Epidemiology, Diagnosis, and Prevention of *Clostridium difficile* Infection

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Disclosures

• Consulting: Merck, Sanofi Pasteur, Rebiotix, Pfizer, Summitt, Daiichi

• Research: Merck, Rebiotix, Sanofi Pasteur
Learning Objectives

• Analyze the importance of *C. difficile* infection on patient outcomes
• Identify the advantages and disadvantages of *C. difficile* diagnostic assays
• Describe the role of the microbiology laboratory in the prevention of *C. difficile* infection
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
  - >50% infants culture positive, 3%-7% healthy adults
  - Cultured from food, water, pets, wild animals
Current Pathogenesis Model for *C. difficile* Infection (CDI)

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

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Total Number of Cases in U.S. Hospitals

Source: AHRQ HCUP data
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

Including CDI diagnosed in hospitals, nursing homes, the community, and recurrent CDI: likely over 700,000 CDI cases in US in 2010
The “Epidemic” Strain

• Several methods of molecular typing
  – NAP1
  – BI
  – 027

• Virulence factors
  – tcdC mutation: more toxin A and B production
  – Binary toxin

• Fluoroquinolone resistance
  – New competitive advantage for old strain?
NAP 1 strain alone does not account for increases in CDI incidence
C. difficile Diagnostics

• Critical role in:
  – C. difficile epidemiology
  – Treatment
  – Infection prevention and control

• Diagnostic test utilization also important
  – Patient selection
## Diagnostics Available

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxin testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxin Enzyme immunoassay (EIA)</td>
<td>Rapid, simple, inexpensive</td>
<td>Least sensitive method, assay variability</td>
</tr>
<tr>
<td>Tissue culture cytotoxicity</td>
<td>More sensitive than toxin EIA, associated with outcomes</td>
<td>Labor intensive; requires 24–48 hours for a final result, special equipment;</td>
</tr>
<tr>
<td><strong>Organism identification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamate dehydrogenase (GDH) EIA</td>
<td>Rapid, sensitive,</td>
<td>Not specific, toxin testing required to verify diagnosis;</td>
</tr>
<tr>
<td>Nucleic acid amplification tests (NAAT) / PCR</td>
<td>Rapid, sensitive, detects presence of toxin gene</td>
<td>Cost, special equipment, may be “too” sensitive</td>
</tr>
<tr>
<td>Stool culture</td>
<td>Most sensitive test available when performed appropriately</td>
<td>Confirm toxin production; labor-intensive; requires 48–96 hours for results</td>
</tr>
</tbody>
</table>
Flaws in Diagnostic Literature Interpretation

• Lack of clinical data
  – Detection of *C. difficile*, not diagnosis of CDI
    • Up to 15% of patients admitted to the hospital are colonized
    • Enhanced sensitivity for *C. difficile* detection may decrease specificity for CDI

• Focus on sensitivity and specificity
  – Not negative predictive value and positive predictive value

Dubberke. AAC. 2015; Peterson, CID. 2007
Types of False Positive Tests for CDI

• Toxigenic *C. difficile* present but no CDI
  – Concern of more sensitive tests
    • GDH
    • NAAT
    • Culture

• Assay result positive but toxigenic *C. difficile* not present
  – Tests that detect non-toxigenic *C. difficile*
    • GDH alone
    • Culture alone
  – Repeat testing
    • Decreasing prevalence leads to decreasing PPV
Enhanced Sensitivity May Decrease Specificity

- Including clinically significant diarrhea in gold standard:
  - No impact on sensitivity
  - Specificity of NAATs decreased from ~98% to ~89% (p < 0.01)
    - Positive predictive value decreased to ~60% (25% drop)

Dubberke. JCM. 2011;
Largest Assay Comparison To Date

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cytotoxicity (CTX) +</th>
<th>CTX -/NAAT +</th>
<th>-/-</th>
<th>(CTX+) vs. (CTX-/NAAT+)</th>
<th>(CTX+) vs. (-/-)</th>
<th>(CTX-/NAAT+) vs. (-/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>435</td>
<td>311</td>
<td>3943</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood count (SD)</td>
<td>12.4 (8.9)</td>
<td>9.9 (6.6)</td>
<td>10.0 (12.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.863</td>
</tr>
<tr>
<td>Died</td>
<td>72 (16.6%)</td>
<td>30 (9.7%)</td>
<td>349 (8.9%)</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>0.606</td>
</tr>
</tbody>
</table>

Planche. Lancet ID. 2013
More Data Indicating Poor Specificity of NAAT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>C difficile Positive</th>
<th>C difficile Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tox+/PCR+ (n = 131)</td>
<td>Tox−/PCR+ (n = 162)</td>
</tr>
<tr>
<td>C difficile-Related Complication or Death Within 30 d, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicationb</td>
<td>10 (7.6)</td>
<td>0</td>
</tr>
<tr>
<td>Deathc</td>
<td>11 (8.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Complication or death</td>
<td>18 (13.7)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Repeat C difficile Testing Within 14 d, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retested</td>
<td>14 (10.7)</td>
<td>61 (37.7)</td>
</tr>
<tr>
<td>Positive toxin test result</td>
<td>3 (2.3)</td>
<td>13 (8.0)</td>
</tr>
<tr>
<td>Treatment Within 14 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole or oral vancomycin, No. (%)d</td>
<td>131 (100)</td>
<td>66 (40.7)</td>
</tr>
<tr>
<td>Duration of metronidazole or oral vancomycin, if treated, median (IQR), d</td>
<td>14 (11-14)</td>
<td>6 (3-11)</td>
</tr>
<tr>
<td>Non-C difficile antibiotic, No. (%)</td>
<td>98 (74.8)</td>
<td>141 (87.0)</td>
</tr>
<tr>
<td>Duration of non-C difficile antibiotic, if treated, median (IQR), d</td>
<td>11 (3-14)</td>
<td>10 (4-14)</td>
</tr>
</tbody>
</table>

Polage. JAMA IM. 2015
## Pre-Test Probability for CDI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-test probability (n)</th>
<th>Low (n=72)</th>
<th>Medium (n=34)</th>
<th>High (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive toxin EIA</td>
<td></td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Positive toxigenic culture</td>
<td></td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Negative EIA and empiric treatment</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative EIA and CDI diagnosed in next 30 days</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>90-day mortality</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Kwon J, et al. SHEA 2014, manuscript in progress
Automatic Repeat Testing: Poor Practice

- Prevalence of disease decreases with repeat testing
- Positive predictive value (PPV) plummets
- Negative predictive value of single toxin EIA >95%

C. difficile Testing Algorithms

• Original intent:
  – Cost containment: GDH -> NAAT

• Part of UK and Europe recommendations
  – GDH or NAAT screen
  – Toxin EIA if screen positive
  – Goal: decrease false positives
Algorithm Interpretation

- GDH or NAAT –
  - Negative for *C. difficile* colonization
- GDH or NAAT + / Toxin –
  - Asymptomatic *C. difficile* carrier
- GDH or NAAT + / Toxin +
  - CDI
## CDI Treatment Stratified by Severity: First CDI Episode

<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/uL) 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/uL) 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 q 8 hrs</td>
</tr>
</tbody>
</table>

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

Fidaxomicin

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

Management of Recurrent CDI

• CDI recurrence is a significant challenge

<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>

• Multiple recurrences
  – Alternate agents
  – Microbial approach

Fecal Microbiota Transplant (FMT)

• Theory: Restoration of fecal microbiota and colonization resistance
• First report 1958
• Numerous 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>

Gough. CID. 2011
### Prospective Trials: Single Dose FMT Efficacy 60%-80%

<table>
<thead>
<tr>
<th>Study</th>
<th>Single dose</th>
<th>Second dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youngster (n=20)</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>Hirsch (n=19)</td>
<td>68%</td>
<td>89%</td>
</tr>
<tr>
<td>Orenstein (n=35)</td>
<td>60%</td>
<td>88%</td>
</tr>
<tr>
<td>Youngster (n=14)</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>Van Nood (n=16)</td>
<td>81%</td>
<td>94%</td>
</tr>
<tr>
<td>Lee (PP n=178, mITT n=219)</td>
<td>62% / 51%</td>
<td>84% / 73%</td>
</tr>
</tbody>
</table>

Status of CDI Prevention Today

• Decrease risk of transmission
  – CDI: Contact precautions
    • Gloves/gowns
    • Dedicated patient equipment
  – Environment decontamination

• Decrease risk of CDI if transmission occurs
  – Antimicrobial stewardship
Clinical Microbiology Laboratory and CDI Prevention

Sethi AJ, ICHE 2010;31:21-7
Clinical Microbiology Laboratory and CDI Prevention

• Alert floor immediately if positive
Minimize False Positives

End of 10d Rx

Vancomycin
Metronidazole
Placebo

Ways to Minimize False Positives

• **DO NOT TEST FORMED STOOLS**
  – No diarrhea = No CDI

• Do not allow automatic repeat testing
  – Require prior authorization
  – Quality improvement project: 90% reduction

• Decrease testing in patients without clinically significant diarrhea
  – Example: alert if recent laxative exposure

• Optimize testing
Different Testing Strategies and False Positives

- Hypothetical scenarios
  - Toxin EIA: sensitivity 85%, specificity 97%
  - NAAT: sensitivity 99%, specificity 89% (CDI)
  - Test 1,000 patients, 100 with CDI (10% prevalence)

<table>
<thead>
<tr>
<th>Testing strategy</th>
<th>True positives</th>
<th>False positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxin EIA</td>
<td>85</td>
<td>27</td>
</tr>
<tr>
<td>NAAT</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>NAAT + then Toxin EIA</td>
<td>84</td>
<td>3</td>
</tr>
</tbody>
</table>
Assist in Antimicrobial Stewardship

• Improve test utilization related to infections
  – Order of tests in drop down list
    • Most appropriate test first
  – Reflex urine cultures: >10 WBC / high power field

• Rapid diagnostics
  – MALDI
  – Rapid tests for resistance mechanisms
  – Respiratory multiplex PCRs

Additional Considerations When Selecting a *C. difficile* Assay

- Patient selection for testing
- Time from bowel movement to proper storage
- Number of specimens
- Frequency able to perform testing
- Not all assays equal
  - Membrane EIAs: ~10% drop sensitivity
  - *C. difficile* strain / toxin gene heterogeneity
Conclusions

• CDI = bad
• Diagnosis: patient first, test second
  – “CDI” assay does not exist
• Clinical microbiology laboratory plays an important role in CDI prevention
• One size does not fit all when selecting an assay