Cholestasis in Infancy

Pathologic Findings and Differential Diagnosis

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Infantile Cholestasis

- Conjugated hyperbilirubinemia and jaundice
- May be noted in the first 2 wk of life.
- Infants present with jaundice, dark urine (conjugated bilirubin), acholic stools, and hepatomegaly.
- In chronic cases: chronic pruritus, symptoms and signs of fat-soluble vitamin deficiency, slow or decreased growth charts.
- In older infants: signs of hepatic fibrosis and cirrhosis: portal hypertension, abdominal distention from ascites, dilated abdominal veins, and esophageal varices may develop.
### Causes of neonatal cholestasis

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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<tbody>
<tr>
<td><strong>Extrahepatic obstruction</strong></td>
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<td></td>
<td>Extrahepatic biliary atresion</td>
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<td></td>
<td>Choledochal cyst</td>
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<td>Insipissated bile/mucus plug</td>
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<td>Cholelithiasis or biliary sludge</td>
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<td>Tumors/masses (intrinsic and extrinsic)</td>
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<td>Neonatal sclerosing cholangitis</td>
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<td>Spontaneous perforation of the bile ducts</td>
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<td><strong>Infection</strong></td>
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<td>Viral</td>
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<td>HIV, cytomegalovirus, herpes, rubella, parvovirus B19, echovirus, adenovirus</td>
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<td><strong>Bacterial</strong></td>
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<td>Urinary tract infection, sepsis, syphilis</td>
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<td><strong>Protozoal</strong></td>
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<td>Toxoplasma</td>
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<td><strong>Metabolic/genetic diseases</strong></td>
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<td><strong>Idiopathic</strong></td>
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<td>Alagille syndrome (syndromic paucity of the interlobular bile ducts or arteriohepatic dysplasia)</td>
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<td>Nonsyndromic paucity of the interlobular bile ducts</td>
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<td>Progressive familial intrahepatic cholestasis, types 1-3 (Byler disease)</td>
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<td>Congenital hepatic fibrosis/Carol's disease</td>
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<td><strong>Disorders of carbohydrate metabolism</strong></td>
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<td>Galactosemia</td>
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<td>Fructosuria</td>
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<td>Type IV glycogenesis</td>
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<td><strong>Disorders of amino acid metabolism</strong></td>
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<td>Tyrosinemia</td>
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<td><strong>Disorders of lipid metabolism</strong></td>
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<td>Wolman, Niemann-Pick, Gaucher</td>
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<td><strong>Disorders of bile acid synthesis</strong></td>
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<td>3-beta-hydroxysteroid dehydrogenase/isomerase deficiency</td>
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<td>4-oxosteroid 5-beta reductase deficiency</td>
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<td>Zellweger syndrome</td>
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<td><strong>Mitochondrial disorders</strong></td>
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<td><strong>Other metabolic defects</strong></td>
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<td>Citrin deficiency</td>
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<td>Alpha-1-antitrypsin deficiency</td>
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<td></td>
<td>Cystic fibrosis</td>
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<td>Hypopituitarism (septo-optic dysplasia)</td>
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<td>Hypothyroidism</td>
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<td><strong>Toxic</strong></td>
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<td>Drugs</td>
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<td>Parenteral nutrition</td>
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<td><strong>Alloimmune</strong></td>
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<td>Gestational alloimmune liver disease (Neonatal hemochromatosis)</td>
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<td><strong>Miscellaneous</strong></td>
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<td>&quot;Idiopathic&quot; neonatal hepatitis</td>
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<td>Shock/hypoperfusion</td>
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<td>Intestinal obstruction</td>
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Etiology

- Extrahepatic or intrahepatic disorders.
- The most common extrahepatic disorder is obstruction.
- Biliary atresia: Obstruction of the biliary tree due to progressive inflammation and sclerosis of the extrahepatic (and sometimes intrahepatic) bile ducts.
- Other bile duct obstruction: Congenital anomalies of the hepatic and biliary ducts e.g. choledochal cysts, Caroli disease, congenital hepatic fibrosis, inspissated bile plugs in CF.
Intrahepatic disorders:

- Neonatal hepatitis syndrome (giant cell hepatitis): An inflammatory condition with numerous metabolic, infectious, and genetic causes; some cases are idiopathic.

- Other disorders: Paucity of bile ducts, familial cholestatic disorders, inborn errors of metabolism, congenital anomalies, total parenteral alimentation and drugs
Extrahepatic biliary atresia

- Cause of >50% of infantile cholestasis
- 1:8-15 000 live births
- Higher in patients of African origin
- Also high in the middle east (Indian J Pediatr 2011;78:171-175; Saudi Med J 2009 ;30:403-408)
Etiology

- Acquired, not inherited.
- Rarely familial; genetic susceptibility
- Unknown etiology.
- Multiple theories:
  - Viruses: CMV, Reovirus type 3, Rotavirus, human papilloma virus types 6 & 8.
  - Dysregulated immune response against viral infection
Diagnostic procedures

- Cholangiography, ERCP, MRCP
- Radionuclide imaging
- Ultrasound
- Liver biopsy: diagnostic in >60% of cases
Pathology

- Features of bile duct obstruction
  - Periportal ductular proliferation
  - Cholestasis
  - Bile plugs in cholangioles and interlobular bile ducts
  - Mixed inflammatory infiltrate with neutrophils infiltration of cholangioles
Other features

- Extramedullary hematopoiesis
- Giant cell transformation
- Pseudoacinar transformation
- Feathery degeneration
- Increased copper
Signs of progressive disease

- Progressive portal and lobular fibrosis
- Bridging fibrosis
- Progressive loss of bile ducts
- Secondary biliary cirrhosis
Treatment

- Porto-enterostomy (Kasai): Re-establish bile drainage after resection of atretic ducts
- Age and degree of liver damage are the most determinant factors
- Has good results especially if done before 60 days of age and before significant fibrosis develops
- There is no correlation between success of portoenterostomy and size of remaining bile ducts
Other causes of large bile duct obstruction: Choledochal cyst

- Congenital ductal dilatation
- Prevalence 1:15000 live births
- High in Asians; female predilection
- May present as abdominal mass
- Histology is similar to EHBA
- Cyst with fibrous wall, 1-2 mm
Neonatal hepatitis

- Idiopathic (>50% of cases): Diagnosis of exclusion
- Infectious: CMV, rubella, Hep B, HSV, varicella, coxsackie virus, toxoplasma and Treponema pallidum.
- Familial (10% of cases): Autosomal recessive
- Metabolic/genetic
- Toxins
- Alloimmune
- Miscellaneous
Pathology

- Liver may be enlarged
- Parenchymal changes: Ballooning, acidophilic bodies
- Giant cell transformation:
  - Diffuse
  - Cytoplasm contains bile
  - May become necrotic and surrounded by neutrophils
- Cholestasis +/- rosetting (usually in zone 3)
- Lobular and portal inflammation
- Extramedullary hematopoiesis
# Comparison of biliary atresia and neonatal hepatitis syndrome

<table>
<thead>
<tr>
<th>Features</th>
<th>Biliary atresia</th>
<th>Neonatal hepatitis</th>
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<tbody>
<tr>
<td>Giant cell transformation</td>
<td>Usually focal</td>
<td>Usually diffuse</td>
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<td>Lobular disarray</td>
<td>Usually mild</td>
<td>May be marked</td>
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<tr>
<td>Cholestasis</td>
<td>Hepatocytes, canaliculi, &amp; ducts</td>
<td>Hepatocytes &amp; ducts</td>
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<tr>
<td>Portal fibrosis</td>
<td>In all portal areas</td>
<td>Absent early</td>
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<tr>
<td>Bile ducts</td>
<td>Proliferation in all portal areas</td>
<td>Rare</td>
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Prognosis

- Depends on etiology
- Variable in idiopathic cases (75% recovery)
- Progression to chronic liver disease in 7% of cases (usually in familial cases)
Persistent cholestasis

- Alagille Syndrome
- Alpha-1 antitrypsin deficiency
- Metabolic causes
- Familial Cholestatic Syndromes:
  - Progressive Familial Intrahepatic Cholestasis
  - Benign Recurrent Intrahepatic Cholestasis
  - North American Indian Cholestasis
  - Norwegian Cholestasis
  - Greenland Eskimo cholestasis
  - Turkish nonsyndromic paucity of interlobular bile ducts
  - Childhood cirrhosis in Arab Israelis
  - Tyrolean infantile cirrhosis
  - Navajo neurohepatopathy
Alagille Syndrome ( Syndromic Bile Duct Paucity)

- Arteriohepatic dysplasia
- Multi-system developmental disorder
- Inherited as autosomal dominant
- Gene localized to chr region 20p12, *JAGGED1* ligand for NOTCH1 receptor
- Mutations detected in as many as 70% of patients
Pathology

- Variable degree of cholestasis
- Portal spaces unexpanded
- Bile ducts may be normal in initial biopsies
- <3 months: Portal inflammation, bile ductular proliferation (may not be present in non-syndromic cases)
- >3 months: bile duct paucity, fibrosis, cholestasis; may be minimal in non-syndromic cases.
- >1 year: 90% paucity
Paucity of intrahepatic bile ducts

- Reduced number of bile ducts in portal tracts to 0 – 0.4 (Normal 0.9 to 1.8)
- Bile ductules should not be counted
- Sufficient representative portal tracts, i.e. minimum of 10.
Additional findings

- Non-specific parenchymal changes: pseudoxanthomatous hepatocytes, giant cell transformation, periportal fibrosis, accumulation of copper, EMH
- Fibrosis starts early in non-syndromic cases
- Progression to cirrhosis is rare.
Non-syndromic bile ducts paucity

- Inherited metabolic diseases: α1-antitrypsin deficiency, inborn errors of bile acid metabolism
- Congenital infections: Rubella, CMV
- Chromosomal abnormalities (Turner, trisomy 21, trisomy 17-18)
- Prune belly syndrome
- Acquired: primary sclerosing cholangitis, Langerhans’ cell histiocytosis, drug-induced, vanishing bile duct injury, allograft rejection, and graft versus host disease
Alpha-1 Antitrypsin Deficiency

- The most common genetic cause of liver disease in childhood
- The most common variant is homozygous Z phenotype (PiZ) or compound heterozygous (SZ)
- Deficiency occurs in 1:2000 – 1:5000 individuals
- May be associated with glomerulonephritis
Alpha-1 Antitrypsin Deficiency

- Conjugated hyperbilirubinemia, acholic stools
- Cholestasis resolves by 6 months of age
- Chronic liver disease with elevated transaminases occur in minority of patients
- Death may occur in 2.5% of cases
Progressive Familial Intrahepatic Cholestasis (PFIC)

- Persistent cholestasis in first year of life
- No evidence of bile duct obstruction
- Three different disease types caused by three different genes:
  - PFIC 1 deficiency (ATP8B1 gene at 18q21): Byler disease
  - BSEP (Bile salt export pump) deficiency (ABCB11 gene at chr 2q24): Byler-like disease
  - MRD3 deficiency (ABCB4 gene at 7q21): high serum \( \lambda \)-glutamate transferase
Clinical features

- Jaundice, therapy-resistant pruritis
- Malabsorption and failure to thrive
- Marked elevation in bile acid levels
- Bilirubin normal or elevated
- Elevations in serum aminotransferases
- $\lambda$-GTP normal in types 1 and 2; elevated in type 3
- Complications by biliary cirrhosis and portal hypertension
Byler disease

- Can be fatal
- First described in Amish children in 1960’s
- Marked elevation in transaminases
- Progressive intralobular fibrosis
- Coarsely granular bile by electron microscopy
PFIC 2 (BSEP Deficiency)

- Described in Saudi patients and Palestinian Arab children
- Gene localized to 2q24
- "Neonatal hepatitis"-like histologic picture
- Filamentous amorphous bile by EM
Benign Recurrent Intrahepatic Cholestasis

- Similar to Byler’s disease, with episodic cholestasis
- Mild disease, permanent liver damage does not develop
- Low or normal serum γ-GT
- BRIC gene localized to 18q21-q22, same like Byler’s (ATP8B1 gene)
Inborn Errors of Bile Acid Metabolism

- Incidence 1-2% of cholestatic disorders
- Familial disorders?autosomal recessive
- Jaundice, poor growth, hepatomegaly
- Elevated serum ALT, AST
- Low urine bile acids
- Chronic cholestatic neonatal hepatitis of indeterminate etiology; varies from mild to severe
- Rapid evolution of neonatal hepatitis to cirrhosis
Bile Acid Synthetic Disorders

**Classical (Neutral) Pathway**
- Cholesterol
- 7α-hydroxycholesterol
- 3α-hydroxy-5-cholestanolic acid
- Cholic acid

**Yamasaki Pathway**
- 27-hydroxycholesterol
- 7α-hydroxycholesterol
- 3α-hydroxy-5-cholestanolic acid
- Cholic acid

**Acidic Pathway**
- Side-chain oxidation
- 3α,7α-dihydroxy-5-cholestanolic acid
- Lithocholic acid
- Chenodeoxycholic acid

**25-Hydroxylation Pathway**
- 25-hydroxylase
- 5α,7α,24,25-tetrahydroxy-5β-cholestanolic acid
- Cholic acid

**Peroxisomal disorders**
- 2-methylacyl-CoA racemase
- Bile acid-CoA ligase
- Bile acid-CoA-amino acid N-acyltransferase

**Bile acid acyl-CoA oxidase**
- Bile acid enoyl hydratase
- Bile acid o xoacyl-CoA thiolase
- Bile acid ligase

**Bile acid CoA/amino acid N-acyltransferase**
- Glycine taurine conjugates of cholic and chenodeoxycholic acids
Morphology

- Neonatal hepatitis-like picture
- Portal infiltrates along the limiting plate
- Sparing of the interlobular and trabecular bile ducts
- Focal proliferation/injury of ductules, usually without ductular bile plugs
- Isolated necrosis of hepatocytes, including giant cells
- Fibrosis, periportal or intralobular
Other Inborn errors of metabolism

- Galactosemia, hereditary fructose intolerance and tyrosinemia
- Mitochondrial hepatopathies: Multi-organ disease
- Hereditary defects of bilirubin metabolism: Crigler-Najjar, Gilbert, Dubin-Johnson syndrome
Acquired Cholestatic Disorders

- Septicemia
- Drug-induced
- Viral hepatitis