Epidemiological Trends in the Healthcare and Community Settings

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Management of Initial and Recurrent Clostridium difficile Infection: Progress and Promise of Novel Pathways
Total Number of CDI Cases in U.S. Hospitals Nationwide Inpatient Sample (NIS)

![Graph showing the total number of CDI cases in U.S. hospitals from 2000 to 2011. The graph indicates a significant increase in cases, peaking at 383,498 cases in 2011.]


The Rate of *C. difficile* Infection is Predicted to Remain High

![Graph showing the national rate of CDI hospitalizations from 2000 to 2014. The graph indicates a consistent increase in cases, with the national rate predicted to remain high.]


*C. difficile* Infection (CDI) Recognized as a Top Priority

- **CDC**: urgent threat, EIP surveillance
- **NIH**: requests for applications for novel therapeutics
- **CMS**: publically reported, may impact hospital reimbursement

Management of Initial and Recurrent *Clostridium difficile* Infection: Progress and Promise of Novel Pathways
CDC Emerging Infections Program (EIP)
Surveillance for CDI

Active population- and laboratory-based surveillance systems in selected counties in 10 U.S. states since 2009

C. difficile is the most commonly identified health care-associated infection (HAI) – 12.1% of all HAIs

NAP1 Strain Type Predicts Outcomes From Clostridium difficile Infection

NAP1 is the most prevalent strain (28.4%) & predicts severe disease, severe outcome & death

↑ C. difficile was responsible for ~half a million infections & ~29,000 deaths in 2011

Estimated U.S. Burden of CDI

Number of cases according to the location of stool collection and inpatient healthcare exposure, 2011

HCA CDI: 293,000
-CD-HCA: 81,300
-NHO: 194,400
-HO: 107,600

CA CDI: 159,700

2/3 were HCA, but only 1/4 had onset during hospitalization

Still Much to Understand

- Diagnosis
  - Patient selection
  - Diagnostic assay
- Prevention
  - Better data needed
  - Challenge: C. difficile is ubiquitous
- Treatment
  - Prevent complications
  - Prevent recurrences
New Perspectives on CDI Pathogenesis and How this Translates to Therapy

Ciarán P. Kelly, MD
Professor of Medicine
Harvard Medical School
Director Gastroenterology Fellowship Training
Director Celiac Center
Beth Israel Deaconess Medical Center
Boston, MA
**C. difficile Infection & Mortality**

![Graph showing US CDI Death Rates](image)

**CDC estimates**

- >500,000 cases annually
- 29,000 CDI-related deaths
- ~100 deaths per million annually

“Urgent Hazard” [highest threat level]

In US, reported deaths related to CDI (according to death certificates) are:
- ×4 deaths related to MRSA
- ×6 deaths related to all other enteric pathogens combined

**US CDI Death Rates**
- Age standardised rates per million population

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**CDI Pathogenesis & Novel Therapy**

- Steps in the Pathogenesis of CDI
- New approaches to prevention & treatment
- Restoring colonization resistance
  - FMT (Fecal microbial therapy)
  - Other bacteriotherapies
- Immunity & immunization
  - Passive immunotherapy
  - Active vaccine

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**Pathogenesis of Clostridium difficile Infection**

- Antibiotic therapy
  - Disturbed colonic microflora
  - Colonization by *C. difficile*
  - Anti-toxin immunity
  - Symptomless carriage
  - Diarrhea & colitis

- “Dysbiosis”
- Exposure
- Toxin effects

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**Management of Initial and Recurrent Clostridium difficile Infection: Progress and Promise of Novel Pathways**
Pathogenesis of Clostridium difficile Infection

Antibiotic therapy

Disturbed colonic microflora (loss of colonization resistance)

Colonization by C. difficile

Toxin A & Toxin B

Symptomless carriage

Diarrhea & colitis

"Dysbiosis"

Antimicrobials
Chemotherapy
Neonatal state
Enteric infection
IBD with colitis

Decreased Diversity of Fecal Microbiome in CDI

Antibiotics Predisposing to CDI: The good, the bad, and the ugly

<table>
<thead>
<tr>
<th>Uncommonly Related</th>
<th>Less Commonly Related</th>
<th>Very Commonly Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Other penicillins</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Sulfonamides</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Trimethoprim</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>Cotrimoxazole</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Macrolides</td>
<td>(2nd and 3rd generation)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
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<tr>
<td>Tigecycline</td>
<td></td>
<td></td>
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</tbody>
</table>


Management of Initial and Recurrent Clostridium difficile Infection: Progress and Promise of Novel Pathways
Fidaxomicin may Cause Less Intestinal Dysbiosis than Vancomycin

*Graph showing* Bacteroides group counts in feces before and after 10 days of treatment with:
- Fidaxomicin (200 mg bid)
- Vancomycin (125 mg qid)


C. difficile Infection: Basic Principles of Management

- Suspect on clinical grounds
- Discontinue non-essential antibiotics
- Confirm presence of toxin-producing *C. difficile* by stool testing (usually PCR or EIA)
- Empiric treatment best avoided UNLESS:
  - Very high clinical index of suspicion
  - OR very severe illness

Non-C. difficile Antibiotics & Response to Therapy: New Data for an Old Rule

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No additional antibiotics</th>
<th>With additional antibiotics</th>
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</thead>
<tbody>
<tr>
<td>Time to resolution of diarrhea (median)</td>
<td>52 hours</td>
<td>96 hours</td>
</tr>
<tr>
<td>% Diarrhea NOT resolved at 10 days</td>
<td>7%</td>
<td>16%</td>
</tr>
<tr>
<td>% Sustained response and no recurrence</td>
<td>25%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Novel Approaches:
Turning to Nature’s Cures for CDI

Antibiotic therapy
↓
Disturbed colonic microflora

Restore colonization resistance

C. difficile exposure & colonization

Toxin A & Toxin B

Symptomless carriage  Diarrhea & colitis


Probiotics to Restore Colonization Resistance and Prevent C. difficile Infection

Antibiotic therapy
↓
Disturbed colonic microflora

Probiotics

C. difficile exposure & colonization

Toxin A & Toxin B

Symptomless carriage  Diarrhea & colitis


Lactobacilli and Bifidobacteria for Prevention of AAD and CDI

UK, National Health Service (NHS) prospective, multi-center, double-blind trial in ≥65-year-old inpatients receiving antibiotics
Randomized to 21 days of:
Probiotic (n=1,470) 6x10^9 organisms per day, multistrain lactobacilli & bifidobacteria mixture or
Placebo (n=1471)
Primary outcomes:
AAD within 8 weeks
CDI within 12 weeks

National Guidelines do not Recommend Oral Probiotics for CDI Prevention or Treatment

<table>
<thead>
<tr>
<th>Episode of CDI</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence</td>
<td>Metronidazole, vancomycin or fidaxomicin</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>Prolonged oral vancomycin (tapering and pulse-dosed) OR fidaxomicin</td>
</tr>
<tr>
<td>Third and subsequent recurrences</td>
<td>Prolonged oral vancomycin (tapering and pulse-dosed) OR fidaxomicin, Vancomycin with rifaximin “chaser”, Fecal microbial transplant</td>
</tr>
</tbody>
</table>

Why?
- Few RCTs
- Most studies single-center
- Reproducibility not shown
- Different agents studied
- Therapeutic indication not always clear


Empiric therapy to “re-establish the balance of nature” within the intestinal flora to correct the disruption caused by antibiotic treatment.

They reported “immediate and dramatic” responses and concluded that “this simple yet rational therapeutic method should be given more extensive clinical evaluation”.

Fecal transplantation by enema for four patients with fulminant, life-threatening, pseudomembranous enterocolitis.

Duodenal Infusion of Donor Feces for Recurrent C. difficile Infection

Fecal microbial transplant by enema for four patients with fulminant, life-threatening, pseudomembranous enterocolitis.

Empiric therapy to “re-establish the balance of nature” within the intestinal flora to correct the disruption caused by antibiotic treatment.

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Duodenal Infusion of Donor Feces for Recurrent C. difficile Infection

Microbiota diversity

FMT Approaches: Bringing Methods to the Madness

- Multiple methods of administration
  - Overall ~75% by colonoscopy or retention enema
  - ~25% by nasogastric tube or upper GI endoscopy
  - Reported efficacy >90% for lower versus >80% for upper routes
- Recent publications provide recommendations for:
  - Donor screening, processing of donor feces, and methods of administration
- “Stool banks” — improve access
  [academic, non-for-profit & commercial]

OpenBiome (www.openbiome.org)

- Established 2013
  - A “public stool bank” operated by the MIT Microbiome Health Research Institute (MHRI)
  - A nonprofit organization
  - Provides processed, frozen stool from rigorously-screened, healthy donors for use in FMT
  - ~$350 per unit (less than screening/processing cost)
  - Goal is to improve ease of access to FMT

Stool banking in your neighborhood
Beyond FMT – Oral Capsules

- Encapsulated feces
- Defined bacterial cultures
- Fecal spores preparation
- Non-toxigenic *C. difficile* spores


Beyond FMT

Bacteriotherapy with a Defined Culture


Non-toxigenic *C. difficile* is Not a Pathogen

Antibiotic therapy

Disturbed colonic microflora

(loss of colonization resistance)

Non-toxigenic *C. difficile*

Toxin

Toxin B

Symptomless carriage

Diarrhea

Colitis

Non-toxigenic *C. difficile* Spores
Nature’s Tailor-made Probiotic?

- **NTCD** (Non-toxigenic *C. difficile*)
  - Spores of strain VP20621
- **Protects hamsters** against colonization by toxigenic *C. difficile* and against CDI

**Phase II trial:**
All with CDI on oral vanco
- **Placebo** (n=43)
- **or NTCD** (Total n=125)
  - $10^4 \times 7$ days (n=41)
  - $10^5 \times 7$ days (n=43)
  - $10^7 \times 14$ days (n=41)

Phase II trial:
All with CDI on oral vanco
- **Placebo** (n=43)
- **or NTCD** (Total n=125)
  - $10^4 \times 7$ days (n=41)
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**Turning to Nature’s Cures for CDI**

- Antibiotic therapy
  - Disturbed colonic microflora
  - *C. difficile* exposure & colonization
  - Toxin A & Toxin B
  - Symptomless carriage
  - Diarrhea & colitis

X *Most Probiotics*

- Restore colonization resistance
  - FMT
  - Infusion
  - Enema
  - Pills
  - Defined cultures
  - Spore preps
  - Fecal
  - Non-toxigenic CD


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**Novel Approaches:**
**Turning to Nature’s Cures for CDI**

- Antibiotic therapy
  - Disturbed colonic microflora
  - *C. difficile* exposure & colonization
  - Toxin A & Toxin B
  - Symptomless carriage
  - Diarrhea & colitis

- Immunize: Active vaccine or passive immunotherapy

Anti-toxin Immunity Protects Against CDI

- High serum anti-toxin in symptomless carriers

- Serum anti-toxin response & protection against recurrent CDI


Intravenous Immunoglobulin Therapy for Recurrent C. difficile Diarrhea

Also used in severe refractory disease
Efficacy not proven – no RCT

Efficacy not proven – no RCT

Treatment with Monoclonal Antibodies Against C. difficile Toxins A and B Prevents Recurrence

Single dose IV infusion used as an adjuvant to standard of care antibiotics

**A C. difficile Toxoid Vaccine**
(inactivated toxins A and B)
**Induces High Serum IgG Anti-toxin**

- Patients
- Vaccine recipients

50 times levels in patients with protective immunity
Young, healthy volunteers
90 days after first dose


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**How Close are These Novel Treatments to Clinical Use?**

**Bacteriotherapy:**
- FMT – already in use
- FMT by pill – already in use
- Defined bacterial mixtures – in development
- Spores of non-toxigenic *C. difficile* – in development

**Immunization:**
- Anti-toxin HuMabs – Phase III trials complete
- *C. difficile* vaccine – Phase III trial ongoing

**CDI: Case History**

- Jackie, a 66-year-old woman
- Multiple medical problems (morbid obesity, type 2 diabetes mellitus, ischemic heart disease & recurrent urinary tract infections)
- Had been stable and feeling well for several months
- Developed oral pain
- Her dentist prescribed clindamycin for a possible dental infection
- Five days after completing the antibiotic she developed mild diarrhea and saw her PCP
CDI Case: Jackie (cont’d)
Which ONE statement is correct?

1. She probably has simple antibiotic-associated diarrhea and so no stool testing is indicated unless the diarrhea persists or worsens
2. If she has not visited a hospital or other healthcare facility recently, her risk for CDI is negligible
3. If stool testing shows the presence of toxigenic C. difficile but her symptoms have resolved, then treatment is not necessary
4. If stool testing shows the presence of toxigenic C. difficile, she should avoid looking after or changing diapers for her 12-month-old twin grandchildren
5. If stool testing shows the presence of toxigenic C. difficile, this indicates that she was likely a C. difficile carrier when she began clindamycin treatment

Take-Home Points

- Key events in CDI pathogenesis include:
  - Loss of colonization resistance
  - Exposure and colonization
  - Toxin production
  - Diarrhea and colitis if not immune
- Antibiotics differ in the degree to which they disrupt C. difficile colonization resistance
- Bacteriotherapies to restore colonization resistance are available and appear effective
- Agents for passive and active immunization are at late stages in development
Recognizing Factors Associated with Poor Clinical Outcomes in CDI

Erik R. Dubberke, MD, MSPH, FSHEA
Associate Professor of Medicine
Director, Section of Transplant Infectious Diseases
Washington University School of Medicine
St. Louis, MO
Back to the Patient

Jackie’s diarrhea resolved without event. When seeing her PCP for a routine visit, she noted some vague side discomfort, but denied urinary urgency, dysuria, suprapubic tenderness or fevers. However, because of her history of UTI, a urine culture was sent. A pan-susceptible E. coli grew and the patient was started on ciprofloxacin.

On day 3 of ciprofloxacin, she developed diarrhea with severe abdominal cramping. She soon was unable to make it to the bathroom. She went to the emergency department. Stool was positive for C. difficile toxins, her WBC was 16,000/µL, and her serum creatinine 2.5 mg/dL.

Which is correct?

1. Most patients diagnosed with UTI actually have a UTI. The cipro was appropriate.
2. The positive test for C. difficile toxin in stool likely represents asymptomatic carriage, not CDI.
3. CDI is no big deal. Metronidazole is an inexpensive and effective treatment.
4. It is possible to risk stratify patients with CDI to select treatments that will optimize patient outcomes.

Two Biggest Challenges in Treating CDI

- Severe CDI
  - Decrease morbidity and mortality
- Recurrent CDI
  - Decrease recurrences
Current Pathogenesis Model for C. difficile Infection (CDI)

- C. difficile exposure
- Antimicrobial(s)
- Asymptomatic C. difficile colonization
- Hospitalization
- CDI

Acquisition of a toxigenic strain of C. difficile and failure to mount an anamnestic antibody response results in CDI.

Factors that Contribute to Poor Outcomes

Host factors
- Age
- Severity of illness
- Immune response

C. difficile
- Germination
- Toxin production
- Binary toxin

Management
- Time to treatment
- Treatment selection
- Concomitant antimicrobials

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- Germination
- Toxin production
- Binary toxin

Management
- Time to treatment
- Treatment selection
- Concomitant antimicrobials


Management of Initial and Recurrent Clostridium difficile Infection: Progress and Promise of Novel Pathways
**Patient Factors Associated with Death**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariable hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAD</td>
<td>1.32 (1.09–1.60)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.17 (1.05–1.27)</td>
</tr>
<tr>
<td>White race</td>
<td>1.22 (1.11–1.35)</td>
</tr>
<tr>
<td>Modified APS</td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>Reference</td>
</tr>
<tr>
<td>3–4</td>
<td>1.09 (0.96–1.24)</td>
</tr>
<tr>
<td>5–6</td>
<td>1.30 (1.14–1.49)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>1.65 (1.46–1.87)</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>1.62 (1.45–1.82)</td>
</tr>
<tr>
<td>3.6–5</td>
<td>1.97 (1.80–2.15)</td>
</tr>
<tr>
<td>Liver disease</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Reference</td>
</tr>
<tr>
<td>Mild</td>
<td>2.59 (1.88–3.54)</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>3.76 (3.05–4.64)</td>
</tr>
<tr>
<td>Diabetes with chronic complications</td>
<td>1.46 (1.16–1.85)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.28 (1.15–1.42)</td>
</tr>
<tr>
<td>Cardiopulmonary disease</td>
<td>1.62 (1.37–1.92)</td>
</tr>
<tr>
<td>Cancer, excluding leukemia or lymphoma</td>
<td>2.44 (2.15–2.75)</td>
</tr>
<tr>
<td>Leukemia or lymphoma</td>
<td>4.92 (3.88–6.33)</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>4.41 (3.47–5.32)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2.88 (2.12–3.91)</td>
</tr>
<tr>
<td>Perioperative sepsis</td>
<td>1.95 (1.52–2.57)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3.17 (2.71–3.71)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>1.31 (1.14–1.50)</td>
</tr>
</tbody>
</table>

**C. difficile Strain and Outcomes**

**Severe CDI**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 y</td>
<td>1.50 (1.21–2.89)</td>
</tr>
<tr>
<td>Healthcare-associated CDI*</td>
<td>1.75 (1.22–2.34)</td>
</tr>
<tr>
<td>Emergency department visit 12 h prior to infection</td>
<td>1.31 (1.01–1.69)</td>
</tr>
<tr>
<td>Medications during 14 d prior to infection</td>
<td>1.06 (0.90–1.26)</td>
</tr>
<tr>
<td>No antibiotic treatment</td>
<td>1.42 (1.05–1.83)</td>
</tr>
<tr>
<td>No infection</td>
<td>1.36 (1.06–1.78)</td>
</tr>
<tr>
<td>NAP1 strain</td>
<td>1.74 (1.26–2.38)</td>
</tr>
</tbody>
</table>

**Severe Outcomes from CDI**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 y</td>
<td>1.71 (1.36–2.19)</td>
</tr>
<tr>
<td>White race</td>
<td>0.49 (0.39–0.61)</td>
</tr>
<tr>
<td>Healthcare-associated CDI*</td>
<td>2.90 (1.63–5.19)</td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.71 (1.38–2.13)</td>
</tr>
<tr>
<td>Any antibiotic during 14 d prior to infection</td>
<td>1.63 (1.04–2.56)</td>
</tr>
<tr>
<td>No infection</td>
<td>1.06 (1.00–2.14)</td>
</tr>
</tbody>
</table>

*Cough, toxic megacolon, or WBC >15K

**C. difficile Strain and Death**

**Death in 14 days**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 y</td>
<td>2.06 (1.80–2.38)</td>
</tr>
<tr>
<td>Epidemiologic classification</td>
<td>2.06 (2.22–2.39)</td>
</tr>
<tr>
<td>Healthcare-associated CDI*</td>
<td>1.00 (0.82–1.31)</td>
</tr>
<tr>
<td>Community-associated CDI*</td>
<td>0.96 (0.74–1.24)</td>
</tr>
<tr>
<td>NAP1 strain</td>
<td>2.01 (1.64–2.48)</td>
</tr>
</tbody>
</table>

**14 day mortality HR ~2.5 for clade 2**

Factors that Contribute to Poor Outcomes

Host factors
- Age
- Severity of illness
- Immune response

C. difficile
- Germination
- Toxin production
- Binary toxin

Management
- Time to treatment
- Treatment selection
- Concomitant antimicrobials

Back to the patient
Which statement is correct?

1. The ciprofloxacin is not indicated. Discontinuing it is an important component of her CDI management.
2. Outcomes of patients positive for toxin are worse than for patients that are toxin negative / PCR positive.
3. This patient has “severe” CDI. Treatment selection will impact her outcome.
4. All of the above.
Impact of Concomitant Antibiotics on Response to CDI Treatment

<table>
<thead>
<tr>
<th></th>
<th>Fidaxo N=391</th>
<th>Vanco N=416</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Clinical</td>
<td>92%</td>
<td>93%</td>
<td>0.80</td>
</tr>
<tr>
<td>Recurrence</td>
<td>12%</td>
<td>23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sustained response</td>
<td>81%</td>
<td>69%</td>
<td>&lt;0.001</td>
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</table>

CA = concomitant antibiotics

Risk Prediction for Severe Outcomes

<table>
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<tr>
<td>Concomitant abx</td>
<td>X</td>
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<tr>
<td>Immunosuppressants</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Comorbidities</td>
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<tr>
<td>Altered mental status</td>
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<td>Hypotension</td>
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<td>Abd pain / tender</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>BM frequency</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Elevated WBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>X</td>
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<tr>
<td>Radiological findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Endoscopy findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>


More Prediction Scores

- ATLAS: age, concomitant antimicrobials, albumin, WBC, creatinine
  - Predict response rate to CDI treatment
- Na: age, WBC, creatinine
  - Predict severe outcomes
- SHEA/IDSA Guidelines
  - WBC ≥15000
  - Cr ≥1.5 × pre-morbid

Ultimate Goal: CDI Severity Scores and Improved Outcomes

- Illinois / Zar score
- Original study: metronidazole response 76% vs. vancomycin 97% (p=0.02)

<table>
<thead>
<tr>
<th>Mild to moderate CDI</th>
<th>Before (N = 144)</th>
<th>After (N = 112)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory disease (N, %)</td>
<td>8 (9.41)</td>
<td>3 (2.68)</td>
<td>Ns</td>
</tr>
<tr>
<td>Death during admission (N, %)</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>Ns</td>
</tr>
<tr>
<td>Length of stay, days (median, range)</td>
<td>11 (1–196)</td>
<td>11 (1–64)</td>
<td>Ns</td>
</tr>
</tbody>
</table>

Recurrent CDI

- Recurrence risk after first episode 15% to 30%
  - Risk increases with additional recurrences
- Associated with worse outcomes
  - Readmissions (RR = 2.5; 95% CI, 2.2–2.9)
  - Costs ($11,631; 95% CI, $8,937–$14,588)
  - Mortality (HR 1.3; 95% CI, 1.1–1.6)

Back to the Patient
Which statement is correct?

1. Infecting C. difficile strain is not associated with risk of recurrent CDI.
2. Anti-toxin antibody levels are not associated with risk of recurrent CDI.
3. It is not possible to identify patients at increased risk for recurrent CDI.
4. Recent exposure to ciprofloxacin may increase this patient’s risk for recurrent CDI.
IgG Response Associated with Decreased Risk for Recurrent CDI

C. difficile Strain and Recurrent CDI

Difficult to Predict Recurrent CDI

- Risk for recurrence already high
- Risk may be influenced by local epidemiology/practices
- No commercially-available assays to measure anti-C. difficile antibody levels
Risk Factors for CDI and Recurrent CDI

Initial CDI
- Age
- Antimicrobials
- Severity of underlying illness
- Immune response

Recurrent CDI
- Age
- Antimicrobials
- Severity of underlying illness
- Immune response

Risk Factors Associated with CDI Recurrence
Findings from Selected Key Publications

<table>
<thead>
<tr>
<th>Increasing Age</th>
<th>Antibiotic Use</th>
<th>Past Hospital / Healthcare Exposure</th>
<th>Host Immunity / Underlying Disease</th>
<th>Severity of Initial CDI Episode / CDI Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per 1 year increment</td>
<td>Systemic concomitant use or continued use of non-C. difficile antibiotics</td>
<td>2+ Hospitalizations in the previous 60 days</td>
<td>Antibody to C. difficile toxin</td>
<td>CDI diagnosis at admission</td>
</tr>
<tr>
<td>&gt;65 or advanced age</td>
<td>High risk antibiotic use at CDI onset</td>
<td>Total inpatient duration before admission* or long hospital stay</td>
<td>Annual severe or fulminant</td>
<td>Stool frequency &gt;3 unformed stools per day</td>
</tr>
<tr>
<td>60-69</td>
<td>Fluoroquinolone use at CDI onset</td>
<td>ER admission + previous MRSA and previous delays or chemotherapy</td>
<td>C-reactive protein &gt;35/26-35/ &lt;=25</td>
<td>Previous C. difficile diagnosis or CDI in the past 3 months</td>
</tr>
<tr>
<td>70-79</td>
<td></td>
<td>Previous gastrointestinal ward admission</td>
<td>ICU at CDI onset‡</td>
<td>Previous CDI diagnosis or CDI in the past 3 months</td>
</tr>
<tr>
<td>&gt;=80</td>
<td></td>
<td>Inpatient vs. outpatient at CDI diagnosis†</td>
<td></td>
<td>C-reactive protein at the time of dx</td>
</tr>
<tr>
<td>&gt;40 years of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* any past admission, >2-13 weeks, >13 weeks
** protective against CDI recurrence
*** creatinine clearance rate

Prediction of C. difficile Recurrence

**TABLE 2** Factors found to predict rCDI in the logistic regression model

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1 year increment)</td>
<td>1.14</td>
<td>1.04 - 1.24</td>
</tr>
<tr>
<td>rCDI (yes)</td>
<td>1.71</td>
<td>1.32 - 2.22</td>
</tr>
<tr>
<td>2+ Hospitalization in prior 60 days (ref: 0 hospitalizations)</td>
<td>1.49</td>
<td>1.08 - 2.06</td>
</tr>
<tr>
<td>New gastric acid suppression at the onset of rCDI</td>
<td>1.99</td>
<td>1.13 - 3.33</td>
</tr>
<tr>
<td>High-risk antibiotics at the onset of rCDI</td>
<td>1.25</td>
<td>1.01 - 1.56</td>
</tr>
<tr>
<td>Fluoroquinolone use at the onset of rCDI</td>
<td>1.31</td>
<td>1.04 - 1.65</td>
</tr>
<tr>
<td>ICU at the onset of rCDI</td>
<td>0.49</td>
<td>0.24 - 0.72</td>
</tr>
</tbody>
</table>

*High-risk antibiotics included all oxazolides, clindamycins, and penicillins.

The validated model had a C statistic of 0.63.

Integrating the New with the Old when Managing CDI

Stuart J. Johnson, MD, FIDSA, DTM&H
Professor, Department of Medicine
Stritch School of Medicine
Loyola University
Chicago, IL
Overview

‘Old’:
- Current guideline recommendations
- Limitations of metronidazole and vancomycin

‘New’:
- Alternative approaches to therapy
- Emerging approaches in treating CDI and reducing the risk of recurrence

Case History, review

Chapter 1:
- 66-year-old woman with multiple medical problems
- Developed mild diarrhea 5 days after finishing a course of clindamycin for a dental infection
- Outcome – resolved without specific treatment

Chapter 2:
- She developed diarrhea with severe abdominal cramping 3 days after starting ciprofloxacin for a questionable UTI.
- Her WBC was 16,000 and serum creatinine 2.5
- Outcome – symptoms resolved after receiving treatment based on severity stratified recommendations, vancomycin 125 mg 4 x daily for 10 days

Case History, continued

Chapter 3:
- 9 days after successfully completing the vancomycin regimen, she again developed diarrhea with abdominal cramping
  - In review of her chart, the ciprofloxacin had been continued to finish a 10-day course of treatment for the ‘UTI’
- She was then treated with vancomycin followed by a taper & pulse regimen
- Unfortunately, she again developed diarrhea 7 days after finishing the vancomycin taper/pulse
What would you recommend now?

1. Fecal microbiota transplant
2. Repeat vancomycin treatment followed by taper/pulse
3. Vancomycin 125 mg QID × 10 d followed by rifaximin 400 mg BID × 14 d
4. Fidaxomicin 200 mg BID × 10 d
5. Fidaxomicin 200 mg BID × 10 d followed by fidaxomicin 200 mg QD × 7 d, then once every other day for 2–3 weeks

History of CDI Guideline Recommendations & Clinical Practice

1995: Hospital Infection Control Practices Advisory Committee (HICPAC):
   • Reduce vancomycin use in hospitals (concern for emergence of vancomycin resistance in other pathogens) (MMWR. 1995;44(RR-12):1-13.)
1995: Society for Healthcare Epidemiology of America (SHEA) Position Paper on CDI:
   • Vancomycin or metronidazole for 10 days is effective
   • Metronidazole may be preferred (Gerding DN, et al. ICHE 1995;16:459-77.)
2010: SHEA/IDSA (Infectious Diseases Society of America) CDI guidelines:
   • Vancomycin is the drug of choice (DOC) for severe disease
   • Metronidazole is DOC for mild-to-moderate CDI
   • 10–14 day course recommended (for slow response to metronidazole) (Cohen SH, et al. ICHE 2010;31:431-55.)

Treatment Guidelines for CDI in Adults: SHEA/IDSA 2010

- Metronidazole is the drug of choice for the initial episode of mild-moderate CDI (500 mg orally TID) for 10–14 days (A-I)
- Vancomycin is the drug of choice for an initial episode of severe CDI. The dose is 125 mg orally QID for 10–14 days (B-I)
- Vancomycin orally (and per rectum if ileus is present) with or without metronidazole IV...for severe, complicated CDI. Vancomycin is dosed at 500 mg (C-III)
- Consider colectomy in severely ill patients... (ideally before) serum lactate rises to 5 mmol/L and WBC rises to 50,000/µL (B-II)

Treatment Guidelines for CDI in Adults: SHEA/IDSA 2010 – Recurrent CDI

- Treatment of the first recurrence is usually with the same regimen as for the initial episode (A-II) but should be stratified by disease severity (C-III)
- Do not use metronidazole beyond first recurrence or for long-term chronic therapy (B-II)
- Treatment of the second or later recurrence with vancomycin using a taper and/or pulse regimen is the preferred next strategy (B-III)
- No recommendations can be made regarding prevention of recurrent CDI in patients requiring continued antimicrobial therapy (C-III)


Limitations of Current Guidelines

- No mention of fidaxomicin
- Limited evidence for recommendations on severe, complicated CDI
- Limited evidence for recommendations on recurrent CDI
- Little mention of fecal microbiota transplant

Limitations of Metronidazole and Vancomycin

- Recurrent CDI after initially effective treatment
- Modest-to-low fecal concentrations of metronidazole
- Potential for resistance (MIC creep with metronidazole)
- Neither treatment directly addresses the main pathogenic mechanism of C. difficile (toxin production)
New Data on CDI Treatment Since Publication of the IDSA/SHEA Guidelines

- Fidaxomicin phase 3 trials, randomized substudy of patients with first CDI recurrence
- Randomized trial of FMT
- Findings from the largest and most rigorous comparison of metronidazole and vancomycin (phase 3 trials of tolevamer)

Phase 3 Multicenter Trials of Tolevamer for CDI randomized, double-dummy, double-blind, active-controlled, parallel-design

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>First dose</th>
<th>All subsequent doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arm</td>
<td>Day 1, single loading dose</td>
<td>Through day 10</td>
</tr>
<tr>
<td>Tolevamer (3.0 gm in 43 mL liquid)</td>
<td>129 mL (8.0 g) plus 1 placebo capsule</td>
<td>1 capsule qid</td>
</tr>
<tr>
<td>Vancomycin (125 mg capsules)</td>
<td>Placebo liquid plus 1 capsule</td>
<td>1 capsule qid</td>
</tr>
<tr>
<td>Metronidazole (375 mg capsules)</td>
<td>Placebo liquid plus 1 capsule</td>
<td>1 capsule qid</td>
</tr>
</tbody>
</table>


Results

- 1118 patients randomized between 2005 & 2007
  - Study 301, n=574 (91 sites in the US & Canada)
  - Study 302, n=544 (109 sites in Europe, Australia, & Canada)
  - 1071 included in the full analysis set (FAS)*
    - tolevamer, n=534
    - metronidazole, n=278
    - vancomycin, n=259

- Patients similarly matched across the 3 treatment arms, but differences noted between studies in terms of age, body weight, inpatient status, and concomitant antibiotic use

*FAS: all randomized patients who received any treatment and who had any post-dose evaluation

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Study 301 (n=543)</th>
<th>Study 302 (n=528)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 ± 17.7</td>
<td>68 ± 16.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age group (&gt;65 years)</td>
<td>46%</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>Gender (F)</td>
<td>52%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Body wt. (kg)</td>
<td>75 ± 24</td>
<td>68 ± 17</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Inpatient</td>
<td>56%</td>
<td>91%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Treatment naïve (yes)</td>
<td>46%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>CDI history (1st episode)</td>
<td>71%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Severe CDI</td>
<td>34%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Concomitant antibiotics (yes)</td>
<td>19%</td>
<td>26%</td>
<td>.044</td>
</tr>
<tr>
<td>Antibiotics during flup (yes)</td>
<td>56%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>CDI Strain (BI, aka RT 027)*</td>
<td>25%</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>

*Prevalence of BI strain in study 301 > 302, but overall distribution of strains was not different

## Results: Clinical Success

![Clinical Success Chart](image)

### Clinical Success

- **P < .001, T vs. M and T vs. V**
- **P = .020, M vs. V**

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
<th>Study 302</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolevamer</td>
<td>72.0%</td>
<td>73.3%</td>
<td>72.7%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>81.3%</td>
<td>80.8%</td>
<td>81.1%</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>46.6%</td>
<td>41.8%</td>
<td>44.2%</td>
</tr>
</tbody>
</table>

*Only patients with diarrhea resolution included in this analysis

## Results: Time to Resolution

![Time to Resolution Chart](image)

### Time to resolution of diarrhea*

- **Tolevamer**
- **Vancomycin**
- **Metronidazole**

*Only patients with diarrhea resolution included in this analysis
Results: Clinical Success by CDI Severity

**Clinical Success by CDI Severity‡ (Combined)**

- **Tolevamer**
  - 78.7*
  - 82.7*
- **Metronidazole**
  - 73.9*
  - 82.2*
- **Vancomycin**
  - 66.3*
  - 78.5*

*P < .001, T vs. M and T vs. V

**Disease severity was based on 3 criteria: stool frequency, white blood cell count, and presence of abdominal pain**


Results: CDI Recurrence

**Recurrence**

- **Tolevamer**
  - 27.1*
  - 23.4*
- **Metronidazole**
  - 18.9*
  - 17.6*
- **Vancomycin**
  - 23.0*
  - 20.6*

*P < .001, T vs. M and T vs. V

†P < .05, T vs. M and T vs. V


Post-hoc Analysis of Vancomycin vs. Metronidazole

Multivariate logistic regression analysis of factors associated with clinical success

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI); P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs B Vancomycin vs Metronidazole</td>
<td>1.575 (1.035, 2.396); P = .0338</td>
</tr>
<tr>
<td>Primary Disease vs Recurrent Disease</td>
<td>1.522 (0.972, 2.477); P = .0636</td>
</tr>
<tr>
<td>Treatment-naive vs Treatment-experienced</td>
<td>1.614 (1.166, 2.212); P = .0031</td>
</tr>
<tr>
<td>Mild/Moderate Disease vs Severe Disease</td>
<td>1.606 (1.032, 2.477); P = .0338</td>
</tr>
</tbody>
</table>

Odds of clinical success greater for B

Odds of clinical success greater for A

Alternative Approaches to Therapy (Recurrent CDI)

- Switch treatment agent
- Tapering/pulsed treatment regimens
- Post-vancomycin chaser regimens
- Host microbiota replacement
- Immune approach

Phase 3 Trial Results of Fidaxomicin vs Vancomycin for CDI

Included patients with first and second CDI episodes

<table>
<thead>
<tr>
<th></th>
<th>Fidaxomicin</th>
<th>Vancomycin</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td>88.2%</td>
<td>88.9%</td>
<td>0.7%</td>
<td>P=NS</td>
</tr>
<tr>
<td>Recurrence</td>
<td>25.3%</td>
<td>26.7%</td>
<td>1.4%</td>
<td>P=0.003</td>
</tr>
<tr>
<td>Sustained cure</td>
<td>74.6%</td>
<td>64.1%</td>
<td>10.5%</td>
<td>P=0.0002</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>87.7%</td>
<td>86.6%</td>
<td>1.1%</td>
<td>P=0.0001</td>
</tr>
<tr>
<td>Recurrence</td>
<td>26.9%</td>
<td>29.8%</td>
<td>2.9%</td>
<td>P=0.005</td>
</tr>
<tr>
<td>Sustained cure</td>
<td>76.6%</td>
<td>73.8%</td>
<td>2.8%</td>
<td>P=0.0002</td>
</tr>
</tbody>
</table>


Rate of Recurrent CDI in Patients Treated for 1st Recurrence of CDI: Randomized Substudy of Phase 3 Fidaxomicin Trials

Caution for Using a Standard Treatment
Course of Fidaxomicin in Patients with
Multiple CDI Recurrences

- Two patients with multiple recurrences given treatment doses of fidaxomicin with improvement but followed by symptomatic recurrence
- Prior regimens
  - 62-YOF: M × 14 d followed by Sb twice, V (many), V tapers (several)
  - 44-YOF: (M × 14 d twice); V × 10 d twice, rifaximin chaser

Alternative Dosing Strategies for Treatment of Recurrent CDI

Randomized, Placebo-controlled Pilot Trial of Rifaximin Chaser Strategy
Fidaxomicin Chaser

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>No. of CDI episodes</th>
<th>Prior CDI Regimens</th>
<th>Duration of CDI treatment up to fidaxomicin chaser*</th>
<th>Outcome (Follow up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67/M</td>
<td>4</td>
<td>M, M, V, V</td>
<td>8 mo (6 mo continuous V until FDX chaser)</td>
<td>Success (10 mo)</td>
</tr>
<tr>
<td>2</td>
<td>80/F</td>
<td>5</td>
<td>M, V, V, V, V</td>
<td>24 mo (5 mo of continuous V until FDX chaser)</td>
<td>CDI recurrence 3 mo later, but was treated for UTI just prior to recurrence</td>
</tr>
<tr>
<td>3</td>
<td>32/F</td>
<td>8</td>
<td>M, M, V, V, R-Rx, V</td>
<td>30 mo (5 mo of continuous V until FDX chaser)</td>
<td>Success (9 mo)</td>
</tr>
</tbody>
</table>

*Following their last CDI episode, patients were 'maintained' on oral vancomycin (V) at a low dose until fidaxomicin (FDX) became available. Vancomycin was stopped and fidaxomicin 200 mg was given BID for 10 d.


68-year-old Woman Developed CDI Following Clindamycin Treatment for Infected Leg Wound (Oct’12)

<table>
<thead>
<tr>
<th>Date</th>
<th>CDI episode/symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/12/12*</td>
<td>1</td>
<td>Metronidazole × 10 days</td>
</tr>
<tr>
<td>12/06/12</td>
<td>2</td>
<td>Metronidazole × 10 days</td>
</tr>
<tr>
<td>12/21/12*</td>
<td>3</td>
<td>Vancomycin × 14 days, then taper (finished 2/27/12)</td>
</tr>
<tr>
<td>03/13/13</td>
<td>4</td>
<td>Vancomycin × 14 days, then fidaxomicin bid × 10 days Fidaxomicin chaser</td>
</tr>
<tr>
<td>04/23/13*</td>
<td>5</td>
<td>Symptoms started 17 days after completing fidaxomicin chaser (frequent, loose stools, became watery with urgency) Fidaxomicin bid × 10 days, then daily × 7 days, then every other day × 14 days Fidaxomicin taper</td>
</tr>
</tbody>
</table>

*Confirmed with positive stool C. difficile PCR assays

Alternative Fidaxomicin Dosing Regimens for Patients with Multiple CDI Recurrences

<table>
<thead>
<tr>
<th>Symptom-free intervals (SFI) &amp; subsequent recurrence rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
</tr>
<tr>
<td>Fidaxomicin Chaser (200 mg bid × 10d)</td>
</tr>
<tr>
<td>Fidaxomicin Taper (200 mg daily × 7d, then q every other day × 26d)</td>
</tr>
</tbody>
</table>

*SFI: Symptom-free interval, days
**p=0.003, compared with non-fidaxomicin taper SFI, Mann-Whitney U test
Treatments prior to the fidaxomicin regimens included: metronidazole, vancomycin, rifaximin chaser, IVIG, fecal transplant, and vancomycin taper (all patients had at least 1 vancomycin taper [mean no. = 2.3])

Emerging Approaches in Treating CDI and Reducing the Risk of Recurrence

- Narrow-spectrum antibiotics
  - Several new antibacterial agents under study
- Microbial approaches
  - FMT (pre-screened donors, capsules)
  - Biotherapeutics (e.g., non-toxigenic C. difficile [NTCD])
- Toxin binders
  - Tolevamer or similar agent as adjunctive therapy?
- Immune approaches
  - Monoclonal antibodies to toxin A and B (actoxumab/bezlotoxumab)

CDI Antibacterial Agents in Clinical Trials: www.clinicaltrials.gov

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sponsor</th>
<th>Drug Class</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB-183,315</td>
<td>Merck &amp; Co.</td>
<td>cyclic lipopeptide</td>
<td>Phase III</td>
</tr>
<tr>
<td>(surotomycin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT-179811</td>
<td>Actelion</td>
<td>quinolonyl-oxazolidinone</td>
<td>Phase III</td>
</tr>
<tr>
<td>(cadazolid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFF571</td>
<td>Novartis</td>
<td>thiopeptide</td>
<td>Phase II</td>
</tr>
<tr>
<td>SMT19969</td>
<td>Summit</td>
<td></td>
<td>Phase II</td>
</tr>
<tr>
<td>CRS3123</td>
<td>NIAID</td>
<td>methionyl-tRNA synthetase inhibitor</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

Phase 3 Trials of Actoxumab/Bezlotoxumab, mAbs as Adjunctive Therapy for CDI

- Patients receiving standard of care for primary or recurrent CDI randomly assigned to one IV infusion of
  - ACT+BEZLO 10 mg/kg each
  - ACT 10 mg/kg alone (MODIFY I)
  - BEZLO 10 mg/kg alone
  - Placebo
- 1st endpoint: recurrent CDI at 12 weeks
- MODIFY I
  - 1452 patients (19 countries); 1412 (97%) received study infusion
- MODIFY II
  - 1203 patients (17 countries); 1168 (97%) received study infusion

Recurrent CDI Rates in Two Phase 3 Trials of Actoxumab/Bezlotoxumab

\[ % \text{ Recurrence} \]

\[ \text{MODIFY I} \]

*ACT+BEZLO vs Pbo: \( p<0.0001 \)

**BEZLO vs Pbo: \( p=0.0003 \)

\[ \text{MODIFY II} \]

*ACT+BEZLO vs Pbo: \( p<0.0001 \)

**BEZLO vs Pbo: \( p=0.0003 \)


CDI Recurrence by Timepoint: Efficacy Sustained Over 12 Weeks

MODIFY I

4 weeks: 19%, 25%, 26%
8 weeks: 12%, 16%, 17%
12 weeks: 10%, 14%, 16%

MODIFY II

4 weeks: 21%, 25%, 26%
8 weeks: 10%, 14%, 16%
12 weeks: 0%, 4%, 5%


Potential Therapeutic Role of Actoxumab/Bezlotoxumab mAbs

- Adjunctive therapy: both phase 2 and phase 3 studies of actoxumab/bezlotoxumab included standard antibiotic therapy for CDI; the potential for this as stand-alone therapy is unknown
- Initial vs. recurrent CDI?
  - Could make a case for use in both settings
- Mild/moderate CDI vs. Severe CDI?
  - Stand-alone therapy in mild cases and avoid any further host dysbiosis by antibiotics?
- Adjunctive therapy for Fulminant CDI?
  - Toxemia has been identified in CDI patients (Yu H, et al. PLoS ONE. 2015;10(4):e0124235); Could toxemia be involved in the often rapid deterioration of these patients?
Summary

- Accumulating data indicate that metronidazole is inferior to vancomycin for treatment of CDI.
- Vancomycin and fidaxomicin are similarly effective for primary CDI and fidaxomicin is superior for sustained response.
- Most patients with recurrent CDI can be managed with currently available anti-infectives (e.g., vancomycin and fidaxomicin) but novel regimens need to be used (e.g., taper, post-vancomycin chaser regimens) and patients need careful follow-up.
- Unresolved issues: In what setting should fidaxomicin and FMT be used?: Primary CDI, 1st, 2nd, 3rd or later recurrence?
- Potential new treatments for CDI include additional narrow-spectrum antibiotics, biotherapeutics (NTCD), and immune-based therapy (mAb).

Notes
Center for Independent Healthcare Education is committed to supporting pharmacists in their Continuing Professional Development (CPD) and lifelong learning. Please use this form to incorporate the learning from this educational activity into your everyday practice.

Continuing Professional Development: a self-directed, ongoing, systematic and outcomes-focused approach to learning and professional development that assists individuals in developing and maintaining continuing competence, enhancing their professional practice, and supporting achievement of their career goals.

CPD Value Statement:
“Pharmacists who adopt a CPD approach accept the responsibility to fully engage in and document their learning through reflecting on their practice, assessing and identifying professional learning needs and opportunities, developing and implementing a personal learning plan, and evaluating their learning outcomes with the goal of enhancing the knowledge, skills, attitudes and values required for their pharmacy practice.”

REFLECT
Consider my current knowledge and skills, and self-assess my professional development needs and goals in the area of Clostridium difficile infection.
PLAN
Develop a “Personal Learning Plan” to achieve intended outcomes, based on what and how I want or need to learn.
Develop objectives that are specific for you, measurable, achievable, relevant to the learning/practice topic, and define the time frame to achieve them.

DO
Implement my learning plan utilizing an appropriate range of learning activities and methods. List learning activities that you will engage in to meet your goals.
List resources (e.g. materials, other people) that you might use to help achieve your goal.

EVALUATE
Consider the outcomes and effectiveness of each learning activity and my overall plan, and what (if anything) I want or need to do next.
Monitor progress regularly toward achievement of your goal.