Case Study: C. diff in IBD Patients

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Case

• 30 year old female with UC admitted with bloody diarrhea, abdominal pain and weight loss
• Diagnosed in 2006→ failed 5-ASA, steroid dependent, allergic to 6-MP
• Started infliximab 14 months earlier with good response though recently has had increasing bloody diarrhea treated with prednisone
• *C. diff* positive treated with metronidazole and then vancomycin without improvement so admitted to hospital where steroids continued
• Repeat *C. diff* positive, treated with fidoxamicin
• Severe UC on sigmoidoscopy w/o pseudomembranes or CMV
Clostridium difficile infection is the most common gastrointestinal infection in patients with IBD
Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases

Diagnosis of CDI

• Two step procedure
  - Transport UNFORMED stool to lab on ice ASAP
  - Options: EIA for C. difficile common antigen (GDH-glutamate dehydrogenase) or EIA for toxin A/B or both
    - If GDH negative, stop
    - If inconclusive or positive – run PCR as confirmatory test

• Test of cure not recommended
• Move toward PCR as primary test for CDI

C. difficile Colonization Rates Higher in IBD Patients

• C. difficile carriage was higher in IBD patients than in healthy volunteers (8 vs 1%) in a study of 122 patients with longstanding IBD in the absence of recent antibiotics or hospitalization

• None developed symptomatic disease in the subsequent six months.

• Possible explanations
  - altered colonic microbial flora, mucosal inflammation, and impaired mucosal innate immunity

Are we over-diagnosing C. diff?

- 1416 hospitalized adults tested for C difficile toxins 72 hours or longer after admission between December 2010 and October 2012
- Patients were characterized as Tox+/PCR+, Tox-/PCR+, or Tox-/PCR-
- Main study outcomes:
  - Duration of diarrhea during up to 14 days of treatment
  - Rate of CDI-related complications (ie, colectomy, megacolon, or intensive care unit care)
  - CDI-related death within 30 days

Are we over-diagnosing C. diff?

• Twenty-one percent (293/1416) of hospitalized adults tested for C difficile were positive by PCR, but 44.7% (131/293) had toxins detected by the clinical toxin test

• The median duration of diarrhea was shorter in Tox-/PCR+ patients (2 days) than in Tox+/PCR+ patients (3 days (P = .003) and was similar to that in Tox-/PCR- patients (2 days), despite minimal empirical treatment of Tox-/PCR+ patients

• No CDI-related complications occurred in Tox-/PCR+ patients vs 10 complications in Tox+/PCR+ patients (0% vs 7.6%, P < .001)

• One Tox-/PCR+ patient had recurrent CDI as a contributing factor to death within 30 days vs 11 CDI-related deaths in Tox+/PCR+ patients (0.6% vs 8.4%, P = .001)

Are we over-diagnosing C. diff?

• Among hospitalized adults with suspected CDI, virtually all CDI-related complications and deaths occurred in patients with positive toxin immunoassay test results.

• Patients with a positive molecular test result and a negative toxin immunoassay test result had outcomes that were comparable to patients without C difficile by either method.

• Exclusive reliance on molecular tests for CDI diagnosis without tests for toxins or host response is likely to result in over-diagnosis, overtreatment, and increased health care costs.

Pseudomembranes are Rarely Seen in IBD Patients

CDI is Increasing in IBD Patients

- Increasing rates of CDI among general population, but rising faster in IBD patients; in this cohort, rate of CDI increased from 1.8% of IBD patients in 2004 to 4.6% in 2005
- CDI-IBD increased from 4% of cases in 2003 to 16% in 2005

ACG C. diff Guideline

• All patients with IBD hospitalized with a disease flare should undergo testing for C. difficile infection. (Strong recommendation and high-quality evidence)

• Ambulatory patients with IBD who develop diarrhea in the setting of previously quiescent disease or in the presence of risk factors such as recent hospitalization or antibiotic use should be tested for C. difficile infection. (Strong recommendation and moderate-quality evidence)

• In patients who have IBD with severe colitis, simultaneous initiation of empiric therapy directed against C. difficile infection, and treatment of an IBD flare may be required while awaiting results of C. difficile testing. (Conditional recommendation and low-quality evidence)

ACG C. diff Guideline

• In patients with IBD, ongoing immunosuppression medications can be maintained in patients with C. difficile infection. Escalation of immunosuppression medications should be avoided in the setting of untreated C. difficile infection. (Conditional recommendation and low-quality evidence)

• Patients with IBD who have a surgically created pouch after colectomy may develop C. difficile infection and should be tested if they have symptoms. (Strong recommendation and moderate-quality evidence)

ACG Guidelines: C. diff Treatment

• No randomized control trials comparing treatment regimens in IBD patients, but in the general population, antibiotic choice is guided by severity of CDI

• Patients with mild-to-moderate CDI should be treated with metronidazole 500 mg orally three times per day for 10 days. (Strong recommendation, high-quality evidence)

• Patients with severe CDI should be treated with vancomycin 125 mg four times daily for 10 days (Conditional recommendation, moderate-quality evidence)

• Vancomycin delivered orally (125 mg four times per day) plus intravenous metronidazole (500 mg three times a day) is the treatment of choice in patients with severe and complicated CDI who have no significant abdominal distention. (Strong recommendation, low-quality evidence)

• Surgical consult should be obtained in all patients with complicated CDI. (Strong recommendation, moderate-quality evidence)

ACG C. diff Recurrences

Treatment of 1 – 2 CDI recurrences

• The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however, vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen. (Conditional recommendation, low-quality evidence)

Treatment of ≥ 3 CDI recurrences

• If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)

FMT for C. diff in immunocompromised Patients

- Cases included adult (75) and pediatric (5) patients treated with FMT for recurrent (55%), refractory (11%), and severe and/or overlap of recurrent/refractory and severe CDI (34%)
- 79% were outpatients at the time of FMT
- In the subset of IBD patients, resolution of CDI occurred in 31 patients (86%) after a single FMT, with an overall cure in 34 (94%)

What to do with Immunosuppressives in CDI IBD Patients

• To date, there is no evidence that immunosuppression with thiopurines or anti-TNF agents are linked to an increase in C. difficile infection

• We recommend stopping or minimizing corticosteroids in the setting of infection because this class of medication may be associated with decreased response to C. difficile therapy

• Due to the potential for worsening IBD, we do not stop the thiopurines or anti-TNFs and will even start biologics in combination with C. difficile treatment if the colitis is severe

Swoger JM, et al. Stopping, continuing, or restarting immunomodulators and biologics when an infection or malignancy develops. Inflamm Bowel Dis. 2014 May;20(5):926-35.
Case Outcome: Repeat *C. diff* negative, colitis worsens and undergoes colectomy where pathology confirms severe UC