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Major Article

Effect of an antimicrobial stewardship intervention on outcomes for patients with *Clostridium difficile* infection

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Background: Although antimicrobial stewardship programs (ASPs) are uniquely positioned to improve treatment of *Clostridium difficile* infection (CDI) through targeted interventions, studies to date have not rigorously evaluated the influence of ASP involvement on clinical outcomes attributed to CDI.

Methods: We performed a quasiexperimental study of adult patients with CDI before (n = 307) and after (n = 285) a real-time ASP review was initiated. In the intervention group, an ASP pharmacist was notified 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 consultation in complicated cases. The primary outcome was a composite of attributable 30-day mortality, intensive care unit admission, colectomy/ileostomy, and recurrence.

Results: A higher percentage of patients in the ASP intervention group had acid-suppressive therapy discontinued (30% vs 13%; $P < .01$). Among patients with severe CDI, more patients in the intervention group received an infectious diseases consultation (17% vs 10%; $P = .04$), received appropriate therapy with oral vancomycin (87% vs 59%; $P < .01$), and vancomycin was initiated earlier (mean, 1.1 vs 1.7 days; $P < .01$). Incidence of the composite outcome was not significantly different between the 2 groups (12.3% vs 14.7%; $P = .40$).

Conclusions: ASP review and intervention improved CDI process measures. A decrease in composite outcomes was not found, which may be due to low baseline rates of attributable complications in our institution.

BACKGROUND

Clostridium difficile is the cause of the most common health care-associated infection, with nearly half a million cases occurring in the United States during 2011.[1,2] *C difficile* infection (CDI) is associated with a nearly 3-fold increase in mortality compared with noninfected controls, and 6%-25% of patients experience recurrent infections.[3,4] Antimicrobial stewardship programs (ASPs) are effective in reducing CDI incidence by decreasing use of high-risk antibiotics.[5] Although prevention of CDI via drug-based stewardship is an important goal, ASPs also have the potential to positively influence the care of patients with CDI. ASPs have been effective in improving patient outcomes in a variety of infections,[6-9] and are also uniquely positioned to improve the treatment of CDI through targeted, evidence-based interventions. Retrospective analyses have postulated that prompt initiation of optimal therapy, decreasing use of concomitant antimicrobial agents and proton-pump inhibitors (PPIs) during CDI treatment, and surgical consultation before CDI has irreversibly progressed may improve clinical outcomes.[10-14] These all represent measures that ASPs are capable of optimizing. In support of this hypothesis, a 2014 Practice Recommendation by the Infectious

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Diseases Society of America and the Society for Healthcare Epidemiology of America encouraged ASP oversight to ensure appropriate severity-based treatment of CDI.[15] However, studies to date have not rigorously evaluated the influence of ASP involvement on clinical outcomes in patients with CDI.[16-20] 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, quasiexperimental study evaluating hospitalized patients with CDI at the University of Michigan Health System (UMHS) before and after implementation of an ASP-directed CDI treatment bundle. UMHS is a 1000-bed tertiary academic medical center with an adult ASP consisting of 3 infectious diseases (ID) physicians, 3 ID pharmacists, and an infection prevention liaison. Adult inpatients aged 18 years or older with CDI from August 1, 2013, to January 31, 2014 (preintervention group), and April 3, 2014, to September 30, 2014 (intervention group), were eligible for inclusion. Patients were excluded if CDI treatment was initiated before admission at UMHS or if CDI testing was performed for screening purposes in a bone marrow transplant patient without active diarrhea. In the intervention group, patients were also excluded if they were discharged before ASP review or if the ASP team 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 Bagdasarian et al.[21] 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 polymerase chain reaction. The GDH and toxin enzyme immunoassay tests were run 4 times daily, whereas the polymerase chain reaction assay was run once daily. Treatment guidelines, developed by the ASP team and approved by the institutional Pharmacy and Therapeutics Committee, were available on the ASP web page and provided recommendations for optimal antimicrobial therapy stratified by disease severity and number of recurrences. Vancomycin was recommended over metronidazole for patients with severe disease and/or ≥2 recurrences. Severe disease was defined as age ≥65 years, white blood count $>15 \times 10^3/mm^3$, albumin ≤2.5 g/dL, serum creatinine ≥1.5 times the premorbid level, treatment for rejection in a solid organ transplant recipient in the preceding 2 months, chronic graft-versus-host disease in a bone marrow transplant recipient, or solid organ transplant and/or bone marrow transplant in the preceding 100 days. Because no consensus exists for defining severe CDI, institutional criteria were adapted from guidelines,[4,22] a clinical trial that compared vancomycin to metronidazole,[23] and local expert opinion. Additionally, the guideline encouraged minimization of concomitant antimicrobial and acid-suppressive therapies and recommended surgical and/or ID 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.

Preintervention group

Before implementation of the ASP initiative, treatment for CDI was at the discretion the patient's primary medical team and the ASP team was not routinely involved in the management of these patients.

Intervention group

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, IL), which provided real-time, automated alerts. An ASP pharmacist reviewed each case once 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 8 a.m.-5 p.m. For alerts received after hours, reviews were deferred until the next business day. Recommendations generally fell within 4 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 were extracted from the electronic medical record. The primary outcome, derived from recommendations from the ad hoc *C difficile* Surveillance Working Group,[24] was a composite of attributable 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 and 8 weeks after the date of the index case. Attribution of mortality, ICU admission, and colectomy/ileostomy to CDI was performed by 2 ID physicians independently (CC and LW), and a third ID physician (TG) adjudicated conflicts.

Process measures that may influence 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 and that 6%-25% of CDI patients experience a recurrence of symptoms.[4,23,25,26] As such, assuming that 20% of the preintervention 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 end point between the ASP intervention and preintervention groups. Dichotomous data, including the primary outcome, were analyzed using a 2-sided Pearson χ^2 or Fisher exact test, as appropriate. Continuous data were analyzed using descriptive statistics and a 2-tailed Student *t* test or Mann-Whitney *U* test, as appropriate. For all analyses, a P value ≤ .05 was considered significant. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

RESULTS

There were 762 positive *C difficile* test results during the study period. Seven patients were excluded because CDI treatment was initiated before admission and 15 were excluded because CDI testing was performed for screening purposes in bone marrow transplant patients. Ninety-nine results from patients with multiple occurrences