**Clostridium difficile** - A Challenge in Long Term Care
Dr. Andrew Simor, University of Toronto
A Webber Training Teleclass

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**Objectives**

- to understand the changing epidemiology and outcome of *C. difficile*-associated diarrhea
- to appreciate the unique features of *C. difficile* in long-term care facilities
- to identify evidence-based strategies for the management and prevention of *C. difficile* infection

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**Clostridium difficile**

- implicated in 20%-30% of antibiotic-associated diarrhea
- major cause of nosocomial infectious diarrhea
- fecal-oral transmission via hands of HCWs and contact with contaminated environment


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**C. difficile- Associated Diarrhea**

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watery diarrhea</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>60-90</td>
</tr>
<tr>
<td>Peritoneal signs</td>
<td>10-20</td>
</tr>
<tr>
<td>Fever</td>
<td>70-80</td>
</tr>
</tbody>
</table>

---

**C. difficile Pathogenesis**

Disruption of normal enteric flora (eg. by antibiotics) with acquisition of toxigenic *C. difficile*

- Toxin A Ab present
- No toxin A Ab
- asymptomatc
- *C. difficile* colonization
- *C. difficile*-associated diarrhea

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**C. difficile-**
Associated Diarrhea

- >80% onset during antibiotic therapy
- may occur with single dose of antibiotic
- may occur after antibiotics discontinued (up to 6 wks later)

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**C. difficile in the Elderly**

- increasing age is a risk factor for acquiring *C. difficile* and for CDAD
  (McFarland, J Infect Dis 1990; Brown, ICHE 1990)
- most patients > 60 yrs of age
- 5-10 fold higher rates of CDAD in older adults; 228/100,000 pop’n. in US in those >65 yrs
  (McDonald, Emerg Infect Dis 2006; Pépin, Can Med Assoc J 2004)

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*McDonald, Emerg Infect Dis 2006*

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C. difficile in LTCFs

- C. difficile prevalence in LTCFs up to 15% (Simor, Clin Infect Dis 1993; Walker, J Am Geriatr Soc 1993)
- Incidence of C. difficile acquisition in LTCFs: 0.2-2.6/1,000 resident-days (Simor, Clin Infect Dis 1993; Laffan, J Am Geriatr Soc 2006)
- In state-wide surveillance (Ohio), approx 50% of CDAD acquired in a LTCF; rate: 2-3/10,000 resident-days (Ohio Dept. of Health; www.odh.state.oh.us/)

Risk Factors for C. difficile in LTCFs

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>O.R. (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics (prior 4 wks)</td>
<td>3.3 (0.03)</td>
</tr>
<tr>
<td>Cephalosporin use</td>
<td>4.7 (0.04)</td>
</tr>
<tr>
<td>Presence of &gt;3 comorbidities</td>
<td>2.0 (0.03)</td>
</tr>
<tr>
<td>Presence of feeding tube</td>
<td>6.5 (0.006)</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>2.5 (0.03)</td>
</tr>
</tbody>
</table>

Simor, Clin Infect Dis 1993; Walker, JAGS 1993

Why are the elderly at risk?

- Impaired C. difficile phagocytosis and toxin neutralizing Ab (Bassaris, Med Microbiol Immunol 1984; Viscidi, J Infect Dis 1983)
- Residence in a closed environment, with limited infection control and housekeeping resources

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Why are the elderly at risk?

- colonization pressure (Dubberke, Arch Intern Med 2007)

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Clostridium difficile - Changing Epidemiology

- increasing incidence and severity in US, Canada, UK, and Europe
- rates doubled in US hospitals 1996-2003: 3.1 to 6.1/100,000 pop’n (p=0.01)
- associated with a hypervirulent epidemic strain (NAP1; PCR ribotype O27; toxinoype III)


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*C. difficile* – Increasing Burden of Disease in U.S. Hospitals

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate per 1,000 admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>4.3</td>
</tr>
<tr>
<td>2004-2005</td>
<td>6.9</td>
</tr>
<tr>
<td>2005-2006</td>
<td>7.3</td>
</tr>
</tbody>
</table>

McDonald, IDSA 2007

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### C. difficile-Associated Diarrhea  
**Increasing Incidence/Severity**

- Centre Hospitalier Universitaire de Sherbrooke:  
  - 2.1/1,000 admissions in 2002  
  - 10/1,000 admissions in 2003  
  - 18/1,000 admissions early 2004  
  (Valiquette, CMAJ 2004)

- Sherbrooke rates increased:  
  - 35.6/100,000 pop’n in 1991  
  - 156/100,000 pop’n in 2003  
  - 866/100,000 pop’n in those ≥65 yrs  
  (Papin, CMAJ 2004)

### Nosocomial C. difficile in Canadian Hospitals

<table>
<thead>
<tr>
<th>Region</th>
<th>Rate per 1,000 admissions</th>
<th>Rate per 10,000 patient-days</th>
</tr>
</thead>
<tbody>
<tr>
<td>East</td>
<td>3.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Central</td>
<td>5.6</td>
<td>8.1</td>
</tr>
<tr>
<td>West</td>
<td>4.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Overall</td>
<td>4.7</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Canadian Nosocomial Infection Surveillance Program, 2007

### Why is there a problem with C. difficile now?

- more virulent strain  
  - clonal outbreak  
  - less susceptible strain  
  - toxin genes; other virulence factors

- changes in how antibiotics are used

- changes in infection control practices or environmental cleaning

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Epidemic *C. difficile*

- Quebec strain: NAP1/027, toxinotype III
  N. Amer. PFGE type 1
- 67% of healthcare facility isolates
  37% of community isolates
  Warny, Lancet 2005

Epidemic *C. difficile*

- binary toxin (significance uncertain, as binary toxin does not cause disease in animal models)
- deletions in *tcdC* gene (associated with higher levels of toxins A and B)
  (Warny, Lancet 2005)
- high-level fluoroquinolone and clindamycin resistance

*C. difficile*

Complications

- acute abdomen, peritonitis
- toxic megacolon
- colonic perforation
- dehydration, hypokalemia, GI bleeding

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**C. difficile Mortality**

- 161 cases/656 controls matched by age, sex, Charlson Comorbidity Index; Sherbrooke Que., 2003-04

<table>
<thead>
<tr>
<th>Mortality (%)</th>
<th>30-day</th>
<th>12-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>23</td>
<td>37</td>
</tr>
<tr>
<td>Controls</td>
<td>7</td>
<td>21</td>
</tr>
</tbody>
</table>

Attributable mortality: 16%

Pépin, CMAJ 2005

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**C. difficile Impact**

- attributable mortality, as high as 16% (Pépin, CMAJ 2005)
- 3 to 11 excess days of hospital stay; $3,700 to $13,675 incremental costs

(Kyne, Clin Infect Dis 2002; O’Brien, ICHE 2007)

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**C. difficile**

**Diagnosis**

- CDAD should be suspected in any hospitalized/LTCF patient with diarrhea who has received antibiotics in the previous 2 months
- Fever is typically present
- Leukocytosis (WBC >20,000) is associated with more severe disease

---

**C. difficile**

**colitis:**

[Image: Thumbprint X-ray]

---

**C. difficile** Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>89-100</td>
<td>84-99</td>
</tr>
<tr>
<td>Cytotoxin assay in cell culture</td>
<td>67-100</td>
<td>85-100</td>
</tr>
<tr>
<td>EIA toxin assay</td>
<td>63-99</td>
<td>75-100</td>
</tr>
</tbody>
</table>

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**C. difficile Diagnosis**

- only diarrheal (unformed) stools should be tested, unless ileus is suspected
- no value to testing stools of patients without symptoms (including “test of cure”), unless investigating an outbreak

**C. difficile Treatment**

- stop antibiotic, if possible
- avoid anti-peristaltic agents (may precipitate toxic megacolon)
- treat only symptomatic patients

**C. difficile Response to treatment**

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>No. cured/No. treated(%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>37/41 (90)</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>39/40 (98)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>29/38 (76)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>30/31 (97)</td>
<td></td>
</tr>
<tr>
<td>Relapse rate (%)</td>
<td>9/66 (14)</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>5/69 (7)</td>
<td></td>
</tr>
</tbody>
</table>

Zar, Clin Infect Dis 2007

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**C. difficile**  
**Treatment**

Typical response to treatment with Vanco/Flagyl is 3-5 days, and up to 10 days for complete resolution of symptoms

---

**C. difficile**  
**Relapse**

- relapse occurs in 5-30% of patients (persistence of spores or re-infection)
- most respond to repeat of initial therapy; 92% will have no further recurrence (Olson, 1994)

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**C. difficile**  
**Relapsing Disease**

- *Saccharomyces boulardii*
- *Lactobacillus GG*
- Vancomycin + rifampin

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### C. difficile - New Agents

- tolevamer (resin that binds toxins)
- macrocyclic antibiotics:
  - ramoplanin
  - OPT-80 (tiacumicin)
- nitazoxamide
- IVIG
- ingestion of non-toxigenic C. difficile;
  donor stool replacement (enema/NG tube)

### Is the most important factor affecting the emergence and spread of C. difficile:

- antibiotic utilization?
- infection control practices?

### Antimicrobial Utilization and C. difficile

- decreasing use of broad-spectrum cephalosporins associated with decreased CDAD
  (McNulty, JAC 1997; Khan, J Hosp Infect 2003; Thomas, CID 2005)
- reduced use of clindamycin associated with decreased CDAD
- change in fluoroquinolones associated with change in CDAD rates (Gaynes, CID 2004)

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**Hand Hygiene**

- 4% chlorhexidine gluconate equivalent to soap/water for removing *C. difficile* from hands (Bettin, ICHE 1994)
- Alcohol-based products are not reliably sporocidal (Larson, AJIC 1999)

---

**Clostridium difficile**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Barriers</strong></td>
<td></td>
</tr>
<tr>
<td>Handwashing</td>
<td>probable</td>
</tr>
<tr>
<td>Gloves</td>
<td>proven</td>
</tr>
<tr>
<td></td>
<td>(Johnson, AJM 1990)</td>
</tr>
<tr>
<td>Gown</td>
<td>no data</td>
</tr>
<tr>
<td>Cohorting</td>
<td>probable</td>
</tr>
</tbody>
</table>

Gerding, ICHE 1995

---

Figure 1. Rate of *Clostridium difficile*-associated diarrhea at a long-term care facility.

*P < .002 for either period of levofloxacin use versus period of gatifloxacin use. (Gaynes, CID 2004)*

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### Clostridium difficile

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environment</strong></td>
<td></td>
</tr>
<tr>
<td>Disinfection of room (hypochlorite)</td>
<td><strong>proven</strong> (Mayfield, CID 2000)</td>
</tr>
<tr>
<td>Use of disposable thermometers</td>
<td><strong>proven</strong> (Brooks, ICHE 1992)</td>
</tr>
<tr>
<td>Endoscopy disinfection</td>
<td><strong>probable</strong></td>
</tr>
</tbody>
</table>

Gerding, ICHE 1995

### Environmental Cleaning

- hypochlorite solutions effective in reducing bacterial load and sporulation
- quaternary ammonium compounds, hydrogen peroxide, and other non-chlorine-containing agents less effective for inactivating spores


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### Clostridium difficile

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use restriction</td>
<td><strong>proven</strong> (Pears, Ann Int Med 1994)</td>
</tr>
<tr>
<td>Use of probiotics</td>
<td>ineffective</td>
</tr>
<tr>
<td>Gut “decontamination” to eradicate C. difficile</td>
<td>ineffective</td>
</tr>
</tbody>
</table>

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C. difficile in LTCFs

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength and Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAD surveillance</td>
<td>BIII</td>
</tr>
<tr>
<td>Antimicrobial use surveillance</td>
<td>BIII</td>
</tr>
<tr>
<td>Prudent use of antibiotics</td>
<td>AII</td>
</tr>
<tr>
<td>Hand hygiene (soap or alcohol gel)</td>
<td>BIII</td>
</tr>
</tbody>
</table>

SHEA Position Paper, Infect Control Hosp Epidemiol 2002

C. difficile in LTCFs

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength/Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation, private room, commode (if feasible)</td>
<td>BIII</td>
</tr>
<tr>
<td>Glove use</td>
<td>AII</td>
</tr>
<tr>
<td>Use of disposable thermometers</td>
<td>AII</td>
</tr>
<tr>
<td>Dedicated patient care items, equipment (if feasible)</td>
<td>BIII</td>
</tr>
<tr>
<td>Environmental cleaning, disinfection with a sporocidal agent (diluted hypochlorite solution)</td>
<td>BII</td>
</tr>
</tbody>
</table>

SHEA Position Paper, Infect Control Hosp Epidemiol 2002

References

Simor, Infect Control Hosp Epidemiol 2002; 23:696-703

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Long Term Care Teleclasses in 2008

February 14
Clostridium difficile Management in Long Term Care

September 11
Surveillance in Long Term Care

December 11
Halting the Spread of MRSA Between Acute Care and Long Term Care

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