
بسم الله الرحمن الرحيم



Chronic infectious diarrhea

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Causes of chronic diarrhes

- **Parasite infection &Protozoal infection**
- **Bacterial infection**
- **Virus infection**
- **Fungal infection**

Causes of chronic infectious diarrhes

- Aeromonas
- Plesiomonas
- Campylobacter
- Giardia
- Amebae
- Cryptosporidium
- Whipple's disease
- Cyclospora
- Microsporidium
- Brainerd diarrhea
- Candidia allbicans
- Blastocystis hominis
- Postinfectious IBS

Giardia duodenalis(Giardia lamlia)

Important cause of:

- **Waterborne**
- **foodborne**
- **Daycare center**
- **International travelers**

risk factors for sporadic giardiasis:

- male-male sexual behavior.
- international travel .
- drinking water from a river, lake, stream, or spring.
- swimming in a natural body of water.
- contact with children in diapers .
- antibiotic use.
- presence of a chronic gastrointestinal condition.

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Entamoeba histolytica

- **The parasite exists in two forms:**
- **a cyst stage(the infective form**
- **a trophozoitestage(the form that causes invasive disease).**
- **Cyst can remain viable in the enviroment for weeks to months,and ingestion of a single cyst is sufficient to cause disease.**

Chronic diarrhea

- **Rarely, intestinal amebiasis may present as a chronic syndrome of diarrhea, weight loss, and abdominal pain without dysentery, lasting for years and mimicking inflammatory bowel disease.**

Diagnostic tests

- **Tools for diagnosis of intestinal amebiasis include**
- **stool microscopy,**
- **stool and serum antigen detection,**
- **stool polymerase chain reaction (PCR),**
- **serology,**
- **colonoscopy with histologic examination.**
- **Serologic testing cannot distinguish between acute, currently active infection and previous infection**



Stool microscopy

- **The demonstration of cysts or trophozoites in the stool suggests intestinal amebiasis, but microscopy cannot differentiate between E. histolytica and E. dispar or E. moshkovskii. In addition, microscopy requires specialized expertise and is subject to operator error**

Amebic colitis: colonoscopic appearance

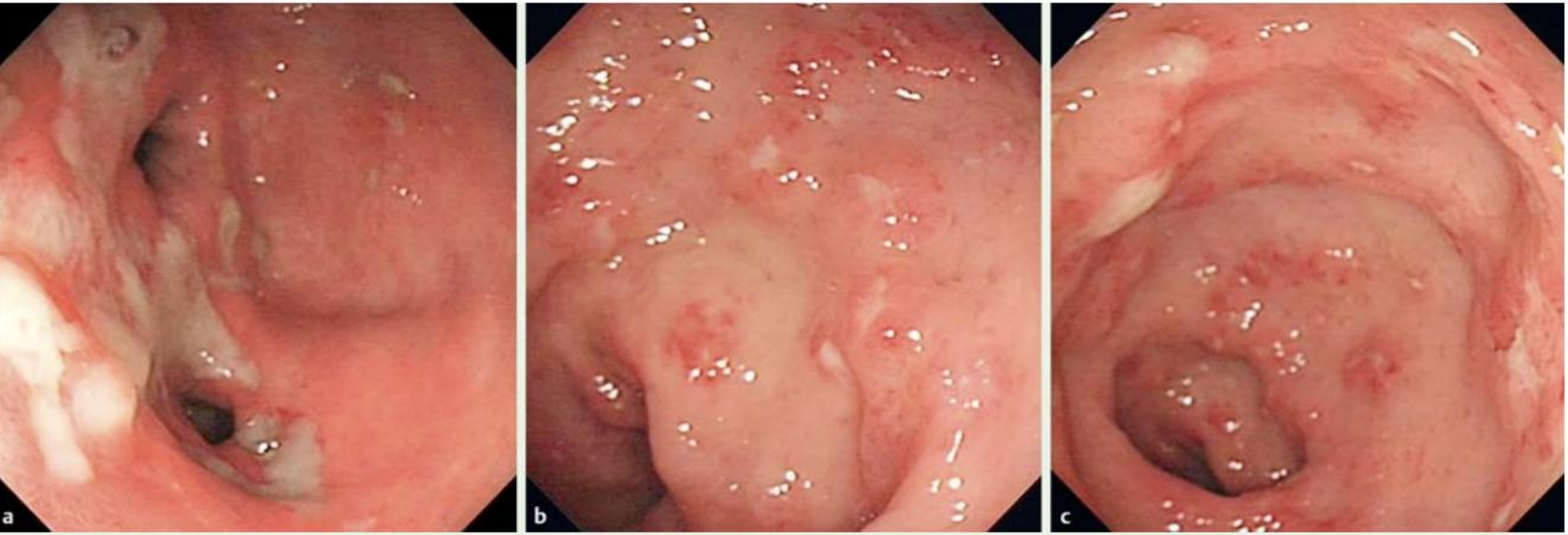
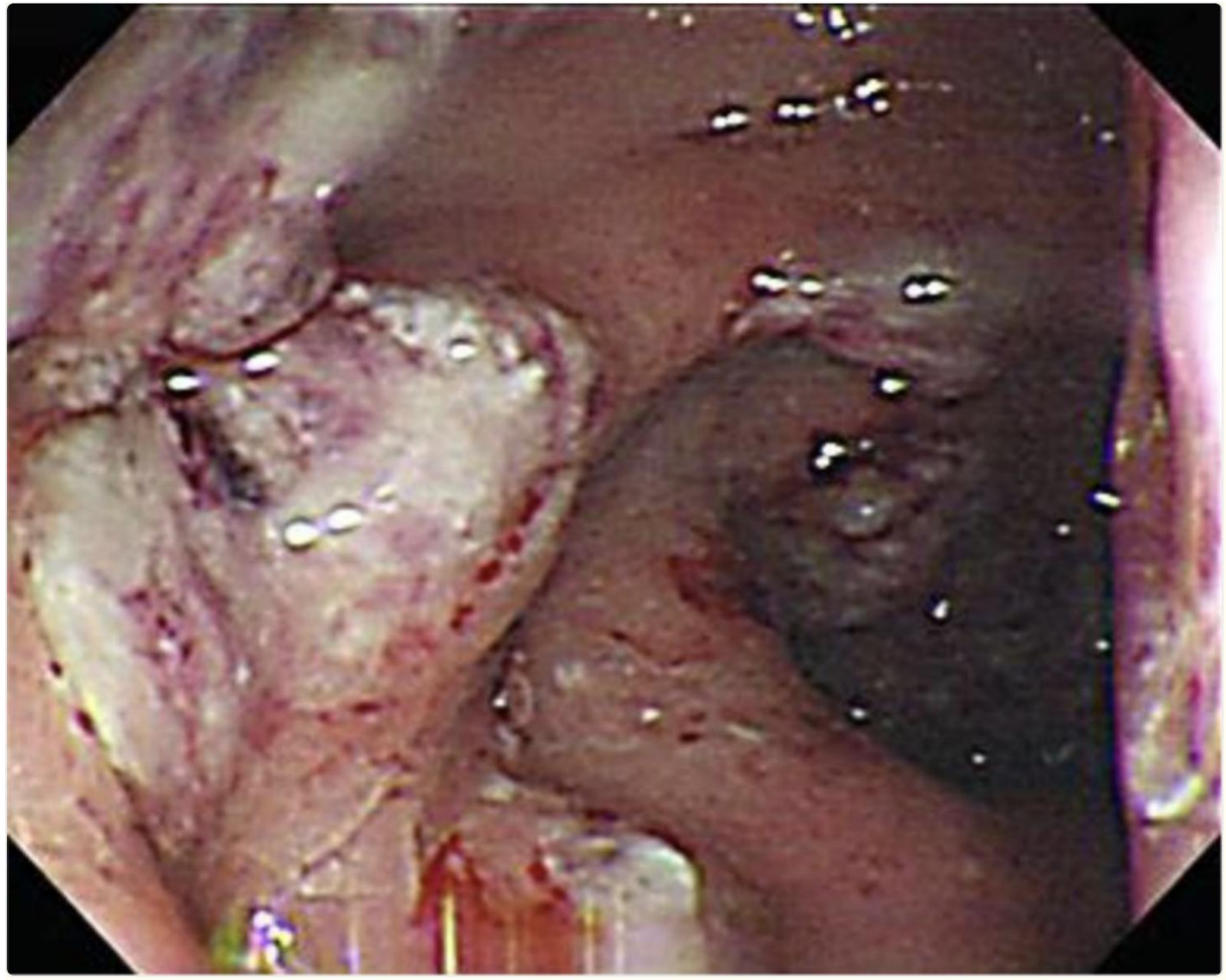


Fig. 1 Colonoscopic views showing multiple discrete ulcers with surrounding erythema in: **a** the cecum; **b** the sigmoid colon; **c** the rectum.



Colonoscopy showed multiple small polyps over the terminal ileum and multiple indurated ulcerations over the rectum and cecum.

Risk factor for Severe disease

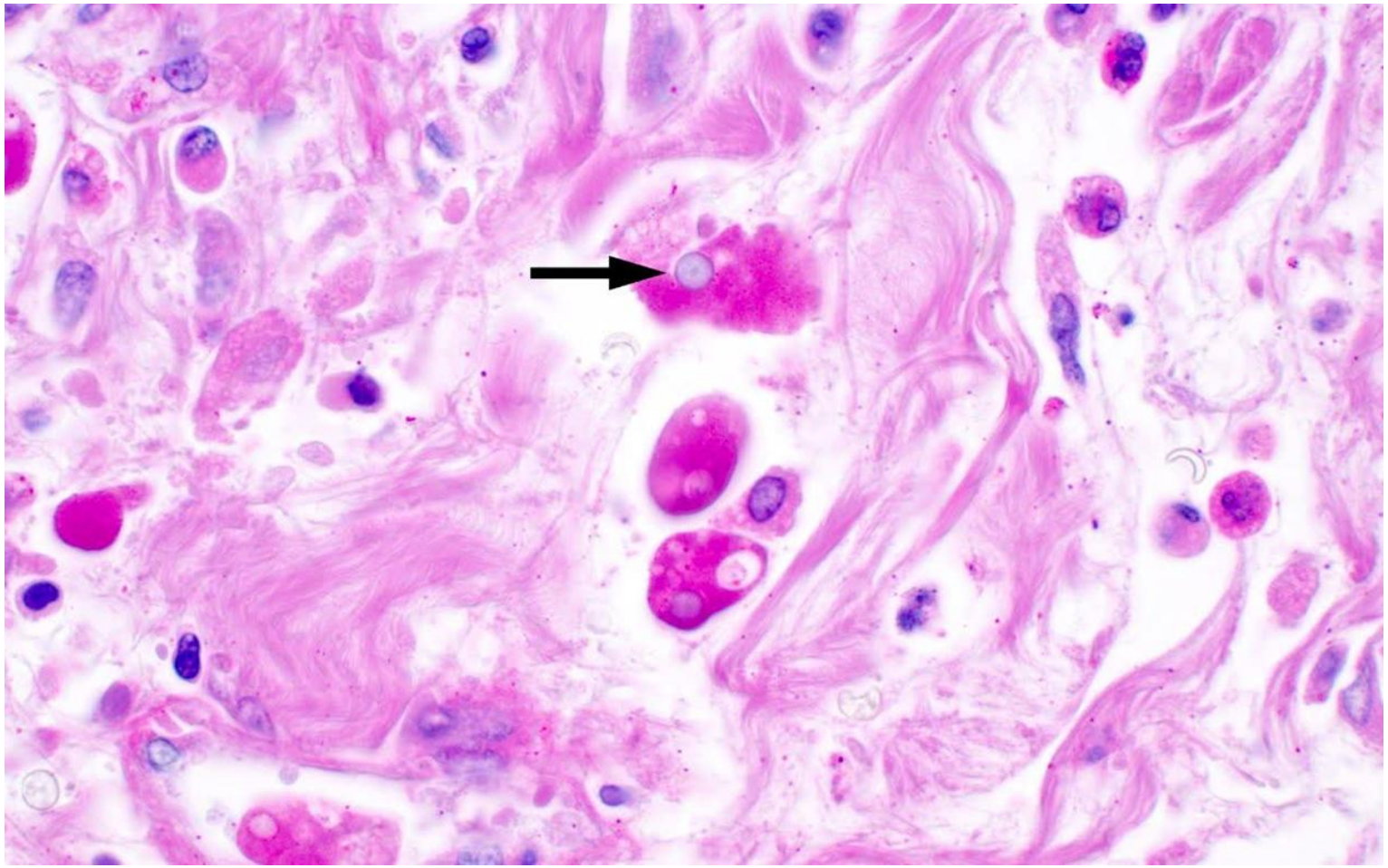
- Young age
- Pregnancy
- Corticosteroid treatment
- Malignancy
- Malnutrition
- Alcoholism
- Malnutition

Amoebic Colitis

- **Flask-shaped ulcers, necrotic exudates**
- **Trophozoites at ulcer base, erythrophagocytosis**
- **May mimic severe ulcerative colitis**
- **Dx: stool O&P, antigen testing, PCR, PAS stain**



PAS stain



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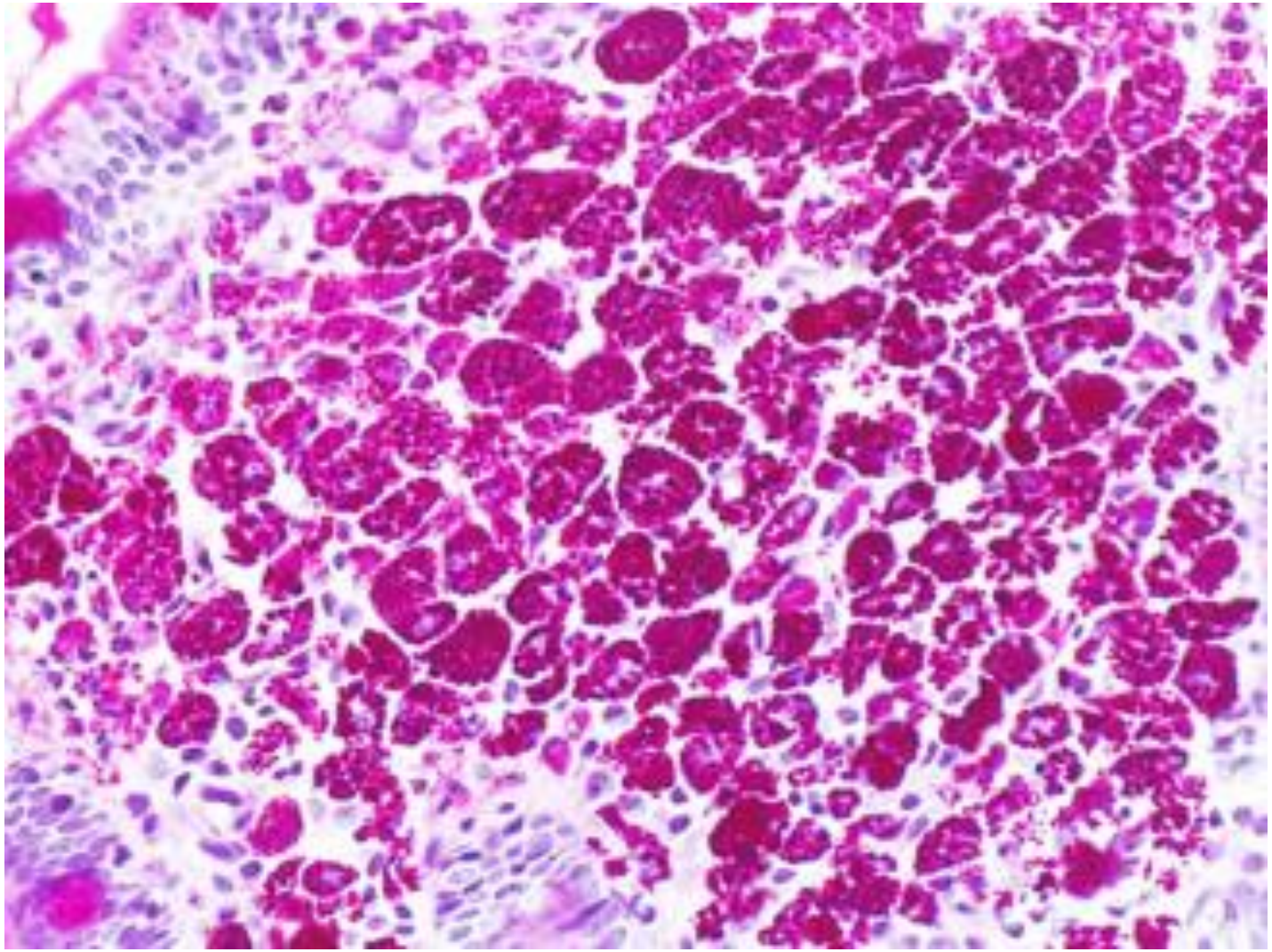
Whipple Disease

- **Foamy macrophages, PAS+ diastase-resistant granules**
- **Villous blunting**
- **Dx: PAS stain, PCR for Tropheryma whipplei**

PAS stain



Strongyloidiasis

- **May show chronic active colitis pattern**
- **Larvae within crypts, eosinophilic inflammation**
- **Steroids can trigger fatal hyperinfection syndrome**
- **Dx: stool larvae, serology, PCR**

Strongyloidiasis

- **chronic asymptomatic infection can be sustained for decades, and clinical manifestations can occur long after the initial infection. In addition, among patients with subclinical infections who subsequently become immunosuppressed, larval reproduction can lead to disseminated infection.**

- **Gastrointestinal symptoms**

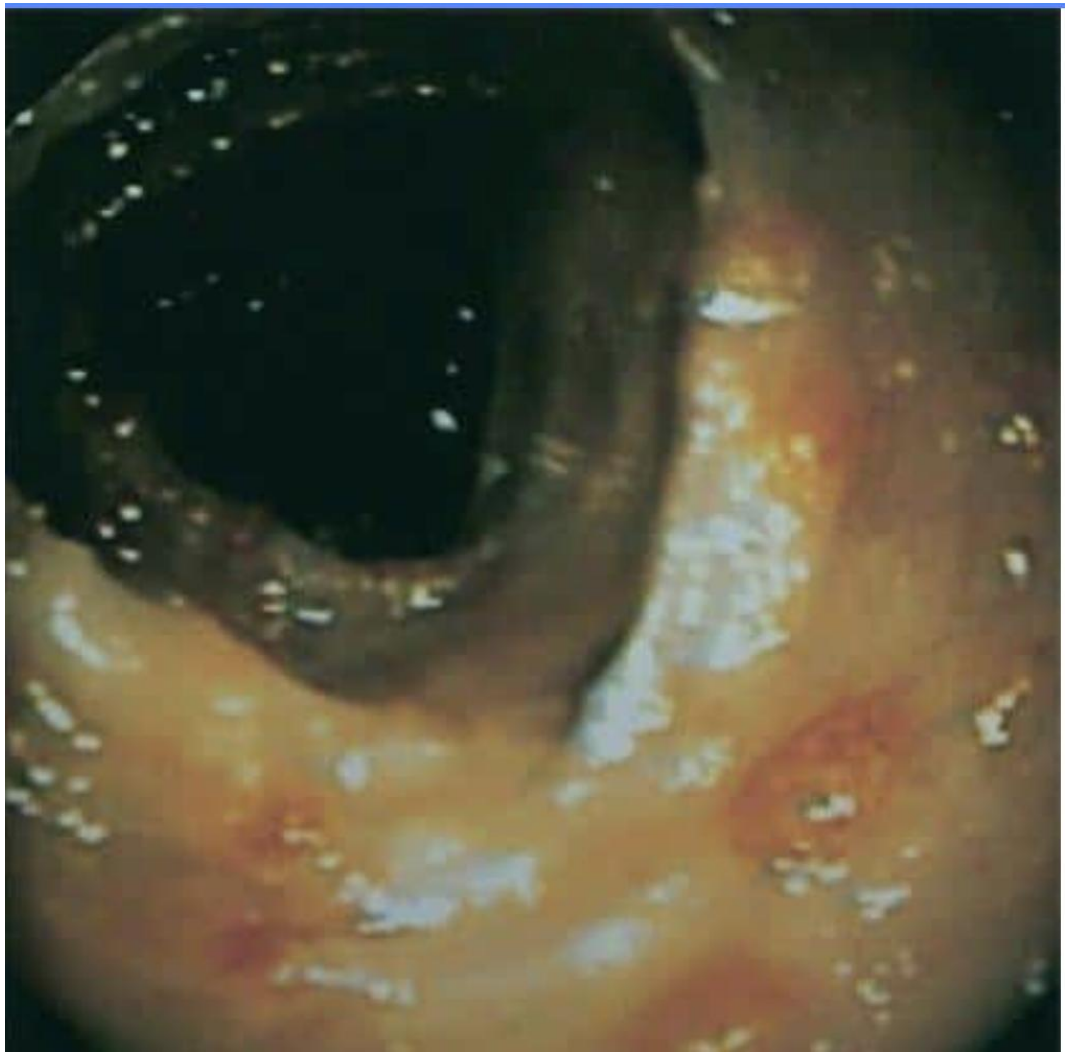
When present, GI symptoms are usually mild. Abdominal pain may be periumbilical

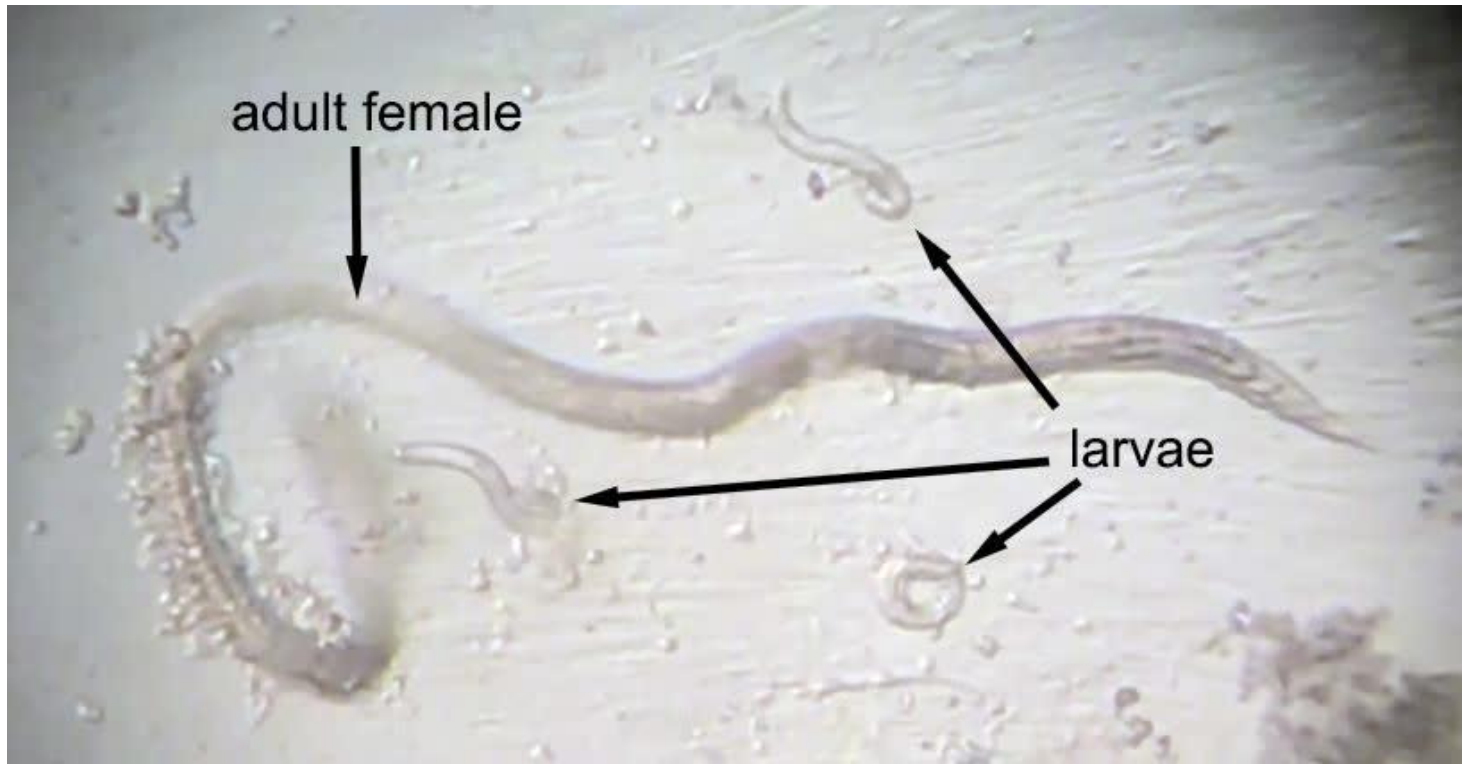
.

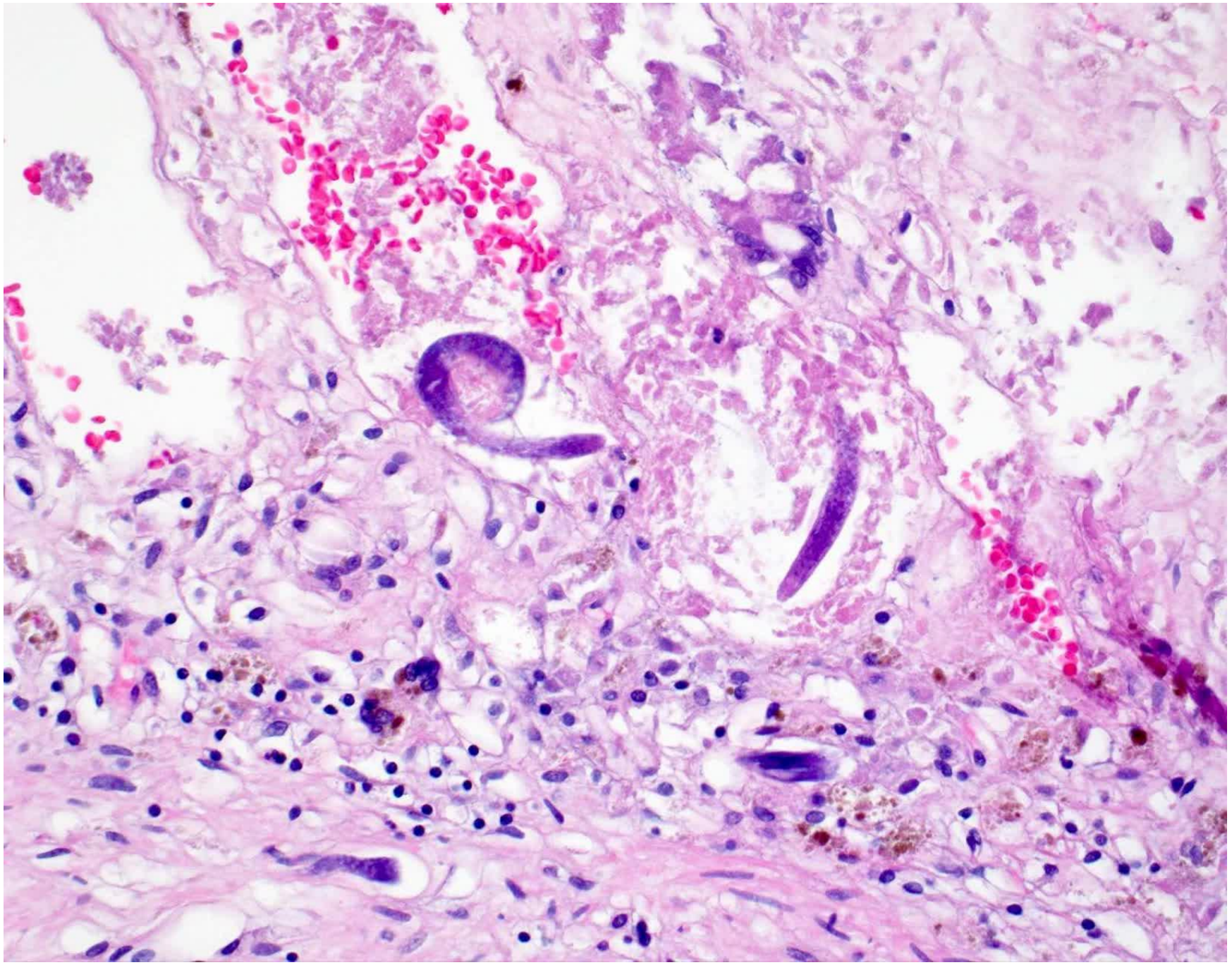
Midepigastric and postprandial pain are likely due to the duodenal localization of adult and larval parasites.

symptoms may include diarrhea, constipation, intermittent vomiting, and borborygmi.

Colon – Edema, loss of vascular pattern, aphthous ulcers, erosions, serpiginous ulcerations, and xanthoma-like lesions . Strongyloides colitis may mimic ulcerative colitis




adult female
larvae



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Post infectious IBS

Risk factors for postinfectious IBS included

- female sex
- history of anxiety
- duration of diarrhea greater than three weeks
- need for hospitalization
- Young age

Clostridium .difficile

Recurrent disease

- **Up to 25 percent of patients experience recurrent C. difficile within 30 days of completing treatmen**

Diarrhea with colitis

- **Watery diarrhea (≥3 loose stools in 24 hours) is the cardinal symptom of CDI. Other manifestations include lower abdominal pain and cramping, low-grade fever, nausea, and anorexia .**
- **Diarrhea may be associated with mucus or occult blood, but melena or hematochezia are rare. Fever is associated with CDI in approximately 15 percent of cases; temperature >38.5°C may occur in the setting of nonsevere or severe CDI**

Clostridioides difficile Colonization vs CDI

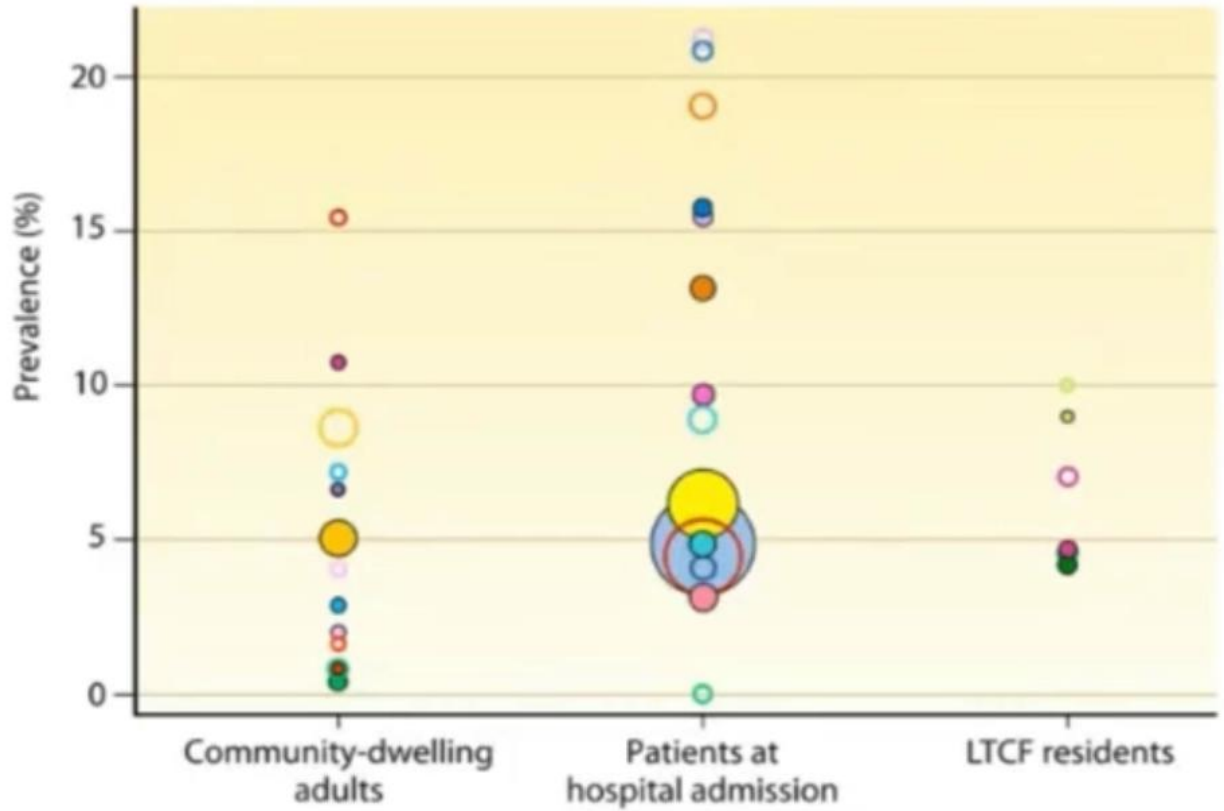
- Colonization: *C. difficile* detected in stool but not causing symptoms
- *C. difficile* infection (CDI): *C. difficile* causing symptoms
  - Diarrhea, etc
- Toxin A and Toxin B
  - Required to cause disease (toxigenic)
  - 20% to 30% of strains non-toxigenic
    - Cannot cause CDI
  - Toxigenic *C. difficile* in stool ≠ CDI



C. difficile colonization prevalence

- Infants: 50%-100%
- Toddlers: 10%-25%
- Healthy adults: 3%-5%
- Hospitalized adults: 5%-15%

- Transient
  - >50% no longer colonized after 3 months
    - True after successful treatment for CDI



Matsuki. International Microbio. 2005; Crobach. Clin Microbio Rev. 2018

Asymptomatic carriage

- **Individuals with asymptomatic carriage of C. difficile shed C. difficile in stool but do not have diarrhea or other clinical symptoms .**
- **Asymptomatic C. difficile carriage occurs in up to 15-20 percent of hospitalized adults and 50 percent of long-term facility residents**

Clostridium difficile

- **Clostridioides difficile is a spore-forming, toxin-producing, and gram-positive anaerobic bacterium that causes antibiotic-associated colitis**

- **CDI can cause a spectrum of manifestations ranging from asymptomatic carriage to fulminant disease with toxic megacolon**

Timing of symptom onset

- **Symptoms of CDI typically, but not always, occur in the setting of antibiotic therapy .Symptoms of CDI may begin during or after antibiotic therapy, and most cases occur within two weeks of antibiotic therapy.**

-

Frequently associated	Occasionally associated	Rarely associated
•Fluoroquinolones •Clindamycin •Penicillins and combinations (broad spectrum) •Cephalosporins (2nd/3rd/4th/5th generation) •Carbapenems	•Macrolides •Penicillins (narrow spectrum) •Cephalosporins (1st generation)* •Trimethoprim-sulfamethoxazole •Sulfonamides •Nitrofurantoin	•Aminoglycosides •Tetracyclines •Tigecycline •Chloramphenicol •Metronidazole •Vancomycin

Timing of symptom onset

However, a lack of antibiotic use does not rule out the possibility of CDI. In one study, approximately 30 percent of patients with community-acquired CDI had not been exposed to antibiotics .

Additional risk factors for CDI include

- **age >65**
- **recent hospitalization**
- **use of proton-pump inhibitors**
- **Severe comorbid disorder**
- **Cancer chemotherapy**
- **Cirrhosis**

Diagnosis of CDI in IBD is extremely challenging

- IBD patients have **~5x higher** risk of CDI (equal for CD and UC)
- Altered traditional risk factors:
  - Younger age
  - Community onset
  - Less likely to have preceding antibiotics

Many studies examined just PCR
? If these represent colonization or CDI?

Lower gastrointestinal endoscopy

- **(flexible proctoscopy, sigmoidoscopy, or colonoscopy) examination may be normal or demonstrate a spectrum of findings, from patchy, mild erythema and friability to severe pseudomembranous colitis (severe inflammation of the inner lining of the bowel**

Extracolonic involvement

Rare cases of C. difficile

- **appendicitis**
- **small bowel enteritis**
- **extraintestinal involvement have been described**

Small bowel involvement with C. difficile enteritis is rare but may occur in older adults and/or patients with multiple comorbidities .

Diagnostics Available

Test	Advantage(s)	Disadvantage(s)
Toxin testing		
Toxin Enzyme immunoassay (EIA)	Rapid, simple, inexpensive, associated with outcomes	Least sensitive method, assay variability
Tissue culture cytotoxicity	More sensitive than toxin EIA, associated with outcomes	Labor intensive; requires 24–48 hours for a final result, special equipment, inter-rater variability
Organism identification		
Glutamate dehydrogenase (GDH) EIA	Rapid, sensitive	Non-toxigenic and toxigenic *C. difficile* detected
Nucleic acid amplification tests (NAAT) (PCR)	Rapid, sensitive, detects presence of toxin gene	Cost, special equipment, does not detect toxin production
Stool culture	Most sensitive test available when performed appropriately	Non-toxigenic and toxigenic *C. difficile* detected; labor-intensive; requires 48–96 hours for results

Interpreting Assay Results

Possible *C. difficile* testing results and interpretation

NAAT-based algorithms	Toxin test	Interpretation
NAAT+	Positive	Patient likely has CDI.
NAAT-	Not performed	Patient does not have CDI.
NAAT+	Not performed	Patient may have CDI. In appropriate setting, treatment may be considered if high clinical suspicion.
NAAT+	Negative	Patient may have CDI or colonization with toxigenic strain. In appropriate setting, treatment may be considered if high clinical
Not performed	Positive	Patient likely has CDI. For children <2 years of age, see FAQ 6.
PCR (polymerase chain reaction) is a type of Nucelic Amplification Test (NAAT) that detects the gene encoding toxin B.		
Toxin tests include: Enzyme immunoassay (EIA) for *C. difficile* toxins (A, B, or A+B) or tissue culture cytotoxicity assays. They detect the toxins that cause CDI. Cytotoxicity assay uses cell culture to determine if there is cytopathic effect when stool is added; an antisera is added to neutralize the cytopathic effect. **When positive, a positive toxin tests usually indicates a patient with CDI if that patient has an appropriate clinical syndrome.**		
GDH-based algorithms	**Toxin test**	**Interpretation**
GDH+	Positive	Patient likely has CDI.
GDH -	Not performed	Patient does not have CDI.
GDH+	Negative	Arbitrated by NAAT. Patient may have CDI or *C. difficile* colonization without CDI. Clinical judgment should be used to determine if treatment is needed.
GDH (glutamate dehydrogenase) is an enzyme produced by toxigenic and non-toxigenic strains of *C. difficile*. This detects all strains of *C. difficile* (both toxigenic and non-toxigenic strains).		

Alonso. Transplant Cell Ther. 2022 May;28(5):225-23

CMV

TRANSMISSION

Cytomegalovirus has been cultured from multiple sites, including

- **urine**
- **blood**
- **Throat**
- **cervix**
- **semen**
- **stool**
- **tears**
- **and breast milk**

Clinical manifestation

The range of clinical disease due to CMV in immunocompromised patients is broad and includes :

- **febrile syndromes**
- **hepatitis**
- **pneumonitis**
- **retinitis**
- **encephalitis**
- **esophagitis**
- **colitis**

GI manifestation

- **CMV has also been implicated as a cause of:**
- **esophagitis**
- **gastritis,**
- **gastric ulcer**
- **gastroparesis**
- **ileitis**
- **Appendicitis**
- **colonic obstruction,**
- **proctitis ,**
- **proctocolitis with perforation ,in patients without underlying immunosuppression.**

Hepatic manifestations

- **Liver function test (LFT) abnormalities are frequently Encountered in patients with symptomatic CMV infection .**
- **Subclinical transaminitis is the most common finding in immunocompetent patients; elevations of alkaline phosphatase and total bilirubin are less typical. Occasionally, patients will present with more significant LFT abnormalities or clinical signs of hepatic dysfunction. Splanchnic vein thrombosis, most commonly involving the portal vein, has also been described as a rare complication of acute CMV-associated hepatitis**

Effect Of CMV Infection On Acute Severe Colitis

- Increased risk of hospitalization
- Increased steroid-resistance
- Increased need for rescue therapy
- Increased risk of colectomy in the short term

- CMV reactivation occurs more often in UC (38%) than in CD (11%)

Risk Factors for CMV in IBD

- **Refractory disease [OR: 4.24; 95% CI: 2.21–8.11]**
- **Immunosuppressive agents such as azathioprine or methotrexate [OR: 1.95; 95% CI: 1.05–3.62]**
- **Age >30 years**

- **Concurrent CMV infection increased the risk of steroid refractoriness by 2.34-fold**
- **Exposure to thiopurines [OR: 1.56; 95% CI: 1.01–2.39] but not to anti-TNF agents increased the risk of CMV reactivation**

J Clin Gastroenterol2017;51:394–401.

Prevalence Of CMV In ASUC

- **CMV IgG Ab in 59.5%**
- **CMV DNA in the inflamed tissue of 38%**
- **CMV DNA tissue load was associated with steroid-refractory disease (risk ratio 4.7; 95% CI 1.2–22.5).**
- **A CMV DNA tissue load > 250 copies/mg was strongly predictive of resistance to IBD Rx**

addition to the cardinal hematologic manifestations of mononucleosis, other abnormalities may also be seen, including:

- **Mild-to-moderate anemia**
- **Reduced haptoglobin levels**
- **Cold agglutinins**
- **Elevated levels of rheumatoid factor**
- **Positive antinuclear antibodies**
- **Thrombocytopenia**
- **Hemolytic anemia**
- **Disseminated intravascular coagulation**

REACTIVATION IN CRITICALLY ILL PATIENTS

CMV reactivation occurs commonly in critically ill patients .

Small observational studies and a systematic review have suggested that CMV reactivation in such patients is linked to

- **increased length of hospital and/or intensive care unit (ICU) stay duration of mechanical ventilation ,**
- **severe sepsis ,**
- **high disease severity and mortality**

INFECTION VERSUS DISEASE

- **CMV infection and disease are not synonymous terms; not all patients with infection develop overt clinical disease**

Infection vs. Disease

- **In most cases, CMV infection is restricted by the immune system**
- **CMV can affect the function of organs (brain, lung, digestive tract, etc.) leading to end-organ disease .**
- **CMV disease need for Rx with antiviral**
- **CMV disease mainly occurs in immunosuppressed patients**
- **In immunocompetent patients rare but may occur after primary infection.**
- **In the case of CMV disease, CMV replication markers are detected in the infected organ**
- **Viremia can be absent, especially when the reactivation occurs primarily in the organ before disseminating to the peripheral blood.**
- **CMV colitis in UC patients should be considered as a CMV disease.**

Blood Tests

Serology

- Most patients have an IgG
- IgM occurs in primary CMV infection
- Little if any role for antibody assays to differentiate infection form dx

PP65 Ag

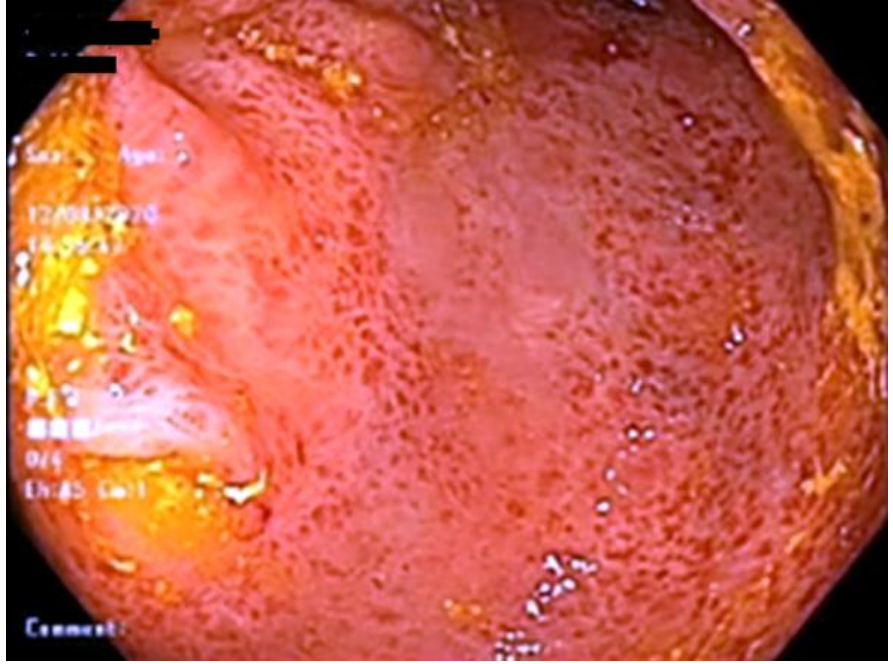
- Not predictive of colonic Dx

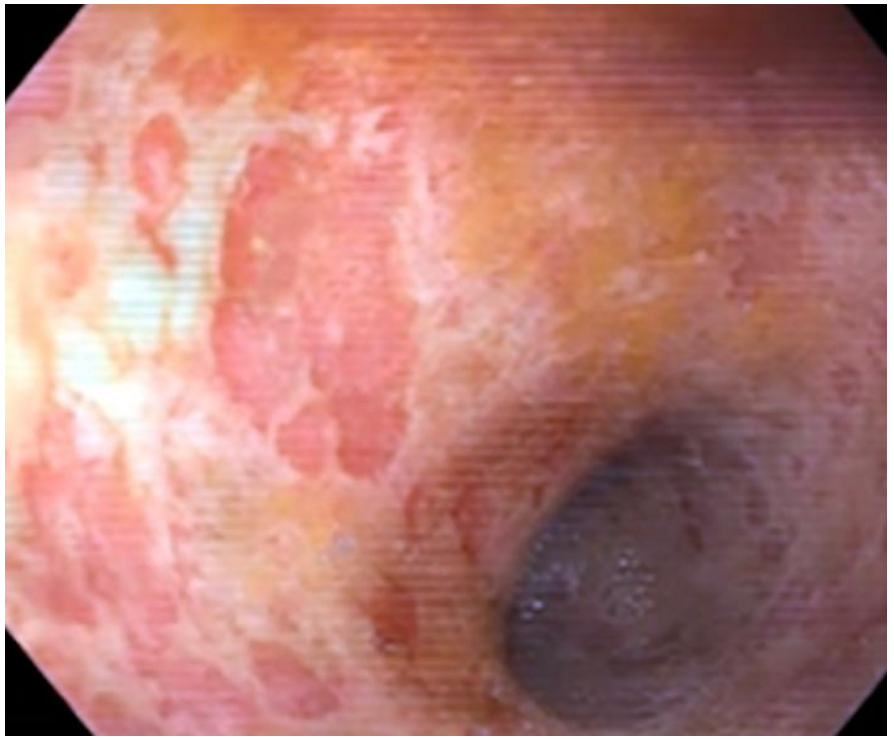
CMV PCR

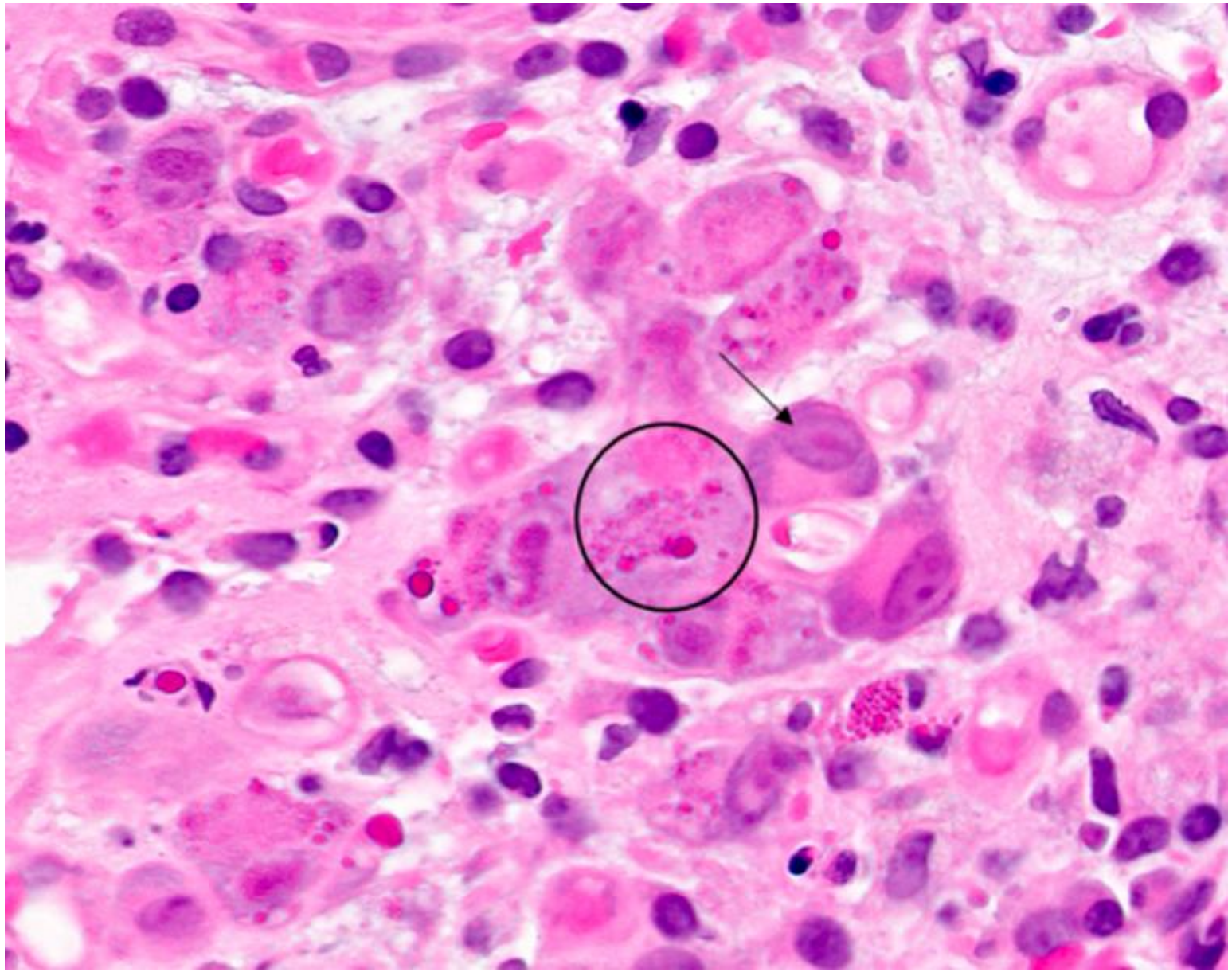
- There is delay in raised load
- Positive value in 48% in those with an IHC diagnosis

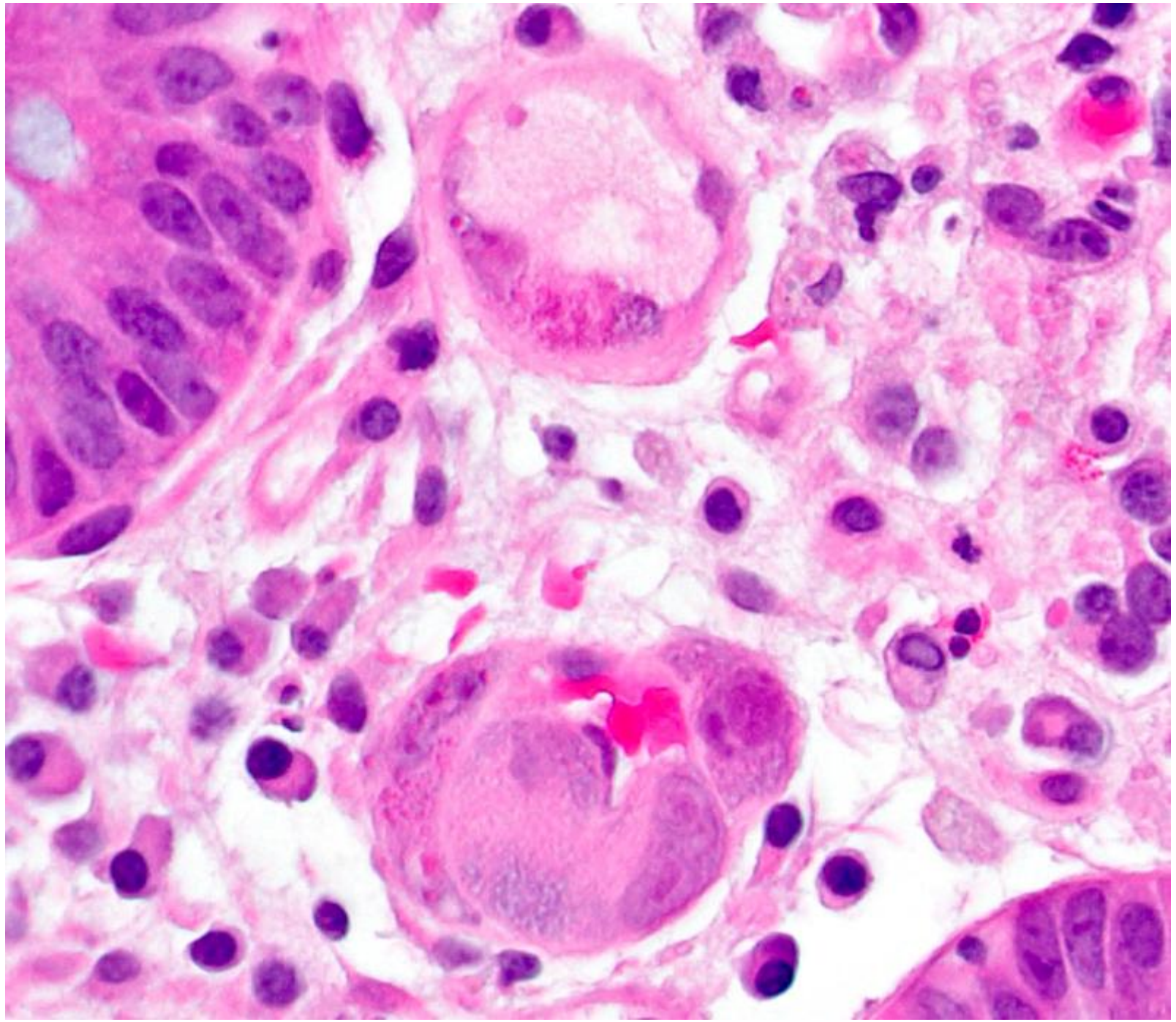
Colonoscopy in IBD

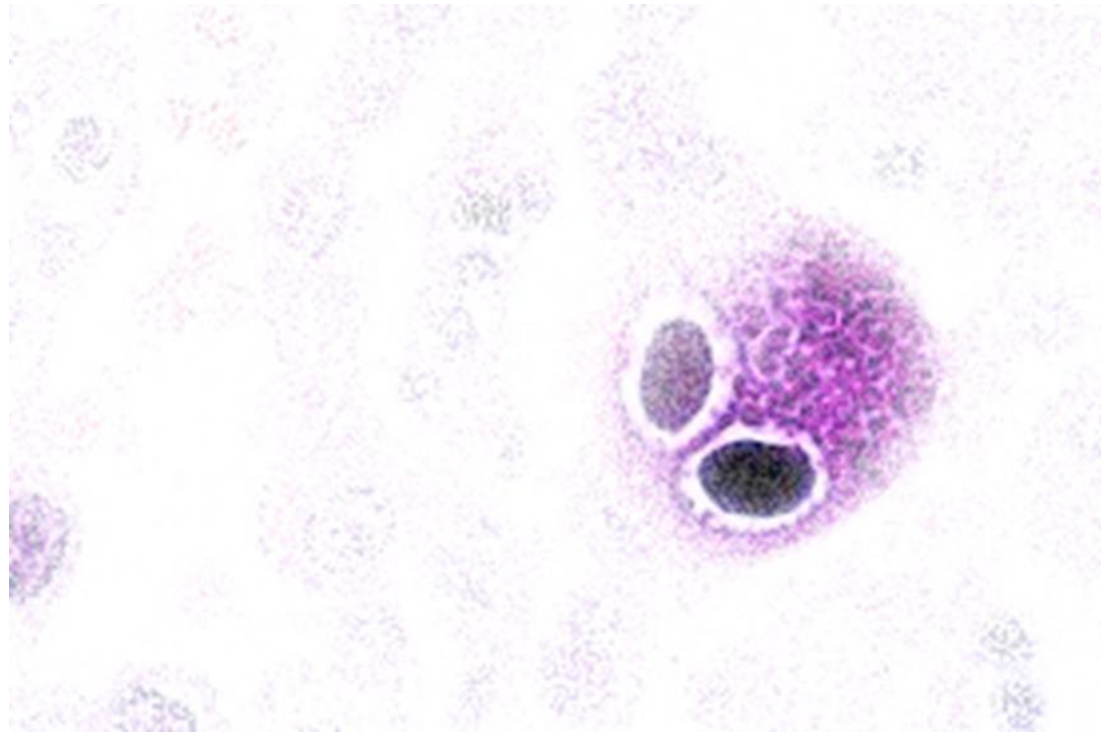
- **Non-specific**
- **Erythema, edema, erosions, ulcers, hemorrhage, mass**
- **Perforation**
- **Similar features in IBD**
- **IBD with and without CMV cannot be distinguished endoscopically (macroscopically).**

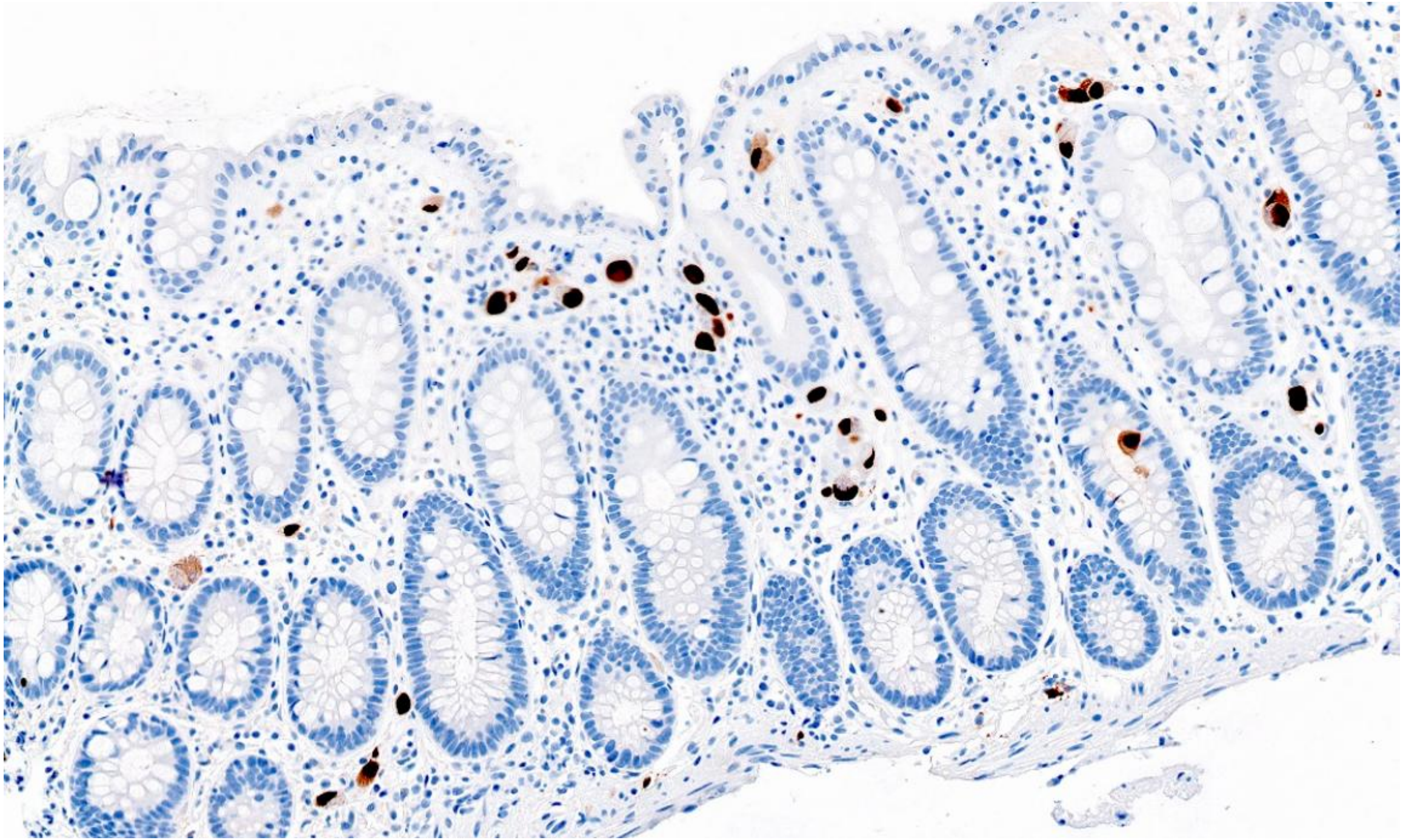












Bx

- **Biopsies from ulcerated areas are more productive**
- **Up to 16 biopsies may be necessary to demonstrate CMV**
- **Possibility to reduce that number by focusing on ulcerated areas**

- **H&E is highly specific 92-100% but has variable sensitivity 10-87%**
- **IHC sensitivity 78-93%**

- **Tissue PCR**

Inflamm Bowel Dis. 2015;21:2833–2838

Am J Gastroenterol. 2011;106:2001–2008

Am J Clin Pathol. 2017;147[1]:96–104

Diagnostic test	Pros	Cons
CMV IgG	Verifies prior exposure to CMV Distinguishes patients with risk for CMV colitis	Uncorrelated with CMV colitis
CMV IgM	Verifies acute infection or reactivation accompanied by viremia	Presents systemic disease
Antigenemia assay	Relatively high specificity for the diagnosis of CMV colitis Takes a short time to obtain results (24 hour) Helpful for predicting clinical course of CMV colitis	Relatively low sensitivity for the diagnosis of CMV colitis
Blood CMV DNA PCR	Noninvasive; endoscopy is not required	Requires a cut-off value for the diagnosis of CMV colitis
Histological H&E staining	High specificity for the diagnosis of CMV colitis	Low sensitivity for CMV colitis Requires many tissue samples and skilled pathologist
Histological IHC staining	Higher sensitivity than H&E for the diagnosis of CMV colitis	Takes a long time to obtain results (3–5 days)
Tissue CMV DNA PCR	Very high sensitivity for CMV detection in colon	Clinical meaning of positivity is unclear
Endoscopy	High sensitivity for the diagnosis of CMV colitis	Low specificity for the diagnosis of CMV colitis
Culture	High sensitivity and specificity for the diagnosis of CMV colitis	Takes a long time to obtain results (2–4 weeks)


Thank you!!