Tuning Down PCR Sensitivity Reduces Treatment for Clostridioides difficile Infection in Toxin-Negative Patients With No Increase in Adverse Outcomes

Matthew M. Hitchcock, MD, MPH;1 Marisa Holubar, MD, MS;1 Lucy S. Tompkins, MD, PhD;1 Niaz Banaei, MD.1,2

Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA;1 Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA

Contact: Matthew Hitchcock
mh286@stanford.edu

Abstract

Background: Studies have shown that toxin detection identifies those who require treatment for C. difficile infection (CDI) and free toxin can be predicted with high negative predictive value from PCR cycle threshold (CT). CT-toxin was introduced at our institution in two phases: from Oct 2016 to Oct 2017, CT-toxin was reported with the PCR result (split reporting) and CDI therapy was discouraged if CT-toxin was negative (PCR+/CT-tox-). Interim analysis showed that CDI treatment had no effect on outcomes in these CT-toxin-negative patients, so starting Nov 2017, only CT-toxin was reported. Outcomes in PCR+/CT-tox- patients treated during split reporting and untreated during the toxin-only period are detailed here.

Methods: Patients tested from Oct 2016 to Feb 2018 with a positive Xpert C. difficile PCR (Cepheid, Sunnyvale, CA) and CT-tox- results were included. Clinical data were collected by retrospective chart review in the split reporting period and prospective review in the toxin-only period and analyzed using SPSS at α=0.01.

Results: Of 186 unique PCR+/CT-tox- patients during split reporting, 99 (53%) were treated, compared to 6 (18%, n=51) in the toxin-only period (p=0.001). In comparing treated patients during split reporting to untreated patients during toxin-only reporting (n=45), there were no significant differences in age, sex, antibiotic use, CDI in the prior 6 months, Charlson Comorbidity Index, patient location, immune status, or data at testing, including WBC count, creatinine, albumin, and stools/day. There were no cases of fulminant CDI in either group and no difference in outcomes (Table 1).

Conclusion: Reporting of CT-toxin alone significantly reduced treatment for CDI compared to split reporting in CT-toxin-negative patients with no increase in adverse outcomes in short-term follow-up. Further study is needed to confirm these findings in a larger cohort.

Background

• Multiple studies have shown that patients who are positive for C. difficile by direct toxin assays have increased duration of diarrhea, longer hospital stays, and increased mortality compared to patients positive by NAAT alone, and the latter patients have outcomes similar to those with negative results by all methods.

• The Stanford clinical laboratory validated the use of the cycle threshold (CT) from the Xpert C. difficile PCR (Cepheid, Sunnyvale, CA) to predict toxin positivity with high negative predictive value at a specified cut-off value.

• From Oct. 2016 to Nov. 2017, the CT-toxin was reported along with the Xpert PCR result at our institution (split reporting), with therapy being discouraged in patients with a PCR+/CT-tox- result, resulting in a treatment rate among these patients of 53%, and an absolute reduction in treatment of PCR+ patients of 15%.

• As interim results showed no difference in outcomes between treated and untreated CT-toxin-negative patients, the CT-toxin result began to be reported alone in Nov 2017. This poster provides the first reported results following this change.

Methods

All unique patients with a positive Xpert C. difficile PCR and a negative CT-toxin result from Oct 2016 to Feb 2018 were included in this study, which covered the split reporting period and the initial months of toxin-only reporting. During the toxin-only reporting period, PCR+/CT-tox- results were reported as a negative result, though the full PCR result could be obtained on request by infectious disease providers. Chart review was performed retrospectively for the patients in the split reporting period and prospectively during the toxin-only period as part of a safety and quality assessment. Treatment status was determined, and patients were followed for 8 weeks after the positive test to evaluate for subsequent development of CT-toxin-positive CDI. Clinical data at testing were also collected. Categorical variables were analyzed with the Chi squared test and continuous variables were analyzed with the Student t-test or Mann-Whitney U test using SPSS v. 24 (IBM Analytics, Armonk, NY). Due to multiple comparisons, a wass set at 0.01. Survival analysis was also performed using SPSS v. 24 at α=0.05.

Results

• Of 186 unique PCR+/CT-tox- patients during the split reporting period, 99 (53%) were treated, compared to only 6 of 51 patients (12%) in the toxin-only period (p=0.001; Figure 1).

• During toxin-only reporting, 3 patients were treated due to recent positive results (2/3 on therapy at time of re-testing), 2 were treated empirically, and 1 was treated for persistent pseudomembranous colitis (PMC).

• There were no significant differences in the clinical attributes or outcomes of the treated patients (n=99) in the split reporting period and untreated patients (n=45) in the toxin-only reporting period (Table 1; Figure 2).

• There were no cases of fulminant CDI in either group (which were seen in CT-toxin-positive patients) and all mortality was attributable to underlying disease states.

Figure 1. Treatment rate of PCR+/CT-tox- patients was significantly lower after shifting from reporting of both PCR and CT-toxin (split reporting) to CT-toxin alone (p=0.001).

Days To Toxin-Positive Conversion Event

• Toxin-only reporting reduces the treatment rate in PCR+/CT-toxin- patients with no increase in all-cause, 30-day mortality or time to diarrheal resolution compared to treated PCR+/CT-tox- patients during the split reporting period.

• The rate of subsequent development of CT-toxin-positive CDI within 8 weeks was low and not significantly different between treatment groups.

Conclusion

• Tuning down PCR sensitivity based on sensitive toxin prediction reduces treatment in PCR+/CT-toxin- patients with no increase in adverse outcomes.

• This study provides direct evidence that PCR+/CT-toxin- patients have similar outcomes regardless of treatment status, suggesting that treatment with anti-C. difficile antibiotics in this group may have limited effect on the rate of later CDI and related complications.

• Further studies in a larger cohort are underway to confirm these initial findings.

• Increasing the C. difficile PCR specificity through toxin prediction appears to be a viable testing strategy to reduce overtreatment.

Table 1. Patient characteristics and clinical/laboratory data at the time of testing, as well as rates of subsequent development of CT-toxin-positive CDI and all-cause mortality in short-term follow-up among CT-toxin-negative patients. Categorical variables are presented as counts with percentages and numerical variables are shown as means with standard deviation except for the Charlson Index, which is shown as median and interquartile range (IQR).

References


