Treatment Rates in a Two-Step *Clostridioides difficile* Diagnostic Testing Algorithm

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Introduction

Clostridioides difficile is a Gram-positive obligate anaerobe long associated with healthcare-acquired infections in the United States. [1] *Clostridioides difficile* infection (CDI) has thus become a key metric for assessing facility cleanliness and iatrogenic infection. *C. difficile* carriage is common, present in approximately 8% of hospitalized patients.[2] Therefore, appropriate patient selection for testing and careful testing procedures is crucial to appropriately identify CDI while avoiding the detection of chronic colonization.

Considerable variability exists among institutions regarding standardized CDI laboratory diagnostic methods. Historically, the gold standard for CDI testing was the clinically inefficient toxigenic culture (TC). [3] This was followed by cytotoxic assays (CTA) and then enzyme-linked immunoassays (EIA), which directly tests for the bacterial toxin.[4] However, EIA use alone was often deemed insufficient and required additional testing to improve sensitivity. [4] Testing for the isoenzyme glutamate dehydrogenase (GDH), specific to the *Clostridioides* species, can be added to EIA toxin testing to improve the sensitivity of the toxin testing result.[5] However, GDH testing alone serves is a poor clinical indicator for CDI, as it does not differentiate those with active CDI vs those colonized with *C. difficile*, and has the potential to identify other close species.[5] Combination toxin EIA and GDH testing improves both sensitivity and specificity for CDI, but can leave clinical uncertainty with incongruent results (ie. GDH+ Toxin- patients).

PCR testing exists as another option for CDI, and identifies Toxin A and Toxin B genes with high sensitivity and produces rapid results.[4] While PCR identifies toxigenic *C. difficile* strains and eliminates those that are non-toxigenic, it fails to identify the active production of toxins. Since toxin production is correlated with active infection, PCR alone is unable to distinguish active infection from colonization.

Current CDI testing guidelines recommendation a multi-step approach that tests for *C. difficile* strains and active toxin production.[1] This can be accomplished with GDH and toxin EIA or PCR and toxin EIA, with some algorithms reflexing to PCR in non-congruent GDH/EIA results. In November 2019, Beaumont Health changed its CDI testing policy to default to GDH and toxin EIA. While PCR remained available, testing could only be performed by consultation of and ordering by an infectious disease physician.

Aims and Objectives

The primary aim of this study is to evaluate the Beaumont Health policy change to a two-step algorithm approach in *C. difficile* testing, comparing treatment rates among test results.

Specific objectives include:

- To compare treatment rates in patients among possible GDH and toxin results
- To analyze treatment patterns in patients with GDH+ and Toxin- results
- To investigate whether patients with GDH+ Toxin- results are prescribed fewer antibiotics based on PCR testing result

We hypothesize that patients with GDH+ Toxin- results will show a limited use of antibiotics, demonstrating that the two-step algorithm helps in minimizing unnecessary treatments in those with presumed *C. difficile* colonization.

Methods

The study was conducted via a retrospective chart review of 7732 hospital encounters in the Beaumont Health System Hospitals Royal Oak, Troy, and Grosse Point from March 2021 through November 2022. The timeframe reflects *C. difficile* policy change that occurred in November 2019 and allows for an adjustment period to limit the impact of COVID-19. Patients included in the study were those over the age of 18 who were admitted to one of the three hospitals and were tested for *C. difficile* infection. Variables collected for each encounter included testing results, length of stay, patient age, race, sex, and prescribed antibiotic treatment. Data was pulled via a secure EMR retrieval program and stored in a locked Sharepoint. IRB approval provided a waiver of patient consent and the study was conducted under IRB 2023-041.

Results

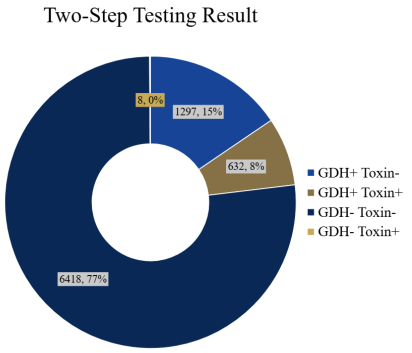

Figure 1. Reported testing result for the two-step, GDH and toxin testing conducted from March 2021 through November 2022.

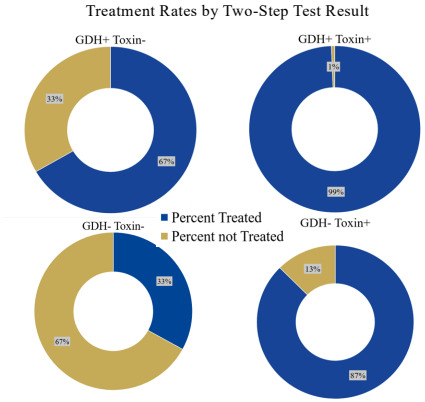

Figure 2. Percent of individuals who had treatment ordered during their hospital stay based on the two-step testing result. Treatments included metronidazole, enteral route vancomycin, fidaxomicin, and rifampin.

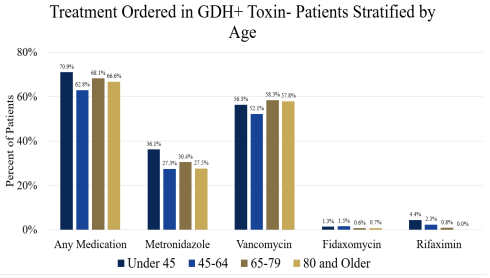

Figure 3. Treatment ordered in patients with GDH+ Toxin- test results during their hospital stay categorized by age at testing order. Percentages are not cumulative as some patients had multiple medications ordered.

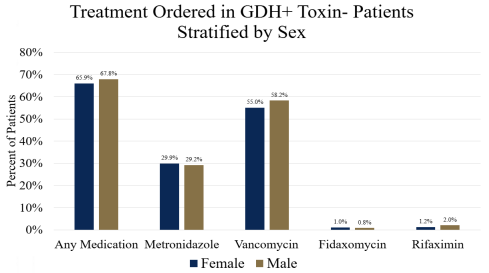

Figure 4. Treatment ordered in patients with GDH+ Toxin- test results during their hospital stay categorized by patient sex. Percentages not cumulative as some patients had multiple medications ordered.

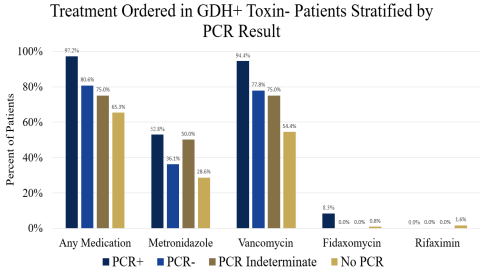

Figure 5. Treatment ordered in patients with GDH+ Toxin- test results during their hospital stay categorized by subsequent PCR testing result. Percentages not cumulative as some patients had multiple medications ordered.

Conclusions

Despite the change in testing to a two-step EIA algorithm in an effort to reduce the treatment of patients colonized with *C. difficile*, two-thirds of GDH+ Toxin- patients were still treated for CDI. Treatment demonstrated little variance among different patient age groups or sex. Patients with PCR testing were more likely to be treated regardless of testing result, and PCR positivity correlated highly with treatment, despite PCR positivity not being indicative of active toxin production. Thus, despite the change in testing, there were high rates of treatment in patients who likely exhibit colonization with *C. difficile* and not active CDI. This highlights the need for continued antibiotic stewardship and additional provider education regarding testing methodology to reduce inappropriate or unnecessary treatment.

This study exhibited limitation in methodology as treatment length and discontinuation were not controlled for. There exists the possibility that treatment in GDH+ Toxin- patients were prescribed prior to final testing result and were later discontinued. The study is also limited as it does not further categorize patients based on immune status or other risk factors known for significant CDI complications. Further research should seek to clarify these sub-categories and expand comparison to treatment rates prior to the new two-step algorithm.

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