New Approaches to Treating C. difficile Infection

Kalpana Gupta, MD, MPH

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

Urgent Threats:

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

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)
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

Kelly CP. JAMA. 2008;301:954-962.

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)
• NAP1 strain testing is not FDA approved yet

<table>
<thead>
<tr>
<th>NAP1 More Virulent</th>
<th>NAP1 More Resistant</th>
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<tbody>
<tr>
<td>Genetic variations enable it to produce:</td>
<td>Particularly to fluoroquinolones:</td>
</tr>
<tr>
<td>Greater quantities (at faster rates) of toxins A (16X) and B (25X)</td>
<td>“Hypervirulent” Wide fluoroquinolone use in recent years has contributed to NAP1 emergence</td>
</tr>
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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.

Kugler J, van Donsel JT. CMAJ. 2006;175:141-146.

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

Kugler J, van Donsel JT. CMAJ. 2006;175:141-146.

Community-Associated C. difficile Connecticut 2006

Clinical features among patients with community-associated C. difficile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>#</th>
<th>%</th>
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<tbody>
<tr>
<td>Abdominal Pain (n=222)</td>
<td>169</td>
<td>(76)</td>
</tr>
<tr>
<td>Vomiting (n=221)</td>
<td>50</td>
<td>(23)</td>
</tr>
<tr>
<td>Diarrhea (n=236)</td>
<td>227</td>
<td>(96)</td>
</tr>
<tr>
<td>Bloody diarrhea (n=209)</td>
<td>48</td>
<td>(23)</td>
</tr>
<tr>
<td>Fever (n=203)</td>
<td>56</td>
<td>(28)</td>
</tr>
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</table>


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
• Could shorten time needed for ingested acid-resistant spores to change to vegetative cells

RR = relative risk

February 8, 2012
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


*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 send a PCR

MMWR / August 10, 2012 / Vol. 61 / No. 31

Sniff Test?

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

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

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

Using a dog’s superior olfactory sensitivity to identify *Clostridium difficile* in stools and patients: proof of principle study

Marie K Borns Consulting; Michel A van Agmael consultant; Hotche Luik canine trainer and psychologist; Hein C van Veen resident; Christina M J S Vandenbroucke-Grauls professor; Yvo M Smulders professor

Department of Internal Medicine, UU University Medical Center, PO Box 7075, 3500 GB Amsterdam, Netherlands; "Team Detection Academy and Research, Animal Behavior and Cognition", BV/HONK, Etten, Netherlands; "Department of Internal Medicine, St Lucas Antwerp Hospital, Antwerp, Belgium; "Department of Medical Microbiology and Infection Control, UU University Medical Centre"
**C. difficile Infection: Signs and Symptoms**

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Mild</th>
<th>Severe</th>
</tr>
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<tbody>
<tr>
<td>Host develops no symptoms, but remains a potential carrier.</td>
<td>Mild to moderate non-bloody diarrhea</td>
<td>Profuse watery diarrhea</td>
</tr>
<tr>
<td>Mild abdominal cramps</td>
<td>Fever, nausea, dehydration often occur</td>
<td>Pseudomembranous colitis OR any 2 of these features:</td>
</tr>
<tr>
<td>+/- low grade fever</td>
<td>Age &gt;60 years</td>
<td>Temp &gt;101°F</td>
</tr>
<tr>
<td></td>
<td>Serum albumin &lt;2.5 mg/dL</td>
<td>Peripheral white blood cell count &gt;15,000 uL</td>
</tr>
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Adapted from Kelly CP. *JAMA*. 2009;301(9):954-962.


**Complications of Severe CDI**

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

**Findings that appear predictive of more serious complications:**
- Increased creatinine
- High white blood cell count
- High lactate level

**SHEA/IDSA Clinical Practice Guidelines**

- **Mild or moderate CDI**
  - Peripheral WBC of ≤15,000/µL and serum creatinine <1.5 times the baseline
- **Severe CDI**
  - Peripheral WBC of >15,000/µL or a serum creatinine >1.5 times the baseline
  - Severe, complicated CDI
  - Shock, ileus, megacolon; hypotension

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


**C. difficile – Treatment Principles**

**Stop other antibiotics, if possible**

**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
- Empircal treatment OK if strong clinical suspicion

**Antimicrobials for CDI**

<table>
<thead>
<tr>
<th>Metronidazole</th>
<th>Vancomycin</th>
<th>Fidaxomicin</th>
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</thead>
<tbody>
<tr>
<td>Approved by FDA for CDI</td>
<td>No, but efficacy supported by early RCTs; equals that of vancomycin</td>
<td>Yes</td>
</tr>
<tr>
<td>Comparative Cost</td>
<td>$</td>
<td>$5</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>
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Fidaxomicin Prescribing Information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201699s000lbl.pdf
Recurrent CDI

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

- Increased risk if antibiotic or proton pump inhibitors

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

Empiric treatment if...

- Fever, distended abdomen, high white blood cell count and high clinical suspicion


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


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


Additional Recurrent CDI Treatment Options

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
- Consider intravenous immunoglobulin, 400 mg/kg, repeated up to 3 times at 3-week intervals
- Consider fecal microbiota transplantation


Fecal Microbiota Transplantation

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


Fecal Microbiota Transplantation (FMT)

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

Figure 2: Rates of Cure without Relapse for Recurrent Clostridium difficile Infection

Figure 3: Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared With Bacteria in Health Donors

**Fecal Microbiota Transplant: Overview**

| Evidence | Multiple observational and randomized studies showing benefit
| Resolution of diarrhea and associated symptoms within 24 hours to 12 days
| Donor fecal microbiota remains stable over a 24-week period |

| Formulations | Slurry
| Pills (RCT preliminary findings at ID Week 2013)

| Routes | Upper GI • Lower GI (enema vs. colonoscope) • NGT

| Who | Patients with severe and recurrent CDI who have failed multiple attempts at conventional antibiotic

| Where | Center of expertise

| Risks | Those associated with NGTs and colonoscopy
| Potential of transmission of infectious agents contained in the stool

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**Fecal Microbiota Transplant: How It’s Done**

**Treatment**

- Oral vancomycin: 500mg BID x 7 days then...
- 3–4 liters of 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 of 200–300 g of stool suspension into colon (but risk of perforation)

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**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

**Fecal Transplant- Mail Order**

http://www.openbiome.org/

- Nonprofit 501(c)(3) organization; MIT/Harvard faculty
- Provides material that is concentrated and packaged for either colonoscopic or nasogastric administration
- $250 per unit of stool
- 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
- 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

**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

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Petrof EO et al. Microbiome 2013, 1:3
Prevention of CDI

- Handwashing!
- Prudent use of antimicrobials
- Addition of probiotics containing viable lactobacilli or Saccharomyces species to antibiotic regimen
  - Cuts incidence of antibiotic-associated diarrhea in half
  - More studies needed to confirm its ability to protect against CDI

Kelly C. *JAMA*. 2008;301(9):954-962.

Which Antibiotics are High Risk?

- Despite recent trends, antimicrobial therapy is still the most important risk factor for CDI.
- Studies conflict when determining agent at highest risk, as many antimicrobials have been linked to increased CDI risk.
- Historically, cephalosporins and clindamycin were associated with highest risk, as well as ampicillin/ amoxicillin.
- Use of multiple antibiotics over longer periods elevates risk.


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
  “Lower Risk” antibiotics
  - Aminoglycosides, macrolides, sulfonamides, tetracyclines

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

Defining 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
  - Insufficient evidence to support use of probiotics to prevent CDI
  - Probiotics did not prevent antibiotic or CDAD in hospitalized patients ≥ 65 getting antibiotics
  - Probiotics reduced CDAD and antibiotic-associated diarrhea (AAD) in patients receiving antibiotics
  - The benefit of probiotics for prevention of CDAD is uncertain

**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

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**CDI 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

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**CDI: Take-Home Points**

- New, more virulent disease strains have made timely diagnosis and treatment more critical:  
  - Diarrhea accompanied by fever or lasting >3 days or should be evaluated and treated  
  - Consider CDI in all pts with persistent severe diarrhea, even if traditional risk factors are absent or in the distant past  
  - Marked leukocytosis suggests more serious disease  
- Patients with confirmed or potential CDI should be vigilantly monitored daily, as rapid deterioration can occur  
- Contact precautions, hand hygiene and environmental disinfection important for prevention/control  
- Prescribe antibiotics prudently

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**CDC FAQs about Clostridium Difficile** [http://www.cdc.gov/HAI/pdfs/cdiff/Cdiff_large.pdf](http://www.cdc.gov/HAI/pdfs/cdiff/Cdiff_large.pdf)