Open Forum Infectious Diseases

MAJOR ARTICLE

Changing Results to Change Results: Nudging Antimicrobial Prescribing for *Clostridium difficile*

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Background. Patients who test positive for *Clostridium difficile* by polymerase chain reaction (PCR), with a negative toxin enzyme immunoassay (EIA), are commonly colonized and do not require treatment. However, clinicians often treat based on a positive PCR result regardless of the toxin EIA result. We evaluated the clinical impact of a microbiology reporting nudge, changing from a report that included both assay results along with treatment recommendations to one that suggested clinicians consider *C difficile* colonization or early infection.

Methods. We conducted a retrospective cohort study of all adult patients admitted to a large multisite community hospital with a positive *C difficile* PCR result and negative toxin EIA from January 1, 2016 to June 30, 2018. We examined total days of therapy (DOT) and impacts on clinical outcomes.

Results. One hundred ninety-nine episodes occurred preintervention and 165 episodes occurred postintervention. The mean DOTs per episode decreased from 13.6 to 7.9 days (difference −5.8 days; 95% confidence interval, −3.9 to −7.6) postintervention, with statistical process control charts suggesting special cause variation. Patients receiving no treatment increased from 6.5% to 23.6% postintervention ($P < .0001$). No significant changes in subsequent toxin positive disease (9.0% vs 6.7%), colectomy (0% vs 0.6%), mortality (7.5% vs 12.1%), or length of stay (18.5 vs 16 days) were observed.

Conclusions. Microbiology reporting nudges raising the possibility of *C difficile* colonization were associated with altered prescribing, reinforcing a postanalytic strategy for invoking change. Decreases in antimicrobial prescribing occurred without increasing subsequent disease or other adverse outcomes, suggesting a safe strategy for decreasing unnecessary treatment of *C difficile* colonization.

Keywords: antimicrobial stewardship; *Clostridium difficile*; laboratory reporting.

Clostridium difficile infection (CDI) is one of the most common causes of healthcare-associated infection. Although rates of other healthcare-associated infection have decreased, rates of CDI have increased more than 200% since 2000 [1, 2]. The increased incidence has corresponded to the increased uptake of molecular assays for *C difficile* detection. Data from the Centers for Disease Control and Prevention show that switching from toxin-based testing to polymerase chain reaction (PCR)-based testing increases CDI incidence by 43%–67% [5]. The clinical relevance of *C difficile* detected by PCR in the absence of detectable toxin is controversial. Studies have shown no difference in patient outcome when a toxin-based enzyme immunoassay (EIA) is utilized with suppression of PCR results [3]. This suggests that exclusive reliance on molecular tests such as PCR to diagnose CDI may result in misdiagnosis and subsequent complications from unnecessary treatment or incorrect diagnoses.

The presentation of microbiology reports has been shown to impact on prescriber behavior [4]. We sought to measure the impact of providing additional interpretation of a positive PCR test result while preserving prescriber autonomy for prescribing when there was a concern of a high pretest probability of active disease and a false-negative toxin EIA result. In March of 2017, we implemented a new reporting protocol that suggests the likelihood of colonization for patients who tested positive for *C difficile* by PCR but had a negative toxin EIA. The purpose of this study was to determine the impact of the nudge from the microbiology laboratory on antimicrobial prescribing and clinical outcomes in this patient population.

METHODS

We conducted a retrospective cohort study at a large tertiary care community hospital, housing approximately 1400 inpatient beds distributed between 2 sites in Mississauga, Ontario, Canada. The study population included all adult patients (>18 years) admitted to hospital with a positive *C difficile* PCR result and negative toxin EIA. The preintervention phase ran from January 1, 2016 to March 28, 2017. The postintervention phase was from March 29, 2017 to June 30, 2018. Patients dying within 24 hours of testing were

Received 20 May 2020; editorial decision 7 December 2020; accepted 15 December 2020.

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Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofaa605

excluded. Recurrent episodes were included if they were off treatment and greater than 7 days from initial testing.

At baseline, if testing yielded a positive PCR but negative toxin EIA (PCR^+/EIA^-) result, laboratory reporting indicated "*Clostridium difficile* cytotoxin B gene detected". It also included treatment recommendations for CDI. On March 29, 2017, PCR^+/EIA^- results were reported as "*Clostridium difficile* organism present but toxin not detected by EIA. Consider *C difficile* colonization or early infection." Treatment recommendations for CDI were no longer included. Throughout the entire study period, testing with a positive toxin EIA had the toxin result reported, along with treatment recommendations. No changes in *C difficile* treatment recommendations occurred at Trillium Health Partners (THP) during the study period (Supplementary Appendix A).

The primary outcome was total days of therapy (DOT) for metronidazole, oral vancomycin, and fidaxomicin. Special cause variation for the intervention was evaluated with statistical process control (SPC) charting for the study period. Secondary outcomes included subsequent toxin positive disease, colectomy, all-cause mortality, and length of stay (LOS). Mortality, possibly attributable to *C difficile*, was assessed by an unblinded infectious diseases physician if there was evidence of active colitis or septic shock without another cause. The χ^2 tests, Mann-Whitney tests, and 2-sample *t* tests were also applied to both primary and secondary outcomes as appropriate. X-mR SPC charting was used to look for special cause variation in DOT, and a P-chart was used to analyze whether the proportion of patients receiving no treatment showed special cause variation.

This was an evaluation of a quality improvement measure that was implemented based on current evidence in the literature. The study included appropriate countermeasures of unintended outcome, including death, colectomy, and recurrent infection to verify the safety of the current intervention.

Patient Consent Statement

This study was approved by the Trillium Health Partners Research Ethics Board with waiver of consent.

RESULTS

One hundred ninety-nine episodes were identified in the preintervention group, and 165 episodes were identified in the postintervention group. Baseline characteristics are presented in Table 1. There were no significant differences in patient characteristics between groups.

The change in distribution of DOTs in the pre- and postintervention groups is demonstrated in Figure 1. Total days of therapy decreased significantly in the postintervention group, from a mean of 13.6 days to 7.9 days (−5.8 days; 95% CI, −3.9 to −7.6). Statistical process control charting suggested special cause variation (Figure 2) at the time of the intervention. The proportion of patients receiving no antibiotic therapy also increased significantly from 6.5% to 23.6% after the reporting change (OR, 4.5; 95% CI, 2.3–8.7). Again, SPC charting indicated special cause variation (Figure 3) at the time of the reporting change.

No significant change in the number of patients who subsequently developed toxin positive disease (9.0% vs 6.7%), patients undergoing colectomy (0% vs 0.6%), or mortality (7.5 vs 12.1%) was seen between the pre- and postintervention groups. The pathology from the patient who underwent colectomy revealed ischaemic bowel as the diagnosis (Table 2). None of the deaths were attributed to *C difficile*. When the entire cohort was evaluated, there was no significant difference in mortality based on whether patients received treatment for *C difficile* (11.5% vs 9.3%; $P = .61$). Hospital LOS (19 days vs 16 days) was not significantly different pre- and postintervention ($P = .14$)

DISCUSSION

Guidelines suggest utilizing a toxin-based EIA along with PCR testing to help clinicians distinguish between active infection and colonization. We theorized that cognitive biases may lead clinicians who see a positive PCR result, even with a negative toxin EIA result, to prescribe unnecessary treatment. In this study, we examined the effects of adopting a toxin-dominant strategy in the way *C difficile* results are communicated to clinicians by suggesting the possibility of colonization in PCR^+/EIA^- patients [6]. Our study demonstrated that a reporting change, attempting to nudge clinicians towards the possibility of colonization in PCR^+/EIA^- patients, was associated with a behavioral change with a decrease in antimicrobial prescribing. A 42.5% reduction (−5.8 days; 95% CI, −3.9 to −7.6) in total days of therapy was seen after the change in reporting. A significant increase in the proportion of episodes with no

Table 1. Comparison of Pre- and Postintervention Cohorts

Characteristic	Preintervention	Postintervention	*P* Value
Age at episode, median (IQR), years	70 (58–82) n = 199	75 (59–82) n = 165	.40
Female sex, %	50.3	55.2	.35
WBC, median (IQR), $\times 10^9$/L	9.95 (6.7–14.1) n = 180	10.0 (6.8–14.1) n = 151	.91
Creatinine, median (IQR), µmol/L	84.5 (61–142.5) n = 180	97.5 (65–165) n = 152	.06
Albumin, g/L	26 (22–31) n = 62	26 (23–30) n = 38	.85

Abbreviations: IQR, interquartile range; WBC, white blood cells.

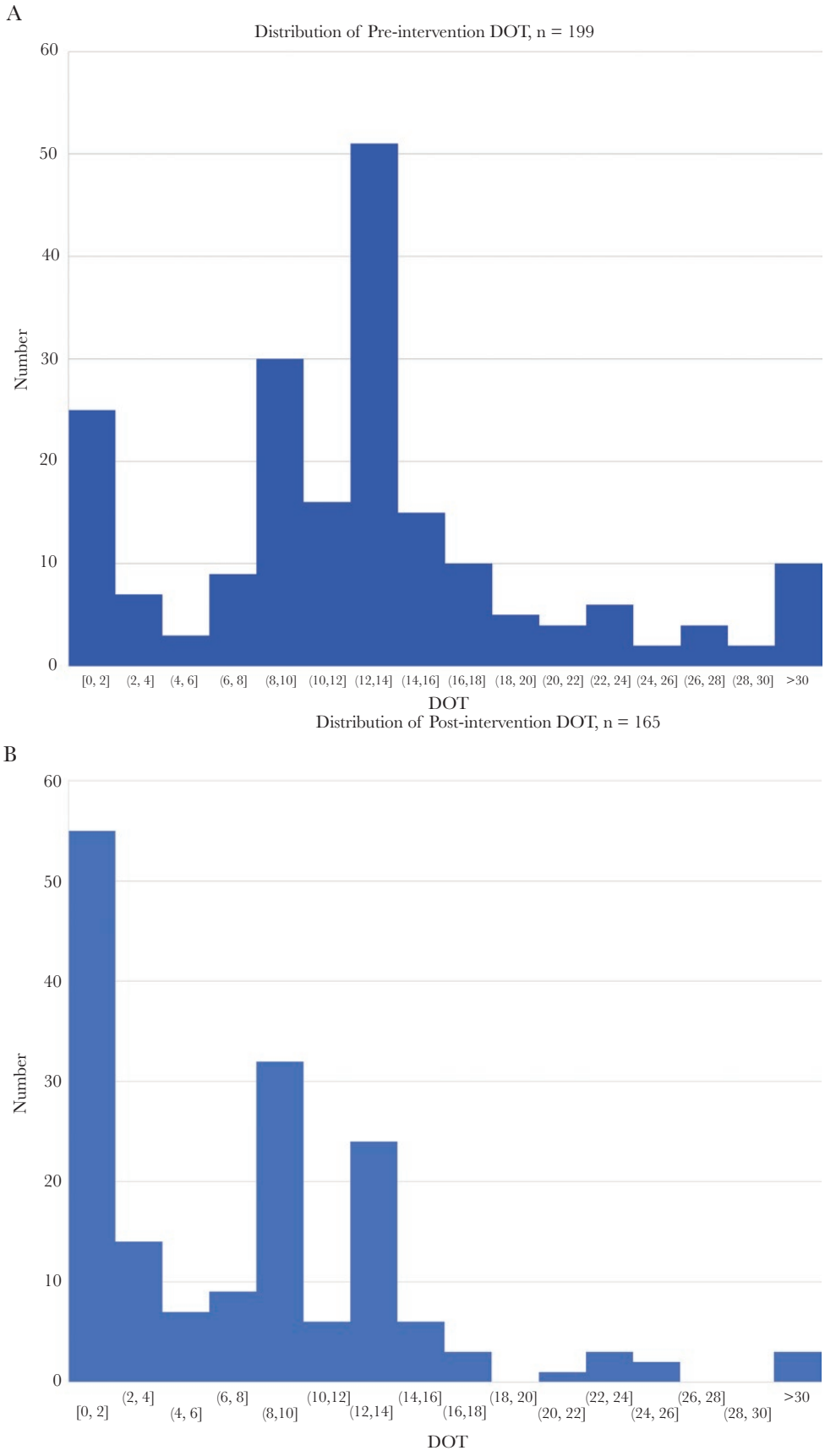

Figure 1. Histogram showing distribution of antibiotic prescribing preintervention (a) and postintervention (b).

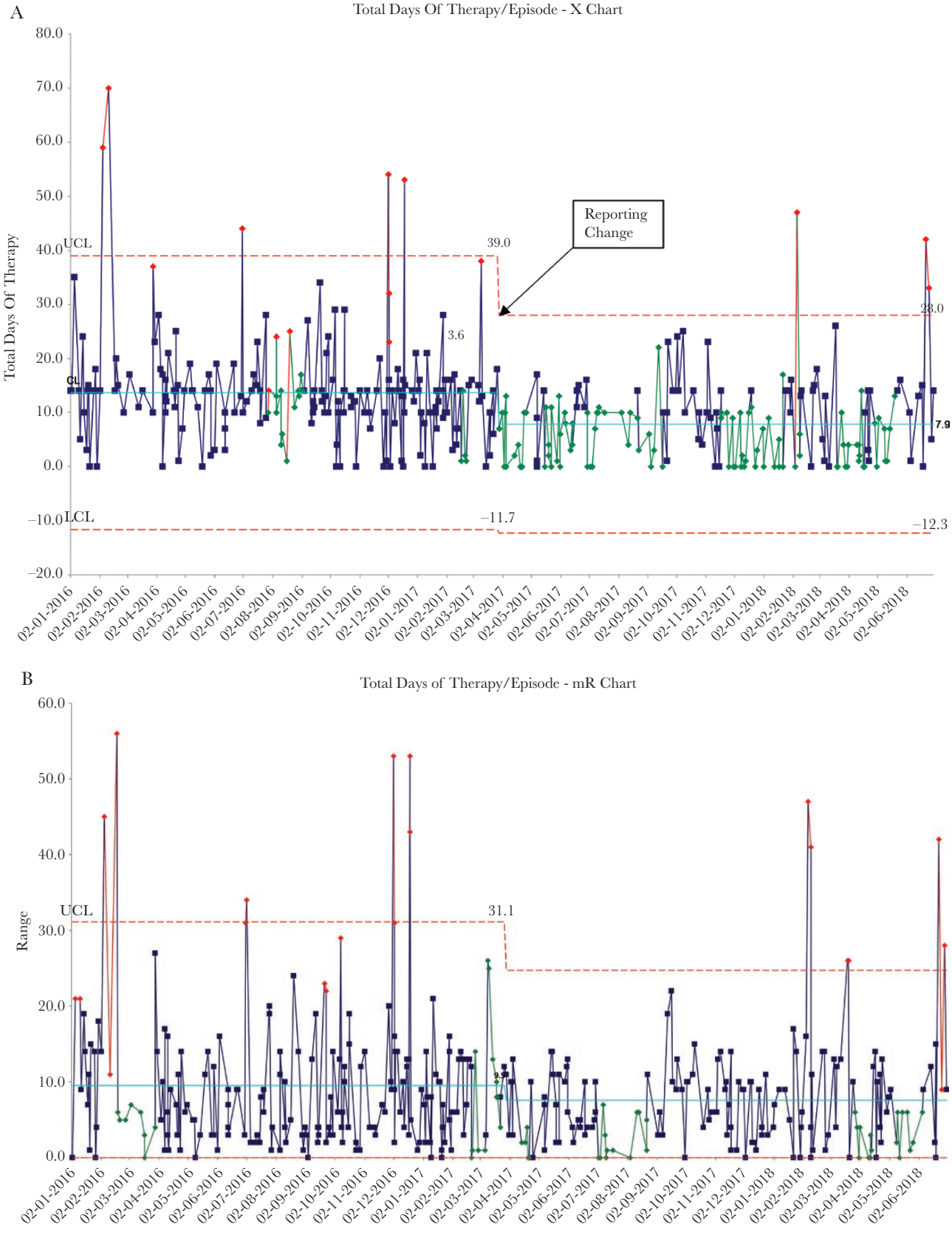

Figure 2. Statistical process control charting of total days of therapy for each individual patient indicating special cause variation at the time of our reporting change. X-mr control charts monitor variation over time identifying whether a process is in control or whether there are special causes of variation. Green points on the X-chart (a) indicate days of therapy with special cause variation that are lower then expected if the process were in control. The mR chart (b) charts the moving range, ie, the difference in consecutive values. Special cause variation on either chart can be considered significant.

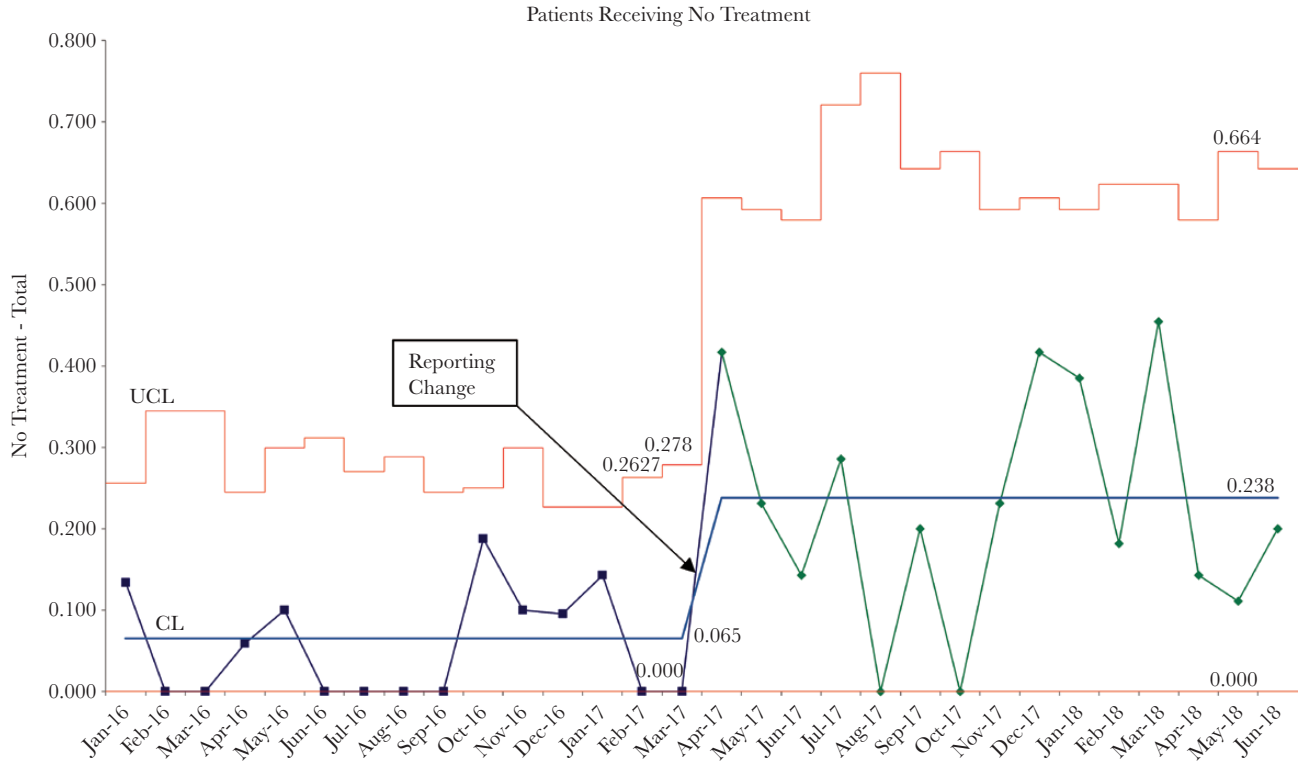

Figure 3. Statistical process control charting of the proportion of patients receiving no antibiotic therapy indicating special cause variation at the time of our reporting change. Green points on the P chart indicate special cause variation, with a proportion of patients receiving no therapy that is higher then expected if the process were in control.

prescribed antibiotics also occurred (odds ratio, 4.45; 95% CI, 2.28–8.68). The SPC charting indicated special cause variation at the time of the reporting change for both outcomes. The SPC charting for DOT also indicated periods and episodes in the postintervention group where there was no special cause variation. We are not able to discern whether this was related to clinical factors or loss of effect from the reporting change. However, there were no other hospital interventions for *C difficile* during the study period, and there was a sustained increase in the proportion of episodes with no treatment, suggesting the change in reporting was having an ongoing impact. Our results are consistent with other reports indicating that providing additional interpretation on microbiology reports can have an impact on prescribing behavior. Interpretation of the test result and treatment decisions were still left to the physician, but the reporting change aimed to encourage alternative thinking and give physicians with a low pretest probability more confidence in choosing to stop or not initiate treatment. The role of various diagnostics was identified in the 2017 Infectious Diseases Society of America Clinical Practice Guidelines for *Clostridium difficile* as an area that required additional research. Analytic interventions are often the focus, but postanalytic interventions such as this are not mentioned but represent an additional avenue for research [7].

Studies have also suggested that basing treatment decisions on toxin testing is safe, but this remains controversial

Table 2. Summary Outcomes Between the Pre- and Postintervention Groups

	Preintervention	Postintervention	OR	
Outcome	N = 199	N = 165	(95% CI)	*P* Value
Total DOT, median days (IQR)	14 (10–16)	8 (1–13)	N/A	*P* < .0001
No antibiotic treatment, n (%)	13 (6.5)	39 (23.6)	4.5 (2.2–8.7)	*P* < .0001
Subsequent toxin positive disease, n (%)	18 (9.0)	11 (6.7)	0.72 (0.33–1.57)	*P* = .40
Colectomy, n (%)	0 (0)	1 (0.6)	N/A	*P* = .27
Death, n (%)	15 (7.5)	20 (12.1)	1.69 (0.84–3.42)	*P* = .14
LOS, median, days	19	16	N/A	*P* = .14

Abbreviations: CI, confidence interval; DOT, days of therapy; IQR, interquartile range; LOS, length of stay; N/A, not applicable; OR, odds ratio.

[3]. Despite a significant decrease in antibiotic utilization and a significant increase in the proportion of episodes receiving no treatment, we did not see any significant difference in adverse outcomes. There was no increase in subsequent toxin-positive disease in the postintervention group or in patients from the whole cohort who received no treatment (data not shown). One colectomy occurred in the postintervention cohort, but pathology subsequently showed ischaemic bowel without evidence of *C difficile*. Death was not attributed to *C difficile* in any of the 35 cases seen in the entire cohort, as judged by an infectious disease physician. Of note, 29 of these patients did receive a course of treatment for *C difficile* (14 of 15 in the preintervention and 15 of 20 in the postintervention, $P = .25$), but the absence of treatment was not associated with an increased risk of death in the whole cohort.

Results are limited by the retrospective nature of the study. Data on resolution of diarrhea could not be reliably obtained from chart review, although previous studies have shown no differences in time to resolution of diarrhea in patients managed with toxin-based testing, even if they are PCR positive [3]. We were unable to confirm whether prescribed antibiotics were taken after discharge. Generalizability may also be limited because these results are from a single institution, although it was made up of 2 sites that had been merged 3 years prior to the study. We used recurrent episodes, as opposed to unique patients, to reflect the impact of the change in reporting in the real-world setting. The presence of duplicate patients may have introduced some confounding. However, there were no significant differences in the number of duplicate patients in either group, and removing duplicate patients did not have a significant impact on outcomes (data not shown). The study was not powered to look at adverse outcomes, and therefore significant differences may not have been detected.

CONCLUSIONS

Our results reaffirm the impact of microbiology reporting on clinician prescribing behavior. Nudging clinicians towards colonization on microbiology reports can decrease antibiotic use in patients that test PCR^+/toxin EIA for *C difficile*. Our cohort also provides additional data on adverse outcomes in this population with no significant changes seen despite a decrease in antibiotic use.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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