Chapter 4. Extra-Hepatic Cholestasis

4.1 Biliary Imaging

Ultrasound

- Ultrasound should be the first test to investigate a patient with **cholestasis** (lack of bile flow), with or without **jaundice**
- It is used to distinguish between **intra-hepatic cholestasis** (where the bile ducts are NOT dilated) and **extra-hepatic cholestasis** (where the bile ducts are dilated)

  NOTE: Primary sclerosing cholangitis can be an exception to this rule, because the extra-hepatic bile ducts often do not dilate due to fibrosis (scarring) of the bile ducts
- Ultrasound is the most sensitive test for the detection of gallstones within the gallbladder, although visualization of the distal common bile duct and head of the pancreas can be difficult in obese patients or if there is gas in the adjacent bowel

Magnetic Resonance Cholangio Pancreatography (MRCP)

- **MRCP** uses heavily T2 weighted imaging to visualize the biliary tree
- Static or slow moving fluid (bile) will be bright on these images
- It can diagnose common bile duct obstruction due to stones or strictures
- MRI can also look for a mass (differentiate benign and malignant strictures)
- It is **non-invasive**, with no ionizing radiation, but some patients are too claustrophobic for MRI
- It is only diagnostic, so if there is a high likelihood of the need for therapeutic intervention, ERCP is preferred

Endoscopic Ultrasound (EUS)

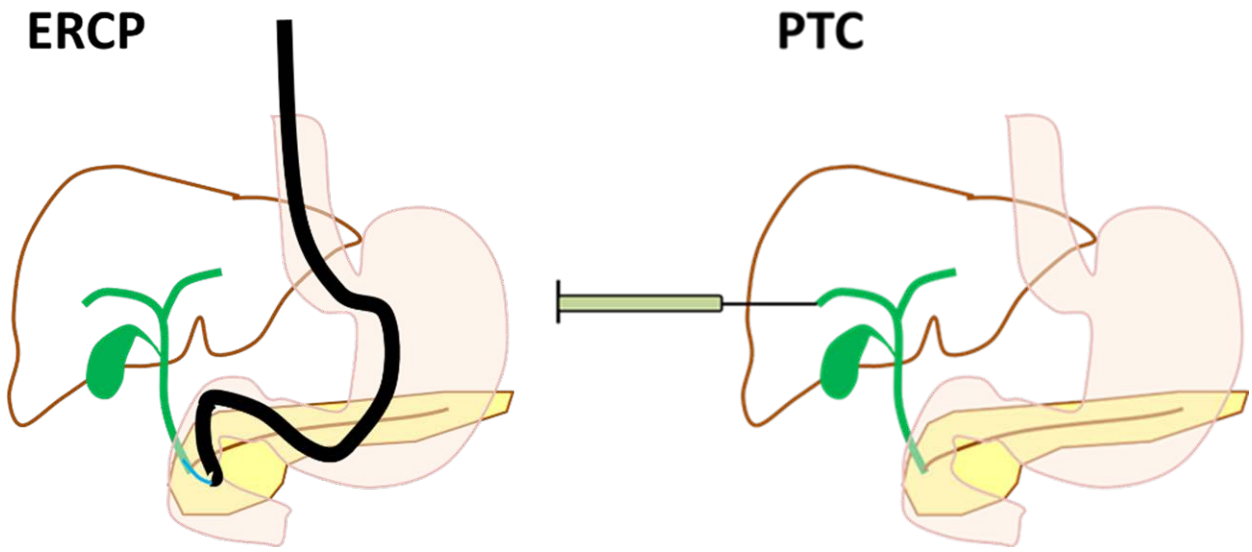
- Small ultrasound probe is situated at the end of a gastroscope
- **Radial probe** is very sensitive for identifying stones in the common bile duct (CBD) and to evaluate masses in the distal bile duct and head of the pancreas
- **Linear probe** allows a needle to be directed in to tissue for sampling of strictures, masses or lymph nodes (to rule out malignancy)

Endoscopic Retrograde Cholangio Pancreatography (ERCP)

- Allows for a **diagnostic cholangiogram**, as dye is injected into the CBD and then X-rays are taken (ionizing radiation), and for **therapeutic intervention** with removal of stones from bile ducts (but not gallbladder), dilation and stenting of strictures to relieve jaundice or cholestasis, and brushing or biopsy of strictures to rule out malignancy
- **Risks of ERCP** include: 1) perforation (1:3000 in esophagus, 1:1000 in duodenum), 2) bleeding ~1% (higher if sphincterotomy performed), 3) pancreatitis ~5% (higher in certain patients, e.g. Sphincter of Oddi dysfunction)

Percutaneous Transhepatic Cholangiography (PTC)

- Needle is inserted directly into the bile ducts (similar to a liver biopsy) to inject dye followed by X-rays to perform the cholangiogram
- The patient is often left with a tube to externally drain bile into a bag
- It is used for patients who fail ERCP and is preferred for some patients with strictures at the hilum (bifurcation of left and right hepatic ducts)
- **Risks of PTC** are similar to liver biopsy (e.g. pain, bleeding) and bile leaks



4.2 Benign Disease

Gallstone disease

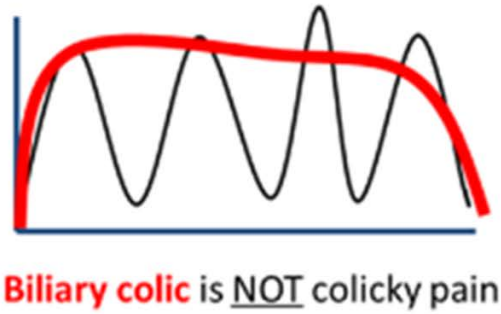
- **Types of Gallstones**
  - **Cholesterol** stones form in the gallbladder when supersaturated bile undergoes nucleation and their growth is promoted by gallbladder stasis (affects 20% of the population)[1]
  - **Black** stones form in the gallbladder or bile ducts as a result of hemolysis (bilirubin acts as the nucleus for formation) and may be seen in cirrhosis
  - **Brown** stones form in the bile ducts in response to infections (bacterial or parasitic)
- **Risks for Cholesterol Gallstones**

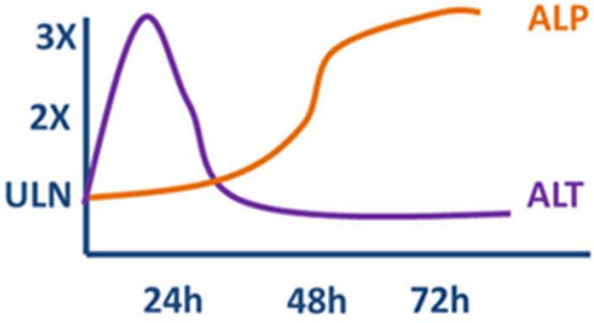
  REMEMBER the 7 Fs = female, fertile, fifty, family, fat, fasting, pharmacology
  - Sex = more common in women than men at all ages
  - Pregnancy = 30% get sludge and 1-3% get gallstones

- Age = 5% of young women vs 25% of those over age 50
- American Indians > Hispanics >> Caucasians
- Obesity = one-third of obese people (BMI >30) have gallstones
- Fasting = rapid weight loss can precipitate gallstones, patients on total parenteral nutrition
- Drugs = ceftriaxone, estrogens, octreotide

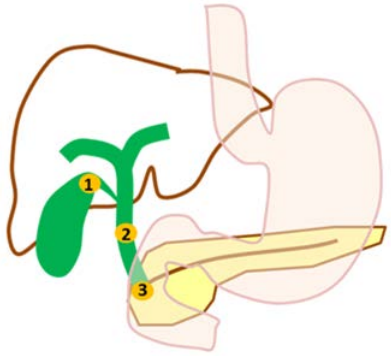
- **Complications of Gallstones**[1]
  - **Biliary colic is NOT a colicky pain**, but rather a steady RUQ pain that comes on slowly and lasts for up to 3-4 hours before subsiding. It can be treated with NSAIDS. Once patients have biliary colic they are more likely to develop other complications from their gallstones and it is an indication for laparoscopic cholecystectomy. Also, patients who have developed acute cholecystitis, cholangitis or gallstone pancreatitis should also undergo cholecystectomy.

    NOTE: With bile duct obstruction, the ALT and AST will be the first tests to rise (as these are preformed enzymes) and the ALP may not rise for 24-48 hours as it is synthesized from biliary canaliculus in response to obstruction.





- **Acute cholecystitis** (see stone location #1) occurs when a stone is lodged in the neck of the gallbladder and the gallbladder becomes inflamed and infected. They will present with fever, RUQ pain, **Murphy's sign** on physical or ultrasound exam (where the patient stops inspiration when inflamed gallbladder hits your hand or the US probe), and a high WBC but liver tests are usually normal (or mildly elevated by sepsis). Treatment is with antibiotics and cholecystectomy.
- **Cholangitis** (see stone location #2) occurs when a stone obstructs the common bile duct. They will present with fever, RUQ pain, jaundice, elevated liver tests and can be septic (with low blood pressure and tachycardia). Patients require antibiotics and immediate ERCP to relieve the obstruction and retrieve the stones from the bile ducts, followed by cholecystectomy within 72 hours.
- **Pancreatitis** (see stone location #3) occurs when a stone passes through or obstructs the pancreatic duct, which joins with the common bile duct at the Ampulla of Vater (Sphincter of Oddi). Patient will present with epigastric pain that radiates into the back, nausea, vomiting, and may have fever, low blood pressure and tachycardia. They will have an elevated **lipase** and may have elevated liver tests and bilirubin. Treatment is with narcotics, IV fluids, and bowel rest (nothing per oral or NPO) although early feeding may improve outcomes. They may need ERCP for stone removal and subsequent cholecystectomy.



Strictures

- **Benign Strictures** (REMEMBER five I's)
  - **Inflammatory** – primary sclerosing cholangitis (PSC) or IgG4 disease *[see Chapter 5.3]*
  - **Iatrogenic** – damaged during cholecystectomy
  - **Ischemic** – with hepatic artery thrombosis (HAT) after liver transplant *[see Chapter 15]* or as a complication of transarterial chemotherapy (TACE) for hepatocellular carcinoma [*see Chapter 13.1]*
  - **Infection** – *Clonorchis sinensis* (Chinese liver fluke) or *Opisthorchis viverrini* (Southeast Asian liver fluke) or *Ascaris lumbricoides* (roundworm)
  - **Idiopathic** – unknown cause
- **Malignant Strictures**
  - Cholangiocarcinoma *[see Chapter 4.3]*
  - Cancer in the head of the pancreas, Ampulla of Vater, or second part of the duodenum

4.3 Malignant Disease

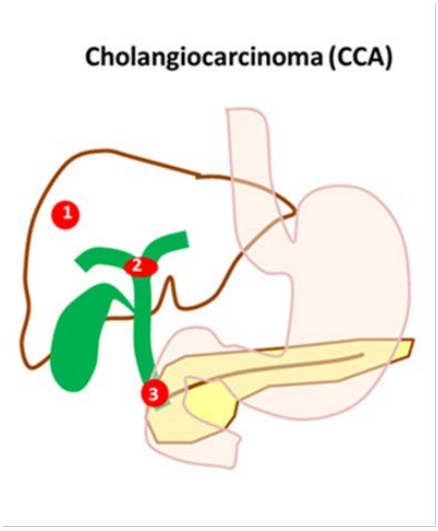
Cholangiocarcinoma (CCA)

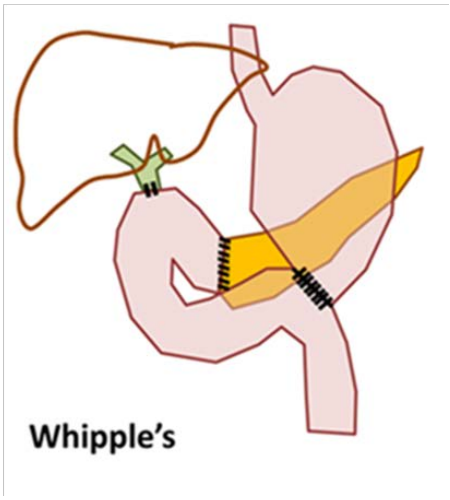
- **Epidemiology**
  - Rare cancer but its incidence is increasing in North America
- **Risks**
  - Chronic inflammation (e.g. PSC, liver flukes) or congenital abnormalities of the bile ducts (e.g. choledochal cysts, Caroli's disease)

- Cirrhosis is the major risk factor for intrahepatic CCA

- **Classification**
  - **Intrahepatic** (iCCA – #1)
  - **Perihilar** (pCCA – #2) previously known as Klatskin tumours
  - **Distal** (dCCA – #3)

- **Management**
  - iCCA can undergo resection, ablation, transarterial chemoembolization (TACE) or receive systemic chemotherapy (gemcitabine & cisplatin)[2] *[see Chapter 13.2]*
  - pCCA may be able undergo partial hepatectomy, and in highly selected cases are candidates for liver transplantation (Mayo Protocol); however, many cases can only be palliated with PTC and stenting with or without chemotherapy
  - dCCA may be able to undergo resection (Whipple's) or can be palliated with ERCP or PTC and stenting with or without chemotherapy





Gallbladder cancer

- **Epidemiology**
  - Rare cancer
- **Risks**
  - Chronic inflammation of gallbladder, PSC or gallbladder polyps
  - If polyps are larger than 1cm the gallbladder should be removed to prevent cancer
- **Management**
  - Gallbladder cancer can be resected (cholecystectomy) and may require partial hepatectomy with removal of the gallbladder
  - Adjuvant chemotherapy with capecitabine improves survival in early stage disease
  - Advanced cases receive chemotherapy similar to CCA

Pancreatic cancer

- **Epidemiology**
  - 4^{th} leading cause of cancer mortality
- **Presentation**
  - If at the head of the pancreas = painless jaundice with cholestasis
  - If in the body or tail of the pancreas = weight loss, back pain, depression
- **Management**
  - Prognosis is quite poor
  - Only resectable if it is not involving the veins and arteries
  - If in the head of the pancreas, surgery requires a Whipple's operation (see above)

- Chemotherapy for advanced cases
- Palliation may require stenting, surgical bypass of obstructed duodenum or bile duct with or without celiac plexus block for pain control

Abbreviations

BMI – Body Mass Index

CBD – common bile duct

CCA – cholangiocarcinoma

dCCA – distal cholangiocarcinoma

HAT – hepatic artery thrombosis

iCCA – intrahepatic cholangiocarcinoma

MRI – magnetic resonance imaging

NPO – nothing per oral

NSAIDs – non-steroidal anti-inflammatory drugs

pCCA – perihilar cholangiocarcinoma

PTC – percutaneous transhepatic cholangiography

TACE – transarterial chemoembolization

WBC – white blood cell

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. *J Hepatol* 2016; 65(1): 146-181.
2. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 2014; 60(6): 1268-1289.