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Glutamate Dehydrogenase for Laboratory Diagnosis of *Clostridium difficile* Infection

We read with interest the paper "Evaluation of the C.Diff Quik Chek Complete Assay, a New Glutamate Dehydrogenase and A/B Toxin Combination Lateral Flow Assay for Use in Rapid, Simple Diagnosis of *Clostridium difficile* Disease" by Sharp and colleagues (10).

Interest in the laboratory diagnosis of *Clostridium difficile* has been encouraged by research that has shown the commonly used toxin enzyme immunoassays (EIAs) to be inadequate when used alone (1, 9).

We agree with Sharp et al. (10) that glutamate dehydrogenase (GDH) is a very sensitive (but poorly specific) assay and can accurately rule out the presence of *C. difficile* in stool samples. Sharp and colleagues (10) used a commercially available combined GDH and toxin A/B assay (C.Diff Quik Chek Complete) in the first step of their testing algorithm, as others have done (2, 8, 11). However, we note that there were no true-positive samples that were GDH negative but EIA toxin positive in the 284 specimens they tested.

We made the same observation in our own study of 500 specimens (3), and others have reported similar results (6, 7, 11). Thus, it is very rare to have a GDH-negative, EIA toxin-positive result for a true-positive sample. Therefore, we believe the toxin component of the C.Diff Quik Chek Complete assay is redundant. We prefer to use the GDH-only assay (C.Diff Chek-60), which is less expensive and allows for automated processing using the Dynex DS2 platform. This saves hands-on time and avoids possible misinterpretation of ambiguous results, since it produces a numerical result.

We note that Sharp and colleagues had one false-positive result with their testing algorithm, giving a sensitivity and specificity of 100% and 99.6%, respectively (10). Using those authors' figures, we calculated performance characteristics using our preferred algorithm of screening with the C.Diff Chek-60 GDH assay, followed by confirmation with GeneXpert PCR, and found a sensitivity and specificity of 100% and 100%, respectively. Furthermore, the GeneXpert system can simultaneously indicate the presence of the potentially "hypervirulent" ribotype 027 strain (4), giving important epidemiological information not provided by the C.Diff Quik Chek Complete test.

Using the Sharp and colleagues' figures for material cost per test (10), we also calculated the cost of each algorithm for testing 284 specimens. Those authors suggested the algorithm would cost $4,200.64, and ours cost slightly less at $3,923.30 (Table 1). Turnaround times for these algorithms would not differ significantly (depending upon degree of batching), but significant reductions may be possible by using GeneXpert as a point-of-care test. Further study is warranted in this area.

It is clear that the GDH test is sufficiently sensitive to work well as an initial screen, but we do not believe any benefit is derived by coupling it with a toxin EIA. Furthermore, a dedicated, automated GDH test is easier to interpret.

In England, we are now seeing a decrease in the prevalence of *Clostridium difficile* infection (which is a mandatory reportable disease) (5), and this will inevitably have an impact upon the positive and negative predictive values of any diagnostic tests. It is critical, therefore, that we have robust, accurate methods of identifying patients with this organism.

TABLE 1. Material cost comparison for two suggested diagnostic algorithms

Diagnostic algorithm	Component assay	Material cost per test ($)	No. of tests required	Total material cost ($)
Chek Complete (GDH plus toxin A/B), followed by PCR	C. Diff Chek Complete	11.50	284	3,266.00
	GeneXpert PCR	33.38	28	934.64
Total cost				4,200.64
Chek-60 (GDH alone), followed by PCR	C. Diff Chek 60	7.35	284	2,087.40
	GeneXpert PCR	33.38	55	1,835.90
Total cost				3,923.30

REFERENCES

1. **Eastwood, K., P. Else, A. Charlett, and M. Wilcox.** 2009. Comparison of nine commercially available *Clostridium difficile* toxin detection assays, a real-time PCR assay for *Clostridium difficile tcdB*, and a glutamate dehydrogenase detection assay to cytotoxin testing and cytotoxigenic culture methods. J. Clin. Microbiol. **47:**3211–3217.
2. **Gilligan, P. H.** 2008. Is a two-step glutamate dehydrogenase antigen-cytotoxicity neutralization assay algorithm superior to the Premier toxin A and B enzyme immunoassay for laboratory detection of *Clostridium difficile*? J. Clin. Microbiol. **46:**1523–1525.
3. **Goldenberg, S. D., P. R. Cliff, S. Smith, M. Milner, and G. L. French.** 2010. Two-step glutamate dehydrogenase antigen real-time polymerase chain reaction assay for detection of toxigenic *Clostridium difficile*. J. Hosp. Infect. **74:**48–54.
4. **Goldenberg, S. D., T. Dieringer, and G. L. French.** 2010. Detection of toxigenic *Clostridium difficile* in diarrheal stools by rapid real-time polymerase chain reaction. Diagn. Microbiol. Infect. Dis. **67:**304–307.
5. **Health Protection Agency.** August 2009. Healthcare-associated infections in England: 2008–2009 report. Health Protection Agency, London, United Kingdom.
6. **Kvach, E. J., D. Ferguson, P. F. Riska, and M. L. Landry.** 2010. Comparison of BD GeneOhm Cdiff real-time PCR assay with a two-step algorithm and a toxin A/B enzyme-linked immunosorbent assay for diagnosis of toxigenic *Clostridium difficile* infection. J. Clin. Microbiol. **48:**109–114.
7. **Larson, A. M., A. M. Fung, and F. C. Fang.** 2010. Evaluation of *tcdB* real-time PCR in a three-step diagnostic algorithm for detection of toxigenic *Clostridium difficile*. J. Clin. Microbiol. **48:**124–130.
8. **Novak-Weekley, S. M., E. M. Marlowe, J. M. Miller, J. Cumpio, J. H. Nomura, P. H. Vance, and A. Weissfeld.** 2010. *Clostridium difficile* testing in the clinical laboratory using multiple testing algorithms. J. Clin. Microbiol. **48:**889–893.
9. **Planche, T., A. Aghaizu, R. Holliman, P. Riley, J. Poloniecki, A. Breathnach, and S. Krishna.** 2008. Diagnosis of *Clostridium difficile* infection by toxin detection kits: a systematic review. Lancet Infect. Dis. **8:**777–784.
10. **Sharp, S., L. O. Ruden, J. C. Pohl, P. A. Hatcher, L. M. Jayne, and W. M. Ivie.** 2010. Evaluation of the C.Diff Quik Chek Complete assay, a new glutamate dehydrogenase and A/B toxin combination lateral flow assay for use in rapid, simple diagnosis of *Clostridium difficile* disease. J. Clin. Microbiol. **48:**2082–2086.

11. **Swindells, J., N. Brenwald, N. Reading, and B. Oppenheim.** 2010. Evaluation of diagnostic tests for *Clostridium difficile* infection. J. Clin. Microbiol. **48:**606–608.

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Author's Reply

We thank Dr. Goldenberg and colleagues for their Letter to the Editor regarding our study and appreciate the substantiation of our data. We agree that the cost of utilizing the C.Diff Quik Chek Complete assay with reflex of discrepant specimens to PCR would approximate the cost of the GDH EIA with PCR reflex for positive results.

However, we believe that the use of the toxin A/B component of the C.Diff Quik Chek Complete assay is not redundant in our setting. We do not batch test samples obtained from inpatients but perform testing on a real-time basis, producing results within 1 h for 88% of specimens which do not need PCR (and within 3 h for those requiring PCR). Production of results within 1 h would be difficult to do when utilizing batch testing with a GDH EIA. As our patient isolation protocols are tied to the laboratory calling for all positive *C. difficile* toxin test results, batch testing would not work in our situation, as this would inappropriately delay the patient being placed into isolation. As pointed out in our article, the decision to batch or test in "real time" is an institutional decision that should be made in conjunction with the laboratory, infection prevention, and other pertinent colleagues.

Of note is that the 027 component of the GeneXpert PCR test is not FDA approved for use in the United States.

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