Updates to pharmacological management in the prevention of recurrent *Clostridium difficile*

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Clinical Impact

- Increasing rates since 2000
- Leading cause of hospital-associated gastrointestinal illness
- Increased length of stay
- 3.2 billion dollars on our health care system
- 57% of residents in long-term care facilities may be carriers

Facing the Facts

- 6-25% experience at least 1 additional episode
  - High as 35%
- After 1 recurrent episode → 40-65% recurrence
- All-cause mortality up to 38%
Objectives

• Recognize common risk factors for recurrent *Clostridium difficile*

• Discuss appropriate regimens for *C. difficile* prophylaxis

• Identify proper regimens for *C. difficile* in specific patient populations
Recurrent *C. difficile*

- Diagnosed *Clostridium difficile* infection (CDI)
- 8 weeks after previous episode
  - Assuming resolution of symptoms
Risk Factors for Recurrent CDI

- Long-term antibiotic treatment
- Hypoalbuminemia
  - < 2.5 g/dL or ↓ > 1.1 g/dL
- Age ≥ 65 years
- Immunocompromised
- Use of proton pump inhibitors (PPI)
- ≥1 CDI episode in past 6 months
- ≥2 previous CDI episodes ever

CDI = Clostridium difficile infection

Am J Gastroenterol 1998; 93: 1873 -76.
Assessment Question

• In addition to antibiotic therapy, which is a risk factor for developing recurrent CDI?
  A. Hyperalbuminemia
  B. Age < 18 years
  C. Prior history of *Clostridium difficile*
  D. Use of probiotics

CDI = *Clostridium difficile* infection
## Guideline Recommendations on CDI Prevention

<table>
<thead>
<tr>
<th>IDSA</th>
<th>American Journal of Gastroenterology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Expert Panel offers no specific recommendation</td>
<td>• Limited evidence for use of probiotics as adjunct therapy</td>
</tr>
<tr>
<td>• Prolong C. <em>diff</em> treatment</td>
<td></td>
</tr>
<tr>
<td>• Oral vancomycin is preferred agent</td>
<td></td>
</tr>
<tr>
<td>• Avoid metronidazole</td>
<td></td>
</tr>
<tr>
<td>• Nontherapeutic levels without active colitis</td>
<td></td>
</tr>
</tbody>
</table>

CDI = *Clostridium difficile* infection
Potential Agents

1994: Probiotic

2016: Vancomycin

2017: Bezlotoxumab
# S. boulardii for C. difficile

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, double-blind, placebo-controlled, parallel-group</th>
</tr>
</thead>
</table>
| Patients        | • Active *C. difficile* ranging from uncomplicated diarrhea to pseudomembranous colitis  
                  • Oral vancomycin or metronidazole |
| Intervention    | • *Saccharomyces boulardii*  
                  • Two 250-mg capsules BID x 4 weeks  
                  • Placebo  
                  • BID x 4 weeks |
| Endpoints       | Primary endpoint  
                  • Recurrence of active *C. difficile* |

*(N = 124)*
S. boulardii for C. difficile

- Rates of Recurrence

<table>
<thead>
<tr>
<th>Group</th>
<th>S. boulardii</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention</td>
<td>6 (19.3%)</td>
<td>8 (24.2%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>9 (34.6%)</td>
<td>22 (64.7%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- Limitations
  - Small study; not powered to detect a difference
  - Unknown dose and duration of antibiotics
  - Unknown dose of vancomycin
  - Surveillance = 4 weeks after study drug discontinuation

### High-Dose Vancomycin with S. boulardii

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, double-blind, placebo-controlled</th>
</tr>
</thead>
</table>
| Patients                 | - Presence of positive *C. difficile* assay and active diarrhea prior to antibiotic therapy  
|                          | - ≥ 1 prior episode of *C. difficile* within the last year |
| Intervention             | - *S. boulardii* 1 gram/day x 4 weeks PLUS  
|                          |   - Vancomycin 500 mg/day x 10 days  
|                          |   - Vancomycin 2 grams/day x 10 days  
|                          |   - Metronidazole 1 gram/day x 10 days |
| Endpoints                | Primary endpoint  
|                          |   - Recurrence of active *C. difficile* |

*(N = 168)*

*Clin Infect Dis* 2000; 31: 1012-17.
High-Dose Vancomycin with *S. boulardii*

### Rates of Recurrence

<table>
<thead>
<tr>
<th></th>
<th>S. boulardii</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose Vancomycin</td>
<td>3 (16.7%)</td>
<td>7 (50%)</td>
<td>0.05</td>
</tr>
<tr>
<td>(n = 32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose vancomycin</td>
<td>23 (51.1%)</td>
<td>17 (44.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>(n = 85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>13 (48.1%)</td>
<td>13 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>(n = 53)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant

### Limitations

- Choice of antibiotic was not randomized
- Unclear duration of antibiotics for other infection

*Clin Infect Dis* 2000; 31: 1012-17.
To Summarize

**Literature**
- Reduced rates of recurrent *C. difficile* infection
- Reduced rate of recurrence with high-dose vancomycin

**Patient**
- Avoid immunocompromised patients
- Avoid critically ill patients
# Prophylaxis with Vancomycin

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, retrospective cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>- Initial or recurrent episode of CDI</td>
</tr>
<tr>
<td></td>
<td>- Subsequently received antibiotics not targeted at <em>C. difficile</em></td>
</tr>
<tr>
<td></td>
<td>- Within 90 days</td>
</tr>
<tr>
<td>Intervention</td>
<td>Vancomycin 125 mg PO QID</td>
</tr>
<tr>
<td>Objective</td>
<td>Whether oral vancomycin as secondary prophylaxis in addition to concomitant antibiotics, could reduce risk of CDI recurrence</td>
</tr>
</tbody>
</table>

N = 551

CDI = *Clostridium difficile* infection

## Prophylaxis with Vancomycin

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Vancomycin Prophylaxis (n = 324)</th>
<th>Vancomycin Prophylaxis (n = 227)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 18-64</td>
<td>78 (24.1%)</td>
<td>45 (19.8%)</td>
</tr>
<tr>
<td>• 65-75</td>
<td>87 (26.9%)</td>
<td>71 (31.3%)</td>
</tr>
<tr>
<td>• ≥75</td>
<td>159 (49.1%)</td>
<td>111 (48.9%)</td>
</tr>
<tr>
<td><strong>Primary Prevention</strong></td>
<td>242 (74.7%)</td>
<td>137 (60.4%)</td>
</tr>
<tr>
<td><strong>Secondary Prevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1</td>
<td>53 (16.4%)</td>
<td>46 (20.3%)</td>
</tr>
<tr>
<td>• ≥2</td>
<td>29 (9.0%)</td>
<td>44 (19.4%)</td>
</tr>
<tr>
<td><strong>Non-C. <em>difficile</em> Infection Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Vancomycin only</td>
<td>76 (24.2%)</td>
<td>94 (42.9%)</td>
</tr>
<tr>
<td>• Vancomycin and metronidazole</td>
<td>81 (25.8%)</td>
<td>90 (41.1%)</td>
</tr>
<tr>
<td>• Metronidazole only</td>
<td>157 (50.0%)</td>
<td>35 (16.0%)</td>
</tr>
</tbody>
</table>

*P < 0.0001
Prophylaxis with Vancomycin

Prophylaxis with Vancomycin

- Vancomycin > 50%
- Vancomycin < 50%
- No Vancomycin

Prophylaxis with Vancomycin

- Vancomycin reduced the risk of *C. difficile* in patients with
  - ≥ 1 prior recurrence of *C. difficile*
  - Duration > 50% of the concomitant antibiotic duration
- Zero benefit was observed in patients who received metronidazole
- Would vancomycin 125 mg PO BID suffice???
## Efficacy of Oral Vancomycin - Brief Report

**N = 203**

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Single center, retrospective cohort study</th>
</tr>
</thead>
</table>
| **Patients** | • Previous documentation of “loose stools” or “diarrhea”  
• Concurrent positive stool test by polymerase chain reaction (PCR)  
• Hospitalized and treated with systemic antimicrobial therapy |
| **Intervention** | • Vancomycin 125-250 mg PO BID  
• No prophylaxis |
Efficacy of Oral Vancomycin - Brief Report

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Oral Vancomycin (n = 71)</th>
<th>Control group (n = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, years</td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td>Probiotics, No. (%)</td>
<td>31 (14)</td>
<td>21 (16)</td>
</tr>
<tr>
<td>Duration of systemic antimicrobial therapy, mean, days</td>
<td>12.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Prior CDI, mean, months</td>
<td>6.14</td>
<td>7.61</td>
</tr>
</tbody>
</table>

CDI = Clostridium difficile infection
Efficacy of Oral Vancomycin - Brief Report

- CDI diagnosed in 3 (4.2%) vs 35 (26.6%), p<0.001
  - 2 ➔ 250 mg PO BID
  - 1 ➔ 125 mg PO BID
- Average duration of prophylaxis: ~1 day after completion of antibiotic therapy
- Limitations
  - Unknown severity or quantity of prior CDI
  - Surveillance period was up to 4 weeks after completion of antibiotic therapy


CDI = Clostridium difficile infection

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To Summarize

**Literature**
- Reduced rates of recurrent *C. difficile* infection
- Benefit seen with BID dosing

**Patient**
- Avoid in acute kidney injury
- Avoid vancomycin allergy
Assessment Question

• Which of the following is not an appropriate regimen used to prevent recurrent *C. difficile* infection?

A. Vancomycin 125 mg PO Daily
B. Vancomycin 125 mg PO BID
C. Vancomycin 125 mg PO QID
D. Vancomycin 250 mg PO BID
Bezlotoxumab (Zinplava™)

- Fully human monoclonal antibody
- Reduce recurrence of *C. difficile*
  - In combination with antibiotics for *C. difficile*
- MOA: Binds to *C. difficile* toxin B
- Dose: 10 mg/kg IV x 1 over 60 minutes
- Preparation: 1000 mg/40 mL single-dose vial

## MODIFY

### MODIFY (n = 1,163)

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, double-blind, placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Primary or recurrent \textit{C. difficile} infection who were receiving oral standard-of-care-antibiotics for 10-14 days • Metronidazole, vancomycin, or fidaxomicin</td>
</tr>
<tr>
<td>Intervention</td>
<td>• Bezlotoxumab • Actoxumab + bezlotoxumab • Placebo</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Primary endpoint • Proportion of participants with recurrent \textit{C. difficile} infection during 12 weeks of follow-up Secondary endpoint • Rate of sustained cure</td>
</tr>
</tbody>
</table>

### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Participants (N = 2559)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard of care antibiotics</td>
<td></td>
</tr>
<tr>
<td>• Metronidazole</td>
<td>1196 (46.7%)</td>
</tr>
<tr>
<td>• Vancomycin</td>
<td>1221 (47.7%)</td>
</tr>
<tr>
<td>• Fidaxomicin</td>
<td>92 (3.6%)</td>
</tr>
<tr>
<td>≥1 Episode of CDI in previous 6 months</td>
<td>704 (27.5%)</td>
</tr>
<tr>
<td>≥2 Previous CDI episodes ever</td>
<td>363 (14.2%)</td>
</tr>
<tr>
<td>Severe CDI</td>
<td>420 (16.4%)</td>
</tr>
</tbody>
</table>

CDI = *Clostridium difficile* infection

**MODIFY**

Subjects w/ CDI recurrence through week 12, (%)

- **Modify II**
  - Act-Bez: 15
  - Bez: 16
  - Placebo: 26

- **Pooled Data**
  - Act-Bez: 15
  - Bez: 17
  - Placebo: 27

P < 0.001

Act-Bez = Actoxumab – bezlotoxumab
Bez = Bezlotoxumab
CDI = *Clostridium difficile* infection
Stratified log-rank test
Actoxumab-bezlotoxumab vs. placebo, P<0.001
Bezlotoxumab vs. placebo, P<0.001

Cumulative Rate of Infusion Recurrence (%)

Weeks after Infusion
Patients with sustained cure through week 12, (%)

Modify II  |  Pooled Data
---|---
Act-Bez  |  Act-Bez
Bez  |  Bez
Placebo  |  Placebo

Act-Bez = Actoxumab – bezlotoxumab
Bez = Bezlotoxumab

MODIFY

- Significantly lower rate of recurrent *C. difficile*
- Higher rates of sustained *C. difficile* prevention through 12 weeks
- Very minimal adverse events were reported
  - 9% overall infusion specific reactions
  - Nausea, headache, dizziness, fatigue, and pyrexia
- Caution in heart failure patients
Patient Care

- 68 YOM admitted for sepsis secondary to bloodstream infection
- PMH: HTN, HFrEF, HIV, aortic valve replacement (7/24/17), C. difficile (7/30/17 – resolved)
- Patient is started on vancomycin and piperacillin/tazobactam
  - Blood Cx: non-lactose fermenting gram negative rods
- Per ID: To continue on antibiotics for 2 weeks following first negative blood culture. Will de-escalate once susceptibilities are known.
Assessment Question

• Based on the presented information, which would be the best option?

A. Prophylaxis is not indicated for this patient
B. Vancomycin 125 mg PO BID
C. Metronidazole 500 mg PO TID
D. Bezlotoxumab 10 mg/kg x 1 + vancomycin 250 PO QID
E. Probiotic + vancomycin 250 mg PO QID
### Take Home Points

<table>
<thead>
<tr>
<th>Indication</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 prior episode of <em>C. difficile</em></td>
<td>• Vancomycin twice daily</td>
</tr>
<tr>
<td>Starting long-term antimicrobial therapy</td>
<td>• Probiotic PLUS vancomycin</td>
</tr>
<tr>
<td>Assess other risk factors</td>
<td>• Avoid metronidazole</td>
</tr>
<tr>
<td></td>
<td>• Bezlotoxumab x 1 PLUS vancomycin</td>
</tr>
</tbody>
</table>
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