Update on Diagnostic Testing for C. difficile and Nosocomial Diarrhea: Where are we now?

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Disclosures

I have received research materials from:

- Cepheid
- TechLab
- Meridian
- Alere
Objectives

After this talk, the participant should be able to:

• Explain the strengths and limitations of tests for *C. difficile* DNA or antigens vs. toxins

• Explain the role of inflammation in *C. difficile* infection and criteria for mild-moderate vs. severe disease

• List 5 common causes of non-*C. difficile* nosocomial diarrhea
Definitions

• Nosocomial diarrhea
  – Onset $\geq 3^{rd}$ hospital day
  – $\geq 3$ diarrheal stools x $\geq 1$ day
  – New diarrhea in hospital due to hospital exposure
  – 10-25% = CDI
  – $\geq 75\%$ due to some other cause

• C. difficile infection (CDI) vs. carrier
<table>
<thead>
<tr>
<th>Nosocomial diarrhea</th>
<th>C. difficile infection (CDI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ~10% of hospitalized pts.</td>
<td>• ~1% of hospitalized pts.</td>
</tr>
<tr>
<td>• ≥3.7 million pts./year</td>
<td>• ~300,000 pts./year</td>
</tr>
<tr>
<td>• Morbidity &amp; mortality:</td>
<td>• Morbidity &amp; mortality:</td>
</tr>
<tr>
<td>- ↑UTI, wound infections</td>
<td>- ~15% complications</td>
</tr>
<tr>
<td>- fluid &amp; electrolyte loss</td>
<td>- ~20% recur</td>
</tr>
<tr>
<td>- ?nutritional impact</td>
<td>- 3-5% attributable death</td>
</tr>
<tr>
<td>• Healthcare costs</td>
<td>• Healthcare costs</td>
</tr>
<tr>
<td>- ↑ hospital days/costs?</td>
<td>- 2-3 hospital days/case</td>
</tr>
<tr>
<td></td>
<td>- 1.1-3.2 billion USD/yr</td>
</tr>
</tbody>
</table>
The spectrum of *C. difficile* disease

- **Asymptomatic**
  - Diarrhea but nl WBC

- **Mild-mod disease**
  - Colitis & \( \uparrow \) WBC/Cr

- **Severe disease**
  - Megacolon, shock

- **Complicated CDI**

  - Shock

60% 40%

- 60% Asymptomatic
- 40% Mild-mod disease
- 33% Severe disease
- 15% Complicated CDI
*C. difficile* disease is mediated by toxins & inflammation
The frequency & severity of *C. difficile* infection has increased.....

- From 2000-2009
  - >200% ↑ CDI cases
  - >400% ↑ CDI mortality

- Associated with:
  - Epidemic BI/NAP1/027 strain
  - Antibiotic use
  - More sensitive tests?

....but colonization and immunity are also common in healthcare settings

Hospitalized patients

<table>
<thead>
<tr>
<th>Susceptible patients (~40%)</th>
<th>Immune patients (~60%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. difficile colonized (~20%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea (~10%)</td>
<td></td>
</tr>
<tr>
<td>CDI (~1-2%)</td>
<td>Diarrhea + carrier (~1-2%)</td>
</tr>
</tbody>
</table>
Available tests for *C. difficile*
Analytical sensitivity vs. clinical specificity *(Dubberke et al. JCM 2011)*

<table>
<thead>
<tr>
<th>Test method</th>
<th>Target</th>
<th>Sensitivity for <em>C. difficile</em> vs. toxigenic culture</th>
<th>Specificity for <em>C. difficile</em> + clinical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxin immunoassay</td>
<td>Toxins A&amp;B</td>
<td>40-92%</td>
<td>93-96%</td>
</tr>
<tr>
<td>Cell culture cytotoxicity</td>
<td>Toxin B&gt;&gt;A</td>
<td>67-86%</td>
<td>93-95%</td>
</tr>
<tr>
<td>DNA amplification</td>
<td><em>tcd</em>B or <em>tcd</em>A</td>
<td>87-100%</td>
<td>84-86%</td>
</tr>
<tr>
<td>Glutamate dehydrogenase</td>
<td>GDH enzyme (log phase)</td>
<td>80-95%</td>
<td>80-85%</td>
</tr>
<tr>
<td>immunoassay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxigenic culture</td>
<td>Bacteria + in vitro toxin production</td>
<td>----</td>
<td>90-92%</td>
</tr>
</tbody>
</table>
Toxin detection

Bacterial detection

Adapted from:
Gyorke et al. JCM 2013
Leslie et al. EJCMID 2012
So, what’s the best diagnostic test…?

Sensitive but specific for active disease

- Historically (1979-2005) - toxin tests favored
  - Gold standard = cell cytotoxin assay
  - Toxin-/C. difficile+ patients = colonized

- Recently (2005-2013) – shift → PCR/NAAT/Ag
  - Gold standard: toxigenic culture
  - Toxin assays only ~40-70% sensitive
So, what’s the best diagnostic test…?

No test is perfect:
  • Toxin tests may miss occasional cases
  • Culture & PCR probably overdiagnose

Both under & overdiagnosis have significant implications
Is there a role for inflammatory markers as adjunctive tests?

LaSala et al. JCM 2012

CR Polage, unpublished data
Definition of severe CDI and risk factors for complications

- Severe CDI as a predictor of complications
  - WBC ≥ 15/mm³ or
  - Cr ≥ 1.5 x baseline

- Other predictors
  - Age ≥ 65 yrs
  - Albumin < 2.5 mg/dL
  - comorbidities, & underlying illness
  - BI/NAP1/027 strain?

Steiner et al. CDLI 2006
## Other causes of nosocomial diarrhea

### Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Diarrhea Frequency</th>
<th>Non-inflammatory diarrhea</th>
<th>Inflammatory diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>8-30%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>5-35%</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>≥20%</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anti-retrovirals</td>
<td>≥20%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Colchicine</td>
<td>80%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cytotoxic chemo</td>
<td>30-80%</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>30-60%</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Laxatives (Mg^{++}, stimulant, osmotic)</td>
<td>≥20%</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Osmotic carbs (sorbitol etc)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>20-60%</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Other causes of nosocomial diarrhea
Underlying illness

- Fecal impaction
- Ischemic colitis
- Opiate withdrawal
- Hypoalbuminemia
- Graft versus host disease
- IBD, IBS, etc.?
Other causes of nosocomial diarrhea
Norovirus

- #1 foodborne gastroenteritis
- Winter vomiting illness
  - Abrupt onset vomiting +/- diarrhea
  - Short duration
- Epi still uncertain in hospitals
  - Outbreaks!
  - Sporadic?
  - Only 50% have vomiting
  - Prolonged in immunocompromised
- RT-PCR is test of choice
Other causes of noscomial diarrhea
toxigenic *Klebsiella oxytoca*

- ~50% strains toxin+
- 1-5% healthy population carry toxin+ strain
- with antibiotics
- Bloody diarrhea & hemorrhagic colitis
  - ~15% bloody AAD
  - 60-80% AAHC

Figure 1. Colonoscopic Images in Two Patients with Antibiotic-Associated Hemorrhagic Colitis.
Panel A shows mucosal edema and hemorrhage in the transverse colon in Patient 1. Panel B shows a close-up of mucosal hemorrhage in the same patient. Panel C shows longitudinal ulceration in the sigmoid colon in Patient 2. Panel D shows rectal sparing in the same patient.

Hogenauer NEJM 2006
Other causes of nosocomial diarrhea
Occasional bacterial causes

<table>
<thead>
<tr>
<th>Organism</th>
<th>Frequency</th>
<th>Testing?</th>
</tr>
</thead>
<tbody>
<tr>
<td>toxigenic <em>C. perfringens</em></td>
<td>≤3%</td>
<td>N/A special request</td>
</tr>
<tr>
<td>toxigenic <em>S. aureus</em></td>
<td>&lt;1%</td>
<td>N/A special request</td>
</tr>
<tr>
<td>toxigenic <em>Bacteroides fragilis</em></td>
<td>? (&lt;5%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Take home messages....

- **C. difficile** testing is evolving
  - Toxin tests are insensitive
  - DNA / bacterial tests are sensitive but non-specific
  - Expect role for adjunctive tests in future

- **Severe CDI defined by** \( \uparrow \text{WBC} \) or Creatinine
  - \( \uparrow \) risk of complications; treat aggressively

- **Many other causes of nosocomial diarrhea**
  - Most are non-infectious due to meds & underlying illness
Questions?

NUMBER 2 IS NUMBER 1 ON OUR AGENDA

GIVE POOP A CHANCE!

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