Clostridium Difficile Infection: Applying New Treatment Guidelines and Strategies to Reduce Recurrence Rate
Objectives

• Summarize the changing epidemiology and demographics of patients at risk for *Clostridium difficile* infection (CDI) recurrence

• More knowledgeably select therapeutic regimens for patients at high risk for recurrent CDI, including validated non-antibiotic agents

• Analyze the impact of the recent changes made to the Infectious Diseases Society of America guidelines on CDI diagnosis accuracy and patient outcomes
Faculty Information

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Dr. Dubberke receives consulting fees from Merck, Rebiotix, Summit, and Synthetic Biologics; and has contracted research for Pfizer.

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Dr. Garey receives consulting fees from Merck, Summit PLC, and Seres Therapeutics.
**C. diff** Incidence Rate

- CDC list of pathogens with pathogens at highest level of risk — based on high incidence and mortality rates
  - Roughly 500,000 cases of *C. diff* per year; 29,000 deaths
  - *C. diff* is the #1 cause of infectious diarrhea for patients hospitalized in all developed countries
  - Often not tested for, more of an emerging disease
  - Considered a global pathogen
Recurrent CDI is Costly: Healthcare Utilization for Recurrent CDI

*Of disease-attributable readmission, 85% returned to the initial hospital for care
What Factors Place Patients at Higher Risk for CDI?

• Patients have 2 main lines of defense against *C. diff*
  - Microbiome — first line of defense
  - Immune system — second line of defense

• Most important risk factor for CDI is antibiotic use
  - Alters the microbiome to where it may no longer protect against CDI

• Conditions, states, or medications that impact immune function place a patient with an altered microbiome at even greater risk for CDI
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)

Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,1 Dale N. Gerding,2 Stuart Johnson,1,2 Johan S. Bakken,1 Karen C. Carroll,1 Susan E. Coffin,1 Erik R. Dubberke,1 Kevin W. Garey,1 Carolyn V. Gould,1 Ciaran Kelly,1 Vivian Loo,5 Julia Shackle Sammons,5 Thomas J. Sandora,11 and Mark H. Wilcox12
PCR Diagnostic Strategies May Detect Patients Colonized with CDI but Not Infected

UK: prospective, multicenter study of suspected CDI patients; fecal samples were evaluated using cytotoxicity assay (CTA), cytotoxigenic culture (CC), or nucleic acid amplification test (NAAT)

Mortality increased significantly in CTA-positive patients (OR 1.61, 95% CI 1.12–2.31)

Clinicians and laboratory personnel agree at the institutional level to not submit stool samples on patients receiving laxatives and to submit stool specimens only from patients with unexplained and new onset >3 unformed stools in 24 h for CDI testing.

- **No**
  - Stool toxin test as part of a multiple step algorithm—usually GDH plus toxin test

- **Yes**
  - NAAT alone or stool EIA toxin test as part of a multiple step algorithm

Why Is Metronidazole No Longer Considered a Drug of Choice for CDI?

• In 2009, a small case series of patients treated with metronidazole showed only a 50% response rate

• A few years later, a randomized, controlled trial compared oral vancomycin with metronidazole, stratified by disease severity
  – In patients with severe CDI, oral vancomycin performed better; changed the 2010 guidelines

• For severe *C. diff*, use oral vancomycin; for mild to moderate, use metronidazole
Metronidazole Shown to Be Globally Inferior to Vancomycin (Tolevamer Phase III RCT)

Treatment Possibilities for CDI

- Probiotics
- FMT
- Narrow-spectrum antibiotics

- Metronidazole
- Vancomycin
- Fidaxomicin

- IVIG
- Monoclonal antibodies vs. C. diff toxins
# Recommendations for Initial Treatment of CDI in Adults

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Supportive Clinical Data</th>
<th>Recommended Treatment</th>
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</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 given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days. Alternate if above agents are not available: metronidazole 500 mg three times daily by mouth for 10 days</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC &gt;15,000 cells/mL or a serum creatinine &gt;1.5 mg/dL</td>
<td>VAN 125 mg given four times daily for 10 days, or FDX 200 mg 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 hours if ileus present</td>
</tr>
</tbody>
</table>

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

Fidaxomicin: Equal Efficacy at Vancomycin to Cure Patients and Lessens the Risk of Recurrence

Any Evidence That Fidaxomicin May Reduce Costs?

Patients 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 re-admissions: Fidaxo: 20.4%; Vanco: 41.3%

Drug acquisition costs
- Vancomycin: $6,333
- Fidaxomicin: $62,112

Hospital re-admission costs
- Vancomycin (183 days): $454,800
- Fidaxomicin (87 days): $196,200

Gallagher et al. AAC. 2015
Real-World Evidence That Fidaxomicin May Reduce Costs?


# Recommendations for Recurrence of CDI in Adults

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Recommended Treatment</th>
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<tr>
<td>First recurrence</td>
<td>• VAN SD if metronidazole was used for the first episode OR</td>
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<tr>
<td></td>
<td>• Prolonged tapered and pulsed VAN if VAN SD was used for first regimen OR</td>
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<tr>
<td></td>
<td>• FDX SD if VAN was used for the first episode</td>
</tr>
<tr>
<td>Second or subsequent recurrences</td>
<td>• VAN in a tapered or pulsed regimen OR</td>
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<tr>
<td></td>
<td>• VAN SD followed by rifaximin 400 mg three times daily for 20 days OR</td>
</tr>
<tr>
<td></td>
<td>• FDX SD OR</td>
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<tr>
<td></td>
<td>• Fecal microbiota transplantation</td>
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Treatment Possibilities for CDI

- Probiotics
- FMT
- Narrow-spectrum antibiotics

- Metronidazole
- Vancomycin
- Fidaxomicin

- IVIG
  Monoclonal antibodies vs. C. diff toxins
Serum Concentrations of IgG Antibodies Against Toxin A, Toxin B, and Non-toxin Antigens

- Single episode
- Recurrent diarrhea

Phase III Studies of Bezlotoxumab (Bezlo): Overall


Actoxumab (acto) is another monoclonal antibody originally studied for the prevention of recurrent CDI.
BEZLO was shown to reduce hospital re-admissions (European Population)

Incremental Cost-Effectiveness Ratio (ICER)

- Cost effectiveness of bezlotoxumab vs. placebo
- ICER represents the average incremental cost per quality-adjusted life-years gained associated with an intervention
- Bezlotoxumab was found to be a cost-effective measure for preventing recurrent CDI, with an ICER of $19,824 per quality-adjusted life-year gained
- Better ICER for patients at increased risk for recurrence
  - ~$15,000 for patients ≥65 years of age
  - ~$13,000 for immunocompromised patients
  - ~$5,000 for immunocompromised patients with a history of CDI in the past 6 months
  - ~ $3,500 for patients ≥65 years of age with a history of CDI in the past 6 months

Conclusions

• *C. diff* remains a significant clinical challenge
• 2017 guidelines had major changes compared with 2010 guidelines
  – Additional guidance for diagnosis of CDI
  – Treatment guidelines
    • Metronidazole no longer is a first-line treatment for CDI
    • Fidaxomicin as a first-line treatment for a first or second episode of CDI or first episode and first recurrence of CDI; not mentioned in 2010 guidelines, not available until 2011
    • Bezlotoxumab is cost-effective and prevents recurrent CDI; will also improve patient outcomes
• Appropriate treatment of *C. diff* is “a team sport”
  – Key role of antimicrobial stewardship team to prevent overuse of antibiotics and develop treatment algorithms
  – Interprofessional team members should collaborate to provide optimal care