7:45 – 8:45 am
New Approaches to Treating C. difficile Infection
SPEAKER
Fred A. Lopez, MD, MACP

New approaches to treating Clostridium difficile Infection
Fred A. Lopez, MD, MACP

Learning Objectives
• Distinguish risk factors for C. difficile infection (CDI) in an outpatient with recent diarrheal symptoms
• Consider the pros and cons of treatment modalities
• Employ prevention measures for clinicians, patients, and households

Case 1: Mr. Murray
70-Year-Old Man

Presents with:
• 4-6 loose stools/day
• Slight fever (100°F) x 5 days
• No unusual physical findings except for mild abdominal pain
• Denies nausea/vomiting, blood in stool, unusual diet or travel in recent weeks

Relevant PMH:
• COPD x 10 years, uses inhaler as needed
• GERD, for which he takes daily proton pump inhibitor (PPI)
• AECB 1-2 times per year – Last episode 6 weeks ago, for which he took a 10-day course of ceftriaxone

Urgent Threats:
1. Clostridium difficile
2. Carbapenem-resistant Enterobacteriaceae
3. Drug-resistant Neisseria gonorrhoeae

Presenter Disclosure Information
The following relationships exist related to this presentation:
► Fred A. Lopez, MD receives royalties from UpToDate® as an author of several chapters.

Off-Label/Investigational Discussion
► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

**C. difficile Infection (CDI)**

- Although *C. difficile* is common in the environment, only 1 - 4% of adults are carriers.
- Normal colonic microflora confers colonization resistance against *C. difficile*.

**Traditional risk factors:**
- Age >65 years and/or underlying illness (weakened immune system).
- Recent antibiotic exposure (up to 3 months prior), resulting in disturbed colonic microflora (dysbiosis).
- Recent exposure to health care settings (hospital, long-term care facility, nursing home).

**New Strain: BI/NAP1**

- Since 2001, severe outbreaks have occurred in health care facilities in the U.S., Canada, and Europe.
- New Strain: North American pulsed-field gel electrophoresis Type 1 (NAP1)

**Community-Acquired CDI: A New Disease Entity**

Less than 1/5 of all disease appears to be community-associated.

**Population-based study in the UK**
- 50% of elderly patients diagnosed with CDI had no history of antibiotic exposure in the 45 days prior to being admitted to hospital for CDI.
- Women at higher risk than men.
- Within the preceding 3 months:
  - 59% had no exposure to antibiotics.
  - 23% had taken a proton pump inhibitor (PPI).
  - Only 59% had visited a facility as outpatients.

**North Carolina County Study**
- 25/100,000 overall incidence of community-associated CDI.
- Women at higher risk than men.
- Within the preceding 3 months:
  - 59% had no exposure to antibiotics.
  - 23% had taken a proton pump inhibitor (PPI).
  - Only 59% had visited a facility as outpatients.

**CDI Risk Factors: A Closer Look at PPIs**

Increasing evidence identifies PPI exposure as an independent risk factor for community-associated CDI.

- Adjusted RR = 2.9 (95% CI, 2.4-3.4) in Canadian general practice database.

Vegetative form of *C. difficile* has been shown to survive in gastric contents with a raised pH.

**February 8, 2012**

**Traditional CDI Risk Factors (cont’d)**

Other factors that disturb colonic microflora can put patients at risk:
- Bowel prep for colonoscopy or surgery.
- Cytotoxic chemotherapy.
- Colitis caused by IBD.

**New Strain: BI/NAP1**

- Genetic variations enable it to produce:
  - Greater quantities (at faster rates) of toxins A (16X) and B (25X)
  - "Hypervirulent" NAP1 More Virulent

- Wide fluoroquinolone use in recent years has contributed to NAP1 emergence.

**NAP1 More Resistant**

- Particularly to fluoroquinolones.


Possible New Modes of Transmission?

Reports of *C. difficile* in food:

- Retail meat in Canada (2007)¹
- Retail meat (both uncooked and ready-to-eat) from supermarkets in Tucson, AZ (2007)²
  - Including about a quarter identified as NAP1 or NAP1-related strains*
  - All isolates were positive for toxins A and B, and binary toxin
- Ready-to-eat (imported) salads in Glasgow, Scotland (2008)³

Notes:

* NAP1 strain testing is not FDA approved yet.


Testing for CDI

- Absence of traditional risk factors no longer rules out CDI
- Testing is merited even in patients who have no known risk factor
- Only diarrheal stools should be tested (unless intestinal ileus is present)

C. *difficile* – Diagnosis Summary

- In patients with new diarrhea, *C. difficile* infection should be in the differential diagnosis
  - Increased risk if antibiotic or health care exposure
- *C. difficile* spores can be carried in the gut
  - Asymptomatic patients should not be tested and do not warrant therapy
- Test stool only in actively symptomatic patients
  - PCR is best test (highly sensitive)
  - EIA less sensitive; if high clinical suspicion, start empiric therapy even if this test is negative, and evaluate with a PCR test

Sniff Test?

*C. difficile* produces a unique odor attributed to a phenol: p. cresol

A dog’s olfactory sense is 300X that of humans

Testing for *C. difficile* Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Speed of Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIA (enzyme immunoassay)</td>
<td>Detects toxin A or toxin A plus B</td>
<td>70-80%</td>
<td>&gt;97%</td>
<td>Hours</td>
</tr>
<tr>
<td>GDH (glutamate dehydrogenase)</td>
<td>Detects a common antigen, not a toxin, of C. difficile; immunoassay is preferred over latex agglutination</td>
<td>70-80%</td>
<td>&lt;90%</td>
<td>Hours</td>
</tr>
<tr>
<td>qPCR (qualitative real-time polymerase chain reaction)</td>
<td>Detects toxin B or toxin regulator genes; commercial and locally developed tests are available</td>
<td>&gt;90%</td>
<td>&gt;97%</td>
<td>Hours</td>
</tr>
<tr>
<td>Anaerobic culture for bioterror C. difficile</td>
<td>Detects Toxin B</td>
<td>&gt;90%</td>
<td>96-97%</td>
<td>2 to &gt;3 d</td>
</tr>
<tr>
<td>Direct stool cytotoxin with tissue culture</td>
<td>Detects Toxin B</td>
<td>70-80%</td>
<td>&gt;97%</td>
<td>2 to &gt;3 d</td>
</tr>
</tbody>
</table>

Using a Dog’s Superior Olfactory Sensitivity to Identify *C. difficile* in Stools and Patients

- 300 patients tested
  - 30 had *C. difficile* infection (by EIA and culture) and 270 controls (negative by EIA and culture)
  - “Cliff” trained to sit or lie down when *C. difficile* detected

How did Cliff do?

- Stool samples: specificity and sensitivity: 100%
- Ward detection rounds
  - Identified 25 of 30 infected cases (83% sensitivity)
  - Identify 265 of 270 controls without infection (98% specificity)

Bomers MK et al. BMJ 2012;345:e7396  doi:10.1136/bmj.e7396

SHEA/IDSA Clinical Practice Guidelines

- Mild or moderate CDI
  - Peripheral WBC of \( \leq 15,000/\mu L \) and serum creatinine \(<1.5 \text{ times the baseline}\)
- Severe CDI
  - Peripheral WBC of \( > 15,000/\mu L \) or a serum creatinine \( > 1.5 \text{ times the baseline}\)
- Severe, complicated CDI
  - Shock, ileus, megacolon; hypotension

SHEA = Society for Healthcare Epidemiology of America
IDSA = Infectious Diseases Society of America

Complications of Severe CDI

- Mild disease can progress to moderate or severe disease.
- Serious, potentially life-threatening complications:
  - Pseudomembranous colitis
  - Paralytic ileus
  - Toxic megacolon
  - Intestinal perforation
  - Septis
- Overall, attributable mortality rate for CDI: 6–15%
- After surgery for complications of CDI, mortality rate rises to 32–50%


C. difficile – Treatment Principles

**Stop other antibiotics, if possible***

**Avoid antimotility agents**

**Supportive Care**
- Fluids
- Diet as tolerated

**Initiate CDI Therapy**
- If diarrhea (or abdominal pain/distension if ileus) and a positive test
- Not just for a positive test in absence of GI symptoms
- Empiric treatment OK if strong clinical suspicion

* Concomitant antibiotics prolong diarrhea and increase risk of recurrence

Antimicrobials for CDI

<table>
<thead>
<tr>
<th>Metronidazole</th>
<th>Vancomycin</th>
<th>Fidaxomicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved by FDA for CDI</td>
<td>No, but efficacy supported by early RCTs</td>
<td>Yes</td>
</tr>
<tr>
<td>Comparative Cost</td>
<td>S</td>
<td>S$</td>
</tr>
<tr>
<td>Form used for CDI</td>
<td>Oral</td>
<td>Oral, intragastric or enema</td>
</tr>
<tr>
<td>Duration</td>
<td>10-14 days</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Notes</td>
<td>Preferred for mild to moderate disease</td>
<td>Preferred and more effective for severe disease; also indicated when metronidazole cannot be used or is not effective</td>
</tr>
</tbody>
</table>

Recurrent CDI

Up to 20-30% of patients with CDI have recurrence within 3 months

- Increased risk with use of antibiotic or proton pump inhibitors

If relapse of diarrhea in patient with recent CDI...

Empiric treatment if...

SHEA/IDSA Clinical Practice Guidelines

First recurrence treated same as initial episode

- Mild or moderate CDI (A-I)
  - Peripheral WBC of ≤ 15,000/µL and serum creatinine <1.5 times the baseline
    - Metronidazole, 500 mg orally 3 times daily X 10-14 d
- Severe CDI (B-I)
  - Peripheral WBC of > 15,000/µL or a serum creatinine >1.5 times the baseline
    - Vancomycin, 125 mg orally 4 times daily X 10-14 d
- Severe, complicated CDI (C-III)
  - Shock, ileus, megacolon; hypotension
    - Vancomycin (orally or NG tube), 500 mg 4 times daily AND metronidazole, 500 mg intravenously every 8 hours
    - Vancomycin by rectum when ileus present

Future Additional Recurrences

- Oral vancomycin, 125 mg 4 times a day for 14 days, followed by rifaximin, 400 mg twice daily for 14 days
- Consider combination therapy with oral vancomycin and oral rifaximin
- Fidaxomicin, 200 mg twice daily for 10 days
- Consider intravenous immunoglobulin, 400 mg/kg, repeated up to 3 times at 3-week intervals
- Consider fecal microbiota transplantation

Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile


Fecal Microbiota Transplantation

- First described in 1958
- Reluctance to accept?
  - Aesthetically unappealing
  - Logistically challenging
  - Lack of efficacy data from randomized, controlled trials

Recurrent CDI Treatment

Second recurrence

- Oral vancomycin tapered over 6 wk
  - 125 mg 4 times daily for 14 d
  - 125 mg 2 times daily for 7 d
  - 125 mg once daily for 7 d
  - 125 mg once every other day for 8 d
  - 125 mg once every 3 d for 15 d
Random assignment to 1 of 3 therapies:

– Initial vancomycin (500 mg PO four times daily X 4 days) followed by bowel lavage and then infusion of donor feces via nasoduodenal tube
– Standard vancomycin therapy (500 mg PO four times daily X 14 days)
– Standard vancomycin therapy (500 mg PO four times daily X 14 days) with bowel lavage

Primary end point
– Resolution of *C. difficile*-associated diarrhea without relapse after ten weeks

Results – Interim Analysis

• 13/16 (81%) in infusion group had resolution of *C. difficile*-associated diarrhea after the first infusion
  – The 3 remaining patients received a second feces infusion from a different donor; resolution in 2/3 patients
• Resolution occurred in 4/13 patients (31%) receiving vancomycin alone and in 3/13 patients (23%) receiving vancomycin with bowel lavage

Results

The trial was closed to new enrollment by its data and safety monitoring board

• 43 of a planned 120 patients had undergone randomization
• Almost all patients in the two control groups had a recurrence

Fecal Microbiota Transplant: How It’s Done Screening

**Screen Donor**
Serum: CBC, hepatitis A, B, and C; HIV-1 and HIV-2, syphilis
Stool: FECAL Giardia antigen, cryptosporidium antigen, acid fast stain for Cyclospora, Isospora, and H. pylori fecal antigen; enteric bacterial pathogens ; O&P; C. diff
Clinical: No antibiotics in past 3 months; no IBD; clinically well

**Screen Recipient**
Hepatitis A and B; HIV-1

Fecal Microbiota Transplant: How It’s Done Treatment

**Oral vancomycin:** 500 mg BID x 7 days then...

3–4 liters of oral polyethylene glycol lavage

200–300 g of donor stool in 200–300 mL of sterile normal saline (homogenize in blender to a liquid consistency)
Administer via enema within 10 minutes of preparation
Retain the enema for at least 6 hours
Repeat daily for 5 days

OR a single infusion by colonoscopy of 200–300 g of stool suspension into colon can be tried if less severe disease (but risk of perforation)
**Fecal Microbiota Transplant (FMT): How to Get It Done**

- Current US FDA Regulations only allow FMT for treatment of *C. difficile* infection that does not respond to standard treatment, unless part of an approved clinical trial
- http://thefecaltransplantfoundation.org/providers-trials

**Fecal Transplant- Mail Order**

- Nonprofit 501(c)(3) organization
- Provides material that is concentrated and packaged for either colonoscopic or nasogastric administration
- Service fee of $250 per treatment to recover the costs of donor screening, lab management, and material preparation
- CPT code 44705, Preparation of fecal microbiota for instillation, including assessment of donor specimen
- Orders are processed and delivered within 5 business days
  - Need to keep frozen
- Current FDA guidance allows use for CDI but new draft regulation may restrict use to stool that is collected and screened by the treating physician
- http://www.openbiome.org/

**Stool Substitute Transplant Therapy for the Eradication of Clostridium Difficile Infection: ‘Repoopulating’ the Gut**

- “Here we report the successful outcome of two patients with recurrent CDI unresponsive to conventional therapy who received a stool substitute, a preparation of 33 different intestinal bacteria isolated in pure culture, from a single healthy donor.”
- Report of 2 patients with recurrent *C. difficile* infection (strain ribotype 078) who were successfully treated with RePOOPulate synthetic stool preparation
  - Both patients remained without symptoms at 6 months post-treatment

**Prevention of CDI**

- Handwashing!
- Prudent use of antimicrobials
- Possible addition of probiotics containing viable lactobacilli or *Saccharomyces* species to antibiotic regimen

**Which Antibiotics are High Risk?**

- Despite recent trends, antimicrobial therapy is still the most important risk factor for CDI.
- Historically, cephalosporins and clindamycin were associated with highest risk, as well as ampicillin/ amoxicillin.

**Which Antibiotics Are High Risk, Given Changing Epidemiology?**

Large recent study of community-based population using Canadian health databases

<table>
<thead>
<tr>
<th>Risk of individual agents</th>
<th>Agent</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>31.8</td>
<td>(17.6-57.6)</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>16.7</td>
<td>(8.3-33.8)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>14.9</td>
<td>(10.9-20.3)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>9.1</td>
<td>(4.8-17.0)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>5.0</td>
<td>(3.7-8.0)</td>
</tr>
<tr>
<td>Penicillins</td>
<td>4.3</td>
<td>(2.8-6.4)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>4.1</td>
<td>(2.4-7.1)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>3.9</td>
<td>(2.5-5.9)</td>
</tr>
</tbody>
</table>

C. difficile Prevention through Antimicrobial Stewardship

Antibiotic Stewardship

- Avoid empirical use of broad-spectrum antibiotics

“High Risk” antibiotics for C. difficile include:

- 3rd generation cephalosporins, fluoroquinolones, and clindamycin

C. difficile Prevention: Probiotics

Formulations of live bacteria and fungi that act by maintaining bowel flora and prevent colonization of pathogens

- *Bifidobacterium* spp., *Saccharomyces* spp., *Lactobacilli* spp
- Larger doses are more effective (>10 billion CFU/day)
- Many formulations available OTC in health food stores


C. difficile Prevention: Probiotics

Conflicting evidence:

- 20 RCTs of probiotics showed
  - 66% reduced risk (RR 0.34 [0.24;0.49]) in C. difficile-associated diarrhea (CDAD) in patients receiving antibiotics
  - No difference in adverse event rates from control groups

- Moderate quality evidence suggests that probiotics are both safe and effective for preventing Clostridium difficile-associated diarrhea

- Probiotics did not prevent antibiotic or CDAD in hospitalized patients ≥ 65 getting antibiotics

- There is insufficient evidence that probiotics prevent CDI.

- Their routine use for the prevention or treatment of active infection is not recommended.


C. difficile Prevention: Probiotics

Give probiotic 2 hours separated from oral antibiotic dose

- Continue probiotics for 3-14 days after end of antibiotic therapy

Risks of probiotic associated infection are minimal

- Rare cases of bacteremia and fungemia
- Avoid probiotics in patients with immune compromise, endocarditis risk, recent GI or heart surgery, acute pancreatitis, diseases that compromise GI barrier function


C. difficile Prevention and Precautions

For Clinicians

- Hand Hygiene! Clean hands with soap and water (preferred) or alcohol based rub before and after caring for every patient *
- Contact precautions (gowns/gloves)
- Environmental disinfection (bleach)
- Limit antibiotics

For Patients

- Hand Hygiene! (yourself and your provider)
- Only use antibiotics when prescribed

For Households

- Hand Hygiene! (yourself and your family)
- Keep high touch surfaces clean

* Alcohol does not effectively kill C. difficile spores

CDI: Take-Home Points

- New, more virulent disease strains have made timely diagnosis and treatment more critical:
  - Consider CDI in all pts with persistent severe diarrhea, even if traditional risk factors are absent or in the distant past
  - Stratify treatment according to severity of disease
    - Marked leukocytosis or increased creatinine or elevated lactate suggests more serious disease
- Contact precautions, hand hygiene and environmental disinfection important for prevention/control
- Prescribe antibiotics prudently