Clinical impact of a pharmacist-led antimicrobial stewardship initiative evaluating patients with *Clostridioides difficile* colitis

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ABSTRACT

Clostridioides difficile is the most common cause of healthcare-associated infection and gastroenteritis-associated death in the USA. Adherence to guideline recommendations for treatment of severe *C. difficile* infection (CDI) is associated with improved clinical success and reduced mortality. The purpose of this study was to determine whether implementation of a pharmacist-led antimicrobial stewardship program (ASP) CDI initiative improved adherence to CDI treatment guidelines and clinical outcomes. This was a single-center, retrospective, quasi-experimental study evaluating patients with CDI before and after implementation of an ASP initiative involving prospective audit and feedback in which guideline-driven treatment recommendations were communicated to treatment teams and documented in the electronic health record via pharmacy progress notes for all patients diagnosed with CDI. The primary endpoint was the proportion of patients treated with guideline adherent definitive regimens within 72 hours of CDI diagnosis. Secondary objectives were to evaluate the impact on clinical outcomes, including length of stay (LOS), infection-related LOS, 30-day readmission rates, and all-cause, in-hospital mortality. A total of 233 patients were evaluated. The proportion of patients on guideline adherent definitive CDI treatment regimen within 72 hours of diagnosis was significantly higher in the post-interventional group (pre: 42% vs post: 58%, p=0.02). No differences were observed in clinical outcomes or proportions of patients receiving laxatives, promotility agents, or proton pump inhibitors within 72 hours of diagnosis. Our findings demonstrate that a pharmacist-led stewardship initiative improved adherence to evidence-based practice guidelines for CDI treatment.

Significance of this study

What is already known about this subject?

- *Clostridioides difficile* infection (CDI) has a significant impact on morbidity and mortality.
- Adhering to clinical practice guidelines is important due to improved mortality with proper treatment in this patient population.
- Antimicrobial stewardship programs (ASP) implementing CDI initiatives have been associated with improvements in adherence to evidence-based therapy.

What are the new findings?

- A pharmacist-led ASP CDI initiative providing prospective evaluation and feedback through verbal recommendations and progress notes documented in the electronic health record significantly increased evidence-based therapy.
- The majority of patients were not treated according to evidenced-based guidelines.
- This ASP initiative did not result in improvements in clinical outcomes including mortality or readmission rates.

How might these results change the focus of research or clinical practice?

- These results demonstrate that ASP CDI initiatives should be implemented into clinical practice to improve adherence to evidence-based therapy which has been shown to improve clinical outcomes, such as mortality. Our model exclusively involves a clinical pharmacist and provides a low cost and efficient method that is not labor-intensive and could be used for other institutions to replicate.

INTRODUCTION

Clostridioides difficile (*C. difficile*) is a spore-forming anaerobic Gram-positive organism transmitted most commonly via the fecal-oral route.[1] *C. difficile* infection (CDI) can vary greatly in severity, ranging from mild diarrhea to pseudomembranous colitis and death.[2] Risk of CDI is greatly increased by use of antibiotics, particularly cephalosporins, clindamycin, and fluoroquinolones. Other risk factors include increased age, immunosuppression, gastrointestinal surgery, and use of acid suppressive agents such as proton pump inhibitors (PPIs).[3] *C. difficile* is the most common cause of healthcare-associated infection and gastroenteritis-associated death in the USA accounting for nearly half a million infections and 29 000 deaths in 2011.[4] Because of its

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significant impact on morbidity and mortality, early diagnosis and appropriate treatment of these infections is vital.

CDI treatment guidelines stratify treatment of CDI based on disease severity and recurrence. During the time of this study, first-line treatment options described in the 2010 Society for Healthcare Epidemiology of America and Infectious Diseases Society of America (SHEA/IDSA) CDI clinical practice guidelines included oral and intravenous metronidazole and oral vancomycin. Oral metronidazole was recommended as first line therapy for patients with mild to moderate CDI, whereas oral vancomycin was first line for patients with severe CDI.[2 5] Multiple studies have found metronidazole to be inferior to vancomycin with regard to clinical success for the treatment of severe CDI, demonstrating the importance of adhering to clinical treatment guidelines.[6–8]

Antimicrobial stewardship programs (ASP) implementing CDI stewardship initiatives have consistently demonstrated improvements in process measures and treatment adherence.[9–13] The UF Health Jacksonville ASP team began a pharmacist-led CDI ASP initiative in August 2016. The purpose of this study was to determine whether routine ASP surveillance and intervention on patients diagnosed with CDI led to improved adherence to CDI treatment guidelines and clinical outcomes.

METHODS

This was a retrospective, quasi-experimental study conducted at UF Health Jacksonville and approved by the University of Florida Health Science Center Jacksonville institutional review board. Adult inpatients with a positive *C. difficile* nucleic acid amplification test (NAAT) admitted between January 1, 2015 and July 31, 2016 (pre-intervention) and September 1, 2016 to February 18, 2018 (post-intervention), who were treated for CDI for at least 72 hours, were evaluated for inclusion. All *C. difficile* tests were ordered at the discretion of the provider and performed in the UF Health Jacksonville Microbiology laboratory using the BD MAX Cdiff Assay (BD Diagnostics, Sparks, MD). Patients were excluded if they were admitted to the intensive care unit (ICU) at the time of CDI diagnosis, but were eligible for inclusion if diagnosed in a non-ICU area and transferred to the ICU at a later time. Patients were also excluded if they were already receiving treatment for CDI at the time of admission, had a documented severe allergy to metronidazole and/or vancomycin, history of predetermined cause of colitis, pre-admission ileostomy or colectomy, unable to tolerate oral therapy throughout the entire treatment duration, pregnant or nursing, incarcerated, taking any investigational medications, or admitted to the UF Health North campus as these beds were not available during the pre-intervention period.

In August of 2016, the UF Health Jacksonville ASP team began evaluating all non-ICU patients diagnosed with CDI. ASP members used prospective audit and feedback with the treatment teams either in person or via the telephone in addition to documenting pharmacy progress notes in the electronic health record (EHR) consisting of guideline driven CDI treatment recommendations. During the study period, official ASP operation hours were weekdays with standard hours of 08:00–16:30. Recommendations for appropriate use of other antimicrobial agents, discontinuation of acid suppressive agents, and avoidance of laxatives were also documented in the EHR.

The primary endpoint was the proportion of patients treated with guideline adherent definitive treatment regimens within 72 hours of CDI diagnosis based on the 2010 SHEA/IDSA CDI treatment guidelines. Definitive treatment regimen was defined as the regimen used for 50% or more of the treatment duration. Oral vancomycin for severe CDI was considered guideline adherent regardless of the dose. Secondary endpoints included time to appropriate therapy, proportions of patients receiving laxatives, promotility agents, and PPIs within 72 hours of diagnosis, length of stay (LOS), infection-related LOS (I-LOS), 30-day readmission rates, and all-cause, in-hospital mortality. Exploratory endpoints included proportion of patients treated with guideline adherent definitive treatment regimens and time to appropriate therapy based on the 2017 SHEA/IDSA CDI treatment guideline update released in February 2018.

During statistical analysis, descriptive summaries were summarized as frequencies and percentages for categorical variables and medians and IQRs for numeric variables. Groups were compared using the Pearson's χ^2 test (or Fisher's exact test if some cell frequencies were small) for categorical data and using Wilcoxon rank sum tests for continuous data. All analyses were done using SAS for Windows V.9.4. An a priori power calculation determined 105 patients per group would be required to show an 18% improvement in adherence to treatment guidelines based on a significance level of 5% and power of 80%.

RESULTS

Of the 776 patients with a positive *C. difficile* NAAT who were screened during the study period, 233 patients were included for analysis. The most common reasons for exclusion were ICU admission at the time of diagnosis (45%), not inpatient status or treatment <72 hours (30%) and other cause for colitis (6%). Baseline characteristics, including CDI risk factors, were similar between groups (table 1). CDI characteristics were similar between groups for all except CDI SHEA/IDSA severity (table 2).

The proportion of patients on a guideline adherent definitive CDI treatment regimen within 72 hours of diagnosis according to the 2010 SHEA/IDSA CDI practice guideline was significantly higher in the post-interventional group (pre: 42% vs post: 58%, p=0.02). The proportion of patients on a guideline adherent definitive treatment regimen at any time during admission was also significantly higher in the post-interventional group (pre: 43% vs post: 61%, p=0.01). The most common reason for non-adherence was utilizing a suboptimal antimicrobial regimen based on severity of infection (pre: 79% vs post: 77%, p=0.80). There was no difference in time to appropriate therapy (median, pre: 3.5 vs post: 3 hours, p=0.82). Overall, there were 119 patients who were on inappropriate initial therapy, and of those, 44 patients (37%) had a change in therapy from the initial regimen. There was no significant difference in the proportion of patients who had a change in therapy from an inappropriate initial regimen between the study groups (pre: 30.6% vs post 43.9%, p=0.18). Patients were most commonly treated definitively with monotherapy (pre: 83% vs post: 84%). Oral metronidazole (pre: 59% vs post:

Table 1 Baseline characteristics

Characteristic	Pre-intervention (n=120)	Post-intervention (n=113)	P value
Age (years)*	63 (49–75)	64 (54–72)	0.78
Female gender†	59 (49)	61 (54)	0.46
Race†			
White	65 (54)	53 (47)	
Black	53 (44)	58 (51)	0.49
Other	2 (2)	2 (2)	
Charlson Comorbidity Index score*	5 (2–7)	5 (3–7)	0.64
Antibiotics received within previous 90 days†	84 (70)	84 (74)	0.46
Recent surgery†	23 (19)	19 (17)	0.64
Immunocompromised†‡	19 (16)	15 (13)	0.71
TPN during admission†	4 (3)	3 (3)	1
Tube feeds started within 72 hours of sample collection†	9 (8)	6 (5)	0.5
Medications received within 72 hours of CDI diagnosis†			
Laxative	30 (25)	23 (20)	0.92
Promotility agent	8 (7)	7 (6)	0.88
PPI	40 (33)	46 (41)	0.21

*Data reported as median (IQR).
†Data reported as n (%).
‡Immunocompromised status included presence of neutropenia, AIDS or current use of immunosuppressive medications.
CDI, *Clostridioides difficile* infection; PPI, proton pump inhibitor; TPN, total parenteral nutrition.

56%) and oral vancomycin (pre: 31% vs post: 44%) were the most common agents used. Intravenous metronidazole (pre: 75% vs post: 89%) and oral vancomycin (pre: 100% vs post: 100%) were the most common agents used for definitive combination therapy.

Table 2 CDI characteristics

Characteristic	Pre-intervention (n=120)	Post-intervention (n=113)	P value
CDI acquirement category†			
Hospital acquired	53 (44)	52 (46)	0.80
Community acquired	67 (56)	61 (54)	
CDI category†			
Primary	111 (92.5)	103 (91)	0.71
Recurrence	9 (7.5)	10 (9)	
Any prior CDI†‡	9 (8)	11 (10)	0.82
Prior CDI at OSH†	6 (5)	5 (4)	
CDI IDSA severity†			
Mild to moderate	39 (33)	41 (36)	0.02
Severe	16 (13)	29 (26)	
Severe, complicated	65 (54)	43 (38)	
CDI ACG severity†			
Mild to moderate	27 (22.5)	26 (23)	0.35
Severe	20 (16.5)	27 (24)	
Severe, complicated	73 (61)	60 (53)	
Time to positive CDI test from hospital presentation (hours)*	52 (26.5–170.5)	56 (30–220)	0.33
Days of CDI therapy*	14 (12–16)	14 (13–15)	0.90

*Data reported as median (IQR).
†Data reported as n (%).
‡Includes patients who had prior CDI episode at UF Health with a positive CDI test documented in the electronic health record and patients with history of CDI episode from outside hospital or clinic.
ACG, American College of Gastroenterology; CDI, *Clostridioides difficile* Infection; ED, emergency department; IDSA, Infectious Diseases Society of America; OSH, outside hospital.

This increase in adherence to guideline-based therapy according to the 2010 SHEA/IDSA guideline resulted in no difference in ICU admission (pre: 12% vs post: 5%, p=0.08), hospital LOS (median, pre: 12 days vs post: 11 days, p=0.99), I-LOS (median, pre: 9 days vs post: 7 days, p=0.37), CDI-related 30-day readmission (pre: 8% vs post: 4%, p=0.20), or all-cause, in-hospital mortality rate (pre: 8% vs post: 3%, p=0.41%) between groups. There was no difference in the proportions of patients receiving laxatives (pre: 25% vs post: 20%, p=0.92), promotility agents (pre: 7% vs post: 6%, p=0.88), or PPIs (pre: 33% vs post: 41%, p=0.21) within 72 hours of diagnosis.

There was no statistically significant difference in exploratory endpoints between groups, including the proportion of patients on a guideline adherent definitive treatment regimen at any time during admission based on the SHEA/IDSA 2017 guideline update (pre: 33% vs post: 42%, p=0.12), with utilization of a suboptimal antimicrobial regimen based on severity of infection the most common reason for non-adherence (pre: 93% vs post: 98%, p=0.10).

DISCUSSION

This study demonstrated that pharmacist-led ASP practices through prospective evaluation and feedback with EHR documentation can have a significant benefit on the management of patients with CDI by improving adherence to evidence-based therapy. Previous published studies have also shown positive outcomes regarding the management of CDI patients through ASP initiatives.[9–12] A recent study conducted by Brumley *et al* evaluated 169 patients with CDI and demonstrated that implementation of an institutional CDI bundle with daily antimicrobial stewardship assessment significantly improved adherence to appropriate CDI treatment (82% vs 64%, p<0.009).[9] Welch *et al* evaluated 592 total adult patients with CDI before and after implementation of a real-time ASP review by a clinical pharmacist.[10] Their efforts led to a significant increase in the proportion of patients with severe CDI appropriately treated with oral vancomycin (87% vs 59%, p<0.01) and earlier initiation of vancomycin (mean, 1.1 vs 1.7 days, p<0.01). Similar to the current study, there were no significant differences in clinical outcomes in either of the aforementioned studies despite these improvements in process measures. Two studies evaluating CDI stewardship efforts have demonstrated improvement in clinical outcomes in addition to process measures.[11 12] Jardin *et al* evaluated 256 total CDI patients before and after implementation of an institutional policy permitting ASP to switch oral metronidazole to oral vancomycin in patients with severe CDI.[11] After implementation of this policy, use of oral vancomycin for severe CDI was significantly increased (91% vs 14%, p<0.0001), and refractory disease was significantly decreased (15% vs 37%, p=0.035); however, there was no significant difference in LOS or in-hospital mortality. Yeung *et al* evaluated 424 total CDI patients before and after implementation of a policy in which a clinical pharmacist recommended appropriate treatment for CDI to the medical team in situations of treatment discordance, which resulted in a significant improvement in treatment concordance (48.1% vs 34%, p=0.01) and a significant reduction in hospital LOS (median 21 vs 30 days, p=0.01).[12]

However, there were no differences in rates of mortality, ICU admission, or colectomy. Although our study showed no difference in clinical outcomes, the majority of patients who were not treated appropriately were treated utilizing an antimicrobial regimen designated for a less severe *C. difficile* infection, which has been associated with worse clinical outcomes, especially in those with severe and severe complicated disease.[13] Wieczorkiewicz *et al* retrospectively evaluated 324 CDI cases and found that patients who were undertreated had significantly lower rates of clinical cure (41.2% vs 55.7%, p=0.033), and significantly higher rates of mortality (24.7% vs 10.1%, p=0.003) and recurrence (44.7% vs 24.8%, p<0.02) compared with patients who were appropriately treated.[13] In our study, readmission and in-hospital mortality rates were low and tended to be lower in the post-interventional group; although the difference was not statistically significant.

At the end of our study period, SHEA/IDSA released an update of the CDI treatment guideline, with oral metronidazole no longer a preferred first-line recommendation for mild to moderate CDI.[14] In the current study, oral metronidazole was the most commonly used agent for patients initiated on monotherapy, and a large proportion of patients, particularly those with severe CDI, were treated utilizing an antimicrobial regimen designated for a less severe *C. difficile* infection based on the 2010 SHEA/IDSA recommendations. With oral vancomycin now recommended as first-line treatment for both mild to moderate and severe CDI, ASPs should explore strategies to automate these more straightforward recommendations via order sets in the EHR or electronic decision support in attempt to lower the proportion of patients receiving inappropriate antimicrobial agents based on severity of *C. difficile* infection which may result in improved outcomes. Additionally, the high rate of oral metronidazole use in this study indicates widespread education efforts at our institution regarding the guideline update are warranted.

Our study includes several limitations. Similar to other studies assessing CDI ASP efforts, the current study was limited by its single-center, retrospective design which poses challenges including controlling for confounding factors in a non-randomized sample and the potential for charting inconsistencies among other inherent limitations. In our study, many patients in both treatment arms were classified as having severe complicated CDI based on 2010 SHEA/IDSA severity criteria. The classification of disease severity can also be subjective based on other clinical scenarios running in parallel with CDI. In addition, prescribers may use one of many different sets of criteria for CDI severity that use some different parameters in severity assessment. In our study, one documented episode of hypotension warranted classification as severe complicated CDI. Providers may have classified CDI severity based on different criteria or attributed an isolated hypotensive episode to another cause and treated the patient as mild to moderate or severe, which may have led to a lower proportion of patients on guideline adherent CDI treatment. Additionally, more patients in the pre-interventional group had severe complicated disease, which may have increased the likelihood of inappropriate treatment in these patients. Due to staffing limitations, ASP screening of CDI patients only occurred on weekdays during day shift, so not all patients diagnosed with CDI during the post-interventional period were evaluated by ASP. We were unable to assess the impact ASP had on discontinuation of laxatives, PPIs, and de-escalation of broad-spectrum antimicrobial agents. Additionally, more than one-fifth of patients received laxatives within 72 hours of CDI diagnosis, potentially resulting in inclusion of some patients who were colonized rather than actively infected with *C. difficile*. Finally, we were only able to follow-up for 30 days; however, risk of CDI recurrence remains high for at least 90 days after initial infection.

In conclusion, our findings demonstrate that a pharmacist-led stewardship initiative can increase adherence to evidence-based practice guidelines for the treatment of CDI. Adherence to evidence-based treatment for CDI has been associated with better clinical outcomes, and institutions should consider implementation of a CDI ASP encouraging appropriate treatment of this patient population.

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