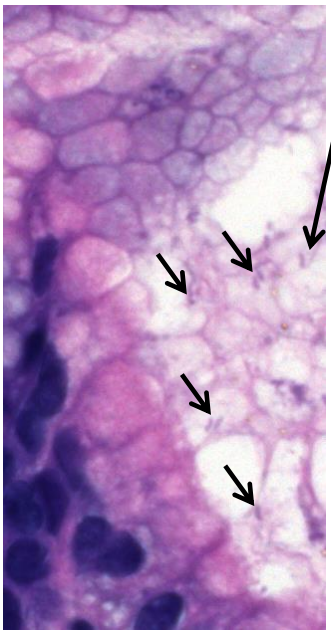
GI Infections

Bacteria

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.** Erosions and **germinal center formation.**

More prevalent in **antrum**

Can cause intestinal metaplasia→ dysplasia→ gastric carcinoma

Can cause MALT lymphoma

***H. heilmannii*→** *milder* inflammation, **corkscrew appearance**

May be acquired from domestic animals. Virtual slide

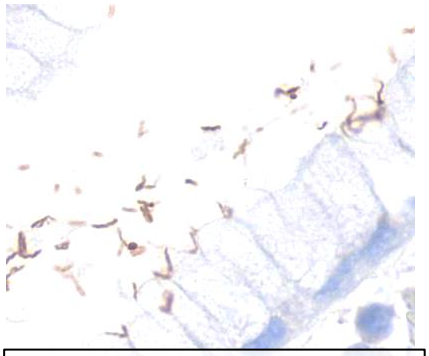
Esp. prevalent in children. Less likely to cause lymphoma.

Both stain with Giemsa, Silver, and same immunohistochemical stain.

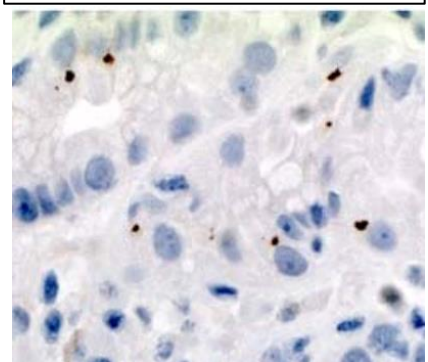
Treat both with triple therapy (2 antibiotics + PPI)

After PPI therapy, there are often *fewer* bacteria.

Also, morphology can change! → Infrequent cocci, intracellular in glands



Usual appearance on IHC: Curvilinear rods in mucus layer adherent to foveolar epithelium and pit lumina



After therapy, can change morphology to intracellular cocci!

Testing options & recommendations: *(from GIPS; PMID: 24141174)*

"Moderate chronic gastritis (i.e., large confluent groups of chronic inflammatory cells identifiable at low magnification) is 97% sensitive and 98% specific for H. pylori infection, with a negative predictive value of 98%."

So, usually only need to get IHC if there is at least moderate chronic inflammation (and you don't see them on H&E).

IHC can also be useful if there is unusual morphology or a low number of organisms (e.g., post-PPI therapy).

IHC is regarded as preferable over other special stains.
(Other stains, like Giemsa, are likely equivalent to H&E in utility).

Not recommended in *normal* stomach, reactive (chemical) gastropathy biopsies, or "up front" (before histologic review)

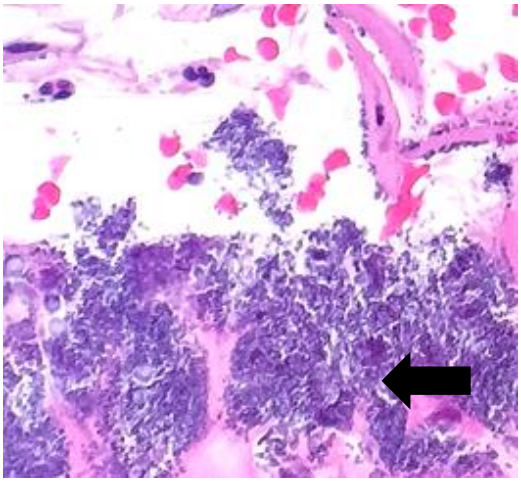
Other "noninvasive" testing options (don't require endoscopy):

Serum antibodies—Good sensitivity. Pretty good specificity too, but remains elevated after eradication.

Stool antigen study—Good sensitivity. Uses antibodies against bacterial antigens in the stool.

Urease breath test—Good sensitivity. Uses radiolabeled urease, which is digested by bacteria.

Normal Flora

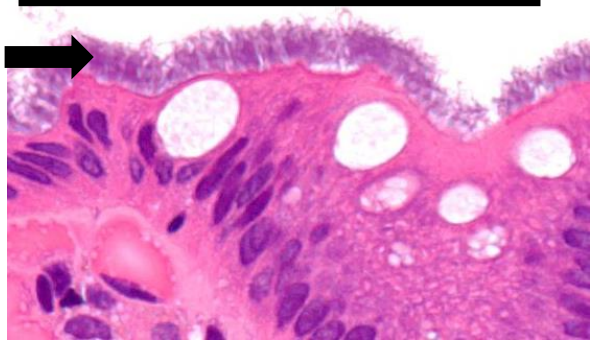


Most "normal" bacteria in the oral cavity and intestines are **gram-negative anaerobes**
On GI biopsies, often see in esophagus and intestines
Bacteroides species are the most common, other common ones include Prevotella and Veillonella.
Other organisms include gram-positive organisms like Streptococcus.

Usually, these are **commensal** and do not cause disease.
Can cause **periodontal disease**

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 gests (e.g., culture, MALDI-TOF, or NAAT) are necessary for identification.

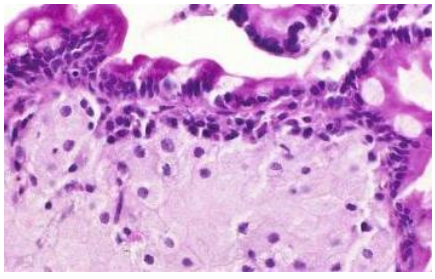
Intestinal Spirochetosis

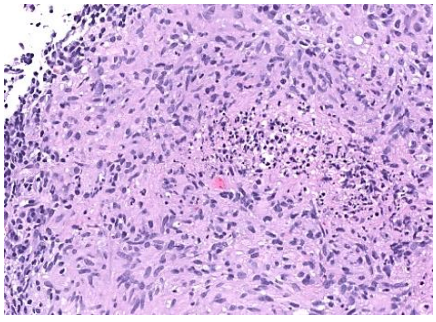


Fuzzy, fringed layer of organisms at surface (Non-invasive)
Variable species, but most are *Brachyspira*
Usually no associated inflammatory infiltrate
Stain with silver stains: Warthin-Starry, Steiner

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. Virtual slide

Mycobacterium





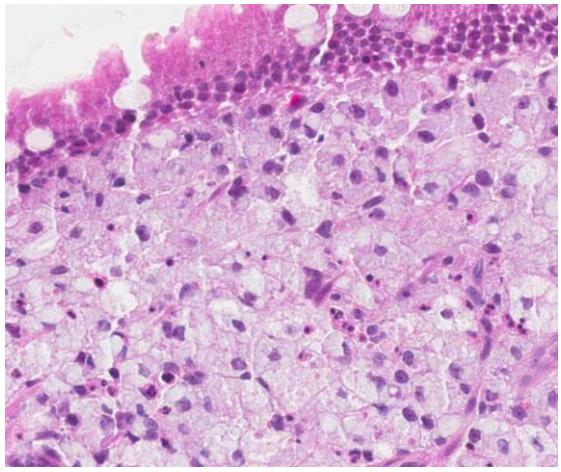
M. avium-intracellulare complex (MAI or MAC)

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
Virtual slide AFB

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



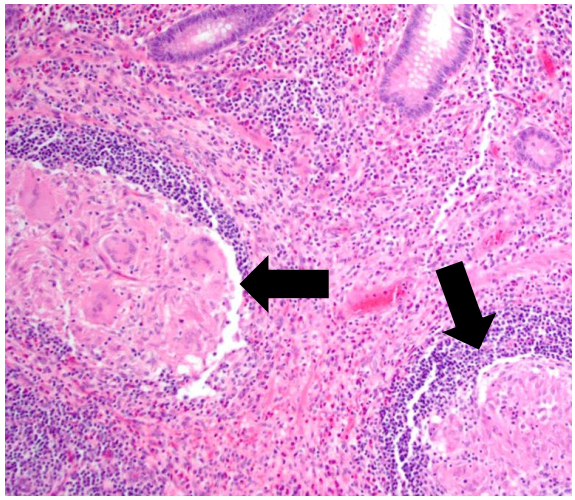
Infection by ***Tropheryma whipplei*** Virtual slide
Present with weight loss, diarrhea, arthritis, lymphadenopathy, endocarditis, and neuropsychiatric issues.
Most common in middle-aged white males with HLA-B27.

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



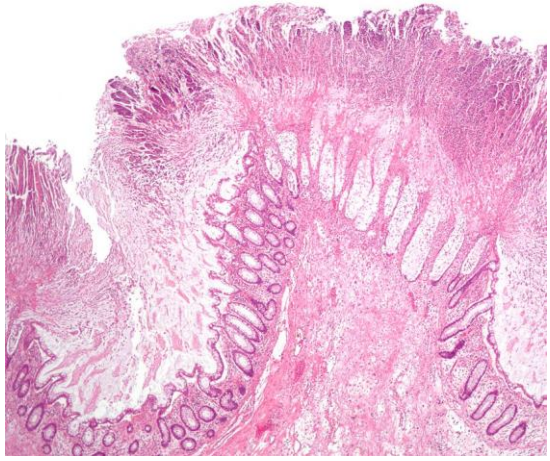
Gram-negative coccobacciform enteric bacteria
Infection caused by food contamination

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 C.Diff Virtual slide

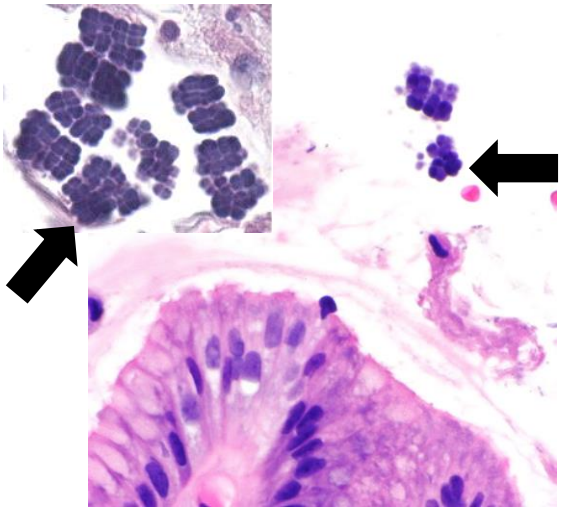
Also caused by some viruses (e.g., norovirus) and parasites

Sarcina

Spherical cells 2-3 µm in diameter
Occur in **tetrads** 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

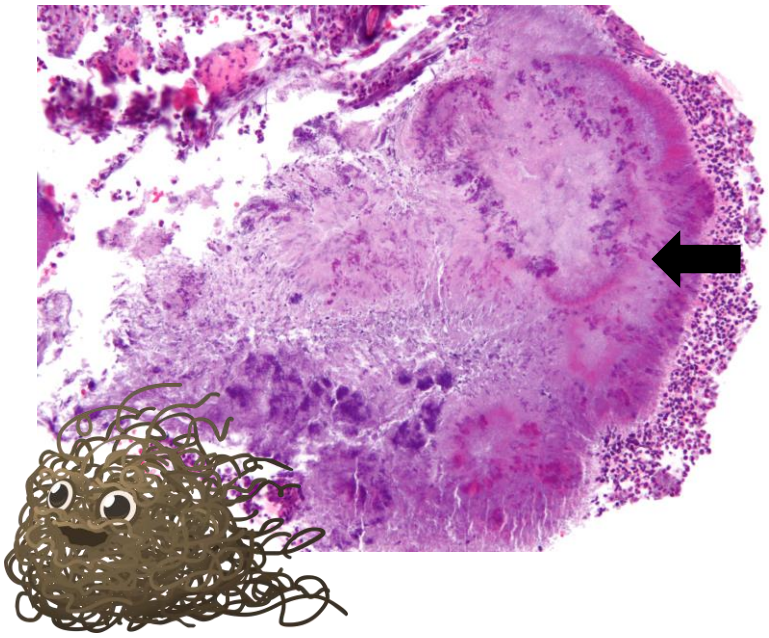
Long, filamentous bacteria that stain purple
Look like "**dust bunnies**"

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.
(can cause Crohn's like inflammation in appendix)

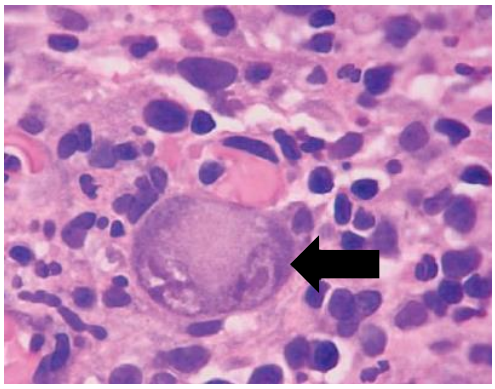
Positive on Gram stain and GMS.
Negative on AFB.

Virtual slide



Viruses

Cytomegalovirus (CMV)



Most common in immunocompromised hosts, esp. AIDS

Often causes ulcerations. Symptoms vary by site:
- Esophagus→ dysphagia, odynophagia
- Stomach/intestines→ Diarrhea, bloody or watery, pain

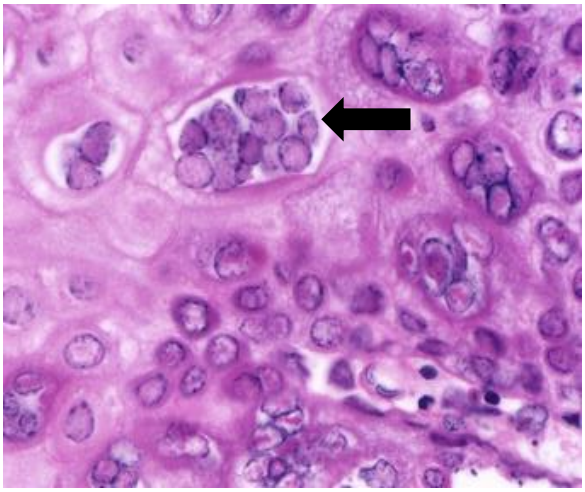
Ulceration, **mixed inflammatory** infiltrate with neutrophils
- if severely immunocompromised, less inflammation

Viral inclusions, preferentially in mesenchymal cells:
- Most commonly endothelium or other stromal cells
- Nuclear→ "Owl's eye" (Cowdry A), pink, nucleolus-like
- Cytoplasmic→ granular and pink to purple, hof-like

Be sure to evaluate for in refractory IBD and GVHD cases

Can also look for with PCR Virtual slide in colon

Herpes Simplex Virus (HSV)

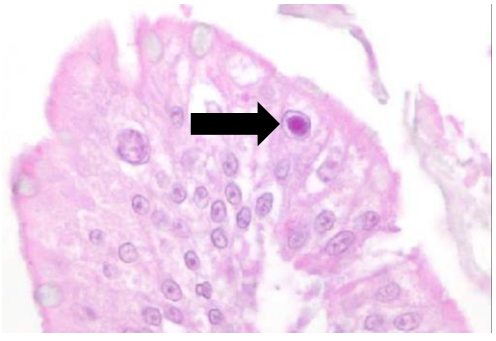


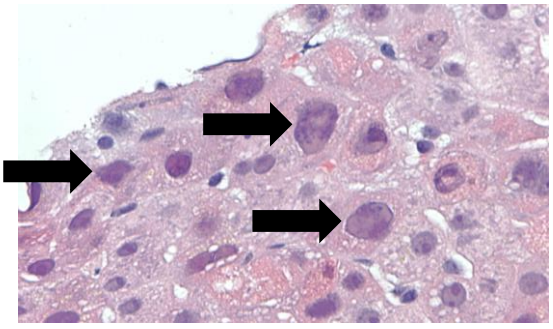
Most commonly causes **ulceration** with variable inflammation, predominantly acute. Can get vesicles in anorectum.

Viral inclusions at edges of ulcers in epithelial cells
3M's→ **M**oulding, (chromatin) **M**argination, **M**ultinucleation

#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 Virtual slide

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.

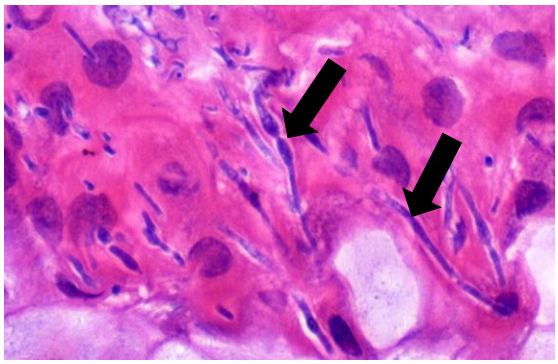
Characteristic **smudgy inclusions** that are basophilic to eosinophilic

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 Virtual slide

Fungus

Candida



Most common infection of the **esophagus**
More common in immunocompromised
Presents with dysphagia/odynophagia

Endoscopy: **white plaques** with associated ulceration

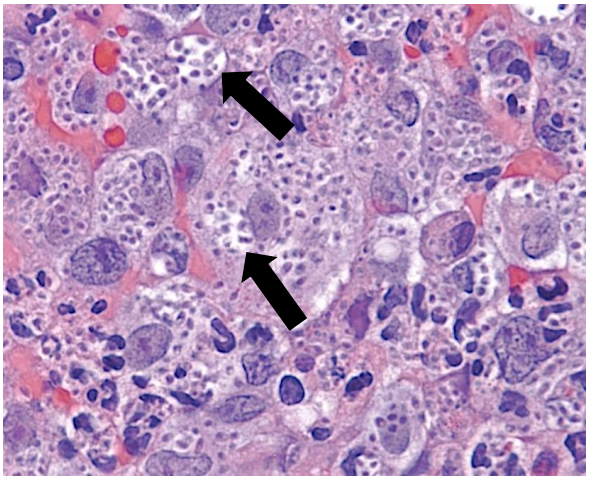
Neutrophilic inflammation, but less if immunocompromised
Parakeratosis common Virtual slide
→ highlighted by PAS-D and GMS stains
→See mix of budding yeast and **pseudohyphae**
(want to see pseudohyphae to call "candida esophagitis")

Histoplasmosis

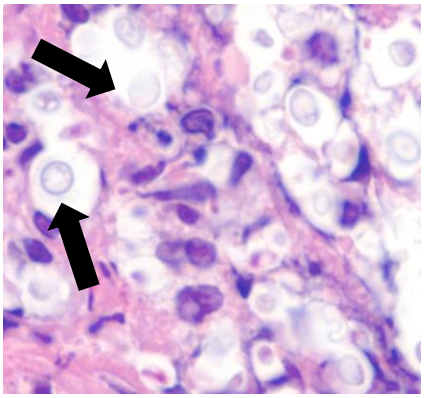
Endemic to Ohio, Missouri, Mississippi river valleys.
Can cause localized or disseminated disease (more common in immunocompromised). Lung most common site, but GI common too.

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 in macrophages
Positive with GMS and PAS



Cryptococcus

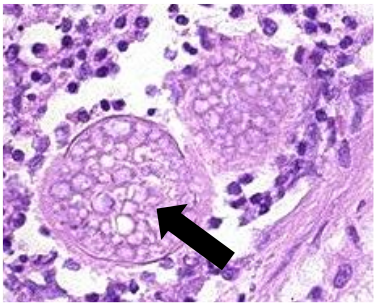


Ubiquitous. Often from avian droppings (*think* "***Pigeons***")
Usually **immunocompromised** (e.g., AIDS, organ transplant, etc…)
Can be localized or disseminated disease.
Other common sites are lung and meninges

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.
Virtual slide

Coccidioides



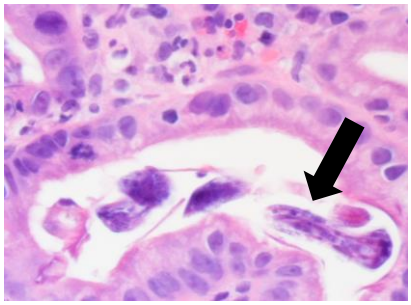
Infection = Coccidioidomycosis

"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. Virtual slide

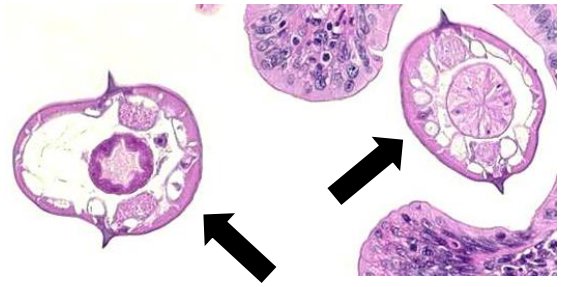
Parasites

Strongyloides



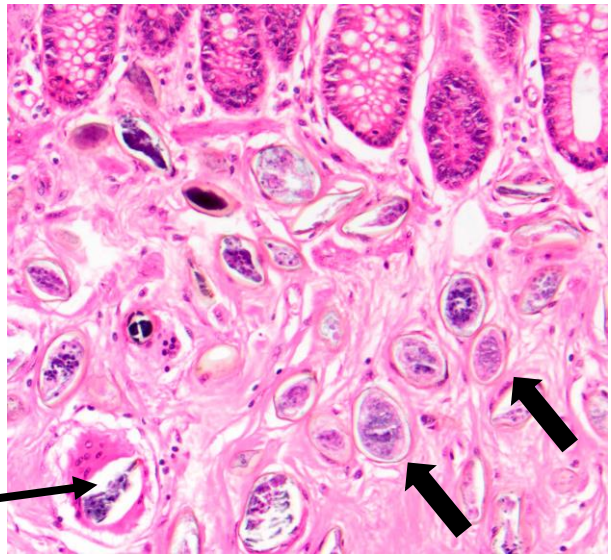
Nematode with worldwide distribution. Very common in Tropics and southeastern US. Often get through skin when barefoot on contaminated soil. Skin→ Lung→ GI tract → Feces → next host (or autoinfect)
Worse in immunocompromised patients
Can be asymptomatic and harbor for >30 yrs
When symptomatic, diarrhea, pain, bleeding
Inflammation with neutrophils and eosinophils often, may resemble IBD
Adult worms, larvae, and eggs all **found *IN* crypts** Virtual slide

Enterobius vermicularis



"Pinworm"
Spread by fecal-oral route. Humans are the only host.
Most common in children.
Often asymptomatic, but can cause anal pruritis
Most commonly seen in **appendix**, often incidentally
Thick cuticle on adult worm
characteristic lateral spikes (ala)
Easily visible internal organs Virtual slide
Even invasive worms cause minimal inflammation

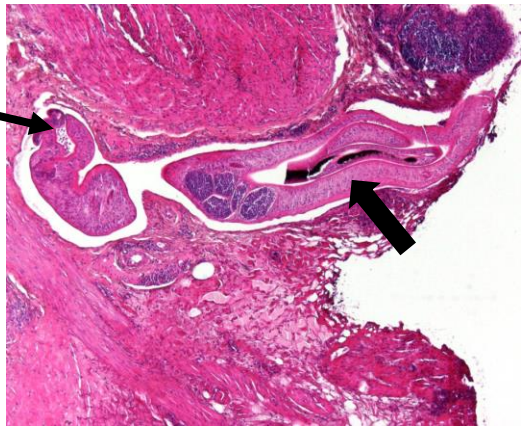
Schistosomiasis



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)

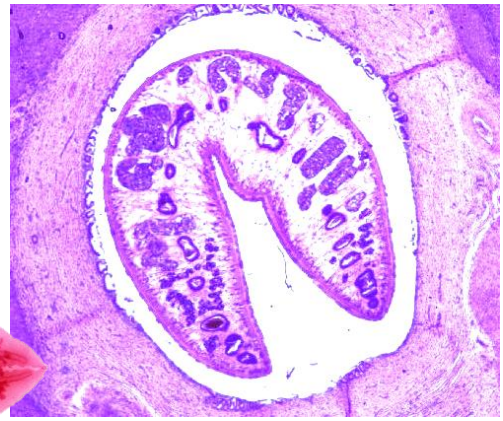
Ova: Found in the wall of the GI or GU tract. Often **calcify** with time. Variable acute, chronic, or granulomatous inflammation. Often prominent eosinophils.
Virtual slide 1 2



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. Lateral knob
Schistosoma haematobium-Usually GU tract. Terminal spine

Liver flukes

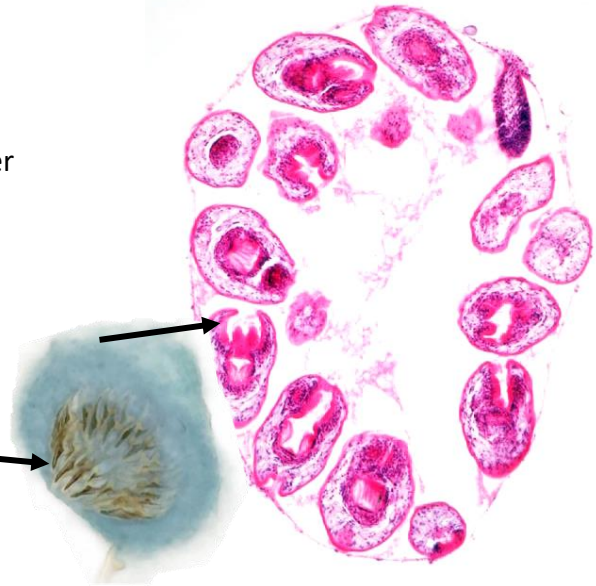


Helminths occlude bile duct→ dilated ducts with wall thickening→ Signs of **biliary obstruction** (jaundice, fever, RUQ pain) → can cause cholangiocarcinoma long-term due to chronic inflammation Virtual slide

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



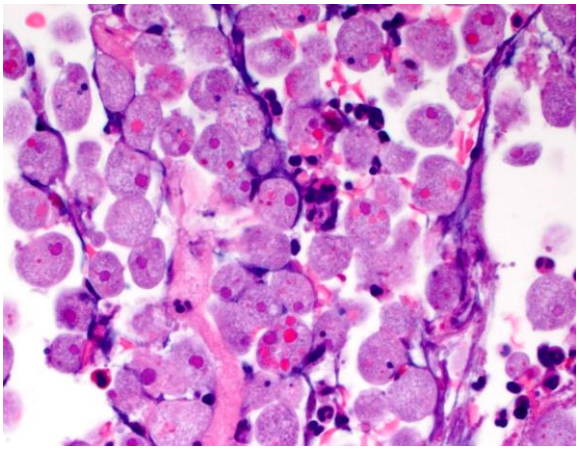
Cestode (**tapeworm**) with wide geographic distribution
Definitive host = **Dogs** (or other carnivore)—humans infected through exposure to feces→ Eggs hatch → larvae travel to liver and form **cysts**→ cysts grow very slowly

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. Virtual slide

Protozoans

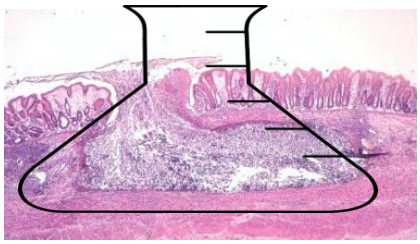
Entamoeba Histolytica



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

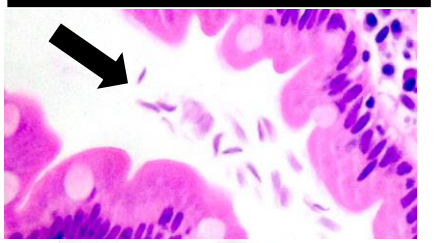
Can be asymptomatic, or cause variably severe **diarrhea**
Can cause amoebic liver abscesses

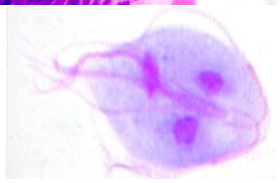
Cause deep "**flask-shaped" ulcers**, extending into submucosa, undermining nearby mucosa.
Architectural distortion may mimic IBD
Often abundant amorphous eosinophilic debris



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

Giardia duodenalis





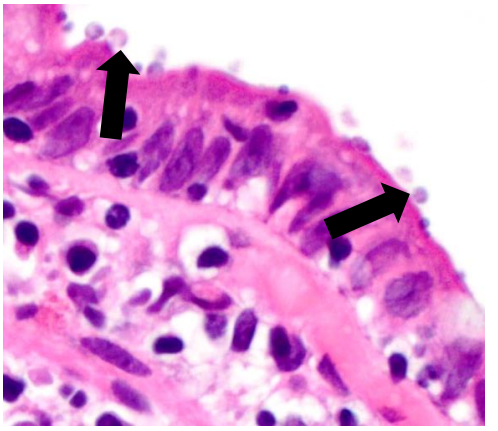
Most common protozoa infection in US.
Usually acquired from **contaminated water**. Can be STD.
More common in kids, with travel, and immunocompromised.
Causes diarrhea (unclear pathogenesis), often watery and foul-smelling.
Can be chronic, esp. if immunocompromised

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

Trophozoites are **pear-shaped with 2 oval nuclei**
Look like **"falling leaves"** in bowel lumen Virtual slide
Organisms stain with CD117

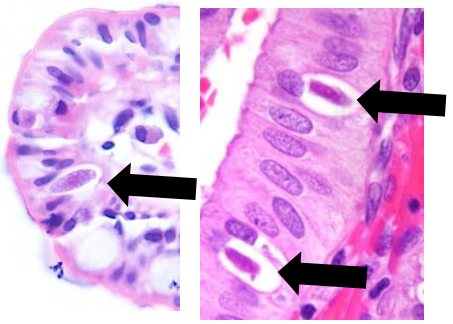
Cryptosporidia

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

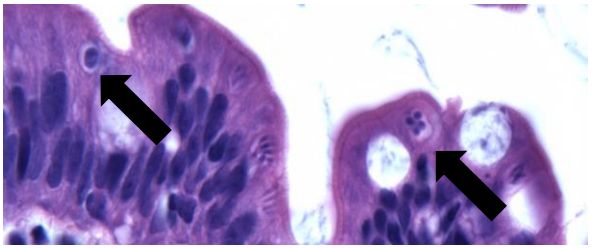
Cystoisospora



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