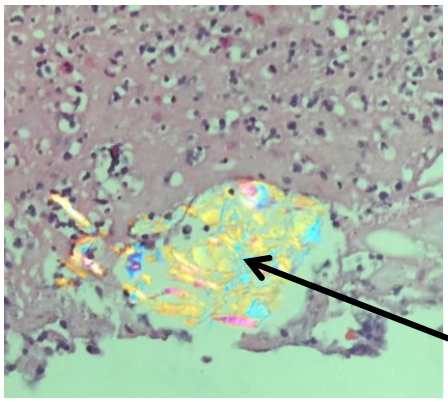
Medication Injury in the GI tract

Non-specific Injury

Pill Esophagitis



Pill retained in esophagus (not enough water or laying supine) → **Caustic/osmotic injury**

Often elderly women → odynophagia and retrosternal pain → strictures and perforation

Often at site of aortic arch (mid-esophagus)

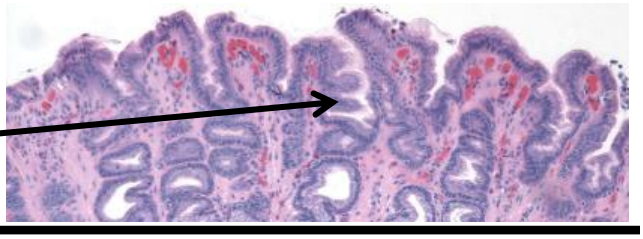
Common offenders: Antibiotics, NSAIDs, Iron, bisphosphonates

Findings: **Ulceration, acute inflammation, granulation tissue**
Helpful finding: polarizable crystalline material (pill fragments)

Reactive (Chemical) Gastropathy

Common offenders: EtOH and NSAIDs

Finding: **foveolar hyperplasia** with corkscrewing glands, mucin depletion, edema, and few inflammatory cells



Colitis

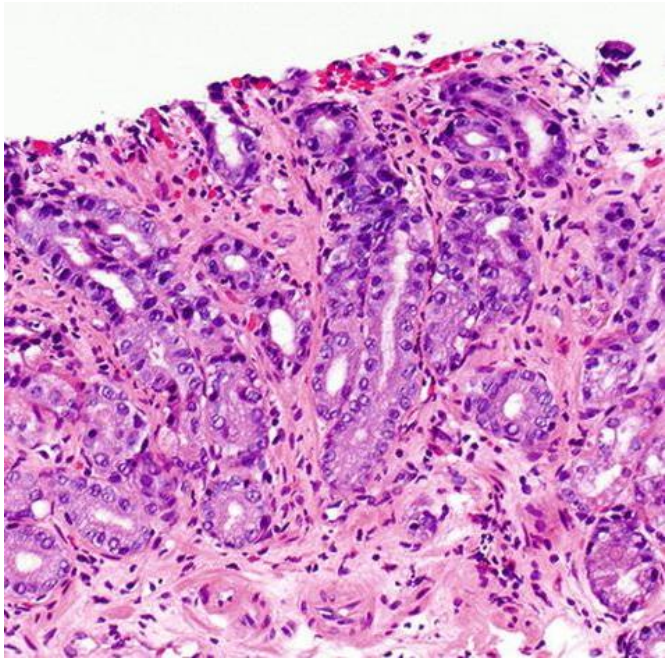
Can cause most patterns of colitis (see separate "Inflammatory Patterns of the GI tract" guide)

Pattern of Colitis	Associated Drug
Eosinophilic colitis	NSAIDs, gold, carbamazepine, antiplatelet agents, estrogens
Lymphocytic or collagenous colitis	NSAIDs, lansoprazole, ticlopidine, ranitidine, simvastatin, flutamide, carbamazepine, sertraline, penicillin, checkpoint inhibitors, Idelalisib
Focal active colitis	NSAIDs, Bowel preparation (esp. oral sodium phosphate), checkpoint inhibitors, Idelalisib
Ischemic colitis	NSAIDs, antibiotics, amphetamines, digitalis, diuretics, chemotherapy, nasal decongestants, constipation-inducing medications, laxatives, vasopressor agents, cocaine, ergotamine, serotonin agonists/antagonists including sumatriptan, estrogen, progesterone, glutaraldehyde, and immunomodulators such as interleukin
Apoptotic colitis	Bowel preparation (esp. oral sodium phosphate), mycophenolate mofetil, laxatives, chemotherapeutic agents (esp. 5-fluorouracil), NSAIDs, cyclosporine, checkpoint inhibitors, Idelalisib
Pseudomembranous colitis	NSAIDs, antibiotic-associated Clostridium difficile colitis
Neutropenic colitis	Chemotherapy

Modified from: Odze and Goldblum's Surgical Pathology of the GI tract, Liver, Biliary tract, and Pancreas. 3rd Edition. 2014.

More Specific Drug Patterns

NSAIDs



Non-Steroidal Anti-Inflammatory Drugs

Inhibit cyclooxygenase→ decrease prostaglandins → decreased mucous, acid neutralizing bicarbonate, and mucosal blood flow → mucosal injury; Also deplete ATP

Inflammation and ulceration in any part of GI tract

Can cause strictures and "Diaphragm disease" (concentric, thin mucosal webs)

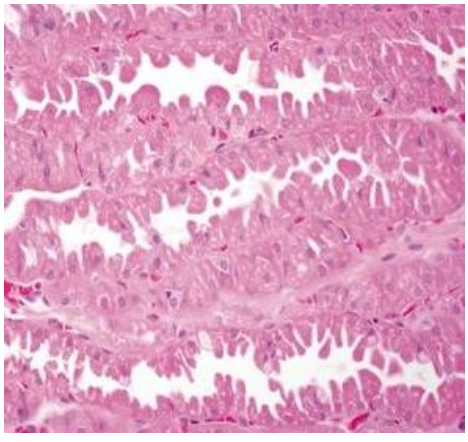
Can cause erosion/ulceration in any part of GI tract

Esophagus→ acute esophagitis, ulceration, stricture

Stomach→ reactive gastropathy, ulceration

Intestines → Mostly active inflammation, with some mild chronic architectural changes, ulceration; lymphocytic/collagenous colitis,

PPI



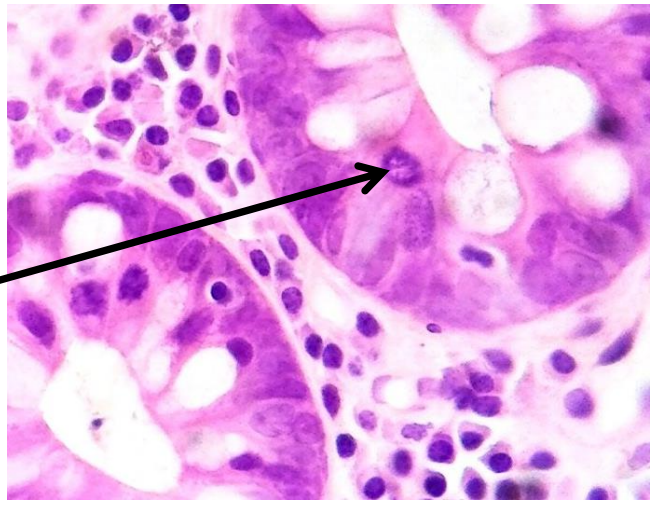
Proton Pump Inhibitor

Used to treat esophagitis and peptic ulcer disease

Inhibit parietal cell acid secretion → less stomach acid → gastrin secretion increases (trying to tell to make more acid) → Parietal cell hypertrophy and neuroendocrine cell hyperplasia

→ Increased fundic gland polyps

Colchicine

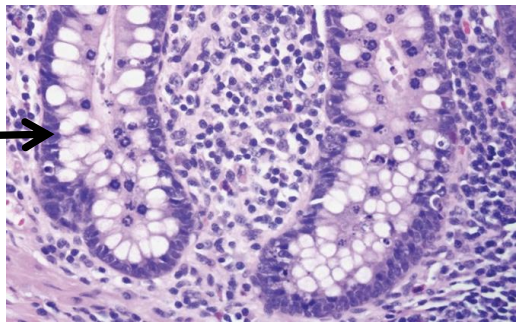


Used to treat gout.

Inhibits microtuble polymerization → interferes with mitosis, chemotaxis, and PMN degranulation

Most characteristic finding: multiple **"arrested" metaphase mitoses,** particularly in "**rings**." Also often apoptotic bodies and lots of reactive changes.

Cytotoxic Chemotherapy



Epithelial atypia, sometimes mimicking dysplasia
Taxol→ ring mitoses like colchicine

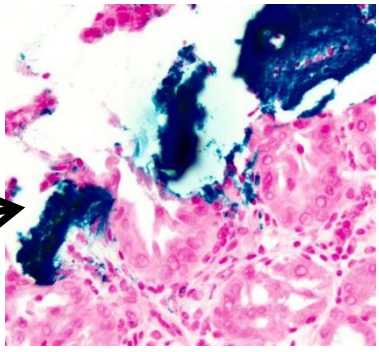
Severe neutropenia can cause "Neutropenic Colitis" where after mucosal damage opportunistic bacteria invade causing necrosis and pneumatosis → often septic shock

Antacids and Sucralfate

Gastric "Metastatic" calcifications (due to Calcium/phosphate imbalances)→ small calcifications under mucosal surface

Iron

Iron appears brown and granular on H&E; Blue on Iron Stain



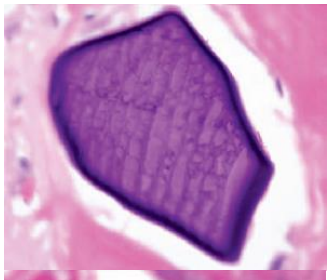
Usually associated with erosion/ulceration. Sometimes reactive chemical gastropathy or chronic gastritis.

Iron Deposition Patterns:
A: Deposition in lamina propria/macrophages → prior mucosal microhemorrhages

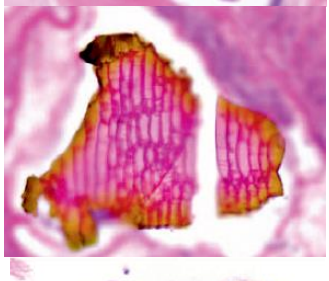
B: Coarse, crystals at surface → Iron pill

C: Subtle, uniform deposition in deep glands → Iron overload

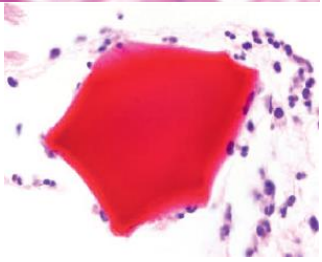
Resins



Kayexalate: Used to treat hyperkalemia in renal failure → causes ischemic and ulcerative changes. Linked to fatalities and perforation, so urgent dx.
Purple on H&E with narrow fish-scale pattern.



Sevelamer: Used to treat hyperphosphatemia in renal failure → Associated with mucosal injury also.
Bright pink to rusty yellow on H&E with irregular fish-scale pattern.



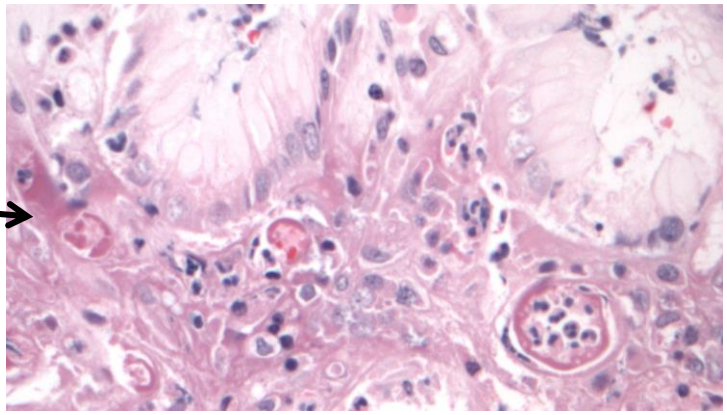
Bile Acid Sequestrants: (e.g., cholestyramine) Binds bile acids (lowers cholesterol). NOT associated with injury
Bright pink/orange on H&E with smooth, glassy texture.

Doxycycline

Superficial mucosal necrosis/erosion

Capillary damage with microthrombi and hyaline necrosis

Background reactive chemical gastritis and chronic gastritis



Angiotensin II Receptor Blockers

The "-artan" drugs: Olmesartan and Losartan
Used to treat hypertension

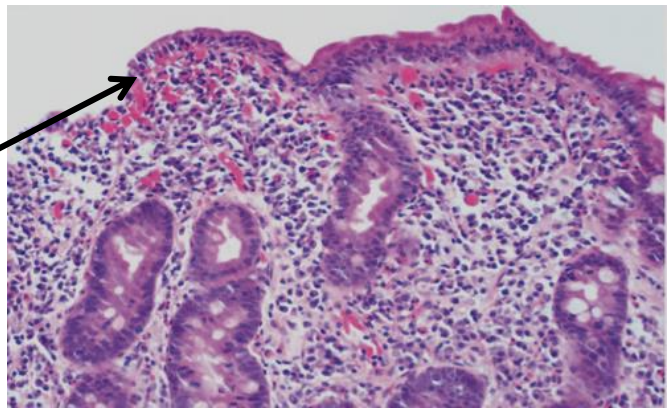
Induces severe diarrhea

Duodenal changes often **indistinguishable from Celiac disease**:

- Villous blunting
- Increased intraepithelial lymphocytes

Often more acute and chronic inflammation in lamina propria

Sometimes see subepithelial collagen deposition



Mycophenolate Mofetil

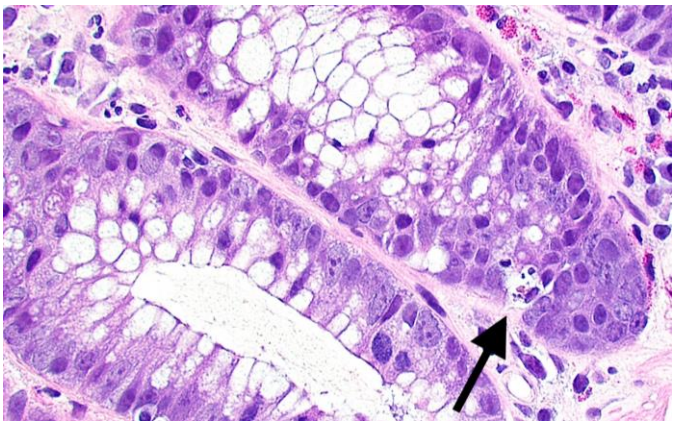
Immunosuppressive drug usually used after solid organ transplantation

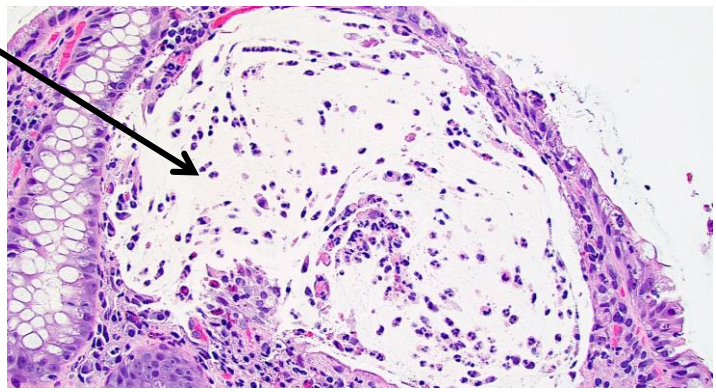
GI toxic→ often limiting use

Resembles GVHD or Crohn's disease:

- **Increased crypt apoptoses**
- Patchy **neutrophilic inflammation**
- Degenerating damaged crypts
- Architectural damage
- Granulomas

More Eos favors drug effect, more apoptoses favors GVHD

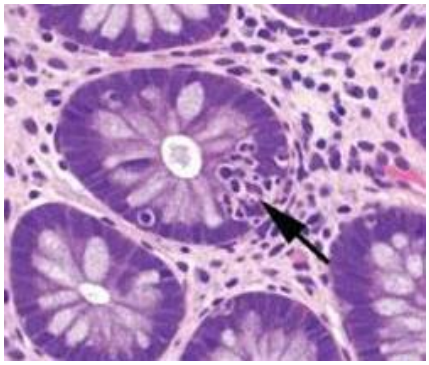




Bowel Prep and Laxatives

Many act through increasing osmolarity of stool → traps water in lumen → loose stool

Mucin depletion
Focal active colitis/cryptitis
Increased **apoptotic bodies**
Erosions

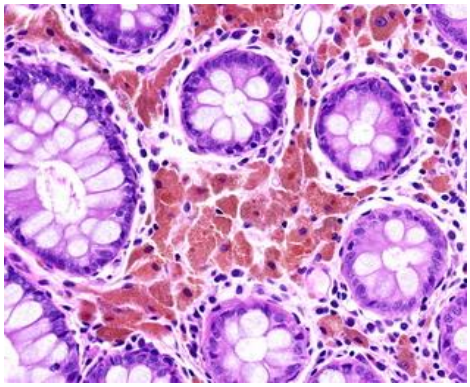


Melanosis Coli

Classically associated with irritant laxatives, **but** actually indicator of increased epithelial cell turnover

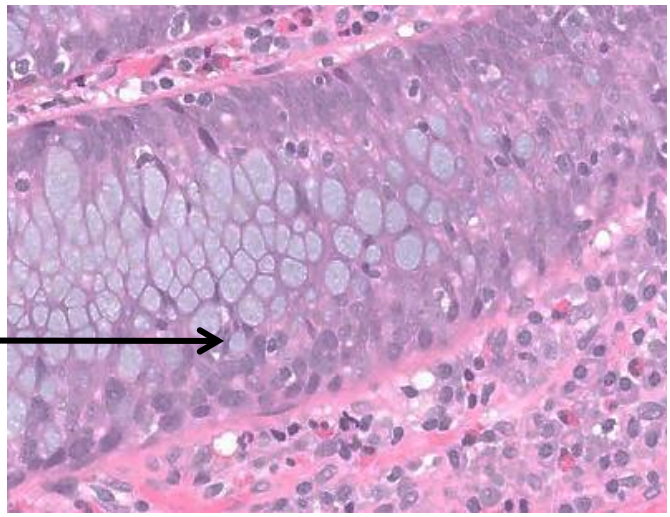
Apoptosis → debris phagocytosed by macrophages → lipofuscin accumulates → looks yellow or brown

Can **see with many drugs** including NSAIDs, etc..



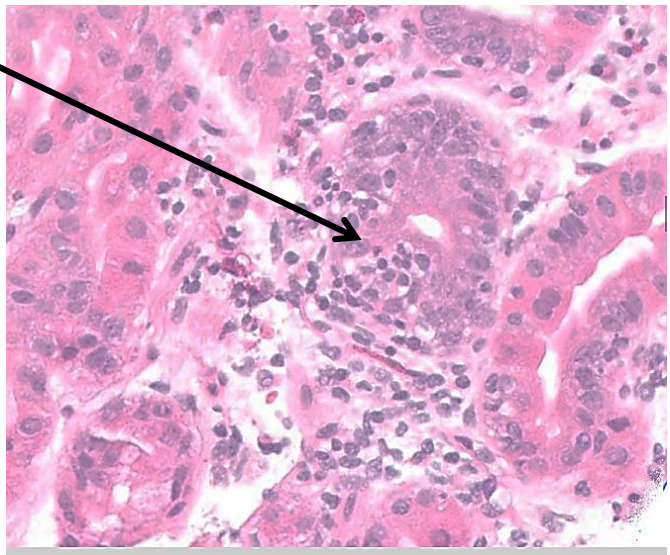
Checkpoint Inhibitors

Anti-PD1, Anti-PDL1, and anti-CTLA therapy
Activate immune tumor destruction, but can also cause autoimmune "immune related adverse events"
Respond to steroids



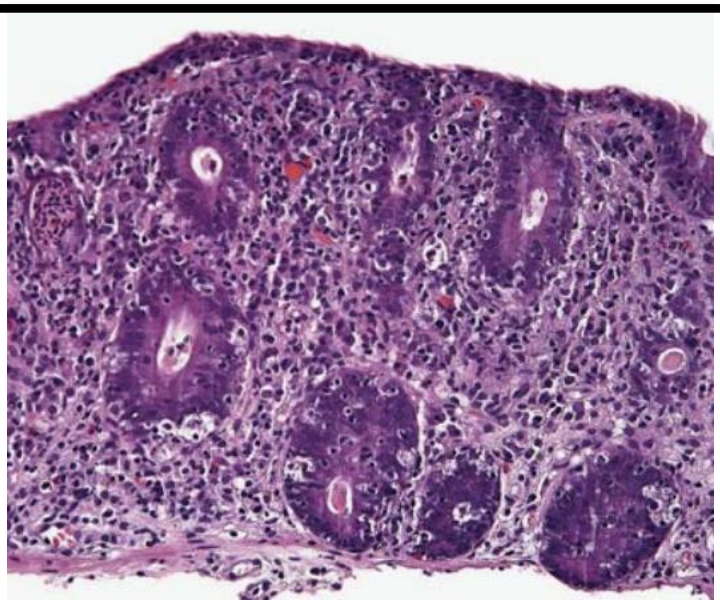
Colon, most patterns including:
- Lymphocytic colitis
- Collagenous colitis
- Acute self-limited colitis
- Apoptotic colitis

Stomach:
- Perigland inflammation/focal enhancing gastritis-pattern
- NOT diffuse



Duodenum:
- Villous blunting
- Increased intraepithelial lymphocytes
- Apoptoses
- Brunner's gland inflammation

Idelalisib

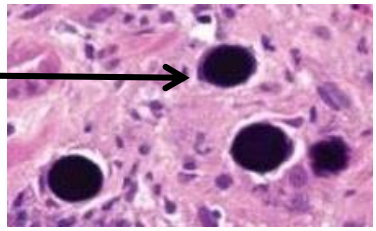


Specific small molecule drug used to treat CLL/SLL and follicular lymphoma

Causes severe diarrhea

Changes seen in colon and small bowel:
- Increased apoptoses
- Lymphocytic colitis
- Focal active colitis/cryptitis

^{90}Yttrium-labeled Microspheres



Appear as uniform dark/opaque perfect circles.

Given by interventional radiology as internal radiation therapy for hepatic malignancies. Often also see radiation injury.

Most common to see in upper GI due to shared circulation with liver

Additional

Diuretics
Decrease circulatory volume→ bowel ischemia at usual watershed areas
See classic ischemic findings: crypt withering, lamina propria hyalinization.

Ergotamine
Given for migraines, induces vasospasm→ causes localized ischemia in GI tract
Small, localized ischemic ulcers. Not in watershed zones.

Gluteraldehyde
Used to disinfect colonoscopes. Used less now. Contact irritant in rectum and colon.

Hormone therapy/Oral contraceptives
Estrogen produces a hypercoagulable state → mesenteric venous thrombosis → ischemic colitis

Table 1. Drug-Induced Colonic Mucosal Injury Patterns and the Most Commonly Offending Medications

Histologic Patterns of Injury	Medication
Mucosal ulcerations, erosions, and strictures	NSAIDs Methotrexate Nonabsorbable drugs: Kayexalate, sevelamer, colesevelam, colestipol, cholestyramine
Increased epithelial apoptosis	Mycophenolate acid Ipilimumab Idelalisib Tumor necrosis factor α inhibitors (etanercept, infliximab) Antimetabolites (methotrexate, capecitabine) NSAIDs Sodium phosphate Taxanes, colchicine
Chronic colitis-like pattern	Mycophenolate acid Ipilimumab Rituximab Tumor necrosis factor α inhibitors (etanercept, infliximab) NSAIDs Idelalisib
Ischemic colitis	Digitalis Estrogen Cocaine Ergotamine Sumatriptan Nonabsorbable drugs: Kayexalate, sevelamer Glutaraldehyde NSAIDs Mycophenolate acid
Focal active colitis/ self-limited colitis	NSAIDs Sodium phosphate Mycophenolate acid Ipilimumab
Microscopic colitis	Proton pump inhibitors (lansoprazole) H2 receptor antagonists Ticlopidine NSAIDs Cyclo 3 Fort Statins Carbamazepine Flutamide Paroxetine Penicillin Selective serotonin reuptake inhibitors Idelalisib
Infectious/necrotizing colitis	Chemotherapy drugs Pegylated interferon and ribavirin Corticosteroids Antibiotics: penicillins, clindamycin, cephalosporins, and trimethoprim-sulfamethoxazole
Mimics of dysplasia and mitotic arrest	Colchicine Taxol Cyclosporine intravenously
Colonic perforation	Corticosteroids Nonabsorbable drugs: Kayexalate

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

From: Marginean EC. The Ever-Changing Landscape of Drug-Induced Injury of the Lower Gastrointestinal Tract. Archives of Pathology & Laboratory Medicine 2016 140:8, 748-758