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Dear Colleague,

IDSA and SHEA recently released new clinical practice guidelines for *Clostridium difficile* testing: [Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America \(IDSA\) and Society for Healthcare Epidemiology of America \(SHEA\)](#). The guidelines provide recommendations and guidance, along with discussion, on the complexity and challenges associated with accurate diagnosis of *C. difficile* infections (CDI).

Immunoassay toxin testing has an important role in CDI diagnosis

C. difficile causes only about 15% or less of diarrheas in hospitalized patients suspected of having CDI. Accurate diagnosis is complicated by the fact that this organism often is present in patients but is not the cause of the diarrhea. The guidelines note this point by stating that “The optimum method for laboratory diagnosis of CDI remains elusive as patients may harbor toxigenic strains and not have clinical disease, an observation that was made in early studies soon after the discovery of *C. difficile*”. As a result, thoughts on the most accurate approach to laboratory testing continue to evolve.

In short, these new guidelines by IDSA and SHEA are in line with the recommendations released recently by the European Society of Clinical Microbiology and Infectious Diseases. Both support the importance of toxin testing as part of multistep algorithm, with the key point being that toxin testing provides the highest predictive positive value (PPV) for CDI. Additionally, multistep algorithms also provide a very high predictive negative value and accurately rule out CDI.

Support for algorithm testing

These diagnostic guidelines are based on recent clinical studies which critically evaluated and compared test results with clinical findings. In the largest study to date, Planche et al. showed that the preferred algorithm compared with culture included a glutamate dehydrogenase (GDH) test or nucleic acid amplification test (NAAT) as a first step to rule out CDI, followed by a toxin test for the highest PPV. The pairing of GDH detection with a toxin test produced results statistically identical to those observed with the pairing of NAAT with toxin detection. Patients who were positive for toxin had a higher case-fatality rate than those who were either toxigenic culture-positive but toxin-negative, or those who were negative by both methods. These findings led the authors to conclude that a positive toxin assay exhibited greater accuracy for CDI and identified patients who needed treatment.

In another large study, Polage et al. noted that CDI is a toxin-mediated inflammatory disease, and that in the absence of toxin, patients had less antibiotic exposure, lower *C. difficile* counts, less inflammation, and milder symptoms despite minimal or no treatment. The authors concluded that most patients with negative toxin test results do not need treatment for CDI, even if *C. difficile* is detected by NAAT or toxigenic bacterial culture. Further, the authors concluded that as many as half of patients positive by NAAT are overdiagnosed and exposed to unnecessary treatment.

These studies and the results of other recent studies (see references below) demonstrate the low PPVs of NAATs, a conclusion recently noted by Kamboj et al. in their analysis of *C. difficile* testing rates. These

studies also support the inclusion of toxin tests as part of an algorithm approach using NAAT or GDH as the initial screen followed by toxin testing.

Better sample selection criteria will improve accuracy of CDI testing in general

The guidelines state that a multistep algorithm offers better PPV over molecular testing, although molecular testing is permitted. The inclusion of stringent sample selection criteria, as recommended in the guidelines for molecular testing, likely will improve accuracy for CDI testing in general, and reduce the number of samples submitted for *C. difficile* testing. Even so, accurate testing of selected samples will continue to be challenging since *C. difficile* can be present in patients with diarrhea but not be the cause of the illness. The inclusion of toxin tests will make testing more accurate.

The importance of immunoassay toxin testing

The detection of toxin production provides the highest accuracy for CDI, based on higher PPV obtained when immunoassay toxin testing is included. The IDSA/SHEA guidelines identified TECHLAB assays as being nearly equivalent in performance to the cell cytotoxicity neutralization assay (CCNA), a gold standard assay that is used as the comparator assay for toxin testing. We support these guidelines and other guidelines which emphasize the importance of toxin testing for accurate diagnosis of CDI.

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