Recurrent *C. difficile* in IBD
How to manage, what to consider:
A Case Presentation

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18 year old Caucasian female with Crohn’s disease

PMH: Juvenile idiopathic arthritis (JIA), asthma

Presents to clinic with worsening abdominal pain x1 week.
HPI

- 6-7 stools/d; liquid to soft w/ blood
- + nausea; - vomiting
- Normal appetite; - weight loss
- No fever
- Tx’d w/ trimethoprim-sulfamethoxazole 1 week prior for reported Klebsiella stool infection at OSH
- Last infliximab infusion 4 weeks ago
Medications

Current GI Medications:
• Infliximab 5 mg/kg every 8 weeks
• Methotrexate 25 mg/mL injection every 7 days
• Saccharomyces boulardii 250 mg oral QD
• Esomeprazole 20 mg oral QD
• Trimethoprim-sulfamethoxazole (for Klebsiella) oral 1 ds BID

Other Meds:
• Albuterol PRN
• Cetirizine 10 mg QD
• Ferrous sulfate oral 325 mg BID
• Folic Acid 1 mg QD
• Sulindac 150 mg BID**
Physical Exam

- **Vitals**: WNL
- **Constitutional**: Well-appearing.
- **Abdominal**: Normal appearance. + Bowel sounds. Soft, no distension, mass, tenderness, guarding, rebound or HSM.
- **Musculoskeletal**: MAE x4. Left knee: swelling with moderate tenderness. Good pulses.
- Remainder of the exam was WNL.
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
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</thead>
<tbody>
<tr>
<td>CRP</td>
<td>19 (H)</td>
<td>&lt;5 mg/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.3 (L)</td>
<td>3.5-5.0g/dL</td>
</tr>
<tr>
<td>Iron</td>
<td>35 (L)</td>
<td>40-160 ug/dL</td>
</tr>
<tr>
<td>Total Iron Binding Capacity</td>
<td>504 (L)</td>
<td>230-430 ug/dL</td>
</tr>
<tr>
<td>WBC</td>
<td>7.0</td>
<td>3.5-11.0 10^3/uL</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>503 (H)</td>
<td>150-450 10^3/uL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.9 (L)</td>
<td>11.5-15.5 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>34.2 (L)</td>
<td>36-47%</td>
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All other labs results are WNL
What is on our Differential Dx?

A) IBD flare/loss of response to therapy
B) CMV Colitis
C) NSAID-induced gastritis
D) *Clostridium difficile* infection (CDI)
Our Diagnosis

A) IBD flare/loss of response to therapy
B) CMV Colitis
C) NSAID-induced gastritis
D) *Clostridium difficile* infection confirmed by CDI toxin B PCR
CDI: A Significant Healthcare Burden

• Leading cause of hospital-associated GI illness
• Increasing cause of community-associated GI illness
• Costs $3.2 billion annually\(^1\)
• Rates of CDI have been increasing since 2000
• ~500,000 infections and 29,000 deaths (2011)\(^2\)
  • ~293,300 cases of health-care-associated CDI
  • ~159,700 cases of community-associated CDI

2. Lessa et. al. NEJM. 2015.
CDI Mechanisms and Host Response

• Disease caused by enterotoxin A and cytotoxin B
  – Interfere with protein synthesis, leading to cell membrane disruption and death¹

• Host immune response to toxins may determine who develops symptoms²
  – ~5% of healthy individuals are colonized with C. difficile²
  – Development of IgG Abs against toxin A may contribute to asymptomatic state³
  – High IgG Abs decrease risk for RCDI by a factor of 44⁴

Emergence of New Resistant Strains

- Many new epidemics of CDI are caused by a novel strain, NAP1/BI/027
  - Hypervirulent
  - Exhibits quinolone resistance
  - Produces a binary toxin
    - Enables increased production of toxin A + B in vitro
  - Increased use of quinolones may have contributed to selection of this strain

CDI in IBD: A Growing Problem

• Since 2000: significant increase in the incidence of CDI in IBD patients

• Recurrent CDI in up to 1/3 of children and adults\(^1\)

• Hospitalization rates for children and young adults with IBD and CDI increased 5-fold (1997-2011)
  – Compared with < doubling of the hospitalization rates for IBD without CDI\(^2\)

2. Sandberg et. al. Inflamm Bowel Dis. 2014.
What Medications are Associated with CDI?

A. Clindamycin
B. Fluroquinololones
C. Sulfamethoxazole-trimethoprim
D. Corticosteroids
E. All of the above
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E. All of the above
“Traditional” Risk Factors:

- Antibiotic use (number and duration)
- Advanced Age (≥ 65 yo)
- Recent/prolonged hospitalization
- Immunosuppression
- Comorbidities
- Proton-pump inhibitors
- NG tubes
Risk Factors are Not the Same in Patients with IBD

• Antibiotic use → less important
  – Abx use preceding CDI is less common
    • 40% of IBD patients vs. 69% in non-IBD patients¹
    • 39% of IBD patients with CDI: no recent Abx use²

• Advanced age and comorbidities
  – Average age of CDI in IBD cohorts significantly lower³

Risk Factors: A Balancing Act In IBD

- **Immunosuppression**
  - Risk of therapy in CDI still **unclear**
    - Maintenance immunosuppressive therapy associated with 2x risk of CDI\(^1\)
    - No association between use immunosuppressive therapy and heightened CDI risk in UC patients\(^2\)
  - **Corticosteroids** may heighten risk of infection
    - Steroid initiation tripled the risk of CDI\(^3\)

- **IBD** itself is an **independent risk factor** for CDI
  - 3x increased risk as compared to non-IBD patients\(^4\)

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Challenges in IBD

- The clinical symptoms of CDI may be indistinguishable from a flare of IBD
- Pseudomembranes are present in only 13% of the patients

Carrion et. al. World J Gastrointest Oncol. 2010.
Who should we test?

- Only patients with diarrhea (≥ 3 liquid stools/day) should be tested for CDI!

- All hospitalized patients with IBD with a disease flare

- Ambulatory patients who develop diarrhea even with no known risk factors

- Patients s/p colectomy and IPAA that are symptomatic

- **Note:** In patients with severe colitis, simultaneous initiation of empiric therapy directed against CDI, and treatment of an IBD flare may be required while awaiting test results

CDI Test Options

1. Nucleic acid amplification tests (NAATs)
   - PRC for toxin genes
   - Sensitivity: 100%  Specificity: 99.2%
   - Superior to A + B EIA testing
   - Risk of false positive even after Tx/asymptomatic pt

2. Toxins A + B Enzyme Immunoassay (EIA)
   - Lower sensitivity and specificity
   - Risk of false positive even after Tx/asymptomatic pt

3. Glutamate dehydrogenase (GDH) screening
   - Used in testing algorithms
   - Unable to distinguish toxigenic and nontoxigenic strains

How would you treat the initial infection?

A. Metronidazole
B. Vancomycin
C. Fidaxomycin
D. Fecal Microbiota Transplant (FMT)
CDI Treatment Paradigms

• Mild-to-moderate:
  – Metronidazole 500 mg PO tid for 10 days
  – Vancomycin 125 mg QID x 10-14 days

• Severe CDI:
  – Vanomycin 500 mg QID x 14 days
  – Vancomycin 125 mg PO qid + metronidazole 500 mg IV tid x10 days

• IBD patients: vancomycin may be considered for first-line treatment
  – Risk of selecting for vancomycin-resistant enterococci

Modifying Therapy in CDI

- Antimicrobial agent(s) should be discontinued
- On-going immunosuppression medications can be maintained
- Escalation of therapy should be avoided during the acute phase

Our Patient’s Course

• Patient treated with metronidazole 500 mg PO tid x 4 days, with no improvement
• Patient transitioned to vancomycin 125 mg PO qid x 10 days

PATIENT IS ASYMPTOMATIC AND NEGATIVE FOR C. DIFF!

Note: repeat testing wasn’t indicated
One Month Later, Her Symptoms Return…

- Admitted with diarrhea ~10 per day moderately bloody
- Increased abd pain; lower crampy pain.
- No fever.
- Nausea for several days prior to admission
- Emesis x 1 in ER

- What could be wrong?
Recurrent CDI, A Recurring Problem

- After initial Tx of CDI, chance of RCDI within 8 weeks is 10 – 20 %

- After 1st recurrence, rates of recurrence increase to 40 – 65 %

- Recurrence can be due to the same or different strain

- RCDI may be due to impaired immune response or alteration of the gut microbiota

CDI Again?! No Easy Answers

- 1st recurrence: treat with same regimen
- 2nd recurrence: pulsed or tapered vancomycin.
- No consensus on optimal pulsed/tapering regimen.
- Severe CDI: vancomycin and surgery consult.

More than 3 Recurrences: Consider FMT

- If there is a 3\textsuperscript{rd} recurrence, \textit{fecal microbiota transplant (FMT)} should be considered\textsuperscript{1}

- Due to reduced efficacy of other antimicrobial therapies, FMT holds promise as effective Tx for RCDI\textsuperscript{2}

- Since 2000, failure rates of metronidazole for uncomplicated CDI have increased from 2.5\% to \( \geq 18\% \)\textsuperscript{2}

FMT for CDI

- Retrospective studies: success rate of 85-95%
- Prospective trial: superiority of FMT to vancomycin
- FMT appears safe and effective in children
- FMT may have increased risk in patients with IBD

Take Home Points

• CDI is on the rise…
  both in the hospital and in the community.
• IBD patients are at increased risk for RCDI.
• CDI presents unique and serious problems for patients with IBD.
• Recurrent CDI demands tailored treatment.
• Always use antibiotics judiciously!
• Always wash your hands!
  – Hand sanitizer isn’t effective against CDI.