Enzyme Immunoassay for C. difficile toxin reduces Lab ID events but fails to detect clinically significant C. difficile infection

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Background: The National Health Safety Network (NHSN) requires reporting of Lab ID events for C. difficile infection (CDI) including all positive clinical tests after day three of hospitalization. Nucleic acid amplification tests (NAAT) that detect genes for toxin A and/or B may be overly sensitive, in some cases detecting C. difficile colonization. Some have advocated for two-stage testing, with positive NAAT tests followed by confirmatory enzyme immunoassay (EIA) to detect the presence of toxin and minimize the downside of false positives (i.e. additional NHSN reports or adverse of antibiotics). We aimed to better understand clinical characteristics of patients with positive NAAT and/or EIA tests.

Methods: Our hospital uses Xpert C. difficile assay (Cepheid), a NAAT method utilizing polymerase chain reaction (PCR), to diagnose CDI on informed stool only. As part of a 6-month quality initiative, we pilot tested the C.DIFF QUIK CHEK COMPLET® test (Alere), an EIA that tests for C. difficile antigen (Ag) and toxin, on all specimens that tested positive by NAAT. We abstracted clinical data from the medical record for a subset of patients who underwent EIA testing.

Results: Over 6 months, 294 patients had a positive test by NAAT. Of these, 258 (87.8%) underwent EIA testing. 67 (26.0%) were Ag+/toxin+, 173 (67.1%) were Ag+/toxin−, and 18 (6.8%) were Ag−/toxin+. Mortality rates were as follows: Ag+/toxin+, 17.9% (12/67); Ag+/toxin−, 13.9% (24/173); Ag−/toxin+, 13.5% (21/160). Among the EIA toxin negative patients who underwent chart review, 81% had 3 or more loose stools within 24 hours, 62% had abdominal pain, nausea, or vomiting, and 27% had a WBC > 15.

Conclusion: The majority of patients testing positive for CDI by NAAT had a negative EIA test for toxin. There was no significant difference in mortality between toxin positive and negative. Those with negative EIA toxin tests often had clinically significant symptoms of CDI. A two-stage CDI testing algorithm with NAAT followed by EIA for toxin may exclude patients with clinically significant CDI but would have resulted in a 75% reduction in reported NHSN LabID events.

Abstract

Background: The National Health Safety Network (NHSN) requires reporting of Lab ID events for C. difficile infection (CDI) including all positive clinical tests after day three of hospitalization. Nucleic acid amplification tests (NAAT) that detect genes for toxin A and/or B may be overly sensitive, in some cases detecting C. difficile colonization. Some have advocated for two-stage testing, with positive NAAT tests followed by confirmatory enzyme immunoassay (EIA) to detect the presence of toxin and minimize the downside of false positives (i.e. additional NHSN reports or adverse of antibiotics). We aimed to better understand clinical characteristics of patients with positive NAAT and/or EIA tests.

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Table 1: Clinical characteristics and outcomes associated with C. difficile Ag/toxin EIA test results among patients who tested positive by NAAT

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Antigen + toxin +</th>
<th>Antigen - toxin -</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or more loose stools within 24 hours prior to test</td>
<td>17.9% (12/67)</td>
<td>13.9% (24/173)</td>
<td>27.8% (5/18)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>88.9% (8/9)</td>
<td>86.4% (19/22)</td>
<td>50% (2/4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>55.5% (5/9)</td>
<td>45.5% (10/22)</td>
<td>25% (1/4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33.3% (3/9)</td>
<td>41.0% (9/22)</td>
<td>0% (0/4)</td>
</tr>
<tr>
<td>WBC &gt; 15</td>
<td>22.2% (2/9)</td>
<td>18.2% (4/22)</td>
<td>75% (3/4)</td>
</tr>
<tr>
<td>Radiology consistent with pseudomembranous colitis or ileus</td>
<td>11.1% (1/9)</td>
<td>31.8% (7/22)</td>
<td>0% (0/4)</td>
</tr>
<tr>
<td>Antibiotics given prior to positive C. difficile test</td>
<td>88.9% (8/9)</td>
<td>95.5% (21/22)</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>Proton pump inhibitor use</td>
<td>66.7% (6/9)</td>
<td>50% (11/22)</td>
<td>75% (3/4)</td>
</tr>
</tbody>
</table>

Results

- Over the 6 month study period, 294 patients underwent C. difficile NAAT testing > day 3 of admission.
- 258 (87.8%) of these underwent EIA testing.
- 67 (26.0%) were Ag+/toxin+, 173 (67.1%) were Ag+/toxin−, and 8 (6.8%) were Ag−/toxin−.
- Table 1 shows clinical outcomes for the patients who underwent chart review.
- There were no significant differences in clinical symptoms among patients based on EIA results.
- There was no significant difference in mortality between those with EIA toxin positive and negative.
- Among the EIA toxin negative patients who underwent chart review, 81% had 3 or more loose stools within 24 hours, 62% had abdominal pain, nausea, or vomiting, and 27% had a WBC > 15.
- If this two-stage testing algorithm had been used to report LabID events to NHSN, it would have resulted in a 75% reduction in LabID events.

Conclusion

- The majority of patients testing positive for CDI by NAAT had a negative EIA test for toxin.
- Those with negative EIA toxin tests often had clinically significant symptoms of CDI.
- A two-stage CDI testing algorithm with NAAT followed by EIA for toxin may exclude patients with clinically significant CDI but would have resulted in a dramatic reduction in reported NHSN LabID events.

References