Prevention and Management of Clostridium Difficile Infection (CDI): The Latest Game Changer to Clinical Practice

Brandon Bookstaver, PharmD, FCCP, FIDSA, BCPS, AAHIVP

Live Activity Handout

2 slides per page

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Prevention and Management of Clostridium Difficile Infection (CDI): The Latest Game Changer to Clinical Practice

ACTIVITY DESCRIPTION
Clostridium difficile infection (CDI) accounts for nearly a half of a million cases annually. Recent guideline updates have occurred leading to changes in guideline preferred regimens for the treatment of CDI. Pharmacists should be aware of these guideline updates. This activity will review some of the more significant changes, identify primary and secondary prophylactic strategies for prevention of CDI, and explore the role of new and emerging therapies.

TARGET AUDIENCE
The target audience for this activity is pharmacists and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:
- Recognize the pathophysiology and current epidemiology of Clostridium difficile infection (CDI)
- Identify appropriate guideline-preferred regimens for CDI treatment.
- Identify prophylactic strategies available for primary and secondary CDI prevention.
- Recognize the role for new and emerging CDI treatment and prevention therapies.

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ACTIVITY TYPE
Knowledge-Based Live Webinar

FINANCIAL SUPPORT BY
Merck & Co., Inc.
Brandon Bookstaver, PharmD, FCCP, FIDSA, BCPS, AAHIVP
Associate Professor, Director of Residency & Fellowship Training,
University of South Carolina SC College of Pharmacy

ABOUT THE AUTHOR
Dr. Brandon Bookstaver is an Associate Professor and Director of Residency and Fellowship Training in the Department of Clinical Pharmacy and Outcomes Sciences at the South Carolina College of Pharmacy, University of South Carolina (USC). Following graduation from the USC College of Pharmacy, he completed PGY1 and PGY2 residencies at Wake Forest University Baptist Medical Center, specializing in Infectious Diseases (ID). Brandon serves as an ID pharmacist at Palmetto Health Richland and director of an ID PGY2 residency and clinical fellowship program. He has over 50 peer-reviewed publications in various areas of ID including antimicrobial stewardship, HIV-related outcomes, hospital-acquired infections including Clostridium difficile, and trainee-related research. He is the co-founder and director of the research network Southeastern Research Group Endeavor (SERGE-45). During his free time, he enjoys spending time with his wife Nicole and baby boy Aaron, running, traveling, and Gamecock athletics.

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Faculty: Brandon Bookstaver, PharmD, BCPS, FCCP, FIDSA

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Conflict of Interest & Disclosures

- Advisory board member for CutisPharma®
- Research consultant for Synthetic Biologics®
- Speaker’s bureau member and advisory board for Melinta Therapeutics®
- Grant recipient from ALK Abello Inc.
- Core faculty for Penicillin Allergy Assessment and Skin Testing Certificate Program

Learning Objectives

- Recognize the pathophysiology and current epidemiology of Clostridium difficile infection (CDI)
- Identify appropriate guideline-preferred regimens for CDI treatment
- Identify prophylactic strategies available for both primary and secondary CDI prevention
- Recognize the role for new and emerging CDI treatment prevention strategies
Increasing Incidence

1-3% of healthy adults are colonized

Lessa FC et al. NEJM. 2015; 72(9): 825-834.
Increasing Incidence

- 1-3% of healthy adults are colonized
- 453,000 cases in LTCF and US hospitals annually
- Results in 29,000 deaths

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Median LOS is 2.8-16.1 days

Increasing Incidence

1-3% of healthy adults are colonized
453,000 cases in LTCF and US hospitals annually
Results in 29,000 deaths
Median LOS is 2.8-16.1 days
Increase continues to grow in community, while in some places we may be seeing a plateauing in hospital onset
History of *C. Difficile* Colitis

- **1966** – Pseudomembranous colitis (PMC) associated with *S. aureus*; treated with oral vancomycin
- **1974** – “New” form of antibiotic associated diarrhea & colitis (predominantly clindamycin), however *S. aureus* not isolated
- **1978** – *Clostridium difficile* identified as etiologic agent
- **2016/2018** – *Clostridium difficile* officially reclassified and renamed as *Clostridioides difficile*


How Does *C. Difficile* Infection (CDI) Occur?

Dysbiosis

- Normal microbiota
- Antibiotics lead to loss of colonization resistance
- Susceptible microbiota
- *C. difficile* spores
- Sporulation
- Vegetative *C. difficile*
- toxin production
- *C. difficile* infection

Available at: https://sites.google.com/a/umich.edu/younglab/research-interests
Risk Factors of Initial CDI

- Antibiotics
  - High risk vs low risk
- Acid suppressing agents
  - PPI vs H2A
- Immunosuppression
  - SOT, BMT
- End stage renal disease
  - HD dependent

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- Age
  - >65? >75? >80?

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  - Female, especially in community-onset disease
  - Mechanical ventilation

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- Age
  - >65? >75? >80?
- Female, especially in community-onset disease
- Mechanical ventilation
- Recent hospital admission
  - Past 60 days

Differential Risk of CDI with Proton Pump Inhibitor Use by Level of Antibiotic Exposure

In 10,479 hospital admissions – PPI increased risk across board in patients on antibiotics.

**Increased risk in patients on ‘low risk’ antibiotics


Antibiotics as Risk Factors

- High-Moderate Risk
  - Clindamycin*
  - Fluoroquinolones
  - Carbapenems
  - Penicillins (+BLI)
- 2nd- & 3rd-Generation Cephalosporins


# Antibiotics as Risk Factors

## High-Moderate Risk
- Clindamycin*
- Fluoroquinolones
- Carbapenems
- Penicillins (+BLI)
- 2nd- & 3rd-Generation Cephalosporins

## Low Risk
- Tetracyclines
- Vancomycin
- Metronidazole
- Linezolid
- Nitrofurantoin
- SMX/TMP

*Additive risks? -- yes likely

*Historically – clindamycin greatest association

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Intersection of Community Onset CDI and Gender

So why the gap in rates of CDI?
Adjusted CDI Rates By Antibiotic Prescriptions

Bottom line:
More antibiotic prescriptions in the community may explain higher incidence in females.

C. difficile Virulence

• Gram-positive anaerobe, spore-forming
  • Infection generally secondary to disrupted normal gut flora

• Toxin A ("enterotoxin") and Toxin B ("cytotoxin")
  • Binary toxin, adhesion factor, and hyaluronidase
  • Pathogenicity Locus (PaLoc) – tcdA and tcdB primarily responsible for encoding of toxins A and B
  • Very possible to have non-toxigenic strains that leads to colonization not infection --- careful on detection

• Ribotyping available to further identify strains
  • Some have greater virulence
**C. difficile** Virulence

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**Recurrent CDI: A Big Issue**

- Initial CDI episode: ~500,000 cases/yr
  - First recurrence: ~20%
  - Second recurrence: ~40%
  - Third or greater recurrence aka “vanc dependent patient”: >60%

**Risk factors**

- Age (eg >75)
- Residence at SNF
- SOT/HSCT recipients
- Multiple co-morbid conditions
- Concomitant antibiotics during initial episode
- Receipt of subsequent course of systemic antibiotic therapy
- Management in outpatient setting

**Risk assessment scores to predict, but none are ready for primetime yet**


**C. difficile strains**
- Toxin A-/B+
- Toxin A+/B-
- Toxin A+/B+
- Binary toxin (3-5%)
Laboratory Diagnosis of *Clostridium difficile* Infections

- Test only patients with **risk factors AND clinical significant diarrhea** (>3 unformed bowel movements / 24 hour period)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Significance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current antibiotics</td>
<td>High</td>
<td>High risk vs low risk agents</td>
</tr>
<tr>
<td>Antibiotics in prior 60-90 days</td>
<td>Moderate</td>
<td>Assessment of antibiotic history is critical</td>
</tr>
<tr>
<td>&gt; 3 BMs / 24 hrs</td>
<td>Case definition</td>
<td>CDI severity correlated with # of BMs</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>High</td>
<td>CDI severity correlation</td>
</tr>
<tr>
<td>SCr &gt; 1.5 times normal</td>
<td>Moderate</td>
<td>CDI-associated renal disease</td>
</tr>
<tr>
<td>Decreasing albumin</td>
<td>Moderate</td>
<td>CDI-associated protein loss</td>
</tr>
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Diagnostic Stewardship for CDI

1) Only test loose/liquid stools (Brecher guidelines)
2) Only test patients with >3 unformed stools plus risk factors
3) Rule-out other reasons for diarrhea in clinically stable patients (eg laxatives, tube feeds)
4) Perform single molecular testing or 2-/3-step algorithm with GDH screening
5) No more than 1 test per week
6) If multiplex available, avoid duplication with individual *C. difficile* tests
7) Do not perform test of cure
8) Stewards (eg Pharmacists, MDs, RNs, etc) should be involved in local *C. difficile* “committees”

### Severity of Disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>IDSA/SHEA Guidelines</th>
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<tbody>
<tr>
<td><strong>Mild/Moderate (aka Non-Severe)</strong></td>
<td>WBC &lt; 15,000 cells/mm³ and SCr &lt; 1.5x pre-CDI level</td>
<td>Serum albumin ≥ 3 g/dL or WBC ≤ 15,000 cells/mm³ and absence of abdominal tenderness</td>
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<td><strong>Severe</strong></td>
<td>WBC ≥ 15,000 cells/mm³ or SCr ≥ 1.5x pre-CDI level</td>
<td>Serum albumin &lt; 3 g/dL PLUS WBC &gt; 15,000 cells/mm³ or abdominal tenderness</td>
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<td><strong>Complicated/Critically Ill/Fulminant disease</strong></td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Attritable to CDI: Admission to ICU, hypotension, T &gt; 38.5°C, ileus/abdominal distention, MS changes, WBC &gt; 35,000 or &lt; 2,000, lactate &gt; 2.2 mmol/L, or EOD</td>
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Primary Prophylaxis Against CDI

Identify patients at high risk for initial CDI and employ preventative strategies.

- Antimicrobial stewardship principles
  - Early de-escalation of antibiotic therapy
  - Narrowest spectrum/targeted empirical therapy
  - Avoiding high risk antibiotics (or using low risk in combination) when not clinically indicated
- Infection control practices
  - Hand hygiene, terminal cleaning
- Appropriate diagnostic algorithms

YES, these do work!!

Still waiting on data to show these really work

https://www.cdc.gov/hai/prevent/prevention.html

Education of clinicians and patients
- Probiotics
- Adding adjunctive antibiotics in combination that have *C. difficile* activity
- Oral beta-lactamases

Still waiting on data to show these really work

https://www.cdc.gov/hai/prevent/prevention.html
Preventing Recurrence At The Time Of Treatment Of Active CDI

Choice of antimicrobial agents:
- Vancomycin (also inc. taper)
- Fidaxomicin
- Metronidazole
- Adjunctive Bezlotoxumab
- FMT

Therapies on horizon:
- Oral beta-lactamases
- C. difficile vaccine

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<td>Metronidazole (MTR) 500mg TID PO x 10-14 days</td>
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<td>VAN 500mg PO QID + MTR 500mg Q8 hours IV; (VAN PR if complete ileus)</td>
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<tr>
<td><strong>Recurrence</strong></td>
<td>Initial – repeat course Multiple – VAN taper</td>
<td>Initial – VAN taper; FDX course Multiple – VAN taper; VAN+rifaximin; FDX course; or FMT (if 3 CDI episode)</td>
<td>Initial – repeat course; 2nd – VAN pulse dosing; 3rd – Fecal microbiota transplant</td>
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**Clostridium difficile** Infection Treatment United States Guideline Comparison
### Clostridium difficile Infection Treatment

#### United States Guideline Comparison

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### Why the Demotion for Metronidazole?

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<th>Study</th>
<th>Comparator Arms</th>
<th>Primary endpoint</th>
<th>Results</th>
</tr>
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<tr>
<td>Wenisch, et al. Clin Infect Dis 1996</td>
<td>Van 500mg PO TID (n=29) vs. MTR 500mg PO TID (n=29) x 10 d</td>
<td>6-day clinical cure</td>
<td>All: MTR 94% vs. VAN 94% (p&gt;0.05) (*Fusidic acid and teicoplanin arms also high success)</td>
</tr>
<tr>
<td>Design: RCT (open label)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Zar F, et al. Clin Infect Dis 2007</td>
<td>Van 125mg PO QID (n=71) vs. MTR 250mg PO QID (n=79) x 10 d</td>
<td>6-day clinical cure + negative Toxin assay</td>
<td>All: MTR 84% vs VAN 97% (p=0.006)</td>
</tr>
<tr>
<td>Design: RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson S, et al. Clin Infect Dis 2014</td>
<td>Van 125mg PO QID (n=259) vs. MTR 375mg PO Q6hr (n=278) x 10 d</td>
<td>10-day clinical success (&gt;48 consecutive hours)</td>
<td>All: MTR 72.7% vs. VAN 81.1% (p=0.02)</td>
</tr>
<tr>
<td>Design: RCT (Combined analysis of 2 studies)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevens VW, et al. JAMA IM 2017</td>
<td>VAN (n=2068) vs. MTR (n=8069)</td>
<td>30-day all cause mortality</td>
<td>All: MTR 10.6% vs. VAN 8.6% (p=0.01)</td>
</tr>
<tr>
<td>Design: Retrospective , propensity matched cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Examining Clinical Cure Rates: Vancomycin vs. Metronidazole

- Meta-analysis of 9 studies examining metronidazole versus vancomycin
- Quality of evidence
  - 3 High quality
  - 6 Moderate quality

Where Should Fidaxomicin (FDX) Fit in Treatment?

- Two, Phase III RCTs of fidaxomicin (200mg PO twice daily x 10 days) compared to vancomycin 125mg PO QID x 10 days
  - Clinical cure, FDX 88% vs Vanc 87% (P=NS)
  - Cure without recurrence, FDX 71% vs Vanc 57% (P=0.0004) → preserves intestinal microbiome and reduces toxin re-expression
  - Consistent across subgroups of other risk factors as well
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Fidaxomicin Role in Therapy
**Cost Effectiveness Must Be Applied in Decision**

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<tr>
<th>Study Identification</th>
<th>Conditions Studied</th>
<th>Cost Effective?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartsch SM et al. CID 2013</td>
<td>No FDX; FDX only and FDX by strain typing; $50,000/QALY threshold</td>
<td>Not as first-line</td>
</tr>
<tr>
<td>Nathwani D et al. JAC 2014</td>
<td>FDX vs vancomycin, incremental cost-effectiveness ratio (ICER) was primary outcome; $30,000 and $45,000/QALY thresholds</td>
<td>60% for severe 68% first recurrence</td>
</tr>
<tr>
<td>Konijeti GG et al. CID 2014</td>
<td>Recurrent CDI, FDX, MTR, Vanc, FMT; $50,000/QALY threshold</td>
<td>No. FDX &lt;$1,359 would meet threshold</td>
</tr>
<tr>
<td>Stranges PM et al. Value in Health 2013</td>
<td>FDX vs vancomycin, $100,000/QALY threshold</td>
<td>Yes. $67,576/QALY</td>
</tr>
<tr>
<td>Gallagher JC et al. Antimicrob Agents Chemother 2015</td>
<td>FDX vs vancomycin as first-line therapy in 2 US hospitals</td>
<td>Yes, average hospital lost was $6,333 per Vanc treated vs $3,286 per FDX treated</td>
</tr>
</tbody>
</table>
Comparison of Primary Treatment Options

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metronidazole</th>
<th>Vancomycin</th>
<th>Fidaxomicin</th>
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<tbody>
<tr>
<td><strong>Guidelines</strong></td>
<td>IDSA now recommends as alternative unless in combo for critically ill</td>
<td>Preferred for non-severe/severe</td>
<td>Preferred for non-severe/severe</td>
</tr>
<tr>
<td><strong>Toxicity &amp; DDI</strong></td>
<td>CNS toxicity, dygeusia DDI (eg warfarin, EtOH, PEG)</td>
<td>Minimal</td>
<td>Minimal; May be some concern if patient has macrolide allergy</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Three times daily</td>
<td>Four times daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td><strong>Formulations</strong></td>
<td>PO (solution, tablets)</td>
<td>PO (reconstitutable suspension, capsules)</td>
<td>PO (tablets)</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$</td>
<td>$5 - $15</td>
<td>$50</td>
</tr>
<tr>
<td><strong>Impact on clinical cure &amp; recurrence</strong></td>
<td>Reduced cure rates esp in severe; equivalent to VAN for recurrence</td>
<td>Equivalent cure rates to FDX; higher rates of CDI recurrence than FDX</td>
<td>Equivalent cure rates to VAN; lower rates of CDI recurrence than VAN</td>
</tr>
<tr>
<td><strong>Impact on resistance &amp; microbiome</strong></td>
<td>High impact on microbiome; rare but some emerging resistance</td>
<td>Moderate impact on microbiome at CDI doses; no real resistance concerns; ? risk of VRE if used widely</td>
<td>Minimal impact on microbiome; no concern for resistance at this time</td>
</tr>
</tbody>
</table>

Potential Concerns with Therapy

- **ADEs**
  - **Metronidazole**: CNS toxicity – overall rare; primarily manifesting as cerebellar dysfunction (77%) or altered mental status (33%)
    - Median duration 54 days; 11% of ADEs in <72 hours of tx.
  - **Vancomycin**: Highly tolerable, limited GI effects; serum [ ] undetectable except in severe renal dysfunction
  - **Fidaxomicin**: rare; concern with macrolide allergy? (Iarikov DE, et al. CID 2014)

- **Drug-drug interactions**
  - **Metronidazole**: EtOH & EtOH/PEG-based solutions; warfarin
  - **Vancomycin**: Cholestyramine
  - **Fidaxomicin**: None known clinically significant

- **VRE colonization** associated with up to 50% of CDI cases
  - Lack of correlation with drug therapy:
    - Look at the inciting antibiotic (or perhaps chemotherapy) not therapeutic antibiotic
    - Increases during therapy, reduced by 2 weeks post-completion

Resistance Concerns with Metronidazole?

- Resistance / reduced susceptibility (MIC>4mcg/mL) to metronidazole has sporadically been reported

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sensitive (CLSI)</th>
<th>Intermediate</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>≤ 8 mcg/mL</td>
<td>16 mcg/mL</td>
<td>≥ 32 mcg/mL</td>
</tr>
<tr>
<td>(CLSI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>≤ 2 mcg/mL</td>
<td>-</td>
<td>&gt; 2 mcg/mL</td>
</tr>
<tr>
<td>(EUCAST)</td>
<td></td>
<td></td>
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<td>Vancomycin</td>
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- Limited correlation between resistance/reduced susceptibility and outcomes

Testing methods create significant variation in susceptibility testing results

Ex: E-test tend to underestimate MIC values for metronidazole and C. difficile

Available at: http://www.eucast.org/eucast_susceptibility_testing/breakpoints/ (Accessed 1 August 2017)

Poll Question Opening
Poll Question Closing

What Role Does Adherence to Therapy Play?

- First, to my knowledge there are no studies evaluating outpatient adherence to CDI therapy
- Outpatient management significantly higher recurrence rates compared to inpatient management
    - Recurrence ~7.5% higher in Study 301 (~50% outpatient) vs. Study 302 (~8% outpatient)
  - Wilcox MH, et al. NEJM 2017
    - Recurrence 9.5% higher among outpatients
### Challenges to Adherence in CDI Treatment

1. **Cost**
2. **Prior authorizations required**
3. **Access**
   - 49 pharmacies within 9 miles of PHR...guess how many had oral vancomycin or oral fidaxomicin?
4. **Taste** if using oral solution for vancomycin
5. **Asymptomatic** if diarrhea resolved

---

**The Challenges to Adherence in CDI Treatment**

1. **Cost**
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3. **Access**
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5. **Asymptomatic** if diarrhea resolved

---

**Huge opportunity here for transitions of care piece for CDI management!**
Vancomycin is certainly superior to metronidazole for severe disease leading to metronidazole being recommended only as an alternative now (IDSA/SHEA guidelines)
- **Reminder**: ACG guidelines aren’t consistent with IDSA

I believe “mild” disease often represents inappropriate testing
- **Solution** = Improve your testing algorithms + education

Choosing the initial agent should be based on risks for recurrence - very possible to have criteria for 2 or 3 risk factors and then use fidaxomicin to help reduce risk of recurrence and maintain cost effectiveness

Need a plan in place for transitions of care if hospitalized

---

### Management of Recurrence

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<tr>
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<tr>
<td><strong>Mild/Moderate (aka non-severe)</strong></td>
<td>Metronidazole (MTR) 500mg TID PO x 10-14 days</td>
<td>VAN 125mg PO QID or Fidaxomicin (FDX) 200mg PO BID x 10 days (MTR listed as alternative)</td>
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<td><strong>Severe</strong></td>
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<td><strong>Complicated/Critically Ill/Fulminant disease</strong></td>
<td>VAN 500mg PO QID + MTR 500mg Q8 hours IV; (VAN PR if complete ileus)</td>
<td>VAN 500mg PO QID plus MTR 500mg IV Q8hrs (Consider rectal VAN if ileus)</td>
<td>VAN 500mg PO QID PLUS MTR 500mg Q8 hours IV PLUS Vanc 500mg PR in 500 cc QID</td>
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<td><strong>Recurrence</strong></td>
<td>Initial – repeat course Multiple – VAN taper</td>
<td>Initial – VAN taper; FDX course Multiple – VAN taper; VAN+rifaximin; FDX course; or FMT (if 3 CDI episode)</td>
<td>Initial – repeat course; 2nd – VAN pulse dosing; 3rd – Fecal microbiota transplant</td>
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Evidence for Vancomycin Taper

- n=163 cases of recurrent CDI
  - Mean # of prior CDI = 3.2 (2.1)
  - Patients received various tx strategies including vancomycin taper to 125mg/day or pulse dosing (every 2-3 days)

- Recurrence rate = 44.6%, median time of 8 days
  - Vancomycin = 54% (45/83)
  - Vancomycin taper = 31% (9/20)
  - Vancomycin pulse dosing = 14% (1/7)

Vancomycin Taper/Pulse Dosing Strategies

- **ACG Guidelines**
  - Vancomycin 125mg PO 4 times daily x 10 days followed by 125mg PO daily every 3 days x 30 days

- **IDSA Guidelines**
  - Vancomycin 125mg PO 4 times daily x 10-14 days
  - Vancomycin 125mg PO BID x 1 week
  - Vancomycin 125mg PO daily x 1 week
  - Vancomycin 125mg PO 2 or 3 days x 2-8 weeks

Fecal Microbiota Transplant

*Rates of Cure without Relapse at 10 Weeks*

- **First Infusion of Donor Feces (N=16)**
  - Percentage Cured without Relapse: 81.3%

- **Infusion of Donor Feces Overall (N=16)**
  - Percentage Cured without Relapse: 93.8%

- **Vancomycin (N=13)**
  - Percentage Cured without Relapse: 30.8%

- **Vancomycin with Bowel Lavage (N=13)**
  - Percentage Cured without Relapse: 23.1%

FMT-related ADE: Belching: (3/16), 19%
Fecal Microbiota Transplant
Rates of Cure without Relapse at 10 Weeks

FMT-related ADE:
Belching: (3/16), 19%

Fecal Microbiota Transplant
Rates of Cure without Relapse at 10 Weeks


Stool Composition: Before and After FMT

**Fecal Microbiota Transplant – Summary of Clinical Data**

- **FMT is highly effective (~90% or >) in treatment of recurrent CDI, severe CDI (> than VAN) and proven in RCTs**
  - Colonoscopy may be better than ND/NG route of administration
  - **References:**

- **Frozen material, including oral capsules, is effective as fresh**
  - **References:**

- **FMT is effective in immunocompromised hosts**
  - **References:**
Fecal Microbiota Transplant – Summary of Clinical Data

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Bezlotoxumab

**Currently approved by the FDA (July 2016)**

Indication: To reduce recurrence of CDI in adults who are receiving antibacterial treatment of CDI and are at high risk of recurrence

- Monoclonal antibody against TcdB (Toxin B)
  - Estimated half-life of 19 days

- Single IV dose, 10mg/kg - developed as an adjunctive therapy to primary treatment to be given during active treatment

- Available as 1000mg/50mL vial
# Bezlotoxumab (BEZ)

## RCT evidence

<table>
<thead>
<tr>
<th>Trial, Patient Pop</th>
<th>Study Arm</th>
<th>Primary Endpoint</th>
<th>Additional Data</th>
</tr>
</thead>
</table>
| **MODIFY I** 1452 pts, 19 countries  
Age ~65 years (47% < 65)  
47% MTR, 47% Vanc | Bezlotoxumab 10mg/kg x 1 IV infusion vs actoxumab 10mg/kg x 1 IV infusion vs both vs placebo (all plus SOC) | 12-week CDI recurrence  
Bez: 17.4%  
Placebo: 27.6% (P=0.0003) | Bez+Act no more effective  
Actox alone not effective  
ADE similar to placebo (mostly GI) |
| **MODIFY II** 1168 pts, 17 countries  
Age ~67 years  
46% MTR, 47% Vanc | Bez 10mg/kg x 1 IV infusion vs both vs placebo (all plus SOC)  
94% received within first 6 days of tx  
67% inpatient/33% outpt. | 12-week CDI recurrence  
Bez: 15.7%  
Placebo: 25.7% (P=0.0003) | Bez+Act no more effective  
ADE similar to placebo (mostly GI) – CHF* |

Note: >90% of patients received within 6 days of therapy; no difference based on day of administration in follow-up analysis

---

*CHF exacerbation: BEZ: 12.7% (15/118) vs 4.8% (5/104)  
Deaths in those with CHF: BEZ: 19.5% (23/118) vs 12.5% (13/104)

Bezlotoxumab Summary Points

- Clinical cure rates not impacted (in fact lower in one study)
- Recurrence significantly lower based on primary endpoint in RCTs - effect most prominently seen in those with > 3 risk factors
  - Higher in outpatients regardless of treatment
- Concomitant systemic antibiotics was not included in primary analysis of initial RCTs - more data needed on this
- Would not recommend using in combination with fidaxomicin
- Caution in CHF - could be Type 1 error, but why risk it? Mechanism still to be determined
- Based on data, giving the drug at any time during therapy is likely appropriate - may be good option at transitions of care?

Summary Points on Recurrence

- **Vancomycin taper/pulse dosing**
  - Taper w/ pulse over 6-8 weeks, QID, BID, daily, TIW...
  - Very limited data on effectiveness, but always positive
  - Adherence? Access? --- transitions of care so vital here

- **Fidaxomicin**
  - Two large RCTs, reduced 28-day recurrence compared to vancomycin
  - Is it cost effective? (Gallagher JC, et al. AAC PMID: 26324268 says yes... others say no)
  - Does it work well in multi-recurrence?

- **Rifaximin chaser**
  - One small RCT study showed decrease (Garey K, et al)

- **Bezlotoxumab**
  - Two large RCTs, reduced 12-week recurrence. Patient selection? Multi-recurrence?

- **Fecal microbiota transplant**

---

37
## Secondary Prophylaxis in CDI

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>• Inexpensive</td>
<td>• PK concerns (as stool forms, fecal concentrations go to 0 mcg/g)</td>
</tr>
<tr>
<td></td>
<td>• Some data when used as part of regimen may reduce acquisition</td>
<td>• ADEs (CNS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Microbiome destruction</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>• Favorable PK (as stool forms, fecal conc increase)</td>
<td>• Access issues</td>
</tr>
<tr>
<td></td>
<td>• Data: 3 studies – mostly favorable outcomes</td>
<td>• Destroys microbiome (less than MTR)</td>
</tr>
<tr>
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<td>• Benign</td>
<td>• Appropriate dose unknown (125mg daily may be ok)</td>
</tr>
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</table>
Oral Vancomycin in Secondary Prophylaxis

- **Scenario:** Patient has a history of CDI (4 months prior) and is now being treated for *E. coli* bacteremia secondary to pyelonephritis.
- **Question:** Should the patient receive oral vancomycin to prevent an episode of CDI?
Oral Vancomycin in Secondary Prophylaxis

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Pop: ~70 yo, prior CDI ~6.5 mo. ago
Vanc proph 125 or 250mg BID (VP) (n=71)
No proph (n=132)
Mean DOV = 13.7d (0.8 post AB)
4-week CDI rates: VP = 4.2% vs Control = 26.6%, OR=0.12, CI 0.04-0.4

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**Renal transplant recipients**
Vanc proph 125mg BID
30-day CDI rates: VPx = 0% (0/12) vs No proph = 8% (2/24)

---

**Pop**: 50% >75yo; Most cases during ‘epidemic’ in Quebec in 2003–2008 including patients with 1 or multiple prior episodes
**Vanc proph 125 mg 4 times daily (mostly)**
Mean DOV = 7 d
**VP n=227, No proph n=324**
90-day CDI rates: Vancomycin prophylaxis 41% reduction (HR=0.59, 0.43–0.80)

**Renal transplant recipients**
Vanc proph 125mg BID
30-day CDI rates: VPx = 0% (0/12) vs No proph = 8% (2/24)
Oral Vancomycin in Secondary Prophylaxis

CDI probability with only 1 prior episode

CDI probability with multiple prior episodes

Bottom line: vancomycin prophylaxis MAY help more in patients who have had multiple prior episodes but data are still sparse.

Oral Vancomycin in Secondary Prophylaxis

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<tr>
<td>Fidaxomicin</td>
<td>• Limited destruction to</td>
<td>• Access &amp; cost issues</td>
</tr>
<tr>
<td></td>
<td>microbiome</td>
<td>• DEFLECT-1 study showed NO</td>
</tr>
<tr>
<td></td>
<td>• Benign (exc. macrolide allergy)</td>
<td>difference in outcomes (abstract data only)</td>
</tr>
<tr>
<td>Probiotics</td>
<td>• Benign</td>
<td>• Do you know what's in them?</td>
</tr>
<tr>
<td></td>
<td>• Readily available</td>
<td>• Poor overall data</td>
</tr>
<tr>
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<td>• Cochrane review supports use</td>
<td>• Ideal dose/mixture unknown</td>
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<td>in pop. w/ &gt;5% incidence</td>
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What About Fidaxomicin As Secondary Prophylaxis

**DEFLECT-1 study**

<table>
<thead>
<tr>
<th>Description of the Event</th>
<th>FDX N=301</th>
<th>PLC N = 299</th>
<th>Wald p-value</th>
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<tbody>
<tr>
<td>Received any CDAD-effective medication, for any reason</td>
<td>12 (4.0)</td>
<td>11 (3.7)</td>
<td>0.4222</td>
</tr>
<tr>
<td>Discontinued due to death or AE</td>
<td>19 (6.3)</td>
<td>16 (5.4)</td>
<td>0.3077</td>
</tr>
<tr>
<td>Missing – other reasons</td>
<td>42 (14.0)</td>
<td>33 (11.0)</td>
<td>0.1397</td>
</tr>
<tr>
<td>Sensitivity analysis 1: CDAD</td>
<td>13 (4.3)</td>
<td>32 (10.7)</td>
<td>0.0014</td>
</tr>
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<td>Primary analysis: CDAD, CDAD-effective medication, deaths/disch., 92 (30.8)</td>
<td>85 (28.6)</td>
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Available at: https://www.bbmt.org/article/S1083-8791(15)01294-X/pdf
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Probiotics

Based on this systematic review and meta-analysis of 31 randomized controlled trials including 8672 patients, moderate certainty evidence suggests that probiotics are effective for preventing CDAD (NNT=42 patients, 95% CI 32 to 56). Our post hoc subgroup analyses to explore heterogeneity indicated that probiotics are effective among trials with a CDAD baseline risk <5% (NNT=12), moderate certainty evidence), but not among trials with a baseline risk >5% (low to moderate certainty evidence). Although adverse effects were reported among 32 included trials, there were more adverse events among patients in the control group. The short-term use of probiotics appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated. Despite the need for further research, hospitalized patients, particularly those at high risk of CDAD, should be informed of the potential benefits and harms of probiotics.

If baseline risk >5%, probiotics are effective (NNT=12, with moderate certainty)...but not among populations with ≤5% baseline risk

Available at: `https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006095.pub4/full`
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If baseline risk >5%, probiotics are effective (NNT=12, with moderate certainty)... but not among populations with <5% baseline risk

31 RCTs, n=8672 patients

PLACIDE trial PMID: 23932219

2800 patients, no difference (Control: 1.2%, Probiotic: 0.9%)

PMID: 20145608

250 pts, probiotic sig decrease (Control: 24%, Probiotic: 5.2%)

Available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006095.pub4/full

Study 1: Healthy, undisrupted gut microbiomes

Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features

Study 2: Healthy, but now disrupted gut microbiomes secondary to antibiotics

Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

Study 1: Available at: https://www.cell.com/action/showPdf?pii=S0092-8674%2818%2931102-4
Study 2: Available at: https://www.cell.com/action/showPdf?pii=S0092-8674%2818%2931105-5
The gut mucosal is commonly resistant to probiotic colonization (person specific) and this is predictable by pre-treatment microbiome (but not stool).

Probiotic colonization is significantly enhanced after antibiotic exposure but after antibiotics, they delay microbiome reconstitution (complete opposite of FMT which enhances quickly).
Potential Concerns with Probiotic Prophylaxis

- Use in immunocompromised hosts
  - Legitimate concern or no?
  - Systematic review in cancer patients (17 studies, n=1530 patients) showed 5 cases of bacteremia/fungemia secondary to probiotic, no attributable sentinel events
  - Sicchasia
- Confirmation of contents
- Regulatory concerns
- Lots of clinical unknowns – best combination, proper dosing, administration with certain antibiotics
- Benefit in populations with low CDI rates (<5%)?
- Benefit in secondary prophylaxis?

Recommended Tertiary Reading on Probiotics

- Review on probiotics in primary & secondary prevention in CDI
- Cochrane Review on probiotics in prevention of CDAD in adults and pediatrics
- Review on research and emerging concepts of probiotics in CDI
  - (Spinler JK, et al. Anaerobe 2016;41:51-7. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5050073/)

Note: Reviews & meta-analyses include most prominent RCT and primary literature, so you’re of course encouraged to explore those specifically.
## Secondary Prophylaxis in CDI

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pro</th>
<th>Con</th>
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<tbody>
<tr>
<td>Metronidazole</td>
<td>• Inexpensive</td>
<td>• PK concerns (as stool forms, fecal concentrations go to 0 mcg/g)</td>
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<td></td>
<td></td>
<td>• ADEs (CNS)</td>
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<td></td>
<td></td>
<td>• Microbiome destruction</td>
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<tr>
<td>Vancomycin</td>
<td>• Favorable PK (as stool forms, fecal conc increase)</td>
<td>• Access issues</td>
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<tr>
<td></td>
<td>• Data: 3 studies – mostly favorable outcomes</td>
<td>• Destroys microbiome (less than MTR)</td>
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<tr>
<td></td>
<td>• Benign</td>
<td>• Appropriate dose unknown (125mg daily may be ok)</td>
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<tr>
<td>Fidaxomicin</td>
<td>• Oral available</td>
<td>• Access &amp; cost issues</td>
</tr>
<tr>
<td></td>
<td>• Limited destruction to microbiome</td>
<td>• DEFLECT-1 study showed no difference in primary outcome, but subset of CDI favorable</td>
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<tr>
<td></td>
<td>• Benign (exc. macrolide allergy)</td>
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<tr>
<td>Probiotics</td>
<td>• Benign</td>
<td>• Poor/inconsistent overall data</td>
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<tr>
<td></td>
<td>• Available</td>
<td>• Ideal dose/mixture unknown</td>
</tr>
<tr>
<td>Limit unnecessary antibiotic exposure</td>
<td>• Zero cost and ADEs</td>
<td>• Still searching...</td>
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## Oral Beta-Lactamases: Therapy on the Horizon

- Over 14 million patients receive IV beta-lactams in US per year

- **Concept:** use of an oral beta-lactamase that is non systemically available to degrade beta-lactam in GI tract and maintain healthy microbiome. One furthest in development = ribaxamase (Phase 3 pending)
Oral Beta-Lactamases: Therapy on the Horizon

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Should I Extend CDI-specific Therapy In Patients On Concomitant Systemic Antibiotics?

- Many “experts” would say yes
- Limited data (1 study to date) suggests no difference in outcomes (Kaki R, et al.) Available at: https://print.ispub.com/api/0/ispub-article/37585
- My opinion is to consider ~5 days of oral vancomycin post concomitant antibiotics
- Is this a reason to consider alternatives to vancomycin (e.g., fidaxomicin, bezlotoxumab)?

When Should I Be Using Combination Therapy?

- In the critically ill for sure!
  - Vancomycin PO plus metronidazole IV significant predictor of lower mortality (Rokas KE, et al. PMID: 26024909)
- No increase in effectiveness and no reduction in recurrence in patients without fulminant disease
  - Li, et al. (PMID: 26444424)
  - Increase costs and ADEs only
- What is strategy for non-responders then?
  1. Is drug getting to site? Need for rectal?
  2. Change drug therapy (oral vancomycin still probably optimal cure)
  3. Look for other causes of diarrhea
  4. Imaging/scope
Prevention

What preventive measures can be taken to reduce the incidence of CDI? What is the best method to identify patients at risk of primary or recurrent CDI? Can administration of probiotics or biotherapeutic agents effectively prevent CDI? What are the most effective antibiotic stewardship strategies to prevent CDI? What are the most effective transmission prevention strategies (i.e., environmental management and isolation) to prevent CDI in inpatient settings? What is the incremental impact of each? Is there a core “bundle” infection control strategy that can be used by a wide range of healthcare facilities? Can vaccination effectively prevent CDI, and what would be the composition of the vaccine and the route of administration? What are systemic or mucosal immunologic markers that predict protection against CDI? What is the role of anti-CDI agents in secondary CDI prevention of CDI patients successfully treated for CDI but who receive subsequent oral, intravenous, or intramuscular antibiotics? What drugs, dosages, and duration? What patient characteristics should be considered for initiating secondary prophylaxis (e.g., age, number of previous CDI episodes, and time since previous CDI episode)? What is the effect of screening patients on admission for C. difficile carriage and isolating positive C. difficile carriers on the incidence of hospital-acquired CDI?

LOTS of unanswered questions in CDI prevention & treatment

TakeHome Points

• CDI is bad...and we want to try to prevent as good antibiotic stewards

• Once the patient has CDI, treatment selection and ensuring continuity of care/adherence is vital

• 2018 IDSA/SHEA guidelines recommend vancomycin or fidaxomicin as first-line therapy for all non critically ill patients

• Use of fidaxomicin and bezlotoxumab (as an adjunct only) should be based on host risk factors for recurrence...and potentially has a role in patients who develop a 1st recurrence to try and break that cycle (alternative to FMT)

• Probiotics are unlikely to be effective and potentially financially toxic

• CDI is bad...and we want to try to prevent as good antibiotic stewards (yes repeated for effect)
prevention & management of CLOSTRIDIUM DIFFICILE INFECTION
the latest game changers to clinical practice

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