Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

A Midday Symposium and Live Webinar conducted at the 2019 ASHP Midyear Clinical Meeting & Exhibition

Monday, December 9, 2019  |  11:30 a.m. – 1:00 p.m.  |  Las Vegas, Nevada

**AGENDA**

11:30 a.m.  
**Welcome and Introductions**  
*Kevin W. Garey, Pharm.D., M.S., FASHP*

11:35 a.m.  
**Epidemiology, Pharmacology, Immunology, and Microbiome Science of *Clostridioides difficile* Infection (CDI): Focus on Prevention of CDI Recurrence**  
*Pablo C. Okhuysen, M.D., FACP, FIDSA*

12:00 p.m.  
**Treatment Plan for CDI Based on Underlying Risk of Recurrence**  
*Kevin W. Garey, Pharm.D., M.S., FASHP*

12:25 p.m.  
**The Great Debate: Is the Future of CDI Treatment and Prevention Focused on Microbiome Restoration Supplements, Antibiotics, or Something Else?**  
*Kevin W. Garey, Pharm.D., M.S., FASHP and Pablo C. Okhuysen, M.D., FACP, FIDSA*

12:50 p.m.  
**Faculty Discussion and Audience Questions**

www.ashpadvantage.com/preventcdiff
Strategies for Prevention and Treatment of Recurrent C. difficile Infection

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Infection Control and Employee Health
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Kevin W. Garey, Pharm.D., M.S., FASHP, Activity Chair
• Merck: Principal investigator

Pablo C. Okhuysen, M.D., FACP, FIDSA
• Merck Sharp and Dohme Corp: Research Grant
• Summit Therapeutics: Principal Investigator
• Pfizer, Merck – Consultant
• Jaguar Health, Inc. - Consultant
• Singulex - Honoraria
• Summit Therapeutics – Research Grant

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Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

Learning Objectives

- Apply concepts of epidemiology, pharmacology, immunology, and microbiome science to stratify patients at risk of developing recurrent *Clostridioides difficile* infection (CDI).
- Develop anti-recurrence strategies for treating patients with recurrent CDI.
- Formulate a treatment plan for CDI based on underlying risk of recurrence.
- Investigate current and future therapeutic targets to prevent recurrent CDI.

Epidemiology, pharmacology, immunology, and microbiome science of *Clostridioides difficile* infection: Focus on prevention of CDI recurrence

Pablo C. Okhuysen, M.D., FACP, FIDSA

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Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**Some Definitions**

- **CDI Case**: Diarrhea, severe ileus or megacolon with: Positive laboratory test and/or, endoscopic/microscopic evidence of pseudomembrane formation (Defined as incident case if no symptoms or negative tests within past 8 weeks)
- **Severe CDI**: Admission to the ICU, colectomy, death within 30 days
- **Recurrent CDI**: Repeated episodes within 2–8 weeks
- **New episode CDI**: Repeat infection after 8 weeks
- **Health Care Onset (HO-CDI)**: Occurring > 72 hr after admission. (rates per 10,000)
- **Community Onset Health Care Facility Associated CDI (CO-HCFA)**: Onset within 28 days after discharge from a health care facility (rates per 100,000). Also includes CO, present on admission and not discharged from the same facility within 4 weeks
- **Community Associated (CA)**
  - No documented overnight stay in a health care facility in the prior 12 weeks (>90% have some form of contact with health care)


**Epidemiology**

- Diarrheal disease-related deaths have increased in the U.S. from 1980 to 2014. In a big part driven by CDI
  - Adjusted mortality from CDI increased 19-fold
- Estimated to cause 500,000 cases per year with 29,000 deaths
- Adds $4.5 billion in excess medical costs
- Has surpassed Methicillin-resistant Staphylococcus aureus (MRSA) as the most common health care associated infection


Case Presentation

A 64-year-old truck driver with maxillary sinus carcinoma and no evidence of disease develops R leg cellulitis and is treated with cephalexin. Two weeks later he develops diarrhea. A rapid diagnostic test (RDT) and toxin A/B enzyme immunoassay (EIA) for Clostridiodes difficile toxin is positive. He is treated with metronidazole and 1 month after completing a 10 day course develops diarrhea with 6 unformed stools, low grade fever, abdominal pain. A RDT and EIA is once again positive. Is this a recurrence, relapse or a re-infection?

Recurrent C. difficile Infection

- Recurrence: Confirmed C. difficile infection within 8 or 12 weeks
- Relapse: Infection with the same strain
- Re-infection: Infection with a different strain
- Other studies define recurrence (15-56 days) and re-infection (>56 days)
Strategies for Prevention and Treatment of Recurrent C. difficile Infection

**Microbiome disruption (antibiotic use) and Exposure to toxigenic C. difficile (Healthcare, community)**

- **Susceptible (40-50%)**
  - No or low Antibodies (Ab) to C. difficile toxin A, B
  - Comorbidities

- **Recurrence (5-40%)**
  - Additional Risk Factors
  - Advanced age, additional antibiotics, ineffective therapy

- **Asymptomatic Carrier**
  - Potential for transmission to others

- **Multiple Recurrences (10-50%)**

- **No Further Episodes (50-90%)**

**First and only episode (60-95%)**

**Not Susceptible (40-50%)**
- Ab to C. difficile and,
- Low co-morbidities

**Asymptomatic carrier**
- Low risk of diarrhea
- Potential for transmission to others

**Increasing rates of rCDI and MRCDI**

- **Due to strains that are:**
  - More resistant to antibiotics
  - Hyper virulent
  - Competitive advantage
- **Other explanations:**
  - Over diagnosis with new molecular based techniques
  - A subset is due to post-infectious irritable bowel syndrome (IBS)
- **30% of recurrences can be linked to a previously identified case**
- **25% can be linked to an asymptomatic carrier**

<table>
<thead>
<tr>
<th>2001-2012 % Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Recurrence</td>
</tr>
<tr>
<td>Multiple rCDI</td>
</tr>
</tbody>
</table>


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Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

### What is Driving the Increase in Frequency and Severity of Recurrent CDI?

- Overuse of antibiotics, particularly fluoroquinolones
- Aging population with more severe conditions
- Increasing number of immunocompromised patients
- Spread of hypervirulent, drug resistant strains
- Spread of strains that have a competitive advantage
- Dietary changes that favor microbiome shifts that allow CDI
- Use of ineffective initial therapy

### Continuing or Restarting Antibiotic Exposure and risk of rCDI

<table>
<thead>
<tr>
<th></th>
<th>No Antibiotics</th>
<th>Antibiotic Course</th>
<th>Antibiotics Stopped</th>
<th>No Antibiotics</th>
<th>Continued or Additional Antibiotic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Flora</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>CDI Risk</td>
<td>-</td>
<td>++++</td>
<td>+++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td><em>C. difficile</em> advantage</td>
<td>-</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>++++</td>
</tr>
</tbody>
</table>

Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics used during follow up</td>
<td>1.76</td>
<td>1.52-2.05</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Fluoroquinolone use</td>
<td>1.42</td>
<td>1.28-1.57</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Age ≥ 65 yr</td>
<td>1.63</td>
<td>1.21-2.15</td>
<td>0.0005</td>
</tr>
<tr>
<td>Proton pump Inhibitor use</td>
<td>1.58</td>
<td>1.13-2.21</td>
<td>0.008</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1.59</td>
<td>1.14-2.23</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Meta-analysis of 33 studies (N=18,530)


What is Driving the Increase in Frequency and Severity of Recurrent CDI?

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- Use of ineffective initial therapy
Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

### Advanced Age as a Risk Factor for rCDI

<table>
<thead>
<tr>
<th>Age group</th>
<th>Estimated Annual Recurrences</th>
<th>Recurrence Rate per 100,000 Persons (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>CA CDI 21,600</td>
<td>HCA CDI 61,400</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-17 yr</td>
<td>1,400</td>
<td>300</td>
</tr>
<tr>
<td>18-44 yr</td>
<td>2,600</td>
<td>3,400</td>
</tr>
<tr>
<td>45-64 yr</td>
<td>6,200</td>
<td>9,000</td>
</tr>
<tr>
<td>≥ 65 yr</td>
<td>11,400</td>
<td>48,700</td>
</tr>
</tbody>
</table>

CA: community associated; HCA: Healthcare associated


### Recurrent CDI in Cancer Patients

- Retrospective, multivariate analysis of 170 patients with 270 episodes of rCDI at MDACC 2016-2018
- Adult patients with diarrhea and NAAT+ and EIA A/B+

<table>
<thead>
<tr>
<th>Characteristics of First Episode</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=170</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>19.9 (2.2-183.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>2.3 (1.1-4.9)</td>
<td>0.035</td>
</tr>
<tr>
<td>NSAID use</td>
<td>4.6 (2.1-9.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>3.5 (1.6-7.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3.8 (11-12.9)</td>
<td>0.035</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>3.7 (1.5-9.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Severe/Fulminant</td>
<td>2.4 (1.1-5.0)</td>
<td>0.022</td>
</tr>
</tbody>
</table>


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Multiple CDI Recurrences in Cancer Patients

- 85/170 cases (50%) had rCDI and 14 /170 cases (8.2%) had MRCDI
- Risk factors for MRCDI included:
  - Previous hospitalization (78% vs. 56%; P=0.009)
  - Immunosuppression (53% vs. 27%; P=0.002)
  - Metronidazole treatment at time of first recurrence (37% vs. 18%; P=0.017)

- MRCDI
  - Required longer courses of therapy (22 vs 17 days; P=0.030)
  - Longer period before being recurrence free (6.6 vs 3.5 months; P=0.025)


CDI in Hematopoietic Stem Cell Transplant Patients

- Most common bacterial pathogen in HSCT patients (8-33%)
- Most patients have a single episode (74%)
- Median onset of 21 days post transplant
- Higher risk with Myeloablative > non myeloablative (37% vs. 24% [OR1.6, 1.1-2.3])
- Allogenic > Autologous
- Pre transplant colonization increases risk
- Frequently follows or precedes sepsis
- Bi-directional relationship with GI graft versus host disease (GVHD)
- Associated with non-relapse-related mortality
- Extends hospital stay (22 vs. 27 days), increased risk of recurrence

Chackrabarti S. Bone Marrow Transplant. 2000; 26:871-6
Antibody Response and Recurrent CDI

- Initial studies showed antibodies to toxin A and B were both relevant
- Advanced age is associated with low antitoxin B antibodies
- Prior episodes of CDI, inpatient status, immunocompromised status and low Ab titers
- Antitoxin B titers at baseline and at week 4 correlate inversely with rCDI
- However 20% of patients with a high Ab response still developed CDI


Antibody Response and rCDI

Baseline Recurrence

Participants with rCDI


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Virulence Locus

- TcdA and TcdB code for toxin A and toxin B
  - Glucosyl transferase domains, bind to Rho and Rac GTPases in cell cytosol
  - Autocatalytic cysteine protease, cleaves host glucosyl transferase
  - CROP domain – needed for cell carbohydrate binding gp96
  - TcdB binds to poliovirus receptor-like 3 protein
  - In human cells deletion of TcdB but not TcdA abrogates toxicity
  - Sequence diversity accounts for variability in toxicity
- TcdR, TcdC and TcdD
  - Suppress or enhance toxin production depending on growth phase
  - TcdC deletions associated with hypervirulence
- Binary toxin (CDT)
  - C. difficile transferase CdtA (ribosyl transferase), CdtB (forms pores)

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**Not all *C. difficile* Strains are the Same**

- *C. difficile* ribotyping
  - First polymerase chain reaction (PCR) gel-based technique developed in 1995
  - Quantifies the differences in length between 16S and 23S rRNA encoding genes at 11 rRNA-encoding operons around the *C. difficile* genome
  - Fluorescent PCR-based ribotyping allows for automated analysis of 113 distinct “F” ribotypes
- Multiple-locus variable number tandem repeat analysis
  - Higher resolution → more recent evolutionary changes
  - Helpful in horizontal transmission/outbreak investigations
- Ribotypes 027, 078, 244 are associated with poor outcomes


**C. difficile** is Ubiquitous and Colonization is Common

- Neonatal pigs, water and soil, meat at the grocery store (7.8%). Ribotype 078
- A recent study done in Houston households found *C. difficile* in:
  - Shoes (25/63; 40%), Bathroom (5/15; 33%)
  - Surfaces (7/37;19%), Dust (4/12;33%)
  - Belonged to 25 different ribotypes
- Neonates peak at 6-12 months (4-70%), luckily not susceptible to disease
- Household pets can carry same isolates as their ill human owners


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### Molecular Epidemiology at a Cancer Center

- Low rates of hyperendemic *C. difficile* strains
- The proportions of NAAT(+) EIA (-) and the infecting ribotypes of *C. difficile* are line of service-specific


Proportion of patients with toxin A/B detected in their stools (blue) at MDACC according to *C. difficile* genotype

Yepez et al. European Congress of Clinical Microbiology and Infectious Diseases. 2019

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![Fig 1. Distribution of clinical outcomes in cancer patients with CDI by *C. difficile* ribotype group and EIA test positive](image)

- G1 F014-020
- G2 F002, F027
- G3 Others
- Severe CDI (55%) and with active malignancy (84.6%)
- PCR+/EIA+ in 34%
  - 31% in G1
  - 46% in G2
  - 42% in G3
- Recurrences 22%
  - EIA+ episode
    - (18/50 vs. 14/97 P=0.005)
  - G1 (27%)
  - G2 (46%)
  - G3 (35%), P=0.003.

**At the Molecular Level, Recurrences or Reinfections?**

- Isolates from 61 patients studied for mixed infection at the molecular level (Mean of 36 colonies per patient)
- At baseline:
  - Mixed infection found in 78% patients with recurrence vs. 36% that did not have a recurrence (OR 6.3 CI 1.4-35.6; P=0.023)
- Variable and mixed infection seen at recurrence and reinfection

Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**What is Driving the Increase in Frequency and Severity of Recurrent CDI?**

- Overuse of antibiotics, particularly fluoroquinolones
- Aging population with more severe conditions
- Increasing number of immunocompromised patients
- Spread of hypervirulent, drug resistant strains
- Spread of strains that have a competitive advantage
- Dietary changes that favor microbiome shifts that allow CDI
- Use of ineffective initial therapy

**Diet and *C. difficile***

- Diet has an important effect on microbiome composition
- Microbiota accessible carbohydrates suppress *C. difficile* growth
- Fiber reduces the presence of *Clostridium XI*
- Dietary trehalose enhances the virulence of epidemic *C. difficile*
- Dysbiosis leads to increased free amino acids such as proline in the gut favoring *C. difficile* growth

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What is Driving the Increase in Frequency and Severity of Recurrent CDI?

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- Spread of strains that have a competitive advantage
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Traditional Risk Factors for rCDI

- Previous CDI
- Continued antibiotics after CDI diagnosis
- Advanced age
- Gastric acid suppression
- Hypervirulent strains
- Severe underlying disease
- Prolonged hospital stays
- Lack of adaptive immune response
- Immunosenescence
- Ineffective initial therapy
Key Takeaways

- *C. difficile* ubiquitous in the environment, frequent colonizer
- Recurrent CDI is on the rise both in frequency and severity
- Recurrent CDI without traditional risk factors also increasing
- Specific ribotypes (078, 244, 027) are associated with poor outcomes, rCDI and decreased response to therapy
- There is a need for improved diagnostic methods that differentiate colonized from infected patients and recurrence from reinfection
- Interventions that do not impact the microbiota are best for CDI treatment and prevention of recurrence

Treatment Plans for CDI based on Risk of Recurrence

Kevin W. Garey, Pharm.D., M.S., FASHP
Let's go back to our case:

A 64-year-old truck driver with maxillary sinus carcinoma and no evidence of CDI develops R leg cellulitis and is treated with cephalexin. Two weeks later he develops diarrhea. A rapid diagnostic test (RDT) and toxin A/B enzyme immunoassay (EIA) for *Clostridioides difficile* toxin is positive.

He is treated with metronidazole and 1 month after completing a 10 day course develops diarrhea with 6 unformed stools, low grade fever, abdominal pain. A RDT and EIA is once again positive.

Is this a recurrence, relapse or a re-infection?

HOW SHOULD WE HAVE TREATED HIM??
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**Therapeutic Goals for *C. difficile* Infection (CDI)**

**Essential:**
- Correct dysbiosis
- Kill the organism
- Adaptive immunity

**Optional but nice:**
- Safe and convenient
- Also affects toxins and spores
- Short vs. long-term use


**There Has Been an Explosion in Treatment Possibilities for CDI**

**Current:**
- Probiotics
- FMT
- Use narrow-spectrum antibiotics
- Metronidazole
- Vancomycin
- Fidaxomicin
- IVIG
- Bezlootoxumab

**Future:**
- 2nd-generation FMT
- Non-tox *C. difficile* M3
- Ecobiotics
- Ridinilazole
- Toxoid vaccines

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**Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)**


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**Treatment for CDI: First Steps**

- Don’t treat asymptomatic patients!
  - Uncertain whether colonization treatment has any effect
  - Treatment may increase colonization/spread!
  - Prophylaxis not well studied
- Stop other antibiotics
  - 15–20% clinical success in mild CDI (alone!)
- Stop proton pump inhibitors (PPIs) and antimotility agents
- Stop/alter use of binding agents (cholestyramine)
  - Can bind vancomycin/metronidazole!

More Recently, Metronidazole has Been Shown to be Globally Inferior to Vancomycin (Tlevamer Phase III RCT)

![Graph showing clinical success and recurrence rates for Tlevamer, Metronidazole, and Vancomycin](Johnson S et al. Clin Infect Dis. 2014; 59:345-54.)

Increased Failure Rate of Metronidazole Also Associated with Increased 30-day Mortality

![Graph showing 30-day mortality rates for metronidazole and vancomycin](Stevens VW et al. JAMA Intern Med. 2017; 177:546-53.)

VA dataset (vancomycin: n=2,068; metronidazole: n=8,069 propensity matched). Patients given vancomycin had a significantly lower risk of 30-day mortality (RR: 0.86, 95% CI: 0.74-0.98). No significant difference in CDI recurrence regardless of disease severity or choice of antibiotic (16.3-22.8%).

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### Strategies for Prevention and Treatment of Recurrent C. difficile Infection

#### Summary of Metronidazole vs. Vancomycin Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>n</th>
<th>Single center</th>
<th>Blinded</th>
<th>Randomized</th>
<th>Metro dose</th>
<th>Vanco dose</th>
<th>Clinical failure</th>
<th>Recurrence</th>
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<tr>
<td>Tauxe, 1983</td>
<td>83–84</td>
<td>MN</td>
<td>101</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>250 mg QD</td>
<td>500 mg QID</td>
<td>2 of 37 (5.4%)</td>
<td>6 of 45 (13%)</td>
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<tr>
<td>Wanisch, 1995</td>
<td>95-96</td>
<td>Austria</td>
<td>62</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>500 mg QD</td>
<td>500 mg QID</td>
<td>2 of 31 (6%)</td>
<td>5 of 31 (16%)</td>
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<tr>
<td>Musher, 2006</td>
<td>06-06</td>
<td>USA (Houston)</td>
<td>34</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>250 mg QD</td>
<td>125 mg QID</td>
<td>6 of 34 (17%)</td>
<td>N/A</td>
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<td>Zar, 2007</td>
<td>07-07</td>
<td>Chicago</td>
<td>150</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>250 mg QD</td>
<td>125 mg QID</td>
<td>13 of 79 (16%)</td>
<td>5 of 66 (14%)</td>
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<tr>
<td>Johnson, 2013</td>
<td>05-06</td>
<td>World</td>
<td>552</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>375 mg QD</td>
<td>125 mg QID</td>
<td>76 of 278 (27%)</td>
<td>43 of 210 (21%)</td>
</tr>
</tbody>
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**TID:** Three time daily; **QID:** Four times daily

#### There May Have Been MIC Creep With Metronidazole Over the Decades

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Time period</th>
<th>Isolates</th>
<th>Metronidazole</th>
<th>Range</th>
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<tbody>
<tr>
<td>All strains</td>
<td></td>
<td></td>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
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<tr>
<td>Hecht et al</td>
<td>Various</td>
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<td>110</td>
<td>0.125</td>
<td>0.025–0.5</td>
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<td>Sweden</td>
<td>1998</td>
<td>50</td>
<td>0.125</td>
<td>0.125–0.25</td>
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<td>Betriu et al</td>
<td>Spain</td>
<td>2001</td>
<td>55</td>
<td>0.5</td>
<td>0.06–1</td>
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<td>Citron et al</td>
<td>USA</td>
<td>2003</td>
<td>18</td>
<td>0.5</td>
<td>0.25–1</td>
</tr>
<tr>
<td>Finegold et al</td>
<td>USA (CA)</td>
<td>2003</td>
<td>72</td>
<td>0.5</td>
<td>0.25–2</td>
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<tr>
<td>Karlowsky et al</td>
<td>Canada (Manitoba)</td>
<td>2007</td>
<td>208</td>
<td>0.5</td>
<td>0.25–4</td>
</tr>
<tr>
<td>Debast et al</td>
<td>Europe</td>
<td>2008</td>
<td>398</td>
<td>0.25</td>
<td>&lt;0.06-2</td>
</tr>
<tr>
<td>Reigadas et al</td>
<td>Spain</td>
<td>2013</td>
<td>100</td>
<td>0.25</td>
<td>0.06-1</td>
</tr>
<tr>
<td>Snydman et al</td>
<td>USA</td>
<td>2011-12</td>
<td>925</td>
<td>1</td>
<td>&lt;0.06-4</td>
</tr>
</tbody>
</table>

**BI/027/NAP1 strains**

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Time period</th>
<th>Isolates</th>
<th>Metronidazole</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citron et al</td>
<td>USA</td>
<td>2004–2005</td>
<td>NR</td>
<td>2</td>
<td>0.5–2</td>
</tr>
<tr>
<td>Debast et al</td>
<td>Europe</td>
<td>2008</td>
<td>0.5</td>
<td>1</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Snydman et al</td>
<td>USA</td>
<td>2011-12</td>
<td>2</td>
<td>2</td>
<td>&lt;0.06-4</td>
</tr>
</tbody>
</table>

**MIC:** minimum inhibitory concentration  

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**Bottom Line:**
*This May Simply be a PK/PD Problem*

- Mean concentrations of metronidazole in stool:
  - <0.25–9.5 µg/g
- \( \text{MIC}_{50} \): 1 µg/mL \( \text{MIC}_{90} \): 2 µg/mL
  - May be higher
- A poor response rate to metronidazole should be expected given these numbers!


**Recommendations for Initial Treatment of CDI in Adults**

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>WBC &lt;15,000 cells/mL and serum creatinine &lt;1.5 mg/dL</td>
<td>VAN 125 mg orally given four times daily for 10 days, or FDX 200 mg orally given twice daily for 10 days Alternatives if above agents are not available: metronidazole 500 mg orally three times daily by mouth for 10 days</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC ≥15,000 cells/mL or a serum creatinine &gt;1.5 mg/dL</td>
<td>VAN 125 mg orally given four times daily for 10 days, or FDX 200 mg orally given twice daily for 10 days</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>VAN 500 mg given four times daily by mouth or nasogastric tube. If ileus, consider adding rectal instillation of VAN. Add intravenous metronidazole 500 mg every 8 hr if ileus present</td>
</tr>
</tbody>
</table>

VAN, vancomycin; FDX, fidaxomicin; SD, standard dose

Explosion in Treatment Possibilities for CDI

**Minus 1**

**Current:**
- Probiotics
- FMT
- Use narrow-spectrum antibiotics

**Future:**
- 2nd-generation FMT
- Non-tox *C. difficile* M3
- Ecobiotics

**Vancomycin**

**Fidaxomicin**

**IVIG**
- Monoclonal antibodies
- vs. *C. difficile* toxins

**Future:**
- 2nd-generation FMT
- Ridinilazole
- Toxoid vaccines

---

**Fidaxomicin: Noninferior to Vancomycin for Clinical Cure and Lower Risk of Recurrence**

- **Clinical cure:**
  - Fidaxomicin: 92.1%
  - Vancomycin: 89.8%
  - *P* = 0.004

- **Recurrence:**
  - Fidaxomicin: 13.3%
  - Vancomycin: 24%

- **Global cure:**
  - Fidaxomicin: 77.7%
  - Vancomycin: 67.1%


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Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

Recurrent CDI is Costly:
Healthcare Utilization for Recurrent CDI

![Graph showing healthcare utilization for recurrent CDI](image)

- First recurrence (n = 64)
- Second or later recurrence (n = 18)

*Of disease-attributable readmission, 85% returned to the initial hospital for care


Increased Healthcare Utilization = Increased Healthcare Costs

![Graph showing increased healthcare utilization](image)

<table>
<thead>
<tr>
<th></th>
<th>Without recurrent CDI</th>
<th>With recurrent CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS: Length of stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDI pharmacologic treatment</td>
<td>$60 (23 – 200)</td>
<td>$140 (30 – 260)</td>
</tr>
<tr>
<td>CDI-attributable hospitalization</td>
<td>$13,168 (7,525 – 24,455)</td>
<td>$28,218 (15,049 – 47,030)</td>
</tr>
<tr>
<td>Total hospitalization</td>
<td>$20,693 (11,287 – 41,386)</td>
<td>$45,148 (20,693 – 82,772)</td>
</tr>
</tbody>
</table>


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Any Evidence That Fidaxomicin May Reduce These Costs?

Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for select patients. CDI-related readmissions: fidaxomicin: 20.4%; vancomycin: 41.3%

Drug-acquisition costs

Vancomycin: $6,333
Fidaxomicin: $62,112
Vancomycin (183 days): $454,800
Fidaxomicin (87 days): $196,200

Hospital re-admission costs


Real-world Evidence That Fidaxomicin May Reduce These Costs?

UK, 2012–13: Seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals

Before Fidaxo After Fidaxo

First line, all episodes

A (n=98) 10.6 3.1
B (n=162) 16.3 3.1
D (n=127) 21.1 12.5

First line, R-CDI

C (n=511) 7.7 8.3
E (n=209) 12.9 11.8
F (n=178) 16.9 9
G (n=278) 5.4 5.8

Selected episodes only


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Strategies for Prevention and Treatment of Recurrent C. difficile Infection

Real-world Evidence That Fidaxomicin May Reduce These Costs?

UK, 2012–13: Seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% and 17.3% to 3.1% and 3.1% in hospitals A and B, respectively (p<0.05, each)


The EXTEND Trial

Extended-Pulsed Fidaxomicin vs. Standard Dose Vancomycin* in Patients >60 years of age

EXTEND: randomized, controlled, open-label, phase 3b/4 trial in patients ≥60-year-old with initial or recurrent CDI confirmed by presence of toxins A or B in stool sample

*Dosage: Fidaxomicin 200 mg oral tablets, twice daily on days 1-5, then once daily on alternate days on days 7-25; Vancomycin 125 mg oral capsules, four times daily on days 1-10

Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**Restore the Microbiome**

Microbiome of non-CDI patients vs. CDI patients

- Total Colony Forming Units (CFU) abundance
- Diversity of microbiologic species
- Other pathogenic organisms

![Healthy Microbiome vs. Recurrent CDI Microbiome](image)

**Recommended Treatment for CDI Recurrence in Adults**

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence</td>
<td>• VAN SD if metronidazole was used for the first episode OR&lt;br&gt;• Prolonged tapered and pulsed VAN if VAN SD was used for first regimen OR&lt;br&gt;• FDX SD if VAN was used for the initial episode</td>
<td>• VAN in a tapered or pulsed regimen OR&lt;br&gt;• VAN SD followed by rifaximin 400 mg orally three times daily for 20 days OR&lt;br&gt;• FDX SD OR&lt;br&gt;• Fecal microbiota transplantation</td>
</tr>
<tr>
<td>Second or subsequent recurrences</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VAN, vancomycin; FDX, fidaxomicin; SD, standard dose


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Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**FMT for Patients with Recalcitrant CDI**

- Before stool transplant: Deaths N/A, # of Recurrence 64 (Range 2–7)
- After stool transplant: 2 (unrelated) deaths, 1 recurrence


---

**Recurrent *C. difficile* Colitis**

Case series involving 18 patients treated with donor stool administered via a nasogastric tube

<table>
<thead>
<tr>
<th></th>
<th>Before stool transplant</th>
<th>After stool transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>N/A</td>
<td>2 (unrelated)</td>
</tr>
<tr>
<td># of Recurrence</td>
<td>64 (Range 2–7)</td>
<td>1</td>
</tr>
</tbody>
</table>

Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**Duodenal Infusion of Donor Feces for Recurrent *C. difficile* Infection**

RCT of oral vanco + FMT (n=16), oral vanco alone (n=13), or oral vanco + bowel lavage (n=13). Study stopped prematurely due to superiority of FMT.

Resolution: no diarrhea without relapse after 10 weeks


**Protocol Utilizing a Staggered and Tapered Antibiotic Treatment Regimen for the Treatment of Recurrent CDI that has Failed to Respond to Standard Antibiotic Therapy**

25 patients with recurrent CDI that were not able to perform FMT. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. The 4 patients who relapsed permanently resolved their diarrhea after a conventional 2-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. All 4 patients remained symptom-free at 12 months of follow-up.


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Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

### Explosion in Treatment Possibilities for CDI: Augment Immune Response!

**Current:**
- Probiotics
- FMT
- Use narrow-spectrum antibiotics
- Vancomycin
- Fidaxomicin
- Monoclonal antibodies vs. *C. difficile* toxins

**Future:**
- 2nd-generation FMT
- Non-tox *C. difficile* M3
- Ecobiotics
- Ridinilazole
- Toxoid vaccines

---

### Serum Concentrations of IgG Antibodies Against Toxin A, Toxin B, and Non-toxin Antigens


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**Monoclonal Antibody: Phase II Study**

![Bar chart showing recurrence rates](image)

- Recurrence at 12 weeks:
  - Monoclonal antibodies (n=101): 7%
  - Placebo (n=99): 25%
  - *P*<0.001


**Phase III Studies of Bezlotoxumab: CDI Recurrence**

![Bar chart showing recurrence rates](image)

- MODIFY I: Bezlotoxumab 17%, Placebo 28%
- MODIFY II: Bezlotoxumab 16%, Placebo 26%
- Pooled Data: Bezlotoxumab 17%, Placebo 27%

*p*<0.001

Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**Bezlotoxumab Was Also Shown to Reduce Hospital Readmissions (European Population)**

![Graph showing reduction in hospital readmissions](image)


**Treatment Conclusions**

- Treatment of CDI is evolving
  - Limit (eliminate) use of metronidazole
  - Bezlotoxumab is here (and can be used in outpatient infusion centers)
  - Complete the triad: Correct dysbiosis

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The Great Debate: Fecal Microbial Therapy or Antimicrobials/Biologics for the Treatment/Prevention of Recurrent CDI?

Kevin W. Garey, Pharm.D., M.S., FASHP
Pablo C. Okhuysen, M.D., FACP, FIDSA

Pro-FMT
Why is Metronidazole Out?

- In a large Veterans Affairs study, vancomycin reduced risk of mortality compared with metronidazole for severe CDI (RR 0.79, 95%CI 0.65-0.97)
- In a three way study vs. tolevamer, metronidazole was inferior to vancomycin for CDI (clinical success 44%, 73% and 81% P = 0.02)
- Metronidazole also associated with Vancomycin-resistant Enterococci (VRE) selection [OR2.0, 95%CI (1.2-3.3), P < 0.009)
- For high risk patients, other options such as fidaxomicin do not select for VRE
- Luminal agents have fewer drug interactions, and are less toxic than metronidazole
- We have newer agents that can treat VRE more effectively
- Anaerobic agents can increase the risk of GHVD following HSCT


Why do Antibiotics Fail so Often?

- Despite high luminal concentrations and in vitro susceptibility, treatment failures are increasingly reported with metronidazole and vancomycin
- Reported rates of antibiotic resistance (3.5%) do not correlate with rates of failure seen in the clinic
- In vitro testing in the lab, may not correlate with activity in the colon due to other factors (method used, antibiotic inactivation, biofilm formation, redox status, etc)
- Isolates from patients with rCDI demonstrate high sporulation, overexpress virulence factors in biofilm, and have reduced susceptibility to vancomycin and linezolid

Pharmacologic Approaches

- All antibiotics available to treat CDI (vancomycin, metronidazole, fidaxomicin) can treat CDI but perpetuate microbiome disruption
- Are associated with toxicities
  - Metronidazole: Neuropathy, CNS disease, nausea, vomiting, altered taste
  - Vancomycin: Small amount can be absorbed, favors VRE
- Taken several times a day, taper and pulse takes a long time, can require maintenance pending FMT
- When NPO, IV metronidazole is only option along with vancomycin enemas
- Can be very expensive, be ready for insurance denials

Fecal Microbiota Transplant

- Anecdotal reports as back as 2,000 years
- 1958 – First report in the medical literature
- 2013 – Meta-analysis showed 89% improvement in 245/278 patients
  - RCT FMT NGT for rCDI vs. vancomycin (91% vs. 34% response)
- 2014 – RCT with oral capsulized, frozen FMT for rCDI
- 2015 – RCT FMT delivered by colonoscopy vs. pulsed vancomycin
- 2016 – RCT Fresh vs. Frozen FMT vs. rCDI
- 2018 – RCT Oral capsule vs. colonoscopy delivered FMT on rCDI

Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**The Microbiome and *C. difficile* Infection**

- Microbial diversity inhibits *C. difficile* growth by:
  - Providing colonization resistance
  - Creating an environment low in succinate, sialic acid and rich in secondary bile acids
  - Rich in Bacteroides, Blautia, Parabacteroides, Coprococcus, Ruminococcus and Oscillopsia

- Antibiotic disrupts this balance and *C. difficile* thrives
  - Decreased commensal production of bacteriocins
  - Loss of Bacteriodetes and Firmicutes
  - Decreased *Clostridium scindens* (7α hydroxylase metabolizes primary bile acids)
  - Decreased *Clostridiales* (clusters IV and XIVa) that produce butyrate
  - Increased *Enterobacteriales*, *Pseudomonadales* and *Lactobacillales*
  - Increased *Incertae sedis* (*Clostridiales* XI)


**A Diverse Microbiome Inhibits *C. difficile***

- In the upper GI tract
  - Limited nutrient environment favors spore formation
  - Primary bile acids (taurocholate) in the upper GI tract signals sporulation through CspC
  - Not all *C. difficile* strains respond to primary bile acids as efficiently
    - Variation in the CspC receptor, Δ CspC cause less disease in a hamster model
- In the colon *C. difficile* growth and toxin production are influenced by
  - Secondary bile acids
  - Amino acids and their metabolites (Proline, Tryptophan, Indoles)
  - Carbohydrates
  - Free fatty acids
  - Oxygen tension
  - Integrity of mucus layer

Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**SCFA: Short chain fatty acids**


What to Make of Controlled FMT trials?

<table>
<thead>
<tr>
<th>Participants (Mean Age, yr)</th>
<th>Antibiotics Prior to FMT (days)</th>
<th>Intervention Modality</th>
<th>N FMT Comparator</th>
<th>Efficacy 1 Treatment (%)</th>
<th>Efficacy &gt; 1 Treatment (%)</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>73.6</td>
<td>63</td>
<td>NGT</td>
<td>16 FMT 13 VAN</td>
<td>81 31</td>
<td>94 ND</td>
<td>Van Nood 2013</td>
</tr>
<tr>
<td>71.7</td>
<td>NR</td>
<td>Colonoscopy</td>
<td>20 FMT 19 VAN</td>
<td>65 23</td>
<td>90 63</td>
<td>Cammarota 2015</td>
</tr>
<tr>
<td>76.7</td>
<td>10-15</td>
<td>Fecal Enema</td>
<td>16 FMT/12 Van</td>
<td>44 58</td>
<td>ND</td>
<td>Hota 2017</td>
</tr>
<tr>
<td>68.4</td>
<td>NR</td>
<td>Colonoscopy or NGT</td>
<td>24 FMT 24 FDX 16 VAN</td>
<td>71 FMT 33 FDX 16 VAN</td>
<td>ND</td>
<td>Hvas 2019</td>
</tr>
</tbody>
</table>

NR: Not reported, ND: not done

Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**FMT Trials on Delivery Methods and Preparations**

<table>
<thead>
<tr>
<th>Participants (Mean Age, yr)</th>
<th>Antibiotics Prior to FMT (t)</th>
<th>Intervention Modality</th>
<th>N FMT Comparator</th>
<th>Efficacy 1 Treatment (%)</th>
<th>Efficacy &gt; 1 Treatment (%)</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 59</td>
<td>NR</td>
<td>Frozen NGT Frozen Colonoscopy</td>
<td>10 10</td>
<td>60 83</td>
<td>80 100</td>
<td>Youngster 2014</td>
</tr>
<tr>
<td>73 811 days</td>
<td></td>
<td>Frozen Enema Frozen Fresh</td>
<td>108 111</td>
<td>53 51</td>
<td>91 86</td>
<td>Lee 2016</td>
</tr>
<tr>
<td>48 55</td>
<td>6-140 wk</td>
<td>Donor colonoscopy Auto colonoscopy</td>
<td>22 24</td>
<td>91 63</td>
<td>ND</td>
<td>Kelly 2016</td>
</tr>
<tr>
<td>75 62 63</td>
<td>NR</td>
<td>Frozen colonoscopy Lyophilized colonoscopy</td>
<td>25 24 23</td>
<td>100 83 75</td>
<td>ND</td>
<td>Jiang 2017</td>
</tr>
<tr>
<td>59 57</td>
<td>1.7-3.8 mo</td>
<td>Frozen capsules</td>
<td>57 59</td>
<td>96 96</td>
<td>ND</td>
<td>Kao 2017</td>
</tr>
<tr>
<td>75 74</td>
<td>NR</td>
<td>Single Donor Colo Multiple Donor Colo</td>
<td>28 28</td>
<td>75 100</td>
<td>100 100</td>
<td>Ianiero 2018</td>
</tr>
</tbody>
</table>

**FMT Risks are Small, Few SAE’s to Date**

- Post infusion symptoms (vomiting, bloating, pain, flatulence)
- Bacterial translocation in immunocompromised hosts
- Transmission of potential pathogens or MDR organisms
- Transmission of carcinogenic bacteria (*pks*-positive *E. coli, BFT *Bacteroides, Fusobacterium*)
- Risks associated with sedation such as aspiration, death
- Off target effects such as obesity, altered hair growth, IBD exacerbations
- Unknown long term effects (autoimmune, neurologic)
- Not FDA approved, done under local IND/IRB overview

SAE: Serious adverse events; MDR: Multidrug resistant; IBD: Inflammatory bowel disease; IND: Investigational new drug; IRB: Institutional review board

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FMT Areas of Uncertainty

- Optimal composition: amount, complexity of communities, anaerobic
- Timing. First vs. subsequent recurrences
- Pretreatment (taper, pulse prior to FMT or not)
- Donor selection
  - Regular, pre-identified, screened donors
  - Stool banks
  - Heterologous > autologous
- Optimal route of delivery
  - Oral, nasogastric, rectal enema, colonoscopy
  - Fresh, frozen, lyophilized
  - Frequency
- Risk/benefit in special populations
- How to regulate/standardize FMT products

FMT and CDI Guidelines

- 2013 - FMT included as an option for rCDI in U.S guidelines
- 2014 – FMT included as an option for rCDI in U.S Guidelines
- 2017 - European consensus conference: rCDI and refractory CDI
- 2018 – IDSA and SHEA guidelines FMT strongly recommended for rCDI
- 2018 – FMT for severe refractory CDI
Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

### FMT Benefits

- Effective, Simple
- Rapid response
- Inexpensive, cost efficient
- Well tolerated
- Low rate of episodes of CDI associated bacteremia
- Patient satisfaction
- Low rate of recurrences
- Endorsed by CDI guidelines
- Commercial standardized products are around the corner

### Pro-Antimicrobials/Biologics
Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

**Remember: Bad things happen when you don’t use antibiotics for CDI!**

- Toxigenic culture positive
- Persistent diarrhea

Indication trial (1978): Randomized controlled trial of vancomycin 125 mg orally four times daily vs. placebo for five days


**Update to 2019: Antibiotics are still needed!**

**Tolevamer Phase III RCT**


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Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

...and we are only getting to the bottom of how these drugs prevent recurrence

Outgrowth of *C. difficile* spores after 1hr exposure to fidaxomicin-bodipy followed by 5 washes prior to 48hr incubation with bile salts.

Fidaxomicin-bodipy is associated with *C. difficile* spore outer layer from three different ribotypes (027, 012, 078). Green: fidaxomicin-bodipy, red: FM4-64, 63X magnification, confocal imaging.

We can focus on primary prophylaxis and secondary prophylaxis (= prevention of recurrent CDI)

C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (1). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (2).

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Primary CDI prophylaxis with fidaxomicin is not that far fetched

Double-blind, randomized controlled study of 600 subjects undergoing HSCT with fluoroquinolone prophylaxis stratified by transplant type (autologous/allogeneic). **Once-daily** oral fidaxomicin (200 mg) or a matching placebo for up to 40 days.


Bezlotoxumab may be even better
(one time infusion has a half life of 3-months (approx.))

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Strategies for Prevention and Treatment of Recurrent *C. difficile* Infection

It is actually getting easier to figure out who to give these (expensive) therapies to (secondary prophylaxis):

- Participants With CDI Recurrence, %
- Bezlo Placebo
- Age ≥65 y Hx CDI (within 6 months)
- Immunocompromised Severe CDI (Zar criteria)
- RT 027/078/244

<table>
<thead>
<tr>
<th>Age ≥65 y</th>
<th>Bezlo</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx CDI (within 6 months)</td>
<td>19.3 39.4</td>
<td>31.6 49.5</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>26.0 41.1</td>
<td>36.0 60.0</td>
</tr>
<tr>
<td>Severe CDI (Zar criteria)</td>
<td>19.0 36.0</td>
<td>15.9 31.5</td>
</tr>
<tr>
<td>RT 027/078/244</td>
<td>28.2 41.1</td>
<td>22.2 37.0</td>
</tr>
</tbody>
</table>


Primary prophylaxis: 30-day risk of CDI among 97,130 hospitalized patients of whom 1,481 developed CDI

<table>
<thead>
<tr>
<th>Individual Antibiotic</th>
<th>OR (ABX Received Y/N)</th>
<th>P-Value</th>
<th>Antibiotic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin/Sulbactam</td>
<td>1.640</td>
<td>0.012</td>
<td>1.7%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1.673</td>
<td>&lt; 0.001</td>
<td>16.1%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1.464</td>
<td>&lt; 0.001</td>
<td>21.8%</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>1.864</td>
<td>&lt; 0.001</td>
<td>3.6%</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2.077</td>
<td>&lt; 0.001</td>
<td>3.2%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1.335</td>
<td>0.020</td>
<td>2.8%</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>1.655</td>
<td>&lt; 0.001</td>
<td>16.6%</td>
</tr>
<tr>
<td>Age</td>
<td>1.009</td>
<td>&lt; 0.001</td>
<td>N/A</td>
</tr>
<tr>
<td>Proton Pump Inhibitor Y/N</td>
<td>1.375</td>
<td>&lt; 0.001</td>
<td>N/A</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>1.208</td>
<td>&lt; 0.001</td>
<td>N/A</td>
</tr>
</tbody>
</table>

OR – odds ratio; ABX - antibiotic


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### Risk of CDI increased from 0.14% to 6.21% in comorbid patients who received high risk antibiotics and a proton pump inhibitor

<table>
<thead>
<tr>
<th>Received High Risk Antibiotic?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Received PPI?</th>
</tr>
</thead>
<tbody>
<tr>
<td>N  Y  N  Y  N  Y  N  Y  N  Y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CDI Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.14 0.58 0.82 0.70 2.31 1.84 0.73 1.33 1.30 2.59 4.04 6.21</td>
</tr>
</tbody>
</table>

- Independent of receipt of high risk antibiotic, more severe Charlson comorbidity index increases CDI risk

---

### Cumulative Risk Index Score and Corresponding CDI Incidence Rate

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Derivation cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDI (-), n</td>
<td>16628</td>
<td>5233</td>
<td>7088</td>
<td>9939</td>
<td>14089</td>
<td>12727</td>
<td>6277</td>
<td>1942</td>
<td>405</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>CDI (+), n</td>
<td>14</td>
<td>19</td>
<td>63</td>
<td>110</td>
<td>208</td>
<td>287</td>
<td>295</td>
<td>132</td>
<td>33</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>CDI Incidence (%)</td>
<td>0.1</td>
<td>0.4</td>
<td>0.9</td>
<td>1.1</td>
<td>1.5</td>
<td>2.2</td>
<td>4.5</td>
<td>6.4</td>
<td>7.5</td>
<td>20.4</td>
<td>0</td>
</tr>
</tbody>
</table>

|       |   |   |   |   |   |   |   |   |   |   |    |
| Validation cohort |   |   |   |   |   |   |   |   |   |   |    |
| CDI (-), n | - | 5250 | 2488 | 3092 | 4361 | 3747 | 1721 | 505 | 104 | 8 | - |
| CDI (+), n | - | 1 | 8 | 25 | 74 | 83 | 71 | 38 | 7 | 2 | - |
| CDI Incidence (%) | - | 0.0 | 0.3 | 0.8 | 1.7 | 2.2 | 4.0 | 7.0 | 6.3 | 20.0 | - |
There are antibiotics in the pipeline that cause even less disruption of the microbiota.

Ridinilazole
Vancomycin


It is true with CDI that you may eventually need a FMT.

Boston, USA: Decreased microbiome diversity observed in patients with recurrent CDI.

But many patients with primary CDI do not have a profound microbiome disruption

These patients should be able to regenerate their own microbiome if we don’t continue to give them high-risk antibiotics and continue the dysbiosis

I would rather regenerate my own microbiota than rely on someone else!

Probiotics delayed recovery of the microbiome compared with spontaneous recovery
AutoFMT was the fastest but usually not applicable in patients with CDI

Drugs (and monoclonal antibodies) are good!

- Disruption of the microbiome is a hallmark of CDI
- But....... this doesn’t mean we need to infuse another persons poop into our patients
  - Primary prophylaxis efficacy has been seen with fidaxomicin (bezlotoxumab really good from a theoretical standpoint)
  - We already know high risk populations (HSCT) and other at-risk populations are becoming more clear
  - Restoration of the microbiome is still in its infancy, we still have lots to learn

REBUTTALS: FMT vs. DRUGS
Key Takeaways

- Key Takeaway #1 – An aging population with frequent health care contacts and exposure to antibiotics, proton pump inhibitors, hypervirulent strains and the use of sensitive rapid diagnostic tests are driving increasing rates of rCDI worldwide
- Key Takeaway #2 – Restoring a rich and diverse microbiome is a vital strategy in preventing rCDI
- Key Takeaway #3 – Newer agents with increased selectivity for *C. difficile* and low collateral microbiome disruption are associated with fewer rCDI
- Key takeaway #4 – Passive immunization with monoclonal antibodies to toxin B is most effective in elderly, immunocompromised patients not infected with hypervirulent strains

Which of these practice changes will you consider making?

- Educate team members on the identification of risk factors that place patients at risk of recurrent CDI
- Educate team members on the emerging and current treatment options for managing patients with recurrent CDI
- Incorporate most current evidence-based guidelines into practice when treating patients with recurrent CDI
- Collaborate with other healthcare professionals to formulate care plans for treating patients with recurrent CDI
- Collaborate with other healthcare professionals to develop strategies to prevent recurrent CDI in patients

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Thank you for joining us!

Claim CE at elearning.org
✓ Deadline: January 31
✓ Code: __________
✓ Complete evaluation
✓ See instructions in handout

Please leave keypads on the chair 😊

For more on this topic visit
www.ashpadvantage.com/preventcdiff
Claiming CE Credit

1. Login to the ASHP eLearning Portal at http://elearning.ashp.org/ with the email address and password that you used when registering for the Midyear. The system validates your meeting registration to grant you access to claim credit.

2. Click on Process CE for the Midyear Clinical Meeting and Exhibition.

3. Enter the Attendance Codes that were announced during the sessions and click Submit.

4. Click Claim for any session.

5. Complete the Evaluation.

6. Once all requirements are complete, click Claim Credit for the appropriate profession.
   - Pharmacists and Pharmacy Technicians: Be prepared to provide your NABP eProfile ID, birth month and date (required in order for ASHP to submit your credits to CPE Monitor).
   - Others (International, students, etc.). Select ASHP Statement of Completion.

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2. Click on the Get Started button.

3. Select the 2019 Midyear Clinical Meeting and Exhibition from the dropdown menu.

4. Select your Exhibiting Company from the list of exhibitors. Your screen will change and you will be then be logged into the ASHP eLearning Portal.

5. Follow the instructions in the section above this, starting with Step Two.

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1. Visit http://elearning.ashp.org, log in or follow the steps to register, and click on My Activities.

2. Enter the Enrollment Code announced during the webinar in the Enrollment Code box and click Redeem. The title of this activity will appear in a pop-up box on your screen. Click on Go or the activity title.

3. Complete all required elements. Go to Step Six above.

Questions? Contact EducServ@ashp.org!
About the Faculty

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Professor and Chair
Department of Clinical Sciences and Administration
University of Houston College of Pharmacy
Houston, Texas

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Dr. Garey is an Adjunct Professor
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Dalhousie University in Halifax, Nova Scotia, Canada, a Doctor
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University of Texas School of Public Health in Austin, Texas.
He completed a pharmacy practice residency at Bassett
Healthcare, Cooperstown, New York and infectious disease
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Dr. Garey has numerous publications in infectious diseases
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international professional conferences. He has received
numerous professional awards including the ASHP Drug
Therapy Research Award, ASHP Best Practices Award in
Health-System Pharmacy, the Society of Infectious
Diseases Pharmacists Impact Paper in Infectious Diseases
Pharmacotherapy Award and the University of Houston
Faculty Leadership award. He is a Fellow of ASHP.

Dr. Garey’s research interests involve clinical and
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Escherichia coli and C. difficile in immunocompro-
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Dr. Okhuysen has served on the board of scientific
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NASA. He has served on the Infectious Diseases
Society of America Publications and Research
Awards Committees and was awarded the
Oswald Avery Award for Early Achievement by the
Infectious Diseases Society of America in 2007.
He has repeatedly received the best teacher award
from fellows in the McGovern and BCM fellowship
programs. In 2018, Dr. Okhuysen received the
UT MDACC Division of Internal Medicine Faculty
Excellence Award.

Additional Activities on Managing Recurrent C. diff Coming Soon
- On-demand activity of today’s live symposium
- Ask the Experts Webinar based on questions from today’s activity
- Expert Interviews

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