Improving Quality of Care for Clostridium difficile Infection: Why a Better Test Means Better Care

Jorge P. Parada, MD, MPH, FACP, FIDSA
Professor of Medicine, Stritch School of Medicine Loyola University Chicago
Medical Director Infection Prevention & Control Program
Co-Director, Antibiotic Stewardship Program
Medical Director, MRSA Clinic
Research Associate, Infectious Diseases and Immunology Institute (InDII)
Loyola University Medical Center

Illinois Campaign to Eliminate Clostridium difficile Webinar
April 2012
Educational Objectives

• Review some basics about microbiology & pathophysiology of *Clostridium difficile* infection (CDI)

• Outline important CDI-related epidemiologic trends

• Share Loyola’s experience with management of CDI

• Review key issues in diagnostic testing & the consequences of inaccurate testing
Disclosures

• Advisory Board to Clarity PSO, Merck
• PI on Clinical Trials for Roche, Astellas, Catheter Connections (no personal/direct financial benefit)
• Speakers Bureau for France Foundation, Robert Michael Educational Institute, Optimer, Cepheid, Cubist, Merck

• Ok, I admit it…I also take pens from displays at conferences
Real Conflict of Interest!

• 9-year-old son…
  - Broken wrist age 4
  - Stitches age 5
  - Staples age 7
Fasten your seat belts…
We’re going fast!
C. Difficile

Vegetative Cells & Endospores
CDI Overview

- **Spore-forming**, anaerobic, gram-positive bacterium

- Causes **toxin-mediated** gastrointestinal infections resulting in diarrhea and colitis
  - Severity ranges from mild colitis to toxic megacolon and death

- Leading cause of healthcare-associated infectious diarrhea in US

- Rivals methicillin-resistant *Staphylococcus aureus* (MRSA) as the most common organism to cause healthcare-associated infections (HAI) in US

CDC. Fact Sheet, August 2004 (updated 7/22/05).
Microbiology of *C. difficile*

**Vegetative Form**

- Can survive in the environment on moist surfaces up to 6 hours\(^2\)
- Susceptible to gastric acid, antibacterial soaps, and alcohol based hand sanitizers\(^3\)

**Spore Form\(^3,4\)**

- Can survive for months on surfaces
- Resistant to gastric acid, antibacterial soaps, alcohol-based hand sanitizers and conventional disinfectants
- Can rapidly change to vegetative form


**Clostridium difficile:** Changing Epidemiology

- Changing face of *C. difficile* infection
  - Increasing incidence
  - Increasing disease severity with substantial morbidity and mortality
  - Infection in “low-risk” populations

- Epidemic strain reported in US, Canada, and Europe

Novel Hypervirulent Strain

- Characteristics of novel epidemic strain:
  - Typed BI/NAP1/027
  - Highly virulent
    - Produces 16-fold higher levels of Toxin A and 23-fold higher levels of Toxin B
    - Produces binary toxin CDT
  - Highly resistant to fluoroquinolones

Epidemiology of CDI in Quebec

Risk for Death and Severe CDI According to Presence of “Epidemic” Strain*

*Epidemic strain=binary toxin positive and partial tcdC deletion.

**Trends were not statistically significant.

States with BI/NAP1/027 Strain of *C. difficile*

Confirmed by CDC ($N=40$)

January 2008

[Map showing states with confirmed BI/NAP1/027 strain of *C. difficile* as of January 2008.]

Centers for Disease Control and Prevention. [www.cdc.gov/ncidod/dhqp/id_Cdiff_data.html](http://www.cdc.gov/ncidod/dhqp/id_Cdiff_data.html)
States With BI/NAP1/027 Strain of *C. difficile* (N=50), October 2008
Impact of C diff on Healthcare Outcomes and Costs

• C diff has repeatedly been documented to cause:
  ◆ Increased length of hospitalization
  ◆ Increased morbidity and mortality
  ◆ Increased costs
  ◆ Lost revenue-blocked beds

• Lawsuits…
$1-3 BILLION
# Economic Burden of CDI

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Per-Episode Costs</th>
<th>Increase in Length of Stay</th>
<th>US Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyne 1998&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-2 medical wards -40 cases</td>
<td>$3,669</td>
<td>3.6 days</td>
<td>$1.1 billion</td>
</tr>
<tr>
<td>O’Brien 2000&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-MA discharge database -3,692 cases</td>
<td>Primary diagnosis: $10,212 Secondary diagnosis: $13,675</td>
<td>3.0 days</td>
<td>$3.2 billion</td>
</tr>
<tr>
<td>Dubberke 2003&lt;sup&gt;3&lt;/sup&gt;</td>
<td>-Nonsurgical patients -439 cases</td>
<td>$2,454 – $3,240</td>
<td>2.8 days</td>
<td>$1.3 billion</td>
</tr>
</tbody>
</table>

Cost of Recurrent CDI

• Patients enrolled into recurrent CDI trial
• Direct costs on outpatient visits, inpatient admissions, labs, and treatments
• 209 patients
  ♦ 2.6 ± 1.9 prior episodes of CDI
• Mean $10,970 per patient
• Mean $3,103 per episode

Additional CDI Cost Issues

• CDI as a “Never Event”??
• CDI currently short-listed for Medicare/Medicaid future “non-reimbursable diagnoses”
• Cost of bed-days lost <=> contact precautions
• Non-acute care facility costs not known
  ◆ Outpatient costs
  ◆ Long-term care facilities
• Increasing CDI severity
• Impact of treatment on CDI costs
  ◆ Does duration of symptoms affect length of stay?
Recurrent CDI

• CDI recurrence is a significant challenge

• Rates of recurrent CDI:
  ◆ 15-25% after first episode
  ◆ 30-45% after first recurrence
  ◆ 40-65% after two or more recurrences

Defective immune response to toxin A

• Generation of an antibody response to toxin A is associated with protection against symptomatic disease and asymptomatic carriage of *C. difficile*

• Following symptomatic infection, many individuals develop anti-toxin A and B antibodies

• Inability to acquire immunity to toxin A increases risk for recurrent disease
  - Individuals with recurrent CDI mount poor anti-toxin responses


C diff Epidemiology
MORE...
MORE...
MORE!
C. Difficile Rates Oct 2006 to June 2008

Memo #1
Memo #2

New Signage & Hand Hygiene Policy
CDI Epidemiology

- Total number of cases of is increasing in the US

US: Overall Incidence

- 3.82/1,000 discharges
- 8.75/1,000 discharges

Graph showing the trend of CDI cases per 1,000 discharges from 2000 to 2008.
US: CDI Incidence by Gender

8.94/1,000 discharges

8.64/1,000 discharges
US: CDI Incidence by Hospital Type and Location

- **CDI cases / 1,000 Discharges**
- **Graphs show the incidence of CDI cases over time for different hospital types and regions.**

**Hospital Type**
- Nonteaching
- Teaching

**Graphs by Region**
- Rural
- Metropolitan

- Small
- Medium
- Large

- Northeast
- Midwest
- South
- West
US: Increasing Case Fatality Rate

Increase in *C. difficile*-Related Deaths

US Age-Adjusted CDI Death Rates

United Kingdom CDI Age-Adjusted Death Rates*


*Death certificates mentioning *Clostridium difficile* and recording *C. difficile* as the underlying cause of death (England and Wales).

Elderly – CDI Incidence & Age

Elderly – CDI Mortality & Age
US Population & Age


Percent Growth in Population

Age 65+

Age < 65
With this in mind...

We formed the:

**The C Diff (reduction) Task Force…**
On the Importance of Planning...
Multidisciplinary TEAM

• Medical champion
• Nursing champions
• Infection preventionists
• Housekeeping
• Laboratory services
• IT services

• Staff & patient education
Infection Control Strategies

• Diagnosis
• Hand hygiene
• Isolation and contact precautions
• Environmental disinfection
• Antimicrobial stewardship
SYSTEMS APPROACH

• Not run around yelling at mistakes…

• **MAKE IT EASY TO DO THE RIGHT THING**

• Empower employees

• Technology: Rapid PCR diagnostic testing

• Develop pathways / systems for *early* specimen collection & flagging results…

• Better IT – leverage emr / informatics
Engaged Surveillance

Dr. Parada

Infection Control Team
C difficile Quality Improvement Collaborative

4/29/2010

Healthcare-associated Infections

HAI Elimination
# Daily C Diff Bundle

**Clostridium difficile Infection**

Cross-transmission minimization bundle

<table>
<thead>
<tr>
<th>UNIT</th>
<th>NAME</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>completing the C diff bundle</td>
<td>completed</td>
</tr>
</tbody>
</table>

Fax Daily to # 63476

**CDIFF STATUS:**
- Suspected (rule out) = S
- Confirmed = C

**Bundle Criterion**

<table>
<thead>
<tr>
<th>BUNDLE CRITERION</th>
<th>YES = Y</th>
<th>NO = N</th>
<th>YES = Y</th>
<th>NO = N</th>
<th>YES = Y</th>
<th>NO = N</th>
<th>YES = Y</th>
<th>NO = N</th>
</tr>
</thead>
</table>

1. CONTACT ISOLATION
   - A. CDI & no CDI patient is in contact isolation in a single room with “Contact Isolation” sign is on door.
   - B. CDI patient has “Use Soap & Water” sign on door.
   - (Note: Two confirmed C. diff positive patients can be co-hosted in a double room)

3. EVERYONE USE PPE
   - Checking all healthcare workers and visitors don PPE (gloves and gowns) before entering CDI & no CDI room and remove PPE after CDI patient care activity.

4. DAILY BLEACH WIPES / SCRUB
   - Service assistants cleaned and disinfected equipment, high touch areas and environment of CDI & no CDI patient today with a chlorine based wipe/solution with scrubbing motion.

5. HAND WASHING
   - Ensuring HCW’s and visitors perform hand washing with liquid soap and water after leaving a CDI & no CDI patient’s room.
How did we do on the final?
49% decrease in CDI Rates

Hospital wide use of Bleach Wipes
July 2008

Use of Cdiff Bundle
February 2009

Hi Touch Investigation Kit
April 2009

Mean = 15.41

Mean = 11.42

Mean = 7.67
Some Words About C Diff Testing
SHEA/IDSA 2010 Guidelines for Diagnosis

- Testing for *C. difficile* or its toxins should be performed only on unformed stool (unless ileus is suspected)\(^1\)

  *Brecher rule:* “If it ain’t loose, it’s of no use”\(^2\)

- Testing asymptomatic patients is not clinically useful\(^1\)

- Test of cure is not recommended\(^1\)

2. Dr. Stephen Brecher, verbal communication.
<table>
<thead>
<tr>
<th>Test</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxin testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzyme immunoassay</td>
<td>Rapid, simple, inexpensive</td>
<td>Least sensitive method</td>
</tr>
<tr>
<td>Tissue culture cytotoxicity</td>
<td>More sensitive than enzyme immunoassay</td>
<td>Labor intensive; requires 24–48 hours for a final result, special equipment</td>
</tr>
<tr>
<td>Organism identification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection of glutamate dehydrogenase (GDH)</td>
<td>Rapid, sensitive, may prove useful as a triage or screening tool</td>
<td>Not specific, toxin testing required to verify diagnosis; may not be optimally sensitive</td>
</tr>
<tr>
<td>PCR</td>
<td>Rapid, sensitive, detects presence of toxin gene</td>
<td>Cost, special equipment, does not necessarily indicate the presence of toxin; indiscriminant testing with PCR is a particular concern</td>
</tr>
<tr>
<td>Stool culture</td>
<td>Most sensitive test available when performed appropriately</td>
<td>Like GDH, may be associated with false-positive results if isolate is not tested for toxin; labor-intensive; not practical for most laboratories</td>
</tr>
</tbody>
</table>
C. difficile Testing in the US

• 95% of USA testing is not cytotoxin or culture
  - LC McDonald et al, EID 12, 409-24, 2006

• 101 microbiology laboratories surveyed
  ◆ 4 (4%) routinely culture for C. difficile
  ◆ 20 culture for special reasons (not as a diagnostic test)
  - P Gilligan, ClinMicroNet, October 31st, 2008
### CDI TESTING...JUST MATH

**CDI (ELISA A + B) Toxin Assay**

- **Sensitivity:** (65-85%) 70%
- **Specificity:** (80-95%) 90%
- **Prevalence:** (15-25%) 20%

<table>
<thead>
<tr>
<th>1000 Diarrhea</th>
<th>200 CDI</th>
<th>800 non-CDI</th>
<th>1000 Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test #1</td>
<td>140</td>
<td>80</td>
<td>220 dx</td>
</tr>
<tr>
<td>Test #2</td>
<td>42</td>
<td>72</td>
<td>334 dx</td>
</tr>
<tr>
<td>Test #3</td>
<td>11</td>
<td>65</td>
<td>410 dx</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>193</td>
<td>217</td>
<td><strong>½ patients!</strong></td>
</tr>
</tbody>
</table>
“Only a crazy person would do the same thing over and over and expect different results.”

Albert Einstein
What is the Consequence of a Low Sensitivity Test?

Goal: Find All Positive

- **EIA** (Sensitivity = 73.3%; Specificity = 97.6%)
  - 5 repeat tests
  - Total true positive = 100
  - Total false positive = 107

- **PCR** (Sensitivity = 93.3%; Specificity = 97.4%)
  - 2 repeat tests
  - Total true positive = 100
  - Total false positive = 49

L Peterson and A Robicsek, Ann Int Med 151:176-9, 2009
## TABLE 2. Comparison of performance results for Xpert *C. difficile*, EIA, and two GDH algorithms compared to toxigenic culture with enrichment by site\(^a\)

<table>
<thead>
<tr>
<th>Site no.</th>
<th>Site assay</th>
<th>(n)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Xpert</td>
<td>Site</td>
<td>Xpert</td>
<td>Site</td>
</tr>
<tr>
<td>1(^{b,c})</td>
<td>Toxin A/B EIA</td>
<td>1,023</td>
<td>94.1</td>
<td>67.5</td>
<td>93.7</td>
<td>92.0</td>
</tr>
<tr>
<td>2(^d)</td>
<td>GDH-EIA</td>
<td>268</td>
<td>91.4</td>
<td>74.3</td>
<td>93.6</td>
<td>94.8</td>
</tr>
<tr>
<td>3(^e)</td>
<td>Toxin A/B EIA</td>
<td>293</td>
<td>92.3</td>
<td>53.8</td>
<td>94.5</td>
<td>97.6</td>
</tr>
<tr>
<td>4(^f)</td>
<td>Toxin A/B EIA</td>
<td>312</td>
<td>91.4</td>
<td>54.3</td>
<td>94.2</td>
<td>95.7</td>
</tr>
<tr>
<td>5(^g)</td>
<td>GDH-EIA-PCR</td>
<td>114</td>
<td>92.3</td>
<td>61.5</td>
<td>96.0</td>
<td>94.1</td>
</tr>
<tr>
<td>6(^b)</td>
<td>Toxin A/B EIA</td>
<td>173</td>
<td>97.0</td>
<td>33.3</td>
<td>93.6</td>
<td>93.6</td>
</tr>
<tr>
<td>7(^h)</td>
<td>Cytotoxin</td>
<td>110</td>
<td>90.9</td>
<td>54.5</td>
<td>94.9</td>
<td>98.0</td>
</tr>
</tbody>
</table>
Extrapolation of Loyola Data

• EIA (Sensitivity = 33%; Specificity = 94%)
  ◆ 13 repeat tests $1,430.00
  ◆ Total true positive = 100
  ◆ Total false positive = 222

• PCR (Sensitivity = 97%; Specificity = 94%)
  ◆ 2 repeat tests $70.00
  ◆ Total true positive = 100
  ◆ Total false positive = 47
Consequences (of an Unreliable EIA)

- Many patients with OUT C diff on Rx and in isolation
  - 1 test: 42% on isolation are false +
  - Costs & Patient Safety

- Many patients WITH C diff NOT on Rx and nor in isolation
  - 1 test: 67% cases not detected
  - Cost & Patient Safety
Consequences

- Undermines confidence in test
  - Physicians will leave test negative patients on isolation and treat them anyway
  - Increased LOS
- Undermines buy-in for use of PPE
- Increased environmental contamination
- Increased C diff transmission
- Increased C diff
How long do nosocomial pathogens persist on inanimate surfaces?
A systematic review
Axel Kramer*1, Ingeborg Schwebke2 and Günter Kampf1,3

Address: 1Institut für Hygiene und Umweltmedizin, Ernst-Moritz-Arndt Universität, Greifswald, Germany, 2Robert-Koch Institut, Berlin, Germany and 3Bode Chemie GmbH & Co. KG, Scientific Affairs, Hamburg, Germany

Email: Axel Kramer* - kramer@uni-greifswald.de; Ingeborg Schwebke - schwebkei@rki.de; Günter Kampf - guenter.kampf@bode-chemie.de
* Corresponding author

<table>
<thead>
<tr>
<th>Type of bacterium</th>
<th>Duration of persistence (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp.</td>
<td>3 days to 5 months</td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td>3 – 5 days</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>up to 6 days</td>
</tr>
<tr>
<td>Clostridium difficile (spores)</td>
<td>5 months</td>
</tr>
<tr>
<td>Chlamydia pneumoniae, C. trachomatis</td>
<td>≤ 30 hours</td>
</tr>
<tr>
<td>Chlamydia psittaci</td>
<td>15 days</td>
</tr>
<tr>
<td>E. coli</td>
<td>7 – 14 days</td>
</tr>
<tr>
<td>MRSA</td>
<td>≤ 1 day</td>
</tr>
</tbody>
</table>
“Quite literally, flipping a coin is more accurate then EIA testing”

“We are not talking about spending more money for a marginally better test. We are talking about continuing to spend money on a useless test (EIA) vs spending money on a very good test.”

“Nobody questions the need for a CT scanner or MRI, simply because they provide so much better diagnostic information…like CT and MRI, PCR is an order of magnitude better test”
Stool Testing for C diff by PCR

Started July 1, 2010
• Utilizing toxin A/B EIA for C. diff toxin diagnosis is insensitive and not recommended as a stand alone test

• Positive A/B EIA for C diff toxin must be confirmed with a positive cytotoxin test or Nucleic Acid Amplified Test (PCR)

• PCR may be used as a stand alone test
Early Experience with PCR

- CDI rates initially increase because of increased sensitivity (true prevalence detection)
- Test volume goes down by 50%
- Test materials cost offset by appropriate utilization of antibiotics and infection control protocols

Belmares J, et al. SHEA 2011; Abstract #150.
Post PCR “Jump” in C diff Rates!

Loyola University Medical Center
Infection Prevention and Control Program
Nosocomial Clostridium Difficile Infection Rates Per 10,000 Patient Days

This information is confidential and to be used for quality improvement purposes only

n=Patient Days
Micro Lab Opportunity Statement

• Decrease Turn Around Time (TAT) for C difficile toxin detection with PCR testing

• Increase sensitivity for the detection of patients with C. diff infections with PCR

• BETTER QUALITY OF CARE
Turnaround Time of Clostridium difficile by EIA June 1-14

**Individuals**
Temporary: UCL=2039.02, Mean=908.19, LCL=-222.65 (not shown) (mR=2)

910 mins
120 mins
Loyola Data

• The mean C diff testing TAT dropped 90%
  ♦ (C diff PCR = 93 min vs EIA Assay = 909 min)

• C diff PCR assay detected 3/4 more positives
  (19% PCR vs 11% EIA)

TAT = Turn Around Time
Pre C diff PCR Testing Average Isolation Days = 339

Post C diff PCR Testing Average Isolation Days = 79

76.7% Decrease
“Impact of real time PCR testing for Clostridium difficile on antimicrobial use and patient management”

Patients tested negative PCR vs EIA (2009 vs 2012)

- Fewer C diff tests sent & less repeat testing (p<0.001)
- Less metronidazole & vancomycin use (p=0.007)
- Fewer C difficile antimicrobial treatment days (p=0.004)
- Less diagnostic radiology testing (Abd X-ray, p=0.013 & CT scan, p=0.002)
- Fewer Infectious Diseases consultations (p=0.033)
- Less Sigmoidoscopy/colonoscopy (p=0.006)
- Lower LOS (21% decrease)
Impact of Rapid C diff PCR at LUMC

- Decreased C diff testing
- Decreased C diff isolation days
- Decrease PPE use
- Decreased blocked beds
- Decreased ancillary testing & ID consultation
- Decreased LOS
- Better antibiotic stewardship
- Plus…decreased anxiety from false + diagnosis
Not Just Wishful Thinking…

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

Real-time polymerase chain reaction testing for *Clostridium difficile* reduces isolation time and improves patient management in a small community hospital

Mary Catanzaro RN, BSMT, CIC*, Justin Cirone BS

*From the Infection Prevention Department, Pocono Medical Center, East Stroudsburg, PA*

---

**Key Words:**
- Isolation reduction
- Accurate testing
- Healthcare-associated infection
- Nosocomial infection

**Background:** The impact of a switch from a toxin A/B enzyme immunoassay (EIA) to a polymerase chain reaction (PCR) method for detection of toxigenic *Clostridium difficile* was assessed for *C difficile* infection (CDI) rates, patient isolation-days, and CDI-related treatment.

**Methods:** A 6-month retrospective study was done on symptomatic patients tested by the toxin A/B EIA and PCR assays. Data on the number of *C difficile* tests ordered, patient isolation-days, and treatment with metronidazole or vancomycin were collected. CDI rates were reported as cases per 10,000 patient-days, and differences between both groups were compared by χ² and Z-test analysis.

**Results:** The CDI incidence was 11.2 and 12.7/10,000 patient-days in the EIA and PCR test periods, respectively (*P* < .36). Health care-associated CDI decreased from 4.6 per 10,000 patient-days during EIA testing to 0.9 per 10,000 patient-days during PCR testing (*P* < .02). A significant decrease in patient isolation-days (*P* < .00001), tests ordered (*P* < .002), and metronidazole treatment for patients with a negative *C difficile* test (*P* < .02) was observed with PCR testing.

**Conclusion:** PCR testing is a viable option for small community hospitals, providing accurate and timely results for patient management and infection control. This can potentially lead to improved outcomes, increased patient satisfaction, and significant hospital cost savings.

Copyright © 2011 by the Association for Professionals in Infection Control and Epidemiology, Inc.
Published by Elsevier Inc. All rights reserved.
C. difficile Testing Take Home Rules

1. Don’t use EIA as a stand alone test
   - Two-step or PCR as stand alone test

2. Don’t test formed stool
   - (only test symptomatic patients = diarrhea)

3. No test of cure
   - (only test symptomatic patients = diarrhea)
Economic Burden of CDI
MORE...
MORE...
MORE!...
THE END