What’s All the Fuss About *Clostridium difficile*?

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Objectives

- *C. difficile* ....the organism
- Host relationships and pathogenesis
- Diagnosis
- Prevention and control
- Patient management
- Updated clinical issues
National Estimates of US Short-Stay Hospital Discharges with *C. difficile* as First-Listed or Any Diagnosis

**Clostridium difficile**

- **Bacterium**
  - Anaerobe
  - Gram-positive spore-forming bacillus

- **Source**
  - Environment
  - Stool flora
Host Relationship

- Disturbed colonic microflora
  - C. difficile exposure & colonize
  - Toxin A & B
  - Diarrhea & colitis
Risk Factors

- Age > 65 years
- Severe underlying disease
  - Prompting hospitalization
- Nasogastric intubation
- Anti-ulcer medications
  - Proton pump inhibitors
- Antimicrobial therapy
  - Clindamycin, 3rd generation cephalosporins, penicillin, fluoroquinolones
- Long hospital stay or long-term care residency

“Clostridium difficile is the most common cause of nosocomial infectious diarrhea.”
**Pathogenesis of C difficile-associated disease**

*Clostridium difficile* is spread via the fecal-oral route. The organism is ingested either as the vegetative form or as hardy spores, which can survive for long periods in the environment and can traverse the acidic stomach.

In the small intestine, spores germinate into the vegetative form.

In the large intestine, *C difficile*-associated disease can arise if the normal flora has been disrupted by antibiotic therapy.

*C difficile* reproduces in the intestinal crypts, releasing toxins A and B, causing severe inflammation. Mucous and cellular debris are expelled, leading to the formation of pseudomembranes.

Toxin A attracts neutrophils and monocytes, and toxin B degrades the colonic epithelial cells, both leading to colitis, pseudomembrane formation, and watery diarrhea.
Virulence Factors

- **Toxin A**
  - Exotoxin
  - Enterotoxic to cells
- **Toxin B**
  - Exotoxin
  - Not as toxic to cells?
- **Multiple strains of *C. difficile***
  - ToxA+/ToxB+
  - ToxA+/ToxB-
  - ToxA-/ToxB+

...only toxigenic strains of *C. difficile* produce disease...
CDI vs Antibiotic-Associated Diarrhea

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diarrhea due to CDI</th>
<th>AAD due to other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Diarrhea; often evidence of colitis (i.e., cramps, fever, and fecal leukocytes)</td>
<td>Diarrhea, usually mild-to-moderate in severity; no evidence of colitis</td>
</tr>
<tr>
<td>CT or endoscopy findings</td>
<td>Often evidence of colitis; no evidence of ileitis</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Results of stool toxin assay</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Epidemiologic pattern</td>
<td>May be epidemic or endemic</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Treatment</td>
<td>Withdrawal of implicated antibiotic May resolve but often persists or progresses</td>
<td>Usually resolves</td>
</tr>
<tr>
<td></td>
<td>Oral metronidazole or vancomycin therapy Often associated with a prompt response</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

*NOTE.* Adapted with permission from the following article published by the Massachusetts Medical Society: Bartlett JG. Clinical practice: antibiotic-associated diarrhea. N Engl J Med 2002;346:334–9. ©Massachusetts Medical Society. All rights reserved.
Clinical Presentation

• Mild disease
  – Non-bloody diarrhea
  – Mild abdominal tenderness

• Severe disease
  – Pseudomembranous colitis
  – Paralytic ileus
    • Ileitis
  – Toxic megacolon
    • Ulcerative colitis
  – Perforation
  – Ascites
Pseudomembranous Colitis

Mushroom-shaped pseudomembrane → “Volcano” lesion

Yellow lesion against hyperemic bowel

H & E, OM 400x
Diagnostics

• Generally....
  ...if stool samples are obtained after hospital day 3, the only enteric pathogen most labs will test for is.....*Clostridium difficile*.....

• Testing not considered a STAT test
  – Batching......but calling all positive results

• Many labs will only test a diarrheic stool specimen

• Follow-up testing of previous positive result not useful
  – Patients remain positive for months
  – Not useful for “proof-of-cure”
## TABLE 1

<table>
<thead>
<tr>
<th>DIAGNOSTIC TEST</th>
<th>TURN-AROUND TIME</th>
<th>SENSITIVITY</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
<td>2 hours</td>
<td>51%</td>
<td>Diagnostic of pseudomembranous colitis</td>
<td>Low sensitivity</td>
</tr>
<tr>
<td>Anaerobic culture</td>
<td>72 hours</td>
<td>89%–100%</td>
<td>Results useful for molecular typing</td>
<td>Does not distinguish toxin-producing strains</td>
</tr>
<tr>
<td>Tissue cytotoxic assay</td>
<td>48 hours</td>
<td>94%–100%</td>
<td>Detects A-B+ strains Gold standard</td>
<td>False-positives</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Results vary with experience of the technologist</td>
</tr>
<tr>
<td>Common antigen</td>
<td>15–45 minutes</td>
<td>58%–92%</td>
<td>Detects A-B+ strains Easy to use</td>
<td>Does not distinguish toxin-producing strains</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cross-reacts with other anaerobes</td>
</tr>
<tr>
<td>Enzyme-linked immunosorbent assay (ELISA)—toxin A</td>
<td>2 hours</td>
<td>80%–95%</td>
<td>Easy to use</td>
<td>Does not detect A-B+ strains</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>ELISA—toxin A + B</td>
<td>2 hours</td>
<td>85%–97%</td>
<td>Detects A-B+ strains</td>
<td>Increased sensitivity for low-level toxin production</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Immunochromatographic toxin A</td>
<td>&lt; 1 hour</td>
<td>60%–85%</td>
<td>Simple to use Rapid</td>
<td>Does not detect A-B+ strains</td>
</tr>
</tbody>
</table>
Relative Sensitivity

Culture >
    Cell cytotoxin >
    Toxin A & B EIA >
    Toxin A EIA >
    Latex agglutination >
    Endoscopy
What about PCR?

• Studies have shown PCR to be less sensitive than the toxin assay
  – Requires a nucleic acid extraction step
    • Complexity of stool matrix a problem
CDI Case Defined

- **Stool characteristic**
  - Diarrhea (most common)
  - No diarrhea
    - Associated with toxic megacolon or ileitis
      - Documented by radiology

- **> 1 of the following**
  - Stool positive for:
    - *C. difficile* toxin
    - *C. difficile* determined to be a toxin producer
  - Pseudomembranous colitis by:
    - Endoscopy
    - Histological exam
Prevention and Control

• Prevent ingestion of the organism
  – Infection control strategies
    • Target environment
    • Personal hygiene
    • Barrier methods

• Reduce the chance of disease in the event of such ingestion
  – Minimize or eliminate antibiotic exposure
    • “Good antimicrobial stewardship”
Questions

- **Clostridium difficile** spores can resist desiccation and can persist on hard surfaces:

  A. 48 hours or less
  B. About 1 week
  C. About 1 month
  D. > 6 months
• The most effective cleaning agent for killing *C. difficile* spores in the environment is:

A. 70% alcohol
B. 10% bleach
C. Hot water and soap
D. Phenol solutions
E. Quaternary ammonium compounds
• The incubation period for *Clostridium difficile* infection is:

A. Less than 1 day
B. 1-7 days
C. 2-3 weeks
D. Unknown
Barrier precautions to prevent the spread of *Clostridium difficile* include:

A. Airborne precautions  
B. Droplet precautions  
C. Contact precautions  
D. Standard precautions only

Duration of isolation controversial...2 days after diarrhea resolves...upon discharge
### Patient Management

#### Table 2

<table>
<thead>
<tr>
<th>DISEASE/HOST CHARACTERISTICS</th>
<th>RECOMMENDED THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild disease</strong></td>
<td>Metronidazole 250 mg by mouth four times a day or 500 mg by mouth three times a day for 10 days</td>
</tr>
<tr>
<td>(No systemic symptoms, only mild diarrhea)</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate disease</strong></td>
<td>Vancomycin 125–500 mg by mouth four times a day for 10 days</td>
</tr>
<tr>
<td>(Fever, profuse diarrhea, abdominal pain, leukocytosis)</td>
<td></td>
</tr>
<tr>
<td><strong>Severe disease</strong></td>
<td>Surgical consult plus intraluminal vancomycin</td>
</tr>
<tr>
<td>(Paralytic ileus, toxic megacolon, dehydration or sepsis)</td>
<td></td>
</tr>
<tr>
<td><strong>Inability to take oral medications</strong></td>
<td>Intraluminal vancomycin with or without intravenous metronidazole</td>
</tr>
</tbody>
</table>

Surgical consult...perforation, toxic megacolon, colonic-wall thickening, ascites....
“Stool infusion therapy” or “fecal transplant” has been shown to be highly effective....
Update Clinical Issues

• Hypervirulent *C. difficile* strain
• Community-associated CDI
• Proton Pump Inhibitors as risk factor
  – Antacids and anti-ulcer drugs
• Medicare issues and CDI
Severe Clostridium difficile--Associated Disease in Populations Previously at Low Risk --- Four States, 2005

Clostridium difficile is a spore-forming, gram-positive bacillus that produces exotoxins that are pathogenic to humans. C. difficile--associated disease (CDAD) ranges in severity from mild diarrhea to fulminant colitis and death. Antimicrobial use is the primary risk factor for development of CDAD because it disrupts normal bowel flora and promotes C. difficile overgrowth. C. difficile typically has affected older or severely ill patients who are hospital inpatients or residents of long-term–care facilities. Recently, however, both the frequency and severity of health-care–associated CDAD has increased; from 2000 to 2001, the rate of U.S. hospital discharge diagnoses of CDAD increased by 26% (1). One possible explanation for these increases is the emergence of a previously uncommon strain of C. difficile responsible for severe hospital outbreaks (2). Although individual cases of CDAD are not nationally reportable, in 2005, the Pennsylvania Department of Health (PADOH) and CDC received several case reports of serious CDAD in otherwise healthy patients with minimal or no exposure to a health-care setting. An investigation was initiated by the Philadelphia Department of Public Health (PDPH), PADOH, and CDC to determine the scope of the problem and explore a possible change in CDAD epidemiology. This report summarizes the results of the investigation in Pennsylvania and three other states, which indicated the presence of severe CDAD in healthy persons living in the community and peripartum women, two populations previously thought to be at low risk. The findings underscore the importance of judicious antimicrobial use, the need for community clinicians to maintain a higher index of suspicion for CDAD, and the need for surveillance to better understand the changing epidemiology of CDAD.

Case Reports

Case 1. A woman aged 31 years who was 14 weeks pregnant with twins went to a local emergency department (ED) after 3 weeks of intermittent diarrhea, followed by 5 days of cramping and watery, black stools 4–5 times daily. Stools specimens tested positive for C. difficile toxin, and the patient was admitted. Her only antimicrobial exposure during the preceding year was trimethoprim-sulfamethoxazole (for a urinary tract infection) approximately 3 months before admission. She was treated with metronidazole and discharged but was readmitted the next day for 18 days with severe colitis, receiving metronidazole, cholestyramine, and oral vancomycin. She improved on vancomycin and was allowed to return home. However, 4 days later she was readmitted with diarrhea and hypotension. She spontaneously aborted her fetuses. Despite aggressive treatment including a subtotal colectomy, intubation, and inotropic medication, the patient died on the third hospital day. Histopathologic examination of the colon demonstrated megacolon with evidence of pseudomembranous colitis.
Hypervirulent *C. difficile* Strain

- North American PFGE Type 1
- Restriction enzyme analysis Type BI
- PCR ribotype 027

Collectively referred to as “NAP1/BI/027 strain”
NAP1 Virulence Attributes

• Hypertoxigenic
  – Toxin A 16x
  – Toxin B 23x
  – Binary toxin

• Hypersporulation capacity

• High-level resistance to fluoroquinolones
  – Leads to outbreaks
States with the Epidemic Strain of \textit{C. difficile} Confirmed by CDC and Hines VA labs (N = 24), Updated 2/9/2007
Community-Acquired CDI

• Less common than nosocomial

• No traditional risk factors
  – “Spontaneous”

• Exposure to hypervirulent strain

• More likely to receive antacids (antiulcer) drugs
What illnesses are invading your community? Here’s an overview of select infections and how to manage them.

By Stacy Coffman, CIC, BS, MBA, SM(ASCP), RM(NRM)

The shifting paradigms for American healthcare moves steadily toward ambulatory care and extra hospital treatment strategies. The line between healthcare-acquired infections and community-acquired infections ever narrows. More inpatients bring infections into the hospital that may be transmitted in the hospital. Some infections are familiar foes with a new twist (e.g., MRSA, VRE, and Clostridium difficile). Some pathogens are emerging regularly, causing infections in either outbreaks or increased endemic proportions (Escherichia coli O157,
Heartburn Drugs Cause Diarrhea?

- Proton pump inhibitors
  - Prilosec
  - Prevacid
  - Nexium

- H2 blockers
  - Zantac
  - Pepcid
  - Tagamet

- Main function is to suppress stomach acid production
  - Gastritis
  - GERD (acid reflux disease)
  - Heartburn

Stomach Acid-Suppressing Medications and Community-Acquired CDAD, England

Deficit Reduction Act of 2005

- Requires an adjustment in Medicare Diagnosis Related Group payments
- For certain hospital-acquired conditions
<table>
<thead>
<tr>
<th>Category of Conditions</th>
<th>Conditions selected for implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CATEGORY</strong></td>
<td><strong>CONDITIONS</strong></td>
</tr>
<tr>
<td><strong>Serious Preventable Events</strong></td>
<td></td>
</tr>
<tr>
<td>Object left in during surgery (998.4 CC)</td>
<td></td>
</tr>
<tr>
<td>Air embolism (999.1 MCC)</td>
<td></td>
</tr>
<tr>
<td>Blood incompatibility (999.6 CC)</td>
<td></td>
</tr>
<tr>
<td><strong>Catheter-Associated Urinary Tract Infection</strong></td>
<td></td>
</tr>
<tr>
<td>(996.64 CC &amp; one of the following specific infection codes: 112.2, 590.10, 590.11, 590.2, 590.3, 590.80, 590.81, 590.9, 595.0, 595.3, 595.4, 595.81, 590.89, 595.9, 597.0, 597.80, 599.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Pressure Ulcers</strong></td>
<td></td>
</tr>
<tr>
<td>(707.00 - 707.01 &amp; 707.09 CCs; 707.02 - 707.07 MCCs)</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Catheter-Associated Infection</strong></td>
<td></td>
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<tr>
<td>(999.31 CC)</td>
<td></td>
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<tr>
<td><strong>Surgical Site Infection - Mediastinitis after Coronary Artery Bypass Graft (CABG) Surgery (a specific surgical site infection)</strong></td>
<td></td>
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<tr>
<td>(519.2 MCC &amp; 36.10-.19)</td>
<td></td>
</tr>
<tr>
<td><strong>Falls and Trauma – Fractures, Dislocations, Intracranial Injuries, Crushing Injuries, and Burns</strong></td>
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<tr>
<td>(Codes will be considered in IPPS FY2009 Proposed Rule)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions being considered for FY2009 IPPS rulemaking</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventilator-Associated Pneumonia (VAP)</strong></td>
</tr>
<tr>
<td>(Codes will be considered in IPPS FY2009 Proposed Rule)</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus Septicemia</strong></td>
</tr>
<tr>
<td>(038.11 + 995.91, 998.59, 999.3 MCCs)</td>
</tr>
<tr>
<td><strong>Deep Vein Thrombosis (DVT) / Pulmonary Embolism (PE)</strong></td>
</tr>
<tr>
<td>(DVT: 453.40-.42 CCs; PE: 415.10 &amp; 415.19 MCCs)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions needing further analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methicillin-Resistant Staphylococcus aureus (MRSA)</strong></td>
</tr>
<tr>
<td>(Codes will be considered in IPPS FY2009 Proposed Rule)</td>
</tr>
<tr>
<td><strong>Clostridium difficile-Associated Disease (CDAD)</strong></td>
</tr>
<tr>
<td>(008.45 CC)</td>
</tr>
<tr>
<td><strong>Wrong Surgery</strong></td>
</tr>
<tr>
<td>(Codes will be considered in IPPS FY2009 Proposed Rule)</td>
</tr>
</tbody>
</table>
“Myth Busters”

• *C. difficile* may infect individuals who are **NOT** taking antibiotics
• Optimal method to diagnose CDI is **NOT** clear
• Alcohol-based gels are **NOT** effective for hand hygiene against *C. difficile* spores
• Vancomycin is **NOT** the recommended initial therapy for CDI
• Current literature does **NOT** support the use of probiotics to treat for CDI
• CDI is **NOT** only a problem in acute care hospital facilities but also long-term care and rehab centers
Recommendations for Control

- Conduct surveillance for CDI
- Early diagnosis and treatment
- Strict infection control practices
- Good antimicrobial stewardship