Jaundice and Cholestasis

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Today’s Goal

• A brief review of the normal metabolism of bilirubin.

• The pathophysiological approach to the patient with hyperbilirubinemia and cholestasis.
• Jaundice means increased serum bilirubin with a subsequent yellowish tinge of the skin and sclera.

• Cholestasis is defined as failure of normal amounts of bile to reach the duodenum. It may cause jaundice, not all jaundice is cholestatic.
Pre-Hepatic
↑ Unconjugated Bilirubin

Hepatic
↑ Conjugated Bilirubin

Cholestatic
Bile unable to reach the duodenum
↑ Conjugated Bilirubin
Pre-hepatic Jaundice
(Unconjugated Hyperbilirubinemia)

- Less apparent
- No itching
- Normal color urine
- ↑ Unconjugated bilirubin
- Normal AST and ALT
- ↑ LDH, reticulocytes
- ↓ Haptoglobin
- Fragmented RBCs

- Hemolysis
- Intra or extravascular
- ↓ Bilirubin uptake
- Shunts, CHF
- Gilbert’s syndrome
- ↓ Bilirubin conjugation
- Crigler-Najjar I & II
Hepatic Jaundice
(Conjugated and Unconjugated Hyperbilirubinemia)

- Apparent jaundice
- ↑ CB and UB
- Dark urine
- ↑ ALT & AST
- Signs and symptoms of liver disease

↓ Excretion
- Dubin-Johnson
- Rotor

Hepatocellular injury
- Hepatitis
- Cirrhosis
Hepatic Jaundice
(Conjugated and Unconjugated Hyperbilirubinemia)

↓ Excretion
• Dubin-Johnson
• Rotor

Hepatocellular injury
• Hepatitis (viral, ETOH, autoimmune)
• Wilson Disease
• Drugs
• Sepsis
• Postoperative jaundice
Cholestatic Jaundice

- Pruritus
- ↑ Bili, alk phos, AST, ALT, cholesterol, bile acids
- Steatorrhea
- Vit. A, D, E, K, malabsorption

Chole = bile
Stasis = stop

- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
- CBD stone
- Neoplasia
- Strictures
- HIV
- PFIC I, II, III
- Parasites
- Systemic
- Medications
- TPN
Cholestasis

Intrahepatic

- Alteration of the patterns of the secretion of bile by the hepatocytes
- Obstruction of the intrahepatic bile ducts

Extrahepatic

- Obstruction of the extrahepatic bile ducts
# Hepatocellular Cholestasis

## Genetic
- $\alpha_1$-antitrypsin deficiency
- Benign recurrent intrahepatic cholestasis
- Byler syndrome
- Cholestasis of pregnancy
- Abnormal bile acid synthesis
- Porphyrias

## Acquired
- Medications
- Cholestatic hepatitis
- Bacterial infections
- TPN
- Paraneoplastic cholestasis
- Postoperative cholestasis
- Miscellaneous
Hepatocellular Cholestasis

Normal HIDA scan
Obstruction of Intrahepatic Bile Ducts

• Primary biliary cholangitis

• Space occupying lesions
  Primary or metastatic liver cancer, lymphoma, amyloidosis

• Vanishing bile duct syndrome
  Allograft rejection, GVHD, Alagille’s syndrome, Idiopathic adult ductopenia, PSC, Hodgkin’s disease, Augmentin

• Cystic fibrosis
Obstruction of Extrahepatic Bile Ducts

- CBD stone
- Pancreatic CA
- Ampullary CA
- Cholangiocarcinoma
- Benign strictures
- Parasites
- PSC
- HIV cholangiopathy
- Lymphoma
- Choledocal cyst
- Biliary atresia
Signs and Symptoms

- Jaundice, dark urine, pale stool
Pruritus

• Generalized, constant or intermittent, exacerbated at night or during warm weather

• Distressing symptom, has lead to suicide

• Pathogenesis controversial
Pruritus

Bile Acids Theory

• ↑Bile acids in skin and blood

• Bile acid-binding resin is effective
Pruritus

Opioid Receptors Theory

- Opiates induce facial scratching in animals
- Endogenous opioids accumulate in cholestasis
- Plasma extracts induce facial scratching in monkeys
- Opioid antagonists relieve pruritus
Steatorrhea

↓ Bile acid concentration in the intestine

↓ Impaired micelle formation

↓ Inadequate fat solubilization

↓ Malabsorption of dietary fats
Vitamin Deficiencies

Malabsorption of dietary fats

↓

Fat soluble vitamin malabsorption

Vitamin A $\rightarrow$ night blindness
Vitamin D $\rightarrow$ bone disease
Vitamin E $\rightarrow$ cerebellar ataxia, peripheral neuropathy, retinal degeneration (in children)
Vitamin K $\rightarrow$ Coagulopathy
Xantomas

- Due to hypercholesterolemia
- Resolve after relieving the obstruction
Hepatic Osteodystrophy

- Osteopenia and osteoporosis
- Multifactorial: Vitamin D, calcitonin, hormonal factors, immobility, reduced muscle mass
- Prevalence: 30%-50%
- Fractures: 7%-10%
- Improves after OLT
Biliary Cirrhosis

- From longstanding obstruction
- Complications of portal hypertension are very common
- Hepatocellular carcinoma is rare
Laboratory Tests

• Hyperbilirubinemia
• ↑ Alkaline phosphatase
• ↑ 5’nucleotidase
• ↑ ALT and AST
• ↑ Bile acids
• ↑ Cholesterol
• ↑ Copper
Diagnostic Approach

• Careful history and physical examination

• Laboratory tests (LFTs, AMA, pANCA, CA 19-9)

• Imaging: US, CT, MRCP/ERCP/PTC

• Liver biopsy
# Management

## Pruritus

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Proposed mechanism of action</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>4–16 g</td>
<td>Binds bile acids and ? other anions</td>
<td>May increase fat malabsorption.</td>
</tr>
<tr>
<td>Ursodiol</td>
<td>13–15 mg/kg</td>
<td>Enrichment of bile salt pool with ursodiol</td>
<td>With cholestyramine, give the two drugs at least 8 hr apart</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>50–100 mg</td>
<td>Sedation</td>
<td>Adjunct, especially for nocturnal pruritus</td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>600 mg</td>
<td>Microsomal enzyme induction</td>
<td>Monitor liver enzymes and blood cell count</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>2–5 mg/kg</td>
<td>Microsomal enzyme induction</td>
<td>Monitor blood levels</td>
</tr>
<tr>
<td><strong>Experimental</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-s-cystinosyl methionine</td>
<td>1,500 mg</td>
<td>? Transmethylation and transsulfuration in hepatocytes</td>
<td>Conflicting clinical results</td>
</tr>
<tr>
<td>Opiate antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>20 mg</td>
<td>Block opiate receptors</td>
<td>Parenteral administration</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>80 mg</td>
<td>Block opiate receptors</td>
<td>Not approved</td>
</tr>
<tr>
<td>Propacetamolen</td>
<td>up to 15 mg</td>
<td>Block afferent spinal signals</td>
<td>Parenteral administration</td>
</tr>
<tr>
<td>Oxcodone</td>
<td>up to 16 mg</td>
<td>Block serotonin 5-HT3 receptors</td>
<td>Anecdotal</td>
</tr>
</tbody>
</table>

Management

Pruritus

- Plasmapheresis/hemoperfusion → Transiently effective

- Phototherapy → Benefit in anecdotal reports

- OLT → Pruritus associated with chronic liver disease, refractory and impacting on quality of life.
Management

Fat and Vitamin Malabsorption

- Adequate caloric intake
- 30-40 grams of fat a day
- Medium-chain triglycerides
- Calcium supplements
- Parenteral vitamin K
- Document and replace vitamins A, D and E
Management

Bone Disease

- Bone densitometry
- Correct vitamin D deficiency
- Calcium supplements
- Biphosphonates → Alendronate
- Calcitonin and fluoride → experimental
- HRT?????
- Prevention through physical exercise, avoid steroids
Management

Extrahepatic Biliary Obstruction

• Relieve the obstruction (ERCP, PTC, surgery)

• Treat the underlying condition
Isolated ↑ bilirubin

Indirect
- Hemolysis
- Medications
- Inherited diseases

Direct
- Dubin Johnson
- Rotor Syndrome
Bilirubin with ↑LFTs

↑↑ ALT AST

Viral serologies
ANA, SMA
Tox screen
Ceruloplasmin
Liver biopsy?

↑↑ Alk phos

Non dilated
Liver bx

Dilated ducts (US)

CT/MRCP
ERCP
Cholestatic vs Hepatocellular

If $R > 5 = \text{Hepatocellular}$
• Suggested reading:

• Harrison’s Principles of Internal Medicine
  Chapter 45: Jaundice

• Sherlock Sheila. Diseases of the Liver and Biliary System