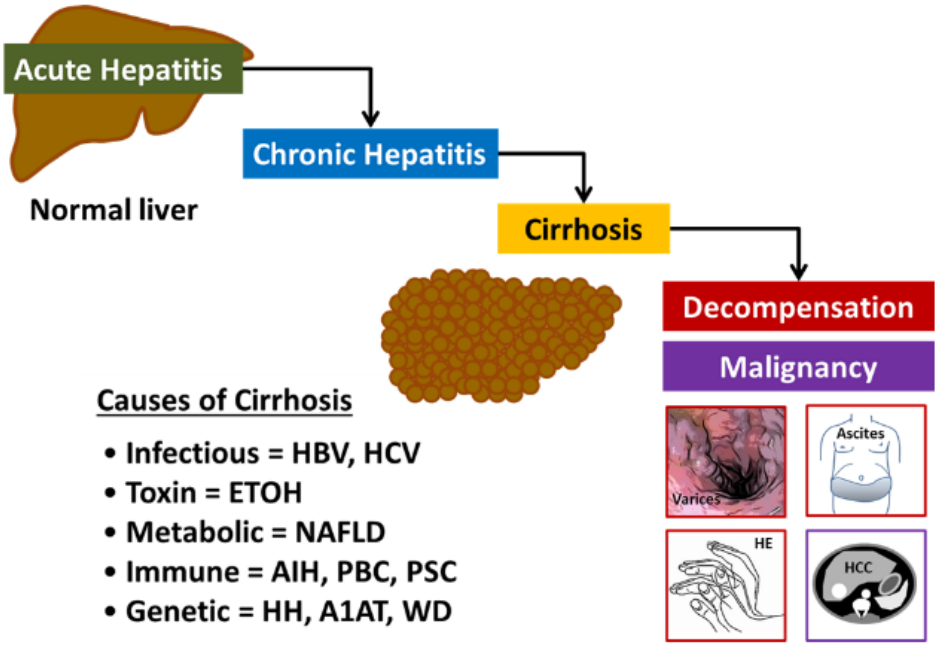
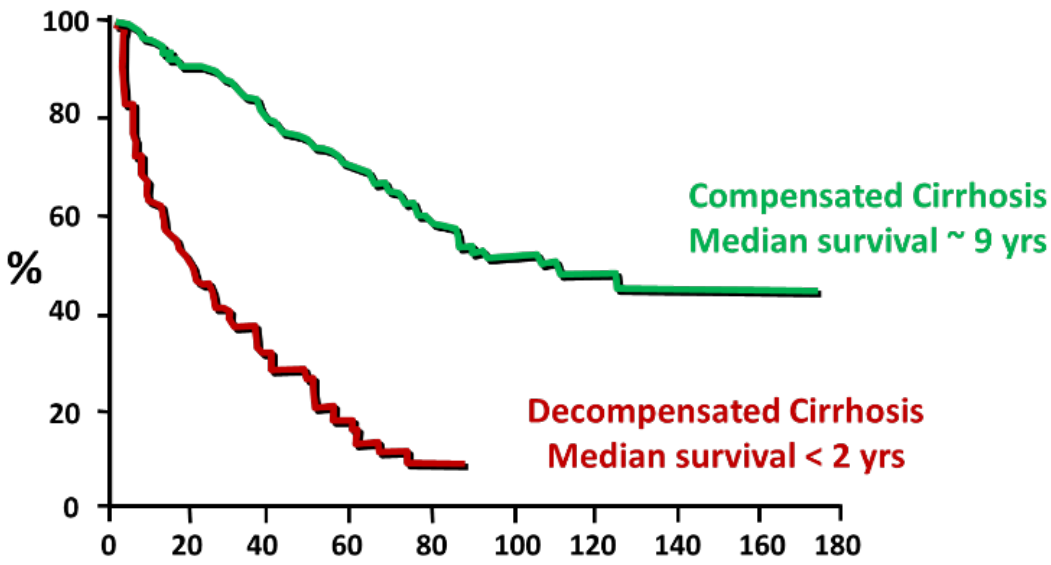
Chapter 2. Clinical Medicine

2.1 Natural History

- Many different things can cause acute liver injury (not just alcohol) and if not self-limiting this can progress onto chronic liver disease
- **Acute hepatitis** may present with jaundice or RUQ pain; however, in many liver diseases this phase is sub-clinical and without symptoms
- **Chronic hepatitis** (ongoing liver inflammation) which persists can results in fibrosis (scar tissue) being laid down by the hepatic stellate cells and over years this can results in **cirrhosis** (severe scarring with regenerating nodules)
- There are many **causes of cirrhosis** including:
  - Viral – hepatitis B virus (HBV), hepatitis C virus (HCV)
  - Toxin – alcoholic liver disease (ETOH = ethanol)
  - Metabolic – non-alcoholic fatty liver disease (NAFLD)
  - Immune – autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC)
  - Genetic – hereditary hemochromatosis (HH), alpha-1 antitrypsin (A1AT) deficiency and Wilson's disease (WD)



- Patients with well **compensated cirrhosis** can remain asymptomatic for many years
  - Compensated cirrhotics have a median survival of nine years
- When cirrhosis become complicated by variceal bleeding (from veins in esophagus or stomach), ascites (fluid accumulation in abdomen), or encephalopathy (confusion or coma) it is called **decompensated cirrhosis** and the natural history is dramatically changed
  - These complications occur at a rate of approximately 5% per year
  - Decompensated cirrhosis has a median survival of less than two years
  - Variceal bleeding, ascites or hepatic encephalopathy are therefore indications for liver transplantation



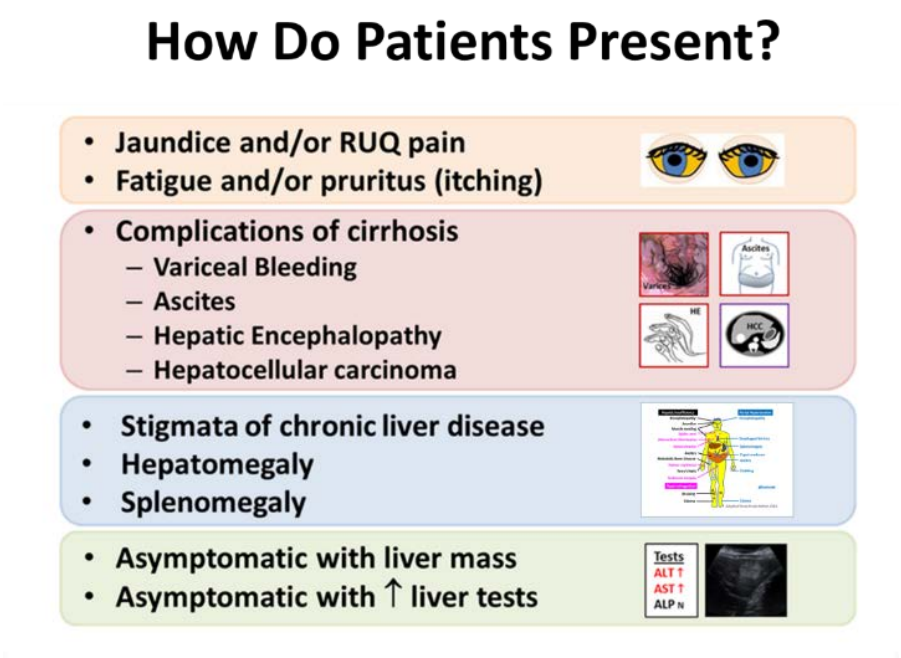
Adapted from Gines P, et al. Hepatology 1987; 7(1): 122-8.

- Patients with cirrhosis are at high risk of primary liver cancer, including hepatocellular carcinoma (HCC) arising from the hepatocytes or cholangiocarcinoma (CCA) from the bile ducts
  - HCC occurs in up to 5% of cirrhotic patients per year
  - These cancers have a very poor prognosis unless diagnosed at an early stage

2.2 Patient Presentations

- Patients with liver damage or blockage of bile flow can present with jaundice (yellowing of eyes and skin), which may or may not be accompanied by pain in the right upper quadrant, or other symptoms such as nausea, fever or pain in the right upper quadrant (RUQ)
- Fatigue is very common in chronic liver diseases, as is pruritus (itching) especially if there is cholestasis (lack of bile flow)

- Patients may present with the signs or symptoms of complications of cirrhosis, including:
  - vomiting blood (hematemesis) or passing black stools (melena) or fresh blood per rectum (hematochezia)
  - ascites (fluid in the belly) which often comes with weight gain and edema (swollen ankles)
  - hepatic encephalopathy (confusion or coma)
  - hepatocellular carcinoma (HCC), which at late stages may present with abdominal pain and weight loss
- Stigmata of chronic liver disease are physical exam findings of patients with cirrhosis which may relate to:
  - hepatic insufficiency
  - portal hypertension
  - high estrogen state seen with cirrhosis
- Hepatomegaly (a big liver) which may be symptomatic or asymptomatic
- Splenomegaly (a big spleen) can be due to portal hypertension
- More commonly, patients are asymptomatic and present with a mass found on abdominal imaging done for other reasons or with high liver tests found on routine blood work
- For more information on these presentations please refer to the SCHEMES



2.3 History Taking

- The causes of injury to organs can be classified by remembering four "I"s and four "M"s
    - Infectious
    - Immune
    - Inflammatory
    - Ischemia
    - Medications (Toxins)
    - Metabolic (Genetic / Congenital)
    - Mechanical
    - Malignancy
- The liver can be affected by infections (mainly viruses), immune disorders (autoimmune), inflammatory conditions (alcohol), ischemia (lack of blood flow), medications or toxins (e.g. acetaminophen), metabolic or genetic disorders (presenting both in children and adults), mechanical (trauma), or malignant diseases (metastatic or primary)
- It is important to remember these things when taking a history from a patient suspected of having liver disease:

- Alcohol consumption
- Drugs
- Viral hepatitis risk factors
- Related medical conditions
- Family history of liver disease
- Review of Symptoms (cirrhosis)

Alcohol history

- Ask about the type and the total amount of alcohol (drinks per day or per week)

  NOTE: all forms of alcohol are equal [12 oz beer = 5 oz wine = 1.5 oz liquor]

- It is important to document:
  - the pattern of drinking (steady vs binge)
  - if there is a history of problem drinking leading to work absenteeism, driving while impaired (DWI) charges, marital problems or social stress with friends and family
  - alcohol withdrawal seizures or delirium tremens (DT) and amnestic episodes ("blackouts")
  - any attempts at quitting and formal alcohol rehabilitation programs
- The CAGE questionnaire (see below) is a validated screening tool to help identify alcoholism
  - Answering YES to 2 or more questions is quite sensitive and specific for alcohol use disorder
  - The "Eye Opener" is the most important question, and may indicate alcohol dependence
  - The AUDIT (Alcohol Use Disorders Identification Test) questionnaire has 10 questions and may be better than the CAGE at identifying alcohol use disorder

    https://auditscreen.org/~auditscreen/cmsb/uploads/audit-english-version-new_001.pdf

1. **Cut Down**
   - **Have you ever felt you should cut down on your drinking?**
2. **Annoyed**
   - **Have people annoyed you by criticizing your drinking?**
3. **Guilty**
   - **Have you ever felt bad or guilty about your drinking?**
4. **Eye Opener**
   - **Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover?**

Drugs

- There are four categories of "drugs" and all may cause liver problems
  - Drugs that are prescribed by physicians
  - Over The Counter (OTC) drugs, with acetaminophen overdoses being the leading cause of acute liver failure (ALF) in North America
  - Complementary Alternative Medicines (CAM), like herbal therapies, which are very commonly used but not well regulated
  - Illicit drugs (injected, snorted, swallowed or smoked) and it is important to ask if a person has ever used IV drugs, even once as a teenager!
- When suspecting drug induced liver injury (DILI) it is important to note when the patient started taking the drug or herbal product, as these usually occur within six months of initiation

Viral Hepatitis Risk Factors

REMEMBER: Hepatitis B or C chronically infects 1 in 12 people worldwide

- It is important to understand the mode of transmission to recognize the risk factors of viral hepatitis acquisition
  - Hepatitis A and E are spread by **fecal-oral transmission** and it is important to ask about:
    - travel to countries where viruses are endemic (Africa, Asia, Mexico or S. America)
    - ingestion of raw seafood (which concentrate the virus)
    - certain sexual practices (anilingus)
  - Hepatitis B, C and D are spread by **parenteral transmission** (through exposure to an infected person's blood) and risks therefore include:
    - patients who received blood products (before the blood supply was safe)
    - persons who inject drugs (PWID), preferred terminology to IV drug user (IVDU)
    - unsafe tattoos or piercings
    - health care workers (HCW) who get needle stick injuries from infected patients
    - unsafe medical equipment (e.g. 15% of Egyptian population infected with HCV by unsafe injections used to treat schistosomiasis)
  - **Sexual transmission** (HBV > HCV) and risks include:
    - multiple sexual partners (MSP)
    - sex trade workers (STW)
    - men who sex with other men (MSM)

    - When taking a sexual history from a patient it is important to be "matter of fact" and you should ask about orientation (heterosexual, homosexual, or bisexual), the number of partners, if "safe sex" is practiced, and if they had sex with a STW
  - **Vertical transmission** (transmission of virus from mother to child at the time of birth) is the main form of transmission of HBV in countries endemic for the virus (Asia and Africa); however, vertical transmission of HCV is rare (<5%) unless the mom is co-infected with HIV
  - **Horizontal transmission** (between children) also occurs in countries endemic for HBV

Related Medical Conditions

- It is important to ask about other medical conditions which may associated with liver disease
  - Non-Alcoholic Fatty Liver Disease (NAFLD) is associated with obesity, diabetes and hyperlipidemia
  - Hemochromatosis is associated with diabetes, arthritis, congestive heart failure, arrhythmias, impotence or bronzing of the skin
  - Primary biliary cirrhosis and autoimmune hepatitis are associated with other autoimmune conditions (thyroid disease, Celiac disease, etc.)
  - Primary sclerosing cholangitis is associated with inflammatory bowel disease in the colon

Family History

- There may be a family history if the patient is affected by a genetic liver condition (e.g. hereditary hemochromatosis, alpha-1 antitrypsin deficiency or Wilson's disease)
- Similarly, some autoimmune liver diseases run in families, as there is a genetic predisposition to developing these conditions
- There may be a family history of alcoholism which may predispose to alcoholic liver disease
- Chronic viral hepatitis (especially hepatitis B) can be spread between family members

Review of Symptoms

- It is important to ask about complications of cirrhosis including confusion (encephalopathy), GI bleeding (from varices or portal hypertensive gastropathy), weight gain with abdominal distention (ascites) or edema, muscle wasting or weight loss

Summary

- The important parts of the history in patients with suspected liver disease

History in Liver Patients

- **HPI**
  - **Jaundice, anorexia, N/V, fever, itch, RUQ pain, fatigue**
- **Social Hx**
  - **Alcohol (ETOH), sexual history, travel, birth place, PWID**
- **Medications**
  - **Prescribed meds, OTC and herbals**
- **Past Med Hx**
  - **DM, arthritis, cardiac, obesity, ↑ lipids, IBD, vaccinations**
- **Family Hx**
  - **Wilsons, hemochromatosis, A1AT def, HBV, liver cancer**
- **ROS**
  - **GI bleed, ascites and edema, confusion, weight loss and muscle wasting**

Abbreviations

HPI = history of present illness: N/V = nausea & vomiting, RUQ = right upper quadrant

Social Hx = social history: ETOH = ethanol, IVDU = intravenous drug use

Medications: OTC = over the counter drugs

Past Med Hx = past medical history: DM = diabetes mellitus, ↑ lipids = hyperlipidemia, IBD = inflammatory bowel disease

Family Hx = family history: A1AT def = alpha 1 antitrypsin deficiency, HBV = hepatitis B virus

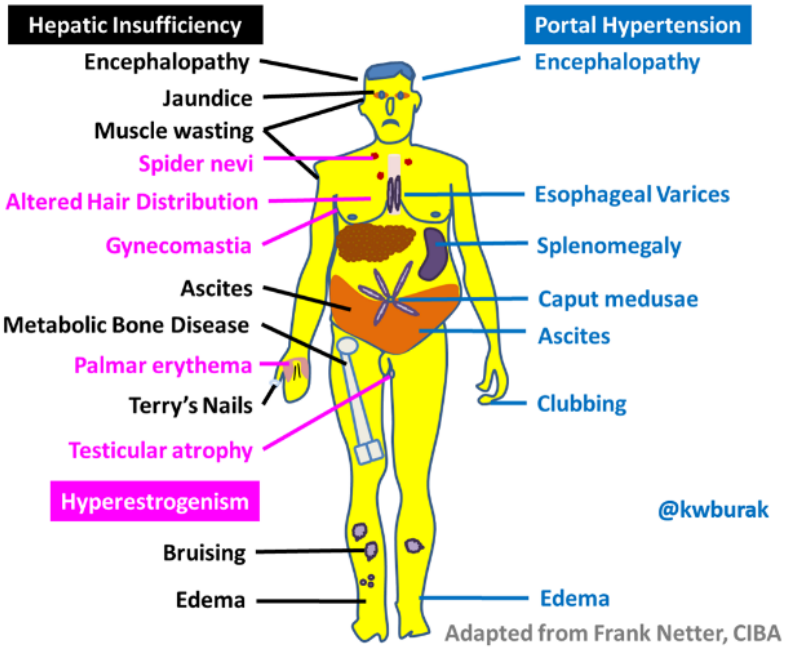
ROS = review of symptoms: GI bleed = gastrointestinal bleeding

2.4 Physical Examination

Stigmata of Chronic Liver Disease

- Physical examination is often normal in patients with liver disease unless they have established cirrhosis, when they may exhibit "**stigmata of chronic liver disease**"
- Cirrhotics may have low blood pressure and a fast heart rate due to hyperdynamic circulation
- Look for jaundice in the sclera of the eyes (bilirubin usually > 50 µmol/L)
- Muscle wasting is common in cirrhotics and is often best seen with loss of the temporalis and deltoid muscles
- There are multiple findings that suggest liver disease and these findings can be due to 1) hepatic synthetic dysfunction, 2) portal hypertension, or 3) altered sex hormone metabolism (*related to high estrogen state)
  - Clubbing = dilation of finger tips and loss of nail bed angle, which may be seen in primary biliary cirrhosis (PBC) or if hypoxic (low oxygen level) from hepatopulmonary syndrome
  - Palmar erythema* = redness of thenar and hypothenar eminence of the palms
  - Terry's nails = increased size of the white "moon" of the nail due to low albumin
  - Dupuytren's contracture = thickening of the sheath surround the finger flexor tendons
  - Spider nevi* = telangiectasia on the skin (usually of upper back and chest or face), which fill from the center
  - Gynecomastia* = enlargement of the breast tissue (most noticeable in men)
  - Altered hair distribution* (most noticeable in men)

- Caput medusa = enlargement of the superficial vessels in the skin of the abdominal wall around the umbilicus (looks like the hair of snakes on Medusa from Greek mythology)
- Hepatosplenomegaly = big liver and spleen
- Ascites = free fluid in the abdominal cavity
- Testicular atrophy*
- Bruising = due to decreased production of clotting factors or low platelets
- Edema = swelling in tissues (usually at the ankles)

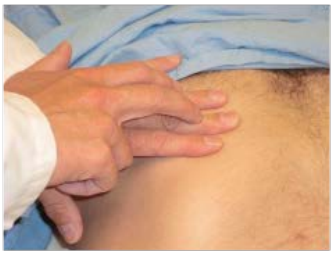


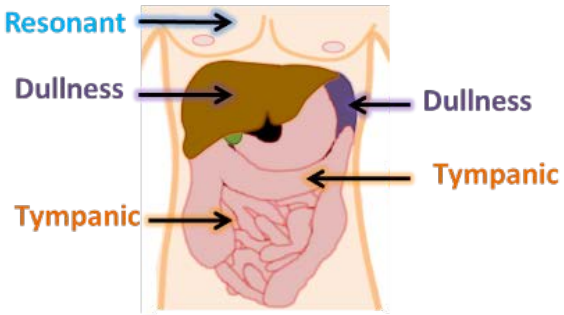
Examination of the Liver

- As the liver is protected by the ribs, the size of the liver is estimated using percussion
- The top of the liver can be found as the percussion note changes from resonant over the lung to dull over the liver

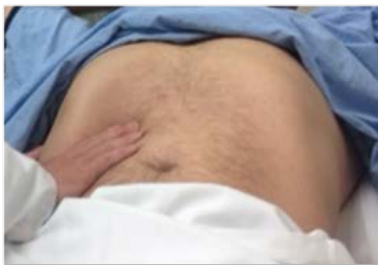
- The bottom edge of the liver can be found as the percussions note changes from dull over the liver to tympanic over the gas in the bowel
- As the liver moves with respiration it is important to measure the span (distance between top and bottom edge) in the same cycle of respiration (inspiration or expiration)
- The bottom of the liver should also be palpated using your fingertips, moving your hand up toward the ribs as the patient breathes in, to feel the liver as it moves down with inspiration
- If you can't feel the liver this way try the Hook technique at the costal margin (wrap your fingers around the edge of the ribs)
- Pay attention to the contour of the liver, feeling for masses, and if the liver edge is tender

Percussion

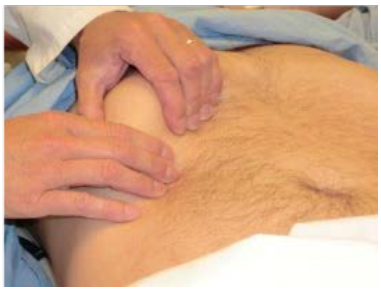




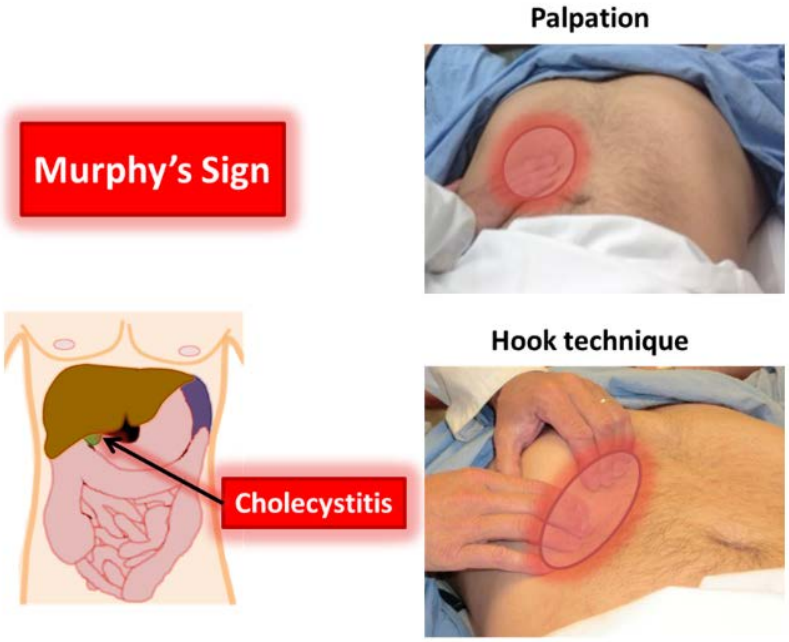
Palpation



Hook technique

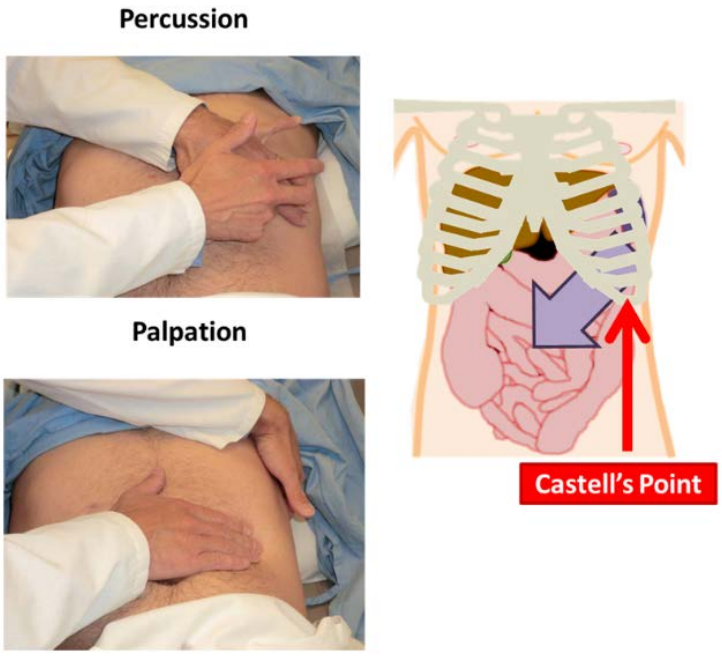


- **Murphy's sign** is described as a sign for acute cholecystitis (inflammation of the gallbladder) where the patient will suddenly stop inspiration when the inflamed gallbladder touches your palpating hand



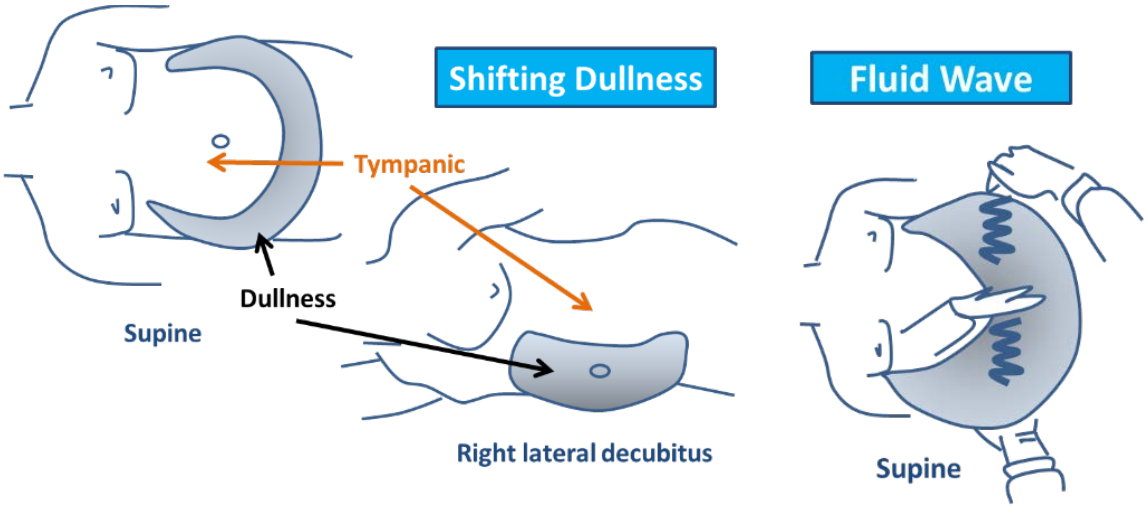
Examination of the Spleen

- An enlarged spleen can be a sign of portal hypertension, which is usually due to cirrhosis
- Whereas the liver tends to enlarge down toward the right lower quadrant (RLQ), the spleen tends to enlarge diagonally across the abdomen (also toward the RLQ)
- The spleen needs to enlarge approximately 2-3 times in size before it can be palpated
- To help palpate the spleen use your left hand to pull up the ribs, while palpating with the right hand
- If needed, the patient could also be rolled onto their right side while employing the Hook technique (similar to examining the liver)
- A dull percussion note at Castell's point (lowest intercostal space in the anterior axillary line) is a sign of splenomegaly



Examination for Ascites

- Ascites (free fluid in the abdomen) is best examined by eliciting "shifting dullness"
  - With the patient in the supine position (on their back) the fluid will settle to the sides resulting in bulging flanks on inspection
  - Starting at the umbilicus, percuss toward the flanks, and notice that the note will change from tympanic over the gas in the bowel to dull over the free fluid
  - Mark on the skin where the change to dullness occurs and then roll the patient on their side (free fluid will shift down)
  - The location of the change in the percussion note (from tympanic to dullness) will move if there is ascites…hence the "shifting dullness"



- The "Fluid Wave" or "Fluid Thrill" can also be done (better for large amounts of ascites)
  - Have the patient (or an assistant) place their hand across the abdomen to block transmission of the wave through the skin and subcutaneous fat
  - Place your left hand on the patients right flank
  - Tap with your right hand and you will feel the "fluid wave" come across the abdomen to lap up against your left hand

Summary

- The important parts of the physical exam in patients with suspected or known liver disease (see below)
- You should be able to

  1) recognize stigmata of chronic liver disease,

  2) examine the liver and spleen and

  3) detect ascites if present

Physical Exam in Liver Patients

- Vitals – cirrhosis may cause hyperdynamic circulation → low BP, high HR
- H & N – jaundice, temporal muscle wasting
- Hands – palmar erythema*, clubbing, Terry's nails, Dupuytren's contractures
- Skin – jaundice, spider nevi*, bruising
- Chest – gynecomastia*, altered hair distribution*
- Abdomen – hepatomegaly, splenomegaly, ascites, caput medusae
- GU – testicular atrophy*

* related to ↑estrogen

Abbreviations:

↑ **lipids** – hyperlipidemia

A1AT – alpha 1 antitrypsin

AIH – autoimmune hepatitis

ALF – acute liver failure

BP – blood pressure

CAM –complementary and alternative medicine

DILI – drug-induced liver injury

DM- diabetes mellitus

DT – delirium tremens

DWI – driving while impaired

ETOH – ethanol (alcoholic liver disease)

Family Hx – family history

GI bleed – gastrointestinal bleeding

HBV – hepatitis B virus

HCV – hepatitis C virus

HCW – health-care workers

HH – hereditary hemochromatosis

HPI – history of present illness

HR – heart rate

IBD – inflammatory bowel disease

IVDU – intravenous drug use(r)

MSM – men who have sex with men

MSP – multiple sexual partners

N/V – nausea and vomiting

NAFLD – non-alcoholic fatty liver disease

OTC – over the counter

Past Med Hx – past medical history

PBC – primary biliary cholangitis

PSC – primary sclerosing cholangitis

PWID – person who injects drugs

RLQ – right lower quadrant

ROS – review of symptoms

Social Hx – social history

STW – sex trade workers

WD – Wilson's disease

WSW – women who have sex with women

Figure Citations:

Natural History

Gines, P, Quintero, E, Arroyo, V. Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 1987; 7(1):122-8.

