

North Carolina Society of Gastroenterology 2024 Annual Meeting



Non-IBD Colitis- "Running Off" a Differential

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Joint Providership



American Society for
Gastrointestinal Endoscopy

Disclosures

- None

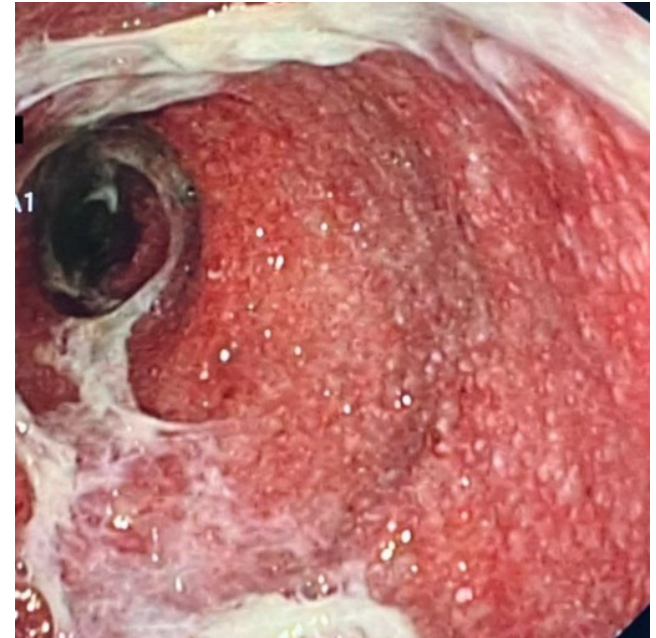
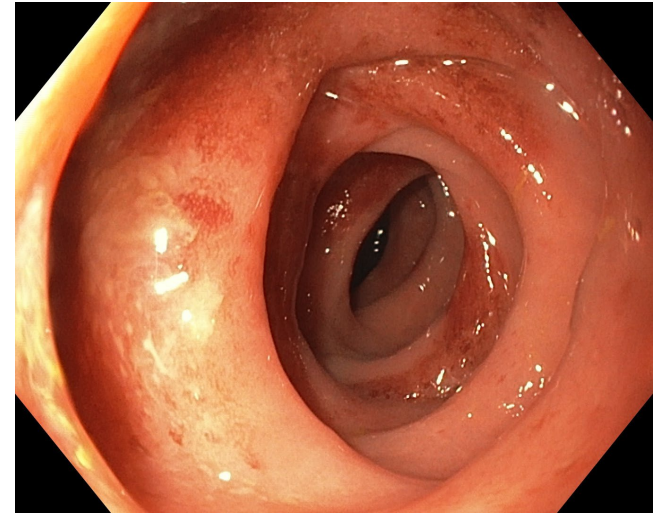
Objectives

- Review the definition and clinical presentation of colitis
- Develop a differential diagnosis for a patient with colitis
- Discuss the diagnosis and treatment of various forms of non-IBD colitis

Definition + Symptoms

Definition

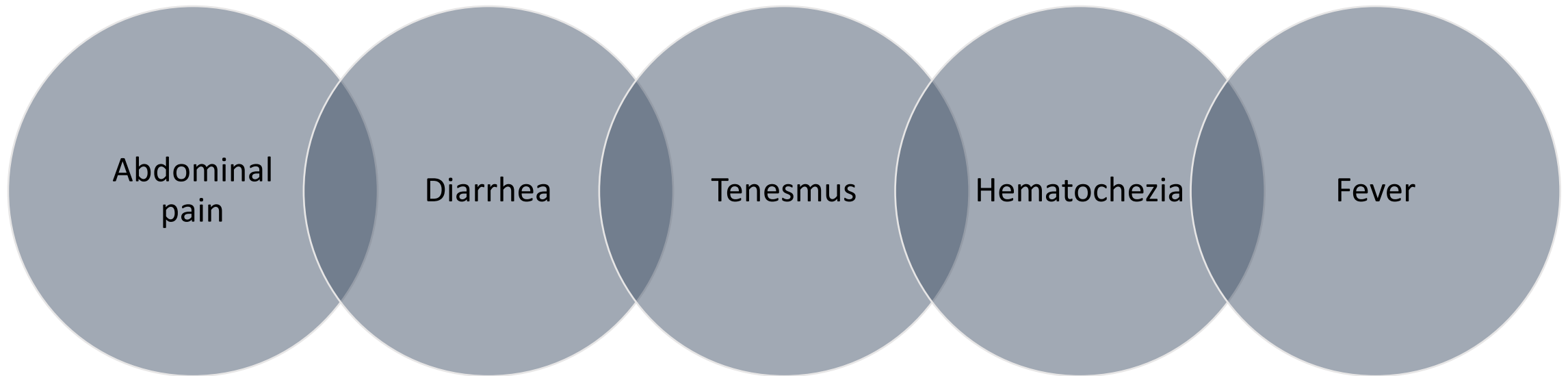
- *Colitis* = inflammation of the colon
- Can be acute or chronic
- May affect all or part(s) of the colon
- Can be based off endoscopic appearance or histologic features
- Endoscopic features:
 - Edematous mucosa
 - Erythema
 - Loss of vascular markings
 - Mucosal friability



© 2020 Wikimedia.org. Available at: https://upload.wikimedia.org/wikipedia/commons/5/58/Segmental_colitis_associated_with_diverticulosis.jpg (Accessed: 20 December 2023).

Losurdo, Giuseppe, et al. "Checkpoint Inhibitor-Induced Colitis: An Update." *Biomedicines*, vol. 11, no. 5, 1 May 2023, p. 1496, www.mdpi.com/2227-9059/11/5/1496, <https://doi.org/10.3390/biomedicines11051496>. Accessed 20 Dec. 2023.

Symptoms



Differential Diagnosis

Infectious

- Viral
 - *CMV*
 - *SARS-CoV-2*
- Bacterial
 - *Campylobacter*
 - *Salmonella*
 - *Shigella*
 - *E coli*
 - *Yersinia*
 - *Tuberculosis*
- Parasitic
 - *Entamoeba histolytica*

Drug-Induced

- NSAIDs
- Check point inhibitors
- Mycophenolate

Radiation

- Urologic
- Gynecologic
- Rectal

Vascular

- Ischemic Colitis

Inflammatory

- Ulcerative Colitis
- Crohn's disease
- Segmental Colitis associated with Diverticulosis (SCAD)
- Microscopic Colitis

Infectious Colitis

Cytomegalovirus

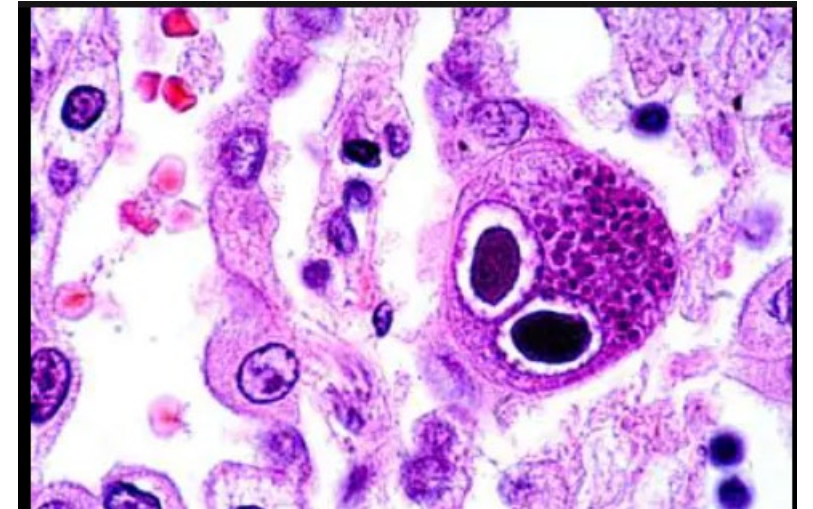
- Most commonly occurs in immunocompromised patients
- Most commonly presents with hematochezia (51%), diarrhea (45%), abdominal pain, fevers
- Pseudomembranes can be present in the colon
- May also be associated with perforation or toxic megacolon

Azer, Samy A., and Faten Limaiem. "Cytomegalovirus Colitis." *PubMed*, Publishing, 2022, www.ncbi.nlm.nih.gov/books/NBK542231/. (Ko et al.)

Ko, J.-H., et al. "Clinical Presentation and Risk Factors for Cytomegalovirus Colitis in Immunocompetent Adult Patients." *Clinical Infectious Diseases*, vol. 60, no. 6, 1 Dec. 2014, pp. e20–e26, <https://doi.org/10.1093/cid/ciu969>. Accessed 7 Apr. 2023.

Cytomegalovirus

- No utility for serologic marker to diagnose CMV colitis
- Gold standard is with biopsies
- Characteristic finding on histology
 - “Owl eye appearance” inclusion body
- Treatment with ganciclovir



Azer, Samy A., and Faten Limaïem. "Cytomegalovirus Colitis." *PubMed*, Publishing, 2022, www.ncbi.nlm.nih.gov/books/NBK542231/. (Ko et al.)

Ko, J.-H., et al. "Clinical Presentation and Risk Factors for Cytomegalovirus Colitis in Immunocompetent Adult Patients." *Clinical Infectious Diseases*, vol. 60, no. 6, 1 Dec. 2014, pp. e20–e26, <https://doi.org/10.1093/cid/ciu969>. Accessed 7 Apr. 2023.

"Cytomegalovirus (CMV): Practice Essentials, Background, Pathophysiology." *EMedicine*, 15 June 2023, emedicine.medscape.com/article/215702-overview?form=fpf.

C difficile

- Leading risk factor is antibiotics
 - MC: Clindamycin, Fluoroquinolones, Cephalosporins, Penicillins, Carbapenems
 - Can present up to 8-10 weeks after antibiotic exposure
- Additional risk factors:
 - Hospitalizations
 - Age 65+
 - Underlying IBD
- There is not always a risk factor!
 - Increasing numbers of community-acquired C difficile

Mada, Pradeep Kumar, and Mohammed U. Alam. "Clostridium Difficile." *PubMed*, StatPearls Publishing, 23 Jan. 2023, www.ncbi.nlm.nih.gov/books/NBK431054

Tedesco, Francis J. "Pseudomembranous Colitis: Pathogenesis and Therapy." *Medical Clinics of North America*, vol. 66, no. 3, May 1982, pp. 655-664, [https://doi.org/10.1016/s0025-7125\(16\)31413-4](https://doi.org/10.1016/s0025-7125(16)31413-4). Accessed 30 July 2021.

C difficile

- Clinical Presentation
 - Acute onset diarrhea, abdominal pain
 - Can present with fulminant colitis (HoTN, ileus, toxic megacolon)
- Diagnostic evaluation
 - Stool antigen and toxin
 - Stool antigen positive, toxin negative = colonized
 - Stool antigen positive, toxin positive = active infection

Mada, Pradeep Kumar, and Mohammed U. Alam. "Clostridium Difficile." *PubMed*, StatPearls Publishing, 23 Jan. 2023, www.ncbi.nlm.nih.gov/books/NBK431054

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C difficile

- Treatment
 - Oral vancomycin 125 mg 4x/day for 10 days
 - Oral fidaxomicin 200 mg 2x/day for 10 days
 - For fulminant colitis:
 - Oral vancomycin 500 mg 4x/day
 - +/- IV metronidazole 500 mg 3x/day
 - *In the setting of an ileus, rectal vancomycin via enema 500 mg 4x/day
- Recurrence is defined as worsening symptoms within 2-8 weeks after completing treatment

C difficile

- Recurrence – 1st time
 - Fidaxomicin if vancomycin previously used, OR
 - Vancomycin pulsed taper
- Recurrence – 2nd+ time
 - Same as 1st episode of recurrence, OR
 - Fecal microbiota transplant (FMT)
 - Delivered via colonoscopy, enema, or capsules

Mada, Pradeep Kumar, and Mohammed U. Alam. "Clostridium Difficile." *PubMed*, StatPearls Publishing, 23 Jan. 2023, www.ncbi.nlm.nih.gov/books/NBK431054

Tedesco, Francis J. "Pseudomembranous Colitis: Pathogenesis and Therapy." *Medical Clinics of North America*, vol. 66, no. 3, May 1982, pp. 655-664, [https://doi.org/10.1016/s0025-7125\(16\)31413-4](https://doi.org/10.1016/s0025-7125(16)31413-4). Accessed 30 July 2021.

COVID-19

- Up to 20% of patients will have GI symptoms (nausea/vomiting, diarrhea, abdominal pain)
 - Of these, up to 30% will have GI symptoms that can last 6+ months
- Can be the cause of hemorrhagic colitis, microscopic colitis, or IBD
 - Suspected due to ACE 2 expression in the GI tract and dysregulated immune response
 - Treatment is unchanged (e.g. budesonide for microscopic colitis)

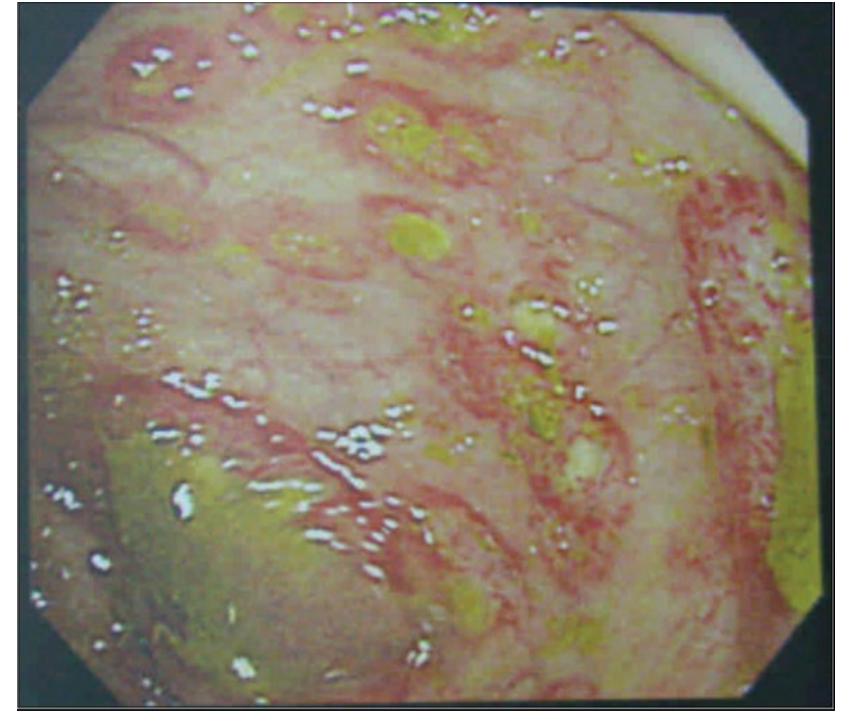
Blackett, J.W. *et al.* (2021) 'Potential long COVID-19 gastrointestinal symptoms 6 months after coronavirus infection are associated with mental health symptoms', *Gastroenterology* [Preprint]. Available at: <https://doi.org/10.1053/j.gastro.2021.10.040>

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Entamoeba Histolytica

- Occurs most commonly in immunosuppression (e.g. AIDS, chronic steroid use)
- Can develop an “IBD-like” presentation (e.g. diarrhea, hematochezia, perforations)
- Also associated with liver abscesses
- Involves any part of the bowel (most commonly ascending colon and the cecum)
- “Flask-shaped” ulcers
- Diagnosed with biopsy, PCR, or stool Ag

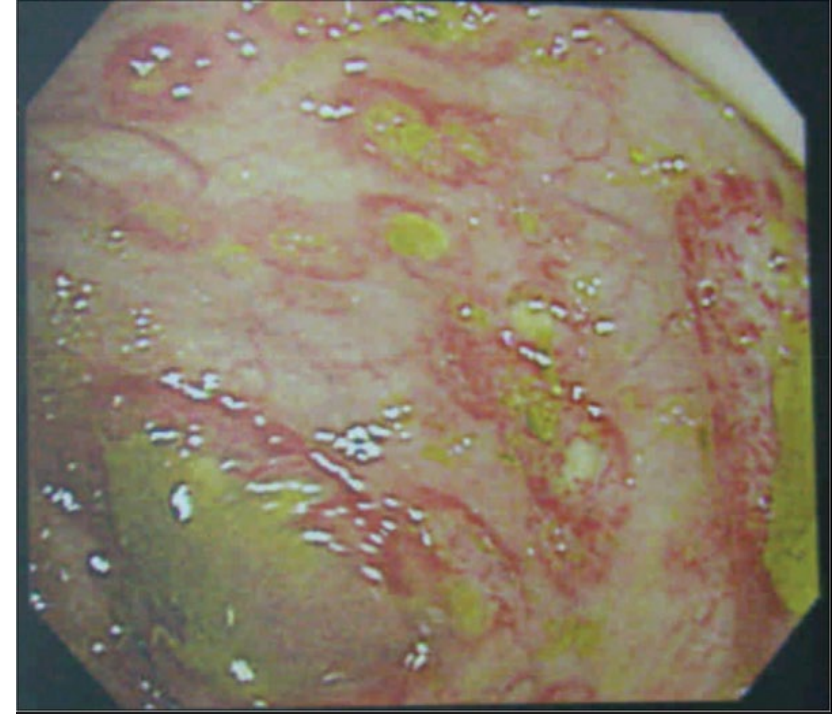


Community transmission and viral load kinetics of the SARS ... - the lancet. (n.d.). [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00648-4/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00648-4/fulltext)

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Entamoeba Histolytica

- Majority (~90%) of cases are asymptomatic
 - Treated with paromomycin
- If symptomatic, recommend treatment with metronidazole followed by paromomycin



Drug-Induced Colitis

Immune Checkpoint Inhibitors

- Cytotoxic T-lymphocyte associated protein 4 (CTLA-4)
 - Ipilimumab and Tremelimumab
- Programmed cell death receptor 1 (PD-1)
 - Pembrolizumab and Nivolumab
- Programmed death ligand 1 (PD-L1)
 - Atezolizumab, Avelumab, and Durvalumab
- Anti-CTLA-4 drugs have the highest adverse event of diarrhea (31-49%)
- Anti-PD-L1 drugs have the highest adverse event of colitis (up to 20%)

Som, A., Mandaliya, R., Alsaadi, D., Farshidpour, M., Charabaty, A., Malhotra, N., & Mattar, M. C. (2019, February 26). *Immune checkpoint inhibitor-induced colitis: A comprehensive review*. World journal of clinical cases. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397821/>

	Diarrhea	Colitis
Grade 1	Increase of < 4 stools/d over baseline	Asymptomatic
Grade 2	Increase of 4-6 stools/d	Abdominal pain, mucus, blood in stool
Grade 3	Increase of ≥ 7 stools/d	Severe pain, fever, peritoneal signs
Grade 4	Life-threatening consequences such as hemodynamic collapse	Life-threatening consequences such as perforation, ischemia, necrosis, bleeding, toxic megacolon
Grade 5	Death	Death

Adapted from Som, A., Mandaliya, R., Alsaadi, D., Farshidpour, M., Charabaty, A., Malhotra, N., & Mattar, M. C. (2019, February 26). *Immune checkpoint inhibitor-induced colitis: A comprehensive review*. World journal of clinical cases. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397821/>

Immune Checkpoint Inhibitor

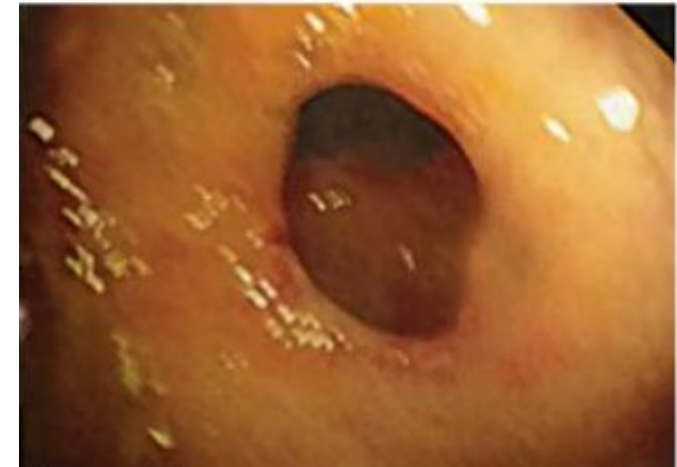
- Ileocolonoscopy is the gold standard
- Normal ileal / colonic mucosa does not exclude diagnosis
- Biopsies should always be obtained
 - Acute colitis is the most common histologic finding
- Infectious etiologies should be evaluated (e.g. pathogen panel, c. diff)

Immune Checkpoint Inhibitor

- Treatment:
 - Holding immunotherapy
 - PO steroids (0.5-1 mg/kg/d)
 - IV steroids (1-2 mg/kg/d)
 - Infliximab 5 mg/kg

NSAIDs

- Thought to occur via inhibition of COX and prostaglandin synthesis, as well as direct drug toxicity (R. colon > L. colon)
- Symptoms can mimic IBD (e.g. abdominal pain, diarrhea, ulceration, strictures, perforation)
- Iron deficiency anemia and malabsorption also occur
- Enteroscopy/Colonoscopy may reveal NSAID-induced diaphragms
 - Thin, concentric ring with luminal narrowing



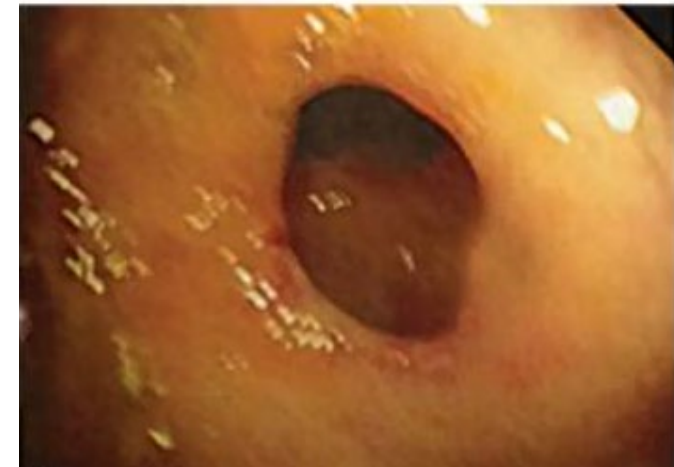
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Goldstein, Neal S., and A. Noel Cinenza. "The Histopathology of Nonsteroidal Anti-Inflammatory Drug-Associated Colitis." *American Journal of Clinical Pathology*, vol. 110, no. 5, 1 Nov. 1998, pp. 622–628, <https://doi.org/10.1093/ajcp/110.5.622>. Accessed 20 Mar. 2020

Farricelli, Laurie, and Dorothy J Sanderson. "Colonic Diaphragm Disease: An Important NSAID Complication to Know." *Federal Practitioner: For the Health Care Professionals of the VA, DoD, and PHS*, vol. 34, no. 3, 2017, pp. 38–40, [www.ncbi.nlm.nih.gov/pmc/articles/PMC6370415/#:~:text=Colonic%20diaphragm%20disease%20\(CDD\)%20is..](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6370415/#:~:text=Colonic%20diaphragm%20disease%20(CDD)%20is..)

NSAIDs

- Biopsies noting granulomas, crypt abscesses/distortion are more likely related to CD
- Treatment is removal of offending agent
 - However, if diaphragms are present, dilation may be required



Tonolini, Massimo. "Acute Nonsteroidal Anti-Inflammatory Drug-Induced Colitis." *Journal of Emergencies, Trauma, and Shock*, vol. 6, no. 4, 2013, p. 301, <https://doi.org/10.4103/0974-2700.120389>. Accessed 20 Mar. 2020.

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Accessed 19 Dec, 2023.

Vascular

Ischemic Colitis

- Can range from superficial mucosal injury to full thickness necrosis
- Most common in ages 60+
- Women > Men
- May have preceding HoTN (e.g. HF, MI, hemorrhage, sepsis)
- Occurs due to watershed area between
 - SMA and IMA (Splenic Flexure - Griffiths point)
 - IMA & Rectal arteries (Sigmoid colon - Sudek's point)
- Splenic flexure is involved in > 75% of cases
- Typical symptoms abdominal pain and hematochezia

Hernandez III, Luis, and James FitzGerald. "Ischemic Colitis." *Clinics in Colon and Rectal Surgery*, vol. 28, no. 02, 25 May 2015, pp. 093–098, www.ncbi.nlm.nih.gov/pmc/articles/PMC4442720/, <https://doi.org/10.1055/s-0035-1549099>
Washington, C. and Carmichael, J.C. (2012) 'Management of Ischemic Colitis', *Clinics in Colon and Rectal Surgery*, 25(4), pp. 228–235. Available at: <https://doi.org/10.1055/s-0032-1329534>.

Ischemic Colitis

- Colonoscopy/Sigmoidoscopy is gold standard to confirm diagnosis
 - Avoid bowel prep and use limited insufflation (CO₂ > O₂)
- Pseudomembranes may be present
- Treatment is largely supportive (e.g. IV fluids, antibiotics)
- If no improvement within 24-48h, surgery may be required
- Mortality ~20%
 - Higher in r. colonic involvement (isolated right colon ischemia – IRCI)
 - May be the first sign of mesenteric ischemia
- IRCI occurs in ~10% of cases

Hernandez III, Luis, and James FitzGerald. "Ischemic Colitis." *Clinics in Colon and Rectal Surgery*, vol. 28, no. 02, 25 May 2015, pp. 093–098, www.ncbi.nlm.nih.gov/pmc/articles/PMC4442720/, <https://doi.org/10.1055/s-0035-1549099>

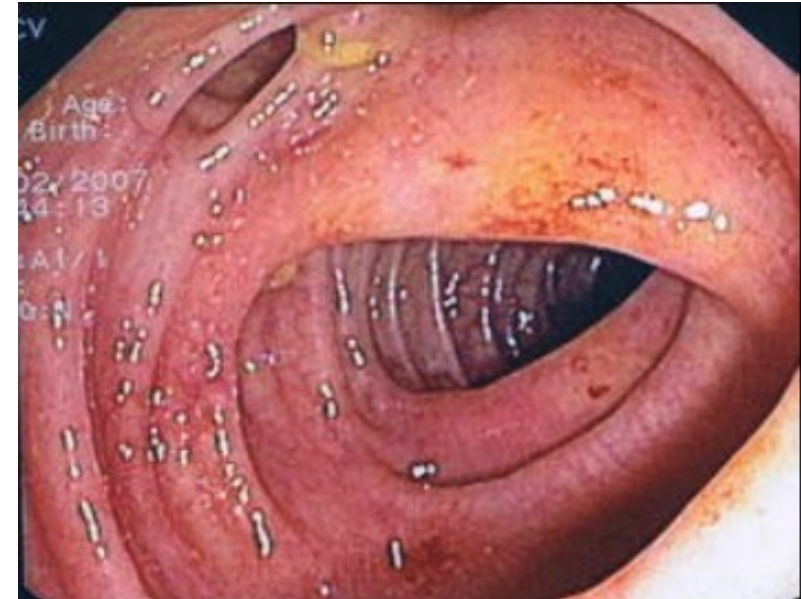
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Sotiriadis, John, et al. "Ischemic Colitis Has a Worse Prognosis When Isolated to the Right Side of the Colon." *The American Journal of Gastroenterology*, vol. 102, no. 10, 1 Oct. 2007, pp. 2247–2252, www.ncbi.nlm.nih.gov/pmc/articles/PMC2805903/, <https://doi.org/10.1111/j.1572-0241.2007.01341.x>.

Inflammatory

SCAD

- SCAD = Segmental Colitis Associated with Diverticulosis
- Over 60% of people 65+ yo have diverticula
 - SCAD occurs in under 2% of people with diverticula
- Male > Female
- Defined by segmental circumferential thickening of the colon with surrounding diverticula
- Patients may have chronic abdominal pain, diarrhea, hematochezia
- Usually left-sided
- Spares rectum
 - Up to 10% patients will have revised diagnosis to IBD



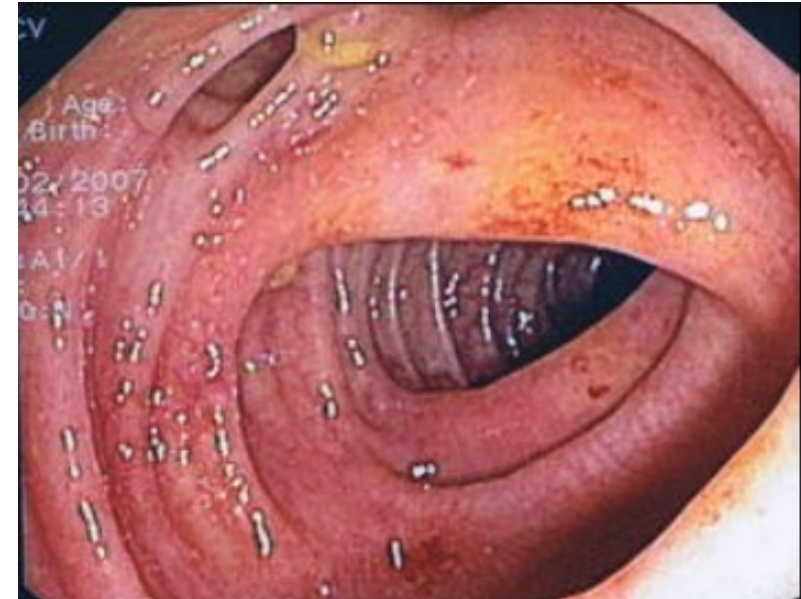
Om Sakhalkar, et al. "Segmental Colitis Associated with Diverticulosis." *Cureus*, 8 May 2023, [www.ncbi.nlm.nih.gov/pmc/articles/PMC10246860/#:~:text=Segmental%20colitis%20associated%20with%20diverticulosis%20\(SCAD\)%20is%20a%20rare%20entity](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC10246860/#:~:text=Segmental%20colitis%20associated%20with%20diverticulosis%20(SCAD)%20is%20a%20rare%20entity), Tursi, Antonio. "Segmental

Colitis Associated with Diverticulosis: Complication of Diverticular Disease or Autonomous Entity?" *Digestive Diseases and Sciences*, vol. 56, no. 1, 22 Apr. 2010, pp. 27–34, <https://doi.org/10.1007/s10620-010-1230-5>. Accessed 8 Mar. 2021

Pereira, Mark C. "Diverticular Disease–Associated Colitis: Progression to Severe Chronic Ulcerative Colitis after Sigmoid Surgery." *Gastrointestinal Endoscopy*, vol. 48, no. 5, Nov. 1998, pp. 520–523, [https://doi.org/10.1016/s0016-5107\(98\)70097-5](https://doi.org/10.1016/s0016-5107(98)70097-5). Accessed 15 Nov. 2020.

SCAD

- Colonoscopy can show interdiverticular mucosal erythema, friability, exudates
- Histology will show chronicity (rectal bx typically normal to contrast with UC)
- Treatment is Ciprofloxacin + Metronidazole for 14 days
- If no improvement, trial of Mesalamine
- Consideration of Prednisone or Budesonide if symptoms persist
- Surgery for refractory cases



Om Sakhalkar, et al. "Segmental Colitis Associated with Diverticulosis." *Cureus*, 8 May 2023, [www.ncbi.nlm.nih.gov/pmc/articles/PMC10246860/#:~:text=Segmental%20colitis%20associated%20with%20diverticulosis%20\(SCAD\)%20is%20a%20rare%20entity,https://doi.org/10.7759/cureus.38724](https://doi.org/10.7759/cureus.38724).

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Lamps, Laura W., and Whitfield L. Knapple. "Diverticular Disease–Associated Segmental Colitis." *Clinical Gastroenterology and Hepatology*, vol. 5, no. 1, Jan. 2007, pp. 27–31, <https://doi.org/10.1016/j.cgh.2006.10.024>. Accessed 19 Oct. 2020.

Microscopic Colitis

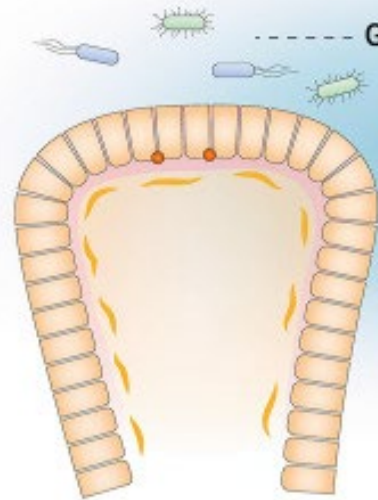
- Two subtypes: Lymphocytic and Collagenous
- Over 70% of MC patients are 60+ yo
- Patients often have chronic diarrhea (do not typically have hematochezia)
- Can be recurrent
- Associated with Celiac Disease, Type 1 DM, Rheumatoid Arthritis
- Several medications associated with MC: PPIs, NSAIDs, SSRIs, Immune checkpoint inhibitors (ICIs)
- May be seen after infection with COVID or COVID vaccination

Marlicz, Wojciech, et al. "Endoscopic Findings and Colonic Perforation in Microscopic Colitis: A Systematic Review." *Digestive and Liver Disease*, vol. 49, no. 10, Oct. 2017, pp. 1073–1085, <https://doi.org/10.1016/j.dld.2017.07.015>. Accessed 4 Mar. 2022.

Nielsen, Ole Haagen, et al. "Microscopic Colitis: Etiopathology, Diagnosis, and Rational Management." *ELife*, vol. 11, 1 Aug. 2022, p. e79397, [elifesciences.org/articles/79397#:~:text=A%20meta%2Danalysis%20has%20revealed,https://doi.org/10.7554/eLife.79397](https://doi.org/10.7554/eLife.79397).

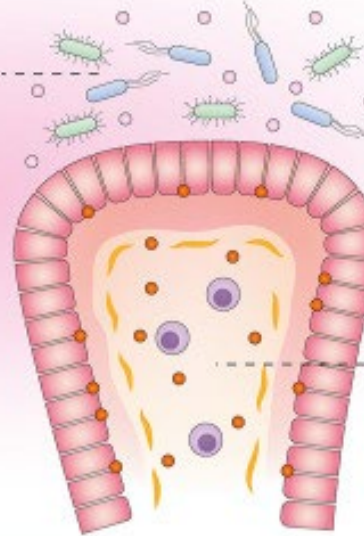
Maslee, Gwen M C, et al. "Increased Risk of Microscopic Colitis with Use of Proton Pump Inhibitors and Non-Steroidal Anti-Inflammatory Drugs." *American Journal of Gastroenterology*, vol. 110, no. 5, May 2015, pp. 749–759, <https://doi.org/10.1038/ajg.2015.119>. Accessed 7 June 2021.

Healthy colon



Gut microbes

Microscopic colitis



Luminal factors

- Drugs
- Dysbiosis
- Bile acids

Mucosal inflammation

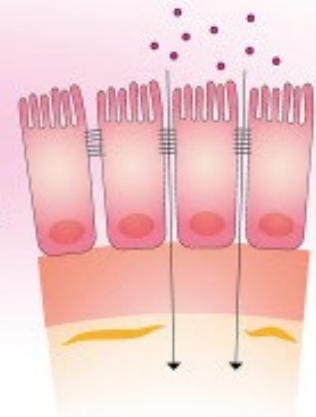
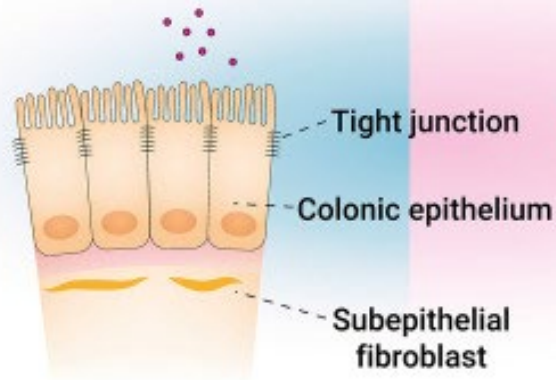
- Pro-inflammatory cytokines incl. TNF- α and IFN- γ
- Subepithelial fibroblasts
- Abundant Tc1/Tc2 and TNF- α producing cells

Host genetic factors

- HLA

Epithelial dysfunction

- Tight junction alterations (leaky gut)
- Malabsorption
- Secretion



Microscopic Colitis

- Gold standard of diagnosis is colonoscopy with biopsy
 - Typically normal endoscopic findings, although can also have macroscopic changes (e.g. mild erythema, loss of vascular pattern, edema)
- Sigmoidoscopy is not sufficient and may miss diagnosis > 20% of patients
- Treatment:
 - First line is Budesonide 9 mg/d for 6-8 weeks (response in >70% of patients)
 - Symptoms typically improve in 1-2 weeks
 - If persistent symptoms after 8 weeks, can consider prolonged course of treatment
 - If symptoms recur, maintenance therapy can be tried at the lowest effective dose
- In clinical remission, not recommended to repeat biopsies

Marlicz, Wojciech, et al. "Endoscopic Findings and Colonic Perforation in Microscopic Colitis: A Systematic Review." *Digestive and Liver Disease*, vol. 49, no. 10, Oct. 2017, pp. 1073–1085, <https://doi.org/10.1016/j.dld.2017.07.015>. Accessed 4 Mar. 2022.

Miehke, Stephan, et al. "Efficacy and Safety of Budesonide, vs Mesalazine or Placebo, as Induction Therapy for Lymphocytic Colitis." *Gastroenterology*, vol. 155, no. 6, 1 Dec. 2018, pp. 1795-1804.e3, <https://doi.org/10.1053/j.gastro.2018.08.042>. Accessed 21 Apr. 2023.

Microscopic Colitis

- Treatment:
 - Bile-Acid Sequestrants 4g up to 3-4x/d – may decrease need for Budesonide dose (up to 50%) or allow for discontinuation (up to 20%)
 - Loperamide as adjunct therapy
 - For refractory cases – Immunomodulators (e.g. Azathioprine or 6-mercaptopurine) or Biologics (e.g. Infliximab, Vedolizumab, Adalimumab, Ustekinumab) can be considered

Marlicz, Wojciech, et al. "Endoscopic Findings and Colonic Perforation in Microscopic Colitis: A Systematic Review." *Digestive and Liver Disease*, vol. 49, no. 10, Oct. 2017, pp. 1073–1085, <https://doi.org/10.1016/j.dld.2017.07.015>. Accessed 4 Mar. 2022. Northcutt, Michael J., et al. "Bile Acid Sequestrant Therapy in Microscopic Colitis." *Journal of Clinical Gastroenterology*, vol. 56, no. 2, 1 Feb. 2022, p. 161, journals.lww.com/jcge/fulltext/2022/02000/bile_acid_sequestrant_therapy_in_microscopic.22.aspx, <https://doi.org/10.1097/MCG.0000000000001496>. Accessed 20 Dec. 2023.

Takeaways

Takeaways

- Colitis can affect part(s) or all of the colon, can be acute or chronic
- Symptoms are non-specific and include abdominal pain, diarrhea, hematochezia, fever
- There are multiple non-IBD etiologies for colitis, including: drug-induced, infections, vascular, or inflammatory
- A thorough history, stool studies, and colonoscopic evaluation with biopsies can help obtain a diagnosis

Review Question

CME/MOC Question:

An 82-year-old woman presents to the ED complaining of severe abdominal pain. She reports she has been taking Ibuprofen 400 mg once daily for the past week due to hip pain. While in the ED, she has a large bowel movement with blood. She denies any infectious contacts, recent travel, or diarrhea. Last colonoscopy was >10 years ago and reportedly normal. Initial vitals: HR 103 bpm, BP 98/62 mmHg, SpO2 98% on RA. Labs: Hgb 13.2.

What is the most likely diagnosis?

- A. Crohn's disease
- B. Segmental Colitis associated with diverticulosis
- C. Ischemic Colitis
- D. C. diff colitis

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Questions?

Thank you!