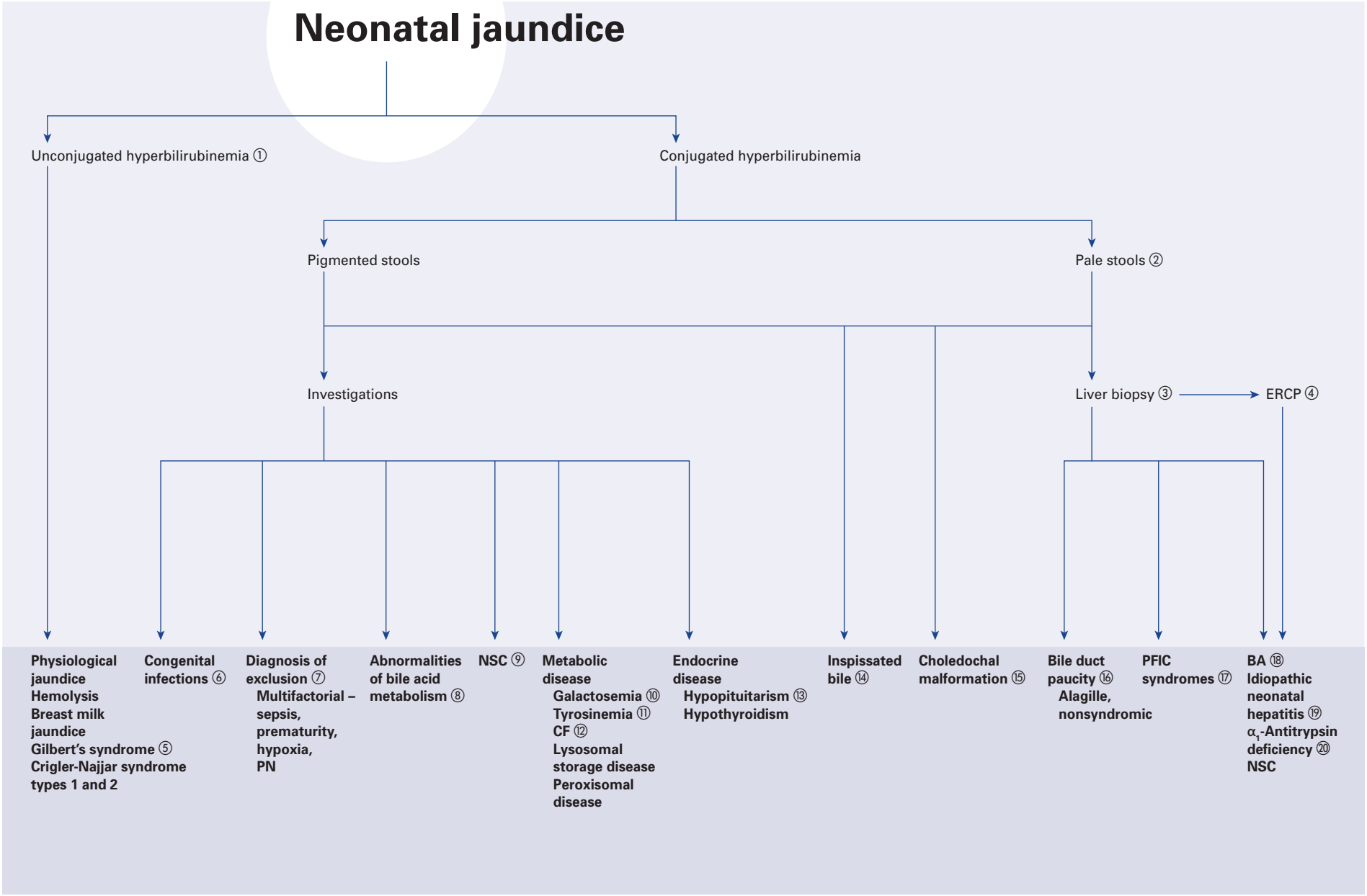
Neonatal jaundice



① —— Unconjugated hyperbilirubinemia occurs in 50% of term and 70% of preterm neonates and is secondary to a combination of rapid red cell breakdown and decreased ability to conjugate bilirubin in the first few days of life. Besides dehydration and sepsis, breast milk may also contribute, possibly due to the inhibition of the conjugating enzyme UDP glucuronosyltransferase. In the case of hemolysis (e.g. secondary to Rhesus disease), normal physiological jaundice is amplified. Neonates with severe unconjugated hyperbilirubinemia should undergo a workup for hemolysis including blood film and reticulocyte count, LDH, uric acid, direct Coomb's test, G6PD deficiency and pyruvate kinase deficiency assays. Treatments include hydration, phototherapy and, in the case of anemia secondary to hemolysis, red cell transfusion. Occasionally, exchange transfusion is required if bilirubin levels are such that the neonate is at risk of kernicterus.
② —— In differentiating BA from other causes of neonatal cholestasis, pale stools are often useful indicating complete obstruction to bile flow.
③ —— A biopsy is diagnostic of extrahepatic BA in 90% of cases. BA is characterized by portal tract expansion, bile duct proliferation and bile plugs. Alagille syndrome may be suspected on the basis of bile duct paucity. Special staining such as diastase periodic acid-Schiff staining is useful for α_1-antitrypsin deficiency (though it may not be positive in biopsies done in the first few weeks of life). Immunohistochemical techniques can be used to aid in the diagnosis of PFIC.
④ —— When a biopsy is equivocal, ERCP may aid in making a diagnosis of BA and avoid the need for laparotomy and intraoperative cholangiogram.
⑤ —— Gilbert's syndrome and Crigler-Najjar syndrome are disorders of the enzyme UDP glucuronosyltransferase 1 which may present in the neonatal period. Gilbert's syndrome usually presents as an exaggerated degree of physiological jaundice. It is generally a benign condition and, aside from phototherapy for neonatal jaundice, does not require any ongoing management. The syndrome is inherited in an autosomal-recessive manner, most commonly caused by homozygosity for the allele polymorphism UGT1A1*28 on chromosome 2: with an extra TA repeat in the TATA promoter region. Polymorphisms of UGT1A6 and 1A7 also occur. Crigler-Najjar syndrome types 1 and 2 may present with severe prolonged hyperbilirubinemia. Type 2 may be distinguished from type 1 as there is a good response to phenobarbitone in the patients, indicating some residual enzyme activity. Crigler-Najjar syndrome is caused by a mutation in either exon 1 or in exons 2–6 of UGT1A and may also affect the metabolism of certain drugs as well as the conjugation of bilirubin. The management of Crigler-Najjar syndrome consists of lifelong phototherapy. Liver transplantation is curative for type 1 but is rarely indicated for type 2.
⑥ —— Congenital infections causing conjugated hyperbilirubinemia and neonatal hepatitis include CMV, toxoplasmosis, rubella and syphilis. These conditions may be associated with other abnormalities such as microcephaly, cataracts, thrombocytopenia, etc. Sepsis and UTI should also be considered in the investigation of an infant with conjugated hyperbilirubinemia.
⑦ —— The most frequent finding in premature or sick neonates with cholestasis is multifactorial (diagnosis of exclusion). A combination of PN, sepsis, hypoxia and prematurity leads to this presentation. Treatment with ursodeoxycholic acid at 10–20 mg/kg b.d. can improve bile flow.
⑧ —— Specific inborn errors of bile biosynthesis may present as neonatal cholestasis. A diminished production of certain enzymes results in a deficient production of primary bile acids that are essential for bile flow. The alternative production of hepatotoxic bile acids may cause liver injury. These abnormalities can be detected by qualitative urinary bile acid analysis. Treatment may involve oral primary bile acid therapy with cholic acid in order to suppress production of toxic bile acids.
⑨ —— NSC is characterized by abnormalities of the intra- and extrahepatic bile ducts secondary to inflammation. This results in obliteration of the ducts and progression to cirrhosis. Familial forms have been described. Though jaundice may initially clear in the first few months, the disease inevitably progresses to end-stage liver disease.
⑩ —— Galactosemia is an autosomal-recessive condition with an estimated prevalence of 1 in 60,000 and can present with early collapse and liver failure once feeding is established. Infants are susceptible to *Escherichia coli* infection. They may also present with conjugated hyperbilirubinemia and, in addition, hemolysis and acidosis. Cataracts can be seen in the neonatal period or present later on in those not on a restricted diet. Diagnosis is made by measuring the galactose-1-phosphate uridyltransferase level. Urinary reducing substances may be useful if the infant has been on a lactose-containing diet. Treatment consists of the complete exclusion of lactose from the diet.
⑪ —— Tyrosinemia type 1 is an autosomal-recessive condition with a prevalence of 1 in 100,000 which may cause liver failure, neurological crisis and hepatocellular carcinoma. Children often present with liver failure within the first few months of life or later with a Fanconi-like syndrome, rickets and growth failure. The deficient enzyme is a fumarylacetoacetate hydrolase. Urine will have high levels of succinylacetone. Treatment is with [2-(2-nitro-4-trifluoromethylbenzoyl)-1,2-cyclohexanedione] and feeds low in phenylalanine and tyrosine.
⑫ —— Infants with CF can sometimes present with conjugated hyperbilirubinemia. The jaundice usually clears within the first few months of life and true CFALD generally occurs later within the first 2 decades of life.
⑬ —— The mechanism by which hypopituitarism causes neonatal cholestasis is unknown, but jaundice may be an important clue and cortisol levels should always be checked in neonates with conjugated hyperbilirubinemia.
⑭ —— Inspissated bile may be secondary to sepsis or hypoxia or occur without risk factors (inspissated bile syndrome). US may show dilated ducts and the presence of inspissated bile. The condition may resolve spontaneously or rarely require radiological intervention (percutaneous transhepatic cholangiography) to flush out the bile duct. Treatment with ursodeoxycholic acid may aid bile flow and improve cholestasis.
⑮ —— Choledochal malformation is a congenital malformation of the extrahepatic ± intrahepatic biliary tract. Type 1c is characterized by a cystic malformation of the common duct, type 1f by a fusiform malformation of the common duct, type IV by both intra- and extrahepatic malformation and type V by intrahepatic bile duct dilatation only.
⑯ —— Alagille syndrome may present with conjugated hyperbilirubinemia in the neonatal period. Typical features on liver biopsy are of bile duct paucity (though neonates can also have a neonatal hepatitis-like picture). Other features are cardiac abnormalities (especially pulmonary stenosis), butterfly vertebrae, posterior embryotoxon and a typical facies. The condition is autosomal dominant, and genetic testing is available. Children often have severe pruritus and hypercholesterolemia.
⑰ —— PFIC encompasses a spectrum of conditions, in which there is a disorder of bile acid transport. PFIC type 1 or FIC1 disease is caused by a genetic mutation in ATP8B1 and is characterized by cholestasis with a normal or low GGT level. Cholestasis, FTT, severe malabsorption, deafness and short stature are characteristic features. Management may include biliary diversion for severe pruritus or liver transplantation. Those with the genetic mutation may also present with a milder form of the disease. These individuals can have episodes of cholestasis and diarrhea precipitated by antibiotics/viral illness. PFIC type 2 or BSEP deficiency is caused by a mutation in ABCB11 and again is a low GGT cholestasis. Immunohistochemical staining of the liver will show poor BSEP staining. Progression of liver disease may be more rapid than with FIC1. PFIC type 3 or multidrug-resistant protein 3 (MDR3) deficiency is caused by a mutation in ABCB4 and is characterized by high GGT cholestasis with progressive liver disease. Immunohistochemical staining reveals an absence of MDR3. There may be some response to ursodeoxycholic acid, but, as with the other two disease types, liver transplantation may be warranted.
⑱ —— BA occurs in 1 of 16,000 children, and its etiology is unknown. Progression to end-stage liver disease is universal without intervention. The Kasai procedure or portoenterostomy within the first weeks of life may establish bile flow and provide medium-term success in 50% of the patients, but only 20% will avoid liver transplantation before their 20th birthday.
⑲ —— Idiopathic neonatal hepatitis is characterized by giant cells on biopsy. This is a diagnosis of exclusion, and the etiology is unknown. Prognosis is usually good. A separate entity of giant cell hepatitis associated with Coomb's-positive hemolytic anemia is thought to have an immunological basis and has a poor prognosis with recurrence of the disease following liver transplantation.
⑳ —— α_1-Antitrypsin deficiency is a disorder of synthesis of a serine protease inhibitor. The disease is autosomal recessive, and the prevalence is 1 in 1,600 to 1 in 2,000 of the (Caucasian) population. Approximately 10–15% of those who are homozygous for the abnormal Z allele will have liver disease of varying severity. Liver abnormalities arise due to the accumulation of abnormally polymerized protein in the endoplasmic reticulum of the hepatocyte. The typical presentation is with neonatal conjugated hyperbilirubinemia. Liver disease can also present later with hepatomegaly, portal hypertension and abnormal synthetic function. Histopathology often demonstrates steatosis, fibrosis and the presence of α_1-antitrypsin, which is seen as periodic acid-Schiff-positive diastase-resistant globules in the endoplasmic reticulum of hepatocytes. Approximately 25% of children who present as neonates will progress to end-stage liver disease in early life; a further 25% may decompensate in the second decade of life.

Selected reading

Brumbaugh D, Mack C: Conjugated hyperbilirubinemia in children. Pediatr Rev 2012;33:291–302.
Lauer BJ, Spector ND: Hyperbilirubinemia in the newborn. Pediatr Rev 2011;32:341–349.