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RESEARCH ARTICLE

An Outcome Evaluation of a Standardized Computerized Prescriber Protocol for the Management of *Clostridium Difficile* Colitis in a Teaching Tertiary Care Facility

Linda Nwachukwu[1], Courtney Armstrong[2], Zachary Mulkey[3], Kristen Fuhrmann[2] and Charles F Seifert[1]*

[1]*School of Pharmacy, Texas Tech University Health Sciences Center, USA*

[2]*UMC Health System, USA*

[3]*School of Medicine, Texas Tech University Health Sciences Center, USA*

***Corresponding author:** *Charles F Seifert, Pharm D, FCCP, BCPS, Professor of Pharmacy Practice & Regional Dean for Lubbock Programs, School of Pharmacy, Texas Tech University Health Sciences Center, 3601 4th Street, STOP 8162, Lubbock, TX 79430-8162, USA, Tel: 806-743-7639, Fax: 806-743-43209, E-mail: charles.seifert@ttuhsc.edu*

Abstract

Purpose: *Clostridium difficile* Infection (CDI) continues to be a major public health concern in the U.S. Despite effective treatment options, there continues to be an increase in *Clostridium difficile* infections, recurrence, and mortality. The purpose of this study was to determine whether a standardized computerized prescriber protocol could improve patient management and outcome as recommended by recent guidelines.

Methods: A retrospective quasi-experimental study of hospitalized adults, between the age of 18 and 89 years, with *C. difficile* infection presenting to a 443 bed tertiary care referral county teaching hospital was conducted prior to and after the implementation of a hospital computerized CDI protocol. Mortality and recurrence of *C. difficile* infection were measured to determine the effectiveness of the protocol.

Results: Eighty percent of patients were treated in accordance with guidelines prior to and post hospital protocol implementation. Patients treated according to the hospital protocol had a reduced mortality (4.0%) compared to patients treated according to Infectious Disease Society of America (IDSA) guidelines prior to protocol implementation (7.8%, $p = 0.0471$) and patients not treated according to the hospital protocol after implementation (11.3%, $p = 0.0158$). As CDI complexity increased, patients were less likely to be treated in accordance with either the IDSA guidelines or the hospital protocol ($p < 0.0001$) and had a higher rate of total complications and mortality.

Conclusions: Our study found that the implementation of a standardized computerized prescriber protocol for the management of *Clostridium difficile* colitis was associated with a lower mortality.

Keywords

Clostridium difficile, IDSA guidelines, ACG guidelines, Infectious diarrhea, Pseudomembranous colitis, Toxic megacolon, Computerized prescriber protocol, EHR based alert, NAP1 strain

Introduction

Clostridium difficile Infection (CDI) continues to be the leading cause of healthcare-associated infectious colitis in the United States, replacing oxacillin-resistant *Staphylococcus aureus* as the most common cause of healthcare-associated infection [1]. With symptoms ranging from mild or moderate self-limiting diarrhea to pseudomembranous colitis and toxic megacolon, *C. difficile* is responsible for 337,000 infections and 14,000 deaths every year [2]. Recurrent symptoms, due to relapse of original infection or reinfection, is one of the greatest and costly challenges of CDI. The estimated cost per infection ranges from $6,000-$9,000 and the estimated total cost per year ranges from $1 billion-$1.6 billion [3]. The cause of recurrent CDI is not well understood; though factors implicated in its development include improper or prolonged antibiotic usage, acid suppressive therapy, prolonged hospitalization, weakened immune system, previous gastrointestinal surgery or manipulation, or serious illness [4].

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The 2010 Infectious Disease Society of America (IDSA) guidelines recommend measures to improve antibiotic prescribing in hospitals [5]. These measures include stratification of patients with confirmed CDI based on age, history, White Blood Cell (WBC) count (15 × 10^9/L), serum creatinine (1.5 times the pre-morbid level), and the presence of complicating factors. While the American College of Gastroenterology (ACG) guidelines reiterate that of the IDSA guidelines, it recommends considering hypoalbuminemia (< 3 g/dL), as opposed to serum creatinine, and a White Blood Cell count (WBC) as additional criteria for disease severity classification [6]. C*. difficile* diarrhea causes a "protein losing enteropathy," and as the severity of diarrhea increases more albumin is lost resulting in hypoalbuminemia [6].

Regardless of which set of guidelines is used in practice, there remains overwhelming evidence of prescribers not complying with such evidence-based guidelines. In fact, only a little over half of recommended care is appropriately provided due to unknown reasons [7]. According to a retrospective case control study conducted by Brown and Seifert, only 52% of patients diagnosed with *C. difficile* were treated in accordance with guidelines. Patients treated in accordance with guideline recommendations not only demonstrated a higher clinical cure rate compared to patients not treated in accordance with guideline recommendations (93.5% and 71.5%, $p < 0.0001$), but showed a significant reduction in mortality (5.6% and 21.8%, $p = 0.00012$) and recurrence (14.0% and 35.6%, $p = 0.0007$) which subsequently resulted in a reduction in total complications (17.2% and 56.3%, $p < 0.0001$) [8].

Developing standardized institution-wide measures should not only improve treatment modality patterns, but also reduce complications. A recently published cohort study conducted by Jardin, et al. examined treatment patterns and patient outcomes after the implementation of a severity-based CDI treatment policy. The policy was associated with both an increased use of appropriate antibiotics, and a decreased rate, from 32% to 15% ($p = 0.035$), of refractory disease in patients with severe CDI [9].

Healthcare facilities and systems have traditionally lacked standardized antibiotic prescribing process measures, and decision support systems to improve quality and efficiency. It seems that most institutions are slow to adopt protocols for *C. difficile* management, despite the evidence-driven recommendations. The primary purpose of this study was to determine if implementation of a standardized computerized prescriber protocol could improve the management and outcomes of patients with *C. difficile* infection and diarrhea.

Methods

A retrospective, nonrandomized, pre-and-post quasi-experimental study of patients between the ages of 18 and 89 years with a primary or secondary diagnosis of intestinal infection due to *C. difficile* from November 1, 2013 to January 31, 2016 was conducted in a 443-bed tertiary care county teaching hospital located in west Texas. November 1, 2013 to October 31, 2014 served as the pre-protocol implementation group and March 1, 2015 to January 31, 2016 served as the post-protocol implementation group. The time period of November 1, 2014 until February 28, 2015 was utilized to pilot test the launched protocol and educate the house staff and prescribers. Patients treated according to the hospital protocol were further separated into those patients treated as the protocol recommended, referred to as "per hospital protocol", and those treated differently than the protocol recommended, referred to as "off hospital protocol".

Study entry criteria

Patients were identified using International Classification of Disease - 9th and 10th Revision (ICD-9 and ICD-10) discharge diagnosis codes of 008.45, and A04.7, respectively; and a positive *C. difficile* Polymerase Chain Reaction (PCR) test. The PCR test used was the Cepheid Xpert® *C. difficile*/Epi test (Sunnyvale, CA). This PCR method detects both the presence of *C. difficile* toxin B and the 027/NAP1/BI strain simultaneously. Laboratory personnel were instructed not to perform the test unless the water in the stool sample touched the sides of the container. Patients were then classified into one of the *C. difficile* infection categories defined by the protocol (mild/moderate, severe, or severe and complicated). Visits were excluded if patients were simply not on any treatment regimen, or for the post-implementation group, the alert for the protocol was suppressed.

Hospital protocol

The hospital protocol for the management of *C. difficile* was developed by a committee comprised of an internal medicine physician, and a team of pharmacists, including the infectious disease pharmacist (Table 1). The protocol was based on recommendations derived from the IDSA guidelines, with components from the ACG guidelines, specifically expanding the severe, and severe and complicated disease classifications. In addition to the IDSA criteria, severe *C. difficile* classification includes the presence or development of, hypoalbuminemia (serum albumin < 3 g/dL) during the course of the disease (Table 1). Severe and complicated CDI was classified in patients who presented with or developed two of the following criteria: intensive care unit admission, ileus, megacolon, required use of vasopressors, fever > 38.5 °C, serum lactate level > 2.2 mmol/L, end organ failure, or mental status changes (Table 1). The protocol also employed the use of high dose oral vancomycin (500 mg) when managing patients with mild-moderate or severe disease with positive North American Pulsed-Field Gel Electrophoresis Type 1 (NAP1) strain (Table 1). The institutional review board (bioethics committee) approved the research protocol to conduct the study as an exempt review (approval number: L16-

Table 1: Abbreviated hospital protocol for the management of patients with *Clostridium difficile*.

Condition	Hospital Protocol Action
If stool sample is positive by Polymerase Chain Reaction (PCR) for *C. difficile* toxin B	**The following computer alert fires:** This patient has a positive stool *C. difficile* toxin by PCR and is currently not receiving antibiotics recommended for treatment Options: 1. Launch *C. difficile* **power plan** 2. Skip for now 3. Document reason to suppress alert A. Patient/Caregiver refused treatment B. Comfort care only C. Believe test result is false positive D. Another treatment is being used E. Antibiotic course completed F. Other
***C. difficile* power plan launched**	**General *C. difficile* management implemented** 1. Contact isolation 2. Discontinue all antidiarrheal agents 3. Discontinue all bile acid sequestrants 4. Discontinue all laxatives or stool softeners 5. Discontinue all acid suppressive therapy 6. Consider discontinuing all antibiotics 7. Consider discontinuing all opiates 8. Fidaxomicin is restricted to infectious disease use only

Initial episode or 1st recurrence **Clinical status: Mild-moderate** 1. White blood cell count < 15,000/mm^3 2. Serum creatinine < 1.5 × Baseline	**Options implemented** 1. Start oral metronidazole 500 mg nasogastric tube/oral tablet every 8 hours × 14 days. 2. If NAP1 strain positive then vancomycin 500 mg nasogastric tube/oral liquid four times a day × 14 days. 3. If unable to tolerate metronidazole or after 5-7 days of treatment and NAP1 negative, use vancomycin 125 mg nasogastric/oral liquid four times a day × 14 days.
Clinical status: Severe 1. White blood cell count ≥ 35,000/mm^3 or 2. Serum creatinine ≥ 1.5 × Baseline 3. &/or Serum albumin < 3 g/dL	**Options implemented** 1. Vancomycin 125 mg nasogastric tube/oral liquid four times a day × 14 days. 2. If NAP1 strain positive then vancomycin 500 mg nasogastric tube/oral liquid four times a day × 14 days.
Clinical status: Severe-complicated 1. White blood cell count ≥ 35,000 of < 2000/mm^3 or 2. Serum creatinine ≥ 1.5 × Baseline & 3. TWO of the following: Intensive care unit admission for *C. difficile* infection, ileus, megacolon, vasopressor, fever ≥ 38.5 °C, serum lactate > 2.2 mMol/L, end organ failure, or mental status changes	**Options implemented** 1. Start both metronidazole 500 mg intravenous piggy-back every 8 hours **+** 2. Vancomycin 500 mg nasogastric tube/oral liquid four times a day × 14 days.
If two or more recurrences:	**Options implemented** 1. Vancomycin 500 mg nasogastric tube/oral liquid four times a day × 14 days. 2. For all types if complete ileus considers adding vancomycin enema 500 mg/100 mL normal saline.

052). The *C. difficile* treatment protocol was approved by the hospital's Clinical Decision Support (CDS) committee independent of the research.

Education of prescribers and house-staff was completed in a 4-week period by physician advocates and by one of the investigators prior to the beginning of the second data collection (L. Nwachukwu). In addition, an EHR-based alert was implemented to prompt the provider to utilize the protocol in the presence of a positive *C. difficile* PCR result and no active therapy (Table 1). Prescribers had the option of launching the protocol and ordering appropriate therapy, skipping the alert as they may not be the primary team managing the patient, or they could suppress the alert, provided a reason was documented. Reasons to suppress the alert included: patient/caregiver refused treatment,

comfort care only, false positive test, another treatment is being used, or antibiotic course completed (Table 1).

Data collection

The primary outcome was the appropriate initiation of antibiotic therapy per the hospital protocol. Treatments were analyzed to determine the impact of the protocol. Patients who received more aggressive treatment than protocol recommendations, based on severity classification, were simply counted as having received appropriate therapy. Secondary outcomes were the reduction in mortality and other complications, including infection recurrence within 4 weeks, and diagnosis of toxic megacolon. Using a standardized data collection sheet, information gathered from the electronic medical record included demographic information, hospital admission and discharge data, vital signs and laboratory values, *C. difficile* infection status, treatment regimen, presence of the NAP1 strain, previous antibiotic exposure, and previous proton pump inhibitor exposure.

Statistical analysis

Continuous data were evaluated with the Shapiro-Wilk test for normality and all were found to be nonparametric. Central tendencies are reported in median (IQR). Nonparametric data were analyzed using Kruskal-Wallis, and Mann-Whitney U test. Chi square (χ^2) or Fisher's exact tests were used to test whether differences existed in nominal data. After these univariate analyses, multivariate logistic regression was undertaken to determine risk factors for hospital mortality. Risk factors significant at the 0.2 level in the univariate analysis were entered into the model. Adjusted odds ratios and their corresponding 95% confidence intervals are reported. All tests were two-tailed, and an alpha < 0.05 was considered statistically significant. All analyses were performed using both the SAS 9.3 (SAS Institute, Cary, NC), and Excel statistics add-on package Analyze-it v 3.90.7 1997-2017 (Analyze-it Software, Ltd., Leeds, UK).

Results

A total of 815 patient visits were identified, of which 762 were eligible for inclusion. Four hundred and fourteen patient visits were included before the implementation of the protocol and 348 were included after the implementation of the protocol (Figure 1). Table 2 shows the patient demographics for "Per Hospital Protocol", and "Off Hospital Protocol" groups after implementation and "Per IDSA Guidelines" and "Off IDSA Guidelines" before implementation. Patients in the before and after protocol implementation groups were similar with respect to median age, sex, and incidence of NAP1 strain. From 2013 to 2016, 206 (27%) isolates were confirmed to have the genes for the binary toxin. The "Off Hospital Protocol" group after implementation, and the "Off IDSA Guidelines" before implementation, had higher Intensive Care Unit (ICU) admissions (65.9% and 67.6%), than "Per Hospital Protocol" and "Per IDSA Guidelines" groups (43.4% and 41.2%, $p < 0.0001$, respectively). Median Simplified Assessment of Physiology Score (SAPS) II score had a similar trend. Also, 182 (44.0%) patients were exposed to a proton pump inhibitor within the previous 8 weeks, prior to the implementation of the protocol.

Eighty percent of patients were treated in accordance with guidelines before and after implementation (80.2% vs. 79.6%, $p = 0.8380$). Implementation of the protocol was associated with a significant overall reduction in mortality [19/348 (5.5%) vs. 41/414 (9.9%), $p = 0.0233$). This reduction in mortality was significant only in patients who were NAP1 strain positive [5/87 (5.7%) vs. 18/119 (15.1%), $p = 0.0348$] and not in patients who were NAP1 strain nega-

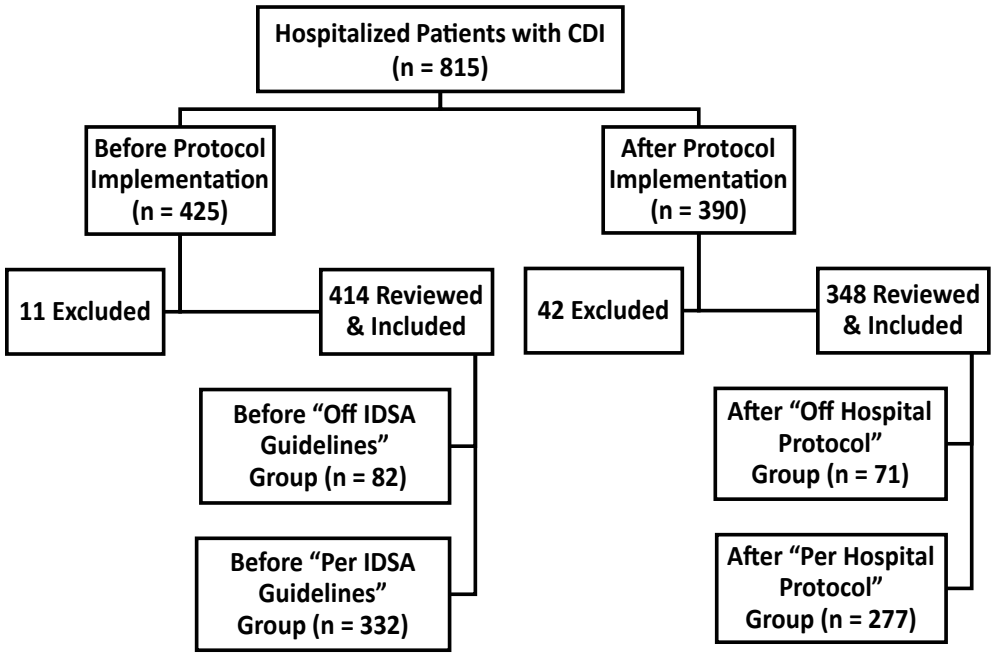

Figure 1: Patients Included in study: Screening, exclusions, and definition of groups.

Table 2: Patient demographics and severity of illness before and after protocol implementation.

Parameters	All (n = 762)	Before "Per IDSA Guidelines" (n = 332)	Before "Off IDSA Guidelines" (n = 82)	After "Per Hospital Protocol" (n = 277)	After "Off Hospital Protocol" (n = 71)	p-value
Median Age (IQR[a]), yrs.	60.5 (24)	62 (27)	58 (21)	60 (22)	60 (28)	0.0720
Race						
White	563 (73.9%)	230 (69.3%)	57 (69.5%)	220 (79.7%)	56 (78.9%)	
African American	55 (7.2%)	22 (6.6%)	6 (7.3%)	21 (7.6%)	6 (8.5%)	
Hispanic	94 (12.3%)	59 (17.8%)	13 (15.9%)	15 (5.4%)	7 (9.9%)	
Other	50 (6.6%)	21 (6.3%)	6 (7.3%)	21 (7.6%)	2 (2.8%)	0.0031
Sex						
Female	422 (55.4%)	187 (56.3%)	47 (57.3%)	145 (52.4%)	43 (60.6%)	0.5625
Severity						
Mild-moderate	537 (70.5%)	279 (84.0%)	20 (24.4%)	233 (84.1%)	5 (7.0%)	
Severe	143 (18.8%)	40 (12.1%)	21 (25.6%)	35 (12.6%)	47 (66.2%)	
Severe and complicated	82 (10.8%)	13 (3.9%)	41 (50.0%)	9 (3.3%)	19 (26.8%)	< 0.0001
NAP1[b] Strain	206 (27.0%)	92 (27.7%)	27 (32.9%)	72 (26.0%)	15 (21.1%)	0.4027
Median SAPS II[c] Score (IQR)	25 (15)	25 (14)	26 (18)	24 (13)	30 (15)	0.0018
ICU[d] Admission	360 (47.2%)	144 (43.4%)	54 (65.9%)	114 (41.2%)	48 (67.6%)	< 0.0001

[a]IQR: Interquartile Range; [b]NAP1: North American Pulsed Field Type 1; [c]SAPS II: Simplified Acute Physiology Score; [d]ICU: Intensive Care Unit.

Table 3: *Clostridium difficile* colitis complications before and after protocol implementation.

Parameters	Before "Per IDSA Guidelines"	Before "Off IDSA Guidelines"	After "Per Hospital Protocol"	After "Off Hospital Protocol"	p-value
All patients	n = 332	n = 82	n = 277	n = 71	
Total complications	14.5%	23.2%	10.5%	16.9%	0.0288
4-week recurrence	8.1%	4.9%	6.9%	8.5%	0.7389
Mortality	7.8%	18.3%	4.0%	11.3%	0.0002
NAP1[a] strain positive	n = 92	n = 27	n = 72	n = 15	
Total complications	20.7%	37.0%	13.9%	20.0%	0.0901
4-week recurrence	14.1%	3.7%	9.7%	6.7%	0.4156
Mortality	9.8%	33.3%	4.2%	13.3%	0.0006
NAP1 strain negative	n = 240	n = 55	n = 205	n = 56	
Total complications	12.1%	16.4%	9.3%	16.1%	0.3416
4-week recurrence	5.8%	5.5%	5.9%	8.9%	0.8323
Mortality	7.1%	10.9%	3.9%	10.7%	0.1294

[a]NAP1: North American Pulsed Field Type 1.

tive [14/261 (5.4%) vs. 23/295 (7.8%), p = 0.2507]. Table 3 compares the complication rates for patients with *C. difficile* before and after protocol implementation. Patients treated according to the protocol had a reduced mortality (4.0%) compared to patients treated according to IDSA guidelines prior to protocol implementation (7.8%, p = 0.0471) and patients not treated according to the protocol after implementation (11.3%, p = 0.0158). These results were consistent among patients who tested positive for the NAP1 strain (9.8% vs. 33.3%, p = 0.0027, 4.2% vs. 13.3%, p = 0.0165, respectively). Outcomes significantly differed between strains as well, but only in the before protocol implementation group. Mortality and ICU admission were significantly increased in patients who tested positive for NAP1 strain compared with patients who tested negative for NAP1 strain (15.1% vs. 7.8%, p = 0.0239; 59.7% vs. 43.1%, p = 0.0022). Patients with mild/moderate CDI were more likely to be treated appropriately compared to patients with severe or severe and complicated CDI in both pre- and post-implementation phases (p < 0.0001) (Figure 2). In both pre- and post-implementation, as the severity of disease worsened, initiation of appropriate treatment regimen decreased, resulting in increased mortality (Figure 3). There was a decrease in patients in the severe group where the protocol was followed from 65.6% to 42.7% post protocol implementation and a subsequent increase in mortality from 1.6% to 6.1%. Four of the five deaths post protocol implementation was in the group of patients where the protocol wasn't followed. Protocol compliance post implementation in the severe & complicated group increased and resultant mortality decreased but neither was significantly different between the protocol groups. Multivariate analysis demonstrated that increasing patient's age, SAPS II score, and classified as having severe and complicated CDI was associated with overall mortality (Table 4). Age and severity were associated with mortality in the pre-protocol population and SAPS II score and severity in the post-protocol population (Table 4).

Discussion

Current guidelines for the management of C. *dif-*

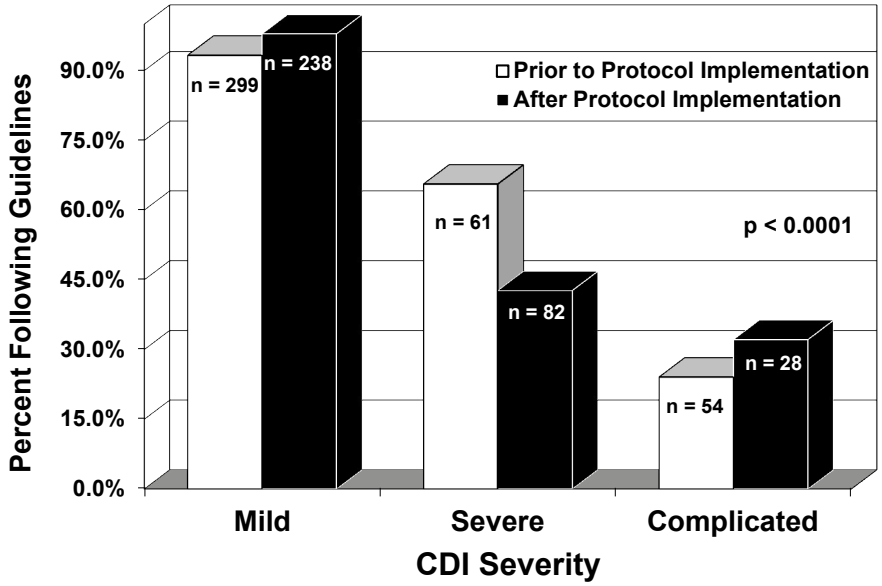

Figure 2: Appropriate initiation of therapy by *Clostridium difficile* diarrhea severity prior to and after protocol implementation.

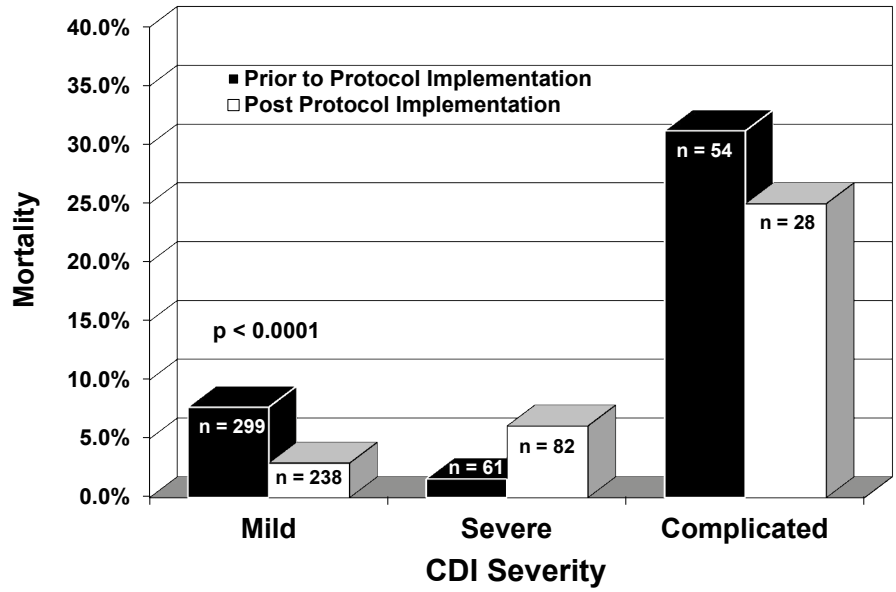

Figure 3: Mortality by *Clostridium difficile* diarrhea severity prior to and post protocol implementation.

Table 4: Multivariate analyses of risk factors for mortality.

Variables	Adjusted Odds Ratio	95% CI	p-value
All patients			
Overall model			< 0.0001
Age	1.033	1.011-1.055	0.0017
SAPS II[a] score	1.048	1.022-1.074	0.0003
Severe & complicated	8.914	4.701-16.90	< 0.0001
Post implementation			
Overall model			< 0.0001
Age	1.070	1.027-1.115	0.0002
Severe & complicated	19.42	5.415-69.65	< 0.0001
Prior to Implementation			
Overall model			< 0.0001
SAPS II score	1.048	1.020-1.076	0.0008
Severe & complicated	3.875	1.727-8.693	0.0002

[a]SAPS II: Simplified Acute Physiology Score.

ficile infection recommend appropriate classification and initiation of oral metronidazole, oral vancomycin, or intravenous metronidazole with oral vancomycin, for mild-moderate, severe, and severe and complicated disease, respectively. Despite effective treatment options, there continues to be an increase in *Clostridium difficile* infections, recurrence, and mortality. The continued increase in incidence, recurrence and mortality, can be attributed to the lack of guideline concordant therapy [8]. For this reason, a standardized computerized protocol was developed and implemented whereby clinicians were alerted to patients with a positive PCR not currently on oral/intravenous metronidazole and/or oral vancomycin therapy. To our knowledge, this is the first study that assessed the effectiveness of a standardized computerized prescriber protocol for the management of *Clostridium difficile* colitis.

Over time, and as demonstrated in this study, there has been an increase in appropriate prescribing patterns since Brown and Seifert's study, thus addressing Brown and Seifert's concerns. Yet, CDI continues to be a major healthcare-related illness, with continued increase in *C. difficile* infection incidence, recurrence and mortality. As seen in our study, there were a total of 815 cases over 23 months of observation. This averages 35 cases a month which is still too high for a 443 bed hospital. The protocol was associated with a decrease in CDI mortality, even without an overall change in prescribing patterns before and after implementation. These results further demonstrate that using clinical guidelines was associated with better care. There still remains a major resistance to treating per protocol, particularly in patients with severe and complicated CDI, a population that warrants it the most. Patients with severe and complicated CDI were more likely to have an ICU admission thus posing the question, why are patients still not being managed as recommended? ICU prescribers at the study's practice site had expressed delay in resuscitation management due to the protocol alert system notifying the need to initiate CDI therapy. However, it can be argued that treatment of CDI and its complications can be managed in the ICU, without delay in resuscitation or vasoactive drug administration.

The study also addressed outcomes in patients with the NAP1 strain. Also, while there remains no current evidence that the NAP1 strain is more resistant to metronidazole or to vancomycin at a dose of 125 mg every 6 hours, the study also looked to evaluate improved outcomes in mild/moderate CDI patients infected with the NAP1 strain, treated with a higher dose of oral vancomycin. For patients who present with a positive NAP1 strain and a mild/moderate severity, the protocol recommended the use of high dose vancomycin. Although limited by the low statistical power, the study found no difference when using a higher dose of oral vancomycin.

This study had notable limitations. First, this was a single-center university-affiliated medical center study, thus these results may not be generalizable to other hospitals or other hospital types. Second, a causal relationship between the implementation of the standardized protocol and an improvement in patient outcomes could not be definitively determined given the study design and sample size. Third, this study was an observational, nonrandomized study. Therefore, unforeseen patient complications could have occurred, contributing to the delay in therapy thus resulting in an increased mortality, specifically in patients with severe and complicated disease severity. Fourth, we were unable to identify post-discharge treatment failures. In spite of these limitations, significant knowledge was gained from implementing and evaluating the standardized computerized prescriber protocol.

Conclusions

Implementation of a standardized computerized prescriber protocol for the management of *Clostridium difficile* colitis was associated with a significant reduction in mortality. With support from stakeholders, including hospital's CDS group, the use of a standardized protocol for management of *C. difficile* should be routinely employed.

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Conflict of interest

All authors report no conflicts of interest relevant to this article.

Presented whole or in part

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