Student Submitted Resources

Gastrointestinal System

Anatomy and Pathophysiology

Kimberley Dejong

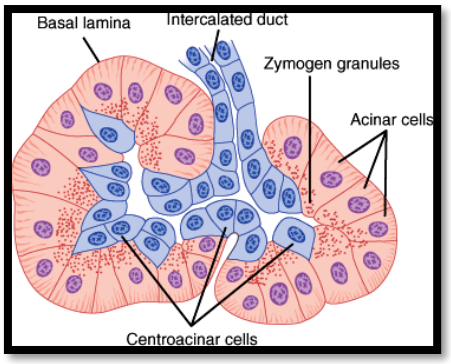
Last Update: June 2017 | File ID: GASTR2017.03

Table of Contents

Histology

- Wall of the GIT consists of 4 concentric layers
  - Mucosa
    - (1) Epithelium: simple cuboidal or simple columnar epithelium with a secretory function
    - (2) Lamina propria: supports vascular mucosal epithelium, contains blood and lymphatic vessels
    - (3) Muscularis mucosae: typically, a double layer of smooth muscle where contraction causes local movement of mucosa
  - Submucosa
    - Layer of connective tissue
    - Contains large blood vessels and lymphatics
    - Contains the submucosal (Meisnner's) nerve plexus
  - Muscularis externa
    - Double layer of smooth muscle
    - Contains myenteric (Auerbach's) nerve plexus
    - Contraction causes peristalsis
  - Adventitia /serosa
    - Connective tissue
- Oesophagus
  - Oesophagus mucosa
    - Non-keratinizing, stratified squamous epithelium (protection against abrasion)
  - Oesophageal muscularis mucosa
    - Upper one third = striated muscle
    - Middle one third = striated and smooth muscle
    - Lower one third muscle = smooth muscle
- Stomach
  - Gastric mucosa
    - Within the mucosa lie gastric glands – simple, branched, tubular that extend from muscularis externa to the bottom of the gastric pits
    - Consist of mucous cells, parietal cells, chief cells and G cells
- Small intestine
  - Duodenum
    - Mucosa: crypts of Lieberkühn (or intestinal glands) that occupy duodenal mucosa
    - Submucosa: Brunner's glands that elaborate alkaline secretions (neutralize acidic chyme propelled by the stomach)
  - Jejunum
    - Mucosa: crypts of Leiberkuhn (or intestinal glands)
    - Submucosa: plicae circulares are circularly arranged transverse folds containing a core of submucosa that extend partially around the lumen
  - Ileum
    - Mucosa: Peyer's patches (aggregation nodules of encapsulated lymphatic tissue) occupy the lamina propria; M cells overlap these Peyer's patches (antigen transporting cells); crypts of Leiberkuhn also

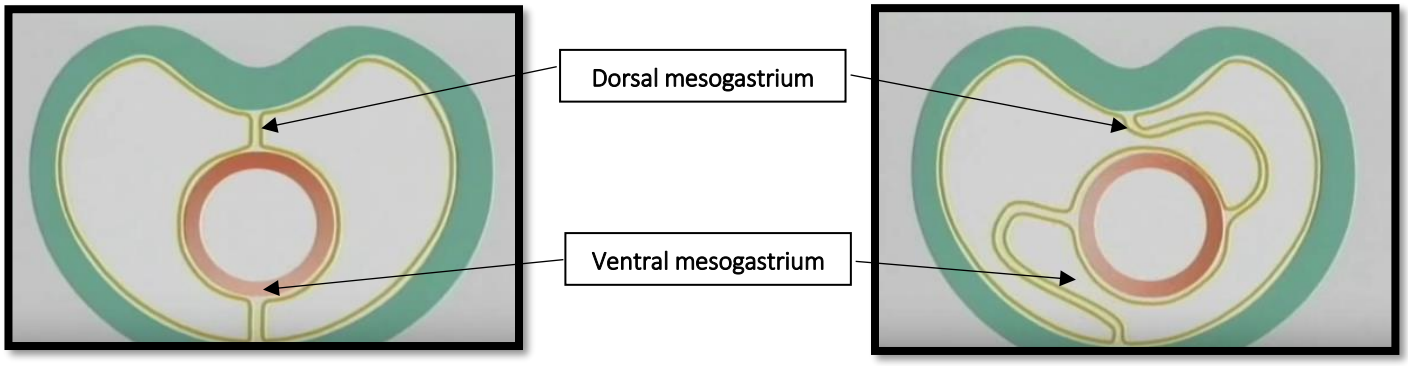
        - Submucosa: plicae circulares
- Large intestine
    - Colon
        - Colonic mucosa: smooth surface with no villi; includes crypts of Leiberkuhn and a muscularis externa
    - Anal canal
        - Mucosa: keratinizing, stratified squamous epithelium
- Pancreas
    - Consists of clusters of acini – which secrete enzymes (Islets of Langerhans)
    - In the middle of each cluster is the centroacinar cells – secretion of electrolytes and water into the pancreatic ductal system
    - Acinar cells surround the centroacinar cells – these synthesize and secrete enzymes
    - Within acinar cells, zymogen granules are found – these contain digestive enzymes or their precursors



GIT embryology

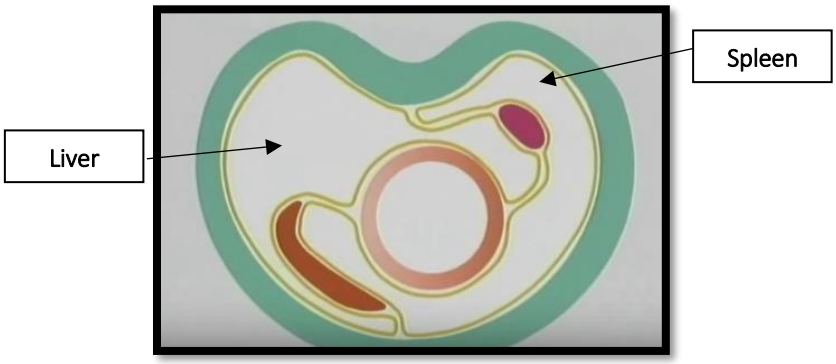
1. The foregut starts as a straight tube, as it develops it rotates on its long axis, lengthens in a double curve and expands to become the stomach and proximal duodenum

2. The foregut has two attachments on the anterior and posterior wall – the dorsal and ventral mesogastrium. As the foregut (red) rotates, the dorsal and ventral mesogastrium rotate with it

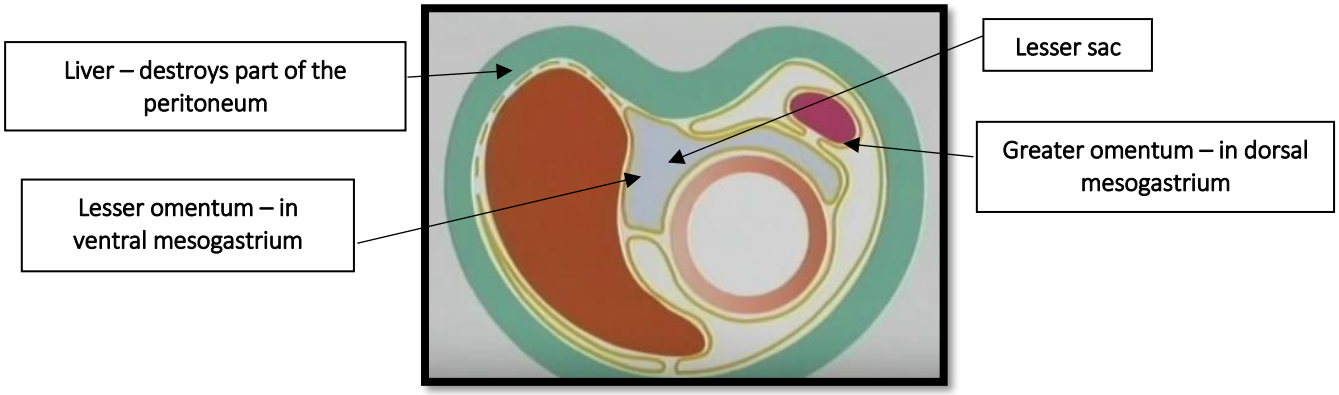


3. The attachment site of the ventral mesogastrium is the lesser curvature of the stomach and the top portion of the proximal duodenum. The attachment site of the dorsal mesogastrium is the greater curvature of the stomach and the underside of the proximal duodenum

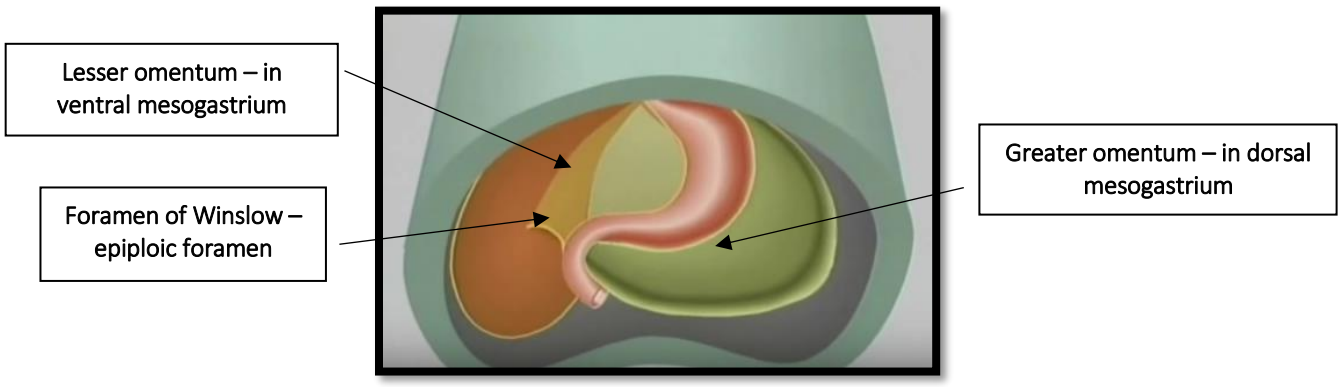
4. While the foregut is developing, the liver develops in the ventral mesogastrium and the spleen develops in the dorsal mesogastrium



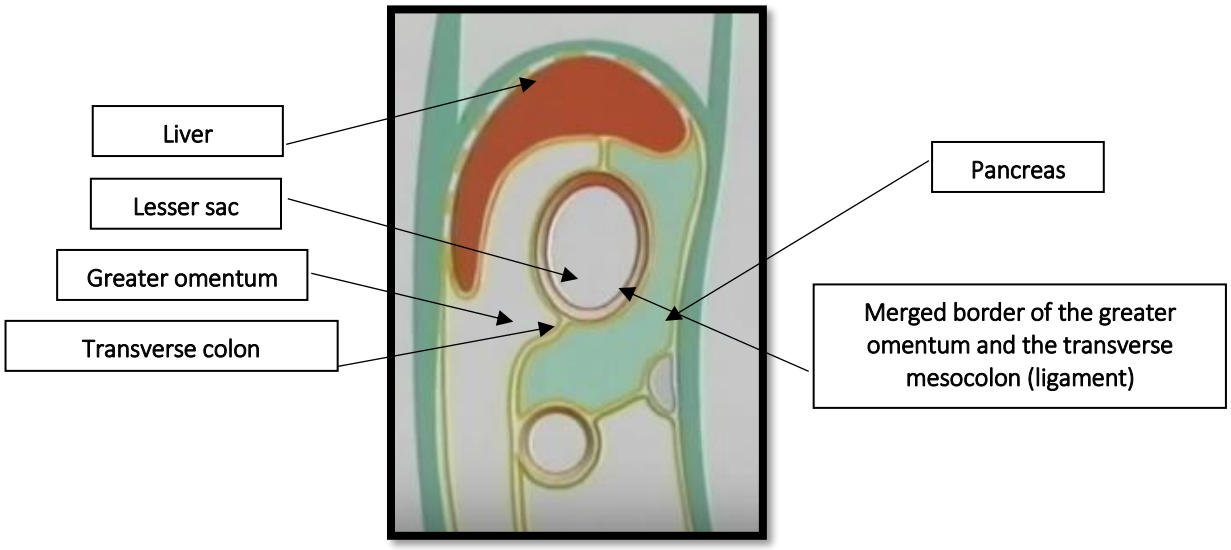
5. The liver grows rapidly, pressing against the body wall obliterating the posterior wall of peritoneum – which leads to the formation of the lesser sac, lying directly behind the stomach. At this point we can distinguish the greater and lesser omentum



6. As the gut develops, the lesser omentum stops growing where the foregut ends in the proximal duodenum. This leaves a free border between the duodenum and the liver – the epiploic foramen (or Foramen of Winslow). The foramen of Winslow allows communication between the greater and lesser omentum

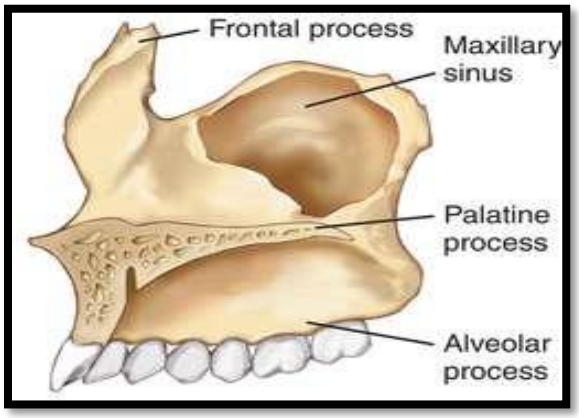


7. At this point, the greater omentum continues to grow. It extends below the transverse colon in a double fold, will its other border merges with the transverse mesocolon (ligament) – while the duplicated layers are dissolved. We are left with the greater omentum stuck to the transverse colon and hanging down below it. The lesser sac still sits behind the lesser omentum and the stomach

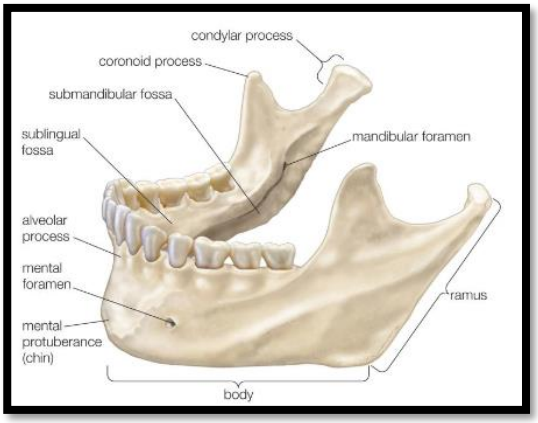


Face and neck anatomy

- Face, mouth and mandible
  - Alveolar process carries teeth of the upper jaw
  - Main body of the maxilla is hollow = maxillary sinus
  - Infraorbital foramen – carries infraorbital nerve and artery
  - Hard palate consists of:
    - Two palatine processes of the maxillae
    - Two horizontal plates of the palatine bones
  - Mandibular foramen is guarded by a small bone – lingula of the mandible

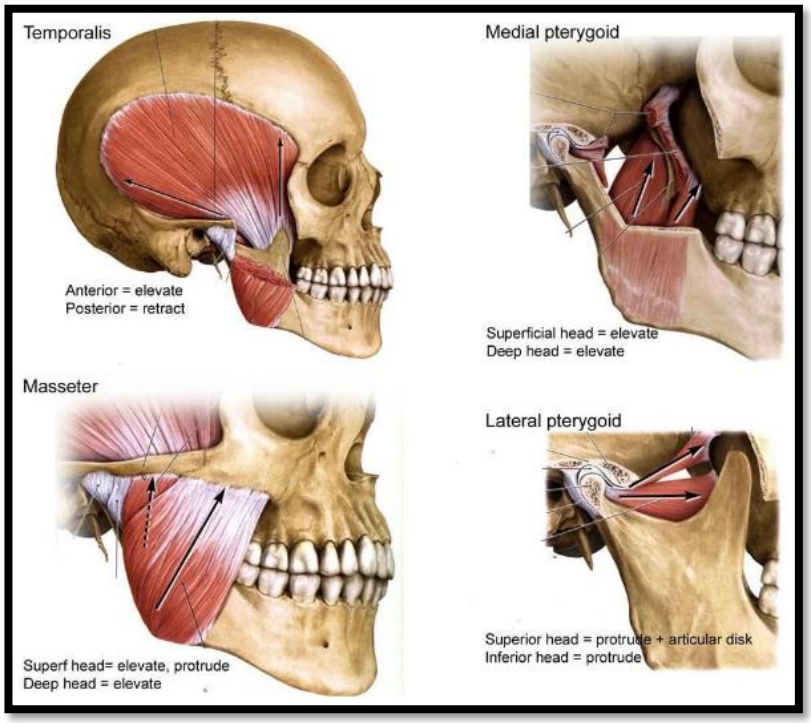


- Teeth
  - 20 child teeth and 32 adult teeth
  - Adult teeth are divided into four quadrants of 8 teeth
  - Each quadrant:
    - 2 incisors (cutting/biting)
    - 1 canine (tearing)
    - 2 premolars (grinding)
    - 3 molars (grinding) – third molar usually appears late in adolescence and is the “wisdom tooth”
  - Innervation
    - Maxillary teeth: CN V2 provides general sensory innervation in a plexus of nerves formed by anterior, middle and posterior superior alveolar nerves

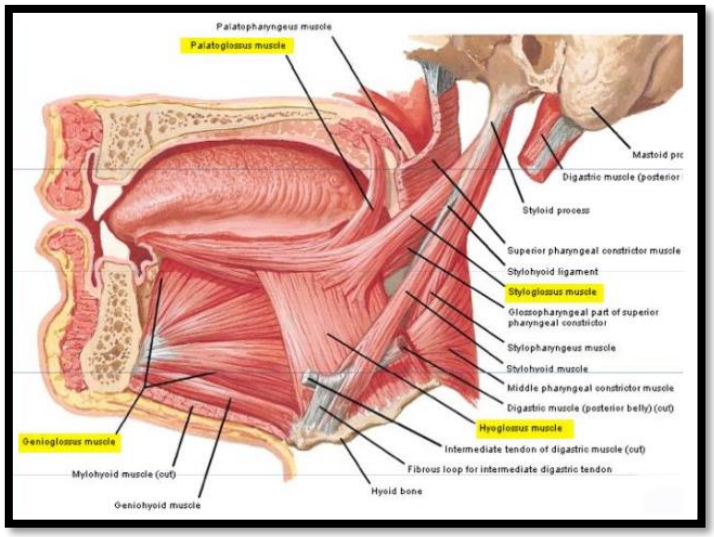


        - Maxillary gingivae: posterior, middle and anterior superior alveolar nerves innervate buccal surface and greater palatine and nasopalatine innervate the lingual surface
        - Mandibular teeth: CN V3 (inferior alveolar branch) provides general sensation
        - Mandibular gingivae: buccal and mental nerves innervate buccal surface; lingual nerve innervates lingual surface
    - Vascular supply (note: veins mirror arteries)
        - Posterior superior alveolar artery
        - Anterior superior alveolar artery
        - Inferior alveolar artery
    - Clinical information
        - Inferior alveolar nerve block administered to patients needing mandible dental work, resulting in numbness of the tongue and oral mucosa
        - Since a maxillary plexus is formed by anterior, middle and posterior superior alveolar nerves – anesthesia is much harder (a greater palatine and nasopalatine nerve block are often administered)

- Hyoid and muscles of mastication
    - Hyoid
        - Does not articulate with any other bone directly
        - Suspended by ligaments from styloid process of the skull
        - Attachments include: mylohyoid, stylohyoid, Hyoglossus, geniohyoid, digastric, omohyoid, sternohyoid and thyrohyoid
    - Muscles of expression
        - Buccinator = cheek muscle, keeps food between the teeth
        - Orbicularis oris = sphincter of the mouth, controlling opening and closure of the lips
    - Muscles of mastication
        - Temporalis
        - Masseter
        - Lateral pterygoid
        - Medial pterygoid



- Tongue
    - Intrinsic muscles
        - Change the shape of the tongue
    - Extrinsic muscles
        - Change the position of the tongue
        - Genioglossus
        - Hyoglossus
        - Styloglossus
        - Palatoglossus



- Pharynx
    - Comprises of three circular muscles stacked inside one another – the constrictors
    - All constrictors are open anteriorly (not a full circle)
    - Constrictors
        - Superior constrictor
        - Middle constrictor
        - Inferior constrictor
    - Vertical muscles that form the pharynx
        - Stylopharyngeus
        - Palatopharyngeus
        - Salpingopharyngeus
    - Innervation
        - Vagus and glossopharyngeal nerves (X and IX), which form the pharyngeal plexus

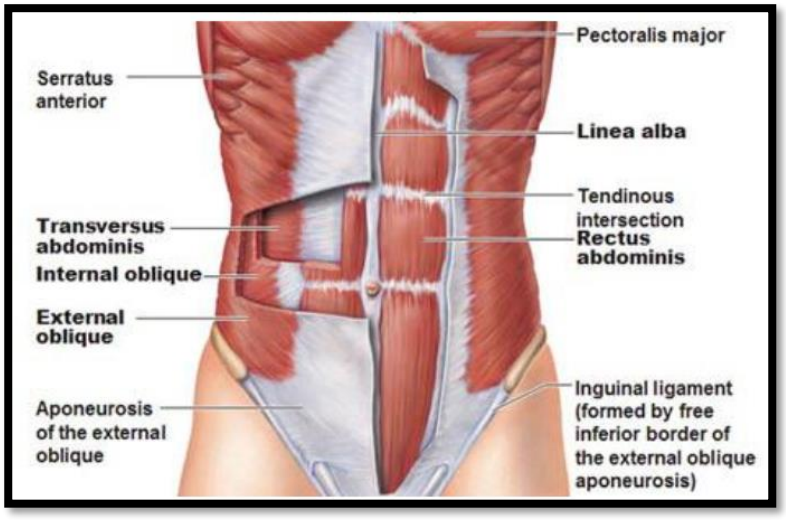
Peritoneal anatomy

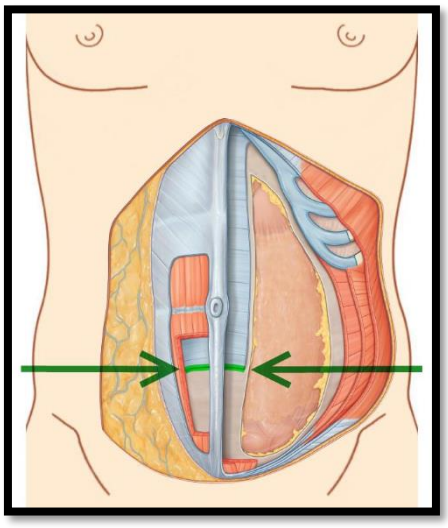
- Peritoneal cavity, abdominal viscera and abdominal wall
    - Peritoneum = serous membrane that consists of two layers
    - Peritoneal sac
        - True peritoneal sac only contains thin film of fluid to allow structures to slide around without friction – there is no actual space – it is a potential space
    - Parietal peritoneum
        - Lines the internal walls of abdominal cavity, forming the peritoneal cavity
        - Completely closed in males and has two openings in females where uterine tubes, uterus and vagina provide passage to outside
        - Reflects off posterior abdominal wall forming a double layer sac housing organs, vessels and lymphatics = mesentery
    - Visceral peritoneum
        - Surrounds the gut tube
        - Produces a serous fluid that lubricates the peritoneal surfaces, enabling organs to slide across one another with minimal friction

- Two types: intraperitoneal (organs suspended from abdominal wall) or retroperitoneal (organs not suspended from abdominal wall)
- Note: surgery involving retroperitoneal structures such as kidneys, can be accessed through the body wall – therefore leaving peritoneum intact and avoiding peritonitis

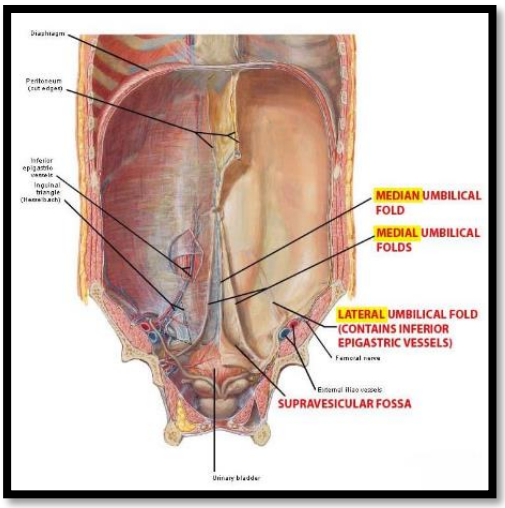
o Anterior abdominal wall

- Layers:
  (1) Skin
  (2) Superficial fascia (where the fat is)
  (3) Deep fascia (usually tightly bound to the muscles and their aponeuroses)
  (4) Abdominal muscles – external and internal oblique's, transverse abdominis, rectus abdominis and posterior muscles including psoas major and quadratus lumborum
  (5) Tranversalis fascia (fascia just deep to the muscles)
  (6) Extraperitoneal fat
  (7) Peritoneum
- Muscles that come around from the sides of the body, to meet the vertical muscles at the front:
  (1) External oblique's – direction of fibers is forwards and down; "hands in pockets", same as the intercostal muscles of the chest wall
  (2) Internal oblique's – direction of fibers is backwards and down, "hips to bra"
  (3) Transversus abdominis – fibers fan out across the inner layer of the abdominal wall, the upper fibres arch upwards and the lower fibers arch downwards, the middle fibres head horizontally
- Rectus sheath formation – upper abdomen
  Anterior rectus sheath is formed by aponeurosis of external oblique and half the internal oblique
  Posterior rectus sheath is formed from transversus aponeurosis and half the internal oblique
- Rectus sheath formation – lower abdomen
  The anterior rectus sheath is formed by all three aponeuroses
  There is no posterior rectus sheath
- Rectus sheath change in the abdomen
  Can clearly see where the anterior and posterior rectus sheaths change over in the abdomen
  Usually halfway between the umbilicus and the pubis >> arcuate line





- Posterior abdominal wall (on the inside of the abdominal wall)
    - Median umbilical ligament >>
      Shriveled piece of tissue that represents a remnant of embryonic urachus (canal that drains urinary bladder of the fetus)
      Extends from the apex of the bladder to the umbilicus on the posterior abdominal wall
    - Medial umbilical ligaments >>
      Paired structures on the posterior abdominal wall, covered by the medial umbilical folds
- Vascular supply
    - Intercostal, lumbar and epigastric arteries = parietal peritoneum
    - Vessels of abdominal aorta = visceral peritoneum



- Gastrointestinal ligaments
    - Lesser omentum
        - Attaches to liver, lesser curvature of stomach and proximal duodenum
        - Referred to as hepatogastric ligament and hepatoduodenal ligament
        - Forms a lesser sac, which is a subdivision of the peritoneal cavity whilst the greater sac is a remaining part of the peritoneal cavity
        - The two sacs communicate via the epiploic foramen of Winslow
    - Greater omentum
        - Attaches between transverse colon and greater curvature of stomach

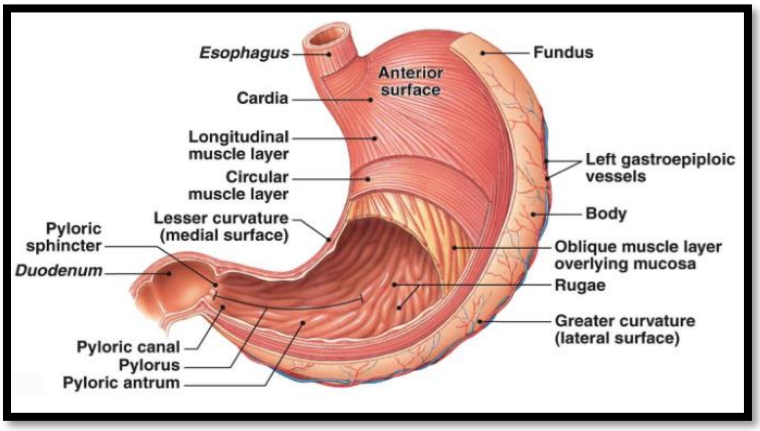
Foregut anatomy

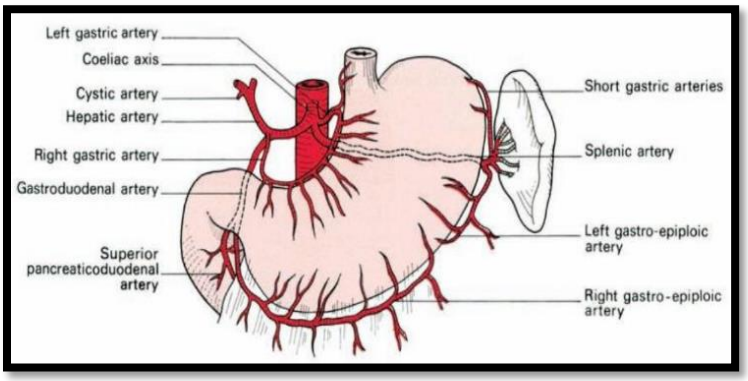
- General details
    - Supplied by celiac trunk and superior mesenteric artery
    - Parasympathetic innervation via the vagus nerve at T12
    - Contains stomach and proximal duodenum, liver, gallbladder, pancreas and spleen

- Oesophagus
    - Total length 25-30cm, depending on length of person
    - Components
        - Cervical oesophagus – skeletal muscle
        - Thoracic oesophagus – smooth muscle
        - Abdominal oesophagus - smooth muscle
    - Course
        - Starts behind cricoid cartilage of larynx, cricopharyngeus muscle, which acts as the upper oesophageal sphincter (note: just above this muscle is a weak area called Killian's area; where a Zenker's diverticulum is located)
        - Descends behind trachea, but in close association
        - Below the tracheal bifurcation, the oesophagus is closely applied to the left atrium of the heart (hence transesophageal echocardiograms are used here for an ultrasonic view of the heart)

- As the oesophagus descends the posterior mediastinum, the aorta swings behind it
- Oesophagus passes through diaphragm at T10 through oesophageal hiatus (formed by right crus – left of midline)
- Junction of oesophagus and stomach = gastro-oesophageal junction/cardia
- Here lie looping fibers of the right crus act as the lower oesophageal sphincter (note: when hiatus is too loose, sliding and rolling hernias can develop)

  - Innervation
    - Left and right vagus nerves approach the oesophagus from each side = form a plexus on surface of oesophagus
    - At diaphragm, plexus emerges as two vagal trunks
    - Left vagus = anterior vagal trunk
    - Right vagus = posterior vagal trunk
  - Vascular supply
    - Branches of inferior thyroid arteries in the root of the neck
    - Branches of bronchial arteries in the chest
    - One or two direct oesophageal branches from the descending aorta
    - Left gastric artery in the lower portion
  - Venous drainage
    - Anastomoses of veins in lower oesophagus with left gastric vein – important porto-systemic anastomoses relevant to portal hypertension

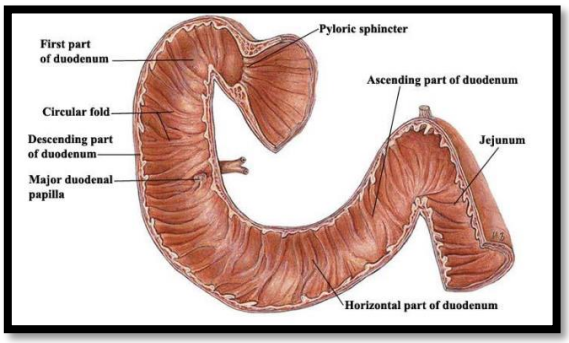


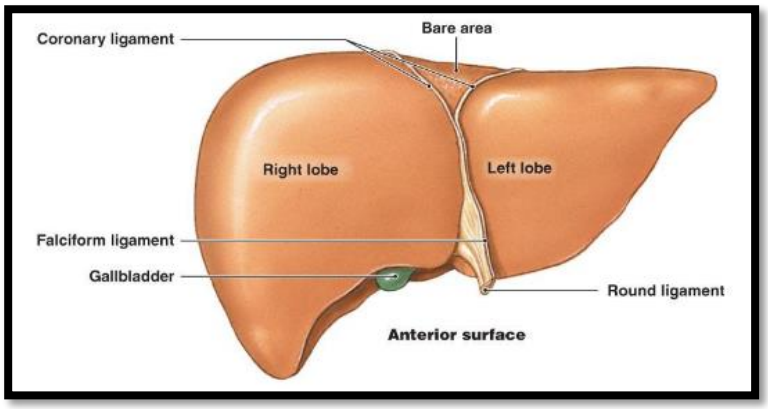


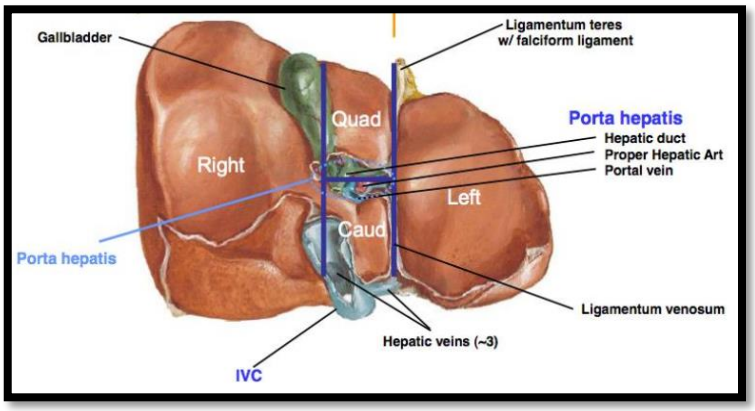
- Stomach
  - Regions
    - Cardia = surrounds the gastro-oesophageal opening
    - Fundus = dome shaped region superior to cardia
    - Body = largest region consisting of a lesser and greater curvature, where the lesser and greater omentum attach respectively
    - Rugae = folds in gastric mucosa in the body of the stomach
    - Pylorus = distal end of stomach containing pyloric sphincter at L1
  - Vascular supply
    - Left gastric artery and right gastric artery = arterial sac around lesser curvature

- Left gastroepiploic artery and right gastroepiploic artery = arterial sac around greater curvature
- Short gastric arteries arising from splenic artery that supply fundus of stomach

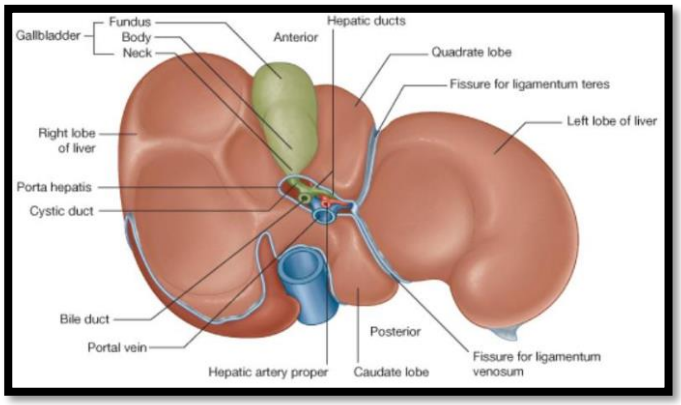
- Duodenum
  - 25cm long
  - Derived of both foregut and midgut
  - Curves around pancreatic head
  - 4 parts:
    - (1) Superior
      Intraperitoneal
      Runs from pylorus
      Contains duodenal cap (large dilation seen on imaging)
      Has a free edge up against the liver, with lesser omentum attached >> hepatoduodenal ligament
    - (2) Descending
      Retroperitoneal
      Site of the junction between embryological foregut and midgut
      Courses in front of the right renal vessels and deep to transverse colon
      Common bile duct receives the main pancreatic duct here
    - (3) Horizontal
      Retroperitoneal
      Turns left and passes horizontally across IVC, aorta and left psoas muscle
    - (4) Ascending
      Retroperitoneal transitioning too intraperitoneal
      Ascends anterior aorta at L2
      As it turns forward it becomes the jejunum >> duodenojejunal flexure







- Liver
  - Location and general considerations
    - Right upper quadrant >> moves down on inspiration
    - 1.4kg in the adult
    - Covered by a fibrous capsule
    - Arises from the ventral mesogastrium during embryological development
  - Lobules and ligaments
    - Attached to inferior surface of right diaphragm dome via coronary ligaments
    - Bare region
      Where the liver is in direct contact with diaphragm
    - Four lobes
      Right, left, quadrate (functionally part of the left lobe) and caudate (functionally separate)
    - Falciform ligament
      Courses between left and right lobes
      This runs from the midline of the anterior abdominal wall, and is attached over the arched surface of the liver
    - Ligamentum teres (round ligament)
      Embryological remnant of the obliterated umbilical vein; lies within Falciform ligament (as above)



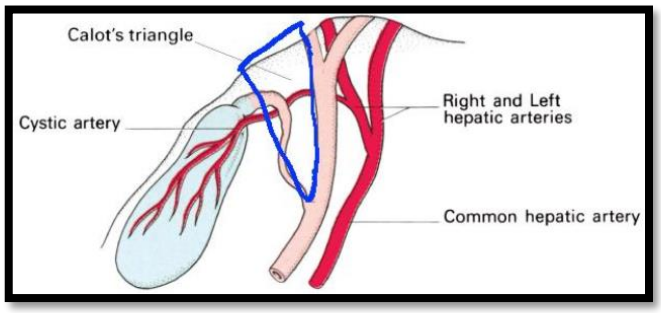
    - Ligamentum venosum
      Contains the remnant of ductus venosus – channel carried blood from the umbilical vein to the IVC, bypassing the liver
    - Underside of the liver there is a H shape of fissures and grooves
      The cross bar of the H is the porta hepatis which is the hilum of the liver (hepatic ducts, portal vein and hepatic artery)
    - Potential space posterior to the liver, in front of the right kidney
      Called the heptatorenal space / Rutherford-Morrison's pouch / Morrison's pouch where fluid can accumulate
  - Macroscopic appearance
    - In life >> large, soft, easily traumatized, reddish in colour
  - Circulation
    - Receives nearly 25% of the body's cardiac output (1500ml per minute) via two sources – venous flow from the portal vein (85%) and arterial flow from the hepatic artery (15%)
    - Portal vein >> venous blood from the small intestine richly with absorbed nutrients – pancreatic venous drainage also drains here
    - Portal vein forms a capillary bed that allows individual hepatocytes to be bathed directly in portal blood
    - The two sources merge within the liver and the combined blood flow exits via the central veins > hepatic vein > IVC
    - The portal triad >> lies between caudate and quadrate lobes; consists of (1) portal vein (2) proper hepatic artery (3) common hepatic duct
  - Innervation
    - Under autonomic control from sympathetic and parasympathetic nerves of the coeliac plexus

- Cellular organisation
  - Parenchyma >> organized into plates of hepatocytes lying in a cage of reticuloendothelial meshwork; each plate is separated by vascular spaces (sinusoids)
  - Sinusoids >> hepatic arterial blood is mixed with portal venous blood
  - Reticuloendothelial meshwork >> endothelial cells, Kupffer cells (liver macrophages), stellate cells (fat storing cells)
- Functional zonation
  - Zone 1 hepatocytes >> receive blood from terminal veins and arteries; exposed to high concentrations of oxygen; very active in gluconeogenesis, oxidative energy metabolism and urea synthesis
  - Zone 2 hepatocytes >> intermediate zone; displays attributes of both zone 1 and 3
  - Zone 3 hepatocytes >> Reached by blood that is leaving the liver via the central vein; exposed to much lower concentrations of oxygen; active in glycolysis and lipogenesis
- Functions
  - Largest gland in the body
  - Energy metabolism > glucose production, glucose consumption, cholesterol synthesis, deamination of amino acids, conversion of ammonia to urea via the urea cycle
  - Protein synthesis > plasma proteins, clotting factors, insulin like growth factor 1, apolipoproteins
  - Transport and storage > drug and poison detoxification, synthesis of VLDL and pre-HDL, clearance of HDL and LDL, uptake and storage of vitamins A, D, B12 and folate
  - Protection and clearance > clearance of bacteria and damaged cells via phagocytosis from Kupffer cells
  - Enterohepatic circulation of bile acids
  - Drug metabolism and secretion
- Receptor mediated uptake
  - Hepatocytes have three sides:
    (1) Apical surface > forms the wall of the bile canniculus
    (2) Basolateral surface > contact with the bloodstream via sinusoids
    (3) Lateral domain > bordered by other two surfaces
  - Each hepatocyte's sides are separated by tight junctions
- Capacity for regeneration
  - Normal liver cells contain very few cells in mitosis
  - When hepatocytes are lost, the rest of the hepatocytes proliferate
  - Therefore, in most cases of fulminant hepatic failure, if the patient survives the acute period, then recovery will be complete

- Gallbladder
  - Location
    - Lies on visceral surface of liver, to the right of the quadrate lobe
    - Lies in a shallow depression >> gall bladder fossa
    - Stores and concentrates bile secreted by liver
    - Has a body, fundus and neck (which leads to cystic duct)
    - Some gall bladders have a small pouch at the junction of the body and neck (Hartmann's pouch) >> pathological as gallstones can get stuck here
  - Bile function and synthesis
    - Digests and absorbs lipids
    - Synthesised and secreted by liver

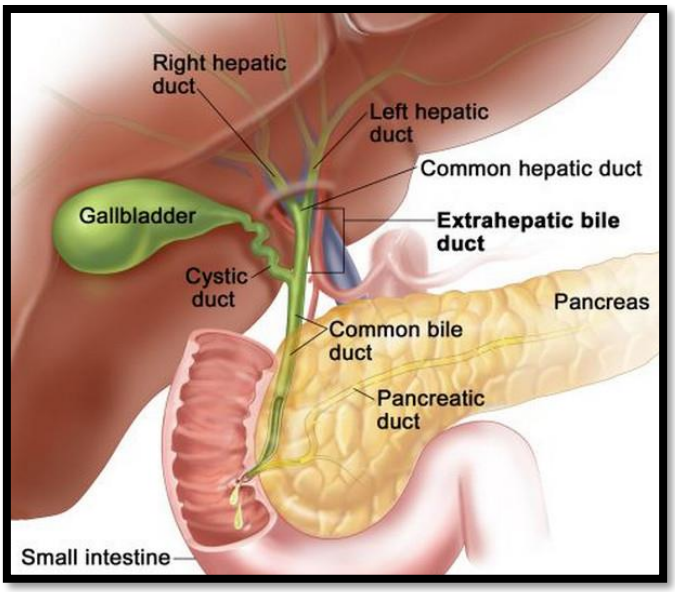
- Stored in gallbladder

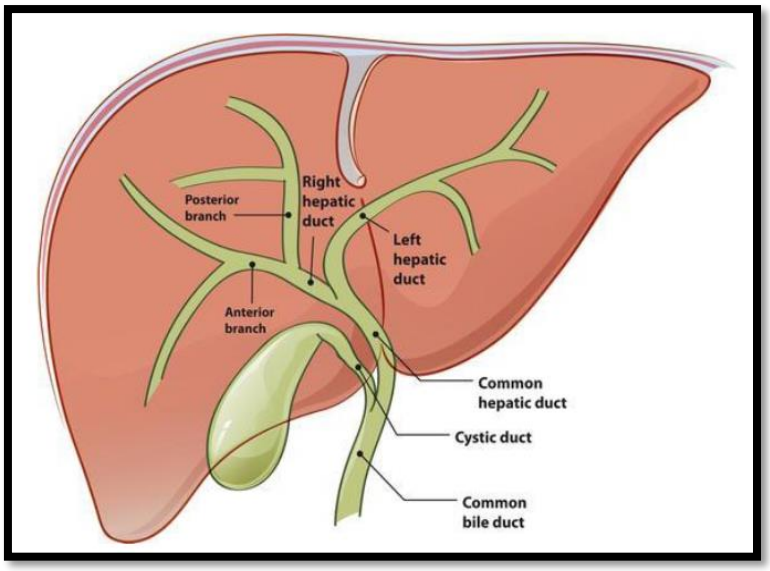
- Bile composition
  - Bile salts
    Cholesterol > primary bile acids > secondary bile acids > bile salts
    Conjugation in liver with amino acids to increase water solubility
    Acts to emulsify dietary lipids
  - Bile pigments >> bilirubin
  - Cholesterol
  - Phospholipids
  - Electrolytes
  - Water



- Bile secretion
  - Mediated via CCK
  - Stimulates contraction of gallbladder and relaxation of sphincter of Oddi > bile flows from gallbladder into duodenum > bile emulsifies lipids
- Bile release
  - Bile released into duodenum when gallbladder is stimulated after eating a fatty meal
  - Bile enters cystic duct which joins common hepatic duct >> becoming common bile duct
  - Common bile duct courses within hepatoduodenal ligament of lesser omentum, where it joins the main pancreatic duct
- Gall bladder blood supply
  - Cystic artery >> a branch of the right hepatic artery
  - Triangle of Calot >> small triangle formed by the cystic duct, inferior portion of the liver and common hepatic duct – this is the region of most anatomical variation and dissection in this triangle is the most common cause of injuries to the bile duct
- Biliary system
  - (1) Right and left hepatic ducts emerge from their corresponding halves of the liver and merge to form the common hepatic duct
  - (2) Common hepatic duct passes down the free edge of the lesser omentum, whilst uniting with the cystic duct from the gallbladder
  - (3) Once the cystic duct has joined the common hepatic duct, it becomes the common bile duct
  - (4) The common bile duct is joined by the pancreatic duct emptying into the second part of the duodenum >> where they unite forms a dilation called “hepatopancreatic ampulla of Vater”

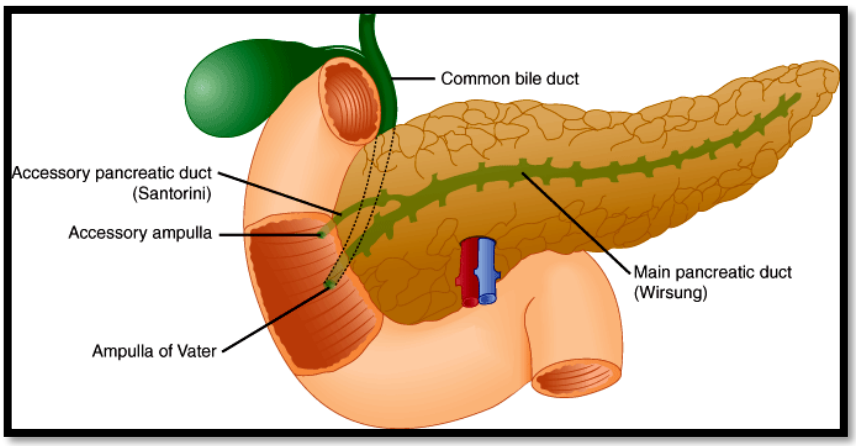
- (5) Around the Ampulla of Vater lies muscle that forms the sphincter of Oddi



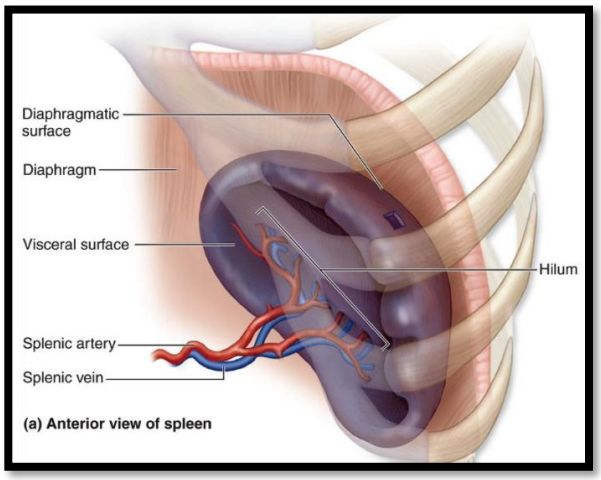


- Pancreas
  - Location and function
    - Retroperitoneal organ at L2
    - IVC, aorta, renal and gonadal vessels lie behind the pancreas
    - Dual – exocrine and endocrine
      Exocrine = produces enzymes that digest carbs, proteins and fats; secreted into main pancreatic duct and into duodenum
      Endocrine = islands of endocrine tissue (pancreatic islets of Langerhans) produce hormones insulin and glucagon; secreted into blood stream via pancreatic vein
  - Anatomy of endocrine pancreas
    - Endocrine pancreas composed of islets of Langerhans (only 1% of total pancreas)
    - More than 70% of insulin secreting beta cells must be loss before dysfunction occurs
    - Four types of islet cells:
      (1) Insulin secreting beta cells (60%)
      (2) Glucagon secreting alpha cells (30%)
      (3) Somatostatin secreting delta cells (9%)
      (4) Pancreatic polypeptide secreting cells (1%)
    - Islets are highly vascularized – one arteriole per islet
    - Islets are highly innervated – S and PS axons are in direct contact
    - Blood from the islets drain to the portal vein
  - Regions
    - Head and neck: nestled near the duodenum, head also contains the uncinate process
    - Body and tail: located anteriorly near left kidney, with the tail touching the spleen
  - Ducts
    - Main pancreatic duct
      Runs from tail to the end, on the posterior surface
      Near the neck, its joined by the bile duct to form Ampulla of Vater within the sphincter of Oddi
      Combined ducts drain into second part of the duodenum via the greater duodenal papilla

- Accessory pancreatic duct
  Can sometimes be present, draining part of the head
  If present, it drains into the duodenum via the lesser duodenal papilla
- Innervation
  - Parasympathetic stimulation via vagus nerve MAY increase exocrine secretions
  - Sympathetic input from T5-T9, increases tone of smooth muscle cells around neck of secretory units



- Spleen
  - Location and appearance
    - Soft, vascular organ
    - Lies against diaphragm and 9^{th}-11^{th} ribs on left side
    - Mostly intraperitoneal
  - Function
    - Formation of red blood cells during fetal and early postnatal life
    - Development of mononuclear leukocytes, lymphocytes and clearance of red blood cells from blood
    - Filters blood, removes iron from hemoglobin
    - Stores blood
  - Regions
    - Left upper quadrant of the abdomen between stomach and diaphragm
    - Hilum >> formed by a lone fissure, where the splenic artery enters and the splenic vein leaves
  - Blood supply
    - Splenic artery >> arises from coeliac trunk
  - Venous drainage
    - Via portal circulation
  - Splenomegaly
    - Increase in RBCs may result in an enlarged spleen
    - Occurs in patients who are diagnosed with diseases that change the shape of RBCs (malaria etc)



Midgut anatomy

- General details
  - Supplied by superior mesenteric artery
  - Parasympathetic innervation via the vagus nerve at L1
  - Contains distal half of duodenum, jejunum, ileum, cecum, ascending colon

- Jejunum and ileum
  - Both suspended from the posterior abdominal wall by the mesentery
  - Arranged in coils, which occupy most of the abdominal cavity
  - There is no fixed line of demarcation between the two
  - Some comparison features:
    - Jejunum tends to have thicker walls
    - Jejunum tends to be emptier than the ileum
    - Jejunum shows windows in the mesentery, with no fat
    - Jejunum has a pattern of blood vessels >> single layer of vascular arcades
    - Jejunum has many circular folds in the mucosa >> pilae circulares (ileum is rather smooth in comparison)
    - Jejunum doesn't have Peyer's patches

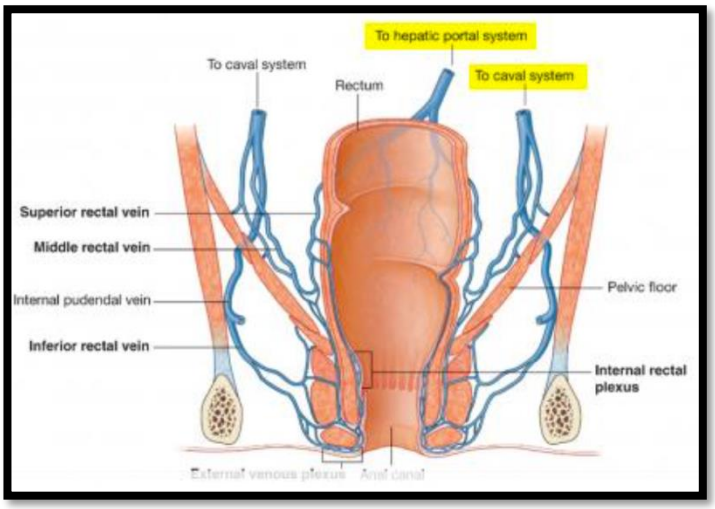
- Cecum and appendix
  - Junction between terminal ileum and cecum >> ileocaecal junction and the ileocecal valve (little mechanical function)
  - Cecum lies in the right illiac fossa and houses the appendix in this region (posteromedial attachment to the cecum)
  - Appendix locations
    - Appendix lies behind cecum >> retrocecal appendix
    - The appendix has its own little mesentery >> mesoappendix, containing appendiceal artery

- Ascending colon
  - Retroperitoneal
  - Extends upwards from the right iliac fossa to the hepatic flexure just below the liver in front of the right kidney

Hindgut anatomy

- General details
  - Supplied by inferior mesenteric artery
  - Parasympathetic innervation via the pelvic nerve at L3
  - Contains transverse, descending and sigmoid colon, rectum and anus

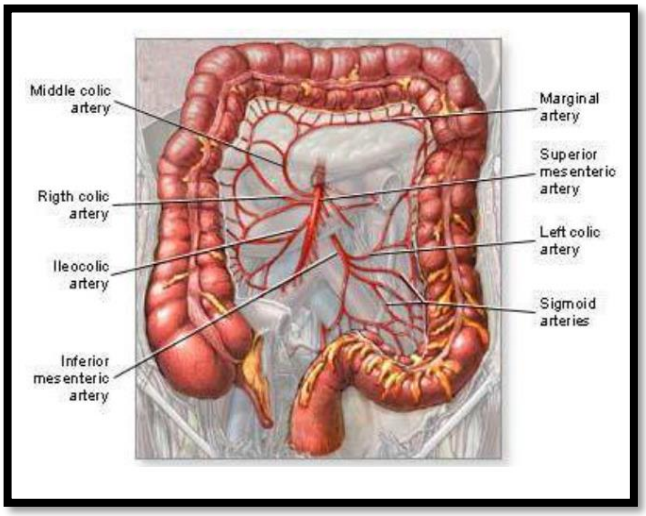
- Transverse, descending and sigmoid colon
    - Transverse colon
        - Extends to the left from the right colic flexure and ends at the left colic flexure
        - Most obvious feature >> its mobility
        - Has a mesentery of its own >> transverse mesocolon
    - Descending colon
        - Usually retroperitoneal
        - Descends to the pelvic brim where the sigmoid colon begins
    - Sigmoid colon
        - Has its own mesentery >> sigmoid mesocolon



- Rectum and anus
    - The sigmoid colon becomes the rectum and anorectal canal at the Rectosigmoid junction >> lined with taeniae coli (distinct banding ribbons)
    - Anorectal canal can drain either into the portal vein (via superior rectal vein) or into the systemic circulation (via the inferior or middle rectal veins)
        - Clinical importance of this portosystemic anastomosis
        - Patients with liver disease that results from portal hypertension can result in varicosities of the middle and inferior rectal veins >> hemorrhoids

Additional intestinal anatomy

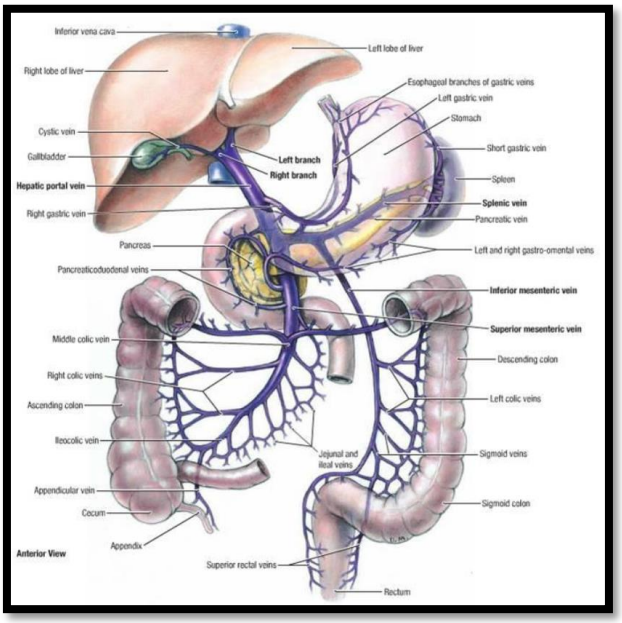
NOTE: THE SMA, CELIAC TRUNK AND IMA ALL FORM ONE ARTERY THAT RUNS AROUND THE MESENTERIC BORDER OF ALMOST THE ENTIRE LARGE INTESTINE. THIS IS CALLED THE MARGINAL ARTERY OF DRUMMOND. THIS IS VITAL TO SEVERAL SURGICAL PROCEDURES INVOLVING RESECTION OF PORTIONS OF THE COLON



- Additional blood supply and venous drainage information – intestines
    - Superior mesenteric and inferior mesenteric veins drain into the portal vein >> which is why the first point of malignant metastasis is the liver instead of the IVC
- The portal vein:
    - Splenic vein and superior mesenteric vein = portal vein
    - Inferior mesenteric vein can join any of these two veins, or their junction >> variable in the body
- Small intestine
    - Supplied by autonomic and sensory fibers
    - Vagal nerve (CNX – parasympathetic) stimulates intestinal movement and secretion
    - Sympathetic stimulation is generally inhibitory – inhibits muscular contractions such as peristalsis and secretions

Hepatic portal system

- General considerations
    - Venous return from almost the entire bowel drains into the portal venous system headed to the liver
- How does the portal system drain blood?
    - Capillary beds of the bowel converge into venules and then veins
    - These veins converge into larger veins
    - The larger veins converge into the superior and inferior mesenteric veins
    - The superior and inferior mesenteric veins are joined by the splenic vein returning from the spleen >> triad forming the hepatic portal vein/portal vein
    - The portal vein reaches the liver and drains entering the porta hepatis zone on the posterior side
    - Once the blood has been processed by the liver, it is drained from the liver by 2-3 large hepatic veins directly into IVC
- Portosystemic anastomoses
    - These are usually low pressure zones – but if the portal system pressures increases, this causes increased pressure within the systemic circulation
    - These zones can develop varices due to this portal hypertension
        - Lower oesophageal varices >> can bleed profusely
        - Paraumbilical varices >> caput medusae
        - Anorectal varices / hemorrhoids >> can bleed or thrombose



Enteric nervous system

- Submucosal nerve plexus
    - Known as Meissner's neve plexus
    - Lies in the submucosa between muscularis mucosal epithelium and inner layer of smooth muscle
    - Regulates GI secretions, blood flow and absorption
    - Receives input from sympathetic and parasympathetic nervous system
- Myenteric nerve plexus
    - Known as Auerbach's nerve plexus
    - Lies in the muscularis externa
    - Regulates GI motility
    - Receives input from sympathetic and parasympathetic nervous system

Associated lymphatics

- Collecting system for lymphatic drainage of stomach and upper intestine = cisterna chyli
- Named so because fatty substances (chyle) accumulate here from upper bowels

- The chyle accumulates in cisterna chyli and then the thoracic duct drains upwards
- Thoracic duct + venous drainage of the neck empty together into the venous circulation = thus malignancies of upper GI tract can spread to the root of the neck

Inguinal region anatomy

- Inguinal ligament
    - Is the rolled under inferior free border of the external oblique aponeuroses, extending between the ASIS to the pubic tubercle
    - Shaped like a gutter

- Attachment sites of the anterior abdominal muscles
    - Internal oblique
        - Extends pass ASIS and along gutter of the inguinal ligament to about 2/3 of the way along the ligament
        - Attach to the pubic tubercle as first part of the conjoint tendon
    - Transversus abdominis
        - Extends along the gutter of the inguinal ligament, but only half way along it
        - Attaches to the pubic tubercle as the second part of the conjoint tendon

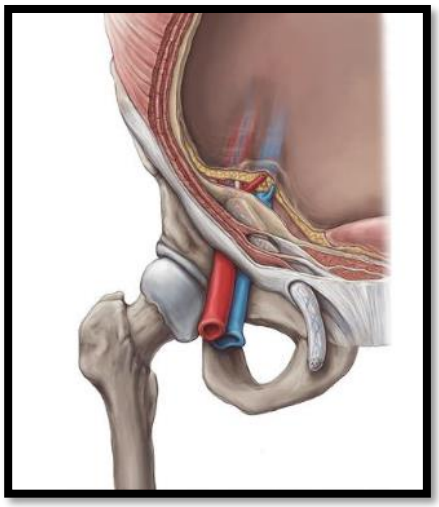
- Inguinal canal
    - Small area lying just above the inguinal ligament
    - It is a pathway through the lower anterior abdominal wall layers
    - 4cm long
    - Starts at the deep inguinal ring and ends at the superficial inguinal ring – running in an oblique direction from entrance to exit
    - Deep inguinal ring
        - Opening in transversalis fascia
        - Lies laterally to the inferior epigastric vessels that arise from the external illiac vessels
    - Superficial ring
        - Inverted V shaped gap between two crura of the external oblique aponeurosis that attach to the pubic tubercle and crest

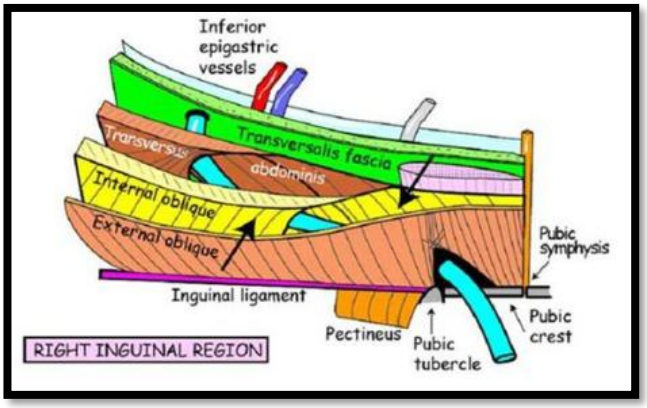
- Contents of the inguinal canal
    - Spermatic cord (males)
        - Ductus deferens passes into deep inguinal ring, is joined by vessels and nerves to form the spermatic cord
        - As it enters the deep ring, it picks up the transversalis fascia which then becomes the fascia covering the cord
        - As the cord travels, it passes below the transversus abdominis muscle fibres
        - As it emerges from the superficial ring it picks up a layer from the edges of the ring, becoming the external spermatic fascia
        - Core components of the spermatic cord:
            (1) Ductus deferens + its arteries and veins
            (2) Testicular artery
            (3) Cremasteric artery
            (4) Pampiniform plexus – leading to testicular vein

(5) Genital branch of the genitofemoral nerve
(6) Lymphatics
(7) Surrounded by three layers of fascia: internal spermatic, cremasteric and external spermatic

- Round ligament of the uterus (females)
- Ilioinguinal nerve
- Fibers from the inguinal ligament – lacunar ligament

- **Development of the gonads**
  - Development
    - Develop in both sexes from the urogenital ridge on the posterior body wall of the embryo >> retroperitoneal
    - Gonads then descend to their final positions >> testes in the scrotum and the ovaries in the pelvis
    - This descent is relative
    - The gonads stay where they are, while the rest of the embryo grows upwards and downwards
  - Attachments
    - Attached to scrotum in the male and the labia majora in the female by a cord called the gubernaculum
    - The gubernaculum guides them on their relative descend and tethers them to lower structures
    - In males, the gubernaculum tethers the testis to the scrotum and the testis is gradually pulled down through the inguinal canal
    - In females, the gubernaculum guides the ovaries towards the uterus
  - Relative outpouchings
    - Outpouching of peritoneum that extends through the deep inguinal ring and inguinal canal and down into scrotum of male >> processus vaginalis
    - Processus vaginalis extends to the testis in the male, most of it being turned into fibrous tissue, but the distal portion remains >> tunica vaginalis
    - This tends to stop in the female at the superficial ring
    - Sometimes the processus vaginalis remains patent and doesn't undergo fibrosis >> gives rise to the Canal of Nuck in females
  - Blood supply
    - Because gonads develop on posterior body wall, they get their blood supply from here
    - Gonadal vessels arise from abdominal aorta
    - Gonadal vessels drained into either IVC directly (right) or indirectly via the renal vein (left)





Physiology of swallowing and motility

- Gastrointestinal motility
  - Contractions
    - Contractile tissue of GIT is almost always smooth muscle which is electrically coupled via gap junctions (rapid cell to cell action potentials)
    - Exceptions for smooth muscle – pharynx, upper 1/3 of oesophagus and external anal sphincter (all have striated muscle)
  - Slow waves
    - Unique feature of GIT smooth muscle
    - Refers to the oscillating depolarization and repolarization of membrane potential of smooth muscle cells
    - Slow waves occur at interstitial cells of Cajal (the "pacemaker" of the GIT)
    - Frequency of slow waves varies along the GIT: stomach has the slowest frequency (3/min), ileum (8-9/min) and duodenum has the fastest frequency (12/min)
    - Mechanism: cyclic opening of Ca+ channels depolarizes the cell membrane, and cyclic opening of K+ channels repolarizes the cell membrane

- Swallowing
  - Oral phase
    - Swallowing under voluntary control of the mouth
    - (1) Food bolus propelled from the mouth to the pharynx via the tongue
    - (2) Somatosensory receptors in the pharynx are activated which initiates involuntary swallowing reflex in the swallowing center in the medulla
  - Pharyngeal phase
    - Swallowing under involuntary control reflex – peristaltic wave of contraction
    - *Breathing is inhibited during this phase*
    - (3) Food bolus is propelled from the pharynx to the oesophagus by the soft palate rising to protect nasopharynx, the epiglottis covering the larynx opening to prevent aspiration, and the upper oesophageal sphincter opening
  - Oesophageal phase
    - Swallowing under involuntary reflex – primary and secondary waves of peristalsis
    - (4) Food bolus is propelled from the pharynx to the lower oesophagus; after which the upper oesophageal sphincter closes to prevent reflux into the pharynx

- Oesophageal motility
  - Overlaps with oesophageal phase of swallowing – under involuntary reflex
  - (5) Food propels down to the lower oesophageal sphincter via sequential contractions of smooth muscle and peristaltic waves
  - *If the primary peristaltic waves do not clear the oesophagus, then a second wave will proceed mediated by the enteric nervous system*
  - (6) Lower oesophageal (cardiac) sphincter relaxes and opens and the orad stomach relaxes via receptive relaxation (decreasing in pressure to pull the food bolus downwards)

- (7) LOS contracts and closes to prevent the bolus from refluxing into the oesophagus

- Gastric motility
  - Functions
    - Oral stomach = fundus and proximal portion; relaxes and receives the food bolus from the oesophagus
    - Caudad stomach = distal portion and antrum; contractions here reduce the size of the bolus and mix it with secretions to initiate digestion
  - (8) Receptive relaxation (a reduction in pressure and increase in volume of the orad stomach)
    - Vasovagal afferent fibers (sensory): mechanoreceptors detect distention of the lower oesophagus and orad stomach by the incoming bolus – they relay sensory information to the CNS via vagus nerve
    - Vasovagal efferent fibers (motor): CNS relays motor information to the smooth muscle walls of the lower oesophagus and the orad stomach via vagus nerve; releasing vasoactive intestinal polypeptide (VIP), which relaxes the LOS and smooth muscle
  - (9) Mixing and digestion
    - Occurs in the caudad of the stomach – which has a thick muscular wall for production of contractions needed to break up the bolus
    - Mixing – contents is propelled to the antrum and then back towards the body of the stomach (retropulsion)
  - (10) Gastric emptying
    - Contractions propel some of the contents through the pylori sphincter and into the duodenum of small intestine
    - Closely regulated to allow time for neutralization of gastric acid in the duodenum
    - H+ receptors detect low pH/high H+ and act via interneurons in the myenteric plexus to slow gastric emptying (allows time for neutralization by pancreatic HCO3-)
    - When fatty acids are encountered in the duodenum, cholecystokinin (CCK) is secreted by I cells in the small intestine to slow gastric emptying (allowing time for acid digestion and absorption)

- Small intestine motility
  - Functions
    - Digestion and absorption of nutrients
    - Mixes chyme with digestive enzymes and pancreatic secretions
    - Propels unabsorbed chyme along GIT
  - Small intestine contractions
    - Segmental contractions (in sections) which splits the chyme and sends it in both directions
    - Sections then relax, and the chyme mixes back together
    - Peristaltic contractions propel intestinal contents along GIT to the large intestine

- Migrating myoelectric complexes (MMCs)
  - Periods of small intestinal contractions that occur during the fasting state (90 min intervals)
  - Helps to clear the small intestine of any residual contents
  - Mediated by motilin

- Large intestine motility
  - Functions
    - Fecal material moves through the cecum > colon (ascending, transverse, descending and sigmoid) > rectum > anal canal

        - Fecal material is excreted
    - Segmentation contractions
        - Mix intestinal contents of the large intestine
        - Occurs in the cecum and proximal colon
        - Contractions associated with characteristic sac-like segments called haustra
    - Mass movements
        - Contents is moved over long distance 1-3 times per day
        - Fecal material in distal colon is semi-solid and moves slowly – consequence of colonic water absorption
    - Defecation
        - Rectosphincteric reflex
        - As rectum fills with fecal material the smooth muscle walls of the rectum contracts and the internal anal sphincter relaxes
        - At this point defecation, does not occur because the external sphincter is still tonically contracted (under voluntary control)
        - Once rectum is 25% full, the urge to defecate occurs
        - Defecation causes smooth muscle wall of rectum to contract and generate sufficient pressure to push material through anal canal

Salivary glands secretions

- Salivary secretions
    - Parotid glands, submandibular glands and sublingual glands
    - Formation of saliva
        - Acinar (pancreatic) cells produce initial saliva composed of water, ions, enzymes and mucous (isotonic)
        - Initial salvia passes from acinus to duct
        - Ductal cells (lining the pancreatic duct) modify initial saliva to produce final saliva by altering various element concentrations (decreasing Na+ and Cl-, increasing K+ and HCO3-) (hypotonic)
    - Salivary enzymes
        - (1) a-amylase – begins initial digestion of carbohydrates
        - (2) Lingual lipase – begins initial digestion of lipids
        - (3) Kallikrein – catalyses proteolytic cleavage of kininogen into bradykinin > potent vasodilator > increases salivary gland activity and blood flow
        - Acinar cells secrete IgA
    - Flow rate and composition
        - Highest flow rates – final saliva resembles plasma (isotonic) > ductal cells have less time to modify the saliva
        - Lowest flow rates – final saliva is most dissimilar to plasma (hypotonic) > ductal cells have more time to modify the saliva
    - Regulation
        - Stimulated both sympathetic and parasympathetic nervous system
        - Sympathetic input to the salivary glands via thoracic segment (T1-T3) where postganglionic nerves release NE > stimulates adenylyl cyclase > increased cAMP > increased secretion

- Parasympathetic input to the salivary glands via facial nerve (CNVII) and glossopharyngeal nerve (CN IX) > increased Ach > stimulates muscarinic receptors > increased IP3 and calcium > increased saliva secretion

Gastric secretions and glands

- Overview
  - Cells of gastric mucosa secrete gastric juice
  - Gastric secretions composed of hydrochloric acid, pepsinogen, intrinsic factor and mucous
  - HCl and pepsinogen = initiate protein digestion
  - Intrinsic factor = required for vitamin B12 absorption in ileum and is the ONLY essential secretion of the stomach; deficiency causes pernicious anemia
  - Mucous = protection for gastric mucosa and lubricates contents
- Gastric glands
  - Oxyntic glands
    - In the body of the stomach
    - Lie within the gastric pits of the stomach
    - These glands contain parietal cells (secrete HCl and IF) and chief cells (secrete pepsinogen)
  - Pyloric glands
    - In the antrum of the stomach
    - Lie within the gastric pits of the stomach
    - Contain G cells (secrete gastrin into systemic circulation) and mucosal neck cells (secrete mucous and HCO3- into pyloric ducts

- Gastric parietal cell
  - Apical membrane
    - Contains H+-K+ ATPase and Cl- channels
  - Basolateral membrane
    - Na+ - K+ ATPase and Cl-/HCO3- exchanger
  - Role of parietal cells
    - Secreting HCl and IF into oxyntic ducts that empty into the stomach, this HCl acidifies gastric contents
  - Parietal cells are activated by
    - Smelling, tasting and conditioned reflexes for anticipated food
    - Distention of the stomach
    - Presence of breakdown products of protein
    - Vagal stimulation
    - Phenylalanine and tryptophan are most potent stimuli for gastric secretion
  - Vagal stimulation – direct pathway
    - Ach is released at synapse and binds to M3 muscarinic receptors > increasing DAG and IP3 second messengers > increasing intracellular calcium > PKC (protein kinase C) breaks down DAG and calcium > HCl secretion is increased
  - Vagal stimulation – indirect pathway
    - Innervation of the gastric G cells > at synapse, gastrin-releasing peptide (GRP) is released
    - GRP increases gastrin secretion indirectly via G cells
  - Vagal stimulation – atropine

        - Atropine inhibits HCl secretion via parietal cells, because it's a cholinergic muscarinic antagonist
    - Histamine
        - Released via enterochromaffin-like(ECL) cells in gastric mucosa > binds to H2 receptors on parietal cells > increase cAMP second messenger > H+K+ ATPase > increases HCl secretion
    - Gastrin
        - Released from G cells of antrum into systemic circulation and is delivered back to the stomach via systemic circulation
        - Stimulates HCl secretion by a) binding to CCK-B receptors (cholecystokinin) on parietal cells or b) binding to CCK-B receptors on ECL cells, increasing histamine and HCl secretion
    - Inhibition of HCl secretion
        - Inhibition of HCl is required when the chyme is being propelled along the GIT from the stomach
        - Somatostatin is secreted by D cells of gastric mucosa to reduce HCl secretion
        - Prostaglandins bind to G proteins on parietal cells to reduce HCl secretion

- Gastric chief cell
    - Function
        - Secrete pepsinogen into oxyntic ducts within the gastric pits of the stomach
        - Pepsinogen = zymogen (inactive enzyme) that must be activated through cleavage
    - Activation of pepsinogen secretion
        - Vagal stimulation = increase in pepsinogen secretion from chief cells
        - Increased hydrogen ions = increase in pepsinogen secretion from chief cells

- Pancreatic secretions
    - Components of pancreatic juice
        - HCO3-, Cl-, Na+ and K+
        - HCO3- is very important as it alkalizes pancreatic juice – which in turn assists to neutralize stomach acid entering the duodenum
    - Enzymes that digest carbohydrates
        (1) Amylase
        Secreted by acinar cells in their active form
        Digest starch bonds of polysaccharides – forming maltose, dextrin's and maltotriose
        These simple sugars are hydrolyzed into glucose by brush border enzymes and then transported across the intestinal wall via Na+ couple transport
    - Enzymes that digest lipids
        (1) Lipase-colipase
        Secreted by acinar cells in their active form
        Hydrolyses triglycerides into fatty acids
        - Phospholipase A2
    - Enzymes that digest proteins (these are all secreted by the zygomen granules within acinar cells)
        - Trypsinogen > trypsin (active)
        - Chymotrypsingoen > chymotrypsin (active)
        - Proelastase > elastase (active)
        - Procarboxypeptidase A/B > carboxypeptidase A/B (active)
    - Regulation of pancreatic juice secretion
        - Two hormones:

(1) Secretin – triggered by gastric acid; acts on centroacinar and acinar cells to raise pancreatic juice pH; also increases secretion of H2O, increasing the volume of pancreatic juice)
(2) Cholecystokinin (CCK) – triggered by peptides, amino acids and fatty acids as they enter the duodenum; activates neurons that control PS signals; directly act on the acinar cells by raising intracellular Ca2+, therefore forcing the secretion of enzymes from zymogen cells

- GI hormones and secretions summary

Hormone	Source	Action	Regulation	Notes
Gastrin	G cells (stomach antrum)	Increase gastric H+ secretion Increase growth of gastric mucosa Increase gastric motility	Increased by stomach distention Increased by amino acids, small peptides Increased by vagal stimulation (GRP) Decreased by a stomach pH of <1.5 Decreased by somostatin	Highly elevated in Zollinger-Ellison syndrome Phenylalanine and tryptophan are potent stimulators
Cholecystokinin (CCK)	I cells (duodenum, jejunum)	Increase pancreatic secretion Increase gallbladder contraction and relaxation of sphincter of Oddi Decrease gastric emptying	Increase by amino acids, small peptides Increased by fatty acids	A patient with cholelithiasis experiences worsened pain after eating fatty food due to the increased release of CCK
Secretin	S cells (duodenum)	Increase HCO3- secretion Increase biliary HCO3- secretion	Increased by H+ in duodenum Increased by fatty acids in duodenum	Increased HCO3- neutralizes gastric H+ in duodenum, essential for fat digestion
Somostatin	D cells (GI mucosa) Delta cells (endocrine pancreas)	Decrease gastric H+ and pepsinogen Decrease pancreatic and small intestine fluid secretion Decreased gallbladder contraction Decrease insulin and glucagon release	Increased by H+ Decreased by vagal stimulation	Inhibitory hormone Antigrowth hormone effects
Glucose dependent insulinotropic peptide (GIP)	K cells (duodenum, jejunum)	Exocrine: decrease gastric H+ secretion Endocrine: increase insulin secretion by pancreatic beta cells	Increased by fatty acids Increased by amino acids Increased by oral glucose	An oral glucose load is utilized by cells more rapidly than an IV glucose load
Vasoactive intestinal polypeptide (VIP)	Parasympathetic ganglia in sphincters, gallbladder and small intestine	Increase intestinal water and electrolyte secretion Increase relaxation of intestinal smooth muscle and sphincters	Increased by distention and vagal stimulation Decreased by adrenergic input	VIPoma is a non-alpha, non-beta islet cell pancreatic tumor that secretes VIP and causes massive diarrhoea

Motilin	Small intestine (upper duodenum)	Increase GI motility Produces migrating motor complexes (MMCs)	Increased in fasting state	
Ghrelin	P/D1 cells (stomach)	Increase growth hormone, ACTH, cortisol and prolactin secretion from pituitary	Decreased before meals Increased after meals	Regulates hunger, meal initiation Lost following gastric bypass surgery Associated with hyperphagia in Prader-Willi syndrome
Neuropeptide Y	Neurones of the SNS	Increase appetite Decrease energy expenditure	Responds to increased ghrelin release	
Glucagon-like peptide 1 (GLP-1)	L cells (endocrine cells of the intestinal epithelium)	Increased glucose-induced insulin secretion from pancreatic beta cells Decreased glucagon secretion Decreased GI motility and secretions Promotes satiety	Secreted in response to meal intake Degraded by dipeptidyl peptidase IV	

Digestion and nutrients

- Micronutrients
    - Compounds that are required for normal function but only in minute amounts. They are typically coenzymes in metabolic processes and can be water soluble, fat soluble, metallic and non-metallic

- Water soluble vitamins
    - Vitamin C
        - Scurvy
          Bleeding and easy bruising (lack of vitamin C => poor wound healing and blood vessel fragility)
          Hair and teeth loss
          Joint pain and swelling
          Fatigue and lack of concentration
    - Thiamine (B1)
        - Beri Beri
        - Wernicke-Korsakoff syndrome
    - Riboflavin (B2)
    - Niacin (B3)
    - Pantothenate (B5)
    - Pyridoxal (B6)
    - Biotin (B7)
    - Folate (B9)
        - Microcytic anemia
    - Cobalamin (B12)

- Absorption of water soluble vitamins
    - Absorbed in the jejunum via classic protein transporters APART FROM B12, which is absorbed in the terminal ileum with intrinsic factor

- Water soluble vitamins that are pH dependent
    - Thiamine (B1)
    - Folate (B9)
    - Pyridoxal (B6)
    - Niacin (B3)

- Fat soluble vitamins

Vitamin	Function	Deficiency	Toxicity
A	Vision (retinol, retinyl esters & retinal only) Gene expression Embryonic development Immune function	Night blindness (reversible) Corneal damage (irreversible) Skin disease	Foetal brain damage Nerve and eye damage in adults Death if extreme intake
D	Maintenance of plasma calcium and phosphorous	Osteoporosis – elderly Ricketts – children	N/A
E	Non-specific antioxidant	Deficiency is rare Takes 2 years in children and 10 years in adults to become symptomatic Mainly causes neurological defects (ataxia, loss of reflexes, decreased sensation, paralysis of eye muscles)	N/A
K	Coenzyme in the synthesis of many enzymes involved in clotting and bone metabolism (post translational carboxylation of proteins)	Common in newborns Prolonged bleeding time	Hypercoagulability

- Vitamin K synthesis
    - Factors 2, 7, 9, 10
    - Protein C and Protein S

- Metallic micronutrients
    - Calcium
    - Magnesium
    - Copper
    - Nickel
    - Zinc
        - It is an important part of over 300 enzymes due to its strong but interchangeable interactions with many ligands
        - Zinc deficiency: poor appetite and weight loss, delayed wound healing, taste abnormalities, mental lethargy, hair loss and dermatitis, diarrhea
        - The immune system worst affected, with deficiency resulting in:

Reduced circulating Ig
Reduced T cell number and functioning
Recurrent infections
Poor wound healing
Increased glucocorticoid secretion

- Non-metallic micronutrients
  - Fluorine
  - Iodine
    - Essential component of the thyroid hormones:
      T3 (triiodothyronine)
      T4 (tetraiodothyronine/thyroxine)
  - Phosphorus
  - Selenium
    - Covalently binds to cysteine to create an selenocysteine, the 21st natural AA
    - Selenocysteine found in peroxidases, reductases, thyroid hormone enzymes and other proteins
    - Deficiency >> Keshan disease (common in China, cardiomegaly and poor functioning of heart)
    - Also, causes promote progression of HIV to AIDS, increases risk of prostate, colon, lung cancer, produces problems in M+F fertility
  - Silica

- Phases of nutrient absorption
  - (1) Intraluminal digestion
    - Proteins, carbs and fats are broken down into forms suitable for absorption
  - (2) Terminal digestion
    - Hydrolysis of carbs and peptides by disaccharides and peptidases in the brush border of the small intestine mucosa
  - (3) Trans epithelial transport
    - Nutrients, fluid and electrolytes are transported across and processed within the SI of the epithelium
  - (4) Lymphatic transport of lipids

- Carbohydrate digestion
  - Overview
    - Carbs = polysaccharides, disaccharides and monosaccharides
    - The intestinal cells can only absorb monosaccharides (glucose, galactose and fructose), which is why digestion is so important
  - Digestion of polysaccharides >> monosaccharides
    (1) Mouth:
    - Carbs are consumed
    - Salivary alpha amylase is secreted to initiate digestion of polysaccharides in the mouth (small role)
    - Polysaccharides are broken down into dextrins, sucrose, lactose and maltose

    (2) Stomach and small intestine:
    - Pancreatic alpha amylase is secreted into the lumen of the duodenum and small intestine to further digest the polysaccharides and disaccharides
    - Intestinal brush border enzymes begin to digest the remaining molecules to monosaccharides
    - Alpha dextrinase catalyses dextrins >> glucose
    - Maltase catalyses maltose >> glucose

- Sucrase catalyses maltotriose >> glucose

(3) Intestinal lining:

- Via active transport, the monosaccharides are absorbed through the intestinal lining into the bloodstream (water soluble) or lymphatics (fat soluble)

- Carbohydrate absorption
  - Glucose and galactose
    - Absorbed by enterocytes via secondary active transport (Na+ - glucose cotransporter; SGLT1)
    - Pass from enterocytes to the bloodstream via facilitated diffusion (GLUT2)
  - Fructose
    - Absorbed by enterocytes by facilitated diffusion (GLUT2)

- Protein absorption
  - Protein degradation via trypsin and pepsin >> become amino acids
  - Amino acids are absorbed by the gut with different transporters, depending on whether they are basic amino acids or large neutral amino acids

- Vitamin and mineral absorption
  - Vitamin B12 (Cobalamin)
    - Absorption occurs at the terminal ileum
    - Requires intrinsic factor (IF)
    - IF deficiency can occur consequently to loss of parietal cells, resulting in a vitamin B12 deficiency and may cause pernicious anemia
  - Iron
    - Absorption occurs in the duodenum by enterocytes (intestinal epithelium) as free iron; free iron binds to apoferritin in the enterocytes; this iron-ferritin complex is transported across the membrane into the bloodstream; here iron binds to transferrin and is taken to the liver for storage
    - Absorption of iron can also be in the form of heme iron into the enterocytes; this is digested by lysosomal enzymes; which then releases free iron; which is bound to apoferritin >> etc
  - Folic acid
    - Absorption occurs in the jejunum
    - Small reserve pool is stored in the liver

Gastrointestinal history

- Abdominal pain
  - PUD pain >> dull or burning in epigastrium that's relived by food and antacids, episodic and may occur at night
  - Pancreatic pain >> steady epigastric pain that may be partly relieved by sitting up and leaning forwards, radiation to the back is common
  - Biliary pain >> epigastric pain, usually is more severe and lasts several hours
  - Renal colic pain >> colicky pain superimposed on a background of constant pain in the renal angle, often with radiation to the groin
  - Bowel obstruction pain >> colicky pain, small bowel obstruction causes more frequent episodes (every 2-3 mins) versus large bowel obstruction frequency (every 10-15 mins), often associated with vomiting, constipation and abdominal distention

- Appetite and weight change
    - Anorexia and weight loss = malignancy, depression
    - Weight loss and increased appetite = malabsorption of nutrients or a hypermetabolic state
    - Disturbance of taste = liver disease

- Early satiation and postprandial fullness
    - Inability to finish a normal meal = gastric disease, including cancer and peptic ulcers
    - Feeling of inappropriate fullness after eating = functional dyspepsia

- Nausea and vomiting
    - Acute symptoms >> GIT infection or small bowel obstruction
    - Chronic symptoms >> pregnancy and drug use (digoxin, opiates, dopamine agonists), gastric outlet obstruction, motor diseases, hepatobiliary disease, psychogenic vomiting (bulimia) and alcoholism
    - Note: vomiting is different from rumination. Rumination is effortless regurgitation of food into the mouth after eating

- Heartburn and acid regurgitation
    - Retrosternal burning pain or discomfort that usually travels up towards the throat
    - Occurs after meals or is aggravated by lying supine
    - Antacids relieve the pain
    - Pain is aggravated by alcohol, chocolate, caffeine, a fatty meal, theophylline, calcium channel blockers and anticholinergic drugs
    - Note >> regurgitation is not to be confused with water brash; which is an excessive secretion of saliva

- Dysphagia
    - Difficulty swallowing (this is different from painful swallowing – odynophagia)
    - Patients may complain of food getting stuck in the oesophagus (anatomical blockage)
    - If the patient complains of progressive dysphagia (stricture, carcinoma or achalasia)
- Diarrhoea
    - Small intestine diarrhoea tends to be non-inflammatory >> linked with ETEC, staph, bacillus, giardia
    - Large intestine diarrhoea tends to be inflammatory >> linked with shingella, salmonella, campylobacter, clostridium diff
    - Watery, high volume stool
        - (1) Secretory diarrhoea >> net secretion of the colon or small bowel exceeds absorption; due to infection, hormonal conditions or villous adenoma
        - (2) Osmotic diarrhoea >> disappears with fasting; occurs due to excessive solute drag; due to lactose intolerance, magnesium antacids or gastric surgery
        - (3) Abnormal intestinal motility >> if patient has thyrotoxicosis or IBS
    - Blood containing stool
        - (1) Exudative diarrhoea >> inflammation of the colon
    - Fat containing stool
        - (1) Malabsorption >> of nutrients and steatorrhea; stools are pale, fatty, extremely smelly and float/hard to flush away
        - Steatorrhea is the presence of more than 7g of fat in a 24-hour collection of stool

- Constipation
    - Ingestion of drugs >> codeine, antidepressants, aluminum or calcium antacids
    - Metabolic or endocrine disease >> hypothyroidism, hypercalcemia, diabetes mellitus, phaeochromocytoma

- Neurological disorders >> autonomic neuropathy, multiple sclerosis, Hirschsprung's disease
- Bowel related >> Carcinoma or partial colonic obstruction

- Pruritus
  - Think about cholestatic liver disease

- Questions to ask:
  - Recurrent vomiting
    - Describe an episode (rule out rumination)
    - How long have the attacks been happening?
    - Does it occur with nausea or without warning?
    - Abdominal pain associated with the vomiting?
    - Does it occur in specific episodes? (Cyclical vomiting syndrome)
    - What does it look like, is it blood stained, bile-stained or felucent (bleeding)?
    - Have you been losing weight?
  - GORD
    - Do you have heartburn? How often does it occur?
    - Does the heartburn occur straight after eating?
    - Is the pain relieved by antacids? (Typical acid reflux)
    - Does the pain radiate across your chest down your left arm or into your jaw? (MI)
    - Have you had trouble swallowing? (Dysphagia)
  - Dysphagia
    - Do you have trouble swallowing solids, liquids or both? (Solids and liquids suggest a motor problem)
    - Where does the holdup occur in your throat?
    - Do you cough or start to choke on starting to swallow?
    - Do you have asthma or hay fever? (eosinophilic Oesophagitis)
    - Have you been losing weight?
  - Diarrhoea
    - How many stools per day do you pass? What do they look like?
    - Do you have to race to the bathroom for a bowel movement? (Urgency in colonic disease)
    - Have you been woken from sleep during the night by Diarrhoea?
    - Have you had problems with leakage of stool? (Fecal incontinence)
    - Have you seen any bright red blood in the stools, or mucous or pus? (Colonic disease)
    - Have you lost weight? (Cancer, malabsorption)
    - Have you had a recent fever, rigor, chills? (Infection, lymphoma)
  - Constipation
    - How often is the bowel movement? Are they hard or difficult to pass? What do they look like?
    - Has your bowel habit changed recently?
    - Any blood in the stool?
    - Any weight loss?
    - Do you have a history of colon polyps or cancer?
  - Hematemesis
    - Before any blood was seen, did you experience any intense retching or vomiting? (Mallory-Weiss tear)
    - Was there fresh blood in the vomitus? Or was the vomitus coffee-stained?

        - Have you passed any black stools or blood in the stool?
        - Have you lost weight?

    - Jaundice
        - Is your urine dark? Are your stools pale? (Obstructive jaundice)
        - Do you have skin itching?
        - Do you drink alcohol? (CAGE questions)
        - Do you have a fever? (Cholangitis)
        - Have you had a change in your appetite? (Malignancy)

- Relevant history
    - Lethargy >> acute or chronic liver disease, anemia
    - NSAID use >> induce bleeding from GIT
    - Other drugs and anabolic steroids
    - Paracetamol overdose >> acute liver cell necrosis
    - Surgical procedures >> jaundice can result or direct damage to bile duct
    - PMH >> IBS; could be a flare up of a past disease
    - Social history >> occupation, like exposure to hepatitis; alcohol history; sexual history
    - Family history >> colon cancer, familial polyps, inflammatory bowel disease, jaundice, anemia, splenectomy, hemolytic anemia, congenital or familial hyperbilirubinemia

Gastrointestinal examination

- Examination anatomy
    - Liver
        - Lower border extends from tip of right 10^{th} rib to just below the left nipple
        - Normally not palpable – may just be able to feel the lower ledge in healthy people
    - Spleen
        - Underlies the 9^{th}, 10^{th} and 11^{th} ribs posteriorly on the left
        - Usually not palpable in health
    - Kidneys
        - Lie anteriorly four finger breadths from midline and posteriorly under the 12^{th} rib
        - Right kidney normally extends 2.5cm lower than the left
        - Lower left pole of right kidney may be felt in healthy people
    - Gallbladder
        - Tip of the 9^{th} costal cartilage
        - Cannot be felt in health
    - Pancreas
        - In retroperitoneum with head tucked into a C shape
    - Aorta
        - Lies in midline and terminates left of the midline at the iliac crest
    - Stomach
        - 1.5m in length
        - Appendix in RLQ

- General appearance
    - Jaundice
        - Yellow discoloration of sclera and skin resulting from hyperbilirubinemia
    - Skin pigmentation
        - Generalized pigmentation can result from chronic liver disease, especially hemochromatosis
        - Addisonian-type pigmentation (sunkissed pigmentation) – sign of malabsorption
        - Freckle like spots around the mouth and buccal mucosa, and on fingers and toes are associated with hamartomas' of the small bowel and colon
        - Brown-black velvety elevations of the epidermis of the neck and axilla – associated with acanthosis nigricans
        - Presence of fragile vesicles appear on exposed areas of the skin – occurs in porphyria cutanea tarda
        - Tense leathery skin – indicates systemic sclerosis associated with GORD or motility disorders
    - Mental state
        - Neurological disturbance can be noticed in hepatic encephalopathy due to decompensated advanced cirrhosis
        - Hepatic encephalopathy >> disturbance in protein metabolism in the liver due to hepatocyte failure or portal-to-systemic shunting, causing a net effect of elevation of centrally acting toxins
- Hands
    - Leukonychia
        - Due to hypoalbuminemia from chronic liver disease, causing opacification of the nail beds
        - Giving them a milky white appearance
        - Compression of capillary flow by extracellular fluid
    - Muehrcke's lines
        - Transverse white lines on the nails, occurring in hypoalbuminemia states
    - Clubbing
        - Indication of cirrhosis, AV shunting in the lungs and cyanosis
        - Caused by IBD, coeliac disease, or nutritional depletion
- Palms
    - Palmar erythema
        - Liver palms – also related to rheumatoid arthritis, polycythemia, raised estrogen levels
        - Redding of the palms involving thenar and hypothenar eminences
        - Soles of the feet can be affected too
        - Can be a normal finding in pregnancy
    - Anemia
        - Palmar crease pallor
        - May result from GI blood loss, malabsorption or chronic disease
    - Dupuytren's contracture
        - Visible and palpable thickening and contraction of palmar fascia causing permanent flexion, most often of the ring ringer
        - Palmar fascia of these patients contains abnormal amounts of xanthine
        - Often bilateral and on the feet
        - Associated with alcoholism and in some manual workers
- Hepatic flap
    - Holding out the arms for 15 seconds

    - Jerky, irregular flexion-extension movements of the hands
    - Associated with hepatic encephalopathy
    - Due to interference with inflow of joint position sense information (proprioception) to the reticular formation in the brainstem
    - Results in rhythmic lapses in postural tone
- Tremor
    - Apparent tremor
        - Wilsons disease
    - Resting tremor
        - Alcoholism
- Arms
    - Large bruises (ecchymoses)
        - Due to clotting abnormalities produced by hepatocellular damage
    - Petechiae
        - Pinhead bruises
        - Associated with chronic excessive alcohol consumption resulting in bone marrow depression; also splenomegaly due to portal hypertension
    - Scratch marks
        - Pruritus
        - Occur in patients with obstructive or cholestatic jaundice, biliary cirrhosis
    - Spider naevi
        - Consist of a central arteriole from which radiate numerous small vessels that look like spider's legs
        - Usually location is in the area drained by the superior vena cava
        - Pressure applied to the area results in blanching of the whole lesion
        - More than two is abnormal >> may indicate cirrhosis, viral hepatitis
        - Differentials for these lesions: Campbell de Morgan spots, venous stars
- Eyes
    - Bitot's spots
        - Yellow keratinized areas of the sclera
        - Result from severe vitamin A deficiency due to malabsorption or malnutrition
        - Retinal damage and blindness can occur
    - Kayser-Fleischer rings
        - Brownish-green rings occurring in the periphery of the cornea, affecting upper pole more than lower
        - Due to deposits of excess copper in the cornea
        - Associated with Wilsons disease (copper storage disease)
    - Xanthelasma
        - Yellowish plaques in the subcutaneous tissue under the eye due to deposits of lipids
        - Pathogenesis: disturbance of lipid metabolism or destruction of the bile ducts, causing decreased lipid clearance by bile
        - Associated with cholestasis, biliary cirrhosis
    - Periorbital purpura
        - Black eye syndrome
        - Characteristic of amyloidosis, very rare
- Salivary glands
    - Parotid enlargement

        - Bilaterally associated with alcoholism, due to fatty infiltration
        - Lumpy parotid gland associated with parotid tumor
        - Mumps can also cause this
    - Submandibular gland enlargement
        - Most often due to calculus or chronic liver disease
- Teeth and mouth
    - Fetor hepaticus
        - Sweet smelling breath
        - Indication of severe hepatocellular disease
        - May be due to methylmercaptans/methinine - substances are known to be exhaled in the breath
    - Lingua nigra (black tongue)
        - Due to elongation of papillae over posterior part of the tongue, which appears dark brown because of accumulation of keratin
        - Bismuth compounds may also cause black tongue
    - Geographical tongue
        - Describes slowly changing red rings and lines that occur on the surface of the tongue
        - Can be a sign of vitamin B2 deficiency
    - Leukoplakia
        - White coloured thickening of the mucosa of the tongue and mouth
        - Premalignant
        - Associated with sore teeth (poor dental hygiene), smoking, spirits, sepsis, syphilis
    - Glossitis
        - Smooth appearance of the tongue
        - Due to atrophy of the papillae resulting from nutritional deficiencies or a rare carcinoid syndrome
    - Macroglossia
        - Enlargement of the tongue
        - Associated with congenital conditions such as Down syndrome and tumor infiltration
    - Apthous ulceration
        - Most common type
        - Begins as a small painful vesicle on the tongue which may break down to form a painful, shallow ulcer
        - Don't indicate serious pathology – but are associated with Crohns disease
    - Angular stomatitis
        - Cracks at the sides of the mouth
        - Caused by deficiencies in vitamin B6, B12, folate and iron
    - Thrush
        - Candida albicans infection
        - Causes white-curd like patches in the mouth that are removed only with difficulty and leave a bleeding surface
        - Caused by immunosuppression, antibiotics, bad oral hygiene and diabetes
- Neck and chest
    - Troiser's sign
        - Large left supraclavicular node (Virchow's node) in combination with carcinoma
    - Gynaecomastia
        - In males, enlargement of the breasts

        - Sign of chronic liver disease, gastric cancer and cirrhosis
- Abdomen
    - Acute abdomen
        - Patient lying very still, with shallow breathing
    - Generalised abdominal distention
        - Caused by things that start with F
        - Fat (gross obesity), fluid (ascites), fetus (pregnant), flatus, faeces, phantom pregnancy
    - Caput Medusae
        - Sign of engorged distended umbilical veins that are responsible for systemic flow due to portal hypertension
        - Very rare
        - Medusa's hair appearance
    - Pulsations
        - Indicate AAA or can be seen in normally thin people
    - Visible peristalsis
        - Can be seen in normal thin people
        - Usually suggests intestinal obstruction
    - Herpes Zoster
        - Vesicles of herpes zoster, in a radicular Patten
    - Sister Mary Joseph nodule
        - Metastatic tumor deposit in the umbilicus
    - Cullen's sign
        - The umbilical black eye
        - Discoloration of the umbilicus where a faintly bluish hue is present
        - Acute pancreatitis
    - Striae
        - Stretch marks seen in Cushing's syndrome
    - Abdominal guarding
        - Guarding from the patient when palpation of the abdomen occurs
    - Rebound tenderness
        - Present when the abdominal wall, having been compressed slowly, is released rapidly and a sudden stab of pain occurs
    - Rigidity
        - Constant involuntary reflex contraction of the abdominal muscles always associated with tenderness
        - Indicates peritonitis
    - Divarication
        - Weakness in the abdominal wall aponeurosis is very common and causes a bulging of the rectus sheath when intra-abdominal pressure increases
    - Shifting dullness
        - Does the dullness on percussion stay there when the patient rolls on their side?
        - If the dull area is then resonant, peritoneal fluid has shifted when being rolled
        - If the dull percussion remains, a more localised and attached pathology is occurring
    - Ascites
        - Detected by bulging of the flanks and shifting dullness
    - Friction rub

        - Indicate abnormality of the parietal and visceral peritoneum due to inflammation
        - Splenic rub indicated a splenic infarct
    - Venous hum
        - Continuous, low pitched, soft murmur that may become louder with inspiration and diminish when more pressure is applied to the stethoscope
        - Can be sometimes heard over large veins
    - Bowel sounds
        - Bowel sounds can be heard all over the abdomen in healthy people – poorly localised, most in the stomach
        - Complete absence of bowel sounds over a 4-minute period indicates paralytic ileus (due to paralyzed bowel)
        - An obstructed bowel will produce a louder, high pitched sound with tinkling quality due to presence of air and liquid
        - Intestinal hurry or rush is characterised by gurgling sounds – diarrhoea based
    - Bruits
        - Higher pitched than a venous hum, non-continuous and well localised
        - Usually due to hepatocellular cancer or intestinal ischemia if heard in the epigastrium
- Gallbladder
    - Murphy's sign
        - Should be sought is cholecystitis is suspected
        - On taking a deep breath, the patient catches his or her breath when an inflamed gallbladder presses on the examiners hand
    - Courvoisier's law
        - If the gallbladder is enlarged and the patient is jaundiced, the cause is unlikely to be gallstones
        - Carcinoma of the pancreas or lower biliary tree is likely to be present
- Kidneys
    - Moves inferiorly on inspiration
    - Are ballotable because of their retroperitoneal position
    - Friction rubs are never heard over the kidneys as they are too posterior
- Bladder
    - Empty bladder is not palpable
    - If palpable – urinary retention
- Rectal examination
    - Hemorrhoids
        - Small, tense, bluish swellings seen on the anal margin
        - Painful due to rupture of a vein
    - Skin tags
        - Associated with hemorrhoids or Crohns disease
    - Rectal prolapse
        - Circumferential folds of red mucosa are visible protruding from the anus
    - Anal fissure
        - Crack in the anal wall
        - Pain can be elicited on DRE
- Faecal contents
    - Melaena
        - Poorly formed, black and tarry with and offensive smell

        - Presence of blood digested by gastric acid and colonic bacteria
        - Usually indicates bleeding from the oesophagus, stomach and duodenum
    - Hematochezia
        - Bright red blood in the stool
        - Results from hemorrhage from the rectum or left colon
    - Steatorrhea
        - Pale, offensive, smelly and bulky stool
        - Often floating
        - Results from malabsorption of fat due to severe pancreatic disease
    - Toothpaste stools
        - Expressed like toothpaste from a tube
        - Condition usually due to severe constipation with diarrhoea
        - Associated with IBS, stricture of Hirschsprung's disease
    - Rice-water stools
        - Can be caused by cholera
        - Results in severe secretory diarrhoea
- Vomitus
    - Coffee ground vomit
        - Can be caused by an old clot, red wine and iron tablets
    - Hematemesis
        - Bright red blood
        - Usually indicates a fresh clot or bleeding from the GIT
    - Yellow-green vomitus
        - Results from the vomiting of bile and upper small bowel contents
    - Feculent vomit
        - Brown offensive material from the small bowel is then vomited
        - A medical emergency due to risk of aspiration
    - Projectile vomit
        - Associated with pyloric stenosis or raised ICP

Oral disorders

- Sjrogens syndrome
    - General considerations
        - Inflammatory disease that affects primarily the salivary and lacrimal glands, causing dryness of the mouth and eyes
        - Thought to be autoimmune T cell related reaction against antigens of the glands
    - Clinical presentation
        - Presents commonly in middle aged women
        - Enlargement of the salivary glands
        - Dryness of the mouth and eyes
    - Associations
        - Epstein-Barr virus

        - Systemic lupus erythematosus
    - Complications
        - 40 x increased risk in developing non-Hodgkin's B cell lymphoma in the marginal zone (MALT lymphoma)

- Sialolithiasis
    - General considerations
        - Salivary gland calculi
    - Clinical presentation
        - Acute swelling and erythema of the duct opening
        - Dry mouth
        - Pain prior to eating or thinking about food (when saliva is mostly produced)

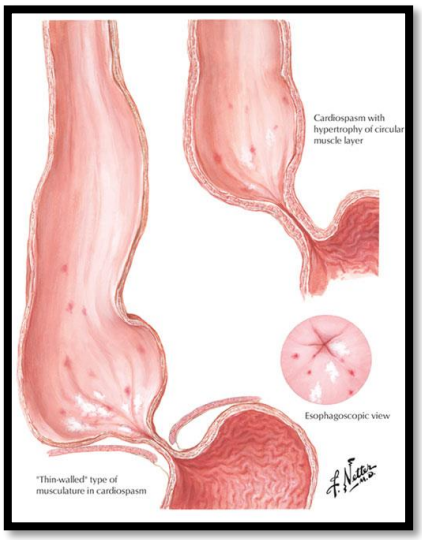
- Pleomorphic adenoma
    - General considerations
        - Common benign salivary gland neoplasm
    - Etiology
        - Most common tumor of the salivary (40%) and parotid glands (60%)
    - Microscopic features
        - Circumscribed lesion, encapsulated mass
        - Neoplastic proliferation of parenchyma glandular cells with malignant potentiality

- Leukoplakia
    - General considerations
        - Condition in which thick, white patches from on the tongue and the lining of the cheeks and mouth
        - Differs from erythroplakia >> red, velvety, eroded area of mucosa, highly associated with malignancy
    - Etiology
        - Most common cause >> smoking
        - Generally self-limiting and will resolve spontaneously
        - 5-25% of leukoplakia findings are malignant
    - Macroscopic features
        - You cannot scrape it off the tongue
        - Thick, white patches

- Hairy leukoplakia
    - General considerations
        - Condition characterised by irregular white patches on the lateral sides of the tongue, due to chronic irritation
    - Macroscopic features
        - Cannot be scraped off
        - Lateral tongue and mouth
        - Not a pre-cancerous lesion
    - Associations
        - Caused by EBV in immunocompromised patients

- Oral squamous cell carcinoma
    - General considerations
        - Oral cancer very commonly found on ventral tongue, floor of the mouth and lower lip, soft palate
    - Etiology
        - Accounts for 95% of cancers in the oral cavity
        - Risk factors >> smoking and chewing tobacco, alcohol, HPV, chewing betel quid and paan (in India)
    - Pathogenesis
        - Develops from dysplastic precursor tumors
        - (1) normal squamous cell epithelium (2) hyperplasia (3) dysplasia (4) tumor in situ (5) malignancy
    - Histology
        - Ranges from well differentiated keratinizing neoplasms to sacromatoid tumors
    - Prognosis
        - Poor
        - Survival rate less than 50% since they are diagnosed a at much later stage compared to other cancers

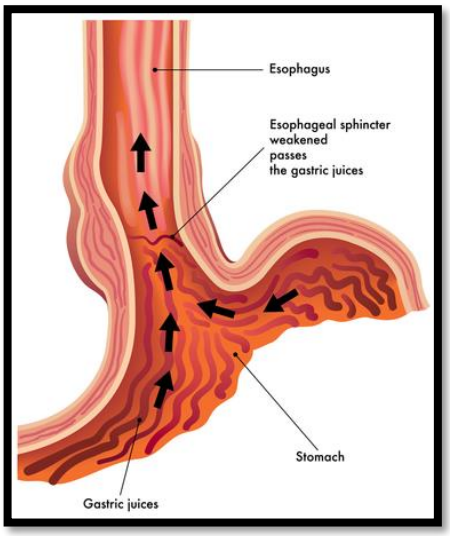
Oesophageal disorders



- Achalasia
    - Clinical presentation
        - Dysphagia
        - Regurgitation
        - Chest pain
        - If not treated: worsening chest pain, severe weight loss, mucosal ulceration, infection and oesophageal rupture and death
    - Etiology
        - Unknown; degeneration of the myenteric plexus and loss of inhibitory neurones may contribute
        - Association with HLA-DQw1
        - Low incidence rate
    - Pathology
        - Sphincter is even more tightly contracted than normal and does not relax properly in response to swallowing because of partial loss of neurons in wall of oesophagus
        - Resulting in functional obstruction
        - Serve radiographic distortion of the oesophagus develops
        - Injection of botulinum toxin into the LOS diminished the excitatory pathways and reduced symptoms
        - Chronic manifestation, results in massive enlargement of oesophagus over time >> increasing its volume capacity for infected material >> high risk of aspiration
    - Associated conditions
        - Chagas's disease
        - Scleroderma
    - Evaluation

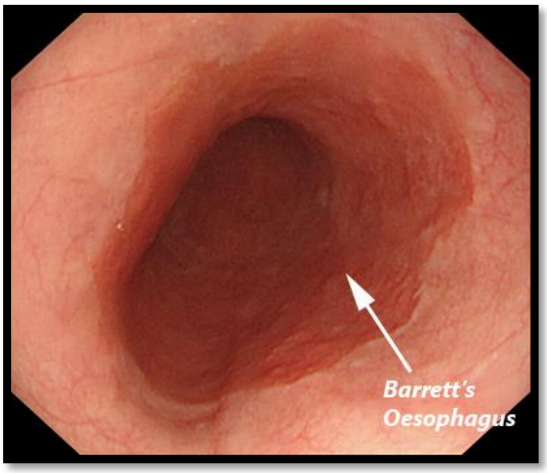
        - Barium swallow test will show = narrowing of distal oesophagus, loss of peristalsis in distal two thirds, dilated proximal oesophagus
        - Manometry studies will show = increased LOS pressure and diffuse oesophageal spasm
    - Treatment
        - Medications to reduce LOS tone >> nifedipine, long acting nitrates, botulinum toxin
        - Surgical >> endoscopic balloon dilation of LOS
    - Complications
        - Oesophageal carcinoma

- Gastro-oesophageal reflex disease (GORD)
    - Clinical presentation
        - Burning chest pain (heartburn) when lying supine, worse at night or after consumption of food of drugs that diminish lower oesophageal tone, improves with antacids
        - Regurgitation
        - May mimic MI or asthma
    - Etiology
        - Caused by conditions where oesophageal mucosa is exposed to persistent acid exposure
        - Causes: disorders that increase the transient relaxation of the LOS or impair reflexes that normally follow transient relaxation of LOS, conditions that increase gastric volume or pressure, delayed gastric emptying, conditions of alkaline injury, hiatal hernia's, obesity, pregnancy

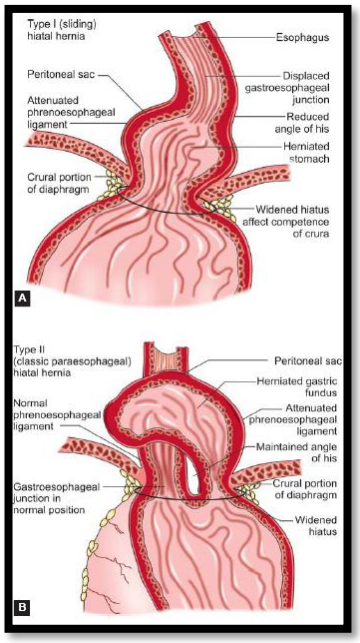


    - Pathology
        - Normally tonically contracted LOS is effective barrier against reflux along with peristaltic waves
        - Barrier is lost when LOS undergoes transient relaxation
        - Recurrent reflux can damage the mucosa >> inflammation and scarring
    - Evaluation
        - Diagnosis based on history given
        - Upper GI endoscopy
        - 24hr intraoesophageal pH probe monitoring >> gold standard
        - Manometry to reveal decreased LOS pressure
    - Treatment
        - (1) lifestyle modification
        - (2) H2 receptor antagonists (ranitidine, cimetidine) or pro-motility agent (cisapride)
        - (3) proton pump inhibitors (omeprazole, lansoprazole)
        - (4) surgical fundoplication or hiatal hernia repair
    - Clinical outcomes
        - Stricture of distal oesophagus
        - Hemorrhage or perforation
        - Hoarseness, coughing and wheezing
        - Barretts oesophagus >> increasing risk of adenocarcinoma

- Barrett's Oesophagus
    - Etiology
        - 10:1 males to females
    - Pathology
        - Complication of chronic GORD
        - Normal squamous epithelium in oesophagus undergoes metaplasia >> metaplastic columnar tissue
    - Evaluation
        - Biopsy >> glandular metaplasia of distal oesophagus due to presence of stomach acid
    - Complications
        - Ulceration leading to stricture formation
        - Increased risk of oesophageal adenocarcinoma



- Hiatal hernias
    - Clinical presentation
        - Similar symptoms to GORD
        - Bowel sounds can be auscultated over left lower lung
        - Present in 80% of patients with reflux
    - Classification
        - Type 1 >> sliding hernia, most common, GO junction slides up into mediastinum through hiatus, loss of diaphragm reinforcement allows reflux of stomach acid
        - Type 2 >> rolling/paraoesophageal hernia, less common, herniation of the fundus of the stomach through the diaphragm parallel to oesophagus
    - Treatment
        - Type 1 >> medical therapy similar to GORD
        - Type 2 >> mandatory surgical repair due to risk of strangulation



Gastric disorders

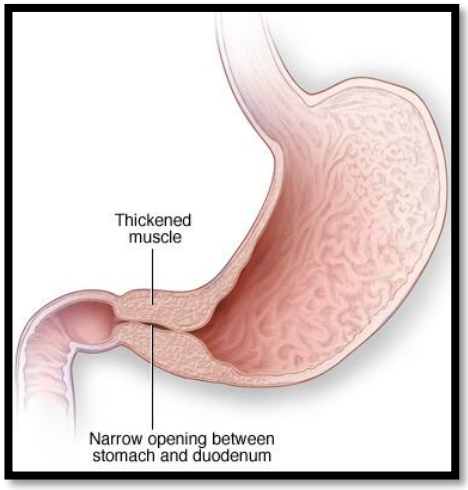
- Upper GI bleed
    - Clinical presentation
        - Hematemesis
        - Hematochezia – passing of fresh blood through the anus, usually in or with stools
        - Hypotension
        - O/E: abdominal pain, anorexia, bloody emesis, dark stools (melena), blood per rectum
    - Etiology
        - Causes >> PUD, gastritis, oesophageal varices, gastric cancer, vascular abnormalities, Mallory-Weis tear
        - Risk factors >> ethanol, tobacco, liver disease, NSAID use, vomiting

- Evaluation
  - NG tube and endoscopy
- Treatment
  - IV fluid resuscitation and transfusion >> restore hemodynamic stability
  - Endoscopy with banding, surgical exploration may be required

- Mallory-Weiss tear
  - General considerations
    - Characterised by upper GI bleeding secondary to longitudinal mucosal lacerations (Mallory-Weiss tears) at the gastroesophageal junction or gastric cardia
  - Risk factors
    - Retching, vomiting, straining, hiccupping, coughing, blunt abdominal trauma and CPR
    - Presence of hiatal hernia
    - Presence of other mucosal lesions
    - Can be caused by medical procedures such as transesophageal echocardiography
  - Pathological mechanisms
    - Tear occurs due to a large, rapidly occurring, and transient transmural pressure gradient along the GO junction
    - A rapid rise in intragastric pressure through precipitating factors causes the transmural pressure gradient to increase dramatically
    - If the force is high enough, a longitudinal laceration will occur
  - Clinical presentation
    - Hematemesis >> following a bout of retching or vomiting (#1 symptom)
    - Melena
    - Hematochezia
    - Syncope
    - Abdominal pain
  - Management
    - Stabilize the patient and monitor vitals
    - Transfuse if necessary
    - Control precipitating factors
    - Endoscopic management >> thermal treatment, epinephrine injection, sclerosing injection, argon plasma coagulation, band ligation, hemoclip placement
    - Angiotherapy
  - Complications
    - MI
    - Hypovolemic shock
    - Death if the bleeding is prolonged and untreated
- Boerhaave syndrome
  - General considerations
    - Spontaneous rupture of the oesophagus typically following forceful emesis
    - Transmural perforation (differs from Mallory Weiss which is non-transmural)
  - Clinical presentation

        - The Mackler Triad >> vomiting, lower thoracic pain and subcutaneous emphysema
        - Plus >> tachycardia, diaphoresis, fever, hypotension
    - Pathophysiology
        - Sudden rise in intraluminal oesophageal pressure produced during vomiting, because of neuromuscular incoordination causing a failure of the cricopharyngeus muscle to relax
        - Commonest location >> left posterolateral wall of the lower third of the oesophagus (2-3 cm proximal to GO junction)
    - Treatment
        - IV fluid resuscitation
        - Broad spectrum antibiotics
        - Prompt surgical intervention
    - Complications and prognosis
        - Mortality rate is high >> is the most lethal perforation of the GI tract
        - Mortality due to subsequent infection
        - Complications: septicemia, mediastinitis, massive pleural effusion, empyema, respiratory distress syndrome, pneumothorax

- Congenital pyloric stenosis
    - Clinical presentation
        - Projectile vomiting – does not contain bile
        - O/E: palpable olive in epigastrium and hyperperistalsis
    - Etiology
        - Not present at birth; develops within first month of life
    - Evaluation
        - Ultrasound is diagnostic
    - Treatment
        - IV fluid resuscitation
        - Electrolyte management pre-operatively
        - Pyloromyotomy >> incision is made in the longitudinal and circular muscles of the pylorus; this loosens the muscle so that food can empty into the small intestine



- Gastritis
    - Clinical presentation
        - Recurrent upper abdominal pain
        - Hematemesis
    - Etiology and classification
        - Acute (erosive) = inflammation and neutrophil infiltration, result of NSAIDs, ethanol, uremia, burns, brain injury and Anisakis worm infestation
        - Chronic (non-erosive) = mixture of plasma cells, lymphocytes and macrophages
            (1) Type A >> fundus/body, caused by pernicious anemia and autoimmune conditions, increased risk of gastric carcinoma
            (2) Type B >> antrum/pylorus, caused by infection and chronic NSAID use, increased risk of MALT lymphoma and adenocarcinoma
    - Pathologenesis (H. pylori)

        - Potential virulence factors >> urease (neutralizes gastric acid by producing ammonia), mucinase (degrades gastric mucosa)
        - General virulence factors >> flagella, adhesins (to attach itself to the cell wall) and LPS (this is where most H. pylori stop, however some may progress)
        - Specific strains of H. pylori may then sit attached to the blood vessel wall and express CagA, this causes an inflammatory response within the host cell
        - Prolonged inflammatory response leads to ulceration
        - Huge correlation between CagA H. pylori strains and oncogenic behaviour (cancer)
    - H. pylori mode of transmission
        - Person-to-person (oral-oral or fecal-oral)
        - Prevalence increased in old age, low SES, domestic crowding and large families, hygiene related
    - H. pylori virulence factors
        - Urease >> neutralizes gastric acid by producing ammonia, to help the bacteria survive
        - Mucinase >> degrades gastric mucous
        - Correlated with CagA >> has a mutagenic effect
        - VacA >> damages local epithelial cells
        - Flagella >> motility
        - Adhesins >> to bind to the host cell
    - Evaluation
        - Endoscopy with biopsy >> gold standard
        - H. pylori detection and culture via stool antigen test or urea breath test
        - The urea breath test >> give the patient a capsule, it has urea in it; if the patient has H. pylori then it will break down the urea in the capsule via urease that it secretes. The breakdown causes there to be radioactive carbon dioxide to be emitted, which can be measured p
    - Treatment

      (1) Acute:
      Triple therapy >> combination of acid lowering drug and 2 antibiotics, over two weeks
      Quadruple therapy >> combination of acid lowering drug and 3 antibiotics, over two weeks
      Acid lowering drug used = omeprazole
      Antibiotics used = amoxicillin, clarithromycin, tetracycline and metronidazole
      Avoidance of gastric irritants
      Misoprostol

      (2) Chronic:
      H. pylori treatment
      Pernicious anemia treatment with vitamin B12
      Stress ulcer treatment

- Peptic ulcer disease
    - Clinical presentation
        - Mid epigastric, gnawing pain
        - Worse with meals
        - Signs of ulcer perforation: pain in right shoulder, rebound tenderness, ileus, peritoneal signs
    - Etiology
        - Common associations: NSAIDs, H. pylori and smoking
    - Classification

        - Gastric ulcers = less common, usually in lesser curvature, higher risk of malignancy, not caused by acid hypersecretion
        - Duodenal ulcers = more common, usually in proximal half, typically due to H. pylori which infects the antrum, low risk of malignancy, caused by acid hypersecretion
    - Pathology
        - Painful sores/ulcers in the lining of the stomach or duodenum
        - Occurs when gastric acid secretion outweighs mucosal defenses
    - Evaluation
        - Culture for H. pylori >> CagA and VacA strains
        - Upper GI endoscopy with biopsy to exclude malignancy
        - Serum gastrin to rule out Zollinger-Ellison syndrome
    - Treatment
        - (1) Stop smoking
        - (2) Mucosal protectors >> bismuths, misoprostol
        - (3) Acid control >> PPIs and H2 receptor antagonists
        - (4) Antibiotics to eradicate H. pylori
        - (5) Surgery >> parietal cell vagotomy
    - Complications
        - Perforations and infection >> air under the diaphragm
        - Hemorrhage >> hematemesis and melena
        - Gastric outlet obstruction

- Zollinger-Ellison syndrome
    - Clinical presentation
        - Like PUD and GORD
        - Diarrhoea present >> acidity in duodenum inactivates pancreatic enzymes
    - Etiology
        - Caused by a malignant duodenal or pancreatic islet cell tumor that ectopically secretes excessive amounts of gastrin
        - Results in increased secretion of acid by parietal cells
        - Associated with multiple endocrine neoplasia type 1
    - Evaluation
        - Increased basal to maximum acid output ratio (BAO: MAO)
        - Increased insulin, glucagon and gastrin on serology
    - Treatment
        - PPIs and chemotherapy
        - Surgical resection of the tumor

- Gastroparesis
    - Clinical presentation
        - Nausea
        - Bloating
        - Vomiting
        - Constipation or diarrhoea

- Etiology
  - Common complication of poorly controlled diabetes mellitus with consequent autonomic neuropathy
- Pathology
  - Gastroparesis = delayed gastric emptying
  - Due to alterations in normal gastric functioning
  - Can occur silently, producing metabolic derangements in the absence of somatic symptoms
- Clinical outcomes
  - Development of bezoars (stony formation) from retained gastric contents
  - Bacterial overgrowth >> resulting in malabsorption and diarrhea
  - Erratic blood glucose control
  - Severe weight loss >> due to nausea and vomiting

- Gastric cancer (usually adenocarcinoma)
  - Clinical presentation
    - Indigestion
    - Nausea or vomiting
    - Dysphagia
    - Postprandial fullness (during or directly after food)
    - Loss of appetite
    - Melena or pallor from anemia
    - Hematemesis
    - Weight loss
    - Palpable enlarged stomach with succussion splash (slushing sound within abdomen on auscultation)
    - Enlarged lymph nodes (Virchow nodes – supraclavicular & Irish nodes – anterior axillary)
    - Periumbilical metastases (Sister Mary Joseph nodule)
  - Etiology
    - Most common cause of cancer-related death in the world
    - More prevalent in Asian and South America than in Western countries
    - Affects men more than women (2:1)
    - Median age at diagnosis 69YO
    - Risk factors >> diet, H. pylori infection (strongest risk factor), smoking, previous gastric surgery, pernicious anemia, radiation exposure, chronic atrophic gastritis, genetics, EBV, obesity, bisphosphonates
    - E-cadherin >> plays an important role in cell adhesion within the body, a mutation linked to gastric cancer and other germ line mutations in CHD1
  - Classifications and frequency
    - Adenocarcinoma (90%)
    - Lymphoma (5%)
    - Stromal tumors/leiomyomas (2%)
    - Carcinoids (1%)
    - Adenocanthomas (1%)
    - Squamous cell carcinomas (1%)
  - Pathology

        - Three oncogenic pathways: (1) proliferation/stem cell (2) NF-kappaB (3) Wnt/beta-catenin
        - Direct extension into the omenta, pancreas, diaphragm, transverse colon, mesocolon and duodenum
        - Peritoneal involvement can occur
        - Easy microscopic spread via lymphatics within the submucosal and subserosal layers of gastric wall
        - Hemotogenous spread commonly results in liver metastases
        - Punched out effect
    - Evaluation
        - Labs >> CBC, electrolyte panel, EnLFTS, tumour markers such as CEA (carcinoembryonic antigen) and CA (cancer antigen)
        - Imaging >> endoscopy, upper GI series, CXR to evaluate for metastases, CT abdomen
        - Biopsy >> at least 6 specimens from around the lesion
    - Histology
        - Signet ring cells filled with mucous
        - Stiffening of the gastric wall
    - Treatment
        - Surgery >> depends on the size, location and local invasion; lymph node dissection
        - Chemotherapy >> Epiribicin/cisplatin/5-FU (platinum analogues)
        - Neoadjuvant, adjuvant and palliative radiotherapy
        - Antineoplastic – antimetabolite >> Fluorouracil
        - Antineoplastic – anti-HER2 >> Trastuzumab
        - Antineoplastic – VEGF inhibitor >> Ramucircumab
    - Complications
        - Metastasis >> supraclavicular nodes (Virchow's nodes), anterior axillary nodes, local invasion into duodenum, pancreas and other retroperitoneal structures
        - Peritoneal or pleural effusions
        - Obstruction of gastric outlet
        - Bleeding in stomach from oesophageal varices
        - Jaundice
    - Prognosis
        - Only a small number of people are cured from the disease
        - Extremely high recurrence rate

Acute abdominal pain

- Main causes of abdominal pain: inflammation, perforation, hemorrhage, ischemia and obstruction

- Types of abdominal pain
    - Visceral (splanchnic) pain
        - From abdominal viscera (solid and hollow)
        - Sympathetic pathways (autonomic pain) transmitted up the celiac plexus and lumbar trunk
        - Can originate from foregut (epigastrium), mid (peri-umbilical) or hindgut (lower abdomen)
        - NOTE: the appendix is considered midgut; therefore, pain is initially felt at the umbilicus

        - Diffuse pain, poorly localised (deep, inside the patient), usually midline and inflammation lowers this threshold
    - Somatic pain
        - From parietal periosteum
        - Spinal nerve pathways (T5-11) and phrenic nerve (C3,4,5)
        - Sharp, intense and well localised pain

- Shifting pain
    - Is felt where the actual organ is
    - Where a distended, inflamed organ can be felt at both the visceral and parietal levels in a shifting pattern

- Referred pain
    - Convergence projection hypothesis – brain wrongly interprets the pain as having come from somewhere else, because of the small portion of innervation that area takes in the spinal cord (lateral and ventral spinothalamic tracts)
    - Examples: biliary colic (scapula pain) and ureteric colic (groin pain)

- Additional symptoms
    - Anorexia/weight loss
    - Nausea and vomiting
    - Constipation/diarrhea
    - Blood per rectum – if patient has acute abdomen and blood per rectum, then they have dead gut until proven otherwise
    - Pale or dark stools
    - Painful spasm – irritable bowel syndrome
    - Chemotherapy
    - Abdominal distention – ascites, intra-abdominal mass, intestinal obstruction
    - Discoloured, hard umbilicus – sister Mary Joseph sign (a result of metastatic pancreatic cancer)

- Be aware of acute gynecology
    - Pregnancy – ectopic and ruptured uterus
    - Infection – pelvic inflammatory disease
    - Endometriosis
    - Ovary torsion or bleed
- Non-abdominal causes of abdominal pain
    - Cardiac
        - Myocardial ischemia/infarction/myocarditis
        - Endocarditis
        - Congestive heart failure
    - Thoracic
        - Pneumonia/pneumonitis
        - PE and infarction
        - Pneumothorax
        - Oesophageal rupture (Boerhaave syndrome) or spasm
        - Emphysema
    - Neurologic
        - Radiculitis

        - Abdominal epilepsy
        - Tabes dorsalis
    - Metabolic
        - Ketoacidosis
        - Uremia
        - Hyperthyroidism
        - Acute adrenal insufficiency
        - Electrolyte imbalance (hypercalcemia)

Peritoneal disease

- Ascites
    - General considerations
        - Pathologic accumulation of fluid in the peritoneal cavity
        - Healthy men have little/no intraperitoneal fluid, whereas women may have up to 20mL depending on the stage of the menstrual cycle
        - Most common cause is secondary to liver disease
    - Etiology
        - Causes (normal peritoneum) >>
            (1) Portal hypertension (hepatic congestion, liver disease or portal vein occlusion)
            (2) Hypoalbuminemia (nephrotic syndrome, protein losing enteropathy)
            (3) Miscellaneous (pancreatic, chylous, bile, nephrogenic ascites)
        - Causes (diseased peritoneum) >>
            (1) Infection
            (2) Malignant conditions
            (3) Other (vasculitis, eosinophilic peritonitis)
    - Pathophysiology hypotheses (in patients with liver disease)
        - Peripheral vasodilation
        - Increased peripheral tone
        - Increased endothelin-1 secretion
    - Clinical presentation (liver disease patient)
        - Increasing abdominal girth
        - Presence of abdominal pain
        - History reveals: portal hypertension, alcohol consumption, transfusions, tattoos, IV drug use, viral hepatitis or jaundice, birth in a hepatitis endemic area
        - O/E (look for): elevated JVP, large tender liver, large abdominal wall veins, palmar erythema, muscle wasting, hepatic flap, frim lymph nodes
    - Evaluation
        - Labs >> abdominal paracentesis, CBC, WBC, albumin and total protein, culture and gram stain bloods, glucose and lactate dehydrogenase
        - Abdominal ultrasound
        - Laparoscopy

- Malignant ascites

- General considerations
  - 2/3 of all malignant ascites cases >> peritoneal carcinomatosis caused by adenocarcinoma of the ovary, uterus, pancreas, stomach, colon, lung or breast
  - 1/3 of all malignant ascites cases >> lymphatic obstruction or portal hypertension
- Clinical presentation
  - Non-specific abdominal discomfort
  - Weight loss
  - Increased abdominal girth
  - Nausea and vomiting
- Evaluation
  - Paracentesis demonstrates low ascites-albumin gradient, increased protein, elevated WCC with lymphocytic predominance
- Treatment
  - Large volume paracentesis
  - Indwelling catheters >> end of life symptomatic relief
  - Intraperitoneal chemotherapy
  - Prognosis is extremely poor >> 10% survival rate at 6 months

- Mesothelioma
  - General considerations
    - Primary abdominal malignant mesothelioma is a rare tumor
    - 70% of cases have Hx of asbestos exposure
  - Clinical presentation
    - Abdominal pain and signs of bowel obstruction
    - Increased abdominal girth
    - Small to moderate ascites
  - Treatment and prognosis
    - Prognosis is poor
    - Surgical debulking of tumor
    - Chemotherapy

GIT infections

- Normal gut flora (these can also be pathogenic)
  - Lactobacillus
  - Streptococcus
  - Bacteroides
  - Bifidobacterium
  - Peptococcus
  - Clostridium
  - E. Coli
    - Most common pathogenic strains include ETEC (enterotoxin), EPEC (adherence factors) and EHEC (secretes Shinga-toxin)
    - Antibiotics not indicated; rest and rehydration

        - Virulence factors: fimbrae, K antigen, LPS endotoxin (septic shock), H antigen (flagella)
    - Klebsiella
    - Proteus
    - Enterococcus
    - Staphylococcus

- Pathogenic gut flora (these bacteria are never seen as residential flora)
    - Salmonella
        - Most common form of food associated diarrhoea with GIT
        - Normally self-limiting (mild serotypes)
        - Some salmonella serotypes can be dangerous; S. typhi and paratyphi; invades the hosts macrophages in Peyer's patches; cause enteric fevers (Typhoid fever)
        - Antibiotics not indicated; rest and rehydration
    - Campylobacter
        - One of the more severe gut bacteria
        - Antibiotics are needed >> especially for severe infection
    - Shigella
        - Consistently invasive
        - Invades the mucosa, uses the host macrophages as a shield, secretes an exotoxin
        - Antibiotics are needed >> especially for severe infection
    - Vibrio cholera
        - Rice water stool
        - Free flowing and constant while bacteria are present
        - Free living in fresh water
        - Secretes an enterotoxin, drawing water along with it as it passes through the GIT, causing mass dehydration
        - Antibiotics not indicated; rest and rehydration

- Pathogenic helminths
    - Enterobius vermicularis (pinworm)
        - Person to person transmission
        - Perianal itchiness
        - Common in crowded areas such as daycare centres
        - Test for eggs in the perianal area (perianal tape test)
        - Treatment with antihelmintics >> mebendazole, albendazole
    - Ascaris lumbricoides (roundworm)
        - Person to person through ingestion of eggs
        - Infections are often asymptomatic
        - Can lead to mechanical blockages, malnutrition and allergies

- Bristol stool form scale
    - Type 1 and 2 – constipation
    - Type 3 and 4 – normal fecal movement (most healthy types)
    - Type 5, 6 and 7 – diarrhoea

- Diarrhoea (gastroenteritis, entercolitis)
  - Definitions
    - Acute <2 weeks
    - Chronic >4 weeks
    - Considered to be greater than 3 to 5 times the patient's normal bowel movements per day
  - Watery diarrhoea (non-inflammatory)
    - No red blood cells present in stool (no inflammation), typically afebrile, large volume, infection is typically in small intestine
    - Pathogens >> enterotoxigenic e. Coli, vibrio cholera, s. aureus, rotavirus, giardia lamblia
  - Bloody diarrhoea (inflammatory)
    - Both red and white blood cells present (inflammation), often febrile, small volume, infection is typically in colon
    - Pathogens >> shingatoxin-producing e. coli, shingella species, salmonella, campylobacter jejuni, clostridium, Entamoeba
  - Clinical manifestations and pathogens

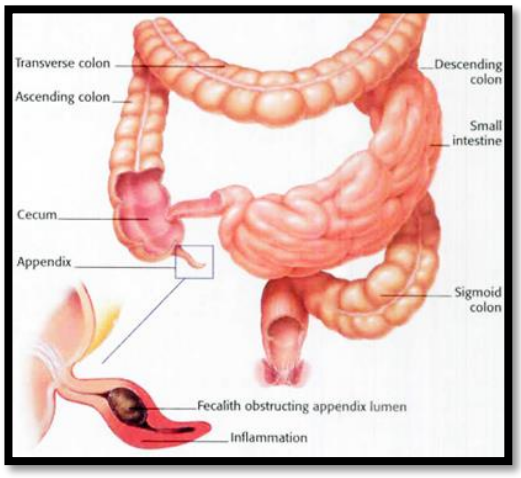
Pathogen	Presentation	Treatment	Comments
Acute non-inflammatory diarrhoea			
Bacteria			
S. Aureus	Vomiting, epigastric pain, diarrhoea	Supportive care	Usually within 6 hours of eating infected food (dairy, mayo, meat)
Bacillus cereus	Vomiting, epigastric pain, diarrhoea	Supportive care	Usually within 6 hours of eating infected food (reheated rice)
ETEC	Afebrile, watery diarrhoea	Ciprofloxacin	Travellers diarrhoea
Viruses			
Norovirus	Afebrile, vomiting, headaches, diarrhoea	Supportive care	Cruise ship and nursing home outbreaks
Rotavirus	Fever and vomiting prodrome, then diarrhoea	Supportive care	Common in children/infants
Protozoa			
Giardia lamblia/duodenalis	Abdominal cramps, flatulence, diarrhoea, stools are fatty and foul smelling, may float	Metronidazole and tinidazole	Diarrhoea may persist for weeks Flagellated protozoan, ovoid shape, two nuclei Can evade immune clearance
Cryptosporidium	Abdominal pain and cramps, watery diarrhoea	Nitazoxanide	Causes of large community-wide outbreaks from contaminated water supply
Acute inflammatory diarrhoea			
Bacteria			
STEC	Bloody diarrhoea, abdominal pain, usually afebrile	None, antibiotics may increase risk of hemolytic-uremic syndrome	Associated with undercooked beef and contaminated produce
Clostridium	Bloody diarrhoea, fever	Oral or IV metronidazole or oral vancomycin	Associated with antimicrobial drug use or community acquired

Shigella	Diarrhoea with blood or pus, abdominal cramps, can be febrile	Ciprofloxacin	Person to person spread
Salmonella	Diarrhoea can be bloody, low grade fever	Ciprofloxacin	Acquired by ingestion of undercooked eggs, raw veges or undercooked poultry
Campylobacter jejuni	Fever, diarrhoea	Ciprofloxacin or azithromycin	Associated with GBS
Protozoa			
Entamoeba	Bloody diarrhoea, fever and abdominal pain	Metronidazole	Can cause hepatic abscesses

- Infection kinetics
  - Vibrio cholera
    - Incubation = 1 to 3d
    - Duration = 5 to 7d
  - ETEC
    - Incubation = 1-3d
    - Duration = 5-10d
  - Campylobacter
    - Incubation = 1-4d
    - Duration = 3-21d
  - Salmonella spp.
    - Incubation = 1-2d
    - Duration = 2-7d
  - Rotavirus
    - Incubation = 1-4d
    - Duration = 4-7d

- Antibiotic associated colitis (pseudomembranous colitis/clostridium colitis)
  - General considerations
    - Common
    - Occurs during the period of antibiotic exposure, is dose related and resolves spontaneously after discontinuation
    - Clostridium diffcile related or due to changes in colonic bacteria fermentation of carbohydrates
    - Most common cause of hospital-acquired infectious diarrhoea
    - Acquired by fecal-oral transmission
  - Clinical presentation
    - Extremely painful for the patient
    - Mild to moderate greenish, foul-smelling watery diarrhoea 5-15 times per day >> with blood
    - Lower abdominal cramps
    - Left lower quadrant tenderness
    - Severe disease >> hemodynamic instability, abdominal distention, pain and tenderness
  - Histological presentation
    - Colon is coated in pseudomembranes, composed of neutrophils and dead epithelial cells

        - Damaged crypts, distended by exudate that erupts like a volcano
    - Evaluation
        - Stool studies >> pathogenic strains of C diff produce two toxins: toxin A (enterotoxin) and toxin B (cytotoxin)
        - Flexible sigmoidoscopy >> severe symptoms
        - Abdominal radiographs and CT
    - Treatment
        - Immediate Rx: discontinue antibiotic therapy; therapy with metronidazole, vancomycin
        - Hand washing
        - Prophylactic probiotics >> lactobacillus bulgaricus
    - Complications and prognosis
        - Progresses quickly
        - Patients can be left with IBS years after the infection
        - Severe colitis may become hemodynamically unstable, experience respiratory failure, megacolon, perforation and death
        - Toxic megacolon >> causes hemodynamic instability and dilation of the colon; presenting with pain, fever, hypotension; can result in perforation and is a medical emergency
- Appendicitis
    - General considerations
        - Inflammation of the vestigial vermiform appendix that extends into the muscularis propria
        - Most common abdominal surgery emergency; therefore, diagnosis usually comes after the appendectomy
        - 10% of population affected
        - Between 10 and 30 YOA
    - Pathophysiology
        - Obstruction of the appendix (infection via parasites, tumor, fecal impaction) leads to an increase in intraluminal pressure
        - Increased pressure causes occlusion of the vessels supplying the appendix, and venous congestion
        - Visceral afferent nerve fibers are activated, which aids in localizing pain to the right iliac fossa
        - Stasis of the luminal contents causes bacterial proliferation and infection
        - If untreated, gangrene and necrosis followed by perforation will occur within 36 hours



    - Clinical presentation
        - Early pain – vague periumbilical pain
        - Within 12 hours – right lower quadrant pain and tenderness, over McBurney's point (shifting pain between these two areas from here on)
        - Anorexia
        - Nausea and vomiting
        - Obstipation >> severe or complete constipation
    - Findings O/E
        - Tenderness and rigidity at McBurney point >> name given to the right side of the abdomen that is one third of the distance from the ASIS to umbilicus (appendix area)
        - Abdominal guarding of right lower quadrant

        - Low grade fever and leukocytosis
        - When asked to cough, patients may be able to localize the painful area >> sign of peritoneal irritation
        - Light percussion may elicit pain and rebound tenderness will elicit pain (this is a last resort, as it will significantly hurt the patient)
        - Positive psoas sign >> pain on passive extension of the right hip
        - Positive obturator sign >> pain with passive flexion and internal rotation of the right hip
    - Atypical presentations
        - Abdominal tenderness may be minimal or elicited in right flank >> anatomical variation of appendix
        - Diagnosis often delayed in elderly as they present with minimal, vague symptoms and mild abdominal tenderness
        - Can be associated with pregnancy >> displacement of the appendix by the uterus
    - Pathogens
        - Predominant organisms are anaerobic >> e. coli, pseudomonas, peptostreptococcus
    - Evaluation and diagnosis
        - Moderate leukocytosis with neutrophilia
        - Microscopic hematuria and pyuria may also be present
        - Abdominal ultrasound and CT >> CT slightly more accurate, can help to pick up perforation or abscesses also
    - Treatment
        - Surgery is a definitive treatment >> laparotomy
        - Conjunction with perioperative broad spectrum antibiotics
    - Complications and prognosis
        - Localised perforation >> abscess
        - Free perforation >> suppurative peritonitis with toxicity
        - Septic thrombophlebitis >> rare
        - Mortality rate is extremely low

- Appendical cancer
    - Etiology
        - Usually indistinguishable from acute appendicitis
        - Carcinoid tumor is most common > adenocarcinoma
        - Carcinoid tumor involves the distal tip of the appendix, causing swelling
        - Pseudomyxoma peritonei >> rare type of cancer than usually begins in the appendix as a small polyp; produces mucinous fluid, eventually spreads throughout the whole tumor, then disseminates into the abdomen

- Enteric fever (typhoid fever)
    - Definition
        - Clinical syndrome comprised of constitutional symptoms (fever, headache, nausea, vomiting, abdominal pain)
        - Significant global health problem
    - Pathophysiology
        - Following consumption of contaminated food, salmonella bacteria enter through the intestinal mucosal epithelium by transcytosis
        - Microbes replicate in the macrophages of Peyer patches, mesenteric lymph nodes and the spleen

        - Bacteremia then occurs with dissemination to the lungs, gallbladder, kidneys and CNS
    - Clinical presentation
        - Prodromal phase with constitutional symptoms, with fever increasing over the next few days
        - During second week, a typical transient rash of pink maculopapular lesions (rose spots) may be seen
        - Splenomegaly and/or hepatomegaly, bradycardia and leukopenia are often observed
    - Pathogens
        - Salmonella typhi ("typhoid fever")
    - Diagnosis
        - History of travel to endemic areas, with compatible presentation
        - Blood cultures and stool cultures
    - Treatment
        - Oral or IV ciprofloxacin OR IV ceftriaxone

- Nausea and vomiting
    - Definition
        - Intense sensation of sickness
    - Pathophysiology
        - Brainstem vomiting center is composed of a group of neuronal areas within the medulla >> area postrema, nucleus tractus solitarius and central pattern generator
        - Four different sources of input:
            (1) Afferent vagal fibers from GIT viscera which may be stimulated by distention, irritation or infection
            (2) Fibers of the vestibular system, which have high concentrations of histamine H1 and muscarinic cholinergic receptors
            (3) Higher CNS centers such as the amygdala, where certain sights, smells or emotional experiences may induce vomiting
            (4) Chemoreceptor trigger zone, located outside BBB in area postrema, which is rich in opioid, serotonin, neurokinin and dopamine D2 receptors – may be stimulated by drugs, toxins, hypoxia, uremia, acidosis and radiation therapy
    - Causes
        - Acute vomiting without abdominal pain >> food poisoning, infectious gastroenteritis, drugs
        - Acute vomiting with severe abdominal pain >> peritoneal irritation, gastric or intestinal obstruction, pancreatobiliary disease
        - Persistent vomiting >> pregnancy, gastric outlet obstruction, gastroparesis
        - Vomiting before breakfast >> pregnancy, uremia, alcohol intake and increased ICP
        - Vomiting immediately after meals >> psychogenic bulimia
        - Vomiting undigested food >> gastroparesis or gastric outlet obstruction
    - Specific examinations
        - Serum electrolytes
        - Flat and upright abdominal x-rays or CT
        - Endoscopy
    - Treatment
        - Most cases are mild and self-limiting
        - Serotonin 5-HT_3- receptor antagonists >> ondansetron, dolasetron
        - Corticosteroids >> dexamethasone
        - Neurokinin receptor antagonists >> aprepitant

- Dopamine antagonists >> phenothiazines

Diseases of the small bowel

- Coeliac disease
  - Definition
    - Permanent dietary disorder caused by an immunologic response to gluten, that results in diffuse damage to the proximal small intestine mucosa with malabsorption of nutrients
    - Attributed to Gliadin triggered, T cell production of cytokines
    - Phase 2 and 3 of the phases of nutrient absorption are affected in coeliac disease
  - Etiology
    - Develops in people with the HLA-DQ2 or DQ8 class II molecules, present in 40% of population
    - Grossly underdiagnosed in adults
  - Clinical presentation
    - Diarrhoea, steatorrhea, malabsorption and weight loss, abdominal distention, weakness, muscle wasting or growth retardation, vomiting, rash
    - Atypical symptoms >> fatigue, depression, iron deficiency anemia, osteoporosis, short stature, delayed puberty, amenorrhea or reduced fertility
    - O/E: pallor due to anemia, easy bruising due to vitamin K deficiency, hyperkeratosis due to vitamin A deficiency, bone pain due to Osteomalacia, or neurologic signs due to vitamin B12 or E deficiency
  - Evaluation
    - Labs >> serology IgA tissue transglutaminase, DQ2/DQ8 genotyping
    - Mucosal biopsy from proximal duodenum (gold standard) – collected from here because this is where the highest amount of dietary gluten absorption occurs
  - Histology
    - Crypt hyperplasia
    - Villus blunting and atrophy
    - Intraepithelial lymphocytosis
  - Treatment
    - Gluten free diet
    - Dietary supplements should be provided in initial stages of therapy
  - Prognosis and complications
    - Usually excellent prognosis >> once diagnosis and treatment is applied
    - Celiac disease may be associated with other autoimmune diseases
    - Associated with higher rates of malignancy – especially lymphoma

- Bacterial overgrowth
  - General considerations
    - Small intestine normally contains small number of bacteria, but bacterial overgrowth can occur and result in malabsorption
    - Causes direct damage to intestinal epithelial cells and the brush border, impairing absorption
    - Causes:
      (1) gastric achlorhydria (absence of HCl in gastric secretions)
      (2) anatomic abnormalities with stagnation

(3) small intestine motility disorders
(4) gastrocolic or coloenteric fistula

- Clinical presentation
  - Asymptomatic
  - Flatulence
  - Weight loss
  - Abdominal pain
  - Diarrhoea and steatorrhea
  - Severe cases may cause significant vitamin and mineral deficiencies
- Diagnosis and treatment
  - Diagnosis made by aspirate and culture of proximal jejunal secretions demonstrating over 10^5 bacterial organisms/mL >> invasive
  - Breath hydrogen and methane tests with glucose or lactose substrates >> less invasive
  - Treatment of 1-2 weeks' oral broad spectrum antibiotics against enteric anerobes >> ciprofloxacin, Norfloxacin, amoxicillin clavulanate
  - If symptoms recur when off antibiotics, cyclic therapy (1 week out of 4) may be needed >> try to avoid antibiotic resistance

- Lactase deficiency
  - General considerations
    - Brush border enzyme that hydrolyses the disaccharide lactose into glucose and galactose
    - Concentration of lactase enzyme levels is high at birth but declines steadily in most people of non-European ancestry during childhood and adolescence
  - Etiology
    - Very common
    - Deficiency may arise from other GIT disorders that affect the proximal small intestinal mucosa >> Crohn's disease, sprue, viral gastroenteritis, giardiasis, short bowel syndrome and malnutrition
  - Clinical presentation
    - Bloating, abdominal cramps and flatulence, osmotic diarrhoea (with high ingestion) after ingestion of milk-containing products
  - Evaluation
    - Hydrogen breath test
    - Diagnosis supported by symptomatic improvement on lactose free diet
  - Treatment
    - Help the patient find their lactase threshold
    - Calcium supplementation is recommended for osteoporotic susceptible patients

- Small bowel obstruction
  - General considerations
    - Inability of the intestinal tract to allow passage of food and bowel contents due to mechanical obstruction or ileus
    - Causes >> stenosis, foreign bodies, strictures, superior mesenteric artery syndrome, adhesions, hernia, intussusception (inversion of the small bowel lining), lymphoma
  - Ileus versus mechanical bowel obstruction

	Ileus	Mechanical obstruction

Pain	Mild to moderate	Moderate to severe
Location	Diffuse	May localize
O/E	Mild distention with/without tenderness, decreased bowel sounds	Mild distention, tenderness, high pitched bowel sounds
Labs	Possible dehydration noted	Leukocytosis
Imaging	May be normal	Abnormal
Treatment	Observation, hydration with/without nasogastric tube	Nasogastric tube and surgery

Diseases of the colon and rectum

- Irritable bowel syndrome
    - General considerations
        - Idiopathic syndrome characterised by chronic (>6 months) abdominal pain or discomfort that occurs in association with altered bowel habits
        - Diagnosis made by chronic abdominal pain with 2/3 features: (1) relieved with defecation (2) onset associated with a change in frequency of the stool (3) onset associated with a change in appearance of stool
    - Pathogenesis
        - (1) Abnormal motility
        - (2) Visceral hypersensitivity - lower visceral pain threshold
        - (3) Enteric infection – can be a "post infectious" IBS from gastroenteritis
        - (4) Psychological abnormalities – depression, anxiety or somatization
    - Clinical presentation
        - Symptoms may be continuous or intermittent >> but it is chronic
        - Abdominal pain >> intermittent and crampy
        - Three categories: (1) IBS with diarrhoea (2) IBS with constipation (3) IBS with mixed constipation and diarrhoea
        - Somatic or psychological complaints >> dyspepsia, heartburn, chest pain, headaches, fatigue, myalgia
    - Evaluation
        - Diagnosis made via criteria
        - Sigmoidoscopy and colonoscopy is indicated for patients with IBS and alarm symptoms >> nocturnal diarrhoea, severe constipation or diarrhoea, hematochezia, weight loss and fever
    - Treatment
        - Reassurance, education and support
        - Dietary therapy for food intolerances
        - Medications >> antispasmodic agents (hyosycamine), antidiarrheal agents (loperamide), anti-constipation (osmotic laxatives), psychotropic agents (oral serotonin reuptake inhibitors), probiotics
        - Cognitive behavioural therapy, relaxation techniques and hypnotherapy
    - Prognosis
        - Learn to cope with symptoms

- Inflammatory bowel disease (Crohn's disease)
    - General considerations

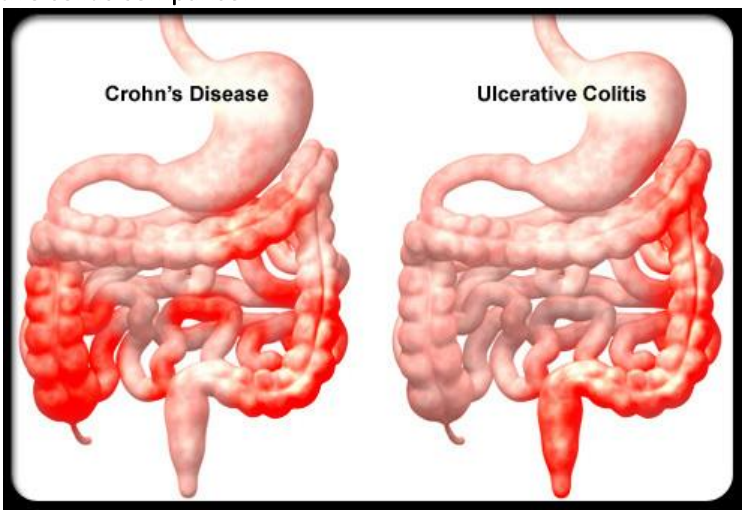
        - Chronic, recurrent disease characterised by patchy transmural inflammation involving any segment of the GIT
        - Some cases involve the terminal ileus; some cases involve the small bowel and the colon
        - Strongly associated with cigarette smoking
    - Etiology
        - White and Jewish people
        - Often presents in early 20's
    - Associated conditions
        - Erythema nosodum
        - Uveitis
        - Ankylosing spondylitis
    - Clinical presentation
        - Variable symptoms due to variation in severity and location
        - Insidious onset and non-contiguous
        - RLQ colicky abdominal pain
        - Watery diarrhoea
        - Weight loss
        - Intestinal obstruction
        - Low grade fever
        - O/E >> penetrating disease and fistula, perianal disease
    - Evaluation
        - CBC, serum albumin, clotting factors, EnLFTS, iron, vitamin B12
        - Colonoscopy >> linear and stellate ulcers, strictures, cobblestone mucosa, skip lesions, creeping fat
        - CT or barium upper GI series
        - Capsule imaging >> patient swallows a pill and it takes pictures along the GIT, before passing out through the rectum
    - Treatment
        - Diet >> well balanced, supplements
        - Medications >> cholestyramine, 5-aminosalicyclic acid agents, antibiotics, corticosteroids, immunomodulation (azathioprine), anti-TNF therapies (infliximab)
        - Surgery >> indicated for patients with chronic obstructive symptoms
    - Complications
        - Abscess formation
        - Small bowel obstruction
        - Abdominal and retrovaginal fistula
        - Perianal disease
        - Carcinoma
        - Hemorrhage
        - Malabsorption

- Inflammatory bowel disease (Ulcerative colitis)
    - General considerations
        - Idiopathic inflammatory condition that involves the mucosal surface of the colon causing bloody diarrhoea

- More common in non-smokers and ex-smokers (smoking acts as a protective barrier)

- Locations
  - (1) Rectosigmoid colitis
  - (2) Left sided colitis – extends to the splenic flexure
  - (3) Extensive colitis – proximal
- Etiology
  - White and Jewish people
  - Slightly more prevalent in females
  - Generally, presents in early 20's
- Pathophysiology
  - Always starts in the rectum and spreads proximally
  - Contiguous
  - Unlikely to have skip lesions (wound/inflammation that it clearly patchy)
- Clinical presentation
  - Highly variable
  - Bloody diarrhoea is the hallmark
  - Mild too moderate >>
    Gradual onset of infrequent diarrhoea with intermittent rectal bleeding and mucous, fecal urgency and tenesmus (continual need to defecate), left lower quadrant cramps relieved by defecation, mild fever, anemia and hypoalbuminemia
  - Severe >>
    More than 6 bloody bowel movements per day, results in severe anemia, hypovolemia and impaired nutrition with hypoalbuminemia, abdominal pain and tenderness
- Evaluation
  - CBC, ESR, hematocrit, serum albumin, p-ANCA positive antibodies
  - Colonoscopy w/biopsy >> diffuse ulcerations only involving mucosa and submucosa, friable mucosal patches, pseudopolyps, crypt abscesses with PMNs, loss of normal vascular pattern
  - Plain abdominal x-ray >> colonic dilation
  - Barium enema >> shortening of the bowel, loss of haustra, small serrations, lead pipe appearance
- Treatment
  - Mild too moderate >>
    Limit caffeine and gas producing vegetables, can be treated with topical mesalamine (5-ASA) or corticosteroids (methylprednisolone), immunomodulatory agents (azathioprine), anti-TNF agents (infliximab), probiotics
  - Severe >>
    Nil by mouth for 24-48 hours, discontinue opioids or anticholinergics, restore circulating volume with fluids, correct electrolyte abnormalities, consider transfusion for anemia, corticosteroid therapy (methylprednisolone or hydrocortisone), anti-TNF agents (infliximab), IV cyclosporine, surgery (total colectomy)
- Complications
  - Toxic megacolon >> develops in 2% of cases, characterised by colonic dilation more than 6cm with signs of toxicity
  - Markedly increased risk of developing colon carcinoma
  - Malnutrition

- Crohns disease and ulcerative colitis comparison



Feature	Crohns disease	Ulcerative colitis
Type of inflammation	Chronic granulomatous inflammation Non-continuous and patchy	Limited mucosal and submucosal involvement; starts in the rectum and extends proximally; lesions are constant and continuous throughout the GIT
Location in GIT	Anywhere from the mouth to the anus	Distal to proximal; begins at rectum and extends to cecum
Gross appearance	Cobblestone mucosa, strictures, creeping fat	Pseudopolyps
Nature of ulcers	Transmural fissuring ulceration extends through muscularis propria; granulomas are evident	Mucosal layers, superficial and broad
Nature of the lumen	Firm thick wall with narrow lumen	Wall is thin with a dilated lumen
Skip lesions and fistula formation	Both present	Neither present
Features of malabsorption	Present with nutritional deficiencies such as B12	Not present
Fibrosis	Present	Absent
Imaging	Cobblestone mucosa, "string sign" showing a narrowed lumen and creeping fat	Lead pipe sign due to loss of haustra
S + S	Diarrhoea with/without blood Colic Right illiac fossa mass Obstruction symptoms (vomiting, pain) Perianal fistula	Tenesmus Urgency Bloody diarrhoea Colic
Genetics	NOD2 and IL23R Seen in ileal Crohns Codes for cytoplasmic element that detects bacteria	HLA
Disease specific complications	Strictures Fistulas Cholelithiasis	Toxic megacolon Primary sclerosing cholangitis Increased risk of colon cancer

	Malabsorption Perianal disease Infertility Kidney stones Gallstones	

- Colonic diverticulitis
  - General considerations
    - Risk increases with age
    - Most commonly involves the sigmoid and descending colon
    - Most common cause of acute lower GI bleed in patients older than 40 YOA
    - Three times more common on the left than the right
  - Pathophysiology
    - Low fiber diet causes chronic constipation > increases intraluminal pressure > muscular hypertrophy > herniation of mucosa through muscular wall
    - True diverticula >> rare herniation that involves full bowel wall thickness
    - False diverticula >> common mucosal herniation's through only the muscular wall containing mucosa and submucosa
  - Associated conditions
    - Collagen disorders (Marfans syndrome)
    - ADPKD
  - Clinical presentation
    - (1) Uncomplicated diverticulosis >> more than 90% of cases and is asymptomatic
    - (2) Diverticulitis >> 10% of cases and is symptomatic
    - Symptoms of diverticulitis >> moderate LLQ abdominal pain, low grade fever, nausea and vomiting, abdominal tenderness, palpable mass, blood in stool
  - Evaluation
    - Colonoscopy
    - CT abdomen
  - Treatment
    - Conservative measures (high fiber intake) with broad spectrum antibiotics
    - Patients with more severe symptoms should be hospitalised >> nil by mouth, nasogastric tube, IV antibiotics, consider surgical management (signs of peritonitis, abscess formation)
  - Complications
    - Fistula may involve surrounding structures
    - Stricture formation in the colon with partial or complete obstruction
    - Peritonitis

- Meckel's diverticulitis
  - General considerations
    - The disease of 2's >> occurs in 2% of population, usually presents in first 2 years of life, found 2 feet from the ileocecal valve, is 2 inches in length, 2 times more common in males
    - Outpouching of the bowel communicating with the lumen, involving all three layers of the bowel wall

        - Caused by failure of involution of the vitelline duct with connects the lumen with the developing yolk sac
    - Clinical presentation
        - Painless rectal bleeding
        - Signs of obstruction
        - RLQ pain – very hard to distinguish this from appendicitis
        - Fecal matter in umbilicus
    - Evaluation
        - Meckel's radionuclide scan – highlights ectopic gastric mucosa
    - Histology
        - Foci of pancreatic and gastric tissue within normal tissue, likely to cause acute inflammation
    - Treatment
        - Surgical excision of the diverticulum

- Polyps of the colon
    - General considerations
        - Discrete mass lesions that protrude unto the intestinal lumen
        - Mostly sporadic, although some may be inherited as part of family adenomatous polyposis (see below)
        - Four pathologic groups:
            (1) Mucosal adenomatous polyps
            (2) Mucosal serrated polyps
            (3) Mucosal non-neoplastic polyps
            (4) Submucosal lesions
        - Of all polyps removed from the population, 70% are adenomatous and mostly come from adenoma and serrated polyps
        - Cancers arise in adenomas after inactivation of APC gene leading to chromosomal instability
        - Cancers arise in serrated polyps when a Kras gene mutation occurs
    - Clinical presentation
        - Mostly asymptomatic
        - Chronic mystery blood loss may lead to iron deficiency anemia
        - Large polyps may ulcerate resulting in intermittent hematochezia
    - Evaluation
        - FOBT (faecal occult blood test) and faecal DNA tests – colorectal screening
        - Barium enema examinations
        - CT colonography
        - Colonoscopy
    - Treatment
        - Most are amendable via colonoscopic removal with biopsy forceps or snare cautery
        - Larger polyps may require surgical resection
        - Follow up colonoscopies are indicated in the following years
    - Complications
        - Perforation during surgery causing clinically significant bleeding – rare

- Peutz-Jeghers syndrome
    - General considerations

        - Rare autosomal dominant disorder characterised by the presence of multiple GI hamartomatous polyps in the GIT and hyperpigmented macules on the lips and oral mucosa (melanosis)
    - Etiology
        - Germline mutation of STK11 / LKB1 (serine/threonine 11) tumor suppressor gene
    - Clinical presentation
        - Hyperpigmentation of the lips and mouth (melanosis)
        - Repeated bouts of abdominal pain
        - Unexplained intestinal bleeding
        - Prolapse of tissue from rectum
        - Menstrual irregularities in females
        - Gynecomastia in males
        - GI intussusception with bowel obstruction
        - Melena
        - Hematemesis
        - Weakness due to anemia
    - Pathophysiology
        - Overexpression of the gene can induce a growth arrest of the cell at the G1 checkpoint in the cell cycle
    - Histology
        - Smooth muscle hyperplasia with elongated, arborized pattern of polyp formation towards the epithelial layer
    - Complications
        - 15x increased risk of developing intestinal cancer
        - Obstruction and infarction
        - Rectal bleeding and ulceration

- Familial adenomatous polyposis
    - General considerations
        - An inherited condition characterised by the early development of hundreds to thousands of colonic adenomatous polyps and adenocarcinoma with a variety of extra-colonic manifestations
        - Autosomal dominant inheritance
        - Syndrome that affects 1:10,000 people
    - Clinical presentation
        - Develop by 15 years and cancer at 40 years
        - Extra intestinal manifestations >> osteomas, soft tissue tumours of the skin, desmoid tumors, Gardner's syndrome, Turcots syndrome
    - Genetic testing
        - Mutation of the APC gene (90% cases)
        - Mutation of MYH gene (8% cases)
    - Treatment
        - Complete proctocolectomy with ileoanal anastomoses

- Lynch syndrome
    - General considerations
        - Also, known as HNPCC – hereditary nonpolyposis colon cancer

        - Autosomal dominant inherited condition
        - Characterised by markedly increased risk of developing colorectal cancer as well as other cancers including endometrial, ovarian, renal or vesical, gastric etc
        - These polyps undergo rapid transformation over 1-2 years from normal tissue > adenoma > cancer
        - Defect of genes that detect and repair DNA base-pair mismatches >> MLH1, MSH2, MSH6
    - Clinical presentation
        - Diagnosed by the Bethesda criteria
    - Treatment
        - Colonoscopies starting at age 25
        - If cancer is found, subtotal colectomy with ileorectal anastomoses

- Hirschsprung's disease
    - General considerations
        - Obstruction secondary too colonic aperistalsis because of no ganglionic cells in the Meissner's submucosal plexus and Auerbach's myenteric plexus
        - 99% of cases localised to the rectum
        - Associated conditions >> Down syndrome and Chagas's disease
    - Clinical presentation
        - Almost always occurs after birth when the newborn is unable to pass meconium
        - Abdominal pain and chronic constipation – due to fecal build up in the dilated zone
        - O/E: absence of stool in the rectal vault on rectal exam
    - Evaluation
        - Rectal biopsy for absence of ganglion cells
    - Treatment and complications
        - Surgical resection of the aganglionic colon segments
        - Complications >> enterocolitis, perforation and peritonitis

- Acute (occlusive) mesenteric ischemia
    - General considerations
        - Medical emergency, challenging diagnosis
        - Mortality rate exceeds 50%
        - Can be categorized as arterial vs venous, embolic vs thrombotic and occlusive vs non-occlusive
        - Additional causes >> adhesions, hernias, malignancy, vasculitis
    - Pathogenesis
        - Caused by reduction in intestinal blood flow >> occlusion, vasospasm, hypoperfusion
        - Most commonly an embolism is involved (50% of cases)
        - Dislodged thrombus from left atrium, left ventricle or cardiac valves
    - Clinical presentation
        - Severe, acute, unremitting abdominal pain strikingly out of proportion to the initial physical findings
        - O/E: abdomen may be soft and nontender, distention, signs of peritonitis, occult blood in stool, transient diarrhoea, nausea, emesis
    - Evaluation
        - Labs are usually normal >> except leukocytosis
        - Initially >> radiograph imaging

        - Gold standard >> mesenteric angiography
    - Treatment
        - Hemodynamic resuscitation, correct of precipitating cause, monitoring, correction of electrolytes and broad spectrum antibiotics
        - Surgical revascularization of ischemic bowel

- Chronic mesenteric ischemia
    - General considerations
        - Result of reduced blood flow due to atherosclerotic narrowing of at least two of three major vessels (celiac trunk, SMA or IMA)
        - Usually, adequate collateral circulation develops to maintain perfusion and avoid intestinal infarction, however in CMI, infarction can develop quickly if thrombosis or embolism occurs
    - Clinical presentation
        - Diagnostic triad >> postprandial pain, weight loss and abdominal bruit
        - Pain is dull, crampy, epigastric and periumbilical that occurs after eating meals – when the gut is most metabolically active
        - Food fear occurs due to the pain resulting in weight loss and cachexia
        - O/E: Hx of PVD, soft abdomen without tenderness during episodes of pain, nausea, emesis, early satiety
    - Evaluation
        - Mesenteric angiography >> demonstration of stenosis in at least two vessels
    - Treatment
        - Gold standard >> open surgical revascularization using aortomesenteric grafting

- Large bowel obstruction
    - Causes
        - Most common cause is neoplasm
        - Volvulus >> twisting of a loop of bowel as its mesenteric point, resulting in luminal and vascular compromise
        - Herniation >> bowel becomes trapped within a defect in the abdominal wall
        - Adhesions to the lumen >> neoplasm, fecal impaction
        - Intussusception >> segment of the intestine is constricted due a proximal piece of intestine that telescopes downwards and invaginates itself upon the bowel distally
    - Pathophysiology
        - Normal bowel contains gas and gastric secretions and food
        - Intraluminal accumulation of these secretions continues even when there is no oral intake
        - As obstruction develops, the bowel becomes congested and intestinal contents fail to be absorbed
        - Vomiting and decreased oral intake follow this
        - Intraluminal pressure exceeds the capillary and venous pressure within bowel wall, absorption and lymphatic drainage decrease and the bowel becomes rapidly ischemic
        - Combining these factors, results in volume depletion with hemoconcentration and electrolyte imbalance
        - Leads to renal failure, septicemia, bowel necrosis and shock
    - Clinical presentation
        - Depends on the site and nature of obstruction
        - Abdominal pain >> usually hypogastric

        - Bowel distention >> accumulation of fluids within the lumen
        - Diminished or absent bowel sounds
        - Vomiting
        - Inability to pass a bowel movement or flatus
        - Constipation
    - Evaluation
        - CBC, EnLFTS, WCC, hematocrit
        - Serum amylase and lipase
        - Blood urea nitrogen and creatinine
        - Abdominal X-ray and CT
    - Treatment
        - Surgical intervention
        - IV fluid replacement and monitor vitals
        - Nasogastric tube
        - Pre-operative antibiotics

- Bowel volvulus
    - General considerations
        - Most commonly in the sigmoid colon and cecum
        - If it occurs in an infant, most likely due to malrotation of the intestines (developmental defect)

- Bowel intussusception
    - General considerations
        - Telescoping of the proximal bowel into the distal bowel, forming an obstruction
    - Clinical presentation
        - Red currant jelly stool – hallmark
    - Pathophysiology in children
        - Usually due to a bowel infection
        - Infection results in enlargement of the bowel lymphoid tissue
        - This forms an anchor point for telescoping of the bowel downwards
    - Pathophysiology in adults
        - Usually due to neoplasia, forming the anchor point, rather than lymphatic involvement

- Carcinoid tumor – carcinoid syndrome (paraneoplastic)
    - General considerations
        - Arises from neuroendocrine organs and neuroendocrine GI epithelial cells
        - It's a paraneoplastic syndrome produced by the hormones from the tumor
        - If carcinoid syndrome is present >> highly likely that there is mets
    - Clinical presentation
        - Vasoactive substances secreted by the tumor result in various symptoms
        - Cutaneous flushing
        - Sweating
        - Bronchospasm
        - Colicky abdominal pain

        - Diarrhoea
        - Right sided cardiac valvular fibrosis

- Hernias
    - General considerations
        - Protrusion of any viscus from its surrounding tissue walls
        - Reducible hernias >> hernia sac is soft and easy to replace back through the hernia neck defect
        - Incarcerated hernia >> firm, often painful and non-reducible by direct manual pressure
        - Strangulated hernia >> develops because of incarceration, presents as severe pain, with signs of bowel obstruction, toxic appearance or skin changes
    - Inguinal hernias
        - Very common (75% of all hernias) – males
        - In males, a patent processus vaginalis can allow small bowel contents or the greater omentum to herniate and reach the scrotum
        - (1) Direct: hernia sac passes directly through a weakness in the transversalis fascia in Hesselbach triangle, causing a bulge forwards; pass medial to inferior epigastric vessels
        - (2) Indirect: hernia passes from the internal inguinal ring into the scrotum; pass lateral to inferior epigastric vessels
    - Ventral hernias
        - Common
        - Develop as result of a defect in the anterior abdominal wall
        - Named per the quadrant they are in
    - Incisional hernias
        - Common
        - Result of excess anterior abdominal wall tension or inadequate wound healing
    - Umbilical hernias
        - Common
        - Mostly acquired due to medical conditions that increase intra-abdominal pressure or congenital defects
    - Femoral hernias
        - Uncommon – females > males
        - Hernia sac protrudes through the femoral canal and produces a mass below the inguinal ring
        - Usually present as a lump below the inguinal ligament, medial to the femoral vein
        - Prone to complications such as incarceration or strangulation
    - Obturator hernias
        - Rare and difficult to clinically diagnose
        - Bowel herniation through the obturator canal, nearly always present as a partial/complete bowel obstruction
        - Typical patient is an eldery fragile female with signs of intestinal obstruction
    - Richter hernia
        - Involves only the anti-mesenteric border of the intestine and a portion of the wall circumference
        - Presents without vomiting or intestinal obstruction due to incomplete involvement of the intestinal wall
        - More prone to strangulation and gangrene – can go undetected
    - Divarication of the recti (diastasis)
        - Patients with a very broad linea alba, which is more pronounced when lying down

        - This is simply the rectus muscles diverging a little >> is not a hernia
    - Treatment
        - Hernial reduction >> IV narcotic analgesia, apply cold packs to the site, grasp and elongate the neck of the hernia, consult surgery if unsuccessful

- Hemorrhoids
    - General considerations
        - Internal hemorrhoids are sub epithelial cushions consisting of connective tissue, smooth muscle fibers and arteriovenous communications between terminating branches of rectal arteries and veins
        - Primary locations: right anterior, right posterior and left lateral
        - External hemorrhoids arise from inferior hemorrhoidal veins located below the dentate line
        - May become symptomatic because of activities that increase venous pressure >> resulting in distention and engorgement of these veins
        - Contributing factors >> pregnancy, straining and constipation, obesity, low fiber diet
    - Stages of development
        - (1) Internal hemorrhoids are confined to the anal canal
        - (2) Over time they gradually enlarge and protrude from the anal opening; firstly, upon straining but they reduce spontaneously
        - (3) Over time the prolapsed hemorrhoids may require manual reduction after bowel movements
        - (4) The hemorrhoids chronically protrude
    - Clinical presentation
        - Bright red blood per rectum >> is uncommon to be prolonged or cause anemia
        - Perianal irritation (if chronically prolapsed)
        - Pain is unusual, only occurring with inflammation and thrombosis
    - O/E
        - External hemorrhoids are visible, non-prolapsed internal hemorrhoids are not visible
        - Look for: fistulas, fissures, skin tags, cancer, dermatitis
    - Treatment
        - Stage one and two can be treated conservatively >> high fiber diet, increase fluid intake with meals
        - Recurrent bleeding >> injection sclerotherapy (elimination of veins), rubber band ligation, electrocoagulation, topical creams, surgical excision of the hemorrhoids

- Anorectal infection
    - General considerations
        - Inflammation of the anal and rectal mucosa (proctitis)
        - Most causes are sexually transmitted
    - Clinical presentation
        - Anorectal discomfort, tenesmus (constant need to evacuate the bowels), mucopurulent discharge
    - Neisseria gonorrhoeae
        - Itching, burning, tenesmus and mucopurulent discharge
        - Cultures taken from the pharynx and urethra in men; pharynx and cervix for women
        - Complications >> strictures, fistulas, perirectal abscesses
    - Treponema pallidum
        - Anal syphilis
        - Perianal pain and discharge

        - VDRL or RPR test positive in most cases
    - Chlamydia trachomatis
        - Similar symptoms too gonorrheal proctitis or can be asymptomatic
        - Can cause lymphogranuloma venerum
        - Diagnosed by serology, culture and PCR of rectal discharge
        - Recommended Rx >> doxycycline
    - Herpes simplex type 2
        - Common
        - Symptoms develop 4-21 days after exposure
        - Severe pain, itching, constipation, tenesmus, urinary retention, radicular pain from lumbar or sacral nerve roots, vesicles in perianal area
        - Diagnosis made via viral culture, PCR or antigen detection assays of vesicular fluid
        - Symptoms resolve within 2 weeks, viral shedding may continue for several weeks
        - Recommended Rx >> acyclovir
    - Condylomata acuminata
        - Anal warts caused by HPV
        - Occur in perianal area, anal canal and genitals
        - Asymptomatic, itching, bleeding or pain
        - Diagnosis made via biopsy of the warts
        - Recommended Rx >> all partners examined and treated, vaccines

- Rectal prolapse
    - Protrusion through the anus of some or all the layers of the rectum
    - Usually due to surgical or traumatic injury or hemorrhoids
    - Complete rectal prolapse requires surgical correction

- Anal fissures
    - General considerations
        - Linear shaped ulcers that are usually less than 5mm in length
        - Usually occur at the posterior midline
        - If they are not midline be suspicious of >> Crohns disease, HIV/AIDS, TB, syphilis or anal carcinoma
        - Acute fissures look like cracks in the epithelium
        - Chronic fissures have fibrosis of the skin and the development of a skin tag at the outermost edge
    - Clinical presentation
        - Severe tearing pain during defecation followed by a throbbing discomfort
        - Mild hematochezia
    - Treatment
        - Fiber supplements
        - Sitz baths
        - Topical nitroglycerin or diltiazem

- Perianal abscess and fistula
    - General considerations
        - Infection of the anal glands can lead to abscess formation

        - Once the abscess is drained, fistulas are often found underlying
    - Clinical presentation
        - Throbbing, continuous perianal pain
        - Erythema, flatulence, swelling
    - Treatment
        - Local incision and drainage

- Perianal pruritus
    - General considerations
        - Perianal itching and discomfort
        - Causes >> poor hygiene, fissures, prolapsed hemorrhoids, skin tags, minor incontinence, over cleaning the area, contact dermatitis, bacterial infections, STIs, candida infection, spicy food, coffee
    - Treatment
        - Cleansing of the perianal area after defecation
        - Piece of cotton wool tucked into the anal opening for comfort and seepage
        - Short course of corticosteroids

- Meconium ileus
    - General considerations
        - Meconium >> dark green substance forming the first faeces of the newborn infant
        - Meconium ileus >> most commonly seen because of cystic fibrosis in babies; meconium is too viscous due to dehydration of the bowel fluids
    - Clinical presentation
        - Inability to pass first meconium
        - Associated with bowel obstruction and cystic fibrosis symptoms

Hepatic disorders

- Bilirubin function
    - Yellow coloured byproduct of hemoglobin metabolism
    - Is elevated in jaundice

- Bilirubin production to excretion
    - Every haem molecule will produce one molecule of bilirubin
    - Occurs mainly in the spleen (macrophages) and liver (Kupffer cells)
    - If the liver cannot excrete conjugated bilirubin – the kidneys will take over

    - Steps of production and excretion
      (1) Haem molecules are taken up by reticuloendothelial cells

      (2) Inside these cells, haem oxygenase enzymes break down the haem, removing iron (which is recycled) and carbon monoxide >> this leaves biliverdin
      NOTE: the detection of carbon monoxide in breath can be used to determine how much haem is being turned into biliverdin

(3) Biliverdin is then converted to bilirubin by the enzyme biliverdin reductase, whilst still in the reticuloendothelial cell

(4) After bilirubin is released from the reticuloendothelial cells, it travels in the blood, bound to albumin
This ensures that no bilirubin is excreted in the urine
NOTE: at very high concentrations, bilirubin can diffuse into the peripheral tissues where its toxic

(5) Bilirubin is then removed from the circulation in the sinusoids by hepatocytes
Passive process, that occurs down a concentration gradient

(6) As soon as bilirubin enters the hepatocyte, it becomes bound to glucuronyl transferase which conjugates the bilirubin ready for excretion
A very small amount of bilirubin evades this process and ends up in the bile as unconjugated bilirubin

(7) Bilirubin is excreted into gastrointestinal system and is deconjugated by bacteria before being reabsorbed in the colon
This process is more likely in the presence of increased bile acids

(8) Most of the bilirubin in the colon is turned into stercobilogens (brown) and urobilogens (colorless)

Alcohol metabolism in the liver

- Basic metabolism
  - Occurs within the cytosol
  - Alcohol converted to acetaldehyde by **alcohol dehydrogenase**
    This reaction requires the reduction of NAD+ to NADH
    Acetaldehyde is essentially a toxin to cells, so causes the side effects
  - About ALDH:
    ALDH1 - found in liver cytosol
    ALDH2 - found in liver mitochondria (MC)
  - Many people of Asian descent are KO for ALDH, thus get acetaldehyde buildup when drinking
  - Acetaldehyde is a vasodilator, causing flushing
  - Also, hits CTZ, causing nausea
  - Acetaldehyde then enters the mitochondria and is converted into acetate by acetylaldehyde dehydrogenase
    This reaction also requires the reduction of NAD+ to NADH
  - What is the rate limiting agent of alcohol metabolism?
    NAD+
- Overflow pathways
  - In situations where there is a heavy EtOH load, there are 2 other systems that metabolize it
    CYP2E1 in the smooth ER
    High Km (low affinity) explains why this system is only active at high alcohol concentrations
    Atalase in the peroxisome
    Not important, as people who are acatalsemic have normal alcohol metabolism
    Both systems lead to a buildup of acetaldehyde, which is one of the factors that causes alcoholic liver disease
- Mechanism of metabolic effects of alcohol metabolism (acute and chronic)
  - NADH is created, thus, the NADH/NAD+ ratio increases; the cell now is in a highly reduced state

- Because ALDH and acetaldehyde dehydrogenase both require NAD+, pathways requiring NADH increase to form more NAD+ (because alcohol is effectively toxic to the cell, the first goal is to remove the alcohol, even if that damages the cell)
- Increased glycolysis (pyruvate > lactate)
  Pyruvate + NADH > Lactate + NAD+
  This can cause lactic acidosis
- Decreased gluconeogenesis
- Pyruvate depleted (see above)
- Oxaloacetate and other TCA intermediates depleted (oxaloacetate > malate to generate NAD+)
- These depletions cause the decreased gluconeogenesis, resulting in **fasting hypoglycemia**
- Increased lipogenesis
- Transient fatty liver
- Decreased protein synthesis

- **Jaundice**
  - General considerations
    - Yellow discolouration of the skin and sclera that occurs when systemic retention of bilirubin produces serum levels above 2.0mg/dL
    - It is classified by the ratio of conjugated bilirubin: total bilirubin
  - Pathophysiology
    - Hepatocytes convert unconjugated (indirect) bilirubin into conjugated (direct) bilirubin
    - This is performed by glucuronyl transferase enzyme
    - Normally bilirubin is not toxic at moderate levels, but dysfunction of hepatocytes and decreased conversion of bilirubin causes an increase bilirubin
    - This can eventually lead to jaundice, kernicterus (deposition of bilirubin in the brain) and death
  - Conjugated bilirubin levels and associations
    - CB <20% = Gilbert's / Crigler Najjar syndromes, physiologic jaundice of the newborn, hemolysis
    - CB 20-50% = viral hepatitis
    - CB >50% = drugs (OCP), Rotor syndrome, primary biliary cirrhosis or obstruction
  - Types of jaundice
    (1) Hemolytic (pre-hepatic)
    Excessive RBC breakdown, more than what the conjugation/excretion system can handle
    Causes: hereditary hemolytic anemia (sickle cell anemia and thalassemia), Rh incompatibility, malaria
    Liver + LFTs normal
    Dark urine and stools >> entire systemic increase in bilirubin
    Often splenomegaly >> increased reticuloendothelial activity
    Pallor normally present

    (2) Hepatocellular
    Inability of the liver to excrete and/or conjugate bilirubin >> due to liver tissue damage
    Causes: viral hepatitis, poisons, drug induced heptatits (paracetamol) and liver cirrhosis
    Levels of both conjugated and unconjugated bilirubin increase

    (3) Obstructive /cholestatic (post-hepatic)
    Obstruction to the bile duct >> the liver can conjugate bilirubin but not excrete it
    Causes: OCP, gallbladder stones, carcinoma of the head of the pancreas, pregnancy, alcohol, drugs
    Presents as elevated conjugated bilirubin in serum, dark urine and clay/light coloured stool

Jaundice Type	Hyperbilirubinemia	Urine Bilirubin	Urine Urobilinogen
Hepatocellular	Conjugated/unconjugated	↑	Normal/↓
Obstructive	Conjugated	↑	↓
Hemolytic	Unconjugated	Absent	↑

- Neonatal jaundice (purexia)
  - Physiologic jaundice in babies
    - Occurs between days 3-5 of life, affecting 50% of neonates
    - Clinically benign
    - This rise in bilirubin is the indirect (unconjugated form)
    - Results from >> increased bilirubin production due to degradation of HbF (foetal hemoglobin) or a deficiency in glucuronyl transferase in the immature liver
  - Pathologic jaundice in babies
    - Jaundice in the first day of life
    - Can be due to direct or indirect hyperbilirubinemia
    - Indirect causes >> Crigler Najjar syndrome, Gilberts syndrome, breastfeeding, hemolytic anemia
    - Direct causes >> Rotors syndrome, infections, metabolic disease (including alpha 1-antitrypsin deficiency)
  - Evaluation
    - Labs >> elevated direct and total bilirubin
  - Treatment
    - Physiologic does not require treatment
    - Pathologic may require phototherapy
  - Prognosis and complications
    - Can lead to kernicterus and is potentially fatal if left untreated

- Acute hepatitis
  - General considerations
    - Inflammatory process causing liver cell death either by necrosis or by triggering apoptosis
  - Etiology
    - Commonly caused by 1/5 major viruses >> hepatitis A, B, C, D or E

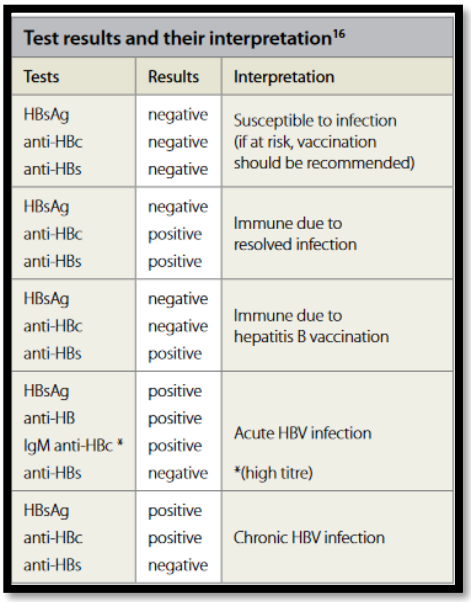
	A	B	C	D	E
Onset	Abrupt	Insidious	Insidious	Insidious	Abrupt
Symptoms	Asymptomatic, nausea and vomiting	Initially like serum sickness, arthralgia, rash, nausea and vomiting	Nausea and vomiting	Fever, nausea and vomiting, jaundice	Arthralgia, rash, fever, nausea and vomiting, jaundice
Virus type	RNA	DNA	RNA	RNA	RNA
Serology	IgM anti-HAV	HBsAg IgM anti-HBc	Screening assay (EIA or CIA) for anti-HCV		

Disease severity	Mild	Moderate	Mild	Can be severe	Severe – especially in pregnant women
Chronic	No	Yes	Yes	Yes	Yes
Associated with malignancy	No	Yes	Yes	Yes	No
Transmission	Oral, sexual	Oral, sexual, percutaneous and perinatal	Percutaneous, sexual and perinatal	Percutaneous and sexual	Oral, percutaneous and perinatal
Vaccine	Yes	Yes	No	No	No
Carrier state	No carrier state	Carrier state common	Carrier state common	Defective virus, depends on having superinfection with HBV	Enteric, epidemic, no carrier state
Liver biopsy	Hepatocyte swelling, monocyte infiltration, Councilman bodies	Granular eosinophilic "ground glass" appearance, cytotoxic T cells mediate damage	Lymphoid aggregates with focal areas of macrovascular steatosis	Similar to HBV	Patchy necrosis

        - Additional, less common causative agents >> EBV, CMV, varicella virus, herpes simplex, rubella, yellow fever
        - Hepatitis can also be drug induced
    - Pathogenesis – viral
        - (1) Viral agent infects the first hepatocyte
        - (2) During the incubation period, intense viral replication in the liver leads to the appearance of viral components (first antigens and then antibodies) in urine, stool and body fluids
        - (3) Liver cell death and inflammatory response result in changes in liver function
    - (1) Prodrome phase
        - 3-4 days
        - (1) Systemic symptoms – malaise, fatigue and mild fever
        - (2) GI symptoms – anorexia, nausea, vomiting, altered sense of olfaction and taste, RUQ discomfort
        - (3) Extrahepatic symptoms – headache, photophobia, cough, hematuria and proteinuria
    - (2) Icteric phase
        - 1-4 weeks
        - Constitutional symptoms improve
        - RUQ pain because of large tender liver
        - Splenomegaly noted in some patients
        - Jaundice – elevation of conjugated bilirubin in the bloodstream
        - Changes in stool colour and urine colour
        - Ecchymoses - coagulopathy, maybe due to loss of vitamin K absorptive capacity from intestine
        - Subtle or profound mental status changes can be seen in severe disease
    - (3) Convalescent phase
        - Complete disappearance of constitutional symptoms but persistent abnormalities in liver function tests

- S+S gradually improve
  - Histology findings
    - (1) Focal liver cell degeneration and necrosis, cell dropout, ballooning and cell shrinking
    - (2) Inflammation of portal areas, with infiltration of mononuclear cells – lymphocytes, plasma cells, eosinophils
    - (3) Prominence of Kupffer cells and bile ducts
    - (4) Cholestasis (arrested bile flow) with bile plugs
  - Severe histology findings
    - Lesion called 'bridging hepatic necrosis' – occurs between lobules, resulting in large areas of hepatic cell loss
    - Severe atrophy and softening of the liver – acute yellow atrophy

- Hepatitis B
  - General considerations
    - Transmitted by infected blood or bodily fluids >> vertical transmission, horizontal transmission (from an infected to unvaccinated household contacts), sexually, percutaneously, salivary transmission (rare) and medically acquired (transfusions and needle stick injury)
    - The virus enters the bloodstream through a break in the skin or through mucous membranes
    - HBV can survive outside the body for up to 7 days
    - HBV is 50-100 times more infectious than HIV
    - 70% of people living with chronic hepatitis B come from overseas countries or as Aboriginal and Torres Strait Islander
  - Natural history (acute)
    (1) Incubation phase
    (2) Symptomatic hepatitis
    Fever, fatigue, anorexia, nausea, dark urine, jaundice, myalgia, RUQ pain
    Elevated aminotransferase levels
    (3) Recovery period
    Normalization of alanine aminotransferase levels (ALT)
    (4) Clearance phase
    HBsAg clears from serum after a few months; this coincides with the development of anti-HBs antibodies
  - Natural history (chronic)



Test results and their interpretation[16]

Tests	Results	Interpretation
HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible to infection (if at risk, vaccination should be recommended)
HBsAg anti-HBc anti-HBs	negative positive positive	Immune due to resolved infection
HBsAg anti-HBc anti-HBs	negative negative positive	Immune due to hepatitis B vaccination
HBsAg anti-HB IgM anti-HBc * anti-HBs	positive positive positive negative	Acute HBV infection *(high titre)
HBsAg anti-HBc anti-HBs	positive positive negative	Chronic HBV infection

Immune tolerance	Immune clearance	Immune control	Immune escape
Positive HBeAg High HBV DNA levels Normal ALT	Fluctuating HBV DNA and ALT levels Positive HBeAg Indicates active, immune mediated cytotoxic response to infected liver cells Patients are at risk of progression to cirrhosis and HCC – consider treatment	HBV DNA is low or undetectable LFTs are normal Patients do not need treatment unless there is advanced liver disease	Negative HBeAg Positive anti-HBe Detectable viral load Patients are at risk of progression to cirrhosis and HCC – consider treatment

  - Testing and interpretation

        - Must gain consent for testing
        - Order HBsAg (surface antigen), anti-HBC (core antibody) and anti-HBs (surface antibody)
        - Interpretation >>
    - Vaccination recommendations
        - Infants
        - Adolescents aged 10-13
        - Men who have sex with men, people with multiple sexual partners, sex workers
        - Aboriginal and Torres Strait Islander people
        - Prison inmates and staff
        - IVD users
        - Travellers to endemic places
        - Health care workers
        - Hemodialysis patients, those who require transplant or transfusions
    - HBV and pregnancy
        - Pregnant women should have screening for HBV in antenatal period
        - Within 12 hours of birth, babies should be given HBIG and HBV vaccine
    - Complications
        - Liver cancer, cirrhosis

- Hepatitis C
    - General considerations
        - Blood borne virus, transmitted via blood-to-blood contact
        - IVDU (95% of cases)
        - Vertical transmission is low (5%)
    - Natural history
        - Acute >> 25% of cases clear the infection spontaneously within 6 months of infection; 75% progress to chronic hepatitis
        - Incidence is expected to increase and peak by 2020
        - Remains underdiagnosed
    - Who should we screen?
        - Patients with abnormal LFTs
        - History of past or current IVDU
        - Received a blood transfusion or blood products before 1990
        - Migrants from high prevalence regions
        - History of tattoos or piercings
        - History of incarceration
        - Children of mothers with HCV
        - Healthcare workers performing exposure prone procedures
    - Examination findings
        - Usually asymptomatic
        - Palmar erythema, Dupuytren's contracture, clubbing, leukonychia, peripheral hair loss
        - Asterixis, Petechiae or ecchymoses, muscle wasting, ankle oedema
        - Jaundice, fetor hepaticus, gynecomastia

        - Parotid enlargement, spider naevi
        - Splenomegaly, ascites, caput medusae
        - Hepatomegaly
    - Treatment
        - No vaccination available
    - Prognosis and complications
        - Is curable, particularly when treated early
        - HVC and HIV co-infection

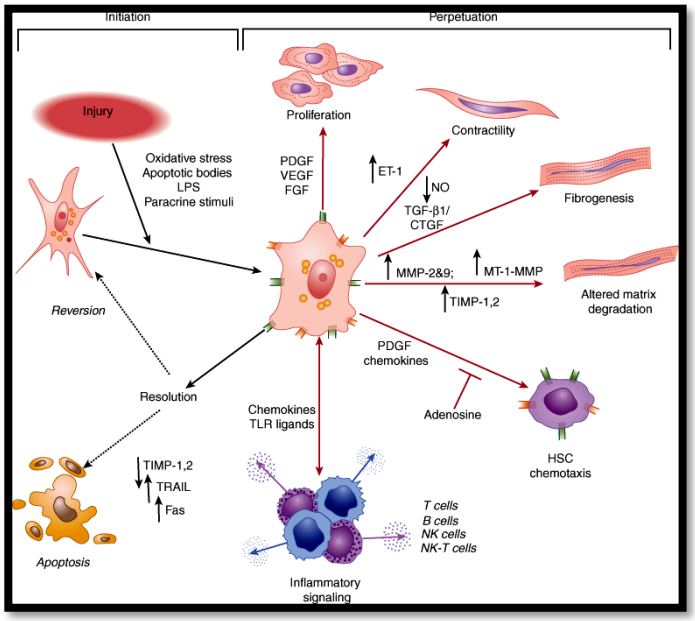
- Chronic hepatitis
    - General considerations
        - Category of disorders characterised by combination of liver cell necrosis and inflammation persisting more than 6 months
    - Etiology
        - Causes:
          Viral – hepatitis B with or without hepatitis D superinfection
          Drugs and toxins – ethanol, acetaminophen, aspirin, amiodarone, methyldopa
          Metabolic and genetic – alpha 1 antitrypsin deficiency, Wilson disease
          Autoimmune or idiopathic
    - Clinical presentation
        - Fatigue, malaise, low grade fever
        - Anorexia and weight loss
        - Mild intermittent jaundice
        - Mild hepatosplenomegaly
    - Histopathology
        - (1) Inflammatory infiltrate of hepatic portal areas with mononuclear cells
        - (2) Necrosis of hepatocytes within the parenchyma or immediately adjacent to the portal areas
    - Complications
        - Progression to cirrhosis
        - Coagulopathy
        - Hypersplenism
        - Ascites

- Hepatic steatosis
    - General considerations
        - Accumulation of triglycerides and other fats in the liver cells
        - Potential mechanisms:
          Decreased mitochondrial fatty acid oxidation
          Increased endogenous fatty acid synthesis or enhanced delivery of FAs to liver
          Deficient exportation of triglycerides as VLDLs
    - 3 classifications
      (1) Alcoholic fatty liver
      (2) Alcoholic hepatitis
      (3) Alcohol-related cirrhosis

- Alcoholic hepatitis (steatohepatitis)
    - General considerations
        - Characterised by progressive inflammatory changes to the liver associated with long term intake of ethanol
        - CAGE questionnaire can be helpful (have you ever felt the need to CUT down; have you felt ANNOYED at the suggestion that you might have an alcohol problem; have you felt GUILTY about excessive drinking; do you need an EYE OPENER in the morning?)
        - Social disruption, including domestic violence, multiple hospital admissions
        - Family history of alcohol abuse is common
    - Clinical presentation
        - Subacute onset of fever, hepatomegaly, leukocytosis, marked impairment of liver function and manifestations of portal hypertension (ascites, encephalopathy and varices)
    - Pathogenesis – ethanol
        - (1) Ethanol disorganises the lipid portion of the cell membrane, leading to adaptive changes in their composition
        - (2) This alters the capacity of liver cells to cope with environmental toxins
        - (3) Oxidation of ethanol produces acetaldehyde, a toxic and reactive intermediate
        - (4) Alters metabolism of cofactors essential for enzymatic activity
        - (5) Induces malnutrition
    - Investigations
        - CBC + WCC – leukocytosis
        - Raised transaminase levels with AST higher than ALT in a ratio of 2:1, but neither above 300 IU/dL
        - Raised Gamma GT on LFTs
        - Elevated bilirubin, hypoalbuminemia and prolonged prothrombin time
        - Ash serum biomarker + serum ethanol
        - Multiple healed fractures of the ribs or clavicle on CXR >> fall related
        - Abdominal US
        - Percutaneous or transjugular liver biopsy
    - Histology findings
        - Zone 3 hepatocytes most affected
        - Hepatocyte ballooning >> foci or cells undergoing swelling and necrosis, filled with fat
        - Mallory-Denk bodies >> tangles of intermediate filaments, visible eosinophilic cytoplasmic inclusions
        - Infiltration of polymorphonuclear leukocytes
    - Treatment and management
        - Abstinence
        - Correction of vitamin deficiencies, high energy and protein diet
        - Immunizations against pneumococcal, meningococcal and influenza – immunocompromised and hyposplenic patients
        - Early referral to specialist care
    - Prognosis
        - Once signs of clinical decompensation occur, patients with alcoholic cirrhosis who stop drinking have a 5-year survival rate of about 60% versus those who do not stop drinking

- Liver cirrhosis and portal hypertension

- General considerations
  - Irreversible distortion of normal liver architecture characterised by hepatic injury, fibrosis and nodular regeneration
- Etiology
  - Hepatitis A, B, C, D, E
  - Alcohol abuse
  - Primary biliary cirrhosis
  - Wilson disease and hemochromatosis
  - Acute fatty liver disease
  - Sarcoidosis
  - Tuberculosis
  - Cholestatic syndromes
  - Drug induced
  - Autoimmune



- Pathogenesis
  - (1) Initation of hepatic stellate (fat storage cells) is provoked by soluble stimuli that include oxidant stress signals, apoptotic bodes, LPS, Kupffer cells and hepatocytes
  - (2) Perpetuation follows – characterised by phenotypic changes including proliferation, contractility, fibrogenesis, chemotaxis and inflammatory signaling
- Clinical presentation
  - Portal hypertension >> due to a rise in intrahepatic vascular resistance
  - Oesophageal varices >> due to portal hypertension
  - Hepatorenal syndrome >> distinct form of kidney injury resulting from renal vasoconstriction that develops in response to the systemic and splanchnic arterial vasodilation in patients with advanced liver disease
  - Coagulopathy and bleeding tendency >> loss of hepatic synthesis of clotting factors; hepatocytes also involved in maintenance of normal coagulation cascade through absorption of vitamin K, necessary to activate clotting factors 2, 7, 9 and 10
  - Encephalopathy >> reversible neuropsychiatric abnormalities due to advanced liver disease or portal-to-systemic shunting
  - Splenomegaly >> consequence of elevated portal venous pressure
  - Pulmonary complications >> hepatopulmonary syndrome, portopulmonary syndrome and hepatic hydrothorax
  - Caput medusae
  - Ascites >> due to portal hypertension; confirmed by presence of serum-to-ascites albumin gradient (SAAG)
  - Bacterial peritonitis >> infection resulting from presence of ascitic fluid in peritoneal space
  - Rectal varices
  - Jaundice >> decreased excretion of bilirubin
  - Spider nevi >> prominent blood vessels with a central arteriole and little blood vessels radiating outwards
  - Dupuytren contractures >> fibrosis of palmar fascia, resulting in permanent flexed ring finger

        - Fetor hepaticus and hepatic flap >> accumulation of ammonia
        - Peripheral oedema >> caused by hemodynamic imbalance following plasma protein [ ] shifts
        - Hypoalbuminemia >> worsening hepatocellular function can result in a drop in [ ] of albumin synthesised by liver
        - Testicular atrophy, loss of sexual hair and Gynaecomastia >> due to decreased clearance of estrogen
    - Histopathology
        - (1) Marked distortion of hepatic architecture
        - (2) Scarring because of increased deposition of fibrous tissue and collagen
        - (3) Regenerative nodules surrounded by scar tissue
    - Treatment
        - Liver transplant
        - Portal shunting
    - Prognosis and complications
        - Increased risk of hepatocellular carcinoma
        - Complications of portal HTN >> oesophageal varices, external hemorrhoids, bacterial peritonitis

- Hepatic encephalopathy
    - General considerations
        - AKA portosystemic encephalopathy
        - Reversible syndrome of impaired brain function caused by advanced liver disease
        - Liver dysfunction results in decreased detoxification capabilities and metabolic abnormalities >> accumulation of ammonia, activation of inhibitory neurotransmitters, impairment of excitatory neurotransmitters
        - Increased risk with >> sepsis, neuroinflammation, alterations to gut flora
    - Clinical presentation
        - Irritability, dementia, seizures, obtundation and coma
        - O/E: hyperreflexia and asterixis
    - Treatment
        - Lactulose >> acidification of gut lumen results in ammonia trapping and less reabsorption
        - Rifaximin >> destruction of the gut bacteria (antibiotic)
        - Protein diet restrictions

- Gilbert's syndrome
    - General considerations
        - Hereditary unconjugated hyperbilirubinemia
        - Due to defect in promotor gene for UGT1A1
    - Clinical presentation
        - Most asymptomatic
        - Occasional recurrent mild jaundice associated with fasting, stress and EtOH intake
    - Diagnosis
        - Made with isolated unconjugated hyperbilirubinemia without evidence of hepatitis or hemolysis
    - Treatment
        - Supportive medical management
    - Prognosis and complications

- No clinical consequences apart from needing to avoid some medications

- Crigler-Najjar syndrome
  - General considerations
    - Infancy disease
    - Hereditary unconjugated hyperbilirubinemia
    - Type 1 = severe jaundice and kernicterus, type 2 = less severe (Arias syndrome)
  - Clinical presentation
    - Neonatal jaundice
    - Sepsis
    - Hypotonia
    - Kernicterus
    - Oculomotor palsy
    - Deafness and poor mental progression/development
  - Evaluation
    - Normal LFTs
    - Unconjugated hyperbilirubinemia
    - Pyloric stenosis might be evident
  - Treatment
    - Plasmapheresis
    - Phototherapy
    - Phenobarbital
    - Liver transplant >> in severe cases
  - Prognosis and complications
    - Kernicterus >> deposition of bilirubin in the brain
    - If severe, patients die within a few years

- Dubin-Johnson/Rotor's syndrome
  - General considerations
    - Hereditary conjugated hyperbilirubinemia due to decreased hepatic excretion
    - Two types:
      (1) Dubin-Johnson syndrome
      Grossly black liver due to the impaired secretion
      Benign
      Autosomal recessive inheritance
      (2) Rotor's syndrome
      Even more mild than DJ syndrome
      Does not cause the black liver
  - Clinical presentation
    - Mostly asymptomatic
    - Patients may become jaundiced during pregnancy or while on OCPs
  - Treatment
    - No treatment is needed

- Reye's syndrome

- General considerations
  - Hepatoencephalopathy associated with aspirin ingestion during a flu-like illness or varicella
  - Usually occurs 4-12 YOA
  - Acute changes seen in liver architecture >> microvascular fatty change
- Clinical presentation
  (1) Prodrome
  Afebrile initially
  Sleepy and lethargic
  (2) Encephalopathy (in order of increasing ICP)
  - Vomiting
  - Stupor
  - Coma
  - Death
- Evaluation
  - Increased transaminases, hypoglycemia
- Treatment
  - Control ICP via mannitol, fluid resus and hyperventilation
- Prognosis and complications
  - Death will occur without aggressive medical management

- Alpha 1 – Antitrypsin deficiency
  - General considerations
    - Autosomal dominant inheritance
    - Misfolded alpha 1 – antitrypsin (AAT)
    - AAT normally functions to inhibit elastase
    - Without AAT, elastase is over active and destroys elastic tissues
  - Clinical presentation
    - SOB
    - Symptoms of cirrhosis
    - Hyperinflated lungs
    - Hepatomegaly
  - Evaluation
    - Spirometry >> decreased FEV1, decreased FEV1/FVC ratio and increases TLC
  - Complications
    - Results in panacinar emphysema
    - The deficiency results in accumulation within the ER in hepatocytes, which causes liver damage and cirrhosis
- Wilson's disease
  - General considerations
    - Disease of free copper accumulation in body tissues (liver, brain, cornea, joints)
    - Autosomal recessive
    - Mutation in ATP7B gene >> causes inadequate copper excretion by liver into bile and failure of copper to enter circulation bound to ceruloplasmin protein
  - Clinical presentation
    - Parkinson like symptoms >> secondary to copper deposits in the putamen

        - Hemiballismus >> secondary to copper deposits in the subthalamic nucleus
        - Dementia >> secondary to copper deposits in cerebral cortex
        - O/E: Kayser-Fleischer rings in the eyes
    - Evaluation
        - Labs >> decreased total serum copper, increased non-ceruloplasmin bound copper, increased urine/serum free copper, hemolytic anemia
    - Prognosis and complications
        - Hepatitis, cirrhosis and carcinoma
        - Fanconi's disease in the proximal tubules

- Hemochromatosis
    - General considerations
        - Disease caused by excess iron deposition in nearly all the tissues of the body
        - Autosomal recessive on chromosome 6
        - Slow course > will usually present in 5th decade of life for men, and 10-20 years post menopause for women
        - Primary = mutation in HFE gene
        - Secondary = accumulation of iron secondary to frequent blood transfusions or alcoholism
    - Clinical presentation
        - Cirrhosis
        - Malabsorption
        - Amenorrhea and decreased libido
        - Arthritis
    - Prognosis and complications
        - Complicated by cardiomyopathy, CHF
        - Increased risk of hepatocellular carcinoma

- Fulminant liver failure
    - General considerations
        - Liver failure and encephalopathy within <8 weeks' onset
        - Caused by: Reye's syndrome, drugs or infection
    - Clinical presentation
        - Vomiting, stupor, coma and death
        - O/E: hepatomegaly and jaundice
    - Treatment
        - Liver transplant

Liver function tests

- Serum bilirubin
    - Haem metabolite
    - Comes in two forms
      (1) Conjugated (direct) – water soluble, and can be excreted by the kidney

(2) Unconjugated (indirect) – insoluble in water and is bound to albumin in blood
- Elevated unconjugated bilirubin – rarely due to liver disease; seen more in hemolytic disorders and genetic conditions such as Crigler-Najjar syndrome
- Elevated conjugated bilirubin – almost always implies liver or biliary tract disease

- Urine bilirubin
  - The only bilirubin that is found in the urine is conjugated
  - Presence of bilirubinuria implies liver disease
  - Urine dipstick for this is extremely accurate

- Blood ammonia
  - Ammonia is produced in the body during normal protein metabolism and by intestinal bacteria
  - The liver plays a role in detoxification of ammonia by converting it to urea, and then excreting it via the kidneys
  - Small correlation between elevated ammonia levels and liver disease and encephalopathy

- Serum enzymes
  - Enzymes that reflect damage to hepatocytes
    (1) AST – aspartate aminotransferase
      - Found in the liver, cardiac muscle, kidneys, brain, pancreas, lungs, leukocytes and erythrocytes
    (2) ALT – alanine aminotransferase
      - Found primarily in the liver and is more specific of liver injury
    (3) In acute hepatocellular disorders, ALT > or equal to AST
    (4) In chronic liver diseases, AST: ALT ratio is normally <1
    (5) An AST: ALT ratio of >2:1 is suggestive of cirrhosis
    (6) An AST: ALT ratio of >3:1 is highly suggestive of alcoholic liver disease
    (7) Causes: infection, alcohol, fatty liver disease, drugs, metal overload, hypoxia, autoimmune conditions
  - Enzymes that reflect cholestasis
    (1) GGT – gamma-glutamyl transferase
    (2) ALP – alkaline phosphatase
    (3) 5'- nucleotidase
    (4) Causes: biliary obstruction, pregnancy, drugs, infiltration of malignancy

- Serum albumin
  - Synthesised by hepatocytes in the liver
  - Half-life of about 20 days
  - Hypoalbuminemia – more common in chronic liver disease

- Serum globulins
  - Proteins made up of immunoglobulins produced by B lymphocytes and alpha and beta globulins produced by hepatocytes
  - Immunoglobulins are increased in chronic liver disease

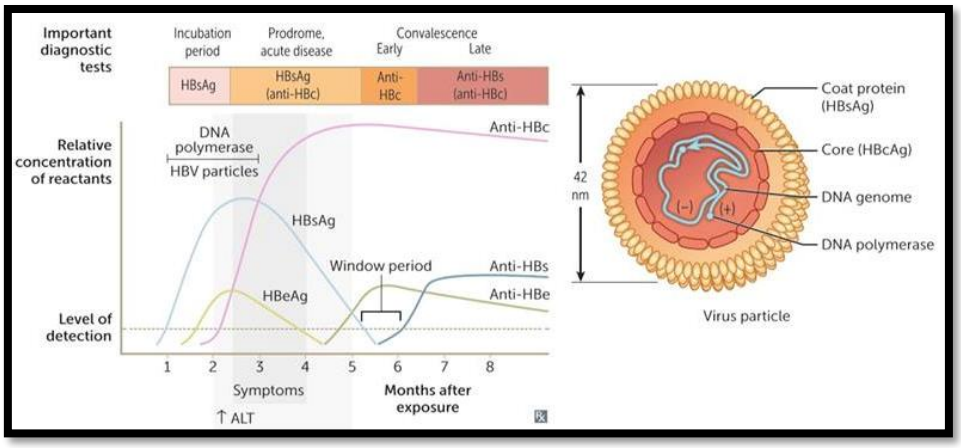
- Coagulation factors
  - All blood clotting factors (except factor VIII – made by vascular endothelial cells) are made by hepatocytes
  - Because of their rapid turnover, measuring these is the single best acute measure of hepatic synthetic function
  - To measure this, we look at serum prothrombin time (PT) – which measures CFs II, VII, IX, X (all vitamin K dependent)
  - This is expressed as INR – international normalized ratio for warfarin

- PT may be elevated in hepatitis and cirrhosis

- Grading liver function
  - Child-Turcotte-Pugh score
  - Per the degree of ascites, plasma concentrations of bilirubin and albumin, prothrombin time and degree of encephalopathy
  - Total score of 5-6 = grade A (well compensated disease)
  - Total score of 7-9 = grade B (significant functional compromise)
  - Total score of 10-15 = grade C (decompensated disease)
  - These grades correlate to 1 to 2-year patient survival: grade A (85-100%), grade B (60-80%) and grade C (35-45%)

	Points		
Parameter	**1**	**2**	**3**
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Bilirubin	<2.0 mg/dL	2.0–3.0 mg/dL	>3.0 mg/dL
Prothrombin time prolongation	<4.0 s	4.0–6.0 s	>6.0 s
Ascites	Absent	Controlled	Refractory
Encephalopathy	None	Controlled	Refractory

- Hepatitis serologic markers
  - HBsAg
    - Antigen found on the surface of HBV
    - This indicates hepatitis B infection
  - Anti-HBs
    - Antibody to HBsAg
    - This indicates immunity to heptatits B
  - HBcAg
    - Antigen associated with the core of HBV
  - Anti-HBc
    - Antibody to HBcAg
    - IgM indicates acute/recent infection
    - IgG indicates prior exposure of chronic infection
  - HBeAg
    - Secreted by the infected hepatocyte into the circulation
    - This is not part of the HBV virion
    - Indicates active viral replication and therefore this person has high transmissibility
  - Anti-HBe
    - Antibody to HBeAg
    - Indicates low transmissibility
  - Anti-HAV (IgM)
    - IgM antibody to HAV
    - Best test to detect the presence of acute hepatitis A
  - Anti-HAV (IgG)
    - IgG antibody indicates prior HAV infection and/or prior vaccination
    - Protects against reinfection



Biliary disorders

- Cholelithiasis
  - General considerations
    - Gallstones
  - Stone classes
    (1) Pigmented stones
    Brown – result from common bile duct infection
    Black – composed of calcium bilirubinate, result of increased liver excretion of bilirubin
    Risk factors – hemoglobinopathies, alcohol cirrhosis
    (2) Cholesterol stones
    Mixed composition
    Risk factors – five Fs, OCPs, north American Indian, rapid weight loss, Crohns disease
  - Clinical presentation
    - Often asymptomatic, discovered incidentally
    - Biliary colic
    - Right upper quadrant pain
    - Nausea
    - Jaundice
  - Etiology
    - Five F's >> female, fat, fertile (multiple pregnancies), fibre (low intake), forty years of age
    - Most are largely composed of cholesterol with/without calcium deposits
    - Sometimes bilirubin stones may form >> in association with other disease
  - Pathogenesis
    Multifactorial: factors that affect bile composition and factors that affect gallbladder motility
    (1) Factors that affect bile composition
    Stasis
    Cholesterol saturation
    Rate of bile formation
    Rate of water and electrolyte absorption
    Bacterial infection
    Estrogen and prostaglandins
    Altered bile salt pool

(2) Factors affecting gallbladder motility
Decreased sphincter of Oddi relaxation
Decreased gallbladder wall muscular contraction
Hormones
Neural control (vagal tone)

- Treatment
  - Cholecystectomy
- Complications
  - Cholelithiasis
  - Peritonitis due to obstruction of the cystic duct
  - Post inflammatory fibrosis
  - Increased risk of carcinoma
  - Calcification of the gallbladder wall
  - Acute and chronic pancreatitis
  - Gallstone ileus

- Primary biliary cirrhosis
  - General considerations
    - Autoimmune destruction of bile ducts in the portal triads
    - Involves granulomatous inflammation and progression to cirrhosis
  - Clinical presentation
    - Pruritus
    - Jaundice
    - O/E: Kayser-Fleischer rings
  - Prognosis and complications
    - Increased risk of hepatocellular carcinoma

- Acute cholecystitis
  - General considerations
    - Acute infection of the gallbladder due to prolonged blockage of the cystic duct
  - Pathogenesis
    - (1) Lodgment of stone in the cystic duct
    - (2) Accumulation of mucous behind stone with bacterial overgrowth
    - (3) Bacterial invasion of the gallbladder wall
    - (4) Perforation of gallbladder with gangrenous necrosis
  - Etiology
    - Caused by: E.Coli, Enterobacter cloacae, clostridium
    - Can rarely occur without stones >> CMV infection in AIDS and severe volume depletion
  - Clinical presentation
    - RUQ pain >> sudden onset, 15-30 mins after eating, steady and aching, radiates to the right scapula
    - Nausea and vomiting
    - O/E: Charcot's triad (RUQ tenderness, fever, jaundice) and positive Murphy's sign
  - Evaluation
    - US is gold standard
    - Labs >> neutrophilic leukocytosis, elevated AST/ALT, elevated bilirubin, elevated amylase

- Treatment
    - IV antibiotics and fluids and electrolytes
    - DO NOT USE MORPHINE FOR ANALGESIA (may worsen pain due to contraction of sphincter of Oddi)
    - Cholecystectomy
- Prognosis and complications
    - Gangrene, fistulas, perforation, sepsis

Pancreatic disease

- Acute pancreatitis
    - General consideration
        - Clinical syndrome resulting from acute inflammation and destructive autodigestion of the pancreas and peripancreatic tissues
    - Etiology
        - I GET SMASHED: idiopathic, gallstones, ethanol, trauma, steroids, mumps, autoimmune, scorpion bite, hyperlipidemia, ERCP, drugs
        - Can result from infectious agents – mumps, hepatitis A, HIV, CMV
        - Familial pancreatitis – rare – usually mutations of the cationic trypsinogen gene
        - Emergence of autoimmune pancreatitis >> type 1 and 2
    - Pathogenesis
        - Pancreatic duct obstruction, acinar cell injury, defective intracellular transport of proenzymes
        - Thought to be involved with the activation of trypsin, causing widespread cellular effects due to the activation of various other mediators
        - Elastase activation >> vascular damage and hemorrhage
        - Chymotrypsin activation >> oedema and vascular damage
        - Lipase activation >> fat necrosis
        - Phospholipase A2 activation >> coagulation necrosis
        - Kalikrenin-kinin activation >> oedema and inflammation
        - Inflammatory mediators >> TNF, IL-1, nitric oxide and platelet activating factor
    - Key morphological features
        - (1) Microvascular leakage causing oedema
        - (2) Necrosis by fat lipases – release of lipases results in splitting of triglycerides found in the peritoneum, then free fatty acids are released to combine with calcium in the interstitial fluid >> causing fat saponification and the chalky white appearance on the outside of the pancreas
        - (3) Acute inflammatory reaction
        - (4) Proteolytic enzyme destruction of the pancreatic parenchyma
        - (5) Destruction of the blood vessels leading to hemorrhage
    - Exists in two forms
        - (1) Interstitial oedematous pancreatitis >> enlargement of parenchyma
        - (2) Necrotizing pancreatitis >> necrosis of parenchyma
    - Clinical presentation
        - Can be mild and self-limiting
        - Abdominal pain – universal hallmark >> intense, deep and searing, radiates to the back

        - Nausea and vomiting >> due to stretching of the pancreatic capsule
        - Marked abdominal distention with/without ileus >> due to peritoneal irritation and electrolyte imbalance
        - Fever >> due to extensive tissue injury, inflammation and necrosis – endogenous pyrogens are released (mostly IL-1)
        - O/E: palpable gallbladder, abdominal tenderness with guarding or rebound tenderness, diminished bowel sounds from ileus, Grey Turners sign (purple discoloration of the flank), Cullen's sign (periumbilical purple discoloration)
    - Evaluation
        - Labs >> elevated serum amylase, lipase
        - CT is gold standard
        - Ranson criteria used to determine prognosis
    - Treatment
        - IV fluids, bowel rest (nil by mouth), BG decompression, antibiotics, oxygen
        - Pain control >> meperidine
    - Early complications
        - Shock >> due to hypovolemia, hypotension, vasodilation
        - Disseminated intravascular coagulation >> tissue factor release may cause activation of plasma coagulation cascade
        - Pulmonary complications >> endothelial cell destruction and increased permeability of alveolar capillary membrane, causes respiratory failure
    - Late complications
        - Pancreatic pseudocysts >> cavities that contain blood, pus or pancreatic juice (can progress to pancreatic abscess)
        - Walled off necrosis >> encapsulated collection of debris
        - Pancreatic ascites >> direct connection develops between the pancreatic duct and the peritoneal cavity
        - Pancreatic fistulas
    - Prognosis
        - Most people recover completely with medical management
        - The pancreas regenerates and returns too normal – apart from some mild residual scarring

- Chronic pancreatitis
    - General considerations
        - Chronic relapsing of inflammation, fibrosis and destruction of the pancreas
        - Damage is irreversible
    - Etiology
        - Alcohol abuse, duct obstruction, pancreas divisum, metabolic disorders, drugs, autoimmune
    - Pathogenesis
        (1) Large duct
            Biliary pancreatic reflux
            Sphincter of Oddi obstruction
        (2) Small duct
            Increased lactoferrin
            Decreased lithostathine (pancreatic stone protein)
        (3) Acinar cell

Toxic metabolites
Stellate cell induced fibrosis

- Macroscopic features
  - Parenchymal fibrosis
  - Reduced number and size of acini
  - Dilation of some pancreatic ducts
  - Relative sparing of the islets of Langerhans
- Clinical presentation
  - Persistent epigastric pain
  - Nausea and vomiting
  - Weight loss
  - Malabsorption
  - Hyperglycemia and diabetes mellitus
  - Bouts of jaundice
- Complications
  - Pseudocyst formation, fistulas, ascites, pleural effusion

- Cystic fibrosis
  - General considerations
    - Autosomal recessive defect
    - Disorder of epithelial transport (dysfunction of chloride channels) affecting fluid secretion in exocrine glands and epithelial lining of the respiratory, GI and reproductive tracts
  - Etiology
    - Most common lethal genetic abnormality of Caucasian populations
  - Changes that occur in the pancreas
    - Abnormal viscous mucosa secretions block the pancreatic ducts resulting in pancreatic insufficiency
    - Ducts become dilated and plugged with eosinophilic mucin
    - This may lead to obstruction by a thick viscous plug, malabsorption, increased fecal loss, foul smelling stools, abdominal distention, poor weight gain

- Pancreatic carcinoma
  - General considerations
    - Known as infiltrating ductal adenocarcinoma of the pancreas
  - Etiology
    - Usually occurs after 50 YOA
    - Men > women
    - Precursor lesion >> PanINS (pancreatic intraepithelial neoplasia)
    - Strongest environmental link >> smoking
    - Additional risk factors >> high intake of saturated fat, exposure to solvents, pesticides, alcohol
  - Pathophysiology
    - Involves the gradual accumulation of genetic defects
    - (1) Telomere shortening
    - (2) Mutation of K-RAS
    - (3) Inactivation of p16

        - (4) Inactivation of p53, SMAD4 and BRCA2
    - Morphological features
        - Most commonly occurs in the head of the pancreas
        - Most are adenocarcinomas
        - Hard, gray-white, stellate, poorly defined masses
        - Generally, obstructs the common bile duct
    - Clinical presentation (in order of likelihood)
        - Severe epigastric abdominal pain
        - Anorexia
        - Unexplained weight loss
        - Jaundice
        - Diarrhoea
        - Weakness
        - Constipation
        - Hematemesis or melena
        - Vomiting
    - Evaluation
        - Elevated ALP, 5'-nucleotidase, LDH, AST, bilirubin, amylase, alpha fetoprotein, and carcinoembryonic antigen
        - Decreased albumin
    - Treatment
        - Surgical resection
        - Systemic chemotherapy
        - Radiation therapy
    - Prognosis and complications
        - Extremely high mortality rate (5-year survival rate 20%)
        - Metastasis
            (1) Hemotogenous spread - liver, lungs
            (2) Lymph node spread – peripancreatic, aortic and extra-abdominal
            (3) Direct invasion – SMAs, portal vein, retroperitoneum, peritoneum, nearby organs

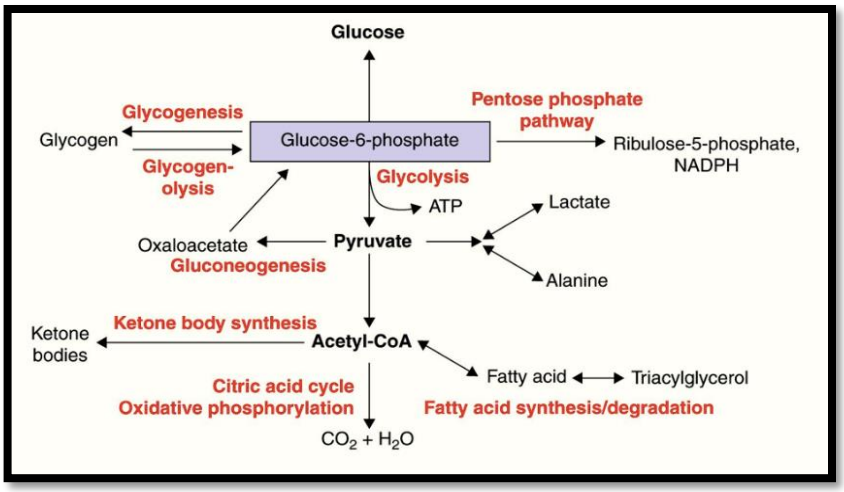
Metabolism and metabolic disease

- Metabolic pathways
    - Anabolic pathway
        - Building compounds
        - Synthesis of larger and more complex compounds from smaller precursors
        - Endothermic reaction
    - Catabolic pathway
        - Breaking down compounds
        - Breakdown of larger molecules, commonly involving oxidative mechanisms
        - Exothermic reaction, producing reducing equivalents mainly via respiratory chain, ATP
    - Amphibolic pathway

- Occurs at the crossroads of metabolism, acting as links between the anabolic and catabolic pathways
- Such as the citric acid cycle

- The fed, fasted and starving states
  - The fed state
    - 4-6 hours after eating, while the products of digestion are being absorbed, there is abundant supply of metabolic fuels
    - In this condition, glucose is the major fuel for oxidation
    - Glucose uptake into muscle and adipose tissue is controlled by insulin (secreted by beta-islet cells in the pancreas in response to increased concentration of glucose in portal blood
  - The fasting state
    - Small fall in plasma glucose
    - As fasting is prolonged, the plasma concentration of ketone bodies increases markedly
    - Glucagon predominant
  - The starving state
    - Dietary glucose and hepatic glycogen have been exhausted, yet the brain still requires glucose
    - Gluconeogenesis can provide the brain glucose
    - Substrates for gluconeogenesis include:
      Liver glycogen
      Lactate
      Glycerol
      Some AA
    - Liver glycogen is exhausted, so isn't viable option in starvation
    - Thus, ketones can be synthesized from the FFAs liberated using glycerol in gluconeogenesis
    - In normal beta-oxidation, FFA are converted to acetyl-CoA and are passed through the CAC
    - However, in starvation, the intermediate carriers within this cycle are limited
    - This shunts acetyl CoA into the ketogenic pathway
    - Because the reaction can progress in both directions, once the ketone reaches the brain, it can be converted back into acetyl CoA and pass through the CAC
  - Starvation past 7 days
    - As starvation continues past 7 days, the favored substrate gluconeogenesis becomes glycerol, resulting in protein sparing and increased concentration of ketones in the blood, reducing the requirement for glucose
    - The shift in fuel utilization is thought to be a result of decreased thyroid hormone secretion
    - Protein loss is usually the cause of death in starvation

	Fed	40 h Fasting	7 Days Starvation
Glucose	5.5	3.6	3.5
Nonesterified fatty acids	0.30	1.15	1.19
Ketone bodies	Negligible	2.9	4.5



- Glucose metabolism
  - Glucose is a major fuel source
  - (1) Dietary glucose
  - (2) Glycolysis
    - (a) Converted to glucose phosphates for further degradation
    - (b) Stored as glycogen in the skeletal muscle and liver
    - (c) Metabolised as part of the pentose phosphate pathway – RNA/DNA synthesis
  - (3) If glucose continues, it is converted to triose phosphates via glycolysis
  - (4) Converted to pyruvate via glycolysis
  - (5) Anerobic tissues metabolise pyruvate to acetyl-CoA
  - (6) Acetyl-CoA enters the citric acid cycle

- Gluconeogenesis
  - Process of synthesizing glucose from non-carbohydrate precursors such as lactate, amino acids and glycerol

- Fatty acid metabolism
  - (1) Triacylglycerol is the body's main fuel reserve
  - (2) Triacylglycerol converted to fatty acids via lipolysis
  - (3) Fatty acids are converted to acetyl-CoA via beta-oxidation
  - (4) Acetyl-CoA has three fates
    - (a) Oxidized via the citric acid cycle
    - (b) Is the precursor for synthesis of cholesterol and other steroids
    - (c) In the liver, it is used to form ketone bodies – important fuels in prolonged fasting and starvation

- Amino acid metabolism
  - (1) Essential amino acids cannot be made in the body and are required through diet – these are broken down via the citric acid cycle
  - (2) Non-essential amino acids can be made in the body via transamination
  - (3) The amino acid then undergoes deamination and amino nitrogen is excreted as urea

- The citric acid cycle
  - All products of digestion are metabolized to a common product – acetyl-CoA, which is then oxidized by TCA cycle

- Summary of metabolic homeostatic reactions

Process	Reaction	Consequence	Hormone
Glycogenesis	Glucose => glycogen	Decrease blood glucose levels	Insulin
Glycogenolysis	Glycogen => glucose	Increase blood glucose levels	Glucagon
Gluconeogenesis	AA => glucose	Increase blood glucose levels	Glucagon
Protein synthesis	AA => protein	Decrease blood AA levels	Insulin
Protein degradation (deamination)	Protein => AA	Increase blood AA levels	Glucagon
Lipogenesis	FA and glycerol => TG	Decrease blood FA	Insulin
Lipolysis	TG => FA and glycerol	Increase blood FA	Glucagon

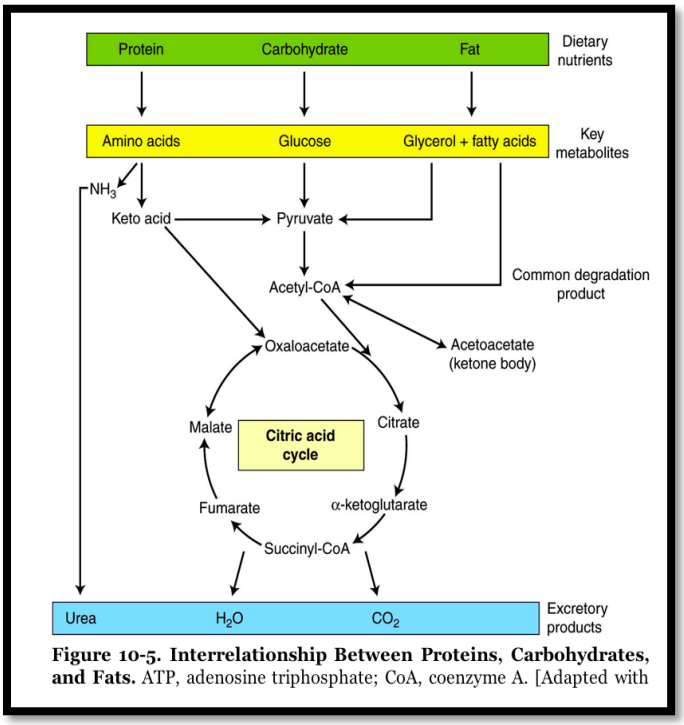


Figure 10-5. Interrelationship Between Proteins, Carbohydrates, and Fats. ATP, adenosine triphosphate; CoA, coenzyme A. [Adapted with

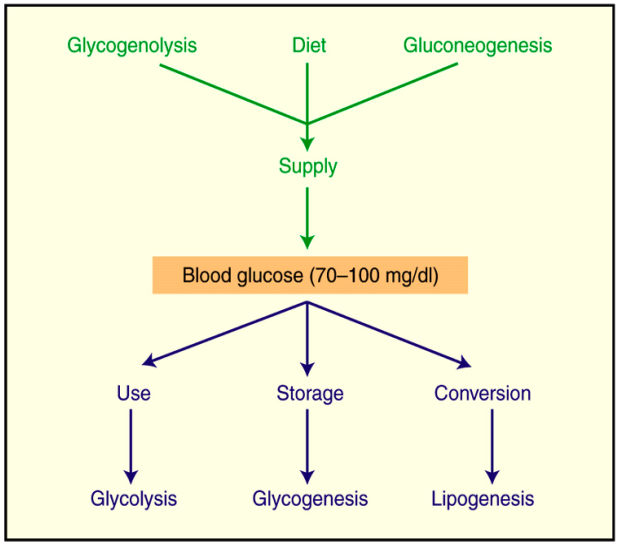


Figure 10-7. Factors Affecting Blood Glucose. [Reproduced with permission from Naik P: Biochemistry, 3rd edition, Jaypee Brothers Medical Publishers (P) Ltd., 2009.]

Several key biomolecules (glucose-6-phosphate or G6-P, pyruvate, and

Lipogenesis	FA and glycerol => TG	Decrease blood FA	Insulin
Lipolysis	TG => FA and glycerol	Increase blood FA	Glucagon

- Insulin synthesis and metabolism
  - Synthesis
    - Insulin = protein with two peptide chains
    - Stages of synthesis
      (1) Precursor to insulin = preproinsulin
      (2) Preproinsulin synthesised in ribosomes and enters ER of beta cells; here its cleaved to form proinsulin

(3) Proinsulin is transported to Golgi apparatus and packaged into vesicles
(4) Whilst inside the vesicle, proinsulin is cleaved in two parts to form insulin

- 50% of insulin is catabolized on its first pass through the liver

- Regulation of insulin secretion
  - Glucose is the primary stimulant of insulin release
  - Stages of regulation
    (1) Glucose enters pancreatic beta cells facilitated by one or more glucose transporters (GLUT1, GLUT2, GLUT3)
    (2) Once in the cell, metabolism of glucose stimulated secretion of insulin
  - Insulin secretion can also be regulated by enteric hormones, such as glucagon-like peptide 1

GLUT transporters	GLUT1- glucose across BBB GLUT2-beta cells, kidney GLUT3-glucose into neurons GLUT4-most body cells, resting skeletal muscle, adipose • Not present in the plasma membrane in the absence of insulin, whereas all others are present • Muscle contraction triggers insertion of GLUT4 into exercising muscle cells in the absence of insulin; important for managing DM

- Mechanism of insulin activation
  - Stages of action
    (1) Insulin binds directly to insulin receptors present on surfaces of target cells (liver, muscle, fat) and nonclassic target tissues (ovary)
    (2) Binding of insulin to its receptors causes activation of the tyrosine kinase region of the receptor
    (3) Activation of tyrosine kinase region causes activation of the whole receptor
    (4) Activation of the insulin receptor initiates a phosphorylation cascade within the cell, beginning with the phosphorylation of a network of docking proteins (insulin receptor substrates) that engages with signaling molecules downstream

- The effects of insulin
  - Fuel homeostasis in liver, muscle and fat
  - Liver
    - Insulin promotes fuel storage by stimulation of glycogen synthesis and storage
    - Inhibits hepatic glucose output by inhibiting gluconeogenesis (glucose synthesis) and glycogenolysis (glycogen breakdown)
    - Insulin stimulates lipogenesis
  - Muscle
    - Insulin promotes storage of glucose by stimulating glycogen synthesis and inhibiting glycogen catabolism
  - Adipose tissue
    - Insulin stimulates lipoprotein lipase >> enzyme that hydrolyses the triglycerides carried in VLDLs

- When is insulin secretion INCREASED?
  - High blood glucose
  - High blood AA (arginine, lysine, leucine)
  - High blood FA
  - Incretins like GIP, which causes insulin secretion in response to oral glucose load

- Parasympathetic activation (vagal stimulation, due to eating)

- When is insulin secretion DECREASED?
  - Decrease in blood glucose
  - Somatostatin
  - Catecholamines

- Glucagon synthesis and metabolism
  - Produced in alpha cells of the pancreas + (intestine and brain)
  - Stages of synthesis
    (1) Proglucagon – precursor protein undergoes proteolytic processing
    (2) Metabolised in liver and kidneys

- Regulation of glucagon secretion
  - Glucagon secretion is inhibited by glucose, somostatin, and two additional beta cell secretory products

- Mechanism of glucagon action
  - Main role is to maintain normal glucose levels during fasting by inducing hepatic glucose production, thus counteracting the hepatic effects of insulin
  - Activation
    (1) Glucagon binds to a GPCR present on the surface of all hepatocytes, activating adenylyl cyclase and generating cAMP
    (2) cAMP activates protein kinase A
    (3) Protein kinase A activated gene transcription for the enzymes responsible for the activity of glucagon in the liver
- Effects of glucagon
  - Counter-regulatory hormone to oppose the effects of insulin
  - Injections used to treat severe hypoglycemia
  - Hepatic effects include:
    (1) Increased hepatic glucose output via release of glycogen stores
    (2) Increased hepatic uptake of amino acids, which fuels gluconeogenesis
    (3) Stimulation of fatty acid oxidation and ketogenesis

- When is glucagon secretion INCREASED?
  - Low blood glucose
  - Ketosis, starvation
  - High blood AA (esp. arginine)
  - CCK (alerts alpha cells to a protein meal)
  - Catecholamines (beta receptors only)

- When is glucagon secretion DECREASED?
  - High blood glucose
  - Insulin presence
  - Somatostatin presence

- Regulation of appetite
  - Energy requirements in a healthy person
    - Amount of energy required in a day is a combination of a person's basal metabolic rate (BMR), activity levels, thermic effect of food, as well as stress, disease, and hormonal status

        - This energy can come from ingested food or stored fat, which the satiety center of the brain determining the favored source
    - What is the site of feeding and satiety regulation?
        - The hypothalamus, specifically various nuclei within the hypothalamus have different effects on feeding
    - What is the major feeding center?
        - Lateral nuclei of hypothalamus
    - What is the major satiety center?
        - Ventromedial nuclei of hypothalamus
    - What is the role of the arcuate nucleus in satiety and feeding?
        - Provides general input to both lateral nuclei and ventromedial nuclei
    - What are the five main inputs to the arcuate nucleus regarding satiety?
        - Blood glucose levels
        - Vagus afferent (signaling of stomach stretch)
        - GI hormones (CCK, peptide YY, insulin)
        - Leptin from adipose tissue, secreted in increasing amounts as the cells grow
        - Ghrelin from the stomach during fasting to stimulate appetite

- BMI
    - BMI = mass (kg) / height $(m)^2$
    - <18.5 = underweight
    - 18.5 – 24.9 = good
    - 25.0 – 29.9 = overweight
    - 30.0 + = obese

- Diabetes mellitus
    - General considerations
        - Heterogeneous disorder defined by the presence of hyperglycemia
        - Diagnostic criteria:
            (1) Fasting plasma glucose of 126 mg/dL or more
            (2) Classic symptoms of hyperglycemia plus a random plasma glucose of 200mg/dL or more
            (3) Plasma level of 200mg/dL or more after an oral dose of 75g of glucose (oral glucose tolerance test)
            (4) HbA1c level of 6.5% or more
    - Pre-diabetes
        - Defined by a fasting blood glucose level of 100-125mg/dL or a 2 hour OGTT glucose level of 140-200mg/dL
    - Type 1 diabetes
        - Pathophysiology
            (1) In early disease, lymphocytic infiltrates of macrophage activating CD4+ cells and cytokine secreting CD8+ cells surround the necrotic B-cells in the pancreas
            (2) The autoimmune destruction of these B-cells occurs gradually over years until there sufficient B-cell mass is lost to cause symptoms of insulin deficiency
            (3) At time of diagnosis, ongoing inflammation is present in some islets, whereas others are atrophic and consist of only glucagon-secreting alpha cells and somatostatin secreting delta cells
    - Type 2 diabetes
        - Pathophysiology
            Two metabolic effects are responsible for hyperglycemia in DMII – target tissue resistance to the effects of insulin and inadequate pancreatic B-cell insulin secretion in the setting of insulin resistance

(1) Nutritional excess of any sources leads to increased free fatty acid storage as triglyceride in adipose tissue
(2) Increased release of various factors from adipose tissue (particularly visceral adipose tissue), drives insulin resistance
(3) Increased insulin resistance causes:
Toxic effects of excess FFAs released from adipose tissue – lipotoxicity
Dysregulated secretion of fat-specific proteins – adiponectin, leptin
Increased production of inflammatory cytokines within adipose tissue – TNF

- Visceral adipose tissue most closes correlated with insulin resistance since its most susceptible to increased lipolysis – therefore the more visceral fat, the higher the likelihood for DMII

- Clinical presentation (both types)
  - No matter the type, both result in deficiency of insulin action and a high glucagon-insulin ratio >> metabolic derangement develops
  - Polyuria and nocturia
  - Polydipsia
  - Polyphagia
  - Weight loss
  - Tiredness
  - Lack of interest and concentration
  - Tingling sensation or numbness in hands and feet
  - Blurred vision
  - Frequent infections and slow healing wounds
  - Hypertension
  - Orthostatic hypertension – due to autonomic neuropathy
  - Diabetic retinopathy
  - Diabetic foot – diminished pedal pulses, foot ulcers, pitting oedema, atropic hair changes, decreased sensation
  - Post-prandial hyperglycemia - inability of insulin sensitive tissues to clear glucose loads
  - Fasting hyperglycemia - occurs when there is severe loss of insulin action and glucagon's effects on the liver are not counterbalanced
- Comparison of type 1 and type 2

Features	Type 1 diabetes	Type 2 diabetes
Age at diagnosis	Childhood	Adulthood
Prevalence	0.2%	11% - common
Risk factors	Genetic susceptibility Viruses (enterovirus, mumps, rubella) Toxic chemicals Exposure to cow's milk in infancy Cytotoxins	Age >45 Obesity Family Hx of DMII Hispanic, native American, Asian American and pacific islander heritage Hx of impaired OGTT Hypertension Dyslipidemia Hx of gestational diabetes/pre-eclampsia Polycystic ovarian syndrome

		Depression Schizophrenia
Pathogenic pathway (described above)	Autoimmune destruction of pancreatic beta cells by T lymphocytes targeting ill-defined B-cell antigens; with resultant severe insulin deficiency	Increased resistance to the effects of insulin at its sites of action and a decrease in insulin secretion by the pancreas Insulin resistance is the hallmark
Beta cell insulin secretion abnormal	Absolute deficiency	Impaired secretion
Insulin resistance	No	Yes
Obese	No	Yes
BMI	Usually <25	>25
Autoimmune diseases	Yes	No
Environmental triggers	Viral infections, dietary exposures, vitamin D deficiency	Obesity
Incidence in offspring (both parents affected)	10%	50%
Genetic loci associated with risk	HLA class II genes Specifically, DR, DQ and DP	Heterogeneous sets of interacting genes: HNF-4-alpha Glucokinase gene HNF-1-alpha IPF-1
Treatment	Insulin treatment Glycemic control Self-monitoring Diet and exercise	Lifestyle modifications Medications (sulfonylureas, incretins, metformin)
Complications	Diabetic ketoacidosis (common) Increased risk of infections Microvascular complications Macrovascular complications Neuropathies	Diabetic ketoacidosis (rare) Hyperosmolar coma Hypoglycemia – from treatment Nephropathy – glomerulosclerosis Neuropathy – autonomic and polyneuropathy Retinopathy Coronary artery disease Cerebrovascular disease Peripheral vascular disease Foot ulcers Infections Skeletal fractures – lower bone mass

- Diabetes treatment (depends on the stage and severity of disease)

Drug class	Drug name	Details	AEs	Type 1 Diabetes	Type 2 Diabetes
Rapid acting insulin	Lispro insulin Glulisine insulin Aspart insulin	Substitutes components of the beta chain to allow the drug to be absorbed more quickly 5-10-minute onset of action		✓	✓

Short acting insulin	Regular insulin	A preparation of zinc insulin crystals in solution 0.5-hour onset of action		✓	✓
Intermediate acting insulin	NPH insulin	Crystalline suspension of human insulin with protamine and zinc 1-2-hour onset of action		✓	✓
Long acting insulin	Lantus Levemir	Does not have a peak, producing a relatively stable level lasting more than 24 hours		✓	✓
Glucose solution		Bolus used to treat hypoglycemia		✓	✓
Biguanide	Metformin	Lowers basal and postprandial plasma glucose levels; by decreasing hepatic gluconeogenesis production	Lactic acidosis		✓
Sulfonylureas	Glyburide Glimepiride	Stimulate insulin release from pancreatic beta cells and probably have the best efficacy for glycemic lowering	Risk of hypoglycemia Weight gain		✓
Glucagonlike peptide – 1 agonists	Exenatide Liraglutide Albiglutide	Stimulate glucose dependent insulin release, reduce glucagon and slow gastric emptying	Nausea Vomiting Weight loss URTI		✓
Meglitinide derivatives	Repaglinide Nateglinide	Similar MOA to above, except shorter acting	Hypoglycemia		✓
Alpha-glucosidase inhibitors		Prevent postprandial glucose surges	GI disturbances		✓
Thiazolidinediones	Rosiglitazone (Avandia)	Insulin sensitizers; thus, requiring the presence of insulin Must be taken for 12-16 weeks to take maximal effect Not used much anymore	Weight gain Oedema Hepatotoxicity		✓
Dipeptidyl peptidase IV inhibitors	Sitagliptin Saxagliptin Linagliptin	Prolong the action of incretin hormones (hormone that stimulates insulin secretion in response to meals – GLP-1 amd GIP)	URTI Weight neutral		✓

    - DMII – Metformin first, then add a drug, then start triple therapy
    - Some people with DMII become insulinpenic and the only thing that can correct this is insulin (red ticks are last resort)
- Pathophysiology of microvascular diabetes complications
    - (1) Increased polyol pathway flux
    - (2) Increased formation of advanced glycation product (AGE)
    - (3) Activation of protein kinase C
    - (4) Increased hexosamine pathway flux
    - Result of these pathways = increase in protein accumulation in vessel walls, endothelial cell dysfunction, loss of endothelial cells and occlusion of the vessels
- Goals of diabetes management
    - Fasting BSL should be 5-7mmol/L
    - Post-prandial BSL should be <10
      Monitor BSL via glucometer

- HbA1c should be 6.5-7%
- Measures glycosylation of hemoglobin (Hb); the higher the BSL, the more glycosylated the Hb; RBC circulate for 3 months, and so taking a HbA1c every 3 months will give a good idea of glycemic control (caveat: HbA1c is not indicative of high and low glucose levels - it is only an average)
- Avoid hypoglycemia
- Tight control of CVS risks
  BP control
  Lipid control
  Obstructive sleep apnea
  Obesity control
  Smoking cessation

- Gestational diabetes
  - General considerations
    - Occurs in pregnant women and tends to resolve once the baby is delivered
    - More common in the second half of gestation, precipitated by increasing levels of hormones such as chorionic somatomammotropin, progesterone, cortisol and prolactin that all have a counter regulatory anti-insulin effects
    - Tested at 24 weeks' gestation via OGTT

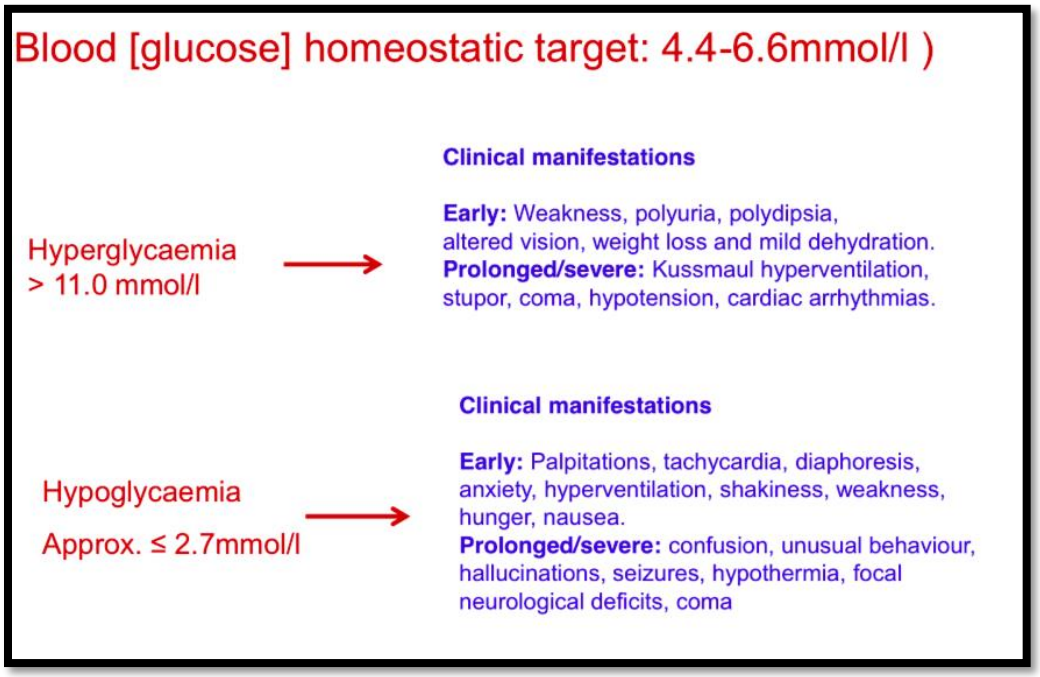
- Latent autoimmune diabetes in adults (LADA)
  - Same pathogenesis as T1DM, but slower autoimmune destruction of B cells
  - Mixed phenotype - older, more range in BMI
  - The disease can be mistaken for T2, patient may have been on oral medications for several months
  - + autoantibodies
  - Eventually need insulin
  - Risk of DKA

- Maturity onset diabetes of the young (MODY)
  - Variety of monogenic mutations in genes controlling glucose sensing and insulin secretion
  - Strong family history
  - Hyperglycemia from a very young age, not discovered until later
  - Responds to sulfonylureas
  - GK (glucokinase mutation)

- Hypoglycemia
  - Complication of insulin treatment in both DMI and II (type I especially prone due to almost absent glucagon response to hypoglycemia)
  - Often occurs with exercise or fasting
  - Symptoms
    - Tremor / shakiness
    - Anxiety
    - Palpitations and tachycardia
    - Sweating
    - Hunger
    - Weakness / fatigue
    - Confusion and headache

        - Difficulty speaking
        - Seizures
        - Night sweats / nightmares / restlessness / morning headache
        - Coma
    - Treatment
        - Rapid oral administration of glucose at the onset of warning symptoms

- Hyperglycemia
    - Clinical presentation
        - Glycosuria
        - Osmotic diuresis
        - Polyuria
        - Dehydration
        - Polydipsia
    - Retinopathy
        - Pathogenesis: proliferating retinal vessels hemorrhage into vitreous fluid, increasing pressure on the macula, leading to blindness
        - Symptoms: asymptomatic until late; curtain falling, floaters, decreased visual acuity
        - Findings: microaneurysms, dot and blot hemorrhages, hard exudates, cotton wool spots, neovascularization, vitreous hemorrhages, macular edema
        - Treatment: improve glucose control, improve BP control, laser, VEGFi, vitrectomy
    - Nephropathy
        - Pathogenesis: hyperglycemia, hyperfiltration, glomerular sclerosis
        - MCC of renal failure/dialysis, as it is asymptomatic until CKD manifests
        - Early stage =>> increased eGFR, increased globerular size and microalbuminuria
        - Late stage >> increasing proteinuria, marked decline in eGFR, uremia
        - Treatment: blood glucose control, BP control, ACEi
    - Neuropathy
        - Pathogenesis: Microangiopathy in small vessels around nerves and altered glucose metabolism in nerves
        - Can present:
          Peripheral >> symmetric length-dependent sensory polyneuropathy or paresthesia
          Gastroparesis
          Autonomic
          Polyradiculopathy mononeuropathy
    - Ischemic heart disease
        - Present normal, with atypical symptoms (SOB, vomiting, HF) or none
        - Treat: glucose control, BP, lipids, smoking cessation, weight-loss, aspirin, stenting
    - Stroke
        - 1.5x risk
        - Treat: typical stroke - anti-platelets, BP, lipids, smoking cessation
    - Peripheral vascular disease
        - Intermittent claudication, gangrenous toe
        - Treat: normal - anti-platelets, BP, lipids, smoking cessation, weight-loss, angioplasty



- Hyperosmolar hyperglycemic state
  - General considerations
    - Hyperglycemia, hyperosmolar, little or no ketoacids
  - Etiology
    - Inadequate treatment of DM and underlying illness
    - Decreased water intake, leading to a gradual, but severe dehydration
  - Pathogenesis
    - From inadequate, but present, amount of insulin and increased regulatory hormones
  - Clinical presentation
    - Irritability
    - Restlessness
    - Stupor
    - Muscle twitching
    - Hyperreflexia
    - Spasticity
    - Seizure
    - Coma

- Metabolic syndrome
  - General considerations
    - Multiplex risk factor that arises from insulin resistance accompanying abnormal adipose tissue deposition and function
    - Major risk factor for chronic diseases
  - Clinical presentation
    - Hypertension
    - Hyperglycemia
    - Hypertriglyceridemia
    - Reduced HDL cholesterol

- Abdominal obesity
- Chest pains and dyspnea
- Acanthosis nigricans, peripheral neuropathy and retinopathy
- Xanthoma's or xanthalasma

- Etiology
  - Risk factors: family history, poor diet and inadequate exercise, African American ethnicity, affects men and women almost equally
  - Caused by adipose tissue dysfunction and insulin resistance
- Evaluation
  - ECG for cardiovascular complaints
  - Cardiovascular risk assessment
  - Sleep related breathing disorder investigations
- Treatment
  - Lifestyle modifications
  - Medications (treatment of co-morbidities)
    (1) Biguanide – Metformin
    (2) Thiazolidinediones – Rosiglitazone
    (3) Statins – Atorvastatin, Lovastatin, Simvastatin
    (4) ACE inhibitors – Captopril, Enalapril, Lisinopril
    (5) Angiotensin II receptor blockers – Losartan, Valsartan
    (6) Lipid lowering non-statin agents – Niacin, Gemfibrozil
    (7) Antiplatelets – Aspirin

- Pediatric metabolic acidosis
  - General considerations
    - Acid base disorder characterised by a decrease in serum pH that results from either a) a primary decrease in plasma bicarbonate concentration or b) an increase in hydrogen ion concentration
  - Clinical presentation
    - Anorexia, weight loss, vomiting, diarrhoea
    - CNS features: headache, lethargy, confusion, AMS, cerebral oedema, seizures
    - Respiratory features: tachypnea, respiratory distress and hypoxemia
    - Tachycardia – due to myocardial depression
    - Dry mucous membranes, delayed capillary refill
    - Failure to thrive
    - Polyuria, polydipsia – fruity fetor
    - Hyperkalemia arrhythmias – due to excess hydrogen ions moving intracellularly and potassium moving extracellularly
    - Oxygen-hemoglobin dissociation curve shifts to the right, decreasing hemoglobin's affinity for oxygen and therefore oxygen is released into the tissues
  - Etiology
    - MUDPILES: methanol, uremia, diabetic ketoacidosis, paraldehyde, iron, lactic acid, ethanol, salicylates
  - Pathophysiology
    - Primary metabolic acidosis
      pH less than 7.35 in the absence of elevated $PaCO_2$
      1/3 mechanisms: (1) increased production of acids (2) decreased excretion of acids (3) loss of alkali

(1) Acutely, medullary chemoreceptors compensate for the acidosis through increased alveolar ventilation – resulting in tachypnea and hyperpnoea
(2) The kidneys begin to compensate 12-24 hours after hyperventilation starts – to reclaim filtered bicarbonate and eliminate daily acid load generated from protein metabolism

- Evaluation
  - ABG – acidaemia
  - CBC, EnLFTS, BUN, creatinine, serum glucose levels and urinalysis
  - Echocardiography – reveal left sided obstructive lesion or cardiomyopathy
- Treatment
  - Bicarbonate therapy (sodium bicarbonate and tromethamine)
  - Thiamine therapy if indicated
  - Hemodialysis
- Complications
  - If untreated, can result in myocardial depression, seizures, shock and multiorgan failure

- Diabetic ketoacidosis
  - General considerations
    - Acute, life threatening complication of diabetes
    - Mainly occurs in patients with DMI but can occur in DMII
    - Complex disordered metabolic state – hyperglycemia, ketoacidosis and ketonuria
    - Anion gap metabolic acidosis
  - Clinical presentation
    - Malaise, generalised weakness and fatigability
    - Nausea and vomiting – may be associated with diffuse abdominal pain, decreased appetite and anorexia
    - Rapid weight loss
    - History of failure to comply with insulin therapy
    - Decreased perspiration
    - Altered consciousness
    - Signs of possible intercurrent infection >> fever, coughing, chills, chest pain, dyspnea, arthralgia
    - O/E: dry skin and mucous membranes, Kussmaul's breathing, decreased skin turgor, decreased reflexes, characteristic acetone breath, tachycardia, hypotension, tachypnea, hypothermia
  - Pathophysiology
    - (1) Occurs because of insulin deficiency that is accompanied by an increase in counter regulatory hormones (glucagon, cortisol, growth hormone, epinephrine)
    - (2) This hormonal imbalance enhances hepatic gluconeogenesis, glycogenolysis and lipolysis
    - (3) Hepatic gluconeogenesis and glycogenolysis results in hepatic metabolism of FFAs as an alternative source of energy, resulting in accumulation of acidic intermediates and ketones >> ketones include acetone, beta-hydroxybutyrate and hydroxy acid
    - (4) Ketone bodies are produced from acetyl co-A within the mitochondria of hepatocytes
    - (5) High levels of acetyl-coA present in the cell inhibits pyruvate complex >> thus inhibiting the citric acid cycle
    - (6) Acetyl-coA is rerouted to ketogenesis
    - (7) Progressive rise in acidic substances causes ketonemia, and eventually exceed the body's capacity to extract them >> overflowing into urine (ketonuria)

        - (8) If not treated, metabolic acidosis occurs with a significant drop in pH and bicarbonate serum levels and Kussmaul's breathing
    - Evaluation
        - Elevated anion gap >> anion gap = [Na + K] – [Cl + HCO3] – where unmeasured anions exceed unmeasured cations in the blood
        - CBC – leukocytosis with intercurrent infection
        - Plasma osmolarity >> elevated
        - Serum potassium >> elevated
        - Serum sodium, chloride and phosphorus >> decreased
        - Possibly elevated >> serum glucose, bicarbonate levels, amylase and lipase levels, ketone levels, serum cbeta-hydrobutyrate levels, blood urea nitrogen and creatinine levels
        - Urine dipstick – ketones present
        - ABG – metabolic acidosis (low bicarbonate and low pH)
        - ECG – DKA can be precipitated by a cardiac event; assess for arrhythmia due to electrolyte imbalance
        - CXR – rule out pulmonary infection
        - CT head – detection for cerebral oedema which requires immediate treatment
        - MRI head – used if altered consciousness is present
    - Management
        - Fluid resuscitation >> saline
            1-3L during first hour
            1L in second hour and then every two hours
        - Reversal of acidosis and ketosis >> sodium bicarbonate
        - Reduction of plasma glucose concentration to normal >> rapid acting (insulin aspart, insulin lispro) and short acting (regular insulin)
        - Replenishment of electrolytes and volume losses >> potassium chloride
        - Identify underlying cause
    - Complications
        - Cerebral oedema is the most common cause of mortality >> if this is established, mannitol should be administered
        - Respiratory distress
        - Infection
        - Cerebrovascular event or MI
        - Late hypoglycemia
        - Hypophosphatemia
    - Prognosis
        - 2% mortality rate in developing countries
        - Worst prognosis is seen in older patients with severe intercurrent illnesses, especially when they aren't placed in ICU

- Glycogen storage disease
    - von Gierke disease
        - Most common
        - Results from deficiency of enzyme glucose-6-phosphotase
        - Impairs the livers ability to produce free glucose from glycogen

        - Convulsions, cyanosis, irritability, pallor, loss of consciousness, apnea and tremors
    - (II) Acid maltase deficiency / Pompe disease
        - Deficiency of a lysosomal enzyme that normally converts glycogen to monosaccharides
        - Results in glycogen accumulation in the tissues
        - Has an infantile, juvenile and adult form
        - Exertional dyspnea, morning headaches, orthopnea, proximal myopathy
    - (III) Forbes-Cori disease or limit dextrinosis
        - Glycogen stored in the liver and skeletal muscle has an abnormal structure
        - Enlargement of the stomach, hepatomegaly, muscular weakness and hypotonia
    - (IV) Andersen disease / amylopectinosis
        - Rare disease that leads to premature death
        - Liver insufficiency and abnormalities of the heart and nervous system
        - Weeks after birth – failure to thrive, hypotonia and atrophy of the muscles
    - (V) McArdle disease
        - Affects skeletal muscles via glycolytic pathway
        - Appears 10-20 YOA
        - Fatigue during physical exertion, muscle cramps, muscle weakness, red-coloured urine
    - (VI) Hers disease
        - Deficiency of hepatic phosphorylase and other enzymes from this cascade activate this disease
        - Minimal symptoms
    - (VII) Tarui disease
        - Phosphofructokinase deficiency located in skeletal muscles and erythrocytes
        - Intolerance to physical activity, muscle cramps, red coloured urine, attacks of rhabdomyolysis

- Galactosemia
    - General considerations
        - Defect in galactose metabolism, usually a deficiency of galactose kinase or galactose-1-phosphate uridultransferase (GALT)
        - This results in elevated serum and urine galactose levels
    - Clinical presentation
        - Infantile cataracts
        - Failure to thrive / poor growth
        - Hepatomegaly
        - Mental retardation >> due to accumulation of galactose derivatives in neurons
        - Milk intolerance
        - Hypoglycemia
        - Proteinuria and liver dysfunction >> due to accumulation of galactose derivatives
    - Treatment
        - Avoidance of dietary galactose

- Phenylketonuria
    - General considerations
        - Phenylalanine hydroxylase deficiency
        - Toxic accumulation of phenylalanine and lack of tyrosine

- Clinical presentation
  - CNS developmental delay
  - Seizures
  - Fair hair, blue eyes, pale >> impairment of melanin synthesis
  - Musky odor
  - Eczema
  - Light sensitivity
  - Higher incidence of pyogenic infections
- Evaluation
- Management
  - Restriction of dietary phenylalanine
  - Supplement with tyrosine

- Maple syrup urine disease (MSUD)
  - General considerations
    - Lack of AA debranching enzymes (isoleucine, valine, leucine) specifically alpha-ketoacids dehydrogenase
    - Toxic accumulation of branched-chain AA, especially leucine, and ketoacids derivatives
    - Can't DISPOSE OF these AA
  - Clinical presentation
    - Poor feeding
    - Severe acidosis
    - Coma
    - Seizures
    - Maple syrup odor to urine
  - Treatment
    - Dietary restriction - no branched chain AA

- Lesch-Nyhan disease
  - General considerations
    - A rare, X-linked recessive disorder caused by defective HGPRT enzyme
    - Pathway that functions to salvage purine metabolites such as hypoxanthine and guanine, preventing them from being unnecessarily degraded and then renally excreted as uric acid
    - The salvage pathway recycles these metabolites to replenish the purine bases guanine and adenine by the action of HGPRT enzyme
  - Clinical presentation
    - Increased uric acid
    - Spasticity
    - Neurological effects
    - Aggressive behavior
    - Self-mutilation
  - Treatment
    - Reduce consumption of purines (meat, poultry, shellfish)
    - Xanthine oxidase inhibitors (allopurinol)