See the Difference in *C. difficile*

**Presenter:**

**Audrey Schuetz, M.D.**  
Professor of Laboratory Medicine and Pathology  
Division of Clinical Microbiology

*Department of Laboratory Medicine and Pathology at Mayo Clinic, Rochester, Minnesota*
Disclosures

• None

Changing Times … Changing Names

• Updated nomenclature for *C. difficile* in 2016\(^1\)
  • *Clostridium difficile* → *Clostridioides difficile*

• Disease = *C. difficile* infection (CDI) or *C. difficile* associated disease (CDAD)

https://www.cdc.gov/cdiff/index.html
Burden of *Clostridioides difficile* Disease

- *Clostridioides difficile* remains the most commonly reported pathogen causing healthcare-associated infections in US hospitals\(^2\)
  - Healthcare-associated CDI cases have been decreasing somewhat since 2015, but community-associated CDI cases have not
  - Mandated reporting of *C. difficile* infections in United States
- Accurate and rapid diagnosis of *C. difficile* infection (CDI) is important!
  - Treat with appropriate antimicrobial agent
  - Discontinue the precipitating antimicrobial agent
  - Institute infection control precautions

Clinical Disease

- Spectrum of clinical findings
  - Diarrhea
  - Pseudomembranous colitis
  - Toxic megacolon
- Antibiotic exposure
  - Clindamycin
  - Broad-spectrum cephalosporins
  - Ampicillin
  - Any antibiotic
Pathophysiology

- Spore-forming Gram-positive rod, obligate anaerobe
- Originally named *Bacillus difficile*
- Spores are ubiquitous!
  - Spread by fecal-oral route, person to person
  - Present on environmental surfaces and on hands of caregivers
  - Resistant to alcohol gels and many hospital disinfectants
  - Persist on inanimate surfaces for several months

Changing Face of *C. difficile*

- Since 2000, rise in severity of disease
- NAP1/BI/027 strain / Hypervirulent strain
  - Compared to non-NAP1 strains:
    - May be associated with increased CDI frequency, more severe disease, and complications
    - Higher rates of fluoroquinolone resistance
    - Produce binary toxin as well as toxins A and B
- Non NAP1 strains have also been associated with severe CDI and production of binary toxin
- Prevalence of various *C. difficile* strains varies according to different geographical regions and patient subsets
**C. difficile Toxins**

- **Toxin A (tcdA gene)***
  - Enterotoxin causes fluid accumulation in bowel
- **Toxin B (tcdB gene)***
  - Cytopathic to (causes distortion of) cells when cultured in the laboratory
- **tcdC gene regulates toxin A and B production***
- **Binary toxin (cdtA and cdtB genes)**

**C. difficile Colonization**

- Asymptomatic carriage can occur with nontoxigenic or toxigenic strains
  - Carriage is predominantly with toxigenic strains
- 0.4%-15% of healthy adults\(^5\) in general population are colonized
  - Percentage increases with particular risk factors, such as elderly, hospital inpatients, long term care facility residents, and others
- 18%-90% of neonates and infants\(^5\) are colonized with *C. difficile*

- The sole presence of *C. difficile* toxins is insufficient for a diagnosis of CDI
- Test only unformed stools when assessing for CDI
Strategies for C. difficile Diagnosis

<table>
<thead>
<tr>
<th>Assay</th>
<th>Target</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleic acid amplification test (NAAT)</td>
<td>C. difficile toxin genes</td>
<td>High sensitivity</td>
<td>Concern for detection of colonization state</td>
</tr>
<tr>
<td>Toxin enzyme immunoassay (EIA)</td>
<td>Toxins A and B</td>
<td>Rapid; easy to perform</td>
<td>Low sensitivity (50-75%)</td>
</tr>
<tr>
<td>Glutamate dehydrogenase (GDH) enzyme immunoassay</td>
<td>Highly conserved enzyme present in all C. difficile</td>
<td>High sensitivity</td>
<td>Poor specificity and only a screening step; GDH assay never used alone</td>
</tr>
<tr>
<td>Cell cytotoxicity neutralization assay (on stool filtrate)</td>
<td>Toxin B primarily but also toxin A to some extent</td>
<td>High sensitivity and specificity</td>
<td>Long TAT (up to 48 hrs); labor-intensive</td>
</tr>
<tr>
<td>Toxigenic stool culture (culture for C. difficile then perform an assay to detect toxin)</td>
<td>Toxigenic C. difficile</td>
<td>High sensitivity</td>
<td>Long TAT (48-96 hrs); labor-intensive</td>
</tr>
</tbody>
</table>

TAT = turnaround time

Culture

**Advantages**
- Highly sensitive
- Allows for molecular typing studies or antimicrobial susceptibility testing

**Disadvantages**
- Recovery of nontoxigenic strains
- Time to results generally 24-48 hours

![CHROMagar™ C. difficile](image)
What is the most sensitive method of diagnosis of CDI in stool specimens from patients likely to have CDI based on clinical symptoms?

Recommendation:
Use a NAAT alone or a multistep algorithm for testing (i.e., GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a toxin test alone when there are pre-agreed institutional criteria for patient stool submission.

What is the best-performing method (i.e., in use positive and negative predictive value) for detecting patients at increased risk for clinically significant C. difficile infections in commonly submitted stool specimens?

Recommendation:
Use a stool toxin test as part of a multistep algorithm (i.e., GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a NAAT alone for all specimens received in the clinical laboratory where there are no pre-agreed institutional criteria for patient stool submission.
**Fidaxomicin**

- Macrolide antimicrobial agent
- Approved for treatment of CDI
- Bactericidal
- Oral administration leads to high fecal concentrations
- Mayo Clinic offers metronidazole and vancomycin susceptibility testing for *C. difficile* from intestinal sources

---

**Testing Guidelines**

- Repeat testing for “test of cure” is not acceptable
- Formed stools should not be tested when used for CDI
- Testing should not be performed on children under 1 year of age
- Laboratories may use more than one testing platform in reflexive or algorithmic approaches
References


