

Propensity-Matched Cost of *Clostridioides difficile* Infection Overdiagnosis

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Background. *Clostridioides difficile* is the leading health care-associated pathogen, but clinicians lack a test that can reliably differentiate colonization from infection. Health care costs attributed to *C. difficile* are substantial, but the economic burden associated with *C. difficile* false positives is poorly understood.

Methods. A propensity score matching model for cost per hospitalization was developed to estimate the costs of both true infection and false positives. Predictors of *C. difficile* positivity used to estimate the propensity score were age, Charlson comorbidity index, white cell count, and creatinine. We used polymerase chain reaction (PCR) cycle threshold to identify and compare 3 groups: (1) true infection, (2) *C. difficile* colonization, and (3) *C. difficile* negative.

Results. A positive test was associated with \$3018 higher unadjusted hospital cost. Among the 3 comparisons made with propensity-matched negative controls (all positives [+ \$179; $P = .934$], true positives [−\$1892; $P = .100$], and colonized positives), only colonization was associated with significantly increased (+\$3418; $P = .012$) cost. Differences in lengths of stay (all positives 0 days, $P = .126$; true 0 days, $P = .919$; colonized 1 day, $P = .019$) appeared to underlie cost differences.

Conclusions. In the first *C. difficile* cost analysis to utilize PCR cycle threshold to differentiate colonization, we found high propensity-matched hospital costs associated with colonized but not true positives. This unexpected finding may be due to misdiagnosis of non-*C. difficile* diarrhea or unadjusted factors associated with colonization.

Keywords. *Clostridioides difficile*; cost analysis; diagnostic stewardship; propensity score matching.

Clostridioides difficile is the most common pathogen causing health care-associated infection and adds substantially to the morbidity, mortality, length of stay, and cost of hospitalized patients in the United States [1, 2]. The *C. difficile* real-time polymerase chain reaction (PCR) stool test, used by >70% of hospitals [3], is highly sensitive but cannot differentiate colonization from infection [4]. Inappropriate *C. difficile* testing in patients with low probability of disease may result in overdiagnosis and unnecessary treatment in up to half of hospitalized patients who test positive, which may contribute to the estimated \$5.4 billion annual health care cost attributed to *C. difficile* infection [4, 5]. *C. difficile* has profound economic impacts on the health care system, including \$3240–\$11 285 attributable cost per hospitalized case [6–10]. However, the economic burden

attributable to *C. difficile* overtesting and overdiagnosis has not been fully quantified [11].

C. difficile colonization can be defined as harboring a *C. difficile* strain capable of producing toxin but without the presence of detectable toxin [12]. Toxin gene PCR-positive patients who are toxin enzyme immunoassay negative are thought to fit the definition of colonization based upon various outcome analyses showing that these PCR/enzyme immunoassay (EIA)-discordant patients have similar outcomes as *C. difficile*-negative patients [4]. The *C. difficile*-colonized patients identified by our study as having a PCR $C_T \geq 30.9$ thus would have been unlikely to have symptoms due to *C. difficile* based on mounting evidence in the literature linking high C_T with low fecal organism burden, negative reference tests, clinical symptoms, and outcomes [13].

Real-time *C. difficile* PCR works by amplifying target DNA sequences through cycled biochemical reactions up to a threshold of detection using a fluorescent probe. The number of cycles required for detection, or cycle threshold (C_T), inversely correlates with organism burden. While the assay was originally designed for a positive/negative result, high C_T (≥ 30.9) is shown to have >98% negative predictive value compared with toxin assays [14] or cell cytotoxicity neutralization assay positivity [13]. Conversely, a low C_T (≤ 28.0) suggests high organism burden and predicts outcomes associated with *C. difficile*

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infection [4, 13, 14]. Thus, we proposed using cycle threshold data from a large cohort of *C. difficile* patients in order to analyze the cost associated with *C. difficile* colonization.

METHODS

Inpatients tested for *C. difficile* (PCR only, GeneXpert [Cepheid, Sunnyvale, CA, USA] platform, with qualitative positive/negative clinical reporting only) between January 1, 2014, and June 30, 2017, were included in the analysis. Notably, a Computerized Clinical Decision Support tool was implemented at the Medical Center for *C. difficile* testing beginning December 2016 (see [15] for details). Baseline and outcome data were collected from the University of Virginia Clinical Data Repository, a database containing administrative, clinical, pharmacy, and laboratory data gathered from the electronic medical record. Cost data were gathered directly from the UVA Finance Department reflecting actual costs attributed to patient accounts. Baseline clinical data included the closest available measurement within ± 48 hours of the test result (if multiple measurements were available, the maximum white blood cell count [WBC], creatinine, lactate, and albumin were used). The Charlson comorbidity index (CCI) was used as an independent variable to estimate comorbidity burden at the time of each test attempt.

C_T values (between 1 and the manufacturer-set maximum of 37.0) for all positive results occurring within the study period have been collected retrospectively using the matched (by MRN, date, and time) to individual positive *C. difficile* PCR test results obtained from the Clinical Data Repository. For hospitalizations with multiple associated *C. difficile* tests, patients were categorized as *C. difficile* positive if they had at least 1 positive result; in patients with multiple repeated positives, C_T was measured from the original result. Secondary analysis of cycle threshold data from 70 PCR samples co-tested using toxin EIA as part of an internal validation study showed results consistent with the literature; a high $C_T \geq 30.9$ optimized the negative predictive value for toxin assay (92%), and a lower C_T cutoff ≤ 28.0 improved the positive predictive value for toxin EIA (to 56%) (Supplementary Figure 1). *C. difficile*-positive patients were categorized into 3 groups, defined as (1) true positive (low $C_T \leq 28.0$), (2) colonized (high $C_T \geq 30.9$), and (3) indeterminate (C_T 30.8–28.1).

The primary outcome was total cost of hospitalization. Secondary outcomes occurring during the remainder of the hospitalization following the *C. difficile* test result were measured including transfer to an intensive care unit (defined as occurring any time during index hospitalization after test result), colectomy, mortality, and length of stay.

A propensity score measures the conditional probability of being assigned to a particular treatment group based upon a set of observed covariates [16]. Matched sampling based on a propensity score removes biases associated with confounding

information in nonrandom samples, with the added advantage of reducing the problem of matching on multiple confounding factors to 1 dimension [17]. Statistical comparisons using propensity score methods work well when observable covariates control for treatment assignment and characteristics of individuals in the treated and nontreated samples overlap [18–20].

To estimate a propensity score, a logistic regression model was created to evaluate the association between clinical covariates and any positive *C. difficile* test. Covariates were chosen for the model based on univariate analyses of baseline characteristics including age, sex, CCI, WBC, eosinopenia (defined as absolute count 0.0 cells/mm^3), lactic acid, creatinine, albumin, and hospital unit location. Relevant covariates included in the final multivariate model (used to calculate propensity scores) were age, CCI, $\text{WBC} \geq 15\,000 \text{ cells/mm}^3$, and creatinine $\geq 1.5 \text{ mg/dL}$ (see Supplementary Table 1 for results of the model applied to each analysis). Costs were then compared across groups using matches based on the propensity score, that is, the predicted value for a positive *C. difficile* test.

P values for categorical variables were obtained using the chi-square test. A Mann-Whitney *U* test was used for median cost comparisons and for non-normally distributed variables. For other variables (age, lactic acid/albumin concentrations), an independent-samples *t* test was used (2-tailed, equal variances not assumed). *P* values for individual cost components were adjusted for multiple comparisons using the Bonferroni method. Analyses were performed using R, version 3.4.1 (R Core Team, Vienna, Austria).

RESULTS

We identified 9419 episodes of hospitalization where *C. difficile* tests were performed in 7079 individual patients. *C. difficile*-positive patients were older (mean, 58.2 vs 56.4 years), had more leukocytosis (25.0% vs 21.6%), had evidence of renal insufficiency (26.2% vs 19.8%), and had higher median CCI (2 vs 1) (Table 1). Unadjusted cost analysis showed that *C. difficile*-associated total hospital costs were significantly higher compared with *C. difficile*-negative patients (median increase, \$3018; *P* = .001) (Table 2).

Our primary analysis with propensity score-matched *C. difficile*-negative controls (Table 3) demonstrated that *C. difficile* colonization was associated with significantly higher (\$3418; *P* = .0118) hospital costs, whereas a true diagnosis of *C. difficile* was not associated with increased cost. Colonized patients also had significantly higher total lengths of stay (1 day; *P* = .0144), length of stay post-test (1 day; *P* = 0.002), and a statistically nonsignificant trend toward higher cost per day (\$119; *P* = .119). Cost determinants that were significantly different between negative and colonized patients (adjusting for multiple comparisons) included Supplies, Surgery, and Components Not Otherwise Specified.

Table 1. Baseline Characteristics

	Negative (n = 7949)	True (n = 911)	Indeterminate (n = 200)	Colonized (n = 359)
Age, mean (SD), y	56.4 (18.9)	58.9 (19.8)	56.3 (19.2)	56.9 (18.4)
Gender, male	3718/7949 (46.8)	448/911 (49.2)	91/200 (45.5)	168/359 (46.8)
Charlson index, median (IQR)	1 (0–4)	2 (0–6)	2 (0–5)	2 (0–6)
Race, %				
White	80.9	80.8	82.5	78.3
Black	16.2	17.1	14.5	20.6
Asian	0.54	0.66	1.50	0.00
Other	2.35	1.4	1.50	1.11
Creatinine \geq 1.5 mg/dL	1572/7949 (19.8)	232/911 (25.5)	60/200 (30.0)	93/359 (25.9)
WBC $>$ 15 000 cells/mm ³	1716/7949 (21.6)	243/911 (26.7)	46/200 (23.0)	78/359 (21.7)
Eosinopenia	2604/4684 (55.6)	345/588 (58.7)	72/124 (58.1)	136/234 (58.1)
Intensive care unit	1546/7949 (19.4)	152/911 (16.7)	52/200 (26.0)	88/359 (24.5)
Lactic acid, mean (SD), ^a mg/dL	2.48 (2.74)	2.39 (2.51)	2.31 (1.86)	2.17 (2.29)
Albumin, mean (SD) ^a	3.03 (0.60)	2.96 (0.59)	3.06 (0.58)	3.00 (0.55)

Data are presented as No./total (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; WBC, white blood cell count.

^aLactic acid missing for 6406 negative, 705 true, 149 missing, and 276 colonized cases. Albumin missing for 4258 negative, 454 true, 99 indeterminate, and 178 colonized cases.

Given observations of significant upward cost skew and the potential for bias due to hospital-onset *C. difficile* infection (by the Centers for Disease Control & Prevention [CDC] definition occurring on hospital day \geq 3, which is known to be 1.5 times costlier than community-onset infection) [21], sensitivity analyses were performed by removing the upper 1% most costly hospital episode outliers and again by excluding lengths of stay $<$ 3 days (focusing only on hospital-onset *C. difficile*); similar trends were observed with each comparison, including higher costs seen in colonized patients compared with *C. difficile* negative (Supplementary Table 2). Post hoc analyses showed that a higher percentage of colonized tests occurred in the ICU compared with their matched negative controls.

DISCUSSION

This is the first cost analysis of *C. difficile* that incorporates PCR C_T data to help differentiate *C. difficile*-colonized cases. While adjusting for age, comorbid conditions, white blood cell count, and creatinine, patients with a high C_T (\geq 30.9) had higher hospital costs compared with matched *C. difficile*-negative patients; this was not seen among patients with a low C_T (\leq 28.0). We did not observe a significant increase in hospital cost associated with any positive *C. difficile* PCR test. These findings suggest that prior cost estimates, by lumping PCR-positive patients together, may have overestimated costs of *C. difficile* infection due to increased cost associated with a significant fraction of patients with *C. difficile* colonization.

Hospital length of stay was significantly longer in colonized compared with negative patients (including post-test length of stay) and appeared to be at least 1 (albeit relatively small) driver to increase cost, as differences in cost components were spread fairly evenly. Although severe complications of *C. difficile*

infection do rarely occur, up to 97% of patients will respond well to conventional treatment, with resolution of diarrhea within 6 days [22]. We hypothesize that misdiagnosis and therefore mismanagement of diarrhea not caused by *C. difficile* led to increased length of stay and cost. Significantly higher cost associated with surgery could also reflect test overuse among surgical patients. Further study regarding potential *C. difficile* misdiagnosis, unadjusted factors associated with cost/colonization, and service-specific testing practices are needed.

We observed no significant increase in cost with *C. difficile* diagnosis (any PCR-positive results), which is in contrast with the historical literature citing *C. difficile* as a costly disease (\$3240–\$11 285 increased attributable cost per hospital episode) [7–10]. However, previous studies that document increased costs to treating *C. difficile* patients likely suffer from selection bias. Important methodological advantages of our study may account for this discrepancy. Our analysis controls for selection bias on 2 important dimensions: First, our sample is drawn exclusively from patients tested for *C. difficile* and thus presumably should have overlapping risk factors for diseases (as evident by their selection by a clinician for testing). Furthermore, our entire pool of potential controls are proven *C. difficile* negative by a PCR with extraordinarily high ($>$ 99%) negative predictive value for *C. difficile* infection. This contrasts with other studies that rely on a more generic population from which to draw their cases/controls on the basis of International Classification of Diseases (ICD) codes, and the accuracy of ICD codes for identifying *C. difficile*-infected patients is mixed [23, 24]. Other cost analyses based on testing were very small (eg, number of *C. difficile* positives $<$ 300) [25, 26] and/or only based on toxin assay instead of PCR [27, 28], which is now used by most hospitals [3]. Second, we employ a propensity

Table 2. Unadjusted Hospital Costs According to *Clostridioides difficile* Diagnosis

	Negative (n = 7949)	All Positive (n = 1470)	True (n = 911)	Indeterminate (n = 200)	Colonized (n = 359)
Total cost, \$	14 516 (1603–51 064)	17 534 (5747–50 355) (P = .0001)	16 159 (5308–46 109) (P = .0925)	16 590 (5243–50 134) (P = .1446)	20 745 (8081–61 457) (P < .0001)

Data are presented as median cost in US dollars (interquartile range). True positive indicates *C. difficile* polymerase chain reaction cycle threshold (C_t) ≤28.0; indeterminate indicates C_t >28.0; colonized indicates C_t ≥30.9. P values reflect comparison with negatives.

Table 3. Propensity-Matched Hospital Costs and Outcomes According to *Clostridioides difficile* Diagnosis

	Negative (n = 4410)	vs	Positive (n = 1470)	P	Negative (n = 2733)	vs	True (n = 911)	P	Negative (n = 1077)	vs	Colonized (n = 359)	P
Total cost, \$	17 355 (4755–55 953)		17 534 (5748–50 355)	.934	18 051 (4750–56 821)		16 159 (5309–46 109)	.100	17 327 (5223–47 359)		20 745 (8081–61 457)	.012
Labs, \$	1458 (468–4193)		1336 (477–3486)	.355	1480 (474–4338)		1177 (434–3285)	.002	1399 (504–3902)		1779 (638–4031)	.999
Pharmacy, \$	1619 (371–5302)		1555 (486–4314)	.999	1666 (383–5617)		1367 (449–3621)	.090	1550 (389–4773)		2182 (646–5331)	.105
Therapy, \$	429 (0–2297)		532 (0–1898)	.999	488 (0–2358)		433 (0–1777)	.999	405 (0–1883)		728 (0–2041)	.053
Radiology, \$	614 (80–1897)		573 (100–1482)	.999	647 (84–1904)		531 (90–1398)	.240	596 (85–1733)		642 (185–1584)	.999
Acute bed, \$	3246 (0–8409)		3774 (0–9200)	.015	3364 (0–8330)		3615 (0–9033)	.887	3590 (0–8625)		4317 (831–9992)	.099
ICU bed, \$	0 (0–14 751)		0 (0–12 122)	.999	0 (0–15 794)		0 (0–11 064)	.158	0 (0–12 730)		0 (0–14 483)	.999
Supplies, \$	273 (0–2367)		387 (52–1939)	.033	324 (0–2466)		341 (39–1697)	.999	305 (0–1795)		469 (62–2306)	.013
Surgery, \$	0 (0–1794)		0 (0–1422)	.999	0 (0–2016)		0 (0–861)	.008	0 (0–1268)		58 (0–2695)	.015
Other, \$	522 (11–2378)		427 (11–2128)	.999	537 (11–2325)		300 (11–1791)	.036	458 (11–2202)		818 (23–2885)	.050
ICU at test	673/4410 (15.3)		218/1470 (14.8)	.690	443/2733 (16.2)		113/911 (12.4)	.013	138/1077 (12.8)		66/359 (18.3)	.009
Length of stay, d	7 (2–17)		7 (3–17)	.126	7 (2–17)		7 (3–16)	.919	7 (2–16)		8 (3.5–18.5)	.019
Post-test	4 (1–10)		4 (2–10)	.001	4 (1–10)		4 (1–10)	.042	4 (1–10)		5 (2–11)	.002
Cost per day, \$	2138 (1364–3306)		2013 (1411–2926)	.003	2143 (1404–3364)		1924 (1366–2766)	< .001	2106 (1428–3177)		2225 (1578–3172)	.119
Inpatient mortality	309/4410 (7.0)		87/1470 (5.9)	.149	213/2733 (78)		56/911 (6.1)	.099	65/1077 (6.0)		22/359 (6.1)	.949
ICU transfer	555/4410 (12.6)		190/1470 (12.9)	.734	342/2733 (12.5)		119/911 (13.1)	.666	123/1077 (11.4)		50/359 (13.9)	.206
Colectomy	61/4410 (1.38)		19/1451 (1.29)	.795	37/2733 (1.4)		11/911 (1.2)	.737	11/1077 (1.0)		6/359 (1.7)	.324

Data are presented as median (interquartile range) or No./total (%). No. values indicate the number of propensity-matched pairs with a 3:1 (negative:positive) ratio. True positive indicates *C. difficile* polymerase chain reaction cycle threshold (C_t) ≤28.0; colonized indicates C_t ≥30.9. "Therapy" refers to combined physical, occupational, and speech services. Abbreviations: ICU, intensive care unit; LOS, length of stay.

score matching technique that is particularly well suited for treatment studies in which the control population may have a range of characteristics that are dissimilar from the treatment sample, but from which a sample with overlapping characteristics can be drawn. The propensity matching allowed us to control for a variety of observable characteristics within each sample in a robust and intuitive manner. In addition, we identified patients with *C. difficile* based on a PCR-only test platform. Nonmethodological reasons for our observed lack of substantial cost attributed to *C. difficile* infection may reflect improvements in therapy (eg, transition to oral vancomycin as preferred initial therapy) [22], evolution of *C. difficile* pathogenicity, or other factors.

Our models included *C. difficile* cases occurring at any point during the hospital episode, and length of stay at *C. difficile* infection onset was not included as a potential confounding variable. In an attempt to parse the effect of hospital-onset infection, a second set of models was created using the subset of tests the CDC defines as hospital-onset, and similar trends were observed, including increased cost in colonized patients (Supplementary Table 2).

There are several significant limitations to this study. As a single-center cost analysis, our findings may reflect institution-specific practices surrounding *C. difficile* diagnosis, prevention, and management, such as our antimicrobial stewardship practices, clinical decision support tool for *C. difficile* testing [15], or institution-specific treatment practices. PCR C_T is an imperfect but practical marker of clinically relevant disease in the absence of a prospectively validated definition for *C. difficile* infection. C_T values (particularly low C_T) may misclassify infection compared with other assays (eg, Senchyna et al. reported a positive predictive value of only 81.7% compared with 3 toxin-based assays using a lower C_T cutoff ≤ 26.8), which may have artificially decreased the cost of true *C. difficile* cases [13]. Treatment data were not analyzed; however, with our hospital's use of PCR-only testing during the study period, the majority of PCR positive patients would have been likely treated for presumed infection. We did not factor long-term cost beyond the index hospitalization, such as hospital readmissions or social costs. Lastly, the increased post hoc percentage of colonized tests that occurred in the ICU compared with their matched negative controls could represent unmeasured or unadjusted factors associated with low-burden *C. difficile*-associated diarrhea, longer length of stay, and higher cost. However, baseline ICU status was intentionally excluded from the propensity model for lack of association with test positivity, and ICU bed-related costs did not account for a significant fraction of the differences in total cost.

Diagnostic stewardship designed to promote evidence-based testing is recommended by consensus guidelines [29] and improves *C. difficile* test utilization [11]. We demonstrated that the intervention was effective and safe and helps providers to accurately identify patients who are less likely

to have *C. difficile* infection (based on C_T data) [30, 31]. The findings of this cost analysis further support a strong financial incentive for diagnostic stewardship practices to prevent unnecessary *C. difficile* tests that are more likely to result in misdiagnosis.

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.

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Patient consent. The study was approved by the institutional review board, and written consent was waived due to the retrospective nature of the study.

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