Biliary Atresia

Karen F. Murray, MD
Professor of Pediatrics
Director, Hepatobiliary Program
Seattle Children's

Biliary Atresia

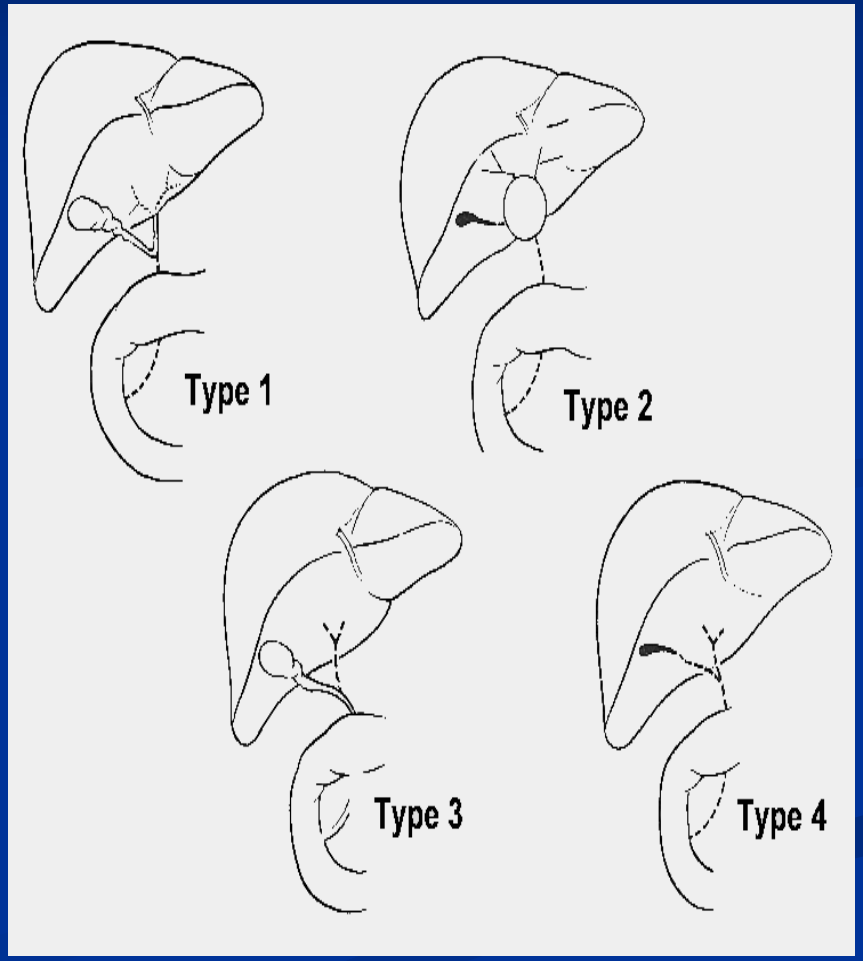
- Incidence: 1/8,000-15,000 live births
- Girls > boys 1.5:1
- The most common cause of surgical obstructive jaundice presenting in the 1st 3 months.
- Leading indication for liver transplantation in infants and children (40-50%)

Biliary Atresia

- **Definition**
  - Progressive sclerosing inflammatory process of extrahepatic and intrahepatic bile ducts causing complete biliary obstruction in the first three months of life
- **Location**
  - Segmental or complete
  - Most commonly involves complete extrahepatic bile duct extending into the hepatic porta

Biliary Atresia: Surgical Anatomy

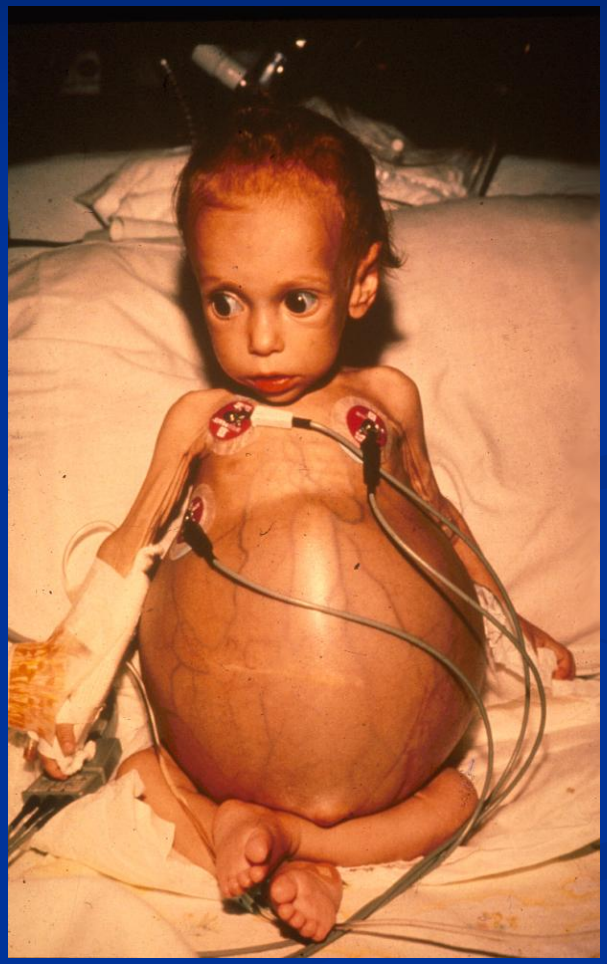
- Type 1 (3%) - common bile duct
- Type 2 (6%) – cyst in hilum communicating with intrahepatic bile ducts
- Type 3 (19%) – GB, cystic duct and common bile duct patent
- Type 4 (72%) – complete extrahepatic atresia



Clinical Presentation

- Healthy term female, growing well
- Jaundiced ≥ 2 week check-up
- Weeks later: jaundiced, hepatomegaly, acholic stools

Biliary Atresia: 100% fatal by 3 yrs if treatment unsuccessful



Biliary Atresia: Phenotypes

- *Embryonic* or *"congenital"* 10-20%
  - Prenatal process causing BD injury
  - Early presentation – born with atretic duct
    - No jaundice free interval
  - Other congenital anomalies
  - Polysplenia (BASM) syndrome
    - 8-11%, 3-4% in Asia

Biliary Atresia: Phenotypes

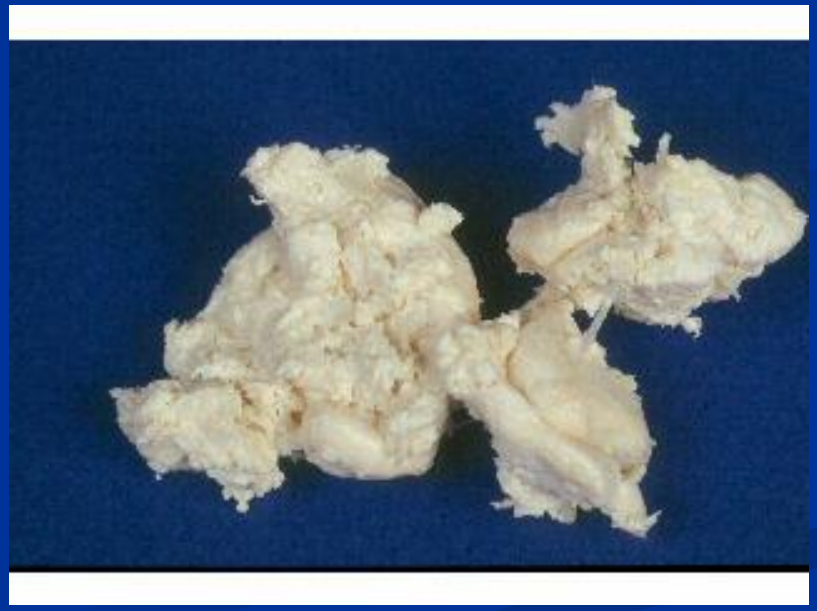
- *Perinatal* or *acquired* 80%
  - Post-natal BD injury
  - Viral or toxic insult
  - Frequently have jaundice-free period
  - No other congenital anomalies

Biliary Atresia: Diagnosis

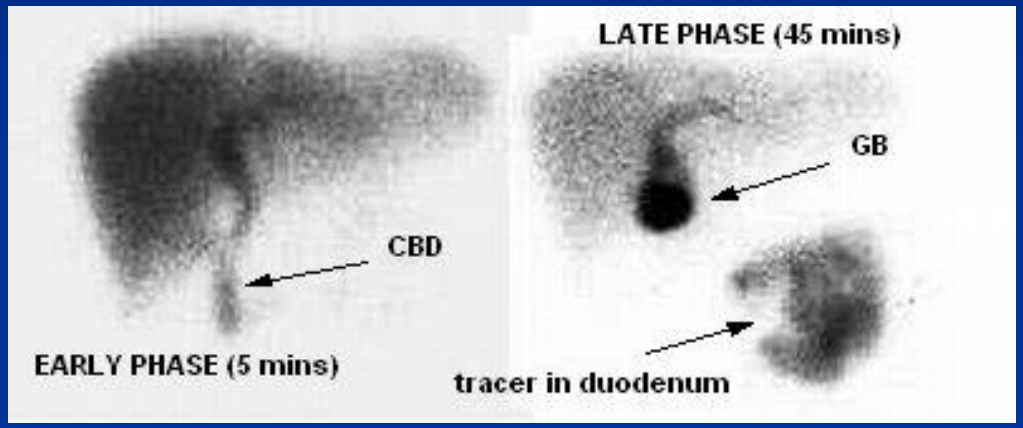
- Within the first 2-3 weeks following birth
- Persistent jaundice
- Acholic stools
- Dark urine

Biliary Atresia: Evaluation

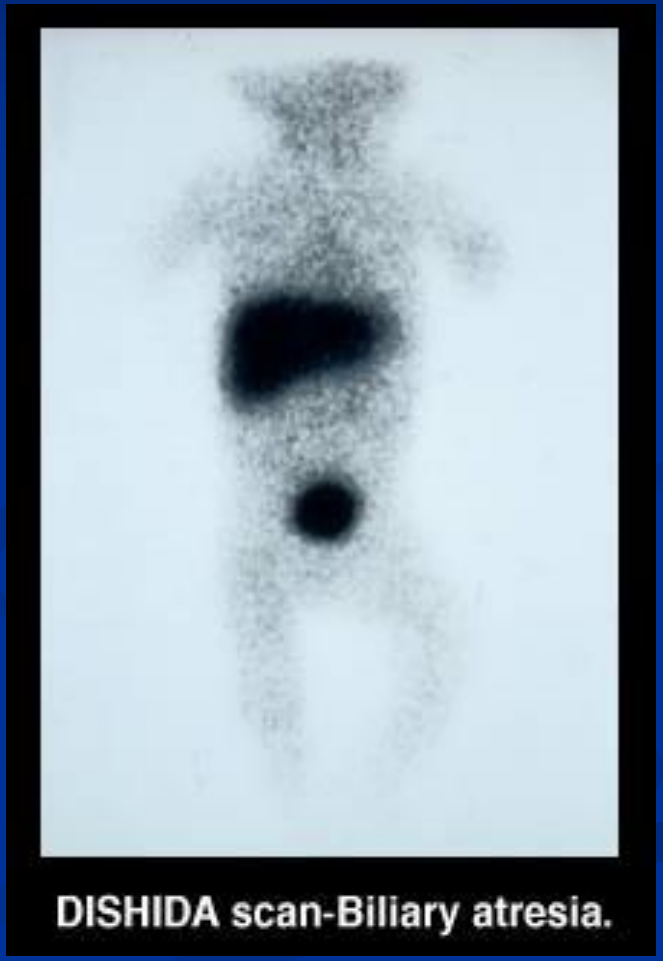
- Laboratory
  - ↑↑ GGT/ALK Phos
  - ↑ ALT/AST
  - ↑ Conjugated Bili
    - > 20% of total
  - Hepatomegaly
- Acholic Stool



Biliary Atresia: Nuclear scan



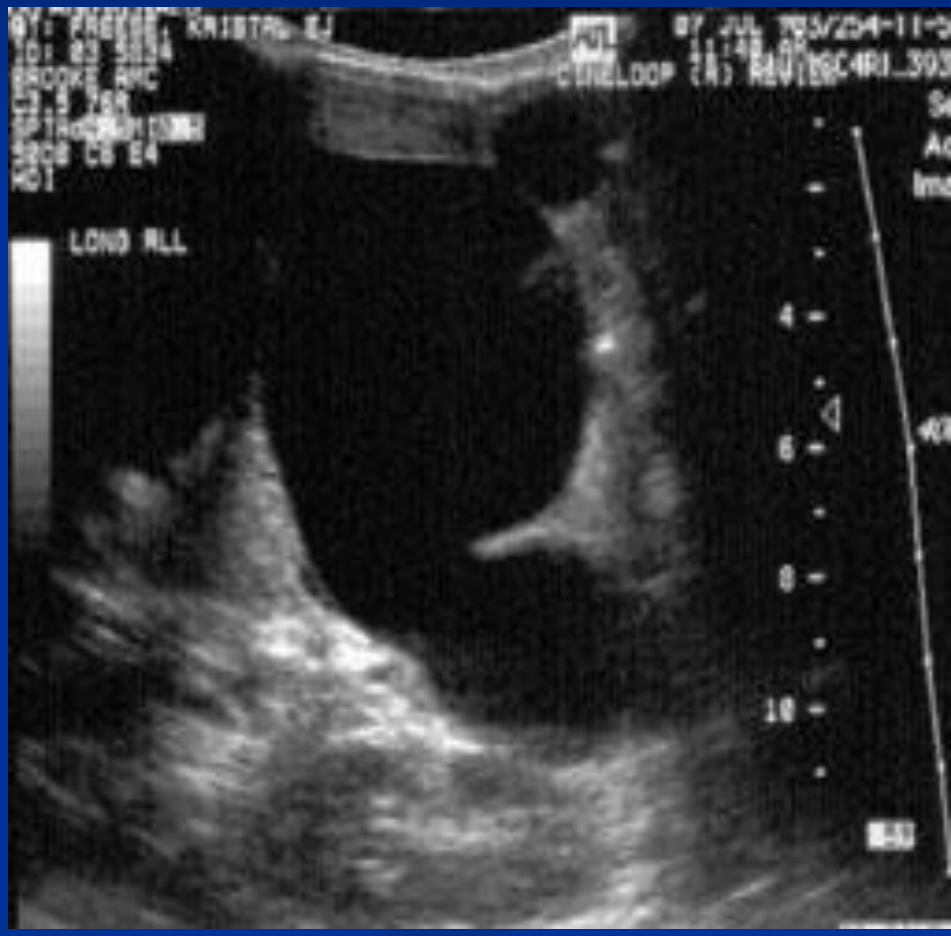
Normal



Biliary atresia

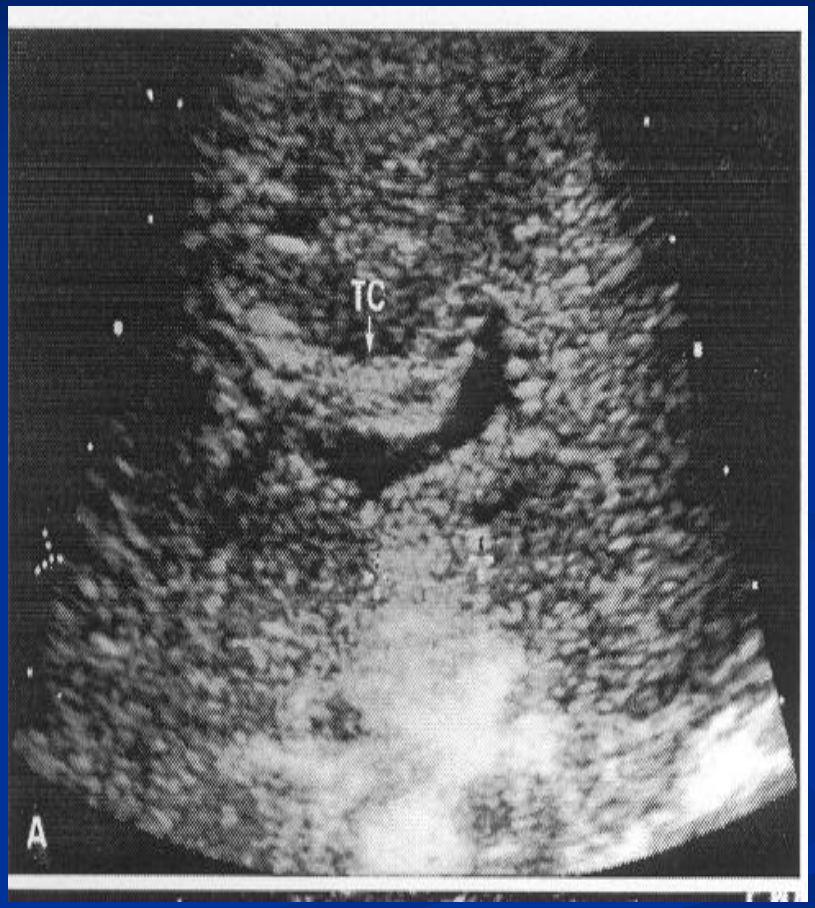
Biliary Atresia: Role of US

- Eval for:
  - biliary dilatation
    - obstruction
  - biliary anomalies
    - choledochal cyst
- "Triangular cord" sign



"Triangular cord" sign

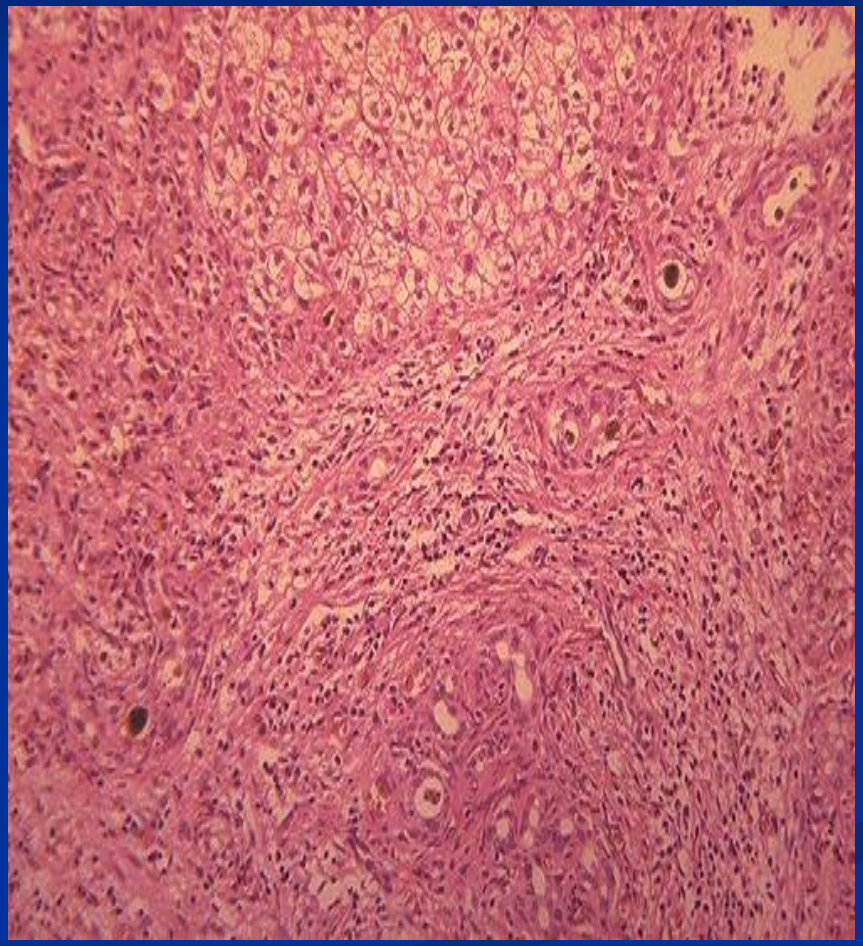
- A triangular/tubular, echogenic density seen just cranial to the portal vein bifurcation in BA
- Simple, noninvasive, inexpensive, timesaving, and reliable



Park et al J Hepatobil Pancreat Surg 2001;8:337
Kotb et al Pediatrics 2001;108:416

Biliary Atresia: Histology

- Portal tract widening
- Biliary duct edema
- Fibrosis
- Bile duct proliferation



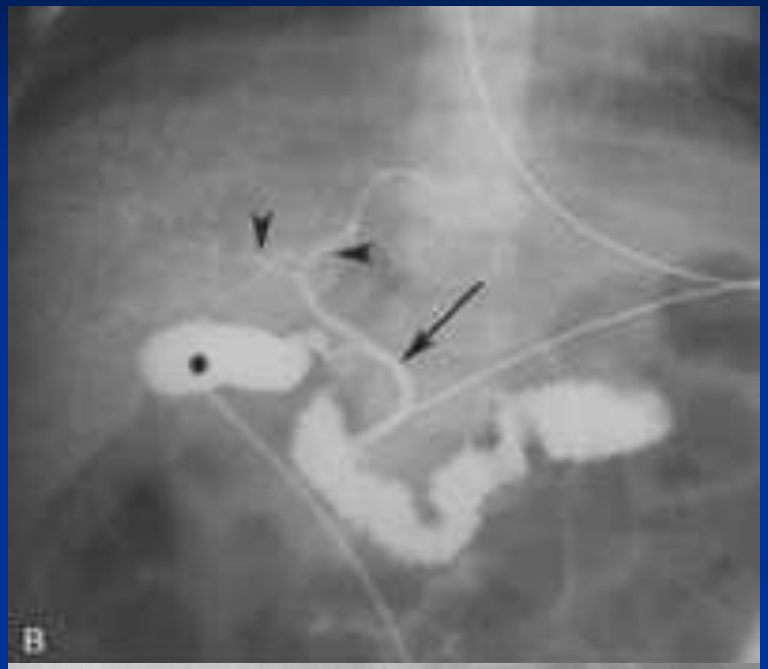
Bile duct proliferation, bile plugs

Biliary Atresia: Cholangiogram

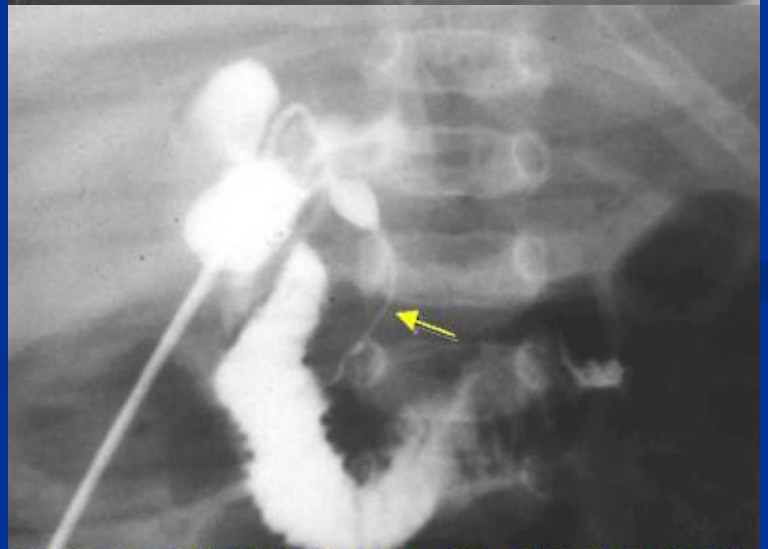
- Cholangiography is standard to assess morphology and patency of the biliary tree

- Can be performed percutaneously, endoscopicly, or intraoperatively

Nl

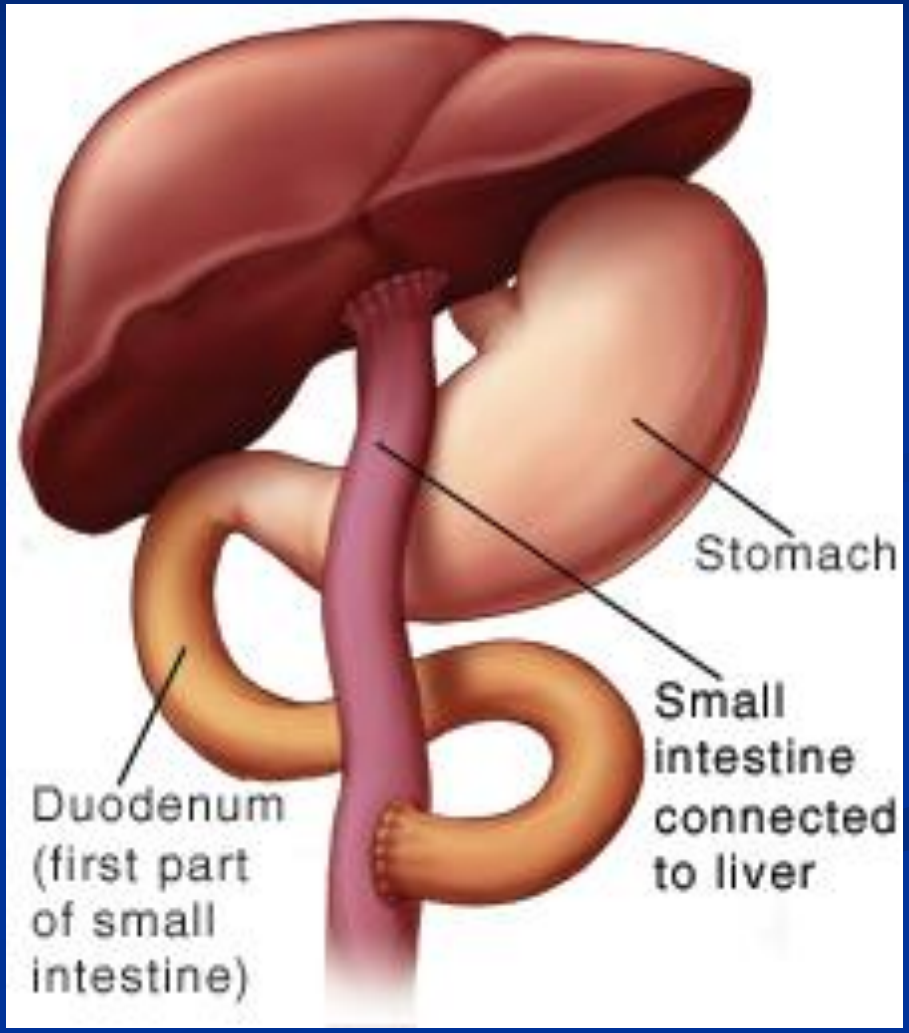


BA

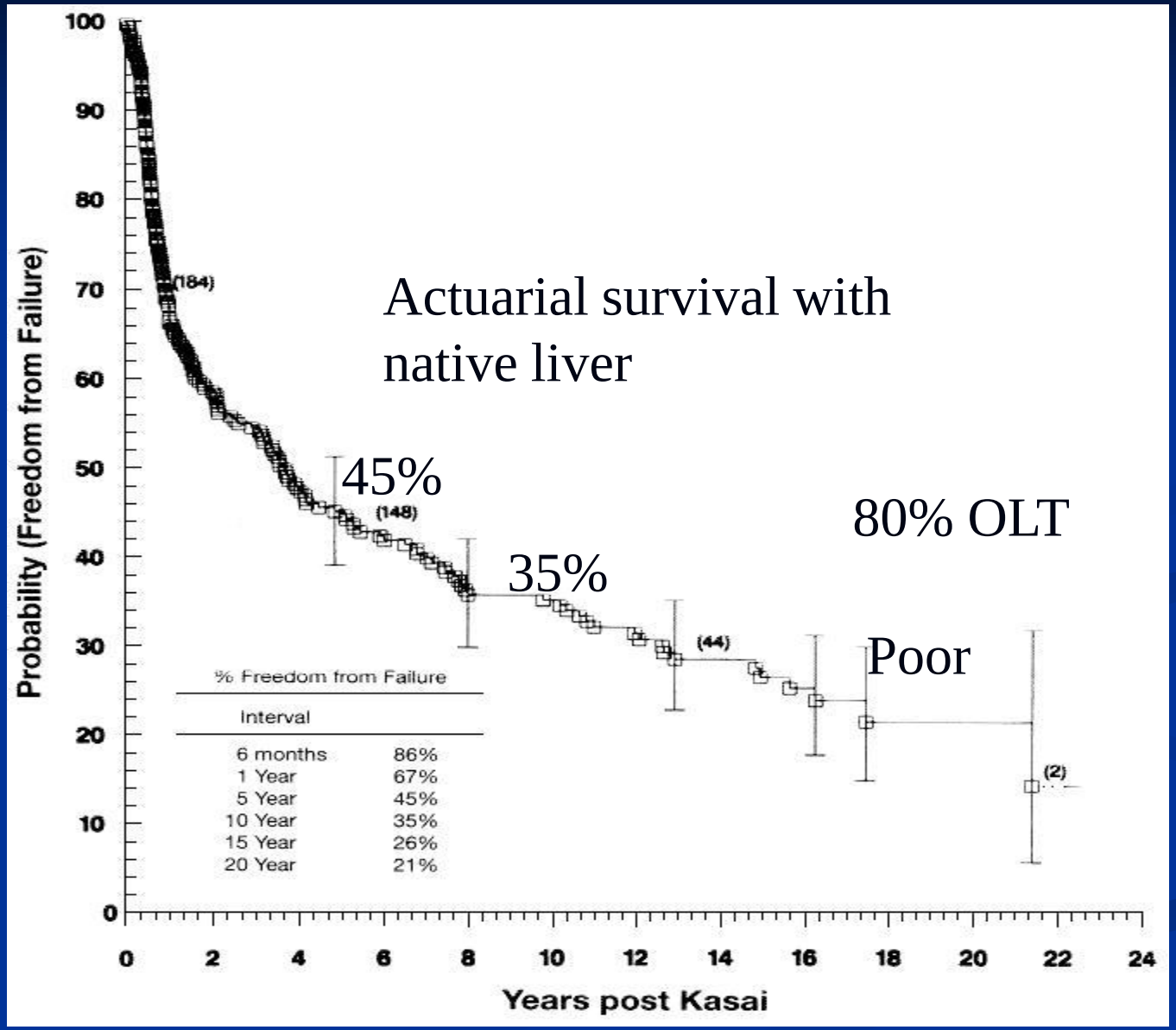


Biliary Atresia Treatment: Kasai Portoenterostomy

- A 45 cm Roux en Y loop anastomosed to the cut edge of the transected liver in the porta hepatis



Survival Post-Kasai: 266 patients



1972-1996 Ann Surg 1997

Prognosticators of a poor post-Kasai outcome

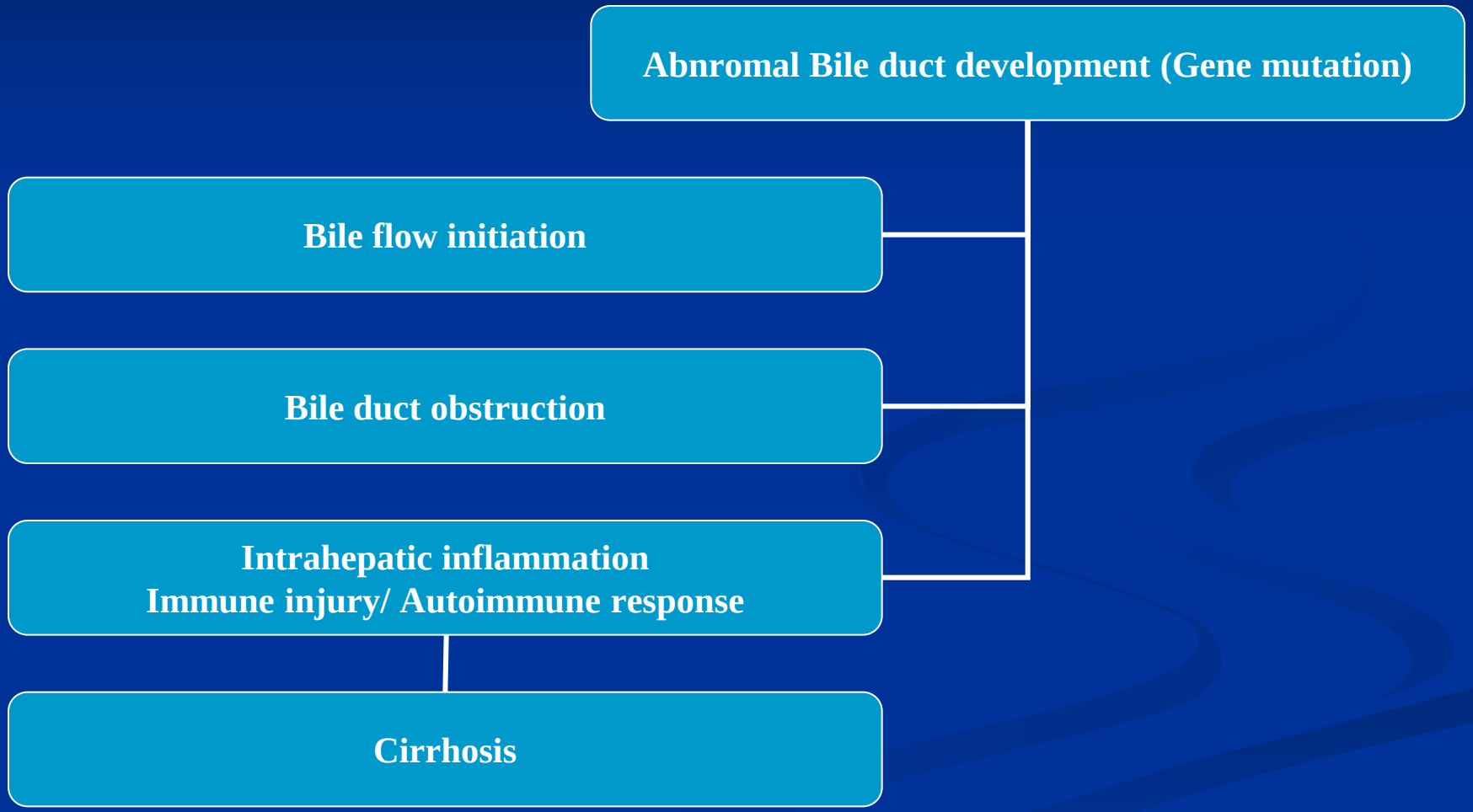
Poor outcome is determined by progressive intrahepatic bile duct disease

- Age/liver injury at Kasai
- Post-Kasai cholangitis
- Other

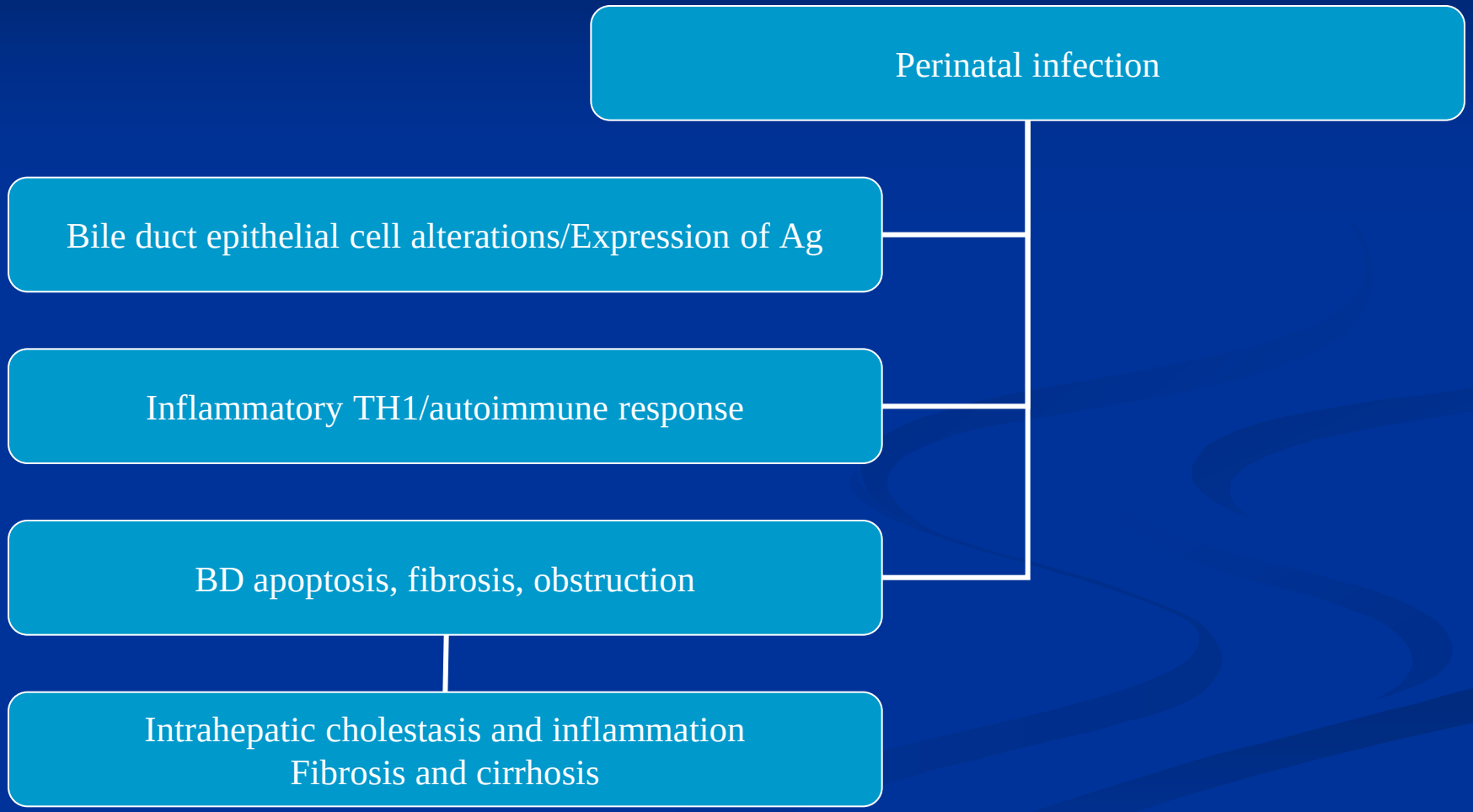
Etiology of Biliary Atresia

- Defective morphogenesis/genetics
  - Laterality sequence genes, Jagged1
- Immune dysregulation
- Autoimmune disease
- Infection-viral, other

“Embryonic” Biliary Atresia
10-20%



"Perinatal" Biliary Atresia 80%



Biliary Atresia: Etiology
Developmental Morphogenesis

- Ductal Plate malformation morphology- failure of normal remodeling at the hepatic hilum
  - *JAGGED1* missense mutations detected in BA patients
- Mouse model (autosomal recessive deletion of the *INV* mouse gene) *
  - Abnormal development of the hepatobiliary system
  - Jaundice
  - Laterality defects
- * No INV mutations detected in human BA, but were in nephronophthisis type 2.

Otto et al.Nat Genet 2003;34:413-420

Biliary Atresia: Etiology

Immunologic

- TH1 cytokines (IL-12, IFN-γ, IL-2, TNF-α) in portal inflammation of BA but not other cholestatic diseases.
- BA liver has up-regulated TH1 pro-inflammatory genes and decreased TH2 genes.

Mack et al. Pediatr Res 2004;56:79-87
Bezerra et al. Lancet 2002;360:1653-1659

Biliary Atresia: Etiology

Autoimmunity

- Antineutrophil cytoplasmic antibodies (ANCA) in the serum of BA.
- anti-Rho antibodies increased in mothers of BA.
- But...family Hx of autoimmunity is no different in BA than other cholestatic diseases.

Vasiliauskis et al. Hepatology 1995;22:87
Burch et al. JPGN 2000;31 (Suppl 2);S108

Biliary Atresia: Etiology

Viral Infection

- Mixed reports of seasonal clustering.
- Increased risk in low birth weight and pre-term infants.
- Many viruses have been investigated and some detected in human BA, but the association less clear.

Biliary Atresia: Etiology

Viral Infection

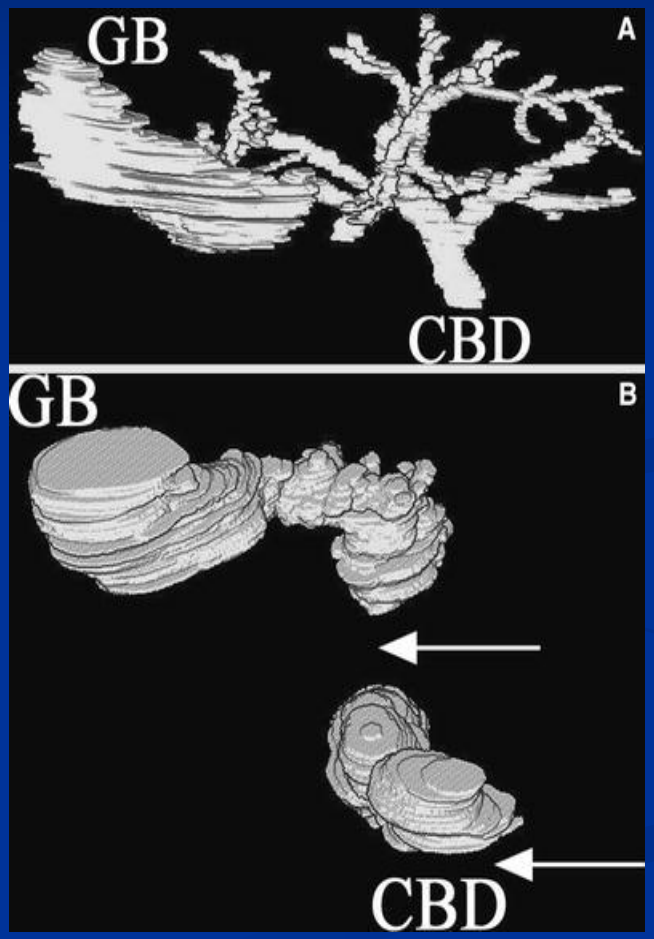
- Reovirus 3:
  - Obliterative cholangiopathy in weanling mice
  - Unsubstantiated in humans: $^{+}$/- detected by RT-PCR
- Rotavirus group C:
  - Rhesus rotavirus (RRV) infection of 12-24 h mice produces BA by 2-3 weeks; inflammation is the same as in humans with BA
  - Detection in human BA by RT-PCR variable

Biliary Atresia: Viral Infection

3D biliary tree in RRV-infected mice

Atresia (*arrows*) at the distal end of the CBD and segmentally at the proximal CBD.

Dilatation of the entire biliary system.



control

RRV-infected

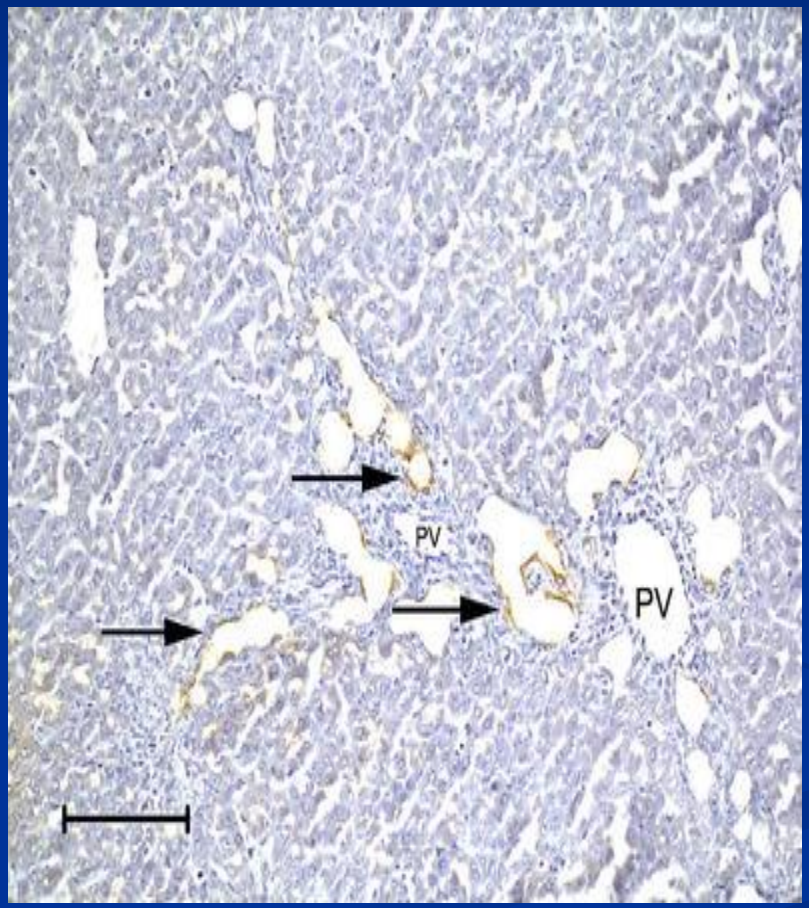
12 days p.i.

Chan et al Pediatr Surg Int 2005;21:615-20

Biliary Atresia: Viral Infection

Liver section from RRV-infected mouse

Bile ducts: denuded of epithelia, and ductular proliferation (*arrows*) around the portal veins (*PV*).



15 days p.i.

Stain: anti-cytokeratin AE1/AE3 antibody (*brown*).

Chan et al Pediatr Surg Int 2005;21:615-20

Biliary Atresia: Complications

- Cholangitis (post-Kasai)
- Portal hypertension
- Intrahepatic biliary cysts (bile lakes)
- Hepatopulmonary syndrome and pulmonary hypertension
- Hepatorenal syndrome
- Malignancies (HCC, cholangiocarcinoma)

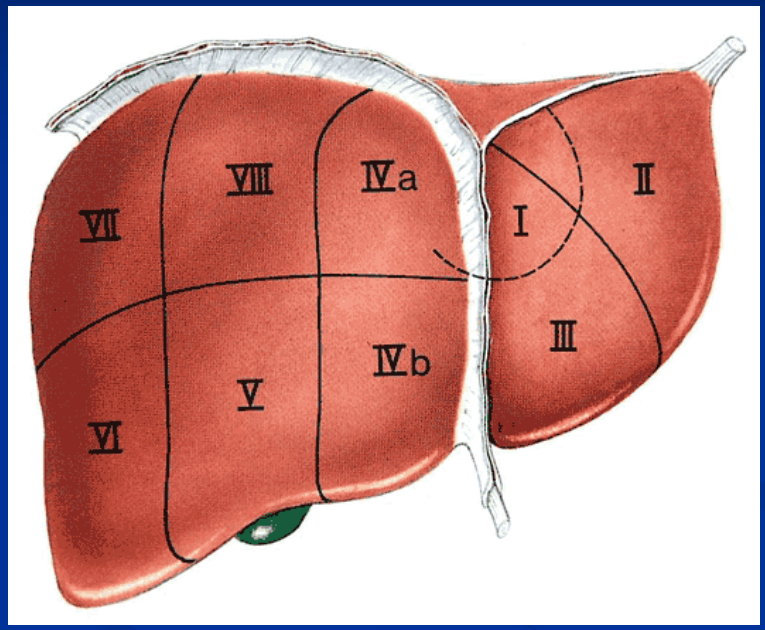
Post-Kasai Treatment : Drugs

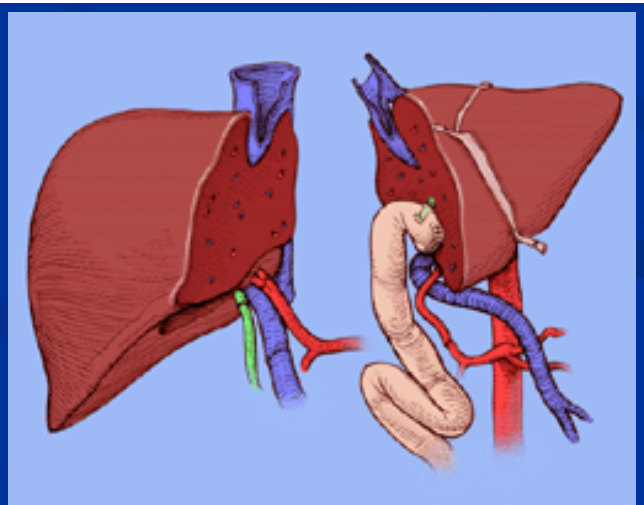
Ongoing controversies

- Use of corticosteroids
  - ChiLDREN (NIH-sponsored placebo-controlled trial of corticosteroid post-Kasai)
- Use of prophylactic antibiotics

Liver Transplantation:
40% in Pediatrics for Biliary Atresia

- Living-related
  - Left lateral segment
- Cadaveric:
  - Whole organ
  - Left lobe (segments 2/3)
  - Left liver (2/3/4)



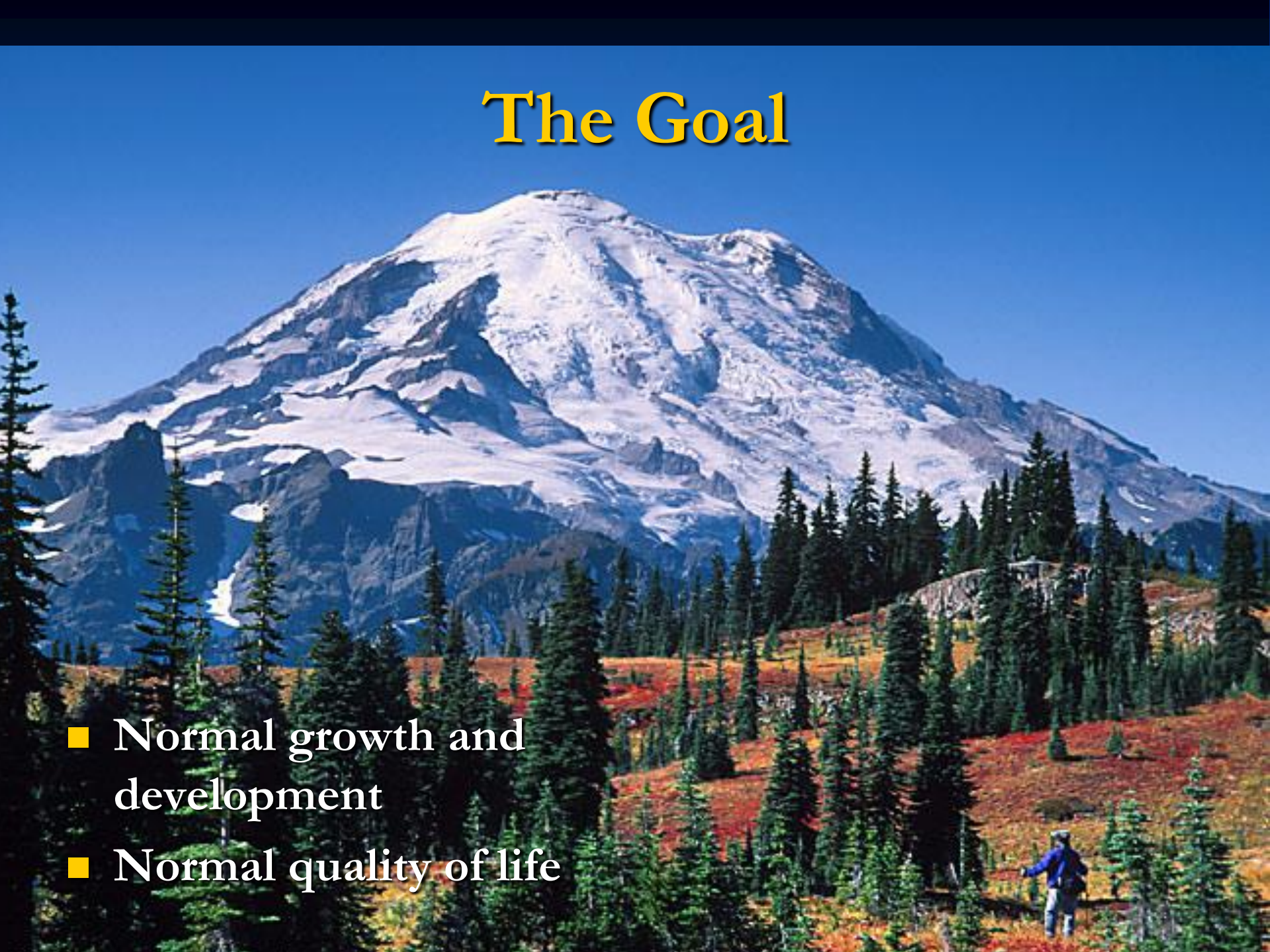


Split liver

Biliary atresia: Survival

- 5 and 10 yr. Survival rates 32% and 27% with native liver
- Overall survival 71%
- With liver transplant, survival rates 85-90%

The Goal



- Normal growth and development
- Normal quality of life