Impact of Targeted Educational Interventions on *Clostridium difficile* Infection Treatment in Critically Ill Adults

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ABSTRACT

Background: *Clostridium difficile* infection (CDI) is a growing clinical and economic burden throughout the world. Pharmacists often are members of the primary care team in the intensive care unit (ICU) setting; however, the impact of pharmacists educating other health care providers on appropriateness of CDI treatment has not been previously examined.

Objective: This study was performed to determine the impact of structured educational interventions on CDI treatment on appropriateness of CDI treatment and clinical outcomes.

Methods: This was a single-center, retrospective, cohort study of patients with CDI in the medical ICU at an academic medical center between January and June 2014 (pre-period) and 2015 (post-period). All patients were evaluated for appropriate CDI treatment before and after implementing pharmacist-provided educational interventions on CDI treatment.

Results: Patients in the post-period were prescribed appropriate CDI treatment more frequently than patients in the pre-period (91.7% vs 41.7%; $p = .03$) and received fewer inappropriate doses of a CDI treatment agent (14 doses vs 30 doses). Patients in the pre-period had a shorter ICU length of stay [1.5 days (range, 1–19) vs 3.5 days (range, 2–36); $p = .01$] and a similar hospital length of stay [9.5 days (range, 4–24) vs 11.5 days (range, 3–56); $p = .30$]. Total time spent providing interventions was 4 hours.

Conclusion: Patients had appropriate CDI treatment initiated more frequently in the post-period. This low-cost intervention strategy should be easy to implement in institutions where pharmacists interact with physicians during clinical rounds and should be evaluated in institutions where interactions between pharmacists and physicians occur more frequently in non-rounding situations.

Key Words— antimicrobial stewardship, *Clostridium difficile* infection, educational intervention, pharmacist intervention

Hosp Pharm 2016;51:901–906

C*lostridium difficile* infection (CDI) is a growing clinical and economic burden across the world.¹ CDI has become the largest cause of health care–associated infections; in 2011, it was

responsible for more than 29,000 deaths.¹ Because of the impact of CDI on hospital length of stay (LOS), mortality, morbidity, and health care costs, appropriate and evidence-based treatment is crucial.

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Treatment options for hospitalized patients with CDI include oral and intravenous (IV) metronidazole and oral vancomycin, with the choice depending on disease severity and previous disease recurrence.^{2,3} In a randomized controlled trial that stratified patients with CDI by disease severity, patients with severe CDI achieved better outcomes when they were treated with vancomycin compared with metronidazole or tolevamer.⁴ The Society for Healthcare Epidemiology of America and the Infectious Disease Society of America recommend oral vancomycin for the treatment of severe CDI, including patients admitted to an intensive care unit (ICU) for CDI.²

Antibiotic use is the single most important risk factor for the development of CDI. Frequently empiric antibiotics are continued for durations longer than the time necessary, thus placing patients at increased risk of developing CDI.⁵ Antimicrobial stewardship programs are a suggested strategy for reducing the incidence of and improving the management of CDI.⁶ However, when the antimicrobial stewardship or infectious diseases team is not consulted to assist with management of a patient with CDI, the patient's primary team must appropriately treat that patient. Outcomes from the implementation of evidence-based guidelines for CDI treatment have varied depending on CDI severity, type of hospital, and education on the guideline.⁷⁻⁹

Pharmacists often are members of the primary care team in the ICU setting; however, the impact of pharmacists educating other health care providers on appropriateness of CDI treatment has not been previously examined. This study was performed to determine the impact of structured educational interventions on CDI treatment, on appropriateness of CDI treatment, and clinical outcomes.

METHODS

Study Design

This single-center, retrospective, cohort study of critically ill patients with confirmed, severe CDI in the medical ICU (MICU) at an academic medical center between January and June 2014 (pre-period) and January and June 2015 (post-period) was approved by the institutional review board. All patients with a positive *Clostridium difficile* toxin, antigen, and/or polymerase chain reaction (PCR) were evaluated for appropriate CDI therapy before and after implementing educational interventions on CDI recognition and treatment. Patients were excluded from analyses if they already were

receiving treatment for CDI upon admission to the MICU, if another service other than an MICU service provided CDI treatment recommendations, or if CDI severity was mild or moderate. CDI was not required to be the primary diagnosis.

Beginning in January 2015, within 2 days of joining the MICU treatment team, a clinical pharmacist provided medical residents and pulmonary/critical care fellows with an educational intervention lasting 5 minutes on guideline-recommended CDI recognition and treatment strategies and a pocket card on CDI recognition and treatment developed by a multidisciplinary team (Figure 1). A clinical pharmacist rounded with the MICU treatment team prior to implementation of this educational intervention; however, no formal intervention of this nature was performed in the pre-intervention period. Appropriate CDI treatment for a critically ill patient was defined as vancomycin by mouth at a dose of at least 125 mg by mouth every 6 hours or 4 times daily in patients who were able to take oral medications or metronidazole IV 500 mg every 8 hours or 3 times daily in patients who were not able to take oral medications.² Because a multitude of factors and patient characteristics could impact the duration of treatment, only the initial agent and dosage were considered when evaluating appropriateness of treatment. Use of rectally administered vancomycin or nonstandard agents (eg, rifaximin, intravenous immunoglobulin) were not considered when evaluating appropriateness of treatment.

Statistical Analysis

The primary outcome was the change in proportion of patients prescribed inappropriate CDI treatment in a MICU between the pre-intervention and post-intervention periods. Secondary outcomes were ICU and hospital LOS, acid suppression therapy (AST) discontinued after CDI diagnosis, and average inappropriate doses of treatment agent. For continuous variables, 2-sample Wilcoxon rank-sum (Mann-Whitney) tests were used; for contingency tables, Fisher's exact tests were used. All statistical tests used a significance level of 0.05 for all statistical analyses. To detect a significant difference in the primary outcome with 95% confidence, 80% power, and an expected 95% of patients in the intervention group and 50% of patients in the control group receiving appropriate initial CDI treatment, a total of 24 patients were needed. All analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Diagnosis of *Clostridium difficile* infection (CDI)

1. Combination of signs and symptoms, confirmed by microbiological evidence of *C. difficile* toxin and toxin-producing *C. difficile* in stools, in the absence of another cause **OR**
2. Colonoscopic or histopathological findings demonstrating pseudomembranous colitis

Clinical pictures compatible with CDI

Diarrhea defined as loose stools, i.e., taking the shape of the receptacle or corresponding to Bristol stool chart types 5–7, and a **stool frequency of three or more stools in 24 or fewer consecutive hours**

Severe CDI

CDI with 1+ specific sign and symptom of severe colitis **OR** a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy, or death

Sign of severe colitis: 1+ of the following unfavorable prognostic factors without evidence of another cause

- Marked leukocytosis (WBC $>15 \times 10^3/\text{mCL}$)
- Decreased blood albumin (serum albumin $<3 \text{ g/dL}$)
- Rise in serum creatinine level (SCr ≥ 1.5 times the premorbid level)

Increased risk of severe CDI

CDI with no signs of severe colitis but ≥ 65 years, serious comorbidity, ICU admission, or immunodeficiency

Recurrent CDI

CDI that re-occurs within 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment

Increased risk of recurrent CDI

Patients with prior CDI, ≥ 75 years, serum creatinine $\geq 1.2 \text{ mg/dL}$, or ≥ 10 unformed bowel movements/24 h

Potential severe complications of CDI

Ileus: severely disturbed bowel function (vomiting & stool absence) + radiological signs of bowel distension

Toxic mega colon: radiological signs of distension of the colon ($>6 \text{ cm}$ in transverse width of colon) and signs of a severe systemic inflammatory response

CDI Treatment Recommendations

Non-severe CDI, initial case: PO metronidazole 500 mg Q8H

Non-severe CDI with risk for recurrent CDI: PO vancomycin 125 mg Q6H

Non-severe CDI when PO route unavailable: IV metronidazole 500 mg Q8H

Severe CDI, initial case: PO vancomycin 125 mg Q6H

Severe CDI when PO route unavailable: IV metronidazole 500 mg Q8H + PO/PR vancomycin 500 mg Q6H

First recurrence of CDI: PO vancomycin 125 mg Q6H

2+ recurrence of CDI: PO vancomycin 125 mg Q6H (+ taper or pulse) **OR** PO fidaxomicin 200 mg Q12H

Definition of CDI treatment response

After therapy either (1) stool frequency decreases or stool consistency improves **OR** (2) parameters of disease severity (clinical, laboratory, radiological) improve and no new signs of severe disease develop

After clinical response, it may take weeks for stool consistency and frequency to become entirely normal.

Appropriate duration of treatment is generally 10-14 days unless second or greater recurrence of CDI.

Figure 1. *Clostridium difficile* infection pocket card. ICU = intensive care unit; PO = oral; Q6H = every 6 hours; Q8H = every 8 hours; Q12H = every 12 hours; WBC = white blood count.

RESULTS

The electronic health records were reviewed for 28 patients who developed and were treated for CDI during the control period (January to June 2014) and intervention period (January to June 2015). Four patients were excluded because they already were receiving CDI

treatment prior to admission to the MICU ($n = 2$) or because the infectious diseases consultant service participated in the recommendation for CDI treatment ($n = 2$), leaving 24 patients included in the study: 12 patients in the pre-educational intervention group and 12 patients in the post-educational intervention group.

Patients in the pre-educational intervention group were older (64.5 vs 50.5 years; $p = .02$) and more frequently diagnosed with CDI by *Clostridium difficile* toxin and antigen tests (67% vs 17%). Most patients in the post-educational intervention group were diagnosed by polymerase chain reaction (33% vs 83%). Most patients in both groups were receiving AST, and all were receiving antibiotic therapy at the time of CDI diagnosis (Table 1).

Patients in the post-educational intervention group were prescribed appropriate, guideline-recommended CDI treatment more frequently than patients in the pre-educational intervention group (91.7% vs 41.7%; $p = .03$) and received fewer inappropriate doses of a CDI treatment agent (14 doses vs 24 doses). In the pre-educational intervention group, AST was stopped in 30% of patients at the time of CDI diagnosis and in no patients in the post-educational intervention group ($p = .09$). The pre-educational intervention group had a shorter ICU LOS

[1.5 days (range, 1-19) vs 3.5 days (range, 2-36), $p = .01$] and a similar hospital LOS [9.5 days (range, 4-24) vs 11.5 days (range, 3-56), $p = .30$]. The carbido-pa was the least stable of the drugs at 22°C while both were stable at 5°C (Table 2).

DISCUSSION

Our study aimed to determine the impact of a pharmacist-provided educational intervention on the appropriate treatment of CDI. In patients with severe CDI who can take medications by mouth or a feeding tube, oral vancomycin is the recommended therapy.² We discovered that patients had appropriate CDI treatment initiated more frequently in the post-educational intervention period than when no formal intervention was provided. In the formal intervention period, all medical residents and pulmonary/critical care fellows received an educational pocket card on CDI management (Figure 1), a 5-minute in-service on CDI treatment reviewing

Table 1. Patient characteristics

Characteristic ^a	Pre-intervention (n=12)	Post-intervention (n=12)	p
Age, median years (range)	64.5 (58-85)	50.5 (43-79)	0.02
Diagnosis			0.02
<i>Clostridium difficile</i> toxin and antigen	8 (67)	2 (17)	
Polymerase chain reaction	4 (33)	10 (83)	
Initial episode of CDI	10 (83)	10 (83)	0.99
Concomitant antibiotic use	12 (100)	12 (100)	0.99
Antibiotics continued at diagnosis	12 (100)	12 (100)	0.99
AST at diagnosis			0.50
H2RA	6 (50)	5 (42)	
PPI	4 (35)	5 (42)	
Antimotility agent at diagnosis	0 (0)	0 (0)	0.99
Oral route available	7 (58)	7 (58)	0.99
Initial CDI therapy prescribed			
Oral metronidazole	3 (25)	1 (8.3)	0.59
IV metronidazole	4 (33)	3 (25)	0.50
Oral vancomycin	6 (50)	10 (83)	0.19

Note: AST = acid suppression therapy; CDI = *Clostridium difficile* infection; H2RA = histamine₂-receptor antagonist; IV = intravenous; PPI = proton pump inhibitor.

^aAll characteristics are presented as n (%) unless otherwise specified

Table 2. Pre- and post-educational intervention outcomes

	Pre-intervention (n=12)	Post-intervention (n=12)	p
CDI treatment appropriately initiated, n (%)	5 (42)	11 (92)	0.03
AST discontinued after CDI diagnosis, n (%)	3 (25)	0 (0)	0.09
Inappropriate doses of treatment agent, median ^a	30	14	-----
ICU LOS, median (range)	1.5 (1-19)	3.5 (2-36)	0.01
Hospital LOS, median (range)	9.5 (4-24)	11.5 (3-56)	0.30

Note: AST = acid suppression therapy; CDI = *Clostridium difficile* infection; ICU = intensive care unit; LOS = length of stay.

^aOnly 1 patient in the post-intervention was initiated on an inappropriate medication for a total of 14 days, which prevented calculation of a p value.

the pocket card, and pharmacist interaction on interdisciplinary, patient care rounds. For comparison, during the non-formal intervention period, all trainees received pharmacist interaction only during the interdisciplinary, patient care rounds.

There was a difference in the ICU LOS but not the hospital LOS between the groups. LOS can be impacted by numerous factors when a small sample of critically ill patients composes the study population. This finding should be interpreted with caution. Knaus et al found a trend toward a significant reduction in hospital LOS ($p = .06$) when a guideline for CDI treatment was disseminated through a local conference and by electronic mail to providers in their hospital.⁹ They included patients throughout the entire hospital rather than just critically ill patients and evaluated a larger patient sample than this study. The guideline adherence at their hospital prior to their intervention was only 38%, which is comparable to our 42%. Physicians more frequently initiated CDI treatment based on a positive PCR rather than positive toxin and antigen test results in the post-educational intervention group, which may be attributable to the pharmacist's focus on the CDI initiative, the availability of the pocket card, or indeterminate results from toxin and antigen tests during the intervention period. We found no difference in acid suppression therapy discontinuation following CDI diagnosis. Although the effects of continuing AST during a case of CDI have not been adequately explored, AST use has been shown to be a possible cause of CDI.¹⁰

Several factors could be responsible for the lack of adherence in the pre-educational intervention group.

Trainees may not be familiar with the guidelines on CDI management or how to assess criteria for disease severity and treatment. In the pre-educational intervention group, IV metronidazole was the most common inappropriately prescribed therapy followed by oral metronidazole. Trainees may have been uncertain of a patient's ability to absorb medications given by mouth at the time of therapy initiation.

There are also a number of potential reasons for adherence issues regardless of the study period. Residents and fellows provide overnight coverage in the ICU with the knowledge that the rounding team will reevaluate all patient care decisions and make appropriate changes in the morning. Trainees may tend to see more value in timely initiation of CDI treatment rather than in choosing the correct agent for treatment. New publications on the treatment of CDI may also affect the care that patients receive⁴; however, not all residents will be aware of these additions to the literature unless they are specifically interested in this area of practice. Finally, there may be attending physicians who chose to treat CDI differently from the guideline recommendations and teach trainees these practices, which is unlikely to change because of this particular educational intervention.

The intervention used in our study required a certain amount of commitment from the pharmacist perspective. The resources utilized in preparation and maintenance of the formal educational intervention program were manageable. Development of all materials included a thorough literature search, literature evaluation, and selection of the most relevant and accurate information. The production of the materials included printing and laminating. The materials were

presented and discussed with residents individually and in small groups on the first days of their service commitment. Due to the nature of changing schedules, some residents working evening shifts were not educated within the desired 2 days. Time spent educating totaled approximately 4 hours over 6 months.

When considering intervention and education in the future, several variables are important. Pocket cards and in-service presentations will need to be updated to incorporate the most updated recommendations and evidence from the literature.⁴ Future plans include the hospitalwide implementation of the initiative. The key points from the pocket card should be integrated into the hospital's computerized physician order entry system to serve as a reminder and to reinforce appropriate CDI treatment. To reach more physicians, pharmacists could provide education at the new resident orientation in June on the management of CDI, including causes, diagnosis, infection control, and treatment elements.

Our study is not without its limitations. The study was conducted at a single center in a single ICU. Furthermore, CDI occurred infrequently in this patient population, resulting in a small eligible sample. We were unable to distinguish between medication orders that were placed when a pharmacist was present on rounds, consulted after hours, or not available to provide a recommendation; however, these scenarios should have existed in each group. This small sample size also made examination of clinical outcomes, such as recurrence of CDI and CDI-associated mortality, infeasible. Despite these limitations, our study highlights the significant impact of an educational intervention on improving guideline-recommended treatment for CDI in an ICU setting.

CONCLUSION

In a study of patients treated for CDI in a MICU before and after a formal educational intervention program was implemented, it was found that patients had appropriate CDI treatment initiated more frequently in the formal educational intervention period. This low-cost intervention strategy can be implemented at institutions where pharmacists interact with physicians on rounding services and should be evaluated in institutions where interactions between pharmacists and physicians occur more frequently in non-rounding situations.

ACKNOWLEDGMENTS

The authors declare no conflicts of interest. There was no funding for this research. The research was approved by the University of Arkansas for Medical Sciences institutional review board (#203793).

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