**GI Infections**

### Helicobacter

- **H. pylori** → slender curved rods
  - Very common: Infects ½ the world population (esp. underdeveloped countries, through person-to-person contact)
  - Acute infection → **Chronic active gastritis with superficial lymphoplasmacytic infiltrate**
  - More prevalent in antrum
  - Often erosions and germinal center formation → can cause MALT lymphoma

- **H. heilmannii** → milder inflammation, corkscrew appearance
  - May be acquired from domestic animals. Esp. prevalent in children.
  - Less likely to cause lymphoma.

Both stain with Giemsa, Silver, and same immunohistochemical stain
Treat with triple therapy (2 antibiotics + PPI)

### Intestinal Spirochetosis

- **Fuzzy, fringed layer** of organisms at surface (Non-invasive)
  - Variable species, but most are Brachyspira
  - Usually no associated inflammatory infiltrate
  - Stain with silver stains: Warthin-Starry, Steiner

Clinical significance is somewhat unclear:
- Diarrhea most common symptom, but unclear if actually causative or coincidental
- Classical association with men who have HIV is also being questioned

### Mycobacterium

- **M. avium-intracellulare complex (MAI or MAC)**
  - Abundant foamy macrophages in lamina propria often distending villi. Can have poorly formed granulomas.
  - Usually immunocompromised (classically AIDS)
  - Present with Diarrhea, malabsorption, and weight loss
  - Organisms stain with AFB, FITE, PAS, and GMS

- **M. Tuberculosis**
  - Classically necrotizing (caseating) granulomas.
  - Coalescence of large granulomas, often with associated cuff of lymphocytes.
  - Organisms stain with AFB & FITE, but culture and/or PCR may be required.
  - Most common in ileocecum with sharply-defined ulcers and strictures (mimicking Crohn’s disease), causing weight loss, fever, abdominal pain, and diarrhea.
  - GI symptoms may precede pulmonary symptoms.
Whipple disease

Infection by *Tropheryma whippelii*
Present with weight loss, diarrhea, arthritis, lymphadenopathy, endocarditis, and neuropsychiatric issues.
Most common in middle-aged white males with HLA-B27.
Most often infects small bowel, but can see changes throughout GI tract and also brain, heart, and lymph nodes.
Massive infiltration of lamina propria by foamy macrophages
Variable acute inflammation.

Organisms stain with PAS. Can also identify with PCR.
(Negative for FITE and AFB, helping differentiate from MAI)

Yersinia

Gram-negative coccobacciform enteric bacteria
Infection caused by food contamination
Most commonly infects ilium, right colon, and appendix.
Can cause ulcers and edema.

Abundant epithelioid granulomas with lymphoid cuffs
Transmural lymphoid aggregates and giant cells common
Usually not necrotizing
→ Closely mimics Crohn’s disease
Stains not helpful→ consider culture, serologies, or PCR
Common cause of granulomatous appendicitis

Acute infectious colitis

“Acute Self-limited Colitis”

Most commonly associated with bacterial enterocolitis
Usually acute onset of diarrhea and abdominal pain.
Often self-limited and resolves within several weeks.
Often discriminated from one another by microbiology testing
(classically culture, but now PCR NAATs)

Classically, Active colitis (cryptitis, crypt abscess formation, epithelial damage), without features of chronicity (preserved architecture, no metaplasia or basal lymphoplasmacytosis).
Nevertheless, can mimic IBD, particularly in the resolving phase

Most common bacteria include (Often food-borne illness):
Campylobacter—most common stool isolate in US.
Salmonella—can cause typhoid fever with hyperplastic Peyer’s patches, ulcers, and necrosis. Less PMNs.
Enterohemorrhagic E. coli (O157:H7)—Shiga-like toxins cause epithelial and endothelial injury→ see fibrin thrombi and ischemic changes→ can cause hemolytic uremic syndrome (HUS) due to endothelial injury and platelet activation causing 1) Thrombocytopenia, 2) Hemolytic anemia, and 3) Kidney injury
Clostridioides difficile—usually after recent antibiotic use. Watery diarrhea with pseudomembranes
Shigella, Yersinia

Also caused by some viruses (e.g., norovirus) and parasites
Sarcina

Spherical cells 2-3 μm in diameter
Occur in tetrad or packets of 8 or more
Most commonly found in the stomach

Unclear if pathogenic. Likely incidental finding.

Often seen in cases of delayed gastric emptying and gastric outlet obstruction
→ Their presence can prompt further investigation as to cause of dysfunction, such as occult malignancy

Actinomyces

Long, filamentous bacteria that stain purple
Look like “dust bunnies”

Frequently seen as incidental bacteria on biopsies or part of mixed flora colonizing lesions, especially in oral cavity.
Associated with poor hygiene.

Uncommon cause of appendicitis.

Positive on Gram stain and GMS.
Negative on AFB.

Normal Flora

Most “normal” bacteria in the oral cavity and intestines are gram-negative anaerobes
On GI biopsies, often see in esophagus and intestines
Bacteroides species are the most common, other common ones include Prevotella and Veillonella.
Other organisms include gram-positive organisms like Streptococcus.

Usually, these are commensal and do not cause disease.

Can cause periodontal disease
Elsewhere, most disease is due to spread to other regions (e.g., endocarditis, abscesses, septic arthritis, pneumonia, etc...)
Often polymicrobial clusters/infections
Highlighted by gram and silver stains
Histologic findings are nonspecific and further microbiology tests (e.g., culture, MALDI-TOF, or NAAT) are necessary for identification.
**Viruses**

### Cytomegalovirus (CMV)

- **Normal hosts**: Common cause of childhood diarrhea.
  - Can cause intussusception due to lymphoid hyperplasia.
- **Immunocompromised hosts**: Diarrhea, potentially leading to disseminated disease (including hepatitis and pneumonitis) and death. Harder to control.
  - Characteristic smudgy inclusions that are basophilic to eosinophilic.
  - Tubular GI tract: Inclusions in surface epithelium, often in goblet cells. Can be round or crescent shaped. Most often in colon with increased apoptosis and epithelial sloughing.
  - Liver: Inclusions in hepatocytes, often at edges of coagulative necrosis.

### Herpes Simplex Virus (HSV)

- Most commonly causes ulceration with variable inflammation, predominantly acute. Can get vesicles in anorectum.
- Viral inclusions at edges of ulcers in epithelial cells:
  - 3M’s → **Moulding** (chromatin) → **Margination**, **Multinucleation**
- #2 most common cause of infectious esophagitis → dysphagia.
- Self-limited in healthy patients; may cause esophageal perforation or disseminate in immunocompromised patients.
- Findings the same in HSV1&2.

### Adenovirus

- **Normal hosts**: Common cause of childhood diarrhea.
  - Can cause intussusception due to lymphoid hyperplasia.
- **Immunocompromised hosts**: Diarrhea, potentially leading to disseminated disease (including hepatitis and pneumonitis) and death. Harder to control.
  - Characteristic smudgy inclusions that are basophilic to eosinophilic.
  - Ulceration, mixed inflammatory infiltrate with neutrophils if severely immunocompromised, less inflammation.

- Be sure to evaluate for in refractory IBD and GVHD cases.
  - Can also look for with PCR.

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*Note: Images and diagrams are placeholders and not actual images from the document.*
### Candida

Most common infection of the **esophagus**

More common in immunocompromised

Presents with **dysphagia/odynophagia**

Endoscopy: **white plaques** with underlying ulceration

**Neutrophilic inflammation with ulceration**, but less if immunocompromised

**Parakeratosis** common

→ highlighted by PAS-D and GMS stains

→ See mix of budding yeast and **pseudohyphae**

### Histoplasmosis

**Endemic to Ohio, Missouri, Mississippi river valleys.**

Can cause localized or disseminated disease (more common in immunocompromised). Lung most common site, but GI common too.

Most common GI site of involvement is ileum. May cause ulcers or mass.

Often **lymphohistiocytic infiltrates** without well-formed granulomas

**Intracellular 2-5 μm fungi**

Positive with GMS and PAS

### Cryptococcus

Ubiquitous. Often from **avian droppings** (think “**Pigeons**”)

Usually **immunocompromised** (e.g., AIDS, organ transplant, etc...)

Can be localized or disseminated disease.

Other common sites are lung and **meninges**

Variable inflammatory response (depending on immune state). Can have granulomas or suppurative necrosis.

4-7μm, very **“pleomorphic” (lots of different sizes)**, round to oval,

Narrow-based buds. Unstained, refringent capsules give “halo” or **“soap bubble”** appearance. Stain with GMS. Capsule stains with mucicarmine

### Coccidioides

**“Valley Fever.”** Found in soil in southwestern United States and South and Central America. Higher risk if immunocompromised. Can have localized or disseminated disease.

In host, spores develop into large, thick-walled endospore-containing **spherules**, which enlarge and rupture. There is often associated granulomatous and chronic inflammation
Parasites

**Strongyloides**

*Nematode* with worldwide distribution. Very common in Tropics and southeastern US. Often get through skin when barefoot on contaminated soil. Skin → Lung → GI tract → Feces → next host (or autoinfect)

Worse in immunocompromised patients

*Can be asymptomatic* and harbor for >30 yrs

When symptomatic, diarrhea, pain, bleeding

*Inflammation with neutrophils and eosinophils* often, may resemble IBD

Adult worms, larvae, and eggs all *found IN crypts*

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**Enterobius vermicularis**

“*Pinworm*”

Spread by fecal-oral route. Humans are the only host.

Most common in children.

Often asymptomatic, but can cause anal pruritus

Most commonly seen in *appendix*, often incidentally

Thick cuticle on adult worm

*characteristic lateral spikes (ala)*

Easily visible internal organs

Even invasive worms cause *minimal inflammation*

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**Schistosomiasis**

Parasitic trematode (fluke)

Any species of “*schisto*” can be found in the gut

Endemic to Africa, Asia and parts of the Americas.

**Highest prevalence in Sub-Saharan Africa and Middle East**

Infected by *contaminated water* through the skin

→ snails are intermediate host

Most patients are *asymptomatic*, but can present with GI bleeding (or hematuria or portal hypertension)

**Ova:** Found in the wall of the GI or GU tract. Often *calcify* with time. Variable acute, chronic, or granulomatous inflammation. Often prominent eosinophils.

**Worms:** often have no reaction to them, *found in veins* (of bowel or bladder) or in liver → lay eggs into urine/stool

Three main species in humans:

Schistosoma mansoni—Usually GI tract. Lateral spine

Schistosoma japonicum—Usually GI tract. Later knob

Schistosoma haematobium—Usually GU tract. Terminal spine
Liver flukes

Helminths occlude bile duct → dilated ducts with wall thickening → Signs of biliary obstruction (jaundice, fever, RUQ pain) → can cause cholangiocarcinoma long-term due to chronic inflammation

Clonorchis sinensis, Opisthorchis species, and Fasciola species
Endemic primarily to Asia and acquired by eating raw or undercooked fish or crawfish
Worms visible to naked eye

Echinococcus

Cestode (tapeworm) with wide geographic distribution
Definitive host = Dogs (or other carnivore)—humans infected through exposure to feces → Eggs hatch → larvae travel to liver and form cysts → cysts grow very slowly
Often asymptomatic, but can get symptoms from mass-effect
Treated with surgical resection; Ruptured cysts are very antigenic → can cause anaphylaxis
Inner most layer contains protoscolices (developing heads of adult tapeworms), which contain 2 circles of hooklets and sucker
This is surrounded by a layer of hyalinized, white laminated, acellular material

Protozoans

Entamoeba Histolytica
Protozoan most common in subtropical and tropical regions
In US, most common in immigrants and travelers
Infected through fecal-oral route/contaminated food/water

Can be asymptomatic, or cause variably severe diarrhea
Can cause amoebic liver abscesses

Cause deep “flask-shaped” ulcers, extending into submucosa, undermining nearby mucosa.
Architectural distortion may mimic IBD
Often abundant amorphous eosinophilic debris

Entamoeba: Round, red, eccentric nucleus
Distinct cell membranes with foamy cytoplasm
Ingested RBCs.
Giardia duodenalis

Most common protozoa infection in US
Usually acquired from contaminated water. Can be STD.
More common in kids, with travel, and immunocompromised
Causes diarrhea (unclear pathogenesis), often watery and foul-smelling.
Can be chronic, esp. if immunocompromised

Usually see trophozoites with no associated inflammation
(sometimes mild villous blunting and chronic inflammation)

Trophozoites are pair-shaped with 2 oval nuclei
Look like “falling leaves” in bowel lumen

Cryptosporidia

Obligate intracellular world-wide parasite.
Can be from contaminated water or person-to-person
Diarrhea→ self-limited in normal hosts, but often chronic/relapsing
with weight loss and cramping in immunocompromised. No good therapy.

Parasites appear as 2-5μm basophilic “blue beads” on lumina apical
surface.
Can see villous blunting and variable inflammatory infiltrate
Enveloped by microvilli→ less microvilli for absorption→ diarrhea

Cystoisospora

Formerly just “isospora”
Obligate intracellular world-wide parasite.
Infected by contaminated food/water
Causes diarrhea, often chronic. Debilitating if immunocompromised
Villous blunting with mixed inflammation and prominent Eosinophils

Variable forms, all intraepithelial:
Some crescent/banana shaped
Others are round with prominent nucleoli

Cyclospora

Protozoan with world-wide distribution that causes diarrhea.
Infection often occurs through contaminated food/water
Variable villous blunting and inflammation
Round (2-3 μm) forms and crescentic merozoites (5-6 μm) in parasitophorous vacuoles

Microsporidia

Fungus that causes intestinal infection, particularly in AIDS patients→
Diarrhea
Small spores (2-3 μm) and larger plasmodia
Located within supranuclear cytoplasm of epithelial cells