Neonatal Cholestasis
“The importance of a timely evaluation”

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OBJECTIVES

• Review the differential diagnosis for neonatal cholestasis.
• Recognize how to timely evaluate the neonate with conjugated hyperbilirubinemia.
• Discuss the therapeutic management of neonates and infants with cholestasis.
Bilirubin Production

- erythrocyte hemoglobin
- muscle myoglobin
- cytochromes catalases

Heme

- CO + Fe

Biliverdin

- heme oxygenase
- biliverdin reductase

Bilirubin

- Albumin

Liver
Bilirubin Uptake, Conjugation, Excretion

1. **UPTAKE**
   - Bilirubin (B) binds to Albumin (Alb) in the sinusoid.

2. **CONJUGATION**
   - Bilirubin (B) enters the hepatocyte.
   - Bilirubin monoglucuronide (B, UDPG) is formed by UDP-glucuronyl transferase (UGT).
   - The conjugated bilirubin (B, G) is transported into the endoplasmic reticulum (E.R.).

3. **EXCRETION**
   - Conjugated bilirubin (B, G) is excreted into the bile canalculus (B.)
Hyperbilirubinemia

1. Increased bilirubin production
2. Reduced bilirubin uptake by hepatic cells
3. Disrupted intracellular conjugation
4. Disrupted secretion of bilirubin into bile canaliculi.
5. Intra/extra-hepatic bile duct obstruction

Lead to Increase in Unconj. Bilirubin

Lead to Increase in Conj. Bilirubin
Hyperbilirubinemia

- Crigler-Najjar Syndrome, Type I - II
- Gilbert’s

- Dubin-Johnson
- Rotor
<table>
<thead>
<tr>
<th></th>
<th>Gilbert</th>
<th>Dubin-Johnson</th>
<th>Rotor</th>
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<tbody>
<tr>
<td>Conjugated bilirubin elevation</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Inheritance</td>
<td>AD/AR</td>
<td>AR</td>
<td>AR</td>
</tr>
<tr>
<td>Defect</td>
<td>UGT1A1 reduced by 10-30 %</td>
<td>Apical Canalicular membrane (MRP2)</td>
<td>Defective bile transport and reuptake (gluthatione)</td>
</tr>
<tr>
<td>Other routine liver function tests</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Age</td>
<td>Clinically apparent after puberty</td>
<td>Puberty Neonates (higher #)</td>
<td>Early Childhood</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Nicotinic acid or rifampin stimulation</td>
<td>-Urine coproporhyrin levels. (high type 1 &gt; 80 %)</td>
<td>-Urine coproporhyrin levels. (high type 1 &lt; 80 %) - NO dark discoloration of liver in biopsy</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Benign</td>
<td>Benign</td>
<td>Benign</td>
</tr>
<tr>
<td>CRYGLER-NAJJAR SYNDROME, TYPE I</td>
<td>CRYGLER- NAJJAR SYNDROME TYPE 2</td>
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<td>----------------------------------</td>
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<tr>
<td><strong>Severe</strong> deficiency of glucuronyl transferase</td>
<td><strong>Moderate</strong> deficiency of glucuronyl transferase</td>
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<tr>
<td>Deep jaundice develops soon after birth.</td>
<td>They will have unremitting jaundice for the whole life.</td>
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<tr>
<td>High serum unconjugated hyperbilirubinemia, &gt;25 mg/dl., <strong>NOT responding to phenobarbital.</strong></td>
<td><strong>Responds to enzyme inducing agents:</strong> phenobarbital</td>
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<tr>
<td>Phototherapy, plasmapheresis are beneficial.</td>
<td>Patients develop normally but some may suffer bilirubin encephalopathy.</td>
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<td>Liver transplantation may be life-saving.</td>
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<td>Death <strong>usually</strong> in the first year or two with kernicterus.</td>
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</table>
Fig. 40.3 Opisthotonus from kernicterus. This is now rarely seen in
- Physiological
- Breast Milk
- Hemolysis
  - Rh
  - ABO
- Hypothyroidism
BEWARE!!

- Dark urine
- Acholic stools
- Hepatosplenomegaly ?
- Abnormal LFTs
Neonatal Cholestasis

• Physiologic definition: Decreased bile flow
• Accumulation of components of bile in the bloodstream.
• Conjugated hyperbilirubinemia developing within the first 90 days of life.
• Conjugated bilirubin > 1.0 mg/dl if TB <5
• Conjugated bilirubin exceeds 20% if TB > 5
• Incidence: 1 in 2500 live births
Approach

1. Intrahepatic or Extra-hepatic etiology?
2. Is this a treatable disorder?
   Surgical/Medical
3. What is the degree of liver injury?
4. Are there complications of cholestasis?
Causes

- Obstruction (Extrahepatic)
- Infection
- Metabolic
- Genetic
- Toxic/Drugs
- Idiopathic
- Alloimmune

Intrahepatic
IDIOPATHIC NEONATAL HEPATITIS

• Prolonged conjugated hyperbilirubinemia without an obvious etiology after a complete evaluation has excluded identifiable anatomic, infectious and metabolic/genetic causes.

• 50 % (1980) down to 15 % (2005) and continues to decrease.
Evolving spectrum of cholestasis

1970-2000

- Idiopathic neonatal hepatitis: 25%
- Biliary atresia: 10%
- A1AT deficiency: 6%
- Syndromic cholestasis: 5%
- "TORCH" syndrome: 2%
- Miscellaneous: 5%

2000...

- Idiopathic neonatal hepatitis: 20%
- Biliary atresia: 25%
- A1AT deficiency: 5%
- Syndromic cholestasis: 15%
- "TORCH" syndrome: 25%
- Miscellaneous: 10%
- PFIC, Alagille, BASD: 25%

2005
CLINICAL PRESENTATION
GOALS OF A TIMELY EVALUATION

• Diagnose and treat known medical and/or life-threatening conditions.
• Identify disorders amenable to surgical therapy within an appropriate time-frame.
• Avoid surgical intervention in intrahepatic diseases.
EVALUATION

– History and physical examination (includes exam of stool color)
– CBC and reticulocyte count
– Total and fractionated bilirubin
– Electrolytes, BUN, creatinine, calcium, phosphate, Mg, P,
– AST, ALT, GGT, Alkaline phosphatase
– Total protein, albumin, cholesterol,
– INR
EVALUATION

• Tests for infectious causes
  – Indicated cultures of blood, urine, CSF
  – TORCH titers
  – Urine for CMV
  – Hepatitis titers.
EVALUATION

• Metabolic work-up
  – Alpha-1-antitrypsin level and phenotype
  – Thyroid function tests
  – Sweat chloride
  – Serum Bile acids
  – Urine/Serum amino acids
  – Review results of newborn metabolic screen
  – Urine reducing substances
EVALUATION

• Radiological evaluation
  – Ultrasonography
    • Patient should be NPO to increase likelihood of visualizing the gallbladder
    • Feeding with exam may demonstrate a functioning gallbladder
  – Hepatobiliary scintigraphy
    • Premedicate with phenobarbital 5-10 mg/kg/d for 3-5 days
EVALUATION

• Invasive studies
  – Percutaneous liver biopsy
  – Percutaneous transhepatic cholangiography
  – Endoscopic retrograde cholangiopancreatography (ERCP)
  – Exploratory laparotomy with intraoperative cholangiogram.
Causes

- Obstruction (Extrahepatic)
- Infection
- Metabolic
- Genetic
- Toxic/Drugs
- Idiopathic
- Alloimmune
Extrahepatic/Obstructive

• Biliary Atresia
• Choledochal Cyst
• Inspissated Bile
• Gallstones/Biliary sludge
• Mass (Hepatoblastoma, Neuroblastoma)
• Spontaneous perforation of Extrahepatic biliary tree
Biliary Atresia

• Progressive scarring of bile ducts outside and inside of the liver that leads to complete blockage of bile flow in the first three months of life.
“Extrahepatic” Biliary Atresia

• 1 in 13,700 live births.
• Complete obstruction of Extrahepatic biliary ducts
  – Progressive sclerosing inflammatory process
    • Infectious, Toxin-mediated inflammatory response, genetic? immune dysregulation (maternal lymphocytes in portal areas), vascular insult?
• Other associated anomalies (10-20%)
  – 10-15% Laterality malformations
    • Asplenia, polysplenia, situs inversus, malrotation, interrupted IVC, CHD
  – 5-10% Other structural anomalies
    • Intestinal atresia, imperforate anus, renal anomalies, CHD
• **Perinatal or “classic” type** (70-85%): Obstruction begins *after* birth. Signs/symptoms develop within 2-4 weeks of age. No associated abnormalities.

• **Embryonic type** (15-30%): Obstructive process begins *in utero*. Cholestatic symptoms present at birth. Associated with congenital anomalies: Situs inversus, polysplenia, malrotation.
Clinical Signs

- Well appearing (initially)
- Jaundice
- Hepatosplenomegaly +/-
- Mild or Moderate Transaminitis
- ↑ GGT and AP
- Acholic stools
Imaging

• Ultrasound
  – Atretic gallbladder
  – Absence of common bile duct
  – Triangular cord sign

• HIDA
  – Phenobarbital 5-10 mg/kg/day x 5 days or does it delay diagnosis?
  – Sensitivity (98%), Specificity (70%)

• Cholangiogram
  – Intraoperative - Assess both proximally into the liver and distally into the bowel to determine patency
  – Percutaneous vs ERCP

Kianafar, Ped Rad 2013
Podder et al, J Nuc Med 2004
Normal Hepatobiliary Imino-Diacetic Acid Scan “HIDA” (hepatobiliary scintigraphy)
Biliary Atresia
Percutaneous Liver Biopsy

- Liver biopsies made early in the course of disease (<6 wks) may be indistinguishable from neonatal hepatitis.
- Bile duct proliferation.
- Following biopsy, diagnosis is confirmed by intraoperative cholangiography (Gold Standard)
Liver Biopsy

- Bile duct proliferation
- Fibrosis

- Canalicular and bile duct bile plugs
- Inflammation
KASAI PROCEDURE

• Roux-en-Y portoenterostomy
• Bile flow re-established in 80-90% if performed prior to 7 weeks-old.
• Bile flow re-established in less than 20% if performed after 12 weeks-old.
• Long-term - 10 yr. survival (no transplant) 20 - 40% (US, France) 50% Japan.
• Liver transplantation - required for 80%
Predictors of Prognosis after Kasai

• Prognosis
  – BA with splenic malformations = worse
  – Serum bilirubin = most predictive at 3 mos
    • Tbili <2 mg/dL, two year survival without transplantation was 84%
    • Tbili ≥6mg/dL, two year survival without transplantation was only 16 percent

Post Operative Management

• Actigall (UDCA) – 15-30mg/kg/day
• Corticosteroids ???
  – NO difference in bile drainage or transplant free survival.
• Nutritional rehabilitation
  – 150% of RDA, MCT oil, High MCT (Progestimil)
  – Vit A,D,E and coags (INR) 2-4 weeks post Kasai
• Prevention of cholangitis
  – Incidence 40-90% but one episode does not predict early transplant.
  – TMP-SMZ (4mg/kg/day trimethoprim divided twice daily)
• Management of portal hypertension
  – Study of 163 children without transplant (mean age 9.2 years)
    • 50% had portal hypertension, 25% history of GI bleeding

James Phillips, MD, Department of Pathology, Hospital for Sick Children.
LIVER TRANSPLANTATION

- Survival rates approach 95% at 1 year and 70% at 5 years.
- Biliary atresia is the most common indication for transplant and may be the initial treatment when detected late or may be used as a salvage procedure for a failed Kasai.
1988-2014 UNOS Database: Liver Transplants (0-17 y/o)
Choledochal Cyst

50-80%
Choledochal Cyst

• 1 in 15,000 live births
• Females > males
• Presents like biliary atresia
  – Can have abdominal pain, vomiting
  – Palpable mass
  – Cholangitis
  – Same progressive disease: Biliary cirrhosis, portal hypertension
  – Can have atresia distal to cyst
• Dg: Ultrasound / MRCP- ERCP / Cholangiogram
• Risk of cholangiocarcinoma
Management

• Early surgical intervention:
  • Type I, IV – complete resection + Roux-en-Y hepatojejunostomy
  • Type II – simple cyst excision
  • Type III (choledochoeles) – sphincterotomy
• Complications
  – Risk of malignancy (0.6-7% postoperative risk)
  – 30% risk of malignancy for Type 1 and IV if not resected
  – Stenosis of biliary-enteric anastomosis
  – Recurrent cholangitis, choledocholithiasis
Causes

- Obstruction (Extrahepatic)
- Infection
- Metabolic
- Genetic
- Toxic/Drugs
- Idiopathic
- Alloimmune

Intrahepatic
Infectious

• Sepsis
• UTI (E.coli)
• TORCH
• EBV,HSV,HIV
• Listeria
• Echovirus
• Enterovirus
• Adenovirus
• Parvovirus
• Hepatitis A,B,C
Metabolic/Genetic

- Galactosemia
- Cystic Fibrosis
- GSD IV
- Tyrosinemia
- Alagille’s Syndrome
- $\alpha_1$-Antitrypsin Deficiency
- Neimann-Pick/Gaucher’s
- Bile acid metabolism/ transport abnormalities
Alagille Syndrome

- "Arteriohepatic Dysplasia"
  - Liver, heart, eyes, face, skeleton, vascular system
- Autosomal Dominant
  - JAG1 mutation on 20p12 or NOTCH-2 mutations
    - Variable penetrance
    - Development and maintenance of biliary epithelium.
- 1 in 70,000 live births
- Some children improve, others progress.
Alagille Syndrome

• Chronic cholestasis (90%)
  – Intrahepatic paucity of bile ducts
  – Intractable pruritus
  – 20% with ESLD

• Cardiac anomalies (85%)
  – Peripheral pulmonic stenosis, tetralogy of Fallot
  – Systemic vascular anomalies (risk of stroke) 15-20 %

• Skeletal abnormalities - Butterfly vertebra (85-90%)

• Ocular abnormalities - Posterior embryotoxin (50-86%)

• Facial findings (95%)
  – Broad nasal bridge, triangular fascies, deep set eyes, small, pointed chin. Can be seen in other intrahepatic etiologies.
Butterfly Vertebra
Ocular

• Posterior embryotoxon

• An abnormal prominence of Schwalbe’s line (cornea-uveal trabecular meshwork). Can be seen in 8-15% of general population

• Iris abnormalities, speckling of retinal pigment epithelium
Clinical Features: Cardiovascular

- PPS Most common cardiac manifestation of AGS.
- TOF, VSD, ASD
Alagille Syndrome

- Cholestasis
  - Pruritis
  - Xanthomas
Moyamoya Syndrome in Children With Alagille Syndrome

American Journal of Neuroradiology
Multiple Cerebral Aneurysms in a Patient with Alagille Syndrome

American Journal of Neuroradiology
Destruction of small bile ducts is a progressive process that injures and obliterates small interlobular bile ducts, resulting in obstructive cholestasis.
Treatment

- Pruritus is seen in 70-80%.
- Ursodiol, Antihistamines, rifampin, bile acid binding resins, naltrexone/naloxone, biliary diversion.
- 40% patients with pruritus is refractory to medical treatment, and resolves only after liver transplantation.
- ESLD develops in approximately 20-30% percent of affected children and is amenable to liver transplantation.
- Malnutrition, with associated growth failure and pubertal delay are common.
- Often requiring nasogastric or gastrostomy feeding/fat-soluble vitamin supplementation.
$\alpha_1$- Antitrypsin Deficiency

- Most frequent genetic diagnosis for which liver transplantation is carried out.
- Mutations in the SERPINA1 gene.
- The "deficiency" state is actually an accumulation of abnormal protein within the ER resulting in liver injury.
- A1AT is an acute phase reactant with plasma concentrations rising 3- to 5-fold during tissue injury and inflammation.
- Normal levels in neonates/infants > 130 mg/dl.
\( \alpha_1 \)- Antitrypsin Deficiency

- 1:1500-5000
- PiMM normal phenotype and PiZZ severe defective phenotype
- Plasma A1AT is *typically* decreased
- Symptoms
  - Jaundice and transaminitis
  - GGT and alk phos may only be mildly elevated
  - Only 10-15% will have liver injury
    - 5% with progressive cirrhosis in 1\textsuperscript{st} year of life
    - 25% resolve, 25% persistent elevation of LFTs, 50% later cirrhosis
Liver affected by AAT

Hepatocytes with granules representing aggregated AAT

Polymerized AAT molecules in a single granule

Treatment

• Supportive management of symptoms resulting from liver dysfunction and the prevention of complications that are generic to all chronic and acute liver diseases.

• Orthotopic liver transplantation with survival rates well over 90% at 1 year and 80% at 5 years.
# Progressive Familial Intrahepatic Cholestasis

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<tr>
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<th>PFIC 1</th>
<th>PFIC 2</th>
<th>PFIC 3</th>
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<tbody>
<tr>
<td><strong>Transmission</strong></td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
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<tr>
<td><strong>Defect</strong></td>
<td>ATP8B1, FIC 1</td>
<td>ABCB11, BSEP</td>
<td>ABCB4, MDR3</td>
</tr>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Infant – Young Child</td>
<td>Neonate</td>
<td>Adolescent</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>Cholestasis, Diarrhea, steatorrhea FTT, pruritis, Pancreatitis</td>
<td>Rapid cholestatic hepatitis FTT, pruritis (later) Risk of HCC</td>
<td>Cholestasis Portal HTN Mild Pruritis Gallstones</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Bland cholestasis Granular bile on EM</td>
<td>Giant cell hepatitis Amorphous bile on EM</td>
<td>Bile duct proliferation Periportal fibrosis Biliary cirrhosis</td>
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<tr>
<td><strong>Labs</strong></td>
<td>Normal GGT AST/ALT &gt;2x</td>
<td>Normal GGT AST/ALT &gt;5x</td>
<td>Elevated GGT</td>
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<tr>
<td><strong>Treatment</strong></td>
<td>Biliary diversion Liver Transplant</td>
<td>Biliary diversion Liver Transplant</td>
<td>Liver Transplant</td>
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<tr>
<td>Disorder</td>
<td>Gene</td>
<td>Estimated Clinical Sensitivity of JaundiceChip*</td>
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<tr>
<td>α-1 Antitrypsin deficiency</td>
<td>SERPINA1</td>
<td>&gt;99%</td>
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<tr>
<td>Alagille syndrome</td>
<td>JAG1</td>
<td>47%</td>
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<tr>
<td>FIC1 deficiency (PFIC1)</td>
<td>ATP8B1</td>
<td>82%</td>
<td></td>
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<tr>
<td>BSEP deficiency (PFIC2)</td>
<td>ABCB11</td>
<td>82%</td>
<td></td>
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<tr>
<td>MDR3 deficiency (PFIC3)</td>
<td>ABCB4</td>
<td>82%</td>
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</table>
# PN-associated liver disease

## Hepatoxic components
- Copper
- Manganese
- Aluminum
- Lipid emulsion
  - Soy phytosterols
- Sepsis/line infections
  - Short bowel → bacterial translocation
- NPO
  - Bacterial overgrowth
  - Loss of GI hormones

## Management
- Decrease trace elements
- Antioxidants
  - Vit A, Vit E, selenium
- Cycle TPN
- Balanced calories
- ↓ Intralipid ~ 1gm/kg/d
- Omegaven
- Meticulous line care
- Prophylactic ethanol locks
- Enteral feeding
  - Continuous feeding
So Many Others...

- Panhypopituitarism
- Mitochondrial DNA depletion syndromes
  - Acute liver failure + hypotonia, apnea, seizures
  - Hypoglycemia, acidosis, increased lactate (Lactate:Pyruvate >20), Ketosis (B-hydroxybutyrate:acetacetate >2), elevated CK
- Mitochondrial respiratory chain enzyme disorders
  - Alpers, Pearson or Chronic diarrhea-villous atrophy syndrome
- Citrin deficiency (neonatal-onset type II citrullinemia) – UCD/Asian
- ARC syndrome (arhdrogryposis, renal dysfunction, cholestasis)
- Gestational alloimmune liver disease (neonatal hemochromatosis)
- Disorders of lipid metabolism (Wolman, Niemann-Pick, and Gaucher diseases)
- Peroxisomal disorder – Zellweger (elevated VLCFA)
Gestational Alloimmune liver disease (neonatal hemochromatosis)

• “Neonatal iron storage disease”
• Hepatic and extrahepatic iron accumulation.
• Iron deposition is a consequence, rather than a cause, of the liver injury.
• Onset is intrauterine, and newborns present with signs of severe liver failure, including coagulopathy, ascites, and hypoalbuminemia.
• Both conjugated and unconjugated.
• Demonstration of extrahepatic iron required for the diagnosis.
• Maternal alloimmune injury (analogous to erythroblastosis fetalis)
• Transplacental passage of specific reactive IgG that activates fetal complement cascade to produce a membrane attack complex and fetal liver injury.
• Rate of recurrence of GALD in pregnancies subsequent to the index case is close to 90 percent.
“Iron is seen within residual hepatocytes, the exocrine pancreas, myocardium and salivary glands”
Treatment

• The combination of exchange transfusion and IVIG is the current treatment of choice.
• Liver transplantation remains an option for infants who do not respond to IVIG treatment.
• Outcomes for infants who do not receive exchange transfusion or IVIG are poor, with approximately 10 percent survival without liver transplantation.
• For pregnant women with a previous pregnancy that resulted in an infant with GALD, gestational therapy (prenatal treatment) with high dose intravenous immunoglobulin (IVIG) dramatically reduces the risk for recurrence of disease. (1 g/kg body weight/week beginning in week 18 of the pregnancy.)
Management of Cholestasis

1. Nutritional support.
3. Treatment of pruritus.
• Nutritional support
  – Supplement calories with medium chain triglycerides (MCT)
  – Treatment and/or prophylaxis for fat-soluble vitamin deficiencies (vitamins A, D, E, and K).
  – Supplemental Ca/P when bone disease is present.
  – Prophylaxis for zinc deficiency.
Management

• **Fat malabsorption**
  - 125-150% RDA
  - High MCT concentration
    • Pregestimil (55%) or Elecare (33%)
  - Vitamin ADEK supplementation
    • Vitamin A 5-25,000 IU/day
    • Vit E 15-25 IU/kg
    • Vit D 4000-8000 IU/day
    • Vit K < 2 years 2.5mg, 2-5 years 5mg, > 5 years 10mg
Treatment

- Management of Cholestasis/Pruritus:
  1. Cholestyramine 250-500 mg/kg/day
  2. Phenobarbital 3-10 mg/kg/day
  3. Ursodeoxycholic acid 10-30 mg/kg/day
  4. Rifampin 10 mg/kg/day
  5. Naloxone/Naltrexone 50 mg daily
TREATMENT

• Management of portal hypertension
• GI Bleeding/ Varices
• - Banding/Sclerotherapy/Beta Blockers
• Ascites
  • Sodium restriction ?
  • Diuretics: spironolactone, furosemide
  • Albumin
How can we improve the time of the initial evaluation?
What is new out there

“Four out of five adults in the US ages 18 to 35—the age of young parents—have a smartphone, and that’s independent of income level”
The idea is not for BiliCam to replace the blood test, but to help parents know if they should take the next step.
QUESTIONS ?