C. Difficile Diagnostic and Clinical Challenges: Is Three Times a Charm?

Barbara DeBaun, RN, MSN, CIC
Cynosure Health
Objectives

- Describe the current laboratory tests utilized to identify C. difficile
- Discuss the benefits and potential weaknesses of current laboratory tests
- Describe the role of sensitivity, specificity and predictive value of laboratory tests
- Describe how the ‘culture of culturing’ can create diagnostic and clinical challenges
Introduction

• 3% - 7% of healthy adults are colonized with *C. difficile*

• Asymptomatic colonization is more common in people with inpatient healthcare exposures

• 4.4% - 15% of people are colonized with *C. difficile* on admission to hospital

• 50% of people who live in a LTC are colonized

• 7% - 21% of hospitalized adults are colonized at some point

• 4% - 15% are asymptotically colonized at the time of admission
To make matters even more challenging...

• Diarrhea is frequent among those with healthcare exposures
• *C. difficile* infection (CDI) affects < 1% of hospitalized patients
• It is cause of diarrhea in only 5%-10% of hospitalized patients who have diarrhea and are tested for *C. difficile*
Highest risk for colonization

- Infants
- Inflammatory bowel disease
- LTC, SNF, rehabilitation residents
- Recent inpatient healthcare
- Antibiotic exposure
- History of prior CDI
- Obesity
- Proton pump inhibitors
- Any condition that disrupts the colonic microbiota
Early Recognition: screening for CDI
Screening for *C. difficile*
Lab Tests for CDI

- 2014: NHSN requires reporting type of test used at your facility for CDI reporting
Laboratory Tests for *C. difficile*

- Cell culture cytotoxicity neutralization assay
  - Detection of free toxin
- Toxigenic stool culture
  - Detection of toxigenic strains of *C. difficile*
- Gold standards
- Long turn around times
- Excessive labor requirements
- Toxigenic culture is not standardized thus can incorporate bias into data analysis
- Primarily used for research
Toxin enzyme immunoassays (EIAs)

- EIA for toxins A and B became widely available in the mid-1980’s
- Quickly became the routinely used diagnostic assay despite poor sensitivity
- Resulted in multiple ordering “C. difficile EIA x 3”
- Many hospitals have abandoned toxin EIAs because of potentially suboptimal sensitivity and concerns for falsely negative results
- Strongly recommended that EIA testing NOT be performed for initial diagnosis
EIA’s

• Negative predictive value of toxin EIA is at least 95%
• Do not automatically repeat testing if first (or subsequent) test results are negative
• Risk for a false-positive test results increases with each round of testing
• Occasional false positive results in low prevalence populations
Glutamate Dehydrogenase Enzyme Immunoassay (GDH)

- Can detect the organism but can’t differentiate toxin + from toxin –
- Can’t be used as a ‘stand-alone’ test to confirm presence of toxigenic strains
- Sensitivity ranges from 75% to >90%
Nucleic acid amplification tests (NAATS)

• PCR (Polymerase Chain Reaction)
• LAMP (Loop-mediated isothermal amplification)
• Most commonly used diagnostic tests for detection of *C. difficile* in US hospitals
• Easy to perform, rapid, highly sensitive
• False negative results are highly unusual
Two-step approach to confirm active infection

PCR or GDH first

Then test for toxin
Studies that compare *C. difficile* diagnostic assays

- Primary problem is lack of data on the patients
- Without clinical data it is not possible to differentiate between asymptomatic *C. difficile* colonization and CDI
Intertwined issues that afflict us today

• Concerns that toxin assays are inadequately sensitive
  • Sensitivity of culture to detect *C. difficile* in stool is much higher than the sensitivity of assays that detect toxin, especially if the patient is an asymptomatic carrier
  • Levels of toxin in stool are lower in asymptomatic carriers than patients with CDI
  • Without clinical data it was thought persons who were culture + but toxin – represented patients with CDI but with a false negative toxin assay
  • When clinical data are available, the vast majority of culture +/-toxin – stools represent asymptomatic colonization NOT CDI
Intertwined issues that afflict us today

- A habit of ordering ‘C. diff x 3’ when testing for *C. difficile*
  - Concern over low sensitivity led to practice of automatic repeat testing for *C. difficile*
Intertwined issues that afflict us today

• A lack of recognition of the importance of the negative and predictive values when interpreting *C. difficile* assay results
  • Each time a test is repeated because the last test was negative, the prevalence of CDI in the population decreases
  • Therefore, the positive predictive value also decreases
  • By the time you get to the 3rd test, there is a <20% chance that a + test represents a true positive
  • Much better to focus on the predictive value of a test rather than the sensitivity
### C. difficile detection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCR Method (BD)</th>
<th>PCR method (Cepheid)</th>
<th>GDH/EIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96%</td>
<td>96%</td>
<td>42%</td>
</tr>
<tr>
<td>Specificity</td>
<td>96%</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>PPV**</td>
<td>100% ?</td>
<td>93% ?</td>
<td>100% ?</td>
</tr>
<tr>
<td>NPV</td>
<td>96%</td>
<td>93%</td>
<td>78%</td>
</tr>
</tbody>
</table>
What is “pre-test probability”?

The probability that THIS SPECIFIC PATIENT has the condition that this test is designed to find
PATIENT 1

- Age 50
- Admitted from home
- No recent prior acute or long term care hospitalization
- 3 loose stools on 4th hospital day
- No antibiotics administered in last 14 days
- Pre-test probability of CDI is 4.4% – 15% (mean 10%)
PATIENT 1

• 68% would be true positives (PPV)
• The false positive rate would be 32%!
• 99.5% would be true negatives (NPV). The false negative rate would be 0.5%

• Note: If the patient had a pre-test probability of 5%, more than one-half of the positive test results would be false.
PATIENT 1: here’s the math

- Test to identify *C. difficile* toxin genes (PCR)
  - Sensitivity = 95%
  - Specificity = 95%
  - Pre-test probability of CDI (prevalence) = 10%

- For a population of 1000 patients like Patient 1:
  - 100 patients would have CDI
  - 900 would not have CDI
  - The test with a sensitivity of 95% would identify 95 of the 100 patients with CDI (95 true positives) and miss 5 of the 100 with CDI (5 false negatives)
  - The test with a specificity of 95% would accurately be negative for the 95% of the 900 patients without CDI (855 true negatives) but would also misidentify 5% of the 900 without CDI as (45 false positives) as falsely having CDI.
PATIENT 2

• Age 80
• Admitted from Skilled Nursing Facility
• 3 loose stools since admission
• On antibiotics for presumed urinary tract infection
• Pre-test probability of CDI is approximately 50%
PATIENT 2

• 95% would be true positives (PPV). The false positive rate would be 5%!

• 95% would be true negatives (NPV). The false negative rate would be 5%.
PATIENT 2: here’s the math

- Test to identify *C. difficile* toxin genes (PCR)
- Sensitivity = 95%
- Specificity = 95%
- Pre-test probability of CDI = 50%

- For a population of 1000 patients like Patient 2:
  - 500 patients would have CDI
  - 500 would not have CDI
- The test with a sensitivity of 95% would identify 475 of the 500 patients with CDI (475 true positives) and miss 25 of the 100 with CDI (25 false negatives)
- The test with a specificity of 95% would accurately be negative for the 95% of the 500 patients without CDI (475 true negatives) but would also misidentify 5% of the 900 without CDI as (25 false positives) as falsely having CDI.
So...Are We Over-diagnosing CDI Cases?

- 90% of hospital onset diarrhea is not due to CDI
  - Tube feeding
  - Laxatives
  - Enemas
  - Medications
  - Other infections
  - Underlying disease
Impact of PCR

• Many patients are admitted as carriers or acquire carrier status after admission

• Polymerase Chain Reaction technology (PCR)
  • Identifies toxin-producing organism
  • Does not identify the presence of the toxin
  • Does not differentiate *C. difficile* associated disease (CDAD) from carrier
CDI Testing Definitions / Methods

• Toxin immunoassay by itself is not sensitive enough, leading to under-diagnosis

• PCR is highly sensitive and specific, but its predictive value is based on the chances a specific patient could have CDI, leading to...
“Among hospitalized adults with suspected CDI, virtually all CDI-related complications and deaths occurred in patients with positive toxin immunoassays.”

“Patients with a positive molecular and a negative toxin immunoassay had outcomes comparable to patients without *C. difficile* by either method.”

“Exclusive reliance on molecular tests without tests for toxins or host response is likely to result in over diagnosis and overtreatment.”
Implications of over-diagnosis

• Higher utilization of Contact Precautions
  • More resources such as single rooms and personal protective equipment
  • Patient anxiety and depression
  • Potential adverse events
  • Fewer interactions with health care workers

• Impact on value-based purchasing decisions
Implications of over-diagnosis

- Patients who do not have CDI will receive CDI treatment
  - Increased risk for drug-related adverse events
  - Selection for MDROs
  - Higher risk for CDI once treatment is stopped
It was Nurse Haggard’s job to collect all the stool samples.
# Charts and Tarts

## Bristol Stool Chart

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Separate hard lumps, like nuts (hard to pass)</td>
</tr>
<tr>
<td>2</td>
<td>Sausage-shaped but lumpy</td>
</tr>
<tr>
<td>3</td>
<td>Like a sausage but with cracks on the surface</td>
</tr>
<tr>
<td>4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>5</td>
<td>Soft blobs with clear-cut edges</td>
</tr>
<tr>
<td>6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>7</td>
<td>Watery, no solid pieces. Entirely Liquid</td>
</tr>
</tbody>
</table>

![Image of Bristol Stool Chart with a pastry version]
The Brecher Guidelines

Look at the stool specimen: If it ain’t loose it’s of no use

Put a thin lab grade stick in the specimen: If the stick falls, test them all
Specimen collection

- Clean, dry plastic jar with screw top lid
- To lab immediately
- Toxins break down quickly at room temperature
- Refrigerate if delay in transporting to lab
When to test for diarrhea:

- **DIARRHEA = ≥ 3 loose stools in ≤ 24 hours** and concern for infectious diarrhea
  - **No**: Do not test, Do not Isolate
  - **Yes**: MD or RN order/initiate CONTACT ISOLATION, Post green C2 sign for 2x/day cleaning
    - **Has patient received laxative in previous 48 hours?**
      - **Yes**: Is diarrhea likely due to laxative?
        - **Yes**: Observe x 24 hours or if strong clinical dif ficile
        - **No**: Send CPE for C. difficile
      - **No**: Send CPE for C. difficile
Laboratory Responsibility

• Test the right patient and the right sample
• Use the right test or combinations of tests
• Ensure only diarrheal stools are tested
• No need to repeat when using highly sensitive test
• No test for cure
• Use an algorithm with a test with good sensitivity first and then a test that detects free toxin
• Create barriers that limit poor practices
  • Reject specimens
  • Don’t allow automatic repeat testing or test of cure
Laboratory Responsibility

• Limit testing to unformed or diarrheal stool specimens
• Evaluate all submitted samples for consistency and reject formed samples
• Limit repeat testing
• Restrict testing of infants <1 year old
• Verify patient screening
Clinician’s Responsibility

• Be aware of what assays are used and how to interpret them
• Strengths and weaknesses
• Impact on patient treatment that is driven by laboratory results
CDI studies that included clinical data

• 35% to 50% of patients tested for *C. difficile* do not have clinically significant diarrhea

• 20% to 40% of patients recently received a laxative

• More studies are needed to compare *C. difficile* diagnostic assays that include high quality data on both patient symptoms and patient outcomes
Should we be screening patients for asymptomatic *C. difficile* colonization?

- Asymptomatic carriers contribute to *C. difficile* transmission and hospital-onset CDI
- We don’t know how much CDI in hospitals originates from asymptomatic vs symptomatic carriers, prior CDI patients, environmental surfaces, healthcare workers, or overgrowth and toxin production from a preexisting endogenous strain
- Lack of studies to guide most effective/best interventions to decrease transmission from asymptomatic carriers
- Unclear optimal sample type/lab test to screen asymptomatic persons
- Active surveillance needs further exploration
The Role of Asymptomatic Carriers

• Up to 70% of infants will transiently carry *C. difficile* in stool in first year of life
• By age 3, rates decline to 3% and remain stable
• Likely that asymptomatic carriers can transmit *C. difficile*
• Risk of transmission likely to be minimal with good compliance with Standard Precautions
• Only 20-30% of new cases of CDI can be linked to a known case of CDI when precautions are followed
How to test for asymptomatic carriage

• Need a screening method that is both rapid and sensitive
• NAATs are only approximately 60-70% sensitive to detect asymptomatic colonization
• Most sensitive method is with broth-enriched selective media but turnaround time is 36 hours
What do you do with the information?

- Do all patients who screen + get placed on Enhanced Contact Precautions?
- Room availability?
- Impact on staffing?
- Impact on patient safety and satisfaction?
What is best test for CDI?

• Good question
• All have advantages and disadvantages
Impact of Diagnostic Assay on HAI Rates

• Choice of test for lab confirmation has MAJOR impact
• Up to 50% of hospitalized patients with toxigenic C. difficile AND diarrhea test NEGATIVE for fecal toxins by immunoassay
• We tend to blame this on the ‘insensitivity of the test’
• BUT...might it actually be C. difficile colonization with an alternative cause for diarrhea?
If No, where is your facility's antifungal susceptibility testing performed? (check one)

- Affiliated medical center
- Commercial referral laboratory
- Other local/regional, non-affiliated reference laboratory
- Not offered by my facility

9. If antifungal susceptibility testing is performed at your facility or an outside laboratory, what methods are used? (check all that apply)*

- Broth macrodilution
- Broth microdilution
- YeastOne colorometric microdilution
- E test
- Vitek 2 card
- Disk diffusion
- Other n/a

10. Is antifungal susceptibility testing performed automatically/reflexively for Candida spp. cultured from normally sterile body sites (such as blood), without needing a specific order or request for susceptibility testing from the clinician? * Y - Yes, N - No

11. What is the primary testing method for C. difficile used most often by your facility's laboratory or the outside laboratory where your facility's testing is performed? (check one)*

- Enzyme immunoassay (EIA) for toxin
- Cell cytotoxicity neutralization assay
- Nucleic acid amplification test (NAAT) (e.g., PCR, LAMP)
- Glutamate dehydrogenase (GDH) antigen plus EIA for toxin (2-step algorithm)
- GDH plus NAAT (2-step algorithm)
- GDH plus EIA for toxin, followed by NAAT for discrepant results
- Toxigenic culture (C. difficile culture followed by detection of toxins)
- Other - Other (specify)

("Other" should not be used to name specific laboratories, reference laboratories, or the brand names of C. difficile tests; most methods can be categorized accurately by selecting from the options provided. Please ask your laboratory or conduct a search for further guidance on selecting the correct option to report.)

12. Does your facility produce an antibiogram (i.e., cumulative antimicrobial susceptibility report)? * Y - Yes

If Yes, is the antibiogram produced at least annually? Y - Yes
If Yes, are data stratified by hospital location? N - No

Infection Control Practices (completed with input from Hospital Epidemiologist and/or Quality Improvement Coordinator):

13. Number of infection preventionists (IPs) in facility**: 1.0
   a. Total hours per week performing surveillance**: 20
Pressure to capture ‘present on admission’
Culture of culturing

• Patient is a frail 84 year old resident of a nearby nursing home
• Recent fall, facial laceration
• History of dementia and psychiatric disease
Physical Exam

- Urinary drainage bag
- Suprapubic catheter
- Unable to urinate
- No discomfort, fever, chills
- Unsteady
- No lower abdomen or back tenderness
Changing the Culture of Culturing

![ICU Cultures and CAUTI Rate Chart]

- **Number of Urine Cultures**
  - Q1-13: 2000
  - Q2-13: 1600
  - Q3-13: 1200
  - Q4-13: 800
  - Q1-14: 400
  - Q2-14: 200
  - Q3-14: 100
  - Q4-14: 50

- **Rate per 1,000 Catheter Days**
  - Q1-13: 4.5
  - Q2-13: 3.5
  - Q3-13: 2.5
  - Q4-13: 1.5
  - Q1-14: 0.5
  - Q2-14: 0.5
  - Q3-14: 0.5
  - Q4-14: 0.5

**Legend**
- Green: Cultures
- Red: CAUTI Rate
Treatment for Positive Urine Cultures in Hospitalized Adults

- Retrospective observational study
- Tertiary academic, county and community hospital
- Asymptomatic bacteriuria (ASB)
- ASB present in 71% of 300 patients with bacteriuria
- ASB treatment was prevalent in all settings
- Associated abnormal urinalysis results with need for antibiotic treatment

Few final thoughts...

- Treat the patient, not the test
- The most expensive test is one that does not work
- Urgent need for a diagnostic test that detects fecal cytotoxin with high sensitivity
- Clinical correlation is essential in the evaluation of any new test for diagnosing *C. difficile* disease
Thank you!
Contact Information

Barbara DeBaun, RN, MSN, CIC
Improvement Advisor
Cynosure Health
bdebaun@cynosurehealth.org