GI Disorders

1. Gastroesophageal Reflux Disease (GERD)

Clinical Presentation

Symptoms:

Sub-sternal burning pain (specific, not sensitive)
- radiates toward the mouth
- precipitated by heavy meals &/or recumbancy
- may be relieved by antacids, milk, or baking soda

Cough (aspiration of gastric contents)
Sour taste after burping
Hoarseness / laryngitis / sinusitis / dental erosions / lung damage

Symptoms associated with complications of GERD:
Odynophagia (ulcerations)
Dysphagia (strictures)

- "Alarm symptoms" that warrant EGD or Barium Swallow are: Weight loss / dysphagia / anemia / early satiety / bleeding

Lab Presentation

Gross Pathology:
Non-complicated → erythema
Complicated → erosions, ulcers, strictures

Histology: epithelial **spongiosis** (increased intercellular fluid), basal hyperplasia; eosinophilic infiltrates

Gastroesophageal reflux is the entrance of gastric contents into the esophagus. Though it occurs in all people to a certain degree without associated with mucosal damage (physiological reflux), in some cases the acidity & digestive enzymes of the gastric juice can damage the esophageal mucosa (pathologic reflux). Natural defenses against pathologic reflux include: 1) the *lower esophageal sphincter*, which normally creates a pressure of 10-40mmHg that opposes reflux – disease may develop if the LES is consistently incompetant (pressures < 5mmHg), under increased gastric pressure and moderately weak (5-10 mmHg), or relaxes unpredictably and inappropriately though its general tone is normal; 2) *luminal clearance mechanisms* such as salivation, submucosal gland secretion of bicarbonate, and peristalsis – since these are inactive during sleep, the potential for reflux damage is greatest at this time; and 3) *epithelial resistance,* composed of structural barriers (glycoprotein-containing cell membranes and tight junctions between cells), acid-extruding mechanisms (Na^+/H^+ and Na-dependent Cl/HCO_3^- antiporters), intracellular bicarbonate buffering, blood flow, and epithelial cell regenerative properties. Severity of reflux is also determined by the quantity & quality of the refluxate – HCL is the major damaging agent (and most GERD patients have a normal acid secretory rate), and the addition of gastric enzymes &/or bile increases the rate and severity of damage, presumably by increasing H^+ influx into epithelial cells. Increased potency of the refluxate is rarely the reason for GERD symptoms, however; delayed gastric emptying may contribute to GERD in some patients by increasing the mean gastric volume.

Complications of GERD include: 1) *ulcerations*, which may be associated with the symptom of odynophagia (pain with swallowing) or evidence of GI bleeding on exam (usually occult, active hemorrhage with hemoptysis &/or melena is rare); 2) *strictures*, which are composed of circular bands of scar tissue underlying the mucosa and are associated with the symptom of progressive dysphagia (begins upon swallowing solids and progresses to swallowing even thin liquids) – impaction with total occlusion is possible; and 3) *Barrett's esophagus*, in which columnar epithelium has replaced the chronically injured stratified squamous epithelium in the lower esophagus (see #2). Risk factors for GERD include ↑ age, male gender, obesity, pregnancy, smoking, collagen vascular disease (i.e. scleroderma), alcohol use, and hiatal hernia.

Drugs that may exacerbate GERD include: anticholinergics, theophylline, diazepanarcotics, CCBs, β-agonists, progesterone (some contraceptives), and α-antagonists (phentolamine).

Treatment

Lifestyle Modifications: elevate HOB, stop smoking, stop EtOH, reduce dietary fat, lose weight if needed, avoid chocolate, peppermint, caffeine, citrus, & tomato.

Medical Therapy:

- *Liquid antacids* prn for symptom relief and possible healing of lesions; compliance is difficult to ensure, however, due to poor taste, bowel-altering side-effects (Mg-containing agents → diarrhea; Al-containing agents → constipation), and limited use in patients with significant renal disease (Al & Mg become toxic);.
  - *Riopan* is a low-Na antacid for salt-restricted pts.
- *H_2-receptor antagonists*
  - may be less effective for GERD-related erosive esophagitis; bid dosing at up to 3x recommended dose is good for moderate-to-severe GERD.
- *Proton-pump inhibitors*
  - superior to H_2-receptor antagonists in reducing acid; good for severe GERD.

Surgical Therapy (*Nissen fundoplication*) to strengthen the LES is indicated when medical tx does not relieve

- Mechanical supports of the LES that oppose reflux include: 1) the phrenoesphageal liamtent (crus of the diaphragm), 2) the acute angle of His, and 3) the intra-abdominal segment of the esophagus; these supports are inactive in patients with a *hiatal hernia* (see #3).
- Anti-cholinergic drugs & certain diseases (e.g. scleroderma) may exacerbate GERD by impairing luminal clearance of refluxate.
- Diagnostic Tests:
  - *Upper endoscopy* is good for evaluating the complications of GERD (strictures, esophagitis, Barrett's esophagus) but not for GERD itself (50% of cases are normal by endoscopy).
  - *24-hour pH probe* has a sens.&spec. of 75-90% and can detect reflux even if the mucosa is normal.
  - *Esophageal manometry* will detect a loose LES (present in 25-50% of patients with GERD).
  - *Barium swallow* is a good test for dysphagia but has low sens.&spec. for GERD.
  - *Empiric trial of proton-pump inhibitor therapy* is the most common test and has the highest sens.&spec. (patients who respond to treatment likely have GERD).
- Weight loss > 10-15lbs suggests squamous cell CA; it is rarely

2. Barrett's Esophagus

Clinical Presentation

Less symptomatic than normal mucosa in GERD.

Lab Presentation

Endoscopy: areas of **salmon coloration in the distal esophagus**;

Histology: **dysplasia** → nuclei are large, pleomorphic, hyperchromatic, with prominent nucleoli and multiple mitotic figures.

Etiology and Pathogenesis

Barrett's esophagus is characterized by metaplastic change of chronically injured stratified squamous epithelium in the lower esophagus to specialized columnar epithelium. It is almost exclusively a complication of GERD and a pre-malignant condition for esophageal adenocarcinoma (though the risk of developing cancer is low) – The risk of developing adenocarcinoma is related to the length of the metaplastic segment and the presence/degree of dysplasia (no dysplasia: 2% risk over 4yrs, low-grade dysplasia: 18% per 4.3yrs, high-grade dysplasia: 34% per 4.5yrs). BE does not spontaneously resolve, nor will surgery stop BE from progressing to cancer.

Treatment

Notes

- BE occurs in about 10-15% of those with weekly GERD.
  - risk for CA is 0.5% / patient / year.
- 10% of pts. with Barrett metaplasia → adenocarcinoma
- 80% of BE occurs in white males.
- If GERD progresses to BE then BE to adenocarcinoma, prognosis is bad.

3. Hiatal Hernia

Clinical Presentation

Symptomatic heartburn in 10% of pts.

Lab Presentation

Etiology and Pathogenesis

A *hiatal hernia* is a protrusion of the stomach into the thorax through an enlarged diaphragmatic hiatus. There are two types: *sliding hiatal hernias* occur when the the gastroesophageal junction and part of the body of the stomach protrudes into the thorax; *paraesophageal hiatal hernias* occur when part of the cardia protrudes into the thorax. Most are benign, but hiatal hernias may be associated with reflux (esp. when supine) and eventual ulceration - 10% of patients are symptomatic.

Treatment

Notes

Epidemiology

- 20% of adults > 60yrs.
- 95% sliding; 5% paraesophageal

- An intact primary barrier (LES) is capable of preventing reflux even in the presence of defects in secondary barriers (such as hiatal hernia).

4. Esophagitis

Clinical Presentation

Erosive esophagitis → chest pain / dysphagia / occ. odynophagia

Lab Presentation

Candidiasis → pseudohyphae & yeast forms seen on H&E or PAS stains; PMNs, necrosis; **white pseudomembranous lesions** grossly

CMV → nucleomegaly & cytomegaly, nuclear & cytoplasmic inclusions; infects fibroblasts & endothelial cells; superficical ulcers grossly

HSV-1 → infects keratinocytes; nuclear "ground-glass" & margination of chromatin; multinucleated cells with nuclear molding; superficical ulcers grossly

Pill esophagitis → pill found on endoscopy; local ulceration

Ingestion of alkaline liquid → liquifactive necrosis with inflammation & saponification; thrombosis → necrosis

Etiology and Pathogenesis

Esophagitis is characterized by inflammatory lesions of the mucosa and may be caused by, infection, drugs, ingestion of toxic chemicals, &/or reflux. Infectious etilogies include HSV, CMV, and candida albicans, all of which preferentially infect immunocompromised patients. Pill esophagitis is often secondary to esophageal dysmotility &/or cardiac enlargement – pills most often associated with esophagitis include tetracycline, KCl, Vitamin C, NSAIDs, and quinine. Corrosive (chemical) esophagitis occurs with ingestion of strongly acidic or alkaline liquid; alkaline solutions are generally worse. First-degree injury refers to injury to the mucosa/submucosa only (and damaged tissue may slough); second-degree injury refers to injury of the submucosa and muscularis propria (ulceration, granulation tissue, fibrosis/stricture may occur); third-degree injury refers to full-thickness necrosis of the tissue.

Erosive esophagitis occurs in 10-40% of GERD patients secondary to a large amount of acid, pepsin, and perhaps duodenal contents refluxing; it is a chronic, relapsing condition that is more common in those with a hiatal hernia and increases the chance of stricture formation or Barrett's esophagus.

Treatment

Erosive esophagitis → PPIs heal 90% of pts. and are safe for long-term use but are expensive.

Notes

5. Esophageal Cancers (Adenocarcinoma & Squamous Cell Carcinoma of the Esophagus)

Clinical Presentation

Adenocarcinoma:

- Progressive Dysphagia (first with solids, then with liquids)
  - usually occurs when 50% of the lumen is occluded
- Weight Loss

Squamous Cell Carcinoma:

- Progressive Dysphagia
- Weight Loss / Anorexia
- Aspiration / Cough

Lab Presentation

Gross Pathology: fungating/ulcerating &/or infiltrating

Histology:

Adenocarcinoma → invasive atypical glands

Squamous Cell Carcinoma → solid & invasive nests/cords of squamous cells in desmoplastic stroma; may show keratin pearls.

Etiology and Pathogenesis

Adenocarcinoma of the esophagus most often arises in the setting of Barrett's eshophagus (see #2); chronic acidic injury induces inflammation, then metaplasia, then ultimately cancer in the distal esophagus. The most common presenting symptom is progressive dysphagia, often accompanied by weight loss. Useful diagnostic studies include endoscopy (for direct visualization and biopsy), barium swallow studies (esp. useful in distinguishing CA from motility disorders), and CT (for preoperative staging in assessing the extent of tumor and involvement of local & distal structures). Esophageal adenocarcinoma is almost always metastatic by the time of diagnosis and the 5yr cure rate is only 7%; surgery is the only chance for cure (the entire columnar lined epithelium should be removed), though RT, chemotx, and placement of an esophageal stent may be useful for palliation. Common nodal metastases are: cervical & supraclavicular nodes for cancer in the upper 1/3 of the esophagus, hilar/tracheal nodes for cancer in the middle 1/3, and gastric/retroperitoneal for cancer in the lower 1/3; local infiltration into the trachea may produce cough, into the aorta may produce hemorrhage, and into the recurrent laryngeal nerve produces hoarseness.

Squamous Cell Carcinoma is the most common neoplasm of the esophagus in the world and the second most common (behind adenocarcinoma) in the US; very high incidences are seen in China & Iran (up to 171/100,000 people). Alcohol and tobacco use are the major risk factors. Early cancer is often asymptomatic, with progressive dysphagia the most common symptom (as in adenocarcinoma). Aspiration &/or cough may develop due to esophageal obstruction or development of tracheo-esophageal fistula. Diagnostic work-up is the same as in adenocarcinoma. Most patients present at a stage that is too advanced for cure; the goal of therapy is palliation – 1yr & 5yr survival rates are 18% and 5%, respectively.

Treatment

Adenocarcinoma:

- Surgery

Squamous Cell Carcinoma:

- Surgery (esophagogastrectomy with esophagogastrostomy)
  - cure rate is low → 5yr survival < 25%
  - perioperative mortality 10-20%
- Radiation (palliative)
- Laser Therapy (palliative in pts. with exophytic tumors)
- Chemotherapy
  - usually cisplatin in combination with radiation &/or surgery
  - rare complete responses have been observed

Notes

Epidemiology: (1% of annual new cancers in the US)

Adenocarcinoma of the Esophagus

- affects whites > blacks, males > females
- incidence ↑s after 40 with each decade; peak incidence is in people age 60-79.
- rate of increase is highest of all tumors
- may be associated with smoking
- slightly more common in US than sqamous cell CA

Squamous Cell CA of the Esophagus

- affects blacks > whites, males > female
- ↑ risk in lower socioeconomic groups
- ↑ risk with tobacco, EtOH, betel nut chewing
- ↑ risk with *tylosis* (hyperkeratosis of palms & soles)
- concomitant/preexisting conditions:
  - achalasia, lye strictures, head&neck squamous CA
  - Plummer-Vinson syndrome, celiac sprue, diverticula

Other Esophageal Growths

1) *Leiomyoma*: smooth muscle with epithelial covering; most are never diagnosed; leiomyoma's can grow to several cm in diameter and occlude the lumen → dysphagia; tx is endoscopic snare or electrocautery, or surgery.
2) *Fibrovascular polyp*: composed of collagen, vascular tissue, and other connective tissue elements with a normal epithelial covering; usually occurs in the proximal 1/3 of the esophagus; can often be removed by endoscopy.
3) *Lipoma*: benign collection of fat in the submucosa; usually asymptomatic; occasionally can cause dysphagia; usually

6. Gastritis

Clinical Presentation

Nausea / Vomiting / Bleeding / Epigastric Pain

Lab Presentation

Blood Tests:

Menetrier's Ds → **severe protein loss**

DCAG → **serum antibodies** to IF &/or parietal-cell antigens

Histology:

DCAG → T-lymphocytes infiltrating gastric mucosa; G-cell hyperplasia (seen on *synaptophysin* stain); intestinal metaplasia

Acute → punctate erosions with hemorrhages

Gross Pathology:

Acute → petechial hemorrhage, erosions (patchy necrosis) mild neutrophilia.

Chronic → thin mucosa with gland atrophy; metaplasia; enlarged lamina propria with lymphocytes

Etiology and Pathogenesis

Gastritis is inflammation of the gastric mucosa caused by agents that directly injure the epithelium &/or interfere with normal protective mechanisms – etiologies include drugs (NSAIDs, chemotherapy), uremia, systemic infections, physiological stress (trauma, burns, surgery), autoimmune mediators, and H.pylori infection. In chronic gastritis, inflammatory epithelial necrosis may lead to gland atrophy, and intestinal metaplasia (dense pink cytoplasm, brush border, goblet cells) may be seen with or without dysplasia &/or cancer.

Diffuse Corporal Atrophic Gastritis represents < 5% of cases of chronic gastritis and is characterized by autoimmune destruction of parietal cells (of the fundic glands) with circulating Abs to IF & parietal cell antigens, pernicious anemia, achlorhydria with secondary hypergastrinemia and antral G-cell hyperplasia (loss of acid-mediated negative feedback on growth), and flattened gastric folds with thin fundic mucosa endoscopically. *Acute Erosive Gastritis* is damage to the gastric mucosa with minimal inflammation histologically, caused by drugs, EtOH, stress, cocaine, radiation, bile reflux, ischemia, portal HTN → congestive gastropathy.

Menetrier's disease is a hypertrophic gastropathy characterized endoscopically by large ridges with histologic foveolar hyperplasia – clinical presentation is vomiting/diarrhea/weight loss/excessive mucus with severe protein loss.

Treatment

Notes

- NSAIDs & H.pylori are the most common causes of gastritis.
- EtOH & smoking ↑ risk & may be etiologies of gastritis.
- G-cells are stained by *synaptophysin*.

7. Peptic Ulcer Disease

Clinical Presentation

Abdominal Pain (60% sensitive)
- non-radiating burning epigastric pain
- often post-prandially & occasionally nocturnal
- relieved by antacids or food

Hemorrhage (15% of patients)

Perforation (7% of patients)

Gastric Retention (from pyloric ulcer or peri-pyloric edema)

Lab Presentation

Gross Pathology:

Benign ulcers → typically have indurated, hyperemic margins with a base containing a white exudate; "starfish pattern" of contracting scar (healed ulcer).

Histology: (four zones)
1. fibrinopurulent exudate
2. necrotic tissue
3. granulation tissue
4. fibrotic tissue

Etiology and Pathogenesis

A peptic ulcer is an erosion in the digestive mucosal surface penetrating through the muscularis mucosa into the submucosa or deeper, caused by physiologic imbalance favoring aggressive factors (H.pylori, NSAIDs, steroids, gastric acid & digestive enzymes, EtOH, smoking) over defensive factors (mucus barrier, cellular resistance, mucosal blood flow, HCO_3^- secretion, GFs, & epithelial restitution). NSAIDs cause PUD primarily by inhibiting COX-1 mediated production of PGI_2 & PGE_2 , stimulants of mucus & HCO_3^- secretion from the gastric and duodenal epithelium as well as mucosal proliferation; NSAIDs also cause direct injury to the epithelium and can damage the microvasculature leading to statis & ischemia. H.pylori causes PUD by elaborating toxins, degrading the mucus layer (by making mucinase), precipitating local inflammation, and inducing increased gastrin & gastric acid secretion (due to a decrease in the # of antral D-cells which produce somatostatin) – HP may also downregulate mucosal defense factors (EGF & TGF-α) that inhibit gastric acid & induce mucosal growth. *Gastric ulcers* commonly develop in the lesser curvature in the body or antrum; *duodenal ulcers* are commonly found within 2-3cm of the pylorus. PUD accounts for 10% of all patients presenting with a digestive disease. Diagnosis is made by endoscopy (>95% sensitivity), which can also be used to biopsy for H.pylori infection. There is little evidence that stress or diet cause ulcers. Ulcers may heal by forming a contracting scar. Complications include: *hemorrhage, perforation* (more common in duodenum, causes peritonitis), and *obstruction* (edema, scar contraction, &/or muscle hypertropy; more common in pylorus).

Treatment

Urgent → endoscopic therapy for acute hemorrhage and surgery for refractory bleeding, perforation, or obstruction.

Medical Therapy:

Acid Reduction → H2 blocker or PPI for 8 weeks

Antibiotics for H.pylori prevent recurrence in 90% of pts.
- for symptomatic patients with documented ulcer

Reduce NSAID use & Quit smoking

Notes

Epidemiology:
- annual incidence in the US: 1.6% (500,000 pts.)
- lifetime incidence: 5-10%
- hospitalization rate stable for DU & increasing for GU
- mortality rate: 15,000 per year; 5-10% in elderly pts. and low for other groups

- Ulcers may occur in the esophagus with reflux or in the jejunum if there is a huge acid load (as in ZES).

- Aberrant gastric mucosa as seen in Meckel's diverticula can produce peptic ulcers in the ileum, usually presenting as lower GI bleeding in kids.

- *H.pylori*: gram-negative spiral rod with 4-6 sheated flagella; adheres only to the gastric epithelium (may be seen outside stomach/duodenum in areas of gastric metaplasia); microaerophilic; expresses urease which cleaves urea to generate ammonia to locally neutralize gastric acid; concentrates at cellular junctions; transmission is probably fecal-oral; seen on silver staining.
  - H.pylori prevalence

normal blood donors	20-55%
active chronic gastritis	100%
duodenal ulcer	>90%
gastric ulcer	60-90%
nonulcer dysplasia	35-60%
gastric cancer	85-95%

8. Zollinger-Ellison Syndrome (Gastrinoma)

Clinical Presentation

Duodenal ulcers (90%)
Diarrhea (15%)
GERD

dysphagia / hypercalcemia / pancreatitis / nephrolithiasis

Lab Presentation

Fasting serum gastrin : > 200 pg/ml
- if > 1,000 pg/ml, no further work-up is necessary
Basal gastric acid output: > 15mmol H^+/hr
Secretin stimulation test: > 200 pg/ml rise

Etiology and Pathogenesis

ZES is characterized by extremely high concentrations of gastrin produced from pancreatic adenomas, resulting in recurrent duodenal & jejunal peptic ulcers refractory to medical therapy. The MEN-1 gene, which codes for a tumor suppressor on chromosome 11q13, has been implicated in 25% of cases of ZES and is associated with pituitary, pancreatic, and parathyroid tumors. Diagnosis is made by deomonstrating hypergastrinemia with hyperchlorhydria & a positive secretin stimulation test (gastrin levels increase after a secretin infusion). Localization of the tumor is done by CT, endoscopic ultrasound, nuclear scan with radiolabled octreotide (somatostatin analogue), or exploratory laparotomy.

Treatment

PPI (omeprazole) plus surgical resection of tumor.

- overall 5yr-survival is 90% if resection is complete, 50% if resection is incomplete.

Notes

- Gastrin-producing tumors can also arise from the intestine (14%) or other sites (9%)
- 80-90% of gastrin-producing tumors are malignant; up to 50% are metastatic at presentation (mets to LNs & liver)
- Chemotherapy is not very effective for ZES.
- MEN-1 is inherited in an autosomal dominant fashion.
- Causes of chronic hypergastrinemia:

Low Gastric Acid	*High Gastric Acid*
pernicious anemia	ZES
chronic atrophic gastritis	antral hyperplasia
pharmacological	chronic renal failure
	short bowel syndrome
	gastric outlet obstruction

9. Gastric Adenocarcinoma

Clinical Presentation

Insidious symptoms:
Dyspepsia / nausea / satiety / anorexia & weight loss

Advanced symptoms:
Vomiting / dysphagia / bleeding / mass

Lab Presentation

Intestinal → cribiform glands with increased mucin

Diffuse → poorly-differentiated, dis-cohesive "signet ring" cells; infiltrative spread of single cells, cell clusters, or sheets; significant fibrosis may be seen
- signet ring cells stain + for mucicarmine (stains mucus)

Etiology and Pathogenesis

Gastric adenocarcinomas (90-95% of gastric malignancies) arise from glandular epithelium of the stomach. They arise in the antropylorus region (50-60%) > cardia (25%) > body-fundus, and the lesser curvature (40%) > greater curvature (12%). Symptoms arise with deeper layer (MP & serosa) involvement & mets, so most are not caught early unless they are seen in screening endoscopy. Diagnosis is usually by upper endoscopy (95-100& sensitive); CT & EUS are useful for staging.

Intestinal gastric adenocarcinoma arises from intestinal metaplasia in the stomach of pts. with chronic gastritis → dysplasia → CA; *diffuse* gastric adenocarcinoma arises from gastric mucous cells and may or may not be associated with desmoplasia. Type of gastric adenocarcinoma is not crucial in determining prognosis.

Treatment

- *Surgery* is the standard of care.
- Chemotx & radiation do not improve survival, but may be palliative (along with endoscopic stenting/ablation).

Future Interventions:
Endoscopic screening in high-risk regions
H.pylori eradication programs
Diet interventions: antioxidants, food prep & refrigeration

Notes

Epidemiology
- 2nd most common cancer worldwide in incidence & mortality
- China accounts for 1/3 of cases
- Low incidence in developed areas & Africa

Risk Factors
- Genetic: inflammatory cytokine genotypes (IL-1β); family history of HNPCC
- H.pylori infection
- Dietary: nitrates, smoked foods, high Na intake; - antioxidants & fruits/vegetables are protective
- Environmental: low socioeconomic status, EBV, smoking
- Clinical: atrophic gastritis, intestinal metaplasia, dysplasia, gastric ulcer, prior partial gastrectomy (> 15 yrs); pernicious anemia.

5yr-survival and (presenting percentage) by TNM stage:
I → 50% (18%)
II → 30% (15%)
III → 15% (35%)
IV → 5% (30%)

10. Gastric Lymphoma

Clinical Presentation

MALToma → dyspepsia / nausea / satiety / anorexia

Bleeding

Lab Presentation

Dense mononuclear lymphocytic infiltrate replaces glands.

Etiology and Pathogenesis

Gastric lymphoma is a lymphoma with the majority of the tumor in the stomach, with or without involvement of contiguous lymph nodes. Primary gastric B-cell lymphomas include MALTomas (gastric marginal zone B-cell lymphomas) & diffuse large B-cell lymphomas; T-cell lymphomas are rare in the stomach. Upper endoscopy is the procedure of choice, with histology & immunophenotyping to confirm MALToma & verify H.pylori infection. Staging is done by CT & EUS.

MALTomas often show indolent growth patterns & have high 5yrDFS after eradication of H.pylori; they may develop into high-grade malignancies, however, where prognosis is worse.

Treatment

Stage I, low-grade MALtoma → eradicate H.pylori

Other → surgery/chemotx/radiation

Notes

Epidemiology

MALToma → 40% of gastric lymphomas; H.pylori infection present in 90%

Diffuse large cell → 50% of gastric lymphomas

Age of onset: 60y, male = female incidence

11. Benign Gastric Neoplasms

Clinical Presentation

Usually asymptomatic, unless large, obstructing, or ulcerated

Lab Presentation

Leiomyoma → smooth muscle proliferation without necrosis or mitotic figures (normal smooth muscle).

GIST → cut surface is tan, flat, with patchy necrosis & hemorrhage; histology → undifferentiated spindle cells (most common), epithelioid cells, or mixed; intact overlying mucosa & submucosa; intracytoplasmic vacuolization may be present

Etiology and Pathogenesis

BGNs may arise from the epithelial (mucosal) or mesenchymal (submucosal) cells; most do not have malignant potential – most gastric polyps do not have to be removed, in contrast to colon polyps. They are found incidentally in 1% of upper endoscopies. Hyperplastic polyps (75% of gastric polyps) have low malignant potential (2%, primarily in polyps >2cm); fundic gland polyps (18%T) have no malignant potential unless they arise in the context of FAP; adenomas (6%) are similar to colonic adenomas & must be resected though they are not the precursor to most gastric adenocarcinoma (unlike in CRC); gastric carcinoid tumors arise from enterochromaffin cells. Common gastric submucosal neoplasms are lipomas (fat), leiomyomas (smooth muscle), and GISTs (which may be malignant as well).

Treatment

GIST tumors → Gleevec (inhibitor of kit-associated tyrosine kinase)

Notes

- Leiomyoma is the most common gastric tumor; it is benign but complications include ulceration & hemorrhage (submucosal tumor stretches & thins overlying mucosa).
- GISTs arise from pluripotent mesenchymal cells & differentiate similar to the interstitial cells of Cajal; tumors often have a c-kit (proto-oncogene) mutation & many will respond to tx with Gleevec; tumors occur anywhere in the GI tract & most are well-circumscribed; no morphologic feature predicts behavior with certainty (even small tumors with no mitotic figures can have mets).

12. Achalasia

Clinical Presentation

Dysphagia (for both solids & liquids)

Lab Presentation

Barium CXR: **air-fluid level** seen in the distal esophagus with **"bird's beak"** representing closed LES; esophageal dilation.

Histo → loss of ganglion cells in dilated portion of distal esophagus; presence of inflammatory cells surrounding residual ganglion cells suggests injury is immune-mediated.

Etiology and Pathogenesis

Achalasia is characterized by a hypertensive LES, incomplete LES relaxation upon swallowing, &/or aperistalsis in the body of the esophagus – as a result of these, patients experience dysphagia for both solids and liquids as well as food/liquid accumulation in the distal esophagus. Achalasia likely results from degeneration of the nerves in Auerbach's plexus; in South America it may result from a neurotoxin from T.cruzi (pathogen responsible for Chagas' disease).

Secondary achalasia refers to blockage of the esophageoduodenal junction by a tumor, most commonly a gastric adenocarcinoma; patients are generally older (> 50y), have a shorter duration of symptoms (< 1y), and lose considerable weight (>15lbs), these clues are not absolutely diagnostic because they can occur with primary achalasia. Endoscopy with biopsy is usually diagnostic but if the tumor is submucosal, exploratory surgery may be required.

Treatment

Medical Therapy:
Nifedipine to relax the LES muscle.

Procedural Therapy:
Pneumatic dilation or *Heller myotomy* to disrupt LES.
Injection of *botox* into the LES may give relief in symptomatic pts.

Notes

- May be associated with development of squamous cell CA.

13. Hirschprung Disease

Clinical Presentation

Abdominal Distention
Vomiting
Constipation

Delayed/Absent passage of meconium

Lab Presentation

Etiology and Pathogenesis

Hirschprung's Ds is a congenital abscence of ganglion cells in a segment of colon caused by defective craniocaudal migration of vagal neural crest cells during embryogenesis and resulting in constant contraction & obstruction of the aganglionic segment. It typically presents in the neonate with delayed or absence passage of meconium.

Treatment

Surgical removal of the aganglionic segment.

Notes

15. Scleroderma

Clinical Presentation

GERD
Esophageal Strictures
Abnormal Motility

Malabsorbtion (10-30%)

Lab Presentation

Etiology and Pathogenesis

Scleroderma is a systemic fibrotic disorder that manifests in the GI tract as smooth muscle atrophy & gut wall fibrosis; pathologic changes are more likely in the circular layer and atropy exceeds fibrosis. Esophageal dysfunction is the most common source of GI symptoms; GERD, strictures, abnormal motility. 10-30% of scleroderma pts. also have evidence of malabsorbtion thought to be due to intestinal stasis with overgrowth of bacteria.

Severe GI problems (inc. malabsorbtion & intestinal pseudoobstruction) occur in 10% of pts, though most pts. are somewhat symptomatic.

Treatment

Notes

- "Woosley is killing me..."
  – Megan H. –

16. Intussusception

Clinical Presentation	Lab Presentation

Etiology and Pathogenesis

Intussusception is the invagination (telescoping) of a segment of colon into the adjoining segment. Idiopathic intussusception usually starts at the ileocolic junction & affects infants and toddlers, thought to be due to a prominent Peyer's patch enlargement by a recent infection; enteroenteral intussusception (jejunojejunal, jejunoileal, ileoileal) occurs in adults and often results from a tumor. Early in the process, lymphatic return diminishes leading to edema of the affected portion of the bowel and when pressure rises to the point where arterial flow is impaired, infarction develops – The mucosa is most sensitive to ischemia since it is furthest from the arterial supply; ischemic mucosa sloughs leading to "current jelly stool" (sloughed mucosa, blood, mucus) and if untreated transmural gangrene and perforation of the leading edge of the intussusception will occur.

Treatment	Notes

20. Volvulus

Clinical Presentation

Lab Presentation

Gross → bowel shows massive dilatation, thinning of the wall, acute congestion & sometimes ischemia with hemorrhagic infarction.

Histo → congestion, ischemia, infarction, ulceration, inflammation with thinning of the mucosal wall

Etiology and Pathogenesis

Volvulus is twisting of the bowel around its mesenteric attachment → bowel obstruction & vascular occlussion (ischemia). In *volvulus neonatorum* torsion leads to gangrene of the small bowel, cecum, & ascending colon; *cecal volvulus* is secondary to a congenital abnormality in the mesenteric attachment; *sigmoid volvulus* (most common site) occurs in pts with a redundant sigmoid colon with a narrow mesenteric attachment.

Treatment

Notes

- Diet rich in fiber is a predisposing factor.

21. Amyloidosis

Clinical Presentation

Bleeding
Gastroparesis
Constipation
Bacterial overgrowth
Malabsorption
Intestinal psuedo-obstruction

Hepatomegaly

Lab Presentation

Gross Pathology: mostly normal; tumor-like mass is rare

Histology: **amyloid deposition** seen diffusely in **Congo Red** staining; filling of blood vessels with amyloid → ischemia & ulceration;

Etiology and Pathogenesis

Amyloidosis is the extracellular deposition of amyloid fibrils as insoluble polymers of soluble precursors – there are multiple types of amyloidosis; in the most common forms of systemic amyloidosis, primary (AL) and secondary (AA), the major sites of involvement are the kidneys, heart, & liver. Most cases of GI amyloidosis are asyptomatic, but manifestations may include bleeding (amyloid infiltration of blood vessels), gastroparesis, constipation, bacterial overgrowth, malabsorption, and intestinal psuedo-obstruction (infiltration of the muscle wall → dysmotility). Hepatomegaly with or without splenomegaly is also common.

Submucosal arterioles are often involved; lumenal narrowing may → mucosal ischemia & ulceration. Extravascular amyloid deposits may be found in the smooth muscle of the MM & MP in the GI tract.

Treatment

Notes

22. Diffuse Esophageal Spasm

Clinical Presentation

Chest pain prominent
Dysphagia common

Lab Presentation

Barium CXR: **"Corkscrew Esophagus"**

Etiology and Pathogenesis

DES is characterized by intermittant & unorganized high-pressure contractions of the esophageal musculature. The LES may functional normally or abnormally with high pressure, incomplete relaxation, or both. DES may result from degeneration of Auerbach's plexus (as does achalasia), and some pts. with many years of DES develop achalasia.

Treatment

Nitroglycerine
- also may use anticholinergics or CCBs

Notes

23. Infectious Diseases in the Immunocompromised GI Tract

Clinical Presentation

Novel Protazoa → debilitiating diarrheal illness with large volumes of watery, non-bloody diarrhea
- diarrhea may be associated with abdominal cramps, weight loss, malaise, & low-grade fever.

MAC → diarrhea, malabsorbtion, weight loss & fever

CMV → diarrhea, fever, hematochezia & abdominal pain

HSV → diarrhea (proctitis)

Candida → dysphagia

Amebiasis → acute colitis, chronic colitis, asymptomatic carrier; blood-bourne dissemination → amebic abcesses in liver or other tissues

CMV: gross → shallow or deep ulcers w/ bleeding/perforation
histo → megalic inclusion cells with "owl's eye" appearance; eosinophilic nuclear inclusions & smaller eosinophilic cytoplasmic inclusions

HSV: gross → small, shallow ulcers with whitish necrotic debris & an erythematous border; histo → "ground-glass" inclusion bodies in multinucleated epithelial cells with nuclear margination; dirty necrosis

MAC → visible on acid-fast stain; LP expanded by a sheet-like infiltrate of macrophages with abundant pale or granular blue-gray cytoplasm; small-bowel villi may be broadened & flattened

Candida → yellow-white plaques grossly; pseudohyphae & yeast forms on biopsy (PAS+); exudate of shed squames, PMNs, neutrophilic debris & pathogen.

Histoplasmosis → lymphocyte infiltrate with small, ovoid yeasts seen in silver staining.

Amebiasis → flask-shaped ulcers extend through MM &

Protozoal causes of AIDS-associated diarrhea include novel protozoa (cryptosporidium, microsporidium, isospora, & cyclospora) as well as "standard" parasites (giardia & entamoeba histolytica); rates of infection with giardia & entameoba are not significantly higher in AIDS pts. than in those who ar e immunocompetant. Cryptosporidium & microsporidium are the most common causes (10-35%) whereas isospora & cyclospora are less common (1-5%). Diagnosis is made by the presence of oocysts in stool specimens with a modified acid-fast stain or in duodenal biopsy (microsporidium is detected by a modified trichrome stain). Isospora is unusual in that it may cause eosinophilia.

MAC is a common mycobacterial infection in HIV-infected pts. with CD4 < 50; infection of the GI tract is usually in presence of disseminated disease and → diarrhea, malabsorbtion, weight loss & fever. Endoscopy may show a "frosted" duodenum. Diagnosis is made by demonstration of MAC by acid-fast staining in the stool or small bowel biopsy. Salmonella, shigella, & campylobacter infections occur more readily in AIDS pts, with salmonella associated with recurrent systemic infections. Histologically, the presentation of MAC is similar to that of Whipple's Ds but lacks the lipid droplets (also Whipple's bacteria are AFB negative).

CMV is one of the most common & serious infections of the GI tract in AIDS. It is seen in up to 15% of pts. with CD4 < 50; the esophagus (shallow, painful mucosal ulcers), colon (mucosal ulcers, watery diarrhea, & in severe cases → deep ulcers with profuse bloody diarrhea requiring colectomy), and stomach are the main sites of infection. Endoscopic findings are variable: from erythema & edema to ulceration or pseudotumor. A common menifestation is colitis characterized by diarrhea, fever, hematochezia & abdominal pain. Diagnosis is made by biopsy. Relapse rate is high. CMV also infects pts. who are treated for IBD with corticosteroids. CMV preferentially grows in endothelial cells & fibroblasts but will grow in other cell lines. Pathogenesis is infection of endothelium with secondary inflammatory changes & subsequent lumen thrombosis → ischemic necrosis of mucosa → ulceration.

HSV infection is most common in the esophagus & rectum; diagnosis requires sigmoidoscopy which reveals small vescicles & progression to erosion that may coalesce into diffuse ulcers with biopsy that reveals intranuclear inclusions in multi-nucleated cells (diagnosis is confirmed by viral culture).

Dysphagia & odynophagia are the most common esophageal symptoms in pts. with AIDS; odynophagia usually implies ulcerating ds or severe esophageal inflammation, whereas dysphagia suggests Candidia infection or non-HIV related disease. Esophageal ulcers are caused by CMV ("punched out ulcers), HSV (multiple punctate ulcers), or HIV idiopathic esophageal ulcers (more common than HSV) – differentiation of IEUs from infectious ulcers is important because the treatment for the former is prednisone; at least 10 biopsies are needed to rule out CMV & HSV.

Amebiasis most often involves the cecum and presents grossly as mucosa with a friable, erythematous granular appearance that resembles idiopathic IBD; there may be small, shallow discrete ulcers or large undermined ulcers separated by normal mucosa.

Treatment

AIDS → HAART (may resolve the diarrhea)

Microsporidium & Cyclospora → TMP/SMX

Cryptosporidium → Azithromycin

Microsporidium → Albendazole

MAC → macrolide + ethambutol

CMV → ganciclovir + foscarnet
- side effects are bone marrow suppression (ganiclovir) & renal toxicity (foscarnet)

HSV → acylclovir, famcyclovir, valcyclovir

Candida → fluconazole or AMB

Idiopathic esophageal ulcers → prednisone or thalidomide

Notes

- The digestive tract is the most commonly affected organ in advanced HIV disease.
- Diarrhea is a common side-effect of HAART.
- HAART accelerates HCV-mediated cirrhosis
- 50-80% of the world's population is + for CMV
- Systemic MAC is associated with liver disease that is usually clinically silent but may present with fever, night sweats, diarrhea, & isolated ALP elevation.

AIDS Biliary Tract Disease

Acalculus Cholecystitis
- usually seen in fasting critically ill patients
- may present in AIDS with intermittant fevers & RUQ pain
- specific pathogen has not been identified

AIDS Cholangiopathy
- *Papillary stenosis* mimics common bile duct gallstones, whereas *sclerosing cholangitis* mimics PSC.
- Presentation is RUQ pain & ↑ ALP but without jaundice
- 75% show biliary tract dilation on ultrasound
- biliary & duodenal epithelium may show cryptosporidium or microsporidium.
- pain from papillary stenosis can be relieved by endoscopic sphincterotomy.

HIV Associated Pancreatitis
- associated with some drugs: ddI, pentamidine, TMP/SMX
- associated with CMV
- elevated amylase is common in HIV & is not specific for pancreatitis; it may be due to EBV-related parotid gland enlargement or macroamylasemia (non-specific binding of amylase & Ig resulting in ↓ renal clearance)

Kaposi's Sarcoma
- histo → densely cellular spindle cell proliferation forming blood-filled, slit-like vascular spaces; spindle cells have only moderate atypia, scattered mitotic figures, characteristic pale eosinophilic hyaline cytoplasmic inclusions.
- associated with HSV-8

25. Intestinal Lymphangiectasia

Clinical Presentation

Lab Presentation

Gross → multiple tiny white flecks (chylous lymph in dilated mucosal lymphatics) seen in duodenal mucosa

Histo → lacteals in intestinal villi are greatly dilated

Etiology and Pathogenesis

Intestinal lymphangiectasia is characterized by dilated lymphatic vessels in the small bowel mucosa; *primary lymphatic vessels* is a rare sporadic, congenital or acquired disorder, in which mucosal lymphatics are widely distended & leak protein/lymphoytes into the intestinal lumen → resulting in hypoalbuminemia & lymphopenia – *secondary lymphangiectasia* may result from retroperitoneal lymph node obstruction by tumor, radiation, or inflammatory processes.

Treatment

Notes

26. Whipple's Disease

Clinical Presentation

Lab Presentation

Histo → small bowel mucosa with macrophages with abundant pale granular cytoplasm (strongly PAS+), expanding the LP & widening the villi (gives the impression of a flat mucosa), lipid droplets scattered in the LP.

Etiology and Pathogenesis

WD is a rare systemic infection caused by *Tropheryma whippleii* (a gram + actinomycete) that may involve virtually any organ but affects the small bowel in most patients, leading to malabsorbtion. Affected organs are infiltrated by macrophages that contain phagocytosed bacteria; the disease process likely represents a defect in macrophage-mediated killing.

Treatment

Notes

27. Giardiasis

Clinical Presentation

Steatorrhea

Lab Presentation

Histo → trophozoites seen on lumenal surface of small bowel & between the villi

Etiology and Pathogenesis

Giardia lamblia is a wide-spread protozoan that is the most common cause of water-bourne diarrhea worldwide; cysts are highly infectious (ingesting 10 cysts can infect you). Cysts resist chlorination but are removed by filtration; direct fecal-oral transmission occurs particularly in day-care centers and among MSMs. Severe giardiasis may be seen in the immunocompromised. Trophozoites form a physical barrier to absorbtion by adhering to the mucosal surface & damage to the microvillus brush border leading to mucosal enzyme deficiency (an acquired lactase deficiency may develop). Diagnosis is made by microscopic examination of duodenal fluid aspirates & stool microscopy (with 3 specimens, sensitivity is 90-95%); ELISA for giardia specific antigen has a sens.&spec. of 95-98%.

Treatment

Notes

28. Cryptosporidiosis

Clinical Presentation

Watery Diarrhea

Lab Presentation

Histo → round, 2-4um PAS+ organisms that are incorporated into the microvillous border of the mucosa of the stomach, small bowel, large bowel, & biliary tract; organisms line both surface epithelium & crypts; most pts. have no villous abnormalities but there may be villous atrophy an intense PMN infiltration
- organisms develop in parasitophorous vaculoles, which replace the microvillous border of the gut & are covered by the host cell membrane (they are intracellular)

Etiology and Pathogenesis

Cryptosporidium is a protozoan parasite that colonizes the brush border of columnar epithelium & causing diarrhea. Oocysts resist cholrination (even treated water can transmit infection); infection is self-limited in immunocompetant persons, but the immunocompromised may fail to clear the infection & develop a chronic watery diarrhea.

Treatment

Notes

29. Carcinoid Syndrome

Clinical Presentation

Episodic cutaneous flushing of the face/neck
Sweating
Diarrhea
Wheezing
Hypotension
Right-sided valvular heart disease

Lab Presentation

Etiology and Pathogenesis

Most carcinoid tumors secrete 5-HT, which with its breakdown product 5-HIAA can be measured in the lab. Carcinoid syndrome results from release of serotonin & other tumor-derived vasoactive compounds from liver mets directly into the systemic circulation via the hepatic vein – the syndrome does not occur if the tumor is confined to the bowel wall or mesentery (secretory products drain into the portal system & are inactivated in the liver). Cardiac disease is a major cause of death in affected pts.

Treatment

Notes

- Only 5% of pts with small bowel carcinoid tumors present with CS.

35. Celiac Disease

Clinical Presentation

Lab Presentation

Gross → flat mucosa with loss of ridges & convolutions

Histo → villus flattening with large numbers of lymphocytes infiltrating the surface epithelium; crypt hyperplasia

Serology → Anti-gliadin (IgA more specific than IgG)
Anti-endomysial Abs

Etiology and Pathogenesis

Celiac disease (celiac sprue) is an immunologically-mediated inflammatory disease of the small bowel mucosa caused by intolerance to a component of gliadin (a storage protein of wheat, barley, & rye) in genetically susceptible individuals. Damage to enterocytes is initiated by breakdown products of gluten & cell-replication in the crypts fails to keep pace with the destruction of enterocytes; this leads to a shortening in height & increase in length of the crypts along with an increased lymphoplasmacytic infiltrate. Celiac disease commonly presents in children, but presentation may be delayed even to old age. Pathologic changes are most severe in the distal duodenum & upper jejunum, decrease distally and may be minimal in distal ileum. Severity of malabsorbtion is dependent upon length of small bowel involvement & correlates with variability in clinical presentation; histologic changes are patchy & multiple biopsy sites are needed to find the characteristic changes.

Pathogenesis is though to proceed as follows: 1) infection or other mucosal injury releases tissue transglutaminase (tTG) from cells in the small bowel lamina propria, 2) tTG enzymatically cross-links glutamine-containing proteins (gliadin has >40% glutamyl residues) creating large gliadin-tTG complexes whict elicit an immune response, 3) antibody to gliadin-tTG complexes interferes with TGF-β activation & thus blocks epithelial maturation (tTG normally activates TGF-β, which regulates maturation of epithelial absorbtive cells), 4) gliadin &/or tTG-gliadin also elicits a cytotoxic lymphocyte response, 5) continued gliadin exposure perpetuates immune-mediated injury. A specific anti-tTG test may soon be available to aid diagnosis.

Treatment

Gluten-free diet.

Notes

- Diagnosis is made via a small bowel biopsy demonstrating villous atrophy & clinical improvement on a gluten-free diet.
- Celiac ds patients shows variable sensitivities to gluten.
- 0.4% of healthy US blood donors have anti-endomysial Abs.

36. Short Bowel Syndrome

Clinical Presentation	Lab Presentation
Etiology and Pathogenesis	
Treatment	Notes

37. Diarrhea (general)

Clinical Presentation

Acute: < 4 months & most often viral or bacterial
Chronic: > 4 months

Inflammatory → multiple mucoid, bloody stools with tenesmus & abdominal cramping

Lab Presentation

Stool Osmotic Gap Measurements:

Na > 90 & osmotic gap < 50 → secretory diarrhea; (or rarely osmotic due to Na2SO4 or Na2PO4 ingestion)

Na < 60 & osmotic gap > 100 → osmotic (if stool volume does not improve onfast suspect Mg ingestion)

Na > 150 & osmolarity > 375 → contamination w/ conc. urine

osmolarity < 200-250 → contamination with dilute urine

Objectively, diarrhea is the quantitiation of an increase in stool weight of greater than 200g per 24hrs; associated symptoms may include urgency, perianal discomfort, cramping or incontinence. Of the 9L of fluid that enter the bowel each day (2L from diet & 7L from intrinsic secretions) only 100mL is excreted in stool – most of the fluid is absorbed along with Na in the small intestine (8L), while 90% of the remainder is absorbed (also with Na) in the large intestine; the capacity of the colon to absorb fluid exceeds by 3x the amount normally delivered to it; the colon also secretes K & the amount of K in the stool exceeds that entering it (but 97% of K delivered to GI tract is absorbed in the small bowel).

IBD may produce diarrhea in a number of ways: loss of absorbtive surface causing increased osmotic load drawing fluid into the lumen, leakage of fluid from damaged blood vessels, & stimulation by inflammatory mediatiors (PGs) to actively secrete fluid.

Inflammatory diarrhea is characterized by the presence of PMNs in the stool; patients may exhibit other signs of a systemic inflammatory response – examples include bacterial diarrhea, pseudomembranous enterocolitis, IBD, radiation colitis, diverticulitis. *Osmotic diarrhea* is chracterized by inability to account for all stool water on the basis of stool electrolytes; this is determined by multiplying 2 times the measured stool Na + stool K and comparing it to the simultaneously measured total stool osmolarity (or an estimated osmolarity of 290mosm/kg water – this gives the "stool osmotic gap", which if it exceeds the calculated osmolarity (usually by 25-50) an osmotic component to the diarrhea is present. Examples of osmotic diarrhea include lactase deficiency, Mg containing antacid or Golytely ingestion, or sorbitol or lactulose ingestion. *Steatorrhea* is a specialized type of osmotic diarrhea characterized by excess stool fat (> 6g / 24hours); this can only be effectively tested when the pt. is eating a "regular" diet containing 100g of fat per day – occuring along with weight loss & evidence of vitamin malabsorbtion (A → night blindness, D → hypocalcemia & osteomalacia, E → RBC fragility, K → ↑ PT), steatorrhea suggests generalized malabsorbtion. Examples of malabsorbtive diarrhea include celiac sprue, Whipple's ds, bacterial overgrowth syndrome, ileal resection > 100cm in length, chronic pancreatitis with pancreatic enzyme deficiency. *Secretory diarrhea* is usually characterized by substantially elevated stool volumes & concomittant hypokalemia; it is diagnosed by finding in a liquid stool that the osmotic gap is < 50 mosm/kg water; another clue to the diagnosis of secretory diarrhea is that it does not resolve significantly by fasting. Examples of secretory diarrhea include laxative abuse, colonic villous adenoma, cholera, VIP secreting tumor (watery diarrhea, achlorhydria, hypokalemia), cholerrheic enteropathy due to bile salts, & fatty-acid induced diarrhea.

Treatment

For bacterial diarrhea → treat with appropriate antibiotic except for Salmonella (tx → prolonged carrier state)

Notes

- Cholera → excessive secretion of small bowel > large bowel
- Cholerrheic enteropathy→ excessive secretion from colon only
- Inflammatory cells in stool → IBD, bacterial
  - inflammatory cells absent → viral, toxin-related

Diagnostic Evaluation of the Patient with Acute Diarrhea

1. Stool Examination
   - i. Inflammatory Cells
     - if present → suggests mucosal disease (IBD, bacterial infection)
     - if absent → suggests viral or toxin-mediated diarrhea
   - ii. O&P (some labs also do antigenic tests for giardia & cryptosporidium)
   - iii. Stool Culture
     - postive culture → treat with appropriate antibiotic except for *Salmonella* (tx → prolonged carrier state)
     - negative culture
       - inflammatory cells present → IBD likely
         - severly ill → r/o toxic megacolon, analyze blood cultures, abdominal XR, treat as IBD
         - not severly ill → colonoscopy after careful & gentle prep, possibly unprepped exam
       - inflammatory cells absent
         - systemically ill → if hx is appropriate with travel to endemic area or if pt. has hypogammaglobinemia, evaluate duodenal aspirate for giardia
         - not systemically ill with no resolution of diarrhea → stop all milk products, tx symptoms & evaluate for chronic diarrhea
2. Sigmoidoscopy
   - Abnormal Mucosa
     - pseudomembranes → check for C.difficile toxin, tx with metronidazole or vancomycin
     - ulcerations/granularity
       - proctitis only → culture for N.gonorrhea, gram stain & culture urethra & pharynx; biopsy
       - more extensive → culture, biopsy for granulomas, non-specific findings of IBD, CMV, parasites

Evaluation of the Patient with Chronic Diarrhea

Outpatient

Stage I

1. Stool Studies: test for fecal leukocytes, O&P, C.difficile toxin, pH, weight in grams for 24hours, fat in 72h collection while patient is consuming 75-100g fat per day
2. Blood Studies: CBC, ESR, electrolytes, BUN, creatinine, thyroid studies (looking for hypothyroidism), gastrin; if diarrhea is > 1L per day +/- hypokalemia, measure VIP, substance P, calcitonin, histamine
3. Urine Studies: 5-HIAA, laxative screen
4. Radiographic Studies: abdominal XR (looking for calcifications of chronic pancreatitis), Barium studies of the UGI, small bowel, and colon.
5. Endoscopic Studies: sigmoidoscopy with biopsy (before the barium studies & without hyperosmotic prep.)
6. Dietary Intervention: lactose-free diet

Stage II (if diagnosis is not appearant after Stage I)

7. Stool Studies: ELISA for giardia antigen, alkalinization assay (for phenolphthalein, found in some laxatives), measurement of stool electrolytes & osmolality.
8. Urine Studies: thin-layer chromatography for bisacodyl, phenolphthalein, anthraquinones
9. Radiologic Studies: enteroclysis, abdominal CT
10. Endoscopic Studies: colonoscopy & ileoscopy with biopsy (for right-sided colitis, amebiasis, Crohn's, & microscopic/collagenous colitis), upper endoscopy with small-bowel biopsy.
11. Other: test of bile acid or other breath test for bacterial overgrowth.

Inpatient

All of the above plus the study of fasting vs. non-fasting component of diarrhea. Hospitalization is required to support the patient with IV fluids during the fast. Secretory diarrhea will often decrease with a fast but the volume will remain over 200 grams of stool over 24hours; osmotic diarrhea will essentially cease with fasting & resume with food intake.

38. Small Bowel Tumors

Clinical Presentation

Most are asymptomatic; symptomatic ones are most likely malignant.

Benign → GI bleeding, intusseption, nonspecific symptoms, pain

Malignant → abdominal pain, intestinal obstruction, intussuseption, occult GI bleeding & weight loss, colicky pain

Lab Presentation

Carcinoid tumor:

Gross path → mets often larger than original tumor; 1/3 are multiple; sessile, umbilicated nodules or polyps; larger tumors may kink bowel wall; cut surface is yellowish, thickened submucosa and muscle layer; large invasion in liver

Histology → small uniform cells growing in nests/cords, trabeculae, tubules, or sheets; fibromuscular hyperplasia with little atypia & bland cigar-shaped nuclei; stain with synaptophysin

Leiomyoma:

Gross path → circumscribed tumors with white/yellow cut surface; may show cysts, whorls, & mucosal thinning and ulceration

Histology → bundles of interlacing smooth muscle fibers with uniform nuclei; a subset can have high cellularity & hyperchromatic nuclei

Diagnostic evaluation usually begins with a barium study of the small bowel; placing air into the colon and compressing the cecal region of the colon provides an air-contrast view of the distal ileum & increases the sensitivity of detecting ileal tumors. An enteroclysis involves placing a nasoduodenal tube and administering the barium through the tube. Endoscopy may be used to detect & biopsy the tumor, whereas CT is used to characterize and stage the tumor – Scanning with radiolabeled octreotide may identify small bowel carcinoid tumors, as does measurement of serum serotonin & urinary 5-hydroxyindoleacetic acid. Arteriography, scintigraphy, and seratonin measurement are also used (carcinoid tumors may secrete seratonin).

Adenoma may be tubular or villous – Tubular adenomas have a low malignant potential and are most commonly found in the duodenum; they may be present with bleeding or obstruction. Villous adenomas have a greater malignant potential. Adenomas associated with *familial polyposis syndrome* have a predilection for the second part of the duodenum and often involve the periampullary region. *Leiomyomas* are single tumors arising from the MM or MP of the small intestine; they usually grow outside of the bowel lumen and do not become symptomatic until they outgrow their blood supply and bleed into the bowel lumen. *Lipomas* are submucosal tumors that arise from serosal or submucosal fat occuring mainly in the duodenum or ileum.

Adenocarcinomas (50% of small bowel cancers) occur most often in the proximal small bowel (except in Crohn's, where they occur in the ileum) and are associated with Crohn's disease, celiac sprue, ilieal conduits, and familial adenomatous polyposis. *Carcinoid tumors* are rare, potentially malignant neuroendocrine tumors most often found in the small bowel in the ileum; most are indolent & asymptomatic, and in symptomatic pts. vague abdominal pain is the most common symptom – carcinoid syndrome occurs in 10% of pts. due to serotonin secretion and is characterized by watery diarrhea, sweating, dyspnea, abdominal pain, hypotension, and right-heart failure with fibrotic plaques on the tricuspid & pulmonic valves (90% of pts. with carcinoid syndrome have metastatic disease, and carcinoid tumors are more likely midugt tumors). *Lymphoma* most often occurs in the small bowel as cancer of nodal origin with secondary involvement of the intestine; B-cell lymphoma is associated with nodular lymphoid hyperplasia, immunoproliferative small intestine disease, and AIDS. T-cell lymphoma is associated with celiac sprue. *Leiomyosarcoma* is the most common sarcoma of the small intestine; tumors generally grow extraluminally and do not cause obstruction (larger tumors behave more malignantly) – tumors are vacular and may present with bleeding.

Treatment

Notes

- Adenocarcinomas occur with most often in males age 50-70.
- Few tumors (1-2% of GI tumors) arise from small bowel.
- Increased risk with adenomatous polyposis syndrome & Crohn's disease.
- 2-5% of polyps removed endoscopically show malignancy (many back-to-back glands with penetration of gland profile through the muscularis mucosa & production of desmoplastic stroma).
- *Ampullary carcinoma* is a small bowel adenocarcinoma arising from the duodenal mucosa, common bile duct, pancreatic duct or head of the pancreas; may be polyploid (often adenoma), ulcerating, or infiltrating & may → obstruction → jaundice &

39. Large Bowel Tumors

Clinical Presentation

Lab Presentation

Gross Pathology:

Hyperplastic polyps → small, pale sessile polyps;

Juvenile polyps → smooth spherical polyp with thin stalk; cut surface shows cystic mucin-filled spaces, vascular congestion & hemorrage

Colorectal CA → polyploid or fungating & exophytic (right) annular (left).

Histology:

Hyperplastic polyps → crypts in upper ½ of polyp have a serrated/convoluted appearance with ↓ed goblet cells; "star shaped" lumens

Juvenile polyps → cystic crypts filled with mucin & PMNs; inflamed LP; ulcerated mucosa with granulation tissue; eroded epithelium

Colorectal CA → adenocarcinoma with desmoplastic stroma and invasion of the bowel wall

Hyperplastic polyps are benign and usually smaller than 5mm in diameter and found in the rectosigmoid region (they are also the most common polyp in the large bowel); pts. with hyperplastic polyps are not more likely to have more proximal colorectal neoplastic polyps (they have no malignant potential). *Juvenile polyps* are non-malignant hamartomas that usually occur in the colon of kids aged 4-14 (they may evert out of the anal canal); 70% present as a single region & 30% as multiple regions – if more than 10 polyps are present the condition is labeled *juvenile polyposis syndrome*, which is associated with genetic abnormalities on chromosome 10 and a possible increased frequency of colon cancer. *Peutz-Jeghers Syndrome* is a congenital disorder (inherited on chromosome 19p as autosomal dominant) associated with intestinal hamartomas and mucocutaneous hyperpigmentation; polyps are not neoplastic but there may be an increased risk of colon cancer. *Adenomatous polyps* are benign, monoclonal neoplasia of the mucosal crypt that occur in the large bowel, small bowel, & occasionally stomach – they are often a precursor lesion to small bowel and colorectal carcinomas (not gastric CA); adenomatous polyps vary in size and may be flat, sessile, or pedunculated (with stalk of mucosa & lamina propria) and usually are paler or darker than the surrounding mucosa; histologically, they may be tubular (most common, closely packed branching tubules with cerebriform apperance at low power), villous, or tubulovillous – nuclei are pleomorphic, hyperchromatic, pseudostratified, and there is loss of cytoplasmic mucin.

Colorectal cancer most often arises from polyps, with villous and larger polyps more likely to be cancerous; removing adenomatous polyps is thought to prevent CRC and is the justification for screening of persons age 50 & older. Screening may consist of fecal occult blood testing, sigmoidoscopy/colonoscopy, &/or newer molecular analysis of cells sloughed from the colorectal epithelium. *Adenocarcinoma* is much more common in the large bowel – 90-95% are sporadic, 5-10% are seen in pts. with *hereditary non-polyposis CRC syndromes*, and 1% in pts. with *adenomatous polyposis syndromes* (pts. develop 100s-1000s of adenomatous polyps by late teens which will become CA if colectomy is not done). Colorectal cancer prognosis can be predicted by: TNM staging, histologic grade, presence of perforation/ulcer, degree of mucin production (mucinous tumors more likely in rectum & sigmoid colon) & whether "signet ring" cells are present, and presence of mets (commonly via the portal circulation to the liver).

Treatment

- *Segmental colectomy* for malignant polyp not completely excised.

Notes

Epidemiology of Colorectal CA:

- Second leading cause of cancer death in the United States.
- men > women; most patients > 50yrs
- lifetime incidence 5-6% and chance of dying 2-3%.
- Risk Factors: age, family history, polyps, IBD, red-meat diet
  - dietary fiber has not been shown to prevent polyps
  - Ca, Se, and folic acid are protective
  - physical activity is protective
  - NSAIDs are protective
  - multiple adenomatous polyps
- Small polyps (< 5mm) rarely contain villous elements or severe dysplasia; larger polyps are associated with ↑ age, distal location, ↑ed villous elements & ↑ed dysplasia.

40. GI Stromal Tumors

Clinical Presentation

Lab Presentation

Gross Pathology: cut surface appears flat and granular with patchy hyalinization, lysis, & hemorrhage

Histology: undifferentiated cellular spindle cell pattern; uniform ovoid to cigar-shaped nuclei with vescicular chromatin; nuclei may be arrayed in palisades; pale eosinophilic cytoplasm with indistinct cell borders
- a minority (more common in stomach) show: epithelioid pattern, sheets of rounded to polygonal cells, uniform round to ovoid nuclei with vescicular chromatin, clear to eosinophilic cytoplasm with distinct cell borders

Etiology and Pathogenesis

GISTs are spindle & epithelioid mesenchymal tumors with little or no evidence of smooth muscle or neural differentiation; they differentiate toward the interstitial cell of Cajal phenotype. GISTs have a c-kit protooncogene mutation that results in overexpression of Kit protein (a tyrosine kinase) → ↑proliferation & ↓ apoptosis; some tumors respond to Gleevec. GISTs occur anywhere in the GI tract (stomach >> small bowel > rectosigmoid > colon > esophagus); most are well-circumscribed (even the malignant ones) with fibromuscular septa that give tumors a lobulated appearance. No GIST can be labeled as benign with absolute confidence.

Treatment

- Some GISTs respond to *Gleevec*

Notes

- Recurrence is common & may occur as late as 20-30 years after surgical excision, even when excision is complete.
- Death results from massive intra-abdominal disease.
- Gastric tumors may show juxtanuclear cytoplasmic vacuoles; they may also become larger without without being malignant

41. GI Bleeding (General)

Clinical Presentation

Shock (25% of blood volume or 1,500mL lost acutely)
Hypotension &/or Orthostatic hypotension
Tachycardia
Hematemesis
Melena (upper GI bleed)
Hematochezia (lower GI bleed)

Lab Presentation

Common causes of upper GI bleeding are: DU, erosive gastritis, varices, esophagitis, GU, & Mallory-Weiss tear – UGI bleeding accounts for 80-90% of GI blood loss. Common causes of lower GI bleeding are: diverticulosis, arteriovenous malformations, colitis, malignancy, hemorrhoids, and post-polypectomy bleeding. NSAIDs and ferrous sulfate tablets (iron supplements) may also cause GI bleeds, as may SSRIs (due to their interference with serotonin uptake by platelets).

Risk factors for poor outcomes from non-variceal UGI bleeding are: age > 60y, severe co-morbidities, inpatient bleeding, persistance hypotension or shock, severe hematochezia with red blood in emesis or per NG tube, transfusion > 6units of blood for single bleeding episode, severe coagulopathy or platelet dysfunction, rebleeding from the same lesion during hospitalization. Variceal bleeding has a higher mortality than other causes (esp. when combined with portal HTN).

Diagnostic studies for evaluation of UGI bleeding: upper endoscopy (most commonly makes diagnosis), NG aspiration, angiography. Diagnostic studies for evaluation of small bowel bleeding: capsule endoscopy, Meckle's scan, small bowel follow through, enteroclysis, angiography, and bleeding scan.

Orthostasis is important because in acute bleeds hematocrit may be normal even with severe blood loss.

Treatment

Prompt fluid replacement for hypovolemia.

Esophageal varices may be banded or sclerosed.

Ulcers may be injected with epinephrine, saline, or alcohol or cauterized endoscopically.

Reduction of portal pressure with a portal decompressive procedure may be helpful in treating varices.

Octreotide may reduce portal pressure in varices.
PPIs may have benefit in pts. who have undergone endoscopic therapy in tx of acute GI bleed.

Surgery may be necessary.

Notes

Epidemiology
- 300,000 hospital admissions anually; most cases upper GI
- 50-150 per 100,000 persons
- 5% require surgery
- 10% require endoscopic therapy
- overall mortality: 5-10%

- Diagnostic procedures include NG tube aspirate, upper endoscopy, and occasionally arteriography.
  - Barium studies are not useful

- Most GI bleeding is self-limited; 80-90% stops within 24h.
  - 25% of pts. with LGI bleeding have recurrent bleeds

- DU → erosion into gastroduodenal artery in area of duodenal bulb.

42. Esophageal Varices

Clinical Presentation

Asymptomatic until bleeding occurs

Lab Presentation

Gross Pathology → varices collapse after death & may be unimpressive on autopsy; seen on ensoscopy

Histology → dilated veins in esophageal wall; thrombi may be visible in rupture.

Etiology and Pathogenesis

Portal venous HTN results in diversion of obstructed blood flow to the systemic veins that anastomose with the portal circulation – esophageal & gastric collaterals are the most important portosystemic shunts. Bleeding occurs when ↑ ↑ pressure ruptures one or more vessels; most bleeding varices are in the distal 1/3 of the esophagus – larger varices have an increased chance of rupture.

Treatment

- β-blockers to ↓ pressure in varices.
- Direct pressure with balloon, injection with sclerosant, or banding of the varices.
  - these procedures are done endoscopically
- Octreotide to ↓ portal pressure.
- TIPS

Notes

- Portal pressure of >12mmHg between the portal vein/IVC is required for varices to rupture & bleed.
- Size of varix is best predictor of variceal hemorrhage

42. Ischemic Colitis

Clinical Presentation

Bowel Obstruction

Lab Presentation

Gross Pathology:

Early acute ischemia → extreme congestion & hemorrhage of the mucosa & submucosa; infarction & ulceration; with progression MP becomes infarcted & may perforate.

Subacute ischemia → areas of ulceration exude a protein-rich fluid which leads to pseudomembrane formation

Chronic ischemia → fusiform strictures (fibrosis)

Histologic progression:

1. mucosal & submucosal edema with hemorrhage
2. epithelial necrosis → crypt miniaturization & hypereosinophilia (when restricted to mucosa, leakage of fibrin & RBCs); necrotic mucosa w/ bacterial colonies mucosa with colonies of bacteria (when severe)
3. pseudomembranes of necrotic tissue, fibrin & blood may form & be hard to distinuish from C.difficile colitis
4. extensive ischemia → coagulative necrosis of MP with risk of colonic perforation
5. healing → fibrosis (prominent in submucosa) leading to

Etiology and Pathogenesis

In the GI tract, the colon is at increased risk of ischemia due to its relatively low-flow blood supply. Causes of ischemia include vascular obstruction (atherosclerosis, vasculitis, thromboemboli, venous thrombosis, diabetic small-vessel disease, vasospasm caused by cocaine abuse), post-hypotensive &/or low-flow states (shock, sepsis), intrinsic/extrinsic obstructions (tumor, adhesions, incarcerated hernia, prolapse, volvulus, impaction), and drugs (NSAIDs, estrogens, digitalis). The "watershed" blood supply areas are the most often affected: the *splenic flexure* (between superior & inferior mesenteric arteries) and *rectosigmoid* (between the inferior mesenteric & superior rectal arteries).

Treatment

Notes

43. Angiodysplasia

Clinical Presentation

Lab Presentation

Gross Pathology: ectatic vessels collapse after resection and are difficult to see; most are > 5mm in diameter

Histology: irregularly shaped clusters of ectatic small arteries, veins, and capillary connections

Etiology and Pathogenesis

Angiodysplasias are aquired telangiectasias (dilated blood vessels) that are common in the cecum & proximal ascending colon – Most are nonpalpable & found incidentally during colonoscopy.

Treatment

Notes

- Most common GI vascular abnormality.
- 2nd leading cause (behind diverticulosis) of LGI bleeding in patients older than 60yrs.
- 75% in cecum & ascending colon; 15% in jejunum & ileum; 10% elsewhere in the GI tract.
- *Hemangiomas* are larger than telangiectasias and diffusely involve large areas of the bowel; histology shows large numbers of blood vessels.

44. Diverticulosis

Clinical Presentation

1-2% of patients develop symptoms.

Lab Presentation

Gross Pathology: see below

Histology: flask-shaped outpouching of mucosa and submucosa through loose connective tissue tunnel in the MP; diverticulitis → mucosal ulceration, granulation tissue, variable inflammation
- peridiverticular abcesses are lined by granulation tissue
- diverticular area shows only mucosa & muscularis mucosa

Barium XR → areas of outpouchings alternating with areas of lumenal narrowing (caused by hypertrophic bands of musuclaris propria).

Etiology and Pathogenesis

Diverticulosis refers to protrusions of the mucosa through the mucosal wall occurring mainly at points of weakness (where muscle wall is penetrated by blood vessels) and forming two rows protruding into the pericolic fat between the mesenteric & antimesenteric taeniae – Taenia coli circular muscle may be thicker than normal, giving a corrugated appearance to the luminal surface. Diverticula often contain pellets of calcified feces, which may contribute to diverticulitis via abrasion or occlusion; diverticulitis may result in: colonic perforation & pericolonic abcess, hemorrhage with erosion into major blood vessels. Complications include: 1) *diverticulitis*, 2) *hemorrhage* – (usually a small amount of occult blood, but bleeding may be sudden & massive if mucosal erosion exposes an artery , 3) *fistulae* secondary to formation of a pericolic abcess & local peritonitis (colovescical fistulae are common), 4) *intestinal obstruction* secondary to lumenal narrowing, & 5) *perforation*.

Diverticula form as high pressures generated in propeling stool with low bulk (low fiber content) weaken the wall over time.

Treatment

- 0.5% of patients require surgery.

Notes

Epidemiology:
- > 1/3 of persons >60y have diverticula; incidence ↑s with age
- high morbidity & low but significant mortality in the elderly
- Low fiber diet → ↑ force necessary to move stool → ↑ed risk
- Most common in the sigmoid colon; diverticula may be single or multiple.
- 15-25% get diverticulitis; 5-15% get diverticular bleeding.

44b. Diverticulitis

Clinical Presentation

Spectrum:
Mild abdominal discomfort / fever / sepsis / perforation with rebound tenderness / death.

Lab Presentation

Etiology and Pathogenesis

Diverticula become infected either secondary to obstruction or to pressure-generated microperforations in the mucosa (and infection of mucosa by intestinal bacteria).

Simple diverticulitis → abdominal pain +/- fever (75% of pts. have simple diverticulitis)

Complicated diverticulitis → simple diverticulitis + perforation, obstruction, abcess, fistula, or a combination of these.

Abdominal XR & CT are highly suggestive in the acute setting; colonoscopy is deferred until after inflammation resolves (due to concerns about perforation).

Treatment

Almost all complicated presentations require surgery.

Surgery may also be needed to manage adhesions resulting from healed episodes of diverticulits.

Notes

Epidemiology:

- Sigmoid (94%), Descending (1%), Transverse (1%), Ascending (2%), Cecum (2%).
- incidence increases markedly with age (40y→5%, 85y→65%)
- much more common in Western than developing world
- 2-5% mortality with the first attack of diverticulitis.
- most who have a single attack will never have another; 30% will have a second attack & surgery is usually necessary.
- Do not do colonoscopy acutely; ↑ pressure could perforate the inflammed diverticulae.

45. Mallory-Weiss Tear

Clinical Presentation

Lab Presentation

Etiology and Pathogenesis

Mallory-Weiss tear is a mucosal tear in the distal esophagus at the gastroesophageal junction, occurring after a bout of retching or vomiting; bleeding results when the tear involves the underlying esophageal venous or arterial plexus – bleeding is usually self-limited with only modest blood loss.

Treatment

Notes

- Relatively common in alcoholics.
- Portal HTN → ↑ed risk of severe bleeding

46. Inflammatory Bowel Disease (Ulcerative Colitis & Crohn's Disease)

Clinical Presentation

Diarrhea
Bleeding
Pain
↓ Weight

UC → **Bloody, mucopurulent diarrhea**;
Bowel movements are frequent & small with urgency
Crampy pain precedes stools
Fever / weight loss / anemia
Abdominal pain (before BMs)

CD → Abdominal pain (frequently postprandial)
Non-bloody diarrhea (small bowel & right colon)
Bloody diarrhea (extensive Crohn's colitis)
Weight loss (↓ed food intake, not malabsorbtion)
Pallor / temoral & interosseus wasting

Childhood presentation → fever/anemia/arthritis/failure to grow

Lab Presentation

XR: may show dilated, edematous colon & free peritoneal air

Barium study:
Chronic UC shows ↓ed distensibility of the involved segment → shortened & tubular lumen; acute inflammation → granularity, spiculation, edema, "collar button" ulcers
Early CD: aphthous ulcers
Later CD: cobblestoning, stricture, fistulae, wall-thickening "string sign",

Lab Findings:
UC →
CD → nonspecific, anemia, iron &/or B_{12} deficiency, thrombocytosis (active ds), hypoalbuminemia (mark of disease severity)

Path: crypts irregularly & less densely distributed as well as variable in diameter, branched, and not necessarily reaching the MM; densely cellular infiltrate of WBCs with plasma cells at base (near MM)

Chronic intestinal inflammation may be caused by a proper immune response to chronic injury (persistant infection or abnormal lumenal contents such as hydrgen sulfide) or an abnormal response to ubiquitous agents (defective mucosal barrier, inflammatory cytokine balance, peripheral immunosuppression, or antigen presentation). IBD is though to arise from potentiating interactions between initiating events (infection, toxin, NSAIDs), perpetuating events (lumenal bacteria, dietary antigens), and immunoregulatory abnormalities to produce tissue damage and clinical symptoms. Up to 40% of pts. with IBD have inflammation outside the bowel.

Ulcerative Colitis is chronic, spontaneously relapsing idiopathic mucosal inflammation that is limited to the colon; the rectum is always involved, and continunous, confluent disease affects the colon to a variable extent. Pathology is characterized by inflammation of the lamina propria with or without epithelial destruction – lymphokine profile is predominantly T_H2. Clinical presentation is shown above; with *proctitis*, there may be blood, mucus, and constipation (due to rectal spasm). The initial attack will be mild in 54% of patients, moderate in 27%, and severe in 19%; >90% of those with a mild first attack will go into remission. Severity & extent of colitis at first presentation affects the likelihood & timing of needing a colectomy; early onset of disease is associated with more complicated ds and increased familial incidence. Endoscopy must be done carefully, as the thinned bowel wall has an ↑ed chance of perforation – endoscopic findings are 1) mild loss of vascular pattern, diffuse erythema, & granularity, 2) moderate "mucopus" collections of yellowish exudate on the mucosa, friability when scope touches, 3) severe, spontaneous bleeding with diffuse ulceration, 4) classic distribution starting in the rectum and extending proximally with confluent inflammation. Screening for dysplasia/cancer should be done when ds has been present for > 8 yrs. The usual course of UC is chronic intermittant attacks that last for weeks to months separated by periods of no activity (pts. with one attack and no recurrence probably do not have UC); a small # have chronic persistant symptoms with no remission despite medical therapy – older pts. have more sustained remissions. Complications of UC are: 1) *perforation,* mostly occuring in the left colon (and more common in toxic megacolon than UC), 2) *toxic megacolon*, where inflammation extends beyond the submucosa into the muscularis → loss of contractility → dilation, with systemic symptoms of fever, tachycardia, leukocytosis & anemia – TM may be exacerbated by antimotility drugs or bowel prep., 3) *malignancy*, with progression from dysplasia to invasive adenocarcinoma without an intervening polyp.

Crohn's Disease is chronic, spontaneously relapsing, idiopathic granulomatous inflammation that may affect any region of the GI tract but has a prediliction for the distal ileum, right colon, and perianal area. Pathology is characterized by acute & chronic transmural inflammation, discrete ulcers, segmental disease, granulomas, and fibrosis – lymphokine profile is predominantly T_H1. Perianal disease (fistulae, fissure, abcesses) are present in 1/3 cases, especially with colonic disease. The ileocecal region is involved in 55% of pts, isolated ileal disease in 30%, isolated colonic ds in 15%, duodenum involved in 10-15% of cases (usually in association with other sites. Endoscopy is useful in diagnosis & evaluation; earliest finding is the aphthous ulcer, followed by deep, linear ulcerations – the rectum may or may not be involved and skip lesions and strictures are often seen. Onset may be insidious, progressive, or fulminant, and symptoms usually spontaneously relapse & remit. Complications of CD include: 1) *absecesses & fistulae*, as a mucosal fissure extends through the intestinal wall (abcesses in 15% & fistulae in 40% of pts.), 2) *obstruction* (esp. in small intestine & the leading indication for surgery) due to mucosal edema & thickening from acute inflammation, progressive fibrosis with chronic inflammation, or impaction of fibrous bolus of food in a stricture, 3) *perianal disease* (fistulous openings in the perianal skin, groin, vulva, or scrotum), 4) *hemorrhage* from ulcerations that may present as iron-deficiency edema, 5) *B_{12}-deficiency* &/or *malabsorbtion* from extensive small bowel involvement. Adenocarcinoma (though less common in CD than UC) is related to mucosal dysplasia and is associated with male sex, extensive disease, both small & large bowel involvement, and long disease history – periodic colonoscopy with biopsy is done for screening.

Treatment

Ulcerative Colitis:

1. Supportive tx → antidiarrheals, antispasmodics, analgesics
2. Sulfasalazine
   - 75% enters colon & 5-ASA is released by bacteria
   - 5-ASA blocks COX, is a free radical scavenger (inactivates PMN-released oxidants), and blocks cytokine synthesis.
   - effective in mild-to-moderate acute attacks of UC, as well as to prevent remission.
3. 5-ASA compounds may be given by enema or suppository
4. Corticosteroids
   - inhibits arachidonic acid release from cell membrane
   - ↓s cytokine synthesis, phagocyte activation, WBC life
   - used for pts. not responding to sulfasalazine
5. 6-MP/Azathioprine
   - used less than in Crohn's because UC can be cured by colonic resection
   - IV cyclosporin may prevent colectomy in fulminant, steroid-refractory UC
6. *Total colectomy* is curative and performed when UC is refractory to medical tx or complicated by dysplasia/CA.
   - ileal pouch-anal anastomosis preserves fecal continence

- 5-ASA, folate, & tight medical control can ↓ risk for CA.

Crohn's Disease:

1. Supportive tx → antidiarrheals
2. Sulfasalazine & 5-ASA agents for active Crohn's
   - delivery to small intestine or colon targeted by new preparations: pentasa (time release) → small bowel &colon
     asacol (pH release) → distal ileum & colon
     dipentum & sulfasalazine → only colon
3. Corticosteroids (do not maintain remission)
4. Metronidazole (for colonic CD & perianal ds)
5. 6-MP & Azathioprine (take 3-4 months to act)
   - cyclosporin A at high doses is effective for severe ds
   - MTX &/or Remicade can be used for refractory ds
6. Segmental resection for obstructions & abcess formation
   - 80% of pts. require surgery within 20yrs
   - also good for refractory ds but there is 85% recurrence
   - 5-ASA, 6-MP, or metronidazole → ↓ operative relapse
   - resection of the distal ileum can → B_{12} deficiency & bile-salt malabsorbtion → colonic secretory diarrhea (< 100cm resected) or fat malabsorbtion (>100cm).

Notes

Epidemiology:

- Incidence: industrial > developing, urban > rural, north > south
  jewish > general population,
  - UC → 2-10 per 100,000 (prevalence 35-100)
  - CD → 1-6 per 100,000 (prevalence 10-100)
- Bimodal age distribution with peak incidence 15-25 and a second peak at 55-65.

Risk Factors:

1. *Genetics:* (CD > UC, genetic heterogeneity for both)
   - 15% of pts. have a first-degree relative affected; lifetime risk: 5-10% for offspring, 8.8% for siblings & 3.5% for parents
   - ↑ed concordance with monozygotic twins
   - ↑ed incidence of HLA-DR_2 in UC, HLA-DQW_4 in CD
2. *Smoking*: UC → ↑ed # of non-smokers & former smokers; frequent onset or flare when quits smoking
   CD → ↑ed # of smokers
3. Oral contraceptives
4. NSAIDs: possible association related to enhanced intestinal permeability or blockade of immunosuppressive PGs
   - 20% of asymptomatic relatives have enhancability to aspirin
5. Appendectomy as a child is protective in UC.

- Measels & anaerobic bacterial infection may be associated with CD; adherent E.coli may be associated with UC.

Pathology	UC	CD
Segmental	never	common
Transmural	rare (fulminant)	common
Granulomas	never	common (60%)
Fibrosis	superficial	transmural
Fissure/fistula	rare	common
Mesenteric fat, LN	never	common
Crypt abcess	common	occasional

Clinical	UC	CD
Rectal bleeding	common	occasional (colon)
Abdominal pain	occasional	common
Palpable mass	rare (CA)	common
Obstruction	rare (CA)	common (SB)
Rectal involvement	>95%	<25%
Ileal involvement	minimal	80%
Perianal Ds	rare	common
SI involvement	rare	common
Extraintestinal Ds	occasional	occasional
Toxic Megacolon	occasional	rare
Recurrence p resect.	never	common
Malignancy	occasional	rare

Inflammation outside the bowel:

1. **Arthritis:** (most often in CD, associated with HLA-B27)
   a. peripheral, pauciarticular, non-deforming: joint pain, swelling & stiffness do not follow the course of ds
   b. spondyloarthritis activity does not follow course of ds.
2. Hepatic: fatty infiltration, pericholangitis (50-80%), chronic active hepatitis, cirrhosis, sclerosing cholangitis (1-4%) in UC (lower frequency in CD)
3. Skin: erythema nodosum, pyoderma gangrenosum
4. Eye: uveitis, iritis, nodular episcleritis
5. Amyloidosis
6. Thromboemboli
7. Gallstones, oxylate renal calculi, right ureteral obstruction related to ileal CD

Pathology of IBD

Ulcerative Colitis:
Gross Pathology:
1. serosal surface is uninvolved & has typical appearance without fat-wrapping
2. colon may be shortened in length due to muscular abnormality
3. mucosal surface shows granular, velvety, hyperemic surface oozing blood with loss of mucosal folds (active UC)
4. well-defined junction between normal & inflamed tissue
5. inflammation is usually worse distally, unless the pt. is treated with steroid enemas
6. linear mucosal ulcerations may separate islands of intact but inflamed mucosa
7. mucosal inflammation is continuous (fibrosis is minimal)
8. inflammatory polyps are common with ulcerations undermining inflamed mucosa (makes mucosa seem elevated)
9. ileal involvement is called "backwash ileitis"; it always occurs along with colonic involvement.

Histology:
1. diffuse inflammatory infiltrate in crypts and LP with involvement of the superficial submucosa
   - neutrophilic cryptitis & crypt abcess; ruptured abcess contributes to ulcer formation
   - dense, diffuse mixed-cell infiltrate in LP (plasma cells may dominate in crypts)
   - crypt distortion (branched & shortened) because of regeneration of damaged crypts
   - ulcerations are broad & shallow (not fissuring)
   - CMV colitis may occur after tx of severe colitis with steroids
2. MP & serosa are free of inflammation

Toxic Megacolon:

Gross → segment of colon (frequently transverse) becomes acutely dilated with marked thinning & fragility of the muscle wall (often with one or more perforations) and peritonitis

Histo → acute inflammation diffusely involving thinned muscle wall; acute serositis

Microscopic Colitis (lymphocytic & collagenous colitis):

Histo → mucosal inflammation with with chronic inflammatory cells in the LP & intraepithelial lymphocytes between the columnar epithelial cells; epithelial cell damage: cell flattening, subepithelial blebs, denuded epithelium; crypts with uniform size, shape & distribution (IBD shows changes in these); collagenous has a subepithelial collagen band > 10um in thickness.

- symptoms correlate with # of inflammatory cells not thickness of collagen band
- chronic watery diarrhea in normal appearing colon
- biopsy findings:

LC → lymphocytic infiltration of colonic epithelium
greater than 20 lymphocytes per 100 epithelial cells

Crohn's Disease:
Gross Pathology:
1. small intestine is ulcerated with strictures & fissuring
2. "cobblestones" formed by fissures surrounding islands of intact mucosa elevated by underlying inflammation & edema
   - this is seen in 25% of CD patients
3. ulcers are serpiginous, **sharp**, & discontinuous (it may take years for these to progress to deep linear ulceration & stenosis); ulcers also show an infiltrate of PMNs
4. small bowel strictures may be short or long, single or multiple; the "string sign" is extensive stricuring of the terminal ileum
5. strictures may be anywhere in the small bowel but most often are found in the ileum
6. may present primarily as a ulcerative, stricturing, or cobblestone form, but lesions are nearly always **discontinuous**
7. bowel wall is thickened with transmural inflammation, sometimes with involvement of serosa & subserosal fat and by fibrosis and adhesions
8. serosal changes may include "tubercules" which represent granulomas histologically
9. **fat-wrapping** (hyperplastic subserosal & mesenteric fat extending around bowel wall to become nearly circumferential) is highly characteristic of CD & correlates well with disease activity
10. regional LNs are frequently enlarged & have granulomas

Histology: (variable)
1. multifocal involvement
2. focal ulceration (some with cobblestoning)
3. **transmural inflammation** (lymphoid aggregates scattered through the bowel wall, esp. in submucosa & subserosa)
   - Crohn's rosary: lymphocytes in line in LP along MP
   - this is seen grossly as well
4. **thickening** of all layers (esp. submucosa) with edema & fibrosis accompanying transmural inflammation → decrease in lumenal area (obstructon)
5. marked hyperplasia of nerve fibers (esp. submucosal & myenteric plexuses)
6. **granulomas** (may be absent in 50% of cases)
   - loose aggregates of epitheloid cells; less well organized than granulomas of infectious processes

47. Constipation (General)

Clinical Presentation

Abnormal stool frequency
Straining with defecation
Passage of hard stool
Incomplete evacuation

Lab Presentation

Etiology and Pathogenesis

Though there is no standard definition, constipation is usually said to be stool frequency less than 3x per week, straining, lumpy/hard stool, sensation of incomplete evacuation, for 12 weeks. Metabolic causes of constipation include: hypothyroidism, DM, pregnancy, hypercalcemia, hypokalemia, uremia, porphyria. Neurogenic causes include: stroke, spinal cord injury, MS, Parkinson's, peripheral neuropathy, autonomic neuropathy, & Hirsprung's disease. Idiopathic causes include: long-term laxative abuse, IBS, pelvic floor dyssynergia, megacolon & megarectum. Medications that cause constipation include: narcotics, antidepressants, anticholinergics, diuretics, NSAIDs, antacids, antihistamines, anti-Parkinson agents, & anticonvulsants. Diagnostic tests include the balloon expulsion study, colonic transit study, anorectal manometry, & defecography.

Infrequent stool → slow transit of fecal material in the colon.

Small, hard, lumpy stool → inadequate fiber &/or intake.

Long, small-caliber, or flat stool → inappropriate relaxation of the puborectalis & external anal sphincter.

Treatment

Counseling about adequate fiber intake (20-35g/day) & encouraging physical activity.

Infrequent BMs or hard stools → *docusate* (stool-softener)

Slow transit → laxatives
- if chronic laxatives are needed, use bulk-forming agents, emollient agents, hyperosmolar or saline laxatives rather than stimulant & anthraquinones.

Pelvic floor dysfuntion → pelvic floor biofeedback

IBS constipation → *tegaserod* (5-HT4 agonist)

Laxatives:
1. Bulk-forming: psyllium, methylcellulose
2. Saline: magnesium sulfate, magnesium phosphate
3. Magnesium citrate
4. Emollient: docusate, mineral oil
5. Hyperosmolar: polyethylene glycol
6. Lactulose
7. Sorbitol
8. Stimulants: bisacodyl, castor oil
9. Anthraquinones: aloe, cascara, senna
10. 5-HT receptor agonist: tergaserod

Notes

Epidemiology
- Most common GI complaint in US.
- women > men; elderly > young; prevalence 2-20%

Types:
Normal Transit
Slow Transit
Outlet Delay

48. Irritable Bowel Syndrome

Clinical Presentation

Only 30% of patients become symptomatic.

Rome II Diagnostic Criteria:
(12wks or more in last 12 months, 2 out of 3 features)
Abdominal Pain that is:
1) relieved with defecation
2) onset associated with change in stool frequency
3) onset associated with change in stool form

Other: abnormal stool passage, passage of mucus, bloating

Lab Presentation

Etiology and Pathogenesis

IBS is characterized by disordered bowel function – patients have an increased motility response in the small & large intestine in response to food, CCK, pentagastrin, rectal distension, and stress. Multiple biological factors have been proposed as mediators: neurotransmitters, gut opiate receptors, and myoelectric reflexes – symptoms appear to occur when there is dysregulation between CNS activity & the intestinal motor/sensory activity. Diagnostic work-up includes H&P, CBC, ESR, blood chemistries, O&P and sigmoidoscopy to rule out other conditions (there are no biological markers for IBS).

Treatment

Mild symptoms with little impairment → diet & education
- medical therapy is useful during exacerbation

Medical Therapy: (manage symptoms)
Diarrhea → antidiarrheals
Constipation → ↑ dietary fiber or laxatives
Abdominal discomfort → anticholinergics or antidepressants

Behavioral Therapy: hypnosis, cognitive-behavioral, biofeedback for muscle relaxation

Notes

Epidemiology:
- worldwide prevalence: 10-20%
- IBS comprises 12% of family practice & 28% GI practice
- female > male; a majority of pts. do not seek health care
  - many patients are high health-care utillizers & have psychosocial problems
- IBS may coexist with organic disease.
- Diagnosis is clinical.

49. Appendicitis

Clinical Presentation

Early Symptoms:
Periumbilical pain / anorexia / nausea & vomiting / maybe fever

Later Symptoms:
Rebound tenderness / guarding / abdominal rigidity

As inflammation becomes transmural, pain localizes to McBurney's point; this shift from periumbilical to localized pain usually takes 4-6 hours.

Long appendix inflamed at the tip → LLQ pain

Retrocecal appendix → back or flank pain

Rovsing's sign → pain in RLQ with palpation of LLQ; indicates RLQ peritoneal inflammation

Lab Presentation

Gross Pathology:
Early change → congestion of small vessels on the serosal surface with hyperemia
Later changes → distal lumen dilated & filled with pus; with transmural involvement the appendix is swollen & hemorrhagic with dull shaggy gray serosal surface; perforation

Histology: edema & congestion of the wall; transmural infiltration by PMNs, often forming small intramural abcesses; mucosal ulceration with local fibrinopurulent peritonitis; vascular thrombosis

Etiology and Pathogenesis

Obstruction of the appendix lumen by a fecalith, poorly-digestible material, or lymphoid hyperplasia of the mucosa → interference with peristaltic drainage → initial mucosal damage → lumen becomes engorged with fluid elaborated from the mucosa → eventually lumenal pressure exceeds venous pressure → ↓↓ venous drainage → ishcemic inflammation & bacterial infection (usually by mixed intestinal flora) spreads from mucosa through the appendix wall. If treatment is delayed, perforation may happen, possibly resulting in severe peritonitis, abcess formation, & sepsis. Vascular thrombosis along with suppurative inflammation & ischemia may lead to gangrenous appendicitis with necrosis of the wall & perforation (more likely in those who have had symptoms >24hrs). Complications include abcess, phlegmon (collection of inflammatory tissue including bowel, necrotis debris, & WBCs), and rupture (15-30% of patients). Diagnostic work-up may include: surgical exploration (mandatory in pts. with acute abdomen), CT, ultrasonography – generally speaking, delaying surgery in a pt. suspected to have appendicitis increases the risk relative to operating early.

Treatment

Notes

Epidemiology

- most common cause of "acute abdomen" in US
- 1/15 people develop this in a lifetime
- 15-25y → males > females; other ages → males = females
- overall incidence in US is declining for unclear reasons

- Diagnosis is not made by colonscopy; air injected into the colon/appendix can cause perforation of inflammed appedix.

50. Infectious Enteritis

Clinical Presentation

Small bowel infection→ watery diarrhea (can look like sprue) & dehydration

Colonic infection → mucoid or bloody diarrhea, tenesmus, lower abdominal pain.

May progress to toxic megacolon.

Lab Presentation

Gross Path → generalized or patchy erythema (may mimic IBD); shallow apthous ulcers; severe ulceration may be seen in severe dysentery or hemorrhagic E.coli.

Histo → edema; PMN infiltration (inc. crypt abcess & cryptitis) mostly in superficial area of crypt; preservation of crypt architechture; minimal ↑ in LP mononuclear cells; crypt miniaturization
no plasmacytes at bases (unlike UC)
thrombosis in small blood vessels & LP
hypereosinophilia of the LP

- Stool culture is important to ID organism.

Primarily caused by *Campylobacter jejuni*, *E.Coli, Salmonella,* & *Shigella*. Bacteria may produce enterotoxins (cause diarrhea by promoting fluid secretion by the crypt epithelium, i.e. cholera toxin) &/or cytotoxins (which damage or kill cells, i.e. toxins of E.coli & Shigella).

Shigella is transmitted fecal-oral & invades epithelial cells, producing a potent cytotoxin. *Shigella dysenteriae* causes ds with significant mortality – it produces a toxin (1,000x more potent than other species) that invades epithelial cells, inhibits protein synthesis, causes cell death, & circulates in the blood stream where it also enhances platelet aggregation→ hemolytic uremic syndrome (MAHA, thrombocytopenia, renal failure). *Shigella flexneri* is less virulent & may cause watery diarrhea or dysentery. *Shigella sonnei* causes a self-limited watery diarrhea with fever lasting 48-72hours.

E.coli O157:H7 is a common cause of sporadic & epidemic disease with a seasonal pattern (peaks between June & September); it is transmitted by undercooked hamburger, unpasteurized milk & apple cider, & fecal-oral. Disease spectrum ranges from asyptomatic infection through mild diarrhea to hemorrhagic colitis complicated by HUS. Toxin is similar to that of Shigella. Gross pathology is edema (with thumbprinting on abdominal XR), erythema, and superficial ulcerations/hemorrhage (usually most severe on rt. side); psuedomembranes may form. Histology is a spectrum of normal areas, PMN & edematous infiltrates resembling any infectious colitis, changes similar to ischemia, and pseudomembranous colitis similar to C.difficile.

Acute diarrhea is usually self-limiting and dx is made by H&P; if the pt. develops systemic toxicity, severe pain, dehydration, or bloody stools, or if symptoms persist more than 24hrs → do CBC, O&P, fecal leukocytes, hemoccult, C.difficile toxin test (if antibiotics given recently), and serum electrolytes (if needed to manage dehydration), sigmoidoscopy (for bloody diarrhea), flat & upright abdominal XR (if there is bloating, severe pain, obstructive symptoms, or suspected perforation).

Treatment

Notes

Incubation times:

- S.aureus & B.cereus→ toxin causes illness 4-6h after ingestion
- Salmonella, shigella, campylbacter, E.coli → 1-2 days
  - these directly invade tissue
- Cholera & enterotoxigenic E.coli → 8-72hrs

51. C.difficile Colitis

Clinical Presentation

Diarrhea & crampy abdominal pain (1wk after antibiotic tx)
Fever / chills / dehydration / abdominal distention

Toxic Megacolon (severe cases, rare)

Lab Presentation

Gross Path → discrete raised indurated creamy-yellow plaques, firmly attached to the underlying mucosa & separated from each other by congested mucosa

Histo → each plaque contains clusters of disrupted crypts; basal portion of each crypt is viable, while the superficial 2/3 is dilated & filled with degerating epithelial cells, mucus, fibrin, PMNs forming the yellow plaques seen grossly
- mucosa between pseudomembranous foci looks normal

- Stool immunoassay for C.dif is highly specific and highly sensitive as well if multiple tests are positive.
- When dx is in doubt, lower endoscopy often shows pseudomembranous plaques.

Etiology and Pathogenesis

Clostridium difficile is a gram(+) spore-forming bacillus; spores are heat-resistant & persist in the environment for months (and are easy to isolate from multiple surfaces in hospitals → high recurrence rate after tx). Overgrowth often happens after antibiotic therapy kills many other constituents of the gut flora. C.difficile makes a potent enterotoxin (toxin A, causes inappropriate colonic secretion & a vigorous inflammatory response) and a cytotoxin (toxin B, 100x more potent than toxin A) that act synergistically to cause ds – gut flora & variation in the ratio of toxins may explain extremely variable course of infection. Psuedomembranous plaques are composed of mucus, fibrin, & inflammatory cells. Diarrhea may be caused even if infection is not severe enough to produce pseudomembranes. A small % of pts. with develop fulminant colitis & toxic megacolon (inflammation involves the entire thickness of the colon, which then loses its muscular tone → dilation & microperforations → possible death)

Stool assays for C.difficile include: *cytotoxin test* (test of choice with sens.&spec. of 94-100% & 99%) and *toxin enzyme immunoassay* (sens.&spec. of 69-87% & 99-100%, less cost with more rapid results) – if results are inconclusive lower endoscopy can be done.

Treatment

Notes

Epidemiology
- develops in 20% of hospitalized patients
- Rarely, ds progresses until it is indistinguishable from ischemic colitis.
- C.difficile is carried by >50% of healthy neonates & some adults without diarrhea.

52. Acute Pancreatitis

Clinical Presentation

Severe mid-epigastric pain that radiates to the back
- exacerbated by food
- accompanied by nausea & vomiting

Fever / jaundice / tachypnea / tachycardia / hypotension

Severe Ds → ecchymoses around the umbilicus & flank
- Flank = Turner's sign
  Umbilical = Cullen's sign

Lab Presentation

Blood tests: **elevated pancreatic enzymes** (may be elevated in urine as well); hypocalcemia (severe ds); leukocytosis; ↑ serum amylase & lipase (not predictive of ds course); ↑ GGT, ↑ alk.phos., & ↑ bilirubin (biliary pancreatitis); hypoxia

Gross Path:
Mild → enlarged pancreas w/ foci of fat necrosis
Severe → large confluent areas of chalky-white fat necrosis along with hemorrhage (can encase pancreas & look like a hematoma); accumulation of peripancreatic fluid (up to 6L) which can be flocculent (suspended particles of necrotic tissue), bloody, &/or purulent.

Histology:
Mild → spotty peripancreatic or perilobular fat necrosis; mild interstitial acute inflammation.
Severe → large areas of fat necrosis & necrosis of pancreatic lobules; necrotic areas may be surrounded by PMNs

Etiology and Pathogenesis

Acute pancreatitis is most commonly caused in the US by cholelithiasis (45%) & chronic alcoholism (35%); tissue autodigestion by enzymes released from inflamed/necrotic pancreatic cells is responsible for the related pathology. Biliary pancreatitis occurs when a gallstone obstructs the ampulla → pancreatic ductal HTN → pancreatic enzyme & bile salt accumulation, activation, & autodigestion of epithelium → enzymes extruded into interstitial space. Gallstone & alcohol pancreatitis present either as *edematous pancreatitis* (mild increase in serum amylase & lipase, resolves within a few days) or *necrotizing pancreatitis*, a serious inflammatory disorder (5% mortality if sterile & 20% mortality if infected). Cytokines including TNF-α & IL-1 mediate pancreatic damage and also may cause symptoms in the lungs consistent with ARDS – organ failure of the liver, intestines, and kidneys are also possible, as lipases released into the bloodstream circulate & cause damage systemically.

Local complications include massive hemorrhage, tissue abcess, pancreatic pseudocyst; systemic complications include retroperitoneal hemorrhage → hypovolemic shock, intravascular coagulopathy (related to circulating proteases), acute renal failure (tubular necrosis), acute respiratory failure (release of phospholipase A_2 with degrading of surfactant), pleural effusion, duct rupture & ascites, hyperglycemia (↓ insulin & ↑ glucagon release), infected necrosis (develops in 30-70% of pts., causes 80% of deaths due to acute pancreatitis, and peaks at about 3 weeks).

Treatment

Supportive Care → IV fluids, gastric acid control, pain meds, & parenteral nutrition.

ERCP to remove the gallstone in gallstone pancreatitis; complete surgical removal of the gallbladder is then necessary.

Surgery debridement of necrotic tissue.

Notes

- The major complication of necrotizing pancreatitis is infection. These patients may be ill for weeks-months and develop multiple complications including pseudocysts.
- CT shows necrosis in pts. with severe ds; it is usually done when symptoms do not resolve within a few days.
- Colocalization in the acinar cells of vescicles containing lysozymes & those containing digestive enzymes is thought to be involved in pathogenesis.
- Ultrasound is the imaging choice for edematous pancreatitis to look for a gallstone, if one is found surgical removal of the gallbladder should be done before the pt. leaves the hospital.
- Get CT/MRI for pts. with necrotizing pancreatitis (in addition to ultrasound)

53. Chronic Pancreatitis

Clinical Presentation

Abdominal pain (results in multiple hospitalizations & meds)
- 2 patterns: chronic persisting
  waxing/waning (recurs every 2 months)
- pain "burns out" after about 20yrs of CP

Nausea / vomiting / weight loss
Jaundice / steatorrhea (stool fat >7g in 24hrs)

Lab Presentation

Gross Path: uneven involvement with affected areas enlarged, indurated, and restricted to the area distal to the obstruction cross-sections show nodular scarring (can resemble the desmoplasia associated with an infiltrating tumor); loss of normal lobulations with distortions & irregular dilatations of the pancreatic duct; calculi seen in pancreatic ducts

Histology: interlobular or perilobular fibrosis; ducts surrounded by fibrosis are dilated with eosinophilic secretions; WBCs may be present in areas of fibrosis; Islets of Langerhans can proliferate (can mimic neoplasm); acinar cell dropout

Blood tests: amylase & lipase may be normal or only slightly increased in these patients.

Abdominal XR: may reveal pancreatic calcification

CT: shows calcifications in pancreas

ERCP: identifies biliary strictures & ductal strictures as well as pseudocysts

Etiology and Pathogenesis

Chronic pancreatitis is associated with irreversible morphologic changes which usually cause pain &/or permanent functional impairment; many pts. have acute exacerbations, but the ds may be painless with fibrosis as the only evidence of inflammation. CP is characterized by irregular, progressive sclerosis with destruction of the exocrine parenchyma that may be focal, segmental, or diffuse. Loss of exocrine & endocrine parenchyma can → malabsorbtion & diabetes. Islets of Langerhans may be preserved over time.

CP may be caused by hypersecretion of enzymes from the acinar cells in absence of increased fluid or bicarbonate secretion, forming a "protein plug" that may calcify & induce inflammation (for this reason, there is a high incidence of CP in patients with cystic fibrosis); stenosis or strictures in the pancreatic duct may create duct HTN, which may also contribute to the pathogenesis of CP. Prolonged exposure to alcohol causes hypersecretion from the acini → ↑ ductal pressure, ↑ protein, strictures.

Complications include endocrine & exocrine pancreatic insufficiency, duodenal obstruction, biliary obstruction (fibrosis), pseudocyst formation, splenic vein or portal vein thrombosis, pancreatic ascites, & fistula.

Treatment

Pain control, pancreatic enzyme replacements with viokase (gives notable pain relief)
- viokase must be given with acid suppression meds (H2-antagonist) because gastric acid degrades viokase;

Low-fat diet

Stent placement in the pancreatic duct may provide temporary relief for pts. with ductal HTN.

Celiac plexus blocks may be beneficial in some pts.

Notes

- Obstruction of the pancreatic duct may cause CP distal to the site of obstruction.
- CP is caused by alcohol in 80% of patients (occurs after 15-20 years); other causes include nutritional deficiency & hereditary pancreatitis (mutations in CF gene).
- CT is the procedure of choice to view glandular texture.
- Check serum albumin & transthyrethin (for malnutrition/dehydration)

54. Pancreatic Pseudocyst

Clinical Presentation

Lab Presentation

Gross Path → usually solitary, unilocular, & round/oval; contents vary from almost colorless or turbid fluid to brown thick fluid (with debris of pancreatic digestion); after removal of fluid, there may be a mud-like material adherent to a shaggy interior cyst wall.

Histo → wall composed of inner layer of fibrin-rich exudate, inflamed granulation tissue or compact fibrous tissue, outer layer of dense collagen which may be continuous with marked fibrosis of the adjacent chronic pancreatitis; no epithelial lining

Etiology and Pathogenesis

A pancreatic pseudocyst is a collection of tubular fluid enclosed by a wall of fibrous tissue or granulation tissue which arises as a result of acute pancreatitis, pancreatic trauma, or chronic pancreatitis. Necrotic tissue becomes walled-off by abdominal anatomic structures → entrapped material broken down by enzyme action (mostly into amino acids) → osmotic pressure drives more fluid in or increased intraductal pressure → localized rupture of duct → leakage of pancreatic fluid → formation of new pseudocyst. Local expansion may compress adjacent structures, causing portal vein thrombosis, jaundice (obstruction of common bile duct), hyperureteronephrosis, & lower extremity edema (compression of the IVC). Complications include hemorrhage, rupture, and infection.

Treatment

Endoscopic drainage, pancreatic duct stent, or surgery to drain the cyst.

Notes

55. Pancreatic Neoplasms

Clinical Presentation

Adenocarcinoma → **painless jaundice** / pruritis / weight loss
back pain / early satiety

Palpable gallbladder (Courvosier's sign) may be present.

Lab Presentation

Serum marker CA19-9 has sens.&spec. of 80% for adenocarcinomas.

Histology:
Ductal Adenocarcinoma:
Well-differentiated → well-formed glands that vary in size & shape lined by columnar-to-cuboidal cells with enlarged, irregular nuclei; glands are haphazardly distributed
Moderate-differentiated → medium-sized duct-like glands with variable architecture & more nuclear and cytologic atypia; incomplete gland formation with a desmoplastic stroma may be present
Poorly-differentiated → more solid growth pattern

Endocrine Tumors: fibrous capsule that may be incomplete; solid, trabecular, or island-like patterns of uniform cells with oval nuclei & inconspicuous nucleoli; infrequent mitotic figures.
- resemble carcinoid tumors

Etiology and Pathogenesis

Pancreatic Ductal Adenocarcinoma is mostly located in the head of the pancreas, producing a hard scirrous mass. Most of these tumors are associated with obstruction & dilatation of the main pancreatic duct and common bile duct; they can also infiltrate to involve the adjacent ampulla, periampullar mucosa &/or distal common bile duct. The skin is a well-known but uncommon area of mets ("sister Mary Joseph" sign = umbilical mets). Complications include weight loss, pain radiating to the back, Courvoisier sign (painless dilation of gallbladder with jaundice due to obstruction of the CBD), & Trousseau syndrome (migratory phelbothrombitis due to a hypercoagulable state accompanying the tumor).

Pancreatic Endocrine Neoplasms may be *β-cell tumors* (most common, usually benign, ↑ insulin → hypoglycemia), *pancreatic gastinoma* (2nd most common, usually malignant, may produce Zollinger-Ellison syndrome), or uncommon tumors: α-cell tumor, Δ-cell tumor, or VIPoma. Gross pathology for all of these is a solitary, well-circumscribed yellow-tan tumor.

Lab values are of little help except to assess the nutritional status of the patient; pancreatic cancer should be resected if at all possible.

Treatment

Palliation → pain control, relief of jaundice, bypass of duodenal obstruction by endoscopy with stent placement.

Resection via the Whipple operation.

Post-operative chemo-and-radiotherapy is performed frequently.
- chemotx is 5-FU or gemcitabine

Notes

- Ductal adenocarcinoma is the most common tumor arising in the pancreas; it most often arises within the duct in the pancreatic head → pts. present with painless jaundice.
- Risk Factors: chronic pancreatitis, K-ras / p53 / p16 / Smad 4 mutations,
- Prognosis is poor for pancreatic CA: 5yr survival is 20%.
  - pts. often present with advanced local disease & mets
  - unresectable ds without tx: 9 months

56. Hereditary Hemochromatosis

Clinical Presentation

Asymptomatic (early disease)

Fibrosis → Cirrhosis (later disease)
Heart failure
Arthritis
Diabetes
Skin Pigmentation
Sexual Dysfunction

Lab Presentation

Gross → hepatomegaly, liver is dark-red/brown

Histo → periportal iron accumulation early with spotty necrosis; no piecemeal necrosis; minimal inflammation; marked increased iron in hepatocytes & bile duct epithelium; fibrosis → cirrhosis; iron accumulation in heart, pancreas, other tissues

Blood tests:
Transferrin saturation → > 50% for women & > 60% for men
↑ ALT, ↑ ferritin

Prussian Blue staining for iron shows deposition in hepatocytes.

Etiology and Pathogenesis

HH is characterized by excessive iron absorbtion in the duodenum leading to toxic accumulation in tissues, especially in the liver, heart, pancreas, joints & pituitary; 20-40 grams of iron accumulates (10x normal). Transferrin becomes fully saturated & iron circulates in non-transferrin bound form which readily enters cells by a non-saturable process. Early disease is asymptomatic, but as iron accumulates excess iron damages cell organelle membranes leading to functional deficits of mitochondria, lysosomes, & microsomes with release of hydrolytic enzymes into the cytosol; hepatic stellate cells are activated to produce collagen with fibrosis maximal periportally – as iron accumulates more is deposited as hemosiderin than ferritin. HH is inherited in an autosomal recessive fashion, most commonly in persons of European ancestry (the heterozygous state may protect against iron deficiency).

Screening is done by measuring transferrin saturation: must be > 50% for women & > 60% for men (usually it is > 90%). Definitive diagnosis is made by measuring the hepatic iron index (umol/g dry weight/age) on the biopsy specimen (homozygous > 1.9, heterozygous < 1.5); molecular diagnosis may be made by DNA probe analysis for C282Y & H63D mutations. Patients having ↑ ALT or ferritin should have a transferrin saturation determination; if this is elevated blood should be sent for hemochromatosis gene testing – causes of secondary iron overload should be excluded. Genetic testing is negative in 20% of pts, and in this case liver biopsy is useful in making the diagnosis as well as staging the amount of fibrosis.

Treatment

- Phlebotomy to reduce total body iron stores; 500ml of whole blood removes 200-250mg of iron.
  - women may be protected by menstruation
- Avoid iron supplements & adhere to low iron diet.

Notes

- The C282Y mutation (on chromosome 6) is the most common in HH.
- Iron stored in all cells as ferritin is not stainable with Perls stain, but aggregates of degraded ferritin make up hemosiderin, which is stainable.
- Total body storage iron: 0.5g (0.3g in liver).
- 1/250 people are homozygous.
- Chelation therapy with desferoxime is usually not effective;
- Family members should be screened for hematochromatosis.

57. Wilson's Disease

Clinical Presentation

Acute or fulminant hepatitis

Chronic hepatitis (with cholestasis & Mallory bodies)

Cirrhosis → portal HTN (varices & ascites)

Neurological disease: tremor/ataxia/apraxia/speech disturbance

Young children may present with behavioral problems

Physial Exam:
Keyser-Fleischer rings
- cresent of golden-brown pigment seen around the cornea
- present in 50% of pts. with neurological symptoms & 50% without

Lab Presentation

- may show hypercalcinuria & nephrocalcinosis

Blood tests: ↓ ceruloplasmin, ↑ Cu (> 100ug/dL/day)

UA: ↑ Cu (> 10ug/dL)

Histo → Rhodanin stain for copper is specific (but present only in 10% of cases); hepatic copper content from biopsy may establish dx (but results may take weeks-months to return); Mallory bodies are seen.

Etiology and Pathogenesis

Wilson's disease is an autosomal recessive disorder of copper metabolism resulting in copper overload & liver injury; incidence of clinical disease is 1 in 30,000 (male > female) and commonly presents in childhood & young adults. The dysfunctional gene product is a copper transporting ATPase (exact site of action is not clear) resulting in biliary excretion of Cu being 25% of normal in WD pts. with intestinal absorbtion not altered – Cu accumulates in mitochondria in the tissues: liver, brain, cornea & kidneys. Cu accumulation results in the production of free radicals that cause oxidative damage.

Early non-specific features are steatosis, lipofuscin deposition, intranuclear glycogen inclusions, & focal necrosis. Diagnosis is made by low ceruloplasmin (not pathogenic or specific) & low total serum copper with high free serum copper; increased urine copper excretion (> 100ug/day) is also seen. Biopsy is not specific but quantitiative copper studies are confirmatory.

Treatment

Copper chelation with pencillamine or trientine (which also increases urinary copper excretion).

Zinc supplements are useful because zinc interferes with the intestinal absorbtion of Cu.

Liver transplantation for pts. with end-stage liver ds or for pts. presenting with acute liver failure.

Notes

- Should be considered in young pts. with elevated aminotransferases, though it is rare.
- Dysfunctional gene chromosome 13, close to the Rb locus.
- The wide spectrum of clinical presentations corresponds to the many different mutations that → dysregulated Cu transport
  - many mutations → gentic testing for Wilson's is difficult & not widely available.

58. Alpha-1-antitrypsin deficiency

Clinical Presentation

Cholestasis of Infancy (most common presentation of liver ds)

Neonatal hepatitis

Liver fibrosis → cirrhosis

Lab Presentation

Histo → α-1-antitrypsin can be found accumulated in the hepatocytes with PAS staining for the intracellular globules.

Etiology and Pathogenesis

(See this one in the Respiratory Notes for COPD)

Treatment

Manage consequences of portal HTN.

Liver transplant for end-stage liver ds.

Notes

- 1 in 40 caucasians carry the allele; 1 in 1,600 are homozygous - genetic defect is on chromosome 14
- It is rare for a pt. to present with both hepatic & lung disease.

59. Granulomatous Liver Disease

Clinical Presentation	Lab Presentation

Infectious granulomas can result from TB (liver is usually involved in miliary TB, characteristic fibrinogranular necrosis is seen only in 30% of cases and acid-fast organisms in < 10%, PCR for mycobacterial DNA is helpful), MAC (numerous organisms on acid-fast stain), histoplasmosis, schistosomiasis (most commonly manifests as portal HTN & granulomas with schistosoma eggs in the portal tract are diagnostic). Granulomatous liver disease also results from sarcoidosis (minimal liver dysfunction with chronic chlolestatic syndrome mimicing PBC in most pts.), drug reactions (similar to sarcoid granulomas), foreign body deposition (barium from extravasation in radiographic studies, talc in IV drug users, silicone from Starr-Edwards heart valves, gold from therapy for rheumatoid arthritis, mineral oil from long-term use as a laxative).

Treatment	Notes
	• Granulomas may be found in 10% of liver biopsy specimens; 13-36% of granulomas are idiopathic

60. Acute Liver Failure

Clinical Presentation

Encephalopathy within two weeks of developing jaundice

Fatigue / scleral icterus / jaundice

Lab Presentation

Blood tests: ↑ AST & ↑ ALT, ↑ INR/PT, ↑ total bilirubin

Acetaminophen toxicity:
arterial pH < 7.3 or PT > 100s & serum creatinine > 300um/L in patients with grade III or IV encephalopathy (severe lethargy or coma)

Non-acetaminophen toxicity:
PT > 100s and 3 of the following: age < 10 or > 40, non-A-non-B hepatitis, drug reactions, interval of jaundice to encephalopathy > 7days, serum bilrubin > 17

Acute Liver Failure is defined in the onset of encephalopathy within two weeks of developing jaundice in a present without a history of cirrhosis; it is also categorized as hyperacute (encephalopathy develops within within 1 week of jaundice), acute (2 weeks), or subacute (2-12 weeks). The most common cause of ALF is acetaminophen overdose, but in 20% of cases no cause is found. HAV & HBV can cause ALF but do not usually cause this severity of liver disease. In young adults (esp. women) autoimmune liver disease & hepatic vein thrombosis (Budd-Chiari syndrome) are causes of acute or subacute LF. Other hepatotoxic drugs (phenytoin) are also causes.

Findings suggestive of portal HTN, spider angioma, ascites, are usually absent; pts. should have a complete neurological exam (esp. looking for asterixis) to look for encephalopathy. Increased PT/INR & bilirubin (indices of synthetic capacity) are more serious than elevated aminotransferases.

One of the most common causes of death in pts. with acute liver failure is cerebral edema resulting in herniation; preventing this is important.

Liver biopsy may be useful in quantifying the amount of necrosis but does not usually give a diagnosis.

Treatment

- Acetaminophen toxicity → n-acetylcysteine
- Encephalopathy → lactulose (d/c if vomiting or abdominal bloating occurs to prevent aspiration)
- Mannitol, phenobarbitol, & elevating HOB to decrease intracranial pressure.
- Liver transplant for pts. with coagulopathy & encephalopathy
  - must be done prior to significant cerebral edema.
- Monitor for hypoglycemia (hepatic glycogen depletion due to hepatocyte necrosis) to prevent seizures.
  - may place pts. on IV glucose tx with 10% dextrose
- Prophylaxis with PPIs; do not give FFP or cryoprecipitate for prophylaxis but do give it for pts.

Notes

- 2,000 cases per year in the US.
- Patients who look well at presentation can die within hours of admission to the hospital.
- Amanita mushrooms can also cause ALF.
- It is critical to not give sedating medications, because if they become lethargic you will not know if it is a side effect of the medication or if encephalopathy is developing.
- If pts. become lethargic but arousable (stage 3) or comatose (stage 4), they should be intubated for airway protection.
- All pts. with ALF should have a liver transplant evaluation.

61. Acute Hepatitis

Clinical Presentation

HAV: viral prodrome / nausea / vomiting / malaise / jaundice

HBV: nausea / vomiting / fatigue / malaise
arthralgias / membranous glomerulonephritis / PAN

HCV: fatigue / mild abdominal pain / anorexia
(> 75% of pts. are asymptomatic)
- autoimmune manifestations: cryoglobulinemia, glomerulonephritis, B-cell lymphoma, diabetes, thyroid ds, lichen planus, porphyria cutanea tarda

Lab Presentation

Blood tests: ↑ AST & ALT; Serology (see below)

Histo → spotty necrosis, lobular sinusoidal inflammation, lobular disarray, +/- cholestasis, variable portal inflammation; **reticulin framework preserved with no fibrosis**.
- zonal necrosis may be associated with drugs with intrinsic hepatotoxicity
- *chronic hepatitis* shows portal-periportal lesions with fibrosis & piecemeal necrosis; HBV → ground-glass hepatocytesm, orcein+; HCV → steatosis, lymphoid aggregates in the portal areas, bile duct injury

Acute hepatitis is inflammation of the entire liver associated with hepatocyte necrosis which resolves within 6mos – Acute hepatitis may be caused by hepatitis viruses, drugs, alcohol, and autoimmune disorders. HAV is an RNA virus that is transmitted by the fecal/oral route; incubation is shorter (6d-6wks) than for viruses that are transmitted parenterally (6wks – 6 mos), and index cases are most infectious prior to clinical symptoms – diagnosis of HAV is made with a positive anti-HAV IgM test; the disease is self-limiting and most pts recover completely (though recovery may take months & be complicated by relapse and cholestatic HAV characterized by intense jaundice & pruritis with ↑ALP).

HBV is transmitted parenterally; diagnosis is made by serology: HBV surface antigen (HBs) is a marker of current infection, anti-HBsAb is signifies resolution of infection, HB core antibody (HBcAb) indicates exposure with IgM indicative of acute exposure, HBe antigen signifies active viral replication, anti-HBeAb indicates resolution of that replication & HBVDNA is a measurement of actual viral load – HBs is detectable prior to the onset of symptoms (or finding of abnormal ALT), as is anti-HBc IgM; the interval between loss of serum HBs & the appearance of anti-HBsAb is known as the "window phase" of infection, and at this time diagnosis is made by finding anti-HBc IgM in the serum. Patients who go on to have chronic hepatitis B are characterized primarily by persistant serum HBs. Most pts. who acquire HBV as an adult will spontaneously recover, 5% will develop chronic infection (and are at ↑ risk for hepatocellular carcinoma), and < 1% will develop fulminant hepatic failure requiring liver transplant. Pregnant women are routinely screened for HBV in the US, since there is a high likelihood of maternal-fetal transmission & infected neonates will become chronic carriers (acquisition of infection as an infant or child is associated with a lower carrier rate).

HCV is also transmitted parenterally and usually produces a chronic disease after infection (unlike HAV & HBV); 25% of HCV pts. will go on to develop cirrhosis & be at risk for liver failure and carcinoma. Diagnosis of HCV is made by the presence of anti-HCV Ab and the finding of HCV-RNA by PCR. HCV screening is recommended for pts. with abnormal ALT, IV drug use (even once), blood transfusions prior to 1992, hemophilia, chronic hemodialysis, organ transplant recipients prior to 1992, healthcare workers with documented exposure, & children born to HCV-positive mothers; screening may be needed for pts. with a history of intranasal cocaine use, tatoos or body-piercings, multiple sex partners or STDs, or long-term partners of infected persons.

Drugs may cause acute hepatitis via intrinsic hepatotoxicity, elicitation of an autoimmune response, causing cholestasis (anabolic steroids & contraceptive steroids), or by an unknown mechanism.

Liver biopsy is necessary to determine grade (of necrosis) and stage (of fibrosis) in hepatitis.

Treatment

- Immune serum globulin can be given to close contacts of pts. diagnosed with HAV (effective if given w/in 2wk)
  - Also give for sexual contacts of an index HBV case.
  - Give vaccine series alone for sexual contacts of chronic HBV pts.

Notes

- HBV is the most common cause, followed by HAV.
- 80% of pts. with polyarteritis nodosa (PAN) have HBV.
- HBV vaccine is recommended for newborns &high-risk adults.
  - failure to elicit an Ab response may be due to previous occult HBV infection, old age, & presence of certain HLAs.
- HAV vaccine must be given 2wks before travel.
- HAV does not cause chronic hepatitis.
- HCV affects more than 70% of IV drug users.
- Markers associated with immunity:
  Anti-HBs, IgG anti-HAV, anti-HEV
- Markers not associated with immunity:

62. Primary Biliary Cirrhosis

Clinical Presentation

Pruritis
Fatigue
Jaundice (usually a later manifestation of ds)
Hyperpigmentation of the skin (25-50% of pts)
- ↑ melanin deposition

Xanthomas (10% of pts., later manifestation)
- hyperlipidemia

Cirrhosis (very advanced disease)

Fat malabsorbtion / steatorrhea / fat-soluble vitamin & Ca deficiency

Blood tests: ↑↑ **ALP**, normal-to-slightly high AST & ALT
↑ bilirubin (late-stage disease);
Anti-mitochondrial antibodies;
IgM hypergammaglobulinemia
- AST & ALT levels have no prognostic import

Histo → patchy destruction of interlobular bile ducts with a mononuclear infiltrate

- Stage 1: florid bile duct lesion
  - lymphoplasmacytic & eosinophilic infiltrate
  - **segmental bile duct damage** with epithelial changes and possible focal ulceration
  - lymphoid follicles; epithelioid granulomas (may impinge on bile ducts); spotty necrosis & hepatitis
  - **no cholestasis**
- Stage 2: ductular proliferation
- Stage 3: scarring
  - portal fibrosis with **ductopenia**
  - chronic portal inflammation; **periportal cholestasis**
  - **↑ Cu & Mallory bodies**
- Stage 4: biliary cirrhosis

Etiology and Pathogenesis

PBC is a chronic, progressive, cholestatic liver disease in which small, intrahepatic bile ducts undergo inflammation and destruction. In contrast to other types of liver disease, 95% of pts. are women with mean age of diagnosis 40-50yrs (PBC is rare with a prevalance 50 cases/million). The cause of PBC may be autoimmune, as associated immunologic abnormalities such as: antimitochondrial antibodies, IgM hypergammaglobinemia, circulating autoantibodies, and decreases in the number & function of suppressor T-lymphocytes – PBC is also associated with a personal or family history of autoimmune disorders. Liver injury results from nonsuppurative destruction of small, intrahepatic bile ducts due to autoimmunity – obstruction of bile flow then leads to chronic cholestasis & toxic hepatocyte injury (as bile acids & copper accumulate), which results in a self-perpetuating cycle of injury, fibrosis, and eventual cirrhosis. 40-50% of patients are asymptomatic at the time of presentation; disease may be detected at this time by an elevated ALP. Liver biopsy can confirm the diagnosis but is most often used for staging & prognostic purposes. Imaging studies are used to exclude extrahepatic causes of cholestasis; larger ducts usually appear normal in size & contour on contrast cholangiography (though smaller ducts are irregular in PBC). Complications include malabsorbtion (which may also ↑ risk for osteoporosis), increased prothrombin time (vitamin K deficiency), and portal HTN (with variceal hemorrhage, jaundice, ascites, & encephalopathy). PBC is a slowly progressive disease that invariably leads to cirrhosis & liver failure (it can present as much as 10 years prior to the onset of symptoms); survival averages 10-20y after symptoms appear & 5-6y after the appearance of jaundice (a major factor in prognosis is serum bilirubin).

Treatment

Ursodiol, a hydrophobic bile acid, delays progression to cirrhosis & improves survival if given early.

Orthoptic liver transplant is the treatment of choice for end-stage liver disease from PBC; 2yr survival is 90-95% & 5yr survival is 70%.

- Immunomodulators (steroids, azathioprine, cyclosporine, MTX) are in trials for PBC; colchicine does not work.

Notes

- Gallstones, strictures, tumors, & PSC must be ruled out.
- Asymptomatic pts. have a longer life-expectancy than symptomatic pts.
- Damage is likely mediated by CTLs against small intralobular bile ducts.

63. Primary Sclerosing Cholangitis

Clinical Presentation

Progressive fatigue
Fluctuating jaundice, nausea, & pruritus

Fever / chills / RUQ pain
- occurs in 10-15% of PSC pts.
- similar to the symptoms of acute bacterial cholangitis

Fatigue / pruritus / fat-soluble vitamin deficiency
- common to all cholestatic diseases

Portal HTN
End-stage liver disease (advanced PSC)

Lab Presentation

Blood tests: ↑ ALP, hypergammaglobinemia (30%),
↑ IgM (40-50%), **pANCA** (90%).

Histo → fibrous obliteration of the small bile ducts, with concentric replacement by connective tissue in an **"onion skin" fibrotic pattern** with fibrous cords alternating with areas of **saccular dilation of bile ducts**; Mallory bodies & ↑ Cu may be seen; piecemeal necrosis & biliary cirrhosis may also be present

PSC is a chronic, progressive, cholestatic liver disease characterized by inflammation, fibrosis, thickening & stricturing of medium sized and large ducts in the intrahepatic and extrahepatic biliary tree. The etiology is likely autoimmune, as pts. have circulating autoantibodies & immune complexes; the most prevalent autoantibodies bind the perinuclear region of neutrophils & are called perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) – the presence of pANCA in 50-80% of UC pts. and 90% of PSC pts. suggests a possible pathogenic link. Other suggested pathogenetic mechanisms include: chronic or recurrent entry of bacteria into the portal circulation, accumulation of toxic bile acids that are abnormally produced by colonic bacteria or chronic viral infection, ischemic damage, and genetic predisposition (HLA-B8, DR3, and DRw54a).

Diagnosis is made by demonstration of the characteristic multifocal stricturing & dilation of intrahepatic &/or extrahepatic bile ducts on contrast cholangiography (ERCP, percutaneous transhepatic cholangiography, or MR cholangiopancreatography) – this pattern may also be seen in cancer, PBC, & ischemic injury, however. The "onion skin" histological lesion is diagnostic but not usually seen; most often, histological abnormalities are similar to those seen in PBC. Liver biopsy is helpful for staging the disease and determining prognosis.

Continued destruction of bile ducts in PSC leads to portal HTN & eventual end-stage liver disease; other complications include those common to the cholestatic diseasea: fatigue, pruritus, steatorrhea, fat-soluble vitamin deficiency, & metabolic bone disease. Other complications include: biliary stricture, cholangitis, cholelithiasis, cholangiocarcinoma (10-15% lifetime risk), and colon cancer in pts. with UC. Median survival is 10yrs from diagnosis, and the course of the disease is usually complicated by multiple bouts of superimposed bacterial cholangitis. Acute deterioration (jaundice & weight loss) in pts. with a dominant stricture seen by cholangiography is a poor prognostic sign & often is associated with cholangiocarcinoma.

Treatment

Treatment is mainly supportive.

Ursodeoxycholic acid may improve symptoms & liver function but does not prolong survival or referral time for liver transplant.

Liver transplant is the treatment of choice; prophylactic colectomy in pts. with UC does not alter the course of PSC.

Notes

Epidemiology

- 50 cases / million persons ; male > female (25%)
- mean age at diagnosis: 40yrs,
- strong association with IBD; 75% of PSC pts. have UC and 5% have CD, but only 3-5% of pts. with UC & 2% of pts. with CD have PSC.
  - clinical course bears no relationship to severity of IBD
  - PSC may develop years after colectomy for UC
- Secondary causes of sclerosing cholangitis: drugs, bile duct cancers, past biliary tree surgery, and opportunistic infections of the bile ducts.
- Liver biopsy often is not specific for PSC vs. PBC.

64. Autoimmune Hepatitis

Clinical Presentation

Fatigue
Acute hepatitis

Hepatomegaly / Jaundice

Lab Presentation

Serology:
Type I → ANA, ASMA
Type II → Anti-LKM1
Type III → ASMA, Anti-soluble liver antigen

↑ serum AST & ALT;
polyclonal hypergammaglobulinemia (IgG predominates)

The etiology of AIH is uncertain; markers of autoimmunity & association with HLA haplotypes HLA-B8, DR3, and DR4 suggest autoimmunity, as does the response of symptoms to immunosuppressive therapy. It is possible that an environmental agent triggers the abnormal immune response. Serologic autoantibodies are useful for diagnosis (and serve as a classification system for AIH) but do not correlate with disease activity or severity – they do not seem to have a role in disease pathogenesis. Type I occurs most frequently in adults (75-85% of cases) whereas type II occurs most often in children. AIH patients often have another autoimmune disorder. Liver biopsy is important to determine activity (grading) & fibrosis (staging) of AIH – there is no specific histologica pattern; AIH may mimic chronic viral hepatitis (periportal mononuclear infiltrate extending into the hepatic lobules termed "piecemeal necrosis"), PSC, or PBC.

AIH usually progresses to liver failure, with a mean survival time of 5 years. ANA & ASMA levels may decrease and transaminase levels may normalize with corticosteroid treatment, but these changes do not predict outcome. Treatment shoudl continue for 1-2 years before considering stopping therapy; relapse is common & long-term maintenance therapy is usually necessary.

Treatment

Corticosteroids may induce remission & prolong life but do not slow the progression to cirrhosis.
- in the setting of chronic viral hepatitis, corticosteroid therapy will be ineffective & increase the viral load.

Liver transplant may be effective, but recurrence post-transplant has been reported.

Notes

Epidemiology
- classically occurs in young women; female > male (20%)
- peaks in children/young adults then again in pts. 50-60yrs old

65. Chronic Liver Failure (General Info)

Clinical Presentation

Complications of portal HTN & decreased hepatic mass:
- Ascites
- Variceal bleeding
- Severe coagulopathy
- Muscle wasting
- Hepatorenal syndrome
- Hepatic encephalopathy

Lab Presentation

Factors associated with the development of ascites are low serum albumin, hepatic outflow obstruction with overproduction of lymph, & portal HTN – patients with cirrhosis who develop ascites need a diagnostic paracentesis (other indications for diagnostic paracentesis: new onset ascites or ascites with clinical deterioration with fever, abdominal pain, or altered mental status). Patients with a serum-ascites albumin gradient of >1.1g/dL have portal HTN (and pts. with a gradient < 1.1 do not); high gradient ascites is associated with cirrhosis, alcoholic hepatitis, cardiac disease, massive liver cancer mets, fulminant liver failure, Budd-Chiari syndrome, and portal vein thrombosis. Low gradient ascites is associated with peritoneal carcinomatosis, TB peritonitis, pancreatic duct leak, nephrotic syndrome, and serositis. About 10% of pts. with cirrhosis will have ascites refractory to routine medical treatment with Na-restriction & diuretics; TIPS or peritoneovenous shunting may be used after at least 2 large-volume paracenteses have been done.

80% of cirrhotics develop varices and 25-40% of them will subsequently experience bleeding; for each bleeding episode, the mortality rate is 30-50% (& risk of recurrent bleeding within 2 years is 50-70%). Esophageal varices most often bleed near the GE junction; factors that predict bleeding include: variceal size, endoscopic features, Child-Pugh-Turcotte classification & portal pressure.

The technical success rate for TIPS in controlling acute variceal bleeding is >90%; the immediate procedure-related complication rate is 10%, complications of TIPS occuring days-months later are hepatic encephalopathy (20-30%), and shunt stenosis or occlusion (40% at 12 months). Hepatic encephalopathy in much more commonly associated with cirrhosis or portosystemic shunt than acute liver failure; in ALF hepatic encephalopathy responds poorly to medical therapy and is associated with cerebral edema. Precipitating factors of HE include: GI hemorrhage, excess protein, alcohol, sedatives/hypnotics, surgery, hepatoma, infection, dehydration, electrolyte imbalance & TIPS.

Treatment of Ascites due to Cirrhosis
- Restriction of dietary Na (2g/day; 20% of pts. respond)
- Spironolactone or Furosemide (90% of pts. respond)

Treatment of Suspected Variceal Bleeding
- Hospitalization with volume-replacement
- Octreotide to ↓ portal blood pressure
  - continue for 3 days to prevent early rebleeding
  - more effective than vasopressin & baloon tamponade
- Endoscopic procedures: ligation or sclerotherapy
  - less effective for gastric varices
  - sclerotherapy → works in 80-95% of pts; no effect on survival; complications are ulcer-bleeding, esophageal stenosis & perforation (20%), mortality 1-3%
  - ligation → works in 90% of pts.; less rebleeding, mortality, & complications than sclerotx.

Treatment to Prevent Recurrent Variceal Bleeding
- β-blockers: ↓ CO & splancnic vasoconstriction
- TIPS: reserved for pts. refractory to endoscopic tx; superior to sclerotx & banding in prevention of rebleeding; may show improved survival.

Notes

- There are no commercial tests available to quantitate hepatic reserve.
- Contraindications to TIPS: severe hepatic failure, right-sided heart failure, primary pulmonary HTN, severe uncontrolled hepatic encephalopathy, advanced portal vein thrombosis.
- Stages of Hepatic Encephalopathy
  1. mild confusion, incoordination
  2. asterixis, personality changes
  3. somnolent, but arousable & disoriented
  4. comatose

66. Cirrhosis

Clinical Presentation

Jaundice
Variceal bleeding
Ascites
Spontaneous bacterial peritonitis
Hepatic encephalopathy
Hepatorenal & hepatopulmonary syndromes
Hypersplenism
Hepatocellular carcinoma

Lab Presentation

Histo → **diffuse hepatic fibrosis** with **regenerative nodules**;

Micronodular → thick, regular fibrous septae separate small (<3mm) uniformly-sized regenerative nodules (early alcoholic cirrhosis).

Macronodular → fibrous septa separate course nodules (>3mm) of various size; nodules may be large and may occasionally contain normal portal structures (cirrhosis from chronic viral hepatitis).

Etiology and Pathogenesis

Hepatocellular injury, whatever the cause, stimulates the stellate (Ito) cells to become fibrogenic, leading the end-stage of chronic liver disease – cirrhosis is the outcome of a number of pathologic processes affecting the liver. Etiology can not be inferred from the morphologic pattern, though micronodular cirrhosis occurs often in early alcoholic disease and macronodular cirrhosis in chronic viral hepatitis. Fibrogenesis is initiated by inflammatory-mediated release of TGF-β and PDGF, which stimulate stellate cells to develop a myofibrogenic phenotype – an initial event in fibrogenesis is the subendothelial accumulation of collagen in the space of Disse leading to "capillarization" of the sinusoids which results in decreased metabolic exchange between blood & hepatocytes. Liver biopsy reveals nodules of regenerative parenchyma without portal areas encased in dense fibrous septa; the sinusoidal endothelium loses its fenestrations → ↓ exchange between the sinusoidal lumen and ↑ vascular resistance, and fibrous connective tissue deposited in the space of Disse also → ↓ exchange & ↑ vascular resistance (↑ compression of the sinusoidal lumen) – The result of these changes is portal HTN and decreased functional capacity of the liver. In advanced cirrhosis, as little as 13% of portal blood flow perfuses the liver & exits via the hepatic veins; the remainder bypasses the liver via collaterals: esophageal & gastric fundic varices, spleen & splenorenal ligament veins, paraumbilical veins (caput medusae), and hemorrhoidal veins.

Treatment

Notes

Non-cirrhotic portal HTN (10% of cases in developed countries)

- Pre-hepatic → splenic & portal vein thrombosis; extrisic compression of the portal vein
- Intra-hepatic → broad range of fibrotic (nodular regenerative hyperplasia, congential hepatic fibrosis), inflammatory (sarcoidosis), infectious (TB, schistosomiasis), and infiltrative (amyloidosis) causes.
- Post-hepatic → Budd-Chiari syndrome, IVC webs or tumors, constrictive pericarditis, cardiomyopathy

67. Alcoholic Liver Disease

Clinical Presentation

Lab Presentation

Fatty Liver → **large lipid droplets primarily in perivenular hepatocyte cytoplasm**; nuclei displaced to the periphery; large & eosinophilic megmitochondria may be present; **lipogranulomas** may be seen (rupture of fat-laden hepatocytes with MPs engulfing the fat).
- no sinusoidal collagen deposition
- no portal fibrosis or inflammation

Steatohepatitis → **fatty liver + Mallory bodies**; single-cell hepatocyte necrosis; lobular infiltrates of PMNs & lymphocytes; **central sinusoidal collagen deposition** (esp. perivenular) with variable portal fibrosis.

Hepatic fibrosis → perisinusoidal fibrosis (fibrosis beginning in the perivenular area and extending in a chicken-wire pattern into the space of Disse)

Alcohol exerts a direct toxic effect on the gut via impairing absorbtion & activation of certain nutrients, increased degredation of some nutrients, and increased vulnerability to certain drugs and hepatotoxins; high EtOH intake also triggers hepatic inflammation and stellate-cell activation, resulting in fibrosis via increased production of reactive oxygen species and decreased endogenous free radical scavengers (centrilobular hepatocytes are most vulnerable) – alcohol is also rich in calories (7.1 kcal/g) but devoid of nutrients, and so high intake can lead to malnutrition (nutritional deficits may also contribute to the toxicity of EtOH & acetaldehyde).

Fatty liver is a relatively harmless accumulation of fat in the liver accompanying a period of heavy drinking; it will resolve within 2-4 weeks of abstention. *Steatohepatitis* is a serious & life-threatening condition that may evolve from fatty liver; it is characterized by fatty liver plus variable amounts of Mallory bodies (aggregates of cytoplasmic intermediate filaments having a characteristic ropy eosinophilic appearance) – clusters of PMNs surrounding hepatocytes contain the Mallory bodies, which indicate irreversible hepatocyte injury (these can persist for weeks-months after abstaining from alcohol).

Chronic alcohol abuse also makes the gut mucosa leaky to bacterial endotoxin → excess toxin in the portal circulation activates Kupffer cells which release additional inflammatory cytokines that further stimulate stellate cell fibrosis.

Treatment

Notes

68. Non-Alcoholic Fatty Liver Disease

Clinical Presentation

Lab Presentation

Histo → macrovescicular steatosis, mixed lobular inflammation, hepatocellular ballooning; lipogranulomas in the lobules and acidophil bodies; perisinusoidal fibrosis; Mallory bodies may be seen

NAFLD encompasses steatosis & steatohepatitis (steatosis + inflammation & ballooning degeneration); associated conditions include obesity, diabetes mellitus, hyperlipidemia, metabolic syndrome, jejunoileal bypass, & massive weight loss. *Metabolic syndrome* is characterized by insulin resistance associated with central obesity, NIDDM, dyslipidemia (↑ TGs & ↓ HDL), and HTN – with each additional component of the metabolic syndrome the risk of steatosis increases exponentially from 1x to 99x.

Insulin resistance (found in pts. with metabolic syndrome) is an independent risk-factor for NAFLD; in insulin resistance lipolysis is increased resulting in increased free fatty-acids delivered to the liver and TG deposition (elevated serum insulin levels suppress disposal of FFAs), and FFAs induce cytP450 CYP2E1 (normally suppressed by insulin) which increases oxidative stress. Severity of fat accumulation correlates with activation of hepatic stellate cells, thus, steatosis per se may activate fibrogenesis; generation of reactive oxygen species and free radicals by induction of cytP450 CYP2E1 leads to expression of pro-inflammatory cytokines (which also induce fibrogenesis) – this process is mediated by free fatty-acids & ketones (high-fat diet or rapid weight loss from dieting, debilitation, intestinal bypass, alcohol abuse, & DM). Diagnosis of non-alcoholic steatohepatitis is made by liver biopsy. Risk factors for development of fibrosis in NASH include: increasing age (>45yrs, 40%), obesity &/or diabetes (60%), and AST/ALT ratio > 1 (66%).

Treatment

Notes

- Non-hepatic steatohepatitis is a diagnosis of exclusion.
- The CDC estimates that 47 million Americans have metabolic syndrome.
- The prevalence of NAFLD is approximately 20%; the prevalence of NASH is 2-3%.
- NASH is a precursor lesion to some types of cryptogenic cirrhosis..

69. Benign Lesions of the Liver

Clinical Presentation

Lab Presentation

Hemangioma → solitary, purple, subscapular nodule; may have variable degrees of fibrosis, calcification, & contraction; cavernous vascular spaces lined by flattened endothelium

FNH → "central scar" on MRI with gadolinium; histology resembles cirrhosis except lesion is focal; stellate scar with proliferating ductules; arteries leading to the nodule show fibromuscular hyperplasia with lumenal narrowing; contains bile ductular structures; no capsule

Simple Cyst → lined by simple cuboidal epithelium

Hepatic Adenoma:

Gross→ well-defined mass with with dilated blood vessels; tumor is variegated pale yellow to tan with necrotic areas, cystic degeneration & hemorrhage.

Histo → hepatocytes arranged in anastomotic 2-3 cell layer trabeculae with **no portal areas or bile ducts**; mitotic figures are absent or very rare; large, tortuous arteries & dilated, thin-walled veins are present & devoid of the usual connective tissue framework; peliosis may be present; encapsulated.

Focal Fatty Change → zones of microvesicular fat surrounded

Hemangiomas occur in 10% of the population and are typically found incidentally; diagnosis is made by gadolinium MRI followed by RBC-tagged scan, or ultrasound followed by RBC study (surgery/biopsy is rarely required to make the diagnosis) – Indications for surgical resection are: symptoms (pain), obstruction, or if diagnosis is uncertain; these lesions rarely spontaneously rupture, so size alone (even > 4cm) is not necessarily an indication for surgery. Complications are rupture & Kasabach-Merritt syndrome (platelet sequestration & consumptive coagulopathy).

Focal Nodular Hyperplasia is more common in women (& may be associated with oral contraceptive use), rarely requires surgical resection, and is diagnosed by MRI (sulfur colloid scan can be used to confirm diagnosis; biospy is rarely needed) – Hypervascular anomalies may play a role in pathogenesis. These lesions may develop from an anomalous arterial branch.

Hepatic Adenoma is more common in women (but rare – 1 case in 10 million people), associated with oral contraceptive use & may regress after d/c oral contraceptives, and is diagnosed by MRI; surgical resection is recommended to prevent hemorrhage & malignant transformation.

Nodular Regenerative Hepatitis is a non-cirrhotic cause of portal HTN; it is reported in 2% of autopsy series, diagnosis is based on liver biopsy, and treatment is supportive.

Simple Cysts occur in 5% of individuals (women > men) and have a benign course; if multiple cysts are present, pts. should be evaluated for polycystic liver disease with imaging studies – cysts rarely require surgical intervention unless they cause obstruction, compression, or bleeding. Simple liver cysts do not have malignant potential. Polycystic liver disease is associated with multiple bile duct hamartomas & a slightly increased risk of cholangiocarcinoma.

Treatment

Notes

- Hemangioma is the most common benign liver tumor.
- FNH is the most common benign hepatic nodule; only 15% are symptomatic.

70. Malignant Tumors of the Liver

Clinical Presentation

Cirrhosis
- except for chronic carriers of HBV

URQ pain / weight loss / presence of hepatic mass
Ascites / spider angioma

Non-hepatic Manifestations: hypoglycemia / porphyria cutanea tarda / hypercalcemia / polycytemia

Hepatocellular Carcinoma:

Gross → tumor nodules are soft, hemorrhagic, bile-stained & may be single or multiple, small or large, with or without a fibrous capsule.

Histo → trabecular: atypical hepatocytes arranged in irregular trabeculae thicker than 2 cell layers; covered by a non-fenestrated endothelial lining; no Kuppfer cells; reticulin network sparse or absent; canaliculi may be bile-filled or require immunostaining to be seen; pale, round, eosinophilic cytoplasmic inclusions (α-1-antitrypsin or fibrinogen); Mallory's hyaline is common;

Hepatoblastoma:

Gross → large, sharply delimited gray-yellow variegated tumor with hemorrhagic areas.

Histo → Embryonal: well-defined clusters of small dark fusiform cells with dense nuclei & scant cytoplasm, arranged in rosettes, cords, or ribbons. Fetal: uniform trabeculae composed of larger polygonal cells with eosinophilic cytoplasm, round uniform nucleus, & distinct nucleolus, alternating light/dark areas of glycogen. Small Cell Undifferentiated: scant

The major risk factor for hepatocellular carcinoma of the liver in the US is cirrhosis (risk for developing CA is 2-5% per year for cirrhotics); in the US chronic HCV infection & alcohol abuse are the primary causes of cirrhosis leading to HCC. *Fibrolamellar HCC* tends to develop in young patients without cirrhosis and who are carriers of HBV; it has a better prognosis than conventional HCC – in fibrolamellar HCC, serum α-fetoprotein is usually normal, and pathologic features include: large cells with abundant eosinophilic cytoplasm with many clear areas of cytoplasm and dense PAS+ cytoplasmic inclusions, and abundant connective tissue occuring as multiple layers of collagen strands alternating with tumor. Patients with cirrhosis are screened for HCC with α-fetoprotein measurements & abdominal ultrasound annually. CT or MRI is used if α-fetoprotein is elevated or liver mass is detected on ultrasound – there are very few conditions that elevate α-fetoprotein (pregnancy, seminoma, HCC).

Diagnosis is made on MRI with gadolinium and liver biopsy is usuallly unnecessary (biospy carries the risk of bleeding & seeding the tumor along the biopsy track. A serum α-fetoprotein should be obtained, but it is normal in one-third of cases. Portal vein thrombosis needs to be excluded because HCC metastasizes to the portal vein (as well as lungs & bone). Chest CT & bone scan are also obtained to look for metastatic disease. Prognosis is based on both tumor staging & extent of underlying liver disease (measured by ascites, serum albumin, and total bilrubin).

Hepatoblastoma is a malignant tumor composed of cells resembling primitive hepatic parenchymal cells; poor prognosis is associated with age <1y, large size, involvement of vital structures, and predominance of small anaplastic cells. Other less common primary malignant tumors include cholangiocarcinoma (occurs in pts. with PSC including those with UC, poor prognosis, treatment is surgical resection), hemangioendothelioma, angiosarcoma, & primary hepatic lymphoma.

Treatment

- surgical resection, ablative tx, liver transplant

Notes

- HCC is the 4th most common cancer worldwide (25% in the US); median age at presentation is 55-65yrs.

71. Extrahepatic Biliary Obstruction (General Info)

Clinical Presentation

Lab Presentation

Gross → dilation of the biliary tree behind the obstruction

Histo: Acute → portal edema with ductal proliferation & neutrophilic infiltrate (cholangitis); perivenular hepatocanalicular cholestasis with **bile lakes**; aggregates of necrotic, bile-filled hepatocytes (bile infarcts)

Chronic → biliary fibrosis, bile ductular proliferation followed by loss of bile ducts (**ductopenia**), biliary cirrhosis (end-stage ds).

Blood tests → ↑ PT (prolonged obstruction)

- ↑ed Cu deposited in liver

Obstruction may be caused by caliculi, tumors, acute pancreatitis, strictures, or extrahepatic cholestatic disease, leading to increased biliary pressure with dilatation of the biliary tree, regurgitaion of bile into the circulation & hepatocyte injury (retained bile salts have detergent properties & are cytotoxic) – liver copper also increases as less bile is secreted; with prolonged obstruction, PT may increase due to vitamin K malabsorbtion.

Treatment

Notes

72. Intrahepatic Bile Duct Diseases (General Info)

Clinical Presentation	Lab Presentation

These include PBC, PSC, sarcoidosis, rejection in liver allograft, graft-vs-host disease in bone marrow transplant pts, and toxin/drug related liver injury. Common features include: insidious onset, jaundice (a late feature), early histologic changes that mirror chronic hepatitis, cholestasis more common in the periportal region, Malloy's hyaline with increased hepatic Cu, biliary fibrosis with eventual biliary cirrhosis and ductopenia.

(For specifics, see entries corresponding to the specific diseases)

Treatment	Notes

73. Gallstones

Clinical Presentation

Cholecystitis → RUQ pain / nausea / fever / leukocytosis

Cholangitis → "Charcot's Triad" of RUQ pain/fever/jaundice
- this is the classic presentation, but others are possible
- cholangitis is a medical emergency that can kill in hours

Gallstone ileus → small bowel obstruction

- Most gallstones will remain asymptomatic for the life of the pt.

Lab Presentation

Gross → Cholesterol stones: yellow-brown stones
Calcium bilirubinate stones: black stones
- these can be seen on XR.

Calcium bilirubinate + FFAs: brown stones
- FFAs produced from bacterial phospholipases reacting with lecithin.
- these stones usually form in the duct itself, rather than in the GB.
- also seen on XR

Gallstones form from increased cholesterol or pigment (bilirubin) in the gallbladder/biliary tree – cholesterol stones are the most common in industrialized countries (80% of all stones). Complications include cystic duct obstruction with acute cholecystitis, gallbladder hydrops (non-inflammatory distention), porceline gallbladder (calcification of gallbladder wall following years of chronic inflammation), gallstone ileus (large gallstone erodes into small bowel & becomes impacted at the ileocecal valve → small bowel obstruction), and choledocholithiasis (common duct bile stone).

Formation of cholesterol stones requires: 1) *supersaturation of bile*, primarily because of hypersecretion of cholesterol by the liver (as in obesity with ↑ HMGCoA-reductase activity); rarely, bile acid deficiency can also lead to hypersaturation (as in intestinal bile salt loss via ileal ds, resection, bypass, or synthetic defects acquired as a result of aging &/or chronic liver ds), 2) *accelerated cholesterol crystal nidus formation*, via an imbalance between promoters (such as mucin) and inhibitors of stone formation, and 3) *gallbladder hypomotility*, as in pregnancy, prolonged fasting, & total parenteral nutrition.

Ultrasound imaging is very sensitive & specific for detecting cholelithiasis; thickening of the GB wall and pericholestatic fluid suggest acute cholecystitis and dilated bile ducts suggest biliary obstruction. Radionucleotide scans are used primarily to detect cystic duct obstruction (secondary to swelling or a stone) in acute cholecystitis; this test is very sensitive & specific unless the patient has been fasting (gallbladder filling may not occur → false positive test). ERCP is the most accurate method for diagnostic evaluation of obstructive jaundice; it also allows for treatment by stone extraction or placement of a stent through the obstruction. Percutaneous transhepatic cholangiogram (PTC) can be useful for obstructive jaundice, especially in cases where ERCP is impossible or unsuccessful.

Treatment

Cholecystitis → urgent cholecystectomy

Porceline gallbladder → elective cholecystectomy reduces risk of developing gallbladder cancer.

Asymptomatic cholelithiasis should not be treated.
- lifetime risk of biliary colic is 20-25%

Notes

- Supersaturation of bile alone is not enough to cause disease.
- 500,000 cholecystectomies per year in US.
- Gallstones commonly become impacted in the cystic duct & at the spincter of Oddi.
- Prevalence: 15% of men, 30% of women.
- Risk factors: female, ↑ age, obesity, multiparity, race (Native American > Caucasian > African American), ileal ds, family hx.
- Risk factors for black-pigmented stones: old age, chronic hemolysis, cirrhosis.
- Risk factors for brown-pigmented stones: chronic biliary infxn,

74. Biliary Tract Tumors

Clinical Presentation

Jaundice
Pruritus
Weight Loss
Abdominal Pain

Lab Presentation

GB CA → diffuse or polyploid; adenoCA with intestinal differentiation common (precursor lesion is intestinal metaplasia → dysplasia).

Cholangiocarcinoma → adenocarcinoma (excluding metastatic adenoCA may be impossible)

Gallbladder carcinoma is the most common biliary tract malignancy; up to 90% of cases are associated with gallstones & chronic cholecystitis (but in US <1% of pts. with gallstones develop GB carcinoma) and large stones (>3cm) increase risk 10x – porceline gallbladder (13-22% develop CA) and chronic Salmonella infection have a particularly strong association with GB CA. The GB has a rich lymphatic drainage leading to early spread to regional nodes. Diagnosis is often unsuspected prior to cholecystectomy for stones, but liver biopsy may show an obstructive pattern or US/CT may show a mass.

Cholangiocarcinoma accounts for 10% of primary hepatic malignancies (cirrhosis is usually not present except in PSC pts.); cholangiocarcinoma may present as a single mass, multiple masses, or diffuse involvement of the portal area – it may remain asymptomatic until later stages and prognosis is poor (though if detected early in the hilar or extrahepatic bile ducts it may be resectable). Predisposing factors include: PSC, UC, parasitic infection with liver flukes, hepatobiliary fibropolycystic disease, thorium dioxide (radioactive contrast material used from 1920s-1950s), and intrahepatic caliculi. Cholangitis is uncommon. A "Klastskin tumor" is a cholangiocarcinoma of the area where the hepatic ducts meet to form the common bile duct.

Treatment

Notes

- GB carcinoma has an increased incidence in Native Americans and Latin Americans.
- Malignancy is second only to gallstones as a cause of biliary obstruction.