

Jaundice

Anatomy

The complexity of the biliary tree can be broken down into much simpler segments. The intrahepatic ducts converge to form the right and left hepatic ducts which exit the liver and join to become the common hepatic duct. The cystic duct branches off the common hepatic duct and drains into the gallbladder. The common hepatic duct continues towards the duodenum, but it is called the common bile duct (CBD) after the take-off of the cystic duct. The CBD then joins the pancreatic duct prior to draining into the second portion of the duodenum.

Obstruction, inflammation, or infection of the biliary tract changes the baseline anatomy and size of the various ducts. The normal calibers of the CBD and pancreatic duct are < 8mm and < 4mm, respectively. The gallbladder wall is typically < 4mm in thickness.

Rokitansky-Aschoff sinuses are epithelial invaginations in the gallbladder wall that form as a result of increased gallbladder pressures.

Ducts of Luschka are biliary ducts that lie in gallbladder fossa and connect directly between liver and the gallbladder. These can result in bile leak after cholecystectomy.

Pathophysiology

Jaundice is the yellowing of the skin and sclera due to abnormally elevated levels of bilirubin in the blood. It can be characterized into three different categories including pre-hepatic, intra-hepatic, or post-hepatic. Pre-hepatic and intra-hepatic causes are known as medical jaundice, while post-hepatic (or obstructive jaundice) is considered surgical jaundice.

PRE-HEPATIC

In pre-hepatic jaundice, there is **excess production** of bilirubin that overtakes the ability of liver to conjugate the bilirubin and excrete into the gut. This is predominantly **unconjugated hyperbilirubinemia**. The most common cause of pre-hepatic jaundice is hemolytic anemia which causes excess heme breakdown.

INTRA-HEPATIC

Intra-hepatic causes are due to parenchymal liver disease with inability to either conjugate or excrete bilirubin. In this case, the fraction of bilirubin that is elevated varies. Viral hepatitis often has a predominantly unconjugated bilirubinemia. A conjugated hyperbilirubinemia is seen with cholestasis from drugs or primary biliary cholangitis.

POST-HEPATIC

In post-hepatic jaundice or **obstructive jaundice**, there is an impediment to the flow of bile due to a partial or complete obstruction of the extrahepatic biliary passage between the liver and duodenum. Obstruction can occur within the biliary ducts themselves or more distal within the pancreas. This is predominantly a **conjugated hyperbilirubinemia**.

Table 1

	PRE-HEPATIC	INTRA-HEPATIC	POST-HEPATIC
PHYSIOLOGY	Excessive hemolysis leading to increased bilirubin delivered to the liver	Defective conjugation Impaired cellular uptake Abnormal secretion	Mechanical obstruction of bile flow causing impaired excretion
ELEVATED BILIRUBIN	Unconjugated	Conjugated and unconjugated is possible	Conjugated
URINE COLOR	Normal	Dark	Dark
STOOL COLOR	Normal	Normal	Acholic
PRURITUS	No	No	Yes

Obstructive (Surgical) Jaundice

Surgical jaundice is suspected over medical jaundice in the following scenarios:

- History of abdominal pain and fevers
- Painless jaundice with weight loss, pruritus, and clay colored stools
- Conjugated bilirubinemia with elevation of alkaline phosphatase and GGT
- An enlarged gallbladder, abdominal mass, and/or lymph node in left supraclavicular area is considered advanced disease

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Jaundice

Distinguishing surgical jaundice from medical jaundice is just the first step in the diagnosis and treatment. Post-hepatic obstruction can be located in several different areas of the biliary tree and can be due to a variety of benign and malignant pathologies outlined below.

Benign:

- Choledocholithiasis
- Mirizzi syndrome
- Bile duct stricture
 - *Chronic pancreatitis*
 - *Primary sclerosing cholangitis*
- Choledochal cyst

Malignant:

- Pancreatic
 - *Solid*
 - *Cystic*
- Cholangiocarcinoma
 - *Klatskin tumor*
- Ampulla of Vater

Pediatric:

- Biliary atresia

Iatrogenic:

- CBD injury following laparoscopic cholecystectomy
- Ischemic stricture from cautery or hepatic artery injury

Diagnosis of Medical vs Surgical Jaundice

Distinguishing between medical jaundice (pre- and intra-hepatic) and surgical jaundice (post-hepatic or obstructive) can be difficult. It is extremely important to obtain a thorough history and physical to help distinguish the underlying pathophysiology of the jaundice.

HISTORY

The history of present illness should elicit a wide range of possible symptoms associated with jaundice. Obstructive jaundice often produces pruritus, pale stools, and dark colored urine. Abdominal pain along with fevers and jaundice is suggestive of obstruction with an associated infection known as cholangitis. A malignant source of obstruction more often presents with painless jaundice and weight loss.

Intrahepatic cholestasis can be due to intrahepatic sources of jaundice or post-hepatic mechanical obstruction making the diagnosis difficult to make on the history of present illness alone. Therefore, a detailed past medical history and social history are warranted. Risk

factors for gallstones and possible choledocholithiasis are important to obtain. This includes obesity, female gender, and age more than 40 years. Prior intraabdominal pathology should be identified, including a history of inflammatory bowel disease, which can have associated hepatic steatosis, cholelithiasis, or primary sclerosing cholangitis. A history of pancreatitis should be noted as this can lead to biliary strictures. Any iatrogenic interventions such as surgery or endoscopy are critical to obtain.

A social history should include current and past alcohol consumption as well as risk factors for transmission of viral hepatitis such as intravenous drug abuse and tattoos.

PHYSICAL EXAMINATION

A thorough but focused physical exam can also help narrow the possible causes of jaundice. This should include a general, abdominal, and rectal exam. The overall general exam allows the clinician to determine the severity of the illness, and the urgency of intervention and level of care required. Also noted on the general exam is jaundice (or icterus) itself. This is defined as the yellowing of skin and whites of the eye (scleral icterus) that accompanies high levels of bilirubin and is typically seen when the levels are greater than 2-3 mg/DL.

A palpable gallbladder, mass in the abdomen or lymph nodes in the supraclavicular area (Virchow's node) are suggestive of a malignancy causing obstructive jaundice. Stigmata of liver failure or portal hypertension such as caput medusa, spider nevi, and ascites are suggestive of a chronic parenchymal liver disease and an intra-hepatic cause of jaundice. The following terminology is important to know when diagnosing jaundice:

Charcot's triad

- Right upper quadrant pain
- Jaundice
- Fever

Reynold's Pentad

- Right upper quadrant pain
- Jaundice
- Fever
- Hypotension
- Altered mental status

Courvoisier's sign/law

- Enlarged, non-tender, and palpable gallbladder in patients with obstructive jaundice due to tumors of the biliary tree or pancreatic head

Murphy's sign

- Positive if patient experiences RUQ tenderness and stops breathing upon inspiration as the gallbladder moves down in contact with the examiner's hand
- Suggestive of acute cholecystitis

Scleral icterus

- Yellowing of the “white of the eye” due to excessive bilirubin in the bloodstream

Caput medusae

- Distended and engorged superficial epigastric veins which appear to be radiating from the umbilicus across the abdomen due to portal hypertension

Rectal varices

- Dilation of submucosal vessels and backflow in the veins of the rectum as the blood shunts from the portal system to the systemic venous system due to portal hypertension

LABORATORY TESTS

Following history and physical exam, laboratory tests should be the next step in proper diagnosis of jaundice. Obstructive jaundice has hallmark findings on the biochemistry profile. It is primarily a conjugated hyperbilirubinemia with the direct bilirubin > 50% of the total bilirubin. There is also an associated elevation of alkaline phosphatase. Depending on the duration of symptoms and severity of obstruction, coagulation can be altered in addition to renal dysfunction. Leukocytosis is more likely seen in infectious and inflammatory causes of obstruction such as cholangitis or cholecystitis.

IMAGING STUDIES

Ultrasound

Ultrasound is the gold standard imaging study for evaluation of the gallbladder. It is able to identify dilated intrahepatic and proximal extrahepatic bile ducts (including CBD) in addition to gallstones. Unfortunately, ultrasound is not optimal for visualization of the distal extrahepatic biliary tree and pancreas due to overlying gas in the duodenum. Therefore, further imaging needs to be obtained for evaluation of the pancreatic head, pancreatic duct, and distal common bile duct.

Cholangiography

Cholangiography is defined as specific imaging of the biliary tree. This is crucial to visualize the entire biliary system and helps delineate the level and possibly the cause of obstruction. Varying techniques include:

MRCP

- Magnetic resonance cholangiopancreatography
- Utilizes T2-weighted MRI which shows static or slow moving fluids as high signal and surrounding tissue as low signal
- Allows for evaluation of the ducts and surrounding liver parenchyma

ERCP

- Endoscopic retrograde cholangiopancreatography
- Upper endoscopic camera is placed through the mouth down into stomach and subsequently the duodenum
- Cannula is placed through ampulla of Vater
- Contrast is injected and x-rays taken to evaluate patency of the ducts

PTC

- Percutaneous transhepatic cholangiography
- Under ultrasound guidance the intrahepatic biliary tree is punctured utilizing a needle with subsequent guidewire placement (L hepatic duct via subcostal location is most common)
- After catheter placement, contrast can be injected for visualization of the biliary tree
- Interventions can be performed after crossing the obstruction with a guide wire including dilation, biopsy, and stent placement
- If the obstruction cannot be passed, a drain can be left in place for drainage/decompression

**** The following are considered advanced imaging for suspected malignancy:**

Contrast enhanced CT abdomen **

This allows for a global assessment of the abdomen. Attention should be focused towards mass lesions in the liver, biliary tract, and/or pancreas. CT also allows for staging of a malignancy by identifying lymph nodes and metastasis.

Endoscopic ultrasound (EUS) **

EUS is sensitive for detecting small lesions in the head of pancreas and surrounding lymphadenopathy. It also allows for a needle biopsy of the lesion when appropriate.

Management of Obstructive Jaundice

The first step in management of obstructive jaundice is based on the acuity of the disease and clinical status of the patient. Patients with hemodynamic instability, coagulopathy, and/or renal dysfunction need to be quickly resuscitated prior to managing the specific etiology of the obstruction. In the presence of cholangitis, often it is difficult to stabilize the patient until the obstruction is relieved and source control of the infection achieved. The following algorithms should be considered.

RESUSCITATION

Presents with cholangitis

Goal = resuscitation

- 1) Intravenous fluids to correct dehydration and pre-renal failure
- 2) Broad spectrum antibiotics - Gram negative coverage is essential
- 3) Correct coagulopathy, if present
- 4) Upon stabilization, decompress biliary obstruction without surgical intervention (ERCP or PTC as described above)
- 5) Further treatment of obstruction based on etiology

Presents with jaundice in the absence of cholangitis

Goal = diagnosis and management of obstruction

- 1) US and blood work to confirm biliary obstruction
- 2) Advanced imaging to identify site and etiology of obstruction if remains unclear

MANAGEMENT OF SPECIFIC ETIOLOGY

Choledocholithiasis

- 1) ERCP with stone extraction from CBD
- 2) Elective cholecystectomy to prevent recurrence (ideally during same admission)

Benign biliary stricture

- 1) ERCP or PTC with balloon dilatation of the stricture with stent placement
- 2) If fails, surgery with biliary-enteric anastomosis

Pancreatic cancer

- 1) Full staging to determine resectability
 - 95% tumors are unsuitable for surgical resection
 - Contraindications for surgery include distant metastases, encasement of SMA or celiac artery vessels
- 2) Neoadjuvant chemoradiation pending staging
- 3) Pancreatoduodenectomy (Whipple procedure) for resectable cases
- 4) Unresectable cases are treated with palliation including biliary stent placement, chemotherapy, and adequate analgesia

Hilar cholangiocarcinoma

- 1) Full staging to determine resectability
 - Contraindications for surgery
 - o Involvement of both right and left hepatic ducts into the liver
 - o Invasion of portal vein and hepatic artery branches to both lobes of liver
 - o Distant metastases

- 2) Bile duct resection with hepatectomy and hepaticojejunostomy to residual lobe is procedure of choice
- 3) Unresectable cases treated with biliary drainage via stent and palliation

Choledochal cysts

- 1) Types I, II, and IV are typically resected due to risk of malignancy
- 2) Types I and IV are completely resected with Roux-en-Y hepaticojejunostomy
- 3) Type II cysts are resected with simple cyst excision
- 4) Type III cysts are only treated if symptomatic which consists of sphincterotomy or endoscopic resection
- 5) Type V cysts are difficult to manage and can require liver transplantation

Questions

1. The common bile duct is:
 - A. The segment of biliary passage from the confluence of the right and left hepatic ducts to the ampulla of Vater.
 - B. The segment of biliary passage from the right hepatic duct to the cystic duct insertion.
 - C. The segment of the biliary passage from the insertion of the cystic duct to the ampulla of Vater.
 - D. The segment of biliary passage from the junction of the right and left hepatic ducts to the ampulla of Vater.
2. A 35-year-old obese and previously healthy woman presents with first episode of right upper quadrant pain and fever. Which of the following is the most appropriate first imaging modality?
 - A. Percutaneous cholangiography and external biliary decompression
 - B. CT abdomen and pelvis
 - C. Magnetic resonance cholangiopancreatography and stent insertion
 - D. Endoscopic retrograde cholangiography and internal biliary drainage with stent
 - E. Ultrasound
3. In jaundice caused by choledocholithiasis, the following biochemical abnormalities are most likely to be seen:
 - A. Increase in GGT and liver transaminases
 - B. Increase in conjugated bilirubin and alkaline phosphatase
 - C. Increase in liver transaminases and alkaline phosphatase
 - D. Increase in GGT and alkaline phosphatase
 - E. Elevated prothrombin time and GGT

4. A 60-year-old man presents with history of pruritus and acholic stools. He has high fever and tenderness in the upper abdomen. Biochemistry shows direct hyperbilirubinemia and elevated CA 19-9 level. Ultrasound exam shows intrahepatic biliary duct dilatation and dilatation of extrahepatic duct to the region of the pancreas. The patient is resuscitated and started on antibiotics. The next best investigation to provide relief is:
- A. CT abdomen and pelvis
 - B. Percutaneous cholangiography and external biliary decompression
 - C. Magnetic resonance cholangiopancreatography and stent insertion
 - D. Endoscopic retrograde cholangiography and internal biliary drainage with stent
 - E. Surgical exploration and biliary drainage
5. All of the following cytokines are mediators of the initial proinflammatory response to infection and injury EXCEPT:
- A. Interleukin 10
 - B. Tumor necrosis factor α
 - C. Interleukin 1
 - D. Interleukin 6
 - E. Interleukin 8

Answers

1. The common bile duct is:
- C.** *The common bile duct is the portion of the biliary tree where the common hepatic duct joins the cystic duct. The common bile duct reaches from this confluence to the duodenum. Its function is to carry bile from the biliary system to the small intestine.*
2. A 35-year-old obese and previously healthy woman presents with first episode of right upper quadrant pain and fever. Which of the following is the most appropriate first imaging modality?
- E.** *Ultrasound is first line imaging technique for right upper quadrant pathology. It is non-invasive, quick, and cost effective. Ultrasound can identify intra and extrahepatic biliary abnormalities. However, it is less sensitive for the distal biliary tree due to the pancreas and gas in the small bowel.*
3. In jaundice caused by choledocholithiasis, the following biochemical abnormalities are most likely to be seen:
- B.** *Choledocholithiasis causes post-hepatic biliary obstruction. This results in elevated conjugated bilirubin and elevated alkaline phosphatase on laboratory tests.*

4. A 60-year-old man presents with history of pruritus and acholic stools. He has high fever and tenderness in the upper abdomen. Biochemistry shows direct hyper-bilirubinemia and elevated CA 19-9 level. Ultrasound exam shows intrahepatic biliary duct dilatation and dilatation of extrahepatic duct to the region of the pancreas. The patient is resuscitated and started on antibiotics. The next best investigation to provide relief is:

D. This patient likely has a malignant pancreatic head mass given the diffuse biliary tree dilation and elevated CA 19-9. After resuscitation and treatment for cholangitis, invasive measures should be taken to decompress the biliary tree. The appropriate next step is ERCP which allows for internal biliary drainage via stent as well as biopsy brushings to help confirm the diagnosis.

5. All of the following cytokines are mediators of the initial proinflammatory response to infection and injury EXCEPT:

A. Proinflammatory cytokines include TNF- α , IL-1, IL-6, and IL-8. These factors induce fever, inflammation, and tissue injury. With time, the cytokines can cause shock and subsequently death. IL-10 is an anti-inflammatory cytokine.

Problems

For each of the problems, answer the following questions:

- What further data should be obtained from the patient's history that gives clues about etiology?
 - What findings would you look for on physical exam?
 - What is your differential diagnosis?
 - What work-up would you recommend (include laboratory tests and diagnostic interventions)?
 - What therapy or treatment would you recommend?
- 1) A 35-year-old woman presents with onset of acute abdominal pain, fever and high colored urine.
- 2) A 65-year-old man presents with itching, anorexia, weight loss, and yellowish discoloration of eyes.

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