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Prolonged jaundice in the preterm infant—What to do, when and why

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Summary
Prolonged jaundice in premature infants (born at <37 weeks gestation) is a frequent clinical problem. The delay in physiological adaptation following premature birth, together with the promotion of breast milk feeds among neonatal units, increases the age at which non-pathological jaundice subsides compared with infants born at term. Sick premature infants can develop cholestasis because of a combination of factors including parenteral nutrition, delayed enteral nutrition, sepsis, the use of umbilical lines and episodes of hypoxia. This pathological jaundice can become apparent within the first few weeks of life. In addition, premature infants are at risk of developing serious liver disease, including extrahepatic biliary atresia, and their diagnosis and management should not be unnecessarily delayed. The paediatrician needs to be aware that premature infants can present with signs of liver disease at any age after birth, from the first week to well beyond the neonatal period.

Practice points

- Liver disease in preterm infants responds to supportive nutritional management. Morbidity and mortality can be reduced by anticipating accompanying problems such as coagulopathy and treating with generous doses of vitamins A, D, E and K
- Many conditions causing cholestasis in preterm infants require specific treatments and interventions, and the outcome can be improved with early diagnosis
- It is important that clinicians actively look for cholestasis in their infants and request a prolonged jaundice screen in any preterm infant who remains jaundiced at 21 days
- The investigation pathway presented will allow a timely referral for infants with severe liver disease while allowing the majority of preterm infants to remain within the care of the neonatal team until they are ready to progress into the big outside world

Research agenda

- To determine the incidence of cholestasis and liver disease in preterm infants

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- To understand how rapidly EHBA progresses after preterm birth in order to make tailored recommendations for timing surgery for this group of small infants
- To revalidate the investigation pathway proposed prospectively

Introduction

Prolonged jaundice in preterm infants, born at less than 37 completed weeks of gestation, is defined as jaundice lasting longer than 21 days. For term infants, prolonged jaundice is defined after 14 days. There are important reasons for this distinction (Table 1). Infants born prematurely have a higher bilirubin load entering the hepatocyte because of reduced erythrocyte survival, increased erythrocyte volume and increased enterohepatic circulation.[1] In addition, the hepatocyte of the preterm infant is less efficient at bilirubin uptake and conjugation, and bile production.[2,3] The delay in the commencement of milk feeds and the attainment of full enteral nutrition may limit intestinal contractility and bacterial colonisation, leading to an increased availability of intestinal bilirubin for uptake by the enterohepatic circulation. Infants receiving either maternal or bank breast milk during the first few weeks of feeding are four times more likely to achieve bilirubin values above 200 μmol/l than those being fed an artificial formula.[4] The promotion of breast milk feeds is widespread within neonatal units, is well accepted by anxious mothers and has numerous advantages in this group.[5]

Prolonged jaundice and liver disease

Prolonged jaundice in any infant can be caused by breast milk jaundice, liver disease or other underlying disorders causing cholestasis. It is important to recognise conditions that require specific treatment as soon as possible (Table 2). There are many other causes listed elsewhere.[3]

There has been a widely held belief among neonatal units that preterm infants do not develop significant liver disease and that conjugated hyperbilirubinaemia occurs secondary to a temporary cholestatic process that does not warrant extensive investigation.[6] A study in a supraregional liver unit looking at a selected group of preterm infants presenting with conjugated hyperbilirubinaemia documented the range of liver diseases found in these infants by using an investigation protocol developed for term infants.[7] These results are summarised in Table 3.

It is apparent that significant liver disease, including extrahepatic biliary atresia (EHBA) and other biliary tract disorders, does occur in preterm infants and that diagnostic delay may occur. This study highlighted both the importance of a structured approach to the investigation of prolonged jaundice and the fact that this approach should be specifically modified for the preterm infant. Other recent studies have even suggested that prematurity is a risk factor for EHBA.[8,9] The Yellow Alert campaign in the UK in 1993 raised general awareness that a delayed diagnosis of EHBA led to late surgery and a poorer outcome. Surgery for EHBA is recommended before 60 days for term infants. The optimal age for biliary atresia in preterm infants is unknown, but they should not be further disadvantaged by unnecessary delay. Data from these studies will be discussed in the subsequent sections.

Table 1 Reasons why physiological adaptation of bilirubin production and metabolism is delayed in preterm infants compared with term infants.

Higher bilirubin load	Erythrocyte survival time shorter Erythrocyte volume increased Enterohepatic circulation increased
Reduced excretion	Uptake of bilirubin by hepatocytes less efficient Conjugation of bilirubin reduced Bile flow slower

Table 2 Conditions causing prolonged jaundice in newborns that require a specific treatment approach and therefore benefit from early diagnosis.

Bile duct abnormalities	Extrahepatic biliary atresia Choledochal cyst Inspissated bile, gallstones Biliary stricture from total parenteral nutrition, Bile duct perforation
Metabolic disorders	Galactosaemia, tyrosinaemia type 1 Cystic fibrosis, α-1-antitrypsin deficiency Bile acid synthetic disorders
Infection	Urinary tract infection, septicaemia Toxoplasmosis, cytomegalovirus Varicella-zoster, human immunodeficiency virus, hepatitis B
Endocrine	Hypopituitarism Hypothyroidism, hypoadrenalism
Toxins/injury	Parenteral nutrition cholestasis Drugs, e.g. chloral hydrate Haemochromatosis Perinatal hypoxia Multifactorial preterm cholestasis
Vascular	Hepatic haemangiomata

Biliary tract disorders in preterm infants

The most common diagnosis amongst the 15 infants with biliary tract disease was EHBA ($n = 6$). The median

Table 3 Liver disease diagnosed in preterm infants at a supraregional liver unit 1990–2001.

	Gestational age group in completed weeks (*n* (%))			
	<27 *n* = 6	27–29 *n* = 12	30–34 *n* = 45	35–36 *n* = 31
Biliary tract disorders				
Extrahepatic biliary atresia			5 (11)	1 (3)
Bile duct stricture	2 (33)			
Choledochal cyst			1 (2)	1 (3)
Alagille syndrome		1 (8)	1 (2)	1 (3)
Bile duct paucity				1 (3)
Neonatal hepatitis				
Isolated	1 (17)	5 (42)	15 (33)	12 (39)
+ total parenteral nutrition changes	1 (17)		1 (2)	
+ hydrops fetalis				2 (6)
+ haemangiomata			1 (2)	
+ maternal lupus			1 (2)	1 (3)
+ maternal diabetes			1 (2)	
+ trisomy 21				1 (3)
Infection				
Cytomegalovirus		2 (17)	2 (4)	1 (3)
Toxoplasmosis				1 (3)
Sepsis			1 (2)	
Metabolic				
α-1-antitrypsin deficiency			2 (4)	1 (3)
Cystic fibrosis			2 (4)	
Galactosaemia			1 (2)	
Dubin–Johnson syndrome				1 (3)
Bile acid disorder			1 (2)	
Haemochromatosis				1 (3)
Endocrine				
Hypopituitarism				1 (3)
Hypothyroidism				1 (3)
Toxins/injury				
Parenteral nutrition	2 (33)	2 (17)	2 (4)	1 (3)
Multifactorial preterm	1 (8)	2 (4)	2 (6)	
Haemolytic disease			3 (7)	1 (3)
Hypoxia			2 (4)	

gestational age was 33 (range 31–36) weeks, and three infants weighed less than 2 kg at birth. These presented with cholestasis and had uniformly elevated γ-glutamyl transferase levels and pale or acholic stools where this was noted. Abdominal ultrasound examination was informative, showing small or absent gallbladders when fasting, or abnormal hepatic echogenicity.

Two further infants required surgery for choledochal cyst. These cysts were easily diagnosed by abdominal ultrasound, and other investigations were rarely necessary.

Four infants had bile duct paucity, three of whom had Alagille syndrome. Alagille syndrome is an autosomal dominant disorder with a variable penetrance and an incidence of 1 in 100 000, and 50% of cases are new mutations. The five major features are chronic cholestasis, characteristic facies (a broad forehead and small chin), vertebral anomalies (butterfly vertebrae, curved phalanges, short ulna), cardiac anomalies (peripheral pulmonary artery stenosis, pulmonary valve stenosis, Fallot's tetralogy, aortic stenosis, ventricular septal defects), and ocular abnormalities (posterior embryotoxin, optic nerve drusen).[10]

Idiopathic/associated neonatal hepatitis

In the great majority of preterm infants in the study who had a liver biopsy, the histological diagnosis was idiopathic neonatal hepatitis. These infants very rarely had acholic stools, and the gallbladder was usually present on fasting ultrasound, although sometimes small. In most instances, there were other possible contributory associations (Table 3). The majority of these infants were growth

restricted at birth (birthweight $<$10th centile) and male. This pattern is in keeping with that of term infants in other studies.[3] Cholestasis had resolved in the majority by 1 year of age, and only one infant had persistently abnormal liver function after 3 years of age.

Given the excellent outcome for these infants from the hepatic point of view, we questioned the need for liver biopsy. We would now consider most of these infants to have multifactorial cholestasis of prematurity and have adapted our investigative protocol specifically for the preterm infant. There is currently a much higher threshold for undertaking liver biopsy in this group.

Multifactorial cholestasis

This category reflects the reality of the setting in which cholestasis develops in the preterm infant. Contributory factors include hepatic immaturity, abnormal bile acid metabolism, interrupted enteral nutrition, possible surgical procedures, sepsis, parenteral nutrition (PN) and multiple drug treatment. This category has recently become more widespread given the change in approach to invasive investigations in this group, especially those without acholic stools or an abnormal hepatic ultrasound. The degree of cholestasis, γ-glutamyl transferase level, stool colour, hepatic ultrasound changes and outcome are very similar to those of infants previously labelled as having idiopathic neonatal hepatitis, and these are likely to be the same hepatic disorder.

Parenteral nutrition cholestasis

Eleven infants had changes in which PN-induced toxicity was the dominant lesion. Seven had classical PN-related liver biopsy changes in isolation, two others also having neonatal hepatitis. Within this group, two infants born at less than 27 weeks' gestation had late presentations from biliary strictures thought to be induced by a prolonged use of PN. The vast majority of infants born at less than 27 weeks' gestation had some degree of PN-related cholestasis.

Haemolytic disease of the newborn

The cholestasis in these infants is often biliary sludge secondary to the increased demand on the biliary system from haemolysis and bilirubin production. These infants may respond to ursodeoxycholic acid (see below), particularly if abdominal ultrasound shows sludge or bile duct dilatation upstream. For the same reasons, gallstones can form. Other contributory features in this group include the use of umbilical venous catheters for exchange transfusion.

Screening tests for prolonged jaundice

The majority of preterm infants with prolonged jaundice have delayed physiological adaptation or breast milk jaundice. The recommended investigations attempt to limit the invasive testing of preterm infants while ensuring that cholestasis and readily treatable conditions are detected early (Table 4).

Table 4 Initial investigations for preterm infants with prolonged jaundice lasting for more than 21 days.

Total and conjugated serum bilirubin
Liver function tests including aspartate transaminase, alanine transferase and γ-glutamyl transferase
Thyroxine and thyroid-stimulating hormone
Galactosaemia screen
Urine for microscopy, culture and sensitivity
Stool specimen in an opaque pot for an experienced observer

Preterm infants with conjugated hyperbilirubinaemia

Conjugated hyperbilirubinaemia is defined when the level of total conjugated bilirubin is above18 μmol/l or over 20% of the total bilirubin.[11] Preterm infants with this biochemical finding should be examined for signs of liver disease including hepatomegaly, splenomegaly, bruising, bleeding, dark urine and pale stools. Clinical findings of facial dysmorphism, congenital heart disease or cutaneous haemangiomata may also be identified and can assist in diagnosis. A chest X-ray can demonstrate the butterfly vertebrae seen in Alagille syndrome, and ophthalmological examination can be supportive.

Conjugated hyperbilirubinaemia (cholestasis) can present at any time after birth and long before the 21-day definition of prolonged jaundice. If there is any clinical or biochemical suspicion of cholestasis, the clinician should investigate as detailed.

Initial investigations for conjugated hyperbilirubinaemia

All infants require the following initial investigations in order to identify any serious consequences of cholestasis, such as coagulopathy, and to diagnose common conditions non-invasively that would benefit from early nutritional support or readily available specific intervention:

- coagulation;
- liver function tests;
- documentation of stool colour;
- hepatic ultrasound;
- a galactosaemia screen if not performed for prolonged jaundice;
- a tyrosinaemia screen;
- α-1-antitrypsin level *and* phenotype;
- thyroxine and thyroid-stimulating hormone if not performed for prolonged jaundice;
- cortisol;
- serum immunoreactive trypsin;
- a TORCH and hepatitis screen.

There should also be liaison with the local liver/gastroenterology unit team.

Investigation pathway for preterm infants with conjugated hyperbilirubinaemia

In the study detailed above, the standard aggressive protocol used for term infants was inappropriate for preterm infants owing to a number of factors, including insufficient blood volume, poor temperature control when attending for isotope scan and limited size for liver biopsy.[7] In addition, the preterm infants were referred and assessed at much greater ages than their term counterparts. Many of them had complications of prematurity requiring periods of respiratory and cardiovascular support. It was appropriate that these infants were allowed to stabilise and grow before they were transferred long distances to a liver unit for further investigation. It also became apparent that many infants would be too small for surgery, and a pragmatic agreement was reached that, in general, infants should weight over 2–2.5 kg before being considered for surgery for suspected biliary atresia. For these reasons, the investigation protocol was modified.[3] More recently, preterm infants have been managed without an early isotope scan because of the difficulties associated with transport to distant sites for the investigation and the increased recognition of the limitations of isotope scanning.

An appropriate investigation pathway for preterm infants with a conjugated hyperbilirubinaemia is shown in Fig. 1.

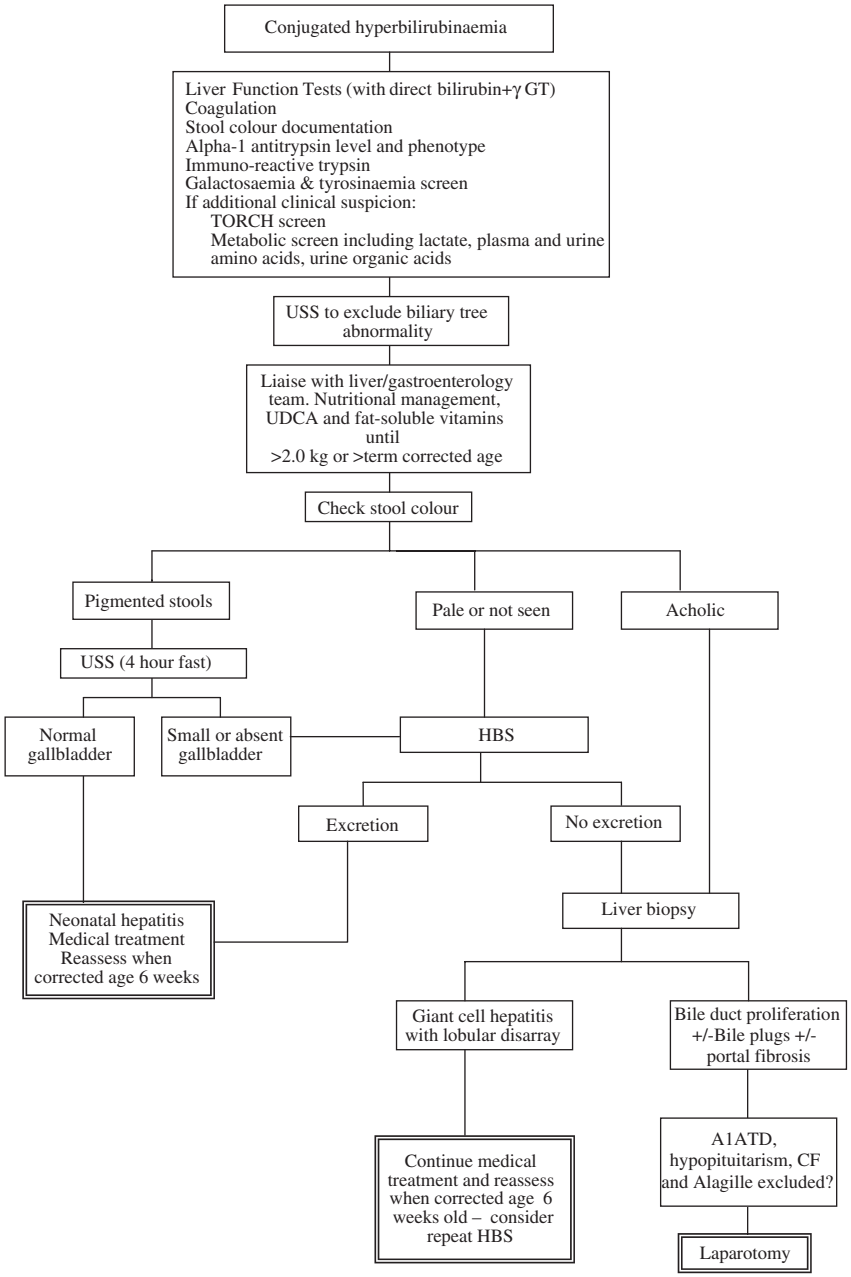

Figure 1 Flow chart for the investigation of the neonatal cholestasis in preterm infants. (Abbreviations. T4, thyroxine; TSH, thyroid stimulating hormone; TORCH, serology for toxoplasmosis, rubella, cytomegalovirus and herpes simplex; HBS, hepatobiliaryscan; A1ATD, α-1-antitrypsin deficiency, CF, cystic fibrosis; USS, abdominal ultrasound; UDCA, ursodeoxycholic acid.)

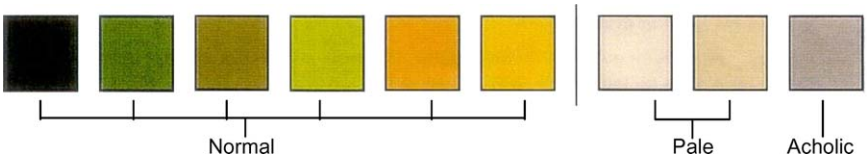

Figure 2 Stool colour chart from the Children's Liver Disease Foundation.

The most important clinical sign is the stool colour, and the most significant initial investigation is coagulation. The latter implies hepatocyte synthetic failure or severe vitamin K deficiency and requires immediate correction to prevent intracranial haemorrhage, which has been documented in infants with liver disease.

Stool colour and isotope scans

Pale or acholic stools are a relative clinical emergency, and the initial investigations as listed above should be instigated in addition to communication with the local liver/gastroenterology unit. Since stool colour and isotope scan results both act as indicators of bile entering the gut, an infant with a pigmented stool will have an excreting isotope scan, and one with acholic stools will have a non-excreting isotope scan. Thus, a clearly documented stool colour, assessed either by an experienced observer or by using a stool colour chart (Fig. 2),[12] can help to identify which infants need urgent investigation and which infants can afford to wait and continue to gain weight with nutritional support in their own neonatal unit without leaving the skills of the neonatal team. Isotope scans will still have a role for infants with persistent cholestasis, particularly if there is any doubt concerning EHBA. An excreting isotope scan completely excludes this diagnosis. Any infant requiring an isotope scan should have 3 days pretreatment with phenobarbitone 5 mg/kg per day to enable optimum resolution.

Abdominal ultrasound

Abdominal ultrasound after a 4-h fast is available in most hospitals. A survey in the West Midlands region noted that 13 out of 14 neonatal units that responded had local access to liver ultrasound; 6 (43%) of these were confident in looking at the size of the gallbladder, and a further 8 (60%) felt they would be if they were provided with simple guidance (pers comm.).

In term infants, an absent or small gallbladder, especially with an irregular wall, is a significant finding and predictive of EHBA.[13] Gallbladder size and contractility have been studied in preterm infants and normal ranges for volume established.[14] A normal gallbladder makes EHBA less likely but not impossible. The liver ultrasound can also identify choledochal cysts, biliary tract dilatation and associated splenic anomalies.

Further investigations

For preterm infants with persistent cholestasis, continuing communication with the local liver team should occur, including a feedback of investigation results and regular liver function tests. This approach should suffice unless the clinical findings change or the cholestasis resolves.

The results of the initial screen and the progression of the cholestasis may dictate the need for further tests, including:

- an ophthalmic review other than for retinopathy of prematurity;
- a karyotype for dysmorphism;
- levels of very long-chain fatty acids for neurological abnormality;
- urinary bile salts;
- an isotope scan, liver biopsy and bone marrow aspirate.

Liver biopsy

This is an extremely important diagnostic investigation and also the most invasive. Liver biopsy has a diagnostic accuracy for EHBA of over 90% if reviewed by an experienced team and is also diagnostic for idiopathic neonatal hepatitis, α-1-antitrypsin deficiency and storage disorders. Owing to the technical difficulties and increased risk for preterm infants, liver biopsies are now deferred wherever possible in this group. Preterm infants with pale or acholic stools should be transferred to a liver unit to have this examination performed as soon as is feasible after the baby becomes eligible for any necessary hepatobiliary surgery. Eligibility includes an infant's coexisting requirement for respiratory support and weight. This decision has to be individualised and agreed on a case-by-case basis.

Preterm infants with pigmented stools are unlikely to require a liver biopsy. Where there is a doubt, careful re-evaluation with regular liver function monitoring and stool colour examination should be undertaken. If the stool colour pales or the stools become acholic, invasive investigations will be indicated. If cholestasis persists, a discussion with the local liver team should consider what further investigations are necessary and whether a liver biopsy should form part of these.

Follow-up

Infants with persistent non-progressive cholestasis or those diagnosed with liver disease, for example α-1-antitrypsin deficiency, can be seen in the outpatient department at an age convenient to the neonatal unit team, patient, family and liver unit. For the majority, this will be after discharge from the neonatal unit.

Management of preterm infants with cholestasis

Nutrition

If surgically correctable lesions are excluded, the main focus of management is to provide adequate nutrition and vitamin support. Owing to reduced bile excretion into the gut, these infants have a malabsorption of long-chain fat and fat-soluble vitamins. The consequences are limited growth, coagulopathy and an exacerbation of disordered preterm bone mineralisation.

If the preterm infant is breast-fed, this should be encouraged unless there is inadequate growth, either weight gain or linear growth. At this stage, a high-calorie diet aiming at 120–150% of the estimated average is recommended, with an increased percentage of fat given as medium-chain triglycerides, such as Pepti-junior. An alternative is to use medium-chain triglyceride fat additives in expressed breast milk.

Preterm infants with moderate-to-severe cholestasis or those not responding to the above approach may require an individually prescribed modular feed. In practice, this feed is usually used only for infants who have been inpatients or are managed as outpatients by the liver team as close contact with liver team dietitians is necessary to monitor this complex regimen.[15]

Vitamins

Fat-soluble vitamins are prescribed in large doses while cholestasis is present and for 3 months following the resolution of jaundice to allow for the delay in the establishment of normal bile flow. The doses required should be adjusted in response to biochemical monitoring of bone metabolism, coagulation and vitamin A and E levels:

- vitamin K 1–2 mg daily;
- vitamin A 2500–5000 IU daily;
- vitamin E 100 mg daily;
- α-calcidol 30–50 ng/kg daily.

Ursodeoxycholic acid

Most preterm infants with cholestasis should be commenced on ursodeoxycholic acid (20–30 mg/kg per day in divided doses) until the jaundice resolves. Ursodeoxycholic acid is a naturally occurring hydrophilic bile acid that stimulates bile flow[3] and has an excellent safety record. It is also used in children with cholestasis associated with cystic fibrosis and has been shown to result in an improvement of biochemical markers of cholestasis, and of symptoms of pruritis in others.[16]

Limitation of parenteral nutrition

It is important to give some enteral feeds to a preterm infant with cholestasis since even a small amount has trophic effects on the gut, reduces bacterial translocation and promotes bile flow.[17] PN should be stopped as soon as sufficient calories can be fed enterally. This is important for all preterm infants with cholestasis and not just those in which PN has been identified as a causative factor.

Specific management

Preterm infants with cystic fibrosis, galactosaemia, tyrosinaemia type 1, and hypopituitarism, hypothyroidism or bile acid disorders will need targeted management in addition to the above. These infants will need lifelong follow-up shared by local teams and specialists in respiratory, metabolic, endocrine and hepatic medicine.

Outcome

Liver dysfunction arising from idiopathic neonatal hepatitis, multifactorial preterm cholestasis and haemolytic disease of the newborn will frequently resolve with supportive nutritional management and ursodeoxycholic acid. PN injury will usually resolve as long as PN can be discontinued. Cholestasis seen with endocrine anomalies often resolves after correction of the hormone imbalance in conjunction with supportive measures. After treating sepsis or supporting an infant through the effects of hypoxia, the liver dysfunction resolves, and the infant's long-term outcome is determined by the effect of released cytokines and secondary injury to the brain.

The metabolic conditions seen in preterm infants (Table 3) require multidisciplinary management. Haemochromatosis is often fatal early on after progressing to acute liver failure. Cystic fibrosis and α-1-antitrypsin deficiency have a high risk of ongoing liver dysfunction, with 40% of the latter group requiring liver transplantation in childhood.[18] The outcome for α-1-antitrypsin deficiency is improved with early aggressive nutritional management, and infants therefore benefit from prompt diagnosis.

Choledochal cysts and biliary stricture respond well to surgical intervention. Unfortunately, infants with either bile duct paucity or early symptomatic Alagille syndrome often progress to liver transplantation.

The outcome of EHBA is determined by age at surgery and the presence of associated abnormalities. Preterm infants should not be disadvantaged by a further unnecessary delay in surgery.

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