CrackCast Episode 28 – Jaundice

Episode overview:

1) Describe heme metabolism
2) List common pre-hepatic/hepatic/post-hepatic causes of jaundice

Wisecracks:

1) What are clinical signs of liver disease?
2) What laboratory tests can be useful in a jaundiced patient?
3) List the triad of acute hepatic failure
4) List and describe 6 critical causes of jaundice
5) What are 3 causes of jaundice in pregnancy?

1) Describe heme metabolism

Jaundice = elevated serum bilirubin

Normal bilirubin metabolism:

- heme products (red blood cells) breaking down → bilirubin
  - very small portion of bilirubin comes from myoglobin (muscles) or maturing erythroid cells
- heme products are oxidied into biliverdin → bilirubin
- bilirubin binds to albumin, then is glucuronidated into the conjugated form in hepatocytes
- conjugated bilirubin is excreted into the biliary system and emptied in the gut
- colonic bacteria metabolize most conjugated bilirubin to urobilogen and stercobilin
  - stercobilin is excreted into the stool
  - urobilinogen is reabsorbed and is excreted into the urine
- remaining conjugated bilirubin is de-conjugated and re-enters the portal circulation to be taken up again by hepatocytes
  - this completes the entero-hepatic circulation of bilirubin

Conjugated bilirubin = direct bilirubin

Unconjugated bilirubin = indirect bilirubin (can cross blood brain barrier) – does not bind albumin

Total bilirubin = direct + indirect
Abnormal Bilirubin Metabolism

Jaundice - usually not obvious until >25 mg/L

- seen in tissues with high albumin concentrations
  - skin, eyes,
  - absent in tears, saliva

Three pathologic processes leading to elevated bilirubin:

1. Overproduction - high levels of heme production
   a. hemolysis
   b. hypoalbuminemia
   c. acidemia
   d. drugs (bind competitively to albumin )
2. Failure of conjugation - hepatocytes unable to take up, conjugate and excrete bilirubin
   a. hepatocellular dysfunction
3. Decreased clearance
   a. biliary excretion problem

- unconjugated levels of bilirubin that is not bound to albumin is able to cross the blood-brain barrier and leads to adverse neurologic effects
  - developmental abnormalities, encephalopathy, death
  - is exacerbated by any condition that leads to increased heme production or a process that competitively decreases albumin/binds to albumin (e.g. drugs or cirrhosis)
- conjugated bilirubin in contrast is non-toxic

2) List common pre-hepatic/hepatic/post-hepatic causes of jaundice

Three pathologic processes leading to elevated bilirubin:

1. Overproduction - high levels of heme production
   a. hemolysis
   b. hypoalbuminemia
   c. acidemia
   d. drugs (bind competitively to albumin )

2. Failure of conjugation - hepatocytes unable to take up, conjugate and excrete bilirubin
   a. hepatocellular dysfunction
      i. Toxins
         1. Tylenol, ETOH
      ii. Vascular:
         2. Budd-Chiari
      iii. Inflammatory/infectious
3. Virus - hepatitis, autoimmune
   iv. Pregnancy related: HELLP / acute fatty liver

3. Decreased clearance -
   a. biliary excretion problem
      i. Gallstone disease: CBD stone, ascending cholangitis

Wisecracks:

1) What are clinical signs of liver disease?

Abnormalities in bilirubin metabolism:
   - Jaundice - usually not obvious until >25 mg/L
     - seen in tissues with high albumin concentrations:
       - skin, eyes,
       - absent in tears, saliva

Symptoms:
   - May be asymptomatic or have:
     - pruritus, malaise, nausea
   - Jaundice with abdominal pain = biliary obstruction or hepatic inflammation
   - Jaundice WITHOUT abdominal pain = pancreatic neoplasm
   - Ask about fit of clothing (ascites) or personality changes

Signs:
   - Skin
     - Sublingual or conjunctival jaundice
   - Signs of liver disease:
     - angiomomas, excoriations, caput medusae, ascites, liver borders and texture, splenomegaly, neurologic examination, asterixis
   - Stages of encephalopathy – see table in Rosen’s

2) What laboratory tests can be useful in a jaundiced patient?

   - GGT = confirms a hepatic source of ALP if ALP is up
     - ALP can also be elevated from bone or placental sources
   - An elevated reticulocyte count can suggest hemolysis
   - Acetaminophen level*** (AST is first to rise)
   - Glucose level
   - Ammonia level - is of limited use and does NOT correlate with degrees of hepatic encephalopathy
   - Ascitic fluid - for analysis
   - Blood cultures - for fever
3) List the triad of acute hepatic failure

- Jaundice
- Encephalopathy
- Coagulopathy (INR > 1.5)

4) List and describe 6 critical causes of jaundice

1) Hepatic
   a) Fulminant hepatic failure
   b) Toxin
   c) Virus
   d) Alcohol
   e) Ischemic insult
   f) Reye’s syndrome

2) Biliary
   a) Cholangitis (ascending infectious)

3) Systemic
   a) Sepsis
   b) Heatstroke

4) Cardiovascular
   a) Obstructing AAA
   b) Budd-Chiari syndrome
   c) Severe congestive heart failure

5) Heme-oncologic
   a) Transfusion reaction (hemolysis)

6) Reproductive
   a) Pre-eclampsia or HELLP syndrome
   b) Acute fatty liver of pregnancy

Empirical management

- Depends on the cause of jaundice and problem:
  - **Bleeding** (in the context of coagulopathy)
    - Transfuse PRBC’s and FFP
  - **Spontaneous bacterial peritonitis**
    - >250 PMN’s per cm3 of ascitic fluid
      - IV ceftriaxone
  - **Acetaminophen toxicity:**
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- N-acetylcysteine
  - **Ascending cholangitis**
    - Antibiotics
    - ***need acute biliary drainage in 24-48 hrs because most antibiotics are excreted***
  - **Choledocolithiasis or strictures**
    - Need for ERCP
    - ***neither CT or U/S is 100% sensitive for choledocolithiasis, but a dilated CBD highly suggests obstruction***
  - **Immune-mediated hemolytic anemia:**
    - Transfuse only if unable to oxygenate and in discussion with hematology
    - Remove any potential offending drugs in the case of G6PD

5) **What are 3 causes of jaundice in pregnancy?**

- **Pregnancy and jaundice = pathology**
  - Potential causes:
  - 1) hyperemesis gravidarum
    - In the first trimester - ?poor nutrition and impaired bilirubin excretion
    - Can have VERY high transaminases (20x ULN)
    - Trxt: fluids and antiemetics and admission if biochemically deranged
  - 2) acute fatty liver of pregnancy
    - In the 3rd trimester
    - Due to microvascular fat accumulation in the liver
    - S+s:
      - Nausea, vomiting, anorexia, jaundice
    - May progress to fulminant hepatic failure
    - Trxt: delivery, patients may need liver transplant!
  - 3) intrahepatic cholestasis of pregnancy
    - Idiopathic cause of jaundice in 2-3rd trimester
    - S+s:
      - Pruritis - trunk, extremities, palms, soles.
      - Acholic stools and dark urine
      - Increased risk of preterm labour or early fetal demise intra-uterine.
    - Trxt:
      - Ursodiol, cholestyramine
      - Vitamin K