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Effect of an Antimicrobial Stewardship Intervention on Outcomes for Patients with *Clostridium difficile* Infection

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Abstract

Background: Treatment of *Clostridium difficile* infection (CDI) is an ideal target for antimicrobial stewardship programs (ASP), as ASPs have been effective in improving care in patients with a variety of infections. Unfortunately, studies to date have not rigorously evaluated the impact of ASP involvement on complications attributed to CDI.

Methods: We performed a quasi-experimental study of adult patients with CDI prior to (n=307) and after (n=285) a real-time ASP review was initiated. In the ASP intervention group, a pharmacist member of the ASP was notified in real time of positive CDI results and consulted with the care team to initiate optimal therapy, minimize concomitant antibiotic and acid-suppressive therapy, and recommend surgical/infectious diseases (ID) consultation in complicated cases. The primary outcome was a composite of 30-day mortality, ICU admission, colectomy/loop ileostomy, and recurrence. A blinded review panel of ID physicians determined whether outcomes were attributed to CDI.

Results: A significantly higher percentage of patients in the ASP intervention group had acid-suppressive therapy discontinued (24% versus 9%, P=0.001), and, in patients with severe disease, significantly more patients in the ASP intervention group received an ID consult (17% versus 10%, P=0.035), received appropriate therapy with oral vancomycin (87% versus 59%, P<0.0001), and vancomycin therapy was initiated earlier (mean 1.05 days vs. 1.70 days, P=0.04), compared to the pre-intervention group. The incidence of the composite outcome was not significantly different between the ASP intervention and pre-intervention groups (12.3% versus 14.7%, P=0.40).

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Conclusions: ASP review and intervention in patients with CDI improved process measures. A decrease in composite outcomes was not found, which may be due to low baseline rates of attributable surgery (0–2%), mortality (2–3%) and ICU admission (4–6%) in our institution.

Keywords

antimicrobial stewardship; *Clostridium difficile*; patient outcomes; oral vancomycin; proton pump inhibitors

Background

Clostridium difficile is the pathogen responsible for the most common health care-associated infection, causing nearly half a million infections in the United States in 2011.[1–2] *Clostridium difficile* infection (CDI) is associated with a nearly 3-fold increase in mortality compared to non-infected controls,[3(Pakyz Pharmacotherapy)] and recurrence occurs in 6–25% of patients (ICHE Guidelines). Antimicrobial stewardship programs (ASPs) are effective in reducing CDI incidence (Faezel JAC 2014), generally by reducing use of high-risk antibiotics. While prevention of CDI via drug-based stewardship is an important goal, ASPs also have the potential to positively impact the care of patients with CDI. ASPs have been shown to improve patient outcomes in a variety of infections (9–11, include Staph aureus ASP bundle project by Nguyen and Nagel). Furthermore, ASPs are uniquely positioned to improve treatment of CDI through targeted evidence-based interventions. For example, retrospective analyses have postulated that prompt initiation of optimal therapy, decreasing use of concomitant antimicrobials and proton-pump inhibitors (PPIs) during CDI treatment, and surgical consultation before CDI has irreversibly progressed may improve clinical outcomes (Barbut 2013, Pop-Vicas Infect Control Epidemiol 2012, Modena J Clin Gastroenterol 2006, Linsky Annals of Internal Medicine, Neal Annals of Surgery). These all represent interventions that ASPs may successfully prioritize to potentially improve outcomes. However, studies to date have not rigorously evaluated the impact of ASP involvement on clinical outcomes in patients with CDI.[18–22] Therefore, the objective of this study was to evaluate clinical outcomes attributed to CDI before and after the implementation of a comprehensive, real-time ASP initiative.

Methods

Patients

The University of Michigan Institutional Review Board approved this study. This was a single-center, quasi-experimental study evaluating hospitalized patients with CDI at the University of Michigan Hospital (UMH) before and after implementation of an ASP-directed CDI treatment bundle. UMH is a 930-bed tertiary academic medical center with an adult ASP consisting of three infectious diseases (ID) physicians, three ID pharmacists, and an infection prevention liaison. Adult patients >18 years old with CDI from August 1, 2013 to January 31, 2014 (pre-intervention group) and April 3, 2014 to September 30, 2014 (intervention group) were eligible for inclusion. Patients were excluded if CDI treatment was initiated prior to admission at UMH or if CDI testing was performed for screening purposes in a bone marrow transplant patient without active diarrhea. In the intervention group,

patients were excluded if they were discharged prior to ASP review or if the ASP was not able to review the patient because the alert did not generate. For patients with multiple occurrences of CDI during the study period, only the first occurrence was included.

Group Descriptions

In both groups, CDI testing was performed at the discretion of the inpatient care team. Microbiology testing on submitted samples was performed using the algorithm described by Solomon (Bagdasarian JAMA 2015). In brief, tests for *C. difficile* glutamate dehydrogenase (GDH) and toxins A or B (by enzyme immunoassay) were performed in all patients. GDH+/toxin– stool tests were subsequently tested for presence of the *tcdB* gene by real-time PCR. Treatment guidelines available on the ASP webpage provided recommendations for optimal antimicrobial therapy stratified by disease severity and number of recurrences (vancomycin recommended over metronidazole for patients with severe disease and multiple recurrences). Severe disease was defined as age ≥ 65, white blood count > 15 X 10^3/mm^3, albumin ≤ 2.5 g/dL, serum creatinine ≥ 1.5 times the premorbid level, treatment for rejection in a solid organ transplant (SOT) recipient in the preceding 2 months, chronic graft-versus-host disease (GvHD) in a bone marrow transplant (BMT) recipient, or SOT/BMT in the preceding 100 days. As no consensus exists for defining severe CDI, institutional criteria were adapted from guidelines (23,24), a clinical trial which compared vancomycin to metronidazole (Zar FA et al, Clin Infect Dis 2007), and local expert opinion. Additionally, the guideline encouraged minimization of concomitant antimicrobial and acid-suppressive therapies, and recommended surgical and/or infectious diseases consultation for patients with multiple recurrences and/or severe or complicated infection. No major changes in Infection Control processes for patients with CDI were instituted during the study period.

Prior to implementation of the ASP initiative, treatment for CDI was at the discretion the patient's primary medical team and the ASP was not routinely involved in the management of these patients. Starting April 2014, pharmacist members of the ASP were notified of positive CDI lab results through clinical surveillance software (TheraDoc Version 4.4, Hospira, Lake Forest, Illinois), which provided real-time, automated alerts. An ASP pharmacist reviewed each case and contacted the medical team, if necessary, with recommendations. ASP review was performed as soon as possible after being alerted on Monday- Friday between the hours of 8am-5pm. For alerts received after hours, interventions were deferred until the next business day. Recommendations generally fell within four categories: prescribing guideline-concordant CDI therapy; discontinuation or de-escalation of non-CDI antibiotics; minimization of acid-suppressive therapy; and recommendation for ID or surgical consultation. ASP members recorded all recommended interventions and the prescriber acceptance rate.

Outcomes

Data was extracted from the electronic medical record. The primary outcome, derived from recommendations from the Ad Hoc Clostridium difficile Surveillance Working Group (McDonald LC, Infection Control and Hospital Epidemiology 2007), was a composite of 30-day mortality, intensive care unit (ICU) admission within 30 days of diagnosis, need for colectomy or ileostomy for complicated CDI within 30 days, or CDI recurrence. Recurrence

was defined as a second occurrence of CDI between 2–8 weeks after the date of the index case. Attribution of mortality, ICU admission, and colectomy/ileostomy to CDI was performed by 2 Infectious Diseases physicians independently (L.W. and C.C.), and a third Infectious Diseases physician (T.G.) adjudicated conflicts.

Process measures that may impact outcomes were also recorded, including use (and time to initiation) of vancomycin in patients with severe disease, discontinuation or de-escalation of non-CDI antibiotic therapy, discontinuation of unnecessary PPI therapy, and ID consultation for patients with severe and complicated CDI.

Statistical analysis

Prior literature has identified that complications due to CDI occur in ~10–15% of patients (Hensgens MPM Clin Micro Infect 2013, Morrison RH Clin Infect Dis 2011) and that 6–25% of CDI patients experience a recurrence of symptoms (Cohen ICHE 2010- guidelines, Zar FA Clin Infect Dis 2007). As such, assuming that 20% of the pre-intervention group would meet the composite outcome, a sample size of ~600 patients was deemed adequate to achieve a significance level of 0.05, power of 80%, and a minimum detectable difference of 8% in the primary composite endpoint between the ASP intervention and pre-intervention groups. Dichotomous data, including the primary outcome, were analyzed using a two-sided Fisher's exact test. Continuous data were analyzed using descriptive statistics and a two-tailed Student's *t*-test. For all analyses, a *P*-value ≤0.05 was considered significant. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

Five hundred ninety-two patients met study criteria for inclusion (307 patients in the pre-intervention group and 285 in the intervention group). Baseline patient characteristics are provided in Table 1. Overall, 39% (232/592) of patients were ≥ 65 years old and 21% (123/592) presented with significant leukocytosis (white blood cell count ≥ 15 $10^3/mm^3$) at time of CDI positivity. 77% (458/592) of patients met criteria for severe disease, while 7% (44/592) of patients presented with complications (hypotensive, ileus, megacolon, and/or peritonitis) and required ICU care at the time of diagnosis. Baseline characteristics between groups were generally similar, although patients in the intervention group were slightly older (mean age 60.1 versus 56.8 years) and less commonly male (48.4% versus 56.7%).

ASP pharmacists provided treatment recommendations for 129 out of 285 patients in the intervention group (45%), and 129 total interventions were accepted in 105 unique patients (81% acceptance rate). Data regarding process measures are provided in Table 2. ASP intervention was associated with a significantly higher rate of PPI discontinuation (30.3% versus 12.6%, $P=0.004$) compared to the pre-intervention group. Among patients with severe CDI, those in the ASP intervention group were more likely to receive appropriate therapy with oral vancomycin (87% versus 59%, $P<0.0001$), and the mean time to initiation of vancomycin therapy was improved (1.05 days versus 1.70 days, $P=0.03$). Additionally, 13 changes to non-CDI related antibiotic therapy (of 133 patients receiving concomitant antibiotics) were made at the time of CDI positivity. The incidence of ID consultation for severe CDI was higher with ASP review (17.2% versus 10.4%, $P=0.03$).

Outcomes are provided in Table 2. In the overall cohort, the crude 30-day mortality was 10.5% (62/592), 30-day ICU admission was 15.0% (89/592), and 30-day colectomy/ileostomy was 0.8% (5/592). The attributable 30-day mortality was 2.4% (14/592), 30-day ICU admission was 4.4% (26/592), 30-day colectomy/ileostomy was 0.7% (4/592), and recurrence rate was 8.8% (52/592). Occurrence of the primary composite outcome was not significantly different between the intervention and pre-intervention groups (12.3 versus 14.7%, P=0.40). In addition, the incidences of the individual components of the composite outcome were not significantly different between groups.

Discussion

This study tested the hypothesis that a comprehensive, real-time ASP initiative would improve outcomes in patients with CDI. Unfortunately, while the initiative improved several process measures, attributable clinical outcomes were not statistically improved with ASP intervention.

Four previous studies have examined the impact of direct ASP intervention on process measures and clinical outcomes in patients with CDI (Brumley, Jardin, Jury, Yeung). In a 2013 pre/post study of 146 patients with CDI, Jury and colleagues demonstrated that targeted ASP intervention could significantly improve measures such as receipt of guideline-adherent treatment (83% baseline vs. 100% intervention, p-value 0.002) and time to treatment initiation (median 4 hours baseline vs. 1 hour intervention, p=0.007). However, the effect of these improvements on measures of clinical outcomes was not assessed (JURY ICHE 2013). Jardin and colleagues evaluated an ASP-driven protocol allowing substitution of oral vancomycin for oral metronidazole in 256 patients with severe CDI. Implementation of the protocol resulted in a significant improvement in vancomycin prescribing (14% pre-intervention vs. 91% post-intervention, p<0.0001). Refractory disease, defined as diarrhea persisting beyond 6 days of therapy, decreased significantly in the intervention group (37% vs. 15%, p= 0.035). However, neither in-hospital crude mortality nor length of stay were significantly improved in the intervention group (JARDIN J HOSP INF 2013). Yeung and colleagues studied the impact of ASP intervention in a pre-post study of 424 patients with CDI. ASP intervention consisted of mandatory clinical pharmacist review of all patients with CDI and recommendation of therapy adherent to the institutional treatment algorithm. This intervention improved overall treatment compliance (34.0% pre-intervention versus 48.1% intervention, p=0.01). All-cause 30-day mortality was not impacted, and although a significant decrease in median length of stay was documented in the intervention group, no analysis was performed to independently ascribe this outcome to ASP intervention (YEUNG JCPT 2015). Most recently, Brumley and colleagues (n=169) evaluated the effect of a CDI treatment bundle with active ASP review targeting similar process measures to those described in the current study, including minimization of concomitant antimicrobial and acid-suppressive therapy, selection of appropriate CDI therapy, and ID or surgical consultation in severe and/or complicated CDI. ASP intervention was associated with an increase in bundle adherence (45% pre-intervention versus 81% intervention, P<0.001), including a higher rate of appropriate CDI therapy and discontinuation of non-essential acid suppressants. No significant differences were noted between groups in mortality, readmission due to CDI, length of stay, or hospital costs (BRUMLEY JAC 2016).

Our study, the largest effort to explore the impact of direct ASP intervention on patients with CDI, enables several conclusions to be drawn when reviewed in context of the prior literature discussed above. First, focused ASP review and intervention in patients with CDI has consistently been shown to improve process measures. Our comprehensive ASP "bundle" resulted in the most diverse array of process measure improvements studied to date, with significant improvements identified in rates of optimal therapy, discontinuation of unnecessary PPI therapy, ID consultation, and time to initiation of appropriate therapy. However, in our study and others, such improvements have not resulted in significant changes in CDI complications. Notably, our study is the first to utilize a composite endpoint of CDI complications, as well as the first to employ a robust process to attribute outcomes to CDI via blinded ID physician review. This lends further strength to the findings. We were also not able to identify significant improvements in outcomes in the subset of patients with severe disease, a population which may be expected to benefit the most from optimization of care (Table 2).

In postulating why ASP intervention has not been successful in improving clinical outcomes, it is instructive to examine the low baseline rates of attributable outcomes (surgery 1.3%, mortality 2.3%, ICU admission 4.6%) in our study. These rates are very similar to those previously attributed to 1,144 cases of CDI at our institution (colectomy 0.4%, mortality 4.3%, ICU admission 4.3%), which lend credence to our results (RAO K CID 2015). However, with such low rates of attributable outcomes, it may be unreasonable to expect ASP intervention to significantly improve results. While the composite outcome was numerically superior in our intervention group (12.3% vs. 14.7% in pre-intervention group), a prohibitively large sample size (~6,000 patients) would be needed to confirm whether this finding is significant.

Perhaps a more appropriate question, however, is whether previous literature would support aligning interventions with a decrease in complications due to CDI. In the two randomized, controlled clinical trials comparing vancomycin to comparator agents (metronidazole and tolevemar), vancomycin has been found to be superior, especially in patients with severe CDI, in terms of clinical cure (generally, resolution of diarrhea by a defined time point), but no significant impact on complications such as mortality, need for colectomy, or recurrence has been demonstrated (Zar, Johnson). A retrospective study of PPIs in CDI found that PPI exposure within 14 days of CDI diagnosis was associated with an increased rate of recurrent disease (25.2% versus 18.5%). However, this finding has not been confirmed in an interventional study, and at least 15 PPIs would need to be discontinued to prevent one CDI recurrence (Linsky AIM). While fidaxomicin has been shown to reduce the rate of recurrence compared to vancomycin, no significant improvements in CDI complications with fidaxomicin therapy have been shown (Louie TJ NEJM 2011, Cornely Lancet ID 2012). As such, perhaps it is not surprising that the only ASP intervention study to identify a robust impact on outcomes in CDI was the trial by Jardin, where increased use of vancomycin therapy in patients with severe disease was associated with a significant decrease in refractory disease (i.e., continued diarrhea) (JARDIN). Given the retrospective nature of our study, we did not collect this data, given the lack of confidence in accurate documentation of stooling frequency in the medical record at our institution.

Our study is subject to the limitations inherent to quasi-experimental studies, including the potential for variation in unmeasured baseline characteristics between groups. Our data reflect practices and outcomes at a single institution, which may not be generalizable to other institutions. Our study did not evaluate the role of other treatment modalities, including fidaxomicin or fecal microbiota transplant. Our ASP reviewed and intervened on each patient only once following notification of positive CDI assay, and further study would be needed to assess the impact of more frequent review. Anecdotally, the rate of non-CDI antibiotic de-escalation would likely increase with ongoing, concurrent review throughout the course of infection.

In conclusion, ASP review and intervention improved process measures, including vancomycin treatment for severe CDI, time to initiation of vancomycin, discontinuation of unnecessary PPIs, and rate of ID consultation for severe CDI. No difference was found in the composite outcome of 30-day attributable mortality, ICU admission, colectomy/loop ileostomy, and recurrence, which may be due to low baseline rates of these complications at our institution. In combination with past literature, the results of our study question whether ASP involvement in the conventional management of CDI is worthwhile. The impact of ASP involvement in positioning alternative therapies remains unknown. Institutions must weigh the costs (including resources that could be diverted elsewhere) with a realistic expectation of the potential benefits of ASP intervention when deciding where to direct resources, especially at institutions with low rates of attributable complications.

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Table 1

Patient Baseline Characteristics

	Pre-intervention (n = 307)	ASP Intervention (n = 285)	*P*
Mean age ± SD (years)	56.8 ± 17.3	60.1 ± 16.7	0.021
Male, No. (%)	174 (56.7)	138 (48.4)	0.044
Comorbidities, No. (%)			
HIV	6 (2.0)	0 (0.0)	0.031
Diabetes	102 (33.2)	91 (31.9)	0.737
Hematologic Malignancy	48 (15.6)	31 (10.9)	0.089
Inflammatory Bowel Disease	28 (9.1)	18 (6.3)	0.203
End-stage Renal Disease	47 (15.3)	35 (12.3)	0.287
Cirrhosis	29 (9.5)	28 (9.8)	0.876
Disease severity measures, mean ± SD			
Temperature (°C)	37.5 ± 0.80	37.5 ± 0.82	0.672
WBC count (10^3/mm^3)	12.2 ± 30.4	11.0 ± 7.7	0.544
Neutrophil count (10^3/mm^3)	8.8 ± 8.3	8.7 ± 6.8	0.821
Albumin (g/dL)	3.2 ± 0.577	3.2 ± 0.570	0.962
Creatinine (mg/dL)	1.4 ± 1.56	1.5 ± 1.64	0.745
Bilirubin (mg/dL)	1.3 ± 2.82	1.6 ± 3.74	0.277
Lactate (mEq/L)	1.5 ± 1.5	1.4 ± 0.7	0.314
Clinical status, No. (%)			
Presence in ICU	37 (12.1)	39 (13.7)	0.553
Mechanically ventilated	25 (8.2)	25 (8.8)	0.783
Severe CDI, No. (%)	231 (75)	227 (80)	0.201
Severe CDI qualifications, No. (%)			
Age ≥ 65	107	125	0.0249
WBC > 15,000	61	59	0.8013
ANC ≤ 500	11	8	0.5925
Albumin ≤ 2.5	41	30	0.2898
SCr ≥ 1.5 times premorbid level	75	82	0.2318
SOT/BMT < 100 days	21	8	0.0231
Chronic GvHD	3	1	0.6248
SOT rejection treatment in past 2 months	1	2	0.6109
Treatment factors, No. (%)			
Surgery service involved	58 (19.1)	49 (17.3)	0.566
Active ID consultation	24 (7.9)	26 (9.1)	0.593
Treatment with PPI	128 (41.7)	112 (39.3)	0.553

Abbreviations: ASP, antimicrobial stewardship program; SD, standard deviation; HIV, human immunodeficiency virus; WBC, white blood cell; ICU, intensive care unit; CDI, *Clostridium difficile* infection; ID, infectious diseases; PPI, proton pump inhibitor

Table 2

Patient outcomes

	All patients			Severe CDI only[a]		
	Pre-Intervention (n=307)	**ASP Intervention (n=285)**	***P***	**Pre-Intervention (n=231)**	**ASP Intervention (n=227)**	***P***
Composite outcome	45 (14.7%)	35 (12.3%)	0.40	35 (15.2%)	31 (13.7%)	0.65
Attributable 30-day mortality	7 (2.3%)	7 (2.5%)	0.89	7 (3.0%)	7 (3.1%)	0.97
Attributable 30-day ICU admission	14 (4.6%)	12 (4.2%)	0.84	13 (5.6%)	12 (5.3%)	0.87
Attributable 30-day surgery	4 (1.3%)	0 (0.0%)	0.12	4 (1.7%)	0 (0.0%)	0.12
CDI recurrence (2–8 weeks)	29 (9.5%)	23 (8.1%)	0.55	20 (8.7%)	19 (8.4%)	0.91
Crude outcomes						
30-day mortality	28 (9%)	34 (12%)	0.265	28 (12%)	34 (15%)	-
30-day ICU admission	43 (14%)	46 (16%)	0.468	40 17%)	45 (20%)	-
30-day surgery	4 (1%)	1 (0.3%)	0.375	4 (1.7%)	1 (0.04%)	-
Mean length of stay ± SD (days)	14.3 ± 17.3	14.7 ± 18.4	0.79	15.5 ±	15.8 ±	0.80
Process measures						
PPI Stopped[b]	11/87 (12.6%)	27/89 (30.3%)	0.004	10/72 (13.9%)	22/77 (28.6%)	0.029
ID Consulted within 72 hours	35 (11.4%)	44 (15.4%)	0.149	24 (10.4%)	39 (17.2%)	0.035
Vancomycin order for severe CDI	-	-	-	136 (59%)	197 (87%)	<0.0001
Mean days to vancomycin order	-	-	-	1.70	1.05	0.03

[a]Due to the small number of patients who presented with complications due to CDI (shock, megacolon, ileus, or peritonitis) such patients were grouped in the “Severe” group.

[b]Defined as PPI discontinuation within 72 hours of positive *C difficile* test in patients who were not discharged during this time period.

Abbreviations: CDI, *Clostridium difficile* infection; ICU, intensive care unit; PPI, proton pump inhibitor; ID, infectious diseases

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