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: **foveal 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)

<table>
<thead>
<tr>
<th>Pattern of Colitis</th>
<th>Associated Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic colitis</td>
<td>NSAIDs, gold, carbamazepine, antiplatelet agents, estrogens</td>
</tr>
<tr>
<td>Lymphocytic or collagenous colitis</td>
<td>NSAIDs, lansoprazole, ticlopidine, ranitidine, simvastatin, flutamide, carbamazepine, sertraline, penicillin, checkpoint inhibitors, Idelalisib</td>
</tr>
<tr>
<td>Focal active colitis</td>
<td>NSAIDs, Bowel preparation (esp. oral sodium phosphate), checkpoint inhibitors, Idelalisib</td>
</tr>
<tr>
<td>Ischemic colitis</td>
<td>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</td>
</tr>
<tr>
<td>Apoptotic colitis</td>
<td>Bowel preparation (esp. oral sodium phosphate), mycophenolate mofetil, laxatives, chemotherapeutic agents (esp. 5-fluorouracil), NSAIDs, cyclosporine, checkpoint inhibitors, Idelalisib</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>NSAIDs, antibiotic-associated Clostridium difficile colitis</td>
</tr>
<tr>
<td>Neutropenic colitis</td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

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 microtubule 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.
**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 apoptosis
- Lymphocytic colitis
- Focal active colitis/cryptitis

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**90Yttrium-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

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**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.

**Glutaraldehyde**

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