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MAJOR ARTICLE

Impact of an Intervention Program on *Clostridioides difficile* Infections: Comparison of 2 Hospital Cohorts

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Background. *Clostridioides difficile* infection (CDI) occurs in various contexts and care settings and is managed by multiple specialists who are not experts in its management. While there are many initiatives to improve the diagnosis and avoid overdiagnosis, there is less focus on the overall management of the infection.

Methods. We studied a cohort of patients with a positive test result for toxigenic *C difficile* in 2 hospitals. Hospital A has a program that provides advice from an infectious disease specialist (IDS) and promotes continuity of care by providing a phone number to contact the IDS. Hospital B does not have any specific CDI program. The evaluation assessed the proportion of patients not treated (carriers or self-limited disease), adherence to Infectious Diseases Society of America guidelines, access to novel therapies, recurrence and mortality rates, and readmission and emergency department visits due to CDI. We assessed the program's effectiveness through a logistic regression model adjusted for covariates chosen by clinical criteria.

Results. Hospital A avoided more unnecessary treatments (19.3% vs 11.5%), provided access to novel therapies more frequently (35.3% vs 13%), and adhered more closely to current guidelines (95.8% vs 71.3%). Although the mortality and recurrence rates did not differ, the absence of an intervention program was associated with greater odds of admission due to recurrence (odds ratio, 4.19; $P = .037$) and more visits to the emergency department due to CDI (odds ratio, 8.74; $P = .001$).

Conclusions. Implementation of a CDI intervention program based on recommendations from IDSs and improved access to specialized care during the follow-up is associated with enhanced quality of CDI management and potential reductions in hospital resource utilization.

Keywords. CDI readmissions; CDI recurrence; *Clostridioides difficile* infection; continuity of care; IDS value.

Clostridioides difficile infections (CDIs) are associated with high rates of relapse, morbidity, and mortality and considerable health care costs [1–4]. CDI can occur in patients admitted to any hospital department, resulting in patients being treated by physicians from multiple specialties [5]. Over the past decade, major diagnostic and therapeutic advances have changed how the disease is managed, making it difficult for nonspecialists to update its optimal management. As a result, poor adherence to guidelines and heterogeneity in patient management have been reported [6, 7].

To date, the majority of antimicrobial stewardship programs for CDI have focused on optimizing diagnostic methods [8–10]. However, few studies have assessed therapeutic interventions for CDI. Most of these studies have focused on substituting medications or implementing protocols with a before-after design, and none of them have compared hospitals or departments with different degrees of expertise [11–16].

At our institution, an intervention CDI support program designed by the Department of Infectious Diseases has been in place for >5 years. We designed this study with the primary objective of assessing the effectiveness of the program by comparing results with those of another hospital in the same geographic region with no such specific program. We wanted to assess differences in the proportion of untreated patients (considered to be colonized), compliance with clinical guidelines, accessibility to new medications, use of hospital resources

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(emergency department visits and readmissions for CDI recurrence), and recurrence and mortality rates.

METHODS

We designed a retrospective cohort study of patients with positive test results for toxigenic *C difficile* in 2 hospitals (hospitals A and B) between 1 January 2021 and 31 December 2021. Hospital A is a 900-bed university referral hospital that offers transplant, cardiac, and neurosurgery services. Hospital B is a teaching hospital with lower complexity and only 380 beds.

At hospital A, a 3-step algorithm based on glutamate dehydrogenase (GDH) as a screening method was employed for diagnosis. When GDH is positive, the toxin is determined, and if the toxin is negative, the discrepancy is resolved by nucleic acid amplification test (NAAT). The diagnosis in hospital B was determined by a positive NAAT result. All positive results are confirmed by toxigenic culture in both hospitals. Neither hospital´s microbiology reports suggest the interpretation of polymerase chain reaction as colonization.

The CDI support program in hospital A has 2 basic elements:

- Assessment and advice for each patient with a positive test result (reports are provided in real time by the microbiology department to the infectious disease specialist [IDS]) to determine whether treatment is needed and, if so, what the most appropriate treatment would be and to review the appropriateness of other antimicrobial treatments
- Accessibility and continuity of care, in which patients receive verbal and written information about CDI in the form of a leaflet

Furthermore, they are provided with a contact phone number to call with any questions, new antibiotic prescriptions, or suspected recurrence. Outpatients with positive *C difficile* test results are contacted by an IDS, avoiding new emergency room visits and delays when starting treatment. Hospital B does not have a similar program. *C difficile* laboratory results are uploaded to the electronic medical record system, and patients are treated by their responsible physicians of any specialty. No IDSs are available at hospital B.

We used standardized definitions according to the clinical setting [15]. Recurrence was defined as the reappearance of symptoms of the disease after symptom resolution from the previous episode, with a positive test result that demonstrated the presence of toxigenic *C difficile* in the stool during the 12 weeks after the end of CDI treatment. The severity of the CDI episodes was established by means of the Zar scale [17]. Immunosuppression was defined as localized solid tumor, metastatic solid tumor, leukemia/lymphoma, HIV, or immunosuppressive treatment (including chemotherapy, corticotherapy, biologic treatment, and immunosuppressive treatment for transplant recipients).

As the current CDI guidelines of the Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases were updated in June 2021 [18, 19] and the previous CDI guidelines of the latter society were published in 2014, we chose to follow the 2018 IDSA guidelines when assessing adherence to clinical guidelines [20]. "Extended" fidaxomicin dosing was considered an appropriate treatment.

Statistical Analysis

Continuous variables are presented as mean with SD and median with IQR. Categorical variables are expressed as absolute frequencies and percentages. Shapiro-Wilk tests were performed to assess normality. Continuous variables were compared by a Student *t* test and Mann-Whitney *U* test according to their distribution. Associations between categorical variables were assessed by a chi-square test or Fisher exact test, when appropriate. Statistical analyses were performed with Stata version 17.0 (StataCorp LP). To evaluate the effectiveness of the program on the different outcomes (recurrence, mortality, and visits to the emergency department or readmission due to CDI), we used an adjusted logistic regression model. Covariate selection was not driven by univariate analysis. According to the clinical criteria, the model was adjusted for patient age, chronic kidney disease status, immunosuppression status, and previous episodes for all primary outcomes. To assess the impact during follow-up on visits to the emergency department and mortality, we also added severity, recurrence, and multiple recurrences. Differences are presented as odds ratios (ORs) and exact confidence intervals.

Patient Consent Statement

This study was approved by the local Medical Research Ethics Committee of the Ramón y Cajal Hospital (318-22). Individual informed consent was not considered necessary by the committee. The information was completed in an anonymized electronic database by physicians from both hospitals.

RESULTS

During the study period, there were 425 instances where toxigenic *C difficile* was detected, with 295 cases identified in hospital A and 130 cases in hospital B.

Out of the 425 recorded episodes, at hospital A there were 164 cases that tested positive for toxin and 131 that tested negative for toxin but positive for NAAT. Among them, 15 toxin-positive cases and 42 toxin-negative/NAAT-positive cases were evaluated as colonized or self-limited CDI and did not receive treatment (19.3%). At hospital B, only 15 cases (11.5%) were identified as carriers or self-limited episodes, thus not requiring treatment. Patients evaluated as carriers or self-limited episodes were different between hospital ($P = .049$).

Table 1. Characteristics and Comorbidities of Patients With Positive Test Results for *Clostridioides difficile*

	Median (IQR) or No. (%)		
	Hospital A (n = 238)	Hospital B (n = 115)	*P* Value
Demographics			
Age, y	73.7 (59.5–83.1)	79.7 (70.4–84.7)	.004
Male sex	106 (44.5)	57 (49.6)	.37
Comorbidities			
None	21 (8.8)	15 (13)	.022
Hypertension	128 (53.8)	77 (67)	.019
Myocardial infarction	27 (11.3)	9 (7.8)	.31
Congestive heart failure	24 (10.1)	32 (27.8)	<.001
Peripheral vascular disease	6 (2.5)	12 (10.4)	.003
Dementia	39 (16.4)	25 (21.7)	.22
COPD	12 (5)	19 (16.5)	<.001
Cerebrovascular disease	26 (10.9)	15 (13)	.56
Connective tissue disease	7 (2.9)	2 (1.7)	.72
Liver disease			
Child–Pugh A	3 (1.3)	1 (0.9)	.99
Child–Pugh B/C	9 (3.9)	0 (0)	.034
Hemiplegia	4 (1.7)	1 (0.9)	.99
CKD stage III or higher	52 (21.9)	24 (20.9)	.83
Diabetes mellitus			
Uncomplicated	44 (18.5)	24 (20.9)	.59
End-organ damage	6 (2.5)	7 (6.1)	.13
Localized solid tumor	39 (16.4)	11 (9.6)	.085
Leukemia/lymphoma	13 (5.5)	2 (1.7)	.10
Metastatic solid tumor	35 (14.7)	8 (7)	.037
HIV	6 (2.5)	0 (0)	.18
Immunosuppressive treatments	52 (21.9)	7 (6.1)	<.001
Immunocompromised	108 (45.4)	25 (21.7)	<.001
Charlson	2 (1–4)	2 (1–4)	.615

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Table 2. Episode Characteristics and Treatment

	No. (%)		
	Hospital A (n = 238)	Hospital B (n = 115)	*P* Value
Clinical setting			.24
Community-associated CDI	48 (20.2)	29 (25.2)	
HCFA			
Community onset	65 (27.3)	26 (22.6)	
Health care facility onset	120 (50.4)	54 (47)	
Indeterminate	5 (2.1)	6 (5.2)	
Episode			.86
First	188 (79)	90 (78.3)	.88
Second	41 (17.2)	19 (16.5)	.87
Multiple recurrences	9 (3.8)	6 (5.2)	.53
Admissions[a]	45 (38.1)	33 (54.1)	.041
Severity			.28
Not severe	172 (72.3)	74 (64.4)	
Severe	54 (22.7)	32 (27.8)	
Fulminant	12 (5)	9 (7.8)	
Diagnosis			
Toxin A/B	149 (62.6)	0 (0)	<.001
NAAT	89 (37.4)	115 (100)	<.001
Main treatment[b]			
Metronidazole	4 (1.7)	11 (9.6)	.001
Vancomycin	143 (60.1)	74 (64.4)	.44
Tapered vancomycin	16 (6.7)	8 (7)	.99
Metronidazole/vancomycin	8 (3.4)	8 (7)	.17
Fidaxomicin	21 (8.8)	14 (12.2)	.34
Fidaxomicin extend	40 (16.8)	0 (0)	<.001
Other combinations	6 (2.5)	0 (0.0)	.18
Bezlotoxumab	23 (9.8)	2 (1.8)	.006
Fecal microbiota transplantation	4 (1.7)	2 (1.8)	.97
Novel therapies[c]	84 (35.3)	15 (13.1)	<.001
Treatment according to guidelines	227 (95.8)	82 (71.3)	<.001

Abbreviations: CDI, *Clostridioides difficile* infection; HCFA, health care facility associated; NAAT, nucleic acid amplification test.

[a]Includes community-associated CDI and community-onset HCFA.

[b]The total is >238 because patients treated with bezlotoxumab or fecal microbiota transplantation were treated with antibiotics for CDI.

[c]Fidaxomicin and bezlotoxumab were considered novel therapies.

Data were examined from the 353 episodes considered to be CDI. The patients in hospital B were older (79.7 vs 73.7 years, $P = .004$). Despite a similar Charlson Comorbidity Index, a different comorbidity profile was observed between the hospitals: hypertension (67% vs 53.8%, $P = .019$), congestive heart failure (27.8% vs 10.1%, $P = .019$), and chronic obstructive pulmonary disease (16.5% vs 5.1%, $P < .001$) were more common in hospital B, whereas patients from hospital A had a greater prevalence of immunosuppression (45.4% vs 21.7%, $P < .001$) and cancer (21.9% vs 11.3%, $P = .017$; Table 1).

The epidemiologic characteristics of the episodes were similar between the hospitals. Nevertheless, the percentage of patients with community-acquired CDI requiring hospital admission was greater at hospital B (54.1% vs 38.1%, $P < .041$). Metronidazole was prescribed more often in hospital B (9.6% vs 1.7%, $P = .001$), while the percentage of patients receiving vancomycin was similar (64.4% vs 60.1%, $P = .44$). The use of novel therapies was notably lower at hospital B (13% vs 35.3%, $P < .001$). Treatment was administered in accordance with the 2018 IDSA guidelines in 95.8% of patients at hospital A and 71.3% of patients at hospital B ($P < .001$; Table 2).

The 12-week recurrence rate for treated patients was similar between the hospitals. Nonetheless, only 35.9% of patients with recurrent CDI treated at hospital A required hospital admission, as opposed to 70.6% at hospital B ($P = .017$). In addition, the proportion of patients who presented to the emergency department for CDI-related problems within 12 weeks of diagnosis was greater in hospital B (35.4% vs 17.2%, $P = .016$). Although the difference was not statistically significant, the mortality rate for patients with CDI at 12 weeks was greater in hospital B (26.1% vs 14.3%, $P = .22$; Table 3).

Although multivariable analyses did not show a statistically significant difference between hospitals in recurrence (OR, 0.89; 95% CI, .47–1.69; $P = .715$), multiple recurrence (OR, 1.45; 95% CI, .40–5.27; $P = .574$), or mortality (OR, 0.73;

Table 3. 12-Week Follow-up of Patients With CDI After Completing Treatment

	No. (%)		
	Hospital A (n = 238)	Hospital B (n = 115)	*P* Value
Recurrence			
12 wk	39 (16.4)	17 (14.8)	.70
Health care associated[a]	15 (38.5)	4 (23.5)	.36
Admissio[b]	14 (35.9)	12 (70.6)	.017
Follow-up visit			
To emergency department	93 (39.1)	48 (41.7)	.63
To emergency department related to CDI[b]	16 (17.2)	17 (35.4)	.016
Mortality			
Overall	50 (21)	23 (20)	.83
Related to CDI[b]	7 (14.3)	6 (26.1)	.22

Abbreviation: CDI, *Clostridioides difficile* infection.

[a]Recurrences that occurred during admission for other reasons.

[b]Over the total number of recurrences, visits to the emergency department and number of deaths.

95% CI, .39–1.37; $P = .371$), the absence of an intervention program was associated with greater odds of any admission due to recurrence (OR, 4.19; 95% CI, 1.09–16.05; $P = .037$) and greater odds of visits to the emergency department due to CDI (OR, 8.74; 95% CI, 2.54–30.04; $P = .001$; Supplementary Table 1).

DISCUSSION

Our research shows that the use of a specific care program for patients with CDI, designed and carried out by an IDS, improves the overall management of patients with CDI.

First, a greater percentage of patients were categorized as colonized (or exhibited self-limited episodes) and therefore did not require antibiotic treatment. Recent studies have shown that treating patients colonized by toxigenic *C difficile* does not eradicate the infection. Instead, it causes substantial changes in the microbiota and promotes environmental contamination by vancomycin-resistant enterococci (VRE) [21]. The variation in diagnostic methodology may have affected the higher proportion of patients in hospital B who received treatment after testing positive, due to the unavailability of toxin determination. However, it is unlikely that the remaining differences observed in the results can be attributed to an overtreatment of colonized cases in hospital B. This is supported by the fact that neither mortality nor recurrences were lower in hospital A and the proportion of severe or fulminant cases was similar. The better compliance with guidelines and lower rate of readmissions or emergency department visits cannot be explained by the different diagnostic methodology.

Second, a larger proportion of patients were treated according to established guidelines and had access to novel therapies. Fidaxomicin became available in the Spanish market in 2014, while bezlotoxumab was introduced in 2018. Therefore, it is not surprising that, under the CDI patient care program, additional novel therapies have been utilized. Both hospitals are affiliated with the same public health care system in Madrid, and guidelines exist for the administration of both medications to high-risk patients with CDI. It is clear that IDSs are familiar with the use of both drugs and are more likely to use them.

Finally, we observed a decrease in hospital resource utilization: fewer patients with community-onset CDI were admitted to the hospital, and the proportion of patients with recurrence who were readmitted to the hospital or received emergency services due to CDI decreased as well.

Recent studies have shown that readmissions drive up the health care costs of CDI [4, 22, 23] and have an enormous impact on patients' quality of life [24]. Thus, reducing readmissions due to *C difficile* recurrence should be a priority [25].

Unlike other published interventions that rely solely on drug substitution or sharing or implementing a local protocol [11–15], our approach includes efforts to promote patient accessibility and continuity of care, as well as an advisory service by an IDS. For example, it can take several days for a general physician to access the information, book an appointment, and treat the patient if a positive *C difficile* test result is identified in the community. Moreover, as oral vancomycin is not available in community pharmacies in Spain and the general physician may not be familiar with the disease [26], the patient is either suboptimally treated or unnecessarily referred to emergency services. Through our program, the IDS receives real-time reports of all positive test results, enabling the specialist to locate the patient and provide treatment without the need for a visit to the emergency department. Similarly, our program helps to avoid readmissions to the hospital or the need for emergency care for patients experiencing recurrent CDI by providing the option for them to call and receive efficient outpatient treatment.

Despite the increased prescription of novel therapies, no reduction in the recurrence rate associated with the program was observed. One possible explanation is that, despite the younger population, hospital A had a greater volume of patients with cancer and immunosuppression than hospital B. In addition, we cannot completely exclude the possibility that hospital A's program, which facilitated patient accessibility, may have allowed more recurrences to be detected, while some patients in hospital B may have remained undiagnosed or been treated in alternative facilities.

Our study has clear limitations as a result of variations between the hospitals that were used in the comparison. While the CDI care program was implemented in a tertiary academic center, the center used for comparison purposes was a smaller center and of lower complexity. Consequently, there were differences in the patient profile as well as the diagnostic methodology employed. Nevertheless, our data enabled us to highlight the advantages of a novel program based not only on expert guidance but also on greater patient accessibility and continuity

of care. These elements are particularly pertinent in the context of CDI, which transcends specialty boundaries. As with other serious infectious diseases, oversight and management by an IDS may result in better outcomes and resource utilization. However, there are almost no studies evaluating the clinical outcomes of a program for CDI managed by an IDS. In this study, we observed a greater proportion of patients who did not receive antibiotics because they were evaluated as colonized, as well as better adherence to clinical guidelines, easier access to novel therapies, and a decrease in hospital resource utilization.

In conclusion, the implementation of a *C difficile* intervention program—integrating real-time recommendations from an IDS and enhancing patient access to specialized advice during follow-up—is associated with improved patient care quality and potential reductions in hospital resource utilization.

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.

Notes

Author contributions. S. K., M. D. C.-L., and J. C. conceived the idea, designed the study, and wrote the manuscript with M. D. C.-L. and L. d. C. carrying out the subsequent analyses. R. E.-S., A. H., S. L., S. M. Q., C. S.-C., M. S. H., and S. M. G. all provided feedback suggestions during manuscript drafting. S. K., M. D. C.-L., and J. C. verified the underlying data. All the authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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