VET 433B GI Block: Icterus

Clinical history of an icteric patient

- Vague clinical signs
  - Weight loss
  - Inappetence
  - Vomiting/Diarrhea
- Can be acute or chronic
- Severe anemia may cause collapse
  - Pre-hepatic (hemolytic anemia etc.)
- PU/PD if there is liver dysfunction
  - Hepatic
- Acholic feces
  - Post-hepatic
  - Uncommon, only seen with a complete biliary obstruction
- Pigmenturia
- People with icterus have described pruritus

Physical exam finding of an icteric patient

- Typically quite, often dehydrate
- If anemic, pale MM may be present
- Icterus is detectible in tissues if the serum bilirubin is > 2mg/dL
  - Sclera *most noticeable
  - Third eyelid
  - Pinnae
  - Mucous membranes (gingiva, soft palate, genitalia)
  - Non-haired skin
- +/- abdominal pain, hepatomegaly, or effusion
- Bleeding/bruising if liver failure is present

Bilirubin Metabolism

1. Heme breakdown in splenic macrophages
   a. Heme oxygenase converts heme into biliverdin releasing Fe^{2+} and CO
   b. Biliverdin reductase converts biliverdin into bilirubin
      i. Overall result is unconjugated bilirubin
2. Transport to the liver

a. Unconjugated bilirubin bound to albumin travel through the plasma and are taken up by hepatocytes in the liver
    i. Once inside the liver cells, bilirubin dissociates from albumin and is processed for excretion
3. Conjugation
    a. The enzyme glucuronyl-bilirubin transferase attached a glucuronic acid molecule to bilirubin forming bilirubin diglucuronide
        i. Overall result is conjugated bilirubin
4. Excreting into bile
    a. Conjugated bilirubin is actively transported via hepatic and cystic ducts which merge to form the common bile duct which leads to the duodenum
5. Intestinal conversion
    a. Intestinal bacteria metabolize conjugated bilirubin into two products
        i. Urobilinogen
            1. Some is reabsorbed and returned to the liver via enterohepatic circulation
            2. Some is excreted by kidneys as urobilin (reason urine is yellow)
        ii. Stercobilin
            1. Gives feces its brown color

Mechanisms of Icterus

Pre-hepatic	**Hepatic**	**Post-hepatic**
Pathologic hemolysis (as opposed to low-grade physiologic removal/hemolysis of senescent RBCs) Hemolytic Anemia	Decreased liver function potentially from a decrease in functional liver mass leading to defective bilirubin handling in hepatocytes Could also be due to functional cholestasis from endotoxins and/or inflammatory cytokines	Extra-hepatic bile duct obstruction or a rupture which could lead to bile peritonitis
Mainly unconjugated bilirubin	Mix of unconjugated and conjugated bilirubin Conjugated > Unconjugated	Mainly conjugated bilirubin
IMHA (intravascular or extravascular) Heinz body anemia (oxidative damage) Transfusion reaction Infectious (Mycoplasma, Babesia) Microangiopathic (DIC, HAS, HW dz) Severe hypophosphatemia (low ATP)	Hepatic lipidosis -C Cholangitis -C FIP -C Neoplasia (lymphoma, MCT) -C&D Acute or chronic toxin -C&D Bacteremia (functional cholestasis of sepsis) -C&D Cholangiohepatitis - D>C Chronic hepatitis - D Copper-associated hepatitis -D	**Obstruction** Severe pancreatitis Gallbladder mucocele Cholecystitis Neoplasia (CBD, pancreas, duodenum) Cholelith Choledocholith Stricture **Rupture**

Snake envenomation Congenital enzyme deficiency (PK, PFK)	Cirrhosis – usually end-stage of another dz process, not a primary diagnosis- D	GB or bile ducts
CBC Regenerative Anemia (3-5 days) Normal total solids RBC morphology changes (Heinz bodies, spherocytes, schistocytes) Icteric +/- hemolyzed plasma Chemistry Hyperbilirubinemia Minimal other changes, possible mild increase in ALT/AST due to anemia-induced hypoxia leading to a reactive hepatopathy	**CBC** Possible microcytosis or mild NNN anemia of inflammation Possible leukogram abnormalities Rarely, mild thrombocytopenia with severe hepatic dysfunction due to decreased TPO Icteric +/- hemolyzed plasma Chemistry Hyperbilirubinemia Increased liver enzymes (rarely not in cats) May also see a decrease in liver function enzymes such as albumin, BUN, cholesterol and glucose	**CBC** Possible microcytosis or mild NNN anemia of inflammation Possible leukogram abnormalities Rarely, mild thrombocytopenia with severe hepatic dysfunction due to decreased TPO Icteric +/- hemolyzed plasma Chemistry Hyperbilirubinemia Often see a significant increase in cholesterol and liver enzymes ALP/GGT > ALT/AST
Treat underlying cause of hemolysis +/- pRBC transfusion	Treat the underlying hepatopathy	Often surgical (mature GB mucoceles, sever cholecystitis, GB rupture, mass severe pancreatitis) Often medical (mild-moderate pancreatitis, mild cholecystitis, immature GB mucocele)

Bile Physiology / Composition

Bile Composition

- Water, bile acids, bile salts, bilirubin, cholesterol, fatty acids, lecithin, electrolytes, and bicarbonate
    - Bile is continually produced, stored and concentrated in the gall bladder
    - Release is stimulated by the hormone CCK just like the pancreatic enzymes
- Bile acids: Steroid acids made by the liver from cholesterol
- Bile salts: salts of the bile acids (Na^+/K^+)

Main Bile Functions

1. Emulsification and digestion of fat (bile salts/acids)
    a. Including the absorption of fat-soluble vitamins
2. Excretion of waste products (bilirubin, cholesterol, drugs, toxins)
3. Bactericidal, alters GI pH

When can you detect icterus

- Normal serum bilirubin < 0.2 mg/dL
- Plasma/serum: bilirubin > ~ 0.5 mg/dL
- Tissues: bilirubin > ~ 2 mg/dL

Urinalysis Findings

- Decreased USG with liver dysfunction and low BUN
- Increased USG with dehydration and normal liver function
- Bilirubinuria
    - Always pathologic in cats
        - Higher renal threshold for bilirubin (9x dogs)
    - Can be physiologic in dogs
        - If noted in an ill dog, look at the serum bilirubin
- Ammonium biurate crystals if PSS
    - Rarely with sever liver dysfunction without shunts

Ultrasound Findings

- *Most important diagnostic to differentiate hepatic vs post-hepatic
- Hepatomegaly with acute liver disease and neoplasia
- Microhepatica with chronic liver disease, especially in dogs
- +/- evidence of pancreatitis, mucocele, masses, choleliths, and duct strictures
- EHBDO: Distention of GB and biliary ducts
    - Anorexia alone can lead to GB distention
- +/- Evidence of bile peritonitis
    - Also abdominocentesis for fluid analysis

Additional Diagnostics

- Plasma ammonia levels to assess for hepatic encephalopathy
- Coagulation panel to further assess liver function and pre-biopsy staging
- Liver FNA/Biopsy if there is hepatic hyperbilirubinemia
- Thoracic radiographs if neoplasia is a differential
- CT scan to further assess the cause of EHBDO or acquired PSS, or or surgery planning
    - Congenital PSS usually have normal bilirubin
- Serum bile acids are generally not necessary with icterus because you should already know that there is dysfunction or biliary obstruction
    - BAs are more indicated with normal bilirubin

- One exception is with IMHA (pre-hepatic) there should be normal bile acids

Kernicterus (bilirubin encephalopathy)

- Refers to neurologic signs that arise from severe hyperbilirubinemia >35mg/dL
- Typically unconjugated bilirubin since it is more lipid soluble
- Leads to toxicity of the gray matter in the brain
- Uncommon!