

BARC DISEASE DEFINITIONS

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| | |
|---|----|
| ASCITES | 6 |
| ALAGILLE SYNDROME | 7 |
| BILIARY ATRESIA | 9 |
| CHOLANGITIS..... | 10 |
| ENCEPHALOPATHY | 11 |
| FAILURE TO THRIVE..... | 12 |
| GASTROINTESTINAL BLEEDING AND ESOPHAGEAL VARICEAL HEMORRHAGE | 13 |
| Gastrointestinal hemorrhage: | 13 |
| Esophageal variceal hemorrhage: | 13 |
| Gastric variceal hemorrhage: | 13 |
| HEPATORENAL SYNDROME | 14 |
| IDIOPATHIC NEONATAL HEPATITIS..... | 16 |
| INBORN ERRORS OF BILE ACID SYNTHESIS | 17 |
| NEONATAL METABOLIC DISEASES..... | 18 |
| Alpha-1-Antitrypsin deficiency | 18 |
| Galactosemia..... | 18 |
| Hereditary Fructose Intolerance..... | 18 |
| Hereditary Tyrosinemia | 18 |
| Neonatal Iron Storage Disease..... | 18 |
| SPONTANEOUS BACTERIAL PERITONITIS (SBP)..... | 19 |
| INFECTIONS ASSOCIATED WITH NEONATAL CHOLESTASIS | 20 |
| ROUTES OF INFECTION..... | 20 |
| ETIOLOGIC AGENTS | 20 |
| Bacterial infections | 20 |
| Urinary tract infection..... | 20 |
| Congenital syphilis..... | 21 |
| Tuberculous hepatitis..... | 21 |
| Toxoplasmosis | 21 |
| Viral infections..... | 21 |
| Cytomegalovirus..... | 21 |
| Herpes hepatitis..... | 22 |
| Rubella | 22 |
| Hepatitis A | 23 |
| Hepatitis B | 23 |
| Hepatitis C | 24 |
| Delta hepatitis (hepatitis D) | 24 |
| Hepatitis E (Enterically transmitted non-A, non-B hepatitis)..... | 25 |
| GB Virus C (Hepatitis G) | 25 |
| Enteroviral hepatitis | 26 |
| Parvovirus hepatitis..... | 26 |
| Human herpesvirus-6 infection..... | 26 |

| | |
|--|----|
| Reovirus-3 infection..... | 27 |
| Paramyxovirus infection..... | 27 |
| Human Immunodeficiency Virus Infection (HIV) | 27 |
| Etiologic Agents Diagnostic Tests..... | 28 |
| Bacteria | 28 |
| Viral infections..... | 28 |

ASCITES

Ascites is the presence of excess fluid in the abdominal cavity. Physical assessment should be by an experienced physician. Ascites is diagnosed by the presence of shifting dullness, ballotable fluid, bulging flanks or a fluid wave. The diagnosis may be confirmed by a successful abdominal paracentesis and/or ultrasound at the discretion of the physician.

ALAGILLE SYNDROME

Alagille syndrome (AGS) is an autosomal dominant disorder characterized by bile duct paucity and cholestasis, along with developmental abnormalities in other organ systems, including the heart, eyes and skeleton. The clinical manifestations of AGS are extremely variable. Many AGS patients who present with neonatal jaundice will have significant cholestatic liver disease during childhood, and about 20% will progress to portal hypertension or liver failure, requiring transplantation. The disease gene for AGS is *Jagged1*, encoding a signaling molecule important for cell fate determination during embryonic development of multiple organ systems.

The reported incidence of Alagille syndrome is 1:70,000. However, the disease is likely to be more common due to the existence of mildly affected individuals who have not come to medical attention.

Major clinical criteria for Alagille syndrome

1. Bile duct paucity: In AGS patients, this finding is present in about 60% of biopsies done in infants less than 6 months of age, and in 95% of biopsies done after 6 months of age.
2. Cholestasis
3. Heart murmur or structural heart disease: In the most recent studies, over 95% of AGS patients have a heart murmur. The murmur of peripheral pulmonic stenosis is most common. The most common structural abnormality is narrowing at some level of the pulmonary vascular tree. Right-sided cardiac lesions, such as tetralogy of Fallot and pulmonic stenosis, are more common than septal defects or left-sided lesions.
4. Ocular anomalies: Examples include, but are not limited to: posterior embryotoxon, Axenfeld's anomaly and Rieger anomaly.
5. Vertebral anomalies (butterfly vertebrae)
6. Facial features: "Inverted triangle," with broad forehead and pointed chin. Facies may be difficult to appreciate in infants.
7. Renal involvement: Overall, reports suggest that about 40 to 50% of patients with AGS have renal involvement. Renal disease may be functional, structural or acquired. Examples include: renal tubular acidosis, solitary kidney and bifid renal pelvis.

The traditional diagnostic criteria for the syndrome, as described by Dr. Alagille, included bile duct paucity plus three major clinical criteria. However, after the discovery of the disease gene, it became apparent that an individual may carry a mutation in *JAG1*, yet not fulfill the clinical criteria for the disease.

Patients meeting the entry criteria for the BARC database will by definition be cholestatic, fulfilling one of the major clinical criteria for AGS.

- Cholestasis and bile duct paucity plus two other major clinical criteria.

- Cholestasis without bile duct paucity, plus three other major clinical criteria. This situation may be common in infancy, when as many as 40% of AGS patients do not demonstrate paucity on biopsy.
- Cholestasis and a relative with Alagille syndrome or a known *JAG1* mutation.
- Cholestasis and a known *JAG1* mutation

BILIARY ATRESIA

Biliary atresia is a chronic progressive cholestatic liver disease of the newborn of unknown cause. The disease is characterized by progressive inflammatory and fibrotic obliteration of extrahepatic and intrahepatic bile ducts that usually leads to chronic cholestasis and ultimately to biliary cirrhosis, portal hypertension, hepatic failure, and death if untreated.

Biliary atresia has its onset during the neonatal period (within the first three months of life). The incidence of biliary atresia is approximately 1 per 8,000-18,000 live births. It is the most common cause of severe liver disease in infants and the major reason for liver transplantation in children, accounting for 50% of all pediatric liver transplants performed in the United States. There is a slight female predominance in cases of biliary atresia and the disease is more common among Asian and African-American children than Caucasian children. Approximately 20% of patients with biliary atresia have other associated anomalies including polysplenia, dextrocardia, and vascular anomalies, and are considered to have a “fetal” form of the disease. Eighty percent of patients have no other congenital anomalies and are considered to have a “perinatal” or “acquired” form of biliary atresia. Biliary atresia is also associated with chromosomal abnormalities, including trisomies.

Diagnostic Criteria:

1. Appearance of jaundice with elevations in serum total and conjugated bilirubin within the first three months of life.
2. Liver biopsy histology compatible with biliary atresia
3. Cholangiographic or histologic demonstration of lack of patency of extrahepatic bile ducts.

CHOLANGITIS

A. Cholangitis:

Fever > 38°C in a child with no other obvious source of infection with:

1. Acholic stools in a child who previously had stool pigmentation
2. Right upper quadrant pain/tenderness
3. Elevation of direct bilirubin by 25% and at least >1.0 mg/dl above previous level baseline

B. Cholangitis with positive culture (blood or liver)

Fever > 38°C in a child with no other obvious source of infection with:

1. Acholic stools in a child who previously had stool pigmentation
2. Right upper quadrant pain/tenderness
3. Elevation of direct bilirubin by 25% and at least >1.0 mg/dl above previous level baseline
4. Positive bacterial culture of blood and liver

C. Possible cholangitis

Fever > 38°C in a child with no other obvious source of infection with at least 2 of the following

1. Acholic stools in a child who previously had stool pigmentation
2. Right upper quadrant pain/tenderness
3. Elevation of direct bilirubin by 25% and at least >1.0 mg/dl above previous level baseline
4. Rise in 2 or more of AST, ALT, alkaline phosphatase or GGTP to 1.5X the upper limit of normal or >25% above baseline values if previously elevated
5. Clinical and biochemical improvement in response to treatment with antibiotics

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Wu ET et al

Subramaniam R et al *J Pediatr Surg* 35:593-97, 2000

ENCEPHALOPATHY

Hepatic encephalopathy is a syndrome observed in patients with cirrhosis of the liver. It is characterized by personality changes, intellectual impairment, and a depressed level of consciousness. An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels. The development of hepatic encephalopathy is explained, to some extent, by the effect of neurotoxic substances, which occurs in the setting of cirrhosis and portal hypertension.

Subtle signs of hepatic encephalopathy are observed in nearly 70% of patients with cirrhosis. Symptoms may be debilitating in a significant number of patients and are observed in 24-53% of patients who undergo portosystemic shunt surgery.

Distinguishing hepatic encephalopathy from other acute and chronic causes of altered mental status may be difficult in patients with cirrhosis. A decision to perform additional neurological studies should be based on the severity of the patient's mental dysfunction, the presence of focal neurological findings (observed infrequently in patients with hepatic encephalopathy), and the patient's responsiveness to an empiric trial with cathartic agents. Even patients with severe hepatic encephalopathy should demonstrate steady improvement in mental dysfunction after an initiation of treatment with lactulose or cathartics derived from polyethylene glycol (PEG).

Differential diagnoses of encephalopathy

1. Intracranial lesions such as subdural hematoma, intracranial bleeding, cerebrovascular accident, tumor, and abscess
2. Infections such as meningitis, encephalitis, and intracranial abscess
3. Metabolic encephalopathy such as hypoglycemia, electrolyte imbalance, anoxia, hypercarbia, and uremia
4. Hyperammonemia from other causes such as secondary to ureterosigmoidostomy and inherited urea cycle disorders
5. Toxic encephalopathy from alcohol, such as acute intoxication, alcohol withdrawal, and Wernicke encephalopathy
6. Toxic encephalopathy from drugs such as sedative hypnotics, antidepressants, antipsychotic agents, and salicylates
7. Organic brain syndrome
8. Postseizure encephalopathy

Adapted from DC Wolf, Hepatic Encephalopathy, e-Medicine, 2003

FAILURE TO THRIVE

Failure to thrive is a description applied to children whose current weight or rate of weight gain is significantly below that of other children of similar age and sex.

Failure to thrive in infants and children is usually noticed when they seem to be dramatically smaller or shorter than other children the same age. In general, the rate of change in weight and height may be a better indicator of a problem than the actual measurements.

Symptoms: Height, weight and head circumference in an infant or young child do not progress normally according to standard growth charts (weight less than 3rd percentile, weight 20 percent below ideal weight for height, or a falloff from a previously established growth curve). Physical skills such as rolling over, sitting, standing and walking are slow to develop. Mental and social skills are delayed.

Signs and tests: A physical examination is done, including height, weight and body proportions. A detailed history is taken, including prenatal, birth, neonatal, psychosocial and family information. A Denver Developmental Screening Test reveals delayed development. A growth chart including all growth parameters and trends since birth is plotted.

Adapted from Medline Plus

GASTROINTESTINAL BLEEDING AND ESOPHAGEAL VARICEAL HEMORRHAGE

Gastrointestinal hemorrhage:

Hematemesis, hematochezia or melena, causing a drop in hematocrit of >5% with either:

Esophageal variceal hemorrhage:

Gastrointestinal hemorrhage and documentation of actively bleeding esophageal varices by esophagoscopy OR identification of esophageal varices and no other identifiable cause of hemorrhage

Gastric variceal hemorrhage:

Hematemesis, hematochezia or melena, causing a drop in hematocrit of >5% with documentation of actively bleeding gastric varices by endoscopy

Adapted from Miga et al J Pediatr 2001;139:291-6

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is the development of renal failure in patients with advanced chronic liver disease, occasionally fulminant hepatitis, who have portal hypertension and ascites. Estimates indicate that at least 40% of patients with cirrhosis and ascites will develop HRS during the natural history of their disease.

Risk factors for developing HRS have been reported based on a large series of patients with cirrhosis and ascites. Patients with marked sodium and water retention, characterized by a low urinary sodium excretion (<5 mEq/L) and dilutional hyponatremia, have a higher probability of developing HRS compared to patients with less sodium and water retention. Another important risk factor is the presence of severe disturbances in the systemic circulation (mean arterial pressure <80 mm Hg) associated with marked activation of the RAAS and SRS. Surprisingly, patients with advanced liver disease, defined by a high Child-Pugh score or worsening albumin, bilirubin, and prothrombin levels, are not at higher risk of developing HRS.

No specific tests establish the diagnosis of HRS. Diagnosis of HRS is based on the presence of a reduced GFR in the absence of other causes of renal failure in patients with chronic liver disease. The following criteria, as proposed by the International Ascites Club, help diagnose HRS:

All major criteria are required to diagnose HRS:

1. Low GFR, indicated by a serum creatinine level higher than 1.5 mg/dL or 24-hour creatinine clearance lower than 40 mL/min
2. Absence of shock, ongoing bacterial infection and fluid losses, and current treatment with nephrotoxic medications
3. No sustained improvement in renal function (decrease in serum creatinine to <1.5 mg/dL or increase in creatinine clearance to >40 mL/min) after diuretic withdrawal and expansion of plasma volume with 1.5 L of plasma expander
4. Proteinuria less than 500 mg/d and no ultrasonographic evidence of obstructive uropathy or intrinsic parenchymal disease

Additional criteria are not necessary for the diagnosis but provide supportive evidence.

1. Urine volume less than 500 mL/d
2. Urine sodium level less than 10 mEq/L
3. Urine osmolality greater than plasma osmolality
4. Urine red blood cell count of less than 50 per high-power field
5. Serum sodium concentration greater than 130 mEq/L

Adapted from:: S Mukherjee, H Roy, Hepatorenal syndrome, e-Medicine

HEPATOPULMONARY SYNDROME

Diagnosis of hepatopulmonary syndrome (HPS) requires documentation of the presence of arterial deoxygenation and intrapulmonary vasodilation.

Pulse oximetry level of $\leq 97\%$ provided a sensitivity of 96% and a specificity of 76% for detecting mild hypoxemia ($pO_2 < 70$ mm Hg).

2D transthoracic contrast echocardiography is the most commonly used technique. Agitated saline, which creates microbubbles visible on echocardiography, is used as a contrast agent. A positive test for intrapulmonary vasodilation occurs when delayed visualization of intravenously administered microbubbles are observed in the left heart (3rd heartbeat after injection).

Michael B. Fallon, Gary A. Abrams. Pulmonary Dysfunction in Chronic Liver Disease. *Hepatology* 2000 • 32 :859:865

IDIOPATHIC NEONATAL HEPATITIS

Idiopathic neonatal hepatitis is an intrahepatic cholestatic disease of the newborn of unknown cause. The term idiopathic neonatal hepatitis is somewhat unsatisfactory. The diagnosis is one of exclusion. Idiopathic neonatal hepatitis should be used only for those cases in which the etiology of the liver disease is undefined and after exclusion of biliary atresia and known causes of neonatal cholestasis such as metabolic, endocrine or infectious diseases. Idiopathic neonatal hepatitis is also known as giant cell hepatitis and is one of many causes of neonatal cholestasis or infantile cholestatic hepatopathy.

Neonatal hepatitis affects newborn infants only. The annual incidence in the United States is approximately 1-2 cases per 10-20,000 live births. Neonatal hepatitis occurs equally in males and females; it may be more common among blacks than whites or Asians. Neonatal hepatitis is often associated with a low birth weight, but the cause-and-effect relationship is unclear. Familial cases (in siblings) occur but should be referred to as "familial neonatal hepatitis" rather than idiopathic neonatal hepatitis as these cases most likely represent cases of genetic disorders, metabolic diseases, forms of progressive familial intrahepatic cholestasis (PFIC) or other undefined entities, and should lead to additional efforts to identify a metabolic or genetic abnormality such as alpha-1-antitrypsin deficiency or an inherited defect in bile acid metabolism.

Diagnostic Criteria:

1. Appearance of jaundice with elevations in serum total and conjugated bilirubin within the first six months of life.
2. Liver biopsy histology compatible with neonatal hepatitis.
3. Exclusion of known causes of the neonatal hepatitis syndrome as shown (at a minimum) by the following:
 - a. Normal alpha-1-antitrypsin level or phenotype
 - b. Elevated total serum bile acid levels
 - c. Normal serum TSH and free T4 levels
 - d. Normal Sweat test
 - e. Negative serum and urine culture for cytomegalovirus; or absence of cytomegalovirus in liver.
 - f. Negative tests for IgM anti-HAV, HBsAg and anti-HCV (in patient or in mother)
 - g. Negative tests for anti-toxoplasmosis
 - h. Absence of extrahepatic biliary atresia and choledochal cyst.
 - i. Absence of family history (in siblings) of neonatal hepatitis
 - j. Absence of obvious congenital abnormalities
 - k. Absence of electron microscopy or histologic findings on liver biopsy of storage disorders (Niemann-Pick type C, Gaucher's, GSD type IV) or of PFIC (e.g., Byler's bile in canaliculi)

INBORN ERRORS OF BILE ACID SYNTHESIS

Definition: Deficiency in one or more steps in the biosynthesis and metabolism of bile acids. The deficiency may result from a primary enzyme deficiency (e.g.: 5 β -reductase deficiency) or secondary to specific organelle dysfunction (e.g.: peroxisomal disorders).

Diagnosis: Low or normal levels of serum bile acids in the setting of cholestasis (as defined by elevated levels of conjugated/direct bilirubin) provide an important clue for a probable inborn error of bile acid synthesis. Specific delineation of the metabolic defect, however, is obtained by the analysis of the urine by fast atom bombardment-mass spectrometry (FAB-MS) and gas chromatography-mass spectrometry (GC-MS).

Clinical manifestations: Clinical spectrum of diseases of bile acid synthesis resulting from defects in modification of the sterol nucleus or side-chain synthesis(*):

| Defective enzyme | No. of cases | Liver disease |
|--------------------------------------|--------------|---|
| 3- β -OH steroid dehydrogenase | 40-50 | Progressive cholestasis; late onset disease; bile acid substitution reverses liver disease |
| Oxosteroid 5- β -reductase | 10 | Early onset of cholestasis; may lead to liver failure; reversed by treatment with cholic acid |
| Oxosteroid 7- α -hydroxylase | 1 | Neonatal cholestasis with bile duct proliferation; rapid progression to cirrhosis |
| 25-hydroxylase* | 2 | Neonatal cholestasis with fibrosis; progression to cirrhosis in older children |
| Ligase deficiency | 2 | Neonatal cholestasis with fibrosis; mild chronic liver disease |

Other disorders include:

1. Cerebrotendinous xanthomatosis: deficiency of C-27 hydroxylase deficiency
2. Familial giant cell hepatitis with defect in the 25-hydroxylase pathway
3. Peroxisomopathies: Zellweger syndrome (ZS), neonatal adrenoleukodystrophy, and Refsum's disease. Only ZS is consistently associated with chronic liver disease.
4. Conjugation (amidation) defect: transient liver disease with primary bile acids only in the unconjugated form.
5. Primary bile acid deficiency caused by defective cholesterol production: deficiency of 7-dehydrocholesterol reductase; liver disease is not a consistent finding.

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2. Bove KE. Liver disease caused by disorders of bile acid synthesis. Clin Liver Dis 2000;4:831-84.

NEONATAL METABOLIC DISEASES

Alpha-1-Antitrypsin deficiency

Liver disease

Low serum alpha-1-antitrypsin levels

PIZZ or PISZ phenotype

Galactosemia

Typical clinical manifestations (liver disease, nutritional failure, cataracts, mental retardation)

Deficiency of galactose-1-phosphate transferase or uridine diphosphate-4-epimerase

Hereditary Fructose Intolerance

Typical clinical manifestations (liver disease, renal tubular defect, nutritional failure, gastrointestinal symptoms, hypoglycemia, acidosis associated with fructose ingestion)

Deficiency of fructose-1,6-bisphosphate aldolase

Hereditary Tyrosinemia

Typical clinical manifestations (liver failure, renal tubular defects, neurologic crises)

Elevated urine succinylacetone

Neonatal Iron Storage Disease

Liver failure of antenatal onset

Iron overload in liver, pancreas and heart

No other explanation for liver disease

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

Diagnosis of SBP is made when the polymorphonuclear cell count in ascitic fluid is $\geq 250/\text{mm}^3$ and the ascitic fluid bacterial culture is positive.

The diagnosis of culture negative SBP is defined as any instance of negative ascitic fluid culture with an ascitic fluid neutrophil count of ≥ 250 neutrophils/ mm^3 .

Bacterascites is defined as any instance of positive ascitic fluid culture with ascitic fluid neutrophil count of < 250 neutrophils/ mm^3 .

The interval between intra-abdominal operation and diagnosis of SBP should be at least 4 weeks. Ascitic fluids should be inoculated into aerobic and anaerobic blood-culture bottles at the patient's bedside. . Secondary bacterial peritonitis, i.e., ascitic fluid infection caused by a surgically-treatable intra-abdominal source, should be excluded.

M Novella, R Sola, G Soriano, M Andreu, J Gana, J Ortiz, S Coll, M Sabat, M C Vila, C Guarner, F Vilardell. Continuous versus inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. *Hepatology* March 1997 • 25 :532-6

Javier Fernández¹, Miquel Navasa¹, Juliá Gómez², Jordi Colmenero¹, Jordi Vila², Vicente Arroyo¹, Juan Rodés¹ Bacterial infections in cirrhosis: Epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* January 2002 • 35 140-8

Bruce A. Runyon Management of Adult Patients With Ascites Caused by Cirrhosis. *Hepatology* 1998;27:264-272

INFECTIONS ASSOCIATED WITH NEONATAL CHOLESTASIS

ROUTES OF INFECTION

The newborn may acquire infection transplacentally in utero, during delivery, or after birth. The study of transplacental infection has been hampered by the latency of many viruses. It has been well established that transplacental passage may result in congenital syphilis, toxoplasmosis, rubella, and cytomegalovirus infections. The secondary liver abnormalities at birth may be inactive due to remote in utero infection with the consequent scarred, cirrhotic liver, or relatively new with an acute hepatitis. An essential factor in the transmission of the infection from the mother to the fetus is the time of maternal infection during the pregnancy. In general, infectious agents cross the placenta best during the third trimester. This is particularly true for syphilis, toxoplasmosis, and hepatitis B virus.

Perinatal acquisition of infection may be due to the upward spread of bacterial agents from vaginitis, endometritis, and placentitis. Inhalation or swallowing of infected amniotic fluid may transmit the infection to the fetus. During labor and delivery, direct contact with pathogens in vaginal or uterine secretions or contaminated blood can result in neonatal infection. *Listeria*, herpes simplex, and cytomegalovirus may be transmitted by this route and cause neonatal hepatitis.

Postnatal infection less frequently results in neonatal hepatitis. Close contact with maternal infecting secretions (oral, nasal, breast milk) is possible. Blood or blood product transfusions may contain agents that could result in a neonatal hepatitis.

ETIOLOGIC AGENTS

Bacterial infections

Both gram-positive and gram-negative organisms have been implicated, with gram-negative bacteria being the most frequent etiologic agents reported. The most frequent bacterial organism isolated resulting in a neonatal hepatitis is *Escherichia coli*. *Streptococcus* group B is only rarely implicated. *Listeria monocytogenes* infection invariably results in hepatic manifestations.

Liver abscesses, the result of hepatic injury from umbilical catheterization, are uncommonly observed. When present, *E. coli* and *Staphylococcus aureus* are the most common pathogens isolated and are presumed secondary to colonization of the umbilical stump.

Urinary tract infection

Neonatal bacterial infections associated with jaundice have frequently been associated with the urinary tract. They commonly present between the second and eighth weeks of postnatal life. These infections are rarely associated with

fever or urinary symptoms. Urinalysis shows pyuria, and urine culture usually reveals *E. coli*. Blood cultures may be transiently positive.

Congenital syphilis

In spite of penicillin and routine maternal screening, congenital syphilis remains a problematic perinatal infection. In utero, transplacental transmission of *Treponema pallidum* spirochetes to the fetus may result in a mild to severe range of symptoms.

Tuberculous hepatitis

Neonatal infection of the liver with tuberculosis is exceedingly rare. Infection may occur by way of placental spread from miliary tuberculosis in the mother or by inhalation with pulmonary involvement or by aspiration of contaminated amniotic fluid.

Toxoplasmosis

Maternal infection with the intracellular protozoan parasite is usually acquired by contact with the oocytes excreted in cat feces or ingestion of inadequately cooked meat (lamb, beef, or pork). Maternal infection may be asymptomatic or mild but is necessary to occur during gestation for congenital toxoplasmosis to develop. Diagnosis may be made prenatally by detection of the parasite in fetal blood or amniotic fluid or from the placenta, cord or infant's peripheral blood using mouse inoculation or polymerase chain reaction (PCR) of its genomic material. Serologic diagnosis can be made by IgM or IgA or persistent (over 12 months) IgG anti-*Toxoplasma* antibody tests determined in the infant's blood. A case of congenital toxoplasmosis diagnosed by the use of exfoliative cytology of neonatal ascites has been reported.

Viral infections

Cytomegalovirus

Cytomegalovirus (CMV) may be acquired transplacentally, at delivery, or postnatally from infected secretions (saliva or breast milk) or from transfusion of blood products. Significant congenital CMV disease has been reported in the offspring of liver transplant recipients. Most congenitally infected infants remain asymptomatic. The minority (5% to 10%) develop clinically apparent infection, but, unfortunately, these may include low birth weight, microcephaly, periventricular cerebral calcifications, chorioretinitis, thrombocytopenia, purpura deafness, and psychomotor retardation. Hepatosplenomegaly and conjugated hyperbilirubinemia are often seen in neonatal CMV infection. The hepatosplenomegaly may be secondary to significant extramedullary hematopoiesis.

Diagnosis of CMV infection includes culture of the nasopharynx, saliva, and urine. Culture of the liver can yield positive results, but the yield is usually not as good as from the urine. The detection of CMV in hepatic tissue can be improved with the use of electron microscopy, viral DNA by PCR, and monoclonal antibody techniques. Serologic tests are also useful for CMV diagnosis. IgM CMV-specific antibodies can be monitored.

Herpes hepatitis

Hepatitis from herpes may present as part of a generalized disease in the newborn. Symptoms may not appear until 4 to 8 days of age, which coincides with the incubation period for herpes. Congenital herpes infection may present with microcephaly and necrotic, ulcerative, vesicular, or purpuric lesions on the mucosal surfaces or the skin. Although the liver may be mildly affected, more often there is jaundice, hepatosplenomegaly, and abnormal coagulation factors. Gastrointestinal bleeding, coagulopathy, encephalitis, and seizures may be present in severe cases. Diagnosis may be confirmed by typical cutaneous lesions, by identification of the virus in skin lesions using direct fluorescent antibody staining or enzyme immunoassay detection of herpes antigens, cell culture and by PCR of herpes simplex viral DNA. Acute and convalescent sera can be tested for rises in herpes simplex antibody titers to confirm acute infection, but serologic diagnosis is less helpful than viral isolation which has become the more rapid diagnostic procedure of choice.

Rubella

The incidence of congenital rubella has diminished due to the widespread use of rubella vaccine. Hepatic involvement in congenital rubella is common. Hepatomegaly is always found, and splenomegaly, jaundice, and cholestasis with a conjugated hyperbilirubinemia and elevated serum alkaline phosphatase and transaminases are frequent accompaniments. Additionally, congenital rubella is associated with ophthalmologic (cataracts, microphthalmia, glaucoma, chorioretinitis), cardiac (patent ductus arteriosus, peripheral pulmonic stenosis, atrial or ventricular septal defects), auditory (sensorineural deafness), and neurologic (microcephaly, meningoencephalitis, retardation) anomalies. Growth retardation, thrombocytopenia, and purpuric skin lesions (blueberry muffin) may be observed.

Humans are the sole source of rubella infection. Postnatal rubella is transmitted by direct or droplet contact with nasopharyngeal secretions. Congenitally infected infants may shed rubella virus in nasopharyngeal secretions and urine for up to 1 year and transmit infection to contacts.

Diagnosis may be made by isolation of virus from the nose by inoculation of appropriate tissue culture. Throat swabs, urine, blood, and cerebrospinal fluid may yield positive cultures, especially in congenitally infected infants. Serologic testing is also useful in confirming the diagnosis. Specific rubella IgM antibody is

indicative of recent postnatal or congenital infection. The use of PCR for prenatal and postnatal diagnosis of congenital rubella is being successfully utilized in research laboratories.

Hepatitis A

Although hepatitis A is a frequent cause of hepatitis in childhood, it is not a frequent cause of hepatitis in the newborn. Acquisition of hepatitis A by blood transfusions has been reported in the neonatal period. In most of the neonates, they developed serologic evidence of acute hepatitis A but were clinically and biochemically asymptomatic. However, in a recent report, a premature infant who developed acute hepatitis A had a severe fatal course with evidence of hepatic necrosis at autopsy.

In general, hepatitis A is spread by the fecal-oral route. Infection occurs at a younger age in lower socioeconomic groups and is endemic in developing countries. Children usually are anicteric and have a milder course than adults. No hepatitis A carrier state exists, and chronic hepatitis A does not occur.

Serologic testing for IgM and IgG specific anti-HAV antibodies are commercially available. Recent infection is denoted by an elevated titer of IgM anti-HAV.

Hepatitis B

Overall in the United States, hepatitis B is an uncommon cause of neonatal hepatitis. However, in certain regions of the United States and parts of the world, it is common for perinatal transmission of the hepatitis B virus to occur from a chronic hepatitis B carrier mother or the mother with acute hepatitis B during the third trimester of pregnancy. Perinatal transmission of hepatitis B is also more likely if the mother is HBeAg-positive and thus has circulating hepatitis B viral DNA circulating in the bloodstream. If the infant does not acquire hepatitis B infection at birth, close contact with other family members places the infant at high risk for acquisition of the virus making pre-exposure hepatitis B immunization imperative.

The majority of infants who develop hepatitis B due to vertical transmission show evidence of HBsAg positivity between 4 and 16 weeks of age and become asymptomatic carriers. However, some infants develop a chronic active form of hepatitis B, and others, with time, develop cirrhosis and hepatocellular carcinoma. A coinfection or superinfection with delta hepatitis (hepatitis D) is also possible. It is rare for perinatally acquired hepatitis B to result in an acute icteric hepatitis. These infants may have a benign course with the development of anti-HBs and loss of HBsAg, or uncommonly may progress to a rapidly fulminant and fatal hepatitis.

Diagnosis of hepatitis B uses commercially available serologic tests for hepatitis B antigens, HBsAg and HBeAg, and antibodies to HBsAg, HBcAg, and HBeAg. In acute infection, HBsAg positivity detects the great majority of cases. However, because HBsAg is also positive in chronic infection, IgM anti-HBc presence can

be used to establish acute or recent hepatitis B infection. Quantitative tests of serum hepatitis B virus DNA by PCR or branched chain DNA methods are commercially available and useful in the selection and monitoring of patients for therapy.

Hepatitis C

The signs and symptoms of hepatitis C are similar to hepatitis A and B and acute disease is associated with jaundice in only 25% of patients and abnormalities in serum liver function test occur less frequent than with hepatitis B infection. Most infections are asymptomatic. Transmission of hepatitis C can occur by way of parenteral administration of blood or blood products, but the majority of cases in the United States are not associated with blood transfusion. High-risk groups for hepatitis C include parenteral drug users, persons transfused with blood or blood products, health care workers who are frequently exposed to blood, and persons with household or sexual contact with an infected person. Perinatal transmission of hepatitis C has been demonstrated. Seroprevalence among pregnant women in the United States is estimated at 1-2% with maternal-fetal transmission at about 5%. Maternal co-infection with HIV has been associated with an increased risk of perinatal transmission of hepatitis C virus. Vertical transmission of hepatitis C virus may depend upon the hepatitis C genotype and the serum titer of maternal viral RNA. The two major tests currently available for the laboratory diagnosis of hepatitis C viral infections are antibody assays for the hepatitis C virus (HCV) and those for detecting and quantitating HCV RNA. The initial antibody test involves a screening enzyme immunoassay (ELISA). If positive, confirmation is made by a recombinant immunoblot assay (RIBA). Both assays detect IgG antibodies; no IgM assays are currently available. Highly sensitive PCR assays for detection and quantitation of HCV RNA and a nucleic-acid based amplification test (bDNA) are commercially available. These tests are costly and not standardized, but may be useful for monitoring patients undergoing therapy and identifying infection early in infants since maternal antibody can cross the placenta and interfere with the ability to detect antibody produced by the infant.

Delta hepatitis (hepatitis D)

Delta hepatitis virus requires infection with hepatitis B virus because the outer coat of the complete delta virus is hepatitis B surface antigen. If delta hepatitis infection occurs at the same time as hepatitis B infection, this is referred to as a coinfection. If delta hepatitis infection occurs in a person who is already chronically infected with hepatitis B infection, this is referred to as a superinfection. Delta hepatitis can be transmitted by parenteral, percutaneous, or mucous membrane inoculation. Delta hepatitis may be transmitted by blood or blood products, intravenous drug use, or sexual contact if HBsAg is present in the person's blood. Transmission of delta hepatitis from mother to newborn infant is unusual. Among families with HBsAg carriers, delta hepatitis may be spread. Delta hepatitis is most commonly found in southern Italy, Eastern Europe, South

America, Africa, and the Middle East. Although there is a high prevalence of hepatitis B infection in the Far East, delta hepatitis is uncommon there. In the United States, delta hepatitis is found most frequently in intravenous drug abusers, hemophiliacs, and immigrants from endemic areas.

Diagnosis of delta hepatitis can be made using a commercially available anti-HDV. IgM-specific anti-HDV and delta antigen tests are available investigational. Differentiation of delta hepatitis coinfection from superinfection can be established by use of IgM anti-HBc, which is present only with acute hepatitis B infection.

Hepatitis E (Enterically transmitted non-A, non-B hepatitis)

Transmission of this virus is by the fecal-oral route. The disease is more common in adults than children and has a significantly high mortality in pregnant women. Cases have been reported in epidemics and have usually been traced to contaminated water. Endemic enterically transmitted non-A, non-B hepatitis has not been reported in the United States.

Diagnosis is established by exclusion of other known causes of acute hepatitis (i.e., hepatitis A, B, C, D). Serologic tests (enzyme immunoassay, Western blot, fluorescent antibody blocking assay) that detect antibody to the hepatitis E virus and hepatitis E viral RNA detection by PCR of stool or serum are available to confirm the diagnosis by contacting the Centers for Disease Control and Prevention.

GB Virus C (Hepatitis G)

Two new viruses belonging to the Flaviviridae family, GB virus C and hepatitis G virus (HGV) were recently discovered. Phylogenetic analysis reveals both viruses are variants of the same viral species and distantly related to hepatitis C virus. While there is considerable evidence demonstrating persistent viral infection, this virus has not been demonstrated to cause disease in humans or other primates. An association with post-transfusion hepatitis has been reported, but most infected children remain asymptomatic. Mother to infant transmission of HGV has been documented resulting in a high viral persistence rate and lack of immune response to the virus. In co-infected mothers with either human immunodeficiency virus or hepatitis C virus and HGV, HGV transmission is frequent and at a higher rate than that for hepatitis C virus. Hepatitis G virus can be transmitted by blood or blood products, injection drug use or sexual contact.

No serologic test is commercially available. An indirect immunoassay, which uses the E2 (envelope) protein as an antigenic target, is available for research purposes. GBV-C RNA can be detected in serum samples utilizing a reverse-transcription, polymerase chain reaction method.

Enteroviral hepatitis

Although many viruses may produce disease in the newborn, only a few viruses are frequently encountered. Among the less frequent viruses, which may on occasion result in nursery epidemics of significant clinical illness, are viruses within the enterovirus classification. These generally include nonpolio enteroviruses including coxsackieviruses, echoviruses and enteroviruses. Transmission may have occurred during the prenatal, intrapartum or perinatal period. A maternal history of a viral syndrome or fever just before delivery may be elicited. Initially the infant may appear healthy and vigorous. However, poor feeding, fever, lethargy, diarrhea, jaundice, and skin rash signal clinical infection. These non-specific signs, however, do not help distinguish these viruses from other bacterial or viral etiologies. In the majority of cases, these infections are benign and self-limited. However, there are reports of death resulting from enteroviral infections in neonates. Fatal and massive hepatic necrosis with failure has been reported with infections of coxsackie group B virus and echovirus groups 6, 9, 11, 14, and 19. These patients demonstrated jaundice, markedly elevated serum transaminases, disseminated intravascular coagulation, and progressive hepatic failure.

Diagnosis is made by viral isolation from the throat, rectum, or other sites of clinical involvement or biopsy material. Tissue culture techniques may not be adequate for viral isolation, and suckling mouse inoculation may be required to isolate the offending virus. Sera for antibody testing during the acute and convalescent period should be collected and stored because a rise in titer for an isolated virus suggests a causal role. Because no common enterovirus antigen is available, serologic screening without viral isolation is generally not done. PCR testing for the presence of enteroviral RNA in cerebrospinal fluid is available in several research laboratories.

Parvovirus hepatitis

Parvovirus B19 is most often associated with erythema infectiosum (fifth disease) and is usually manifested by mild systemic symptoms, fever, and the distinctive "slapped cheek" rash. However, parvovirus B19 has been reported to cause liver disease ranging from an acute hepatitis to fulminant hepatitis with an associated aplastic anemia.

Laboratory diagnosis can be made by testing for B 19 parvovirus IgM antibody. IgG serum antibody indicates prior infection and immunity. Investigational assays using the polymerase chain reaction or nucleic acid hybridization techniques are useful for detecting chronic infection.

Human herpesvirus-6 infection

Human herpesvirus-6 infection has been identified as the etiologic agent for roseola infantum (exanthema subitum, sixth disease). Young children usually present with an acute febrile illness for several days with rapid defervescence

followed by an erythematous maculopapular rash lasting 1 to 2 days. Chronic hepatitis in an infant associated with human herpesvirus-6 has been reported. The presence of human herpesvirus-6 DNA in liver tissue was confirmed by both in situ hybridization and by polymerase chain reaction.

Reovirus-3 infection

The concept of infantile obstructive cholangiopathy postulated by Landing suggests a common etiologic agent for several neonatal liver diseases including biliary atresia and neonatal hepatitis. Reovirus 3 has been proposed as a candidate virus serving as an etiologic agent for biliary atresia and neonatal hepatitis. Infection of weanling mice results in hepatic lesions similar to those observed in neonates with neonatal hepatitis. Several early studies suggested elevated reovirus 3 antibody titers in the sera of infants with biliary atresia and neonatal hepatitis. Reovirus type 3 was also detected in the porta hepatitis of an infant with biliary atresia and in a monkey infected with reovirus that developed biliary atresia. However, this association has not been confirmed. Studies utilizing molecular techniques have yielded mixed results. If reovirus type 3 infection results in biliary atresia or neonatal hepatitis in human newborns, only some of the cases can be attributed to its presence.

Paramyxovirus infection

Ten patients with an unusual form of giant cell hepatitis associated with a severe clinical course have been reported. Two of the patients were infants 5 months and 7 months of age. Both infants had features of autoimmune chronic active hepatitis, and one infant also had evidence of autoimmune hemolytic anemia. Histopathologic and electron microscopic evaluation of the liver biopsies of these infants showed the presence of syncytial multinucleated giant cells replacing hepatocyte cords most prominently in the centrilobular region, as well as severe acute and chronic hepatitis with bridging necrosis of hepatocytes, ballooning and dropout of hepatocytes, cholestasis, and small round cell inflammation within the lobule. Ultrastructural studies revealed the presence of viruslike structures within the giant cells resembling the nucleocapsids of paramyxoviruses. Inoculation from one of the patients into two chimpanzees failed to induce biochemical or histologic evidence of hepatitis. However, in one animal, an increase in titer of antibodies to measles virus and parainfluenza 4 was found. The giant cells in these infants were larger and of different morphology than the giant cells usually encountered in neonatal hepatitis and biliary atresia. Paramyxoviruses should be considered in patients with severe sporadic hepatitis.

Human Immunodeficiency Virus Infection (HIV)

HIV infection in children is associated with a broad spectrum of disease and a varied clinical course. Acquired immunodeficiency syndrome (AIDS) represents the most severe form. The great majority of cases of AIDS in children are due to

vertical transmission from an infected mother. Other infections (i.e., hepatitis B and C) may be transmitted to the newborn more efficiently when the mother is co-infected with HIV. Other routes of HIV transmission include sexual contact with an infected individual and exposure to infected blood or blood products. Clinical manifestations of HIV infection often involve the gastrointestinal tract and the liver and include generalized lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, oral candidiasis, recurrent diarrhea, parotitis, cardiomyopathy, hepatitis, nephropathy, central nervous system disease, lymphoid interstitial pneumonia, recurrent invasive bacterial infections, opportunistic infections, and malignancies.

While liver involvement is frequently observed in HIV infection, whether the liver lesions are primary or secondary to opportunistic infection in an immunosuppressed host is difficult to determine. Diagnosis of HIV infection is made by serum antibody tests (enzyme immunoassays) except in children younger than 18 months because of passive maternal antibody acquisition across the placenta. Western blot or immunofluorescent antibody tests should be used for confirmation of positive results. In young children (less than 18 months), the preferred tests are HIV culture and detection of HIV genomic sequences by PCR.

Etiologic Agents

Diagnostic Tests

Bacteria

E. coli most common

Blood and urine cultures

Congenital Syphilis

Spirochetes in skin or mucosal lesions
Treponemal antibody tests serum
or CSF

Tuberculous hepatitis

Mantoux skin test, chest x-ray, culture

Toxoplasmosis PCR, IgM, IgA or IgG (persistent) in serum

Viral infections

Cytomegalovirus

Culture nasopharynx, saliva, urine, liver
CMV antigen, IgM-CMV antibody,

PCR

Herpes PCR, cell culture, antibody titers

Rubella Virus isolation from nasopharynx, cultures urine, blood, CSF, IgM-rubella antibody

Hepatitis A IgM/IgG anti-HAV antibody

Hepatitis B HBV DNA, HBsAg, HBeAg, HBsAb, HBcAb, HBeAb

Hepatitis C HCV RNA PCR, anti-HCV antibody (ELISA/RIBA)

Hepatitis D HBsAg, anti-HDV

Hepatitis E HEV RNA PCR (CDC), anti-HEV antibody

Hepatitis G (GBV-C) GBV-C RNA PCR, E2 protein (research)

TTV (Transfusion transmitted virus) PCR (research)

Enteroviral hepatitis Viral isolation throat, rectum, PCR (research)

Parvovirus hepatitis B19 parvovirus IgM antibody, PCR (research)

Human herpesvirus-6 PCR, in situ hybridization liver

Reovirus-3 PCR, antibody

Paramyxovirus histopathology, electron microscopy liver

HIV (human immunodeficiency virus) anti-HIV antibody, PCR, culture