AIM: To assess adherence with the the Society for Healthcare Epidemiology of America (SHEA)/the Infectious Diseases Society of America (IDSA) guidelines for management of *Clostridium difficile* (C. difficile)-associated disease (CDAD) at a tertiary medical center.

METHODS: All positive *C. difficile* stool toxin assays in adults between May 2010 and May 2011 at the University of Maryland Medical Center were identified. CDAD episodes were classified as guideline adherent or non-adherent and these two groups were compared to determine demographic and clinical factors predictive of adherence. Logistic regression analysis was performed to assess the effect of multiple predictors on guideline adherence.

RESULTS: 320 positive *C. difficile* stool tests were identified in 290 patients. Stratified by disease severity criteria set forth by the SHEA/IDSA guidelines, 42.2% of cases were mild-moderate, 48.1% severe, and 9.7% severe-complicated. Full adherence with the guidelines was observed in only 43.4% of cases. Adherence was 65.9% for mild-moderate CDAD, which was significantly better than in severe cases (25.3%) or severe-complicated cases (35.5%) (*P* < 0.001). There was no difference in demographics, hospitalization, ICU exposure, recurrence or 30-d mortality between adherent and non-adherent groups. A multivariate model revealed significantly decreased adherence for severe or severe-complicated episodes (OR = 0.18, 95%CI: 0.11-0.30) and recurrent episodes (OR = 0.46, 95%CI: 0.23-0.95).

CONCLUSION: Overall adherence with the SHEA/IDSA guidelines for management of CDAD at a tertiary medical center was poor; this was most pronounced in severe, severe-complicated and recurrent cases. Educational interventions aimed at improving guideline adherence are warranted.

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Key words: *Clostridium difficile*; Metronidazole; Vancomycin; Adherence to the Infectious Diseases Society of America Guidelines; Hospital Acquired Infections

Core tip: This study assesses a tertiary care medical center’s adherence with updated guidelines on the management of *Clostridium difficile* (C. difficile)-associated diseases in adults. We found that overall adherence is poor, especially in patients with severe disease. Factors associated with poor adherence and limitations of current guidelines are identified. Our data suggests that educational interventions aimed at improving *C. difficile* guideline adherence are warranted.
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**INTRODUCTION**

*Clostridium difficile* (*C. difficile*) is the major infectious cause of nosocomial diarrhea and can cause prolonged hospital stays, renal failure, toxic megacolon, and death. In 1995, the Society for Healthcare Epidemiology of America (SHEA) published a clinical position paper on *C. difficile*-associated disease (CDAD). Based on data from small, randomized, controlled studies showing no outcome-difference when comparing metronidazole and vancomycin, the 1995 position paper considered them equally effective; however, it stated, “metronidazole may be preferred to reduce the risk of vancomycin resistance among other organisms in hospitals.” Updated clinical practice guidelines for the management of CDAD in adults were published in 2010 by SHEA and the Infectious Diseases Society of America (IDSA). The 15-year interval between the two sets of recommendations was marked by dramatic changes in CDAD epidemiology and outcomes, with increases in prevalence, severity, and therapy resistance; emergence of hypervirulent strains may have contributed to these trends. Additionally, new data suggested vancomycin might be superior for CDAD treatment in some cases. *Zak et al.* prospective, randomized, comparative efficacy study of metronidazole vs vancomycin demonstrated superiority of vancomycin for the treatment of severe CDAD. These results influenced the 2010 SHEA/IDSA guidelines that recommended vancomycin as first-line treatment for severe CDAD, while maintaining a recommendation for metronidazole in mild-moderate cases. These guidelines recommend treating an initial recurrence in the same manner as the initial episode, and a second recurrence with vancomycin in a tapering and/or pulsed regimen.

The 2010 SHEA/IDSA recommendations promote significant clinical practice changes. Since adherence to the guidelines may affect patient outcomes and infection control, we sought to determine adherence with the updated SHEA/IDSA CDAD guidelines at a tertiary care medical center.

**MATERIALS AND METHODS**

The Institutional Review Board of the University of Maryland Baltimore approved this study and waived the requirement for informed consent. All positive *C. difficile* stool tests (Quick Check A/B Toxin Assay; Wampole Laboratories, Princeton, New Jersey) in adults between May 2010 and May 2011 at the University of Maryland Medical Center were retrospectively identified. Medical charts were reviewed for demographics, clinical information, and adherence to CDAD guidelines.

Classifications defined in the updated 2010 SHEA/IDSA guidelines were used. These guidelines define mild-moderate CDAD as the presence of a white blood cell count ≤ 15000/mm³ and a serum creatinine level ≤ 1.5 times the premorbid level. Conversely, severe CDAD is defined by the presence of a white blood cell count ≥ 15000/mm³ or a serum creatinine level ≥ 1.5 times the premorbid level. Severe-complicated CDAD is defined by the presence of hypotension, shock, ileus, or megacolon. According to the guidelines, the correct treatment for mild-moderate CDAD is metronidazole 500 mg orally three times per day for 10-14 d. For treatment of severe CDAD, recommended treatment is oral vancomycin 125 mg four times per day for 10-14 d. For severe-complicated CDAD, the recommended treatment is oral vancomycin 500 mg four times per day in addition to intravenous metronidazole 500 mg every eight hours. If complete ileus exists, then rectal administration of vancomycin should be considered. Patients with a first recurrence are recommended to receive the same treatment as per their initial episode. For a second recurrence, vancomycin in a tapered and/or pulsed regimen is recommended.

Specific data collected included age, gender, disease severity as defined by the 2010 SHEA/IDSA guidelines, location of treatment (stratified into outpatient, hospital ward or intensive care unit), non-CDAD antibiotic treatment during the month preceding diagnosis, presence of immunosuppression, if the episode was a recurrence, 30 d mortality, and agent selection and dosage of CDAD treatment. CDAD episodes were classified as guideline adherent if treatment provided was with the correct agent(s) at the correct dosage(s). If one of these parameters was not in accordance with the guidelines, then the treatment regimen was deemed non-adherent. Partial adherence was defined as the patient receiving the correct antibiotic, but at the wrong dose. Patients stratified into adherent and non-adherent groups were compared to determine demographics and clinical factors predictive of guideline adherence. Logistic regression analysis was performed to assess the effect of multiple predictors on guideline adherence (SAS, version 9.2).

**RESULTS**

About 320 positive *C. difficile* stool tests were identified in 290 patients (average age 57.6 years, 43.1% female). Of the cases, 95.9% were in hospitalized patients and 15.6% were identified as a recurrence. Stratified by disease severity criteria set forth by the SHEA/IDSA guidelines, 42.2% of cases were mild-moderate, 48.1% severe, and 9.7% severe-complicated. Most (80.6%) of the severe-complicated cases met this criterion due to hypotension or shock. Full adherence with the guidelines was observed in 43.4% of cases; 65.9% for mild-moderate, which was significantly better than in severe (25.3%) and severe-complicated cases (35.5%) (*P* < 0.001) (Figure 1). Of the severe CDAD cases, 55.3% were managed incor-
Figure 1  Rates of adherence with the 2010 the Society for Healthcare Epidemiology of America/the Infectious Diseases Society of America guidelines stratified by severity of Clostridium difficile-associated disease: (A) Mild-moderate, (B) Severe, and (C) Severe-complicated. Compliance was significantly better in mild-moderate vs severe or severe-complicated disease, P < 0.001.

Table 1  Comparison of demographics, disease severity, and other clinical factors between guideline adherent and guideline non-adherent groups  n (%)  

| Demographics          | Guideline Compliant, n = 139 | Guideline Non-compliant, n = 181 | Unadjusted P value | Adjusted P value |
|-----------------------|------------------------------|----------------------------------|--------------------|------------------|
| Mean ± SD, yr         | 56.8 ± 14.1                  | 59.4 ± 16.2                      | 0.13               | 0.81             |
| Female                | 61 (44.2)                    | 77 (58.8)                        |                    |                  |
| Disease severity      |                              |                                  |                    |                  |
| Mild-moderate         | 89 (65.9)                    | 46 (34.1)                        | < 0.001            | < 0.001          |
| Severe                | 39 (25.3)                    | 115 (74.7)                       |                    |                  |
| Severe-complicated    | 11 (35.5)                    | 20 (64.5)                        |                    |                  |
| Severe +              | 50 (27.0)                    | 135 (73.0)                       |                    |                  |
| Other factors         |                              |                                  |                    |                  |
| Hospitalized          | 133 (43.3)                   | 174 (56.7)                       | 0.84               |                  |
| ICU                   | 60 (40.0)                    | 90 (60.0)                        | 0.24               | 0.08             |
| Prior antibiotics (<30 d) | 88 (39.1)              | 137 (60.9)                       | 0.02               | 0.08             |
| Recurrence            | 17 (34.0)                    | 33 (66.0)                        | 0.14               | 0.04             |
| Immunosuppressed      | 57 (51.8)                    | 53 (49.2)                        | 0.03               | 0.49             |
| 30-d mortality        | 15 (41.7)                    | 21 (58.3)                        | 0.82               |                  |

1On unadjusted analysis, mild-moderate disease is compared to both severe and severe complicated disease. On adjusted analysis, mild-moderate disease is compared to the combination of severe and severe-complicated disease.

difference for prior antibiotics or IS status.

DISCUSSION

Our results reveal poor overall adherence with the 2010 SHEA/IDSA guidelines for management of CDAD at a tertiary care academic medical center. Guideline adherence is worst in severe, severe-complicated, and recurrent CDAD. Our data suggests a lack of familiarity with current guidelines, as most providers continue to treat all initial episodes of CDAD with metronidazole, which was suggested as preferable by the 1995 SHEA clinical position paper on CDAD management. In fact, over half of our severe CDAD population, which should be treated with vancomycin, was incorrectly treated with metronidazole. This also explains the significantly improved adherence observed in mild-moderate patients whose treatment was not changed by the updated guidelines. We considered other possible causes of guideline non-adherence, such as the high cost of vancomycin and concern for vancomycin-resistance in other organisms, which has been shown to be significant in other nosocomial settings[10,11]. While the cost of branded oral vancomycin is approximately fifty-fold higher than oral metronidazole, our pharmacy routinely administers the generic intravenous formulation orally, which reduces the cost-difference dramatically[12], and makes cost concerns negligible. This finding also suggests an increased need for more intensive antibiotic stewardship, as not all incidences of non-adherence are likely due to knowledge. Antibiotic stewardship has been proposed as an effective method of increasing compliance at medical centers[13-15]. The exact impact of concerns over vancomycin resistance in other organisms on prescribing practices at our institution is unknown. We suspect this impact is small, as research on vancomycin use for CDAD has been conflicting with regards to rates of colonization and infection with resistant organisms[16-18].

Partial adherence with the guidelines, where the correct drug was chosen but an incorrect dosage was administered, occurred frequently as noted in Figure 1. The dosage of vancomycin chosen was often higher than recommended by the guidelines. While this is a form of
In 1995, the Society for Healthcare Epidemiology of America (SHEA) published guidelines that suggested that oral Vancomycin be preferred in cases of severe and severe-complicated disease, but adherence to these new guidelines is unclear at this time. In this study, the authors observe compliance to the new 2010 guidelines at a tertiary medical center.

Innovations and breakthroughs
Despite advances in health care sanitation technique, Clostridium infections continue to increase. In this study, the authors observed that compliance to the updated 2012 SHEA/IDSA guidelines is poor at the tertiary care hospital, suggesting a need for increased education and antibiotic stewardship for providers. The authors also identified specific areas that the guidelines fail to address clearly; end-stage renal disease patients and patients who are significantly immunosuppressed.

Applications
By recognizing poor compliance at our tertiary care facility, steps can be made to increase education and antibiotic stewardship at other facilities. In addition, the study suggests the guidelines should be updated to include the aforementioned patient populations with specific guidelines pertaining to their management.

Terminology
Compliance in the study is defined as using the proper dosage (both strength and frequency) in the proper duration for a specific C. difficile-associated diarrhea (CDAD) infection. The guidelines define mild to moderate CDAD as the presence of a white blood cell count ≤ 15000/mm^3 and a serum creatinine level ≤ 1.5 times the premorbid level. Conversely, severe CDAD is defined by the presence of a white blood cell count > 15000/mm^3 or a serum creatinine level > 1.5 times the premorbid level. Severe-complicated CDAD is defined by the presence of hypotension, shock, ileus, or megacolon.

Peer review
The authors report the results of a study conducted to assess adherence with the SHEA/IDSA guidelines for management of CDAD at a tertiary medical center. The study is well-designed, includes sufficient number of patients and the paper is well written. Despite the fact that the study is single-centered, and includes only hospitalized patients which reduces its generalizability (as mentioned by the authors), the results are considerable. This is a worthy study and appears of high clinical interest.

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