Pearls and pitfalls in the diagnosis and management of *Clostridium difficile* infection

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Disclosures

- **Consulting:** The Medicines Company, Basilea Pharmaceutica

- **Scientific Advisory Board:** Motif Bio

- **Adjudication committee:** Achaogen

- **Grant support:** NIH, FDA

- **Royalties:** UpToDate

- **Employment:** Duke University
Overview

• *C. difficile* diagnostic testing – who to test and how to do it

• Treatment – when to use oral vancomycin and when to start thinking about FMT
From a recent ID discussion board:

“Given the financial ramifications of hospital acquired C. difficile infection, our hospital decided to aggressively screen for C. difficile infection in patients who are to be admitted, to avoid hospital attribution if they subsequently found to be positive… Since then, we have seen a large number of patients presenting with various illnesses to include Pneumonia, Heart failure, Respiratory failure or even altered mental status, who test positive by Nucleic Acid Testing.”
Patient CD

- A 63yo female presents to the ED with heart failure. She was recently treated with cipro at another facility for UTI. Screening for *C. difficile* is performed via PCR and is positive. What do you do?

A) Initiate treatment with oral vancomycin
B) Assess for diarrhea and, if absent, ignore the test result
C) Send confirmatory stool culture for *C. difficile*
D) Complain about the perverse incentives we face when practicing medicine
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Testing modalities for *C. difficile*

- The challenge in testing for *C. difficile* is in distinguishing colonization from disease

- This is compounded by:
  - the fact that culture is not routinely performed
  - Not all strains are toxigenic
  - Ancillary tests like fecal leukocytes are not useful
Colonization ≠ Disease

• Asymptomatic carriage occurs in:
  – 3-5% of healthy individuals
  – ~20% of hospitalized patients
  – ~50% in longterm care facilities

• For every 1 patient with CDI, at least 9 others are colonized
  – It is thus imperative to consider your pretest probability of disease before you test
Pathophysiology

Antimicrobial (s) → C. difficile acquisition → Hospitalization → Asymptomatic C. difficile colonization (85%) → CDI (15%)

C. difficile Infection

- Onset during antimicrobial administration or after discontinuation
  - Days to weeks to months later
- Watery stools ≥ 3 or more/day that persists for >24 hours
- Lower abdominal cramping
- Fever
- Leukocytosis

Kelly, CP et al. NEJM 2008; 359: 1932-40
Testing modalities for *C. difficile*

- **Toxin detection (the “old” way)**
  - EIA for *C. difficile* GDH antigen (produced by all *C.diff* strains)
  - EIA for *C. difficile* toxins A and B
  - Toxin degrades rapidly at room temperature, impacting results of testing
  - **Sensitivity ~ 75% / Specificity >99%**

- **Molecular testing (the “new” way)**
  - PCR for toxigenic strains (*tcdB* gene for toxin B)
  - *Qualitative test only! Does not distinguish active toxin production or a certain quantitative threshold of toxin production*
One possible algorithm (though your lab may do it differently)

Patient with diarrhea and risk factor(s) for *C. difficile* infection

Send stool for
- GDH antigen test (EIA)
- Toxin A and B test (EIA)

- GDH positive
  - Toxin positive
  - GDH positive
  - Toxin negative
  - GDH negative
  - Toxin positive
  - GDH negative
  - Toxin negative

  Indeterminant result

  Perform PCR for *tcdB* and *tcdC* genes

  PCR positive
  - Testing consistent with *C. difficile* infection
  PCR negative
  - Testing not consistent with *C. difficile* infection
Impact of change from toxin to molecular test on CDI rates

- 22 DICON hospitals: 10 switched compared to 12 that did not switch

aIRR 1.56 (95% CI 1.28-1.90)
Original Investigation

Overdiagnosis of Clostridium difficile Infection in the Molecular Test Era

Christopher R. Polage, MD, MAS; Clare E. Gyorke, BS; Michael A. Kennedy, BS; Jhansi L. Leslie, BS; David L. Chin, PhD; Susan Wang, BS; Hien H. Nguyen, MD, MAS; Bin Huang, MD, PhD; Yi-Wei Tang, MD, PhD; Lenora W. Lee, MD; Kyoungmi Kim, PhD; Sandra Taylor, PhD; Patrick S. Romano, MD, MPH; Edward A. Panacek, MD, MPH; Parker B. Goodell, BS, MPH; Jay V. Solnick, MD, PhD; Stuart H. Cohen, MD
Comparison of molecular and toxin tests

• Study objectives:
  – What is the natural history of PCR+/toxin- patients?
  – How do patient outcomes compare to PCR+/toxin+ patients?
  – How do patient outcomes compare to PCR-/toxin- patients?
  – **Do PCR+/toxin- patients require treatment for CDI?**

• Methods:
  – Clinical cultures submitted for *C. difficile* testing >=72 hours after admission
  – EIA toxin A/B and PCR performed on all unformed stool specimens
  – **Only toxin result was reported to clinicians**
1416 Included in study

293 *C. difficile* positive (21%)

131 Tox+/PCR+\(^a\)

Baseline
- 115 Diarrhea
- 16 <3 Stools per 24 h

15-Day follow-up (diarrhea)
- 109 Resolved
- 6 Diarrhea
- 15 Discharged with diarrhea
- 1 Died with diarrhea

30-Day follow-up (mortality)
- 96 Alive
- 14 Died
- 21 Unknown

162 Tox-/PCR+\(^a, b\) (55%)

Baseline
- 121 Diarrhea
- 41 <3 Stools per 24 h

15-Day follow-up (diarrhea)
- 148 Resolved
- 2 Diarrhea
- 12 Discharged with diarrhea
- 0 Died with diarrhea

30-Day follow-up (mortality)
- 120 Alive
- 23 Died
- 19 Unknown

1123 Tox-/PCR-\(^a, c\)

Baseline
- 773 Diarrhea
- 350 <3 Stools per 24 h

15-Day follow-up (diarrhea)
- 1048 Resolved
- 16 Diarrhea
- 57 Discharged with diarrhea
- 2 Died with diarrhea

30-Day follow-up (mortality)
- 751 Alive
- 98 Died
- 274 Unknown
No. at risk
Tox+/PCR+ 131 62 41 29 25 8
Tox-/PCR+ 162 60 29 21 10 2
Tox-/PCR- 1123 328 172 99 42 23
Treatment and Outcomes of Tox- versus Tox+ Patients

- 100% of Tox+ patients received treatment
- 40% of Tox- patients received any anti-CDI treatment
  - Majority received only partial treatment course

Table 3. Nondiarrheal Outcomes and Treatment by Clostridium difficile Test Group

<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>Complication-related complication or death within 30 d, No. (%)</td>
<td>10 (7.6)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3 (0.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>11 (8.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Complication or death</td>
<td>18 (13.7)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>3 (0.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Polage JAMA Intern Med. 2015; 175(11):1792-1801
Potential harms of unnecessary testing/treatment for CDI?

– Unnecessary antimicrobial exposure
  • Toxicities (metronidazole)
  • Antimicrobial resistance (VRE)
  • Continued disturbance of GI flora
  • Cost

– Patient anxiety
  • Some patients remain colonized for a long time and will repeatedly test positive; this leads to high anxiety state
Summary: *C. difficile* diagnostics

- Not all PCR+ patients (even those with diarrhea) require treatment.

- We need smarter diagnostics that assess disease activity, not just presence of toxigenic *C. difficile*.

- In the meantime, what can we do to improve the specificity of CDI testing for clinically active disease?
DUH *C difficile* infection data

- Review of cases diagnosed between days 4-10 of hospitalization
  - 71 (29%) were diagnosed on hospital day 4 or 5
  - 27 (38%) of those were receiving laxatives
C. difficile Testing Pearls

<table>
<thead>
<tr>
<th>Appropriate</th>
<th>Inappropriate</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Testing patients who have 3 or more diarrheal stools in less than 24 hours that persists</td>
<td>• Testing patients who have fewer than 3 diarrheal stools in 24 hours</td>
</tr>
<tr>
<td></td>
<td>• Sending repeat tests after obtaining a negative test within the last 7 days</td>
</tr>
<tr>
<td></td>
<td>• Testing soft or formed stool samples</td>
</tr>
<tr>
<td></td>
<td>• Performing a “test-of-cure” on patients after they have been treated</td>
</tr>
<tr>
<td></td>
<td>• Testing patients who have diarrhea when they are also on stool softeners or laxatives or those who have just recently been started on tube feeds</td>
</tr>
<tr>
<td></td>
<td>• As part of a fever of unknown origin work-up in patients without diarrhea</td>
</tr>
<tr>
<td></td>
<td>• Test that was ordered &gt;24 hours ago – but not sent because patient has not had any stool</td>
</tr>
</tbody>
</table>
CDI Testing Algorithm

*if clinical concern for toxic megacolon, consider abdominal imaging/surgical consultation

**septic shock, WBC > 15, and/or Cr > 1.5x baseline without other cause
Next steps at DUHS

• Electronic decision-support
  • BPA to fire when *C difficile* PCR test is ordered and patient has received laxative within 24 hours with recommendation to place on empiric isolation, discontinue laxatives, and observe if patient without signs/symptoms of severe CDI
  • Orders for *C difficile* PCR with auto-discontinue if not collected within 24 hours; ordering provider will have to renew order if patient condition still warrants test

• Education
  • Nurse and provider groups
  • Update Custom ID website to include testing algorithm
TREATMENT
General Principles of CDI Treatment

- Confirm the diagnosis using appropriate testing criteria
- Discontinue inciting antibiotics, when able
- If antibiotics cannot be discontinued, consider oral vancomycin prophylaxis
  - Reduced risk of CDI recurrence in those who received prophylaxis compared to those who did not (4.2% vs. 26.6%, OR 0.12, p < 0.001)
- Do not perform “test of cure” assays
- Stop unnecessary proton-pump inhibitors

# Daily Cost of Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Brand</th>
<th>Dosage</th>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidaxomicin</td>
<td>Dificid</td>
<td>200mg po BID × 10 days</td>
<td></td>
<td>$341.60</td>
</tr>
<tr>
<td><strong>Metronidazole</strong></td>
<td>Flagyl</td>
<td>500 mg po TID × 10-14 days</td>
<td></td>
<td>$2.20</td>
</tr>
<tr>
<td>Vancomycin (125mg capsule)</td>
<td>Vancocin</td>
<td>125 mg po q6H × 10 days</td>
<td></td>
<td>$127.30</td>
</tr>
<tr>
<td>Vancomycin (250mg capsule)</td>
<td>Vancocin</td>
<td>250 mg po q6H × 10 days</td>
<td></td>
<td>$234.75</td>
</tr>
<tr>
<td>Vancomycin oral solution</td>
<td>--</td>
<td>250 mg po q6H × 10 days</td>
<td></td>
<td>$8.00</td>
</tr>
</tbody>
</table>
Disease Severity

- No consensus definition
- WBC > 15K, serum creatinine ≥1.5x pre-morbid level
- WBC > 20K
- RCT vanco vs. metro
  - One point for: age >60, T >38.3, Albumin < 2.5mg/dl, WBC >15K within 48 hours;
  - Two points for pseudomembranous colitis on endoscopy
  - Patients with 2 or more points considered “severe”
- ≥ 10 BM per day, WBC ≥ 20K, or severe abdominal pain

Non-severe Disease
(WBC <15,000, creatinine <1.5x baseline)

- Metronidazole 500 mg orally every 8 hours x 10-14 days
  *or*

- If intolerance to metronidazole...
  - oral vancomycin 125mg orally every 6 hours (lower dose oral vancomycin is equivalent to 500mg po q6hr in eradication)

- IV Metronidazole 500 mg every 8 hours can be used if patient is NPO (drug has biliary excretion)

- IV Vancomycin is not effective in *C. difficile* infection

Severe Disease

• Oral vancomycin 125mg every 6 hours x 14 days

• If ileus suspected, add metronidazole 500 mg IV every 8 hours.

• If severe ileus/toxic megacolon and patient is critically ill:
  – add intracolonic vancomycin 500mg in 100ml normal saline every 4-12 hours via retention enema (foley catheter with 30cc balloon in rectum, inflate, instill vancomycin, clamp x 60min then deflate and remove)

• Surgical evaluation

Initial Relapse

- Confirm diagnosis
  - evaluate for other causes of diarrhea i.e. IBD, other infections
- Repeat same antibiotic course given for initial infection
- Relapse is common and occurs in 15-35% of patients after the first episode
- 45% of patients who have one relapse will experience a subsequent relapse
- 65% of patients who have another relapse will experience a subsequent relapse

Brandt et al. GASTROINTESTINAL ENDOSCOPY Volume 78, No. 2 : 2013 ; 240-249
Second Relapse

• Confirm diagnosis

• Tapering/pulsed oral vancomycin:
  – 125 mg po 4 times daily x 7 days
  – 125 mg po 2 times daily x 7 days
  – 125 mg po daily x 7 days
  – 125 mg po every other day x 7 days
  – 125 mg po every 3 days x 14 days

Subsequent Relapse

• Oral vancomycin 125 mg po 4 times daily x 14 days, followed by

• Rifaximin 400 mg po twice daily x 14 days

Fidaxomicin

- Bactericidal against *C. difficile*
- Narrower antimicrobial spectrum than metronidazole or vancomycin
- Phase 3 RCT: Fidaxomycin (200 mg po bid) vs. vancomycin (125mg po qid)
  - Similar clinical cure rates (88.2 vs 85.8%)
  - Recurrence occurred less often with fidaxomicin among patients with non-NAP1 strains
  - $3000 per course of treatment!

“a course of fidaxomicin would need to cost ≤$150 to be cost-effective in the treatment of all CDI cases and between $160 and $400 to be cost-effective for those with a non-NAP1/BI/027 strain”
Role for Probiotics?

• No good evidence exists that probiotics are effective for primary or secondary CDI prevention
  – RCTs have not confirmed benefits suggested by observational data

• Products are not standardized and may be costly

• Fungemia is a risk so probiotics are not recommended for:
  – Hospitalized patients
  – Patients with central venous catheters
  – Neutropenic patients
Emerging Therapies

- Monoclonal Antibodies
  - Not available for clinical use
- Tigecycline
- Fecal Microbiota Transplantation
- Stool Substitutes
- Non-toxigenic *C. difficile*
- Bile salt analog blocks germination (CamSA)
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FMT Pathophysiology

- Residential flora help prevent exogenous bacteria from establishing colonization through various mechanisms
  - “colonization resistance”

- Antibiotics and other factors (GI surgery) disrupt the normal balance of colonic flora (90% strict anaerobes)

- \textit{C. difficile} spores can germinate and lead to infection

- Treatment involves more antibiotics (perpetuating imbalance of colonic flora – “dysbiosis”)

- Fecal microbiota transplantation restores normal balance
Efficacy – It works!

• Gough et al
  – Systematic Review
  – 317 patients, 27 case series and case reports
  – Resolution of symptoms in 92% cases
  – No significant adverse events reported

• Kassam et al
  – Systematic Review and Meta Analysis
  – 273 patients, 11 studies
  – 245/273 (89%) with symptom resolution
  – No significant adverse events reported

...although not perfectly

Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent *Clostridium difficile* Infection: An Open-Label, Randomized Controlled Trial

Susy S. Hota,1,2,4 Valerie Sales,2,3,4 George Tomlinson,4,5 Mary Jane Salpeter,1,6 Allison McGeer,2,7,8 Bryan Coburn,2,4,9 David S. Guttman,10,11 Donald E. Low,2,7,8,9 and Susan M. Poutanen2,7,8

- RCT of patients with recurrent CDI, randomized to 14 days oral vanc followed by FMT enema, vs 6 week oral vanc taper
- Trial terminated for futility after just 30 patients (planned N=138)
- 9/16 (56.2%) recurrence rate with FMT vs 5/12 (41.7%) with vanc taper

Hota et al, Clin Infect Dis 2017;64(3):265-271
Possible indications for FMT

- Recurrent or relapsing CDI
  - At least 3 episodes of mild to moderate CDI and failure of a 6- to 8-week taper with vancomycin with or without an alternative antibiotic (eg, rifaximin, nitazoxanide)
  - At least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity

- Moderate CDI not responding to standard therapy for at least a week

- Severe (and perhaps even fulminant C. difficile colitis) with no response to standard therapy after 48 hours

Bakken JS et al. Clinical Gastroenterology and Hepatology 2011;9:1044-1049
Treatment take-home messages

• Optimize treatment conditions:
  – Stop other antibiotics, PPIs

• Use oral vancomycin for severe disease

• Recurrences are common and the optimal treatment strategy is unclear