C. difficile
Re-emergence of an Old Pathogen

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Associate Hospital Epidemiologist
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March 13, 2008
Infection Control Timeline

Big Bang
10 billion and 20 billion years ago

Many uneventful years elapse

Hotel-Dieu:
Paris hospital founded in the 7th century

Circa 600 AD

Big Bang
10 billion and 20 billion years ago
History: Advances in Surgical Infection Control

Joseph Lister introduced antiseptics in 1867
William Halstead introduced gloves in 1890
Johannes Mikulicz introduced masks in 1897
Infection Control Timeline: *The Modern Era*

- **First antibiotics, sulfonamides & penicillin, developed in the late 1930s**
- **1978:** *C. difficile* associated toxin discovered in the stool of patients with antibiotic-associated pseudomembranous colitis
- **1980:** R.P Wenzel MD Founded Society of Healthcare Epidemiology; applied epidemiologic techniques to infection control
- **1961:** MB Edmond Born in West Virginia...
Clostridium difficile

- **Clostridium difficile** is a gram-positive, anaerobic, spore-forming bacillus that is responsible for the development of antibiotic-associated diarrhea and colitis.
Epidemiology

- *C. difficile* cultured from the stool of 3% of healthy adults and up to 80% of healthy newborns and infants
- Stool carriage of *C. difficile* reaches 16–35% among hospital inpatients.
- *C. difficile* persists in the stools of 10–40% of patients with CDAD regardless of antibiotic treatment
- Contaminated environmental surfaces, other patients with CDAD and hand carriage on the part of healthcare personnel are important reservoirs for cross transmission


Epidemiology of CDAD

- *C. difficile* is the leading cause of nosocomial enteric infection
- Three million new cases of *C. difficile* diarrhea and colitis in United States hospitals per annum.
- CDAD affects 10% of hospitalized patients

Hospital-acquired *Clostridium difficile*-associated disease in the intensive care unit setting: epidemiology, clinical course and outcome

- Historical cohort study on 58 adults with CDAD occurring in intensive care units at VCUMC.
- In ICU patients with CDAD, advanced age and increased severity of illness at the onset of infection were independent predictors of death.
- The in-hospital mortality was 27.6%.

Marra A, Edmond MD, Wenzel RP and Bearman G. *BMC Infectious Diseases* 2007, 7:42
Risk Factors and Pathophysiology

• *C. difficile* is more likely to cause clinical disease in patients who are newly exposed

• Patients who are already colonized with *C. difficile* typically remain asymptomatic during their hospital stay

Risk Factors and Pathophysiology

• The association of developing *C. difficile* infection following exposure to antibiotic is well defined
  – The probability of CDAD is greatest with Clindamycin and Ampicillin
  – Fluoroquinolones are now increasingly associated with CDAD

## Antibiotics and CDAD

<table>
<thead>
<tr>
<th>Highly associated</th>
<th>Moderately Associated</th>
<th>Rarely Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Other Beta-lactam antibiotics</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Sulfonamides</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Erythromycin</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Trimethoprim</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td>Quinolones</td>
<td>Metronidazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>
Toxins

- **Enterotoxin A**
  - Causes fluid accumulation in the bowel
- **Cytotoxin B**
  - Cytopathic toxin
    - Promotes cell lysis and death

*C. difficile* endospores
Pathophysiology

- *C. difficile* toxins A and B are large proteins (308 kDa and 275 kDa)
- Both toxins adhere to receptors on the human colonocyte brush border and cause:
  - Necrosis
  - Shedding of cells into the GI lumen
Risk Factors and Pathophysiology

- Receipt of antibiotics
- Disruption of microflora in colon
- Exposure and colonization by *C. difficile*
- Release of toxins A and B with resultant mucosal injury
Carrier State

- Once infected, 2/3 of infected hospitalized patients remain asymptomatic
  - Carriers are reservoirs of toxigenic organisms
- Routine treatment of carriers is not recommended
  - The carrier state can be eliminated by use of vancomycin, however, culture positivity returns upon cessation of the antibiotic
  - Treatment of carriers may be employed during hospital outbreaks
    - Elimination of the organism from the hospital environment


Antibiotic Associated Diarrhea Without Colitis

• Common in hospitalized patients
• Diarrhea is mild
  – 3-4 loose watery stools per day
  – Cramping
• Physical examination is normal with only minimal lower abdominal tenderness
• Fever, leukocytosis, and dehydration are mild or absent
• *C. difficile* toxins present in stool
• Sigmoidoscopic examination is normal
Antibiotic Associated Colitis Without Pseudomembrane Formation

- Abdominal pain, nausea, anorexia
- Profuse watery diarrhea of 5 to 15 watery bowel movements per day
- Left or right lower quadrant abdominal pain and cramps
- Fever and dehydration
- Sigmoidoscopic examination may reveal a nonspecific diffuse or patchy erythematous colitis without pseudomembranes
Pseudomembranous Colitis

- Appears as raised yellow or off-white plaques ranging up to 1 cm in diameter scattered over the colorectal mucosa
- Similar clinical symptoms of diarrhea, fever, leukocytosis and abdominal pain
Histopathology of pseudomembranous colitis

- The pseudomembrane membrane is composed of fibrin
- Adheres to the damaged colon surface and blocks the absorptive surface layer further adding to diarrhea

http://www.pathguy.com/~tdemark/0075.htm
Pseudomembranous colitis

Axial CT images show distention and significant colonic wall thickening of the transverse and sigmoid colon
Fulminant Colitis and Toxic Megacolon

• 2 or 3 percent of patients
• Marked leukocytosis (>30,000 to 40,000 WBC/microL)
• Fever, chills, dehydration and metabolic (lactic) acidosis
• Diarrhea is prominent
  – However, diarrhea is less prominent in patients with ileus and secondary pooling of secretions in the dilated, adynamic colon
Toxic Megacolon

- Diagnosis based upon the finding of an enlarged dilated colon
  - >7 cm in its greatest diameter
- Accompanied by severe systemic toxicity

http://www.cfpc.ca/cfp/2004/Nov/_images/Fig0376_104_A.jpg
Definition of Disease Severity

• Severe disease
  • WBC count >20,000 cells/microL
  • Elevated serum creatinine

• Point (score) assignment system in clinical trial
  – > 2 points = severe disease
    – 1 point assigned each
      » age >60 years
      » T>38.3°C
      » Albumin <2.5 mg/dL
      » WBC >15,000 cells/microL
    – 2 points assigned for endoscopic evidence of pseudomembranous colitis or treatment in the ICU

Diagnosis: Cytotoxicity Assay

• The gold standard for the identification of C. difficile cytotoxins
• Diarrheal stool is prepared so that present toxins are added to monolayers of cultured fibroblast cells
  – If present, the toxin will exert a cytopathic effect
• High sensitivity (94 to 100 percent) and specificity (99 percent)
• Laborious, time consuming and used mostly as a research tool

Diagnosis: ELISA for Toxin Detection

• More rapid assays with comparable sensitivity (70 to 90 percent) and specificity (99 percent)
• Some detect Toxin A only
  – Toxin A variant strains (toxin A-negative, toxin B-positive strains) relatively infrequent
    • (1-2% of all isolates)

Recent data suggests that CDAD has made an epidemiologic resurgence.
Emergence of Highly Toxigenic Strain

- Hospital and nursing home outbreaks of severe disease particularly in elderly patients
- Strain is generally resistant to fluoroquinolones
- Prior receipt of fluoroquinolones is a risk factor
- Associated with an increase in length of hospitalization
- Increase in mortality
- 10% of case patients required admission to the ICU
- 2.5 percent underwent an emergency colectomy
Toxin gene-variant and highly toxigenic strains - NAP1/BI/027

- A highly toxigenic strain of *C. difficile* that produces about 15 to 20 times the amount of toxins A and B
  - Caused nosocomial and community outbreaks in North America, Great Britain, and the Netherlands
    - Toxinotype III
    - North American PFGE type 1 (NAP1)
    - Restriction enzyme analysis type "BI"
    - PCR-ribotype 027

Toxin gene-variant and highly toxigenic strains - NAP1/BI/027

• Genes
  – \( tcdA \) Toxin A
  – \( tcdB \) Toxin B
  – \( tcdC \) porin gene
    • Partial deletions of \( tcdC \)
      – The expression of \( tcdA \) and \( tcdB \) is down regulated by the \( tcdC \) gene

Mechanism for the overproduction of toxins in the NAP1/BI/027 strain is a partial deletion in the \( tcdD \) gene resulting in overproduction toxins A and B
A Predominantly Clonal Multi-Institutional Outbreak of *Clostridium difficile*-Associated Diarrhea with High Morbidity and Mortality

- Prospective study in 12 Quebec Hospitals to determine the incidence of nosocomial CDAD and its complications.
- Case-control study performed to determine risk factors
- All *C. difficile* isolates were PFGE typed

A Predominantly Clonal Multi-Institutional Outbreak of *Clostridium difficile*-Associated Diarrhea with High Morbidity and Mortality

<table>
<thead>
<tr>
<th>Results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total # of episodes</strong></td>
<td>1719 Episodes of <em>C. difficile</em> diarrhea</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>22.5 per 1000 hospital admissions</td>
</tr>
<tr>
<td><strong>30 day attributable mortality</strong></td>
<td>6.9 %</td>
</tr>
</tbody>
</table>

A Predominantly Clonal Multi-Institutional Outbreak of *Clostridium difficile*-Associated Diarrhea with High Morbidity and Mortality

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>3.8</td>
<td>2.2-6.6</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>3.9</td>
<td>2.3-6.6</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1.6</td>
<td>0.5-4.8</td>
</tr>
<tr>
<td>Penicillins -beta lactamase inhibitor</td>
<td>1.2</td>
<td>0.7-2.3</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>1.4</td>
<td>0.3-6.3</td>
</tr>
</tbody>
</table>

A Predominantly Clonal Multi-Institutional Outbreak of *Clostridium difficile*-Associated Diarrhea with High Morbidity and Mortality

• Antibiotic susceptibility:
  – A predominant, fluoroquinolone resistant strain was found in 129/157 isolates (82.2%)

• Genetic typing
  – 82.2% of isolates with identical PFGE pattern
  – Binary toxin genes and partial deletion of tcdC gene were present in 132 isolates (84.1%)

Mortality attributable to nosocomial *C. difficile* - associated disease during an epidemic caused by a hypervirulent strain in Quebec

<table>
<thead>
<tr>
<th></th>
<th>30 Day Mortality</th>
<th>12 Month Mortality</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>23.0% (37/161)</td>
<td>7.0% (46/656)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CDAD</td>
<td>37.3% (60/161)</td>
<td>20.6% (135/656)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Attributable mortality</td>
<td>16.7% (95% confidence interval 8.6%-25.2%).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
An Epidemic, Toxin Gene–Variant Strain of *Clostridium difficile*

- 187 *C. difficile* isolates were collected from eight health care facilities in six states with CDAD outbreaks between 2000 and 2003
  - PFGE performed on isolates
    - B1/NAP Strain Identified
  - Antibiotic susceptibilities performed

An Epidemic, Toxin Gene–Variant Strain of *Clostridium difficile*

Table 1. Isolates of *Clostridium difficile* According to Health Care Facility and the Proportion of Isolates Belonging to the B1/NAP1 Strain.

<table>
<thead>
<tr>
<th>Health Care Facility</th>
<th>Date of Onset of Outbreak</th>
<th>No. of Isolates Tested</th>
<th>BI/NAP1 Strain no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgia</td>
<td>Oct. 2001</td>
<td>46</td>
<td>29 (63)</td>
</tr>
<tr>
<td>Illinois</td>
<td>July 2003</td>
<td>14</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Maine, Facility A</td>
<td>March 2002</td>
<td>13</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Maine, Facility B</td>
<td>July 2003</td>
<td>48</td>
<td>30 (62)</td>
</tr>
<tr>
<td>New Jersey</td>
<td>June 2003</td>
<td>12</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Oregon*</td>
<td>April 2002</td>
<td>30</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Pennsylvania, Facility A</td>
<td>2000–2001</td>
<td>18</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Pennsylvania, Facility B</td>
<td>Oct. 2003</td>
<td>6</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>187</td>
<td>96 (51)</td>
<td></td>
</tr>
</tbody>
</table>

*Isolates were not collected until after the peak of the outbreak.*

51 % of all isolates tested were of the B1/NAP Strain

An Epidemic, Toxin Gene–Variant Strain of *Clostridium difficile*

![Graph showing distribution of minimum inhibitory concentrations of levofloxacin for Current (Obtained after 2000) BI/NAP1 and Non-BI/NAP1 *Clostridium difficile* isolates.](image)

States with BI/NAP1/027 strain of C. difficile (N=38), November, 2007

Updated Nov. 9, 2007

http://www.cdc.gov/ncidod/dhqp/id_Cdiff_data.html
Treatment
Discontinuation of antibiotics

• Prior to the discovery of effective antimicrobial therapy:
  – In 1974, a report of 20 patients with pseudomembranous colitis, all patients recovered following the cessation of clindamycin therapy

• The efficacy of stopping other antibiotics has not been by further studies but is widely recommended

Metronidazole

• Oral metronidazole was widely recommended as the drug of choice for most cases of CDAD
  – High in vitro activity against *C. difficile*
  – High concentrations in the stool after both oral and IV administration
Vancomycin

- Poorly absorbed after oral administration
  - Virtually no serum concentration achieved via oral dosing.
    - Systemic toxicity is minimal
- High fecal concentrations have been documented and are known to be therapeutic
- Use is a significant risk factor for the VRE GI colonization
- More expensive than metronidazole
Treatment of *C. difficile* with Vancomycin

• Large series published in 1984
  – 189 patients with CDAD
    • 183(97%) responded to vancomycin therapy
      – Defervescence was observed after 24-48 hours
      – Diarrhea resolved after 1-13 days
        » Mean time to resolution was 4.5 days

Bartlett JG. *Rev of Infec Dis* 1984;6 (suppl1) 2S235-41
Prospective randomised trial of metronidazole versus vancomycin for Clostridium-difficile-associated diarrhea and colitis

• 101 patients with C. difficile-associated diarrhea or colitis were prospectively randomised to:
  – 10-day oral courses of
    • metronidazole, 250 mg four times a day
    • vancomycin, 500 mg four times a day.

• Participants:
  – 52 patients received vancomycin
  – 42 patients received metronidazole
  – 7 did not complete the trial

**Prospective randomised trial of metronidazole versus vancomycin for Clostridium-difficile-associated diarrhea and colitis**

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metronidazole N=42</td>
<td></td>
</tr>
<tr>
<td>Failure (N)</td>
<td>2</td>
<td>0.20</td>
</tr>
<tr>
<td>Relapses (N)</td>
<td>2</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Vancomycin N=52</td>
<td></td>
</tr>
<tr>
<td>Failure (N)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Relapses (N)</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

* Metronidazole and vancomycin have equivalent efficacy and relapse rates and are tolerated to a similar extent by patients with C-difficile-related diarrhea and colitis

# Relatively Poor Outcome after Treatment of *Clostridium difficile* Colitis with Metronidazole

<table>
<thead>
<tr>
<th>Study results</th>
<th>N</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients observed</td>
<td>207</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients cured</td>
<td>103 (50%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients with symptoms of colitis for 10 days despite treatment</td>
<td>46 (22%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients with a recurrence within 90 days</td>
<td>58 (28%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>27%</td>
<td>N/A</td>
</tr>
<tr>
<td>Mortality comparing complete responders vs incomplete clinical responders</td>
<td>21% vs 33%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Prospective, observational study of 207 patients who were treated with metronidazole for *C. difficile* colitis

Increasing Risk of Relapse after Treatment of *Clostridium difficile* Colitis in Quebec, Canada

60-day probabilities of recurrence among patients with *Clostridium difficile* associated diarrhea treated with only **metronidazole**, comparing 1991-2002 to 2003-2004 (top).

Treatment with only **vancomycin** during 1991-2002 to 2003-2004 (bottom).

Clinical Infectious Diseases 2005;40:1591-1597
Vancomycin vs Metronidazole?

- Randomized, prospective, double blinded placebo controlled trial
- Treatments
  - Oral metronidazole 250mg QID x 10 days
  - Oral vancomycin 125mg QID x 10 days
- Outcomes
  - Clinical cure/ recurrence
    - Stratified by disease severity

## Vancomycin vs Metronidazole?

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clinical Cure</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metronidazole</td>
<td>Vancomycin</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Mild CDAD</td>
<td>90%</td>
<td>98%</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>N=81</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe CDAD</td>
<td>76%</td>
<td>97%</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>N=69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disease severity scoring system: one point each was given for age >60 years, temperature >38.3°C, serum albumin <2.5 mg/dL (25 g/L), or peripheral white blood cell count >15,000 cells/microL within 48 hours of enrollment. Two points were given for endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit. Patients with >2 point considered to have severe disease.

# TABLE 2. Comparison of vancomycin and metronidazole for *Clostridium difficile* infection.

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic levels</td>
<td>&gt; 500 mcg/mL</td>
<td>0–10 mcg/mL</td>
</tr>
<tr>
<td><em>In vitro</em> activity</td>
<td>≤ 1.0 mcg/mL</td>
<td>≤ 1.0 mcg/mL</td>
</tr>
<tr>
<td>FDA-approved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Unbeaten</td>
<td>Beaten</td>
</tr>
<tr>
<td>Mild disease</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Severe disease</td>
<td>Superior</td>
<td>Inferior</td>
</tr>
<tr>
<td>Relapse rate</td>
<td>10%–25%</td>
<td>10%–25%</td>
</tr>
<tr>
<td>Cost/day (AWP)</td>
<td>$36/$17</td>
<td>$10</td>
</tr>
<tr>
<td>Promotion of VRE</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AWP=average of wholesale price; FDA=Food and Drug Administration; VRE=vancomycin-resistant enterococci.
Nitazoxanide vs Metronidazole

Nitazoxanide – oral antiprotozoal agent

Prospective, randomized, double blind study

Treatments:
Metronidazole 250mg po QID x 10 days
Nitazoxanide 500mg bid x 7 days
Nitazoxanide 500mg po bid x 10 days

Nitazoxanide was at least as effective as metronidazole in treating *C. difficile* colitis

Musher et al, Clinical Infectious Diseases, 2006:43: 421-7
Relapse- Increasingly More Common

- Relapse of CDAD occurs in 10-50% of patients
  - Likely due to persistence and germination of *C. difficile* spores
  - However, up to 50% of relapses may be due to reinfection with a new strain of *C. difficile*

Mylonakis et al. *Archives of Int Med.* 2001; 161:525-33
Malnick SDH. *Annals of Pharmacotherapy.* 2002;36:1767-75
Relapse

• Risk factors
  – From prospective studies
    • Increasing age
    • Abdominal surgery
    • Prior episodes of CDAD
  – From retrospective studies
    • Leukocytosis
    • Renal failure
    • Female gender

Young G et al. Gastroenterology 1986;90:1098-9
## Relapse

- There are no evidence based guidelines for the treatment of multiple relapses

<table>
<thead>
<tr>
<th>1st Recurrence</th>
<th>Repeat metronidazole therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Repeat Vancomycin therapy</td>
</tr>
<tr>
<td></td>
<td>Nitazoxanide</td>
</tr>
</tbody>
</table>

| Multiple Recurrences   | Dose titration of vancomycin  |
|                        | Vancomycin or metronidazole with probiotic agent |
|                        | Vancomycin + colestipol       |
|                        | Vancomycin+rifaximin          |
|                        | Fecal transplantation         |
Vancomycin

- Dose titration with pulse dosing
  - Week 1: 125mg QID
  - Week 2: 125mg BID
  - Week 3: 125 mg QD
  - Week 4: 125mg QOD
  - Weeks 5 and 6: 125 mg every 3 days

- Intermittent administration of antibiotics permits germination of residual spores on the off days.
- With the reintroduction of antibiotics, the organism is consequently destroyed.

Interruption of Recurrent *Clostridium difficile*–Associated Diarrhea Episodes by Serial Therapy with Vancomycin and Rifaximin

- **Rifaximin** is a semisynthetic, rifamycin-based non-systemic antibiotic, poorly absorbed
- One recent study
  - 8 women with 4–8 episodes each of CDAD
  - 2 week course of rifaximin following vancomycin therapy
  - 7 of 8 patients experienced no further diarrhea recurrence.
- Rifaximin has been shown to cause minimal changes in fecal flora, possibly suppressing the recrudescence of vegetative *C. difficile* growth

Probiotic Therapy

• Randomized placebo controlled trial
  – \textit{S. boulardii} (500 mg twice daily for 4 wk) was administered in combination with metronidazole or vancomycin in 124 patients with CDAD.

• Results:
  – No effect on the relapse rate in 64 patients treated for a first episode of CDAD
  – Significant reduction in the relapse rate in patients with at least 1 prior episode of CDAD (35\% vs. 65\%; \(p = 0.04\)).

McFarland et al. \textit{JAMA} 1994;271:1913-8
Anion Binding Resins

- Resins bind toxins produced in CDAD
- Bowel flora are not altered by resins
- Anion-exchange resins bind vancomycin and resin must be taken two or three hours apart
Treatment of recurrent antibiotic-associated pseudomembranous colitis

- 11 patients with relapses of antibiotic-associated pseudomembranous colitis
  - Treated with a tapering dose schedule of vancomycin and colestipol
- All patients responded and were asymptomatic at least 6 wks

Tedesco FJ. Am J Gastroenterol 1982 Apr;77(4):220-1
Fecal Transplantation

• Case series over nine years involving 18 patients with recurrent *C. difficile* colitis treated with donor stool via nasogastric tube
  – 90 days of follow up:
    • 2 patients died of unrelated illnesses.
    • 1 recurrence in 16 patients
    • No adverse effects associated with stool treatment

Aas et al. *Clinical Infectious Diseases* 2003;36:580–585
Fecal Transplantation

Table 3. Preparation of stool transplant recipient and description of the transplantation procedure.

<table>
<thead>
<tr>
<th>Procedure Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat the stool transplant recipient with vancomycin hydrochloride capsules (250 mg q8h) starting 4 days before the transplantation procedure. The last dose should be given on the evening before the transplantation.</td>
</tr>
<tr>
<td>Treat with omeprazole capsules (20 mg po) on the evening before and on the morning of the stool transplantation.</td>
</tr>
<tr>
<td>Immediately before the stool transplantation, a nasogastric tube is placed. Radiography should be used to verify that the tube tip position is in the gastric antrum.</td>
</tr>
<tr>
<td>A total of 25 mL of the transplantation stool suspension is aspirated into a syringe and instilled into the recipient via the nasogastric tube.</td>
</tr>
<tr>
<td>After the stool instillation, the nasogastric tube is flushed with 0.9 N NaCl. The nasogastric tube is then withdrawn.</td>
</tr>
<tr>
<td>The patient is permitted to resume a normal diet and all customary physical activities immediately after discharge from the gastroenterology clinic.</td>
</tr>
<tr>
<td>The patient should be evaluated 14–28 days after transplantation with a routine outpatient interim history, physical examination, and stool examination for presence of Clostridium difficile toxin.</td>
</tr>
</tbody>
</table>
Clinical outcomes of intravenous immune globulin in severe *Clostridium difficile*-associated diarrhea

- Retrospective analysis of 79 patients with CDAD
- Standard therapy for severe CDAD including intravenous metronidazole, oral vancomycin, or vancomycin enema
  - 18 patients received IVIG treatment (200-300 mg/kg)
  - 18 matched patients with similar CDAD severity but did not receive IVIG treatment
- There were no statistical differences in clinical outcomes:
  - Mortality, colectomies, and length of stay

Surgery

- Surgical intervention is warranted in the setting of peritoneal signs, severe ileus, or toxic megacolon.
- From retrospective data-
  - Colectomy most beneficial in:
    - Immunocompetent patients
    - Age >65 years
    - WBC > 20,000 cells/microL
    - And/or a plasma lactate between 2.2 and 4.9 meq/L

# Treatment summary

| Mild CDAD            | • Discontinue offending antibiotic  
<table>
<thead>
<tr>
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<th>• Oral Metronidazole</th>
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| Moderate to severe   | • Oral vancomycin                
|                     | • Oral metronidazole              
|                     | • IV metronidazole (ileus) + oral vancomycin via NG tube  
|                     | • Antibiotics + IVIG              |
| 1st Recurrence       | • Repeat metronidazole therapy    
|                     | • Repeat Vancomycin therapy       
|                     | • Nitazoxanide                    |
| Multiple Recurrences | • Dose titration of vancomycin    
|                     | • Vancomycin or metronidazole with probiotic agent  
|                     | • Vancomycin + cholestipol        
|                     | • Vancomycin+rifaximin            
|                     | • Fecal transplantation           |
| Severe ileus, toxic megacolon | • Surgical evaluation for complete colectomy |


Infection Control and C. difficile
The inanimate environment is a reservoir of pathogens

Recovery of MRSA, VRE, C. diff, CNS and GNR

Devine et al. Journal of Hospital Infection. 2001;43;72-75
Lemmen et al Journal of Hospital Infection. 2004; 56:191-197
The inanimate environment is a reservoir of pathogens

Recovery of MRSA, VRE, CNS. C. diff and GNR

Lemmen et al Journal of Hospital Infection. 2004; 56:191-197
Walther et al. Biol Review, 2004
Hand Hygiene

- Single most important method to limit cross transmission of nosocomial pathogens
- Multiple opportunities exist for HCW hand contamination
  - Direct patient care
  - Inanimate environment
Hand Hygiene

*Clostridium difficile*

- Hand washing with antiseptic impregnated soap is preferred method for hand hygiene
- Alcohol based hand sanitizers do not consistently and adequately remove *Clostridium difficile* spores.
Contact Precautions for drug resistant pathogens.

Gowns and gloves must be worn upon entry into the patient’s room.

Visitors: Report to nurse before entry

- Handwashing after all patient / environmental contact and glove removal.
- Gloves required for all patient / environmental contact.
- Long sleeved gown required for all patient / environmental contact.
Terminal Disinfection of Patient Rooms Harboring Drug Resistant Pathogens

• All touchable surfaces and all equipment in the room should be cleaned thoroughly at the time of patient discharge using a hospital approved disinfectant

• Sodium hypochlorite (bleach) preferred over Quaternary Ammonium products

• Goal: Decontamination of inanimate environment
# Antibiotic Restriction

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>Restriction of third generation cephalosporins has been successful in reducing CDAD rates</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Fluoroquinolone use appears to be a class effect in outbreaks caused by the NAP1/BI/027 strain. Restriction of entire FQ class likely needed for effective control</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>During <em>C. difficile</em> outbreaks in the 1990s, clindamycin restrictions were followed by reductions in CDAD</td>
</tr>
</tbody>
</table>

*Settle, CD et al. Aliment Pharmacol Ther 1998; 12:1217.31*
*Khan, R. Cheesbrough, J Hosp Infect 2003; 54:104.32*
Triple Threat to *C. difficile*

- Hand Hygiene
- Antibiotic Restriction
- Disinfection of Inanimate Environment

Decrease in colonization pressure, environmental contamination and cross transmission
Summary

• *C. difficile* has become a resurgent nosocomial pathogen
• New data suggest that CDAD is now associated with both hyper-virulence and an increased rate of relapse
• Evidence based treatment guidelines do not exist for the management of CDAD
Summary

- Newer data suggest that oral vancomycin may now be preferred over metronidazole for severe CDAD
- For recurrent CDAD, multiple treatment options exist, none significantly superior than the others
- Meticulous hand hygiene, terminal disinfection and antibiotic restriction is the cornerstone of effective prevention and infection control
The End