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Reduced *Clostridioides difficile* Tests Among Solid Organ Transplant Recipients Through a Diagnostic Stewardship Bundled Intervention

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: *Clostridioides difficile* infection (CDI) is a frequent complication of solid organ transplantation, especially in the early post-transplantation period. Overdiagnosis of CDI is likely common in hospitals using nucleic acid amplification testing (NAAT), potentially leading to unnecessary iatrogenesis and cost. Recently, multiple studies have shown that computerized clinical decision support (CCDS)-based interventions can significantly reduce inappropriate *C. difficile* testing and healthcare facility-onset CDI events across hospitals and health systems. We aimed to determine if a CCDS-based intervention could reduce *C. difficile* testing and surveillance infection events among recent solid organ transplant recipients, a population at high risk for CDI. We also sought to determine the safety of the CCDS intervention.

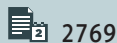
Material/Methods: Quasi-experimental census-adjusted interrupted time-series analyses were performed retrospectively to examine testing and CDI events pre- and post-intervention. Mortality and readmissions rates were also examined.

Results: A significant 33% relative reduction in tests and a nonsignificant trend towards fewer CDI events were observed following the intervention, without significant differences in mortality or 30-day readmission. A review of patients with positive *C. difficile* NAATs after prevented tests revealed no specific adverse events attributable to a possible delay in CDI diagnosis.

Conclusions: CCDS may be a helpful and safe adjunctive strategy to reduce unnecessary testing in accordance with guideline recommendations among solid organ transplant recipients.

MeSH Keywords: *Clostridium difficile* • Decision Support Systems, Clinical • Organ Transplantation

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Background

Clostridioides difficile (formerly *Clostridium difficile*) is the major pathogen causing healthcare-associated infection (HAI) in the USA, leading to significant morbidity, mortality, and cost [1]. Solid organ transplant (SOT) recipients suffer a higher incidence of *C. difficile* infection (CDI) compared to other hospitalized and postoperative patients [2,3]. CDI in SOT patients occurs most frequently during the first 3 months following transplantation, when antimicrobial use and immunosuppression tend to be highest [3,4].

Molecular detection of *C. difficile* toxin genes through highly-sensitive nucleic acid amplification testing (NAAT) is a common diagnostic approach for CDI. However, since NAAT can also detect toxigenic *C. difficile* in samples from asymptomatic carriers (patients who are colonized with *C. difficile* but do not have CDI), and CDI overdiagnosis is thought to be common. Recent studies suggest that up to 50% of hospitalized patients with a positive NAAT for *C. difficile* may not benefit from treatment [5,6]. To our knowledge, whether this is true in SOT recipients has not been reported. Positive tests in colonized patients who are not infected could lead to overtreatment and increased healthcare expenditures. Additionally, for SOT patients, unnecessary CDI treatment may lead to downstream drug reactions, immunosuppressant disruption, prolonged hospitalization, and promote antimicrobial resistance such as vancomycin-resistant enterococci [7].

CDI overdiagnosis could be explained by inappropriate testing of patients who are colonized with *C. difficile* and have low pre-test probability for infection. Improvement of diagnostic utilization using diagnostic stewardship is an increasingly recognized approach that hospitals use to reduce diagnostic error and cost [8]. Computerized clinical decision support (CCDS) systems, incorporated in the computerized physician order entry system, are one method to guide diagnostic decision-making.

Here we report a successful CCDS-based intervention used to decrease inappropriate *C. difficile* testing in a SOT recipient population.

Material and Methods

Intervention

The CCDS tool was designed as part of a system-wide effort to address *C. difficile* infection and improve test utilization based on established institutional criteria for appropriate *C. difficile* testing [9]. The 2-part CCDS first presented a duplicate order alert screen that listed any *C. difficile* result within 28-days. Next, algorithmized questions were presented to the ordering

providers in a step-wise fashion that were designed to encourage appropriate testing based on the 2010 Infectious Diseases Society of America (IDSA) *C. difficile* guidelines [10]. The ordering provider was encouraged to complete an order when they could attest that the patient had diarrhea (defined as ≥ 3 liquid stools within 24 hours) and either signs or symptoms of *C. difficile* infection (e.g., fever, abdominal discomfort, leukocytosis) or risk factors for infection (e.g. recent antibiotic exposure, abdominal surgery, age >60 years). This process would also be consistent with the recently updated 2017 IDSA and Society for Healthcare Epidemiology of America (SHEA) *C. difficile* guidelines which recommend NAAT testing alone (versus a multistep algorithm) and should only be performed on stool submitted from patients that meet “preagreed institutional criteria” for diagnostic testing [11]. A test was allowed to be ordered regardless of responses. Per laboratory protocol, non-liquid stool specimens would be rejected, and a test would not be performed. NAAT was done using the GeneXpert platform (Cepheid, Sunnyvale, CA, USA). In addition, during the intervention period, peroxyacetic acid/hydrogen peroxide-based cleaner was adopted hospital-wide, and antimicrobial stewardship performed CDI case reviews with feedback to providers; no other *C. difficile* or SOT-specific infection prevention measures were implemented during the study period.

The CCDS was bundled with educational efforts involving all nurses and other licensed independent practitioners (including flyers, a demonstration video, and emails) and a quality improvement project lead by graduate medical education (GME) house staff [9]. A *C. difficile* electronic display was produced for the institutional patient safety and quality dashboard that depicted real-time testing rates (including positive, duplicate, and prevented test attempts). The dashboard was visible to all hospital staff and administration with specific service line ascriptions, including transplant.

Study design

A quasi-experimental retrospective cohort study was done to analyze inpatient rates of *C. difficile* tests among patients that received a SOT between January 2014 and December 2017 at University of Virginia Health System (UVAHS), before and after introduction of a CCDS tool. The UVAHS Charles O. Strickler Transplant Center is a comprehensive transplant program that performed on average 185 adult SOTs per year (range 137–239) during the study period (49% kidney, 33% liver, 10% lung, 6% heart, 2% kidney/pancreas, and $<1\%$ pancreas). Monthly rates of NAAT orders, results, and order attempts prevented by the CCDS occurring over a 24-month pre-intervention period (December 2014 to November 2016) were compared to a 13-month post-intervention period (December 2016 to December 2017) after CCDS implementation on December 5, 2016.

Table 1. Demographic characteristics for *C. difficile* tests done on solid organ transplant recipients, pre- and post-intervention.

Baseline characteristics	Total tests		P
	Pre-(n=322)	Post-(n=169)	
Age, years, mean (SD)	52.7 (15.0)	49.4 (16.2)	.028
Gender, male (%)	198/322 (61.5)	92/169 (54.4)	.131
Transplant (%)			
Liver	141/322 (43.8)	34/169 (20.1)	<.001
Lung	69/322 (21.4)	44/169 (26.0)	.267
Kidney	43/322 (13.4)	57/169 (33.7)	<.001
Heart	45/322 (14.0)	16/169 (9.5)	.150
Pancreas	0/322 (0)	6/169 (3.6)	<.001
Multiple organ	24/322 (7.5)	12/169 (7.1)	.887
Time from Transplant, median days (min, IQR, max)	57.5 (3, 16–190, 931)	59 (3, 23–196, 1432)	.296

SD – standard deviation; min, minimum; IQR – interquartile range; max, maximum.

Outcomes

Our primary outcomes were the relative reduction in the rate of *C. difficile* tests and National Healthcare Safety Network (NHSN) reported CDI events. CDI events included combined community-onset (occurring on hospital day ≤ 3 in a patient not hospitalized within 28 days), community-onset health-care facility-associated (CO-HCFA) (occurring on hospital day ≤ 3 in a patient hospitalized within 28 days), and health-care facility-onset (occurring on hospital day ≥ 4) [12]. Secondary outcomes included all-cause mortality and 30-day readmission rates. Quantitative real-time polymerase chain reaction (qRT-PCR) cycle threshold values of positive results were also analyzed as a marker of pathogen burden in each group [5,13].

Analysis

Orders were labeled as prevented if providers initiated a NAAT order but aborted the order before it was electronically submitted. Baseline characteristics, all-cause mortality, 30-day readmission, and monthly rates of testing and CDI events were compared between the intervention groups [12].

Tests and CDI events were dated by order and collection date, respectively. Monthly rates were calculated using hospitalized patient-days for the cohort. *P* values were obtained using χ^2 test for categorical variables, independent samples *t*-test for continuous variables with normal distributions (2-tailed, equal variances not assumed), and Mann-Whitney U test for variables without a normal distribution (time from transplant to test, tests per patient, cycle threshold). In addition, interrupted

time series analyses were performed using quasi-Poisson models to assess change in total test and CDI events between pre- and post-intervention periods, using an offset of patient days. Statistical software R, version 3.4.1 (R Core Team, Vienna, Austria) was used to perform analyses. This study received approval from the UVa Internal Review Board (#20082) with a waiver of consent.

Results

Characteristics of the study population

Among the cohort of 769 patients, a total of 14 944 and 8822 SOT inpatient days were measured throughout the pre- and post-intervention periods, respectively. 27% (211 out of 769) of the cohort was tested at least once for *C. difficile* during the period of observation (139 individual patients during pre-intervention, 87 patients during post-intervention), resulting in a total of 491 inpatient tests (322 pre-intervention, 169 post-intervention). Baseline characteristics of patients at the time of each test were similar between groups, with the exceptions of older age, a higher percentage of liver transplants and lower percentages of kidney and pancreas transplants in the pre-intervention group (Table 1).

Primary outcomes

The CCDS bundled intervention was accompanied by a 33% reduction in the rate of *C. difficile* tests (189 results per 10 000 patient days pre-intervention versus 124 per 10 000 patient

Table 2. Testing rates and mortality, pre- and post-intervention.

	Total tests and events/patient days (average monthly rate per 10,000 patient days)		P
	Pre	Post	
Tests (total)	300/14,944 (203.3)	119/8,822 (135.6)	<.001
Liver	130/4,370 (289.7)	23/1,840 (133.0)	.001
Lung	68/1,855 (374.1)	34/1,632 (202.8)	.003
Kidney	41/3,508 (117.6)	36/2,342 (149.4)	.415
Heart	41/3,658 (119.4)	13/1,934 (58.5)	.066
Pancreas	0/0 (0)	3/41 (1000.0)	–
Multiple organ	20/1,553 (113.1)	10/1,033 (122.9)	.880
Rejected by lab	22/14,944 (15.4)	12/8,822 (14.4)	.878
Duplicate negatives	13/14,944 (8.4)	1/8,822 (1.3)	.004
Duplicate positives	5/14,944 (3.3)	0/8,822 (0)	.023
Prevented tests	–	38/8,822 (43.1)	–
CDI LabID Events (total)	45/14,944 (35.0)	15/8,822 (17.3)	.113
CO	9/14,944 (6.5)	3/8,882 (3.9)	.407
CO-HCFA6	11/14,944 (7.4)	3/8,822 (3.3)	.135
HO	25/14,944 (17.3)	9/8,822 (10.0)	.298
PCR cycle threshold, med (min, IQR, max)*	24.4 (18.1, 21.8-28.2, 36.2)	26.0 (18.6, 22.0-27.6, 36.8)	.651
Tests per patient, med (min, IQR, max)	1 (1, 1–2, 20)	1 (1, 1–2, 6)	.801
Mortality	49/14,944 (31.2)	35/8,882 (37.4)	.742
30-day readmission	546/14,944 (367.7)	284/8,882 (324.7)	.081

CDI LabID Events – *C. difficile* Infection National Healthcare Safety Network-reported Laboratory-Identified Events; CO – community-onset; CO-HCFA – Community-Onset Healthcare Facility-Associated; HO – healthcare facility-onset; med – median; min – minimum; IQR – interquartile range; max, maximum; PCR – polymerase chain reaction. * Cycle threshold data were missing for 4 pre-intervention results.

days post-intervention; $P < 0.001$) (Table 2). There was a trend towards reduced LabID CDI events (including NHSN-defined community-onset, community-onset healthcare facility-associated, and healthcare facility-onset) that was not statistically significant (35 per 10 000 patient days pre-intervention versus 17 positives per 10 000 patient days post-intervention; $P = 0.113$) [12]. Quasi-Poisson models of testing rates and CDI events demonstrated similar findings ($P < 0.001$ and $P = 0.122$, respectively) (Figure 1).

Out of 169 test attempts during the intervention period, 38 tests (22.5%) were prevented by the CCDS and 12 tests (7.1%) were rejected by the laboratory. Specific CCDS provider responses for prevented tests were not recorded; however, among the

119 orders completed during the intervention period, 7 tests (5.9%) were ordered despite guidance by the CCDS indicating an inappropriate test (3 for lack of diarrhea, 3 for lack of signs/symptoms of CDI, and no CDI risk factors, and 1 test for a duplicate of negative test).

Secondary outcomes

Duplicate-negative results (defined as any negative result ≤ 3 days after a previous negative) decreased from 8.4 per 10 000 patient-days (13 duplicate negatives) pre-intervention to 1.3 per 10 000 patient-days (1 duplicate negative) post-intervention ($P = 0.004$). Duplicate positive results (≤ 14 days after prior positive) decreased from 3.3 per 10 000 patient-days

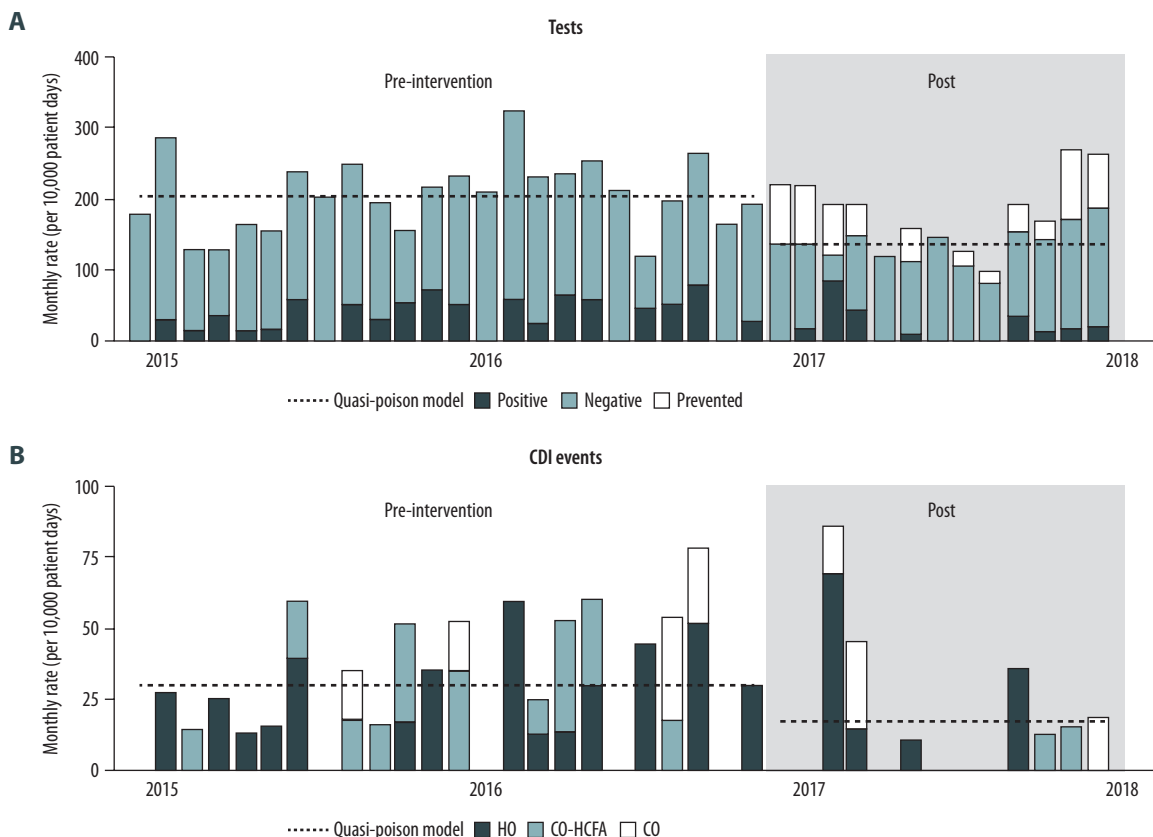


Figure 1. Monthly *Clostridium difficile* testing and surveillance, pre- and post-intervention. (A) *C. difficile* tests (by positive/negative result or prevented) and (B) *C. difficile* infection (CDI) events (by event type). Dotted lines depict predicted values using quasi-Poisson models. Note: 3 duplicate positive results were not counted as National Healthcare Safety Network reported CDI events.

(5 duplicate positives) pre-intervention to 0 duplicate positives post-intervention ($P=0.023$). The rate of laboratory rejection of stool samples was unchanged post-intervention (15.4 per 10 000 patient days versus 14.4 per 10 000 patient days; $P=0.878$). All-cause mortality rate was not statistically different between groups (31.2 per 10 000 patient days pre-intervention versus 37.4 per 10 000 patient days post-intervention; $P=0.742$) and there was a nonsignificant trend towards fewer 30-day readmissions (367.7 per 10 000 patient days pre-intervention versus 324.7 per 10 000 patient days post-intervention; $P=0.081$). Cycle thresholds were not statistically different between groups.

An in-depth review of prevented test patients identified 3 instances in 2 patients in which a subsequent positive result occurred within a week of the prevented test. A full clinical summary is provided in Table 3. In the first instance, a patient with aspiration pneumonia had a positive *C. difficile* NAAT 1 day after a prevented test. The Infectious Diseases consult team concluded that the test was likely to be a false positive and

recommended that *C. difficile* treatment be withheld. The patient clinically improved and diarrhea stopped without CDI-specific treatment. Of note, the cycle threshold value for the test was 27.8.

Patient 2 had 2 different instances in which a prevented test was followed by a positive result for *C. difficile* within the subsequent week. In the first instance, an increase in diarrhea and abdominal cramping prompted reconsideration for testing 3 days after a prevented test. Interestingly, the cycle threshold was just below the maximum cycle threshold cutoff of 37.0, suggesting that patient was likely colonized but not infected with *C. difficile* at that time. In the second instance, a duplicate *C. difficile* test was not indicated, because the patient had a positive *C. difficile* test at another facility 2 days prior and had already begun treatment for recurrent CDI. The cycle threshold for this result was 25.3.

Table 3. Case descriptions of patients with prevented tests, who are subsequently positive within 7 days.

Patient/episode	Time delay (H: M)*	Pertinent signs/symptoms prior to prevented test	Clinical changes during delay	PCR CT	Subsequent hospital course
1	25: 43	64yo female s/p DDKT developed bilious emesis on POD #6. CT demonstrating ileus, and hypoxemia, leukocytosis (WBC 26)	Repeat CT showed pneumonia and started on pneumonia-directed antibiotic therapy. WBC and clinical status improved	27.8	Loose bowel movement tested positive for <i>C. difficile</i> , but was felt to be a false positive. CDI-specific treatment was withheld at the direction of the Infectious Diseases consult team, and the patient clinically improved
2/a	73: 43	64yo female s/p DDKT admitted 1mo after transplant for delayed graft function. CT abdomen demonstrated post-operative fluid collections concerning for infection	Increased episodes of loose stools noted by providers	36.8	Treated with oral vancomycin. Subsequent kidney biopsy demonstrated acute antibody-mediated rejection for which she was treated with immunosuppression and plasma exchange. Renal function improved partially
2/b	2: 39	Acute-onset nausea, vomiting diarrhea developed 4wks after completing 10d of treatment for the above CDI episode. Diagnosed with recurrent CDI at outside hospital and retreatment was begun with oral vancomycin prior to transfer to our institution. For unclear reasons, testing was performed again	None	25.3	Treated for dehydration, recurrent CDI, and diarrhea improved. Intraabdominal fluid collections were sampled and confirmed presence of intraabdominal abscess. Discharged 4d later with a course of intravenous antibiotics

* Defined as the time between prevented test order and subsequent test order that resulted positive. H – hours; M – minutes; PCR – real-time polymerase chain reaction cycle threshold; yo – year-old; s/p – status-post; DDKT – deceased-donor kidney transplant; CT – computed tomography; WBC – white blood cell count; CDI – *Clostridium difficile* infection.

Discussion

We observed significantly decreased overall testing for *C. difficile* among SOT patients following introduction of a CCDS that targeted inappropriate testing. Rates of pre-intervention testing among our SOT cohort (203 tests per 10 000 SOT patient days) were similar to our general inpatient population (208 tests per 10 000 general inpatient days), as was the 33% reduction in overall testing for SOT (compared to a 41% reduction in general inpatients) [9]. Duplicate testing (both positives and negatives) was also significantly reduced post-intervention, with a notable reduction in the maximum range of tests per patient from 20 to 6 tests. In addition to reduced tests, we observed a 51% decline in the rate of all CDI events that was not statistically significant.

While our hospital-wide efforts were not tailored specifically to address *C. difficile* testing in SOT patients nor targeted to SOT providers, it is important to assess the impacts of the

intervention in this patient population. Diarrhea is common following SOT, occurring in 20–50% of all recipients, and is associated with increased graft loss and mortality [14]. Post-transplant diarrhea is often a challenging diagnostic dilemma, with an infectious etiology identified in only a third of cases (most commonly *C. difficile*, cytomegalovirus, or norovirus) [15,16]. Potential noninfectious causes of diarrhea among SOT recipients can be numerous, including drug side effects such as mycophenolate mofetil. We observed exceptionally high testing rates among lung and liver transplant recipients before and after CCDS, possibly owing to predisposing factors for diarrhea in these subpopulations, such as cystic fibrosis-related pancreatic insufficiency and the use of osmotic laxatives, respectively.

High NAAT CT values (i.e., >26.4–28.0) are associated with low pathogen burden, negative toxin A/B enzyme immunoassay, negative cell culture cytotoxin neutralization test, non-clinically severe CDI, shorter time to resolution of diarrhea, and could indicate *C. difficile* colonization rather than infection [5,17–19].

The similar median cycle thresholds observed in each group may reflect the small number of positive results and underlying high rates of colonization rather than a lack of difference in post-test probability for CDI as a result of the intervention.

We identified only 3 instances in 2 patients when a positive *C. difficile* NAAT followed a prevented test. In one instance, a duplicate positive test was inappropriately ordered. In the other 2 instances, the cycle threshold was elevated, suggesting *C. difficile* colonization rather than infection.

These results suggest that CCDS-based interventions can be effective and safe when used in the evaluation of diarrhea in organ transplant recipients, a patient population at high risk for *C. difficile* infection and *C. difficile*-associated complications. While CCDS-based interventions are generally considered safe [20], patient harm has occurred [21]. We and others have previously demonstrated that CCDS interventions can reduce unnecessary testing by 30% or more [12,22]; however, another guideline-based alerts have not significantly changed test utilization [23]. A range of factors may influence the success and safety of a diagnostic stewardship tool for *C. difficile*, such as which aspects of the guidelines are stressed, provider engagement/feedback, algorithmized design to minimize unnecessary clicks, and whether there are “hard stops” banning certain tests. We suspect the success a tool relates to a number of these factors.

Limitations

Our study offers a unique understanding of the impact of a particular diagnostic stewardship approach to *C. difficile* testing in a high-risk population. To our knowledge, this is the first report of the effects of CCDS-based diagnostic stewardship amongst SOT recipients. However, there are several limitations. As a quasi-experimental study, we could not account for time-varying confounding variables apart from the intervention and the longer-term durability of these findings is unknown. While the prevention of 38 tests could be linked to the CCDS tool, the overall reduced rate of testing may be attributed to our overlapping efforts. Impacts of individual aspects of our bundled intervention (CCDS tool, trainee involvement, provider education, electronic dashboard) could not be separately analyzed.

The reduction in CDI events theoretically represents hindrance of potential false-positives but could also reflect improved infection control efforts or prevention of appropriate testing. CCDS has not been associated with patient harm due to delayed or missed CDI treatment; however, many *C. difficile* diagnostic stewardship studies have not systematically addressed patient safety [24,25]. Furthermore, SOT patients are at higher risk for CDI and CDI-related complications compared to other patient populations and CDI doubles the risk of graft

loss [2,3,26]. The lack of specific encounter-level baseline data such as medications and comorbidities were a significant limitation to our study. Although complicated outcomes related to potential missed or delayed CDI diagnoses were not systematically examined in our SOT cohort, it is reassuring that 30-day readmission and all-cause mortality were not significantly increased post-intervention. Further, the 6.1% mortality rate among patients identified as having at least 1 prevented test (2 deaths/33 patients) was similar compared to the 7.9% cohort mortality rate. In addition, no instance could be identified in which prevention of a test led to delayed *C. difficile* diagnosis with adverse outcomes. Patient 1 was felt to have had a false positive result and clinically improved without CDI-directed treatment. An increase in gastrointestinal symptoms for Patient 2 led to reconsideration of testing in one instance, and repeat testing while being treated for CDI occurred in the second instance. However, it is possible that patients with a prevented test had CDI but were never tested in our institution and/or did not meet either of the primary adverse outcomes – all-cause mortality or 30-day readmission.

Future studies for CDI and other healthcare-associated infections (HAI)-related diagnostic stewardship should ideally involve measures of outcomes of patients at highest risk for potential complications, such as those with prevented tests [8].

Conclusions

Clinical criteria play a key role in the accurate interpretation of *C. difficile* tests [27]. One way to improve *C. difficile* diagnostic accuracy is to prevent tests from occurring that are clinically irrelevant or in patients that have low pretest probability for disease [8].

CCDS-based diagnostic stewardship may be helpful and cost effective in reducing unnecessary testing among patients at high risk for disease, such as SOT patients [28]. Additional studies are required to establish efficacy, safety, and the optimal diagnostic stewardship approach for this and other high-risk populations.

Acknowledgement

Multiple clinical departments at the UVA Health System were responsible for the concept, development, and implementation of the computerized clinical decision support tool including the Antimicrobial Stewardship Program, *C. difficile* Coalition, Graduate Medical Education Trainees, and Bioinformatics.

Conflict of interest

None.

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