

Chapter 4: The Jaundiced Baby

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Neonatal jaundice is a common finding in general paediatrics. Many babies, as many as 30–50% of normal term newborns, have transient jaundice 3–5 days after birth. This unconjugated hyperbilirubinaemia is due to immaturity of the hepatic enzyme glucuronosyl transferase, which is responsible for glucuronidation of bilirubin. Unconjugated hyperbilirubinaemia occurring later in the perinatal period may be associated with breast feeding, so-called ‘breast-milk jaundice’. Elevated blood levels of unconjugated bilirubin can be due to haemolysis, sepsis, hypothyroidism or pyloric stenosis. In contrast, conjugated hyperbilirubinaemia nearly always reflects hepatic dysfunction, which may be due to many different disorders, such as the neonatal hepatitis syndrome, biliary atresia or duct paucity syndromes, all of which have different long-term outcomes. The nature of the liver disease must be determined as early as possible in order to start appropriate treatment or provide supportive therapies. The best current practice is to investigate jaundice in any infant who is 14 days old, to determine whether unconjugated or conjugated hyperbilirubinaemia is present.

Unconjugated hyperbilirubinaemia

Bilirubin, a breakdown product of haem, is extremely toxic. When it binds to cellular macromolecules, as in neural tissue, it causes damage, disrupts metabolic processes and leads to cell death. As bilirubin is normally tightly bound to albumin in the vascular compartment, concentrations of free bilirubin, which is capable of diffusing into brain tissue, are extremely low. Several parameters influence the level of free bilirubin: production of unconjugated bilirubin, the serum albumin concentration, and the concentration of bilirubin competitors that also bind to albumin. These include: commonly used drugs such as sulphonamides, frusemide and benzoate; free fatty acids, including lipid infusions for total parenteral nutrition; and other breakdown products from red cell haemolysis. Premature infants are more vulnerable to bilirubin neurotoxicity than term infants, a tendency that may be potentiated by dehydration, which causes hyperosmolality, acidosis and hypoxia. Kernicterus is the most serious consequence of severe unconjugated hyperbilirubinaemia, and develops secondary to binding of bilirubin in specific areas of the brain such as the basal ganglia. It may be fatal

or cause severe movement disorders (choreoathetosis), mental retardation and deafness.

Physiological jaundice

As hepatic bilirubin glucuronosyl transferase activity is low at the time of birth, nearly all newborn babies have hyperbilirubinaemia in the first week of life. Unconjugated bilirubin predominates whereas serum conjugated bilirubin is low or undetectable (Keffler *et al.* 1998). Approximately half of term babies are jaundiced; more severe jaundice (serum bilirubin $\geq 200 \mu\text{mol/l}$) occurs in 8–20% in the first week of life (Maisels *et al.* 1988). Factors associated with severe jaundice include breast feeding, exaggerated perinatal weight loss ($>7\%$ of birth weight), maternal diabetes mellitus, bruising, and induction of labour with oxytocin. The severity and duration of jaundice may be increased in infants born prematurely. Infants of Oriental, Inuit, or North American Indian extraction tend to have more severe jaundice, with as many as 24–54% developing serum bilirubin $>200 \mu\text{mol/l}$. In general, physiological jaundice peaks on day 3 of life, although hyperbilirubinaemia may persist as long as 2 weeks.

The mechanism(s) of such severe physiological jaundice remain uncertain, and while environmental factors cannot be entirely excluded, genetic control of bilirubin production and clearance appears to be most important (Kaplan *et al.* 2002b). There may be increased bilirubin load due to shortened red blood cell lifespan (Kaplan *et al.* 2002a), increased activity of the enterohepatic circulation, and inefficient uptake of bilirubin by hepatocytes due to relatively immature expression of ligandin, which mediates uptake of organic anions, in addition to immaturity of hepatic bilirubin glucuronosyl transferase. Infants who have abnormalities in the bilirubin glucuronosyl transferase which cause Gilbert's syndrome (Burchell & Hume 1999) alone or in addition to glucose-6-phosphatase dehydrogenase deficiency (Kaplan *et al.* 1997; Kaplan & Hammerman 1998) are at greater risk for severe physiological jaundice and breast-milk jaundice.

Treatment

Treatment may not be necessary in most cases. Phototherapy should be initiated for normal term infants only when serum total bilirubin is $>300 \mu\text{mol/l}$. The decision is complex and depends not only on the bilirubin concentration and its rate of increase, but also on the weight and gestational age of the infant, postnatal age, the rate at which bilirubin is generated and the adequacy of bilirubin–albumin binding. Numerous clinical trials have demonstrated the effectiveness of phototherapy for decreasing unconjugated hyperbilirubinaemia (bilirubin $>300 \mu\text{mol/l}$) in term infants (Tan 1975; Brown *et al.*

1985) and in premature babies with serum bilirubin $>200 \mu\text{mol/l}$. Body temperature and fluid status must be monitored closely; fluid loss may be excessive, mainly because of increased insensible loss and additionally due to frequent watery stools. Eye patches are required. The baby may be more irritable, especially as normal parental interaction is often interrupted. For babies of ethnic extraction in whom severe unconjugated hyperbilirubinaemia may commonly occur even in the absence of haemolysis, exchange transfusion remains a viable therapy to prevent kernicterus (Yeung 1985), although tin-protoporphyrin treatment has also been used (Rubaltelli *et al.* 1989; Galbraith *et al.* 1992). Exchange transfusion may be required to prevent possible kernicterus in any baby with severe unconjugated hyperbilirubinaemia.

Breast-milk jaundice

Moderately severe unconjugated hyperbilirubinaemia associated with breast feeding is common, occurring in 0.5–2% of healthy newborn babies. Jaundice may develop after the fourth day of life (early pattern) or towards the end of the first week of life (late pattern) and usually peaks around the end of the second week of life. Jaundice may overlap with physiological jaundice or be protracted and last 1–2 months.

The aetiology remains uncertain. Contamination of breast milk with steroids such as pregnanediols appears unlikely. Breast milk may contain endogenous substances, such as free fatty acids, which displace bilirubin in the intestinal contents and enhance the enterohepatic circulation of bilirubin, although increased free fatty acids were not found in freshly expressed breast milk from mothers of infants with breast-milk jaundice (Jalili *et al.* 1985). An alternative hypothesis is that breast milk contains β -glucuronidase, leading to deconjugation of glucuronide moieties from conjugated bilirubin and subsequent reabsorption of bilirubin (Gourley & Arend 1986). Breast-fed babies have less frequent stools and eliminate less bile in faeces than bottle-fed babies (De Carvalho *et al.* 1985), which may increase bilirubin reabsorption and contribute to hyperbilirubinaemia. More frequent breast feeding may enhance gut motility and stool output.

The diagnosis is clinical: an exclusively breast-fed infant with unconjugated hyperbilirubinaemia, normal conjugated bilirubin, haemoglobin and reticulocyte counts, no maternal blood group incompatibility, and a normal physical examination except for jaundice. The diagnosis is supported by a drop in serum bilirubin ($\geq 50\%$ in 1–3 days) if breast feeding is interrupted for 48 h (Lascari 1986). Breast-milk jaundice lasting 1–2 months requires surveillance by the physician to exclude liver disease, although pale stools, if noted, are highly suggestive of important liver disease.

Systemic disease

Unconjugated hyperbilirubinaemia is frequently associated with systemic disease. Haemolysis of any aetiology increases the bilirubin load and includes: rhesus and ABO incompatibility with Coombs' positivity; glucose-6-phosphate dehydrogenase deficiency; erythrocyte membrane defects; and spherocytosis. Severe haemolytic disease of any aetiology can result in severe jaundice associated with kernicterus and requires aggressive treatment with phototherapy and/or exchange transfusion. Bruising, haemorrhage into brain or lung tissue, and neonatal polycythaemia also increase the bilirubin load.

The association of unconjugated hyperbilirubinaemia with congenital hypothyroidism is based on early observations (Weldon & Danks 1972). The mechanism of jaundice is not known, but thyroid function should be evaluated in any neonate with jaundice.

Unconjugated hyperbilirubinaemia is also found with pyloric stenosis and other forms of upper intestinal obstruction, which resolves rapidly after pyloric myotomy (Bleicher *et al.* 1979). The mechanism remains uncertain. A likely explanation is that these infants have Gilbert syndrome and develop unconjugated hyperbilirubinaemia due to reduced oral intake (Labrune *et al.* 1989; Trioche *et al.* 1999).

Other pathological conditions associated with unconjugated hyperbilirubinaemia include sepsis, hypoxia, hypoglycaemia, galactosaemia and fructose intolerance.

Inherited disorders

Crigler–Najjar syndromes

Crigler–Najjar syndromes type 1 and 2 are autosomal recessive conditions which lead to unconjugated hyperbilirubinaemia due to a deficiency of the enzyme bilirubin uridine diphosphate glucuronosyl transferase (UDPGT). In Crigler–Najjar type 1 there is effectively no UDPGT present; in type 2 the defect is partial.

The genetic basis for these diseases has been elucidated since the structure of the human bilirubin glucuronosyl transferase gene has been established (Owens & Ritter 1992; Ritter *et al.* 1992, 1993). Humans have two such genes (B-UGT1 and B-UGT2); B-UGT2 appears to play little if any role in bilirubin glucuronidation and is not responsible for induction of enzyme activity in Crigler–Najjar type 2 due to phenobarbital. B-UGT1 and 2 are members of a glucuronosyl transferase superfamily. In these genes exon 1 relates to substrate specificity, for example, for bilirubin, exons 2–5 code for the carboxy-terminal domains common to all glucuronosyl transferases. The clinical phenotype of Crigler–Najjar type 1 can result from mutations in exons 2–5, resulting in a trun-

cated non-functional enzyme, or in exon 1, resulting in complete loss of substrate recognition for bilirubin. Genetic heterogeneity in this condition has been striking (Aono *et al.* 1993; Labrune *et al.* 1994). The genetic defect in Crigler–Najjar type 2 is somewhat subtler. Mutations leading to Crigler–Najjar type 2 appear to change the affinity of the enzyme for its substrate (Seppen *et al.* 1994; Guldutuna *et al.* 1995).

Clinical features and diagnosis Both conditions present early in the perinatal period with a rapid rise in bilirubin despite phototherapy. Kernicterus may develop in the perinatal period, particularly if treatment is delayed or if associated with dehydration or sepsis. Type 1 is much more severe than type 2, with peak serum bilirubin levels at 250–850 $\mu\text{mol/l}$. In Crigler–Najjar type 2 serum bilirubin is lower (200–300 $\mu\text{mol/l}$) and may reduce by ~40% when phenobarbitone is administered.

Liver function tests, including conjugated bilirubin, are normal. Liver histology is normal except for occasional bile plugs. Confirmation of the diagnosis may be obtained by detection of the enzyme deficiency in liver or estimation of bilirubin mono- and diglucuronides in bile aspirates. Bilirubin diglucuronides are not present in bile in type 1 but can be found in type 2 (Sinaasappel & Jansen 1991).

Management Treatment for Crigler–Najjar type 1 consists of aggressive use of measures to remove bilirubin with either phototherapy or exchange transfusion. Effective phototherapy depends on delivering radiant energy from light of wavelength 400–500 nm to the skin. Irradiance is not related to the brightness of the lights; the quantity of irradiation is inversely related to the distance between the lights and the infant. Skin pigmentation does not influence effectiveness of treatment. The development of lighted mattresses (Hughes-Benzie *et al.* 1993) has facilitated treatment and permitted early discharge from hospital. The use of tin-protoporphyrin has been advocated as an alternative treatment, which works by interfering with the generation of bilirubin from haem (Kappas *et al.* 1988; McDonagh 1988).

The aim of therapy is to maintain bilirubin levels low enough (<300 $\mu\text{mol/l}$) to prevent kernicterus, which may require up to 15 h of phototherapy a day. Intercurrent infections with rapid increases in bilirubin should be managed with plasmapheresis or exchange transfusions.

Liver transplantation, including auxiliary transplantation, is a long-term option if damage to the nervous system has been avoided (Chapter 20) and may improve quality of life. It is the only effective method for preventing kernicterus. Hepatocyte transplantation has limited success (Fox *et al.* 1998).

In Crigler–Najjar type 2 prolonged treatment with phenobarbitone (5–10 mg/kg/day) may provide cos-

metic improvement, but treatment is not usually required as kernicterus is rare.

Outcome Sudden late neurological deterioration in Crigler–Najjar type 1 may occur even if management of hyperbilirubinaemia has been meticulous. Late intrahepatic cholestasis has been reported. The outcome following liver transplantation is excellent.

Gilbert's syndrome

This condition manifests with mild variable unconjugated hyperbilirubinaemia, with total serum bilirubin levels ranging from 30 to 90 $\mu\text{mol/l}$. It is a heterogeneous condition in which the responsible gene defect has been identified: the presence of an extra TA tandem repeat in the promoter region of the bilirubin UDP glucuronosyl transferase 1 gene (Bosma *et al.* 1995). Instead of having the normal six repeats, seven are present. Although this promoter region abnormality is the prevailing abnormality in individuals of European extraction, a different genetic picture exists in Asians in whom mutations within the coding region of bilirubin UDP glucuronosyl transferase 1 gene have been found associated with Gilbert's syndrome (Burchell & Hume 1999).

Clinical features There is mild jaundice which is exacerbated by dehydration, intercurrent illness or fatigue. Patients often complain of vague abdominal pain, lethargy and general malaise for which no good cause has been found. It is more common in males than females; most children present in adolescence. Serum aminotransferases are normal and biopsy is unnecessary. Infants homozygous for the genetic abnormality of Gilbert syndrome have a greater increase in jaundice in the first 2 days of life than heterozygotes or non-affected infants (Bancroft *et al.* 1998; Monaghan *et al.* 1999; Roy-Chowdhury *et al.* 2002). Asian infants with Gilbert's syndrome associated with coding region mutations in the bilirubin glucuronosyl transferase gene are also more prone to physiological or breast-milk jaundice (Akaba *et al.* 1999; Maruo *et al.* 1999, 2000; Sutomo *et al.* 2002).

Treatment No treatment is required, but families often require reassurance.

Conjugated hyperbilirubinaemia

Conjugated hyperbilirubinaemia nearly always indicates liver disease, which may be due to the neonatal hepatitis syndrome, biliary atresia or duct paucity syndromes.

The nomenclature for neonatal liver disease is problematic. The term 'neonatal jaundice' causes confusion with physiological jaundice, while 'neonatal cholestasis' is imprecise. In the first 3–4 months of life every infant has

some degree of neonatal cholestasis on a physiological basis, which is multifactorial. Hepatocellular pathways of bile acid conjugation and biliary secretion are immature, and uptake of bile acids and other organic anions by hepatocytes is inefficient, leading to high concentrations of bile acids in blood; the circulating bile acid pool is contracted, and ileal uptake of bile acids is underdeveloped (Suchy *et al.* 1981; Balistreri *et al.* 1983). The term 'neonatal hepatitis' is inadequate because hepatic inflammation is not prominent in every condition. The term 'neonatal hepatitis syndrome' (NHS) is now used as it conveys the similarity of the clinical illness in infants and suggests a broad spectrum of causative disease processes.

Neonatal hepatitis syndrome (NHS)

The neonatal hepatitis syndrome is now the term given to non-specific hepatic inflammation, which develops secondary to many different aetiologies, including intrauterine infection, endocrine disorders and inborn errors of metabolism. Causes of the neonatal hepatitis syndrome and diagnostic approach are summarized in Fig. 4.1 and Table 4.1. Treatment is summarized in Table 4.5. (p. 61).

Clinical features

Conjugated hyperbilirubinaemia may present at any time after birth. If detected in the first 24 h of life infection is usually the cause. Most causes of the neonatal hepatitis syndrome have a similar presentation:

- Jaundice, which may not be obvious at first.
- Dark urine and pale yellow stools. Abnormal stool colour, though suggestive of liver disease, is neither a specific nor a reliable feature.
- Infants may be small for gestational age, especially those with Alagille's syndrome, metabolic liver disease and intrauterine infection (see Plate 1, Atlas: p. 440).
- Failure to thrive or poor feeding.
- Dysmorphic features in trisomy 18, trisomy 21, Alagille's syndrome, Zellweger syndrome, and with certain congenital infections.
- Hypoglycaemia in metabolic liver disease, hypopituitarism or severe liver disease.
- Hepatomegaly.
- Splenomegaly (the spleen may also be palpated in healthy babies 1–2 cm below left costal margin). An impalpable spleen in an infant with severe cholestatic jaundice may suggest extrahepatic biliary atresia with polysplenia.
- Ascites is rarely evident except in metabolic liver disease (Chapter 5).
- Cardiac murmurs or neurological abnormalities are associated with specific congenital syndromes.
- Bleeding from vitamin K deficiency or thrombocytopenia.

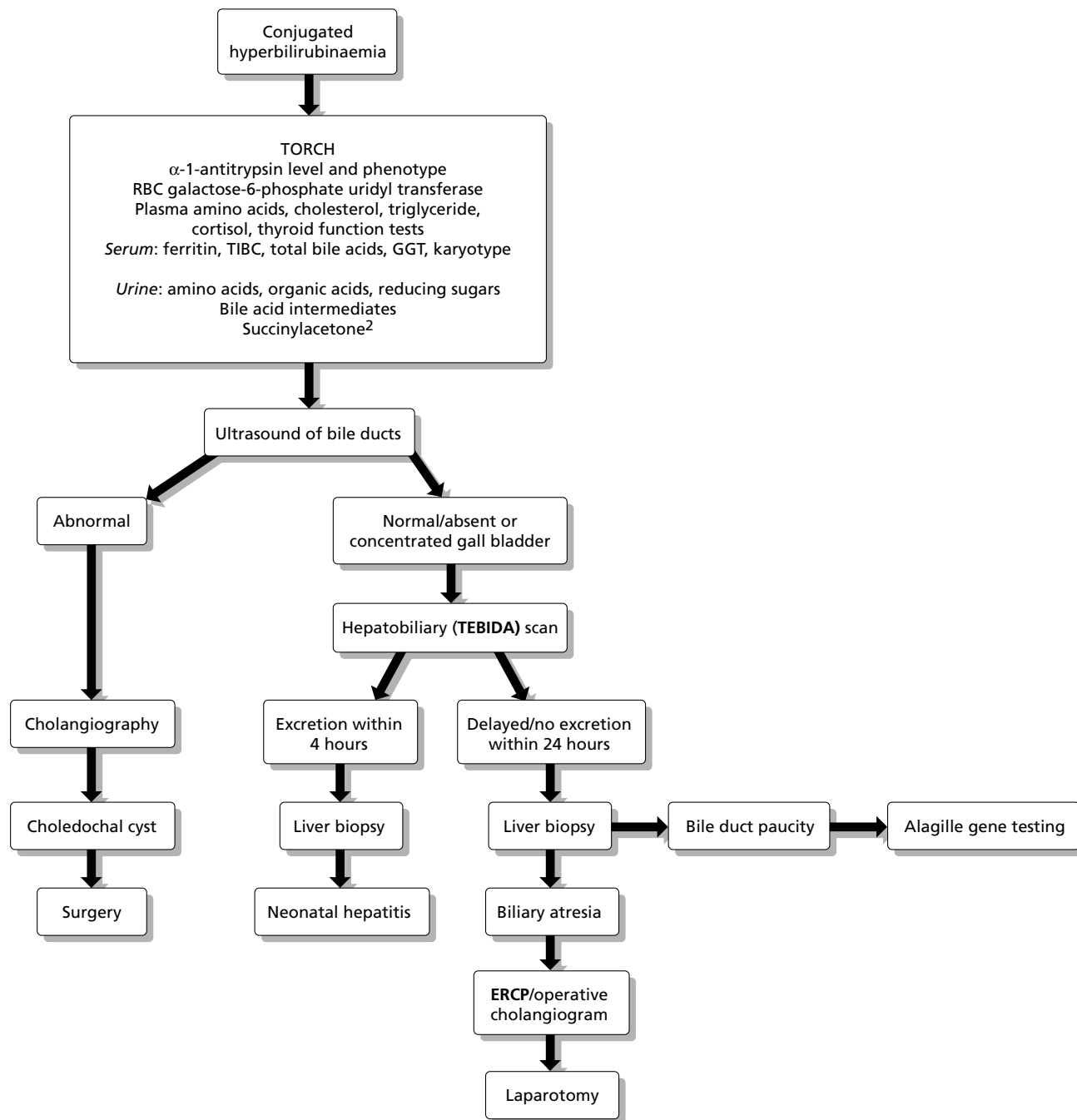


Fig. 4.1 Investigation of conjugated hyperbilirubinaemia in the neonate. TORCH, Serology for toxoplasma, other, rubella, cytomegalovirus and herpes simplex viruses; TIBC, total iron-binding capacity; GGT, gamma-glutamyl-transpeptidase; TEBIDA, Technetium trimethyl-1-bromo imino diacetic acid; ERCP, endoscopic retrograde, cholangiopancreatography.

Investigations

The following investigations and findings are used in determining a diagnosis of neonatal hepatitis syndrome:

- The cardinal feature is conjugated hyperbilirubinaemia of any degree. Even a mildly elevated conjugated bilirubin ($\geq 20 \mu\text{mol/l}$) in the absence of unconjugated hyperbilirubinaemia may indicate significant hepatic disease.
- Serum aminotransferases are frequently elevated 2–4 times normal, but they may be within normal limits for age. Higher elevations suggest an infectious process.
- Serum alkaline phosphatase may be normal or only mildly elevated. Higher levels may indicate biliary atresia or rickets.

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Table 4.1 Neonatal liver disease syndrome: differential diagnosis and diagnostic approach

Disease	Major diagnostic strategy
<i>Congenital infection</i>	
Toxoplasmosis	IgM-specific antibodies
Rubella	IgM-specific antibodies
Cytomegalovirus	Urine for viral culture, IgM antibodies
Herpes simplex	EM/viral culture of vesicle scraping
Syphilis	STS, VDRL, FTA-ABS, long-bone films
Human herpesvirus-6, herpes zoster	Serology, PCR
Hepatitis B	HBsAg, anti-HBc (IgM), HBV DNA
Hepatitis C	HCV RNA by RT-PCR
Human immunodeficiency virus	Anti-HIV, immunoglobulins, CD4 count
Parvovirus B19	IgM antibodies
Syncytial giant cell hepatitis	Giant cell hepatitis on liver biopsy
Enteric viral sepsis (echoviruses, Coxsackie A and B viruses, adenoviruses)	Appropriate serology, CSF for viral culture
<i>Genetic</i>	
Trisomy 18, (21), cat-eye syndrome	Karyotype
<i>Endocrine</i>	
Hypopituitarism (septo-optic dysplasia)	Low cortisol, TSH and T4
Hypothyroidism	High TSH titre; low T4, free T4, T3
<i>Structural</i>	
Extrahepatic biliary atresia	Delayed or absent excretion on hepatobiliary scan, biliary obstruction on histology
Caroli cyst, choledochal cyst	Ultrasound, cholangiography
Neonatal sclerosing cholangitis	Cholangiogram
Hair-like bile duct syndrome	Cholangiogram
Spontaneous perforation of CBD	Ultrasound, paracentesis, biliary ascites
Inspissated bile syndrome	Coombs' test, other evidence for haemolysis, dilated bile ducts
<i>Duct paucity syndromes</i>	
Alagille syndrome	Echocardiogram, posterior embryotoxon, CXR for 'butterfly vertebrae'
Non-syndromic duct paucity	Bile duct paucity on histology
<i>Metabolic</i>	
α_1 -Antitrypsin (AAT) deficiency	Serum AAT concentration, PI type
Cystic fibrosis	Sweat chloride, immunoreactive trypsin
Galactosaemia	Galactose-1-6-phosphate uridylyltransferase
Tyrosinaemia	Serum tyrosine, methionine, alpha-fetoprotein, urine succinylacetone
Hereditary fructosaemia	Liver biopsy: EM, enzyme activities
Glycogen storage disease, type IV	Liver biopsy
Niemann–Pick, type A	Bone marrow aspirate, sphingomyelinase
Niemann–Pick, type C	Storage cells in BM aspirate, liver, rectal Bx
Wolman disease	Abdominal X-ray of adrenal glands
Primary disorders of bile acid synthesis	Urinary bile acid intermediates by FAB-MS
Byler disease	GGT, genetic testing
Zellweger syndrome	Very-long-chain fatty acid studies
<i>Immune</i>	
Neonatal lupus erythematosus	Anti-Ro and anti-La antibodies (in infant and mother)
NH with autoimmune haemolytic anaemia	Coombs' test, giant cell hepatitis

AAT, α_1 -antitrypsin; Bx, biopsy; CBD, common bile duct; CXR, chest X-ray; EM, electron microscopy; FAB-MS, fast-atom bombardment-mass spectroscopy; FTA-ABS, fluorescent treponemal antibody, absorbed; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; HCV, hepatitis C virus; PI, protease inhibitor; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase-polymerase chain reaction; STS, standard test for syphilis; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory.

- Serum gamma-glutamyl transpeptidase (GGT) may be elevated, but reference values for GGT change during the first 3 months of life and may be difficult to gauge. It does not reliably distinguish bile duct obstruction from hepatocellular injury in the infant. Normal or low GGT suggests Byler disease or progressive familial intrahepatic cholestasis (see below).
- Blood glucose may be normal or low. Hypoglycaemia suggests metabolic liver disease, hypopituitarism or poor hepatic reserve.
- Serum albumin is usually normal unless there is severe prenatal disease.
- Prothrombin and partial thromboplastin times are usually normal unless there is associated vitamin K deficiency (haemorrhagic disease of the newborn) or severe liver disease.
- Bilirubin is present in urine.
- Screening investigations for known causes of neonatal hepatitis syndrome may be diagnostic (Fig. 4.1).
- Abdominal ultrasound scan (after 4-h fast) to detect gall bladder size. Usually present unless there is severe intrahepatic cholestasis or biliary atresia (see Plate 2, Atlas: p. 440).
- Radioisotope scan to demonstrate hepatic uptake (may be reduced in NHS) and biliary excretion (may be delayed more than 4–6 h in NHS if there is severe cholestasis, and more than 24 h, or indefinitely, in biliary atresia) (see Plate 3, Atlas: p. 440).
- Liver biopsy. This is frequently the most informative investigation in neonatal hepatitis syndrome (Lichtman *et al.* 1987). If the liver is difficult to palpate, or if situs inversus abdominis is present, an ultrasound-guided biopsy should be performed. Information provided by liver biopsy includes: the severity of hepatocellular injury and extent of fibrosis; evidence for infiltrative or storage disease; and type of biliary damage (bile ductular proliferation vs. small duct paucity). Care should be taken to obtain a large enough specimen with adequate numbers of portal tracts to assess changes in the small bile ducts. Histological findings vary depending on the aetiology. Most diseases will have conspicuous cholestasis with bile staining within the hepatocytes, and bile plugs within bile canaliculi and bile ductules. Hepatocytes may demonstrate a variable degree of multinucleated giant cell transformation and rosette formation on the hepatocytes. There may be a degree of extramedullary haematopoiesis. Although biliary ductular proliferation is said to be prominent in bile duct obstruction, it also occurs in children with a neonatal hepatitis syndrome, particularly those with α_1 -antitrypsin deficiency, cystic fibrosis and endocrine deficiency. Paucity of bile ducts is a feature in Alagille's syndrome (see Plates 4 and 6, Atlas: pp. 441 and 442, respectively).

Infection

Toxoplasmosis, rubella, cytomegalovirus, herpes simplex ('TORCH') infections

Congenital infections grouped under the acronym 'TORCH' often have very similar clinical features: hepatosplenomegaly, jaundice, pneumonitis, petechial or purpuric rash, and a tendency to prematurity or poor intrauterine growth. A presentation with fulminant hepatic failure in the newborn period is common with herpes simplex infection. Whenever possible, direct identification of viral infection or measurement of specific IgM antibodies should be sought for rapid diagnosis; relying on conventional TORCH titres is less preferable.

Toxoplasmosis Congenital toxoplasmosis is comparatively rare. Maternal infection in the third trimester is more likely to cause fetal infection than infection earlier in pregnancy. Neonatal hepatitis is an important feature but may be less obvious than central nervous system involvement with chorioretinitis (with large pigmented scars), hydrocephaly or microcephaly. Intracranial calcification is usually prominent, leading to convulsions, nystagmus and evidence of increased intracranial pressure. Liver biopsy may demonstrate a non-specific hepatitis or portal fibrosis with biliary ductule proliferation. Spiramycin therapy may prevent progression of central nervous system and liver disease. Prognosis depends on the extent of neurological or optic disease.

Rubella Congenital infection with rubella virus is now rare because of immunization. It may cause intrauterine growth retardation, anaemia/thrombocytopenia, congenital heart disease (patent ductus arteriosus or pulmonary artery stenosis), cataracts, chorioretinitis ('salt and pepper' appearance), mental retardation and sensorineural deafness. Hepatosplenomegaly is usual. Liver histology shows typical giant-cell hepatitis. The disease may be self-limited or progress to cirrhosis.

Cytomegalovirus Cytomegalovirus is the most commonest cause of congenital infection, affecting 1–2% of newborns, most of whom are asymptomatic. Those with evident disease may have intrauterine growth retardation or be premature (Hart *et al.* 1991). Fetal ascites (Binder *et al.* 1988; Sun *et al.* 1990) may occur. Cytomegalovirus rarely causes acute liver failure in the newborn.

Clinical findings include: petechial rash, hepatosplenomegaly, and jaundice in 60–80%. Cytomegalovirus infection often affects the central nervous system, producing microcephaly, intracranial calcification, and chorioretinitis; progressive sensorineural deafness or cerebral palsy may develop later in childhood. Primary infection in the second and third trimesters ap-

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pears to cause more severe fetal disease than recurrent infection.

Liver biopsy demonstrates a giant cell hepatitis; the classical inclusion bodies are rarely seen in neonatal infection. In a study of liver tissue in infants with neonatal hepatitis or extrahepatic biliary atresia, Chang *et al.* (Chang *et al.* 1992) found cytomegalovirus DNA in 23 of 50 infants with neonatal hepatitis by polymerase chain reaction, but in only two of 26 with extrahepatic biliary atresia, and in none of control specimens. Although differentiation from biliary atresia is usually easy, cytomegalovirus may be associated with extrahepatic biliary atresia. In one report of fraternal twins, both had congenital cytomegalovirus infection: one had hepatitis only and the other presented with 'late' pattern extrahepatic biliary atresia (Hart *et al.* 1991). In addition, 25% of infants with extrahepatic biliary atresia were found to have cytomegalovirus infection and were referred later than those without cytomegalovirus infection (Tarr *et al.* 1996). Cytomegalovirus is a candidate virus for causing 'late' presentation extrahepatic biliary atresia as it can infect bile duct epithelial cells directly and increase expression of MHC class II antigens (Arnold *et al.* 1992; Domiati-Saad *et al.* 2000). Infants with congenital cytomegalovirus infection and persisting conjugated hyperbilirubinaemia should have extrahepatic biliary atresia excluded.

Conclusive diagnosis requires cytomegalovirus to be cultured from the infant within the first 4 weeks of life. Serological studies and clinical features provide support for the presence of cytomegalovirus infection but do not distinguish congenital from early postnatal infection (Table 4.1).

In most children cytomegalovirus hepatitis is mild and resolves completely. A few children develop hepatic fibrosis (Zuppen *et al.* 1986; Le Luyer *et al.* 1990) or non-cirrhotic portal hypertension (Ghishan *et al.* 1984). Intrahepatic calcification has been reported (Alix *et al.* 1978). Cirrhosis with chronic cholestasis necessitated liver transplantation in one child. Persisting neurodevelopmental abnormalities become the main problem in the majority of patients (Conboy *et al.* 1987).

Herpes simplex In the newborn this virus causes a severe multisystem disorder with encephalitis, severe hepatitis, or acute liver failure (Miller *et al.* 1970; Benador *et al.* 1990) due to either type 1 or type 2 virus, although type 2 virus shed from the infected cervix at birth is more common. Liver biopsy shows areas of necrosis with viral inclusions in intact hepatocytes; however, profound coagulopathy may preclude biopsy. Scrapings from vesicular skin lesions reveal herpes simplex virus, but these typical herpetic skin, mouth or eye lesions may not be present in neonates. Antiviral treatment with acyclovir should be administered to avert the otherwise high mortality.

Syphilis

Congenital syphilis is now rare in the developed world. It causes a multisystem illness, which may include intrauterine growth retardation and subsequent failure to thrive, severe anaemia and thrombocytopenia, nephrotic syndrome, periostitis, nasal discharge ('snuffles'), skin rash, diffuse lymphadenopathy, and hepatomegaly. Jaundice may be present within 24 h of birth or develop after treatment (Long *et al.* 1984). Jaundice may be severe (Wolf *et al.* 1997). Some babies with congenital syphilis never develop jaundice but present with a typical rash on palms and soles or only with fever, as well as prominent hepatomegaly (Dorfman & Glaser 1990). Central nervous system involvement occurs in up to 30% of infants.

Liver histology in untreated congenital syphilis may reveal numerous treponemes in hepatic tissue, but after treatment with penicillin, giant-cell hepatitis without detectable treponemes is the usual finding. Diagnosis involves serological testing, including the Venereal Disease Research Laboratory (VDRL) test and confirmatory testing for specific antitreponemal antibodies. Radiographs of long bones may show typical bony abnormalities in the first 24 h of life and aid rapid diagnosis (Table 4.1).

Varicella

Varicella may occur in newborn infants if maternal infection occurs within 14 days of delivery. It tends to be more severe in premature infants and is mild in term infants after 10 days of age. Early presentation or protracted disease in an infant of any gestational age may lead to a fatal outcome. This severe disease is characterized by jaundice, and extensive skin and multisystem involvement, especially pneumonia. In fatal cases hepatic parenchymal involvement can be demonstrated (Brunell 1983; Feldman 1986).

Hepatotropic viruses: hepatitis A, B and C

In general, infection with hepatotropic viruses in neonates does not cause jaundice unless there is acute liver failure or severe hepatitis. Neither hepatitis A nor B have been associated with NHS or biliary atresia (Balistreri *et al.* 1980).

Hepatitis A Hepatitis A is rare in the neonate but congenital infection may occur if the mother is infected 1–2 weeks before delivery (Watson *et al.* 1993). The typical picture in the early neonatal period is a non-specific diarrhoeal illness, as shown by rare outbreaks of transfusion-related hepatitis in premature infants (Klein *et al.* 1984; Noble *et al.* 1984).

Hepatitis B Vertical hepatitis B infection is subclinical in the neonatal period; prompt administration of both hepatitis B immune globulin and hepatitis B immunization provides protection against chronic infection in 93% of infants at risk. Infants who fail this regimen may have been infected transplacentally. Without immunoprophylaxis, infants may become chronic carriers or develop acute hepatitis B or fulminant hepatic failure after a 3- to 4-month incubation period (Dupuy *et al.* 1975; Mollica *et al.* 1977; Shiraki *et al.* 1980; Delaplane *et al.* 1983) (Chapter 7).

Hepatitis C Hepatitis C is not a cause of neonatal hepatitis syndrome. A study of 33 infants with either idiopathic neonatal hepatitis or extrahepatic biliary atresia revealed only one (with extrahepatic biliary atresia) positive for anti-hepatitis C virus (anti-HCV) antibodies and for virus by reverse transcriptase-polymerase chain reaction (RT-PCR) (A-Kader *et al.* 1994). Similar studies in Taiwan, where hepatitis C is endemic, found no anti-HCV-positive infants among 42 with neonatal hepatitis and 11 with extrahepatic biliary atresia, by second-generation enzyme-linked immunoassay (Chang *et al.* 1993). Vertical transmission of hepatitis is less common than in hepatitis B viral infection. Jaundice does not occur.

Human immunodeficiency virus (HIV) infection

Although infants with congenital HIV infection may present with hepatosplenomegaly, conjugated hyperbilirubinaemia in the neonatal period is rare. A case of neonatal hepatitis was attributed to HIV infection despite concomitant congenital cytomegalovirus infection (Witzleben *et al.* 1988); an increased incidence of congenital cytomegalovirus infection has subsequently been found in HIV-infected infants. Congenital HIV infection may present clinically as hepatitis with jaundice although later than in the neonatal period, typically at ~6 months of age (Persaud *et al.* 1993).

Parvovirus B19 infection

Congenital parvovirus B19 infection may cause profound anaemia leading to hydrops (Essary *et al.* 1998) and fetal death. The spectrum includes conjugated hyperbilirubinaemia, hepatomegaly, severe coagulopathy, dermal erythropoiesis ('blueberry muffin' rash), anaemia and perinatal distress (Silver *et al.* 1996). Liver biopsy showed diffuse sinusoidal fibrosis, siderosis, little giant-cell transformation of hepatocytes but excessive extramedullary haematopoiesis (Metzman *et al.* 1989; Langnas *et al.* 1995; White *et al.* 1995). Despite features of early hepatic insufficiency, serum aminotransferases may be low or near normal. Diagnosis is made by PCR for presence of parvovirus 19, although placental histology may suggest prenatal

parvovirus infection. Outcome depends on severity of infection.

Human herpesvirus-6 (HHV-6) infection

Human herpesvirus-6 causes exanthem subitum, a common but usually benign febrile illness in infants; other HHV-6 infections are common and self-limited without a rash. Acute liver failure has been reported (Asano *et al.* 1990; Aita *et al.* 2001).

Syncytial giant-cell hepatitis

'Syncytial giant-cell hepatitis' denotes severe liver disease attributed to paramyxovirus infection. The clinical liver disease varies with the age of the patient: in children, fulminant hepatic failure is common, while rapidly progressive chronic hepatitis occurs in adults. Infants may have features of a chronic active hepatitis or autoimmune haemolytic anaemia.

In neonates, syncytial giant-cell hepatitis is associated with a severe hepatitis, which does not meet the criteria for fulminant liver disease (Chapters 5 and 7). Hepatitis with moderately elevated serum aminotransferases progresses to chronic cholestasis and decompensated cirrhosis over 6–12 months.

Liver histology and electron microscopy show both the characteristic syncytial-type giant cells and viral inclusions consistent with the morphology of paramyxoviruses (Phillips *et al.* 1991; Sussman *et al.* 1994; Hicks *et al.* 2001). Formation of giant multinucleated hepatocytes is a characteristic response of infantile hepatocytes to injury, which is not often seen in hepatitis in adults. Syncytial giant cells differ from the giant cells of neonatal hepatitis because the outline of the liver cell plates remains evident, with indistinct, 'smudged' borders between the cells. They may form because of cell fusion secondary to paramyxovirus, in the same way as other viruses such as respiratory syncytial virus and measles virus.

Spontaneous recovery is uncommon. Treatment with the antiviral agent ribavirin appeared efficacious in one case (Roberts *et al.* 1993). Most babies require liver transplantation before the end of the first year of life.

Enteric viral sepsis (echovirus, Coxsackie viruses, adenoviruses)

The enteroviruses cause systemic viral infection in the newborn period, and severe hepatitis with acute liver failure may be a prominent feature. Incidence is greatest at the seasonal peak incidence of echovirus infections (late summer to early autumn). The infant's mother may relate development of abdominal pain just prior to onset of labour. Vertical infection near the time of birth is associated with more severe disease in the infant. Most infants

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with enteric viral sepsis present between 1 and 5 weeks old. The infant is lethargic and jaundiced, with very high serum aminotransferases and severe coagulopathy; meningitis is usually present. Echovirus serotypes 3, 6, 7, 9, 11, 14, 19 and 21 have all been reported in severe infections with hepatitis (Modlin 1980; Gillam *et al.* 1986; Modlin & Kinney 1986). Echovirus serotype 11 appears to be most virulent for newborns.

Coxsackie A and B viruses are capable of causing an identical clinical picture, although myocarditis or heart failure suggests Coxsackie virus infection. Adenoviruses (Matsuoka *et al.* 1990) and herpes simplex infection (either type 1 or 2) also cause the same severe hepatitis (Benador *et al.* 1990). Mortality with acute liver failure is of the order of 85–90%. Meticulous supportive care is essential (Chapter 14). Infants who recover may develop severe cholestatic jaundice. Subsequent hepatic function in survivors appears entirely normal.

Bacterial infection outside the liver

Conjugated hyperbilirubinaemia may occur with sepsis or localized extrahepatic infection, such as a urinary infection, that is inapparent (Hamilton & Sass-Kortsak 1963; Franson *et al.* 1985; Garcia & Nager 2002). Serum aminotransferases may be slightly elevated; hepatosplenomegaly is uncommon. Jaundice may also occur with streptococcal and staphylococcal infections and Gram-negative bacterial septicaemia.

Infants with galactosaemia may present initially with jaundice and Gram-negative septicaemia, often due to *Escherichia coli* or *Klebsiella* species. Other typical features of galactosaemia may not be obvious. Galactosaemia should be investigated in any infant with conjugated hyperbilirubinaemia associated with sepsis by measuring erythrocyte galactose-1-phosphate uridyl transferase.

Listeriosis

Congenital infection with *Listeria monocytogenes* typically involves the liver. Although meningitis is the predominant clinical feature of the systemic disease, infants have hepatosplenomegaly and are sometimes jaundiced. Pneumonia is usually present. A history of maternal illness is common. Liver biopsy may reveal simply a diffuse hepatitis or, more commonly, diffuse areas of focal necrosis. Diagnosis is made by isolating the organism from blood, cerebrospinal fluid (CSF) or liver. Treatment is with penicillin.

Tuberculosis

Congenital tuberculosis is rare, but since the prevalence of tuberculosis in women of child-bearing age has risen in the past few years, tuberculosis in infants may become

more common. Newborn infants may be infected by aspirating infected amniotic fluid or cervical secretions at the time of delivery.

Practical criteria for diagnosis are a proven tuberculous infection in a newborn baby with at least one of the following: lesions in the first week of life; primary hepatic complex or caseating granulomas in the liver; tuberculous infection of the placenta or maternal genital organs; and exclusion of postnatal infection by investigation of contacts (Cantwell *et al.* 1994).

Hepatomegaly is common in infants with tuberculosis, but jaundice is rare and indicates severe disease. Respiratory distress, poor feeding and fever are frequent. Mortality approaches 30%; a quadruple antitubercular antibiotic regimen *excluding* ethambutol is recommended. A high index of suspicion appears to be required for diagnosis, as tuberculosis in this age group often has atypical clinical features (Gogus *et al.* 1993).

Endocrine disorders

Hypothyroidism

Hypothyroidism is usually associated with an unconjugated hyperbilirubinaemia but may be associated with the neonatal hepatitis syndrome and should be excluded in every patient (Fig. 4.1).

Hypopituitarism

Pituitary–adrenal dysfunction is associated with neonatal hepatitis syndrome in 30–70% of patients (Herman *et al.* 1975; Leblanc *et al.* 1981b; Kraehe *et al.* 1992; Sheehan *et al.* 1992; Ellaway *et al.* 1995). The cause of the hypopituitarism is variable. It is due to hypothalamic dysfunction in some; deficiency of anterior and/or posterior pituitary function may be present; a child with adrenal insensitivity to adrenocorticotropin was also described (Lacy *et al.* 1993). Clinical features include: conjugated hyperbilirubinaemia; hypoglycaemia in the perinatal period, which is usually symptomatic and persistent; and septo-optic dysplasia, which is a neuro-optical malformation that includes ventral midline developmental defect (absence of the septum pellucidum or corpus callosum) and hypoplasia of one or both optic nerves which is associated with hypopituitarism. There may also be midline facial abnormalities, nystagmus and microgenitalia in boys (see Plate 5, Atlas: p. 441).

The diagnosis is confirmed by detecting an extremely low random or 09.00h cortisol in association with a low thyroid-stimulating hormone (TSH) and thyroxine (T4). Liver biopsy usually reveals typical giant-cell hepatitis, but severe cholestasis may be present with dilated bile canaliculi and hepatocellular necrosis. There may be delayed excretion on radioisotope scanning (Kumura *et al.*

1987). Hormone replacement is essential and includes thyroxine, corticosteroids and occasionally growth hormone. Progression of the disease to cirrhosis and portal hypertension has been reported in those children who had delayed or no hormone replacement.

Chromosomal disorders

Trisomy 18

Trisomy 18 is associated with growth retardation, skeletal abnormalities and complex congenital heart disease. Both giant-cell hepatitis and extrahepatic biliary atresia have been reported (Alpert *et al.* 1969; Ikeda *et al.* 1999). In one infant with trisomy 18 serial liver biopsies suggested late evolution of neonatal hepatitis to extrahepatic biliary atresia.

Other cytogenetic abnormalities, including trisomy 13, deletion of the short arm of chromosome 18 and 49 XXXXY (Silveira *et al.* 1991), have been reported in association with extrahepatic biliary atresia.

Trisomy 21

The association between trisomy 21 and neonatal cholestasis or extrahepatic biliary atresia (Henriksen *et al.* 1981) is not well substantiated. Recently, severe hepatic fibrosis associated with transient myeloproliferative disorder has been reported with Down's syndrome (Ruchelli *et al.* 1991; Becroft 1993), raising the possibility that hepatic fibrogenesis might be due to high concentrations of growth factors derived from megakaryocytes.

Cat-eye syndrome

Cat-eye syndrome is a highly variable malformation syndrome associated with a small supernumerary bisatellited marker chromosome derived from duplicated regions of chromosome 22. Major features may include coloboma of the iris and other facial malformations involving the eyes, anal atresia with fistula, complex congenital heart disease and renal malformation. There is considerable phenotypical variability. Extrahepatic biliary atresia has been reported in association with this disorder. A candidate responsible gene in this condition has recently been identified as the human homologue of *CECR1*, which is an insect gene encoding growth factors. The expression pattern of *hCECR1* in heart, cranial nerves and notochord and later in fetal liver, lung and kidney implicates it as leading to cat-eye syndrome when it is overexpressed (Riazi *et al.* 2000).

Idiopathic neonatal hepatitis

In up to 25% of infants presenting with conjugated hyper-

bilirubinaemia before 3 months of age, no aetiology is found, and these infants are considered to have idiopathic neonatal hepatitis. If cholestasis is severe, differentiation from extrahepatic biliary atresia and other cholestatic conditions is important. Infants with idiopathic neonatal hepatitis are more likely to be premature or small for gestational age than those with extrahepatic biliary atresia (Mowat *et al.* 1976), perhaps reflecting a genetic disorder or an intrauterine infection. An important subset of idiopathic neonatal hepatitis includes instances where more than one child in a single family is affected, accounting for 5–15% of cases in most series.

Liver biopsy shows an extensive giant-cell transformation of hepatocytes with inflammation, but bile ducts appear generally normal. A few infants with histologically severe inflammation also have small bile duct paucity. In general, it may not be easy to differentiate between severe idiopathic neonatal hepatitis and extrahepatic biliary atresia. An intraoperative cholangiogram may be required, and there is no evidence that diagnostic laparotomy for assessment of the extrahepatic biliary tree is adverse for infants with idiopathic neonatal hepatitis.

The prognosis is generally good. Mortality is 13–25% (Deutsch *et al.* 1985; Chang *et al.* 1987; Suita *et al.* 1992). Predictors of poor prognosis include: prolonged severe jaundice (beyond 6 months of age); acholic stools; familial occurrence; persistent hepatomegaly; and severe inflammation on biopsy. Peak bilirubin level is not necessarily predictive of outcome, and the prognostic importance of ductopenia has not been rigorously investigated. Septic complications may lead to decompensation. The long-term outlook for infants surviving the first year of life with little evidence of chronic liver disease is very good.

Neonatal hepatitis in preterm infants

Idiopathic neonatal hepatitis does occur in preterm babies, some of whom will have cholestasis due to immaturity of the biliary tree. They may be prone to hypoglycaemia and have a functionally immature gastrointestinal tract resulting in difficulties with feeding. It is important to differentiate this condition from other known causes of NHS and, in particular, extrahepatic biliary atresia. The prognosis is generally good.

Structural abnormalities

Extrahepatic biliary atresia

Extrahepatic biliary atresia (EHBA) is the cause of liver disease in ~25% of infants presenting with neonatal hepatitis syndrome and is the most important differential diagnosis. Early diagnosis is vital as the Kasai portoenterostomy is less likely to be successful the later it is performed (Mieli-Vergani *et al.* 1989; Chardot *et al.* 1999).

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EHBA involves a progressive destruction of the extrahepatic bile ducts, with scarring, obliteration and concomitant damage to small and medium-sized intrahepatic bile ducts. The disease is classified according to the extent of damage at diagnosis. In type 1, damage is limited to the distal common bile duct (also known as 'correctable'); in type 2 damage is limited to the common hepatic duct; in type 3, which is the most common, the entire extrahepatic biliary tree is involved. Type 1 accounts for ~10% of EHBA, and type 2 is extremely rare (Chapter 18).

EHBA is found worldwide in all racial groups, with an incidence of 1 in 8000–15 000 live births. For discussion of aetiology and pathogenesis see Chapter 18.

Clinical features

The clinical presentation of EHBA is unremitting, progressive jaundice in an infant who usually looks well. The main features are:

- Normal birth weight and gestational age in the majority. Preterm infants can have EHBA.
- Jaundice, which is present from shortly after birth, continuous with physiological jaundice. There may be some variability in intensity; however, jaundice can be readily identified in affected infants by 4 weeks of age.
- Yellow or dark urine with increasingly pale stools, which eventually become acholic. Initially there may be variation in stool colour, which may be confusing.
- Hepatomegaly is always present; the liver is usually firm.
- Splenomegaly is a late sign and implies some degree of hepatic fibrosis.
- Failure to thrive despite adequate feeding.
- Cardiovascular anomalies (ventricular or atrial septal defects) in 30%.
- Polysplenia syndrome; this includes preduodenal portal vein, situs inversus, absence of inferior vena cava and malrotation (Chapter 18).
- Bleeding from vitamin K-responsive coagulopathy, which is more common in breast-fed infants who did not receive vitamin K at birth.
- Ascites and pruritus are late complications indicating progression to cirrhosis.

Diagnosis

A diagnosis of EHBA involves the following investigations and findings:

- Serum conjugated bilirubin at presentation ranges from 40 to 200 $\mu\text{mol/l}$.
- Serum aminotransferases are always abnormal: concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are typically in the range of 80–200 iU/l.

- Serum alkaline phosphatase is usually elevated (range 500–800 iU/l) due to biliary damage or rickets.
- Gamma-glutamyl transpeptidase is usually elevated ($\times 10$ normal).
- Serum albumin is usually normal.
- Cholesterol may be elevated but triglycerides are normal.
- Prothrombin time is normal although 5–10% of cases present with vitamin K-responsive coagulopathy.
- Blood glucose is usually normal.
- Hepatic ultrasound, after a 4-h fast, may not demonstrate a gall bladder or only a contracted gall bladder (see Plate 2a, Atlas: p. 440); it rarely shows a dilated extrahepatic biliary tree, consistent with distal, 'correctable' atresia; dilated intrahepatic bile ducts are uncommonly found. Abnormal vascular anatomy consistent with the polysplenia syndrome may be seen.
- Hepatobiliary scanning, using TEBIDA, following phenobarbitone pretreatment (5 mg/kg/day for 3–5 days) fails to demonstrate passage of the radiolabelled substance into the intestinal tract over a 24-h period (see Plate 3b, Atlas: p. 440). Although hepatobiliary scanning has high sensitivity, scanning may appear normal if performed very early in the disease process in late-pattern extrahepatic biliary atresia (Clarke *et al.* 1997; Gilmour *et al.* 1997). It may also fail to show bile drainage in severe idiopathic neonatal hepatitis or bile duct paucity syndromes.
- Percutaneous liver biopsy is essential and has high diagnostic specificity. Features of bile duct obstruction (bile ductular proliferation, bile plugs in small bile ducts, portal tract oedema) are usually obvious, along with variable fibrosis and some giant-cell transformation (see Plate 4b, Atlas: p. 441). The earlier the liver biopsy is performed, the more difficult it may be to interpret. When the hepatobiliary scan shows no drainage and the liver histology is ambiguous, close clinical surveillance is required to determine the evolution of disease.
- Uncertain cases require cholangiography, usually intraoperative, although endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and MR cholangiography are possible alternatives (Derkx *et al.* 1994; Norton *et al.* 2002) (Chapter 18).

Management

Therapy consists of nutritional and family support. Palliative surgery, the Kasai portoenterostomy, should be carried out, if possible, to establish biliary drainage. See Chapter 18 for operative details and postoperative management.

Optimally, the diagnosis of EHBA must be established before the infant is 5–7 weeks old, so that the Kasai portoenterostomy can be performed by 6–8 weeks of age. The

operation should not be withheld from infants of 10–12 weeks of age because successful palliation can be achieved in one-third of patients. It is probably not indicated after 14 weeks of age, but every child should have a laparotomy to confirm the diagnosis and exclude unusual anatomy that might be amenable to surgical reconstruction. In one series there was no improvement in outcome associated with very early (before the infant is 40 days old) operation (Davenport *et al.* 1997). Contrary to initial impressions, the presence of the polysplenia syndrome does not in itself predict that the Kasai operation is likely to fail (Karrer *et al.* 1991; Vasquez *et al.* 1995).

Complications and outcome

The complications include recurrent cholangitis, malnutrition secondary to malabsorption, and progression to cirrhosis and portal hypertension. Patients with a well-functioning portoenterostomy appear to have some risk of recurrent cholangitis at any age despite prophylaxis. In one series, children with correctable atresia appeared unusually susceptible to septicaemia, presumably due to bacterial cholangitis.

Since damage to intrahepatic bile ducts is progressive irrespective of whether or not bile drainage is re-established, even children with a successful Kasai operation may be expected to develop biliary cirrhosis. Portal hypertension with variceal haemorrhage occurs in many long-term survivors, and endoscopic injection sclerotherapy or band ligation may be required.

In ~40% of children, a Kasai portoenterostomy fails to establish biliary drainage. These children remain cholestatic and develop the complications of fat malabsorption with subsequent protein-energy malnutrition, and should be referred immediately for liver transplantation (Chapter 20).

Five-year survival after Kasai portoenterostomy is 40–60% (Houwen *et al.* 1989). Patients in Japan (Nio *et al.* 1996) and elsewhere (Davenport *et al.* 1997) have survived 20 years or more after a portoenterostomy without liver transplantation: most are well and asymptomatic, with normal growth and psychosocial development, but have evidence of chronic liver disease. A few women have had babies after apparently uncomplicated pregnancies.

The majority of children will require liver transplantation at some stage, especially if the Kasai portoenterostomy has not been successful.

Choledochal cyst

Choledochal cyst refers to a group of congenital malformations of the biliary system. There are five major forms (Todani *et al.* 1977). Choledochal cysts may be identified

in the fetus by prenatal sonography (Bancroft *et al.* 1994; Stringer *et al.* 1995; Burnweit *et al.* 1996) (see also Chapter 18).

Clinical features and diagnosis

The triad of symptoms associated with choledochal cyst consists of jaundice, abdominal mass and pain, but this is an unusual presentation in the neonatal period. There is female predominance (female: male is 5:1). Most affected infants have jaundice, abdominal mass or distension, and acholic stools (Stringer *et al.* 1995; Todani *et al.* 1995), and differentiation from biliary atresia or choledocholithiasis is important.

The diagnosis is made by identifying the choledochal cyst by ultrasound examination of the liver in a jaundiced infant (see Plate 2b, Atlas: p. 440). Cholangiography, either percutaneous or endoscopic, confirms the diagnosis (see Plate 3c, Atlas: p. 440). Hepatobiliary scanning has limited utility for diagnosis. Liver function tests are compatible with biliary obstruction.

Treatment and outcome

Treatment is aimed at removing the cyst as much as possible (Chapter 18). Excision of the cyst with hepaticoenterostomy offers the best outcome (Lipsett *et al.* 1994; Miyano & Yamataka 1997; Yamataka *et al.* 1997). Complications are less with early surgical intervention. Surgery should be performed promptly in infants diagnosed prenatally who have conjugated hyperbilirubinaemia. If the infant remains free of jaundice, elective surgical resection of the choledochal cyst may be postponed until the infant is ~1 month old, but it should not be greatly delayed. Although ~50% of infants with prenatally identified bile duct dilatation have hepatic fibrosis, and a few have cirrhosis, most of these infants do well. A minority of infants may have correctable biliary atresia, and close follow-up is warranted.

Caroli disease

Caroli disease (also known as type 5 choledochal cyst) denotes congenital saccular dilatations of the intrahepatic bile ducts, without hepatic fibrosis or portal hypertension. It is often associated with autosomal recessive polycystic kidney disease. Caroli disease is rarely evident in infancy, but associated jaundice may be due to acute cholangitis. Some newborn infants with severe autosomal recessive polycystic kidney disease have extensive cystic bile duct changes, but renal insufficiency dominates the clinical picture. Ultrasound of the liver is often adequate for diagnosing Caroli disease; cholangiography is confirmatory. Outcome is related to the severity of renal disease (Chapter 9).

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Congenital hepatic fibrosis, often associated with these same bile duct abnormalities (Caroli syndrome), may present in infancy with hepatomegaly and either autosomal recessive polycystic kidney disease or systemic hypertension. Jaundice and abnormal serum aminotransferases are uncommon (Alvarez *et al.* 1981). Outcome is variable and depends on the progression of hepatic and renal disease (Chapter 9).

Cholelithiasis and choledocholithiasis

Choledocholithiasis was reported in four of 62 children with neonatal hepatitis syndrome (Lilly 1980). Two of these infants had structural abnormalities of the extrahepatic bile ducts (correctable biliary atresia in one and choledochal cyst in the other). Stones were of the bilirubinate type. The stones were removed without difficulty by standard methods once the diagnosis was secured. Subsequent reports indicate that choledocholithiasis is not rare in infants (Debray *et al.* 1993; Bohle 1995; Rescorla 1997). Haemolysis, fasting and total parenteral nutrition may be contributing factors, in addition to anatomical abnormalities. The obstructing gallstone may not contain enough calcium to be seen on a plain abdominal X-ray, but ultrasound usually (though not consistently) identifies the gallstone or shows dilatation of the biliary tree due to obstruction.

Treatment may not be required if the stones are asymptomatic or pass into the duodenum without intervention (Monnerie & Soulard 1995). Prolonged obstruction or cholangitis require surgery (Ishitani *et al.* 1996; Wilcox *et al.* 1997). Alternatives to surgical treatment include ursodeoxycholic acid (20 mg/kg/day); and percutaneous drainage after percutaneous transhepatic cholangiogram with lavage of the bile ducts and ERCP combined with sphincterotomy in older infants (Wilkinson 1996). Adequate antibiotic treatment is required to avoid bacterial cholangitis (Chapter 18).

Inspissated bile syndrome

'Inspissated bile syndrome' is the term traditionally given to conjugated hyperbilirubinaemia complicating severe jaundice associated with haemolysis, usually due to rhesus factor or ABO incompatibility or erythrocyte membrane abnormalities. A multifactorial cause cannot be entirely excluded as these infants are often premature and present complex medical problems. Intrahepatic cholestasis is found on liver biopsy, and cholestasis may be due to direct hepatocellular toxicity of unconjugated bilirubin. The outlook is generally good, although early reports showed cirrhosis in some infants.

Obstruction of the extrahepatic biliary system with dried-out highly viscous bile has been reported in cystic fibrosis (Davies *et al.* 1986; Evans *et al.* 1991). Diagnosis is

usually made by demonstrating dilated bile ducts on ultrasound or cholangiography. Treatment includes ursodeoxycholic acid (20 mg/kg/day) or surgical or percutaneous lavage (Chapter 18).

Spontaneous perforation of the common bile duct

This condition usually presents as a severe acute illness resembling acute peritonitis with abdominal pain and distension, jaundice and fever, but may present as neonatal hepatitis syndrome with abdominal distension in addition to jaundice and acholic stools (Stringel & Mercer 1983). Biliary ascites is pathognomonic. Bacterial superinfection greatly increases the morbidity of this condition. Hepatobiliary scan may indicate the site of leakage and typically shows no drainage into the intestinal tract. In some cases perforation is associated with distal choledocholithiasis. Surgical repair is usually curative (Lloyd & Mickel 1980) (Chapter 18).

Neonatal sclerosing cholangitis

Neonatal sclerosing cholangitis (NSC) was first reported in 1987 with a few subsequent reports (Amedee-Manesme *et al.* 1987; Sisto *et al.* 1987; Maggiore *et al.* 1988; Mulberg *et al.* 1992; Baker *et al.* 1993). The aetiology of this condition is unknown but may have a genetic basis (Baker *et al.* 1993). Currently the true nature of neonatal sclerosing cholangitis remains uncertain, although scepticism as to whether the entity exists seems unwarranted. In one case non-specific autoantibodies were detected (Bar Meir *et al.* 2000).

NSC is distinguished from childhood primary sclerosing cholangitis by the presentation in early infancy with conjugated hyperbilirubinaemia which then resolves. The clinical picture includes:

- Jaundice, which subsides within 3–6 months (Amedee-Manesme *et al.* 1987). Although some children with childhood primary sclerosing cholangitis present as infants (Wilschanski *et al.* 1995), they have not had early cholestatic jaundice.
- Recurrent hyperbilirubinaemia develops 1–2 years later or in mid childhood (8–10 years old).
- Development of hepatosplenomegaly, biliary cirrhosis and portal hypertension.

Laboratory investigations indicate obstructive biliary disease with elevated serum alkaline phosphatase and gamma-glutamyl transpeptidase. Endoscopic or percutaneous cholangiography demonstrates beaded irregularity of medium to large intrahepatic bile ducts in all patients and in extrahepatic ducts in 80%. Liver histology shows portal fibrosis with ductal proliferation developing into biliary cirrhosis.

Surgical treatment with Kasai portoenterostomy is not indicated and nutritional and supportive management is

required. The majority of children require liver transplantation at some stage.

Hair-like bile duct syndrome

This very rare disorder is known as extrahepatic biliary hypoplasia (Krant & Swenson 1973; Lilly 1976) or 'hair-like bile duct syndrome'. Infants present with conjugated hyperbilirubinaemia and features suggesting extrahepatic biliary atresia, but are found at laparotomy to have an intact but disproportionately small extrahepatic biliary tree. In some reports the extrahepatic bile duct was described as thickened. The clinical course is similar to that of neonatal sclerosing cholangitis: resolution of jaundice, development of biliary cirrhosis, progressive cholestasis with recurring jaundice, portal hypertension, and hepatic insufficiency. A Kasai portoenterostomy is not indicated for these children.

Bile duct paucity syndromes

Alagille's syndrome

Alagille's syndrome (syndromic duct paucity, Watson–Miller syndrome, arteriohepatic dysplasia) is a genetic disorder with autosomal dominant transmission but highly variable expression. Alagille's syndrome was identified in the early 1970s (Watson & Miller 1973; Alagille *et al.* 1975) because of the unusual association of congenital heart disease, usually peripheral pulmonary artery stenosis, with neonatal cholestasis. Alagille's syndrome is thought to be rare, occurring in 1 in 100 000 live births. This is probably a gross underestimate, reflecting only those with disease severe enough to be recognized clinically.

Genetic basis The genetic basis for Alagille's syndrome has been determined. Analysis of multiple kindreds indicates autosomal dominant inheritance, with essentially complete penetrance but highly variable expression. There is no evidence for anticipation or imprinting in the pattern of expression. The proportion of new mutations is uncertain, estimated at 15% to $\geq 50\%$ (Dhorne-Pollet *et al.* 1994; Elmslie *et al.* 1995). The gene defect has been localized to the human *JAG1* gene which is on the short arm of chromosome 20 (20p12) (Li *et al.* 1997; Oda *et al.* 1997).

JAG1 is the human homologue of the rat gene *Jagged 1*. It codes for a ligand of Notch 1, which is one of four members in a family of transmembrane proteins with epidermal growth factor (EGF)-like motifs. Alagille's syndrome is the first childhood disorder identified with a mutation in a ligand for a Notch protein. The expression of Notch 1 and its ligand includes many of the organs potentially abnormal in Alagille's syndrome. *JAG1* is expressed in adult heart and kidney; it is not expressed in adult liver, but it is

in fetal liver (Li *et al.* 1997; Pollet *et al.* 1997). Haploinsufficiency of *JAG1* causes Alagille's syndrome. Dosage of Notch ligands is critical in development, and this may contribute to the clinical diversity of Alagille's syndrome. Mutations result in truncated and thus inactive proteins; residual gene expression cannot compensate, leading to the phenomenon of haploinsufficiency (Spinner *et al.* 2001). Many mutations are sporadic. No clear relationship between genotype and phenotype has been found, although the Delta/Serrate/Lag-2 (DSL) domain in the *JAG1* protein may influence the severity of liver disease (Crosnier *et al.* 1999; Colliton *et al.* 2001; Crosnier *et al.* 2001; Yuan *et al.* 2001).

Clinical features Alagille's syndrome is fairly benign in the majority of children. The majority of patients with clinically important Alagille's syndrome have conjugated hyperbilirubinaemia in the neonatal period (Deleuze *et al.* 1995; Emerick *et al.* 1999). The main clinical features are as follows (see Plate 6, Atlas: p. 442):

- Cholestasis, which may be sufficiently severe to produce acholic stools and dark urine.
- Characteristic facies, which consists of a broad forehead, deep-set eyes, mild hypertelorism, straight nose and small pointed chin. The facies may not be evident in the first months of life and the classic childhood appearance differs from the adult form.
- Skeletal abnormalities, which include 'butterfly' vertebrae due to failure of fusion on the anterior arch of the vertebral body, are commonly found in the thoracic spine (Sanderson *et al.* 2002). There may also be a decrease in the interpedicular distance in the lumbar spine, spina bifida occulta, short distal phalanges and fifth finger clinodactyly, and short ulna.
- Eye findings may be very diverse (Hingorani *et al.* 1999). Posterior embryotoxon, an abnormal prominence of Schwalbe's line (junction of Descemet's membrane with the uvea at the angle of the anterior chamber), is most common and requires slit-light examination for detection. It is not pathognomonic since it occurs in 8–15% of normal persons. Optic disc drusen, which are calcific deposits in the extracellular space of the optic nerve head, are common in Alagille's syndrome and are not found in other cholestatic conditions. They are detected by ocular ultrasound examination (Nischal *et al.* 1997). Abnormal retinal pigmentation without evidence of functional retinal degeneration may occur. Strabismus, ectopic pupil and hypotrophic optic discs with or without abnormal retinal vessels have also been reported.
- Cardiac disease includes peripheral pulmonary artery stenosis, severe hypoplasia of the pulmonary artery branches (Silberbach *et al.* 1991; McElhinney *et al.* 2002), Fallot's tetralogy, pulmonary valve stenosis, aortic stenosis, ventricular septal defect, atrial septal defect and anomalous pulmonary venous return. The severity of

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cardiac disease varies between patients and careful assessment is required, particularly if liver transplantation is contemplated.

- Chronic cholestasis with pruritus, fat malabsorption, occasionally exacerbated by exocrine pancreatic insufficiency.
- Failure to thrive in association with intrauterine retardation.
- Severe malnutrition present in ~50% of patients may be part of the syndrome or secondary to fat malabsorption or gastroesophageal reflux.

Minor features Apart from the main aspects of Alagille's syndrome outlined above, a number of other features may be present. These are:

- Renal disease, which includes defects in urinary concentrating function, nephrolithiasis, or structural abnormalities such as small kidneys or congenital single kidney, or renal cystic disease. Histological examination may reveal a membranous nephropathy or lipid accumulation in the kidney (mesangiolipidosis).
- Delayed puberty or hypogonadism.
- Abnormal cry or voice.
- Mental retardation, learning difficulties or antisocial behaviour.
- Vascular anomalies, including decreased intrahepatic portal vein radicals, coarctation of the aorta and other arterial abnormalities, and Moya Moya disease (Connor *et al.* 2002).
- Neurological abnormalities, such as peripheral neuropathy, may be related to vitamin E deficiency from severe chronic cholestasis.
- Hypothyroidism and pancreatic insufficiency.
- Recurrent otitis media (Quiros-Tejeira *et al.* 1999).
- Recurrent chest infections, perhaps secondary to gastrointestinal reflux and aspiration pneumonia.
- Xanthomata secondary to hypercholesterolaemia.

Diagnosis The diagnosis of Alagille's syndrome is based on the characteristic clinical features, but laboratory investigations may indicate:

- Conjugated hyperbilirubinaemia in neonates, which may improve with age.
- Aspartate aminotransferase and alkaline phosphatase concentrations are usually elevated ($\times 10$ normal).
- Gamma-glutamyl transpeptidase concentration elevated 3–20 times normal.
- Serum cholesterol and triglyceride may be raised to values three times the upper limit of normal.
- Serum albumin and prothrombin time are normal except in decompensated disease.
- Abdominal ultrasound may be normal or show a small contracted gall bladder.
- Radioisotope scanning may show delayed or no excretion if intrahepatic cholestasis is severe.

- Liver biopsy classically shows reduced numbers of small (i.e. portal) bile ducts and in neonates there may be giant-cell transformation and cholestasis. In some infants (up to 20%) ongoing damage to small bile ducts may be found, or bile ductular proliferation suggestive of extrahepatic bile duct obstruction. The diagnostic histological findings may become obvious only with age (Deutsch *et al.* 2001). Alternatively, the number of portal tracts may be reduced. Periportal or centrilobular fibrosis is usually absent in infancy but progressive disease with biliary cirrhosis develops in 15–20% of patients. Differentiation from extrahepatic biliary atresia may be difficult on histological grounds alone, particularly if there is significant bile ductular proliferation (see Plate 6, Atlas: p. 442).

Management It is essential to exclude extrahepatic biliary atresia, which may be difficult in infants with severe cholestasis, acholic stools and non-excreting hepatobiliary scanning. Endoscopic or operative cholangiography may identify a patent extrahepatic biliary tree. Portoenterostomy is not indicated as this rarely improves bile flow and may increase portal fibrosis because of recurrent cholangitis.

Specific management of Alagille's syndrome is dependent on the distribution and severity of associated disease. Severe cholestasis requires supportive management (see p. 60–3). Nutritional support with feeding via a gastric tube may be highly effective (Duche *et al.* 1999). Hypercholesterolaemia usually responds to a modified fat diet; gastroesophageal reflux requires standard medical or surgical management. Cardiac anomalies may require corrective surgery, with balloon dilatation or surgical correction of pulmonary valve or pulmonary artery stenosis. Children with Alagille's syndrome are prone to bleeding episodes without necessarily having definite abnormalities of coagulation (Berard & Triolo 2000; Lykavieris *et al.* 2003). Special caution must be exercised with respect to head trauma. Renal disease requires specific management as indicated.

Outcome The outcome of Alagille's syndrome depends on the hepatic and extrahepatic disease. The majority of children have a benign course. Most estimates put overall mortality at 20–30%, due to cardiac disease, intercurrent infection or progressive liver disease (Hoffenberg *et al.* 1995; Emerick *et al.* 1999; Lykavieris *et al.* 2001). Early reports of outcome minimize the role for liver transplantation. Liver transplantation should be reserved for patients with hepatic failure, intolerable pruritus unresponsive to medical treatment, and severe growth failure. Liver transplantation can be complicated by associated heart disease, renal impairment or vascular anomalies. Catch-up growth after transplantation often occurs (Cardona *et al.* 1995; Holt *et al.* 1997; Quiros-Tejeira *et al.* 2000) (Chapter 20).

Non-syndromic duct paucity

In a full-term neonate with small bile duct paucity in whom Alagille's syndrome has been excluded, various disorders may cause portal ductopenia (small duct paucity), known as 'non-syndromic duct paucity'. These disorders (Table 4.2) fall into the broad categories of infection, genetic (with chromosomal abnormalities), and metabolic diseases (Kahn *et al.* 1986). When idiopathic neonatal hepatitis is clinically severe, bile duct paucity may also be present.

Among congenital infections cytomegalovirus is the most important cause (Finegold & Carpenter 1982; Dimmick 1993) and cytomegaloviral inclusions may be found in bile duct epithelial cells. Chromosomal abnormalities associated with duct paucity include trisomy 18 and 21. Metabolic disorders associated with duct paucity in the infant are diverse and include α_1 -antitrypsin deficiency (usually indicates more severe liver disease and a poor prognosis), Byler syndrome, and rarely cystic fibrosis or Zellweger syndrome. Duct paucity may also develop in late stages of extrahepatic biliary atresia following a Kasai portoenterostomy or in primary sclerosing cholangitis.

Small bile duct paucity may develop in infants as a result of graft vs. host disease (Shulman *et al.* 1988) or other immunological injury complicating allogeneic bone marrow transplant or a stem-cell transplant in the perinatal period. Occasionally this develops without features of graft vs. host disease (Wulffraat *et al.* 1997).

Where no specific associated condition can be found,

Table 4.2 Causes of non-syndromic paucity of bile ducts in infants

Prematurity
Infection
Cytomegalovirus (CMV)
Rubella
Syphilis
Hepatitis B
Metabolic
α_1 -antitrypsin deficiency
Cystic fibrosis
Zellweger syndrome
Byler syndrome
Ivemark syndrome
Prune belly syndrome
Hypopituitarism
Genetic: chromosomal disorders
Trisomy 18, 21
Partial trisomy 11
Monosomy X
Immune-related: graft vs. host disease
Severe idiopathic neonatal hepatitis
Isolated/idiopathic

then isolated non-syndromic bile duct paucity can be diagnosed. These children are supposed to have a less favourable outlook than children with Alagille's syndrome, with persistent severe cholestasis and progressive liver damage. The relationship of childhood non-syndromic duct paucity to idiopathic adult ductopenia, which has recently been described and may be familial, remains uncertain (Ludwig *et al.* 1988; Bruguera *et al.* 1992).

Metabolic liver disease

α_1 -Antitrypsin deficiency

This autosomal recessive condition is the most common inherited cause of neonatal hepatitis syndrome. Deficiency occurs in 1 in 1600–2000 live births in North American and European populations, but it is less common in people of other ethnic backgrounds. The protease inhibitor, α_1 -antitrypsin, is a glycoprotein that is mainly produced in the liver. Only a small proportion of individuals with α_1 -antitrypsin deficiency ever develop liver disease, but it is the main cause of emphysema in early adulthood.

Aetiology and genetics

A member of the serpin superfamily, α_1 -antitrypsin binds and inactivates leucocyte elastase. More than 75 variants have been reported. The deficiency status is caused by a mutation in the gene at the PI locus on chromosome 14. There is impaired secretion of the mutant gene product, which can be demonstrated in the hepatocyte (periodic acid–Schiff (PAS)-positive diastase-resistant granules). The most common deficiency variant is 'Z', a slow-moving protein on electrophoresis, with a point mutation resulting in a single amino acid substitution (lysine replacing glutamic acid at position 342). Some variants such as M_{Malton} and M_{Duarte} show only subtle differences from the normal 'M' electrophoretically and may be difficult to recognize.

Structural variants of α_1 -antitrypsin are classified according to the protease inhibitor (PI phenotype) system. More than 75 variants have been reported, most of which are not associated with clinical disease. Liver disease is associated with PI ZZ in the majority of cases. It may occur with PI SZ at a relatively young age and with PI FZ and PI MZ later in adulthood (Gourley *et al.* 1989; Primhak & Tanner 2001).

The pathogenesis of liver disease is unknown, although studies in transgenic mice indicate that liver injury is caused by the intracellular accumulation of the abnormal α_1 -antitrypsin gene product (Carlson *et al.* 1989). The Z mutation causes abnormal folding of the α_1 -antitrypsin molecule so that it is caught in the endoplasmic reticulum (Lomas *et al.* 1992; Perlmutter 1996). Since

not everyone with PI ZZ α_1 -antitrypsin develops liver disease, additional factors such as increased production and decreased removal of abnormal α_1 -antitrypsin within hepatocytes might accelerate liver damage. One possible mechanism involves the serpin–enzyme complex (SEC), which is activated by α_1 -antitrypsin–elastase complexes and by inflammatory mediators such as substance P (Perlmutter 1994). When activated, it increases α_1 -antitrypsin synthesis. Since α_1 -antitrypsin is an acute-phase reactant, any inflammatory process might increase its production. Defects in hepatocellular proteasome action or other mechanisms for removing abnormal proteins from the endoplasmic reticulum might account for excessive accumulation of abnormal α_1 -antitrypsin in hepatocytes. New treatments are envisioned based on these mechanisms, including administration of chemical chaperones (Burrows *et al.* 2000; Perlmutter 2002).

Clinical features

Neonates with α_1 -antitrypsin deficiency who develop liver disease present with

- Conjugated hyperbilirubinaemia (see Plate 1, Atlas: p. 440).
- Intrauterine growth retardation.
- Severe cholestasis with totally acholic stools; differentiation from extrahepatic biliary atresia may be difficult. The rare infant has been reported with both α_1 -antitrypsin deficiency and extrahepatic biliary atresia (Nord *et al.* 1987).
- Hepatomegaly is usual at presentation, but splenomegaly is unusual unless significant hepatic fibrosis develops.

Approximately 2% of infants present with a vitamin K-responsive coagulopathy, which is more likely in those infants not given prophylactic vitamin K at birth or who are breast fed. The coagulopathy may be obvious, with bruising and bleeding from the umbilicus, or the initial presentation may be an intraventricular haemorrhage. There is a rapid response to intravenous vitamin K (Hope *et al.* 1982).

Diagnosis

Biochemical evaluation demonstrates a mixed hepatocellular/obstructive pattern with raised aminotransferases, alkaline phosphatase and gamma-glutamyl transpeptidase.

Radiological investigation may demonstrate severe intrahepatic cholestasis with a contracted gall bladder on abdominal ultrasound and delayed or absent excretion of radioisotope on hepatobiliary scanning.

In homozygotes the diagnosis is confirmed by demonstrating low serum α_1 -antitrypsin levels (normal >1.0 g/l) and determining the phenotype (PI) by isoelec-

tric focusing. Confusion may occasionally arise if α_1 -antitrypsin levels are increased secondary to hepatic inflammation because it is an acute-phase reactant, but in practice this is rarely a problem with homozygotes.

Liver biopsy typically demonstrates a giant-cell hepatitis in which the characteristic PAS-positive diastase-resistant (PASD) granules are detected in the hepatocytes, often noted as early as 6–8 weeks (see Plate 6, Atlas: p. 441). Occasionally PASD-positive inclusions are found in individuals without the Z allele because of an M variant associated with hepatocellular α_1 -antitrypsin retention (Roberts *et al.* 1984).

Management

Management consists of nutritional support, fat-soluble vitamin supplementation, treatment of pruritus and cholestasis as required (see p. 60–3). Patients and parents should not be permitted to smoke, and phenotype inhibitor zz (PIZZ) individuals should be protected from secondary smoke. It is usual to offer family screening for families wishing to have further children. Parents are obligate heterozygotes, thus there is a 25% chance of each subsequent fetus being affected. Antenatal diagnosis by chorionic villus sampling is now available using synthetic oligonucleotide probes specific for the M and Z gene or by restriction fragment length polymorphism (Povey 1990).

Prognosis

The prognosis is varied. The long-term outlook for many infants with α_1 -antitrypsin deficiency is good, although a certain proportion of infants with early jaundice develop chronic liver disease (Moroz *et al.* 1976; Odievre *et al.* 1976; Ghishan & Greene 1988; Volpert *et al.* 2000). The outcome falls into four general categories (Psacharopoulos *et al.* 1983). Approximately half do well: of these infants, half are entirely normal and the other half have mildly abnormal serum aminotransferases but no progression of liver disease. The other half do poorly. Of the infants with poor prognosis, half develop persisting cholestasis with progressive hepatic decompensation and may die or require live transplantation in the first year of life. In the other half, jaundice resolves but serum aminotransferases are abnormal; the liver and spleen remain enlarged. These infants develop cirrhosis with eventual hepatic insufficiency. The small group of children with α_1 -antitrypsin deficiency who present later in infancy or in childhood with hepatomegaly, without neonatal jaundice, usually have early cirrhosis and a poor prognosis.

Early prognostication of individual infants with α_1 -antitrypsin deficiency is difficult. Standard indicators of hepatic decompensation, such as persistent or recurring jaundice, hepatosplenomegaly, prolonged prothrombin

time (PT), and elevated serum aminotransferases, are only helpful later in the course of disease (Nebbia *et al.* 1983). A retrospective analysis of 85 children with neonatal hepatitis and α_1 -antitrypsin deficiency showed that very elevated serum alanine aminotransferase, prolonged PT, and very low serum α_1 -antitrypsin concentration at presentation were associated with poor outcome; girls generally had a worse outcome than boys (Ibarguen *et al.* 1990). In another study of children with neonatal hepatitis, persisting elevation of serum aminotransferases and serum GGT through 6–12 months of age, or presence of bile ductular proliferation, bridging fibrosis or cirrhosis on the initial liver biopsy presaged rapidly progressive liver disease (Francavilla *et al.* 2000). Infants in whom jaundice or hepatomegaly resolves before the age of 6 months are likely to have a good outcome, but those with prolonged jaundice, cirrhosis or bile duct paucity pursue a downhill course. Infants whose liver disease appears to resolve should still be monitored for development of splenomegaly, as this may herald advancing hepatic fibrosis. Children with α_1 -antitrypsin-associated cirrhosis may remain stable for some time but may decompensate precipitously. Evaluation for liver transplantation should be considered early for these children. They tolerate liver transplantation well, although attention to potential kidney disease associated with α_1 -antitrypsin deficiency is required through the early post-operative period (Prachalias *et al.* 2000).

Cystic fibrosis

Abnormalities of liver function tests or hepatic pathology are found in one-third of infants with cystic fibrosis (Chapter 11). The spectrum of hepatic pathology includes: giant-cell hepatitis; extrahepatic bile duct obstruction by inspissated bile; massive hepatic steatosis

usually without conjugated hyperbilirubinaemia, and paucity of small (portal tract) bile ducts. The clinical presentation is with jaundice, hepatomegaly, failure to thrive and extrahepatic biliary tract obstruction similar to extrahepatic biliary atresia due to plugging of the common bile duct by abnormal bile (Davies *et al.* 1986). Early studies suggested that infants with severe liver disease had meconium ileus, which is supported by more recent data obtained at autopsy in patients similar with respect to pulmonary function, nutritional status and Schwachman score (Maurage *et al.* 1989). Children with cirrhosis had a statistically significant relationship between incidence of mucous plugs in liver tissue histologically and meconium ileus in infancy or distal intestinal obstruction syndrome later in life. Occurrence of neonatal hepatitis syndrome in itself does not necessarily predict early development of cirrhosis.

Another rare lesion in cystic fibrosis in infancy is paucity of intrahepatic bile ducts ('non-syndromic duct paucity') (Furuya *et al.* 1991), raising the possibility that there is an inherent abnormality in the small bile ducts in cystic fibrosis.

Severe hepatic steatosis has been reported in infants with cystic fibrosis who are typically not jaundiced. In one case, carnitine deficiency was found, and the steatosis improved with carnitine supplementation (Treem & Stanley 1989).

Primary disorders of bile acid synthesis

Inherited defects in the enzymes involved in bile acid synthesis lead to neonatal hepatitis syndrome or to chronic cholestasis later in childhood. A number of new entities have been identified (Table 4.3), largely facilitated by fast atom bombardment-mass spectroscopy (FAB-MS) of urine to identify unusual intermediates arising from

Table 4.3 Primary disorders of bile acid synthesis

Enzyme	Cellular location	Features	Treatment
3 β -Hydroxy- Δ^5 -C ₂₇ -steroid dehydrogenase/isomerase	Endoplasmic reticulum ('microsomal')	Severe neonatal hepatitis; normal serum GGT; low serum total bile acid concentrations; no pruritus	Cholic acid \pm UDCA initially
Δ^4 -3-Oxosteroid 5 β -reductase	Cytoplasm ('cytosolic')	Severe cholestasis, coagulopathy; elevated serum total bile acid concentrations	Cholic acid
24,25-Dihydroxy-cholanoic cleavage enzyme	Endoplasmic reticulum	Severe giant-cell hepatitis; normal serum GGT; elevated serum cholesterol; low serum total bile acid concentrations	Cholic acid
C ₂₇ -Hydroxylase	Mitochondria	Cerebrotendinous xanthomatosis: No liver disease	–

GGT, Gamma-glutamyl transpeptidase; UDCA, ursodeoxycholic acid.

deranged bile acid synthesis. Although rare, these diseases can be treated by supplementation of critical bile acids if the diagnosis is made early in the course of disease.

Aetiology

Bile acid synthesis involves the conversion of cholesterol to the primary bile acids, cholic and chenodeoxycholic acid. This takes place in hepatocytes, and enzymes in the process are variously located in the endoplasmic reticulum ('microsomal'), the cytoplasm ('cytosolic'), mitochondria or peroxisomes. The initial, and rate-limiting, step is a change in the steroid nucleus: hydroxylation of cholesterol at the C₇ position by the microsomal enzyme 7 α -hydroxylase. Further modifications can then be categorized as involving the steroid nucleus or the side chain. Side-chain abnormalities are found mainly with mitochondrial or peroxisomal disorders. Cerebrotendinous xanthomatosis is due to deficiency of the mitochondrial enzyme C₂₇-hydroxylase, leading to abnormal side-chain modifications; neonatal cholestasis and jaundice do not occur in this disease. Autosomal recessive mutations in two enzymes associated with steroid nucleus modifications at early stages of bile acid synthesis have been associated with severe neonatal liver disease. Two other inborn errors of bile acid metabolism have been described in single patients presenting with neonatal liver disease. An infant with NHS progressing rapidly to biliary cirrhosis with a low-normal serum GGT was found to have oxysterol 7 α -hydroxylase deficiency: the liver disease did not improve with cholic acid treatment and required liver transplantation (Setchell *et al.* 1998). Rather mild NHS with profound fat-soluble vitamin deficiencies was found with deficiency of peroxisomal 2-methylacyl-CoA racemase (Setchell *et al.* 2003). The bile acid profile was similar to that found with Zellweger syndrome (alligator bile), and treatment with cholic acid was effective. NHS with a defect in bile acid conjugation (ligase deficiency) has also been observed (Bove 2000).

3 β -Hydroxy- Δ^5 -C₂₇-steroid dehydrogenase/isomerase deficiency This microsomal enzyme is the second in the bile acid synthetic pathway. Infants lacking it present with jaundice and acholic stools in the first few days of life (Buchmann *et al.* 1990); neonatal hepatitis may be histologically severe (Clayton *et al.* 1987) or the cholestatic disease may be somewhat more indolent, resembling progressive intrahepatic cholestasis and therefore presenting later in childhood (Horslen *et al.* 1992; Jacquemin *et al.* 1994b). One patient was reported with rickets and fat-soluble vitamin deficiencies in the absence of jaundice (Akobeng *et al.* 1999). Typically affecting infants and children, this deficiency produces excessive amounts of C₂₄-bile acids with a 3 β -hydroxy- Δ^5 structure. Biochemically they have normal serum GGT and low serum total bile

acid concentrations, and clinically have no pruritus. Treatment with chenodeoxycholic acid (Ichimiya *et al.* 1990; Horslen *et al.* 1992) or ursodeoxycholic acid (Jacquemin *et al.* 1994b) has been reported, but the preferred treatment strategy is cholic acid with or without ursodeoxycholic acid. This may improve bile flow and prevent cirrhosis and hepatic decompensation.

Δ^4 -3-Oxosteroid 5 β -reductase deficiency Δ^4 -3-Oxosteroid 5 β -reductase is an important cytosolic enzyme in the bile acid synthetic pathway. The original description of this disorder included two infants with early severe cholestasis and coagulopathy (Setchell *et al.* 1988); subsequent reports have included infants with a clinical presentation resembling perinatal haemochromatosis (Shneider *et al.* 1994; Siafakas *et al.* 1997). In this disorder Δ^4 -3-oxo bile acids are overproduced and may be hepatotoxic. Serum GGT is usually, but not invariably, normal. Liver biopsy may reveal abnormal bile canaliculi in a focal, 'mosaic' pattern. Treatment with cholic acid (with or without ursodeoxycholic acid) appears beneficial in patients without iron overload (Daugherty *et al.* 1993).

There is a diagnostic subtlety in identifying patients with this genetic disorder because hepatocellular levels of Δ^4 -3-oxosteroid 5 β -reductase drop with progressive severe liver disease (Clayton 1994). Thus for diagnostic reasons, as well as therapeutic ones, diagnostic testing should be performed as early as possible.

24,25-Dihydroxycholanoic cleavage enzyme deficiency Infants have been described with a defect in the 25-hydroxylase pathway (Clayton *et al.* 1995) and excess production of a bile alcohol with an abnormal, eight-carbon side chain. Jaundice and hepatomegaly were noted in the first week of life; serum GGT was normal but alkaline phosphatase and cholesterol were elevated; biliary and serum bile acid concentrations were low; hepatobiliary scanning showed no drainage; pruritus later developed. Liver biopsy revealed severe giant-cell hepatitis with cholestasis. Treatment with chenodeoxycholic plus cholic acid appeared beneficial.

Treatment

Treatment consists of nutritional support, therapy for cholestasis and with specific bile salts aimed at compensating for a defective synthetic pathway.

Byler disease (progressive familial intrahepatic cholestasis)

Byler disease was originally described as a disorder of intrahepatic cholestasis in an American Amish kindred named 'Byler': clinical features included pruritus, steatorrhoea, poor growth and inexorable progression to

cirrhosis in early childhood (Clayton *et al.* 1969). Non-Amish children were later reported with similar clinical characteristics (Tazawa *et al.* 1985; Maggiore *et al.* 1987; Winklhofer-Roob *et al.* 1992; Whittington *et al.* 1994; Bourke *et al.* 1996). A prominent finding was a low or normal serum GGT, which was discordant with the severe cholestasis. Low or normal serum cholesterol is also characteristic and may identify patients reported prior to 1969 (Gray & Saunders 1966). Nomenclature is problematic, especially as Byler disease is itself clinically somewhat variable and is probably only one of several diseases with progressive intrahepatic cholestasis that are clinically similar but mechanistically different. The term 'progressive familial intrahepatic cholestasis' (PFIC) has the advantage of being more general, but it is not strictly applicable until there are at least two affected children in a family.

Genetics

Recent genetic studies, mainly using a shared segment strategy for identifying a common mutation, have identified a group of diseases with progressive intrahepatic cholestasis in childhood with low GGT (PFIC-1 and PFIC-2) and one variant with high GGT (PFIC-3). Other high-GGT disorders exist and require further definition genetically (Chen *et al.* 2001). Most patients with Byler disease have a mutation on chromosome 18q21-22 in the *FIC1* gene (Bull *et al.* 1998). *FIC1* encodes a P-type ATPase (ATP8B1) involved in aminophospholipid transport between membrane leaflets. *FIC1* is expressed in numerous tissues including the gastrointestinal tract, pancreas and lung. Mutations in *FIC1* are also responsible for Greenland Eskimo cholestasis (Ornvold *et al.* 1989; Klomp *et al.* 2000). Mutations in *FIC1* are often the cause of benign recurrent intrahepatic cholestasis, a disease mainly of adults but sometimes symptomatic in childhood (Carleton *et al.* 1995; Bull *et al.* 1997; van Ooteghem *et al.* 2002).

Clinical features

Byler disease (PFIC-1) presents with conjugated hyperbilirubinaemia in the first 3–6 months of life. The degree of jaundice may vary. Hepatomegaly persists, although progression to cirrhosis is variable. Fat-soluble vitamin deficiencies, including rickets, may be severe. Pruritus is problematic and refractory to most treatment. Growth retardation may not be evident initially. Children with Byler disease have persistent diarrhoea with fat malabsorption and protein loss, bouts of pancreatitis, and poor growth leading to short stature. Sensorineural hearing loss may occur. Cirrhosis usually develops in early childhood and liver transplantation is required. After liver transplant, pancreatitis may still occur, and the diarrhoea may get worse.

Diagnosis

The serum GGT is repeatedly normal, as is serum cholesterol. The total serum bile acid concentration is elevated. However, the concentration of chenodeoxycholic acid in bile from these patients is extremely low (Tazawa *et al.* 1985; Jacquemin *et al.* 1994a). Sweat chloride may be elevated (Lloyd-Still 1981). Liver biopsy shows little inflammation but has canalicular bile plugs of distinctive colour on routine histochemical staining, with a characteristic granular appearance on electron microscopy. Small duct paucity may be found. The main differential diagnosis is from an inborn error of bile salt metabolism (see above).

PFIC-2 Some children with intrahepatic cholestasis and normal serum GGT do not have this 18q mutation. Instead they have a mutation in a gene found on chromosome 2q24 (Strautnieks *et al.* 1997). These children differ from those with Byler disease in some respects: they do not have pancreatitis or diarrhoea. There is evidence of inflammation with giant-cell hepatitis, fibrosis and ductular proliferation on liver biopsy. The PFIC-2 gene has now been identified as encoding a bile canalicular transporter, the human bile salt export pump (BSEP, ABCB11), an ATP-binding cassette transporter formerly known as sister of P-glycoprotein (SPGP) (Strautnieks *et al.* 1998; Jansen *et al.* 1999). A variety of functional disturbances in bile salt excretion due to different mutations leads to clinical disease (Wang *et al.* 2002).

PFIC-3 A further group of children has been identified with progressive intrahepatic cholestasis but elevated serum GGT (Jacquemin *et al.* 1997). Onset may occur later in childhood, but presentation in infancy is common. In children with PFIC-3 jaundice may be less prominent than pruritus; despite the clinical appearance of biliary tract obstruction, imaging reveals a normal biliary tree. Portal fibrosis with or without bile ductular proliferation is prominent on liver biopsy. Mutations in the P-glycoprotein MDR-3 gene (*ABCB4*) have been identified, and mutations resulting in a truncated protein appear to be associated with more severe disease than missense mutations (Jacquemin *et al.* 2001). The affected protein is the bile canalicular membrane translocator of phospholipids, and PFIC-3 patients have bile phospholipid concentrations which are <15% of normal. Most children with severe disease require liver transplantation.

Treatment and outcome

Treatment is as for other cholestatic disorders (see below). Treatment with ursodeoxycholic acid appears to be beneficial in many, if not most, patients with any PFIC disorder. Some children may have relief of pruritus following biliary diversion (Melter *et al.* 2000) provided it is per-

formed prior to development of significant hepatic fibrosis. Liver transplantation is indicated for those children with decompensated disease.

Aagenaes syndrome

Aagenaes syndrome is a very rare disorder with cholestasis and lower limb oedema. It was initially reported in a Norwegian kindred but has also been reported in children of Norwegian descent and in other ethnic groups (Aagenaes *et al.* 1968; Sharp & Krivit 1971; Vajro *et al.* 1984; Morris *et al.* 1997; Aagenaes 1998). The principal features are neonatal hepatitis syndrome evolving to a chronic cholestatic condition and a lymphatic disorder perhaps due to abnormal development of hepatic lymphatics. The lymphatic abnormalities may present clinically later than the jaundice and include localized lower limb lymphoedema like Milroy disease, a more subtle disorder with generalized oedema despite normal serum albumin, or haemangioma(s) and/or lymphangioma(s).

The neonatal hepatitis evolves into a cholestatic problem with pruritus and fat-soluble vitamin deficiencies which require treatment. While the initial cholestasis resolves in early childhood, recurrent bouts of cholestasis, similar to benign recurrent cholestasis, and lymphoedema become a prominent problem in adulthood. Chronic liver disease with portal hypertension has not been reported. Abnormal development of hepatic lymphatics has been postulated as part of the pathogenesis of this condition. The genetic basis of this familial cholestatic disorder remains unknown, but the genetic locus has been mapped to chromosome 15q (Bull *et al.* 2000).

North American Indian familial cirrhosis

Chronic cholestatic liver disease was described in 14 North American Indians living in north-western Quebec, Canada. Familial clustering of disease incidence was prominent and consanguinity a possible factor. Nine of the 14 presented with neonatal conjugated hyperbilirubinaemia, and in these infants jaundice disappeared during the first year of life. Chronic cholestatic disease was similar in all 14: hepatosplenomegaly, pruritus, facial telangiectasia, and eventually portal hypertension. Serum aminotransferases, alkaline phosphatase and bile acids were elevated, but serum cholesterol was normal in most patients. Serum gamma-glutamyl transpeptidase data were not reported. Electron microscopy revealed widening of the pericanalicular microfilament cuff, not unlike changes due to phalloidin intoxication (Weber *et al.* 1981). A subsequent report indicated most had moderate elevation of serum cholesterol and elevated GGT (Drouin *et al.* 2000). Liver disease typically progresses to biliary cirrhosis in this disorder, although liver transplantation is often not required in the first decade of life. The gene

mutated in this disorder has recently been identified: it is *FLJ14728*, conventionally called cirhin, on chromosome 16q22, and it encodes a protein of unknown function which localizes to mitochondria (Chagnon *et al.* 2002). It may be appropriate to classify this disorder as one of the PFIC disorders (e.g. PFIC-4).

A second apparently different cholestatic disease has been described in North American Indians from various regions of Ontario, Canada (Phillips *et al.* 1996). Most belong to a single extended kindred and presented as infants with conjugated hyperbilirubinaemia and hepatomegaly; in some jaundice was transient and chronic cholestatic disease developed later in childhood. Two unrelated North American Indian children appeared to have extrahepatic biliary atresia clinically and at laparotomy. Increased concentrations of zinc were found in hepatic parenchyma obtained at the time of liver transplantation in all patients. The pathogenesis of this zinc-overload cholestatic liver disease remains to be determined.

Zellweger syndrome

Zellweger syndrome is the prototype of the peroxisomal biogenesis disorders, characterized by multiple abnormalities of peroxisome function. The molecular and cell biology of these disorders is complex, involving multiple *PEX* genes which encode peroxins, proteins required for peroxisome assembly. Zellweger syndrome is most often associated with mutations in *PEX1* and *PEX6* (Moser 1999; Gould & Valle 2000; Preuss *et al.* 2002). Bile acid synthesis is abnormal because of selective or generalized deficiency of the peroxisomal enzymes involved in side-chain modification. In Zellweger syndrome C_{27} bile acids accumulate: principally, trihydroxycoprostanic acid (THCA) and dihydroxycoprostanic acid (DHCA). These would ordinarily undergo side-chain modification in the peroxisome to chenodeoxycholic acid and cholic acid. It is a rare disorder with an incidence of 1 in 100 000. Sexes are affected equally.

Clinical features and diagnosis

Multiple systems besides the liver are affected: features include profound hypotonia, facial dysmorphism with a high forehead and large fontanelles, developmental delay, seizures, bony abnormalities such as epiphyseal calcifications, and cystic malformations in the brain and kidneys (see Plate 7, Atlas: p. 442). Failure to thrive and feeding difficulties are common. In the first 3 months of life, hepatic involvement may not be prominent, although some babies have persistent conjugated hyperbilirubinaemia (Naidu *et al.* 1988). Fifty percent of infants are not jaundiced but have hepatosplenomegaly with evidence of poor hepatic synthetic function.

The diagnosis is confirmed by demonstrating abnormal bile salt metabolites using FAB-MS or the detection of very long-chain fatty acids in serum. Hepatic histology may be normal, although there may be excess iron deposition. Hepatic fibrosis is typical. Paucity of the small (portal) bile ducts may be found. Electron microscopic studies of liver reveal the absence of peroxisomes in hepatocytes. Mitochondria may appear abnormal. These infants may develop cirrhosis, although extrahepatic features of the syndrome typically overshadow the hepatic disease.

Treatment and outcome

Treatment is supportive, as death is inevitable. Liver transplantation is contraindicated because of the multi-system disease. Attempts to produce peroxisomes with hypolipaeic drugs were not successful (Lazarow *et al.* 1985). Primary bolus therapy with cholic and chenodeoxycholic acid may produce some initial improvement but does not prolong life (Setchell *et al.* 1992).

Niemann–Pick disease, type A or type C

There are two types of Niemann–Pick disease (A and C) associated with neonatal liver disease. Type B is defined as a juvenile-adult form of sphingomyelinase deficiency without neurological features (see also Chapter 12).

Niemann–Pick type A

This is due to lysosomal sphingomyelinase deficiency. Clinical features include hepatosplenomegaly, failure to thrive and progressive neurological deterioration. Jaundice is unusual. Fetal ascites has been reported (Meizner *et al.* 1990).

Niemann–Pick type C

Niemann–Pick type C is secondary to a disorder of cholesterol esterification (Pentchev *et al.* 1985). There are two subtypes characterized by different mutations (Millat *et al.* 1999; Naureckiene *et al.* 2000). Correlation of genotype with phenotype is complex (Millat *et al.* 2001a,b). The gene product of *NPC1* appears to mediate trafficking of sterols and various other substrates out of lysosomes to other subcellular compartments (Neufeld *et al.* 1999). Numerous animal models exist for type C Niemann–Pick disease. Recent studies in a mutant mouse strain suggest that in addition to abnormal cholesterol homeostasis, peroxisomal function is impaired. This appears to develop at an early stage of the disease and may influence disease progression (Schedin *et al.* 1997). Some infants may have a similar pattern of disease (Sequeira *et al.* 1998).

Clinical features and diagnosis Two-thirds of infants present with prolonged cholestasis, hepatomegaly and a particularly prominent splenomegaly; some may have fetal ascites (Maconochie *et al.* 1989; Kelly *et al.* 1993). They appear neurologically normal at birth, although subsequent motor and speech development may lag (Semeraro *et al.* 1986; Kelly *et al.* 1993). In one Indo-Pakistani kindred, type C Niemann–Pick disease was associated with extrahepatic biliary atresia and meconium ileus in two of three affected infants (Adam *et al.* 1988). The remainder of affected children present with isolated splenomegaly with or without neurological symptoms.

Liver biopsy shows a histologically severe neonatal hepatitis, pericellular fibrosis and pseudoacinar formation (Rutledge 1989). The diagnosis is confirmed by identifying the characteristic PASD-resistant material in Kupffer cells and hepatocytes, which may be difficult to identify in neonates. It may be easier to detect the foamy storage cells in bone marrow aspirate. Neuronal storage is usually present at birth and may be demonstrated in the ganglion cells of a suction rectal biopsy, which demonstrate typically pleomorphic lamella cytoplasmic inclusions (Kelly *et al.* 1993) (see Plate 8, Atlas: p. 442).

Studies of cholesterol esterification in the patient's cultured fibroblasts are definitive.

Management and prognosis In most infants liver disease resolves and jaundice disappears in the first year of life. Neurological symptoms become obvious by 5 years of age. Most children develop loss of upward gaze due to vertical supranuclear ophthalmoplegia, which is regarded as a pathognomonic sign. Other neurological complications include ataxia, convulsions, developmental delay and dementia. Most children die in early adolescence from bronchial pneumonia rather than liver failure. There is no specific treatment, although a low-cholesterol diet has been suggested. Liver and bone marrow transplantation are ineffective. Genetic counselling is essential and antenatal diagnosis is available by chorionic villus biopsy (Vanier *et al.* 1989) or by gene analysis (Vanier 2002).

Wolman disease

Wolman disease, and the associated milder disease, cholesterol ester storage disease, are both due to deficiency of lysosomal acid lipase (also known as acid esterase, cholesterol esterase, or sterol esterase). Inheritance is autosomal recessive; some mutations in the lysosomal acid esterase gene capable of causing severe functional deficiency have been identified (Anderson *et al.* 1994). Babies with Wolman disease are not usually jaundiced but have deranged liver function, hepatosplenomegaly, persistent diarrhoea and poor growth; calcified adrenal glands are found radiologically. The majority die in early infancy.

Citrullinaemia, type II

Citrullinaemia is due to deficiency of argininosuccinate synthetase. The classic form of citrullinaemia (type I) presents in infancy or childhood as a urea cycle disorder with hyperammonaemia. Jaundice is rare. The disorder is due to mutations in the argininosuccinate synthetase gene on chromosome 9q34. A second form of citrullinaemia has been described, which occurs mainly in adults, who present with fatty liver, hepatitis and iron accumulation. Type II citrullinaemia is due to a deficiency in citrin, a carrier protein of unknown function associated with the urea cycle, encoded by the gene *SLC25A13*. Several mutations in this gene have been identified in adults with the type II citrullinaemia. Recently infants with NHS were found to have type II citrullinaemia, confirmed by genetic analysis (Tazawa *et al.* 2001; Ben-Shalom *et al.* 2002; Saheki & Kobayashi 2002; Tamamori *et al.* 2002). A distinguishing feature was the presence of steatosis and iron deposition histologically. Liver disease was severe enough in one infant to require liver transplantation.

Toxic injury**Total parenteral nutrition-associated cholestasis**

Progressive cholestasis in infants receiving total parenteral nutrition without any enteral nutrition occurs mainly in critically ill, often premature infants.

Aetiology

Total parenteral nutrition-associated cholestasis is more likely to develop with increasing degree of prematurity and longer duration of exclusive dependence on total parenteral nutrition to meet nutritional needs. The setting of severe gastrointestinal disease (such as recurrent necrotizing gastroenteritis, gastroschisis or intestinal atresias), which may lead to recurrent bouts of sepsis or require surgical resection(s), or a short gut syndrome signals an especially difficult situation as these infants often cannot avoid protracted use of total parenteral nutrition. The more premature the infant is, the more underdeveloped are hepatocellular mechanisms of bile formation, leading to the development of total parenteral nutrition-associated cholestasis. Factors which amplify this physiological inefficiency by interfering with enterohepatic circulation of bile acids may contribute to the pathogenesis of total parenteral nutrition-associated cholestasis. Depending on gestational age, fetal patterns of bile acid biosynthesis may persist: synthesis of the toxic bile acid, lithocholic acid, may be higher than in older infants.

Fasting interrupts the enterohepatic circulation, diminishes the output of gut hormones needed for normal

hepatobiliary function, and may promote small bowel overgrowth by bacteria that are capable of producing endotoxin or modifying endogenous bile acids to more toxic chemicals. Bacterial translocation may occur. All these mechanisms are compounded by systemic factors such as hypoxia or hypoperfusion, localized infection or septicemia, and medications used to treat these sick infants. Specific nutritional deficiencies may also play a role: lack of taurine, essential fatty acids, carnitine, and antioxidants such as vitamin E, selenium and glutathione (Sokol *et al.* 1996).

It is not clear whether specific components in the total parenteral nutrition solution are toxic. High concentrations of amino acids do not necessarily promote more rapid protein synthesis and may be toxic to hepatocytes. Lipid preparations are probably not toxic as such, although some sources of lipid may be tolerated better than others; however, accumulation of lipofuscin in Kupffer cells appears to be due mainly to the lipid component.

Clinical features and diagnosis

Most infants present with conjugated hyperbilirubinaemia and hepatomegaly in the context of prolonged parenteral nutrition. Cholestasis may be so severe that extrahepatic biliary tract obstruction is mimicked with acholic stools. Serum aminotransferases, alkaline phosphatase and GGT are usually elevated, whereas albumin and coagulation times are usually normal unless affected by extrahepatic disease.

The diagnosis is relatively straightforward. A careful history mapping out feeding history, all other medications and intercurrent illnesses is essential. Other causes of neonatal hepatitis syndrome should be considered and excluded. Abdominal ultrasound may be normal or demonstrate a contracted gall bladder. If cholestasis is severe, there may be delayed excretion on a hepatobiliary scan. Liver biopsy shows cholestasis with hepatocellular necrosis, abundant lipofuscin, some fatty infiltration, mild giant-cell transformation, portal inflammatory infiltrate, and some bile ductular proliferation with or without portal fibrosis. Electron microscopy may reveal cholesterol crystals in hepatocytes.

Treatment

Treatment continues to be empirical. If possible, some oral nutrition should be introduced: even dextrose in water given in very small boluses (2–5 ml) every few hours is beneficial. Oral or nasogastric feeding with a highly digested formula may be commenced concurrent with continued total parenteral nutrition. The components of the total parenteral nutrition solution should be reviewed carefully to be sure that amino acid requirements are being met but not exceeded and that essential

fatty acids and trace metals are supplied. Taurine and carnitine can be supplemented. Protecting the total parenteral nutrition solution from light, and cycling total parenteral nutrition administration are other simple strategies. Extreme care to avoid central venous catheter sepsis is critically important. There may be benefit from treating small bowel overgrowth with metronidazole, although no controlled trials are available; metronidazole is preferable to gentamicin. Once some oral intake is established, ursodeoxycholic acid (20 mg/kg/day) may promote bile flow and improve cholestasis, but there are few reports in children (Cocjin *et al.* 1993).

In general, recovery is slow, unless parenteral nutrition can be discontinued. Infants totally dependent on total parenteral nutrition because of massive bowel dysfunction due to severe inherited disorders of motility or short gut syndrome will develop progressive liver disease, cirrhosis and portal hypertension, which may be exacerbated by intercurrent portal vein thrombosis. Cirrhosis may be averted by either innovative bowel surgery or successful intestinal transplantation, and this should be considered at an early stage before a combined liver-intestine transplant may be needed (Chapter 21).

Other complications of total parenteral nutrition

Other complications of total parenteral nutrition include: generation of 'biliary sludge' (material appreciated by sonography as echogenic, resembling a stone but without typical acoustic shadowing) (Matos *et al.* 1987); cholelithiasis (Whittington & Black 1980; Roslyn *et al.* 1983); or acalculous cholecystitis (Thurston 1986) (Chapter 18). Extensive abdominal surgery leading to short gut syndrome or resection of the ileocaecal valve as well as longer duration of parenteral nutrition may predispose to biliary tract disease. Regular ultrasound examination of the biliary tree at 4- to 6-week intervals during prolonged use of total parenteral nutrition may be of value in such patients. Spontaneous resolution of gallstones sometimes occurs in infancy, and thus surveillance of the asymptomatic infant is often appropriate, instead of immediate surgery (Debray *et al.* 1993).

Drug-induced hepatotoxicity

Drug hepatotoxicity as a cause of neonatal hepatitis syndrome is poorly documented. Prolonged chloral hydrate administration is associated with conjugated hyperbilirubinaemia in newborns, without other signs of liver toxicity (Lambert *et al.* 1990). Drug exposure might occur via breast milk, which has been reported for carbamazepine (Merlob *et al.* 1992; Frey *et al.* 2002).

Cholelithiasis in infants has been attributed to certain drug therapies including prolonged use of frusemide (Whittington & Black 1980; Callahan *et al.* 1982) or various

antibiotics such as ceftriaxone (Schaad *et al.* 1988). Without choledocholithiasis, jaundice is unusual.

Immune causes

Neonatal lupus erythematosus

Neonatal lupus erythematosus is due to passage of maternal anti-Ro and anti-La antibodies across the placenta leading to damage to fetal tissues, which express Ro and La antigenic determinants. The heart, skin and liver are most likely to be involved, rarely with thrombocytopenia and leukopenia (Silverman & Laxer 1997). Congenital heart block is the most dramatic cardiac manifestation. A rash resembling discoid lupus erythematosus may be present in the newborn period or develop some weeks later. Hepatic involvement, evident in ~10%, is often limited to elevated serum aminotransferases, but neonatal hepatitis syndrome is found (Laxer *et al.* 1990; Evans & Gaskin 1993). Occasionally this is severe enough to mimic extrahepatic biliary tract obstruction, with acholic stools and non-draining hepatobiliary scan (Rosh *et al.* 1993). In severe cases a clinical phenotype of neonatal haemochromatosis may be found (Schoenlebe *et al.* 1993). Deposits of associated antibodies (anti-Ro and/or anti-La) may be found in affected liver tissue by immunofluorescence (Selander *et al.* 1998). Transient unexplained isolated conjugated hyperbilirubinaemia in the perinatal period and later presentation at 2–3 months old with transient elevations of serum aminotransferases are other possible clinical presentations (Lee *et al.* 2002). In most infants the liver disease resolves completely between 6 and 12 months of age, as the maternal antibodies are degraded. Mild fibrosis was found in one child on repeat liver biopsy.

The diagnosis of neonatal lupus erythematosus is difficult in the child who does not have congenital heart block, a typical skin rash or a history of maternal systemic lupus erythematosus or Sjögren's syndrome. The risk of neonatal lupus erythematosus in subsequent pregnancies appears variable, estimated at 10–50%.

Autoimmune haemolytic anaemia with giant-cell hepatitis

This condition is rare and poorly defined as only about 10 children with this complaint have been reported in the English language literature. Most are infants aged 6–24 months or more. Pallor, jaundice and hepatosplenomegaly are the important clinical findings. The autoimmune haemolytic anaemia is Coombs' positive, but autoantibodies typical of autoimmune hepatitis are not present (Bernard *et al.* 1981). Viral studies are generally negative, although it is possible that the disease is related to syncytial giant-cell hepatitis attributed to paramyxoviral infection (Phillips *et al.* 1991). Liver biopsy

reveals extensive giant-cell transformation with fibrosis. Some patients have responded to treatment with prednisolone and azathioprine (Brichard *et al.* 1991), but the disease has frequently been refractory to immunosuppressive treatment and may recur following liver transplantation.

Miscellaneous causes

Vascular disorders

Budd–Chiari syndrome

Budd–Chiari syndrome is rarely diagnosed in infants (Jaffe & Yunis 1983; McClead *et al.* 1986; Gentil-Kocher *et al.* 1988) but may be due to endophlebitis from a venous catheter or associated with neoplasia, septicaemia or fungal infection (Brocart *et al.* 1974); membranous obstruction of the inferior vena cava probably represents previous thrombosis of the vessel. A prothrombotic disorder may be present (Dahms *et al.* 2002). Hepatic vein thrombosis may rarely occur due to other intra-abdominal congenital abnormalities (Yonekura *et al.* 1998). Affected children usually have hepatomegaly, splenomegaly or ascites; jaundice is more common in infants.

Budd–Chiari syndrome must be differentiated from veno-occlusive disease, where the vascular blockage is at the level of terminal hepatic venules, as opposed to larger hepatic veins. Veno-occlusive disease is rarely reported in infants, although an infant with congenital leukaemia developed veno-occlusive disease after treatment with antineoplastic drugs.

Severe congestive heart failure

The role of chronic passive congestion, or functional hepatic venous obstruction, in neonatal hepatitis syndrome is difficult to assess. Babies with severe chronic congestive heart failure may develop moderate hepatomegaly or hepatosplenomegaly, as well as ascites. Jaundice is uncommon (Chapter 15). Infants with acute circulatory failure associated with severe congenital heart disease or shock may develop elevated serum aminotransferases, coagulopathy and jaundice with mild to moderate conjugated hyperbilirubinaemia (Jacquemin *et al.* 1992), which resolves rapidly once hepatic perfusion is restored.

Neonatal asphyxia

Neonatal conjugated hyperbilirubinaemia with mild elevations of aminotransferases is associated with severe neonatal asphyxia (Vajro *et al.* 1997; Jacquemin *et al.* 1998). Conjugated hyperbilirubinaemia jaundice developed within 6 days of birth, and was protracted. Hepatobiliary

scanning showed bile drainage. Spontaneous resolution typically occurs.

Neoplasia

Primary hepatic neoplasms rarely present with the neonatal hepatitis syndrome, although mesenchymal hamartoma may present with hyperbilirubinaemia in the neonatal period (Chapter 19). Rhabdomyosarcoma of the biliary tree rarely presents in infancy, but jaundice and acholic stools are the major clinical features. Any neoplasm which obstructs bile flow may cause jaundice (Finegold 1994). Langerhans cell histiocytosis is associated with sclerosing cholangitis in children and may present in early infancy with jaundice (Leblanc *et al.* 1981a). Jaundice rarely occurs with neuroblastoma, erythrophagocytic lymphohistiocytosis, or neonatal leukaemia.

Consequences of cholestasis

Many infants with neonatal liver disease will have a mild self-limiting disease, but those children with progressive disease, or following unsuccessful Kasai portoenterostomy, will develop significant fat malabsorption with consequent protein malnutrition. It is important to establish baseline anthropometric examinations in order to detect and prevent early malnutrition. This is best evaluated by using a combination of weight (may be imprecise because of fluid retention), height (may be useful for assessing chronic malnutrition), triceps skin fold (to evaluate fat stores), and mid-arm muscle area (to evaluate protein stores). Mid-arm circumference is a reliable marker of malnutrition in children under 5 years old.

The effects of chronic cholestasis are extensive: failure of biliary excretion of bilirubin, bile salts and cholesterol leads to jaundice, pruritus and xanthomata; decreased bile salts in the intestine leads to malabsorption of long-chain triglycerides and consequent fat malnutrition. Malabsorption of fat-soluble vitamins is inevitable (Table 4.4). If cirrhosis develops, then protein malnutrition and muscle wasting are likely.

Management of neonatal liver disease

Management should be supportive and, whenever possible, definitive. Disorders for which specific medical or surgical therapies are available are summarized in Table 4.5.

Nutritional support

The main aim of nutritional support is to provide sufficient calorie intake to reverse or prevent fat malabsorption and protein malnutrition. In extrahepatic biliary

atresia resting energy expenditure runs ~30% higher than in normal infants of the same age and sex (Pierro *et al.* 1989). Thus an aggressive approach to feeding is required, including nasogastric supplementation if oral feeding cannot meet caloric needs (Kaufman *et al.* 1987).

Infants with severe cholestatic jaundice require special

formulas to ensure that calorie intake is 120–150% EAR (estimated average requirement) using either a standard infant formula with appropriate supplements or a modular feed in which individual constituents can be added according to requirement. A nearly elemental formula containing medium-chain triglycerides, which can be absorbed regardless of luminal concentrations of bile acids, is preferable. Caloric density can be increased further by concentrating the formula or adding starch powder (glucose polymer). If the infant is satisfactorily breast-feeding this should be encouraged with supplementation using a highly digestible high-caloric-density formula.

Table 4.4 Consequences of chronic cholestasis and cirrhosis

Aetiology	Clinical manifestations
Reduced excretion of bilirubin, bile acids	Pruritus, jaundice
Fat malabsorption	Steatorrhoea, loss of fat stores
Essential fatty acid deficiency	Peeling skin rash
Vitamin A deficiency	Conjunctival and corneal drying, abnormal retinal function, night blindness
Vitamin E deficiency	Peripheral neuropathy, ophthalmoplegia, ataxia, haemolysis
Vitamin D deficiency	Osteopenia, rickets, fractures
Vitamin K deficiency	Bruising, epistaxis, coagulopathy
Hypercholesterolaemia	Xanthomata
Increased protein catabolism	Muscle wasting, motor development delay, growth failure

Fat-soluble vitamin supplementation

All infants with chronic cholestasis, whether jaundiced or not, require supplementation with fat-soluble vitamins. These can be provided as water-soluble preparations of vitamins A, D, E and K given orally (Kaufman *et al.* 1987), or less commonly, as parenteral supplementation (Alagille 1985) (Table 4.6). Vitamin levels should be monitored to ensure adequate absorption and prevent toxicity.

Vitamin A This is provided in a water-soluble preparation. Toxic levels may lead to hepatic fibrosis or pseudotumour cerebri.

Table 4.5 Neonatal liver disease syndrome: specific treatments

Disease	Major diagnostic strategy
<i>Infection</i>	
Toxoplasmosis	Spiramycin
Cytomegalovirus	Gancyclovir, if severe
Herpes simplex	Acyclovir
Syphilis	Penicillin
Bacterial infection elsewhere (sepsis)	Appropriate antibiotic(s)
Tuberculosis	Quadruple antitubercular therapy (not ethambutol)
Syncytial giant-cell hepatitis	Ribavirin (unproven benefit)
<i>Endocrine</i>	
Panhypopituitarism (septo-optic dysplasia)	Corticosterone, thyroxine, growth hormone
<i>Structural</i>	
Extrahepatic biliary atresia	Kasai portoenterostomy before 8–12 weeks old
Choledochal cyst	Surgical resection
Choledocholithiasis	Surgical removal
Spontaneous perforation of CBD	Surgical repair
<i>Metabolic</i>	
Primary disorders of bile acid synthesis	Bile acid supplementation
<i>Toxic</i>	
TPN-associated cholestasis	Enteral feeding; metronidazole; ursodeoxycholic acid
Drug-induced	Stop causative drug
<i>Immune</i>	
Neonatal hepatitis with autoimmune haemolytic anaemia	Prednisolone + azathioprine

CBD, Common bile duct; TPN, total parenteral nutrition.

Table 4.6 Oral regimens for supplementation of fat-soluble vitamins in infants with chronic cholestasis

Vitamin	Regimen	Features of toxicity
A	Water-soluble preparation 5000–25 000 units/day	Hepatotoxicity; pseudotumour cerebri; dermatitis
D	Vitamin D 800–5000 units/day or 25-hydroxyvitamin D ₃ 3–5 µg/kg/day	Hypercalcaemia: lethargy, cardiac arrhythmia, nephrocalcinosis
E	TPGS 15–25 IU/kg/day or α-tocopheryl 25–200 IU/d/day	(None known) (Polyethylene glycol: hyperosmolarity if renal impairment)
K	2.5 mg twice per week 5 mg daily	(Clotting diathesis?)

TPGS, Tocopheryl polyethylene glycol succinate.

Vitamin D This is usually provided as alfacalcidol (1,25-dihydroxy-vitamin D), although the administration of 25-hydroxy-vitamin D may be more effective (Heubi *et al.* 1989). Vitamin D production in the skin can be enhanced through sunlight or sunlamp exposure, even for babies who are jaundiced (Kooch *et al.* 1989). Absorption of water-soluble vitamin D may be enhanced by simultaneous administration of alpha tocopheryl polyethylene glycol succinate formulation of vitamin E (Argao *et al.* 1992).

Vitamin E Vitamin E transferred via the placenta to the fetus may keep the infant replete until the age of 3 months, but the sufficiency of maternal stores varies from baby to baby. Most babies require supplementation after 2 months of age or earlier if the baby was born preterm. Vitamin E linked to polyethylene glycol 1000 through a succinate linkage, alpha tocopheryl polyethylene glycol succinate (TPGS), has the best bioavailability in severe cholestasis (Sokol *et al.* 1987a,b) as its absorption depends on simple passive absorption of polyethylene glycol independent of bile acids in the intestinal lumen. This formulation is not universally available and the more traditional oral supplement vitamin E acetate may not be as quickly absorbed. Coagulation should be monitored closely in all infants with cholestasis, who should receive oral vitamin K prophylactically. Infants receiving rifampicin for pruritus should receive extra vitamin K.

Other dietary measures

It is reasonable to place an infant with conjugated hyperbilirubinaemia on lactose-free formula until the results of testing for galactosaemia are known; however, interrupting breast feeding is problematic. Brief use of a more restrictive diet is sometimes justifiable: an infant with severe neonatal hepatitis syndrome might be placed on a lactose-free/low-protein formula (to minimize aromatic amino acid intake) until the results of tests for both galac-

tosaemia and hereditary tyrosinaemia type I are available.

Special diets are used life-long for children with inborn errors of carbohydrate and amino acid metabolism. Supplementation with specific bile acids may arrest liver damage in inborn errors of bile acid metabolism (Suchy 1993).

Pruritus

Pruritus due to severe cholestasis interferes with the infant's sleep and compromises quality of life. It is often difficult to treat; local measures such as non-perfumed skin cream may help. For infants with some duct patency and bile flow medical therapy includes:

- Cholestyramine (1–4 g daily) is effective but is unpalatable. The mechanism of action is to bind bile salts in the intestinal lumen, thus interrupting the enterohepatic circulation and reducing bile salt concentration. Side-effects include malabsorption of fat-soluble vitamins and drugs, folic acid deficiency, constipation and acidosis. Cholestyramine can cause intestinal obstruction or hypernatraemia in small infants; adequate fluids must be given with it.
- Ursodeoxycholic acid (UDCA) may be effective when given in a dose of 15–30 mg/kg/24 h. It is thought to have a choleric action but is not universally effective. UDCA may transiently increase pruritus.
- Phenobarbitone (5–10 mg/kg/day) may stimulate bile salt-independent bile flow and decrease jaundice and control pruritus. However, it is relatively ineffective, causes sedation and may exacerbate rickets.
- Biliary diversion may be effective in some conditions, including PFIC and Alagille's syndrome (Emerick & Whittington 2002).
- Rifampicin (5–10 mg/kg/day) relieves pruritus in at least 50%, producing a significant improvement in the remainder (Yerushalmi *et al.* 1999). Results are variable and experience in young infants limited (Banks *et al.* 1989;

Gregorio *et al.* 1993). Rifampicin inhibits uptake of bile acids by hepatocytes and alters their metabolism (Hoensch *et al.* 1985; Wietholtz *et al.* 1996). Side-effects include hepatotoxicity in 5–10% and thrombocytopenia. The urine may turn an orange–red colour.

- Phototherapy with infrared or ultraviolet radiation may improve pruritus if given for 3–10 min daily.
- Antihistamines are largely ineffective but as they cause drowsiness may be useful at night. Toxic side-effects include cardiac dysrhythmias.

Family and psychological support

Specific attention to the infant's developmental needs is often beneficial. Physiotherapy may improve gross motor development while infant stimulation programmes enhance the mental development for infants who require frequent hospitalization. Family education and support are essential, particularly for children with progressive illness requiring liver transplantation.

Indications for liver transplantation

The indications for liver transplantation are severe cholestasis, decompensated liver disease and intractable pruritus (Chapter 20). Orthotopic liver transplant is often the only definitive treatment for severe infantile liver disease and can be performed safely in the first year of life (Casavilla *et al.* 1994; Colombani *et al.* 1996; Bonatti *et al.* 1997), especially if nutrition has been maintained well. In those who are malnourished, catch-up growth occurs after liver transplantation, including patients with Alagille's syndrome (Holt *et al.* 1997; D'Antiga *et al.* 2002). The role of gene transfer therapies for genetic disorders causing the neonatal hepatitis syndrome requires further clarification.

Inherited disorders of bilirubin conjugation

These rare disorders are characterized by benign conjugated hyperbilirubinaemia and an unexplained abnormality of coproporphyrin metabolism. Clinical features include jaundice, which may be exacerbated by stress, intercurrent illness, pregnancy and oral contraceptives. There are no other clinical or laboratory features of liver disease. The diagnosis is made as described below.

Dubin–Johnson syndrome

Dubin–Johnson syndrome is due to mutations in the human gene *MRP2*, which encodes the bile canalicular membrane transporter for anion conjugates (Kartenbeck *et al.* 1996; Paulusma *et al.* 1997). (Some initial reports used the terminology 'canalicular multispecific organic anion

transporter', or cMOAT, for this transporter.) Numerous mutations have been described, most of which cause functional deficits though defects in protein maturation and localization (Hashimoto *et al.* 2002; Keitel *et al.* 2003). Neonatal hepatitis syndrome has been reported rarely in Dubin–Johnson syndrome (Shieh *et al.* 1990; Regev *et al.* 2002). Treatment of severely affected neonates with ursodeoxycholic acid may be beneficial. Diagnosis is hampered by the difficulty in recognizing the typical melanin-containing pigment in the liver during infancy as little accumulates until later in childhood. Bromosulphophthalein sodium retention in the serum at 45 min is generally between 10 and 20%. Coproporphyrin excretion in urine is normal, but the ratio of coproporphyrin III to coproporphyrin I is reversed, with coproporphyrin I accounting for >75% of the total urinary coproporphyrins (Haimi-Cohen *et al.* 1998). Abdominal computed tomography scan showing high attenuation in the liver may provide important supporting evidence for the diagnosis in an infant (Shimizu *et al.* 1997). Liver histology in older children demonstrates a typical melanin-containing pigment, which is found predominantly in the centrolobular region.

Rotor syndrome

Rotor syndrome is also characterized by conjugated hyperbilirubinaemia without cholestasis but does not have pigment accumulation in the liver. The pathogenesis of Rotor syndrome remains unclear but is related to a defect in bilirubin secretion. Neonatal hepatitis syndrome has not been reported in infants with Rotor syndrome. The diagnosis is made by estimating the bromosulphophthalein sodium retention in serum, which is 30–50% at 45 min after injection, or by measuring urinary coproporphyrin excretion, which is generally increased, with a particular increase in coproporphyrin I. No treatment is required for either disorder apart from reassurance.

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