Discovering the Optimal Approach to Diagnosing Clostridium difficile Infection (CDI)

PRESENTED BY: NATHAN A. LEDEBOER, PHD, D(ABMM)

PROFESSOR OF PATHOLOGY AND VICE CHAIR
DEPARTMENT OF PATHOLOGY
MEDICAL COLLEGE OF WISCONSIN

MEDICAL DIRECTOR, MICROBIOLOGY AND MOLECULAR PATHOLOGY
WISCONSIN DIAGNOSTIC LABORATORIES AND FROEDTERT HEALTH

MEDICAL DIRECTOR, CLIENT SERVICES AND REFERENCE SERVICES
WISCONSIN DIAGNOSTIC LABORATORIES
MILWAUKEE, WI
Learning objectives

After this webinar, you will be able to:

• Review the clinical background of C. difficile and its role as a pathogen in human health
• Identify various ways in which C. difficile can be accurately diagnosed
• Discuss the revised treatment recommendations for C. difficile
• Evaluate the role of the 2018 modifications to the NHSN reporting criteria for healthcare-associated C. difficile
**Clostridium difficile** infection (CDI)

- **Gram-positive, spore forming anaerobic bacillus**
- **First linked to disease in 1978**
- **Frequently causes diarrheal illness in hospitalized patients, patients with IBD or those treated with Abx**
- **Causes wide range of illness**
  - Diarrhea
  - Pseudomembranous colitis
  - Toxic megacolon
  - Systemic symptoms: fever, nausea, malaise, anorexia
- **New research shows**
  - Decreasing effectiveness of metronidazole therapy
    - 50% success with single course of treatment
    - 2 clones of metronidazole resistant *C. difficile*
- **Part of the GI Flora in**
  - 1-3% of healthy adult
  - 70% of children < 12 months
The financial and human impact of *C. difficile*

<table>
<thead>
<tr>
<th>Type of Onset</th>
<th>Number of Annual Cases</th>
<th>Cost</th>
<th>Number of Annual Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital – onset, hospital acquired (HO-HA)</td>
<td>165,000</td>
<td>$1.3 B</td>
<td>9,000</td>
</tr>
<tr>
<td>Community-onset hospital acquired (CO-HA) [4 weeks of hospitalization]</td>
<td>50,000</td>
<td>$0.3 B</td>
<td>3,000</td>
</tr>
<tr>
<td>Nursing home-onset</td>
<td>263,000</td>
<td>$2.2 B</td>
<td>16,500</td>
</tr>
</tbody>
</table>
Number one risk factor for *C. difficile* in healthcare – antibiotics

<table>
<thead>
<tr>
<th>Very commonly related</th>
<th>Less commonly related</th>
<th>Uncommonly related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>Sulfa</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Macrolides</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Carbapenems</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Other penicillins</td>
<td>Chloramphincol</td>
</tr>
<tr>
<td>Fluoroquinolons</td>
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</tr>
</tbody>
</table>

- 96% of patients with CDI receive ABX within 14 d of symptoms
- 100% of patients receive within 3 months
C. difficile testing methods

- Anaerobic stool culture
  - With testing of recovered isolates for cytotoxin production
- Cell culture cytotoxicity assay
- Toxin testing
  - EIA (enzyme-linked immunosorbent assay)
  - Glutamate dehydrogenase (GDH)
- PCR
Anaerobic stool culture (toxigenic culture)

• “Gold standard”
• Specimens can be heated to enhance spore formation before plating
• Specimens plated on specific media
  o Usually cycloserine-cefoxitin-fructose agar +/- horse blood
• Incubated anaerobically
  o For up to 5 days for final negative
• Colony appearance
  o Yellow, spreading
• *C. difficile* isolates recovered for cytotoxin production
  o grown in chopped-meat broth and supernatant passed through filter to determine toxigenicity
  o Supernatant purified and added to shell vials to observe for cytotoxic effect
• Turn around time 5 days or more
Anaerobic stool culture - *C. difficile*
## Anaerobic culture (toxigenic culture) sensitivity and specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison Method</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peterson, et al.</td>
<td>≥3 positive test results*</td>
<td>100 (85.9-100)</td>
<td>92.9 (88.2-95.9)</td>
<td>68.2 (52.3-80.9)</td>
<td>100 (97.5-100)</td>
</tr>
<tr>
<td>Stamper, et al.</td>
<td>Used as “gold standard”</td>
<td></td>
<td></td>
<td></td>
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*Peterson study evaluated 4 tests: 1. Anaerobic culture; 2. Cell culture cytotoxicity; 3. EIA; 4. Real-Time PCR
Cell culture cytotoxicity assay

• Cells of specific origin incubated in shell vials with sample (liquid from centrifuged stool) and buffer
  o MRC-5 cells (fetal lung cells)
  o Human foreskin fibroblasts

• Shell vials examined for cytotoxic effect

• Toxin B presence can be confirmed with neutralized cytotoxic activity in a control well containing the antitoxin
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<tbody>
<tr>
<td>Peterson, et al.</td>
<td>≥3 positive test results*</td>
<td>90.0 (72.3-97.4)</td>
<td>97.0 (93.2-98.8)</td>
<td>81.8 (63.9-92.4)</td>
<td>98.5 (95.2-99.6)</td>
</tr>
<tr>
<td>Stamper, et al.</td>
<td>Toxigenic anaerobic culture</td>
<td>67.2 (55.4-79.0)</td>
<td>99.1 (98.1-100)</td>
<td>93.2 (85.7-99.9)</td>
<td>94.4 (92.0-96.8)</td>
</tr>
<tr>
<td>Eastwood, et al.</td>
<td>Toxigenic anaerobic culture</td>
<td>86.4 (79.1-91.9)</td>
<td>99.2 (97.9-99.8)</td>
<td>2% prev-67.7 10% prev-92.0</td>
<td>2% prev-99.7 10% prev-98.5</td>
</tr>
</tbody>
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*Peterson study evaluated 4 tests: 1. Anaerobic culture; 2. Cell culture cytotoxicity; 3. EIA; 4. Real-Time PCR*
Enzyme Immunoassays (EIAs)

- One of the most frequently used diagnostic tests for CDI for past 10 years
- Initially targeted toxin A
- Disease-causing strains producing toxin B alone were identified
- EIAs updated to test for both toxins
- Cost $128 (clinical charge)
- Turn around time 4-6 hours
EIA sensitivity and specificity

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<tr>
<td>Peterson, et al.</td>
<td>≥3 positive test results</td>
<td>86.7 (68.4-95.6)</td>
<td>98.5 (95.3-99.6)</td>
<td>89.7 (71.5-97.3)</td>
<td>98.0 (94.6-99.4)</td>
</tr>
<tr>
<td>Eastwood, et al.</td>
<td>Toxigenic anaerobic culture</td>
<td>60.0-81.6</td>
<td>91.4-99.4</td>
<td>2% prev (16.8-69.0) 10% prev (47.0-92.4 )</td>
<td>2% prev (99.3-99.6) 10% prev (95.6-97.9)</td>
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*Peterson study evaluated 4 tests: 1. Anaerobic culture; 2. Cell culture cytotoxicity; 3. EIA; 4. Real-Time PCR

Generally accepted sensitivity of EIA 60-70% compared to toxigenic culture
Glutamate Dehydrogenase (GDH)

- “Common antigen” test
- Alternative to traditional EIA-meant to be more sensitive
- Uses EIA or latex agglutination technology
- Sensitivity 69-100%
  - Generally accepted as 80% sensitive
  - 100% sensitivity not using toxigenic culture as gold standard
- Specificity low
- 2 or 3-stage technique (based on presumed high sensitivity)
  - GDH initial test
  - Retest positives with more specific test
    - EIA
    - PCR
- Eastwood et al
  - Sensitivity 87.6%
  - Specificity 94.3%
## PCR sensitivity and specificity

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<td>100 (97.5-100)</td>
</tr>
<tr>
<td>Stamper, et al.</td>
<td>Toxigenic anaerobic culture</td>
<td>83.6 (74.3-92.9)</td>
<td>98.2 (96.8-99.6)</td>
<td>89.5 (81.5-97.4)</td>
<td>97.1 (95.3-98.9)</td>
</tr>
<tr>
<td>Eastwood, et al.</td>
<td>Toxigenic anaerobic culture</td>
<td>88.5 (80.3-93.6)</td>
<td>95.4 (92.9-97.0)</td>
<td>2% prev 28.1 10% prev 68.0</td>
<td>2% prev 99.7 10% prev 98.7</td>
</tr>
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*Peterson study evaluated 4 tests: 1. Anaerobic culture; 2. Cell culture cytotoxicity; 3. EIA; 4. Real-Time PCR*
C. difficile: An old bug providing contemporary clinical and laboratory challenges

- Persons with ≥ 3 unformed BM within 24 hours with risk factors for CDI (Clinically Significant Diarrhea)
- ↑ WBC, ↑ creatinine, ↓ albumin, antibiotics, IBD, surgery and older age
- Patients who completed therapy who still have CSD
- Do not perform tests on everyone with diarrhea
  - Consider non-infectious etiologies
Alternative causes of diarrhea in the hospitalized patient

• Careful selection of the patient is important:
  
  - 20-44% are receiving laxatives
  
  - 36-50% do not have significant diarrhea
  
  - tube feeding can cause liquid stools
Who to test

- “Judicious use of *C. difficile* testing is important because a *C. difficile* colonization state exists and can be common.”
- One study showed nearly 50% of hospitalized patients had *C. difficile* in their stool by the end of 4 weeks despite no symptoms of CDI.
- Testing should be reserved for patients with ≥3 loose stools per day for at least 1-2 days.
- “Stools taking the shape of the container”
- Number of EIA tests is controversial.
- Wait 7-14 days between samples from a single patient after positive result and treatment.
- Currently requests can be limited to one PCR per 5-7 days.
The challenges of *C. difficile* testing

- Incidence and severity of *C. difficile* increasing
- Disease caused by toxin production
  - Diagnostic Challenge, do labs detect toxin versus organism
    - Detection of organism increases sensitivity
    - Detection of toxin increases clinical specificity
- What’s the Best Test(s)?

Key points

Point-Counterpoint: What Is the Optimal Approach for Detection of Clostridium difficile Infection?

Ferric C. Fang, Christopher R. Polage, Mark H. Wilcox
Departments of Laboratory Medicine and Microbiology, University of Washington School of Medicine, Seattle, Washington, USA; Department of Pathology and Laboratory Medicine, University of California Davis School of Medicine, Sacramento, California, USA; Leeds Teaching Hospitals, NHS Trust, and University of Leeds, Leeds, United Kingdom

- NAAT-based testing often increases reported CDI infection rates at healthcare institutions
- Performance of any test can be significantly altered based on pre-analytical factors
- NAATs and culture-based methods are more sensitive but less specific than toxin assays, whereas toxin assays are less sensitive but more specific than NAATs
  - We don’t know what the best strategy is in relation to sensitivity versus specificity!
- Data suggest that patients testing positive by NAAT without active CDI may be more likely to spread C. difficile
NHSN reporting

• Facilities may choose to monitor *C. difficile* where *C. difficile* testing in the laboratory is performed routinely only on unformed (specifically, conforming to the shape of the container) stool samples
  - NO CHEATING!! Facilities are allowed to implement active surveillance protocols for epidemiology, but these results should not be reported in NHSN as Community Acquired *C. difficile*!

• All inpatient locations – outpatient locations can be reported, but must be mapped accordingly

• BIG CHANGE FOR 2018
  - When using a multi-testing methodology for CD, the final result of the last test will determine if the CDI positive laboratory assay definition is met.
    - So if using NAAT + toxin testing, only toxin results are reported to NHSN
  - CAUTION – This may change the institution’s SIR or Standardized Infection Ratio
The clinical challenges of *C. difficile* testing

- 490 HO-CDI LabID events during 452,587 patient-days
  - 284 (58%) were true HO-CDI
  - 206 (42%) were classified as nontrue (either inappropriate (90.5%) or delayed testing (9.5%))
What the guidelines said and did not say

• Shifts in guidance
  o Potential Major Change in Recommended Testing Strategy, but Weak Evidence – Expect Future Updates as New Data Emerges
    – Underscores the need for outcome studies in NAAT+/Toxin Negative Patients
  o Patients with unexplained and new-onset ≥3 unformed stools in 24 hours are the preferred target population for testing for CDI – Weak Evidence
  o Do not perform repeat testing (within 7 days) during the same episode of diarrhea and do not test stool from asymptomatic patients, except for epidemiological studies – Strong Evidence
  o In routine or endemic settings, perform hand hygiene before and after contact of a patient with CDI and after removing gloves with either soap and water or an alcohol-based hand hygiene product
    – Addition of alcohol-based products new, based on weak evidence – MAJOR shift for Infection Prevention
The 2017 IDSA guidelines, lab testing

Clinicians and laboratory personnel agree at the institutional level to not submit stool specimens on patients receiving laxatives and to submit stool specimens only from patients with unexplained and new onset ≥ 3 unformed stools in 24 h for testing for CDI.

- **Stool toxin test** as part of a multiple step algorithm (i.e. GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a nucleic acid amplification test (NAAT) alone.

- **NAAT alone OR stool toxin test** as part of a multiple step algorithm (i.e. GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a toxin test alone.

*Approved stool EIA toxin tests vary widely in sensitivity. Laboratories should choose a toxin test with sensitivity in the upper range of sensitivity as reported in the literature [146-149, 156].

From: Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)
Clin Infect Dis. Published online February 15, 2018. doi:10.1093/cid/cix1085
So how should healthcare facilities adopt to this shift?

• First, stop and take a breath!
• This is really test stewardship – We need to provide the right test for the right patient
Test stewardship can work

- Test Stewardship can reduce ordering
  - Alert versus Hardstop
    - Effectiveness of alert can wane over time

- Alter/Hardstop Values
  - Fires on third day of admission
  - Evaluates for documented diarrhea
  - Evaluates for laxative use
  - Also can consider elevated temperature
So how should healthcare facilities adapt to this shift?

• First, stop and take a breath!
• This is really test stewardship – We need to provide the right test for the right patient
• The Lab can Also Help!
It all comes down to the poo….

• Evaluate specimens that arrive in the Lab, only accept those specimens that take the form of the transport container.

• Establish acceptance criteria
  o Specimens submitted within 7 days of a previous test should not be repeated
    – Some centers have limited testing on patients with a positive NAAT to 14 or 21 d before retesting – Needs Further Study

• Use IT solutions to help
  o Alerts or Best Practice Alerts can help, but “Notification Fatigue” can occur
  o Consider “Hard Stops” that prevent the provider from ordering without providing a reason
  o Consider Including “Mandatory Consultation” with ID or Lab Director if test is flagged as an inappropriate order – Can be difficult, but can improve culture.
So how should healthcare facilities adopt to this shift?

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- This is really test stewardship – We need to provide the right test for the right patient
- The Lab can Also Help!
- Use your IT Department to Help
- Education of Physicians and Nurses

<table>
<thead>
<tr>
<th></th>
<th>Baseline Period</th>
<th>Intervention Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive PCR (n = 80)</td>
<td>Negative PCR (n = 80)</td>
</tr>
<tr>
<td>≥3 stools documented on day of test,* No. (%)</td>
<td>18 (45)*</td>
<td>42 (52)</td>
</tr>
<tr>
<td>Any laxative within 48 h of test, No. (%)</td>
<td>20 (30)</td>
<td>33 (41)</td>
</tr>
<tr>
<td>Age [y], median (IQR)</td>
<td>54 (46-71)</td>
<td></td>
</tr>
<tr>
<td>Unit, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floor</td>
<td>37 (68)</td>
<td></td>
</tr>
<tr>
<td>Stepdown</td>
<td>4 (80)</td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>9 (23)</td>
<td></td>
</tr>
<tr>
<td>Service, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>33 (83)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>7 (18)</td>
<td></td>
</tr>
<tr>
<td>Concomitant PPI, No. (%)</td>
<td>26 (65)</td>
<td></td>
</tr>
<tr>
<td>Documented clinical rationale for testing,* No. (%)</td>
<td>36 (90)</td>
<td>68 (92)*</td>
</tr>
<tr>
<td>Treatment Concordance,* No. (%)</td>
<td>29 (73)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic carriage</td>
<td>0/4 (0)</td>
<td></td>
</tr>
<tr>
<td>Mild–moderate infection</td>
<td>24/28 (86)</td>
<td></td>
</tr>
<tr>
<td>Severe infection</td>
<td>6/7 (57)</td>
<td></td>
</tr>
<tr>
<td>Severe complicated infection</td>
<td>1/1 (400)</td>
<td></td>
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</tbody>
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Buckel et al, ICHE, 2015; 36(2): 217-221

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• This is really test stewardship – We need to provide the right test for the right patient
• The Lab can Also Help!
• Use your IT Department to Help
• Education of Physicians and Nurses
• Antimicrobial Stewardship
Questions?

Presented by: Nathan A. Ledeboer, PhD, D(ABMM)
nledeboe@mcw.edu

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