Cholestasis Ddx

- **Congenital:** CMV, Toxo, Rubella, HSV, Syphilis, HIV
- **Acquired:** UTI, Sepsis
- **Metabolic:** A1AT, CF, Galactosemia, Tyrosinemia
- **Obstructive:** Biliary Atresia, Choledochal cysts, Inspissated bile syndrome
- **Cholestatic syndromes:** Alagille, Progressive familial intrahepatic cholestasis
- **Plus:** Hypothyroidism, Hypopituitarism, TPN, drugs, shock, heart failure

Genetics

- AD mutation (20p12.2 deletion, haploinsufficiency) of JAG1 with 94% penetrance, 15% sporadic mutations.
- JAG1 codes for a NOTCH1 receptor ligand, and are known to play a role in early cellular fate determination. Signaling pathway disruption and developmental error account for much of the phenotype.

Clinical Presentation: Cholestasis and pruritis within one year after birth, characteristic facies

Systems

- **Hepatic**
  - Bile duct paucity is the main histologic finding and causes the conjugated hyperbilirubinemia. Presence of jaundice is associated with increased morbidity and mortality—bile is building up in the liver due to bile duct paucity and is hepatotoxic. Might not be present in infancy.
- **Cardiac Abnormalities**
  - Peripheral Pulmonic Stenosis
- **Craniofacial**
  - Prominent forehead and pointed chin. Eyes are deep set and dysmorphic (eccentric pupils, chorioretinal atrophy).
- **Skeletal**
  - Butterfly vertebrae
  - Foreshortening of the fingers
- **Ocular**
  - Posterior embryotoxon (opaque ring (CT bundle) around the margin of the cornea)
  - Iris abnormalities
  - Fundus hypopigmentation
- **Renal**
  - Renal dysplasia
  - RTA
  - VUR
  - Urinary obstruction
**Diagnosis:** Bile duct paucity plus three of five clinical criteria (cholestasis, cardiac defects, skeletal abnormalities, opthalmologic abnormalities, characteristic facial features.

**Treatment:**

- Ursodeoxycholic acid
  - Stimulates bile flow and reduces cholestasis
  - May displace toxic bile acids from hepatocytes
- Rifampin
  - Reduces pruritis by unknown mechanism
- Organ transplantation is definitive treatment and is often required

**Patient Resources:**

- Support Alagille Syndrome Alliance.
  - www.alagille.org
  - Community tab – Family Map
- National Organization for Rare Disorders

**References/Information of Interest:**

