Best practice update on Clostridium difficile Infection (CDI): Focus on Prevention, Treatment and Recurrence

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FACULTY

Kevin Garey, Pharm.D., M.S., FASHP
Professor and Chair
Department of Pharmacy Practice & Translational Research
University of Houston College of Pharmacy
Houston, Texas
VIEW BIO

A. Krishna Rao, M.D., M.S.
Assistant Professor
Division of Infectious Diseases, Department of Internal Medicine
University of Michigan Medical School
Ann Arbor, Michigan
VIEW BIO

WEBINAR INFORMATION

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- Webinar registration link
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- CE webinar processing information
Best practice update on *Clostridium difficile* Infection: Focus on Prevention, Treatment, and Recurrence

Kevin Garey, Pharm.D., M.S.  
Professor and Chair  
University of Houston College of Pharmacy  
Houston, Texas

A. Krishna Rao, M.D., M.S.  
Assistant Professor  
Division of Infectious Diseases  
Department of Internal Medicine  
University of Michigan Medical School  
Ann Arbor, Michigan

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- **Kevin Garey**
  - Merck, Inc., Summit Therapeutics, and Tetraphase: Research Support

- **Krishna Rao**
  - Merck, Inc.: Research support (Co-investigator)
On average how many patients with Clostridium difficile infection (CDI) do you provide care to each month?

a. None—I am not directly involved in patient care  
b. 1-10 patients/month  
c. 11-20 patients/month  
d. 21-30 patients/month  
e. More than 30 patients/month

Learning Objectives

• Review updates of Clostridium difficile infection (CDI) guideline recommendations  
• Apply antibiotic stewardship strategies for the primary prevention of CDI  
• Discuss treatment of CDI with a focus on sustained clinical response

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**Clostridium difficile** infection (CDI)

- Caused by Gram-positive, spore-forming bacillus
- Acute, infectious colitis with features ranging from asymptomatic colonization to diarrhea to fulminant colitis and death
- Diagnosis = compatible syndrome + organism in stool
- 450,000 cases/year
- 35,000 deaths/year
- $1.5 billion/year

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**Pathogenesis of CDI**

FMT=Fecal microbiota transplantation

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Recurrent Disease

- Definition: initial resolution of symptoms followed by clinical re-emergence with positive testing >2 weeks but <8 weeks from the index episode
- Happens in up to 25%


Recurrent Disease

- 2\textsuperscript{nd} Recurrence: 30-45\% of 1\textsuperscript{st}
- 3\textsuperscript{rd} Recurrence: 45-60\% of 2\textsuperscript{nd}
- \leq 5\% of all pa. ents → chronic, recurrent pa. ern
- No universal treatment algorithm

Who should be tested: Symptomatic patients

- Diarrhea
  - >=3 loose bowel movements (BM) per 24 hours
  - No alternate explanation
- Ileus + leukocytosis
- Colitis on imaging
- Acute abdomen with bowel wall thickening
- Toxic megacolon
- Pseudomembranes on endoscopy

Who should not be tested?

- Asymptomatic Patients
- Patients with Colonization
  - 60-70% of infants
  - 3% of healthy adults
  - 20-50% of adults in LTACs
  - Treatment not recommended
    - Doesn’t decrease risk of CDI
    - Doesn’t affect epidemiology or spread

LTAC=Long term acute care


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Who should **not** be tested?

- While on therapy
- Immediately following therapy (prolonged shedding)
  - Up to 50% of patients 6 weeks after completion of therapy
  - 10-20% become long term carriers
  - Repeat testing for “cure” and retreatment not recommended during this period unless accompanied by symptoms


Who should **not** be tested?

- Post-infectious IBS
- Long-term asymptomatic colonization following CDI occurs
  - Following treatment and recovery, transient irritable bowel syndrome (IBS) symptoms in 35%
  - Rarely persists as post-infectious IBS
  - Difficult to distinguish from recurrent CDI


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**Controversy: Inflammatory Bowel Disease**

- Asymptomatic carriage common (20-50%)
- CDI can mimic a flare
- CDI can trigger a flare
- Do you treat CDI, flare, or both?
  - Gastroenterologists divided evenly


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**Differential Diagnosis**

- **Antibiotic associated diarrhea**
- *Klebsiella oxytoca*
- post-infectious IBS
- IBD
- Celiac disease
- Ischemic colitis
- Collagenous Colitis
- Cytomegalovirus (CMV) colitis
- Routine enteric pathogens
- Parasitic pathogens
  - right risk factors or exposures (Giardia / Cryptosporidium)
- Carcinoid syndrome / other hypermotility states
How to test: Not all stools

• Some labs only test diarrheal stool

<table>
<thead>
<tr>
<th>Observation</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Look at the stool specimen</td>
<td>If it ain’t loose, it’s of no use</td>
</tr>
<tr>
<td>Put a thin lab grade stick in the specimen</td>
<td>If the stick stands, the test is banned</td>
</tr>
<tr>
<td></td>
<td>If the stick falls, test them all&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Table 2. The Brecher Guidelines*


How to test: Different assays

• Can find organism, toxin, genes, or a combination

• Organism:
  – GDH EIA + toxin EIA
  – Toxin B Gene PCR
  – GDH EIA alone not sufficient (nontoxigenic strains)

• Toxin: toxin EIA (rarely used alone now and **not recommended**)

GDH=Glutamate dehydrogenase; EIA=Enzyme immunoassay; PCR=Polymerase chain reaction

NAAT/PCR

- Can be used to detect toxigenic *C. difficile*
- Performance characteristics good
- Sensitivity / Specificity high (>90%)
- Does not detect toxin
  - Colonization vs. true disease?
  - Better prognosis?
  - Too sensitive? Real disease specificity?
- **Should be rejecting formed stools if this is your only test**

NAAT=Nucleic acid amplification test


Indications for Endoscopy with Biopsy

- Evaluating for other diseases on differential.
- High clinical suspicion for *C. difficile* with negative laboratory assays
- Ileus or minimal diarrhea
- Visualization of pseudomembranes sometimes insufficient
  - Get histology!
**Diagnosis Summary**

- Lab testing alone will not make the diagnosis
- Must integrate results with clinical picture
- Test only symptomatic patients
- Don’t “test for cure” and be aware of post-infectious IBS
- Repeat testing usually not indicated
- Endoscopy may be helpful when uncertainty exists or with ileus

**1. Treatment for CDI: First Steps**

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

2. Classify Episode

- Note history of CDI
  - 1st or subsequent recurrences, alters therapy
  - Would consider vancomycin +/- taper or fidaxomicin
  - May need to plan / coordinate outpatient care for long courses


3. Classify CDI Severity

- Severe CDI Clinical Features
  - IDSA criteria
    - WBC >15,000 cells/mL
    - Acute kidney injury (AKI) (SCr >1.5 x premorbid level)
  - Other criteria
    - Age >65
    - Albumin <2.5 g/dL
    - Fever
    - Colonic thickening / Severe abdominal pain
    - Pseudomembranous colitis
3. Classify CDI Severity

- Complicated CDI
  - IDSA criteria
    - Hypotension / shock / sepsis
    - Ileus / megacolon
  - Other features
    - Peritonitis
    - Bowel perforation

Source: NIH 2011

4. Pick your treatment based on recurrence and severity

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Supportive Clinical Data</th>
<th>Recommended Treatment&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Strength of Recommendation/ Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>Leukocytosis with a white blood cell count of &lt;15,000 cells/mL and a serum creatinine level &lt;1.5 mg/dl.</td>
<td>• VAN 125 mg given 4 times daily for 10 days, OR • FDX 200 mg given twice daily for 10 days • Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days</td>
<td>StrongHigh</td>
</tr>
<tr>
<td>Initial episode, severe&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Leukocytosis with a white blood cell count of ≥15,000 cells/mL or a serum creatinine level ≥1.5 mg/dl.</td>
<td>• VAN 125 mg 4 times per day by mouth for 10 days, OR • FDX 200 mg given twice daily for 10 days</td>
<td>StrongHigh</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>• VAN: 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.</td>
<td>Strong/Moderate (oral VAN); Weak/Moderate (rectal VAN); Strong/Moderate (intravenous metronidazole)</td>
</tr>
</tbody>
</table>

First recurrence
- VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR
- Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (e.g., 125 mg 4 times per day for 10–14 days, 2 times per day for a week, and then every 2 or 3 days for 2–8 weeks), OR
- FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode

Second or subsequent recurrence
- VAN in a tapered and pulsed regimen, OR
- VAN: 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR
- FDX 200 mg given twice daily for 10 days, OR
- Fecal microbiota transplantation<sup>c</sup>

<sup>a</sup>new in 2018


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No recommendation for the following

- Probiotics for prophylaxis or treatment
- Antibiotic prophylaxis
- Rifaximin
- Tigecycline
- Nitazoxanide
- Bezlotoxumab (although it was approved by FDA at the time the IDSA/SHEA guidelines were finalized)


Surgery Consult Indications?

- Complicated or suspected complicated CDI
- Clinical deterioration
  - Worsening abdominal distention/pain and/or peritonitis
  - Bowel obstruction
  - Intubation
  - Vasopressor requirement
  - Mental status changes
  - New or worsening Acute Kidney Injury
  - Worsening Lactate > 5mmol/L
  - Persistent or worsening leukocytosis (WBC ≥35,000 cells/mm³)
  - Hirschsprung’s disease
- Failure to improve with standard therapy within 5 days as determined by resolving symptoms and physical exam, resolving WBC/band count

Surgery Consult Outcome

- Loop ileostomy + anterograde vancomycin enemas
  - New colectomy-sparing procedure
  - Non-inferior to colectomy
- Full/partial colectomy


The Best Defense is a Good Offense

How to prevent CDI in the first place?
**C. diff** and Antibiotics

Is exposure to C. diff a rare (chance) event with a particular ‘hypervirulent’ strain?

How much antibiotic exposure do you need to be at risk (and which antibiotics)?

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**How do patients get infected in the first place?**

*Where are C diff strains coming from?*

- Leeds, England: Whole genome sequencing of 1223 cases of CDI. This allows for a highly discriminatory way to see where *C. diff* strains are coming from.

Is C. diff ubiquitous in our environment?

- We hypothesized the community environment may contain a large burden of *C. difficile* contamination.
- We recently completed a large field study to assess community environmental contamination of toxigenic *Clostridium difficile*.

Results, number of samples

<table>
<thead>
<tr>
<th>Isolate source</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental</td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>1173</td>
</tr>
<tr>
<td>Chain stores</td>
<td>230</td>
</tr>
<tr>
<td>Fast-food restaurants</td>
<td>125</td>
</tr>
<tr>
<td>Parks</td>
<td>540</td>
</tr>
<tr>
<td>Clinical isolates</td>
<td>613</td>
</tr>
</tbody>
</table>

Community environmental contamination of toxigenic *C. difficile*

![Bar graph showing contamination levels in different environments.](image)

**p<0.001 compared to either chain stores, fast-food restaurants, or other commercial stores


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Home environmental contamination of toxigenic *C. difficile*

![Bar graph showing contamination levels in different home environments.](image)

**p<0.001 comparing shoe soles and doorsteps to cleaning supplies, kitchen and restroom samples


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Ribotype distribution of clinical vs. environmental *C. difficile* isolates

CDI update #1: *C. diff* is ubiquitous

How much antibiotic exposure do you need to be at risk (and which antibiotics)?
Next: Welcome to the wonderful world of the microbiome!

Welcome to a whole new area of 'omics' science!

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Gut microbiota: 16S RNA sequencing

**Formiculates:**
- Mostly good (C. diff is a formicate)
- Mostly spore formers (think: probiotic)
- Usually largest component of microbiota

**Bacteroidetes**
- Mostly good (Bacteroides predominates)
- Non-spore forming
- Usually tied for largest component

**Actinobacteria**
- Mostly good
- Not very common, sort of the ugly stepsister of the healthy microbiota

**Proteobacteria**
- Good in small quantities (this is E. coli, Klebsiella, etc.)
- This is where the ‘overgrowth’ occurs after antibiotic therapy

Microbiome analysis is all about abundance, diversity, and types of organisms present

Microbiome of non-CDI patients vs. CDI patients

Total colony forming units (CFU) abundance
Diversity of microbiologic species
Other pathogenic organisms

The microbiome of recurrent CDI patients is much less diverse

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

The microbiome “organ” continues to be damaged with recurrent CDI

Michigan: 93 patients with CDI. Fecal microbiome diversity during initial infection (A) and during follow up period

What else do we have in our damaged microbiome?

Canada: Number of antibiotic resistant genes (ABR) present in stool samples from patients with recurrent CDI before and after FMT (n=8)
Now that we have an understanding of how microbiome studies work, we can apply this technology to better understand how antibiotics kill our microbiota and what we can do about it!

C. Diff colonization in mice exposed to a variety of antibiotics for 5 days

5 days of antibiotics are more than enough to completely change the microbiota

...and this disruption is more than enough to support C diff colonization

Schubert et al. Mbio. 2015;6:e00974
The effect on the microbiome starts almost immediately

- 14 healthy volunteers given ceftaroline-avibactam X 7 days
- Changes in microbiota assessed over 21 days


We are now able to predict the antibiotics most likely to cause CDI!!

- Any antibiotic that kills firmicutes and/or bacteroides will almost immediately increase CDI risk
- Thus: the most common antibiotic used with these properties will be the most likely to be associated with CDI
Antibiotics that increase CDI risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kills firmicutes</th>
<th>Kills bacteroidetes</th>
<th>Commonly used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin-sulbactam</td>
<td>Yes</td>
<td>Yes</td>
<td>Medium</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes and increasing</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Yes</td>
<td>Yes</td>
<td>Not as much</td>
</tr>
</tbody>
</table>

Which antibiotics are risk factors at our hospital?

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

<table>
<thead>
<tr>
<th>Individual Antibiotic</th>
<th>OR (ABX Received (Y/N))</th>
<th>P-Value</th>
<th>Antibiotic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin/Sulbactam</td>
<td>1.640</td>
<td>0.012</td>
<td>1.7%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1.673</td>
<td>&lt; 0.001</td>
<td>16.1%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1.464</td>
<td>&lt; 0.001</td>
<td>21.8%</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>1.864</td>
<td>&lt; 0.001</td>
<td>3.6%</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2.077</td>
<td>&lt; 0.001</td>
<td>3.2%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1.335</td>
<td>0.020</td>
<td>2.8%</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>1.665</td>
<td>&lt; 0.001</td>
<td>16.6%</td>
</tr>
<tr>
<td>Age</td>
<td>1.009</td>
<td>&lt; 0.001</td>
<td>N/A</td>
</tr>
<tr>
<td>Proton Pump Inhibitor (Y/N)</td>
<td>1.375</td>
<td>&lt; 0.001</td>
<td>N/A</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>1.208</td>
<td>&lt; 0.001</td>
<td>N/A</td>
</tr>
</tbody>
</table>

OR = odds ratio; ABX - antibiotic

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

<table>
<thead>
<tr>
<th>Received High Risk Antibiotic?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Received PPI?</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>CDI Incidence (%)</td>
<td>0.14</td>
<td>0.58</td>
</tr>
</tbody>
</table>

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

We can now update an old slide with newer antibiotics

If I was a betting man, I would guess that carbapenems will be the ‘cause’ of the next C. diff epidemic.
CDI update #1 and #2: 
*C. diff* is ubiquitous and antibiotic risk happens quickly

Stewardship approaches to protect the microbiome

<table>
<thead>
<tr>
<th>Stewardship intervention</th>
<th>Will it work to decrease CDI rates</th>
<th>Caveat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic time-out</td>
<td>Yes</td>
<td>Get an initial microbiome hit that persists but perhaps faster restoration</td>
</tr>
<tr>
<td>Rapid diagnostics</td>
<td>Yes</td>
<td>Especially if get rid of early, broad-spectrum antibiotic use</td>
</tr>
<tr>
<td>IV to PO conversion</td>
<td>Maybe</td>
<td>Only if switch to oral that doesn't damage microbiome (aka, no cipro or amox-clav, please)</td>
</tr>
<tr>
<td>Formulary restriction</td>
<td>Yes</td>
<td>Most evidence supports this approach</td>
</tr>
<tr>
<td>Anything that slows down carbapenem use</td>
<td>Yes</td>
<td>No caveats here, this is always a good idea when you can do it!!</td>
</tr>
</tbody>
</table>

## Stewardship interventions and CDI rates

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Stewardship method</th>
<th>Pre-intervention</th>
<th>Post-intervention</th>
<th>Reduction in CDI rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>USA</td>
<td>Restrictive use</td>
<td>15.8</td>
<td>1.9</td>
<td>88%</td>
</tr>
<tr>
<td>1997</td>
<td>UK</td>
<td>Restrictive use</td>
<td>5.3</td>
<td>2.3</td>
<td>57%</td>
</tr>
<tr>
<td>1998</td>
<td>USA</td>
<td>Restrictive use</td>
<td>11.5</td>
<td>3.3</td>
<td>71%</td>
</tr>
<tr>
<td>2003</td>
<td>UK</td>
<td>Restrictive use</td>
<td>14.6</td>
<td>3.4</td>
<td>77%</td>
</tr>
<tr>
<td>2003</td>
<td>USA</td>
<td>Prospective audit and feedback</td>
<td>2.2</td>
<td>0.3</td>
<td>86%</td>
</tr>
<tr>
<td>2004</td>
<td>UK</td>
<td>Restrictive use</td>
<td>46</td>
<td>22</td>
<td>52%</td>
</tr>
<tr>
<td>2004</td>
<td>USA</td>
<td>Restrictive use</td>
<td>1.32</td>
<td>0.51</td>
<td>61%</td>
</tr>
<tr>
<td>2007</td>
<td>UK</td>
<td>Prospective audit and feedback</td>
<td>NR</td>
<td>NR</td>
<td>65%</td>
</tr>
<tr>
<td>2007</td>
<td>Canada</td>
<td>Restrictive use</td>
<td>2.03</td>
<td>0.82</td>
<td>60%</td>
</tr>
<tr>
<td>2011</td>
<td>UK</td>
<td>Restrictive use</td>
<td>2.22</td>
<td>0.45</td>
<td>80%</td>
</tr>
<tr>
<td>2012</td>
<td>Canada</td>
<td>Prospective audit and feedback</td>
<td>1.12</td>
<td>0.71</td>
<td>37%</td>
</tr>
<tr>
<td>2013</td>
<td>UK</td>
<td>Restrictive use</td>
<td>2.40</td>
<td>1.2</td>
<td>50%</td>
</tr>
</tbody>
</table>

## Clinical studies examining CDI bundles

<table>
<thead>
<tr>
<th>Study</th>
<th>CDI setting</th>
<th>Population</th>
<th>Control bundle</th>
<th>Effect size (Before/after)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bishop, 2013</td>
<td>Endemic</td>
<td>Surgical inpatients (17,145)</td>
<td>Resident rounding, hand hygiene, stop PPI, ASP</td>
<td>2.8/1000 pd 1.8/1000 pd</td>
</tr>
<tr>
<td>Koll, 2013</td>
<td>Endemic</td>
<td>Adult inpatients (14,591)</td>
<td>Contact precautions, hand hygiene, isolation, environmental cleaning</td>
<td>12/10,000 hosp 8/10,000 hosp</td>
</tr>
<tr>
<td>Abbett, 2009</td>
<td>Endemic</td>
<td>Adult inpatients (881)</td>
<td>Contact precautions, hand hygiene, EVS, vancomycin for Rx</td>
<td>1.1/1000 pd 0.66/1000 pd</td>
</tr>
<tr>
<td>Salgado, 2009</td>
<td>Epidemic</td>
<td>Adult inpatients</td>
<td>Contact precautions, EVS, hand hygiene</td>
<td>1.8/1000 pd 1.2/1000 pd</td>
</tr>
<tr>
<td>Weiss, 2009</td>
<td>Epidemic</td>
<td>Adult inpatients</td>
<td>EVS, contact isolation, ASP</td>
<td>37.3/1000 pd 14.5/1000 pd</td>
</tr>
<tr>
<td>Muto 2007</td>
<td>Epidemic</td>
<td>Adult inpatients</td>
<td>EVS hand hygiene, contact isolation, ASP</td>
<td>7.2/1000 pd 3.0/1000 pd</td>
</tr>
</tbody>
</table>

PPI=proton pump inhibitor; EVS=Environmental services

Despite our best stewardship efforts, patients are still going to get CDI

....and many of them will get recurrent CDI

Fecal Microbiota Transplantation—The Solution?

- 1983 FMT enema (Schwann A et al., 65 y/o woman with CDI; better in 24 hr)
- 1991 NG tube (Aas, Gessert, Bakken)
- 2000 colonoscopy (Persky, Brandt)
- 2010 self-administered enemas (Silverman, Davis, Pillai)
- Slow acceptance due to concerns over safety and acceptability (no longer true?)

FMT: Fecal Microbiota Transplantation

- A consideration for recurrent CDI refractory to medical therapy
  - Only FDA approved indication

- Not proven in severe CDI or primary CDI
- Mechanism of action poorly understood
- Appears to be safe and effective

First Word: FMT is Effective

- 92% of patients had resolution, 89% after 1 treatment and 5% after retreatment
- 4% had a relapse; 87.5% had resolution with retreatment.
- No serious adverse events

FMT Goes Randomized Controlled Trial (RCT)

- The study was stopped early
- Off-protocol FMT offered to patients in other treatment arms (n=18):
  - 83% cure rate


Another FMT RCT stops early

- Open label RCT
- Stopped after 39 patients
- 90% efficacy in FMT arm vs. 26% in vancomycin arm

Frozen vs. Fresh?

- 219 patients enrolled in RCT
- Cure 75% frozen, 70.3% fresh (mITT)
- Noninferiority reached
- Context and issues in editorial:

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Expanded Evidence for Frozen Fecal Microbiota Transplantation for Clostridium difficile Infection
A Fresh Take
Preeti N. Malani, MD, MS, Krishna Rao, MD, MS
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mITT=Modified intention to treat


FMT route?

- Small RCT comparing nasogastric to lower route showed no difference (n=20)
- Overall cure 90%

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Hold on a second: placebo and/or non-Bacterial FMT works?

- 90% cure with patients’ own stool in recent RCT
- Filtered stool confirmed on culture and PCR to be bacteria-free: cured 5 patients


Does FMT really work that well?

- Prior studies used non-standard comparators (2 weeks of vancomycin, chronic recurrence)
- No better than vancomycin taper in recent RCT on acute CDI patients, although enema only
- The authors on difference with prior RCTs not using a placebo control arm (emphasis mine):
  “Without a control arm in either trial, it is not known what proportion of patients would have been symptom-free had their antibiotics been simply discontinued.”

FMT: Open Questions

- Who benefits the most? Unknown
- Long term safety? Unknown
  - Microbiota associated with diabetes mellitus, obesity, cancer, atopic/autoimmune disorders
- Safe in immunocompromised? Possibly
  - Concern in patients with IBD raised
- Effective / safe for primary / severe CDI?
  - Yet to be established
- Optimal route, preparation, and stool characteristics unknown
- Other indications?
  - Beyond scope of this talk

Despite the fact that FMT is awesome, it is not available for everyone

.....any other strategies we can use?
Serum concentrations of IgG antibodies against toxin A, toxin B, and non-toxin antigens

Kyne et al. *Lancet* 2001;357:189-93

Monoclonal antibodies: phase II study


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Phase III studies of actoxumab (acto) and bezlotoxumab (bezlo):
Overall


BEZLO was also shown to reduce hospital readmissions (European population)

SOC=Standard of care

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

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

- **Clinical Outcomes**
  - Extended-pulsed fidaxomicin (n=177)

- **Recurrence**
  - Day 12
  - Day 40
  - Day 55
  - Day 90

- **Sustained clinical cure**
  - Day 40
  - Day 55
  - Day 90


Conclusions

- New IDSA/SHEA guidelines de-emphasize use of metronidazole and increased use of vancomycin and fidaxomicin
- Antimicrobial stewardship strategies have been shown to be effective to decrease CDI rates, use science to your advantage
- FMT, novel uses of indicated agents (fidaxomicin), and new treatment modalities (bezlotoxumab) may help decrease the burden of recurrent CDI
Which of these practice changes will you consider making?

- Discuss with colleagues the disease burden of CDI
- Educate staff on the emerging and current treatment options for managing patients with CDI
- Incorporate most current evidence-based guidelines into practice when treating patients with CDI
- Apply emerging evidence and treatment recommendations for managing patients with CDI
- Collaborate with other healthcare professionals to achieve optimal outcomes for preventing and treating patients with CDI

Thank you for participating!

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- Archive of today’s webinar coming mid-November
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