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Wong RJ, et al. Clinical manifestations of unconjugated hyperbilirubinemia in term and late preterm infants. . Accessed April 2, 2018.Maisels MJ, et al. Hyperbilirubinemia in the newborn infant ≥ 35 weeks' gestation: An update with clarifications. Pediatrics. 2009;124:1193.American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297.Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. American Academy of Pediatrics. . Accessed April 2, 2018.Hay WW, et al., eds. The newborn infant. In: Current Diagnosis & Treatment: Pediatrics. 23rd ed. New York, N.Y.: McGraw-Hill Education; 2016. . Accessed April 2, 2018.Wong RJ, et al. Evaluation of unconjugated hyperbilirubinemia in term and late preterm infants. . Accessed April 2, 2018.Maisels MJ. Managing the jaundiced newborn: A persistent challenge. Canadian Medical Association Journal. 2015;187:335.Muchowski KE. Evaluation and treatment of neonatal hyperbilirubinemia. American Family Physician. 2014;89:87.Biliary atresia. National Institute of Diabetes and Digestive and Kidney Diseases. . Accessed Jan. 13, 2020.Wong RJ. Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology. . Accessed Feb. 5, 2020.Picco MF (expert opinon). Mayo Clinic. Feb. 5, 2020. CausesSymptoms Risk factorsDiagnosisTreatmentPreventionFAQsOutlookNewborn jaundice is when a baby's skin and eyes turn yellow from too much bilirubin. It usually resolves as their liver matures and they start feeding, but if it persists, there may be another cause.Share on PinterestRyan S. Christie/FlickerIn most cases, jaundice (also called hyperbilirubinemia) in newborns will disappear within 2 to 3 weeks. The higher the bilirubin levels are, the more the baby is at risk for brain damage.Bilirubin is a yellow pigment produced during the typical breakdown of red blood cells. In older babies and adults, the liver processes bilirubin, passing it through the intestinal tract. However, a newborn's still-developing liver may not be mature enough to do this.There are two types of newborn jaundice: physiological and pathological.Physiological jaundice is the most common, accounting for 75% of cases. This just means the baby's metabolism cannot clear out bilirubin as quickly as it is produced. This type typically develops in a few days and clears up on its own in a few weeks when the breakdown of red blood cells slows and liver function improves.On the other hand, pathological jaundice means that there is another underlying condition that's causing a problem with filtering out bilirubin. This type may show up in the first 24 hours after birth.Pathological jaundice can also be caused by certain medications, such as certain antibiotics.The first sign of jaundice is the yellowing of a baby's skin and eyes, which may start in the face before spreading across the body. With physiological jaundice, the yellowing may begin and peak within 2 to 5 days after birth. With other causes, it may begin closer to birth.However, this yellowing can be harder to see in darker skin tones. Another way to tell is by pressing your finger lightly on the baby's skin. The spot should briefly appear paler. If it looks more yellow, it's likely a sign of jaundice.Share on PinterestLaura Dwight / Alamy Stock PhotoIf you have concerns or are unsure, contact your baby's doctor, particularly if the whites of their eyes look yellow.If untreated, severe newborn jaundiced can lead to acute bilirubin encephalopathy, which is caused by the toxic levels of bilirubin in the brain. A baby may get a fever, act listless and lethargic, have a shrill cry, refuse to feed, and curve their neck and body backward. This can, in turn, progress to kernicterus, which is permanent brain damage.In the United States, many hospitals discharge birthing parents and newborns after 24-48 hours before jaundice may become very apparent. If the baby has not developed jaundice within 72 hours of delivery, they're less likely to have the pathological form. But they can still develop the physiological form, leading to complications.Once you're home, contact your doctor if you notice the following symptoms:Jaundice spreads or becomes more intense.Your baby develops a fever over 100°F (38°C).Your baby's yellow coloring deepens.Your baby feeds poorly, appears listless or lethargic, and makes high-pitched cries.There are some things that can increase the chance of a newborn developing physiological jaundice. premature birthhistory of newborn jaundice in siblingsbeing male assigned at birth (MAAB)being of Asian descentIn addition, certain risk factors can increase your baby's chance of developing severe jaundice, which may be physiological or pathological. These include:jaundice within 24 hours after birthbirth before 40 weeks, with the chance increasing the earlier the baby is borntreatment with phototherapy or a history of a sibling being treated with phototherapy for jaundicefamily history of inherited red blood cell disorders such as G6PD deficiencydifficulty breastfeeding or chestfeedingbruising on the head or scalp from the birthhaving Down syndromeBeing born bigger than average for gestational age (macrosomia)Though distinct yellow coloring confirms that a baby has jaundice, additional tests may be needed to determine the severity.Babies who develop jaundice will get a bilirubin blood test to determine the levels of bilirubin in their blood. Additional tests may be needed to see if a baby's jaundice is due to an underlying condition. This may include testing your baby for their complete blood count (CBC), blood type, and Rh incompatibility.Additionally, a Coombs test may be done to check for antibodies that show an elevated risk of increased red cell breakdown (hemolysis).Mild jaundice will usually resolve on its own as a baby's liver matures. Frequent feedings (at least 8 times a day) will help babies pass bilirubin through their bodies.More severe jaundice may require other treatments. Phototherapy (light therapy) is a common and highly effective method of treatment that uses light to break down bilirubin in your baby's body.In phototherapy, your baby will be placed on a special bed under a blue spectrum light while wearing only a diaper and special protective goggles. A fiber-optic blanket may also be placed underneath your baby.In very severe cases, an exchange transfusion may be necessary. In this procedure, a baby receives small amounts of blood from a donor or a blood bank.This replaces the baby's damaged blood with healthy red blood cells. This also increases the baby's red blood cell count and reduces bilirubin levels.In addition, if there's an underlying cause, the baby will need to be treated for the condition to resolve symptoms.Physiological jaundice can't be prevented. But you can reduce the chance of development by frequently feeding your newborn, which can help their bilirubin pass through the body more quickly. If you or your doctor thinks there is a likely underlying issue that could cause jaundice in your newborn, there are tests that can verify this so that you or the baby can get preventive treatment if appropriate. For example, during pregnancy, you can have your blood type tested to rule out the possibility of Rh incompatibility. If you're Rh-negative, you can get intravenous immunoglobulin during pregnancy.Newborns that develop jaundice can have a pale-colored stool, but not often. Most newborns with jaundice will have the same color stool as newborns without jaundice. It may begin as black, dark brown, or dark green in the first few days, and then transition to yellow or orange-colored stool. For this reason, it can be hard to recognize jaundice from the stool color alone.A newborn with jaundice may have dark yellow urine. As you feed the baby, it should become colorless. Make sure your baby is having at least six diapers daily.In addition to the yellowing of the skin, jaundice also causes the yellowing of the white part of the eyes.Most cases of physiological newborn jaundice will clear away, often without treatment. Frequent feedings will help it resolve. But your doctor will still monitor your baby to make sure it is improving.The outlook of pathological jaundice depends on the underlying cause and what treatment the baby requires. In both cases, without immediate treatment, complications can begin to develop.The most recent guidelines by the American Academy of Pediatrics (AAP) recommend that all newborn babies be examined for jaundice at least every 12 hours after birth and until their discharge from the hospital Neonatal jaundice is a clinical manifestation of elevated total serum bilirubin, termed neonatal hyperbilirubinemia, which results from bilirubin that is deposited into an infant's skin. The characteristic features of neonatal jaundice include yellowish skin, sclerae, and mucous membranes. Jaundice derives from the French word jaune, meaning yellow. Neonatal jaundice is the most frequently encountered medical condition in the first 2 weeks of life and a common cause of readmission to the hospital after birth.

[1] Approximately 60% of term and 80% of preterm newborns develop clinical jaundice in the first week after birth.[2] Neonatal jaundice is usually a mild, transient, and self-limiting condition known as physiologic jaundice. However, this should be distinguished from the more severe pathologic jaundice. The two types of neonatal hyperbilirubinemia are unconjugated hyperbilirubinemia (UHB) and conjugated hyperbilirubinemia (CHB).When neonatal jaundice is clinically identified, the underlying etiology of neonatal hyperbilirubinemia must be determined. In most neonates, unconjugated hyperbilirubinemia is the cause of clinical jaundice. However, some infants have conjugated hyperbilirubinemia, which is always pathologic and signifies an underlying medical or surgical etiology. Failure to identify and treat pathologic jaundice may result in bilirubin encephalopathy and associated neurological sequelae. The causes of pathologic UHB and CHB are numerous and varied. Preterm infants and those with congenital enzyme deficiencies are particularly prone to the harmful effects of unconjugated bilirubin on the central nervous system.[3][4]Unconjugated hyperbilirubinemia is diagnosed by assessing bilirubin levels with a transcutaneous measurement device or blood samples for total serum bilirubin. Conjugated hyperbilirubinemia is typically diagnosed through laboratory studies, including serum aminotransferase, prothrombin time, urine cultures, tests for inborn errors of metabolism, and, in some cases, imaging studies. Severe hyperbilirubinemia can cause bilirubin-induced neurological dysfunction (BIND) and, if not treated adequately, may lead to acute and chronic bilirubin encephalopathy.

[5] Phototherapy and exchange transfusions are the mainstays of treatment of UHB, and a subset of patients also respond to intravenous immunoglobulin (IVIG). Treatment of CHB is more complex and depends on the etiology of the jaundice. Despite advances in the care and management of hyperbilirubinemia, it remains a significant cause of neonatal morbidity and mortality.[6]The underlying etiology of neonatal jaundice is neonatal hyperbilirubinemia, which has 2 distinct types: unconjugated and conjugated hyperbilirubinemia, also known as indirect and direct hyperbilirubinemia, respectively. (See Image. Metabolic Pathway for Bilirubin in the Hepatocyte). Unconjugated Hyperbilirubinemia Unconjugated (ie, indirect) hyperbilirubinemia (UHB) is the more common type and is either physiologic or pathologic. Physiologic jaundice accounts for 75% of neonatal hyperbilirubinemia and results from a physiologic alteration in neonatal bilirubin metabolism. Healthy adults have a total serum bilirubin (TSB) level of less than 1mg/dL. In neonates, normal TSB levels are comparatively higher, with age-dependant levels. Even healthy full-term newborns have an increased bilirubin load due to higher red blood cell (RBC) mass and decreased RBC lifespan. Metabolic bilirubin clearance is also compromised due to impaired activity of uridine diphosphate glucuronosyltransferase (UGT), the enzyme needed for bilirubin conjugation. The activity level of the newborn UGT enzyme is approximately 1% that of an adult.[7] Moreover, neonates also have increased enterohepatic circulation, further contributing to elevated TSB levels. Physiologic jaundice typically appears in full-term infants 24 hours after birth, peaks at around 48 to 96 hours, and resolves by 2 to 3 weeks.[2] Conversely, pathologic unconjugated hyperbilirubinemia occurs within the first 24 hours after birth when the TSB level is >95% on age-specific bilirubin nomograms or increases ≥5 mg/dL/day or >0.2 mg/dL/hour.[8] Based on the mechanism of bilirubin elevation, the etiology of unconjugated hyperbilirubinemia can be subdivided into the following 3 categories: increased bilirubin production, decreased bilirubin clearance, and miscellaneous. Increased Bilirubin Production The production of bilirubin can increase secondary to immune-mediated hemolysis caused by blood group incompatibilities (eg, such as ABO and Rhesus (Rh) incompatibility) and nonimmune mediated hemolysis, which is caused by RBC membrane defects (eg, hereditary spherocytosis and elliptocytosis), RBC enzyme defects (eg, glucose-6-phosphate dehydrogenase [G6PD], pyruvate kinase deficiencies), sequestration-like cephalohematoma, subgaleal hemorrhage, intracranial hemorrhage, polycythemia, and sepsis. Exaggerated immune or nonimmune mediated hemolysis is the most common cause of pathologic hyperbilirubinemia. Immune-mediated hemolysis occurs with blood group incompatibility as ABO/Rh incompatibility and causes hemolytic disease of the newborn (HDN). In HDN from ABO incompatibility, preformed maternal anti-A and anti-B antibodies of the immunoglobulin G (IgG) subclass cross the placenta and cause hemolysis and UHB in newborns with blood types A, B, or AB. Although the direct antiglobulin test (DAT) aids diagnosis, the sensitivity and positive predictive value for severe UHB are low.[9] ABO incompatibility between mother and fetus exists in about 15% of pregnancies, but HDN occurs in only about 4% of newborns with ABO incompatibility.[10] In Rh incompatibility, an Rh-negative mother, exposed to Rh-positive RBCs during a previous pregnancy, becomes sensitized and develops antibodies against Rh antigen. Initially, sensitization produces IgM antibodies that cannot cross the placenta. However, during subsequent pregnancies, IgG antibodies cross the placenta, causing RBC hemolysis in a fetus with Rh-positive blood. The Rh antigen is very immunogenic, and the resultant HDN is usually severe, often leading to hydrops fetalis or severe UHB in newborns. Prevention of neonatal UHB caused by immune-mediated hemolysis begins in pregnancy with the recognition of mothers at risk for developing Rh antibodies. The American College of Obstetricians and Gynecologists (ACOG) recommends that all Rh-negative pregnant women receive anti-D immune globulin at 28 weeks gestation and again after delivery if the infant is Rh-positive or the blood type is unknown.[11]Nonimmune causes of UHB include RBC enzyme defects, RBC membrane defects, hemoglobinopathies, sepsis, sequestration, and polycythemia. Glucose-6 phosphatase dehydrogenase (G6PD) deficiency is the most common RBC enzyme defect, transmitted as an X-linked recessive trait. G6PD protects RBCs against oxidative damage by generating NADPH (nicotinamide adenine dinucleotide phosphate hydrogenase) from NADP (nicotinamide adenine dinucleotide phosphate). When exposed to oxidant stressors like illness, certain medications, dyes, and foods such as fava beans, G6PD deficient RBCs are hemolyzed, causing anemia and hyperbilirubinemia. More than 200 different mutations cause G6PD deficiency.[12] The clinical presentation differs depending on the variant, and some newborns may develop severe hyperbilirubinemia and bilirubin encephalopathy. Pyruvate kinase deficiency (PKD) is another condition that causes hemolysis and may present as UHB in newborns. PKD is an autosomal recessive (AR) disorder interfering with glycolysis and cellular energy production. In PKD, RBCs have shortened life spans, resulting in hemolytic anemia and UHB.[13]Conditions causing UHB due to RBC membrane defects include hereditary spherocytosis (HS) and hereditary elliptocytosis (HE). HS (ie, Minkowski Chauffard disease) is the most common RBC membrane defect caused by RBC membrane protein mutations.[14] Most cases are transmitted as an autosomal dominant (AD) trait and can present in the neonatal period with UHB.[15] Hereditary elliptocytosis is another type of RBC membrane defect caused by structural membrane protein mutations in which elliptical-shaped RBCs are trapped in the spleen, leading to extravascular hemolysis and elevated TSB. HE is usually asymptomatic but may cause UHB in the neonatal period.[16] Etiologies that cause RBC sequestration (eg, cephalohematoma, subgaleal hemorrhage, and intracranial hemorrhage) are also risk factors for neonatal UHB due to increased bilirubin load. Polycythemia is another condition associated with an increased risk of UHB in newborns, associated with intrauterine growth restriction (IUGR), infants of diabetic mothers (IDM), large for gestational age (LGA) infants, maternal smoking, high altitude, twin to twin transfusions, and placental transfusion (eg, delayed cord clamping and umbilical cord milking). Studies show that delayed cord clamping reduces the incidence of postnatal anemia and leads to improved neurodevelopmental outcomes among term and preterm infants.[17][18] Delayed cord clamping has gained popularity but may also increase the risk of hyperbilirubinemia.[19][20] Decreased Bilirubin Clearance Indirect hyperbilirubinemia due to decreased bilirubin clearance usually results from quantitative or qualitative defects in the uridine diphosphate glucuronosyltransferase (UGT) enzyme. Gilbert syndrome and Crigler–Najjar syndrome type I and II are 3 disorders resulting from an abnormality of the UGT enzyme. Gilbert syndrome is the most common due to a mutation in the UGT1A1 gene leading to decreased UGT production and subsequent unconjugated hyperbilirubinemia.[21] Gilbert syndrome typically presents as mild jaundice at times of physiologic stress in the absence of hemolysis or liver dysfunction. However, presentations during the neonatal period are rare and usually associated with G6PD deficiency.[22][3] Crigler-Najjar syndrome type I is an AR disorder resulting from a complete absence of UGT activity. Affected patients present with severe hyperbilirubinemia in the first few days of life, often leading to bilirubin encephalopathy. Patients with Crigler-Najjar syndrome type II retain some of the activity of UGT enzymes; therefore, their TSB levels are not as elevated as in patients with the type I variant, and bilirubin encephalopathy rarely develops.[23] Miscellaneous Causes Other etiologies of UHG include congenital hypothyroidism, sulfa medications, ceftriaxone, penicillins, intestinal obstruction, pyloric stenosis, breast milk jaundice, and suboptimal intake with breastfeeding. Infants of mothers with diabetes are at higher risk of developing unconjugated hyperbilirubinemia. Jaundice secondary to breastfeeding and breast milk are 2 other common etiologies of UHB in newborns. Breastfeeding jaundice, known as suboptimal intake hyperbilirubinemia, occurs in the first week of life due to inadequate breast milk consumption, leading to dehydration and occasionally hypernatremia.[7] Poor intake decreases intestinal motility and elimination of bilirubin in the stool. Conversely, breast milk jaundice occurs late in the first week after birth, peaks in the second week, and usually resolves by 2 weeks of age, though the condition may persist for up to 3 months. Breast milk jaundice is rarely pathologic and is associated with adequate intake and good weight gain.[24] Inhibition of the UGT enzyme by pregnanediol and the deconjugation of conjugated bilirubin in the intestines by beta-glucuronidase present in breast milk is thought to be the primary underlying pathophysiology.[25][26]Other miscellaneous causes of UHB include infants of mothers with diabetes (IDM), gastrointestinal obstruction, congenital hypothyroidism, and certain medications. IDM often have polycythemia, with an increased incidence of jaundice.[27] UHB in congenital hypothyroidism is related to decreased bilirubin hepatic uptake, impaired UGT activity, and sluggish gut motility, while gastrointestinal obstruction promotes increased bilirubin recycling by augmenting enterohepatic circulation. When prescribed in the neonatal period, certain medications may worsen UHB by displacing bilirubin from albumin, affecting albumin binding.[28] Sepsis can also predispose a newborn to UHB by causing oxidative damage to RBCs and increasing bilirubin load.[29]Additionally, most infants with clinical UHB have a combination of 2 or more predisposing contributing factors, including prematurity, a history of jaundice requiring phototherapy in parents or siblings, Asian ethnicity, male gender, and exclusive breastfeeding.[2] Preterm infants are at increased risk of bilirubin encephalopathy and kernicterus and require close monitoring, although there is insufficient data and a lack of consensus guidelines on managing UHB in preterm infants.[30][31] Because of the increased risk of neurotoxicity, the TSB threshold for initiation of phototherapy is lower than for term infants. However, bilirubin is an antioxidant and may have a physiologic role in neonates.[32][33] Keeping TSB levels low by aggressive treatment in preterm infants may reduce this antioxidant level and potentially worsen retinopathy of prematurity. Moreover, reduced antioxidant status is also associated with chronic lung disease and neurological injury. Therefore, treating UHB in premature neonates is challenging without evidence-based guidelines. The most recent clinical practice guidelines for managing hyperbilirubinemia of the American Academy of Pediatrics in 2022 included only infants >35 weeks of gestation.[34][30] Conjugated Hyperbilirubinemia Conjugated hyperbilirubinemia (CHB), also referred to as neonatal cholestasis, is characterized by the elevation of serum conjugated (ie, direct) bilirubin (>1.0 mg/dL) due to impaired hepatobiliary function. Distinguishing CHB from UHB is critical because cholestatic neonatal jaundice is almost always pathologic and warrants prompt evaluation and treatment.[35] The causes of CHB are extensive and typically classified into the following categories:Infection: Congenital infections (eg, syphilis, toxoplasmosis, HIV, herpes virus, and rubella) should be included in the differential diagnosis of neonatal cholestasis, especially when stigmata of congenital infection, including growth restriction, coagulopathy, skin rash, or thrombocytopenia, are present. Cytomegalovirus (CMV) is also a common congenital infection with many manifestations. Most infected newborns are asymptomatic, but hepatomegaly and CHB may indicate hepatic involvement.[36] Carefully reviewing maternal history, specific serologies, and viral culture results aid diagnosis. Urine and blood cultures are also a component of the diagnostic evaluation, as urinary tract infections and septicemia can cause CHB in neonates. Additionally, microcirculatory changes in the liver, a direct effect of bacterial products, and toxins released by bacteria are thought to be the possible mechanisms of cholestasis in patients with UTI.[37]Obstruction of biliary flow: Conditions with this underlying pathophysiology include biliary atresia, choledochal cysts, neonatal sclerosing cholangitis, and neonatal cholelithiasis. Biliary atresia (BA) is the most common cause of conjugated hyperbilirubinemia in infants, with an incidence that varies by geographic location.[38] Taiwan, the region with the highest incidence, has a reported frequency of 1 in 6000 live births. In the United States, the incidence is about 1 in 12,000 live births.[39] The etiology of BA is not well understood, but genetic factors, viral infections, toxins, chronic inflammation, and autoimmune injury to bile ducts seem to play a role in the pathogenesis. The disease involves both intra-hepatic and extrahepatic bile ducts and classically presents around 2 to 4 weeks after birth with pale stools and jaundice. The initial ultrasound examination may reveal an absent gallbladder and the classic "triangular cord" sign, a ductal remnant of the extrahepatic bile duct.[40] Early diagnosis is critical to maximizing the response to the Kasai operation (ie, hepatic portoenterostomy).[41] If surgery is delayed until after 90 days of life, 70% of patients will establish adequate bile flow.[42] Choledochal cysts can also cause biliary flow obstruction. The intrahepatic and extrahepatic bile ducts are dilated when choledochal cysts are present, and ultrasonography can detect cysts with normal or dilated intrahepatic bile ducts as opposed to the sclerosed ducts of biliary atresia. However, cystic biliary atresia may resemble choledochal cysts.[43] Neonatal sclerosing cholangitis (NSC) is a rare form of cholangiopathy that presents in infancy with CHB, hepatosplenomegaly, pale stools, and high serum gamma-glutamyltransferase activity (GGT).[44] Neonatal cholelithiasis is another rare entity that causes significant direct hyperbilirubinemia.[45]Genetic: There are several genetic etiologies (eg, Alagille syndrome, alpha-1 anti-trypsin deficiency, galactosemia, fructosemia, Tyrosinemia type 1, cystic fibrosis, progressive familial intrahepatic cholestasis [PFIC], Aagenaes syndrome, Dubin-Johnson syndrome, bile acid synthesis disorders [BSAD]) that commonly result in CHB. Alagille syndrome (ALGS) is an AD disorder caused by mutations in the JAG1 or NOTCH2 genes, leading to a lack of interlobular bile ducts.[46] With an incidence of 1 in 30,000 live births, ALGS is the most common cause of familial intrahepatic cholestasis, though CHB in patients with ALGS may resolve with age.[47][35] Characteristic clinical features include butterfly vertebrae, congenital heart defects (eg, peripheral pulmonic stenosis), kidney involvement, dysmorphic features (eg, broad forehead and a small pointed chin), and posterior embryotoxon of the eye. Gamma-glutamyl transferase (GGT) levels are elevated, often up to 20 times the standard value. Occasionally, patients with cystic fibrosis (CF) present with cholestasis because of abnormal bile that plugs the bile ducts.[48] In developing nations where newborn screening with immunoreactive trypsinogen is unavailable, neonatal cholestasis may be the first clue to diagnosing CF. Alpha-1-antitrypsin deficiency is the most common genetic cause of cholestasis and can mimic biliary atresia in early infancy. Accumulation of anti-trypsin polymers in the hepatocyte endoplasmic reticulum of a patient with the PIZZ genotype leads to apoptosis of hepatocytes, ultimately resulting in cholestasis and cirrhosis later in childhood.[49] As with ALGS, cholestasis may improve with age. Galactosemia, fructosemia, and tyrosinemia type 1 are a few of the inborn errors of metabolism known to cause cholestasis in neonates. Newborns with galactosemia can present with cholestatic jaundice, cataracts, hepatomegaly, failure to thrive, renal tubular acidosis, and Escherichia coli sepsis after ingesting galactose from milk.[50] Galactose-1-phosphate uridyl transferase (GALT) deficiency leads to the accumulation of toxic galactose metabolites in multiple organs. The presence of urine-reducing substances suggests galactosemia, but GALT activity in the liver or erythrocytes confirms the diagnosis. Neonatal cholestasis is a presenting feature in hereditary tyrosinemia type 1, another AR disorder caused by a deficiency of the enzyme fumarylacetoacetate hydroxylase. Other characteristics of this disorder include renal Fanconi syndrome, hepatomegaly, coagulation abnormality, and the risk of hepatocellular carcinoma in untreated older patients.[51]Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of 3 genetic disorders involving canalicular hepatobiliary transport that presents with cholestasis.[52] Types 1 and 2 usually manifest in the neonatal period, while type 3 presents later in infancy. Affected patients with PFIC frequently develop cirrhosis and end-stage liver disease during childhood. In diagnostic studies, the GGT level is within the normal range in types 1 and 2 and elevated in type 3 patients. PFIC type 1 is caused by a mutation in the ATP8B1 gene, which encodes the FIC1 protein, whereas PFIC type 2 is caused by a mutation in the ABCB11 gene, which encodes for the bile salt excretory protein (BSEP). PFIC type 3 is caused by a mutation in the ABCB4 gene, which encodes for the multi-drug resistant-3 protein (MDR3).[53] Aagenaes syndrome, also known as lymphedema cholestasis syndrome (LCS), is another idiopathic familial intrahepatic cholestasis syndrome characterized by neonatal cholestasis and lymphedema in the lower extremities. Aagenaes syndrome is transmitted as an autosomal recessive (AR) trait usually seen in individuals of Norwegian descent.[54] Dubin-Johnson syndrome (DJS) is a rare AR disorder caused by a mutation in the ABCC2 gene, which codes for a non-biliary ion transporter in the liver. A unique feature of DJS is a black-colored liver and the excretion of coproporphyrin 1 in urine.[55] Bile acid synthesis disorder (BASD) results from a deficiency of an enzyme involved in synthesizing bile acids from cholesterol. BASDs are an uncommon cause of cholestasis, but many are curable with medical therapy.Miscellaneous: Other conditions that may cause CHD include idiopathic neonatal hepatitis, parenteral nutrition-induced cholestasis, gestational alloimmune liver disease, neonatal hemochromatosis, and hypotension. Parenteral nutrition-associated cholestasis (PNAC) is a significant iatrogenic cause of cholestasis in preterm infants managed with parenteral nutrition (PN). PNAC is present in about 20% of neonates receiving PN for 2 weeks or longer.[56] Duration of PN use and intestinal failure are 2 independent risk factors for PNAC. Though the mechanism is not entirely clear, likely being multifactorial, abnormal bile salt metabolism due to prematurity and the harmful effects of PN components are thought to be the main culprits.[57] Other factors, including sepsis and necrotizing enterocolitis, can also potentiate liver injury.[58] Gestational alloimmune liver disease (GALD), which causes almost all cases of neonatal hemochromatosis, is a fulminant alloimmune disorder and results from intrahepatic and extrahepatic iron deposition, leading to liver failure.[59] In GALD, maternal IgG immunoglobulin against fetal hepatocytes crosses the placenta, causing complement-mediated damage to fetal hepatocytes. Characteristic features involve signs of liver failure, including hypoglycemia, coagulopathy, hypoalbuminemia, cholestatic jaundice, edema, and elevated liver enzymes. GALD has a risk of recurrence in subsequent pregnancies of approximately 90% and can result in fetal or neonatal death.[60] The term idiopathic neonatal hepatitis is used when the etiology of neonatal cholestasis cannot be ascertained after an extensive diagnostic evaluation. Newer diagnostic tools enable more precise diagnoses, with fewer cases of neonatal cholestasis now classified as "idiopathic."[42] Unconjugated hyperbilirubinemia is frequently encountered in the neonatal period. About 80% of term and preterm newborns will present with clinical jaundice with a TSB >5 mg/dL.[2][61] However, only approximately 10% of neonates require phototherapy.[62] Physiologic jaundice is the most frequent cause of clinical jaundice after the first day of life, estimated to account for 50% of cases.[63] Approximately 15% of breastfed infants will develop physiologic UHB lasting >3 weeks.[64]Only a minority of jaundiced newborns have pathologic hyperbilirubinemia. Severe hyperbilirubinemia, commonly defined as a TSB>25 mg/dL, occurs in approximately 1 out of 2500 live births. Among these, ABO incompatibility, followed by G6PD deficiency, is the most frequently identified cause.[65] Newborns with Southeast and East Asian ancestry have higher recorded TSB levels than Black or White infants.[66][67] Neonatal jaundice also appears more common in infants living at high altitudes and around the Mediterranean Sea, especially in Greece.[68][69] Acute bilirubin encephalopathy occurs at a rate of approximately 1 in 10,000 live births, and the incidence of chronic bilirubin encephalopathy is comparitively lower, estimated at 1 in 50,000 to 100,000 live births.[70] However, developing nations report higher rates of kernicterus, a permanent neurologic condition.[71]Conjugated hyperbilirubinemia is much less common than UHB, with an incidence of around 1 in 2500 term infants.[72] The most frequently identified cause of cholestatic jaundice in the neonatal period is biliary atresia, accounting for an estimated 25% to 40% of all cases, followed by infections and PN-induced cholestasis.[35][73] Approximately 60% to 70% of patients with BA will require liver transplantation in childhood, remaining the most common indication for a pediatric liver transplant.[74]Bilirubin is produced from the catabolism of heme, a breakdown product of hemoglobin, in the reticuloendothelial system (RES). First, heme is converted to biliverdin, releasing iron and carbon monoxide via the action of the enzyme heme oxygenase.[75] Biliverdin is then converted to bilirubin by the enzyme biliverdin reductase. This hydrophobic unconjugated bilirubin binds to albumen, is transported to the liver, and is conjugated with glucuronic acid in the smooth endoplasmic reticulum by the enzyme uridine diphosphate-glucuronosyltransferase (UGT). Conjugated bilirubin is water soluble and is excreted in bile, passed into the gastrointestinal (GI) tract, and eliminated in feces. Some conjugated bilirubin is deconjugated in the GI tract by beta-glucuronidase and reabsorbed through the enterohepatic circulation.[76]Newborn infants have higher TSB levels than adults due to higher hemoglobin levels at birth, a shorter RBC life span, and limited conjugating ability of the neonatal liver.[77] Healthy, full-term newborns typically have peak serum bilirubin concentrations of 5 to 6 mg/dL compared to adult levels of 35 weeks gestation include:[8]A bilirubin level in the high-risk zone before hospital dischargeJaundice in the first 24 hours after birthMaternal-fetal blood group incompatibilityGestational age