and (3) progressive hepatocellular damage leading to portal hypertension and eventual liver failure (Figure 49-3). Currently, no specific therapy either reverses existing cholestasis or prevents ongoing damage; therefore, therapy is empiric and aimed at improving nutritional status, maximizing growth potential, and minimizing discomfort.⁹¹ The success of this therapeutic intervention is limited by the residual capacity of the liver and by the rate of progression of the underlying disorder. The success is enhanced by introducing these measures in a timely fashion, namely as soon as abnormal weight gain is anticipated.

PRURITUS

Significant clinical morbidity may result from pruritus, and its management is a difficult and sometimes frustrating clinical problem. In some patients, the impairment in quality of life is so severe that liver transplant is indicated. The cause of cholestatic pruritus is not clear.^{92,93} It has been reported that skin and serum levels of bile acids did not differentiate between patients with or without pruritus,⁹³ arguing against bile acids as direct pruritogens. Endoge-

nous opioids have been implicated as mediators of pruritus, specifically cholestasis-induced pruritus.⁹⁴ Similarly, the serotonin neurotransmitter system has also been identified as one potential factor.⁹⁵ With these recent findings, new approaches to the management of cholestasis-induced pruritus are emerging.

Therapy directed at decreasing the concentrations of bile acids may be efficacious in some patients because of the nonspecific action of these agents. The anion exchange resin cholestyramine has been used historically to interrupt enterohepatic circulation. Because its use entails a complicated regimen, it is seldom used in pediatrics.

Phenobarbital, in therapeutic doses of 5 to 10 mg/kg/d, stimulates bile acid-independent flow and decreases the bile acid pool size.⁹⁶ The drug has not been consistently efficacious in relieving pruritus in intrahepatic cholestasis. The sedative side effects of phenobarbital may be a limiting factor in its usefulness. As a rule, its use in cholestasis is becoming more infrequent. The use of rifampin (10 mg/kg/d), which inhibits hepatic uptake of bile acids, has also been tried with variable success in relieving pruritus.^{97,98} Like phenobarbital, it is a microsomal enzyme inducer, with the advantage of not having a sedative effect. Related side effects are minimal, but worsening biochemical liver markers can be suggestive of rifampin-induced hepatitis.⁹⁹

Ursodeoxycholic acid (UDCA), which alters bile acid composition, has been shown to be beneficial in the relief of pruritus in studies of adults with primary biliary cirrhosis.¹⁰⁰ Preliminary studies, using 15 to 30 mg/kg/d, suggest that it may be of benefit in ameliorating pruritus in childhood cholestasis as well.^{101,102} In our center, UDCA is routinely prescribed to all children with cholestasis for its potential cytoprotective effect on hepatocytes, as well as its

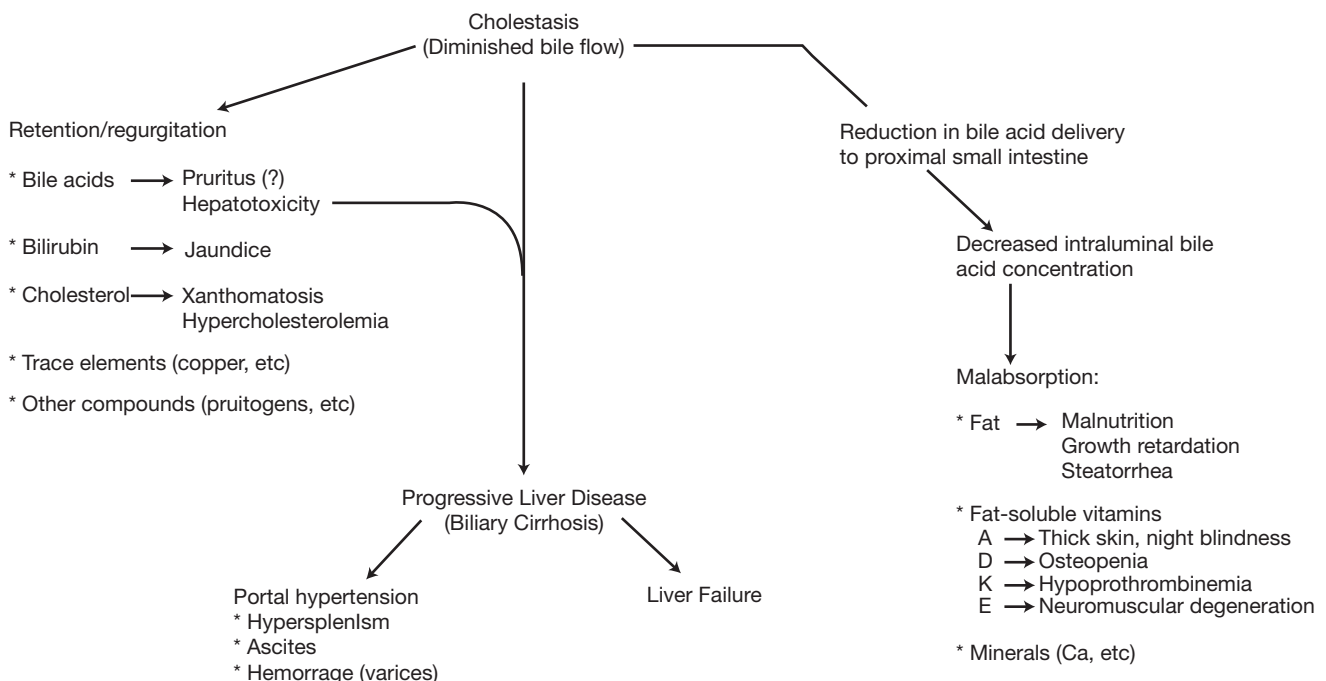


FIGURE 49-3 Clinical sequelae of chronic cholestasis. Numerous consequences of cholestasis become clinically manifest and result from retention of substances excreted in bile, reduction of intestinal bile acids, and progressive damage to the liver. See text for relationship between bile acids and pruritus.

role in relieving pruritus. The current trend is toward the higher dose of 30 mg/kg/d, although there is no documented evidence that the effect is dose dependent.

As mentioned above, interest in the role of the opiate receptor system in pruritus of cholestasis was prompted by the results of studies in which opioid antagonists relieved pruritus.^{98,102} The presumed mechanism of action is that they prevent the binding of endogenous opioid agonists, which have been shown to be elevated in cholestasis. The three known opioid antagonists (naloxone, nalmefene, and naltrexone) have been studied and have demonstrated an alleviating effect, although none have completely abolished pruritus. There are problems associated with the use of opioid antagonists: they precipitate a withdrawal-like effect, and a “breakthrough” phenomenon has been described, which consists in an exacerbation of the pruritic symptoms after an initial improvement. Thus, determining the appropriate dose and management can be difficult, and consultation with anesthesia may be appropriate.⁹⁹ As mentioned earlier, there have been some studies implicating serotonin in the pathophysiology of pruritus. As such, the use of ondansetron in the relief of pruritus has been studied with some promising results, but more studies are required to confirm these findings.⁹⁹

For those children with intrahepatic cholestasis and intractable pruritus unresponsive to therapy, partial external biliary diversion has been performed.¹⁰³ Patients with progressive intrahepatic cholestasis had a good response, with relief from itching and concomitant improvement in their biochemical tests of liver function and histology. In a retrospective review performed at our center, patients and parents reported a marked improvement in quality of life, as defined by school attendance and interactions with peers.¹⁰⁴ Finally, there have been anecdotal reports on the efficacy of a variety of other therapies, including phototherapy and plasmapheresis.

MALABSORPTION AND MALNUTRITION

Lipids. One of the major and more immediate complications of chronic cholestasis is fat malabsorption related to decreased intraluminal bile acids, which leads to malnutrition and fat-soluble vitamin deficiency. Decreased excretion of bile acids leads to a low intraluminal micellar concentration; therefore, long-chain triglyceride lipolysis and absorption are ineffective. Medium-chain triglycerides (MCTs) are more water soluble than their long-chain counterparts and are therefore readily absorbed by the gastric and intestinal mucosa in the face of low intraluminal concentrations of bile acids, making them a more adapted source of fat calories; MCTs can best be administered as MCT-containing formulas. MCT oil alone is insufficient because it does not contain essential fatty acids. In those children who are unable to take in sufficient calories orally, nocturnal enteral feeding has been shown to improve nutritional indices in many patients with chronic liver disease.¹⁰⁵

Liposoluble Vitamins. Intestinal absorption of fat-soluble vitamins (A, D, E, and K) that require solubiliza-

tion by bile acids into mixed micelles is also compromised, and supplementation of at least two to four times the recommended daily allowance is often necessary (Table 49-6). Serum vitamin levels and laboratory tests such as serum calcium and phosphate levels and prothrombin time are useful indices of adequate supplementation. Chronic vitamin E (α -tocopherol) deficiency has been associated with a progressive neuromuscular syndrome characterized by areflexia, cerebellar ataxia, posterior column dysfunction, and peripheral neuropathy.^{106,107} The most reliable index of vitamin E status is the ratio of serum vitamin E (mg/dL) to total serum lipids (g/dL) because elevated lipids, as seen in chronic cholestasis, allow vitamin E to partition into the nonpolar phase (plasma lipoprotein fraction), artificially raising the serum vitamin E concentration. In infants and children less than 12 years of age, a ratio of less than 0.6 mg/g indicates vitamin E deficiency.¹⁰⁸ In those children who do not respond to supplementation of vitamin E by traditional methods, oral administration of a water-soluble form of vitamin E, *d*- α -tocopherol polyethylene glycol 1000 succinate (TPGS), has been found to correct biochemical vitamin E deficiency in doses of 15 to 25 IU/kg/d.¹⁰⁹ In truly refractory cases, an admixture of all fat-soluble vitamins with TPGS may be more beneficial than administration of the supplement alone.¹¹⁰ Although there are no data to support its use in neonatal cholestasis, vitamin E is part of the antioxidant armamentarium prescribed in many forms of acute and chronic liver disease.¹¹¹ Careful consideration should be given to fat-soluble vitamin replacement in the nutritional management of these patients because intracranial bleeding from vitamin K deficiency is still a frequent cause of death in infants and toddlers with cholestasis.

Carbohydrates. In animal models of biliary atresia, as much as a 20 to 30% decrease in brush border enzyme activity has been observed. Thus, although there is no published evidence to this effect in human subjects, one should consider changing the carbohydrate composition of the formula if the infant is demonstrating signs consistent with lactose intolerance. This is particularly important because the infant with cholestasis requires as much as 130% of the caloric intake of age-matched controls (as much as 150 kcal/kg/d), 60% of which should be in carbohydrate form.

TABLE 49-6 RECOMMENDED ORAL VITAMIN SUPPLEMENTATION

VITAMIN	PREPARATION, DOSE
Fat soluble	
Vitamin A	Aquasol A: 3,000–25,000 IU/d
Vitamin D	Cholecalciferol: 500–5,000 IU/d or 25-Hydroxycholecalciferol: 3–5 μ g/kg/d
Vitamin K	Phytonadione (K1): 2.5–5 mg every other day
Vitamin E	Aquasol E: 50–400 IU/d or TPGS 15–25 IU/kg/d
Water soluble	Twice the recommended daily allowance

TPGS = *d*- α -tocopherol polyethylene glycol 1000 succinate.

Protein. Infants with cholestasis require a normal proportion (20–30%) of their diet in protein form. However, unless malnutrition is so severe, there is no evidence to suggest that protein hydrolysates are necessary. One study in a rat model suggested that adding branched-chain amino acids to the formula may impact growth and nitrogen retention favorably.¹¹² There is no such evidence in human subjects.

Other Vitamins and Nutrients.

1. **Calcium.** In spite of aggressive liposoluble enteral or parenteral vitamin replacement, most children with cholestasis suffer from severe osteopenia, often leading to pathologic fractures.^{113,114} Thus, both additional calcium and magnesium¹¹⁵ supplementation is advisable, ensuring that the child or infant receives at least 1,000 to 1,300 mg/d of calcium and 8 to 16 mg/kg/d of elemental magnesium. The time at which the supplement is taken is critical because it has been suggested that UDCA may affect calcium absorption negatively. Finally, monitoring a patient's calcium-phosphorus status using urinary indices and parathyroid hormone may be indicated because serum levels may not always be accurate because of acid-base abnormalities or hypoalbuminemia.
2. **Zinc.** Because of increased intestinal losses and fat malabsorption, zinc deficiency is more prevalent in cholestasis than is commonly thought. Because zinc is a common cofactor in numerous enzymatic reactions, including in the liver, zinc deficiency may further exacerbate the underlying liver disease.
3. **Iron.** Iron deficiency is common in these children. Early on, this may be due to insufficient dietary intake. As the course of the disease progresses, however, this is more often the sign of occult, or overt, gastrointestinal bleeding.

PORTAL HYPERTENSION

In most patients with biliary atresia, and in certain patients with intrahepatic cholestasis, progressive fibrosis and cirrhosis ultimately lead to the development of portal hypertension, the most clinically significant sequelae being ascites and variceal hemorrhage. The medical management of ascites should be dictated by patient comfort and by the relative risk of peritoneal bacterial infection. The judicious use of sodium restriction and diuretics may be helpful in controlling the accumulation of ascites. Initial steps include restricting dietary sodium intake to 1 to 2 mEq/kg/d and introducing a diuretic such as spironolactone, which inhibits the effects of aldosterone. We usually start with 3 to 5 mg/kg/d divided into 3 to 4 doses and increase the dose as needed up to 10 to 12 mg/kg/d to maintain an increased urinary sodium-to-potassium ratio. Refractory ascites with respiratory compromise may be managed by therapeutic paracentesis with concomitant administration of an intravenous colloid such as albumin.¹¹ Albumin has been shown in adult studies to play a role in the preservation of renal function in large-volume paracentesis and to have a protective effect against the risk of spontaneous bacterial peritonitis.¹¹⁶ Used together with furosemide, it participates in the elimination of free water and sodium while avoiding the prompt recurrence of ascites.¹¹⁶

Esophageal and gastric varices are a potentially life-threatening complication of portal hypertension. Acute variceal hemorrhage is managed in an intensive care unit with intravenous fluids and blood products, gastric lavage, and intravenous vasopressin infusion (0.3 U/1.73 m²/min) as indicated. Balloon tamponade, used for severe or prolonged hemorrhage, may be associated with significant complications such as esophageal rupture, airway obstruction, and pulmonary aspiration. Endoscopic sclerotherapy is being used more extensively in infants and children for the acute and ongoing management of esophageal varices and may be superior to surgical alternatives,¹¹⁷ particularly if eventual liver transplant is anticipated. Although not available for the infant population, banding is also used routinely in older children. However, to date, there is no literature to suggest that prophylactic banding or sclerotherapy is preferable to managing varices on an ad hoc basis following a bleed. This topic is covered in greater depth in Chapter 59, "Treatment of End-Stage Liver Disease." Gastric varices are not amenable to this therapy. There has also been interest in long-term administration of β -blocking agents such as propranolol to reduce portal pressure and prevent recurrent variceal bleeding in adults,^{102,103} but the results have been variable, and there is limited experience in children. Furthermore, β -blockade may impede appropriate cardiovascular compensation in the event of an acute bleed and is therefore not used routinely in infants. In refractory hemorrhage, pediatric patients may be stabilized using intravenous octreotide, starting at 1 μ g/kg/(min) and increasing as needed. Patients should be closely monitored for hyperglycemic side effects. The use of octreotide can be a convenient tool while the patient awaits emergent liver transplant.

Orthotopic liver transplant has become a viable option for infants and children who progress to end-stage liver disease.^{118,119} The ability to determine the optimum time in the clinical course to pursue transplant requires careful monitoring and sequential evaluation of hepatic function. Although no one specific functional measure has been shown to reliably assess hepatocellular reserve, prognostic scores have been developed for predicting outcome without transplant. These scores may be compared with operative survival statistics for a particular patient group and thus aid in decision-making. In infants and children with end-stage liver disease, the deciding factor in timing organ transplant is usually organ availability. Therefore, it is important to carry out evaluation early in the course to develop supportive strategies and to stratify based on clinical criteria.

The major limiting factor for successful transplant in infants has been the supply of appropriately sized organs. This situation has been somewhat alleviated by introduction of the techniques of segmental or volume reduction liver transplant, living donor transplant, and "split" organ donation.¹²⁰ More effective means for supporting and monitoring infants with chronic liver disease are needed. Ultimately, a better understanding of the pathophysiology of specific underlying disease processes may

lead to more efficacious treatment of the sequelae of persistent infantile cholestasis and to therapeutic interventions that will prevent or reverse the development of chronic liver disease.

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