CONGENITAL

Fistula. Fistulas often occur together with atresias. Atresias are where a tube (in this case the esophagus) ends in a blind pouch. A Fistula is where a tube connects to another tube. A Tracheoesophageal fistula is a connection between the trachea and the esophagus. Over 80% of these lesions occur with atresia of the proximal esophagus, and a fistula of the distal esophagus to the trachea. This means that when the baby swallows, the food goes into the trachea! This is pretty clear early on, presenting with dysphagia (spitting up, not vomiting, food), and Coughing + Cyanosis during feeding. Air in stomach may be seen as well. This must be surgically corrected, which is easy to do.

Webs. Esophageal webs are simply extensions of mucosal epithelium into the lumen of the esophagus. They act as nets which can catch food trying to be swallowed. This presents with dysphagia and foul breath as the food that gets stuck putrefies in the esophagus. Webs are associated with Plummer-Vinson Syndrome from the Heme block, presenting with iron deficiency anemia and an increased risk for squamous cell carcinoma. These will persist into adulthood.

Achalasia. This is a failure of the LES to relax. When food is swallowed, it cannot pass into the stomach, causing distension of the esophagus (megaesophagus) and dysphagia. Over time, the food is pushed through the tight sphincter. It is caused by death of ganglionic cells in the LES. It is corrected surgically by either placing a stent or resecting the faulty zone. Presents with a “bird’s beak” appearance of the gastro-esophageal junction on gross and with barium swallow.

HEMORRHAGE

Mallory-Weiss Tears. These are longitudinal hemorrhages often found at the gastro-esophageal junction in patients who undergo severe retching. Patients at highest risk include alcoholics and bulimics (differential is based on age, cirrhosis, and palmar calluses on hands). These are usually not fatal, and will spontaneously heal as will the hemorrhage.

Esophageal Varices. Caused by portal hypertension associated with liver failure and cirrhosis, the formation of porto-caval shunts produces hemorrhoids, caput medusa, and esophageal varices. These tortuous and distended veins of the esophagus are prone to rupture. Small mechanical manipulation (swallowing) is enough to cause them to tear, vomiting (cirrhotic liver from alcoholic) has the greatest risk. With rupture, these cause fatal hemorrhage presenting as hematemesis and melena. This is a surgical emergency. The people at risk for developing them (alcoholics) are also at risk for tears.
ESOPHAGITIS

GERD. Gastroesophageal Reflux Disease is where the acidic content of the stomach refluxes through the LES, and damages the esophagus. Reflux is caused by a weakened LES, allowing the reflux. Slowing of gastric emptying (overeating or fatty meals), Sliding Hiatal Hernias, Weakening of LES (chocolate, alcohol, cigarettes), and laying down all ↑ symptoms of GERD. On inspection, there may be simple hyperplasia (increased redness). A buzzword for reflux is on histologic section, called basal zone hyperplasia (the germ cells of the basal layer are revved up to accommodate the damage done to the mucosal epithelium by the acid). Patients often complain of a retrosternal/epigastric burning which is alleviated by food. While a nuisance, GERD in and of itself does not do much. However, it is the driving stimulus which leads to Barrett’s Metaplasia.

Barrett’s Esophagus. In the continuum between GERD and cancer lays Barrett’s Esophagus. Continual acidic damage to the musical epithelium induces a metaplastic change from squamous epithelium to gastric/intestinal epithelium. This is a columnar epithelium with goblet cells. This change in tissue is a protective measure; this tissue can withstand the acidic contents of the stomach. On endoscopy it appears as a velvety salmon-colored epithelium that is often difficult to spot. Patients will state that they had epigastric burning for decades, which then stopped spontaneously. Yay! They aren’t burning anymore, but unfortunately, this metaplasia is precancerous, giving rise to the dysplasia that accompanies adenocarcinoma (30-40x ↑ Risk for Adenocarcinoma).

Chemical. This is sort of the “other” pile for esophagitis, and is low yield. In addition to the acid from the stomach, if you drink battery acid or ingest lye, you can irritate the lining of the esophagus (wow, no kidding).

CANCER

Squaumous Cell Carcinoma. This is the leading esophageal cancer worldwide, falling behind adenocarcinoma in the U.S. It is a typical squamous cell carcinoma that progresses through dysplasia, carcinoma in situ, then to full blown carcinoma. It resembles all other squamous cell carcinomas up to this point, with some unique symptoms since it’s on the esophagus. Weight Loss is common to all tumors, but Hemorrhage and Dysphagia are more unique to the esophagus. While these symptoms are not unique to SCC, when a patient progresses from solid foods to liquids with progressive difficulty, AND has a weight loss, it is most likely cancer. You will have to look to see if it is SCC or Adenocarcinoma.

Adenocarcinoma. This is the leading esophageal cancer in the US, gaining ground over SCC because of our obese population and accelerated rates of GERD. While this tissue looks like duodenum/gastric tissue (columnar epithelium with glands) it presents very much like SCC. Dysphagia, Hemorrhage, and Weight Loss all point towards a tumor. A history of GERD or Barrett’s makes you suspect for Adenocarcinoma over SCC, but you will have to do a biopsy to determine it. Up to this point, treatment of the reflux with proton pump inhibitors would have been curative, reversing the damage to the esophagus and reversing metaplasia. Once adenocarcinoma has formed, therapy is no longer curative. Resection is required (often a poor prognosis).
CONGENITAL

**Diaphragmatic Hernia.** This is a congenital defect represented by a *hole in the diaphragm* though which the *stomach or intestine* may herniate. If severe enough, the bowel may compress and inhibit the development of the lungs, leading to *pulmonary hypoplasia*. If allowed to persist, it may even cause strangulation or incarceration of the bowel that has herniated through. Usually occurs on the *left side*. We learned about this in Pulmonary Block, “Foramen of Morgagni and Bochdalek.”

**Hiatal Hernia.** *Sliding Hiatal Hernias* are usually acquired hernias of the stomach through the diaphragm. This causes the stomach to rise above the LES, opening the LES and permitting reflux. It is one of the risk factors for GERD. There is no risk of strangulation or incarceration. In a *nonsliding hiatal hernia*, pieces of the stomach other than the cardia herniate through the diaphragm increasing risk of strangulation and incarceration of the stomach, which lead to ischemia and infarction.

**Pyloric Stenosis.** This is *either congenital* (at birth) or *acquired* (tumor or ulcer at the pyloric valve). Regardless of the cause, the patient is unable to push food through the outlet valve of the stomach, resulting in *nonbiliary projectile vomiting after eating* (the stomach is still contracting, but the pylorus won’t open, so the gastric contents have to go somewhere, which is back out the hole). Look for an *abdominal olive-like mass* in the vignette. Treat with *myotomy* to resect excess muscle in the way.

**Menetrier’s Disease.** A disease of *middle-aged men* which is represented by *large gastric folds* throughout the body and fundus. There is a proliferation of mucous cells, replacing the chief and parietal cells. There is an *increased risk of gastric cancer*, ↓*acidic content*, and *hypochloridia* of the stomach. This produces a *protein losing enteropathy* malabsorption.

**Zollinger-Ellison.** A *gastrin-secreting tumor* of the *pancreas*, causing *increased rugal fold size* and an ↑*acidic content* of the stomach. This patient is at risk for *multiple peptic ulcers*. Gastrin levels will be elevated in blood at all times, inducing proliferation of the chief cells. Treated with PPIs and resection. If the patient has *multiple* or *intractable duodenal ulcers*, and H. Pylori is not present as an option choice or the test for it is negative, look for evidence of this disease.
GASTRITIS

Acute Gastritis. This is inflammation of the superficial mucosal barrier. It is caused by lapse of mucosal barrier (NSAIDs, Ischemia, Duodenal Regurgitation) or increased acidic environment (↑Parietal cells in Zollinger-Ellison). There may be erosion of the mucosal layer, ulceration into the deeper layers, or hemorrhage. This is usually an upper GI bleed, presenting as melena (dark tarry stools). These patients will present with an epigastric pain, usually alleviated by food.

Acute Peptic Ulcer. If gastritis gives way to an ulcer, it is given a special category. Ulcers are usually punched-out lesions; well circumscribed holes in the gastric mucosa. They are associated with the same risk factors as acute gastritis; just now we have a deeper hole. In order to be an ulcer, the lesion must erode past the muscularis mucosae. When due to trauma or burns, it is called Curling’s Ulcer. When due to increased intracranial pressure, it’s called Cushing’s Ulcer. These ulcers are common in the ICU setting. Remove the offending stressor for treatment. See ULCERS for more information on ulcers.

Chronic/Atrophic Gastritis. There is chronic inflammation of the mucosa that leads to atrophy of the folds. There are two important types. Type A is the fundic type, caused by the generation of autoantibodies to the parietal cells and/or intrinsic factor of the fundus and body. This kills the parietal cells, causing the resultant loss of folds and reduction in stomach acid. This leads to malabsorption. You will see flattened rugal folds. Under the scope you can see lymphocytes and the absence of parietal cells. This is called pernicious anemia when there is B12 deficiency. Type B is the antral type, and is far more high-yield than Type A. Type B is “Bug” type. It is caused by H. Pylori Infections. H. pylori is associated with Atrophic Gastritis, Gastric Ulcers, Duodenal Ulcers, Gastric Carcinoma, and even MALTomas. It is an ugly bug discussed in the GI infection section. Some highlights are included here. H. Pylori lives within the mucous layer and secretes urease that cleaves urea, offering its own buffer. It also has two cytotoxic proteins that damage the epithelial layer of the stomach. You can see the gram-negative rods in the gastric mucosa. The bugs’ presence leads to a chronic inflammatory infiltrate in an attempt to get rid of the bugs. Regardless of the stage (except for carcinoma), antibiotics are curative. To test if the patient has H.Pylori or not, do a urease breath test (H. Pylori can chop up radioactive urea into CO₂ which the patient breathes out)

ULCERS

Chronic Peptic Ulcers (general ulcer features). These are benign holes (benign as in they are not cancer) in the GI tract. Risk factors include smoking, NSAIDs, Aspirin, and H Pylori Infections. There are two main types of ulcers: gastric and duodenum. As a gastroenterologist you can just scope them and see where they are. For the test, you are most likely going to get a history, and will have to determine whether or not it is Gastric (hurts with food) or Duodenal (hurts 1-3 after food). Treatment involves cessation of drugs, antibiotics for H Pylori, and possibly protein pump inhibitors. Ulcers can hemorrhage, causing an upper GI bleed. Ulcers can penetrate the wall, forming fistulas with nearby organs or perforating into the peritoneum. Perforation is shown as air under the diaphragm.
**Gastric Ulcers.** There is an association with H. Pylori in about 75% of the cases, the rest are due to drugs and smoking. There is a small, well-circumscribed “punched-out” lesion in the stomach, typically near the antrum. There is a burning, gnawing epigastric pain that is made worse by eating. Food in the stomach causes acid secretion, leading to pain. In fact, pain is the worst right before you eat, where you think about food, your body prepares for food and secretes acid, but there is no food to buffer the acid.

**Duodenal Ulcers.** This is much more common than stomach ulcers. There is a near 100% association with H pylori but also with increased acid secretion. It is caused by the inability of the duodenum to neutralize stomach acid. Since the acid is greatest at the entry point, the proximal duodenum is mostly often involved, usually on the anterior wall. This will likely perforate, and show air under the diaphragm. There is a gnawing epigastric pain that comes on hours after eating and is relieved by eating. Remember, if H. Pylori is absent, another etiology is Zollinger-Ellison.

**TUMORS**

**Gastric Carcinoma.** Gastric carcinoma is a natural progression from chronic inflammation of the stomach, most often associated with H Pylori and Nitrosamine Ingestion (smoked fish in Japan). It is most common in the antrum (50%) or along the lesser curvature (40%). Treatment for the chronic inflammation and antibiotics for H. Pylori could have prevented this transition; once cancerous, resection is the only cure. Unfortunately, gastric carcinomas do not present with symptoms until it is too late. The gross appearance is unique in that there is linitis plastica, a thickening of the mucosal layer of the stomach. There are two subtypes of Gastric carcinoma: intestinal and diffuse. Intestinal Type is well differentiated intestinal metaplasia associated with H Pylori infection, and is the less malignant form. Diffuse Type is much worse, and demonstrates poorly differentiated cells with signet ring cells. If caught early (which is almost never) there is a good prognosis with resection. Unfortunately, it is usually diagnosed late, whereby the muscularis propria has already been invaded, leading to metastasis. The metastasis goes to two places. It can be found at a clavicular lymph node called Virchow’s Node, or it can be found in the ovaries (called a Krukenburg Tumor). For Gastric Carcinoma, think H. Pylori, Nitrosamine, Antrum, Virchow’s Node, Signet Ring Cells, Linitis Plastica, and Krukenburg Tumor.

**MALToma.** This is a non-hodgkin’s lymphoma of the stomach caused by H Pylori. This is tricky. Because we talk so much about chronic gastritis and gastric carcinoma in relation to H Pylori, we miss the fact that this tumor has the highest association with H. Pylori infections.

**Stromal Tumors.** Referred to as GIST, this is a tumor of the interconnective tissue. It is rare, and only gains attention because it is the result of an overactive tyrosine kinase pathway (just like CML) which can be treated with Gleevac/Imatinib (just like CML).

**Metastasis.** Metastasis to the stomach is rare. The most common are lymphomas that originate outside the stomach (i.e. not MALTomas). Pay more attention to the Virchow’s Node and Krukenburg tumor which are metastasis from the stomach.
MECHANICAL OBSTRUCTION

**Volvulus.** A Volvulus is the **twisting of bowel** about itself. It essentially ties a kink in the bowel. It also causes a twisting of the mesentery, **twisting and obstructing the blood vessels** leading to malabsorption and **ischemia**. It is common in the sigmoid colon and the cecum. If you do not untwist the bowel, it will **infarct** and patient death will result from **perforation and peritonitis**.

**Intussusception.** This is a **telescoping of bowel into itself.** When this occurs, the lumen is narrowed (normal segment has the intussuscepted segment inside it) causing obstruction. Worse, the blood vessels to the intussuscepted segment is **impinged**, leading to **ischemia** and **infarction**. This is most common in **infants and children** occurring at the terminal ileum, where the pyre’s patches are enlarged. When it happens in adults, there is usually a polypt or cancer. There will be **abdominal pain, obstruction**, with a **courant-jelly stool** (lots of mucus and blood in the stool).

**Incarcerated Hernia.** Defined as a segment of bowel protruding through a hernia, becoming **trapped**. Incarceration is a mild form, whereby the bowel protruded through a segment of abdominal muscle, then the muscle contracted, preventing the bowel from returning. This causes **obstruction**. There is an increased risk of **strangulation**, where the blood vessels are cut off and the bowel becomes ischemic. Incarceration and strangulation are often used interchangeably on the exam, so be careful.

**Herschbrung’s Disease.** This is a congenital disease whereby the distal colon is **lacking autonomic ganglia** of the enteric nervous system. This is a problem involving the **failure of neural crest cells to migrate** to their intended destination. Without innervation, there can be no peristalsis, no movement. It is as if the food hits a “dead-end.” The **unaffected segment is enlarged** while the **affected segment is normal**. As stool is pushed towards the affected segment, it hits a brick wall. More stool backs up, but nothing can get through the affected segment, so the unaffected segment must dilate. This results in a **megacolon**. Neurons will never migrate, so the affected segment must be **resected**. This occurs in **neonates**, presenting with constipation and a **lack of passage of stool and muconium**. Eventually, if the backup is allowed to progress long enough, the patient will **vomit feces**. While megacolon will be present on barium enema, to be certain of the diagnosis, there must be **absence of Myenteric and Auerbach Plexuses**. This is required because “megacolon” may occur in other disease states: Chagas disease and toxic megacolon. If in a question stem you have a baby + megacolon, your diagnosis is Herschbrung’s.
Celiac Sprue. This is an immune disease that produces an allergic reaction to wheat gluten, specifically, gliadin. It causes a mucosal inflammation that produces flat atrophic villi with narrowed crypts, limiting absorptive capacity of the small intestine. There is a strong correlation with other IgA Immune Diseases such as dermatitis herpetiformis. Avoidance of wheat gluten will be completely curative. There is no treatment except avoidance of gliadin. Classic presentation is an infant with malabsorption or failure to thrive who also presents with foul smelling, fatty stool called steatorrhea. This is caused by malabsorption of fats, which also leads to vitamin deficiencies of the fat-soluble vitamins (A, D, E, and K).

Tropical Sprue. This has similar features histologically to Celia Sprue (loss/atrophy of villi), but we aren’t sure how it happens. It is found in the tropics (thus its name), and is suspected to be due to an infection. We think it might be E Coli. It responds very well with antibiotics and vitamins. It LOOKS like celiac sprue on histology, but has nothing to do with autoimmunity or associated IgA diseases.

Whipple’s Disease. This is a rare infectious disease that involves multiple organs (joints, lungs, heart, brain) but mainly involves the small intestine thus producing a malabsorption syndrome. The causative organism is Tropheryma Whippeli (thus the name), and it affects rural, male workers of the Caribbean leaving us with a presumptive “tropical farmer’s disease.” This barely exists in life, but is a Board favorite. The patient will present with diarrhea, weight loss, and malabsorption. On scope, a biopsy will show mucosal lining with abundant distended macrophages and there will be complete villi. The organism lives inside macrophages, so many macrophages will be recruited to kill the remaining organisms. This may in fact cause an obstruction, both of the GI tract and of the sphincter of Oddi. A PAS-stain will highlight the rod-shaped organisms. The treatment is long-term antibiotics.

Inflammatory Bowel Disease. This is a trick subject since not a lot is known about it. For now, we consider two independent forms of the disease: Ulcerative Colitis and Crohn’s Disease. Whether these are the same disease, a variant thereof, or even different diseases, is not certain. All you need to know is that (a) inflammation leads to diarrhea and malabsorption and (b) the differences between the two.

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<thead>
<tr>
<th>COMPARING CROHN’S AND ULCERATIVE COLITIS</th>
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<tbody>
<tr>
<td>Crohn’s Disease</td>
</tr>
<tr>
<td>Population</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>Spread</td>
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<td>Micro</td>
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<tr>
<td>Gross</td>
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<td>Inflammation</td>
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<td>Cancer</td>
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<td>Presentation</td>
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MISCELLANEOUS

Ischemic Bowel Disease. When blood flow is reduced either from an embolus, thrombus, or hypotension, most of the GI tract has good collateral circulation. However, there are end arteries of the bowel, that, when affected, will lead to ischemia and infarct. The regions at most risk are the watershed areas such as the splenic flexure. This results in a hemorrhagic infarction that produces a very bloody diarrhea and abdominal pain with eating (mesenteric angina) with a poor prognosis. Occurring in older individuals spontaneously, or younger trauma victims, surgical resection is the only means of treatment, with a 50% survival rate. Patient will present with mesenteric angina after eating.

Hemorrhoids. Talked about in the Liver section, these are varices of rectal veins. It occurs with portal hypertension due to liver failure or with increased strain (such as pregnant females). These may thrombose or bleed, producing a bright red bloody diarrhea. However, they are generally benign, treated for symptoms only (with OTC meds like Preparation H).

Angiodysplasia. Rare, tortuous vessels affecting the cecum or right colon that produce 20% of all lower intestinal bleeding. Found in the 6th decade of life, they span the submucosa and mucosa. These vessels are sort-of Telangiectasias. The treatment is surgical resection. Associated with CREST (Telangectasia).

DIVERTICULA

Meckel’s Diverticula. This is a congenital defect of the small bowel, commonly encountered in children. They are basically a remnant of the vitelline duct. Most Meckel’s are completely asymptomatic, encountered on autopsy. However, sometimes there may be pancreatic or gastric mucosa, which may bleed, presenting with bright red blood. These are fairly common in the general population (2%) and a small proportion (2% of that 2%) will have cancerous material. This is a true diverticulum.

Colonic Diverticula. This is an acquired defect of the large bowel, commonly encountered in adults. This is caused by an increased luminal pressure for any reason (constipation, for example). The big risk factor is a low-fiber diet. It takes time to occur, so it appears after 50. It commonly occurs in the right side of the colon. It can mimic cancer (alternating diarrhea and constipation, bloody diarrhea). Because these outpouchings eventually get feces stuck in them, there may be infection or simple inflammation, a process called diverticulitis which is painful. This diverticulitis may lead to an abscess. The wall of the colon has limited tensile strength. As the Diverticulum continues to be pushed on, its wall thins, and may perforate, leading to peritonitis. Picture this as a blood vessel aneurysm, only in the colon, filled with poo instead of blood.

CANCER

Is colon cancer going to be on the Exam/USMLE? You bet. It’s the number 3 cancer, and number 3 cancer killer in the US. But before you get cancer, you get polyps called colonic adenomas. These are benign growths, but over time, they will become malignant, turning into colonic adenocarcinoma. Let’s start off with Benign Neoplasms and the Polyposis Syndromes (FAP, Turcots, Gardners), and then tackle carcinomas.
**Adenomatous Polyps.** Synonymous with colonic adenomas they tend to asymptomatic polyps growing in the colon. They may become abraded and bleed, which is invisible to the naked eye. On a digital rectal exam, occult blood is found. On gross, there are two forms of polyps: sessile and pedunculated. **Sessile Polyps** are flat and have no stalk. They are more sinister and are likely to carry adenocarcinoma (“sessile are sinister”). **Pedunculated Polyps** are usually larger and have a stalk. On micro there are two forms of polyps: tubular adenomas and villous adenomas. **Tubular Adenomas** have tubules within the polyp, appearing as “normal” colonic tissue (just larger or growing off a stalk). **Villous Adenomas** have a higher risk for cancer. Sessile and Villous = bad, Pedunculated and Tubular = not as bad. Finally, the **larger the polyp, the higher incidence for malignancy.** In general, heme occult blood is discovered on routine inspection or when a patient comes in for fatigue (chronic iron deficiency). Once discovered, the patient is guaranteed an endoscopy. Polyps, when found, are excised and sent to histology.

**Familial Adenomatous Polyposis (FAP).** This is an autosomal dominant disorder, a mutation of the APC gene, whereby 100s to 1000s of polyps form in the colon, discovered usually by adolescence. The entire colon will be full of polyps. There is a high chance for dysplasia given the sheer number of polyps, and prophylactic colectomy is indicated. If you don’t take their colon out, they are guaranteed to have colon cancer by 40, and be dead by 45. There are some variants of this polyposis syndrome, which follow.

FAP-variant = **Gardner.** FAP + Benign osteomas of the jaw, fibromatosis of the abdomen + benign epithelial inclusions cysts of the skin.

FAP-variant = **Turcots.** This is a rare variant that is autosomal recessive version of FAP. The characteristic finding is 1000s of polyps in your colon together with a tumor in the brain, which is usually medulloblastoma. This is NOT a metastasis from the colon, but is instead another tumor in the brain. Remember that TURcots wears a TURban on his head, where the BRAIN is.

**Hereditary Nonpolyposis Colorectal Cancer (HNPCC).** This is an autosomal recessive mutation of the DNA mismatch repair genes. These patients will get colon cancers, but there will not be any polyps. They are also at risk of endometrial and ovarian cancers.

**Peutz-Jeghers.** Patients present with hyperpigmented lesions on the lips and the oral mucosa, presenting as dark spots on lips and mouth. You will give this person an endoscopy, usually of the small intestine. This patient will have multiple polyps, but they are not premalignant; they are hamartomous polyps. The reason you want to make this diagnosis so you can look for cancers somewhere else other than the colon, such as lungs and skin.

**Colon Adenocarcinoma.** Risk factors include a low-fiber, high red meat, low fruit and vegetables and of course, having Adenomatous polyps in the colon. With any polyposis syndrome, HNPCC, or ulcerative colitis you are likely to increase your chance of cancer. There are multiple genetic mutations. The APC gene (FAP), the k-ras oncogene, the DCC gene, and the p53 gene are all implicated in colon cancer. Great, lots of little tidbits that don’t mean anything or are repeats from before, that’s why nothing was in bold. The real kicker is in differentiating right vs left colon cancer. **Right Sided Cancer** is the more dangerous cancer. Because stool is softer, and more liquid, this cancer does not cause obstruction, so the patient has no complaints. The polyps can get large and ulcerate, releasing microscopic blood into
the stool (caught by guiac stools). **Left Sided Tumors** produce a thickened wall and a narrowed lumen, termed stricture. This causes **obstruction**. As the feces backs up, it gets stuck, until it is shot through as diarrhea. Thus **alternating constipation** (obstruction) and **diarrhea** (forces its way through) is indicative of left sided cancer. It is called a **napkin ring** tumor since it surrounds the entire lumen, constricting it, much like a napkin ring at a fancy restaurant. If you do a barium enema, you will see a **narrowing** where the tumor is, termed an **apple core narrowing**. Regardless of the side of the tumor, cancer is determined by occult blood, followed by endoscopy, followed by histologic sectioning. Colon cancer tends to **metastasize to the liver** (remember portal vasculature).

**Carcinoid Tumors**. Carcinoid tumors we first learned about in Lung cancer. They can also occur in the colon and intestines. In fact, they are most common in the colon, but can often appear in the appendix or terminal ileum. **Before they metastasize**, serotonin is sent to the liver, where it is degraded, so no serotonin syndrome is felt. **After they metastasize**, the Carcinoid does not have the first pass metabolism, and serotonin is allowed to escape into the inferior vena cava. Remember, when the Carcinoid was in the lung or the adrenal gland, there was no liver to clear the serotonin, so the symptoms were felt immediately. When in the colon **you must first have metastasis to the liver** before Carcinoid symptoms can be felt. The syndrome is **flushing, cramping, nausea, vomiting, diarrhea**, and **fibrosis of the heart and valves**. When it came from the lung, the left heart was affected. Now it comes from the colon/liver, so the right heart is affected. It is diagnosed by the presence of **5-HIAA in the urine**, a product of serotonin metabolism (5HT → 5-HIAA).
JAUNDICE

By definition, a patient will not become jaundiced until a patient’s bilirubin becomes elevated. The classic presentation is yellow skin (jaundice) and scleral icterus (yellow eyes). The major cause of Jaundice is elevated bilirubin. That can be because (a) too much gets produced (b) not enough gets taken out of the blood (c) not enough gets conjugated by the liver, and (d) defective excretion. Clinically, when bilirubin is elevated, you must determine whether the bilirubin is conjugated or unconjugated.

Unconjugated bilirubin is dangerous bilirubin. It is lipid-soluble so it can penetrate the blood brain barrier, it cannot be excreted in the urine, and causes kernicterus (degeneration and death of the brain).

Conjugated bilirubin is safe bilirubin. It is water-soluble so it cannot penetrate the blood brain barrier, it can be excreted in the urine, and while turning yellow is disconcerting, it is not fatal. There are four diseases that cause unconjugated bilirubinemia (Gilbert, Crigler-Najjar, Physiologic Jaundice of the Newborn, and any Hemolytic anemia). Everything else is conjugated.

Hemolytic Anemia. An increase in red blood cell turnover, from any cause, results in a production of bilirubin. Bilirubin comes from heme degradation. This excess load must be eliminated by the liver. Even if the liver is completely functional, if severe enough, the bilirubin levels may elevate above the maximum threshold for the liver. Since the bilirubin backs up in the blood without having gotten to the liver, it will most likely be unconjugated bilirubin. Of the bilirubin that reaches the liver, the large concentration secreted into the bile duct leads to pigment gallstones (supersaturation of bilirubin).

Physiologic Jaundice of the Newborn. Neonates have nonfunctioning livers; the ability to conjugate does not fully develop until about 2 weeks of age. Therefore, neonates are normally a little yellow. Since RBCs last 120 days, the risk of jaundice causing damage is low. The risk for kernicterus increases when the baby is a premature delivery. In addition, if the neonate has a superimposed hemolytic anemia, they will have an increased load, leading to jaundice. The treatment is phototherapy.

Erythroblastosis Fetalis. Rh- mom has an Rh+ baby. She develops antibodies to baby’s red blood cells. Nothing happens to this baby. The second Rh+ baby gets attacked by mom’s antibodies, causing hemolytic anemia. With baby’s reduced physiologic function at birth, jaundice and kernicterus arise.

Gilbert Syndrome. This is a common autosomal recessive disorder. It is caused by a mutation in the promoter region, TATA box sequence, for the UGT conjugation protein. This means there is only a little bit of the protein that takes unconjugated bilirubin and makes it into conjugated bilirubin. PreTest anD Rapid Review (not Robbins) says there is something to do with conjugation AND uptake into the liver. Whatever the mechanism, this is generally asymptomatic. When there is a physiologic stressor (infection), the patient may have bouts of jaundice, but for the most part, this patient lives a normal life.
Cirrhotic-Najjar. There are two types. Both are rare autosomal recessive genetic disorders that have to with deletion or downregulation of the UGT conjugation protein. In Type 1 there is a complete absence (deletion) of the UGT protein, while in Type 2 there is only a partial loss. Type 1 is fatal as there is an accumulation of unconjugated bilirubin leading to kernicterus.

Dubin-Johnson. This is a benign autosomal recessive genetic disorder that is the most tested on Board exams. It has a defective cannalicular transport protein (bilirubin is able to get into the liver, be conjugated, but has trouble getting out of the hepatocytes into bile). This causes a black pigmentation of the liver, but only episodic jaundice with a stressor. It has no clinical consequences.

Rotor Syndrome. In every review book I saw, it always said “its another Dubin-Johnson”

OBSTRUCTION

Biliary Tract Obstruction. So far we have covered increased production (hemolytic anemia), decreased uptake (hypoperfusion), decreased conjugation (genetic disorders), and now we move into the outflow obstruction disorders. Any obstruction can lead to the decreased removal of bilirubin. For example, gallstones, tumors, or even parasites (Clinorchis Sinensis) can block the output of bile into stool. This causes jaundice, icterus, and clay colored stools. Because the bilirubin gets conjugated, but cannot be excreted in the stool, it is excreted in the urine, turning the urine a dark brown color.

Primary Biliary Cirrhosis. Automimmune disease characterized by granulomas of intrahepatic bile ducts. Being autoimmune, there is a female domination, and a serologic Antimitochondrial autoantibody (AMA) maker. There is a lymphocytic granulomatous destruction of interlobular bile ducts. The patients will present with pruritis, xanthomas, and jaundice/icterus, usually in the female patient.

Primary Sclerosing Cholangitis. Disease of unknown pathogenesis characterized by segmental inflammation and fibrosis causing destruction of the intra and extra hepatic bile ducts. There is an onion skinning of the bile ducts on histologic section (concentric fibrosis around the bile ducts). There is a strong association with ulcerative colitis.

Cirrhosis of the liver is defined as nodular liver with islands of regenerating parenchyma within spreading fibrosis. The progression to fibrosis is easy to understand: lymphocytes start in the portal tracts, move out into parenchyma, and finish their spread in the hepatic vein. Where lymphocytes go, fibrosis follows. Stage 1 is defined as periportal fibrosis; lymphocytes exit the portal tracts and invade parenchyma, damaging the hepatocytes at the limiting plate. Stage 2 is septal fibrosis whereby the lymphocytes spill into parenchyma. Stage 3 is bridging fibrosis where multiple septal fibroses converge on each other. Stage 4 is complete cirrhosis, defined above. With cirrhosis, the liver is shrunken and nodular, which may be macronodular (Hep infections) or micronodular (alcohol). Other etiologies exist. With cirrhosis comes liver failure. The liver is the major outlet of blood from the portal system. With fibrosis, blood flow is reduced, so esophageal varices (esophagus), hemorrhoids (anus), and caput medusa (abdomen) arise to get blood through collaterals. Clotting factors are not made, so there is an elevation of the PTT. Albumin is not made, so there is limited oncotic pressure, allowing for edema, especially in the abdomen, called ascites. Finally, the backup of blood causes splenomegaly. We already encountered the role of liver failure and jaundice.
Hep A. Hepatitis A causes only acute hepatitis. It lasts about 3-4 weeks, causes dark urine, jaundice, clay-colored stools, elevated liver enzymes, etc. but has no real long term effects. Hepatic injury is by T cell mediated Cytotoxicity clearing the virus. There is no risk of carrier or chronic state, though acute hepatic failure has resulted. You get this fecal-oral. There is no treatment, but there is an inactivated vaccine and Hep A Immunoglobulins can be administered if caught at exposure. There is a vaccine.

Hep B. There is a lot to know for this one & is massively board relevant. Hep B is a hepatitis virus that can cause acute, chronic or carrier states. It is spread through bodily secretions (STD), or injected drug use. The virus spreads through viremia and targets only the hepatocytes. Most of Hep B cases resolve spontaneously with clearing of the virus associated with an acute hepatitis. Acute hepatitis is described as jaundice, dark urine, clay colored stools, hyperbilirubinemia. The virus does not do anything to the liver. It is your own immune response (cell mediated Cytotoxicity) clearing the virus that causes hepatocellular damage. If you suffer severe acute hepatitis you are likely to clear the virus, if you suffer mild symptoms, you will have a chronic infection. The strength of the immune response is dependent on the status of your T cell immunity. Very young children are screwed. 5 or older have a developed immune system to prevent it. You must use serology to determine state. The dane particle is the virion itself (a 42nm particle with the DNA, core protein [HBC], surface antigen [HBS], and the envelope). There is another secreted protein (HBe) that tricks the immune system and is 22nm. The body forms antibodies to all 3 antigens (HBcAg, HBSAg, HBeAg). If you have IgM anti-anything, you are in the acute stage. If you have Anti-HBc but HBSAg you are chronically infected. Anti-HBS-IgG means immunity. There is a period called the HBsAg Window where there amount of antibodies = the amount of antigen, and neither is detected. This lasts about 2 months and follows the acute phase. There is a recombinant vaccine that can be coadministered with Hep A vaccine. Anti-HBs Ig is given to neonates of infected mothers and accidental needle sticks for prophylaxis. Interferon, lamivudine and adefovir are given to reduce the risk of hepatocellular carcinoma, but there is no cure. There is a vaccine.

Hep C. Abundant in homosexual males, transmitted via blood (transfusions), injectable drugs (usually Hep B) and via sexual contact. Unlike Hep A (which is always acute) and Hep B (which is usually acute) Hep C will always establish a chronic infection. Hepatitis is caused by inflammation and cell mediated cytotoxicity and viral clearance. Hepatocellular carcinoma is associated with this Hepatitis as well. Mutations are abundant creating variability in the major envelope protein leading to immune system escape. There is no vaccine. Treatment is similar to Hep B chronic treatment (interferon and ribavirin).

Hep D, A bunk virus that requires an existent infection or coinfection with Hep B for its reproduction. Coinfection makes the Hep B infection worse (↑HCC, Cirrhosis), and a superinfection may be fatal.
ALCOHOLIC LIVER DISEASE.

Steatosis. This is completely reversible. If the patient abstains from drinking, they will revert to normal. The liver is enlarged, swollen, and yellow on gross with vacuoles of fat inside hepatocytes. Continued use of alcohol produces fibrosis, which is irreversible.

Alcoholic Hepatitis. This is an acute illness that usually follows a heavy drinking binge. There is a great variability in symptoms. It can be asymptomatic, but usually there is RUQ pain, jaundice, hepatomegaly, malaise and anorexia. They may even undergo fulminant liver failure, which is potentially fatal. Hepatocytes will demonstrate hydropic change, also called ballooning degeneration. Pink cytoplasmic inclusions, called Mallory Bodies, are common. While not unique, they are nearly pathognomonic for alcoholic hepatitis. There will be inflammatory cells (usually neutrophils) within fatty change. The prognosis is good; if you go on one binge nothing may happen. However, if you don’t lighten up the liquor load, you will progress to cirrhosis. Ballooning + Mallory Bodies + Neutrophilic Rxn = EtOH Hep.

Alcoholic Cirrhosis. This will be a micronodular cirrhosis. While the size of the nodules may correlate to the history of alcohol consumption, there may be no way of telling where the cirrhosis came from. Frequent bouts of necrosis and inflammation result in a shrunken fibrotic liver (see page 12).

METABOLIC LIVER DISEASE

Wilson’s. It is an autosomal recessive mutation of the WD gene (Wilson’s disease) on chromosome 13. The gene product, ATP7B, is responsible for copper extrusion, and is a Cu-Transporting-ATPase. When the body has too much copper it dumps it into the bile for excretion. In Wilson’s disease, the ability to transport copper from hepatocytes into the bile is lost. Our blood has a natural copper buffer, called ceruloplasmin. At first, these patients accumulate copper that is displaced by ceruloplasmin. As the ability to buffer the copper is overwhelmed by copper levels, the copper deposits in organs. The first place is in the liver (uptake is fine, Cannalicular extrusion is broken), forming a brown liver. Copper also likes to deposit in the brain (basal ganglia) and in the eye (Kayser-Fleischer rings). Because ceruloplasmin is being used up by an excess of copper in the blood, because the liver can take up copper, and because copper can be excreted in the urine at super-high levels, lab values will show ↓ceruloplasmin, ↑hepatocyte Cu, ↑Urine Cu. Note that the serum copper is not useful. Because this is a liver genetic disorder, transplant is curative. Copper Chelators may work.
Hemachromatosis. There are two forms: primary/hereditary and secondary. The primary form is an autosomal recessive disorder of the HFE gene on chromosome 6. The most common mutation is a Cystine to tryptophan mutation at 282, a so called C282Y mutation. It normally codes the “we have enough iron” signal. With the mutation, enterocyte programming defaults to increased dietary absorption. Because there is no way to get iron out of the body once it’s in, you are screwed. These patients present with a classic triad: (1) micronodular cirrhosis with increased risk for HCC, (2) diabetes mellitus from iron deposition in the pancreas, and (3) skin bronzing from iron deposition in melanocytes. There will be an ↑Serum iron and a ↓TIBC (transferritin). Liver and pancreas are the most severely affected, but there will be brown to black organs all over the body. Liver will stain positive for iron with Prussian blue. Treatment is phlebotomy since there is much iron in blood. Since this is a liver genetic disease, transplant is curative.

α-1-Antitrypsin Deficiency. This is an autosomal recessive disorder whereby the misfolding of α1-AT results in entrapment in hepatocytes. Made by the liver, this antiprotease cannot get into the blood. There are many variants, two of which you must know, M (good) and Z (bad). The normal is PiMM (homozygous). The worst case is PiZZ (homozygous mutation). In between is PIMZ (heterozygous). This produces an increased risk for micronodular cirrhosis / HCC and Panacinar emphysema. On micro, PAS positive eosinophilic inclusions within hepatocytes are pathognomonic. These patients should not smoke or drink alcohol; liver transplant is curative.

HEMODYNAMIC LIVER DISEASE

Budd-Chiari Syndrome. Also known as hepatic vein thrombosis, this is an occlusion of the outflow vein. This usually results in death. This is a coagulopathy and shares the same etiology as most coagulopathies (cancer, pregnancy, oral contraceptives) as well as others (Polycythemia Vera), There is Centrilobular congestions with necrosis, as the blood backs up and swells up the liver.

Chronic Passive Congestion of the Liver. Covered in the cardiovascular block, with right sided heart failure, venous return is decreased, the blood pools, and creates nutmeg liver. Long-standing congestion results in cardiac cirrhosis.

OTHER

Nonalcoholic fatty liver (NAFL) / Nonalcoholic SteatoHepatitis (NASH). Both name the same thing: a fatty change of the liver without the presence of alcohol. This happens in people who are obese or are diabetics. This demonstrates steatosis on micro and may lead to cirrhosis. This can be remembered simply as “fat people get fat livers.”

Autoimmune Hepatitis. Unknown etiology, though there is Antinuclear Antibodies (ANA) and Anti Smooth Muscle Antibodies (SMA) in the blood stream. Has a female preponderance and responds well to steroids. If you see a woman with hepatitis, without alcohol or viral serology, think au toimmune.

Drug-Induced. “Drugs can cause Hepatitis.” This was not present in Kaplan, and had exactly one slide in lecture. Guess what it said...
NODULAR HYPERPLASIA

Focal Nodular Hyperplasia. A large singular nodular growth that has a central fibrotic scar, this hyperplasia is not a neoplasm. It occurs in women more than men, is often well-demarcated though poorly-encapsulated, and appears paler than the normal liver.

BENIGN TUMORS

Hemangiomas. The most common primary tumor. It is a subcapsular, red (lots of blood vascular) and spongy tumor. They tend to be asymptomatic incidentally on CT scan or autopsy.

Liver Cell Adenoma. Most common in young women, usually using oral contraceptives or who are pregnant. This tumor grows in response to estrogen. This can cause hemorrhagic rupture, and peritoneal irritation. Because it is benign, it will not metastasize, but it can still cause problems. When resected, they usually do not recur. The neoplasm look like a normal liver but lack portal tracts. Withdrawal of oral contraceptives or the termination of pregnancy will cause the tumors to regress.

MALIGNANT TUMORS

Metastatic. The most common tumor of the liver. The most common tumors that go to the liver are lungs, skin, and colon. The liver has such a large blood supply (artery and portal vein) that metastases are abundant. When looking at a liver, if there are small and multiple tumors, it is most likely metastasis.

Hepatoblastoma. This is a tumor of early childhood (blastoma is fetal) and is fatal in one year if not resected. This can throw you off because there may be an elevated AFP (which is usually indicative of HCC). However, in a kid with AFP elevations, you can safely assume Hepatoblastoma (a 5 year old has not had the opportunity to drink alcohol for 20 years to develop cirrhosis). This, like focal nodular hyperplasia, presents with a large mass with a central fibrotic scar, but is poorly differentiated mesenchymal or fetal tissue and is the same color as the rest of the liver.

Angiosarcoma. This blood vessel tumor resembles angiosarcomas anywhere in the body. They can happen to occur in the liver. When in the liver, there is a particularly poor prognosis (<1 year). It is commonly associated with carcinogenic exposure (vinyl chloride, arsenic, mushroom toxin).
Cholangiosarcoma. This is a tumor of the biliary tree, effecting both intra and extra hepatic biliary trees. It is often diagnosed late in the disease, presenting as a painless jaundice with clay-colored stools. It is associated with chronic inflammatory diseases of the biliary tree (primary Sclerosing cholangitis, Ulcerative Colitis and Clinorchis Sinensis infection). This carries a dismal prognosis.

HEPATOCELLULAR CARCINOMA

Hepatocellular Carcinoma. Most common in Asia (where hepatitis infections are high), this is a tumor caused by continued inflammation. Much like a liver can progress to cirrhosis, a chronically inflamed liver can progress to HCC. Infection with Hep B, C, or D significantly increase the risk of the developing the tumor. Anything that causes cirrhosis (Hep infection, Alcohol, Wilson’s, A1AT, Hemachromatosis) can cause this cancer. It is detected by elevated AFP (α-fetoprotein) in the serum. They love to invade blood vessels (even into and up the IVC), but they rarely metastasize. A special variant, called Fibrolamellar HCC occurs in kids, but has a much better prognosis.

GALL STONES

Cholesterol Stones. These are stones formed from an excess of cholesterol in the bile, a bile supersaturated with cholesterol. A good test question would be the risk factors: being female, on oral contraceptives, being pregnant, increasing age, or being Native American. There are others (see the outline review sheet), but these are the big guns. Cholesterol stones appear as yellow-green stones within the gallbladder. The clinical consequences of cholesterol stones are the same as for pigment stones, discussed below. Think “Fat, Forty, and Fertile,” is a pretty prominent mnemonic.

Pigmented Stones. These are formed of calcium salts and unconjugated bilirubin. To get bilirubin into the bile duct, it must first be conjugated. Therefore, getting unconjugated bilirubin in the bile ducts requires deconjugation within the lumen or have an overload of unconjugated bilirubin (where unconjugated bilirubin escapes in bile ducts anyway). Therefore, chronic hemolytic anemia (unconjugated production), cirrhosis (general liver failure), and infections of biliary tree (Clinorchis Sinensis) are risk factors. These are black (usually sterile and radio-opaque) or brown (from infection and radio-lucent), often found in the gallbladder. Clinical features for all gallstones continues below.
Stones Clinical Features. If they are really tiny stones, they will escape down the biliary tree and out in the feces (you don’t know you have them). Super large stones never leave the gallbladder, and are generally asymptomatic. Medium sized stones can obstruct the neck of the gallbladder (cholecystitis) or may obstruct the biliary tree (choledocholithiasis). If there is an obstruction down near the sphincter of Oddi, there may be complete pancreatic obstruction, resulting in acute pancreatitis. Likewise, regions proximal to the obstruction may become infected. There is an upper right quadrant abdominal pain, which is usually colicky, though most stones go asymptomatic for decades (which is why you can open a gallbladder and see hundreds of stones). Btw, the buzzword for acute pancreatitis is saponification.

INFLAMMATION

Acute Cholecystitis. This is an inflammation of the gallbladder because of an obstruction. If that obstruction is a stone, then it is called calculous; if there is no stone, it is called acalculous. There will be biliary colic (URQ pain), especially with fatty meals. An inflamed gallbladder may become necrotic and/or perforate giving rise to peritonitis. With the obstruction to flow, the risk of superinfection increases, which may produce a cholangitis, or hepatic infection. Patient will have Murphy’s Sign: as the palpate inhales, you palpate deeply. With disease the patient will suddenly stop inhaling (from pain).

Chronic Cholecystitis. This is ongoing or recurrent bouts with acute cholecystitis. There will be fibrotic thickening of the walls of the gallbladder (porcelain gallbladder) and mucosal outpouchings (Rokitansky-Aschoff Sinuses). Risk, clinical, and treatment are the same as for acute cholecystitis.

Ascending Cholangitis. This is a bacterial infection that ascends the biliary tree, infecting the biliary tree and even the liver. These patients have biliary colic, nausea, vomiting, high fever, and shaking chills. This is usually caused by gastrointestinal flora (E.Coli, Bacteroides, or Klebsiella). In addition to all the symptoms above, infection of the biliary tree can lead to pigmented stones.

CANCERS

Carcinoma of Gallbladder. This is a rare disease occurring in the elderly, often in the 7th decade of life. They are frequently asymptomatic. However, a large palpable painless gallbladder is strongly indicative of cancer. There may of course be obstruction of the gallbladder with similar presentation (which may in fact be indistinguishable from cholecystitis). These grow either as an infiltrative type (in and around the duct) or Exophytic (into the lumen). Since they are in the gallbladder, they are unlikely to cause obstruction. The prognosis is terrible, often having already metastasized or seeded locally. Since this is from a glandular tissue, it is an adenocarcinoma.

Carcinoma of the Extrahepatic Bile Duct. There are bile ducts inside and outside the liver. If you get a cancer of the bile ducts within the liver, it is called Cholangiosarcoma (above). Regardless of the location, the tumor is the same. These tumors arise as a result of long term inflammation. In Asia, where they are the most common, they are caused by Clinorchis Sinensis liver fluke infection. In the US there is the greatest association with ulcerative colitis / primary Sclerosing cholangitis which often occur together. These are actually inside the lumen, and can therefore cause obstruction, causing jaundice. The main buzzword for this is painless jaundice.