Neonatal Liver Disease

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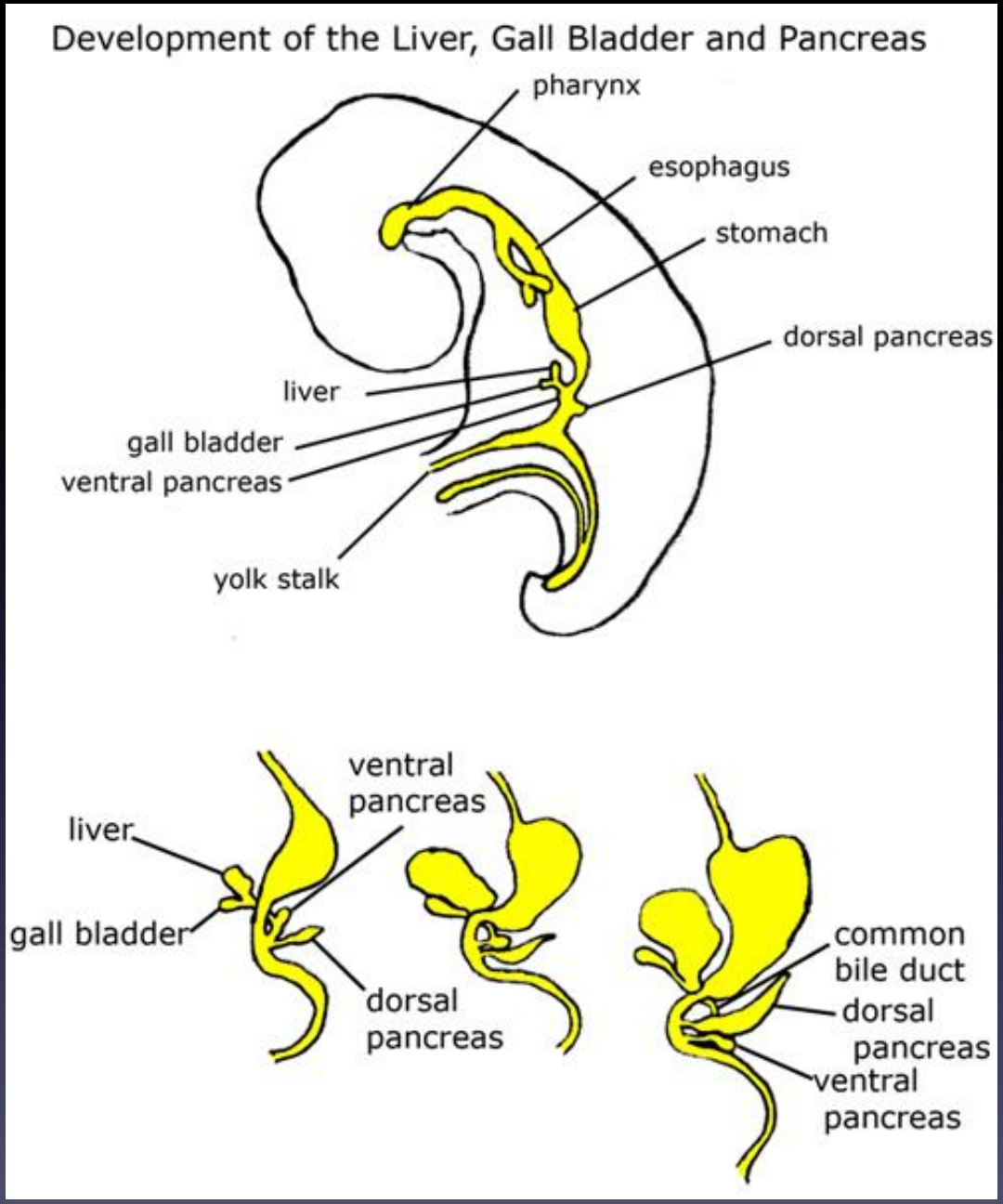
Outline

- Embryology
- Etiologies of neonatal liver disease
- Approach to neonate/infant with liver disease

- Liver is derived from **endoderm.**
- **It** forms from a diverticulum (bud) which branches out from the primitive gut.
- The pancreas develops dorsally, while the liver bud develops ventrally.


Development of the Liver, Gall Bladder and Pancreas
pharynx
esophagus
stomach
dorsal pancreas
liver
gall bladder
ventral pancreas
yolk stalk
liver
ventral pancreas
gall bladder
dorsal pancreas
common bile duct
dorsal pancreas
ventral pancreas

- The liver metabolizes nutrients absorbed from the gut : first organ to receive intake.
- It removes toxic compounds which are absorbed by modifying them so they are soluble.

- At birth the hepatocyte is already specialized with two surfaces:
  - Sinusoidal side: receives and absorbs a mixture of oxygenated blood and nutrients from the portal vein;
  - Canalicular side :delivers bile and other products of conjugation and metabolism (especially drugs) to the canalicular network which joins up to the bile ductules.

Neonatal liver diseases

Neonatal liver disease

- The estimated incidence of neonatal liver disease is as high as 1 in 2,500 live births.

Presentation

- Jaundice /Cholestasis
- ALT/AST rise
- Coagulopathy

Risk factors

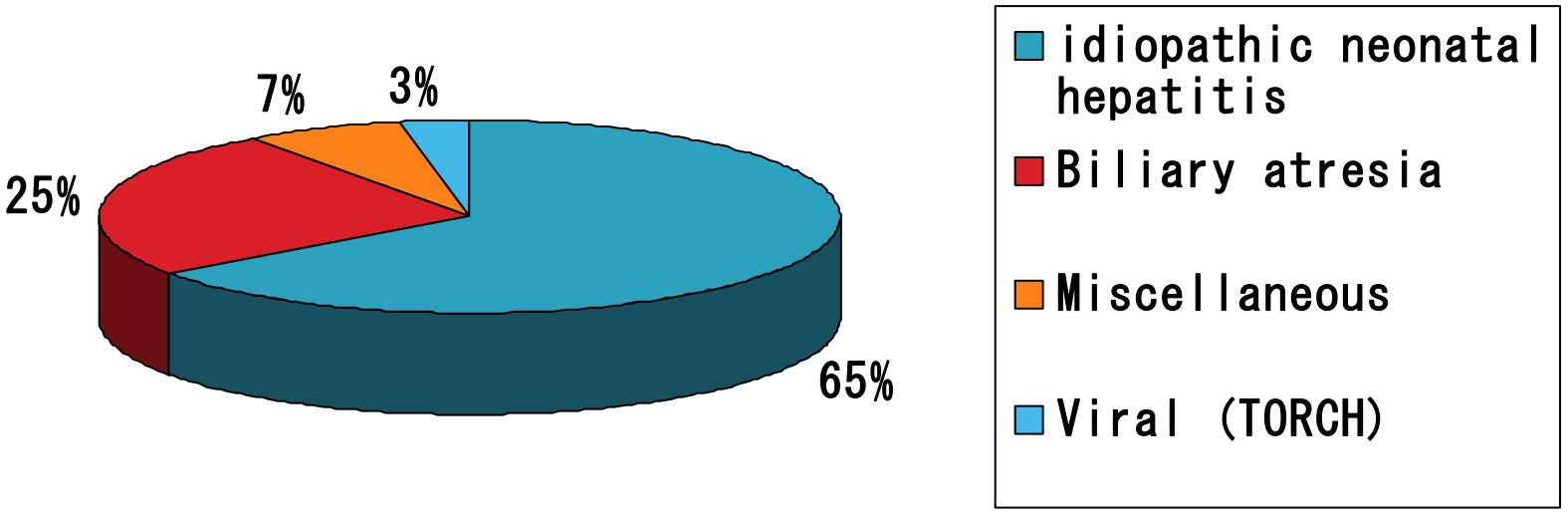
- Prematurity
- NPO
- Prolong TPN
- Intestinal injury
- Sepsis and inflammation
- Hypoxia
- Hepatotoxic medications

Neonatal Hepatitis

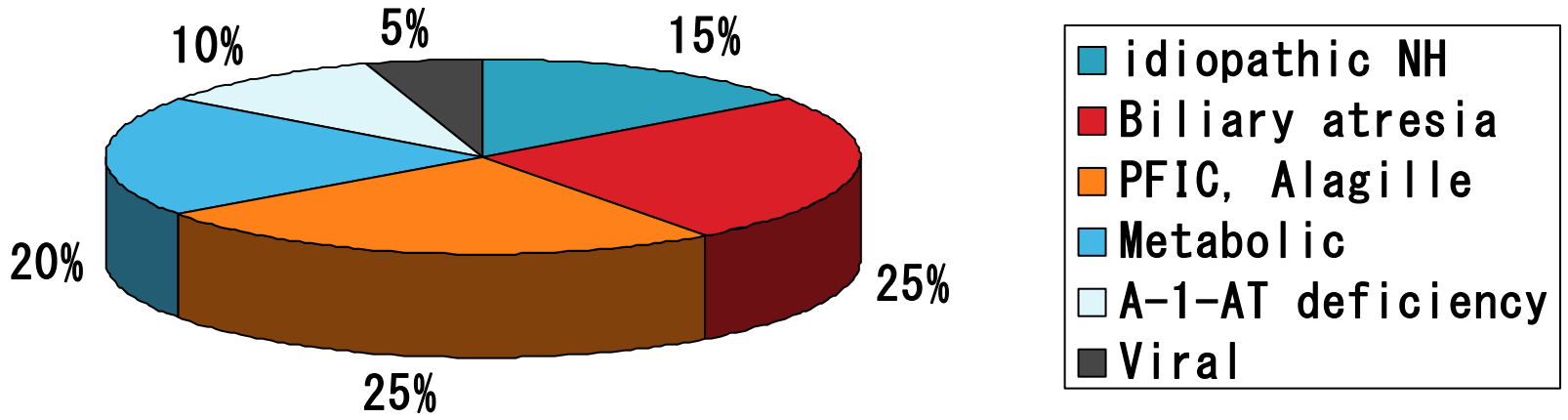
- Nonspecific collective term for intrahepatic cholestasis due to all various etiologies in an infant or neonate.
- Idiopathic neonatal hepatitis

Differential Dx of neonatal cholestasis

in 1970



Differential Dx of neonatal cholestasis in 2004



- Cholestasis: physiological reduction in canalicular bile formation or flow.

- Can be caused by defects in
  - Intrahepatic production.
  - Transmembrane transport of bile.
  - Mechanical obstruction to bile flow.

- Cholestasis: is primarily manifested as conjugated hyperbilirubinemia.

- Conjugated hyperbilirubinemia in a neonate is defined as:
  - Serum conjugated bilirubin concentration greater than 17.1 micromol/L if the total serum bilirubin is 85.5 micromol/L
  - Or greater than 20 percent of the total serum bilirubin if the total serum bilirubin is 85.5 micromol/L.

Etiologies

- Obstructive cholestasis:
  - Biliary atresia:
    - Occurs in 1 in 10,000 to 20,000 infants
    - Obliteration or discontinuity of the extrahepatic biliary system, resulting in obstruction to bile flow
    - Cause is unknown
    - Important to diagnose BA early as ideal time for successful Kasai is 45-60 days

- Alagille syndrome:
  - dominantly inherited disorder of variable expressivity. The gene has been identified as the Jagged1 (JAG1)
    - congenital cardiac defects (PPS)
    - posterior embryotoxon in the eye
    - dysmorphic feaures
    - butterfly vertebrae.
  - Liver biopsy will show bile duct paucity
  - liver transplant for hepatic decompensation, bone fractures, pruritus, and xanthomas

- Choledochal Cyst
  - Can be diagnosed with ultrasound
- Inspissated bile
- Cystic fibrosis
- Neonatal sclerosing cholangitis
- Congenital hepatic fibrosis/Caroli’s disease

Non obstructive

- **Idiopathic neonatal giant cell hepatitis**
  - Histologic appearance of widespread giant cell transformation
  - non-specific and may be associated with infectious, metabolic, and syndromic disorders
  - Needs close follow up and may self resolve
- Infection
  - Sepsis
  - Cytomegalovirus, HIV, Toxoplamosis, Syphilis

- Genetic/metabolic disorders
  - α1-antitrypsin deficiency (A1AT)
  - Tyrosinemia
  - Galactosemia
  - Hypothyroidism
  - Progressive familial intrahepatic cholestasis (PFIC)
  - Cystic fibrosis
  - Panhypopituitarism
- Toxic/secondary
  - Parenteral nutrition-associated cholestasis

PFIC

- Three conditions comprise the currently known group of biliary transport defects
  - **PFIC I:** Mutations in the FIC1 gene (ATP8B1)
    - FIC1 mediates the flipping of aminophospholipids from outer to inner hemi-leaflet of the canalicular membrane
    - FIC1 is located on other tissues including the pancreas and intestine leading to other extrahepatic signs and symptoms

- **PFIC II** have defects in the canalicular bile salt export pump (BSEP) caused by mutation in *ABCB11*
  - BSEP is responsible for transporting bile acids from inside the hepatocyte into the bile canaliculus

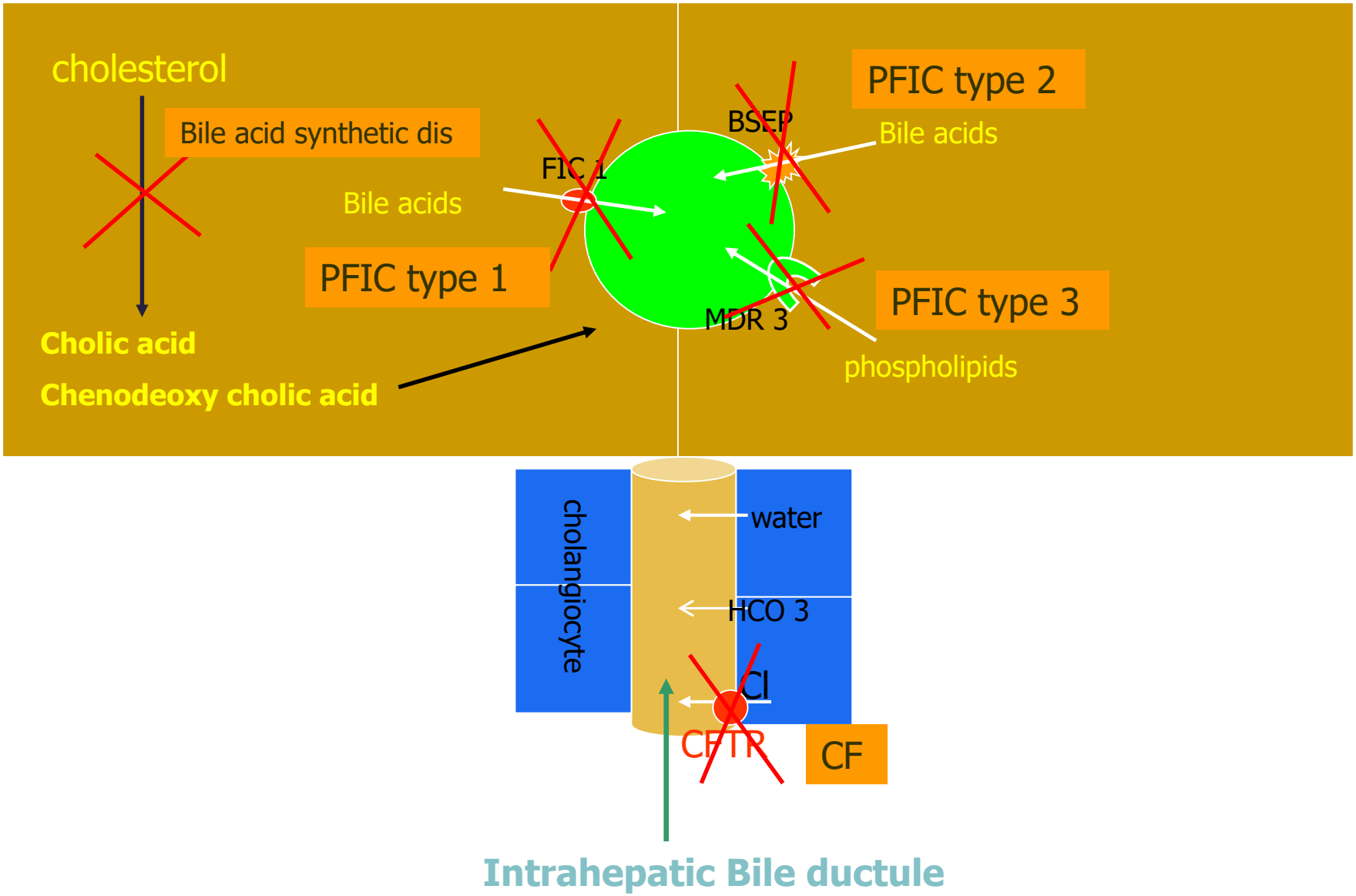
- **PFIC III** caused by mutations in ABCB4
  - Encodes multidrug resistance-associated protein 3 (MDR3) and mediates the flopping of aminophospholipids from inner to outer hemi-leaflet of the canalicular lipid bi-layer

- Liver disease in PFIC results from the effects of hepatocellular accumulation of bile acids

Table 3. **Forms of Progressive Familial Intrahepatic Cholestasis (PFIC)**

	PFIC1	PFIC2	PFIC3
Genetics	Autosomal recessive	Autosomal recessive	Autosomal recessive
Serum gamma-glutamyl transferase	Low	Low	High
Bile	Low bile acids	Low bile acids	Low phospholipids
Gene	*FIC1*	*BSEP*	*MDR3*
Gene product	P-type ATPase (function unknown)	Bile salt pump	Phospholipid transporter (membrane flippase)
Cell localization	Apical: gut, bile duct cells, canalicular membrane	Canalicular membrane	Canalicular membrane
Clinical course	Neonatal onset, variable progression	Neonatal onset, rapid progression	Neonatal or later onset with cholestasis, variable progression
Pruritus	++++	++++	±
Histology	Pseudoacinar pattern of hepatocytes, canalicular cholestasis, coarsely granular bile in bile canaliculi on electron microscopy	Giant cell transformation of hepatocytes, amorphous or dense bile in bile canaliculi on electron microscopy	Portal fibrosis, bile ductular proliferation

Pathophysiology



TPN Cholestasis

- occurring in almost 50% of infants whose birthweights are less than 1,000 g.
- onset often seen after 2 weeks of receiving TPN
- pathogenesis of TPN-associated cholestasis is multifactorial.

- TPN-associated cholestasis has the potential to lead to progressive liver disease and cirrhosis.

TPN-associated cholestasis:

- Precise etiology remains unknown
- • Risk factors are well-characterized:
    - Prematurity
    - Lack of enteral feeds
    - Intestinal surgery
    - Repeated bouts of sepsis
    - Lipid loads

Treatment: Cycling parenteral nutrition

- *Proposed benefits:*
  - Theoretical decreased risk of cholestatic liver disease
    - 2-6 hour cycle off PN promotes GI hormones
    - Improved quality of life at home
- • *Caution:*
  - No prospective, randomized controlled trials confirming the hepatoprotective effect of PN cycling
- - Monitor for hypoglycemia during cycles off PN in patients with end-stage liver disease

Treatment: Ethanol locks to central lines

- Bactericidal and fungicidal via denaturing of cell membranes
- Benefits include ease of acquisition, low cost, and low likelihood of promoting antibiotic resistance
- Potential adverse effects include CNS depression, arrhythmias, local venous irritation, and flushing
- Effective alone or in combination with other agents for eradication of various microorganisms

Novel Lipid emulsion SMOF

- S: Soybean oil
- M: MCT oil
- O:O live oil
- F:Fish oil

- SMOFlipid 20% was safe/well tolerated
- Decreased plasma bilirubin in SMOFlipid20% cohort vs. IL cohort
- Increased ω3 FA and α-tocopherol status in SMOFlipid20% cohort vs. IL cohort without changing lipid peroxidation.

Acute neonatal liver failure

- Galactosemia
- Tyrosinemia
- Neonatal haemochromatosis
- Haemophagocytic lymphohistiocytosis and congenital leukaemia
- Septicemia and shock
- Giant cell hepatitis with hemolytic anemia
- HHV-6, Hepatitis B, Adenovirus, Parvovirus
- Mitochondrial hepatopathy
- Vascular malformations and congenital heart disease
- Maternal overdose (paracetamol)
- Hypocortisolism

APPROACH TO INFANT WITH LIVER DISEASE

History

- H/o Neonatal infection
  - UTI, sepsis and viral infection
- Feeding history and history of weight gain
  - metabolic disease can cause anorexia, FTT, and jaundice
- Bowel history
  - Vomiting - metabolic disease, pyloric stenosis, bowel obstruction
  - Delayed stooling—CF, hypothyroidism
  - Diarrhea—infection, metabolic disease, PFIC1, CF
  - Clay colored stool—biliary obstruction

- Dark urine color

- Source of nutrition
  - Composition of formula:
    - Galactose containing → galactosemia
    - Fructose or sucrose containing → hereditary fructose intolerance

- Lethargy
  - Hypothyroidism, panhypopituitarism, sepsis, or infection
- Excessive bleeding
  - coagulopathy, vitamin K deficiency
- Similar problem with parents or among siblings
  - A1AT deficiency, Alagille syndrome, cystic fibrosis, PFIC
- Consanguinity
  - Risk for autosomal recessive inheritance

- Maternal infection that can affect baby
  - TORCH infections, occassionally HBV
- Cholestasis of pregnancy
  - May be seen in PFIC
- Past ABO or Rh disease, or Rh negative

Physical examination

- Global assessment of general health and nutrition status
  - Dysmorphic findings (Alagille's)
- HEENT
  - Slit-lamp findings (Alagille's , cataracts)
- Chest/heart
  - Murmur or evidnece of congenital heart disease (biliary atresia, Alagille's)
- Abdomen
  - Liver and spleen size and consistency
  - Distention, Ascites, Abdominal wall vasculature

- Skin
  - Jaundice, bruising, petechiae, rashes
- Neurologic
  - General assessment of vigor, tone, and symmetry
- Diaper
  - Dark urine (conjugated hyperbilirubinemia)
  - Pale or clay colored stool (cholestasis, rule out obstruction)

Investigations

- Total and direct bilirubin
- LFT, GGT
- Synthetic function
  - PT/PTT, glucose, albumin
- CBC
- Urine and blood culture
- Viral serologies
  - TORCH infections, HBsAg, CMV, HIV if indicated
- UA
- Urine reducing substances
- Thyroid function studies
- Alpha-1-antitrypsin
- Sweat chloride or mutation analysis for CF gene
- Follow-up newborn screen

Radiological investigations

- Ultrasound with dopplers
  - Choledochal cyst
  - Portal vein thrombosis
  - For Biliary Atresia
    - Triangular cord sign (TC) - obliterated fibrous ductal remnant in the porta hepatis
    - May demonstrate absence of the gallbladder and no dilatation of the biliary tree

- HIDA scan
  - Consider biliary atresia if good hepatic uptake with no evidence of excretion into the bowel at 24 hours
  - Not specific for biliary atresia
  - Pretreatment with phenobarbital (5 mg/kg/day for 5 days) to increase biliary secretion may help minimize false positives

- Refer to Hepatology
- May need:
  - Liver biopsy
    - For BA → portal tract fibrosis, edema, ductular proliferation, and cholestasis with the appearance of bile plugs
  - Intra-op cholangiogram
  - Further work up for cholestasis including directed genetic testing

General Principles in management of childhood cholestasis

- Should aim for a caloric intake of 125 – 150% of the recommended dietary allowance based on ideal body weight.

- Supplement fat soluble vitamins :
  - Vit A : 5000 – 25000 IU/ day.
  - Vit D3 : 1200 – 4000 IU/day.
  - Vit E : 15 – 5 mg PO every other day.
  - If oral form is not available give Vit K injection every 2 – 3 weeks at a dose 2 – 5 mg IV/IM.

- Management of Pruritus
  - Ursodeoxy cholic acid 20 mg / kg / day BID
  - Antihistamines
    - Hydroxyzine 2 – 5mg / kg / day.
    - Diphenhydramine 5 – 10 mg / kg / day.
  - Phenobarbitone 5 mg / kg / day BID.
  - Rifampicin 10 mg / kg/ day.
  - Cholestyramine 250 – 500 mg / kg / day.

Summary

- It is essential to detect liver disease in an infant through a careful history, physical examination, and fractionation of the serum bilirubin
- Many intrahepatic disorders, such as congenital infection and inborn errors of metabolism can lead to cholestasis
- Early recognition and diagnostic evaluation of the cholestatic infant is needed to manage the complications