10:45 – 11:45am

C. Difficile Infection in the Community

SPEAKER
Fred A. Lopez, MD, MACP

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Clostridium difficile Infection in the Community

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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 cefadroxil

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

**C. difficile Infection (CDI)**

>200% increase in CDI diagnoses


**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
- Collitis caused by IBD

Kelly CP. *JAMA*. 2009;301:954-962.


**C. difficile Transmission**

*C. difficile* is shed in feces as spores that survive for up to 2 years on any contaminated surface

**Toxin A:** Attracts neutrophils and monocytes

**Toxin B:** Degradates colonic epithelial cells, causing cell death

Both toxins lead to:

- Inflammation
- Fluid and mucus secretion
- Mucosal damage
- Watery diarrhea
- Pseudomembrane formation

**Pathogenesis of CDI**

1. Ingestion of spores transmitted from other patients via the hands of healthcare personnel and environment
2. Germination into growing (vegetative) form
3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon
4. Toxin A & B Production leads to cellular damage & pseudomembrane

**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

**NAP1 More Virulent**

Genetic variations enable it to produce:

- Greater quantities (at faster rates) of toxins A (16X) and B (25X)

**NAP1 More Resistant**

Particularly to fluoroquinolones:

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


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.

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


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Community-Acquired C. difficile
Connecticut 2006

Clinical features among patients with community-associated C. difficile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</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>
</tbody>
</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


Possible New Modes of Transmission?

Reports of C. difficile in food:
- Retail meat in Canada (2007)²
- 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.
C. difficile in the Hospital Setting

- Researchers at hospital in England sampled the air and environmental surfaces near patients with symptomatic Clostridium difficile infection
  - Compared any organisms found with those in patient fecal samples by molecular typing
- One hour of air sampling: C. difficile in 6 of 50 patients with confirmed CDI (12%).
- Of the 10 patients who had sampling extended to 10 hours, 7 had C. difficile detected
  - In five cases, similar organisms isolated from feces, the environment, and the air
- C. difficile was not detected in the air in areas adjacent to patients without CDI.


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)


Testing for C. difficile Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Sensitivity (F)</th>
<th>Specificity (F)</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; 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 toxigenic C. Difficile</td>
<td>Detects Toxin B</td>
<td>&gt;90%</td>
<td>95-97%</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>


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 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)
    - Identified 265 of 270 controls without infection (98% specificity)

Bomers MK et al. BMJ 2012;345:e7396 doi: 10.1136/bmj.e7396
**C. difficile Infection: Signs and Symptoms**

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
<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>Serum albumin &lt;2.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Temp &gt;101°F</td>
<td>Peripheral white blood cell count &gt;15,000 uL</td>
</tr>
</tbody>
</table>

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

**Pseudomembranous Colitis**

- Inflammation caused by *C. difficile* toxins produces a pseudomembrane on top of injured areas of bowel mucosa, consisting of:
  - Inflammatory cells
  - Fibrin
  - Bacterial and cellular components
- Typically in distal colon; sometimes in proximal colon
- Appears as a greenish-yellow exudate covering areas of the mucosa

**SHEA/IDSA Clinical Practice Guidelines**

- Mild or moderate CDI
  - Peripheral WBC of ≤ 15,000/uL and serum creatinine <1.5 times the baseline
- Severe CDI
  - Peripheral WBC of > 15,000/uL 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*
- 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


**SHEA/IDSA Clinical Practice Guidelines for Initial Episode of CDI**

- Mild or moderate CDI (A-I)
  - Peripheral WBC of ≤ 15,000/uL 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/uL 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

### Antimicrobials for CDI

<table>
<thead>
<tr>
<th></th>
<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; equals that of vancomycin1,2,3</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Comparative Cost</td>
<td>$</td>
<td>$$</td>
<td>$$$$</td>
</tr>
<tr>
<td>Form used for CDI</td>
<td>Oral IV for severe or complicated disease</td>
<td>Oral, intragastric or enema</td>
<td>Oral</td>
</tr>
<tr>
<td>Duration</td>
<td>10-14 days</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>
<td>Equal efficacy to vancomycin but may have lower recurrence rates</td>
</tr>
<tr>
<td></td>
<td>Nausea (11%)</td>
<td>Vomiting (7%)</td>
<td>Abdominal pain (6%)</td>
</tr>
</tbody>
</table>


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### Case 2: Mr Conti

- 60-year-old man with COPD and diabetes
- Hospitalized for a COPD exacerbation 2 weeks ago
- Presents for post-hospitalization follow-up
- His COPD is stable
- Was told he had C. difficile while in the hospital and finished his course of oral metronidazole* last week
- Reports that he has no more diarrhea

*Metronidazole is not FDA-approved for treatment of CDI.

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### 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 a patient with recent CDI... test for CDI recurrence

Empiric treatment if... fever, distended abdomen, high white blood cell count and high clinical suspicion

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### 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


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### 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


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### 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

**Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile**


**Study Design**

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

**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: 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)¹

**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


Fecal Microbiota Transplant: How It's Done

**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; Cdiff

**Screen Recipient**
- Descripted

**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)

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

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
- Orders are processed and delivered within 5 business days
- Need to keep frozen
- Current FDA guidance allows use for CDI
- New draft regulation may restrict use to stool that is collected and screened by the treating physician

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

In Illinois:

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Center for Advanced Medicine
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http://www.uchospitals.edu/physicians/david-rubin.htm

Eugene Yen, MD
North Shore University Health System
Evanston, IL
http://www.northshore.org/research/investigators/eugene-yen-md/

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http://www.uchospitals.edu/physicians/david-rubin.htm

Eugene Yen, MD
North Shore University Health System
Evanston, IL
http://www.northshore.org/research/investigators/eugene-yen-md/
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

Which Antibiotics are High Risk?

• Despite recent trends, antimicrobial therapy is still the most important risk factor for CDI.1
• 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.2
• Use of multiple antibiotics over longer periods elevates risk.3

Which Antibiotics Are High Risk, Given Changing Epidemiology?

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

Risk of individual agents:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>31.8 (17.6-57.9)</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>16.7 (8.3-33.6)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>14.9 (10.9-20.3)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>9.1 (4.9-17.0)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>5.0 (3.7-8.9)</td>
</tr>
<tr>
<td>Penicillins</td>
<td>4.3 (2.8-6.4)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>4.1 (2.4-7.1)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>3.9 (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
“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

Conflicting evidence:
• 20 RCTs of probiotics showed1
  – 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 CDI4
• Probiotics did not prevent antibiotic or CDAD in hospitalized patients ≥ 65 getting antibiotics5
• Probiotics reduced CDAD and antibiotic-associated diarrhea (AAD) in patients receiving antibiotics2
• 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 Summary

Clinicians: 6 Steps to Prevention

1. Prescribe and use antibiotics carefully. About 50% of all antibiotics given are not needed, unnecessarily raising risk of C. difficile infections.
2. Test for C. difficile when patients have diarrhea while on antibiotics or within several months of taking them.
3. Isolate patients with C. difficile immediately.
4. Wear gloves and gowns when treating patients with C. difficile, even during short visits. Hand sanitizer does not kill C. difficile, and hand washing may not be sufficient.
5. Clean room surfaces with bleach or another EPA-approved, spore-killing disinfectant after a patient with C. difficile has been treated there.
6. When a patient transfers, notify the new facility if the patient has a C. difficile infection.


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

* Alcohol does not effectively kill C. difficile spores

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


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