Patterns of GI Tract Injury

Esophagus

**Benign Incidental Findings:**
*Gastric “Inlet Patch”*- Heterotopic gastric mucosa in esophagus

**Pancreatic Heterotopia/Metaplasia**

**Glycogenic Acanthosis** – Epithelial hyperplasia with abundant, enlarged superficial glycogenated cells; clinically appears white

**Acute Esophagitis**

*Intraepithelial Neutrophils with Erosion/Ulceration*

**GERD** Often scattered Eos (usu. < 15/HPF), Intercellular edema, Basal cell hyperplasia, Elongation of vascular papilla. Worse distally (near GEJ).

**Infections**
- Candida - Look for fungal hyphae, Get PAS-D/GMS
- HSV - Look for Molding, Multinucleation, Margination in epithelial cells.
- CMV – Look for inclusions in mesenchymal cells.

**Medications** (“Pill esophagitis”) Look for crystals, resins, and pill fragments; Polarize to help looking for foreign material.

**Eosinophilic Esophagitis**

*Increased intraepithelial Eosinophils* (report per HPF)

**GERD**
Eos typically < 15/HPF, Intraepithelial T lymphocytes (“squiggle cells”), Intercellular edema, Basal cell hyperplasia, Elongation of vascular papilla. Worse distally (near GEJ).

**Eosinophilic Esophagitis**
Typically >20 Eos/HPF. Often eosinophilic microabscesses with degranulation. Often diffuse or worse proximally. Associated with “Atopic Triad” (Allergies, Asthma, Eczema). Presents with dysphagia, chest pain, food impaction, which may cause a food aversion. Endoscopically can appear as rings or furrows (“Trachealization/felinization”)

**Allergies/Systemic autoimmune disorders**

**Medication Reaction**

*Note:* As EoE and GERD can appear identical on a single bx, close clinical and endoscopic correlation is often necessary to distinguish between the them!
**Parakeratosis Pattern**

**GERD**
Eos typically < 15/HPF, Intraepithelial T lymphocytes ("squiggle cells"), Intercellular edema, Basal cell hyperplasia, Elongation of vascular papilla. Worse distally (near GEJ).

**Candida Esophagitis**
Look for fungal hyphae at surface and get PAS-D or GMS, particularly in immunosuppressed individuals. Budding yeast are NOT good enough!

**Esophagitis Dissecans Superficialis ("Sloughing Esophagitis")**
Superficial "mummified" layer (with ghost nuclei) with variable necrosis and minimal inflammation. Clinically can be quite dramatic with extensive peeling and fissuring. Has been associated with thermal injury, medications, and some autoimmune conditions.

**Esophageal Leukoplakia**

**Lymphocytic Pattern**

**GERD**

**Lichen Planus**
Band-like ("lichenoid") infiltrate at junction between epithelium and submucosa. Dyskeratotic keratinocytes ("Civatte bodies") are common. Associated with cutaneous LP, certain medications, and viral infections. Often older women. Risk of dysplasia → SCC

**Graft Versus Host Disease**
Donor T lymphocytes attack host tissue. Typically present with Rash, Diarrhea, elevated LFT’s. Intraepithelial lymphocytes with dyskeratotic keratinocytes and scattered apoptotic bodies. Make sure CMV IHC is neg.

**Crohn’s Disease**
Look in lamina propria for granulomas

**“Contact Mucositis”**
May be a generalized response to mucosal injury, for example to an allergy to a medication or food.

**Other**
CVID, Celiac disease, Dysmotility, Etc...
**Stomach**

**Oxyntic Mucosa** (90% of stomach)
- Present in body/fundus
- Pink parietal cells make acid and intrinsic factor (B12 uptake)
- Purple chief cells make pepsinogen

**Antral Mucosa**
- Present in distal antrum and cardia
- Gastrin-secreting G cells are found ONLY in antrum
- Usu. extremely few inflammatory cells, except at the gastric cardia, which commonly has some chronic inflammation.

**Reactive (Chemical) Gastritis/Gastropathy**

*Foveolar hyperplasia ("corkscrew glands"), Mucin depletion, Edema, Minimal inflammation, Extension of smooth muscle bands between glands*

Often caused by **chemical irritation** by bile reflux, Medications (particularly NSAIDs), or alcohol.

**Portal Hypertensive Gastropathy**
- Above findings, plus dilated vessels in lamina propria. Seen in patients with portal hypertension.
- Endoscopically like “snake skin”

**Gastric Antral Vascular Ectasia ("GAVE")**
- Endoscopically looks like a watermelon. Fibrin thrombi present in lamina propria capillaries.

**Acute Gastritis**

*Intraepithelial Neutrophils often with Erosion/Ulceration*

**Helicobacter pylori**
- Acute gastritis with characteristic **superficial** lymphoplasmacytic inflammation and prominent **lymphoid aggregates**. Most common in Antrum. Look hard in pits and consider getting Helicobacter IHC.
- Risk of MALT and dysplasia/carcinoma.

**Helicobacter heilmanni**
- Less acute inflammation. More common in kids. Organisms are longer, more tightly spiraled, and less numerous

**Medications**
- Esp. NSAIDs. Often associated ischemic or reactive changes.

**“Focally Enhanced Gastritis”**
- Focally injured glands surrounded by inflammation. Associated in kids with IBD, particularly Crohn’s disease.

**CMV**
Chronic Gastritis

**Helicobacter pylori**
Acute gastritis with characteristic superficial lymphoplasmacytic inflammation and prominent lymphoid aggregates. Most common in Antrum.

**Autoimmune Metaplastic Atrophic Gastritis (AMAG)**
Also known as autoimmune gastritis. Autoantibodies destroy parietal cells/oxyntic mucosa → No intrinsic factor → B12 deficiency → Pernicious anemia.

Body-predominant injury with loss of oxyntic mucosa and **Deep** chronic inflammation → Intestinal and pyloric metaplasia & ECL cell hyperplasia → Can make neuroendocrine tumors (type I)

Gastrin stain can help confirm sample came from body (negative) and not antrum (positive).

**Medications**
Esp. NSAIDs. Often associated ischemic or reactive changes.

**Other**
CVID, Celiac disease

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**Lymphocytic Gastritis**

*Intraepithelial Lymphocytes*

**Helicobacter pylori**

**Celiac Disease**

**Medications** (E.g., Ticlopidine, Olmesartan)

**HIV**

**Other Immune-mediated Disorders**
CVID, Crohn’s Disease, Lymphocytic colitis, etc...

**Lymphoma**

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**Collagenous Gastritis**

*Increased subepithelial collagen band with Intraepithelial Lymphocytes* (can highlight with trichrome stain)

**Collagenous colitis/enteritis**

**Celiac Disease**

**Medications** (E.g., Olmesartan)

**Helicobacter**

**Other Immune-mediated Disorders**
**Eosinophilic Gastritis**

*Increased Eosinophils*

Although there is no strict cut-off, >30/HPF is likely too many and any in the epithelium, submucosa, or muscle is abnormal.

**Eosinophilic Gastritis/Gastroenteritis**

Diagnosis of exclusion. Can be associated with Eosinophil-rich inflammation in other organs (e.g., esophagus and/or small bowel). Layer of bowel involved determines symptoms.

**Helicobacter**

**Parasites**

**Connective tissue diseases/Vasculitis**

**Food Allergies**

**Medications**

**Inflammatory bowel disease** (particularly Crohn’s)

**Oxyntic Gland Hyperplasia**

Dilated oxyntic glands with hypertrophic parietal cells with “snouts”

**Single/Sporadic Polyp → Fundic Gland Polyp**

Associated with Proton Pump Inhibitor use (increases gastrin levels through feedback, causing parietal cell hypertrophy).

Extremely low risk of dysplasia/progression

**Innumerable or Dysplastic? Consider a Syndrome:**

**Familial Adenomatous Polyposis** Can become dysplastic, but still low rate of progression to carcinoma

**MutYH-Associated Polyposis**

**Zollinger-Ellison Syndrome**

Gastrinoma (usu. in small bowel) causes increased acid secretion and ulcers. Associated with MEN1.

**Foveolar Hyperplasia**

“Corkscrew glands”, Mucin depletion, Edema

**Single/Sporadic Polyp → Hyperplastic Polyp**

Associated with background inflammatory injury. extremely low risk of dysplasia/progression

**Innumerable or Dysplastic? Consider a Syndrome:**

**Ménétrier's Disease** Whole stomach, protein-losing enteropathy

**PTEN Syndromes (Cowden’s, etc...)**

**Cronkhite-Candada Syndrome**

**Juvenile Polyposis**

**Peutz-Jeghers Syndrome**
**Small Intestine**

**Quick Checklist:**
- Villi? Long and skinny? Go away or blunt with Celiac Disease
- Goblet Cells? Go away with autoimmune enteropathy
- Intraepithelial lymphocytes? Increased in Celiac (and others)
- Plasma cells? Go away with CVID
- Critters? Look between villi and on surface for Giardia, etc.
- Vessels ok? Look for amyloid and vasculitis
- Endocrine cells? Go away with endocrine dysgenesis

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**Acute Duodenitis**

**Neutrophils in duodenal epithelium**

**Peptic Duodenitis**

Additionally see Gastric foveolar metaplasia and chronic inflammation. Associated with excess gastric acid and/or *Helicobacter*

**Infection** Most commonly *Helicobacter* (can lead to ulcers → Peptic Ulcer Disease). Sometimes Adenovirus, CMV, or other viruses.

**Medications** Most commonly NSAIDs

**Inflammatory bowel disease** (particularly Crohn’s)

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**Acute Ileitis**

**Neutrophils in ileal epithelium**

**Medications** Most commonly NSAIDs

**Infection** Including common stool pathogens (bacterial and viral)

**Inflammatory bowel disease** Crohn’s disease is more likely to impact TI (so look for granulomas, and signs of chronicity, including pyloric gland metaplasia). In UC, there is typically inflammation in the nearby cecum (that is thought to “backwash”)

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**Eosinophilic Gastroenteritis**

**Increased Eosinophils**

Although there is no strict cut-off, >60/HPF is likely too many and any in the epithelium, submucosa, or muscle is abnormal

**Eosinophilic Gastroenteritis**

Diagnosis of exclusion. Can be associated with Eosinophil-rich inflammation in other organs (e.g., stomach or colon). Layer of bowel involved determines symptoms.

**Parasites**

**Connective tissue diseases/Vasculitis**

**Food Allergies**

**Medications**

**Inflammatory bowel disease** (particularly Crohn’s)

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**Eosinophilic Gastroenteritis Symptoms**

<table>
<thead>
<tr>
<th>Layer</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Mucosa</td>
<td>Diarrhea, malabsorption</td>
</tr>
<tr>
<td>Muscle</td>
<td>Ileus</td>
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<tr>
<td>Serosa</td>
<td>Ileus and ascites</td>
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</tbody>
</table>
Chronic Injury

**Architectural distortion:** crypt branching, dropout, and pyloric gland metaplasia often with villous blunting and a basal lymphoplasmacytosis

**Often starts to look like colon with IBD!**

**Inflammatory Bowel Disease**

Chronic ACTIVE inflammation, with cryptitis and crypt abscesses. Particularly Crohn’s in the TI (and small bowel in general). Look for granulomas and transmural inflammation in resections.

**“Diaphragm Disease”** Due to NSAIDS

Mild → erosions with associated acute inflammation
Severe → multiple episodes can cause scarring → stenosis
Usu. Less chronic inflammation than Crohn’s

**Medications**

Mycophenolate – Immunosuppressant (often given after transplantation) that can cause epithelial/crypt damage with increased apoptosis → causes diarrhea

**Ischemia** Severe pain. Coagulative necrosis. Crypt withering. Lamina propria hyalinization and hemorrhage. Reperfusion brings acute inflammation.

**Radiation** Most sensitive to damage. Endothelial injury → edema, fibrin, and ischemic changes with enlarged/bizarre nuclei.

**Graft vs. Host Disease (GVHD)** Donor T-lymphocytes attack host bowel. First see apoptotic bodies in crypts. Severe damage shows crypt abscess, crypt distortion, and epithelial destruction.

**Graft Rejection** Host T-lymphocytes attack donor bowel. Similar to GVHD: Inflammation (mostly lymphs) with crypt destruction and apoptosis.

**“IPAA” findings** *(given to patients with UC or FAP)*

Usu. NOT given to Crohn’s patients as high risk of complications

**Pouchitis** Acute and chronic inflammation of ileal reservoir. Unclear etiology, but often treated with antibiotics/probiotics.

If refractory, consider Crohn’s.

**vs**

**Cuffitis** Chronic active inflammation of rectal cuff, attributed often to residual/recurrent UC.

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<table>
<thead>
<tr>
<th>Lerner System for Grading GVHD</th>
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<tbody>
<tr>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>4</td>
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Malabsorption

Villous atrophy with increased intraepithelial lymphocytes (IEL)

Causes Diarrhea clinically often with weight loss.

**Gluten Sensitive Enteropathy (Celiac Disease)**
Gluten exposure triggers inflammation, primarily in duodenum. Positive serology for: Antigliaden, Tissue transglutaminase (TTG), and antiendomysial (EMA) (if not IgA deficient!). Associated with haplotypes HLA-DQ2 or DQ8 (absence both of these essentially excludes diagnosis). Number of IEL typically >20/100 enterocytes. “Crescendo” at tip of villi.

**Other Protein Sensitives** (e.g., cow milk, soy, eggs)
Often increased Eosinophils in mucosa

**Peptic duodenitis**

**Medications** (e.g., Olmesartan and NSAIDs)

**Small Bowel Bacterial Overgrowth** excess anaerobic bacteria (often caused by decreased acid and dysmotility) digest bile and carbohydrates $\rightarrow$ variable local damage and bloating

**CVID** Immunodeficiency with impaired B-cell differentiation. Usually plasma cells ABSENT $\rightarrow$ low serum Ig’s $\rightarrow$ recurrent infections.

**Tropical Sprue** Unknown etiology, but likely infectious. After travel to Africa, Asia, or South America. Must exclude other infections.

**Autoimmune Enteropathy** Gut autoantibodies $\rightarrow$ often absent goblet or Paneth cells. Most common in infants.

**Foamy Macrophages** “Foamy” macrophages in mucosa

**Mycobacterium avium intracellulare (MAI)** Get a FITE stain! Immunocompromised/AIDS-defining opportunistic infection.

**Whipple Disease** Get a PAS/D stain! *Tropheryma whipplei* causes an infection often afflicting adult white men $\rightarrow$ arthralgias, weight loss, diarrhea. Treat with antibiotics.

**Nonspecific Macrophages**

**Dilated Lacteal** Engorged/dilated lymphatics

**Primary Lymphangiectasia** Poorly understood. Dilated lymphatics $\rightarrow$ lymph/albumein leakage into gut $\rightarrow$ diarrhea and protein-losing enteropathy.

**Secondary Lymphangiectasia** Similar manifestations as primary, but secondary to obstruction, tumor, adhesions, stricture, prior surgery, etc....
Colon

Crypts should be oriented parallel to one another, perpendicular to the surface (like test tubes), resting on the muscularis mucosae

<table>
<thead>
<tr>
<th>Regional Variation</th>
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</thead>
<tbody>
<tr>
<td><strong>Right Colon</strong></td>
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<tr>
<td>More lymphocytes</td>
</tr>
<tr>
<td>Paneth cells normal</td>
</tr>
<tr>
<td>Fewer goblet cells</td>
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</tbody>
</table>

Some architectural distortion and muciphages in the rectum is considered **normal**.

Focal Active Colitis

*Rare collections of neutrophils in crypt epithelium*  
(Otherwise normal)

**Medications** (esp. NSAIDs)

**Acute Self-limited Colitis** Resolves in <4 weeks. Usually infectious (e.g., *Campylobacter*, *Salmonella*, *Shigella*, or *Yersinia*) with abrupt onset and coinciding fever.

**Bowel preparation artifact**

**Ischemic Colitis**

**IBD** Usu. More insidious onset.

Acute Colitis

*Extensive cryptitis and crypt abscesses, WITHOUT features of Chronicity*

**Infection** Usu. acute bacterial or viral infections (e.g. CMV, *Salmonella*, *Shigella*, *Campylobacter*, etc...), so make sure this has been evaluated clinically. Often food contamination (fecal-oral). May see Pseudomembranes.

**Medications** Esp. NSAIDs. Also Resins (Kayexalate and Sevelamer) and Ipilimumab.

**IBD** Usually has features of chronicity, so would have to be emerging (very recent onset) or partially treated.
Chronic Active Colitis

Active colitis with features of Chronicity

Features of Chronicity include: Architectural distortion (crypt branching, loss, and shortening), basal lymphoplasmacytosis, and Paneth cell or pyloric metaplasia

Inflammatory Bowel Disease (IBD)

Chronic systemic autoimmune inflammatory disease. On a mucosal colonic biopsy, can be impossible to distinguish Crohn’s from UC and must rely on clinical/endoscopic impression. Look for Granulomas and Dysplasia. (See IBD handout for Crohn’s vs UC)

Infection

Always rule out CMV in refractory IBD (along with other causes clinically)

Diverticular Disease

Most common in older patients in sigmoid colon. Can mimic IBD with Diverticulitis and Segmental Colitis Associated with Diverticulosis (SCAD).

Diversion-Associated Colitis

In bowel diverted from fecal stream (causes short chain fatty acid deficiency). Usu. see florid lymphoid hyperplasia with prominent germinal centers.

STD Proctocolitis

Sexually Transmitted Diseases: Esp. Syphilis and lymphogranuloma venereum (Chlamydia). Often tons of plasma cells.

Cord Colitis Syndrome

After Umbilical cord transplantation. Often see granulomas.

Medications

NSAIDs, Ipilimumab, and resins

Ischemic Colitis

Superficial epithelial damage, Crypt withering, Lamina propria hyalinization and hemorrhage.

Occasional pseudomembranes and acute inflammation (with reperfusion)

Ischemia

Due to poor perfusion. Most common in “watershed” areas (splenic flexure, rectosigmoid, and ileocecal regions) in older patients with vascular occlusion or low-flow states.

Infection

*E.coli O157:H7* (EHEC)—Endothelial damage from toxin → Fibrin thrombi often seen. Associated with Hemolytic Uremic Syndrome (Anemia, low platelets, renal failure)

*C. Difficile*—Pseudomembranes, less hyalinization and crypt withering

Medications

Esp. NSAIDs. Also Resins (Kayexalate and Sevelamer) and Ipilimumab.
Eosinophilic Colitis

Increased Eosinophils

Although there is no strict cut-off, >60/HPF is likely too many and any in the epithelium, submucosa, or muscle is abnormal.

**Eosinophilic Colitis/Gastroenteritis**
Diagnosis of exclusion. Can be associated with Eosinophil-rich inflammation in other organs (e.g., esophagus and/or small bowel). Layer of bowel involved determines symptoms.

**Parasites**

**Connective tissue diseases/Vasculitis**

**Food Allergies**

**Medications**

**Systemic mastocytosis**

**Inflammatory bowel disease** (particularly Crohn’s)

Lymphocytic Colitis

*Increased intraepithelial lymphocytes*

**Lymphocytic Colitis** Watery diarrhea with normal endoscopic findings. Increased intraepithelial lymphocytes (>20 lymphs/100 epithelial cells). Classically older women.

**Collagenous Colitis** Watery diarrhea with normal endoscopic findings. Increased intraepithelial lymphocytes with *Increased subepithelial collagen layer* (irregularly thickened, trapping inflammatory cells, vessels, and fibroblasts). Highlight with trichrome stain.

**Medications** (e.g., NSAIDs, Olmesartan, SSRIs, etc...)

**Viral Infections**

Granulomatous Colitis

*Granulomas!* Rule out infection with FITC and GMS/PAS-D

**Crohn’s Disease** Loose, non-necrotizing. Seen in less than ½ of cases. *Note:* In UC can see granulomatous reaction to crypt rupture!

**Infections** Esp. if Necrotizing! Rule out fungi and mycobacteria. Look around for parasites (e.g., Schistosomiasis)

**Nonspecific mucosal injury**

**Medications**

**Sarcoidosis**

**Cord Colitis Syndrome**

**Diverticular disease**

**CVID and Chronic Granulomatous Disease**
Pigments and Inorganic Material

**Iron**
*Appears brown and granular on H&E; Blue on Iron Stain*

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, so urgent dx.
*Purple on H&E with narrow fish-scale pattern.*

**Sevelamer**: Used to treat hyperphosphatemia in renal failure → Associated with mucosal injury.
*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.*

**Calcium**
*Appears dark purple and often cracked on H&E; Black on von Kossa*

*Can be*: Metastatic (in normal tissue due to high serum calcium levels), dystrophic (in damaged tissue due to injury), or idiopathic

**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.
Melanosis

Coarse, brownish black pigment in cytoplasm of macrophages.

Consists of deposited Lipofuscin. Although classically associated with laxative use, can be seen in any disorder with increased epithelial cell turnover, including constipation.

Tattoo

Very black, coarse granules in macrophages, often with a foreign body giant cell reaction.

Used to mark lesions endoscopically for later identification.

Muciphages

Mucin-containing macrophages in lamina propria

Presumably cleaning up after epithelial injury and turnover. Very common, especially in rectum.

Air

"Pseudolipomatosis"

Empty spaces, without a foreign body reaction.
Attributed to insufflation artifact. No associated nuclei (not fat).

Pneumatosis Cystoides Intestinalis

Empty spaces, WITH a foreign body reaction.
(which means it happened in vivo!!)
Often iatrogenic or infectious cause.