Clostridium difficile Infection: Burden, Diagnostics and Recurrence

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Georgia Emerging Infections Program Conference
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Disclosures

- Nothing to disclose
Outline

- Diagnostic testing for CDI
  - Change to more sensitive methods
  - Colonization vs Infection
  - Implications for providers, laboratories, and infection control
- Burden of CDI
  - National estimates
  - Multiple recurrences
- CDI trends in metro Atlanta
  - Impact of changing diagnostics on incident and recurrent case counts
C. Difficile Infection (CDI)

- A leading cause of healthcare-associated infections
- Clinical syndromes
  - Asymptomatic ➔ severe diarrhea ➔ death
- Recurrence
  - 15-30% of all CDI have a recurrence
- Changing diagnostics
  - More sensitive methods
  - Increased incident rates
- Public reporting
  - Soon tied to reimbursements
Diagnostic tests for *C. difficile* Infection
Reference tests

- **Cell culture cytotoxicity neutralization assay (CCCNA)**
  - Detects free toxin in feces
  - Cell culture, look for cytopathic effect, see if effect is neutralized by antibodies to toxins

- **Toxigenic culture**
  - Detects organisms (spores) that produce toxins
  - Labor and time intensive

Diagnostic tests for *C. difficile*

- **Enzyme immunoassay (EIA):**
  - Detects toxin A and B
  - Inexpensive but low sensitivity (as low as 60%)

- **Nucleic acid amplification test (NAAT):**
  - Molecular test (PCR, LAMP) for toxin-producing gene (e.g. *tcdA* or *tcdB*)
  - High sensitivity, but expensive
  - Unable to discern carriage vs true infection

- **Glutamate dehydrogenase immunoassays (GDH):**
  - Detects conserved antigen common to toxigenic and non-toxigenic strains
  - Only used in combination with another test

- **Algorithms:**
  - GDH/EIA
  - GDH/NAAT, GDH/EIA/NAAT
  - Higher sensitivity than EIA while controlling cost

## Comparison of methods

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIA</td>
<td>Low</td>
<td>Moderate</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>GDH</td>
<td>High</td>
<td>Low</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>NAAT</td>
<td>High</td>
<td>Low/moderate</td>
<td>$$$</td>
<td>Colonized vs infected?</td>
</tr>
<tr>
<td>Algorithms</td>
<td>Moderate/High</td>
<td>Moderate/High</td>
<td>$</td>
<td>Multiple versions</td>
</tr>
</tbody>
</table>
Colonization ≠ Infection

- Asymptomatic colonization is common
  - 2% of community dwellers
  - 7-18% of admitted patients
    - Highest in those previously admitted
  - 20% of discharged patients
  - Up to 50% of long term care facility residents
    - Ratio of asymptomatic colonized to CDI: 7:1

- Diarrhea is common in hospitals
  - 12% of hospitalized patients have diarrhea
  - Not all diarrhea is CDI
    - *C. difficile* responsible in 4-30%

Natural history

Colonization, Infection and Shedding
Outcomes after colonization

Shedding of *C. difficile*
Stool, skin and environment

Colonizers shed less than infected patients

<table>
<thead>
<tr>
<th></th>
<th>Patients with CDI contaminating:</th>
<th>Asymptomatic colonizers contaminating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin</td>
<td>Environment</td>
</tr>
<tr>
<td>Medical ward</td>
<td></td>
<td>49%</td>
</tr>
<tr>
<td>LTCF residents</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td>Acute care</td>
<td>83%</td>
<td>67%</td>
</tr>
<tr>
<td>Oncology unit</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

• Who should be tested?
• Which stool should be tested?
• Who is transmitting the bacteria?
• What should we do with asymptomatic colonizers?
• What happens next?
Who should be tested?

Providers:
- Inappropriate ordering
  - 36% of pts with CDI tests did not have clinically significant diarrhea
  - 20% were on a laxative
- TEST OF CURE IS NOT RECOMMENDED!

Laboratories:
- Stool rejection policies of formed stool
  - Often implemented with NAAT testing
  - Repeat testing limitations
    - Recent positive tests: clinical cure?
    - Recent negative test: high sensitivity of initial NAAT test

Dubberke J Clin Microbiol 2011
Which stool to test?

- 3\textsuperscript{rd} loose stool in 24 hrs (IDSA/SHEA guidelines):
  - Improved diagnostic yield of true infection
  - Later isolation $\Rightarrow$ increase transmission (?)
- 1\textsuperscript{st}-2\textsuperscript{nd} loose stool in 24 hrs (European guidelines):
  - Early isolation and treatment
  - Over diagnose colonization $\Rightarrow$ over treat CDI, underdiagnose other causes

Who is transmitting the bacteria?

- Whole genome sequencing of all CDI in Oxfordshire, England
  - 1,223 cases from 2007-2011
  - Non-outbreak setting
  - Excellent, well-established infection control measures
  - Antibiotic stewardship
- 45% of CDI cases were genetically distinct from previous cases
  - Transmission from sources other than symptomatic patients
    - Asymptomatic colonizers? The environment?

Eyre et al. NEJM 2013
Potential interventions for asymptomatic colonization

- Screening and isolation
  - Expensive (NAAT testing) or delayed (cultures)
  - Resource intensive with unknown benefit
  - Can we identify the super-shedders?
- Decolonization
  - Treatment does not eradicate colonization
  - CDI treatment contributes to dysbiosis → patient harm
- Skin and environmental disinfection
- Antibiotic stewardship interventions

Future directions in diagnostics

- Canines?
- Biomarkers
  - Lactoferrin
  - Calprotectin
  - Cytokine analyses
- Reverse algorithms
  National Health Service (England)
  - NAAT or GDH first (screen)
    - If positive then EIA
  - NAAT+ and EIA+ = *C. difficile* infection
  - NAAT+ and EIA- = “potential fecal excretor”
    - Do not need CDI treatment, other causes should be considered
    - But may consider isolation precautions
- Diagnostics will evolve:
  - Relies on lab-provider-epidemiologist communication
Burden of CDI

In the United States and in Atlanta
Epidemiological Classification

HCFO (Healthcare Facility Onset)
- CDI ≥ three days after admission to hospital,
- Stool collected at LTCF or LTACH,
- Or admitted from LTCF
  - **HO (Hospital Onset):**
    - CDI in acute care setting
  - **LTCFO (Long-term Care Facility Onset):**
    - Stool collected in LTCF
    - Or admitted from LTCF

CO (Community Onset):
- CDI in outpatient setting,
- Or within first 3 days of hospitalization
  - **CO-HCFA (Community Onset-Healthcare Facility Associated):**
    - Healthcare exposure 12 weeks prior to CDI
    - Overnight stay in healthcare facility or resident of LTCF
  - **CA (Community Associated):**
    - No healthcare exposure 12 weeks prior to CDI
    - No overnight stay nor resident of LTCF

LTCF: long term care facility/skilled nursing facility
LTACH: long-term acute care hospital
CDI in the US in 2011

- Incident cases: ~453,000 cases in US
  - 65% health care-associated
  - 24% health care onset
  - NAP1 more common in healthcare associated disease than community associated
- First recurrences: ~ 83,000 cases
- Deaths after CDI: ~29,300 cases
- CDI rates:
  - All CDI: 147 cases/100,000 persons
  - > 65 yo: 627 cases/100,000 persons
  - Females: 163 cases/100,000 persons
  - White: 162 cases/100,000 persons
  - First recurrences 27 cases/100,000 persons
  - Deaths: 10 cases/100,000 persons

Lessa F et al, NEJM 2015
National estimates of CDI

CO-HCA: community onset- health care associated; NHO: nursing home onset; HO: hospital onset

Lessa F et al, NEJM 2015
Survey of health care associated infections (HAI) in acute care facilities

- One day survey of 183 hospitals; 11,282 patients
- 4% (452 patients) had 1 or more HAI
- Most common pathogen:
  - C. difficile (12%)
  - S. aureus (11%)
  - Klebsiella (10%), E. coli (9%), Enterococcus (9%), Pseudomonas (7%), Candida (6%)
- Types of infection:
  - Pneumonia (22%)
  - Surgical site infections (22%)
  - Gastrointestinal infections (17%)
    - 71% due to CDI
- Device-associated infections: 25%
- Estimated 648,000-721,800 HAI in US hospitals in 2011

Magill S et al, NEJM 2014
Multiple CDI Recurrences
Risk for multiple recurrences in metro Atlanta 2010-2013

• Initial cases
  • No history of previous positive
  • Age >18 years old
  • Followed minimum 3 months. Average 24.5 months

• Initial episode:
  • 11,945 initial cases
  • 60% female
  • 49% >65 years old

• Recurrence:
  • Any subsequent positive >14 days from initial (or a recurrent test)

Reddy SC et al, ID Week 2014
Risk of Recurrent CDI
By Age (n=11,945)

* * Compared to 18-45 yo: p<0.05
Increased Risk for Subsequent Recurrences

<table>
<thead>
<tr>
<th>Recurrence Level</th>
<th># at risk</th>
<th># with subsequent recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 Recurrence</td>
<td>11,945</td>
<td>2,629</td>
</tr>
<tr>
<td>≥ 2 Recurrences</td>
<td>2,629</td>
<td>834</td>
</tr>
<tr>
<td>≥ 3 Recurrences</td>
<td>834</td>
<td>329</td>
</tr>
<tr>
<td>≥ 4 Recurrences</td>
<td>329</td>
<td>136</td>
</tr>
</tbody>
</table>

Percent with Recurrence:
- ≥ 1 Recurrence: 22%
- ≥ 2 Recurrences: 31.7%
- ≥ 3 Recurrences: 39.4%
- ≥ 4 Recurrences: 41.3%
When do Recurrences Occur?
Cumulative Proportion of 1\textsuperscript{st} Recurrence by Time from Initial
In patients with >1 year of follow up (n=9,745)

The median number of days to 1\textsuperscript{st} recurrence was 39 days (IQR: 24-85)
Patients go to different labs!

- >30% of 1st recurrences were diagnosed at a different lab than the initial episode
- Single laboratory site analyses could underestimate risk of recurrent disease
C. Difficile Infection in Metro Atlanta

Impact of Changing Diagnostics
CDI Rates by Age Group 2010-2014*

*2014 data incomplete and uses 2013 population estimates
Rates by County
2010-2014*

HD3 Counties, Georgia

*2014 data incomplete and uses 2013 population estimates
Case counts by Race
2010-2014*

Number of CDI cases

White
Black
Other

2010
2011
2012
2013
2014*

*2014 data incomplete
Case counts by Epidemiologic classification 2010-2014*

Number of CDI cases

<table>
<thead>
<tr>
<th>Year</th>
<th>Community Associated</th>
<th>Community Onset- Healthcare Facility Assoc</th>
<th>Hospital Onset</th>
<th>Long Term Care Facility Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>500</td>
<td>400</td>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>2011</td>
<td>600</td>
<td>500</td>
<td>400</td>
<td>300</td>
</tr>
<tr>
<td>2012</td>
<td>700</td>
<td>600</td>
<td>500</td>
<td>400</td>
</tr>
<tr>
<td>2013</td>
<td>800</td>
<td>700</td>
<td>600</td>
<td>500</td>
</tr>
<tr>
<td>2014*</td>
<td>900</td>
<td>800</td>
<td>700</td>
<td>600</td>
</tr>
</tbody>
</table>

*2014 data incomplete
### 2010 – 2011 NAP 1 Strain Distribution

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th></th>
<th>2011</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percent</td>
<td>N</td>
<td>Percent</td>
</tr>
<tr>
<td>NAP 1</td>
<td>11</td>
<td>26.3%</td>
<td>71</td>
<td>27.1%</td>
</tr>
<tr>
<td>NAP 1-related</td>
<td>2</td>
<td>4.7%</td>
<td>17</td>
<td>6.5%</td>
</tr>
<tr>
<td>Other</td>
<td>29</td>
<td>69%</td>
<td>174</td>
<td>66.4%</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>100%</td>
<td>262</td>
<td>100%</td>
</tr>
</tbody>
</table>

#### 2011 Strain Distribution

- **NAP 1**: 27%
- **Unnamed**: 28%
- **NAP 2**: 1%
- **NAP 3**: 1%
- **NAP 4**: 11%
- **NAP 5**: 0%
- **NAP 6**: 6%
- **NAP 7**: 1%
- **NAP 8**: 2%
- **NAP 9**: 3%
- **NAP 10**: 2%
- **NAP 11**: 9%
- **NAP 12**: 1%
- **Unk**: 1%
- **NAP 1-related**: 7%
Incident and Recurrent CDI
Sept 2009 - July 2014

CDI case count

Incident CDI  Recurrent CDI
% Incident cases by diagnostic method

*Sept-Dec 2009; Jan-July 2014
Are Changes in Diagnostic Testing Associated with Increased Incident and Recurrence Rates?

- Labs switched to PCR
- New Lab(s) added
Incident CDI by laboratory classification
Sept 2009- July 2014

- All incident CDI
- Switch labs
- Nonswitch labs

CDI case count

2009 2010 2011 2012 2013 2014
## Characteristics of switch/non-switch labs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NAAT switch n=12</th>
<th>Algorithm switch n=4</th>
<th>Non-switch n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facilities that labs serve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-affiliated lab</td>
<td>12</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Reference labs</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Stool rejection policies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reject formed stool</td>
<td>11</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Reddy SC et al. Southern Regional Meeting 2015
Ratios of CDI counts after and before switch

Count ratio after/before switch date

Incident CDI
Non-switch | NAAT-switch | Algorithm-switch

Recurrent CDI
Non-switch | NAAT-switch | Algorithm-switch

*: p<0.05. Error bars represent range for non-switch and algorithm-switch labs. For NAAT-switch represent 95%CI
Ratios of CDI counts after and before switch

p=0.55

*: p<0.05. Error bars represent range for non-switch and algorithm-switch labs. For NAAT-switch represent 95%CI
Changing Diagnostics and Case counts

- After switching to NAAT, labs had increasing CDI counts
  - Incident CDI rate increased by 71%
    - 95%CI: 22-104%
  - Recurrent CDI rate increased by 113%
    - 95%CI: 60-180%
  - Increase in CDI rate was similar between recurrent and incident CDI (p=0.55)

- Labs switching to algorithm tests and to NAAT had similar increases in CDI rates
  - Median incident CDI increase of 47%
    - Range 40-77%
  - Median recurrent CDI increase of 89%
    - Range 25-150%

- No temporal increase in CDI in non-switch labs
What happens after the initial increase due to NAAT testing?

- Several studies suggest that improved diagnostics eventually lead to lower CDI rates
- Presumably due to improved isolation and infection control measures for patients with *C. difficile* in the stool
  - One study showed:
    - Decrease in HCA CDI
    - Reduction in patient isolation days
    - Fewer tests ordered
    - Reduction in duration of empirical metronidazole therapy

Conclusions

- CDI causes almost half a million infections in the US per year
  - Still a significant cause of HAI, but also significant burden is seen in the community
  - Multiple recurrences are common
- NAAT methods are more sensitive but context is crucial
  - Policies for when to test
  - Colonization ≠ Infection, but may still be important
  - NAAT testing increase rates initially, but may not stay elevated
  - Diagnostics will continue to evolve
    - Impact on labs, clinical practice, infection control, and epidemiology
Questions?

Thank you to:

- Zirka Smith
- Olivia Almendares
- Wendy Baughman
- Andrew Revis
- Catherine Espinosa
- Michelle Wiles
- Monica Farley
Extra slides
Georgia Emerging Infections Program (EIP)  
CDI Surveillance

- Active population and laboratory-based surveillance for positive C. difficile tests in 8 county metro Atlanta area
- All positive tests of residents in catchment area
  - 3.8 million persons under surveillance
  - 35 labs serving inpatients and outpatients
    - 45 Acute care facilities
    - 80 long term care facilities
    - >650 outpatient centers
- CDI surveillance started September 2009
Should NAP/ribotype be shared?

- Few NAAT methods are able to discern NAP1/ribotype 027 strains, should labs result this information?
- Who will use it?
- Infection preventionists: NAP1 may help identify a potential cluster, but given reasonably high prevalence in populations, may not help guide interventions
- Clinicians: fidaxomicin vs vancomycin: fidaxomicin had lower recurrence rates than vancomycin, particularly in non-NAP1 strains
Carriage/Colonization vs Infection

- Colonization: persistence of bacteria in colon
- Carriage: transient passage of bacteria
- A single test does not differentiate
- In healthy community dwellers who had an initial positive *C. difficile* test, only 16-33% had a positive test on repeat testing
Public reporting of CDI rates

- Rates of healthcare facility onset CDI in hospitals are now being published through Medicare
- Standardized infection ratio (SIR) adjusts for:
  - Community onset CDI prevalence rate
  - Facility bedsize
  - Medical school affiliation
- Test type:
  - NAAT vs EIA vs other
  - Categorizes labs that use algorithm testing as NAAT labs

<table>
<thead>
<tr>
<th></th>
<th>No. of Infections Reported (A)</th>
<th>Number of Patient Days</th>
<th>Predicted No. Infections (B)</th>
<th>Standardized Infection Ratio (SIR)</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>155</td>
<td>165245</td>
<td>168.563</td>
<td>0.920</td>
<td>No Different than U.S. National Benchmark</td>
</tr>
</tbody>
</table>

Standardized infection ratio (SIR) national benchmark = 1. Lower SIRs are better. A score of (0) – meaning no C.diff. infections – is best.

Increased CDI Rates Compared to 2010
By Year, Test Method and Initial vs Recurrent

<table>
<thead>
<tr>
<th>Year</th>
<th>Initial Cases per Year</th>
<th>1st Recurrent Cases per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>226</td>
<td>36</td>
</tr>
<tr>
<td>2011</td>
<td>273</td>
<td>60</td>
</tr>
<tr>
<td>2012</td>
<td>277</td>
<td>63</td>
</tr>
<tr>
<td>2013</td>
<td>293</td>
<td>79</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate per month</th>
<th>% EIA</th>
<th>Rate per month</th>
<th>% EIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td></td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td>2013</td>
<td></td>
</tr>
</tbody>
</table>

*2013 initial rate calculated from 1/13-9/13
Treatment of Sampled* Incident CDI 2010-2013

*Healthcare facility onset cases are sampled 1:10