Objective

• Discuss risk factors for development of C. difficile infection

Outline

• Epidemiology and Pathogenesis
• Clinical Presentation
• Diagnosis and Management
• Infection Control and Prevention
• Summary
**Epidemiology**

- *Clostridium difficile* is the causative agent of antibiotic associated colitis (CDAD).
- Identified in 1978 and attributed to Clindamycin.
- 1989-1992 – Highly clindamycin resistant "J strain" implicated in a large outbreak in the USA.
- Penicillins, cephalosporins, and fluoroquinolones became implicated with their widespread use.
- 2003-2006 – rise of hypervirulent strains, refractory to standard therapy (NAP1/BI/027) in USA and Europe.
- NAP1 associated with fluoroquinolone use.

**Epidemiology**

- Incidence of CDAD per 100,000 persons rose 4-fold from 1991 to 2003 and 10-fold in those over age 65.
- In hospitalized patients the incidence rose from 3-12 per 1000 person to 25-43 per 1000 person during the same time period.
- Cases were associated with more severe disease requiring ICU care and colectomy for toxic megacolon.
- Mortality rates as high as 16%.
- 2005: strain 078 identified in Netherlands and associated with disease in a younger population and community associated.

**National Rate of CDAD hospitalization per 1000 non-maternal, adult discharges**

[Graph showing the national rate of CDAD hospitalization per 1000 non-maternal, adult discharges from 2001 to 2012 with observed and projected rates indicated.]

Discharge rate for *Clostridium difficile* infection from US short-stay hospitals by age

![Graph showing discharge rate for Clostridium difficile infection by age](image)

**FIGURE 1. Percentage of Clostridium difficile infection (CDI) cases (N = 10,342), by inpatient or outpatient status at time of stool collection and type/location of exposures** — United States, Emerging Infections Program, 2010

<table>
<thead>
<tr>
<th>Type/Location of exposure</th>
<th>Outpatient exposure only</th>
<th>Inpatient exposure</th>
<th>No health-care exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community onset</td>
<td>45.0%</td>
<td>20.7%</td>
<td>34.3%</td>
</tr>
<tr>
<td>Nursing home onset</td>
<td>40.2%</td>
<td>41.2%</td>
<td>18.6%</td>
</tr>
<tr>
<td>Hospital onset</td>
<td>50.4%</td>
<td>31.3%</td>
<td>18.3%</td>
</tr>
<tr>
<td>No health-care exposure</td>
<td>55.3%</td>
<td>55.3%</td>
<td>55.3%</td>
</tr>
</tbody>
</table>

**Mortality: Demographics**

<table>
<thead>
<tr>
<th>Demographic group</th>
<th>CDI-related deaths, no. (%)</th>
<th>Age-adjusted mortality rate per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>12.50 (8)</td>
<td>11.9</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td></td>
<td>18.53 (8)</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>Native American</td>
</tr>
<tr>
<td></td>
<td>1.56 (4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Age group</td>
<td>1-14</td>
<td>15-44</td>
</tr>
<tr>
<td></td>
<td>17 (1)</td>
<td>24 (1)</td>
</tr>
<tr>
<td></td>
<td>0.74</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Note: This table includes only non-institutionalized individuals 14 years of age or older.
Microbiology

- Gram Positive Rod
- Anaerobic
- Spore forming
- Toxin producing
- Difficult to culture
- Extra-colonic—spore form
  - Resistant to heat, acid, Abx
- Colonic – vegetative form
  - Toxin A (enterotoxin)
  - Toxin B (cytotoxin)
- Essential for virulence
- C. difficile is part of this microbial ecosystem in up to 70% of infants and 3% of normal adults

Pathogenesis

- Normal colonic bacterial flora disrupted by antibiotics or anti-neoplastic agents with antimicrobial activity
- Colonization with toxigenic strain of C. difficile (not typically covered by most antibiotics)
- Mucosal injury and inflammation
  - Exotoxins A and B
  - Binds to intestinal epithelial cells
  - Causes disruption of cell structure (cytoskeleton) of WBCs and mucosal epithelial layers
  - Destroys the “tight junction” between cells
  - Fluid leak, mucosal injury, and inflammation

References:

- Brito et al. J Infect Dis. 2002;185(9):1297
Transmission

- C. difficile carriers (20-50% of hospitalized adults) act as reservoir for environmental contamination
- Fecal oral route through ingestion of spores
- Organism survives in patient rooms, on hands, stethoscopes, and fomites
- Patient to patient transmission
- About half of transmission are associated with symptomatic infection

Gerding et al. Infect Control Hosp Epi 1995; 16:459
Ko et al. JID 1999: 179:42

Risk Factors

- Prior antibiotic us (within 5 days of start and up to 10 weeks after cessation)
- Hospitalization
- Advance age
- Severe illness
- Gastric acid suppression
- Enteral feeding, GI surgery, obesity, chemotherapy
- Recurrence: >75 yrs old; >10 unformed stools/day, Cr. >1.2mg/dL

Kromhout et al. CID 2013; 57:499

Community Associated CDAD

- No hospitalization within 1 year
- Women, younger age and healthier
- No prior antibiotic exposure within 12 weeks (1/3rd)
- Little or no outpatient exposure (50-60%)
- PPI use (1/3rd)
- Exposure to antibiotics in animal feed?

Chitnis et al. JAMA Intern Med 2013; 173:1359
CDC. MMWR. 2005;54:1201
Gould et al. CID 2010; 51:577
Diagnosis

- Presence of moderate to severe diarrhea or ileus AND
  - A stool test positive for C. difficile toxins or toxigenic C. difficile
    - Enzyme immunoassays for toxins A and B (sensitivity 75% – results in a couple of hours)
    - Polymerase chain reaction (PCR) – sensitivity 95% with rapid turnaround
    - Enzyme immunoassay for the C. difficile common antigen, glutamate dehydrogenase (GDH)
    - Cell culture cytotoxicity assay (Gold standard—takes 2 days)
    - Selective anaerobic culture – not practical for clinical purposes
  - OR
  - Endoscopic or histologic findings of pseudomembranous colitis
  - Risk for perforation
- Only loose, watery, or semi-formed stool should ordinarily be tested for C. difficile unless an ileus is suspected (stool swab)
- C. difficile toxin degrades at room temperature and may be undetectable within two hours after collection. Stool specimens should be kept at 4°C if delay is anticipated.

C. difficile "life cycle"

Clinical Presentation

- Variable—from Asymptomatic carrier state to severe disease (toxic megacolon)
  - Mild CDAD
    - Profuse watery diarrhea (<10 watery stools a day)
    - Lower abdominal pain
    - Cramping
    - Low grade fever
    - Leukocytosis
  - Severe disease
    - Fever (>38.5°C)
    - >10 bowel movements/day
    - WBC >15K-20K
    - Age >60 years
    - Serum creatinine >1.5x baseline
    - Serum albumin <2.5mg/dL
    - Signs of systemic toxicity
    - Toxic megacolon
    - Endoscopic findings of pseudomembranous colitis

References:
- Cohen et al. Infect Control Hosp Epidemiol 2010; 31:431
- Debast et al. Clin Microbiol Infect 2014; 20 Suppl 2:1
- Zar et al. CID 2007; 45:302
# Antibiotics Associated with CDAD

<table>
<thead>
<tr>
<th>Frequently associated</th>
<th>Occasionally associated</th>
<th>Rarely associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Macrolides</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Trimethoprim</td>
<td>Tetacyclines</td>
</tr>
<tr>
<td>Penicillins (broad spectrum)</td>
<td>Sulfonamides</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Cephalosporins (broad spectrum)</td>
<td>Metronidazole</td>
<td>Vancomycin</td>
</tr>
</tbody>
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**Treatment for several disease**

- **Vancomycin 125mg PO QID vs 500mg PO QID**
  - Vancomycin maintains consistently high levels in the stool compared to metronidazole
- **Intracolonic vancomycin**
- **IV metronidazole in combination with oral vancomycin**
- **Addition of fidaxomicin 200mg PO BID?**
- **Surgery**
  - Subtotal colectomy
  - Diverting loop ileostomy and colonic lavage

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**Alternative therapies**

- Anion-binding resins (tlevamer, colestipol, cholestyramine)
- IVIG – contains C. difficile antitoxin
- Probiotics – *Lactobacillus (Bifidobacteria)* or *Saccharomyces boulardii*
  - Suppression of C. diff growth
  - Inhibit toxin production and binding to colonic wall
  - Immunomodulation
- Fecal biotherapy
  - Severe and recurrent disease
  - Human synthetic stool (33 enteric pathogens)
  - Stool from healthy donors
  - Via enema, UGI (NGT), colonoscopy

**References**

- Goldenberg et Cochrane Database Syst Rev. 2013;5:CD006095
Infection Control Strategies

• Surveillance
  o Category
    • Healthcare facility (HCF) onset/associated
    • Community onset, HCF associated
    • Community onset/associated
  o Hospitals receiving Medicare & Medicaid payments are required to report CDI outbreaks using the National Healthcare Safety Network (since 2013)
  o Public reporting to Hospital Compare website (2014)

• Prevention
  o Early detection (clinical and laboratory diagnostic) and isolation
  o Contact precautions
  o Hand hygiene (soap and water, not just alcohol-based gels)
  o Environmental cleaning
  o Chlorhexidine baths

• Antibiotic stewardship
  • Avoidance of gastric acid suppression

Boyce et al. MMWR Recomm Rep. 2002;51(RR-16):1

Environmental disinfection and hand hygiene

• C. diff spores are able to attach and persist on environmental surface for as long as 6 months
• C. diff contamination was found on environmental surfaces in 49% of rooms occupied by CDAD patients and in 29% of asymptomatic carriers
• Heaviest contamination are bedrails and floors, but can be anywhere
• Common hospital cleaning agents (ammonium based or surfactant based detergents are NOT sporicidal and may encourage sporulation
• Chlorine-based disinfectants and high concentration, vaporized hydrogen peroxide are sporicidal
• Warm soapy water and glove use

Gerding et al. CID 2008:46 (Suppl 1)

Community Prevention

• CDAD patient – strict hand hygiene
• Avoid using the same toilet as family members if active diarrhea
• Sanitize common areas (sinks, countertops, etc) with bleach:water (1:10) mixture
• Children with diarrhea should not be sent to daycare/school

Gerding et al. CID 2008:46 (Suppl 1)
Summary

- Patients with C. difficile infections need to be in isolation and on CONTACT precautions.
- Handwashing with soap/water is more effective than alcohol-based hand-gels for killing C. difficile spores.
- Environmental cleansing with Chlorine-based solutions are effective.
- Health care providers should practice wise ABX stewardship to prevent the development of C. difficile infections.

Questions?

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