Evaluation and Management of the Patient with Painless Jaundice

Sean W.P. Koppe, MD
Northwestern University Feinberg School of Medicine
8/11/12
Bilirubin

- ~ 80% bilirubin production from hemoglobin breakdown (unconjugated bilirubin)
- Unconjugated bilirubin mostly bound to albumin and then taken up into hepatocytes in concentration dependent fashion (facilitated diffusion)
- Within hepatocytes, bilirubin conjugated (made water soluble) and excreted into bile ducts against concentration gradient (active transport)
- Too much within hepatocytes can prevent more from coming in
Bilirubin Elevation

Non-Liver issue
- Increased bilirubin production
  1. Hemolysis
  2. Hematoma absorption

Liver related issue
- Impaired uptake/conjugation/secretion
  1. Hereditary
     - Gilbert’s (common)
     - Crigler-Najjar II (very rare)
  2. Liver dysfunction
     - Liver damage/disease
     - Drug effect

Bile duct issue
- Common duct obstruction
  - Stones
  - Cancer
  - Stricture
Unconjugated Hyperbilirubinemia

Direct bilirubin < 20% of Total bilirubin

- Hemolysis
  - Rarely will give bilirubin >5
  - Should generally be clinically evident (i.e. dropping hemoglobin)
  - Peripheral smear, Coombs test, haptoglobin, LDH, AST
Unconjugated Hyperbilirubinemia
Direct bilirubin < 20% of Total bilirubin

- Gilbert’s
  - Common “disorder”
    - ~ 10% certain ethnicities homozygous for mutations
    - ~ 5% will actually manifest elevated bilirubin
  - Typically, Total bilirubin ~ 3-5 mg/dL range
  - Chronic, recurrent finding
    - Fasting, illness, stress can exacerbate
  - Bilirubin conjugated via UDP-Glucuronosyltransferase (UGT1A1)
    - Gene testing for UGT1A1 available (~ $300-400)
Initial Evaluation

- **History**
  - “Sick” or healthy (inpatient ICU/sepsis?)
  - Old or young
  - Medications (antibiotics, supplements, herbals?)
  - Alcohol
  - Discomfort, nausea, fevers?
  - Recurring problem or new finding

- **Exam**
  - Evidence for underlying liver disease?
    - Angiomata, palmar erythema, ascites
Initial Evaluation

- Labs (initial)
  - Other liver tests elevated?
    - Direct Bilirubin < 20% of Total -- unconjugated
    - Isolated bilirubin may point to hemolysis, Gilbert’s
    - Bilirubin/Alkaline phosphatase >> ALT/AST
      - Cholestatic liver disorder or Drug reaction
      - Obstructed bile ducts
    - Mixed liver test abnormalities or high ALT/AST
      - Hepatocellular liver disorder or drug reaction
    - INR corrects with vitamin K?
      - Yes, supports biliary obstruction
      - No, you have a sick liver
Initial Evaluation

- Imaging
  - U/S initial evaluation unless malignancy suspected (weight loss, older age?)
  - CT vs. MRCP?
- Additional labs (if no evidence for obstructive process)
  - Viral hepatitis serologies
  - ANA, smooth muscle, quantitative immunoglobulins, AMA
  - Work up for other causes of liver disease?
    - Wilson’s, Alpha-1-antitrypsin, hemochromatosis
Evaluation

- ERCP vs. liver biopsy vs. observation
  - Fevers, RUQ pain, obstructive features on imaging then likely ERCP
  - If drug toxicity suspected and INR normal could consider observing once medication discontinued
    - Elevated INR or failure of liver tests to start improving generally prompts liver biopsy
Case 1

- 34 year old male with no medical problems presents with jaundice. Feels otherwise well. Active, no weight loss. (+) pruritus
  - Medications: none
  - Social History: Married, drinks heavy on the weekends but not much during the week.
  - Exam: Vitals stable, healthy appearing, muscular build, no angiomata, no ascites, no edema
  - Total Bilirubin 28.4 mg/dL, Direct Bilirubin 18.1
  - ALT 66, AST 100, Alkaline phosphatase 340, albumin 3.1 mg/dL
  - INR 1.3
Why itch?

Case 1

- Differential
  - Alcohol?
    - Heavy on weekends?
    - AST:ALT 2:1?
  - Herbals, etc?
    - No medications?
  - Viral hepatitis?
Case 1

- Acute hepatitis panel (-) [no Hep A/B/C]
- RUQ U/S: mild hepatomegaly, normal echotexture, normal spleen, no biliary dilation
  - Normal echotexture (no obvious fat)
  - Normal spleen (no obvious portal hypertension)
  - No biliary dilation, should I get MRCP or ERCP?
- Vitamin K 10 mg x 3 (oral or SQ?) ➔ INR 1.0
- Alkaline phosphatase > 300? Only drinks heavy on weekends?
- Looks healthy…..works out a lot…..anabolic steroids
Case 2

- 62 year old male presents to his PCP with yellow eyes. No abdominal pain. No fevers. (+)fatigue for 1 week, lost ~ 5 lbs over past week
  - Medical History: HTN, Hyperlipidemia
  - Medications: Amlodipine (3 years), Simvastatin (5 years), no herbals/supplements
  - Social History: 1-3 drinks per night
  - Exam: afebrile, no angiomata, no palmar erythema
Case 2

- **Labs:**
  - Total Bilirubin 21.4, Direct Bilirubin 16.3, Alkaline phosphatase 204, ALT 640, AST 410
  - INR 1.9, Albumin 2.9, Creatinine 1.4, Platelet 230
  - Viral hepatitis Serologies (-)
  - RUQ U/S: normal appearing liver and spleen. No biliary, dilation, trace ascites

- **Wife arrives…..**
  “Do you think it is from that tylenol? He had a dental abscess 3 weeks ago and was taking some pain pills”
  - Taking 2-4 pills hydrocodone/acetaminophen per day x 5 days
  - Finished amoxicillin/clavulanate ~ 10 days ago
## Drug Induced Liver Injury

<table>
<thead>
<tr>
<th>300 Subjects with Drug Induced Liver Injury</th>
<th># Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/Clavulanate</td>
<td>23</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>13</td>
</tr>
<tr>
<td>INH</td>
<td>13</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>9</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>6</td>
</tr>
<tr>
<td>Valproate</td>
<td>6</td>
</tr>
<tr>
<td>Interferon beta</td>
<td>6</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>5</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>5</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>5</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>5</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>5</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>4</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>4</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>4</td>
</tr>
<tr>
<td>Atomoxetine, azithromycin, oxacillin, atorvastatin, etanercept, mercaptopurine, minocycline</td>
<td>3</td>
</tr>
<tr>
<td>Allopurinol, amiodarone, amoxicillin, antithymocyte globulin, doxycycline, nevirapine, ranitidine, celecoxib, desflurane, buproprion, fluoxetine, fluconazole</td>
<td>2</td>
</tr>
</tbody>
</table>

Case 3

- 68 year old female with dementia admitted from nursing facility with jaundice. Poor historian but does not appear in pain. Has lost ~ 10 lbs in past month. Not eating as much lately per staff.
  - Medical history: Dementia, HTN, CAD
  - Medications: Donepezil, Amlodipine, Aspirin
  - Exam: afebrile, no angiomata, no abdominal tenderness
Case 3

- Labs:
  - Bilirubin 6.8, Direct Bilirubin 4.1, Alkaline phosphatase 350, ALT 82, AST 74
  - INR 1.4, Albumin 3.4, Creatinine 1.1
  - RUQ U/S: cholelithiasis, normal appearing liver and spleen, mild common bile duct dilation
  - CA 19-9 ~ 3 times upper limit normal
  - Vitamin K; INR normalizes
Case 3

- MRI/MRCP: some motion artifact, normal appearing liver and spleen, mild intra and extra hepatic biliary dilation, filling defect in distal common bile duct. 0.6 cm pancreatic cyst, mild lymphadenopathy

  - Cancer?… CA 19-9 high, weight loss

- ERCP: choledocholithiasis. Sphincterotomy with sweep of stone and sludge from distal duct

- Liver tests normalize, weight improves, CA 19-9 normalizes
Take Home Points

- Ask...and ask again about pills
  - How long on medications?
  - Any medications within past month?
  - Supplements/Herbals?
- Alcohol? (does the pattern fit?)
- Young vs. Old, “sick” vs. well
- Any evidence for chronic liver disease
  - Angiomata on exam
  - Splenomegaly, low platelets, past liver problems?
Take Home Points

- Trial vitamin K (SQ)
  - INR better with vitamin K? (obstruction or malnourished)
  - INR no better or worsening…… worry
- Fever?
- Any hint of biliary problem – ERCP (or EUS)
- Bilirubin
  - “It’s like gas prices. It goes up real fast but takes a long time to come down” (Edward S. – patient of mine)