About the Disease

*Clostridium difficile* is a healthcare-associated infection (HAI) typically brought on by exposure to antibiotics in the healthcare setting. *C. difficile* is present in 13 of every 1,000 hospital inpatients.1 The bacteria can live harmlessly in the gut of infants and adult carriers, but causes severe diarrheal disease in susceptible patients. *C. difficile* typically produces two toxins, known as toxins A & B, that damage the cells of the colon and result in diarrheal illness. The key feature of *C. difficile* disease is clinically significant diarrhea and testing should only be performed on patients with at least three diarrheal stools in the past 24 hours (unless bowel obstruction is suspected).2

*C. difficile* testing remains challenging. For many years, immunoassay testing for toxins A & B has been the common laboratory practice for diagnosis. However, testing only for toxins by immunoassay is no longer considered sensitive enough to be used as a stand-alone test.2 This lack of sensitivity led to requiring multiple serial samples to confirm a negative result. Advancements in diagnostics and disease understanding have created many options for laboratories to use to test for *C. difficile* and often overcome the need for testing multiple samples for an accurate diagnosis.

GDH Sensitivity

Glutamate dehydrogenase (GDH) antigen testing is a highly sensitive method for detecting the presence of *C. difficile* bacteria.

- All *C. difficile* bacteria produce GDH antigen in large quantities, making it easily detectable by current laboratory tests with superior performance to older methodologies like latex agglutination.
- Not all strains of *C. difficile* can produce toxins, so GDH positive samples must be tested for toxin or the gene responsible for toxin production. This process is known as algorithm testing.
- GDH is as sensitive as PCR for detecting possible *C. difficile* infections, and the negative predictive value (NPV) is equal to PCR as well.3,4 A negative GDH test can be reliably reported immediately, as recommended by the American Society for Microbiology (ASM).2

The Complete Diagnostic Picture

Algorithm testing provides a more complete diagnostic picture than molecular testing alone.

- Algorithm testing is a 2-step process. Incoming samples are screened for GDH. Positive samples are then tested for toxin or a gene encoding for toxin, while GDH-negative samples are reported as negative for *C. difficile*.
- The GDH algorithm improves testing sensitivity compared to toxin testing alone and reduces false positives associated with molecular testing.
- Samples positive for both GDH and Toxin, and samples negative for both GDH and toxin, are reported immediately with no further testing needed. Samples positive by the GDH screen yet negative for toxin should be confirmed by another method.
- The *C. DIFF QUIK CHEK COMPLETE®* test offers simultaneous GDH and Toxin testing in a single rapid cassette. It is ideal for algorithm testing, providing reportable results on the majority of samples while reducing the cost and time burden of molecular testing.
Faster Turnaround Time, Reduce Hospital Costs and Improve Infection Rate with Algorithm Testing

Implementation of an algorithm incorporating the C. DIFF QUIK CHEK COMPLETE® test resulted in the following statistics at JT Mather Hospital in Port Jefferson, NY:

- **Turnaround Time**: 66% decrease
- **Overall Hospital Costs**: 32% reduction
- **Testing Volumes**: 42% decrease
- **C. difficile Infection Rate**: 40% decrease

GDH & Molecular Testing Methods

Multiple independent studies have compared the results of GDH screening, molecular techniques, and algorithm methods to laboratory reference standards and clinical symptoms. They consistently show that GDH and molecular tests are equally sensitive and can be similarly relied upon to detect possible C. difficile infections.

Assay sensitivity and negative predictive value (NPV) compared to reference assays

<table>
<thead>
<tr>
<th>Study</th>
<th>GDH</th>
<th>Tox A/B (Frozen)</th>
<th>Cepheid Xpert®</th>
<th>BD GeneOhm®</th>
<th>Meridian Illumigene®</th>
<th>Reference Assay</th>
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<tbody>
<tr>
<td>Dubberke, et al.4</td>
<td>100 sens. 100 NPV</td>
<td>94.3 sens. 99.2 NPV</td>
<td>100 sens. 100 NPV</td>
<td>100 sens. 100 NPV</td>
<td>97.1 sens. 99.6 NPV</td>
<td>Toxigenic Culture plus diarrhea</td>
</tr>
<tr>
<td>Dubberke, et al.4</td>
<td>100 sens. 100 NPV</td>
<td>84.0 sens. 97.0 NPV</td>
<td>98.0 sens. 99.6 NPV</td>
<td>98.0 sens. 99.6 NPV</td>
<td>96.0 sens. 99.2 NPV</td>
<td>4 assays positive</td>
</tr>
<tr>
<td>Swindells, et al.3</td>
<td>100 sens. 100 NPV</td>
<td>61.1 sens. 95.0 NPV</td>
<td>100 sens. 100 NPV</td>
<td>94.4 sens. 99.2 NPV</td>
<td>--</td>
<td>Toxigenic Culture</td>
</tr>
<tr>
<td>Sharp, et al.6</td>
<td>100 sens. 100 NPV</td>
<td>60.0 sens. 99.2 NPV</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>GDH, Tox A/B, PCR all positive</td>
</tr>
<tr>
<td>Quinn, et al.7</td>
<td>100 sens. 100 NPV</td>
<td>78.3 sens. 96.8 NPV</td>
<td>--</td>
<td>95.7 sens. 99.3 NPV</td>
<td>--</td>
<td>2 of 3 positive; Toxigenic Culture, BD PCR, homebrew PCR</td>
</tr>
</tbody>
</table>

Sensitivity is the probability that a test will give a positive result for patients who are positive by the reference assay. NPV is the probability that a patient with a negative test result is also negative by the reference assay.
Molecular Results May Not Indicate Active Disease

- Molecular testing detects the gene encoding for toxin, not the toxin itself. When the gene is detected, there is no indication if toxins are actively being produced or even if there are any viable bacteria present.
- Molecular tests can remain positive for months following treatment and clinical cure, reducing the clinical utility of molecular results in recently treated patients. ²

In a study of 400 samples submitted for *C. difficile* testing from hospitalized patients, Kvach and colleagues reported: ¹³
- Eighteen patients were PCR positive but negative for toxin production based on the cytotoxicity assay gold standard. Treatment decisions were based on the cytotoxicity result.
- Seventeen of the 18 patients had no evidence of disease or adverse consequences despite the lack of treatment.
- One patient was diagnosed with *C. difficile* disease 22 days after the study sample was collected.

Asymptomatic carriers of *C. difficile* present a special challenge for the clinician and the laboratory as the presence of the toxin gene does not mean there is active *C. difficile* disease.
- Carriers may be tested due to inappropriate sample submission - including patients with recent laxative use, those lacking clinically significant diarrhea, or patients recently treated for *C. difficile* infection. This can lead to unnecessary and potentially harmful treatment.
- The rate of carriers in the hospital often exceeds the number of actively infected patients.² Up to 70% of newborn infants, 32% of cystic fibrosis patients, and up to 20% of residents in long-term care facilities are asymptomatic carriers of *C. difficile*.³⁵,¹¹
- Carriers should not be given antibiotic therapy to clear the *C. difficile* colonization. Decolonization attempts are often ineffective and increase the risk to the patient of acquiring a pathogenic infection.¹²
- Carriers are less likely to contaminate their environment than actively infected patients. Isolation of carriers is not strictly necessary.¹²

False Positive Results

All molecular tests have a risk of false positive results. False positive results lead to overtreatment and may expose patients to needless antibiotics or disrupt the treatment of other illnesses.
- False positive results divert infection control resources and can lead to false impressions if *C. difficile* rates are reported.⁴
- Algorithm testing improves the accuracy of *C. difficile* diagnosis by reducing the number of false positives associated with molecular testing alone.⁴ Screening with GDH will eliminate the majority of samples from needing further testing, reducing the risk of a false positive result.

Topics for Consideration

*C. difficile* only produces toxins when needed, primarily in response to lack of nutrients.¹⁴
- If *C. difficile* has sufficient food it will not produce toxin, resulting in a state where the bacteria are present and have the genes to make toxin, but the toxins themselves are unlikely to be detected.
- The toxins cause *C. difficile* disease, and without toxin production any patient symptoms are likely due to a secondary cause.
C. difficile Testing Algorithm

Contact your local Account Executive at 877.441.7440 or visit www.alere.com today.

Product ordering information

<table>
<thead>
<tr>
<th>Alere #</th>
<th>Product</th>
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<tr>
<td>30550C</td>
<td>C. DIFF QUIK CHEK COMPLETE® – Rapid, 50 tests</td>
</tr>
<tr>
<td>30525C</td>
<td>C. DIFF QUIK CHEK COMPLETE® – Rapid, 25 tests</td>
</tr>
</tbody>
</table>

References

6. Uettwiller-Geiger DL. The Clinical Laboratory Plays a Key Role in Reducing Clostridium difficile Hospital Associated Infection (HAI) Rates by Implementing a Simultaneous Two Test Algorithm for Rapid Identification of C. difficile. AACC Annual Meeting, July 2011