

BRIEF REPORT

Performance of severity of illness classification for *Clostridium difficile* infection to predict need-for-colectomy or inpatient death

Adnan Khan, MD, Ahmad Elashery, MD, Shyam Kapadia, MD and Subhash Chandra, MD*

Internal Medicine Residency Program, Department of Medicine, Greater Baltimore Medical Center, Towson, MD, USA

Background: In current state of practice, disease severity assessment for *Clostridium difficile* infection (CDI) lacks consensus between different organizations. In the latest guidelines for management of CDI, authors have proposed a new disease severity classification. This classification has been derived from expert opinion and includes previously reported patient related factors that predict unfavorable outcome in CDI.

Objective: To evaluate the performance of new disease severity classification to predict CDI-related colectomy or in-patient deaths.

Methods: This observational study was performed at a 300-bed community hospital catering to a suburban population. All the adult patients discharged during October 2005 through September 2012 and diagnosed with CDI were included in the study. Cases of CDI were identified using the billing database. Demographic and clinical characteristics of CDI cases were extracted from medical chart reviews performed by two physician researchers. Cases were classified as mild-to-moderate, severe, or severe and complicated CDI. Major outcomes measured were in-patient deaths and colectomy attributed to CDI. For risk stratification, each variable of severe and complicated CDI was counted.

Results: In total, 59,897 patients were discharged from our hospital during the study period; 894 of them were diagnosed with CDI. Mean age of CDI cases was 74 years (standard deviation 15 years), 345 (39%) were male, and median length of hospital stay was 7 days (interquartile range 4–13). One hundred ninety-one patients (21%) were classified as mild-to-moderate, 93 patients (10%) as severe, and 610 patients (68%) as severe and complicated. In total, 14 patients underwent colectomy for CDI and 53 patients expired. In 35 of these patients, the cause of death was thought to be CDI. The combined outcome (CDI-related colectomy and/or death in hospital) occurred in 47 patients. None of the patients in mild-to-moderate disease or severe disease had combined outcome. On severe and complicated cases, as the score increased, rate of combined outcome increased significantly ($z = 12.7, p < 0.0001$). On plotting receiver-operating curve, the simple variable count had area under the curve of 0.91.

Conclusion: The newly proposed disease severity classification for CDI categorized more than two-thirds of patients as severe and complicated. Increase in number of severe and complicated classifying variables increases the chance of adverse outcomes significantly. Patients meeting only one variable could be potentially treated as a severe case instead of severe and complicated. This data needs to be validated prospectively before could be used in clinical practice.

Keywords: *Clostridium difficile* infection; Severity of Illness; Need for colectomy; inpatient mortality

*Correspondence to: Subhash Chandra, Greater Baltimore Medical Center, 6565 N. Charles Street, Towson, MD 21204, USA, Email: subhash.budania@gmail.com

Received: 20 April 2014; Revised: 8 June 2014; Accepted: 16 June 2014; Published: 31 July 2014

C*lostridium difficile* infection (CDI) is the most common hospital-acquired infection, outnumbering the incidence for methicillin-resistant *Staphylococcus aureus* (1). CDI is no longer a disease of old and frail people only. Emergence of highly virulent strains of *C. difficile* is affecting relatively healthy and

young individuals who were considered low risk in the past (2). CDI imposes a huge financial and health burden. Annual estimate of excess acute care use in the United States was \$4.8 billion in 2008 (3). Apart from financial burden; it also adds significant mortality and morbidity (4). Hospital-acquired CDI increases length of

hospital stay and hospital mortality. All-cause 30-day mortality was reported to be 15% or more in 15 independent studies with CDI-attributable mortality of 5.7–6.9% (4).

The clinical spectrum of CDI ranges from a mild diarrheal illness to a fulminant colitis, leading to shock and possible death. A classification system for disease severity in CDI has been recommended by different organizations and has been updated frequently over the past two decades. Society of Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) last published scales were in 2010, and American Journal of Gastroenterology published updated guidelines in management of CDI in 2013 (5, 6). Stratification of severity guides first line antimicrobials, oral versus parenteral administration of antimicrobials, the need for hospitalization and level of care. In guidelines endorsed by the American College of Gastroenterology (ACG), authors have proposed a new stratification for severity of CDI cases that classify cases into mild-to-moderate, severe, and severe and complicated. The classification system was developed based on expert opinion and consensus amongst authors, and till date there is no study available which has validated its performance.

In the current study, we aimed to evaluate performance of the proposed classification of severity in CDI in an unselected cohort of CDI cases from a community hospital.

Methods

Study design and site

This retrospective observational medical review study was performed in a 300-bed community hospital. The hospital catered to a suburban population. An institutional review board approved the study and need-for-consent was waived due to its null risk nature.

Cases identification

All the cases with discharge diagnosis of CDI between October 2005 and September 2012 were included. Cases were identified by billing database. All the patients who were discharged from medical service, including intensive care unit, with a primary or secondary diagnosis of international disease classification 9th clinical modification code 0.008 were included.

Outcomes

Primary outcome measured was CDI-related inpatient mortality. Death was attributed to CDI if cause of death was septic shock without any other identified source of infections apart from *C. difficile* and perceived as most likely cause of death by at least two physicians. Secondary outcome was need-for-colectomy for CDI.

Data extraction and synthesis

Two physician researchers reviewed electronic medical charts of all the cases, independently and in duplicate. Severity of illness was determined based on patients' most abnormal parameters. Cases were categorized into mild-to-moderate, severe, and severe and complicated as per the classification proposed in ACG guidelines (Box 1) (5). In severe and complicated cases, numbers of qualifying variables were counted. Because physician-documented altered mental status was not available consistently in medical charts, it was decided not to include it while scoring.

Box 1. Scoring systems for *C. difficile* infection severity

2013 – American College of Gastroenterology (5)

Mild-to-moderate disease: Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria

Severe disease: Serum albumin < 3 g/dl plus one of the following:

- 1) WBC \geq 15,000 cells/mm³
- 2) Abdominal tenderness

Severe and complicated disease: Any of the following attributable to CDI:

- 1) Admission to intensive care unit for CDI
- 2) Hypotension with or without required use of vasopressors
- 3) Fever \geq 38.5°C
- 4) Ileus or significant abdominal distention
- 5) Mental status changes
- 6) WBC \geq 35,000 cells/mm³ or < 2,000 cells/mm³
- 7) Serum lactate levels > 2.2 mmol/l
- 8) End-organ failure (mechanical ventilation, renal failure, etc.)

2010 – Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) (6)

Mild-to-moderate disease: WBC \leq 15,000 cells/mm³ and a serum creatinine level < 1.5 times the pre-morbid level

Severe disease: WBC \geq 15,000 cells/mm³ and a serum creatinine level > 1.5 times the pre-morbid level

Severe and complicated disease: Hypotension or shock, ileus, megacolon

Measures of central tendencies are reported using mean with standard deviation (SD) or median with inter-quartile range (IQR) based on normality of distribution.

Trend analysis was performed by Cochran-Armitage test. Area under the receiver-operating curve was used to assess the performance of variable count in severe and complicated cases. Data analysis was performed using JMP statistical package version 9 (SAS Inc., Cary, NC).

Results

In total 59,897 patients were discharged from medical service during the study period; 894 of them were coded for discharge diagnosis of CDI, primary or secondary. Mean age of CDI cases was 74 years (SD 15 years), 345 (39%) were male, median length of hospital stay was 7 days (IQR 4–13), and 53 of these cases expired in the hospital (Table 1).

Severity of illness

Based on ACG 2013 severity of illness classification, 191 patients (21.4%) were classified as mild-to-moderate, 93 patients (10.4%) as severe, and 610 patients (68.2%) as severe and complicated (Table 2). When these patients were classified based on 2010 guidelines by SHEA and the IDSA, only 244 patients (27%) were in severe and complicated category.

A total of 14 cases (1.6%) underwent colectomy for CDI. Of 53 patients with CDI who expired before discharge, in 35 patients cause of death was perceived to be CDI. The combined outcome (CDI-related colectomy and/or death in hospital) occurred in 51 patients. None of the patients in mild-to-moderate disease or severe disease had combined outcome. On severe and complicated cases, as the number of qualifying variables increased, rate of combined outcome increased significantly, $z = -12.1$, $p < 0.0001$ (Fig. 1). On plotting receiver-operating curve, the sum of variable count has area under the curve of 0.91 for combined outcome (Fig. 2). At the cut-off score of 2 or more, the score demonstrated sensitivity of 100% and specificity of 49.4% in predicting inpatient death or need for colectomy. Using this cut-off point, 285 (46.7%) patients could be safely included in severe category from severe and complicated category.

Table 1. Clinical and demographic characteristics of the cohort of *C. difficile* infection

Variables	Observations (<i>n</i> = 894)
Age, mean (SD)	74 (15)
Gender, male (%)	345 (39)
Length of hospital stays, median (IQR)	7 (4–13)
Outcomes, <i>n</i> (%)	
• Colectomy attributable to CDI	14 (1.6)
• All cause inpatient deaths	53 (5.9)
• Inpatient deaths attributable to CDI	35 (3.9)
• Colectomy and/or deaths attributable to CDI	47 (5.3)

Table 2. Classification of patients into severity of illness based on 2010 clinical practice guidelines for *C. difficile* infection in adults by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America compared to 2013 guidelines by American College of Gastroenterology (5, 6)

Severity of illness	2010 Guidelines (6), <i>n</i> (%)	2013 Guidelines (5), <i>n</i> (%)*
Mild to moderate	235 (26.3)	191 (21.4)
Severe	415 (46.4)	93 (10.4)
Severe and complicated	244 (27.3)	610 (68.2)

*Altered mental status was not available for severity assessment.

Discussion

Summary of results and clinical implication

Assessment of severity of illness in CDI is very essential in choosing treatment and assigning level of care for the patient. Current guidelines in management of CDI recommend combination of oral vancomycin and intravenous metronidazole in severe and complicated cases and oral metronidazole in mild-to-moderate cases (5). Current study results show that proposed classification in 2013 ACG guidelines, classify more than two-thirds of the cases into severe and complicated category. Only one-fourth of the cases were classified as severe and complicated as per 2010 guidelines. The new classification moves a big proportion of patients from severe category as per earlier classification to severe and complicated category.

Study results demonstrate that not all the severe and complicated cases are the same. Patients meeting higher number of variables of severe and complicated CDI category have significantly higher rate of adverse outcome. Cases, which met only one criterion of severe and complicated category, did not have any adverse

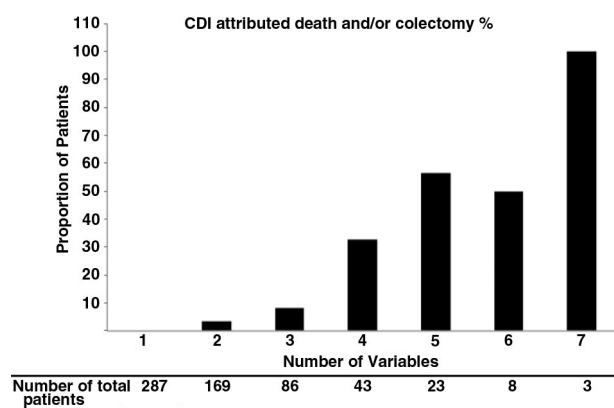


Fig. 1. Percentage of patient undergoing CDI-related colectomy and/or death in hospital based on qualifying variable count in severe and complicated class as per 2013 American College of Gastroenterology guidelines.

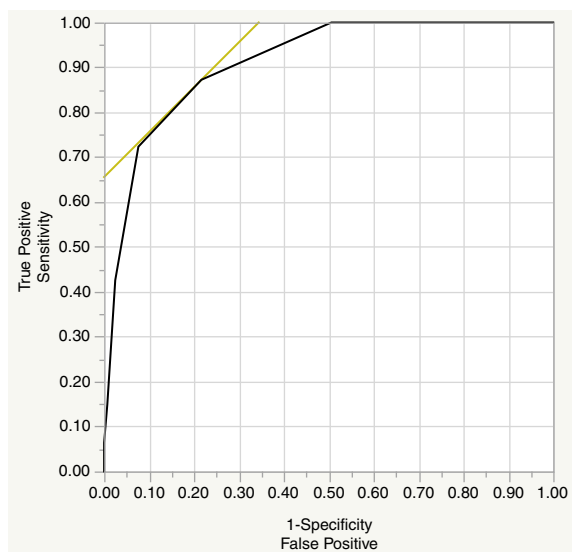


Fig. 2. Receiver-operating curve demonstrating prediction of adverse outcome but increase in cumulative score in severe and complicated cases of CDI.

outcome. If one categorizes them as severe instead of severe and complicated, patients meeting severe and complicated criteria decrease by half. Appropriate classification has huge implications as single antimicrobial (oral vancomycin) should be sufficient whereas cases which meet two of more criteria should be treated with dual therapy and assigned higher level of care (5).

Strengths and limitations

We included an unselected adult population of patients who were admitted to a community hospital. Henceforth, study results have good external validity as most patients of CDI in the United States are treated in community hospitals. Data were extracted, in duplicate and independently. Outcome and severity of illness assessment was done blindly to eliminate bias. The major limitation of the study is that data for altered mental status was not available. If data on altered mental status were available, it would have placed the same or higher number of patients into severe and complicated category. Henceforth, findings of the current study would have been strengthened, if anything. In addition, the retrospective nature of study did not allow impact of treatment allocation on outcomes.

Conclusion

In the management of CDI, stratification of severity of illness is essential. The proposed severity of illness classification in 2013 guidelines endorsed by ACG aggressively labels patients as severe and complicated cases. A simple measure of counting the number of criteria patients meets from the severe and complicated category has potential for better risk stratification. Patients meeting only one criterion appear to have similar outcome as patients in the severe category. This approach could eliminate a big portion of the cases from the severe and complicated category that has a huge implication on appropriate allocation of health care resources and financial stability of healthcare. Additional methodologically sound studies are needed before using these findings in clinical practice.

Conflict of interest and funding

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

Financial Disclosure: None.

References

1. Miller BA, Chen LF, Sexton DJ, Anderson DJ. Comparison of the burdens of hospital-onset, healthcare facility-associated *Clostridium difficile* infection and of healthcare-associated infection due to methicillin-resistant *Staphylococcus aureus* in community hospitals. *Infect Control Hosp Epidemiol* 2011; 32(4): 387–90.
2. Lessa FC, Gould CV, McDonald LC. Current status of *Clostridium difficile* infection epidemiology. *Clin Infect Dis* 2012; 55(Suppl 2): S65–70.
3. Dubberke ER, Olsen MA. Burden of *Clostridium difficile* on the healthcare system. *Clin Infect Dis* 2012; 55(Suppl 2): S88–92.
4. Mitchell BG, Gardner A. Mortality and *Clostridium difficile* infection: a review. *Antimicrob Resist Infect Control* 2012; 1(1): 20.
5. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol* 2013; 108(4): 478–98; quiz 499.
6. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; 31(5): 431–55.