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:
    - angiomas, 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

- INR , PTT
- AST, ALT

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:**

        - 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 choledocolithasis, 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