CLINICAL RESEARCH STUDY

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Effect of Treatment Variation on Outcomes in Patients with *Clostridium difficile*

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ABSTRACT

PURPOSE: New guidelines for the treatment of *Clostridium difficile*-associated diarrhea were published by the Infectious Disease Society of America (IDSA) in 2010, however, there has been no literature evaluating the effectiveness of these guidelines. The purpose of this study was to examine the clinical outcomes of *Clostridium difficile* infection including death, *C difficile* infection recurrence, toxic megacolon, and surgery between patients who received guideline-concordant therapy vs guideline-discordant therapy.

METHODS: Retrospective case-control study of hospitalized adults with *C difficile* infection presenting to a 420-bed tertiary care referral county teaching hospital. Patients were identified by International Classification of Diseases-9th Revision codes, and included if they were ≥18 years of age and treated for *C difficile* infection during their hospital visit. Complication rates (death, infection recurrence, toxic megacolon, and surgery) of patients with *C difficile* infection were measured to determine if following the IDSA guidelines improves outcomes.

RESULTS: Only 51.7% of the patients' prescribers followed the 2010 IDSA guidelines. Patients whose prescribers followed the IDSA guidelines experienced fewer complications than patients whose prescribers strayed from the guidelines (17.2% vs 56.3%, $P < .0001$). This difference was mainly due to a reduction in mortality (5.4% vs 21.8%, $P = .0012$) and infection recurrence (14% vs 35.6%, $P = .0007$). Patients who presented with severe and complicated disease received guideline-based therapy significantly less often than patients with mild disease (19.7%, 35.3%, and 81.2%, respectively, $P < .0001$).

CONCLUSIONS: There was a significant reduction in *C difficile* infection recurrence and mortality when prescribers followed the IDSA/Society for Healthcare Epidemiology of America guidelines for treatment of *C difficile* infection.

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KEYWORDS: *Clostridium difficile*; Infectious diarrhea; Treatment guidelines

Clostridium difficile is a Gram-positive, anaerobic, cytotoxin-producing bacterium that is of growing concern to the health care industry. It has been a common cause of nosocomial infections for decades and historically has experienced a stable epidemiological profile. However, increased disease incidence and severity combined with reduced response to standard therapies have identified *C difficile* infections as a target for increased study and invigorated control.[1]

C difficile infection is now the leading cause of infectious nosocomial diarrhea in industrialized countries worldwide.[2] In the US, the incidence of *C difficile* infection increased from 5.5 to 11.2 cases per 10,000 population between 2000 and 2005.[3] *C difficile* infection-related age-adjusted fatality rates nearly doubled from 1.2% to 2.2% over this same 5-year time period.[3] More recent evidence has shown that the national rate of *C difficile* infection hospitalizations per 1000 nonmaternal, adult discharges has more than doubled in the last 10 years (5.6 vs 12.1).[4] Also, many outbreaks responsible for the increased rates of *C difficile* infections involve a highly virulent strain referred to as the North American Pulsed Field type 1 (NAP-1) strain. The NAP-1 strain

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produces as much as 10 times more toxin than other *C difficile* strains, causing more severe infections.[1] These alarming trends show why containing *C difficile* infections has become a top priority in the acute care setting.

C difficile infections are not only becoming more common and more serious but are also becoming increasingly more difficult to treat. The standard treatment for *C difficile* infection remains metronidazole or oral vancomycin. Fidaxomicin, a newly developed treatment option for *C difficile* infection, was not approved for use at the time of guideline publication. In the past, these drugs have had similar cure rates of over 90%. Concern over the development of vancomycin resistance left the less-expensive metronidazole option as the most commonly used first-line treatment.[5,6] However, an observational study has shown that the *C difficile* infection failure rate of metronidazole may be as high as 50%, evoking the question of vancomycin superiority.[7] Furthermore, rates of *C difficile* infection recurrence are also on the rise. An analysis of *C difficile* infection in Quebec, Canada demonstrated that the recurrence rate in patients >65 years of age increased from 28.9% during 1991 to 2002, to 58.4% during 2003 and 2004.[8] Moreover, cure rates between metronidazole and vancomycin may differ in certain patients. A recent study stratified patients by *C difficile* infection severity, and compared the effectiveness of the 2 different regimens. The response rates for vancomycin and metronidazole in patients with mild infections were similar (98% and 90% respectively, $P = .36$). However, in patients with severe infections, vancomycin showed a significantly higher response rate than metronidazole (97% and 76%, respectively, $P = .02$).[9]

In 2010, the Infectious Disease Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) published guidelines outlining treatment recommendations for patients with *C difficile* infection.[10] The guidelines recommend stratification of all patients with confirmed *C difficile* infection based on history, infection severity, and the presence of complicating factors. Recent guidelines released in April of 2013 from the American College of Gastroenterology echo the IDSA/SHEA guidelines.[11] Patients experiencing a mild or moderate first occurrence, or first recurrence, should be treated with oral metronidazole. Those experiencing a severe first occurrence, or first recurrence, should be treated with oral vancomycin. Patients with a history of more than one recurrence should be treated with oral vancomycin regardless of infection severity, and their treatment should conclude in a pulsed or tapered manner to prevent further recurrence. Lastly, patients experiencing a severe and complicated infection should be treated with intravenous metronidazole and oral vancomycin, with or without rectal vancomycin administration. Specific guideline recommendations can be seen in **Table 1**. It is unknown if the guidelines have influenced current practices and prescribing patterns or improved patient outcomes. *C difficile* infection is associated with several complications, including infection recurrence, need for surgery, toxic megacolon, and death.[1] We hypothesized that guideline-concordant therapy may lead to a reduction of these complications compared with guideline-discordant therapy.

CLINICAL SIGNIFICANCE

- Only 51.7% of prescribers followed the Infectious Disease Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) guidelines for the treatment of *Clostridium difficile* infections.
- Patients whose prescribers followed the IDSA/SHEA guidelines had a significant reduction in mortality (5.4% vs 21.8%, $P = .0012$) and *C difficile* infection recurrence (14% vs 35.6%, $P = .0007$).
- Patients who presented with severe and complicated disease received guideline-based therapy significantly less often than patients with mild disease (19.7%, 35.3%, and 81.2%, respectively, $P < .0001$).

METHODS

We conducted a retrospective case-control study of patients who were diagnosed with an intestinal infection due to *C difficile* from hospital stays between April 1, 2011 and October 1, 2011. Patients were identified by the International Classification of Diseases-9th Revision discharge diagnosis code of 008.45 (intestinal infection due to *C difficile*).[12] Patients were included if they were at least 18 years of age, and received treatment for *C difficile* infection. All data were collected from electronic health records from a single 420-bed tertiary care referral county teaching hospital in west Texas. The following information was gathered from medical records using a standardized data collection sheet: demographic information, hospital admission and discharge dates, previous hospital admissions within 12 months, daily vital signs and laboratory values, *C difficile* infection status, *C difficile* polymerase chain reaction, presence of NAP-1 strain, *C difficile* infection treatment regimens, *C difficile* infection history, previous antibiotic exposure, previous proton pump inhibitor exposure, Simplified Acute Physiology Score (SAPS-II), *C difficile* infection recurrence, subtotal colectomy, ileostomy, or any other surgical intervention intended to cure a *C difficile* infection, development of toxic megacolon, and 30-day all-cause mortality. This study was approved by the appropriate Institutional Review Board.

The primary aim of this study was to determine if guideline-concordant therapy reduces the rates of complications compared with guideline-discordant therapy. Patients were classified retrospectively into one of the previously mentioned *C difficile* infection categories defined in the IDSA/SHEA guidelines (mild or moderate, severe, or severe and complicated). Infections were classified into their