**Clostridium difficile Infection: A Review of Treatment Options and Preventative Measures**

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SEPTEMBER 29, 2017

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**Learning Objectives**

- Identify risk factors for primary and recurrent *Clostridium difficile* infection (CDI).
- Recommend an appropriate empiric antimicrobial regimen based on *Clostridium difficile* infection severity.
- Discuss the role of the gut microbiome and its relation to CDI.
- Identify the agents available that show promise for the reduction of recurrent CDI

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**Clostridium difficile Pathogenesis**

- Gram-positive, anaerobic, spore-forming bacillus
- Generally exists as a spore in nature but can change to toxin-producing form (vegetative)
- Enterotoxins A&B damage the intestinal mucosa, causing inflammation and characteristic CDI-associated symptoms
- Disruption of gut microbiome is highly associated with *Clostridium difficile* infection
  - 96% of symptomatic patients received antimicrobials within 14 days of diarrhea according to one study
Infection vs Colonization

- Colonization, rather than actual infection with *Clostridium difficile* is not uncommon
- Defined as positive test for *Clostridium difficile* but absence of symptoms

Clostridium difficile Infection

- 2009 data from the Agency for Healthcare Research and Quality indicates that for patients with any CDI diagnosis:
  - 12.8% were readmitted with CDI within 30 days
  - 17.2% were readmitted with CDI within 90 days
  - Nearly 50% of patients diagnosed with CDI were readmitted for any cause within 90 days

Clostridium difficile Infection

- According to a study recently published in NEJM:
  - CDI was responsible for nearly 500,000 infections and associated with 29,000 deaths in 2011
  - Especially harmful in patients ≥65 y/o with healthcare onset
    - ~25% developed recurrence in 14 to 56 days
    - ~12% died within 30 days of initial diagnosis
Risk Factors for CDI

• Acquisition
  o Exposure to *Clostridium difficile*
    - Healthcare settings
    o Acute and long-term care
    o Transmission due to poor infection control practices
    o Poor hand hygiene
    o Failure to follow isolation protocols
    o Inadequate sterilization of equipment

• Disruption of the gut microbiome
  o Antibiotic exposure
  o Advanced age
  o Acid suppressing drugs (especially proton pump inhibitors)
  o Cancer chemotherapy and other immunosuppressants
  o Gastrointestinal surgery or manipulation of the GI tract
  o Tube feeding

Antibiotic Risk

• Exposure to antibiotics increases CDI risk up to 3 months
• The number of antibiotics (abx) prescribed increases CDI rate
  o A study measuring antibiotic exposure and risk of CDI up to 60 days after discharge (with 1 antibiotic as reference) had a hazard ratio of:
    - 2.5 for exposure to 2 abx
    - 3.3 for exposure to 3 or 4 abx
    - 9.6 for exposure to 5 or more abx
• Although nearly all antibiotics can cause CDI, fluoroquinolones, cephalosporins, clindamycin, and other broad spectrum antibiotics are most frequently associated.

The Human Gut Microbiome

• Human gut microbiome consists of up to 35,000 bacterial species
• Function of normal microbiome includes
  o Nutrient metabolism
  o Drug metabolism
  o Antimicrobial protection
    o Prevents overgrowth of pathogenic strains
  o Immunomodulation
  o Maintaining integrity of the gut barrier and structure of gastrointestinal tract
The Human Gut Microbiome

- Diseases associated with alterations in the microbiome:
  - Irritable bowel syndrome
  - Inflammatory bowel disease
  - Obesity and type 2 diabetes mellitus
  - Colorectal cancer
  - *Clostridium difficile* infection

Clinical Presentation

- **Mild-moderate CDI**
  - Diarrhea
  - Abdominal cramps
  - Fever
  - Leukocytosis
  - Colitis

- **Severe CDI**
  - Paralytic ileus/bowel perforation
  - Hypoalbuminemia
  - Electrolyte disturbances
  - Renal failure
  - Sepsis
Diagnosis and Testing

- Presence of symptoms (3 or more cases of watery diarrhea/unformed stool required)
- Positive diagnostic test
  - Nucleic acid amplification test (NAAT) for toxin genes such as polymerase chain reaction (PCR) deemed superior for detection
    - But may be oversensitive, detecting colonization as well
  - Two-step testing (glutamate dehydrogenase) followed by toxin A and B enzyme immunoassay may also be performed, but less sensitive

Infect Control Hosp Epidemiol 2010;31(5):431-55

Diagnosis and Testing

- Repeat testing strongly discouraged
  - <5% of repeat tests are positive after an initial negative
- Test of cure should not be performed
  - Toxin can be found in stool up to 30 days after resolution of symptoms


Testing Pitfalls and Considerations

- Only 20-30% of antibiotic associated diarrhea is CDI
- Significant percentage of patients are colonized, especially in acute healthcare and long term care facility settings
- Patients frequently receive drugs that cause diarrhea on their own
  - Laxatives
  - Chemotherapeutic agents
  - Proton pump inhibitors
  - Drugs in liquid form (containing sorbitol, etc)
  - Antibiotics
    - Did the antibiotic cause Clostridium difficile infection or just cause diarrhea in a patient colonized with Clostridium difficile?
    - Symptomatology beyond diarrhea should be considered when possible
### Treatment Options - Metronidazole

#### Advantages
- Cost
- Non-inferior to vancomycin for mild-moderate CDI

#### Limitations
- Treatment failures increased from 3% to >18% since 2000
- Limited fecal concentrations
- Dose-dependent peripheral neuropathy, neurotoxicity
- Side effects
- Inferior to vancomycin for severe CDI
- Drug interactions
- Recurrence rate ≥20%

### Treatment Options - Vancomycin

#### Advantages
- High fecal concentrations
- Effective for mild-severe CDI
- FDA-approved standard of care
- Limited side effects

#### Limitations
- Cost
- Recurrence rate ≥20%
- Possible overgrowth of vancomycin-resistant enterococcus
### Treatment Options - Fidaxomicin

#### Advantages
- Limited activity against normal GI flora
- Post-antibiotic effect
- Blocks gene transcription and thus toxin production
- Limited side effects
- Improved response rate for patients on concurrent antibiotics

#### Limitations
- Cost!
  - Much more expensive than oral vancomycin
- Recurrence rates similar to vancomycin for NAP1/B1/027 strains
- Efficacy for patients with multiple recurrences

### NAP1/B1/027 vs non-NAP1 isolates

- Compared with non-NAP1 isolates, NAP1 strains exhibit
  - Hypervirulence
  - Increased production of toxins A&B, as well as a binary toxin
  - High-level fluoroquinolone resistance
  - And more associated with fluoroquinolone exposure
  - Increased risk of severe disease, severe outcome, and mortality
  - Increased risk for recurrence

### Recurrent CDI

- Up to 25% of patients will have recurrence within 30 days after completion of therapy
- After the first recurrence, risk of further recurrences is 40-65%
- Likely primarily due to altered colonic microbiota and remaining spores
- Treatment options and courses of therapy become more complicated with multiple recurrences
Recurrent CDI

- Risk factors
  - Age ≥65
  - Fluoroquinolone or other high risk antimicrobial exposure
  - Proton pump inhibitors
  - Community-onset, healthcare-associated CDI
  - >1 hospitalization within 60 days
  - BI/NAP1/027 strain
  - Severe underlying disease
  - Immunosuppression
  - Previous recurrence of CDI

Treatment of Recurrent CDI

- First recurrence
  - Same agent used initially

- Second recurrence
  - Pulsed/tapered dosing (usually oral vancomycin)
    - Example: oral vancomycin 125 mg QID x 10 days, followed by BID x 7 days, daily 7 days, etc

- 3 or more recurrences
  - Pulsed/tapered dosing of vancomycin
  - Fecal transplant

Fecal Transplant

- Transplant of stool from a healthy donor to a patient with CDI
- Studies appear to show high degree of efficacy, but long-term follow up is limited
  - Brandt, et al showed primary cure rate of 91%, secondary cure rate of 98%
  - Systematic review by Gough, et al had resolution rate of 89% after 1 treatment (Kassam and colleagues showed a near identical cure rate)
  - Several (very) small recent studies have not found fecal transplant to be more efficacious than standard therapy
Other Potential Options

- **Fidaxomicin**
  - Macrolide antibiotic that has comparatively minimal effect on normal flora of colon
  - Selective favorable data for lower rates of recurrence as primary CDI regimen

- **Bezlotoxumab**
  - Human monoclonal antibody that binds to *Clostridium difficile* toxin B
  - Approved for reduction of recurrence in high-risk patients
  - Is NOT approved for treatment of CDI
    - Adjunctive only

Fidaxomicin

- Compared with oral vancomycin had a recurrence rate of 15.4% vs 25.3% (first episode)
  - Driven by non NAP1 CDI
- For treatment of first recurrence:
  - 19.7% second recurrence rate for fidaxomicin vs 35.5% for vancomycin in per protocol analysis
  - Both groups had >90% initial clinical cure rate
  - Included NAP1 patients

Bezlotoxumab

- Evidence of superiority for prevention of recurrence compared with placebo (absolute risk reduction):
  - MODIFY I: 17% vs 28% for placebo
  - MODIFY II: 16% vs 26% for placebo
- Even greater impact in the following groups:
  - Age ≥65 (16% ARR, 51% RRR)
  - ≥1 recurrence in past 6 months (16.1% ARR, 39.2% RRR)
- Smaller absolute risk reduction in:
  - No CDI in past 6 months (7.4% ARR, but 35.5% RRR)
    - Recurrence rate of 13.5% vs 20.9%
Prevention of *Clostridium difficile* Infection

- **Improve environmental factors**
  - Isolation compliance
  - Hand hygiene (handwashing, not alcohol foam or liquid)
  - Equipment sterilization procedures
  - UV light technology
    - Kills a number of bacteria including *Clostridium difficile*, VRE, and MRSA, as well as other organisms
    - A study done in hematology/oncology units showed an incidence rate ratio of 0.48 compared with non-study units.

- **Reduce modifiable risk factors**
  - De-escalate from high-risk antibiotics when able
  - Reduce antibiotic duration
  - Reduce number of antibiotics
  - Minimize acid-suppressing drugs as able

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*Clostridium difficile* Infection Risk Factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A+ (no.)</th>
<th>A− (no.)</th>
<th>Code-based rate*</th>
<th>Adjusted code-based rate*</th>
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<tbody>
<tr>
<td>Defined daily dose, median (IQR)</td>
<td>18 (7)</td>
<td>162 (57)</td>
<td>Ref</td>
<td>Ref</td>
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<tr>
<td>&lt;7.5</td>
<td>18 (7)</td>
<td>162 (57)</td>
<td>1.1 (1.5, 4.8)</td>
<td>1.1 (1.5, 4.8)</td>
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<td>7.6 to 17.9</td>
<td>09 (37)</td>
<td>296 (127)</td>
<td>1.1 (3.0, 4.9)</td>
<td>1.1 (3.0, 4.9)</td>
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<tr>
<td>≥18.0</td>
<td>08 (35)</td>
<td>175 (78)</td>
<td>5.5 (2.6, 9.0)</td>
<td>5.5 (2.6, 9.0)</td>
</tr>
<tr>
<td>Antibiotic days, median (IQR)</td>
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<td>2.0 (1.3)</td>
<td>Ref</td>
<td>Ref</td>
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<tr>
<td>&lt;4</td>
<td>06 (24)</td>
<td>231 (97)</td>
<td>1.1 (2.8, 4.6)</td>
<td>1.1 (2.8, 4.6)</td>
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<td>4.1 to 7</td>
<td>41 (17)</td>
<td>303 (123)</td>
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<td>1.5 (3.8, 7.4)</td>
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<tr>
<td>8.1 to 15</td>
<td>37 (16)</td>
<td>307 (121)</td>
<td>5.5 (2.1, 9.0)</td>
<td>5.5 (2.1, 9.0)</td>
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<td>≥16</td>
<td>91 (35)</td>
<td>147 (76)</td>
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<td>5.5 (2.6, 9.0)</td>
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<td>Number of antibiotics, median (IQR)</td>
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<td>2 (1)</td>
<td>Ref</td>
<td>Ref</td>
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<tr>
<td>3</td>
<td>34 (15)</td>
<td>267 (106)</td>
<td>3.7 (1.6, 8.3)</td>
<td>3.7 (1.6, 8.3)</td>
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<tr>
<td>4 or 5</td>
<td>54 (24)</td>
<td>476 (201)</td>
<td>3.7 (1.6, 8.3)</td>
<td>3.7 (1.6, 8.3)</td>
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<tr>
<td>5 or more</td>
<td>80 (30)</td>
<td>1157 (452)</td>
<td>11.6 (7.7, 17.4)</td>
<td>11.6 (7.7, 17.4)</td>
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Prevention of *Clostridium difficile* Infection

• Probiotics:
  o Proposed benefits:
    ▪ Stimulate host immune function
    ▪ Prevent invasion of GI mucosa by pathogenic flora
    ▪ Compete with *C. difficile* for nutrients
  o Literature mixed for evidence of efficacy
  o Multi-strain appears to be more effective than single strain
  o Current guidelines do not recommend routine use for CDI prevention based on current evidence
    ▪ Last guideline update was in 2013, and current updates are underway.

2013 Cochrane Review
Conclusions

- *Clostridium difficile* is a potentially deadly infection that arises from disruption of gut microbiome
  - Especially consequential in patients ≥65
- Recurrence rate of *C. difficile* can range from 20-25% for first recurrence to 40-65% for additional recurrences despite guideline-recommended therapies
- Several recent advances in therapy may have a role in preventing recurrence compared with standard therapies
- Minimization of disruption of gut microbiome is critical to prevent initial and recurrent infections with *C. difficile*

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