# Inflammatory Bowel Disease Potpourri: A Vignette-Based Discussion

*Manuel Y. Lam, Edward R. Feller, MD FACG, John R. Lonks, MD, Samir A. Shah, MD, FACG*

**Crohn's disease (CD) and ulcerative colitis** (UC) can cause abdominal pain, diarrhea, rectal bleeding and a variety of systemic manifestations. Most patients require chronic medical therapy and are managed in the outpatient setting. Some present with signs and symptoms from an uncomplicated exacerbation of IBD; others present with clinical features that seem unrelated to IBD or its medications. However, these manifestations may be associated with an acute, severe, sometimes life-threatening complication that requires prompt intervention. We describe a few clinical vignettes to showcase several common and not so common emergencies and medical complications in IBD.

**Case 1.** *A 43-year-old man with a long-standing CD presents to his primary care physician with the complaint of right hip pain and a slight limp. His surgical history is significant for resection of a small bowel stricture and enterocutaneous fistula 4 years ago. His post-operative course was uncomplicated, and he declined treatment with 6-mercaptopurine. Several weeks ago, he began to have abdominal cramping and diarrhea, which rapidly improved after prednisone was started at a walk-in clinic. His doctor wants to avoid NSAIDs because in the past they led to flare-up of his Crohn's; the patient has also tried acetaminophen without relief. Instead, the physician makes an orthopedic referral. X-ray of the hip is normal. A CT scan demonstrates a psoas abscess in the right iliopsoas region. He is hospitalized and intravenous ampicillin/sulbactam and vancomycin were started. A percutaneous drain was inserted into the abscess and left in situ for several days. Culture grew* Escherichia coli *and* Bacteroides fragilis. *He is discharged on oral amoxicillin/clavulanic acid, and his condition improves.*

In contrast to a patient who presents with an acute perforation of the bowel and free air in the abdomen, a patient with fistulizing CD, as in this case, commonly presents with an encapsulated intra-abdominal abscess. Intestinal contents may leak through transmural sinus tracts into surrounding structures, very commonly the iliopsoas muscle, which is anatomically contiguous to the ileocecal junction. It has been estimated that over one-third of patients with CD will develop a fistula during the course of their disease,[1] and over half of those will develop an intra-abdominal abscess.[2]

The clinical manifestations of an intra-abdominal abscess are often difficult to distinguish from an exacerbation of CD. Patients in either scenario may present with abdominal pain and tenderness, fever, and an elevated white blood cell count. Corticosteroids may blunt the inflammatory response, masking the typical signs and symptoms of infection, including fever. Generally, patients with CD, especially those on corticosteroid therapy, presenting with increased abdominal pain or fever should have abdominal and pelvic CT or MR enterography. Those patients with hip/groin pain or difficulty with hip flexion must have deep pelvic and groin imaging to exclude an iliopsoas abscess complicating fistulizing CD. Aseptic necrosis of the hip secondary to steroid use must also be considered. A delay in diagnosis may result in increased morbidity and mortality and longer hospital stays.[3]

A combined medical and surgical approach is the therapy of choice in these cases. Initially, management includes broad-spectrum antibiotics and percutaneous drainage. However, since an abscess is formed via a perforation of the bowel wall, nearly 50% of those patients managed medically ultimately require subsequent resection of the fistula and affected bowel segment.[4]

*A week later, the patient returns to the ER with diarrhea and abdominal pain. CT reveals new thickening in the transverse, descending and sigmoid colon.* Stool *Clostridium difficile toxin test is negative. Steroids and empiric oral metronidazole are started. The next day, a flexible sigmoidoscopy shows nonspecific inflammation and ulcers. No pseudomembranes are seen. However, stool aspirate sent for C. difficile toxin test and sigmoid biopsy confirms the diagnosis of C. difficile. The steroids are discontinued, Metronidazole is changed to oral Vancomycin with rapid improvement in symptoms.*

Infection with enteric pathogens account for approximately 10% of relapses in patients with IBD; *Clostridum difficile* has been implicated in more than half of these infections [5]. Infection with *C. difficile* may trigger a flare of IBD requiring hospitalization[6] and increase the risk of colectomy (20% in one series).[7] The incidence and severity of *C. difficile* infection appears to be increasing among patients with IBD, resulting in increased morbidity and mortality.[7,8] Contrary to past reports that hospitalized patients were primarily susceptible to infection, the majority of IBD patients actually contract *C. difficile* in the outpatient setting. The most significant risk factor seems to be a prior history of colitis itself independent of previous antibiotic treatment. Therefore, all patients presenting with relapse of IBD should be evaluated for *C difficile*.

*C. difficile* may be difficult to distinguish from an IBD relapse given the similar symptoms (diarrhea, abdominal pain, and low grade fever). In fact, typical pseudomembranes may not be seen on endoscopy, especially if the patient is im-

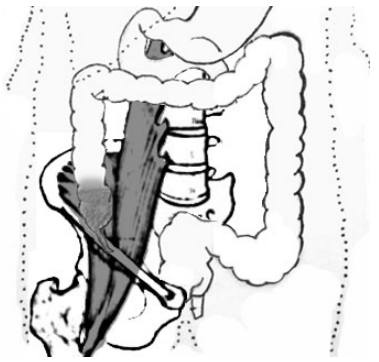


**Diagram:** The iliopsoas muscle is anatomically contiguous to the ileocecal junction.

munosuppressed. Furthermore, failure to promptly diagnose *C. difficile* infection in patients with IBD can lead to inappropriate treatment with corticosteroids and worsening of colitis. Therefore, it is important to exclude *C. difficile* infection in patients with apparent exacerbations of IBD.[7,8] Colonic biopsy and stool aspirate for *C. difficile* toxin testing should be done if initial stool tests for *C difficile* are negative. Oral vancomycin is superior to oral metronidazole for severe *C. difficile*. [9]

**Case 2.** *A 31-year-old woman with ileal Crohn's complicated by perianal disease presents to her internist with fever, chest pain, malaise and a dry cough. She has been in remission on infliximab therapy for one year. Of note, she had a negative PPD and normal CXR prior to starting treatment. Recently, she visited her family in Ohio. No family members were sick. She had not been on antibiotics recently. The internist orders a chest x-ray, which shows upper lobe haziness. He orders urine antigen test for Histoplasmosis and sends the patient for direct hospital admission. The infectious disease and pulmonary consults confirm Histoplasmosis. Infliximab is discontinued. She is started on amphotericin B and subsequently improves.*

**Tumor necrosis factor (TNF)** plays a critical role in host defense and granuloma formation. Thus, a possible adverse event following the use of TNF-alpha inhibitors is the development of granulomatous infections, such as tuberculosis and histoplasmosis.

Tuberculosis is the opportunistic infection most strongly associated with TNF-alpha inhibitors. A Spanish database of over 1500 patients treated with TNF-alpha inhibitors estimates an annual TB incidence of 1% following initiation of infliximab, an incidence rate up to 90 times higher than what is expected in the general Spanish population .[10] A United States registry of over 10,000 rheumatoid arthritis patients with over 16,000 person-years of follow-up estimates that the incidence rate of TB before infliximab became available was 6.2 cases per 100,000 person-years. Among infliximab-treated patients, there is an eightfold elevation in risk to as high as 52.5 per 100,000 person-years .[11] However, once TB screening was instituted before initiation of TNF-alpha inhibitors, the incidence rate waned.[10]

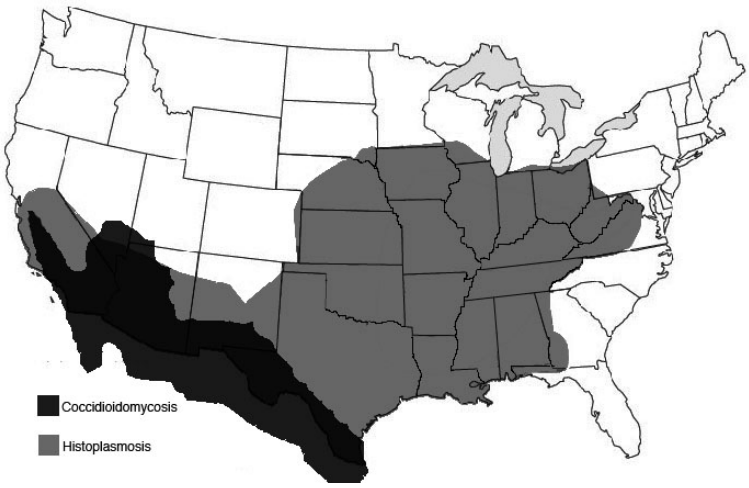
Most cases of TB were reported within 3 months of initiating TNF-alpha inhibitors; this would suggest that most cases were caused by reactivation of latent infection rather than newly acquired infection. According to the **Centers for Disease Control and Prevention (CDC),** patients should be evaluated for latent infection with a tuberculin skin test before initiating anti-TNF-alpha therapy. However, a negative tuberculin skin test does not exclude the possibility of latent infection. Initiation of empiric treatment in consultation with an infectious disease specialist should be considered in high-risk groups (eg., prisoners, homeless, previous resident of or traveler to a high-prevalence country, etc.) before therapy with a TNF-alpha inhibitor.[12]

Clinicians should consider TB in any patient on anti-TNF-alpha agents who has a febrile or respiratory illness. Both extrapulmonary and disseminated TB are also more common in patients treated with TNF-alpha inhibitors than in immunocompetent patients .[13] A few cases of TB enteritis mistaken for an IBD flare have been treated with infliximab, resulting in death.[14] If active TB is diagnosed, anti-TNF-alpha therapy should be temporarily discontinued until treatment for active TB has been initiated and the patient's condition has improved.[12]

In addition to TB, invasive opportunistic fungal infections are important considerations in any patient undergoing treatment with anti-TNF-alpha therapy. In 2008, **the Food and Drug Administration (FDA)** issued a warning about the risk for pulmonary and disseminated histoplasmosis, coccidioidomyscosis, blastomycosis, aspergillosis, candidiasis, cryptococcosis, and other invasive fungal infections in patients taking TNF-alpha inhibitors. The FDA identified 240 reports of patients diagnosed with histoplasmosis who had been treated with TNF-alpha inhibitors. There was a delay in diagnosis and treatment in 21 of these cases, resulting in 12 deaths among these 21 patients.[14]

Among cases of histoplasmosis and coccidioidomycosis in the United States, (1) most patients resided or travelled in endemic regions, and (2) nearly all were concurrently on immunosuppressive agents.[15,16] These patients should be advised to have a low threshold for seeking medical attention. Typical signs and symptoms of possible systemic fungal infection include fever, malaise, sweats, weight loss, cough, shortness of breath, pulmonary infiltrates on chest x-ray, or shock. In these patients, clinicians should be vigilant to stop anti-TNF-alpha therapy; start a complete diagnostic workup in consultation with an infectious disease specialist; and consider empiric antifungal treatment until the pathogens are identified. At this time, there are no recommendations for baseline testing for *Histoplasma capsulatum* or *Coccidioides immitis* in residents of endemic areas before initiation of anti-TNF-alpha therapy.

*Histoplasma capsulatum* is found worldwide. In the United States, Histoplasmosis is endemic in the Ohio and Mississippi River valleys. Histoplasmosis is acquired through inhaling conidia, usually found in the soil of these endemic regions.




Map: Distribution of Regions Endemic with Histoplasmosis and Coccidioidomycosis in the United States.

*Coccidioides immitis* is a dimorphic fungus found in the southwestern United States (Arizona, California, Nevada) and parts of Central and South America.

**Case 3.** *A 54-year-old man with long-standing UC had done well for many years on mesalamine alone until a bout of gout treated with indomethacin sixteen months ago flared up his colitis. He required two courses of steriods and the eventual addition of azathioprine to wean off the steroids. He now presents to his family physician with a second bout of gout in his left great toe. He is treated with colchicine, which improves his pain. He is referred to a rheumatologist. At his evaluation, he forgets to bring his list of medications. He is prescribed allopurinol, which he immediately fills at a 24-hour pharmacy near the office. Three weeks later, his gastroenterologist calls to discuss a depressed WBC on routine blood work. His azathioprine is temporarily stopped. Given the gout, a joint decision is made with the rheumatologist to continue allopurinol. Two weeks later, his WBC is normal, and azathioprine is restarted* at one-third the previous dose with serial blood work monitoring.

**Azathioprine** (**AZA**) is a pro-drug, converted *in vivo* to the active metabolite 6-mercaptopurine (6-MP). AZA and 6-MP are both active purine synthesis inhibitors, which inhibit the proliferation of cells, especially leukocytes. The typical doses used in inflammatory bowel disease are 2.0-2.5 mg/kg for AZA and 1.0-1.5 mg/kg for 6-MP.

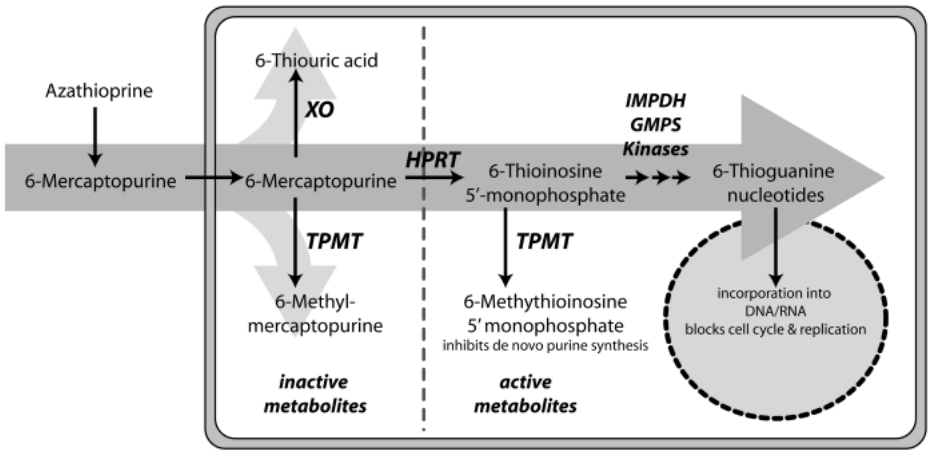



Diagram: Metabolism of Azathioprine
XO = xanthine oxidase, TPMT = thiopurine methyltransferase, HPRT = hypoxanthine phosphoribosyltransferase; IMPDH = inosine monophosphate dehydrogenase, GMPS = guanosine monophosphate synthetase

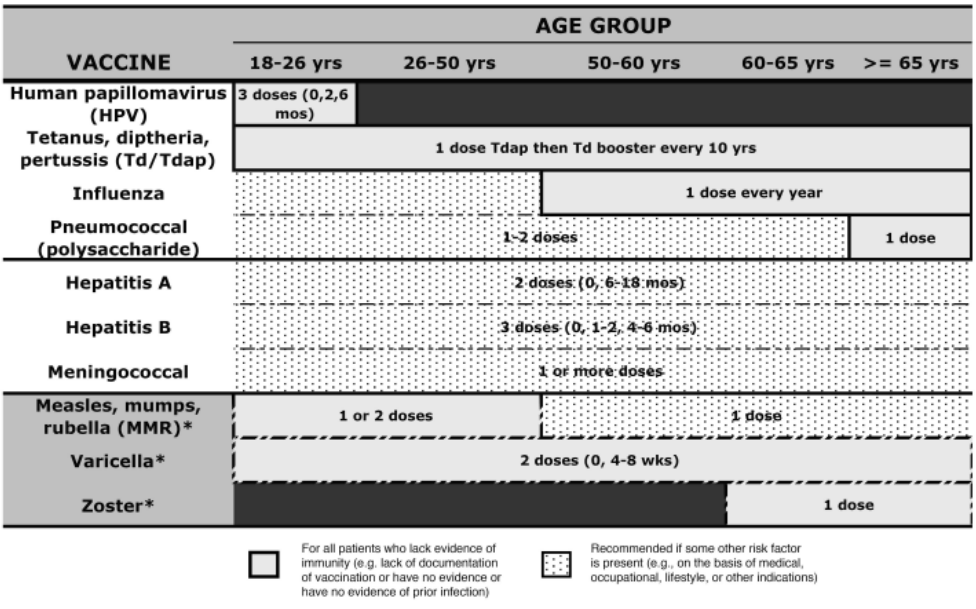



Table: Immunization Guidelines for Immunocompetent Adults, by vaccine and age group
Adapted from CDC's Recommended Adult Immunization Schedule [21]
* Live vaccines should be avoided in *immunocompromised* children and adults with IBD.

However, lack or inhibition of either of these enzymes causes 6-MP to be preferentially metabolized to produce higher levels of 6-TG, which then leads to bone marrow suppression. Thus, it is important to consider drug-drug interactions. For example, allopurinol inhibits XO. Thus, concomitant use of allopurinol and AZA/6-MP should be avoided.[17] However, if the patient has severe gout and allopurinol must be used, a reduced azathioprine dose by at least 50% may be used.

6-MP is further metabolized along the competing routes catalyzed by xanthine oxidase (XO), thiopurine methyltransferase (TPMT) and hypoxanthine-guanine phosphoribosyltransferase (HGPRT). HGPRT produces thioguanine nucleotides, such as 6-thioguanine (6-TG), which are incorporated into both the RNA and DNA of rapidly dividing cells inducing cell cycle arrest and cell death. Bone marrow suppression secondary to AZA or 6-MP correlate with elevated 6-TG levels. Conversely, XO and TPMT deactivate 6-MP and render several inactive metabolites, including 6-thiouracil (6-TU) and 6-methylmercaptopurine (6-MMP), respectively.

| General Recommendations for Immunosuppressed IBD patients | |
|---|---|
| Tetanus, diphteria, pertussis | 1 dose Tdap then Td booster every 10 years |
| Human papillomavirus | 3 doses for women < 26 yo |
| Influenza | Annually |
| Pneumococcal | 1-2 doses |
| Hepatitis A | Consider in all patients |
| Hepatitis B | Consider in all patients |
| Meningococcal | If risk of exposure |
| **Avoid live vaccines!** | |
| Measles Mumps Rubella | |
| Varicella | |
| Zoster | |
| Yellow Fever | |
| Oral typhoid | typhoid Vi is safe. |
| Smallpox | |
| Adenovirus | |
| Bacille Calmette-Guerin | |

Table: General Recommendations for Immunosuppressed Adults with Inflammatory Bowel Disease

AZA/6-MP is eventually discontinued in many of these patients. Similarly, TPMT genotype or phenotype testing may be assessed in all patients before starting AZA or 6-MP to prevent toxicity by identifying patients with low or absent TPMT enzyme activity.[18,19] Approximately, 11% are heterozygous, have low TPMT ezyme activity, and thus require lower dosing. One in 300 is homozygous for TPMT genetic mutations, has no activity, and should not receive AZA or 6-MP.

Regardless of testing for enzyme activity or metabolite assays, all patients must receive frequent monitoring of **complete blood count (CBC)** and **liver function tests (LFTs)**—weekly CBCs for the first month and eventually CBCs and LFTs every 2-3 months when on a stable dose regimen.

***Several months later, he is doing well. He asks his primary care doctor during his annual physical exam whether he should receive a flu shot. Since the patient is immunosuppressed on azathioprine, his doctor informs him that a flu shot is safe and recommended along with a pneumonia vaccine.***

Recombinant and inactived vaccines are safe in patients on either an immunosuppressant (i.e. AZA, 6-MP, MTX, or steroids) or an anti-TNF agent (infliximab, adalimumab, certolizumab pegol). However, live vaccines should be **not** be used in an IBD who is on treatment with:[20]

1. glucocorticoids (prednisone 20 mg/d equivalent) for 2 weeks or more and within 3 months of stopping,
2. effective doses of 6-MP/AZA and within 3 months of stopping,
3. methotrexate and within 3 months of stopping,
4. an anti-TNF agent and within 3 months of stopping, or
5. significant protein-calorie malnutrition.

## References


1. Schwartz DA, Loftus EV, Jr., et al. *Gastroenterol* 2002;122(4):875-80.
2. Ribeiro MB, Greenstein AJ, et al. *Ann Surg* 1991;21:32-6.
3. Mallick IH, Thoufeeq MH, Radjendran TP. *Postgrad Med J* 2004;80:459-62.
4. Garcia JC, Persky SE, et al. *J Clin Gastroenterol* 2001;32:409.
5. Mylonaki M, Langmead L, , et al. *Eur J Gastroenterol Hepatol* 2004; 16:775-8.
6. Ananthakrisnan AN, McGinley EL, Binion DG. *Gut* 2008;5:205-10. Epub 2007 Sep 28.
7. Issa M, Vijayapal A, et al. *Clin Gastroenterol Hepatol.* 2007;5:345-51.
8. Rodemann JF, Dubberke ER, et al. *Clin Gastroenterol Hepatol* 2007; 5:339-44.
9. Zar FA, Bakkanagari SR, et al. *Clin Infect Dis* 2007; 45:302-7. Epub 2007 June 19.
10. Gomez-Reino JJ, Carmona L, et al. *Arthritis Rheum* 2003; 48:2122-7.
11. Wolfe F, Michaud K, et al. *Arthritis Rheum* 2004;50:372-9.
12. Centers for Disease Control and Prevention. *MMWR* 2004;53:683-6.
13. Keane J, Gershon S, et al. *NEJM* 2001;345:1098-104.
14. Food and Drug Administration MedWatch.: http://www.fda.gov/cder/drug/InfoSheets/HCP/TNF_blockersHCP.htm
15. Lee JH, Slifman NR, et al. *Arthritis Rheum* 2002;46:2565-70.
16. Bergstrom L, Yocum DE, et al. *Arthritis Rheum* 2004;50:1959-66.
17. Black, AJ, McLeod, HL, , et al. *Ann Intern Med* 1998; 129:716.
18. Cuffari C, Dassopoulos, T, et al. *Clin Gastroenterol Hepatol* 2004; 2:410.
19. Ragab AH, Gilkerson E, Myers M. *Cancer Res* 1974; 34:2246.
20. Sands BE, et al. *Inflamm Bowel Dis* 2004;10:677-92.
21. Centers for Disease Control and Prevention. *MMWR* 2007;56:Q1-Q4.



*Manuel Y. Lam is a fourth year medical student at The Warren Alpert Medical School of Brown University.*

*Edward R. Feller, MD FACG, is Clinical Professor of Medicine and Adjunct Clinical Professor of Community Health, The Warren Alpert Medical School of Brown University, and Director, Division of Gastroenterology, at Miriam Hospital.*

*John R. Lonks, MD, is Associate Professor of Medicine, The Warren Alpert Medical School of Brown University.*

*Samir A. Shah, MD, FACG, is Clinical Associate Professor of Medicine, Warren Alpert Medical School of Brown University.*


### Disclosure of Financial Interests

Manuel Y. Lam, Edward R. Feller, MD, and John R. Lonks, MD, have no financial interests to disclose.

Samir A. Shah, MD, FACG. Speaker's bureau: Abbott, Elan, Procter&Gamble, Prometheus, UCB.

**Discussion of off-label usage of drug:** Metronidazole is not FDA-approved for treatment of *Clostridium difficile.*

## Correspondence:


Samir A. Shah, MD, FACG
Gastroenterology Associates, Inc.
44 West River Street
Providence RI 02904
phone: (401) 274-4800
e-mail: samir@brown.edu