# Chapter 9

# Gastroenterology step 1 notes

## Embryology and Anatomy of the GI Tract

### Embryology:

- The gastrointestinal tract is very long
- For it to be confined in the small abdominal cavity, a lot of developmental steps that involve herniation, return of midgut and rotation need to occur
- At the 6th week, the rapidly growing midgut herniates through the umbilical ring (a physiologic hernia)
    - The principle is simply to have more space for the midgut to develop
- At the 10th week, the midgut returns to the abdominal cavity
    - First rotation occurs around the superior mesenteric artery 270 degrees counterclockwise
- The other two parts of the developing GI tract are the foregut (before the midgut) and the hindgut (after the midgut)
- The foregut becomes everything from the pharynx to the proximal duodenum
    - Liver, gallbladder, and pancreas originates from the foregut
    - The proximal duodenum buds out (the different buds develop into these accessory digestive organs)
- The midgut becomes the distal duodenum up to the first two thirds of the transverse colon (the splenic flexure)
- The hindgut develops into last one third of the colon to the pectinate line
    - The pectinate line separates the GI endodermal origin from the skin of the anus which is ectoderm

Area above the pectinate line:

- The superior rectal artery from the inferior mesenteric artery supplies the area above the line. Venous drainage is via the superior rectal vein → inferior mesenteric vein → portal vein
- Chronic constipation and straining → dilatation of the branches of the superior rectal vein → internal hemorrhoids which are painless
- Tumors above this line are adenocarcinomas → drainage via the lymphatic vessels to the internal iliac lymph nodes (internal nodes)

Area below the pectinate line:

- Perianal perineum is supplied by the pudendal nerve and pudendal blood supply
- Inferior rectal artery from the pudendal artery. Venous drainage is via the inferior rectal vein to the pudendal vein to the iliac veins and inferior vena cava
- Dilatation of these veins → external hemorrhoids which are painful
- Anal fissures are tears in the anal mucosa below the pectinate line:
    - Blood streaks on toilet paper
    - Painful pooping
    - Mostly are located posteriorly
    - Associated with chronic constipation and low-fiber diet
- Squamous cell carcinoma → lymphatic spread to the inguinal lymph nodes (external nodes)

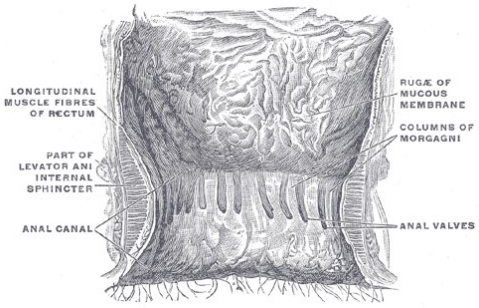



Figure 1: Pectinate line anatomy. Source: https://en.wikipedia.org/wiki/Pectinate_line#/media/File:Gray1080.png

### Anatomical Structure of the GI Tract:

The gastrointestinal (digestive) tract starts from the mouth and ends at the anus. The main purposes of the GI tract are to allow food and nutrients to enter the body, pass it to the stomach, early digestion, passing food to the small intestine for further digestion and absorption, further breakdown of food in the large intestine and finally exiting the end product in the form of stool through the anus.

The GI Tract:

- The mouth, and pharynx (some digestion of the carbohydrates starts here)
- Esophagus (a tube for food to pass to the stomach)
- The stomach which stores food, and starts the process of digestion via proteases and acidic secretions

- The duodenum where bile and pancreatic secretions come to help digest food further
- The jejunum and ileum where further digestion of food takes place and absorption of nutrients takes place
- Colon where broken food starts to form into stool to be passed by the anus

## Layers of the GI Tract:

Mucosa:

- The lining of the GI tract "epithelium" which can be stratified squamous, or columnar depending on which part is being analyzed (form intestinal villi)
    - The intestinal villi increase the surface area of the intestine → more absorption
- The lamina propria
- The muscularis mucosa

Submucosa:

- Contains the submucosal glands which secrete fluids
- The Meissner submucosal nerve plexus (important in controlling digestive tract secretions and hormones

Muscularis externa:

- Auerbach myenteric nerve plexus (peristalsis and GI motility)

Outer layer:

- Serosa for intraperitoneal structures
- Adventitia for retroperitoneal structures
- Blood vessels and lymphatic run through this layer to supply the GI tract

Ulcers versus Erosions:

- These two pathologies are descriptions of almost the same thing but differ in the depth of the lesion
- Erosions are confined to the mucosa
- Ulcers can extend to the submucosa, muscularis externa or even all the way through the serosa (perforation)

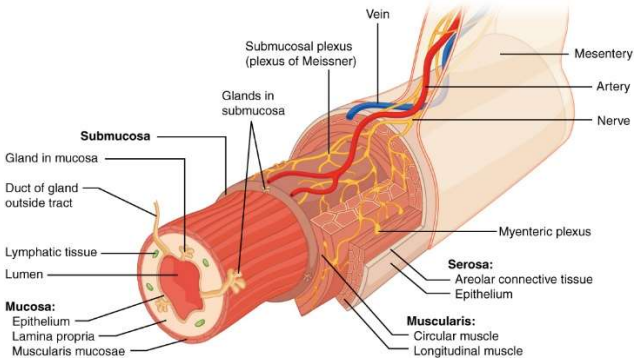



Figure 2: Layers of the GI tract. Source: https://commons.wikimedia.org/wiki/File:2402_Layers_of_the_Gastrointestinal_Tract.jpg

## Histology:

Esophagus:

- Nonkeratinized stratified squamous epithelium → to protect from abrasions

Stomach:

- Gastric glands which secrete acid

Duodenum:

- Villi and microvilli – increase absorptive surface
- Brunner glands which secrete bicarbonate and are found in the submucosa:
    - Fluid passing from the stomach is acidic
    - It is important to neutralize this acidity for next-step digestive enzymes related to the breakdown of fats
    - Also, to protect the duodenum from ulcers' formation

Lieberkühn crypts:

- These are important for the small intestine
- Continuous regeneration and replacement of enterocytes is needed
- These crypts have stem cells that are capable of replacing the enterocytes and goblet cells
- Bacterial pathogens might be present in the food, accordingly, Paneth cells found in the duodenum secrete defensins, lysozyme and tumor necrosis factor to provide some innate nonspecific immunity

Jejunum:

- Plicae circularis and crypts of Lieberkühn

Ileum:

- Peyer patches which are lymphoid aggregates in the lamina propria (important in fighting pathologic microorganisms)
- Largest number of goblet cells in the small intestine to secrete mucous and lubricate the passing food

Colon:

- The villi are absent (no need to absorb any more nutrients)
- Water absorption still occur to harden the stool
- Abundant goblet cells for lubrication

## Blood Supply to the GI Tract:

Blood supply and innervation of the developing gut:

- The foregut is supplied mainly by the celiac trunk and innervated by the vagus nerve
- The midgut is supplied by the superior mesenteric artery and also innervated by the vagus nerve
    - A pad of fat exists between the duodenum and the superior mesenteric artery
    - Protects the superior mesenteric artery from being compressed when food is passing through the duodenum
    - In severely malnourished people, this visceral fat might be lost
    - Postprandial pain due to intermittent compression of the superior mesenteric artery will result in what is known as superior mesenteric artery syndrome
- The hindgut is supplied by the inferior mesenteric artery and innervated by the pelvic nerve
- Sympathetic nerve supply of the foregut and midgut is from the thoracic splanchnic nerves
- Sympathetic nerve supply of the hindgut is from the lumbar splanchnic nerve

Celiac trunk:

- Common hepatic, splenic and left gastric arteries
- Anastomoses between the left and right gastroepiploic and left and right gastric arteries

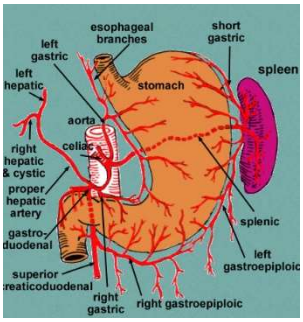



Figure 3: Branches of the celiac trunk. Source: www.wesnorman.com/celiactrunk.htm

Portosystemic anastomoses:

- Studying these anastomoses is important because patients with portal hypertension will develop varices involving these veins
- Mainly, in the esophagus, umbilicus and rectum

Esophagus portosystemic anastomoses:

- Left gastric vein with the azygos vein
- In portal hypertension, esophageal varices can develop

Umbilical portosystemic anastomoses:

- Paraumbilical vein with the small epigastric veins of the anterior abdominal wall
- Caput medusae is the clinical sign in patients with portal hypertension

Rectum portosystemic anastomoses:

- Superior rectal vein with middle and inferior rectal veins
- Anorectal varices can develop in patients with portal hypertension

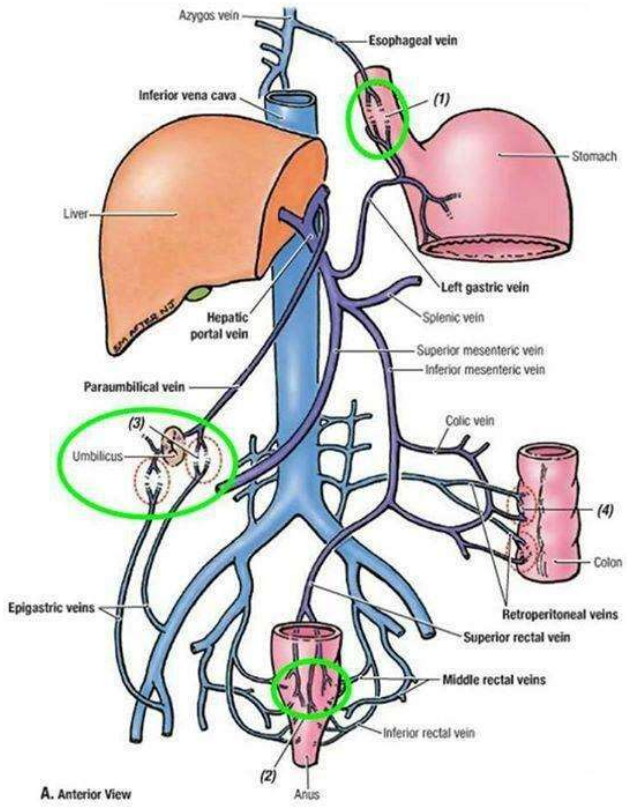



Figure 4: Portosystemic anastomoses. Source: https://pbs.twimg.com/media/BKo3gyTCYAAWyEh.jpg

## Ligaments of the GI Tract:

- These ligaments are important because they connect different GI organs to the abdominal wall or to each other
- They keep the different organs in their place

| ligament | Structures within the ligament | Connection | Notes |
|---|---|---|---|
| **Gastrocolic** | - Gastroepiploic arteries | - Greater curvature of the stomach and transverse colon | - Part of the greater omentum |
| **gastrosplenic** | - Short gastric, and left gastroepiploic vessels | - Greater curvature of the stomach and the transverse colon | - Part of the greater omentum<br>- Separates the greater and lesser sacs on the left |
| **splenorenal** | - Splenic artery and vein<br>- Tail of pancreas | - Spleen to the posterior abdominal wall | |
| **falciform** | - Ligamentum teres hepatis<br>- Patent paraumbilical vein | - Liver to anterior abdominal wall | - A derivative of the ventral mesentery |
| **hepatoduodenal** | - Proper hepatic artery<br>- Portal vein<br>- Common bile duct | - Liver to the duodenum | - The ligament can be compressed between thumb and index fingers to control intraoperative bleeding in Pringle maneuver<br>- Borders the omental foramen<br>- Part of the lesser omentum |
| **Gastrohepatic** | - Gastric blood vessels | - Liver to the lesser curvature of the stomach | - Separates the greater from the lesser sacs on the right<br>- Part of the lesser omentum |

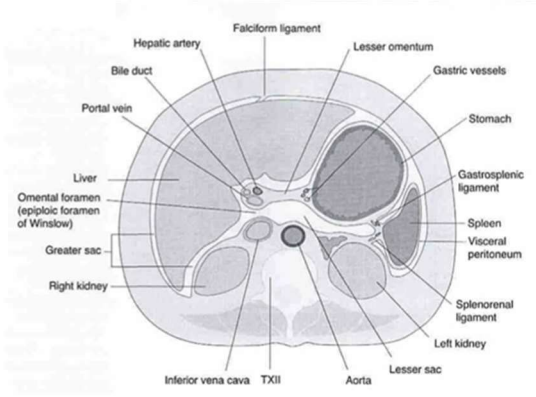



Figure 5: Gastrointestinal ligaments. Source: https://step1.medbullets.com/gastrointestinal/110003/gastrointestinal-ligaments

## Retroperitoneal Structures:

- Structures that do not have a mesentery
- Include GI and non-GI structures
- Injuries can cause blood or gas in the retroperitoneal space
- They are:
    - Suprarenal glands
    - Aorta and inferior vena cava
    - 2nd to 4th parts of the duodenum
    - Pancreas except tail
    - Ureters
    - Descending and ascending colon
    - Kidneys
    - Thoracic portion of the esophagus
    - Part of the rectum

## Developmental Anomalies of the GI Tract

### Tracheoesophageal Fistula

Definition:

A congenital malformation of the trachea and esophagus where there is an abnormal communication between the two tubes. Tracheoesophageal anomalies can be classified into the following types.

Types:

Esophageal atresia with distal tracheoesophageal fistula:

- Most common type (85%)
- Presents with polyhydramnios in utero
    - Esophageal atresia makes the fetus unable to swallow amniotic fluid
- If not diagnosed antenatally, the diagnosis is often obvious after the first feeding:
    - Drooling and choking associated with nonbilious vomiting
- The abdomen becomes distended because the distal TEF allows air to enter the stomach
    - Can be confirmed by plain radiography
- Neonates can become cyanosed secondary to laryngospasm:
    - Laryngospasm develops in response to reflux aspiration
- The diagnosis can be confirmed by failure of passing a nasogastric tube into the stomach

H-type tracheoesophageal fistula:

- A TEF without esophageal atresia
- Resembles the letter H

Pure esophageal atresia without a tracheoesophageal fistula:

- Esophageal atresia or stenosis
- A plain radiograph will reveal a gasless abdomen with possible collapse of the stomach

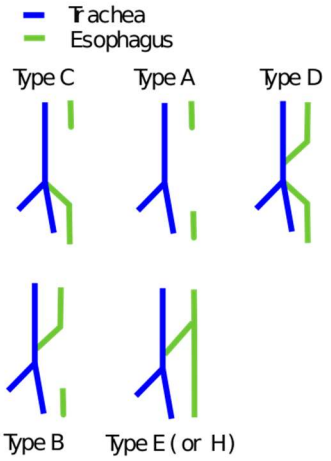



Figure 6: The different types of TEF. Source: https://en.wikipedia.org/wiki/Tracheoesophageal_fistula

## Ventral Wall Defects:

Failure of rostral fold closure:

<u>Ectopia cordis:</u>

- Very rare with an estimated incidence of 8 per million births
- The heart is located partially or totally outside the thorax
- The heart can be found in the neck, chest or abdomen
- Most neonates die and there is no recommended treatment

- Early surgical intervention might be successful in a minority of the cases

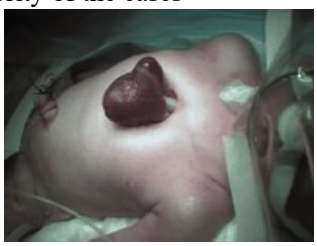


Figure 7: Complete thoracic ectopia cordis. Source: https://doi.org/10.1016/s1010-7940(02)00811-4

Failure of caudal fold closure:

Bladder exstrophy:

- 1 in 10,000 to 50,000
- Male to female ratio is 6:1
- Risk of bladder exstrophy in the offspring of an individual with corrected bladder exstrophy is increased by 500 times
- Presentation:
    - A defect in the abdominal wall with an exstrophied bladder and a portion of the urethra
    - Separation of the pubic symphysis
    - External rotation of the pelvis
    - In females, narrowed vaginal orifice, bifid clitoris and divergent labia
- Primary closure is the treatment whenever feasible

Long-term complications:

- Vesicoureteral reflux
- Bladder spasm
- Bladder calculus
- Recurrent urinary tract infections

Figure 8: Bladder exstrophy in a female. Source: https://en.wikipedia.org/wiki/Bladder_exstrophy

Failure of lateral folds closure:

Gastroschisis:

- Definition:
    - Extrusion of abdominal contents through an anterior abdominal wall defect typically on the right of the umbilicus without peritoneum or amnion covering
- Not associated with chromosomal abnormalities
- Often an isolated finding

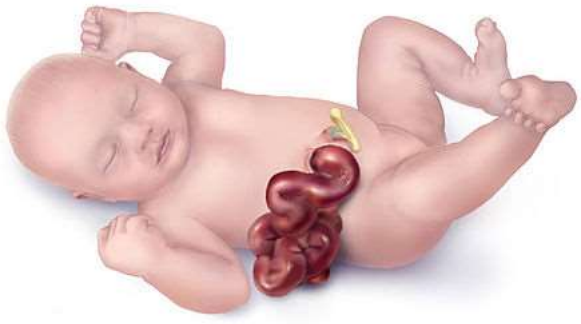


Figure 9: Gastroschisis. Source: https://en.wikipedia.org/wiki/Gastroschisis

Omphalocele:

- Definition:
    - Failure of the lateral walls of the abdomen to migrate at the umbilical ring which results in midline herniation of the abdominal contents into the umbilical cord. Covered by peritoneum
- Associated with chromosomal abnormalities such as trisomies 13 and 18
- Associated with other structural malformations of the heart, genitourinary and neural tube systems

Figure 10: Omphalocele. Source: https://en.wikipedia.org/wiki/Omphalocele

Congenital umbilical hernia:

- Failure of the lateral folds of the abdomen to close at the umbilical ring which results in a small defect
- Most often close spontaneously

### Pancreatic Anomalies:

Normal development:

- The pancreas is derived from the foregut
- Ventral buds form the uncinate process and main pancreatic duct
- The dorsal pancreatic bud becomes the body, tail, isthmus and accessory pancreatic ducts
- Both buds contribute to the pancreatic head

Annular pancreas:

- Abnormal rotation of the ventral pancreatic bud which fails to meet the dorsal bud
- A ring of pancreatic tissue is formed which encircles the 2nd part of the duodenum
- It can result in duodenal narrowing → obstruction and vomiting

Pancreas divisum:

- Failure of fusion between the ventral and dorsal parts of the pancreas which is supposed to happen at 8 weeks
- Mostly asymptomatic and is common in the general population
- Patients might develop chronic abdominal pain and chronic pancreatitis

### Gastrointestinal Hormones and Secretions

### Gastrointestinal Regulatory Substances

These are gastrointestinal endocrine hormones (substances released into the blood to affect distant targets).

### Gastrin:

Definition and source:

Gastrin is a hormone that is released by G-cells in the pyloric antrum of the stomach, duodenum and pancreas. It is a polypeptide hormone.

Regulation:

- Stomach mechanical distention in response to food or a change in the stomach's pH (alkalization) stimulates the release of gastrin
- Presence of aminoacids and peptides (from food) and vagal stimulation by gastrin-releasing peptide also stimulate the release of gastrin
- A very low pH (< 1.5) inhibits the release of gastrin

Action:

- It is clear from the mechanism of regulation that the main effect of gastrin would be to increase acid ($H^+$) production by the parietal cells
- To protect the stomach from the increased acid production, gastrin also stimulates the growth of gastric mucosa
- Finally, gastrin is known to increase gastric motility in an attempt to move the food from the stomach to the duodenum

Clinical correlation:

- Conditions that increase the pH of the stomach such as chronic proton pump inhibitor use, or atrophic gastritis will increase the release of gastrin
- Zollinger-Ellison syndrome results in hypergastrinemia secondary to a gastrinoma

### Somatostatin

Definition and source:

A polypeptide hormone synthesized and released by D cells which are found in the pancreatic islets and gastrointestinal mucosa.

Regulation:

- Its release is increased by increased acidity of the stomach juices
- Decreased by vagal stimulation

Actions:

- Again, the main action of somatostatin is obvious from its regulation mechanisms, it is to decrease gastric acid production and secretion
- It also decreases the production of pepsinogen, pancreatic and small intestine fluid secretion, gallbladder contraction, insulin and glucagon release

Clinical correlation:

- Somatostatin inhibits the release of growth hormone and other hormones
- Octreotide, a somatostatin analog, is used in the treatment of acromegaly, variceal bleeding and carcinoid syndrome

### Cholecystokinin

Definition and source:

An endocrine hormone released by the I cell of the duodenum and jejunum.

Regulation:

- Increased release by presence of fatty acids and aminoacids in the duodenum

Actions:

- The name of the hormone and its regulation mechanism gives away its main action, which is to facilitate fat digestion
- It increases pancreatic secretion and gallbladder contraction (to release bile) and relaxes the sphincter of Oddi (to allow for the passage of pancreatic secretions and bile into the duodenum)
- It decreases gastric emptying (allowing more time for the pancreatic enzymes to digest fat)

### Secretin:

Definition and source:

A polypeptide hormone release by the S cells in the duodenum.

Regulation:

- Increased release by the presence of fatty acids and acidic fluid in the duodenum

Action:

- Increases the release of bicarbonate to neutralize gastric acid in duodenum
    - This is important because pancreatic enzymes cannot work in an acidic environment
- Decreases gastric acid secretion
- Increases bile secretion

### Motilin:

Definition and source:

A polypeptide hormone that is released by the small intestine.

Regulation:

- Increased release in fasting

Action:

- As the name implies, it increases intestinal peristalsis by producing migrating motor complexes

Clinical correlation:

- Erythromycin is used to stimulate intestinal peristalsis
- This antibiotic is a motilin receptor agonist

### Vasoactive Intestinal Polypeptide:

Definition and source:

This polypeptide is released by parasympathetic ganglia found in the gallbladder, small intestine and the different GI sphincters.

Regulation:

- Increased release by mechanical distention of the GI tract and vagal stimulation
- Inhibited release by adrenergic input

Actions:

- Increases intestinal water and electrolyte secretion
- Relaxes intestinal smooth muscle and GI tract sphincters

Clinical correlation:

- VIPomas are pancreatic tumors that secrete vasoactive intestinal polypeptide
- From the understanding of the actions of this hormone, one can conclude that patients with this type of tumor will have watery diarrhea and hypokalemia
- Achlorhydria will develop (loss of $H^+$ in exchange for $K^+$ by the kidneys)

### Nitric oxide:

Clinical correlation:

- This regulatory substance is a very potent smooth muscle relaxer
- Its release stimulates the relaxation of the lower esophageal sphincter
- Loss of nitric oxide secretion is implicated in the pathophysiology of achalasia where there is an increase in the lower esophageal sphincter tone

### Ghrelin:

Source:

This polypeptide hormone is released by the stomach.

Regulation:

- Increased production in fasting state
- Decreased production when there is food in the stomach

Actions:

- Increases appetite

Clinical correlation:

- Decreased production after gastric bypass surgery → decreased appetite and weight loss
- Increased production in Prader-Willi syndrome → weight gain

### Glucose-Dependent Insulinotropic Peptide:

Definition and source:
A peptide hormone released by the K cells in the duodenum and jejunum.

Regulation:

- Increased release by the presence of fatty acids, aminoacids and glucose in the lumen of the duodenum and jejunum

Actions:

- Decreases gastric acid secretion (hence, the other name gastric inhibitory peptide)
- Increased the release of insulin by the pancreatic beta-cells

Clinical correlation:

- It has been noted that oral glucose load results in a higher insulin response than IV glucose
- This hormone is thought to be responsible for the higher insulin response of oral glucose load compared to IV

### Gastrointestinal Secretory Products:

- These are products that aid in digestion or absorption.

### Gastric Acid:

Definition and source:
HCl which is released by the parietal cells in the stomach.

Regulation:

- Increased production by histamine, vagal stimulation and gastrin
- Decreased production by somatostatin, gastric acid inhibitor peptide, and prostaglandin

Actions:

- Decreases the pH of the stomach which is important for the activation of other important digestive enzymes

Clinical correlation:

- Antihistamines, prostaglandin analogs and PPIs work on different targets to decrease acid production by the parietal cells and are used in the treatment of peptic ulcer disease

### Pepsin:

Definition and source:
A digestive enzyme that is released by the chief cells of the stomach.

Regulation:

- Its production is increased by vagal stimulation and presence of acid in the stomach
- It's released in an inactive form known as pepsinogen
- Pepsinogen is converted to the active form pepsin in the presence of acid ($H^+$)

Action:

- Protein digestion

### Bicarbonate:

Definition and source:
This buffer is secreted by the mucosal cells lining the stomach, duodenum, pancreas and salivary glands. It is also released by Brunner glands in the duodenum.

Regulation:

- Increased release is stimulated by pancreatic and biliary secretions, which are stimulated by secretin

Action:

- Neutralizes the acid in the lumen of the duodenum which is important for the activation of the pancreatic digestive enzymes

### Intrinsic Factors:

Definition and source:
This binding protein is released by the parietal cells of the stomach. Same cells that secrete acid.

Clinical correlation:

- The absorption of vitamin $B_{12}$ by the terminal ileum requires the binding of vitamin $B_{12}$ to intrinsic factor
- Autoimmune destruction of parietal cells results in chronic atrophic gastritis → loss of intrinsic factor
- Failure of absorption of vitamin $B_{12}$ by the terminal ileum → pernicious anemia

## Common Oral Pathologies

### Cleft Lip/Palate

Definition:

A cleft lip deformity is often associated with a cleft palate. An occult cleft is the incomplete separation of the lip with distortion but no separation of the vermillion border. An incomplete cleft lip is lip separation through the vermillion border with downward displacement of the ala and an intact nasal sill. A complete cleft lip has complete separation of the lip and nasal sill.

Etiology:

- The nose and lip come from the 1st and 2nd pharyngeal arches
- Cleft lips and palates occur due to lack of fusion of the medial nasal process of the frontal nasal prominence with the maxillary process during embryogenesis

Epidemiology:

- Usually on the left side
- 0.1% overall risk
- More common in Asian populations
- 29% have associated congenital malformations

Risk factors:

- Maternal use of phenytoin, steroids, tobacco, and alcohol
- Maternal malnourishment

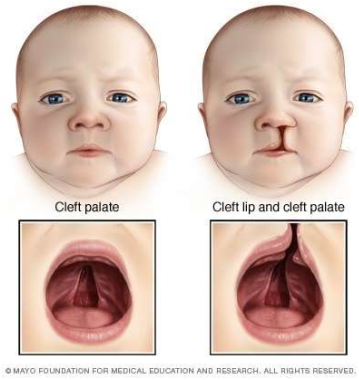



Figure 11: Isolated cleft palate, and cleft lip/palate. Source: Mayo Clinic

## Aphthous Stomatitis

Definition:

Recurrent painful aphthous ulcers known as canker sores on the non-keratinized oral mucous membranes.

Epidemiology:

- 20% of the general population
- More common in females
- Most often occurs in the second and third decades of life
- Can be a manifestation of other systemic diseases such as:
    - Behcet disease
    - Systemic lupus erythematosus
    - Reactive arthritis
    - Crohn disease

Risk factors:

- Iron, vitamin B6 and B12 deficiencies
- Thiamine or zinc deficiency
- Nonsmokers
- Smokers who quit smoking
- Poor oral hygiene

Triggers:

- Local trauma
- Emotional or physiologic stress
- Exposure to allergens
- Exposure to foods containing cinnamon, cheese, citrus or figs

Pathology:

- Immune-mediated ulcers by T-cell and neutrophil dysfunction

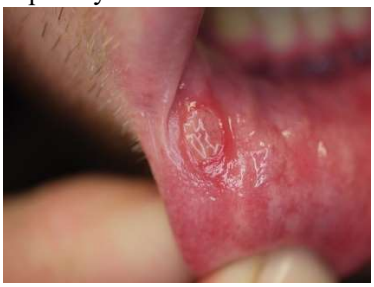


Figure 12: Aphthous ulcer. Source: https://www.ncbi.nlm.nih.gov/books/NBK431059/

## Behcet Disease

Definition:

An oculo-oro-genital syndrome with chronic remitting and relapsing inflammation.

Epidemiology:

- More common in Mediterranean ancestries especially Turkey
- Prevalence in Turkey is as high as 420 per 100,000
- Age of onset is in the second or third decade

Etiology:

- Unknown cause
- Autoimmune disease triggered by a dysregulated immune response to HSV, streptococcus or staphylococcus infection
- Genetic predisposition in HLA-B51 carriers

Immunologic findings in Behcet disease:

- Autoantibodies against intermediate filaments of mucous membranes

- Immune complexes deposition in the involved sites
- Decreased complement levels
- Immunoglobulin complement deposition within and around small blood vessels (vasculitis)
- Decreased ratio of CD4+/CD8+

Leukocytoclastic vasculitis is pathognomonic of Behcet disease.

Presentation:

- Multiple aphthous ulcers
- Genital ulcers on the scrotum in males, and vulva and vagina in females
- Ocular involvement in the form of conjunctivitis, uveitis, retinal vasculitis, and posterior uveitis → the latter can lead to blindness
- Non-deforming arthritis of the medium and large joints which is asymmetric, sterile, and seronegative
- Deep venous thrombosis, oro-genital ulcers and eye disease is highly suggestive of Behcet disease

Diagnosis:

Recurrent oral aphthous stomatitis plus two of the following:

- Recurrent painful genital ulcers
- Ocular involvement
- Skin lesions such as erythema nodosum, or a positive Pathergy test (a sterile pustule after local trauma to the skin)
- Cerebral infarctions or sterile meningoencephalitis

Treatment:

- Topical antibiotics and corticosteroids for ulcers
- Topical corticosteroids for ocular disease
- Colchicine, and NSAIDs for articular disease
- Systemic steroids for vascular, or CNS disease
- Immunomodulators or immunosuppressive drugs are reserved for refractory cases

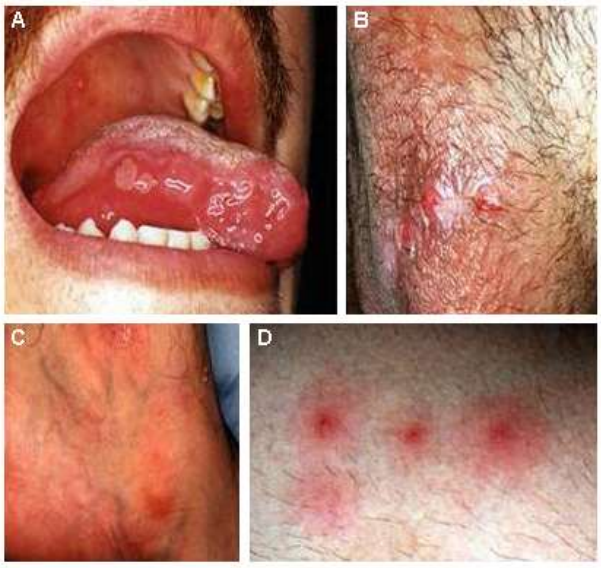



Figure 13: Behcet disease clinical presentation. Source: BMJ Best Practice

Herpetic Ulcers:

- Most cases of primary HSV-1 infection are asymptomatic
- Orolabial herpes is most often due to HSV-1 (few cases have been attributed to HSV-2)
- The most common manifestation is aa cold sore or a fever blister

Primary orolabial infection:

- Most often asymptomatic
- Viral prodrome of malaise, fevers, and tender lymphadenopathy
- Painful grouped vesicles on an erythematous base
- May progress to pustules, erosions and ulcerations
- Within two to six weeks, lesions crust over, and symptoms resolve

Recurrent orolabial infection:

- Milder than primary infection
- 24-giyr prodrome of tingling and burning
- Classically the vermillion border of the lip is affected

Treatment:

- Oral valacyclovir two grams twice daily for one day

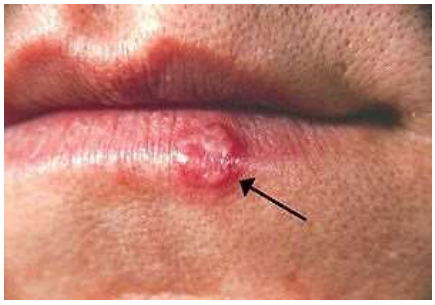


Figure 14: Orolabial herpes. Source: https://en.wikipedia.org/wiki/Herpes_labialis

## Leukoplakia and Other Causes of White Tongue

Oral thrush:

- Caused by candida albicans
- More common in patients with a CD4+ count less than 500/$mm^3$
- On physical examination, the lesion can be scrapped off
- Pseudohyphae on microscopy

Leukoplakia:

- A pre-malignant condition
- Oral hairy leukoplakia is caused by EBV in a patient with HIV
- The white plaque cannot be scrapped off
- More often on the lateral part of the tongue
- Can be classified into two types:
    - Homogenous leukoplakia → less likely to progress to malignancy
    - Non-homogenous leukoplakia → high malignant potential


Figure 15: Hairy leukoplakia versus oral candidiasis. Source: https://hellomrdoctor.com/hairy-leukoplakia/

## Mumps:

Mumps is caused by a viral agent. The diagnosis is suspected in patients with one of the following:

- Parotitis, acute salivary gland swelling, orchitis or oophoritis
- Positive laboratory test result in an asymptomatic patient

The diagnosis is probable in patients with parotitis or orchitis lasting two days or more and one of the following:

- Positive IgM antibodies against mumps
- Linkage to another confirmed or probable case in the patient's group or community
- An outbreak of mumps

The diagnosis is confirmed in patients with a positive reverse transcription PCR of mumps and any of the following:

- Acute parotitis
- Aseptic meningitis
- Encephalitis
- Orchitis
- Oophoritis
- Mastitis
- Pancreatitis

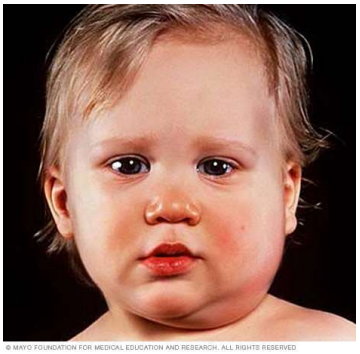


Figure 16: Parotid gland swelling in an infant with mumps. Source: Mayo Clinic

## Sialolithiasis:

Definition:

Stone formation in a salivary gland duct which results in obstruction. Can occur in parotid, submandibular or sublingual glands. A single stone is more commonly seen in Wharton duct of the submandibular gland.

- Caused by trauma or dehydration

Presentation:

- Periprandial pain
- Swelling of the obstructed gland

Treatment:

- NSAIDs
- Gland massage
- Warm compresses
- Instruct the patient to eat sour candies which promote salivary gland flow

Sialadenitis:

- The obstructed salivary gland might become infected
- Most often a staph infection
- Antibiotics might be needed

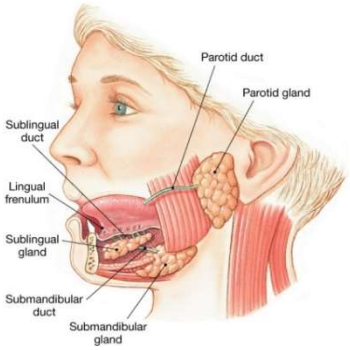



Figure 17: Anatomy of the salivary glands and ducts. Source: http://medifitbiologicals.com/sialolithiasis/

## Sjogren's Syndrome:

Definition:

A systemic autoimmune disorder that presents with sicca symptoms (dryness of the eyes and mouth).

Etiology:

- Genetic predisposition
- Epstein-Barr virus infection

Pathology:

- Focal lymphocytic sialadenitis (autoimmune inflammation of the salivary glands)
- Predominantly T-lymphocytes
- Involvement of other exocrine glands including the lacrimal glands
- Decreased production of tears and saliva

Presentation:

- Feeling of a foreign body in their eyes and a dry mouth
- Absence of tears
- Keratoconjunctivitis sicca on slit-lamp exam
- Schirmer test help in confirming ocular dryness
- Enlarged parotids or submandibular glands
- Polyarthritis, lower extremity purpura, and peripheral neuropathies

Diagnosis:

- Schirmer test and slit-lamp exam
- Positive ANA and RF (non-specific)
- Positive SS-A and SS-B (SS-A is specific for Sjogren's syndrome)
- Gold standard: minor salivary gland biopsy to show focal leukocytic sialadenitis

Treatment:

- Symptomatic treatment with artificial tears, oral and vaginal moisturizers

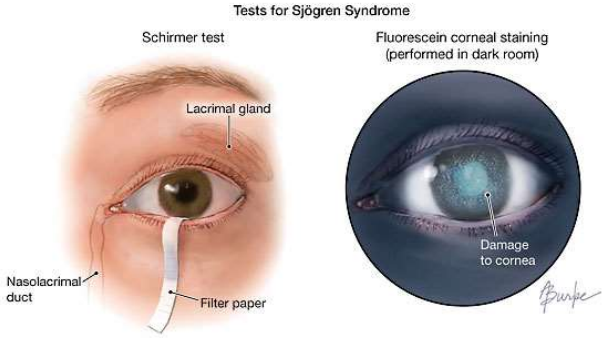



Figure 18: Schirmer test and slit-lamp exam in Sjogren's syndrome. Source: https://jamanetwork.com/journals/jama/fullarticle/186301

## Salivary Glands Neoplasia

Definition:

Salivary gland neoplasms are rare, and they can be benign or malignant. The pathohistological diagnosis is important for prognostic and treatment purposes.

The salivary glands can be divided into major salivary glands and minor salivary glands:

- The major salivary glands include the parotids and the submandibular and sublingual glands
- The minor salivary glands are about 600 to 1000 in number and are found across the oral cavity, palatine tonsils, pharynx and larynx

Epidemiology:

- 1% of head and neck tumors
- Incidence is 1.5 per 10,000
- 75% are benign – most commonly pleomorphic adenomas
- Tumors arising from the small salivary glands are more likely to be malignant

Pathophysiology:

- Radiation exposure, even in low-dosages, might be a risk factor for pleomorphic adenoma and other salivary gland neoplasms
- Warthin's tumor appears to be more common in smokers
- Epstein-Barr virus appears to be a risk factor for undifferentiated salivary gland carcinoma

Pleomorphic Adenoma:

- The most common benign salivary gland tumor
- Most commonly affects the parotid gland
- Variable appearance on histopathology → pleomorphic
- Well-differentiated tumor with parenchymatous glands and myoepithelium in a stroma of chondromyxoid composition
- May undergo malignant transformation

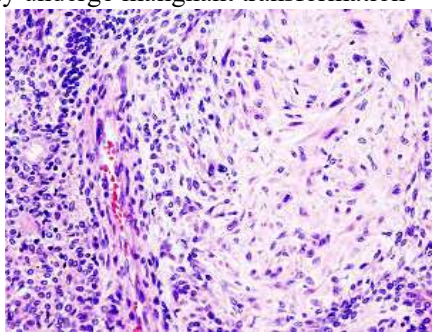


Figure 19: Pleomorphic adenoma. Source: https://en.wikipedia.org/wiki/Pleomorphic_adenoma

Diagnosis:

- Fine-needle aspiration has excellent sensitivity (90%)
- US, CT and MRI for staging

Treatment:

- Surgical resection
- The tumor should be handled gently → if rupture occurs intraoperatively, this can lead to recurrence
- Potential for malignant transformation → should be resected if identified

Warthin's Tumor:

- Also known as papillary cystadenoma lymphomatosum
- The second most common benign salivary gland tumor
- Most commonly affects the parotid gland
- More common in older people with history of cigarette smoking
- A well-differentiated tumor with germinal centers, cystic spaces, lymphocytosis, and condensed chromatin in the nuclei
- 10% are bilateral and 10% are multifocal
- The tumor is slow growing as compared to other salivary gland tumors

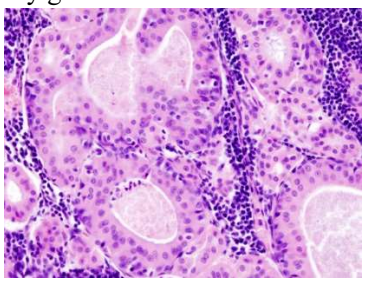


Figure 20: Warthin's tumor. Source: https://en.wikipedia.org/wiki/Warthin%27s_tumor#/media/File:Warthin_tumor_(1).jpg

Mucoepidermoid Carcinoma:

- Most common malignancy of the parotid gland
- The second most common malignancy of the submandibular gland
- Mainly two types of cells: mucous and squamous cells
- Based on the degree of differentiation, the tumor can be classified into low, intermediate and high-grade
- Slow-growing tumor that is associated with cytomegalovirus

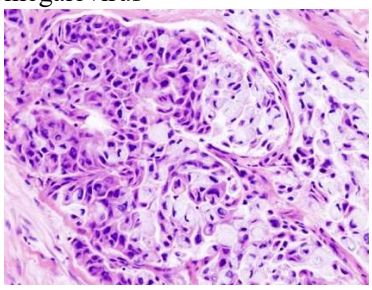


Figure 21: Mucoepidermoid carcinoma. Source: https://en.wikipedia.org/wiki/Mucoepidermoid_carcinoma#/media/File:Mucoepidermoid_carcinoma_(2)_HE_stain.jpg

Adenoid Cystic Carcinoma:

- Second most common malignancy of the salivary glands
- Most common malignancy of the submandibular gland

- Distant metastasis to the eyes, lung, brain and sinuses are common
- Treatment is surgical resection with or without radiation
- The prognosis is very poor

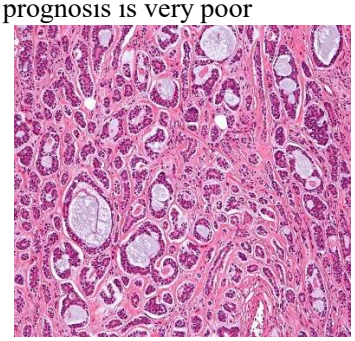


Figure 22: Adenoid cystic carcinoma. Source: https://en.wikipedia.org/wiki/Adenoid_cystic_carcinoma#/media/File:Adenoid_cystic_carcinoma_-_intermed_mag.jpg

## Duodenal Atresia

### Definition

Duodenal atresia is the congenital absence or closure of the lumen of the duodenum.

### Epidemiology

- The estimated incidence is 1 in every 5000 to 10,000 live births
- Up to 40% of them occur in infants with Down syndrome
- 8% of infants with Down syndrome have duodenal atresia

### Clinical Presentation

- During pregnancy, the mother presents with polyhydramnios
- It is caused by the inability of the fetus to swallow the amniotic fluid and absorb it
- After birth, the newborn presents with upper abdominal distension and bilious vomiting
    - Because the most common site of duodenal atresia is below the insertion of the common bile duct, vomiting usually has bile
    - In pyloric stenosis, the obstruction is before the common bile duct → non-bilious vomiting

### Complications

- The prognosis is very good
- Complications and prognosis are dependent on the presence of other congenital anomalies

### Diagnosis:

- Radiography is the imaging modality of choice to confirm the diagnosis of duodenal atresia in a newborn with bilious vomiting
- The abdominal radiograph shows two large air-filled spaces which is known as the double-bubble sign
- The two air-filled spaces are the stomach and proximal duodenum
- The pyloric sphincter separates the two bubbles from each other
- Air is absent in the distal duodenum

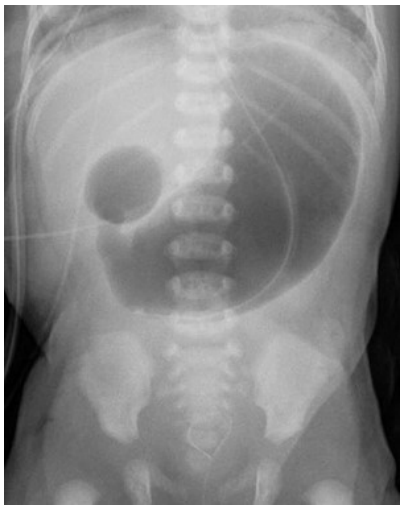


Figure 23: Double-bubble sign on an abdominal radiograph of a newborn with duodenal atresia. Source: https://en.wikipedia.org/wiki/Duodenal_atresia

- Jejunal and ileal atresia can also occur and are often caused by ischemic necrosis → segmental resorption

### Treatment:

- Stomach aspiration via a nasogastric tube
- IV fluids because the newborn will be dehydrated
- Duodenoduodenostomy is the definitive treatment
    - Not urgent

## Hypertrophic Pyloric Stenosis

### Definition

Hypertrophic pyloric stenosis (HPS) is a condition affecting infants that is characterized by an abnormally thickened pyloric portion of the stomach and manifests as obstruction to gastric emptying. Infants present in the first two to twelve weeks of life with forceful projectile nonbilious vomiting after feeding.

## Epidemiology

- The estimated incidence is 2 to 4 per 1000 live births
- Less common in African and Asian populations
- Male to female ratio is 4:1
- HPS is more common in bottle-fed infants, in rural populations, and in the summer months
- There is ongoing debate on whether the condition is acquired or congenital
- HPS is the most common cause of gastric outlet obstruction in infants

Possible risk factors:

- Firstborn child
- Male gender
- Maternal exposure to macrolides

## Pathophysiology

- The exact etiology is unknown
- It is hypothesized that the exposure of an abnormal pyloric tissue to enteric feeding is the trigger of the condition, and that the pathogenesis needs two to twelve weeks to cause significant obstruction
- Deficiency of nerve terminals and peptide-containing nerve fibers in the pyloric portion of the stomach
- Decreased production of mRNA for nitric oxide synthase and a decrease in the interstitial cells of Cajal in the muscular layer of the pylorus has been described
- Increased production of insulin-like and platelet-derived growth factors → myocyte hypertrophy
- These pathologies eventually lead to the following:
    - Impaired relaxation of the pylorus muscle
    - Subsequent hypertrophy of the pylorus muscle

## Clinical Presentation

- Infants aged 2 to 12 weeks present with forceful projectile nonbilious vomiting
- Palpation reveals a hypertrophic pylorus → often described as an olive
- The olive sign is present in 99% of the infants and is diagnostic of HPS
- The child's hips should be flexed to relax the abdominal wall
- Figure 1 shows how the olive is palpated in HPS
- Visible peristaltic waves

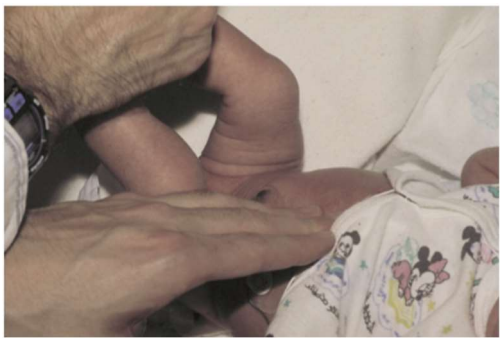


Figure 24: Palpation for the olive sign in an infant with HPS. Source: DOI: 10.1053/j.sempedsurg.2006.10.004

## Diagnosis:

- Ultrasonography is the imaging modality of choice with an accuracy of 100%
- Ultrasonography reveals a thickened and lengthened pylorus that fails to relax

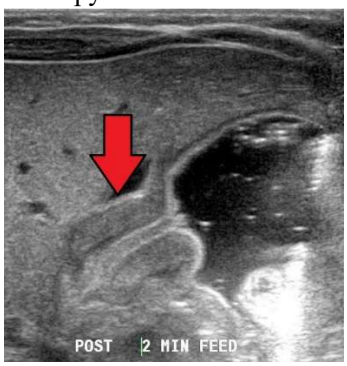



Figure 25: Ultrasonography in an infant with HPS showing a thickened and lengthened pylorus. Source: https://en.wikipedia.org/wiki/Pyloric_stenosis#/media/File:Pyloric-stenosisLocal.jpg

- Infants develop hypokalemia and metabolic alkalosis due to the loss of stomach acid in vomiting
- The kidney conserve sodium at the expense of hydrogen ions → paradoxical aciduria
- Known as hypokalemic hypochloremic metabolic alkalosis
- Barium swallow study reveals a string-sign

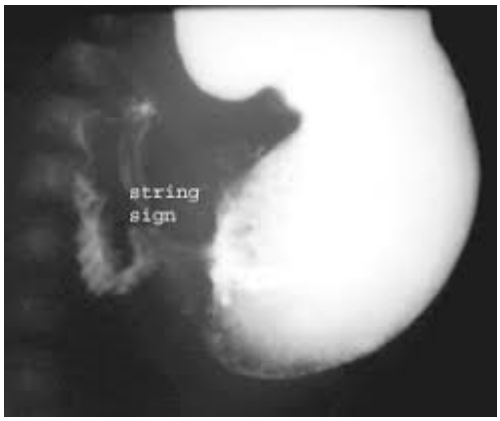



Figure 26: String-sign in HPS. Source: https://meddiction.com/knowledgebase/pyloric-stenosis/

## Treatment:

- Fluid resuscitation is important to break the cycle of hypokalemic hypochloremic metabolic alkalosis and aciduria
- Definitive treatment is pyloromyotomy

## Liver Tissue Architecture

### Hepatic Lobules

A hepatic lobule is the small division of the liver at the microscopic scale. These are the building blocks of liver parenchyma and they consist of a portal triad, hepatocytes arranged in linear cords in a capillary network, and a central vein.

Portal triad:

- The functional unit of the liver
- Consists of three vessels "interlobular artery, interlobular vein and a bile duct
- Figure 1

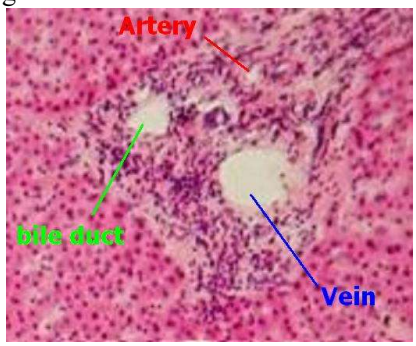



Figure 27: Portal triad. Source: https://en.wikipedia.org/wiki/Portal_triad#/media/File:Portal_triad.JPG

## Cellular Composition of the Liver:

- The apical surface of the hepatocytes faces bile canaliculi
- The basolateral surface faces sinusoids
- The functions of the hepatocyte are dependent on its hepatic zone

Kupffer cells:

- Specialized macrophages
- Located in the sinusoids
- Figure 2

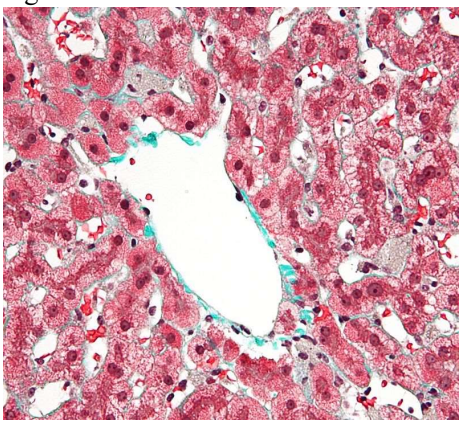


Figure 28: Black arrow points to a Kupffer cell. Source: https://en.wikipedia.org/wiki/Kupffer_cell#/media/File:Kupffer_cells_high_mag_cropped.jpg

Hepatic stellate cells:

- Found in the space of Disse
- Store vitamin A
- Produce extracellular matrix when activated
- Responsible for hepatic fibrosis
- Figure 3

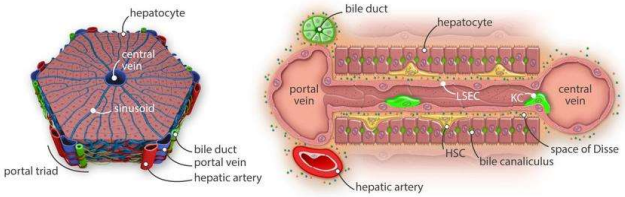



Figure 29: Acinus architecture. Source: https://www.researchgate.net/figure/The-liver-lobule-and-acinus-Schematic-representation-of-a-liver-lobule-and-a-diagram_fig1_318301214

## Hepatic Zones:

- Hepatic acini can be divided into different metabolic zones

- The definition of a zone is the imaginary line connecting two portal triads and extending towards the two adjacent central veins
- Figure 4

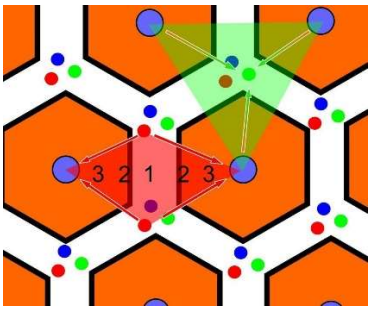



Figure 30: The red diamond-shaped acinus is what we refer to when we talk about hepatic zones. Zone 1 is nearest to the portal triads. Zone three is nearest to the central vein. Source: https://en.wikipedia.org/wiki/Lobules_of_liver#/media/File:Liver_scheme1.jpg

Zone I:

- Periportal zone
- Hepatocytes in this zone are mainly concerned with gluconeogenesis, beta-oxidation of fatty acids, and cholesterol synthesis
- Most oxygenated part of the acinus
- First site to be affected by viral hepatitis
- First site to be affected in ingested toxins such as cocaine
- This is the affected zone in hemochromatosis where hemosiderin is deposited

Zone II:

- An intermediate zone
- Necrosis of zone II → yellow fever

Zone III:

- Pericentral vein (centrilobular) zone
- Least oxygenated zone → first to be affected by ischemia
- Highest concentration of cytochrome P-450
- Responsible for the metabolism of medications and toxins such as ethanol, halothane, rifampin, and $CCl_4$
- Most affected site in alcoholic hepatitis

Note: Bridging fibrosis starts from the central vein and progresses to the portal triad (zone III before zone I).

## Liver Function Tests:

- There are two important enzymes within the hepatocytes
- Aspartate transaminase and alanine transaminase
- Destruction of the hepatocyte results in elevation in the blood levels of these two enzymes
- Alanine transaminase (ALT) is more specific to the liver than aspartate transaminase (AST)

## Jaundice:

## Bilirubin Physiology:

- RBCs are destroyed in the reticuloendothelial system and heme is extracted
- Heme is metabolized by heme oxygenase (in macrophages) to biliverdin
- Biliverdin is reduced to bilirubin
- Bilirubin at this stage is unconjugated and it is water insoluble → it needs to be bound to albumin in the bloodstream
- Unconjugated bilirubin-albumin complex is taken up by the liver
- UDP-glucuronosyltransferase converts it to conjugated bilirubin which is water soluble
- Direct bilirubin is bilirubin-glucuronate
- Indirect bilirubin is unconjugated bilirubin
- Conjugated bilirubin enters the gastrointestinal tract in the bile
- It gets converted to urobilinogen by the gut bacteria
- 80% of urobilinogen is excreted in the feces as stercobilin → brown color of the stool
- 20% is reabsorbed into the bloodstream
    - 10% of this will go to the kidneys to be excreted in the urine in the form of urobilin which gives the urine its characteristic yellow color
    - 90% will enter the enterohepatic circulation to be recycled by the liver

## Causes of Jaundice:

Definition:

Jaundice is the yellowish discoloration of the skin, mucous membranes and conjunctiva which occurs when serum bilirubin levels become higher than 3 mg/dL.

- Most cases of acute jaundice are due to intrahepatic pathologies such as acute viral hepatitis, alcoholic liver disease and drug-induced liver injury
- 45% of the cases are due to extrahepatic causes such as gallstone disease, hemolysis, and malignancy

Unconjugated hyperbilirubinemia:

Increased bilirubin production:

- Too much bilirubin is being produced that the conjugation machinery fails to keep up
- Increased red blood cell destruction
- Red blood cell membrane disorders, enzyme disorders, hemoglobin disorders, or autoimmune hemolysis
    - Cold reactive, warm reactive, or drug-induced hemolysis
    - Sickle cell anemia or thalassemia
    - G6PD deficiency
    - Pyruvate kinase deficiency
    - Spherocytosis
    - Myeloproliferative neoplasms such as polycythemia vera
- Increased heme metabolism → large amounts of unconjugated bilirubin → overwhelmed conjugating machinery → clinical jaundice

Impaired bilirubin conjugation:

- Normal RBC turnover
- Gilbert syndrome is caused by a deficiency in UDP-glucuronosyltransferase
    - Benign condition with jaundice and unconjugated hyperbilirubinemia when fasting or after strenuous exercise
- Crigler-Najjar syndrome is more severe
- Ingestion of UDP inhibitors such as protease inhibitors → clinical jaundice in patients with Gilbert syndrome
- Physiologic jaundice in newborns

Conjugated hyperbilirubinemia:

Intrahepatic causes:

- Viral hepatitis
- Alcoholic liver disease (steatosis, hepatitis or cirrhosis)
- Nonalcoholic steatohepatitis
- Drug-induced liver injury
- Sepsis
- Primary biliary cirrhosis
- Autoimmune hepatitis
- Ischemic hepatitis
- Wilson disease or hemochromatosis (cirrhosis)
- Hepatocellular carcinoma or metastatic disease to the liver

Extrahepatic causes:

- Choledocholithiasis
- Biliary strictures
- Biliary atresia
- Cholangitis
- Choledochal cysts
- Gallbladder carcinoma
- Cholangiocarcinoma
- Pancreatic head adenocarcinoma
- CMV or HIV infections

## Pathophysiology

- Jaundice occurs when there are disruptions in the metabolic pathway of unconjugated bilirubin production, uptake by the liver, conjugation by the liver, or secretion of conjugated bilirubin

## Clinical Presentation

- Enquire about alcohol and drug use
- Differentiate between intrahepatic causes (alcoholic liver disease, viral hepatitis) and extrahepatic causes (common bile duct stones or cholangitis)
- The physical examination aims to identify the cause of jaundice
- Examination and history taking can help in the identification of the cause, but there are no specific clinical findings to suggest conjugated over unconjugated hyperbilirubinemia

## Diagnosis

Initial diagnostic workup of a jaundiced patient:

- Complete history and physical examination
- Measure total, direct and indirect bilirubin
- AST, ALT and ALP
- GGT
- Synthetic liver function tests (INR, prothrombin time, albumin)

Further diagnostic workup for unconjugated hyperbilirubinemia:

- Mainly an elevation in indirect bilirubin

- Peripheral smear, direct antibody tests to exclude hemolysis
- G6PD enzyme testing
- If hemolysis is unlikely, consider Gilbert or Crigler Najjar syndrome as the diagnosis

Further diagnostic workup for conjugated hyperbilirubinemia:

- Mainly an elevation in direct bilirubin
- Laboratory testing for viral hepatitis
- Ultrasonography
- Treat the cause if possible

## Achalasia

### Definition:

Achalasia is a neurodegenerative motility disorder of the esophagus that results in deranged esophageal peristalsis and loss of lower esophageal sphincter function. The lower esophageal sphincter fails to relax due to the loss of the myenteric (Auerbach) plexus.

### Epidemiology:

- Rare
- Incidence ranges between 0.5 to 1.2 per 100,000 per year
- Equal frequency in both genders
- Possible bimodal peak in incidence in those aged around 30 and 60 years
- The incidence of achalasia is rising which could be due to the increased awareness about the condition

### Pathophysiology:

- The exact etiology is unknown
- The end-point pathology regardless of the exact trigger is the destruction of the inhibitory parasympathetic neurons in the myenteric Auerbach plexus

Autoimmune diseases and achalasia:

- Autoimmune diseases such as systemic lupus erythematosus and uveitis are found to be more common in patients with achalasia
- In some patients, the myenteric plexus is invaded by T-cell infiltrates and there is an increase in the expression of human leukocyte antigen class II antigens
- Autoantibodies are more often found in patients with achalasia than the general population

Infectious agents:

- Chagas disease can present with achalasia
- Varicella zoster virus and Guillain-Barre syndrome can precede achalasia in some patients

Genetic predisposition:

- A triad of achalasia, alacrimia and adrenocorticotrophic hormone resistant adrenal insufficiency has been described

### Clinical Presentation

- Patients present with dysphagia → cardinal symptom of achalasia | solids before liquids
- Chest pain
- Nocturnal cough due to the regurgitation of undigested food into the trachea
- Weight loss

### Diagnosis

- Esophageal manometry is the gold standard in the diagnosis of achalasia:
  - Aperistalsis and failure of relaxation of the lower esophageal sphincter

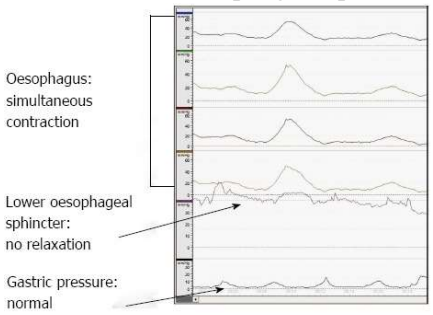



Figure 31: Esophageal manometry findings in achalasia. Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3793135/

- Endoscopy is important to exclude other causes of dysphagia such as carcinoma of the esophagus
- Barium esophagogram can show the pathognomonic bird's beak sign in the distal esophagus with proximal esophageal dilation:
  - A late finding in established achalasia
  - Its absence does not rule out achalasia

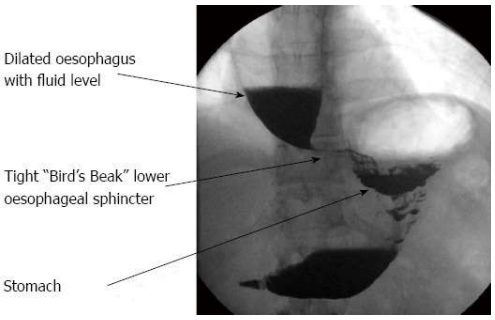



Figure 32: Barium esophagogram showing bird's peak sign in achalasia. Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3793135/

## Treatment:

- Pneumatic balloon dilatation or surgery
- If surgical intervention is not feasible:
    - Long-acting nitrates or calcium channel blockers – limited efficacy
    - Endoscopic injection of botulinum toxin to relax the lower esophageal sphincter → short-term improvement only

## Complications

- Aspiration pneumonia
- Megaesophagus
- Increased risk of squamous cell carcinoma:
    - Increased levels of nitrosamines produced by bacterial overgrowth due to stasis of food in achalasia
- Increased risk of adenocarcinoma when achalasia is treated successfully:
    - Successful treatment of achalasia often leads to GERD

## Esophageal Complaints

### Introduction:

Esophageal complaints are common. They are usually benign and do not indicate serious disease. The most common esophageal symptom is heartburn, however, in this discussion we will focus on two esophageal-specific complaints: dysphagia and odynophagia.

### Dysphagia

Definition:

Difficulty swallowing → food is unable to pass from the esophagus to the stomach. Dysphagia is usually caused by a structural abnormality of the esophagus, i.e. achalasia for instance. History and physical examination can correctly identify the cause in 80 to 85% of the patients.

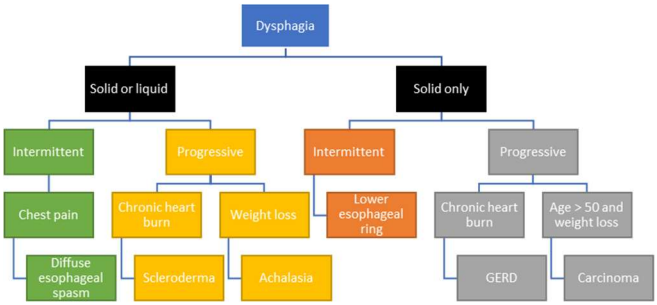
Mechanism:

- Primary and secondary peristaltic contractions of the esophagus propel food down to the stomach
- Loss of these contractions result in dysphagia
- Mechanical obstruction of the esophageal lumen due to an intraluminal mass, i.e. tumor, or stricture can also result in dysphagia

Causes:

- Mechanical obstruction:
    - Benign esophageal strictures
    - Webs and rings (associated with iron deficiency)
    - Neoplasms
- Motility disorders:
    - Achalasia
    - Spastic motility disorders of the esophagus
    - Scleroderma
    - Chagas disease
- Other causes:
    - Diabetes
    - Alcoholism
    - GERD

Approach to a patient with dysphagia:




Diagnosis:

- Barium swallow
- Endoscopy
- pH monitoring
- Esophageal manometry

### Odynophagia:

Definition:

Painful swallowing. It can range from a dull retrosternal ache on swallowing to stabbing pain radiating to the back.

Usually caused by an inflammatory process of the esophageal mucosa.

Causes:

- Caustic ingestion:
  - Acid
  - Alkali such as lye
- Pill-induced esophagitis:
  - Doxycycline
  - Potassium chloride
  - Quinidine
  - Iron sulfate
  - Zidovudine
  - NSAIDs
- Radiation
- Infectious:
  - Candida albicans or HSV in healthy individuals
  - Candida, HSV, CMV, EBV, tuberculosis, protozoan or idiopathic in HIV patients
- Severe ulcerative esophagitis secondary to GERD
- Esophageal carcinoma

Some of these causes can cause odynophagia and dysphagia at the same time.

Diagnosis:

- Endoscopy

## Esophagitis:

### Definition:

Esophagitis is a term that refers to the inflammation of the esophageal mucosa. It is associated with heartburn, chest pain, dysphagia and odynophagia. The most common cause of esophagitis is gastroesophageal reflux disease (GERD). Here, we focus on the other types of esophagitis that are not caused by GERD.

### Eosinophilic Esophagitis:

- Immune-mediated inflammatory disease
- Eosinophilic infiltration of the esophageal mucosal layer
- Annual incidence is 7 per 100,000
- The most common symptom is dysphagia for solid foods
- Family history of allergies

Diagnosis:

- Endoscopy demonstrates multiple esophageal rings that resemble the rings found in the trachea
- If a biopsy is taken, it would reveal eosinophilic infiltration with more than 15 eosinophils in high-power-field

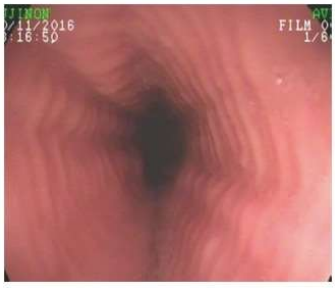


Figure 33: Trachealization of the esophagus as seen on endoscopy in eosinophilic esophagitis. Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5423037/

### Esophagitis in Crohn's Disease:

- Crohn's disease affects the entire GI tract
- It is an inflammatory bowel disease
- Up to 3% of patients with Crohn's disease have esophagitis

Diagnosis:

- Endoscopy reveals multiple aphthous erosions and ulcerations
- The erosions are far from the esophago-gastric junction
- Fistulae might be found between the esophagus and mediastinum, pleural cavity or bronchi
- Biopsy might reveal non-caseating granulomas in 10% of the cases

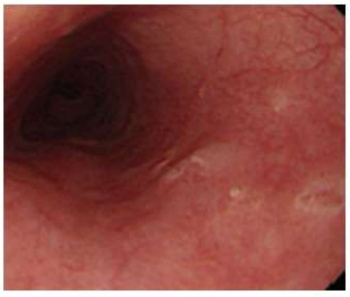


Figure 34: Aphthous ulcers on endoscopy in a patient with esophagitis and Crohn's disease. Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5423037/

### Drug-Induced Esophagitis:

- Antibiotics such as doxycycline, amoxicillin, ciprofloxacin, metronidazole and rifaximin
- NSAIDs
- Anti-hypertensives including spironolactone and furosemide
- Bisphosphonates
- Warfarin

Diagnosis:

- Endoscopy reveals ulcers and erosions of the middle portion of the esophagus

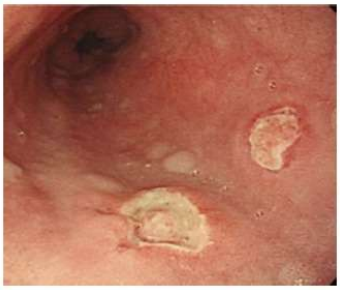


Figure 35: Ulcers in a patient with drug-induced esophagitis. Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5423037/

Treatment:

- This type of esophagitis is easily treated with PPIs, antacids and the discontinuation of the offensive drug

### Infectious Esophagitis:

- Rare in immunocompetent individuals
- Herpes simplex virus is the most common viral agent responsible for esophagitis in immunodeficient patients especially those with HIV infection
    - Multiple shallow ulcers in the lower third of the esophagus
    - More common in men
    - Can be accompanied by fever
- Candida can also cause esophagitis in immunocompromised patients
    - Endoscopy reveals multiple yellow plaques covering the entire esophagus
- Bacterial esophagitis is very uncommon. Staphylococcus aureus, and staphylococcus epidermidis can cause esophagitis in immunocompromised patients or in those who have been receiving long-term $H_2$ blockers or PPIs
- Treatment with the appropriate antimicrobial is possible once the etiological diagnosis is made:
    - Fluconazole for candida esophagitis
    - Acyclovir for HSV esophagitis

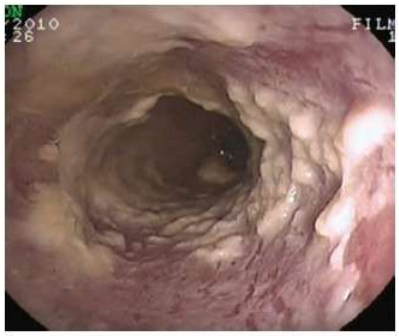


Figure 36: Candida esophagitis. Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC542303/

### Caustic Injury Esophagitis:

- Most commonly caused by alkaline liquids
    - Colliquative necrosis → destruction of mucosa within few seconds → microvascular thrombus formation within 48 hours
- Acidic substances can also cause esophagitis
    - Coagulative necrosis and eschar formation
- Most common alkaline agent is household detergents
- Picosulfate, a laxative, can cause caustic injury esophagitis
    - Must be properly dissolved in water before ingestion

### Other Types of Esophagitis:

- Chemotherapeutic agents such as dactinomycin, bleomycin, daunorubicin, 5-flourouracil, methotrexate and vincristine can cause esophagitis secondary to oropharyngeal mucositis
- Thoracic irradiation can cause esophagitis
    - Progressive fibrosis and degeneration of blood vessels, smooth muscle cells, and nerves

## Gastroesophageal Reflux Disease

### Definition:

Gastroesophageal reflux disease (GERD) is defined as symptoms due to mucosal damage caused by abnormal

reflux of gastric contents into the esophagus. It can be classified into non-erosive and erosive reflux disease.

## Epidemiology:

- The prevalence can be as high as 20%
- Western countries have higher prevalence of GERD (10 to 20%) than Asian countries (5%)
- These figures are based on the symptomatic diagnosis of GERD without the confirmation of the diagnosis by endoscopy

## Pathophysiology:

- Transient decrease in lower-esophageal sphincter tone → gastric acid reflux
- Associated with asthma

## Clinical Findings:

Typical GERD symptoms:

- Acid regurgitation – water brash
- Heartburn

Atypical GERD symptoms:

- Epigastric fullness
- Epigastric pain
- Dyspepsia
- Nausea
- Bloating
- Belching

Extraesophageal symptoms:

- Chronic unexplained cough
- Bronchospasm
- Wheezing
- Hoarseness
- Sore throat
- Asthma
- Laryngitis
- Dental erosions due to acid reflux

## Diagnosis:

The diagnostic test is dependent on the patient's presentation and the presence or absence of alarm symptoms.

Alarm symptoms:

- Dysphagia
- Odynophagia
- Iron deficiency anemia
- Weight loss
- Vomiting blood

PPI trial:

- Patients with classic GERD symptoms and no alarm symptoms can be prescribed a PPI. If symptoms resolve → the diagnosis of GERD is confirmed

Upper endoscopy:

- Patients with typical symptoms of GERD who are unresponsive to PPIs should get an upper endoscopy
- This will help in the classification of the patient into erosive or non-erosive reflux disease
- Patients with alarm symptoms should receive an upper endoscopy as first-line diagnostic test

Esophageal pH monitoring:

- If the patient's symptoms persist but they are atypical of GERD, esophageal pH monitoring is indicated

Barium esophagram:

- GERD patients with dysphagia → to exclude peptic strictures

Esophageal manometry:

- Patients who will receive surgical intervention for GERD must not have achalasia or scleroderma

## Treatment:

- The treatment approach includes lifestyle modification, medical therapy and surgical therapy

Lifestyle modifications:

- Weight loss
- Elevation of head of bed
- Avoidance of nighttime meals
- Elimination of trigger foods (chocolate, caffeine and alcohol)
- Helpful, but rarely enough to control GERD symptoms

Pharmacological therapy:

- Patients with erosive reflux disease should receive a proton pump inhibitor such as omeprazole or lansoprazole
- Proton pump inhibitors block the H/K ATPase pump in the gastric parietal cell → acid suppression

- $H_2$ blockers such as ranitidine are helpful in non-erosive reflux disease
- PPIs can still be needed on-demand in non-erosive reflux disease
- Antacids such as aluminum hydroxide, magnesium hydroxide, and calcium carbonate have limited efficacy in GERD

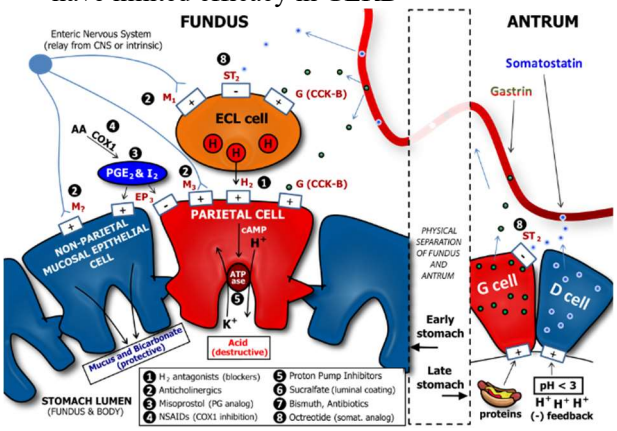



Figure 37: The main targets of the pharmacological treatment of GERD. Source: https://en.wikipedia.org/wiki/Gastric_acid#/media/File:Determinants_of_Gastric_Acid_Secretion.svg

Surgery:

- Considered in patients who cannot tolerate medical therapy, who have medically-refractory GERD, or in patients with GERD and a large hiatal hernia
- Traditional fundoplication is an old procedure used in the treatment of medically-refractory GERD but it has a lot of complications
- LINX Reflux Management System augments the lower esophageal sphincter by the placement of a titanium bracelet with magnetic cores around the LES

## Complications:

- Erosive esophagitis
- Peptic stricture
- Barrett's esophagus
- Esophageal adenocarcinoma in Barrett's esophagus
- Pulmonary disease

## Esophageal Cancer:

### Definition

Esophageal cancer is an aggressive malignancy and a leading cause of cancer-related death. In the Western countries, adenocarcinoma is more common than squamous cell carcinoma.

- Esophageal squamous cell carcinoma is more common worldwide and affects upper two-thirds of the esophagus
- Esophageal adenocarcinoma is more common in Western countries and affects lower third of the esophagus

### Epidemiology:

- 8th most common cancer worldwide
- 6th most common cause of cancer-related deaths
- Incidence of esophageal adenocarcinoma (EAC) of the distal esophagus is 2.8 per 100,000 in men
- The ratio of esophageal squamous cell carcinoma of the upper esophagus to EAC of the distal esophagus is 0.4:1 in the West
- EAC is becoming more common because:
  - GERD incidence is increasing
  - Obesity incidence has increased
- 5-year survival is 15%

Risk factors:

- Male dominant disease
- Male to female ratio is 3:1
- EAC is five times more common in Caucasians than in any other race
- Esophageal squamous cell carcinoma is more common in Chinese and Asian individuals
- A body mass index > 30 is a risk factor for EAC
- GERD → Barrett's esophagus → EAC
- Smoking and alcohol are risk factors for squamous cell carcinoma of the esophagus
- HPV infection in esophageal squamous cell carcinoma
- H. pylori infection is protective against EAC
- NSAIDs might be protective against EAC

### Barrett's Esophagus:

- The risk of EAC increases by 60-fold in patients with GERD who develop Barrett's esophagus
- Barrett's esophagus is more common in men
- Replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (non-ciliated columnar with goblet cells)

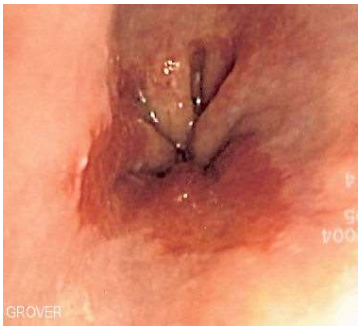



Figure 38: Barrett's esophagus as seen on endoscopy. Source: https://en.wikipedia.org/wiki/Barrett%27s_esophagus#/media/File:Barretts_esophagus.jpg

### Clinical Findings:

- Patients present with progressive dysphagia (solids before liquids)
- Some patients might present with bloody vomiting
- Weight loss
- Clearly, the symptoms are very non-specific → the diagnosis is usually delayed

### Diagnosis:

- The symptoms of esophageal cancer are similar to GERD with alarm symptoms
- Accordingly, most patients will hopefully receive an upper endoscopy in the early diagnostic workup
- Once the diagnosis is confirmed by endoscopy, a biopsy might be taken
- CT and PET are the next step to determine the local extension of the tumor (CT) and distant metastasis (PET)
- Endoscopic ultrasound is no longer recommended

### Treatment:

- Most patients are diagnosed when they have dysphagia
    - Dysphagia usually occurs in T2 or T3 stage (late presentation)
    - Neo-adjuvant chemotherapy or radiotherapy are indicated
- Surgery is indicated as the following:
    - Barrett's esophagus without EAC:
        - Radiofrequency ablation
    - EAC confined to the mucosa:
        - Endoscopic submucosal dissection
    - Other Tx stages that are superficial:
        - Minimally invasive esophagectomy
    - Locally advanced esophageal cancer:
        - Multimodal treatment with chemotherapy and debulking surgery
- A stent might be placed if stenosis occurs

## Acute and Chronic Gastritis

### General Characteristics of Acute Gastritis:

Acute gastritis is a non-specific term that refers to different diseases that cause inflammatory damage to the gastric mucosa. Acute gastritis can be classified into:

- Erosive gastritis which can be superficial, deep or hemorrhagic
- Non-erosive gastritis which is caused by Helicobacter pylori – H. pylori most often causes chronic not acute gastritis

Superficial acute gastritis:

- The symptoms are often absent or non-specific such as epigastric discomfort, nausea and vomiting
- The inflammation is confined to the mucosa
- The diagnosis is confirmed by endoscopy and biopsy
- No place for radiological evaluation
- Microscopic appearance does not correlate with the clinical picture
- It is often caused by alcohol, bile reflux, or is drug-induced

Severe erosive gastritis:

- Severe epigastric pain, vomiting and hematemesis are often present
- CT scan is helpful in confirming the diagnosis
- Endoscopy reveals deep ulcerations

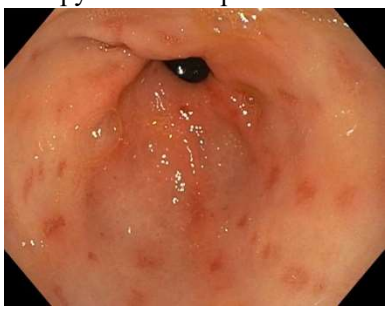


Figure 39: Erosive gastritis of the antrum. Source: https://pictures.doccheck.com/com/photo/38008-erosive-gastritis-antrum

## Causes of Acute Gastritis:

Reactive acute gastritis:

- Caused by NSAIDs and aspirin
- Most often confined to the greater curvature of the stomach
- NSAIDs interfere with arachidonic acid pathway → reduced prostaglandins which are needed for mucosal wall protection

Alcohol-induced acute gastritis:

- Heavy drinking can damage the mucosal layer of the stomach lining
- This can lead to ulceration
- Additionally, acute bacterial gastritis caused by Escherichia coli, Pseudomonas aeruginosa, and other bacteria is seen in patients who drink massive amounts of alcohol → phlegmonous gastritis

Hemorrhagic and ulcero-necrotic acute gastritis:

- These types of acute gastritis are seen in critically ill patients
- Major burns can result in massive water loss → hypovolemia → decreased perfusion to visceral organs including stomach → ischemic injury and ulcer formation – Curling ulcer
- Can resemble the ulcers seen in NSAIDs but involve the fundus of the stomach instead of the greater curvature
- Traumatic brain injury can also result in hemorrhagic acute gastritis either by similar mechanisms or due to severe physical stress: increased vagal stimulation → increased Ach → increased $H^+$ production
- This type of ulcer is also known as Cushing's ulcer

## Diagnosis of Acute Gastritis:

- Endoscopy is the first diagnostic test
  - Ulcers
  - Hyperemia
  - Erosions
  - A biopsy can be taken
- Urease breath test is used to screen for H. pylori infection → can cause non-erosive acute gastritis
- IgG and IgM antibodies specific to the suspected offending organism

## Treatment of Acute Gastritis:

- Misoprostol can be used for the prevention of NSAID-induced gastritis
- Antacids
- $H_2$ blockers
- Proton pump inhibitors
- Discontinuation of the offending agent: alcohol, NSAIDs if possible, or other drugs
- Adequate IV fluid replacement in major burns' patients

## Chronic Gastritis and its Types:

- Chronic gastritis is non-erosive
- While H. pylori may cause acute gastritis, it is most often associated with chronic gastritis
- 90% of chronic gastritis are attributed to H. pylori infection
- 10% of chronic gastritis are autoimmune → can cause pernicious anemia due to intrinsic factor deficiency → vitamin B12 deficiency

H. pylori chronic gastritis and cancer:

- H. pylori chronic infection results in chronic non-erosive non-atrophic gastritis in the early stages
- Eventually, atrophic gastritis occurs in the antrum, corpus or both
- Intestinal metaplasia occurs in the atrophic regions
- Dysplasia in the form of intraepithelial neoplasia occurs
- The final step would be stomach cancer
- Mucosa-associated lymphatic tissue lymphoma is also seen in chronic H. Pylori infection

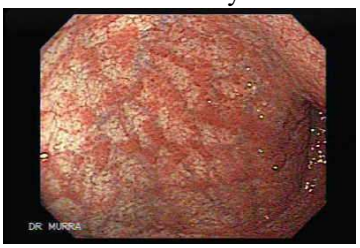



Figure 40: Chronic gastritis with atrophic gastritis. Atrophic gastritis is confirmed by biopsy. Source: https://www.gastrointestinalatlas.com/english/cronic_gastritis.html

## Treatment of Chronic Gastritis:

- The most important treatment is the eradication of H. pylori

- Triple therapy with amoxicillin, clarithromycin and omeprazole is an option

## Peptic Ulcer Disease:

### Definition:

Peptic ulcer disease refers to the injury of the stomach or duodenum secondary to acid. In the past, it was hypothesized that peptic ulcer disease is caused by a hypersecretory acidic environment. The current understanding of peptic ulcer disease emphasizes that the cause is H. pylori infection.

### Epidemiology:

- Annual incidence is 0.1 to 0.3%
- Life-time prevalence is 5 to 10%
- The incidence is decreasing after the introduction of new therapies for the eradication of H. pylori

### Pathogenesis:

- H. pylori infection, NSAIDs and aspirin are the main risk factors for peptic ulcer disease (PUD)
- Zollinger-Ellison syndrome can cause duodenal ulcers
- H. pylori secretes different proteins which activate the H+K+/ATPase channel or the calcitonin-gene related peptide sensory neurons
- The effects are increased acid production by the gastric parietal cells
- In some cases, hypochlorhydria can develop → ulcers are still seen
- H. pylori also secrete urease which increases the pH of the stomach → more suitable for the viability of other bacteria
- NSAIDs can cause peptic ulcer disease by the following mechanism:
    - Reduced prostaglandins → decreased protective lining of the stomach → ulcer formation
- Zollinger-Ellison syndrome is characterized by hypergastrinemia → stimulates gastric parietal cells to produce more HCl

The following table shows the differences between gastric and duodenal PUDs.

| | **Duodenal PUD** | **gastric pud** |
|---|---|---|
| **h. pylori** | 90% - hypertrophy of Brunner glands | 70% |
| **cancer risk** | Not increased | Increased |
| **other causes** | Zollinger-Ellison syndrome | NSAIDs |
| **presentation** | Pain decreases with meals | Pain increases with meals |
| | Weight gain | Weight loss |

### Clinical Presentation:

- Feeling hungry, and nocturnal abdominal pain in duodenal ulcers
- Postprandial abdominal pain, nausea, vomiting and weight loss in gastric ulcers
- Asymptomatic in the elderly

Hemorrhage:

- Can occur in gastric and duodenal ulcers
- Posterior duodenal ulcers can cause hemorrhage more often than anterior duodenal ulcers
- Most common PUD complication
- Gastric ulcers usually erode the left gastric artery
- Duodenal ulcers typically erode the gastroduodenal artery
- Can manifest as melena or hematemesis
- Mortality can be as high as 20%

Obstruction:

- Ulcers in the pyloric channel or duodenum
- Patients present with gastric outlet obstruction

Perforation:

- More often in anterior duodenal ulcers than posterior ulcers
- An erect abdominal radiograph can reveal free-air under the diaphragm
- Irritation of the phrenic nerve → pain can refer to the shoulder
- Can result in peritonitis → shock → death

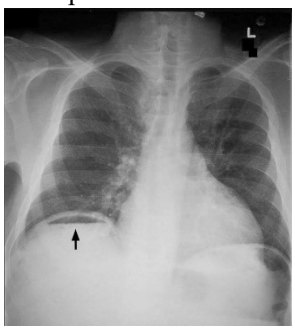


Figure 41: Air under the diaphragm in a patient with a perforated PUD. Source: https://upload.wikimedia.org/wikipedia/commons/3/3c/Pneumoperitoneum_modification.jpg

### Diagnosis:

Endoscopy:

- Gold standard for the diagnosis of PUD
- A biopsy can be taken to confirm the presence of H. pylori
- Rapid urease tests

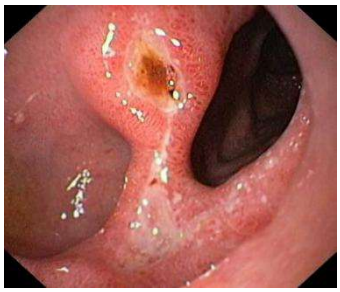


Figure 42: A PUD on upper endoscopy. Source: https://emedicine.medscape.com/article/181753-workup#c7

H. pylori non-invasive tests:

- H. pylori is the most common cause of PUD
- This led to the development of noninvasive tests to screen for H. pylori
- Urea breath test and stool antigen tests are available

Supporting tests:

- Barium swallow test – do not order if you suspect a perforation
- Blood gastrin levels – if Zollinger-Ellison syndrome is suspected

Treatment:

- Offending agents such as NSAIDs, alcohol, smoking or caffeine need to be stopped
- Triple or quadruple therapy to eradicate H. pylori:

Triple therapy:

- PPI plus amoxicillin plus clarithromycin for two weeks

Quadruple therapy:

- PPI plus amoxicillin plus clarithromycin plus metronidazole for two weeks

Other treatments:

- Bismuth can be added to the previous regimens
- $H_2$ blockers, misoprostol, and sucralfate are used as adjunct treatments
- Bismuth and sucralfate increase the production of $HCO_3$ in the base of the ulcer and provide physical protection

## Celiac Disease

### Definition:

Celiac disease is a chronic inflammatory autoimmune disorder of the small intestine due to the ingestion of dietary gluten products in susceptible people. An abnormal adaptive immune response against gluten-containing grains is the hallmark of the disease. Unlike other inflammatory conditions of the GI tract, gluten-induced enteropathy is completely reversible if complete avoidance of gluten is possible.

### Epidemiology:

- One of the most frequent genetically based disorders in humans
- The estimated prevalence is 1 to 2% in the United States
- Most cases remain undiagnosed

Risk factors for celiac disease:

- Family history
- Diabetes mellitus type-1
- Down syndrome
- Anemia
- Osteoporosis
- Northern European descent

### Pathology:

- 90% of patients with celiac disease express HLA-DQ2, the remainder express HLA-DQ8
- History of rotavirus infection in the first year of life appears to increase the risk
- Gluten is composed of prolamines (gliadins) and glutenin.
- An autoimmune response against gliadin appears to be the pathology:
    - Elicit T-cell responses
    - Induces the production of cytokines
    - Intestinal injury
- Histopathology:
    - Decreased enterocyte height
    - Crypt hyperplasia
    - Villous atrophy
    - Increased intraepithelial T lymphocytes
- Dermatitis herpetiformis:
    - An inflammatory cutaneous disease
    - Associated with celiac disease
    - Diffuse, symmetrical polymorphic lesions of erythema, urticarial plaques, herpetiform vesiculae and blisters
    - Erosions and excoriations

- Typically occur in the third decade of life

### Clinical Presentation

Typical celiac disease symptoms:

- Chronic diarrhea and steatorrhea
- Failure to thrive
- Abdominal distention
- 12 to 18 months of age

Atypical symptoms:

- Symptoms secondary to malabsorption:
  - Vitamin A, D, E and K deficiency
  - Vitamin $B_{12}$ deficiency
  - Anemia
  - Osteopenia
- Short stature
- Recurrent abortions
- Hepatic steatosis
- Recurrent abdominal pain
- Dermatitis herpetiformis

### Complications:

Osteoporosis:

- Most common complication
- Caused by abnormal calcium absorption due to defective calcium transport
- Vitamin D deficiency (ADEK deficiency)
- Can be prevented by avoiding gluten-containing products during childhood

Enteropathy-associated intestinal T cells lymphoma:

- A very important complication
- Complete avoidance of gluten-containing products might decrease the risk

Collagenous sprue:

- Increased deposition of collagen in the extra-cellular matrix

Refractory sprue:

- T-lymphocytes express only CD3 and not CD8 – normal T-lymphocytes typically express both antigens

Other complications:

- Non-Hodgkin lymphoma
- Small bowel adenocarcinoma
- Ulcerative jejunoileitis → hemorrhage, obstruction or perforation

### Diagnosis:

Serologic tests:

- Antitissue transglutaminase antibodies (anti-tTGA) IgA antibodies
  - 97% sensitivity, 96% specificity and 98* accuracy
- IgA anti-endomysial has 100% specificity
- Anti-gliadin antibodies are no longer recommended due to low specificity and sensitivity
- Deamidated gliadin peptides can be used to increase certainty of the diagnosis

Histology:

- Gold standard to diagnose celiac disease in adults
- Villous atrophy, crypt hyperplasia, decreased enterocyte height, and lymphocytes' infiltrates of the small-bowel mucosa
- Normal villi with intraepithelial T-lymphocytes can be seen in other conditions:
  - Autoimmune enteritis
  - NSAID-induced enteropathy
  - Helicobacter pylori infection in the stomach

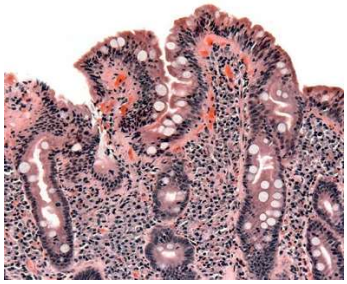


Figure 43: Histopathology in celiac disease. Source: https://en.wikipedia.org/wiki/Coeliac_disease#/media/File:Coeliac_path.jpg

Other tests:

- HLA-DQ2 and DQ8 testing → if negative in an asymptomatic patient, celiac disease can be ruled out
- In vitro gluten challenge test

### Treatment

- Life-long gluten-free diet

## Crohn's Disease

### Definition:

Crohn disease (CD) is a chronic inflammatory bowel disease characterized by skip lesions and can affect any

part of the gastrointestinal tract from the mouth to the anus. The inflammation is described as transmural.

## Epidemiology:

- Annual incidence ranges from 3 to 20 per 100,000
- More common in the industrialized world
- Slightly higher predominance in women
- More common in Ashkenazi Jews

Risk factors for celiac disease:

- Gastrointestinal infections, NSAIDs and antibiotics can increase the risk of CD by changing the gut microbiome
- Salmonella and campylobacter infections appear to carry the highest risk of developing CD in the next year
- Cigarette smoking doubles the risk of developing CD
- Diets that are high in sugar, omega-6 fatty acids, polyunsaturated fatty acids, oil and meat
- Family history
- NOD2 gene polymorphisms

## Pathology:

- Can affect any part of the GI tract
- Transmural inflammation:
    - Non-stricturing – inflammatory
    - Stricturing
    - Penetrating
- Cobblestone mucosa, creeping fat, and bowel wall thickening
- Linear ulcers and fissures
- String-sign on barium swallow
- Histopathology: noncaseating granulomas and lymphoid aggregates. Th1 mediated
- Malabsorption and increased risk of colorectal cancer

## Clinical Presentation:

Location:

- 50% - terminal ileum and colon
- 30% - small bowel only
- 20% - isolated colon disease
- Less than 10% of the patients might present with isolated perianal complaints, upper GI disease, or extraintestinal manifestations
- Up to 25% of patients with CD have perianal disease

Gastrointestinal symptoms and signs:

- Abdominal pain
- Diarrhea
- Weight loss
- Low-grade fever
- Fatigue
- In patients with stricturing disease:
    - Small bowel obstructions
    - Lack of fistulas and bowel movements
    - Nausea and vomiting
- In patients with penetrating disease:
    - Fistulas
        - Diarrhea in enteroenteric fistula
        - Urinary tract infection in enterovesicular fistula or enterouretheral fistula
        - Passage of stool from vagina in enterovaginal fistula
        - Drainage from skin in enterocutaneous fistula
    - Abscesses
- Bloody stool can be seen in severe colonic CD, however this is more common with ulcerative colitis

Extraintestinal manifestations of CD:

- Arthritis:
    - 25% of the patients
    - Peripheral and axial skeleton
    - Type I: flares with disease activity | a pauciarticular arthritis involving < 6 joints
    - Type II: involves more than 6 joints and is chronic | not related to disease activity
    - No synovial destruction
- Skin manifestations:
    - Erythema nodosum – mirrors luminal disease
    - Pyoderma gangrenosum – independent of luminal disease
- Primary sclerosing cholangitis:
    - More commonly seen in UC
    - Not related to luminal disease
    - Can result in cirrhosis, portal hypertension, cholangiocarcinoma and colon cancer
- Uveitis
- Scleritis

- Osteoporosis and vitamin $B_{12}$ deficiency
- Deep vein thrombosis
- Nephrolithiasis
- Failure to thrive in children

### Diagnosis:

- A clinical diagnosis
- Endoscopy is helpful and can reveal the following:
  - Skip lesions
  - Varying degrees of inflammation (erythema, friability, erosions and ulcers)
  - Luminal strictures
  - Fistulae
- Biopsy:
  - Non-caseating granulomas only in 25% of the patients
  - Lymphocytes, plasma cells, granulocytes, and distortion of the crypt architecture are other findings
  - Paneth cell metaplasia → chronicity of CD
- Imaging:
  - Computed tomography enterography
  - Magnetic resonance enterography
  - Small-bowel barium studies
- Serology:
  - Current recommendation is to not perform serologic testing in CD
  - Anti-saccharomyces cerevisiae antibodies
- Laboratory supporting findings:
  - Elevated ESR and CRP

### Treatment:

5-aminosalicyclic acid:

- Sulfasalazine, oral mesalamine, and rectal mesalamine
- Inhibit cyclooxygenase and lipoxygenase → decreased production of pro-inflammatory prostaglandins and leukotrienes by the arachidonic pathway
- Dose-related side effects: headache, epigastric pain, nausea, vomiting and rash
- Idiosyncratic side effects: hepatitis, autoimmune hemolysis, aplastic anemia, agranulocytosis and pancreatitis

Corticosteroids:

- Induction of remission in CD
- Budesonide → lower systemic bioavailability

Immunomodulators:

- Azathioprine
- Methotrexate
- Infliximab
- Adalimumab

Antibiotics:

- Metronidazole
- Ciprofloxacin

Surgery in stricturing and fistula-forming CD

## Ulcerative Colitis

### Definition:

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of the colon where there is diffuse friability and superficial erosions of the colonic wall and is often associated with colonic bleeding.

### Epidemiology

- Annual incidence ranges from 9 to 20 per 100,000
- Has a greater prevalence in adults when compared to Crohn's disease
- Peak incidence in those aged 15 to 30, and those aged between 50 to 70 years
- Appendectomy reduces the risk of ulcerative colitis
- Cigarette smoking appears to be protective against ulcerative colitis

### Pathology

- Defects in colonic mucin and tight-junctions → increased uptake of luminal antigens
- The lamina propria has an increased number of activated and mature dendritic cells which express Toll-like receptors (TLR2 and TLR4)
- Th2 response
- TNF-alpha, interleukin 13, and natural killer T-cells also play a role
- Continuous involvement of the colon, with universal involvement of the rectum
- Starts from the rectum and moves proximally
- Mucosal and submucosal inflammation
- Loss of haustra → lead pipe appearance on imaging

Histopathology:

- Lymphocytes, plasma cells and granulocytes infiltrate the mucosa and submucosa
- No skip lesions
- Goblet cell depletion
- Crypt abscesses
- No granulomas
- Confined to the colon

Complications:

- Fulminant colitis
- Toxic megacolon
- Perforation
- Colonic cancer:
    - 2% risk after ten years of diagnosis
    - 8% after 20 years
    - 30% after 30 years
    - Cancer risk is dependent on the disease's duration and extent

## Clinical Presentation

Gastrointestinal symptoms and signs:

- Bloody diarrhea
- Urgency and tenesmus
- Abdominal pain
- Weight loss
- Fever

Extraintestinal manifestations of UC:

- Episcleritis, scleritis and uveitis
- Arthritis:
    - Peripheral
    - Type I: flares with disease activity | a pauciarticular arthritis involving < 6 joints
    - Type II: involves the axial skeleton | not related to disease activity
    - No synovial destruction
- Skin manifestations:
    - Erythema nodosum – mirrors luminal disease
    - Pyoderma gangrenosum – independent of luminal disease
- Primary sclerosing cholangitis:
    - Not related to luminal disease
    - Can result in cirrhosis, portal hypertension, cholangiocarcinoma and colon cancer
    - P-ANCA positive

## Diagnosis:

- A clinical diagnosis
- Endoscopy is helpful and can reveal the following:
    - Continuous colitis with a friable mucosa and superficial or deep ulcerations
- Biopsy:
    - Lymphocytes, plasma cells, and granulocytes confined to the mucosa and submucosa
- Imaging:
    - Double-contrast barium enema → lead pipe appearance
- Serology:
    - P-ANCA positive in patients with PSC
    - ASCA antibodies – also found in CD
    - Elevated levels of carcinoembryonic antigen in an active flare
- Supporting laboratory findings:
    - Elevated ESR and CRP

The following table shows the current classification of UC.

| Extent stage | Endoscopic description | Note |
|---|---|---|
| **E1** | Proctitis | Symptoms of the disease are also graded from S0 (remission) to S3 (severe UC) |
| **E2** | Left-sided or distal colitis | |
| **E3** | Pancolitis | |

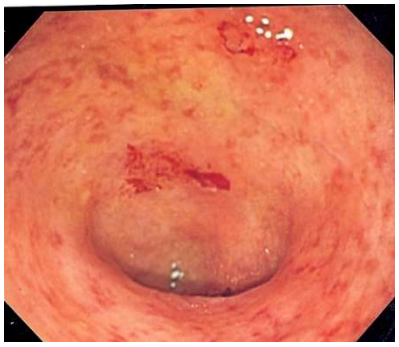


Figure 44: Colonoscopy in UC. Source: https://en.wikipedia.org/wiki/Ulcerative_colitis#/media/File:UC_granularity.png

## Treatment:

5-aminosalicyclic acid:

- Sulfasalazine, oral mesalamine, and rectal mesalamine
- Inhibit cyclooxygenase and lipoxygenase → decreased production of pro-inflammatory

prostaglandins and leukotrienes by the arachidonic pathway
- Dose-related side effects: headache, epigastric pain, nausea, vomiting and rash
- Idiosyncratic side effects: hepatitis, autoimmune hemolysis, aplastic anemia, agranulocytosis and pancreatitis

Corticosteroids:

- Budesonide → lower systemic bioavailability

Immunomodulators:

- Azathioprine
- Methotrexate
- Infliximab
- Adalimumab

Surgery can be curative because the disease is confined to the colon. Indications for surgery:

- Failure of medial therapy
- Fulminant colitis, toxic megacolon or perforation
- Uncontrollable bleeding
- Strictures
- Growth retardation in children

## Acute Appendicitis

### Definition:

Acute appendicitis is the acute inflammation of the appendix. The most common etiology is the obstruction of the appendix lumen by a fecolith which leads to infection because of bacterial overgrowth.

### Epidemiology

- One of the most common surgical emergencies and causes of an acute abdomen
- More common in the Western world
- Mainly affects teenagers and young adults
- Lifetime risk is 6%

### Pathology

Etiology: from most common to least common

- Fecoliths
- Lymphoid hyperplasia
- Intestinal worms
- Carcinoid tumors

Pathology:

- The most commonly involved bacterial organisms are E. coli and B. fragilis
- Obstruction of the appendix → continue production of mucous → the appendix enlarges and become infected → inflammation of the appendix → the appendix becomes fragile and can rupture
- The swelling of the appendix impairs the venous drainage and eventually the arterial supply of the appendix → ischemic injury of the appendix → increased risk of perforation
- The afferent fibers supplying the appendix come from the T10 sympathetic level → initially periumbilical pain
- Eventually, the swollen appendix irritates the parietal peritoneum → pain localizes to the right lower abdominal quadrant

### Clinical Presentation

Symptoms:

- Right lower quadrant pain – right iliac fossa pain
- Nausea
- Vomiting
- Anorexia
- Constipation – remember the most common cause is a fecolith which is hardened stool
- Pelvic appendix → urinary frequency, suprapubic pain and diarrhea

McBurney's sign:

- McBurney's point is 1/3 the distance from the right anterior superior iliac spine to umbilicus
- Deep tenderness in this point is indicative of acute appendicitis

Rovsing's sign:

- Deep palpation of the left iliac fossa causes pain in the right iliac fossa

Obturator sign:

- The leg of the patient is flexed and internally rotated
- Cause pain in acute appendicitis

Digital rectal examination:

- Right-side tenderness in the case of a low-lying pelvic appendix

Psoas sign:

- The patient is instructed to flex the hip against resistance or the hip is extended passively
- If the position of the appendix is retrocecal → positive psoas sign

### Diagnosis

- A clinical diagnosis

- CT scan can be used to confirm the diagnosis and shows edema in the appendix wall and peri-appendix fluid collections
- Other diagnostic studies are indicated to exclude other possible diagnoses of acute abdomen:
    - β-hCG to rule out ectopic pregnancy
    - Ultrasound
    - KUB to rule out kidney or ureteric stones
- Leukocytosis is often present

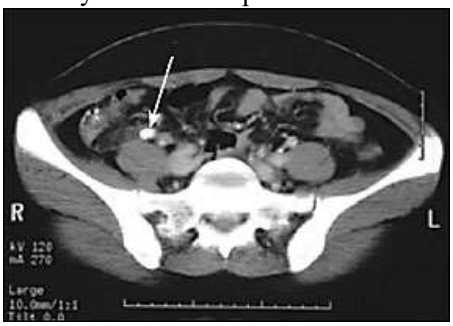



Figure 45: Abdominal CT in acute appendicitis revealing peri-appendicular fluid collection and a fecolith. Source: https://www.aafp.org/afp/2005/0101/p71.html

### Treatment:

- Keep the patient NPO
- Start antibiotics
- IV fluids
- Laparoscopy appendectomy is the definitive treatment
    - There is no medical management of acute appendicitis

## Diverticular Diseases

### Definitions:

Diverticulum:

A blind pouch protruding from the GI tract with communication with the lumen of the tract. Acquired diverticula of the esophagus, stomach, and colon are false diverticula.

True diverticulum:

A diverticulum that has all the three layers of the gut wall. Meckel's diverticulum is an example. They are congenital.

False diverticulum:

A diverticulum that only has the mucosa and submucosa layers of the gut wall. Diverticular diseases of the colon are an example of false diverticula.

Asymptomatic diverticulosis:

An incidental finding of colonic diverticula on imaging or colonoscopy. They are not treated.

Diverticulitis:

An inflammation of a diverticulum. Can be acute or chronic. Occurs in 10% of patients with diverticulosis.

Symptomatic uncomplicated diverticular disease:

Chronic diverticulosis with chronic abdominal pain but no acute diverticulitis or overt colitis.

Segmental colitis associated with diverticulosis:

Non-specific segmental inflammation in the sigmoid colon associated with multiple diverticula. Does not need to involve the diverticula.

### Epidemiology:

- Diverticular disease is the 16$^{th}$ most common cause of death among gastrointestinal diseases
- More than 2.5 million outpatient visits annually are related to diverticular diseases
- More than 300,000 emergency department visits per year are due to acute diverticulitis
- Asymptomatic diverticulosis is the most common finding on colonoscopy, especially in people older than 40 years

### Pathogenesis:

Weakened colonic wall structure:

- The diverticula are mucosal and submucosal herniations in the colonic wall muscle layer
- Through the points of entry of blood vessels (vasa recta) into the muscularis externa
- Most of the diverticula are found in the sigmoid colon
- Family history appears to play an important role suggesting the contribution of genetics
- Age is perhaps the single most important risk factor for diverticular disease

Environmental risk factors:

- Low dietary fiber intake can result in constipation and straining
- This can elevate the intracolonic pressures
- It can result in diverticulosis
- The consumption of higher amounts of dietary fiber in a patient with established diagnosis of

diverticulosis decreases the frequency of hospital admissions and death
- Obesity appears to be a risk factor. It has been reported that obese people have shifts in gut microbiota which might explain the increased risk of diverticular disease in obese individuals
- Diets high in fat and red meat might increase the risk of diverticulosis

Pathophysiology of diverticulitis:

- Obstruction of the diverticulum by a fecalith
- Irritation of the mucosa, low-grade inflammation, venous congestion and further obstruction
- This is known as uncomplication diverticulitis
- Complicated diverticulitis is classified as:
    - Diverticular abscess
    - Diverticular fistula
    - Colonic obstruction
    - Diverticular perforation

## Clinical Presentation:

Diverticulosis is most often asymptomatic, i.e. an incidental finding on colon imaging studies.

Symptomatic uncomplicated diverticular disease (Diverticulosis):

- Fatigue
- Painless bloody stools
- Abdominal pain

Diverticulitis:

- Left lower quadrant pain
- Fever
- Symptoms related to the complications:
    - A perforated diverticulum will result in severe abdominal pain, guarding and possibly a high-grade fever
    - An abscess can be felt as a left lower quadrant tender mass and it can result in high-grade fever
    - A fistula might result in pneumaturia

Segmental colitis associated with diverticulosis:

- Inflammatory stenosis of the sigmoid colon → obstruction

## Diagnosis:

Diverticulosis:

- Usually asymptomatic or associated with mild non-specific symptoms
- Accordingly, most cases are incidentally diagnosed after colonic imaging is performed for other reasons
- CT or colonoscopy

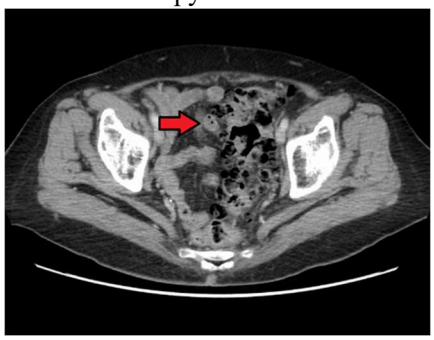


Figure 46: CT scan showing diverticulosis of the sigmoid colon. Source: https://en.wikipedia.org/wiki/Diverticulosis#/media/File:DivertDiseaseMark.png

Diverticulitis:

- CBC might reveal leukocytosis
- Anemia in case of hemorrhage
- An abdominal radiograph can reveal air-fluid levels (obstruction) or free air under the diaphragm (perforation)
- CT can confirm the diagnosis
- Barium studies are to be avoided → in case of perforation, barium can cause chemical peritonitis

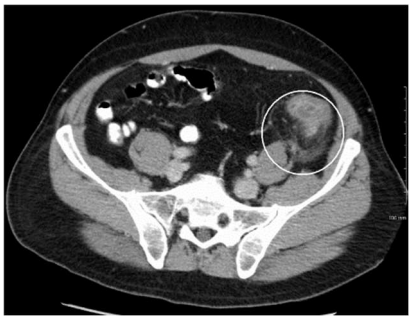


Figure 47: CT scan showing diverticular wall thickening, a sign of inflammation, in diverticulitis. Source: https://en.wikipedia.org/wiki/Diverticulitis#/media/File:Diverticulitis.png

## Treatment:

Symptomatic diverticulosis:

- Increase dietary fiber intake
- Avoid NSAIDs if the patient has past medical history of diverticulitis

- Vigorous physical activity and weight loss lower the risk of diverticulitis

Diverticulitis:

- Antibiotics such as metronidazole in selected cases
- In severe cases, consider keeping the patient NPO (bowel rest)
- IV fluids to prevent dehydration
- Blood transfusions in case of anemia secondary to hemorrhage

Surgery:

- Usually reserved for patients with a perforated diverticulum secondary to diverticulitis
- Hartmann's procedure:
    - The inflamed area is resected, and a stump is formed
    - After the inflammation resides (6 weeks), the two parts of the colon are re-connected

## Zenker's Diverticulum

### Definition:

A Zenker's diverticulum (ZD) is a false diverticulum of the esophagus that develops in the hypopharynx between the cricopharyngeal muscle and the inferior pharyngeal constrictor muscle. It involves only the mucosa and submucosa without the muscular layer of the esophagus. It can occur in other locations in the esophagus.

### Epidemiology:

- Rare
- More common in patients aged between 70 and 90 years
- More common in men
- Extremely rare before the age of 40

### Pathology:

Etiology:

- Abnormal physiology and structure of the cricopharyngeus muscle due to aging → dehiscence of the muscle during swallowing → Zenker's diverticulum
- The Killian triangle between the thyropharyngeal and cricopharyngeal parts of the inferior pharyngeal constrictor is the most commonly affected location

Pathophysiology:

- During swallowing, the intrabolus pressure is increased → elevated hypopharyngeal pressure → herniation of the mucosa and submucosa at the weakened point just above the cricopharyngeus muscle | this could be due to esophageal dysmotility
- The sac of the diverticulum is lined by stratified squamous epithelium
- The submucosa is fibrous
- Ulcerations might be seen in the diverticulum

### Clinical Presentation:

- Retention of food particles in the diverticulum:
    - Regurgitation
    - Halitosis
    - Aspiration
    - Difficulty swallowing
    - Recurrent cough
- Long history of dysphagia often precedes the diverticulum → esophageal dysmotility
- A visible lump might be seen in the neck

### Diagnosis:

Barium swallow studies:

- An outpouching will be seen on the radiograph
- Diagnostic

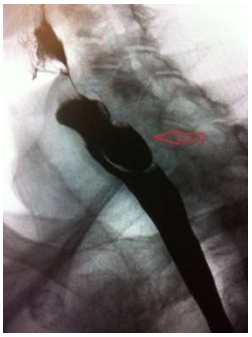


Figure 48: A Zenker's diverticulum as seen on a barium swallow study. Source: https://en.wikipedia.org/wiki/Zenker%27s_diverticulum#/media/File:Zenker22015Lateral.JPG

Upper endoscopy:

- Indicated in the presurgical evaluation of the patient
- Used for the staging of the diverticulum based on its size

### Treatment:

- Asymptomatic diverticula < 2 cm do not require any treatment
- Symptomatic diverticula that are small in size and associated with dysphagia:
    - The patient's symptoms are most likely secondary to esophageal dysmotility not the diverticulum

    - Botulinum toxin injection might decrease the dysphagia
- All other diverticula need to be surgically removed

## Meckel's Diverticulum:

### Definition:

A Meckel's diverticulum occurs when the omphalomesenteric duct in the developing embryo fails to completely obliterate. It is the most common congenital anomaly of the GI tract and it is found in the small intestine. Acid secretion from the ectopic gastric mucosa within the diverticulum can lead to GI bleeding and abdominal pain. This is a true diverticulum.

### Epidemiology:

- Most common congenital anomaly of the GI tract
- Patients with other congenital malformations are at increased risk of having a Meckel's diverticulum
- Estimated prevalence is 2%
- If it becomes symptomatic, most patients present in the first decade of life

### Pathology:

- Incomplete obliteration of the omphalomesenteric duct:
    - This duct connects the yolk sac to the gut
    - At 7 weeks of gestation, it separates from the intestine
    - If this does not occur, a Meckel's diverticulum might occur
    - An omphalomesenteric cyst is cystic dilation of the incompletely obliterated vitelline duct
- The rule of 2's:
    - Two-times more common in females
    - Two-times more common to be symptomatic in males
    - Two-inches long
    - Two-feet from the ileocecal valve
    - 2% of the population
    - Typically presents within the first two years of life
    - May have two types of specialized epithelia (gastric or pancreatic)
- The presence of acid-secreting gastric mucosa can result in GI bleeding and right-lower quadrant pain secondary to ulceration

### Clinical Presentation:

- Typically, asymptomatic, identified at the time of an appendectomy
- May present with hematochezia or melena
- Right lower quadrant abdominal pain
- Intussusception
- Volvulus
- Small-bowel obstruction

### Diagnosis:

- Meckel radionuclide scan:
    - Technetium-99m is injected
    - It is absorbed by ectopic gastric mucosa
    - Visualization of the Meckel's diverticulum
    - Co-administration of cimetidine, or ranitidine increases the uptake of the radioactive contrast
    - Pertechnetate can be also used
- Radioactive tagged RBCs can identify the source of bleeding in a patient with ongoing lower GI bleeding
- These tests are rarely needed because the diagnosis of a Meckel's diverticulum is assumed in any child younger than 2 years of age who presents with painless lower GI bleeding

### Treatment:

- IV fluids replacement to prevent shock
- Blood transfusion might be needed
- Surgical excision is the treatment of symptomatic Meckel's diverticulum

## Hirschsprung's Disease

### Definition:

Hirschsprung's disease (HD) is caused by failed migration of colonic ganglion cells during gestation which results in a congenital megacolon.

### Epidemiology:

- More common in boys
- Family history of the disease is a very important risk factor
- 1 in 5000 live births
- Short-segment disease is the most common form
    - Confined to the rectosigmoid region of the colon
- Long-segment disease passes the sigmoid
- Most patients present in infancy

### Pathology:

Etiology:

- Polymorphisms or mutations in the RET proto-oncogene on chromosome 10q11.2

- Associated with MEN type IIA
- More common in patients with Down syndrome
- Other neurologic conditions linked to Hirschsprung disease:
    - Congenital deafness
    - Hydrocephalus
- Can be associated with other congenital malformations such as:
    - Meckel's diverticulum
    - Imperforate anus
    - VSDs
    - Renal agenesis
    - Cryptorchidism
    - Waardenburg's syndrome
    - Neuroblastomas
    - Ondine's curse

Pathology:

- Failure of ganglion cells to migrate cephalocaudally through the neural crest within the 4th to 12th week of gestation
- Absence of ganglion cells → colon is unable to relax → proximal portion becomes dilated | a transition zone
- The Auerbach and Meissner plexuses are absent

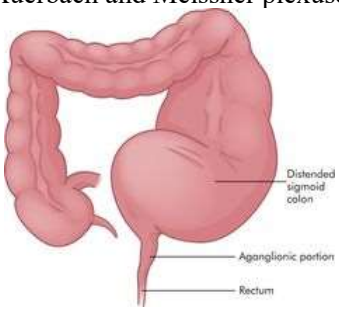



Figure 49: Megacolon in Hirschsprung's disease. Source: https://www.pinterest.com/rachel491/hirschsprungs-disease/

## Clinical Presentation:

Symptoms during infancy:

- Bilious vomiting
- Enterocolitis-associated diarrhea
- Failure to pass meconium within the first 24 hours of life
- Infrequent explosive bowel movements
- Jaundice
- Progressive abdominal distention
- Tight anal sphincter
- Empty rectum

Symptoms in older children:

- Absence of soiling
- Chronic progressive constipation with onset in infancy
- Failure to thrive
- Fecal impaction
- Progressive abdominal distention

## Diagnosis:

- Plain abdominal radiography shows a dilated small or large bowel
- Contrast enema radiographs are diagnostic:
    - Normal in the first 3 months of life
    - Shows dilation of the normal colonic portion
    - The aganglionic portion appears normal
    - A transition zone can be identified
- The diagnosis must be confirmed by a rectal suction biopsy

## Treatment:

- Serial rectal irrigation followed by surgery

# Volvulus

## Definition:

Volvulus occurs when a loop of the intestine (usually the colon) twists around itself and the mesentery that supports it causing a closed-loop obstruction.

## Epidemiology:

- More common in Africa and in people on high-fiber diets
- The estimated annual incidence in the United States is 2 to 3 per 100,000
- Most patients are old
- The most commonly affected portion is the sigmoid colon. Sigmoid volvulus is seen in older chronically constipated patients
- Cecal volvulus is uncommon and presents with small-bowel obstruction
- Midgut volvulus is the most common type in infants and is caused by intestinal malrotation
- Segmental volvulus occurs in any age and is due to intestinal adhesions

Risk factors:

- Intestinal malrotation, Hirschsprung's disease, or abdominal adhesions
- Mega-colon due to other causes
- Pregnancy
- High-fiber diet in chronically constipated patients

## Pathology:

- The most well-studied mechanisms of volvulus are related to chronic constipation and high-fiber diet

- Chronic constipation → dilated sigmoid colon → more susceptible to torsion
- Repeated attacks of torsion → shortened mesentery and formation of adhesions
- The sigmoid colon gets twisted and entrapped in that position → volvulus
- Distension of the affected part → increased compression on mesenteric blood vessels → bowel ischemia, acidosis and eventually necrosis

### Clinical Presentation:

Cecal volvulus:

- Nausea
- Vomiting
- Lack of flatus

Sigmoid volvulus:

- Constipation
- Abdominal distension due to accumulation of gas and fluid
- Patients are usually old, bedridden and debilitated
- Bloody stool
- Prolonged volvulus will result in peritonitis and bleeding per rectum → sigmoid colon ischemia/necrosis

### Diagnosis:

- Abdominal radiograph might reveal a bent inner tube or a coffee-bean sign
- A barium enema will reveal a bird's peak
- CT and endoscopy in selected cases where the cause of bowel obstruction is suspected to be colonic cancer

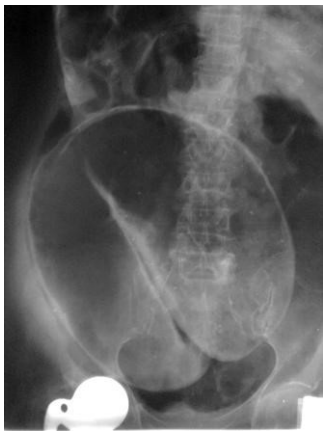


Figure 50: Coffee-bean sign in sigmoid volvulus. Source: https://radiopaedia.org/articles/coffee-bean-sign-sigmoid-colon

### Treatment:

- Sigmoidoscopy or a barium enema
  - High recurrent rate
  - Bowel resection within the next two days is recommended
- Cecal volvulus requires early surgical intervention
- Mortality even after surgical resection can still be as high as 15%

## Intussusception

### Definition:

Intussusception occurs when part of the intestine folds into the section next to it. It usually involves the small bowel. Patients present with abdominal pain that comes and goes, bloody stools and symptoms and signs suggestive of small bowel obstruction.

### Epidemiology:

- Usually a disease of infants and young children
- 2000 infants younger than one year develop intussusception each year in the United States
- Most cases occur before the age of five months
- Rare after the age of 18 months
- Intussusception in adults is most often due to a neoplasm

Risk factors:

- Most cases are of unknown cause
- Infections
- Altered motility
- Meckel's diverticulum
- Duplication
- Polyps
- Appendicitis
- Hyperplasia of Peyer's patches
- Older rotavirus vaccines

### Pathology:

- In most cases, the ileum enters the cecum
- Rarely, the ileum or jejunum prolapses into itself
- A peristaltic action of the intestine pulls the proximal segment into the distal segment → more prolapse of the proximal intestine into the distal portion
  - The portion of the intestine that prolapses is known as the intussusceptum
  - The part that receives the prolapse is known as the intussuscipiens

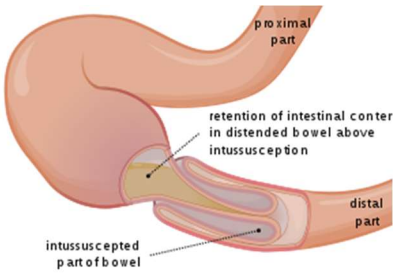



Figure 51: Telescoping of a proximal bowel segment into a distal segment. Source: https://en.wikipedia.org/wiki/Intussusception_(medical_disorder)

- The trapped portion of the small bowel can become ischemic
    - Sloughing of the gut
    - Red currant jelly – occurs in a minority of the patients

### Clinical Presentation:

Early symptoms:

- Periodic "colicky" abdominal pain
- Nausea
- Bilious vomiting
- Pulling legs to chest to ease the pain

Later symptoms:

- Rectal bleeding
- Red currant jelly stool
- Sausage-shaped mass on physical examination

Very delayed presentation:

- Bowel ischemia → necrosis → sepsis
- Patients might develop a fever

Henoch-Schoenlein purpura:

- Severe abdominal pain
- Other symptoms and signs suggestive of HSP

### Diagnosis:

- A clinical diagnosis
- Ultrasound is the diagnostic modality of choice for intussusception:
    - Target sign or doughnut sign
    - 3 cm in diameter
- Air enema is used for diagnosis and treatment

### Treatment:

- Barium, water-soluble or air-contrast enemas are diagnostic and therapeutic
    - 80% success rate
    - 10% recurrence within the next 24 hours
- Surgery:
    - Manually squeezing the telescoped part might solve the issue
    - If not possible, the affected portion of the bowel might be removed

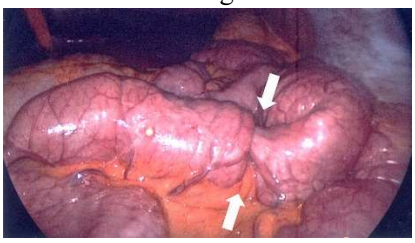


Figure 52: Intussusception on laparoscopy. Source: http://sgc2014.kongress-poster.ch/posters/retrograde_intussusception_of_the_roux_limb_a_rare_complication_after_laparoscopic_rouxeny_ga/

## Other Intestinal Diseases:

### Meconium Ileus:

Patients with cystic fibrosis due to a delta F508 mutation are more likely to develop exocrine pancreatic insufficiency and meconium ileus during the neonatal period.

- The cause of meconium ileus is multifactorial
- Increased absorption of fluid because of the abnormal CFTR channel → dehydration of the intraluminal intestinal contents → formation of a meconium plug → obstruction of the intestine and prevention of stool passage at birth

Presentation:

- Prolonged neonatal jaundice
- Early lung infections
- Failure to pass stool at birth
- Other signs suggestive of cystic fibrosis:
    - Undescended testicles
    - Pancreatic insufficiency

The diagnosis can be confirmed by abdominal radiography.

### Necrotizing Enterocolitis:

Definition:

Life-threatening illness affecting neonates and caused by bacterial invasion into the intestinal wall.

Epidemiology:

- Most common life-threatening emergency of the GI tract in neonates

- Most cases present in the first second to third week of life
- Prematurity, low-birth weight, and formula feeding are the main risk factors
- Worldwide incidence is 0.3 to 2.4 per 1000 live births
- Mortality ranges from 10 to 50%
- Severe cases with perforation and sepsis have a 100% mortality rate

Pathology:

- Bacterial invasion into the intestinal wall
- Inflammation and cellular destruction of the intestinal wall
- GI tract immaturity in premature infants play a role
- Histopathology reveals:
    - Bacteria within the intestinal wall
    - Tissue ischemia and necrosis
    - Microperforations → pneumatosis intestinalis "air within the wall of the intestine"

Presentation:

- Decreased appetite, vomiting, diarrhea and increased abdominal girth
- Bloody stools
- Systemic signs of sepsis:
    - Respiratory failure
    - Circulatory collapse
    - Cyanosis
    - Coma
- Abdominal distention and tenderness
- Visible intestinal walls
- Erythema of the abdominal wall

Diagnosis:

- Abdominal plain radiographs:
    - Dilated loops
    - Pneumatosis intestinalis – visualization of small amounts of air within the bowel wall
    - Portal venous air – poor prognostic sign
    - Free air in the abdomen – perforation

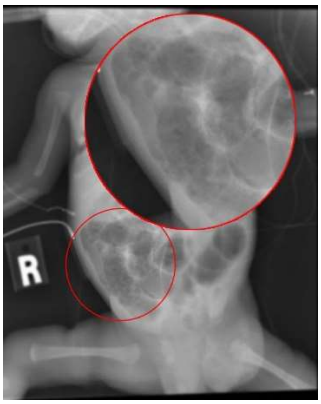



Figure 53: A neonate with necrotizing enterocolitis. Source: https://en.wikipedia.org/wiki/Necrotizing_enterocolitis

- Laboratory findings:
    - Leukopenia
    - Hyponatremia
    - Low serum bicarbonate
    - Negative blood cultures

Treatment:

- Stop all enteral feeding → NPO
- Placement of a nasogastric tube to decompress the bowels
- Intravenous broad-spectrum antibiotics (ampicillin, gentamicin plus "clindamycin or metronidazole")
- Parenteral nutrition
- Laparotomy in unresponsive cases and resection of nonviable bowel

## Imperforate Anus:

- Patients with trisomy 21 might develop GI tract anomalies:
    - Duodenal atresia or stenosis
    - Annular pancreas
    - Imperforate anus
- Imperforate anus is diagnosed in the neonatal period
- Can be associated with other anomalies:
    - Vertebral abnormalities
    - Cardiac defects
    - Tracheal or esophageal fistulas/atresia
    - Renal abnormalities
    - Limb defects

## Colon Cancer:

### Polyps:

Tubular adenomas:

- 80% of neoplastic colonic polyps
- Has a stalk and an adenoma or a cap
- Less likely to become cancerous
- When seen on colonoscopy, they are usually resected and sent for histological examination
- May present with occult bleeding
- Caused by chromosomal instability due to spontaneous mutations in the APC and KRAS genes

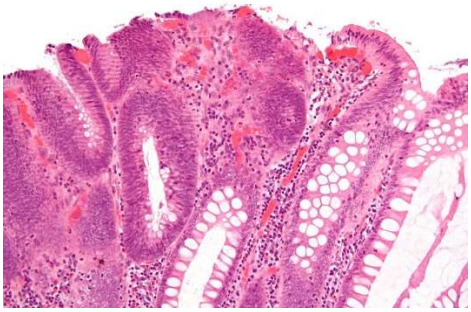


Figure 54: Tubular adenoma histology. Source: https://en.wikipedia.org/wiki/Colorectal_polyp#/media/File:Tubular_adenoma_2_high_mag.jpg

Villous polyps:

- 20% of neoplastic colonic polyps
- Sessile in configuration
- Finger like projections
- More likely to become cancerous

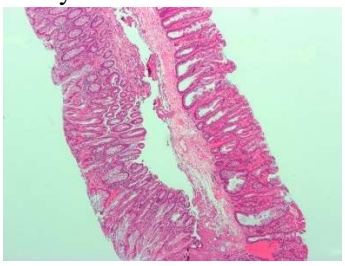


Figure 55: Villous adenoma histology. Source: https://en.wikipedia.org/wiki/Colorectal_polyp#/media/File:Sessile_serrated_adenoma.jpg

## Colon Cancer Epidemiology

- Third most common cancer in the United States
- Most patients are > 50 years of age
- 25% have family history of colon cancer

Risk factors:

- Cigarette smoking
- Inflammatory bowel disease – especially ulcerative colitis
- Large villous polyps
- Juvenile polyposis syndrome
- Genetic predisposition

## Molecular Pathways of Colon Cancer:

Microsatellite instability pathway:

- 15% of the cases
- Mutations or methylation of mismatch repair genes
    - The DNA needs to be replicated when the cell divides
    - During the process of replication, matching of nucleotides is important
    - Sometimes, accidents can occur where there is a mismatch
    - DNA polymerases checks the newly formed DNA strand scanning for mismatches
    - It cleaves off any mismatches
    - When these DNA polymerases are defective, microsatellite instability occurs
- MLH1 gene mutations
- Cause Lynch syndrome
- Serrated "villous" polyps can become carcinogenic via this pathway in sporadic colorectal carcinoma

Chromosomal instability pathway:

- 85% of the cases
- Mutations in the APC gene are implicated in the adenoma-carcinoma sequence
- Once an adenoma develops, the chance that it will become cancerous increases if both KRAS and APC mutations occur
- The final step in this pathway is the loss of tumor suppressor genes like p53 → development of an adenocarcinoma
- The size of the adenoma is predictive of the risk of progression to cancer (> 4 cm has a 40% risk of becoming cancerous)
- The degree of dysplasia in an adenoma is also predictive of progression to cancer

## Genetic Predisposition to Colon Cancer:

Familial adenomatous polyposis:

Familial predisposition to the formation of multiple adenomatous polyps. The colon is riddled with adenomatous polyps.

- Autosomal dominant mutation of the APC gene on chromosome 5q21
- 100% risk of developing colon cancer
- Thousands of polyps start to arise after puberty
- Prophylactic colectomy

Gardner syndrome:

- Familial adenomatous polyposis plus osseous and soft tissue tumors (mandibular osteomas)
- Congenital hypertrophy of the retinal pigment epithelium
- Fibromatous abdomen
- Impacted or supernumerary teeth

Turcot syndrome:

- Familial adenomatous polyposis plus brain malignant tumors (gliomas or medulloblastomas)

Peutz-Jeghers syndrome:

- Numerous hamartomas throughout the GI tract
- Hyperpigmented mouth, lips, hands or genitalia
- Increased risk of breast, colorectal, stomach, small bowel and pancreatic carcinoma

Hereditary non-polyposis colorectal cancer (HNPCC):

- Lynch syndrome
- Autosomal dominant mutation of DNA mismatch repair genes → microsatellite instability
- 80% develop colorectal carcinoma
- Proximal colon is always involved
- Patients can also develop endometrial, ovarian and skin cancers

Clinical Presentation:

- Asymptomatic
- Hematochezia
- A recent change in the characteristics of stool
- Constipation
- Iron deficiency anemia secondary to occult blood loss

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Note: A patient who presents with incidental iron deficiency anemia and is older than 50 years should be presumed to have colon cancer until proven otherwise if a clear cause of the anemia is not easily identifiable.

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- Rectosigmoid more often than ascending more often than descending colon
- Patients are at risk of developing S bovis bacteremia

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Note: Ascending colon cancers are usually exophytic and the present with iron deficiency anemia/weight loss, whereas descending colon cancers are infiltrating masses that cause partial obstruction and hematochezia.

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Diagnosis:

- Male patients older than 50 years and postmenopausal females with iron deficiency anemia should be screened for colon cancer

Low-risk patients screening:

- Colonoscopy at age 50
- Alternatives:
  - Flexible sigmoidoscopy
  - Fecal occult blood testing
  - Fecal immunochemical testing
  - CT colonography

Patients with a first-degree relative with colon cancer:

- Colonoscopy at age 40 or 10 years prior to the age of diagnosis of colon cancer in their relative

Diagnosis:

- Direct visualization of the lesion on colonoscopy
- Confirmed by biopsy
- An apple core lesion on barium enema

Figure 56: Apple-core lesion on barium enema radiography in a patient with colon cancer. Source: https://radiopaedia.org/articles/apple-core-sign-colon-1

Tumor markers:

- CEA tumor marker for monitoring of recurrence

- Not indicated for screening

## Liver Cirrhosis and Portal Hypertension:

### Definition:

Liver cirrhosis is characterized by fibrosis and nodule formation of the liver due to chronic hepatic injury. There is diffuse bridging fibrosis maintained by stellate cells alternating with regenerative nodules. The normal liver architecture is disrupted, and synthetic liver functions are deranged.

Epidemiology:

- The estimated prevalence of liver cirrhosis in the United States is between 0.15 to 0.27%

### Etiology:

Fatty liver diseases:

- Alcoholic liver disease
- Non-alcoholic fatty liver disease

Viral:

- Hepatitis B
- Hepatitis C
- Hepatitis D

Autoimmune:

- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- IgG4 cholangiopathy

Storage diseases:

- Hemochromatosis
- Wilson disease
- Alpha-1-antitrypsin deficiency

Other causes:

- Recurrent bacterial cholangitis
- Bile duct stenosis
- Budd-Chiari syndrome
- Right-heart failure
- Porphyria

### Pathophysiology:

Main cells involved in hepatic cirrhosis:

- Hepatocytes
- Hepatic stellate cells
- Sinusoidal endothelial cells
- Kupffer cells

Fibrosis:

- Stellate cells when exposed to pro-inflammatory cytokines transform into myofibroblasts
- They deposit collagen
- Bridging fibrosis occurs

Role of Kupffer cells:

- Kupffer cells are satellite macrophages
- They release pro-inflammatory cytokines in response to viral hepatitis which activates the stellate cells responsible for bridging fibrosis
- Damaged hepatocytes also release reactive oxygen species and inflammatory mediators that activate hepatic stellate cells

Vascular regulation abnormalities in cirrhosis:

- Portal hypertension
- Dysregulation of the systemic and splanchnic circulation:
    - Increased production of NO in the systemic and splanchnic circulation → vasodilation → decreased vascular resistance
    - Activation of the RAAS → increased water and sodium retention → a hyperdynamic circulation
    - Increased venous return to the heart by the formation of collaterals

Progression of liver cirrhosis:

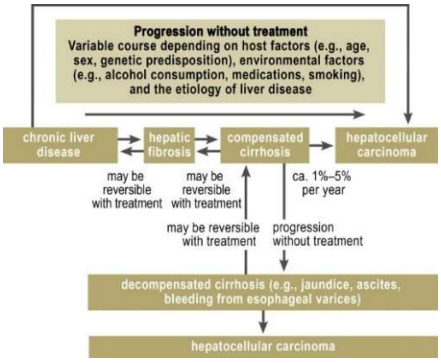


Figure 57: Hepatic fibrosis can progress to cirrhosis which can become decompensated and eventually lead to hepatocellular carcinoma. The goal of treatment is to prevent the progression, transform a decompensated patient to a compensated cirrhotic patient, or to cause regression of the disease. Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3583179/

Histopathology:

- Micronodular cirrhosis:
    - < 3 mm in dimeter nodules
    - Seen in alcoholic liver disease and hemochromatosis
- Macronodular cirrhosis:
    - Irregular nodules some > 3 mm in diameter
    - Viral hepatitis and alpha-1-antitrypsin deficiency
- Micronodular cirrhosis can progress to macronodular type

## Portal Hypertension:

Pathophysiology:

- Chronic fibrosis and abnormal vaso-regulatory mechanisms of the liver result in an elevation in the portal pressure
- Collateral circulation becomes more important and a hyperdynamic circulation occurs
- Nitric oxide and endothelin-1 act on hepatic stellate cells:
    - They control relaxation (NO) and contraction (endothelin-1) of the sinusoids
    - In liver cirrhosis endothelin-1 production is increased whereas NO production is decreased
    - This results in increased intrahepatic vasoconstriction and resistance
    - Portal hypertension occurs
    - If not treated, vascular remodeling by hepatic stellate cells occurs
    - Eventually, collateral circulation is formed

Collateral circulation and portal hypertension:

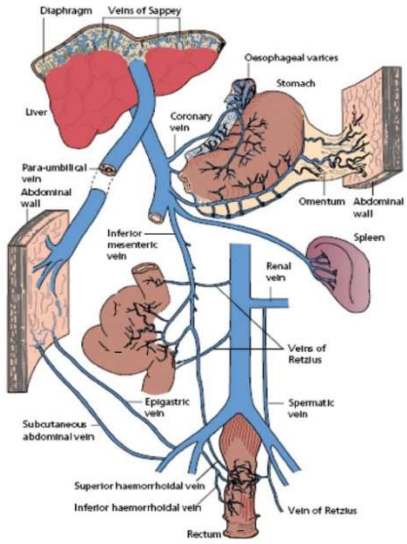


Figure 58: The porto-systemic anastomoses in the esophagus, stomach, spleen, skin, and hemorrhoidal veins. Source: http://www.mmj.eg.net/article.asp?issn=1110-2098;year=2017;volume=30;issue=1;spage=116;epage=121;aulast=El

## Clinical Presentation:

Compensated cirrhosis:

- Asymptomatic cirrhosis detected by labs, physical examination or imaging
- Possible findings on examination are hepatomegaly or splenomegaly

Decompensated cirrhosis:

- Skin:
    - Jaundice
    - Spider angiomas
    - Palmar erythema
    - Purpura and petechiae
- Neurologic:
    - Hepatic encephalopathy and asterixis
- Gastrointestinal:
    - Nausea and vomiting
    - Dull abdominal pain
    - Fetor hepaticus
- Renal:
    - Hepatorenal syndrome
- Hematologic:
    - Thrombocytopenia
    - Anemia
    - Coagulation disorders
    - Hypersplenism due to splenomegaly

- Cardiovascular:
  - Cardiomyopathy and peripheral edema
- Reproductive:
  - Testicular atrophy and gynecomastia in men
  - Amenorrhea in women
- Portal hypertension:
  - Esophageal varices, which may bleed causing hematemesis
  - Gastric varices which can bleed resulting in melena
  - Caput medusae
  - Anorectal varices
  - Ascites
- Metabolic:
  - Hyponatremia
  - Hyperbilirubinemia

Typical findings in liver cirrhosis:

- Cutaneous signs of liver disease
- A firm enlarged liver on palpation
- Presence of risk factors for liver disease

### Spontaneous Bacterial Peritonitis:

- Common in decompensated hepatic cirrhosis
- Potentially fatal
- Bacterial infection in patients with cirrhosis and ascites
- Presents with fever, abdominal pain, ileus and worsening encephalopathy
- Most often caused by aerobic gram – organisms such as E. coli or Klebsiella. In rare cases, it can be caused by streptococcus
- Diagnosed by paracentesis which shows a neutrophil count > 250 cells/$mm^3$
- First-line treatment is a 3rd generation cephalosporin such as cefotaxime

### Diagnosis:

Ultrasonography:

- Inhomogeneity of hepatic tissue
- Irregular hepatic surface
- Caudate lobe enlargement and splenomegaly

Advanced liver disease:

- Thrombocytopenia
- Hypoalbuminemia
- Elevated INR
- Elevated bilirubin concentration
- ALT and AST will be normal or mildly elevated "most hepatocytes are lost"

Esophagogastroduodenoscopy:

- Visualization of esophageal varices
- Assessment of risk of bleeding
- Should be performed at time of diagnosis before onset of variceal bleeding

Biopsy:

- Contraindicated in most cases, unless the etiology of liver disease is unclear, and the patient is not in decompensated cirrhosis
- Not useful in end-stage liver cirrhosis

### Treatment:

The goal of management in patients with early liver disease is to prevent the progression of liver fibrosis to cirrhosis.

- The treatment is based on the etiological diagnosis
- Antiviral therapy in cirrhosis due to hepatitis B or C
- Treatment of iron or copper overload in hemochromatosis and Wilson disease respectively
- Abstinence from alcohol to prevent alcoholic cirrhosis

## Liver Function Tests

### Introduction:

- The main function of the liver is to detoxify toxins and metabolites, synthesize proteins and to produce other biologically important enzymes
- The liver plays an important role in lipid and glucose metabolism
- Liver function tests are helpful in understanding the type of liver injury the patient might have and the most likely cause
- The main classification based on the abnormalities seen in liver function tests are into cholestatic and hepatocellular pathology

### Differential Diagnosis in Patients with Abnormal Liver Function Tests:

Hepatocellular pattern:

- Elevations mainly in alanine transaminase (ALT) and aspartate transaminase (AST)
- Viral hepatitis, vascular causes of liver injury, autoimmune hepatitis and storage-disease related hepatitis result in ALT-predominant pattern

- Alcoholic hepatitis, cirrhosis, and non-hepatic causes present with AST-predominant elevations
- Non-hepatic causes of elevated AST:
    - Hemolysis
    - Myopathy
    - Thyroid disease
    - Exercise

Cholestatic pattern:

- Elevations mainly in alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and bilirubin

## Pathophysiology of the Components of Liver Function Tests:

AST:

- Present in cytosolic and mitochondrial isoenzymes
- Found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, lungs, pancreas, leucocytes and red blood cells
- Not sensitive or specific for liver disease

ALT:

- A cytosolic enzyme found mainly in the liver
- Released after hepatocellular injury, not necessarily cellular death

ALP:

- A member of the family of zinc metalloenzymes
- Concentrated in the microvilli of the bile canaliculus, bone and intestines
- Non-specific for biliary disease

GGT:

- Located on the membranes of cells with high secretory or absorptive activities (biliary tree)
- More specific for biliary disease than ALP

Bilirubin:

- Lysis of the hemoglobin within the red cells by the reticuloendothelial system results in the formation of unconjugated bilirubin
- It is transported to the liver while bound to albumin
- Bilirubin gests conjugated in the liver to form bilirubin glucuronide which can be secreted into the bile and gut
- Conjugated bilirubin is water-soluble, i.e. can be found in the urine

Synthetic function tests:

- Albumin (10 grams are synthesized by the liver per day)
- Prothrombin time which can be elevated in cirrhosis
- Mainly dependent on factors II, V, VII and X which are synthesized by the liver

## Clinical Correlation:

Alcoholic hepatitis:

- AST:ALT ratio is 2:1 or more
- Elevated GGT levels increase the certainty of the diagnosis

Medication-induced hepatitis:

- Very high AST and ALT levels
- Synthetic liver dysfunction

Viral hepatitis:

- Mainly elevations in ALT
- Can be seen in any form of acute hepatitis caused by hepatitis A, B, C, D, E, EBV or CMV

Autoimmune hepatitis:

- Elevated liver function tests without an apparent cause
- Check for the following autoantibodies:
    - Anti-smooth muscle antibody
    - Anti-liver/kidney microsomal antibodies

Non-alcoholic fatty liver disease:

- AST:ALT ratio is 1:1, but both are elevated
- Other tests are normal
- Dyslipidemia
- Type 2 diabetes mellitus

Hemochromatosis:

- Elevated ALT levels more than AST
- Elevated serum ferritin level
- Transferrin saturation > 45%

Wilson disease:

- Abnormal liver function tests
- Low serum ceruloplasmin level
- > 100 micrograms of copper per 24 hours in urine
- Liver biopsy is needed to confirm the diagnosis

## Reye Syndrome

### Definition:

Reye syndrome is a rare fatal pediatric illness that is characterized by acute noninflammatory encephalopathy and fatty liver failure.

Epidemiology:

- Rare
- Peak age of onset is 5 to 14 years
- Estimated incidence is 0.11 per 100,000

Pathology:

- Most commonly preceded by a viral illness such as influenza A or B
- More than 80% of those who develop Reye syndrome have taken aspirin in the preceding three weeks
    - After the widespread warnings against aspirin use in viral illness in children, the incidence of Reye syndrome has dropped dramatically
- Viral illness → mitochondrial injury perpetuated by aspirin → inhibition of fatty-acid metabolism
- The encephalopathy is due to hyperammonemia secondary to hepatic failure:
    - Hyperammonemia may induce astrocyte edema → cerebral edema → elevated ICP

Clinical Presentation:

Stage 1:

- Persistent vomiting
- Lethargy and nightmares
- Confusion

Stage 2:

- Stupor, disorientation and delirium
- Hyperreflexia
- Hyperventilation

Stage 3:

- Coma

Stage 4:

- Dilated fixed pupils
- Deep coma with decerebrate rigidity

Stage 5:

- Paralysis
- Seizures
- Death due to respiratory arrest

Diagnosis:

Diagnostic criteria:

- Acute noninflammatory encephalopathy documented by:
    - An alteration in consciousness and
    - CSF containing 8 or less leukocytes/$mm^3$
- Liver biopsy only on autopsy to confirm the diagnosis
- Three-fold or more increase in serum glutamic-oxaloacetic transaminase or serum glutamic-pyruvic transaminase levels
- Elevated serum ammonia

Other diagnostic clues:

- Elevated AST, ALT and bilirubin
- Abnormal coagulation studies
- Elevated lipase and amylase
- Hypoglycemia

Treatment

- Supportive care and close monitoring
- Correction of hypoglycemia
- Treatment of severe acidosis by sodium bicarbonate
- Phenylacetate-sodium benzoate to treat hyperammonemia
- Correction of coagulopathies

Treatment of cerebral edema:

- Head elevation to 30 degrees
- Mannitol or hypertonic saline
- Analgesia or sedation
- Seizure treatment with antiepileptics

Hereditary Hyperbilirubinemias

Bilirubin Physiology

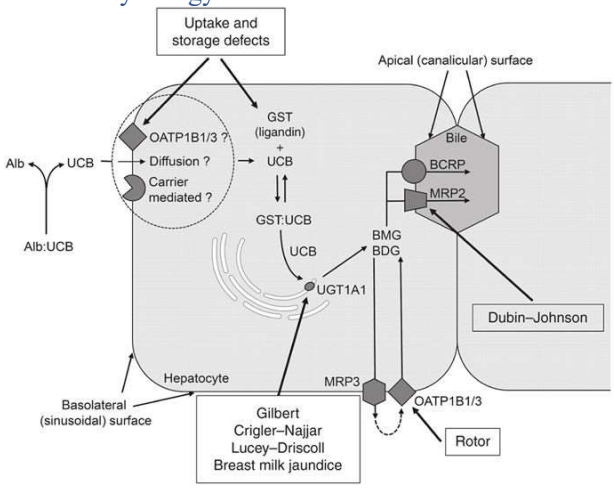


Figure 59: Genetic disorders affecting bilirubin clearance. Source: https://www.nature.com/articles/pr2015247

- Hemoglobin is broken down by the reticuloendothelial system into unconjugated bilirubin
- Unconjugated bilirubin is water-insoluble → it is bound to albumin
- Hepatocytes take the circulating bilirubin into the cell for conjugation
- UDP-glucuronosyltransferase is responsible for the conjugation of bilirubin
- Conjugated bilirubin is water soluble and it needs to be transported into the lumen of a bile canaliculus
- Diseases affecting bilirubin uptake, conjugation, or intracellular transportation will result in hereditary hyperbilirubinemias

### Gilbert Syndrome:

Pathology:

- Mild decrease in UDP-glucuronosyltransferase conjugation
- Impaired bilirubin uptake

Presentation:

- Common and benign
- Patients are often asymptomatic
- Mild jaundice only with stress or fasting
- Laboratory testing reveals elevated unconjugated bilirubin without hemolysis

### Crigler-Najjar Syndrome:

Type I:

- Absent UDP-glucuronosyltransferase
- Presents very early
- Patients die within a few years
- Jaundice, kernicterus, and markedly elevated unconjugated bilirubin
- Treated with plasmapheresis and phototherapy
- Liver transplantation is curative

Type II:

- Markedly decreased, but not absent, UDP-glucuronosyltransferase
- Symptomatic unconjugated hyperbilirubinemia
- Responds to phenobarbital which increases the liver production of UDP-glucuronosyltransferase

### Dubin-Johnson Syndrome:

Pathology:

- Defective liver excretion of conjugated bilirubin

Presentation:

- Conjugated hyperbilirubinemia
- Dark or black liver
- Benign

### Rotor Syndrome:

Pathology:

- Impaired intracellular transportation of conjugated bilirubin
- Impaired hepatic uptake of unconjugated bilirubin

Presentation:

- Mild symptoms
- Normal liver color

### Wilson Disease:

#### Definition:

Wilson disease is an autosomal recessive disease that results in excess copper buildup in the body with primary involvement of the liver and basal ganglia. It is also known as hepatolenticular degeneration.

#### Epidemiology:

- Incidence is 1 in 30,000
- Carrier frequency is 1 in 90
- Consanguineous marriages increase the risk
- Age at presentation ranges from 4 to 40 years

#### Pathology:

Etiology:

- A mutation in the hepatocellular-copper-transporter ATP7B gene on chromosome 13
- Important for the transportation and excretion of copper into the bile to be excreted in stool
- 95% of copper excretion is by the liver

Pathophysiology:

- Copper is unable to leave the body → accumulates in the liver and spills into the circulation to accumulate into other organ systems:
  - Subthalamus
  - Putamen
  - Cortex
  - Kidneys
  - Cornea
- Excess copper increases the formation of toxic hydroxyl groups → increases oxidative stress:
  - Liver damage → liver failure/cirrhosis
  - Cortical damage → behavioral abnormalities
  - Basal ganglia damage → movement disorders

    - Corneal damage → Kayser-Fleischer rings
- ATP7B is important because it links copper to ceruloplasmin to be released into the bloodstream and removing the excess of copper by secreting it into bile
- When defective, ceruloplasmin is secreted without being bound to copper → rapidly degraded in the bloodstream
- Damage of the lenticular nucleus and the liver → hepatolenticular degeneration

### Clinical Presentation:

- Positive family history in some patients
- Abdominal pain
- Jaundice
- Weakness
- Personality changes
- Migraines
- Seizures
- Movement disorders
- Hemiballismus

Physical examination:

- Stigmata of chronic liver disease
- Kayser-Fleischer rings (also seen in primary biliary cirrhosis) – due to copper deposition in Descemet membrane of cornea
- Muscle rigidity and spasticity due to basal ganglia involvement
- Bluish discoloration of the base of fingernails

Figure 60: Kayser-Fleischer ring in Wilson's disease. Source: https://en.wikipedia.org/wiki/Kayser–Fleischer_ring#/media/File:Kayser-Fleischer_ring.jpg

### Diagnosis:

Ceruloplasmin level:

- Less than 20 mg/dL

Confirmation of the diagnosis:

- Kayser-Fleischer rings, and
- Urinary copper levels > 100 micrograms per dL, and
- Serum ceruloplasmin level < 20 mg/dL
- If in doubt, order a liver biopsy

### Treatment:

- Chelation therapy with penicillamine or trientine
- Oral zinc supplementation

## Hemochromatosis:

### Definition:

Hereditary hemochromatosis is an autosomal recessive disorder that affects the body's regulation of iron. It is the most common genetic disease in whites. Iron overload in men is 24 times more common as compared to women with hemochromatosis.

### Epidemiology:

- The estimated prevalence in whites is 0.64 to 2.06%
- The estimated prevalence in other ethnic groups is from 0 to 0.1%
- 6% of those who develop cirrhosis secondary to hemochromatosis develop hepatocellular carcinoma
- The risk of hepatocellular carcinoma is 20 times higher in patients with hemochromatosis
    - Most important cause of death

### Pathology:

Iron physiology:

- Iron is important for normal cellular functions and metabolism
- It is part of hemoglobin, myoglobin and the cytochrome P450 system
- Total body iron levels are precisely regulated
- When disrupted, toxic levels of iron accumulate in different body organs

Etiology:

- Abnormal expression of the HFE protein responsible for regulating hepcidin (important for iron regulation) – chromosome 6
    - A missense mutation at aminoacids position 282
    - Production of C282Y
    - Decreased hepcidin expression in response to elevated iron levels
    - Unregulated control of iron levels
    - 90% of the patients have this mutation

Pathology:

- Excess iron deposition in the heart causes restrictive cardiomyopathy, diastolic dysfunction,

dysrhythmias and conduction defects → AV block and bradyarrhythmias can be seen
    - Reversible if recognized and treated before onset of overt HF
- Excess iron deposition in hepatocytes → hepatocyte toxicity → fibrosis → cirrhosis
    - 20-fold increased risk of hepatocellular carcinoma compared to the general population
    - Prognosis is largely dependent on the presence of cirrhosis
- Deposition of iron in the pancreas → bronze diabetes triad:
    - Cirrhosis
    - Diabetes
    - Bronze skin pigmentation
- Impaired iron sensing → increased intestinal absorption of iron despite elevated levels → increased ferritin and total body iron and decreased TIBC → elevated transferrin saturation

Clinical Presentation:

- Abdominal pain
- Amenorrhea
- Ascites
- Arthralgias due to calcium pyrophosphate deposition in metacarpophalangeal joints
- Cardiomyopathy
- Cirrhosis
- CHF
- Spider nevi, palmar erythema and bronze skin pigmentation
- Diabetes mellitus
- Hypogonadism, hypothyroidism and other endocrine dysfunctions
- Splenomegaly and hepatomegaly
- Weakness
- Weight loss
- Hepatocellular carcinoma

---

Note: Most patients are older than 40 years and become symptomatic only when total body iron > 20 g

---

Diagnosis:

Who should be screened?

- Symptomatic patients
- Asymptomatic patients with abnormal iron study results
- Patients with a first-degree relative diagnosed with hereditary hemochromatosis

Serum ferritin and transferrin saturation:

- Transferrin saturation ≥ 45%
- Serum ferritin levels are elevated

Confirmation:

- HFE gene testing focusing on C282Y mutation

Liver transaminase levels:

- When elevated, combined with the above findings, a liver biopsy might be indicated if serum ferritin ≥ 1000 ng/mL
- Prussian blue stain is used in liver biopsy

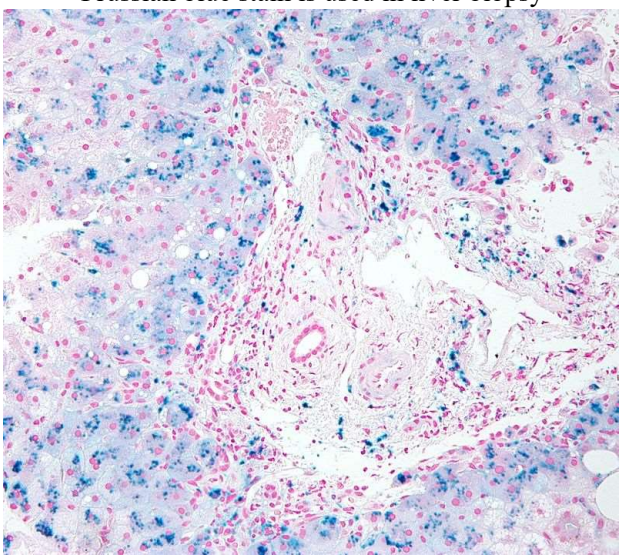

Figure 61: Liver biopsy in hemochromatosis. Source: https://en.wikipedia.org/wiki/Iron_overload#/media/File:Hemosiderosis_high_mag.jpg

Monitoring:

- Regular evaluation of liver, heart, and endocrine function
- Screening hepatic ultrasonography

Iron study results in hemochromatosis:

| **iron** | **ferritin** | **transferrin%** | **tibc** | **transferrin** | **hemoglobin** |
|---|---|---|---|---|---|
| High | High | High | Low | Low | Normal |

Risk of cirrhosis in hereditary hemochromatosis:

- Normal serum ferritin level → risk of cirrhosis is 0
- Elevated serum ferritin, but normal ALT/AST, platelet count and no excessive alcohol use → 45%
- Elevated serum ferritin, ALT or AST, and thrombocytopenia but no excessive alcohol use → 80%
- Elevated serum ferritin, ALT or AST, thrombocytopenia, and excessive alcohol use → > 80%

### Treatment:

Treatment goals:

- Maintain serum ferritin between 50 to 150 ng/mL (complete eradication of the risk of cirrhosis!)
- Maintain hemoglobin level > 12.5 g/dL

Treatments:

- Repeated phlebotomy to maintain normal serum ferritin levels
- Chelation therapy with deferasirox, deferoxamine or oral deferiprone

## Primary Sclerosing Cholangitis

### Definition:

Primary sclerosing cholangitis (PSC) is characterized by chronic bile duct destruction that leads to end-stage liver disease. Up to 80% of the cases are associated with inflammatory bowel disease.

### Epidemiology:

- Estimated incidence in high-prevalence areas such as northern Europe is 1.3 per 100,000
- Estimated prevalence is 16.2 per 100,000
- 60% of the patients are men
- Median age at onset is 30 to 40 years
- Associated with inflammatory bowel disease
- Most patients are non-smokers

### Pathology:

- Progressive chronic injury of the small, medium and large bile ducts
- Inflammatory and obliterative concentric fibrosis known as onion-skinning → biliary strictures
- Early in the disease, the changes are mainly seen in the portal tracts
- The inflammatory infiltrate includes lymphocytes, plasma cells and neutrophils
- The ongoing inflammation results in periportal fibrosis, loss of bile ducts, and disorganized ductular proliferation → eventually cirrhosis
- Increased risk of biliary tree malignancy
  - Not related to disease duration or severity of biliary fibrosis
- More often with ulcerative colitis

### Clinical Presentation:

- Liver specific symptoms such as itch, jaundice and pain
- Non-specific symptoms such as fatigue
- Most patients have history of inflammatory bowel disease
- Most patients are identified by imaging and biochemical testing

### Diagnosis:

Cholestatic pattern on liver function tests:

- AST and ALT might be elevated
- ALP and GGT are markedly elevated
- Conjugated hyperbilirubinemia

Supporting laboratory tests:

- A positive p-ANCA
- Elevated IgM level

Imaging:

- MRI cholangiography is the gold standard diagnostic modality nowadays
  - Most cases are diagnosed early nowadays before the classical picture of generalized beading of the biliary tree and stenosis can be seen on cholangiography
- Endoscopic cholangiography is used for intervention
  - Alternating strictures and dilation with beading of the intra and extrahepatic bile ducts

Liver biopsy:

- If endoscopic cholangiography is normal and you still suspect PSC, a liver biopsy can help in confirming the diagnosis

Colonoscopy:

- Full colonoscopy is indicated in any patient with PSC with no prior history of inflammatory bowel disease
- If the diagnosis of inflammatory bowel disease has been established, colonoscopy should be performed every year after the diagnosis of PSC
  - Presence of PSC in a patient with inflammatory bowel disease increases the risk of colon cancer

## Treatment:

Biliary interventions:

- Antibiotic prophylaxis during endoscopic retrograde cholangiography is mandatory
  - Typically, ciprofloxacin
- Long-term antibiotics only in patients with recurrent cholangitis
  - Alternate between amoxicillin-clavulanic acid, ciprofloxacin and co-trimoxazole
- Endoscopic interventions are indicated for dominant biliary strictures and for the early diagnosis of malignancy
  - Increased risk of cholangiocarcinoma and gallbladder cancer

Liver transplantation:

- Indications:
  - Decompensated cirrhosis
  - Intractable cholangitis
  - Biliary obstruction
  - Hepatocellular carcinoma
- Recurrence rate after transplantation is 20% within 5 years

## Gallstones:

### Outline:

- Definition
- Epidemiology
- Pathology
- Clinical Presentation
- Diagnosis
- Treatment

### Definition:

Gallstones, also known as cholelithiasis, are hardened deposits composed of bile that form within the gallbladder.

### Epidemiology:

- Gallbladder stones are more common in middle-aged and older individuals
  - The most common type is cholesterol stones
  - Biliary cholesterol saturation increases with age
  - As people age, the activity of cholesterol 7α hydroxylase decreases → increased risk of cholesterol gallstones
- Women during fertile years are twice as common to develop gallstones than men
  - Estrogen increases cholesterol saturation in the bile and decreases gallbladder movement → cholestasis → formation of gallstones
- Ethnic variability:
  - Most common in native Americans
  - Extremely rare in Asians

Risk factors:

- Female gender during reproductive years
- Use of estrogen containing contraceptives or hormonal replacement therapy
- Obesity, especially in women:
  - Increased activity of HMG CoA reductase → increased biliary secretion of cholesterol → increased risk of gallstones
- Rapid weight loss → increased hepatic secretion of cholesterol into bile → gallbladder bile sludge and formation of gallstones
- Increased intake of fat and refined carbohydrates combined with decreased intake fiber appears to be a risk factor for gallstones
- Sedentary lifestyle
- Drugs:
  - Fibric acid derivatives such as clofibrate
  - PPIs
  - Ceftriaxone
- Diabetes:
  - Elevated levels of triglycerides increase the risk of gallstones

### Pathology:

- Gallstones form when the bile is oversaturated with cholesterol or when there is an increased production of bilirubin
- Gallbladder stasis is an important factor

Cholesterol stones:

- 80% of all gallstones
- Up to 20% are radiopaque due to calcification

Pigmented stones:

- Increased production of bilirubin
- Seen in hemolytic diseases
- Associated with Crohn's disease, chronic hemolysis, alcoholic cirrhosis, biliary infections and total parenteral nutrition
- Black on gross examination
- Most of them are radiopaque
  - Brown gallstones are due to infection and are radiolucent

Complications:

- Larger stones can obstruct the gallbladder → cholecystitis
- Smaller stones can be dislodged and obstruct the common bile duct → cholangitis; or the pancreatic exocrine duct → acute pancreatitis

Biliary colic:

- Increased production of CCK after a fatty meal → contraction of the gallbladder → stone impaction into cystic duct → right upper quadrant pain, nausea and vomiting

Clinical Presentation:

- Most patients are asymptomatic – silent stones → require no treatment in most cases
- Recurrent episodes of right upper quadrant or epigastric pain → biliary colic
- Biliary colic characteristics:
    - Intermittent impaction of a stone in the cystic duct
    - Right upper quadrant pain that increases in intensity over 30 minutes to few hours
    - Possible pain referral to the shoulder blades or below the right shoulder (Boas' sign)
    - Attacks occur after a fatty meal and always at night

Acute cholecystitis as a presentation of gallstones:

- Most commonly caused by E. coli and bacteroides species
- Severe right upper quadrant pain, nausea, vomiting, fever and leukocytosis
- May progress to gangrene and perforation in some patients

Choledocholithiasis:

- The stone might lodge in the common bile duct
- Obstructive jaundice
- May be painless in some patients

Other presentations:

- A fistula between the gallbladder and duodenum might form
- Gallstones can be dislodged directly into the duodenum → obstruction of the duodenum → Bouveret's syndrome

Diagnosis:

- History of biliary colic or a presentation of acute cholecystitis or choledocholithiasis are suggestive of gallstones disease

Ultrasonography:

- Most often tool used in the diagnosis of gallstones disease and cholecystitis
- Specificity and sensitivity of 90 to 95%
- Can demonstrate the presence of common-bile-duct stones, bile-duct dilatation, and show thickening of the gallbladder wall

Nuclear studies:

- Technetium-99 m
- Hepatic iminodiacetic acid (HIDA) or disopropyl iminodiacetic acid (DISIDA)
- Provide functional information about gallbladder contraction → helpful in acalculous cholecystitis

Other diagnostic tests:

- A complete blood count might reveal leukocytosis
- Elevated bilirubin and ALP or GGT in patients with obstructive jaundice

Treatment:

Elective cholecystectomy:

- Patients with recurrent episodes of biliary colic should undergo elective cholecystectomy
- Children with asymptomatic gallstones should undergo elective cholecystectomy:
    - Almost all of them will eventually become symptomatic
- Asymptomatic gallstone disease in patients with sickle cell disease
- During surgery for morbid obesity
- Laparoscopic cholecystectomy is the treatment of choice

Choledocholithiasis

Definition:

Choledocholithiasis is the presence of a stone, or stones, within the common bile duct. It is the indication of cholecystectomy in up to 22% of the patients.

Pathology:

- Gallstones can be classified into cholesterol stones, mixed, or pigmented stones
- Primary choledocholithiasis is the formation of a biliary stone within the biliary tree without the presence of gallstones
- Secondary choledocholithiasis occurs when gallstones are ejected from the gallbladder to be later lodged within the common bile duct

- Primary choledocholithiasis is most often due to brown stones (infectious etiology)

Complications:

- Acute pancreatitis
- Cholangitis

### Clinical Presentation:

Charcot's triad: in acute cholangitis

- Right upper quadrant pain
- Jaundice
- Fever

Biliary pancreatitis:

- Acute pancreatitis with marked elevation in serum amylase and lipase levels

Note: In most patients, history of established gallstone disease is present.

### Diagnosis:

Findings highly suggestive of choledocholithiasis:

- Charcot's triad
- A common bile duct stone on transabdominal ultrasound
- Serum bilirubin > 4 mg/dL

Liver function tests:

- Early elevation in AST and ALT
- In persistent biliary obstruction → marked elevation in ALP and bilirubin

Imaging:

- Transabdominal ultrasonography
- MR cholangiopancreatography
- Endoscopic retrograde cholangiopancreatography shows multiple filling defects in the common bile duct – gold standard for the diagnosis of choledocholithiasis

Supporting tests:

- CBC can show leukocytosis in patients with acute cholangitis

### Treatment:

Goals of treatment:

- Removal of the biliary stone
- Early recognition and treatment of complications:
  - Obstructive jaundice
  - Acute pancreatitis
  - Acute cholangitis

Endoscopy:

- Capable of treating 90% of the cases
- Endoscopic sphincterotomy (sphincter of Oddi) and endoscopic papillary balloon dilation → stone extraction

Surgery:

- Laparoscopic common bile duct exploration or laparoscopic-assisted trans-gastric endoscopic retrograde cholangiopancreatography (LA-ERCP)

## Acute Pancreatitis

### Definition

Acute pancreatitis is characterized by premature activation of the exocrine enzymes of the pancreas which results in inflammation.

### Epidemiology:

- Approximately, 50,000 persons are admitted every year for acute pancreatitis
- 40% are caused by choledocholithiasis
- 35% are caused by chronic alcohol use or abuse
- 4% are caused by ERCP
- Mortality rate in mild acute pancreatitis is less than 1%
- Mortality rate in severe acute pancreatitis is 30%

Bad prognostic features:

- Hemorrhagic pancreatitis
- Multiorgan dysfunction
- Necrotizing pancreatitis

### Pathology:

Anatomy and physiology:

- The pancreas has endocrine and exocrine functions
- It releases digestive enzymes into the duodenum
- A pancreatic duct runs from the pancreatic tail to enter the duodenum
- In some cases, the pancreatic duct is joined by the common bile duct before entering the duodenum
  - This anatomical variation means that a gallstone might pass from the common bile duct to the pancreatic duct, obstructing the latter

Pathophysiology:

- Premature activation of exocrine digestive enzymes in the pancreas → acute reversible inflammation
- The most common causes are gallstones and alcohol

- Other less common causes include:
    - Trauma
    - Steroids
    - Mumps
    - Autoimmune disease
    - Scorpion sting
    - Hypertriglyceridemia
    - Hypercalcemia
    - ERCP – as a complication
    - Sulfa-containing drugs, and protease inhibitors

Complications:

- Acute renal failure
- Acute respiratory distress syndrome
- Ascites
- Disseminated intravascular coagulation
- Ileus
- Pancreatic necrosis
- Pseudocyst formation
- Mesenteric venous or splenic venous thrombosis
- Sepsis
- Peritonitis
- Fistula formation

## Clinical Presentation:

Pain:

- Sudden onset left upper quadrant abdominal pain
- Periumbilical, epigastric or pain radiation to the back have been described
- Painless in some patients
- The pain worsens after eating fatty foods and eventually becomes constant

Other symptoms and signs:

- Nausea and vomiting
- Clay-colored stools → obstructive choledocholithiasis
- Decreased urine output → multiorgan dysfunction

Examination:

- Fever
- Hypotension
- Tachypnea and tachycardia
- Diaphoresis
- Severe abdominal tenderness and guarding
- Jaundice

Cullen sign:

- Ecchymosis and edema in the subcutaneous tissue around the umbilicus

Grey Turner sign:

- Ecchymosis of the flank

## Diagnosis:

Initial workup:

- A complete blood count → leukocytosis
- Lipid profile
- Lipase level → specific for pancreatic injury – 3 times the upper normal limit
- Amylase level is elevated, but is not specific for pancreatic injury
- Hypocalcemia

Etiological diagnosis:

- Contrast-enhanced computed tomography → confirms the diagnosis
- Ultrasonography → gallstones

Further testing after establishing the cause:

- ALP, bilirubin level, MRCP and ERCP if the cause is gallstone

Prognostic labs:

- Arterial blood gas
- Calcium level
- CRP
- Interleukin-6 and 8
- LDH level
- Urinalysis

---

Note: Lipase or amylase levels need to be three times the upper normal limit for the diagnosis of acute pancreatitis. A lipase to amylase ratio of more than 4 is suggestive of an alcoholic cause of pancreatitis.

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Urinary trypsinogen activation peptide (TAP) has prognostic value

## Treatment:

- Bowel rest
- IV fluid therapy:
    - Potassium or dextrose might be needed in addition to normal saline
- Analgesia:
    - Acute pancreatitis can be quite painful to the patient
- Nasogastric tube suction
- Antibiotics:
    - Need to include metronidazole
- Surgery in necrotic pancreatitis or in the management of pancreatitis complications

Pancreatic pseudocysts:

- Has no true epithelial cell lining
- Formed by an inflammatory process → scarring and entrapment of pancreatic juices in the cyst
- Diagnosed by the finding of an elevated amylase level after the resolution of acute pancreatitis
- Cysts larger than 5 cm or those that persist for more than 6 weeks should be aspirated or surgically excised

## Acute Cholecystitis:

### Definition:

Acute cholecystitis is the acute inflammation of the gallbladder wall secondary to cystic duct obstruction by an impacted gallstone.

### Epidemiology:

- The most frequent complication of gallstone disease
- One third of all surgical emergency hospital admissions
- 18.5% of all intra-abdominal source of infection
- Biliary stones are the main etiology
- The risk of acute cholecystitis in patients with gallstones disease is 1% per year
- The risk of acute cholecystitis in symptomatic gallstone disease is 20% per year → the rationale behind elective cholecystectomy in symptomatic gallstone disease

### Pathology:

Pathophysiology:

- A gallbladder stone is impacted at the infundibulum or the cystic duct → obstruction → continued mucin production and gallbladder distention → increased intraluminal pressure in the gallbladder → impaired micro and microcirculation perfusion of the gallbladder
- This results in serosa edema, mucosal sloughing, venous congestion and ischemic changes in the gallbladder wall
- This environment is optimum for bacterial overgrowth, most often E. coli and bacteroides species
- Necrosis of the gallbladder wall might result in gangrene and perforation, two feared complications of acute cholecystitis

Complications:

- Gallbladder perforation → peritonitis and sepsis
- Emphysematous cholecystitis
- Gangrene of the gallbladder wall

### Clinical Presentation:

Pain:

- Right upper quadrant pain
- Positive Murphy's sign
  - Inspiratory arrest on RUQ palpation because of pain
- Pain may radiate to the shoulder plates or under the right shoulder region

Other symptoms and signs:

- The patient should <u>not</u> be jaundiced, unless there is concomitant obstruction of the common bile duct

### Diagnosis:

Initial workup:

- Leukocytosis
- Elevated CRP level

Scoring:

- The goal of scoring is to predict who is going to develop gangrenous cholecystitis
- The following five parameters are the main risk factors for gangrenous cholecystitis:
  - Age > 45 years
  - Heart rate > 90 per minute
  - Gallbladder thickness on ultrasound > 4.5 mm
  - Leukocytosis
  - Male gender

Imaging:

- No role for plain radiography
- Abdominal ultrasound is the first-line imaging in acute cholecystitis
  - Presence of gallstones
  - Increased gallbladder wall thickness
  - Positive Murphy's sign on abdominal ultrasound
- CT is useful in confirming the diagnosis of emphysematous or gangrenous cholecystitis
- Cholescintigraphy – not readily available but has excellent accuracy
  - The gallbladder is not visible in acute cholecystitis

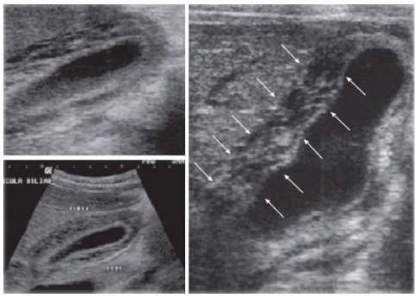

Figure 62: Abdominal ultrasound findings in acute cholecystitis. Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5442405/

Treatment:

- Keep the patient NPO
- IV fluids
- Analgesia
- Antibiotics
- Urgent cholecystectomy is recommended over delayed cholecystectomy
    - Laparoscopic approach is superior to open approach

Acute Acalculous Cholecystitis:

- Bile stasis in the gallbladder, or hypoperfusion to the gallbladder wall
- Seen in critically ill patients
- Confirmed by the presence of cholecystitis on HIDA scan or ultrasonography without the presence of gallstones

Chronic Pancreatitis:

Definition

Chronic pancreatitis is a progressive fibrotic inflammatory disease of the exocrine pancreas which eventually results in the destruction of the pancreas and adversely affects the endocrine pancreas. Chronic pancreatitis is a possible complication of recurrent acute pancreatitis or can be primary and insidious in onset.

Epidemiology:

- Estimated incidence is 4 per 100,000 per year
- Prevalence is 41.67 per 100,000
- Men are more likely to develop chronic pancreatitis
- African Americans have a higher frequency of chronic pancreatitis than whites

Risk factors:

- Alcohol is the single most important risk factor/cause of chronic pancreatitis and is responsible for 50% of the cases alone, and an additional 40% of the cases combined with other risk factors
- Smoking
- Family history
- Ductal obstruction by inflammatory strictures, benign tumors or malignancies

Pathology:

Etiology:

- Calcific pancreatitis:
    - Alcohol, alone or with other risk factors (90%)
    - Smoking
    - Genetic – cystic fibrosis
- Obstructive pancreatitis:
    - Trauma
    - Tumors
    - Recurrent acute pancreatitis due to any cause
- Autoimmune
- Idiopathic

Pathophysiology:

- Increased viscosity of the interlobular and intralobular secretions secondary to a failure in ductal bicarbonate secretion → formation of protein-rich plugs
- Ductal obstruction by the formed protein plugs → inflammation → pancreatic parenchymal fibrosis
- Ductal obstruction increases the pancreatic ductal intraluminal pressure → hypoperfusion to the acinar cells → ischemic injury to the pancreas
- Eventually, the exocrine and endocrine pancreas are destroyed → pancreatic exocrine and endocrine deficiency

Complications:

- Diabetes mellitus
- Fat-soluble vitamin deficiency (A, D, E and K)
- Pseudocysts
- Steatorrhea – when 90% of the exocrine pancreas is lost

Clinical Presentation:

- Recurrent acute pancreatitis
- Steatorrhea
- Weight loss

- Type 3C diabetes mellitus due to the destruction of beta-cells (similar to type 1 in that there is absolute insulin deficiency)
- Anorexia

### Diagnosis:

Initial workup:

- Fecal elastase 1 – low specificity and sensitivity
- Serum lipase and amylase – normal or elevated

Imaging:

- Abdominal CT scan shows pancreatic atrophy and calcifications

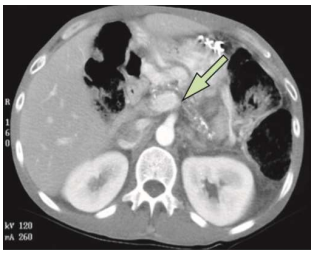

Figure 63: Abdominal CT showing pancreatic calcification, atrophy and a dilated pancreatic duct. Source: http://dx.doi.org/10.1016/S0140-6736(16)00097-0

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Note: The diagnosis in most cases of chronic pancreatitis is obvious, i.e. recurrent episodes of acute pancreatitis and alcoholism. Imaging can confirm the diagnosis.

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### Treatment:

- Patients with chronic pancreatitis often have intractable pain
  - Opioids are often needed
  - Celiac ganglion block
- Exocrine pancreatic replacement therapy:
  - Trypsin and lipase
- Diet containing medium chain fatty acids:
  - Their digestion is not dependent on pancreatic enzymes
- Treatment of complications such as diabetes and pseudocysts
- Referral of the patient to an alcohol abstinence program if possible:
  - Continued alcohol intake → increased risk of pancreatic cancer → very poor prognosis

## Pancreatic Cancer

### Definition:

Pancreatic cancer is an adenocarcinoma arising from the pancreatic ductal system.

### Epidemiology:

- Fourth leading cause of cancer death in the United States
- 5-year survival is 5 to 15%
- Is responsible for more than 300,000 deaths per year in the United States
- Highest incidence of pancreatic cancer is in those older than 70 years
- 90% of the patients are older than 55 years

Risk factors:

- Alcohol
- Physical inactivity
- High consumption of red meat
- Cigarette smoking

### Pathology:

Etiology:

- Smoking is responsible for 20% of pancreatic cancers and is the most important risk factor
- Diabetes
- Obesity
- Chronic pancreatitis
- Occupational exposures
- Genetic predisposition:
  - Family history
  - Lynch syndrome
  - Peutz-Jeghers syndrome
  - Von Hipaul Lindau syndrome
  - MEN1

Pathology:

- Most often it is an adenocarcinoma
- Can also be serous, sero-mucinous or mucinous
- 90% are duct cell adenocarcinomas (disorganized glandular structure with cellular infiltration)
- Two thirds arise in the pancreatic head
- Associated with tumor markers CEA and CA 19-9

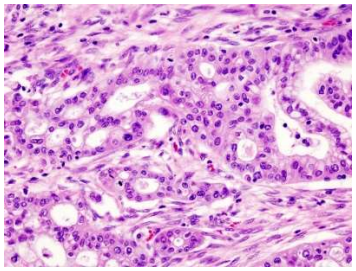

Figure 64: Histopathology in pancreatic adenocarcinoma showing disorganized glandular structure with cellular infiltrates. Source: https://en.wikipedia.org/wiki/Pancreatic_cancer#/media/File:Pancreas_adenocarcinoma_(4)_Case_01.jpg

### Clinical Presentation:

- Painless jaundice (70%)
- Weight loss
- Abdominal pain
- Weakness
- Pruritus
- Anorexia
- A palpable, non-tender distended gallbladder (Courvoisier sign)
- Acholic stools and dark urine → obstruction of the CBD
- Recurrent DVT → pancreatic cancer creates a hypercoagulable state
- Migratory thrombophlebitis (Trousseau syndrome)

### Diagnosis:

Initial workup:

- Elevated ALP, conjugated bilirubin, and liver function test abnormalities
- Elevated amylase and lipase levels
- Elevated CA 19-9 and CEA levels (CEA is less specific)

Imaging:

- Multidetector computed tomography is the imaging modality of choice to diagnose and evaluate pancreatic cancer
- PET CT to look for metastasis, which are often present at time of diagnosis

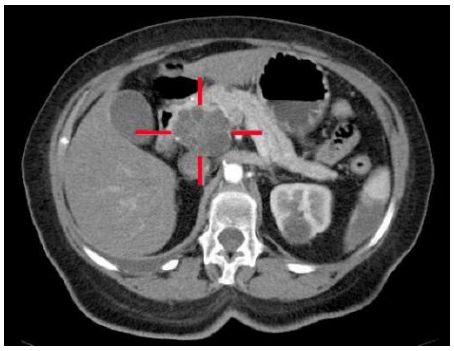

Figure 65: Abdominal CT showing an adenocarcinoma of the head of the pancreas. Source: https://en.wikipedia.org/wiki/Pancreatic_cancer#/media/File:MBq_cystic-carcinoma-pancreas.jpg

### Treatment:

- Whipple procedure for tumors located in the head of the pancreas
  - Pancreaticoduodenectomy
- Postoperative chemotherapy with 5-florouracil and gemcitabine
- Postoperative radiotherapy
- Involvement of the hepatic artery renders the cancer unresectable
- Average survival after diagnosis is 1 year
  - Extremely bad prognosis

## Small Bowel Obstruction

### Definition:

Small bowel obstruction (SBO) is defined as any luminal obstruction from the duodenum to the terminal ileum.

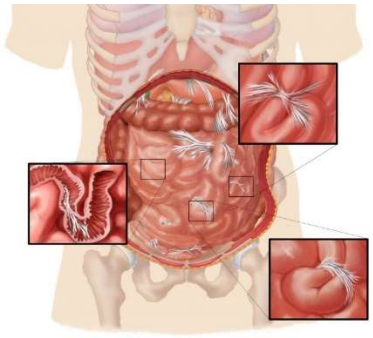

Figure 66: Adhesions are the most common cause of SBO. Source: http://www.clearpassage.com/avoid-surgery/avoid-surgery-for-small-bowel-obstruction/

### Epidemiology:

- 15% of hospital admissions for abdominal pain are due to SBO
- Approximately, 300,000 hospital admission annually

- 75% are caused by postoperative adhesions
- Malignancy, Crohn disease, and hernias account for the remainder of the cases in the Western world
- In the developing world, the most common cause is hernia followed by adhesions, tuberculosis and least common are malignancy, Crohn disease and parasitic infections

## Pathology:

Etiology:

- Intraabdominal adhesions postoperatively → typically 4 weeks post-surgery
- Malignancy (10%)
- Incarcerated groin hernias (10%)
- Inflammatory bowel disease, volvulus and miscellaneous causes account for the remainder of the cases
- Pediatric causes of small bowel obstruction:
    - Congenital atresia
    - Pyloric stenosis
    - Intussusception

Pathology:

- An SBO leads to proximal dilation of the intestine
    - Accumulation of GI secretions and air
    - Stimulation of cell secretory activity
- Increased intraluminal pressure → increases peristalsis above and below the obstruction → early diarrhea and flatus
- Proximal SBO → vomiting
- Prolonged SBO → increased intraluminal hydrostatic pressure → increased pressure in capillary beds → third-spacing of fluid, electrolytes and protein into the intestinal lumen → dehydration
- Severe dehydration in SBO is the main determinant of morbidity and mortality
- Continued distention of the small bowel leads to twisting on the mesenteric pedicle → strangulated SBO → arterial occlusion, ischemia and necrosis → if untreated, perforation, peritonitis and death

## Clinical Presentation:

- Nausea and vomiting, typically bilious
- Constipation or obstipation → a late finding
- Abdominal distention with visible peristalsis
- Fever and tachycardia are seen in patients with strangulated SBO
- Intermittent abdominal pain which may progress to become constant
- Presence of signs of peritoneal irritation such as rebound tenderness or guarding → bowel ischemia

## Diagnosis:

Laboratory workup:

- Serum electrolytes which can be impaired in patients with third-space fluid loss and dehydration
- Elevated BUN and creatinine levels in dehydrated patients
- Serum lactate levels which may be elevated in ischemic bowel injury
- CBC which may show leukocytosis in prolonged SBO secondary to bacterial overgrowth and infection

Imaging:

- Upright plain abdominal radiography which might show air-fluid levels or absence of gas in the small bowel
- Multi-slice CT has excellent sensitivity in diagnosing SBO
    - Helpful in detecting complications of SBO such as ischemia, perforation, and mesenteric edema
- Ultrasonography, which as a specificity of 100% (good for exclusion of SBO)
- Barium studies should be cautiously used:
    - Barium is very irritating/toxic to the peritoneum in case of perforation

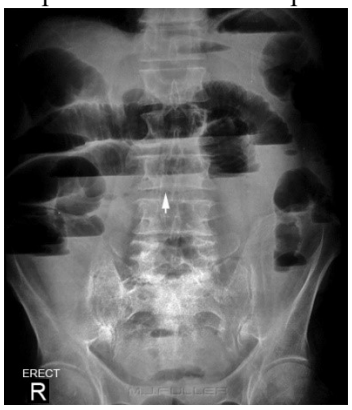


Figure 67: Multiple air-fluid levels on a plain radiograph indicative of SBO. Source: Wikiradiography

Treatment:

Note: The etiological diagnosis is important because treatment is usually tailored to the cause of SBO.

Initial treatment:
- IV fluids to replace third-space loss

Nonoperative treatment:

Inflammatory bowel disease associated SBO:
- High-dose steroids
- Bowel rest

Malignancy:
- Usually a metastatic tumor

Operative treatment:
- Strangulated SBO → surgical emergency
- Obstipation → complete SBO → early surgical intervention
- Laparoscopy is superior to open laparotomy

Prevention:
- The most common cause of SBO is postoperative adhesions
- Limiting laparotomy by utilizing minimally invasive techniques and laparoscopy has been proven to decrease the incidence of SBO

## Acute Mesenteric Ischemia

### Definition:

Acute mesenteric ischemia can only occur in patients with preexisting comorbidities. It can be classified into 4 types: acute superior mesenteric artery thromboembolic occlusion, mesenteric arterial thrombosis, mesenteric venous thrombosis and nonocclusive mesenteric ischemia.

### Pathology:

Etiology:

Mesenteric arterial occlusion:
- Embolism in patients with atrial fibrillation or arterial embolic disease
- Congestive heart failure
- Digitalis therapy
- Hypercoagulable state
- Hypovolemic shock

Venous thrombosis:
- Portal hypertension
- Trauma
- Hypercoagulable state
- Chronic renal failure
- Intra-abdominal inflammation

Pathology:
- Atherosclerotic vascular disease → atheroma formation → plaque rupture and thrombosis → blockage of the lumen of the artery
- Embolism from another source such as a mural thrombus in atrial fibrillation → occlusion of the superior mesenteric artery
- Hypercoagulable states:
  - Factor V Leiden
  - Antithrombin III deficiency
  - Protein C deficiency
- Ischemic injury to the affected part of the bowel → small bowel necrosis → sloughing of the mucosa presents as currant jelly stools

### Clinical Presentation:
- Postprandial pain
- Abdominal pain out of proportion to findings
- Nausea and vomiting
- Hemodynamic instability
- Established diagnosis of other comorbidities

Complications:
- Sepsis
- Septic shock
- Necrosis and perforation of part of gut
- Death – remember these patients have other comorbidities

### Diagnosis:

Laboratory workup:
- CBC: leukocytosis
- Elevated lactate levels
- Elevated serum amylase and LDH levels

CT angiography confirms the diagnosis

### Treatment:

Classical signs of mesenteric ischemia on history and CT in an unstable patient:
- Transfer the patient to the OR immediately or to endovascular therapy

Stable patients with classical signs of mesenteric ischemia:
- IV fluids
- Antibiotics
- Anticoagulants

- Early endovascular intervention

Insidious onset or vague symptoms:

- Anticoagulation
- IV fluids
- Bowel rest
- Repeat CT
- Treatment of the possible causes
- Exploratory laparotomy in unresponsive cases

## Primary Biliary Cirrhosis

Outline:

- Definition
- Epidemiology
- Pathology
- Clinical Presentation
- Diagnosis
- Treatment

### Definition:

Primary biliary cirrhosis (PBC) is an autoimmune progressive cholestatic liver disease characterized by cholestasis, circulating anti-mitochondrial antibodies and nonsuppurative destructive cholangitis and interlobular bile duct destruction.

### Epidemiology:

- More common in women
- Median age of diagnosis is 50 years
- Estimated prevalence in the United States is 400 per million
- Much less common in Africa or Asia with an estimated prevalence of 20 per million

Risk factors:

- Recurrent urinary tract infections
- Cigarette smoking
- Alcohol consumption could be protective!
- Family history
- Presence of other autoimmune diseases such as Raynaud syndrome or Sjogren syndrome
- HLA-DR7 and DR8
- HLA-DR11 and DR13 are protective

### Pathology:

Pathology:

- Autoimmune reaction which might be triggered by recurrent E. coli infections
- Lymphocytic infiltrate and granuloma formation in the biliary ductal system → destruction of lobular bile ducts
- Associated with other autoimmune disorders

### Clinical Presentation:

- Fatigue is present in most patients:
  - Could be caused by elevated inflammatory cytokines and excessive manganese deposits in the globus pallidum
- Pruritus:
  - Caused by cholestasis
- Jaundice
- Xanthomas
- Osteoporosis
- Dyslipidemia:
  - Reduction in biliary secretion of cholesterol
  - Hypercholesterolemia and hyperlipidemia

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Note: Prognostic models such as the Mayo Risk Score take into account the patient's age, bilirubin, and edema severity in determining which patients should be considered for a liver transplantation. Fortunately, most patients nowadays do not need a liver transplantation.

---

### Diagnosis:

Diagnostic criteria: Two of the following are needed

- Anti-mitochondrial titer > 1:40
- ALP > 1.5 times the upper limit of normal for > 24 weeks (cholestatic liver disease)
- Nonsuppurative destructive cholangitis and interlobular bile duct destruction on liver histology

Stages of PBC on histology:

1. Portal inflammation
2. Increased size of periportal lesions with interface hepatitis
3. Distortion of hepatic architecture with fibrous septa
4. Cirrhosis

Inflammation in PBC:

- Mainly lymphocytes
- Some mononuclear cells

- Near the basal membrane of the cholangiocytes (which undergo necrosis and destruction)
- Granuloma formation due to lymphohistiocytic cells

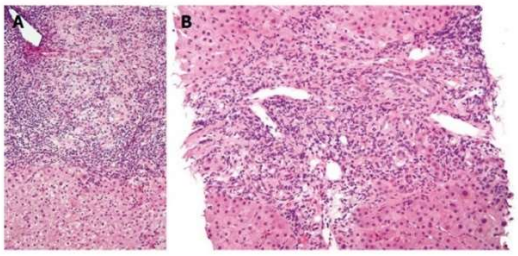


Figure 68: Lymphocytic infiltrates around the small bile ducts in a patient with early PBC. Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4419097/

### Treatment:

UDCA therapy:

- Ursodeoxycholic acid
- Protection of cholangiocytes
- Stimulation of biliary secretions of bile acids
- Can cause diarrhea

Corticosteroids:

- Useful in patients with interface hepatitis

## Hepatocellular Carcinoma:

### Definition:

Hepatocellular carcinoma is a primary liver cancer that is increasing in frequency in parallel to the increasing incidence of chronic liver disease and cirrhosis.

### Epidemiology:

- Fifth most common cancer
- Second cause of cancer-related death
- Most of the cases are due to chronic viral B and C hepatitis
- Estimated incidence in men is 11.5 per 100,000
- Estimated incidence in women is 3.9 per 100,000
- Male to female ratio 3:1
- Most common present in the elderly
- HCV is the most common cause in the United States

---

Note: Most common cause of liver malignancy is metastatic disease from other sources.

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### Pathology:

Etiology:

- Strong association with chronic HBV and HCV infection
- Associated with other causes of cirrhosis such as excessive alcohol consumption and coinfection with HDV
- Cigarette smoking increases the risk
- Environmental exposure to aflatoxin
- Treatments that prevent hepatic cirrhosis in at-risk patients decrease the risk of hepatocellular carcinoma

Pathology:

- Chromosomal instability or single nucleotide polymorphism in a patient with chronic liver disease predispose him/her to tumorigenesis
- Mainly signaling pathways JAK/STAT, WntB-catenin, and mTOR
- Hepatocellular carcinoma displays significant genomic heterogeneity → failure to develop targeted therapy
- Presence of gene mutations in the tumor suppressor gene p53 is associated with poor prognosis
- Can resemble fibrolamellar hepatic tumors:
  - More common in the young
  - Not associated with chronic hepatitis
  - Normal alpha-fetoprotein levels
  - Mostly resectable

### Clinical Presentation:

- Initially asymptomatic or symptoms and signs of chronic liver disease
- Upper abdominal discomfort and distention
- Weight loss
- Fever
- Anorexia
- Early satiety
- Diarrhea

---

Note: Acute liver decompensation in a patient with compensated cirrhosis = suspicion of a hepatocellular carcinoma.

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Paraneoplastic syndromes:

- Hypoglycemia
- Erythrocytosis
- Hypercalcemia
- Severe watery diarrhea

Diagnosis:

Assessment of the severity of liver disease:

- Synthetic liver function tests such as albumin and prothrombin time
- Bilirubin levels
- AST and ALT

Diagnosis in high-risk patients:

- MRI or CT
- An increased alpha-fetoprotein level
- Biopsy is not required if the MRI shows characteristic findings on T2 imaging

Diagnosis in low-risk patients:

- MRI, CT or ultrasound
- If a hepatic tumor/nodule is identified, biopsy must be taken
- The diagnosis can be confirmed only by biopsy

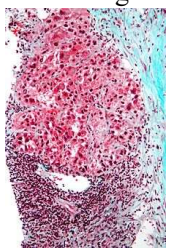
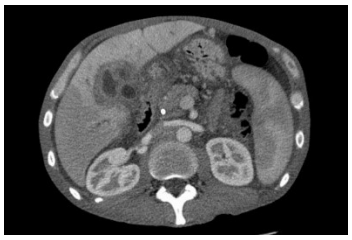
A  B 

Figure 69: A. Histopathology examination of a liver biopsy showing a hepatocellular carcinoma. B. CT showing a hepatocellular carcinoma. Source: https://en.wikipedia.org/wiki/Liver_cancer#/media/File:CT_cholangioca.jpg

Treatment:

- Surgical resection if possible (20% of the patients)
- Chemotherapy and radiotherapy
- Liver transplantation

Liver Adenoma:

- Most common in middle-aged women
- More common in pregnant women or those taking estrogen-containing oral contraceptives
- The diagnosis is confirmed by ultrasonography which reveals a mass with well-defined borders
- Some patients might have elevations in AST/ALT or GGT
- Most people are asymptomatic
- Symptomatic treatment is indicated which may be hormonal therapy or resection

Hernias:

Definition:

A hernia is a protrusion of a part or a structure through tissues that normally contain it. A hernia has a sack, a neck and contents. The complications of hernias are related to these three features (for example, does the hernia have a narrow long neck as in femoral hernia or a wide short neck?).

The most commonly seen hernial contents are fat and bowel, however any abdominal structure or organ can herniate.

Incarcerated hernia:

Non-reducible hernia that fails to be reduced back to the abdomen or pelvis after applying pressure.

Strangulated hernia:

A hernia that has its neck compressed → compromised venous return and congestion → compromised arterial supply → ischemia → necrosis

- Tenderness
- Erythema
- Fever

Epidemiology:

- The lifetime risk of a spontaneous abdominal hernia is 5%
- Hernia repair procedures are the second most common abdominopelvic operation in the United States
- More than one million repairs per year
- Inguinal hernias are way more common in males than in females
    - 10% are bilateral
    - 70% of all abdominal wall hernias
- Femoral hernias are more common in females; however, inguinal hernias remain more common in females than femoral hernias
    - 15% of abdominal wall hernias
- The remainder of the abdominal wall hernias can be classified as umbilical, epigastric and incisional types
- Strangulation, a possible complication, is more common in internal hernias such as diaphragmatic hernias

## Pathology:

- Increased intraabdominal pressure is the main predisposing factor for the development of an abdominal hernia in adults. It can be caused by:
  - Obesity
  - Chronic cough
  - Bladder outlet obstruction
  - Ascites
- The second important predisposing factor is a weakened abdominal musculature which can be caused by:
  - Previous surgery
  - Trauma
  - Aging
  - Impaired wound healing
- The typical presentation of an uncomplicated abdominal hernia is:
  - A lump that appears and increases in size with coughing, standing or straining
  - The lump reduces spontaneously or with manual manipulation by the patient or the surgeon

## Inguinal Hernias:

Anatomy of the inguinal canal:

- The deep internal ring is found in the transversalis fascia, lateral to the inferior epigastric vessels
- The spermatic cord gets its internal spermatic fascia from the transversalis fascia
- Another opening is found in the transversus abdominis muscle
- The spermatic cord pierces the transversus abdominis muscle and the internal oblique muscle
- It drags with it a layer of the internal oblique → cremasteric muscle and fascia
- Finally, it passes through the external inguinal ring found in the aponeurosis of the external oblique muscle → forms the external spermatic fascia

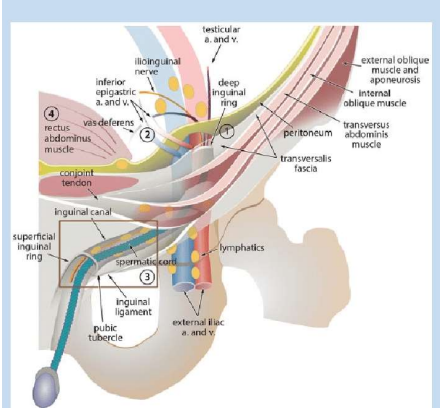



Figure 70: Anatomy of the inguinal canal. 1. Indirect inguinal hernia. 2. Direct inguinal hernia. 3. Femoral hernia. 4. Spigelian hernia. Source: https://www.researchgate.net/figure/Diagram-of-the-inguinal-canal-IC-and-its-contents-The-deep-inguinal-ring-is-formed-by_fig1_318615287

Indirect inguinal hernia:

Definition:

A hernia that goes through the internal inguinal ring, external inguinal ring, and into the scrotum.

Anatomical landmarks:

- Lateral to the inferior epigastric vessels
- Covered by all 3 layers of spermatic fascia
- Follows the path of descent of the testicles

Etiology:

- Failure of closure of the processus vaginalis

This type of hernia is more common in males and can be diagnosed in infants or in adults.

Direct inguinal hernia:

Definition:

The hernia protrudes through the parietal peritoneum directly (inguinal or Hesselbach triangle).

Anatomical landmarks:

- Medial to the inferior epigastric vessels
- Lateral to the rectus abdominis muscle
- Only covered by the external spermatic fascia
- Only passes through the external inguinal ring
- Hesselbach triangle:
  - Inferior epigastric vessels laterally

- Lateral border of rectus abdominis medially
- Inguinal ligament inferiorly

Etiology:

- More common in older men
- Caused by weakened abdominal muscles and transversalis fascia

### Femoral Hernia:

Definition:

A hernia that protrudes below the inguinal ligament through the femoral canal.

Anatomy landmarks:

- Below and lateral to the pubic tubercle
- Below the inguinal ligament
- Medial to the femoral vessels

Clinical significance:

- More common in females
- More likely to be incarcerated or strangulated than inguinal hernias because of their narrow and long neck

### Diaphragmatic Hernias:

The previously discussed hernias were defined as protrusions through the abdominal wall. Diaphragmatic hernias are internal hernias.

Definition:

Abdominal structures enter the thorax via a congenital defect of the pleuroperitoneal membrane or from a trauma. It is more common on the left side.

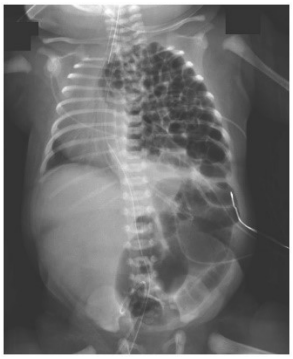


Figure 71: Congenital diaphragmatic hernia. The left-lung is often hypoplastic. Source: https://www.nejm.org/doi/full/10.1056/NEJMicm1701321

Hiatal hernia:

- The stomach herniates upward through the esophageal hiatus of the diaphragm
- Can result in acid reflux

Sliding hiatal hernia:

- The gastroesophageal junction is displaced upward
- The gastric cardia slides into hiatus
- Known as hourglass stomach
- Most common type
- Can result in gastroesophageal reflux disease

Paraoesophageal hiatal hernia:

- The gastroesophageal junction is normal in position
- The fundus protrudes through the hiatus into the thorax
- More likely to strangulate

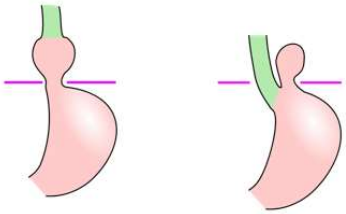


Figure 72: An illustration of the two hiatal hernias. Source: https://en.wikipedia.org/wiki/Hiatal_hernia#/media/File:Hiatus_hernia.svg