Understanding *Clostridium difficile* Infections: Are We There Yet?

Erik R. Dubberke, MD, MSPH, FSHEA
Associate Professor of Medicine
Director, Section of Transplant Infectious Diseases
Washington University School of Medicine
St. Louis, MO

**Historical Perspective**

- 1935: *Bacillus difficilis* first described
- 1943 – 1978: Antibiotic associated colitis (AAC) / pseudomembranous colitis (PMC)
- 1978: *Clostridium difficile* identified as causative agent of AAC/PMC
  - Cytotoxicity cell assay developed
- 1981: Oral vancomycin FDA-approved for treatment of *C. difficile* infection (CDI)
- 1982: Oral metronidazole as effective as oral vancomycin
- 1984: Toxin EIAs approved
- 2000 – present: Increasing incidence and severity of CDI
- 2007: Surveillance definitions developed
- 2007: First double-blinded trial of CDI treatment published (Zar)
- 2009: Nucleic acid amplification tests approved
- 2011: Fidaxomicin FDA-approved
- 2011: First diagnostic assay comparison where patients prospectively evaluated and included regardless of diarrhea severity
**Clostridium difficile**

- Gram-positive, spore-forming rod
- Obligate anaerobe
- Toxin A and Toxin B
  - Required to cause disease (toxigenic)
  - *C. difficile* infection (CDI, formerly CDAD)
    - Toxigenic *C. difficile* in stool ≠ CDI
- Ubiquitous: infants, pets, livestock, wild animals, food, water

**Current Pathogenesis Model for CDI**

Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic immune response against toxins results in CDI.


**Total Number of Cases in U.S. Hospitals**

**Nationwide Inpatient Sample (NIS)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>138,954</td>
</tr>
<tr>
<td>2001</td>
<td>181,901</td>
</tr>
<tr>
<td>2002</td>
<td>205,369</td>
</tr>
<tr>
<td>2003</td>
<td>228,737</td>
</tr>
<tr>
<td>2004</td>
<td>252,115</td>
</tr>
<tr>
<td>2005</td>
<td>275,493</td>
</tr>
<tr>
<td>2006</td>
<td>301,056</td>
</tr>
<tr>
<td>2007</td>
<td>329,638</td>
</tr>
<tr>
<td>2008</td>
<td>351,449</td>
</tr>
<tr>
<td>2009</td>
<td>365,013</td>
</tr>
<tr>
<td>2010</td>
<td>383,498</td>
</tr>
<tr>
<td>2011</td>
<td>398,000</td>
</tr>
</tbody>
</table>

Increasing CDI Severity

- Outbreaks of severe CDI in US, Canada, Ireland, England, Netherlands, France, Germany
- Sherbrooke, Quebec, Canada outbreak, 2003
  - 16.7% attributable mortality
- St. Louis, endemic, 2003
  - 5.7% attributable mortality
  - 2.2-times more likely readmitted
  - 1.6-times more likely discharged to nursing home


Costs of CDI

- Attributable inpatients costs of initial CDI (2012 USD)
  - $3,327 to $9,960 per episode (limited to studies with more robust methodology)
- Attributable inpatient costs of recurrent CDI (2010 USD)
  - $11,631
  - Driven by readmissions
- Other costs not yet quantified
  - CDI outside of the hospital
  - Increase in transfers to skilled nursing facilities at hospital discharge
  - Lost time from work (patient and/or caregiver)


CDI is a Top Priority

- CDC: urgent threat, EIP surveillance
- NIH: requests for applications for novel therapeutics
- CMS: publically reported, may impact hospital reimbursement
Role of the Hospitalist

- ~50% of CDI cases are managed in the hospital
- Diagnose CDI
- CDI treatment
  - Cure now
  - Prevent recurrences in the future
- Prevention
  - Adherence to contact precautions
    - Gowns, gloves, stethoscope
    - Encourage/prompt others

Still Much to Understand

- Diagnosis
  - Patient selection
  - Diagnostic assay
- Prevention
  - Better data needed
  - Challenge: C. difficile is ubiquitous
- Treatment
  - Prevent complications
  - Prevent recurrences

Infection Control Measures to Prevent C. difficile Infection: What Really Works?

Scott R. Curry, MD
Medical Director of Fecal Microbiota Transplant Program
University of Pittsburgh Medical Center, Presbyterian
UPMC Health System
Pittsburgh, PA
### Ubiquity of Toxigenic C. difficile

<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>Toxigenic C. difficile (%)</th>
<th>concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic animals</td>
<td>200</td>
<td>3 (1.5)</td>
<td>?</td>
</tr>
<tr>
<td>Farm animals</td>
<td>524</td>
<td>4 (0.8)</td>
<td>?</td>
</tr>
<tr>
<td>Fish</td>
<td>107</td>
<td>0</td>
<td>?</td>
</tr>
<tr>
<td>Soil</td>
<td>104</td>
<td>9 (8.6)</td>
<td>&gt;2 cfu / 1gm</td>
</tr>
<tr>
<td>Hospitals</td>
<td>380</td>
<td>72 (18.9)</td>
<td>≥1 cfu / 24 cm²</td>
</tr>
<tr>
<td>Nursing homes</td>
<td>275</td>
<td>4 (1.5)</td>
<td>?</td>
</tr>
<tr>
<td>Houses</td>
<td>350</td>
<td>3 (0.9)</td>
<td>?</td>
</tr>
<tr>
<td>Dorms</td>
<td>200</td>
<td>3 (1.5)</td>
<td>?</td>
</tr>
<tr>
<td>Water*</td>
<td>110</td>
<td>36 (32.7)</td>
<td>5 cfu/100 mL</td>
</tr>
<tr>
<td>Vegetables</td>
<td>300</td>
<td>5 (1.7)</td>
<td>?</td>
</tr>
</tbody>
</table>

* Fresh water from lakes, rivers, seawater; no chlorinated tap water samples positive

**7/106 (6.7%) Healthy Subjects with Toxigenic C. difficile Allegheny County, PA 2012**

<table>
<thead>
<tr>
<th>Positive subject</th>
<th>Visit</th>
<th>Toxigenic culture</th>
<th>C. difficile NAAT (illumigene)</th>
<th>tcdC genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 POS</td>
<td>&gt;2 x 10⁵</td>
<td>NEG</td>
<td>tcdC 5</td>
</tr>
<tr>
<td>2</td>
<td>2 NEG</td>
<td>&lt;10</td>
<td>POS</td>
<td>tcdC 30</td>
</tr>
<tr>
<td>3</td>
<td>1 POS</td>
<td>8.7 x 10⁵</td>
<td>NEG</td>
<td>tcdC 15</td>
</tr>
<tr>
<td>4</td>
<td>2 NEG</td>
<td>&lt;10</td>
<td>POS</td>
<td>tcdC 14</td>
</tr>
<tr>
<td>5</td>
<td>1 POS</td>
<td>3.8 x 10⁴</td>
<td>POS</td>
<td>tcdC 53</td>
</tr>
<tr>
<td>6</td>
<td>1 POS</td>
<td>8.6 x 10⁴</td>
<td>NEG</td>
<td>tcdC 3</td>
</tr>
<tr>
<td>7</td>
<td>1 POS</td>
<td>1.1 x 10⁵</td>
<td>NEG</td>
<td>tcdC 10</td>
</tr>
</tbody>
</table>


Infective dose for C. difficile in the mouse model is 5-10 spores/cm²

**Longevity of C. difficile Spores**

Viability of *C. difficile* spores stored in 50% ethanol (left) or dried on metal disks (right).

*Perez et al. J AOAC Int. 2011;94(2):618-626.*

---

**C. difficile is Tough to Kill**

- Standard hospital disinfectants (NH3)
- Isopropyl alcohol 70%
- Ethanol 80%
- INEFFECTIVE

- Strong oxidizing agents:
  - H₂O₂ 10%
  - 5000 ppm bleach
  - Prolonged contact time (15 minutes)

*Wilcox et al., ICUH. 2008;28(8):921-25.*

---

**C. difficile as Nosocomial Infection**

- 728 patients admitted
- 300 not enrolled
- 241 excluded
- 59 refused
- 428 enrolled
- 112 *C. difficile* positive
- 316 *C. difficile* negative
- 83 incident nosocomial
- 23 non-incident nosocomial
- 6 community-acquired

Asymptomatic 52 (63%)
Diarrhea 31 (37%)
Asymptomatic 14 (81%)
Diarrhea 9 (39%)
Diarrhea 3 (50%)

CD Epidemiology: Background

- Widespread in environment
- Hospitals/clinics are major reservoirs
- Nearly indefinitely viable
- Difficult to disinfect
- Large reservoir of asymptomatic carriers
- Spread primarily on the hands of healthcare workers
- Transmitted by fecal-oral route

WHAT INTERVENTIONS ARE EFFECTIVE?

Community-acquired *C. difficile*?

<table>
<thead>
<tr>
<th>setting</th>
<th>year</th>
<th># cases</th>
<th>% cases</th>
<th>Rate per 100,000 person-years*</th>
<th>abx exposure (3 mos.)</th>
<th>exposed to healthcare facilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connecticut</td>
<td>2006</td>
<td>241</td>
<td>?</td>
<td>6.9</td>
<td>68%</td>
<td>29%</td>
</tr>
<tr>
<td>Manitoba</td>
<td>2005-6</td>
<td>275</td>
<td>27.3%</td>
<td>23.4</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>VA/Durham NC</td>
<td>2005</td>
<td>109</td>
<td>20%</td>
<td>21.46</td>
<td>51%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Reading, UK</td>
<td>2008-9</td>
<td>54</td>
<td>?</td>
<td>12.9</td>
<td>31.5%</td>
<td>27.8%</td>
</tr>
</tbody>
</table>

* Hospital-acquired disease ~0.1-50 cases/10,000 patient-days, i.e. 500-5000x higher incidence in hospital populations

Prospective Study of *C. difficile* Contribution to Outpatient Diarrheal Illness

- All outpatients with acute diarrheal illnesses at Yale and Hopkins ER and clinics May 2001-Sept 2004
- 43/1091 (3.9%) participants with + EIA tests for CDI
  - Only 7 had no recognized risk factors
  - Only 3 (0.27%) had no risk factors and no co-infection (rotavirus, norovirus, *C. perfringens*)

“An evolving picture of widespread, frequent CDI among outpatients without risk factors should be tempered by these findings.”

CD in Hospitals

- CD is the most common cause of acute care HA diarrhea
  - accounts for ~15–30% of all abx-associated diarrhea
  - more than 300,000 cases/year.

- Reported incidence – 1 to 30/1,000 discharges
  - No real national benchmarks
  - Target Rate # CDI/1,000 discharges
    - OMG Rate >20

<table>
<thead>
<tr>
<th>Target Rate</th>
<th>OMG Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
</tr>
</tbody>
</table>

- Reported incidence – 1 to 30/1,000 discharges
  - No real national benchmarks
  - OMG Rate >20 >33

* Based on a average LOS of 6 days

- Relapses occur in 20%–30% of cases


Audience Question

Handwashing with soap and water for 30 seconds is as effective at preventing C. difficile transmission as wearing gloves.

1. TRUE
2. FALSE
3. Beats me.

Answer: False!

- Handwashing = 2 log₁₀ reduction in C. difficile CFU on palmar surfaces of volunteers, never in complete eradication
- Alcohol hand-rubs =no intervention
- Prospective controlled study of vinyl gloves vs. enhanced education for care of CDI patients
  - Incidence CDI fell from 7.7 to 1.5/1000 discharges on glove wards
  - Incidence fell from 5.7 to 4.2 cases/1000 discharges on control wards (p<0.015)

Effect of Glove-Wearing by Personnel on 2 Wards vs 2 Control Wards

The Pittsburgh Story

- Hospital-acquired (HA) CD infection (I) rate began increasing in 2000
- Peaked in 2000 at 10.4 cases/1000 discharges
- From ’99 to ’00 annual incidence increased significantly from 2.7 to 7.2 (p<0.05; 95% CI=2.1–3.6)

- Accompanied by an increase in AE rate from 0.15 to 0.61 cases/1000 discharges (p<0.01; 95% CI 1.31–14.3)
- Half of the colectomy cases were associated with CD death

- No obvious changes in patient population, cleaning or infection control policies.
- The only formulary changes were switching ceftazidime to cefepime and cipro to levofloxacin.

“The Epidemic Strain”

- REA type BI, Ribotype 027, PFGE type NAP-1, tcdC=1, MLST=1
  - In US (Chicago) pre-2001 isolates 0.3% BI/NAP1/027
  - Post-2001 outbreak isolates in US hospitals 10-75% BI/NAP1
  - Similar 2002-4 Quebec outbreak described

- Outbreak isolates associated with nonsense mutations in tcdC, negative regulator of toxin B
- Contain extra toxin outside PaLoc= binary toxin (cdt)
- Produces 16-20X toxin A and B in vitro during both growth phases.

McDonald LC, Killgore GE et al. NEJM. 2005;353: 2433-41.
Loo VG et al. NEJM. 2005;353: 2442-2449.
Epidemic Strain *C. difficile* May Not be Associated with Worse Clinical Outcomes

<table>
<thead>
<tr>
<th>N (% epidemic)</th>
<th>year</th>
<th>endpoint</th>
<th>multivariate OR* setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>236 (25)</td>
<td>2004-6</td>
<td>death, colectomy, or ICU admission</td>
<td>0.74 (0.3-1.7) Boston</td>
</tr>
<tr>
<td>123 (41)</td>
<td>2006</td>
<td>Shock, colitis, ileus, PMC</td>
<td>2.07 (0.6-6.8) England</td>
</tr>
<tr>
<td>205 (42)</td>
<td>2001-2005</td>
<td>Attributable death, colectomy</td>
<td>2.10 (0.6-6.9) UPMC</td>
</tr>
<tr>
<td>478 (57)</td>
<td>2005</td>
<td>death or CDI-attributable death</td>
<td>2.1 (0.98-4.6) Québec</td>
</tr>
</tbody>
</table>

*odds ratio for severe outcome associated with epidemic strain

**Curry JR, unpublished data**

The Pittsburgh CD Story

Unlike Vegas, What Happens in Pittsburgh Doesn’t Stay in Pittsburgh

What We Knew

- Hospitals are major reservoirs
  - ~20% to 40% of hospitalized patients become colonized
- Iatrogenic Risk Factors – Things we do to the patient
  - Antibiotics, Antibiotics, Antibiotics, especially… PCN, clindamycin, and cephalosporins
  - Prolonged hospital/long-term care stay
  - Sharing a room with an infected patient
  - Gastrointestinal surgery or manipulation
    - Repeated enemas
    - Prolonged NG insertion
    - Decreased stomach acidity – PPIs/H2 Blockers
- Spread primarily on the hands on HCWs
- Transmitted by fecal-oral route

C. *difficile* spores have been recovered from:
  - Hospital toilets/commodes
  - Metal bedpans
  - Floors
  - Thermometers

Spores can exist on surfaces for months

CDC Fact Sheet. August 2006 (updated 7/15/06).
Action Plan

Stop and Think!

- Review of Literature
- Multidisciplinary Team Assembled
  - Infection Control
  - Pharmacy
  - Microbiology
  - Environmental Services
  - Administration/ Clinical leadership
  - Clinical Staff
    - MDs
    - Nursing
    - Respiratory Care
    - Ancillary Care
  - Risk management
- What changed?
  - Patients
  - The bug
  - The HCWs
- Set Benchmarks

Antibiotic Trend Analysis Results

Total DDDs for Quinolones* and Incidence of HA CD cases, 1/96–4/01

The quinolone formulary change was accompanied by a significant increase in quinolone use (p<0.001) which preceded the C. difficile outbreak by 9 months. Cephalosporin and clindamycin use did not change significantly (data not shown).

*Cipro, oflox, and levo (combined)

Study Components

1. Matched case-control study
   - To characterize a CDI outbreak
   - Identify associated risk factors
   - 203 case-control sets
2. Inpatient antibiotic utilization trends
   - To determine whether the outbreak coincided with changes in antibiotic consumption
3. A microbiologic component
   - Assess for resistant strains
   - Molecular subtyping to evaluate for horizontal transmission

Matched Case-Control Study Results - Multivariate Analysis

8 variables in the final model were significant

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>OR</th>
<th>95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Continuous variable</td>
<td>1.02/y</td>
<td>1.006-1.037</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>83 (40.9)</td>
<td>59 (29.1)</td>
<td>2.1</td>
<td>1.2-3.6</td>
</tr>
<tr>
<td>Transplant</td>
<td>44 (21.7)</td>
<td>18 (8.9)</td>
<td>5.8</td>
<td>2.3-14.6</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>21 (10.3)</td>
<td>8 (3.9)</td>
<td>5.6</td>
<td>1.8-15.8</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>159 (78.3)</td>
<td>54 (26.6)</td>
<td>2.4</td>
<td>1.3-4.4</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>32 (15.8)</td>
<td>13 (6.4)</td>
<td>4.8</td>
<td>1.9-12.0</td>
</tr>
<tr>
<td>H2 Blockers</td>
<td>159 (78.3)</td>
<td>141 (69.5)</td>
<td>2.0</td>
<td>1.1-3.5</td>
</tr>
</tbody>
</table>

*Like historical studies, exposure to ceftriaxone and clindamycin were independent RFs.
*Additionally, levofloxacin was found to be significant

Levofloxacin was the most widely prescribed abx during the study period (59% of cases)


Microbiology

- CD isolates
  - In addition to CD toxin testing, began CD culturing 3/2001
  - Very labor-intensive process
  - TAT- 5 days
- On average, ~300 cultures were done per month
  - Positivity rate of 10% to 20%
- CD isolate collection
  - >7000 of CD isolates have been collected and stored

Had The Bug Changed?

- 135 C. difficile isolates were typed
  - REA types 2 and 4, differed from each other by a single band
  - Represent ~5% of all HA CD isolates (Outbreak strain)
A subset of isolates underwent additional testing and were consistent with the epidemic BI strain

What to Do?  
What Works?

Infection Control Preventative Measures

<table>
<thead>
<tr>
<th>IC Measure</th>
<th>Intervention efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrier precautions</td>
<td></td>
</tr>
<tr>
<td>Gloves1</td>
<td>Proven</td>
</tr>
<tr>
<td>Handwashing2,3</td>
<td>Probable</td>
</tr>
<tr>
<td>Private room/isolation4-6</td>
<td>Probable</td>
</tr>
<tr>
<td>Environmental cleaning</td>
<td></td>
</tr>
<tr>
<td>Rooms7-10</td>
<td>Proven</td>
</tr>
<tr>
<td>Commodes</td>
<td>Untested</td>
</tr>
<tr>
<td>Single-use rectal thermometers11</td>
<td>Proven</td>
</tr>
<tr>
<td>Endoscope disinfection12,13</td>
<td>Probable</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Antibiotic restriction14,15</td>
<td>Proven</td>
</tr>
<tr>
<td>Metronidazole tx for asymptomatic carriers16</td>
<td>Ineffective</td>
</tr>
</tbody>
</table>


What we did: The Muto Bundle

1. CD education module/RN test authority/CD email alerts/1:100 NaOCl cleaning/isolation precautions
2. CD management team (SWAT team)
3. Monitoring of isolation compliance
4. Computer flagging to enhance cohorting CD patients
5. First year of isolates collected by micro
6. Antibiotic management team piloted
7. Hand washing for CD patients (no ETOH)
8. Real-time lab alerts to floor for isolation
9. Full implementation of AMP/1:10 NaOCl cleaning  

**CDC Summary of Prevention Measures**

### Core Measures
- Contact precautions for duration of illness
- Hand hygiene in compliance with CDC/WHO
- Cleaning and disinfection of equipment and environment
- Laboratory-based alert system
- CDI surveillance
- Education

### Supplemental Measures
- Prolonged duration of contact precautions*
- Presumptive isolation
- Evaluate and optimize testing
- Soap and water for HH upon exiting CDI room
- Universal glove use on units with high CDI rates
- Bleach (sporicide) for environmental disinfection
- Antimicrobial stewardship program

*Not included in CDC/HICPAC 2007 Guideline for Isolation Precautions

---

**CONTACT PRECAUTIONS**

*(IN ADDITION TO STANDARD PRECAUTIONS)*

- **Private Room**
  - A private room is indicated; however patients infected with the same organism may share a room if necessary.

- **Gloves**
  - Wear gloves for contact with the patient and/or environment.
  - Change gloves after contact with infective material.
  - Remove gloves before leaving the patient's environment.

- **Gown**
  - Wear if you anticipate that your clothes will have contact with the patient, environmental surfaces, or items in the patient's room.
  - Remove gown before leaving the patient's environment.

- **Wash Hands**
  - Use antiseptic product immediately after glove removal and before leaving the patient's environment.

- **Transport**
  - Limit the movement/transport of patients to essential purposes only. During transport, ensure that all precautions are maintained at all times.

- **Equipment**
  - Dedicate the use of patient-care equipment to a single patient. If common equipment is used, clean and disinfect between patients.

---

**Rationale for Soap and Water: Lack of Efficacy of Alcohol-Based Handrub Against C. difficile**

<table>
<thead>
<tr>
<th>Intervention 1</th>
<th>Intervention 2</th>
<th>Mean Log reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm water and plain soap</td>
<td>No hand hygiene</td>
<td>2.14 (1.74-2.54)</td>
</tr>
<tr>
<td>Warm water and plain soap</td>
<td>Alcohol-based handrub</td>
<td>2.08 (1.49-2.67)</td>
</tr>
<tr>
<td>Cold water and plain soap</td>
<td>No hand hygiene</td>
<td>1.68 (1.46-2.28)</td>
</tr>
<tr>
<td>Cold water and plain soap</td>
<td>Alcohol-based handrub</td>
<td>1.62 (1.49-2.22)</td>
</tr>
<tr>
<td>Warm water and antibacterial soap</td>
<td>No hand hygiene</td>
<td>1.57 (1.10-1.96)</td>
</tr>
<tr>
<td>Warm water and antibacterial soap</td>
<td>Alcohol-based handrub</td>
<td>1.50 (1.20-1.80)</td>
</tr>
<tr>
<td>Cold water and plain soap</td>
<td>Antibacterial handrub</td>
<td>1.41 (1.09-1.71)</td>
</tr>
<tr>
<td>Warm water and antibacterial soap</td>
<td>Antibacterial handrub</td>
<td>1.40 (1.08-1.73)</td>
</tr>
<tr>
<td>Warm water and plain soap</td>
<td>Warm water and antibacterial soap</td>
<td>1.63 (1.02-2.02)</td>
</tr>
<tr>
<td>Antibacterial handrub</td>
<td>Warm water and antibacterial soap</td>
<td>1.62 (1.17-2.06)</td>
</tr>
<tr>
<td>Alcohol-based handrub</td>
<td>Cold water and plain soap</td>
<td>1.51 (1.23-1.80)</td>
</tr>
<tr>
<td>Cold water and plain soap</td>
<td>Warm water and antibacterial soap</td>
<td>1.59 (1.10-2.07)</td>
</tr>
<tr>
<td>Warm water and plain soap</td>
<td>Cold water and plain soap</td>
<td>0.56 (0.33-0.80)</td>
</tr>
<tr>
<td>Alcohol-based handrub</td>
<td>Warm water and plain soap</td>
<td>0.56 (0.33-0.80)</td>
</tr>
</tbody>
</table>


---

14
Asymptomatic carriers had significantly higher rates of environmental and skin contamination than did noncarriers but < patients with CDAD. Carriers of epidemic and nonepidemic CD strains had similar skin and environmental contamination (67% vs. 55%; \(p=0.78\) and 55% vs. 62%; \(p=0.52\) respectively).


Environmental Cleaning: Options

- Sodium hypochlorite/bleach (B) – 5500 ppm
  - Caustic to the environment
    - Furniture, mattresses, equipment, etc.
    - Leaves a salt precipitate upon evaporation

- \(\text{H}_2\text{O}_2\) +/- Peracetic/Peroxyacetic acid (PA)
  - EPA approval for use in healthcare settings
  - Decreased contact time with addition of PA: \(\leq 5\) minutes
  - Disrupts cell wall permeability
  - Use has been limited because of its vinegar odor

Sporicidal Switch
Sodium hypochlorite/bleach → H₂O₂ → Peroxyacetic acid (PA)

1. No change in CDI rates
2. Promotion of the "NEW SMELL OF CLEAN" was instrumental.
3. No damage to furniture or equipment
4. Staff were particularly fond of the one-step cleaning

Real-World Bleaching...
Percentage of Positive Environmental Cultures for Clostridium difficile after Housekeeping Cleaning with Bleach

- 47% of high-touch surfaces in 3 hospitals were cleaned
- Sustained improvement in cleaning of all objects, especially in previously poorly-cleaned objects, following educational interventions with the environmental services staff
- The use of environmental markers is a promising method to improve cleaning in hospitals

Assess Environmental Cleaning
- Ensure that environmental cleaning is adequate and high-touch surfaces are not being overlooked
- Fluorescent environmental marker to assess cleaning showed:
  - 47% of high-touch surfaces in 3 hospitals were cleaned
  - Sustained improvement in cleaning of all objects, especially in previously poorly-cleaned objects, following educational interventions with the environmental services staff
- The use of environmental markers is a promising method to improve cleaning in hospitals
Tru-D SmartUVC
Adjunct to Terminal Cleaning

• UV-C utilizes short-wavelength radiation that is germicidal
• Destroys 99.9% to 99.99% of targeted pathogens
  • 3–4 log_{10} disinfection
• Targets surfaces and shadows
• Automated and safe
• Remote activation
• Sensor and Lock on Door
• Cannot transmit through glass

UVC Disinfection

• Room Decontamination with UV radiation
• Evaluation of an Automated UVC Device for Decontamination of CD and Other HCA Pathogens in Hospital Rooms
• Rapid Hospital Room Decontamination Using Ultraviolet (UV) Light with a Nanostructured UV-Reflective Wall Coating
• Decontamination of Targeted Pathogens from Patient Rooms Using an Automated UVC-Emitting Device
• Terminal Decontamination of Patient Rooms Using an Automated Mobile UV Light Unit
• Decontamination with Ultraviolet Radiation to Prevent Recurrent CDI in Two Roommates in a Long-Term Care Facility

Enhanced IC Measures

• Expanded duration of contact isolation to entire LOS - July 2000
• Require bleach cleaning for CD+ patient rooms
  • 1:100 dilution – May 2001
  • 1:10 dilution – July 2003
• Routine monitoring of isolation compliance - July 2001
• Require handwashing with soap and water (not alcohol-based sanitizers) for care of CD+ patients
  • Implemented May 2003
  • Room Signage

HANDWASHING, WITH SOAP AND WATER, IS REQUIRED PRIOR TO LEAVING THIS ROOM

Increased Case Finding
Early Identification

- Expanded CD ordering authorization to RNs – Implemented 7/00
- CD Alert - Email sent by the Medical Director to clinicians requesting consideration of CD testing on high-risk patients
  - Previous CDI
  - Extended antibiotic use
  - Leukocytosis, leukopenia or bandemia
    - Patient readmitted within 14 days with a WBC >10,000
    - A LOS >7 days and WBC >10,000 or <2000 and bandemia >10%
  - 13,302 alerts have been sent through 9/05

Informatics Tools

- Electronic flagging of CD+ patients
  - To assure maintained isolation during entire inpatient stay
  - Implemented November 2001
- Automatic real-time CD+ notification
  - Generated from Laboratory Information System directly to the patient care unit
    - Fax, email, and digital page available, soon phone voice message
  - Patient CD+ result and need for Contact Precautions
  - Requirements for CD isolation at our facility listed on the fax and email
  - Implemented March 2003
- Linked comment to all CD+ lab results stating isolation requirements
  - Implemented March 2003

UPMC PUH
Risk of CD Diarrhea According to Antibiotic Class

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Odds Ratio (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>5.4</td>
</tr>
<tr>
<td>Clinda</td>
<td>4.8</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Canadian Experience
Risk of CD Diarrhea According to Antibiotic Class

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>3.8</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>3.9</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1.6</td>
</tr>
<tr>
<td>Macrolides</td>
<td>1.3</td>
</tr>
</tbody>
</table>


Targeted Antibiotic Restriction

- Levofloxacin, clindamycin and ceftriaxone were found to be associated with increased risk of HA CD in our case-control study.
- Require prior approval for inpatient use
  - Implementation began October 2002
  - Fully implemented by July 2003
- Antibiotic usage
  - Defined daily doses (DDDs)/per 100 patient-days are calculated monthly and annually
  - Individual antibiotics and class usage is followed

The Antibiotic Management Team achieved significant reductions of all antibiotics identified as high risk
2004: Quinolones - 50%; Clindamycin - 75%; Ceftriaxone - 35%
2006: Quinolones - 38%; Clindamycin - 68%; Ceftriaxone - baseline

Use of Multilocus Variable Number of Tandem Repeats Analysis Genotyping to Determine the Role of Asymptomatic Carriers in Clostridium difficile Transmission

- 3006 high-risk patients at UPMC screened
  - 314 (10.4%) positive for C. difficile
  - 226 (7.5%) found only on screening tests
  - 56 HA-CDI cases during screening
    - 17 (30%) linked to known CDI patients by MLVA
    - 16 (29%) linked to carriers by MLVA
    - Balance of cases of unknown origin
Asymptomatic Toxigenic CD Positivity Rate

- CD was cultured 292/3003 (10%) patients
- 210/3003 (7.0%) of patients with no known CD history were positive
  - CD identified 7.5 days prior to discharge (945 un-isolated pt-days)

Where did they get it?
- Toxigenic CD was recovered from 5/6 rooms sampled at 15/30 sites.
- In 4/5 patients – At least 1 environmental isolate matched the patient’s perirectal swab
- Effective universal bleach cleaning may interrupt transmission to the next room occupant

DID IT WORK?

Peak – 2000
CD Bundle was implemented over time
CD HAI rate significantly ↓
\[ OR = 1.6, CI = 1.3-2.0, p=0.00003 \]
By 2007 - 64% reduction from peak

Conclusions

• A new epidemic CD strain has emerged worldwide, causal role not established
• Traditional risk factors like age, cephalosporin and clindamycin use still play a role
  – Newer risk factors like fluoroquinolone and PPI use have also been identified
  – Newly described at-risk populations have been identified
• Infection Control Measures associated with reduction in HA CDI rates
• Unknown which components were necessary and sufficient:
  – Antimicrobial restriction
  – Enhanced environmental cleaning
  – Glove use
  – Hand hygiene
  – Patient isolation
• Future directions
  – Technical advances in environmental cleaning
  – Enhanced vertical controls (such as for VRE/MRSA)

Preventing CDI

OUTCOME

Recognizing Patient Risk Factors for *C. difficile* Infection, Recurrence, and Complications

Ciarán P. Kelly, MD
Professor of Medicine
Harvard Medical School
Director Gastroenterology Fellowship Training
Director Celiac Center
Beth Israel Deaconess Medical Center
Boston, MA
**CDI: Understanding Patient Risk for Complications and Recurrence**

- Pathophysiology of *Clostridium difficile* infection (CDI)
- Risk factors that predict severe complications of CDI
- Features of severe and of severe complicated (fulminant) CDI
- Management of fulminant CDI
- Pathophysiology of recurrent CDI
- Risk factors that predict recurrent CDI

**Pathogenesis of C. difficile Infection (CDI)**

- Antibiotic therapy
- Disturbed colonic microflora (loss of colonization resistance)
- *C. difficile* exposure & colonization
- Toxin A & Toxin B
- Symptomless carriage
- Diarrhea & colitis
- Highest risk in healthcare facilities
- Chemotherapy
- Neonatal state
- Enteric infection
- IBD with colitis

**Antibiotics Predisposing to CDI:**

<table>
<thead>
<tr>
<th>Uncommonly Related</th>
<th>Less Commonly Related</th>
<th>Very Commonly Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Other penicillins</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Sulfonamides</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Trimethoprim</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>Cotrimoxazole</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Macrolides</td>
<td>(2nd and 3rd generation)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*References*


Marked Increases in Severe CDI in the US

- US Annual CDI-Related Hospitalizations
- US CDI Death Rates

- 14,000 deaths per annum in US per CDC estimate
- x 4 annual deaths related to MRSA
- x 6 annual deaths related to all other enteric pathogens combined


Immunity to *C. difficile* Toxins is Associated with Symptomless Carriage


Predicting Severe Complications of CDI

- Derivation cohort – 263 CDI subjects in Boston
- Validation cohort – CDI subjects in Houston (n=225) & Dublin (n=150)

Severe outcomes – CDI-related ICU admission and/or Colectomy and/or Death.

Prediction score
- 1 for Age ≥65 years
- 1 for WBC ≥20,000 cells/μL
- 1 for Creatinine ≥22 mg/dL

Score: 0 1 2 3

(73% accurate)

C. difficile Infection: Factors Contributing to Increased Incidence and Severity

Host factors
- Age
- Immune response
- Underlying disease

C. difficile bacterial factors
- Virulence
- Sporulation
- Antibiotic resistance

Environment
- Antibiotic use
- PPI use
- Burden of spores


Severe CDI: Case Presentation
- 87-year-old man undergoes hip replacement surgery following fractured femur
- Medical history: diabetes mellitus, COPD & severe CAD with congestive heart failure
- POD #6: diarrhea. Stool test positive for toxigenic C. difficile
- WBC 18,200 cells/µL, creatinine 1.9 mg/dL (baseline 1.2)
- Treated with oral vancomycin 125 mg q6h
- 36 hours later, he develops nausea, abdominal distension and hypotension.
- His WBC is now 34,700 cells/µL and creatinine is 2.7 mg/dL

How would you change his management at this time?

1. Increase oral vancomycin dose to 500 mg q6h
2. Discontinue oral vancomycin as it is not effective and change to oral metronidazole 500 mg q8h
3. Continue oral vancomycin 125 mg q6h and add oral metronidazole 500 mg q8h
4. Increase oral vancomycin dose to 500 mg q8h and add IV metronidazole 500 mg q8h
5. Increase oral vancomycin dose to 500 mg q6h, add IV metronidazole 500 mg q8h and request a surgery consultation
### CDI: SHEA – IDSA Treatment Guidelines

<table>
<thead>
<tr>
<th>CDI Severity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mild to moderate</td>
<td>Metronidazole 500 mg 3 times per day PO 10–14 days</td>
</tr>
<tr>
<td>2. Severe</td>
<td>Vancomycin 125 mg 4 times per day PO 10–14 days</td>
</tr>
</tbody>
</table>
| 3. Severe, complicated (fulminant) | Vancomycin 500 mg 4 times per day PO or by nasogastric tube or enema plus Metronidazole 500 mg q8h IV


### CDI: Determining Disease Severity

**Severe**
- Marked leukocytosis
  - >15,000 in severe CDI
  - >25,000 increased fatality
- High (>1.5 mg/dL) or rising (50% increase) serum creatinine
- Severe diarrhea
  - >10 bowel movements/day
- Severe abdominal pain or distension
- Fever >101ºF
- Low serum albumin (<2.5)

**Fulminant (Severe complicated)**
- Not responding to therapy
- Toxic megacolon
- Hemodynamic instability
- Organ failure
- Ileus
- CT with
  - Colonic thickening
  - Ascites
- Pseudomembranes on colonoscopy


### Colonic Distension and Small Bowel Ileus in Fulminant *Clostridium difficile* Colitis

Severe / fulminant CDI may present as an acute abdomen and/or small bowel and colonic ileus (mimicking acute colonic pseudo-obstruction)
- Little or no diarrhea
- Sigmoidoscopy usually diagnostic

When Standard Therapy Fails in Fulminant CDI: Unproven Adjunctive Treatments

1. Tigecycline
   - Loading dose of 100 mg IV
   - Then 50 mg two times per day

2. IVIG (Intravenous immunoglobulin infusion)
   - 400 mg/kg body weight x 1

3. FMT (Fecal microbiota transfer)

---

Diverting Loop Ileostomy and Colonic Lavage:
An alternative to total abdominal colectomy in refractory CDI

**Colectomy versus:**
- Loop ileostomy
- Intraoperative colonic lavage with warmed polyethylene glycol 3350/ electrolyte via the ileostomy
- Post-op antegrade vancomycin instillation via ileostomy

42 patients
- 83% by laparoscopy
- 93% colon preserved
- 19% mortality
  - versus 50% mortality in historical controls (odds ratio, 0.24; p=0.006).

Severe CDI: Case Presentation

- 87-year-old man undergoes hip replacement surgery following fractured femur
- Medical history: diabetes mellitus, COPD & severe CAD with congestive heart failure
- POD 6: diarrhea. Stool test positive for toxigenic *C. difficile*
- WBC 18,200 cells/µL, creatinine 1.9 mg/dL (baseline 1.2)
- Treated with oral vancomycin 125 mg q6h
- 36 hours later he develops nausea, abdominal distension and hypotension
- His WBC is now 34,700 cells/µL and creatinine is 2.7 mg/dL.
Back to Audience Question

How would you change his management at this time?
1. Increase oral vancomycin dose to 500 mg q6h
2. Discontinue oral vancomycin as it is not effective and change to oral metronidazole 500 mg q6h
3. Continue oral vancomycin 125 mg q6h and add oral metronidazole 500 mg q6h
4. Increase oral vancomycin dose to 500 mg q6h and add IV metronidazole 500 mg q8h
5. Increase oral vancomycin dose to 500 mg q6h, add IV metronidazole 500 mg q8h AND request a surgery consultation


Recurrent CDI: Case Presentation

- Our 87-year-old patient with severe complicated CDI responded to intensive medical management.
- He was transferred to rehab where he completed 14 days of oral vancomycin and was treated for a UTI with ciprofloxacin.
- Five days later, he developed diarrhea, nausea, vomiting, abdominal distension and his WBC was elevated at 17,200 cells/µL.
- He was transferred back to the acute care hospital where he responded well to aggressive treatment for recurrent CDI (oral vancomycin and intravenous metronidazole).
- Prior to transfer he asks if there is a risk for yet another recurrence of CDI.

Audience Question

What is his risk for a second recurrence?
1. Less than 10%
2. 10 to 20%
3. 20 to 30%
4. 30 to 70%
5. Greater than 70%
Antibiotic therapy
Disturbed colonic microflora (loss of colonization resistance)

Recurrence
C. difficile exposure & colonization
Toxin A & Toxin B
Symptomless carriage
Diarrhea & colitis
Antibiotic treatment

Recurrence C. difficile Infection

• Common: ~25% of patients treated with metronidazole or vancomycin suffer a recurrence
  – Recurrence rates after fidaxomicin lower (~15%)
• Mechanisms of recurrence:
  – NOT primarily due to antimicrobial resistance
  – Instead, antimicrobial therapy perpetuates dysbiosis
• Same strain as initial episode (relapse) or a new strain (re-infection)
• Several patient risk factors for CDI recurrence have been identified

Risk Factors for Recurrent CDI

• Previous episode of recurrent CDI
• Additional antibiotic use (perpetuates dysbiosis)
• Aged 65 years or over
• Impaired immune response to C. difficile toxins
• Prolonged hospitalization
• Severe underlying disease
  – ICU admission
  – Immunocompromised
  – Renal impairment
• Acid anti-secretory medication?
Meta-analysis of Risk Factors for Recurrent CDI

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non- (C.) difficile antibiotics after diagnosis of CDI</td>
<td>4.23</td>
<td>2.10–8.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acid antisecretory medications</td>
<td>2.15</td>
<td>1.13–4.08</td>
<td>0.019</td>
</tr>
<tr>
<td>Older age</td>
<td>1.62</td>
<td>1.11–2.36</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

Factors were evaluated only if studied in at least 3 publications that met the quality inclusion criteria:
- Fewer than 3 studies evaluated:
  - Disease severity (Horn’s index)
  - Anti-toxin immune response


Prospective Derivation and Validation of a Clinical Prediction Rule for Recurrent Clostridium difficile Infection

Predictors of recurrence:
- 1 for Age >65 y
- 1 for Severe underlying disease (Horn’s index)
- 1 for Additional antibiotic use

Score         Recurrence rate (validation cohort)
0             0%
1             17%
2             31%
3             67%

Predictive accuracy (in validation cohort): 72%
Score of 0 or 1 versus 2 or 3 [95% CI: 59.2 to 82.4%]


High Serum IgG Anti-toxin A Levels are Associated with a Lower Risk for Recurrent \(C.\) difficile Diarrhea

For a level <1.23
Odds ratio = 0.8 (95% CI, 3.5 – 6.6)

Prior CDI Recurrence and Recurrence Risk

- Recurrence rate
- Initial episode
- First recurrence
- Second recurrence
- ~25%
- ~40%
- >50%

Whether treated with Metronidazole or Vancomycin


Back to Audience Question

What is his risk for a second recurrence?
1. Less than 10%
2. 10 to 20%
3. 20 to 30%
4. 30 to 70%
5. Greater than 70%

Refractory and Fulminant (CDI):
Key Points

- CDI has become an increasingly common and lethal infection (usually nosocomial & iatrogenic).
- Factors that predict severe outcomes in CDI include older age (>65 years), high WBC (>20,000 cells/μL) and high creatinine (>2 mg/dL).
- Severe complicated (fulminant) CDI can result in SIRS (systemic inflammatory response syndrome), hypotension, organ failure and toxic megacolon.
- Vancomycin therapy is indicated in severe CDI – metronidazole is not an appropriate sole therapy.
- In refractory CDI, timely surgical intervention can be lifesaving.
Risk Factors for Recurrent CDI: Key Points

- Antibiotic treatment for antibiotic-induced CDI perpetuates dysbiosis and predisposes to recurrence.
- Recurrent CDI is common.
  - ~25% after a 1st CDI episode
  - ~35% after a 2nd CDI episode
  - ~50% after a 3rd or subsequent CDI episode
- Host immune responses (anti-toxin antibody production) can protect against recurrent CDI.
- Factors that predict a higher risk for recurrence include prior recurrences, additional (concomitant) antibiotic use, older age, and severe underlying disease.

A Patient-Centered Approach for Managing CDI: Balancing the Old with the New

Erik R. Dubberke, MD, MSPH, FSHEA
Associate Professor of Medicine
Director, Section of Transplant Infectious Diseases
Washington University School of Medicine
St. Louis, MO

Case

- 70-year-old female nursing home resident
- Developed diarrhea: six Bristol 7 stools/day
- Completed ciprofloxacin for a UTI 5 days prior
- In ED noted to be dehydrated
  - IV fluids started
  - WBC = 13.5K cells/μL
- Stool positive for C. difficile toxin
**CDI Treatment**

- Historically two main treatments
  - Metronidazole
  - Oral vancomycin (not intravenous)
- Response rates equal until 2000
  - Initial cure in 85% to 95%
  - Recurrence in 15% to 30%

**Increased Reports of Metronidazole Failures**

<table>
<thead>
<tr>
<th>Study</th>
<th>Response</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez</td>
<td>61/99 (62%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mushar</td>
<td>161/207 (78%)</td>
<td>47/161 (29%)</td>
</tr>
<tr>
<td>Pépin</td>
<td>323/435 (74%)</td>
<td>109/323 (34%)</td>
</tr>
<tr>
<td>Belmares</td>
<td>72/102 (71%)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Vancomycin vs. Metronidazole for Severe CDI

- First double-blind trial of metronidazole vs. vancomycin

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>No. of patients cured</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Mtz group 37/41 (90)</td>
<td>30/40 (98)</td>
</tr>
<tr>
<td>Severe</td>
<td>26/38 (70)</td>
<td>30/43 (97)</td>
</tr>
<tr>
<td>All</td>
<td>63/79 (84)</td>
<td>60/83 (97)</td>
</tr>
</tbody>
</table>


CDI Treatment Stratified by Severity

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>Leukocytosis (WBC &lt;15,000 cells/µL) or SCr level &lt;1.5 times premorbid level</td>
<td>Metronidazole 500 mg 3 times per day PO for 10–14 days</td>
</tr>
<tr>
<td>Severe</td>
<td>Leukocytosis (WBC ≥15,000 cells/µL) or SCr level ≥1.5 times premorbid level</td>
<td>Vancomycin 125 mg 4 times per day PO for 10–14 days</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin 500 mg 4 times per day PO or by nasogastric tube plus metronidazole 500 mg IV q8h</td>
</tr>
</tbody>
</table>


Metronidazole Also Inferior For Non-Severe CDI

Vancomycin superior to metronidazole on multivariable analysis, including controlling for clinical severity (p=0.013)

A Word on Vancomycin Dose

- Vancomycin concentration at 125 mg QID >100 times higher than MIC for C. difficile
- Time-dependent killing
  - No additional benefit beyond 4–10 × MIC
- Higher concentrations may kill more "non-susceptible" bacteria

Fidaxomicin

- Novel antimicrobial: macrocyclic
- Narrow spectrum: No activity against Gram-negatives
  - Sparing of Bacteroides spp., bifidobacterium, clostridial clusters IV and XIV
- Decrease in recurrences
  - Patients with multiple recurrences were excluded

Impact of Concomitant Antibiotics on Response to CDI Treatment

<table>
<thead>
<tr>
<th></th>
<th>No CA</th>
<th>Fidaxo N=391</th>
<th>Vanco N=416</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td>92%</td>
<td>93%</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>12%</td>
<td>23%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sustained response</td>
<td>81%</td>
<td>69%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CA</th>
<th>Fidaxo N=90</th>
<th>Vanco N=102</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td>90%</td>
<td>79%</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>17%</td>
<td>29%</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Sustained response</td>
<td>72%</td>
<td>59%</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

CA = concomitant antibiotics
Fidaxomicin in Oncology Patients

Clinical cure: fidaxomicin 85%, vancomycin 74% (p=0.065)
Recurrence: fidaxomicin 14%, vancomycin 30% (p=0.018)
Sustained clinical response: fidaxomicin 74%; vancomycin 52% (p=0.003)

Case Continued

- The patient responded to the 10-day course of vancomycin you prescribed
  - Diarrhea recurred 7 days later, stool was positive for *C. difficile*, responded to metronidazole at the nursing home
- Diarrhea recurred 5 days after metronidazole stopped
  - Ten Bristol 7 stools/day
  - Transferred back to the ED
  - Stool positive for *C. difficile* toxin

Audience Question

What do you do?

1. Metronidazole 500 mg PO q8h for 60 days
2. Vancomycin 125 mg PO q8h for 10 days then taper over several weeks
3. The pharmacy will finally let me prescribe fidaxomicin: fidaxomicin 200 mg PO q12h for 10 days
4. More feces
Management of Recurrent CDI

- CDI recurrence is a significant challenge
- Rates of recurrent CDI:
  - 20% after first episode
  - 45% after first recurrence
  - 65% after two or more recurrences

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence</td>
<td>Treat as first episode according to disease severity</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>Treat with oral vancomycin taper and/or pulse dosing</td>
</tr>
</tbody>
</table>


First Step: Educate and Confirm Symptoms are from CDI


Abrupt Stop vs. Taper or Pulse of Vancomycin

- Mean number of CDI episodes 3 ± 2.1 (range 1–14)
- Relative Risk of Relapse = 0.51 (95% CI: 0.29–0.90)

### Alternative/Adjunctive Therapies

- **Probiotics:** RCTs of *Lactobacillus* and *Saccharomyces boulardii* without benefit
- **Cholesterol binders:** No better than placebo
- **Rifaximin:** Initial treatment and “Chaser” to prevent recurrence; *caution – rapid development of resistance*
- **Nitazoxanide:** Non-inferior to metronidazole and vancomycin in small trials; no clear advantage
- **Tigecycline:** Case reports for severe CDI; mixed results
- **IVIG:** Severe or recurrent infections; mixed results

### Tens Days of Fidaxomicin May Not Be Enough for Recurrent CDI: Potential Role for Chaser or Taper

![Graph showing efficacy of fidaxomicin]


### Fecal Microbiota Transplant (FMT)

- **Theory:** Restoration of fecal flora and colonization resistance
- **First report in 1958**
- **Several recent reviews of published reports**

<table>
<thead>
<tr>
<th>Method</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>55/62 (88.7%)</td>
</tr>
<tr>
<td>Enema</td>
<td>105/110 (95.4%)</td>
</tr>
<tr>
<td>Gastric or duodenal tube</td>
<td>55/72 (76.4%)</td>
</tr>
<tr>
<td>Rectal catheter</td>
<td>44/46 (95.6%)</td>
</tr>
<tr>
<td>&gt;1 method</td>
<td>19/21 (90.5%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>6/6 (100%)</td>
</tr>
</tbody>
</table>

Recent FMT Trial

- At least one relapse
- Open label
  - 4 to 5 days of vancomycin, bowel prep, FMT (duodenal tube)
  - 14 days of oral vancomycin
  - 14 days of vancomycin with bowel prep at day 4 to 5

<table>
<thead>
<tr>
<th>Method</th>
<th>Number prior episodes</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single infusion of feces</td>
<td>3 (1–5)</td>
<td>13/16 (81%)</td>
</tr>
<tr>
<td>Vancomycin only</td>
<td>3 (1–4)</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>Vancomycin and lavage</td>
<td>2 (1–9)</td>
<td>3/13 (23%)</td>
</tr>
</tbody>
</table>


FMT: The Devil is in the Details
(and hopefully not in the stool)

- Sounds simple
  - Poop is readily available
  - All you have to do is mix it with saline, filter it, and infuse away
- FDA/IRB
  - IND no longer required, but patients must be informed FMT is experimental therapy, not all risks are known, and sign a consent form
  - Whether IRB approval is needed is up to local IRB
- Donor screening
  - Consent prudent: if determined to be not eligible, recipient will know the donor has an excluding condition, such as HIV
  - Not covered by insurance: Charges may approach $2000
- Stool prep/delivery
  - Body fluids must be handled like biohazard level 2 substance – prepared in biohazard hood
  - Good manufacturing practice
  - Fresh versus frozen
- Cleaning of materials to process stool

Investigational Therapies: Surotomycin

- Non-absorbed antimicrobial
  - Lipopeptide
- Phase 2 study
  - 250 mg BID with 50% reduction of recurrent CDI compared to vancomycin
    - 17% versus 35%; p<0.035
- Phase 3 studies ongoing
Investigational Therapies: LFF571

- Non-absorbed antimicrobial
  - Thiopeptide
- Phase 2 study
  - 200 mg QID versus vancomycin 125 mg QID


Investigational Therapies: Nontoxigenic C. difficile (NTCD)

- Recurrence rate if became colonized with NTCD: 2%
- Recurrence rate if not colonized with NTCD: 31%


Investigational Therapies: Monoclonal Antibodies (mAbs)

- Study of mAbs in 200 CDI patients receiving metronidazole or vancomycin
- Recurrence rates:
  - 7% in mAb group vs. 25% in placebo group

Investigational Therapies: C. difficile Toxoid Vaccine

Dose response relationship with survival


Investigational Therapies: C. difficile Toxoid Vaccine

• Seroconversion rates in young vs. elderly healthy subjects (50 μg dose)

<table>
<thead>
<tr>
<th>Study 008</th>
<th>Study 009</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–55 yrs; median age = 26</td>
<td>≥65 yrs; median age = 70</td>
</tr>
<tr>
<td>Seroconversion Rate (%)</td>
<td>Seroconversion Rate (%)</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Day</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>100</td>
<td>75</td>
</tr>
</tbody>
</table>


Conclusions: CDI Treatment

• Initial episode
  – Enthusiasm for metronidazole quickly waning
  – Vancomycin remains highly efficacious for initial episode
  – Role of fidaxomicin: potential populations
    • Risk for recurrence
    • Risk for decreased treatment response
• Recurrent CDI
  – Potential approach: vancomycin taper → fidaxomicin taper → FMT
• Many agents being investigated
  – Initial treatment
  – Prevent recurrence
  – Primary prevention