2007

# Severity of Clostridium difficile-associated disease (CDAD) in allogeneic stem cell transplant recipients: Evaluation of a CDAD severity grading system

Erik R. Dubberke
*Washington University School of Medicine in St. Louis*

Justin Sadhu
*Washington University School of Medicine in St. Louis*

Robert Gatti
*University of Missouri - Kansas City School of Dentistry*

Kimberly A. Reske
*Washington University School of Medicine in St. Louis*

John F. DiPersio
*Washington University School of Medicine in St. Louis*

***See next page for additional authors***

Severity of Clostridium difficile—Associated Disease (CDAD) in Allogeneic Stem Cell Transplant Recipients: Evaluation of a CDAD Severity Grading System •

Author(s): Erik R. Dubberke , MD, Justin Sadhu , BS, Robert Gatti , BS, Kimberly A. Reske , MPH, John F. DiPersio , MD, PhD, Steven M. Devine , MD, Victoria J. Fraser , MD

Reviewed work(s):
Source: *Infection Control and Hospital Epidemiology*, Vol. 28, No. 2 (February 2007), pp. 208-211
Published by: The University of Chicago Press on behalf of The Society for Healthcare Epidemiology of America
Stable URL: http://www.jstor.org/stable/10.1086/511792
Accessed: 19/04/2012 17:14

CONCISE COMMUNICATION

# Severity of *Clostridium difficile*–Associated Disease (CDAD) in Allogeneic Stem Cell Transplant Recipients: Evaluation of a CDAD Severity Grading System

**Erik R. Dubberke, MD; Justin Sadhu, BS; Robert Gatti, BS; Kimberly A. Reske, MPH; John F. DiPersio, MD, PhD; Steven M. Devine, MD; Victoria J. Fraser, MD**

The purpose of this study was to develop and test a *Clostridium difficile*–associated disease (CDAD) grading system based on presenting symptoms in allogeneic stem cell transplant recipients. Patients with severe CDAD had significantly shorter median survival times and more adverse outcomes than patients with mild or moderate CDAD.

*Infect Control Hosp Epidemiol* 2007; 28:208-211

*Clostridium difficile*–associated disease (CDAD) is the most common infectious cause of healthcare-associated diarrhea.[1] Allogeneic stem cell transplant recipients may be at increased risk for severe CDAD because of their immunocompromised state. However, studies of CDAD in hematopoietic cell transplantation patients disagree about the incidence of, severity of, and risk factors for CDAD.[2-10] A lack of differentiation between mild cases and severe cases of CDAD may explain some of these discrepancies. To address this deficiency and to further study CDAD outcomes among allogeneic stem cell transplant recipients, we developed and validated a grading system for CDAD severity using a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE) and based on the presenting clinical CDAD symptoms.

## METHODS

The study was conducted at Barnes-Jewish Hospital, a 1,250-bed, tertiary care hospital in St. Louis, Missouri. A retrospective cohort study was performed that included all allogeneic stem cell transplant recipients who developed their first episode of CDAD between August 1, 2001, and July 31, 2003. Cases were identified prospectively by the infection control department. Patients were excluded if they had a history of CDAD before the study period. A case of CDAD was defined by a stool toxin assay positive for *C. difficile* toxin (Tech Lab). The decision to order a *C. difficile* toxin assay was made by the patient's treating physician on the basis of the patient's symptoms and risk factors. In addition, the microbiology laboratory tests stool samples for *C. difficile* only if the stool sample conforms to the container in which it is sent (ie, is unformed).

Patients' medical records were reviewed to collect information on demographic characteristics, underlying disease status, symptoms, infections, complications, medications received, and outcomes. Infections were defined using the Centers for Disease Control and Prevention National Nosocomial Infections Surveillance System definitions.[11,12] Patients were followed up for 180 days after the date of CDAD diagnosis to identify infections and determine mortality. Diarrhea was defined as 3 or more loose bowel movements per day, for at least 48 hours. Response to CDAD therapy was defined as either a decrease in diarrhea by half or resolution of ileus and resolution of any other associated symptoms.

The CDAD severity grading system was developed by modifying the criteria for grading diarrhea and colitis in the CTCAE. The CTCAE is a standardized method of reporting adverse events in cancer patients.[13] Hypothermia (temperature of 35.6°C or less, or 35.9°C or less for more than an hour) was added as a criterion for grade 3 colitis. The nursing notes for the transplantation ward include an intake and output assessment. Because intestinal output is recorded only if diarrhea is present, total daily intestinal output was included in the determination of diarrhea severity: 500 mL or less of intestinal output per day was included in the definition of grade 1 diarrhea; 501 to 1,000 mL in the definition of grade 2; 1,001 to 2,000 mL in grade 3; and more than 2,000 mL in grade 4. Mild CDAD was defined as grade 1 diarrhea and/or colitis. Moderate CDAD was defined as grade 2 diarrhea and/or colitis. Severe CDAD was defined as grade 3 or higher diarrhea and/or colitis. All symptoms had to be present within 48 hours of the time CDAD was diagnosed to be included in the grading scale. For statistical analyses, mild and moderate cases were grouped together and compared with the severe cases.

Statistical analyses were performed with SPSS statistical software, version 12.0 for Windows (SPSS). Statistical tests used included the $\chi^2$, Fisher exact, Mann-Whitney *U*, and Kaplan-Meier tests. *P* values less than or equal to .05 were considered statistically significant. The Washington University Human Studies Committee approved this study.

## RESULTS

Thirty-seven allogeneic stem cell transplant recipients met the inclusion criteria. Sixteen patients (43%) were classified as having mild or moderate CDAD and 21 (57%) as having severe CDAD. No significant differences at baseline were noted between patients who developed mild or moderate CDAD and patients who developed severe CDAD with respect to demographic characteristics, underlying disease, reason for admission, transplant donor source (sibling vs unrelated),

TABLE. Outcomes for Patients With *Clostridium difficile*–Associated Disease (CDAD)

| Outcome | Patients with mild or moderate CDAD ($N = 16$) | Patients with severe CDAD ($N = 21$) | $P$ |
|---|---|---|---|
| Therapy | | | |
| Responded to therapy | 15 (94) | 19 (91) | 1.0 |
| Responded to therapy after >2 days | 5 (31) | 14 (67) | .05 |
| Treated with Mtz only | 11 (69) | 8 (38) | .06 |
| Treated with Mtz plus Vm or Vm only | 4 (25) | 12 (57) | .05 |
| Duration of treatment, mean days | 13 | 16 | .30 |
| CDAD relapse[a] | 5 (31) | 5 (36) | 1.0 |
| Acute renal failure (creatinine level, ⩾2.0 mg/dL) | 0 (0) | 7 (33) | .01 |
| Acute liver dysfunction (total bilirubin level, ⩾4.0 mg/dL) | 1 (6) | 5 (24) | .20 |
| BSI rate, cases per 1,000 patient-days[b] | 5.7 | 11.5 | .06 |
| BSI due to enteric organism[bc] | 4 (31) | 14 (82) | .004 |

NOTE. Data are no. (%) of patients, unless indicated otherwise. BSI, bloodstream infection; Mtz, metronidazole; Vm, vancomycin.

[a] Among the patients alive at discharge (mild to moderate CDAD, 16 patients; severe CDAD, 14 patients).

[b] Includes only BSI after onset of CDAD (relative rate, 2.0 [95% confidence interval, 1.0-4.1]).

[c] Of the total number of BSIs (patients with mild to moderate CDAD, 13 cases of BSI; patients with severe CDAD, 17 cases of BSI). BSI in patients with mild or moderate CDAD was caused by coagulase-negative *Staphylococcus* (6 cases), *Klebsiella pneumoniae* (2), *Klebsiella oxytoca*, *Escherichia coli*, methicillin-resistant *Staphylococcus aureus*, viridans group *Streptococcus*, and *Stomatococcus* species. BSIs in patients with severe CDAD were caused by vancomycin-resistant enterococci (5 cases), coagulase-negative *Staphylococcus* (3), *Enterococcus faecalis* (2), *Candida albicans* (2), *Candida tropicalis* (2), *K. pneumoniae*, *K. oxytoca*, and *Pseudomonas aeruginosa*.

days since transplantation, graft-versus-host disease, neutropenia at the time of CDAD diagnosis, or number of days hospitalized before CDAD. The CDAD symptoms seen most frequently within 48 hours of diagnosis were diarrhea (in 31 patients [84%]), fever (in 13 [35%]), and abdominal pain (in 9 [24%]).

Patients with severe CDAD had significantly more adverse outcomes than did patients with mild or moderate CDAD (Table). Patients with severe CDAD were more likely to be treated with metronidazole and vancomycin or vancomycin alone than were patients with mild or moderate CDAD ($P = .05$). Compared with patients with mild or moderate CDAD, a larger number of patients with severe CDAD required more than 2 days to respond to therapy ($P = .05$), and more of these patients had acute renal failure after the onset of CDAD ($P = .01$). Patients with severe CDAD had a higher rate of bloodstream infection (BSI) after CDAD (11.5 vs 5.7 cases per 1,000 patient-days; relative rate, 2.0 [95% confidence interval, 1.0-4.1]). Significantly more cases of BSI due to enteric organisms occurred among patients with severe CDAD than among patients with mild or moderate CDAD ($P = .004$). The median survival time after CDAD was 266 days for patients with mild or moderate CDAD and 55 days for patients with severe CDAD (log-rank $P = .003$) (Figure).

## DISCUSSION

This study is the first, to our knowledge, to provide a method for grading CDAD severity in allogeneic stem cell transplant recipients. Previously published CDAD severity grading systems were developed on the basis of outcomes and characteristics seen in patients with CDAD throughout their clinical course.[14,15] The grading system presented herein was developed on the basis of clinical presentation (symptoms present within 48 hours before or after CDAD diagnosis). Application of this system identified patients at increased risk for adverse events associated with CDAD. Patients with severe CDAD were more likely to be treated with vancomycin or metronidazole plus vancomycin than were patients with mild or moderate CDAD. Metronidazole is first-line therapy for CDAD at our institution, and vancomycin is used for severe or refractory CDAD. The increased use of vancomycin among patients with severe CDAD suggests that the treating physicians perceived these patients' symptoms to be more severe than those of other patients or refractory to metronidazole therapy. Significantly more patients with severe CDAD required more than 2 days to respond to antimicrobial therapy and experienced acute renal failure after CDAD onset than did patients with mild or moderate CDAD.

Significantly more cases of BSI caused by enteric organisms

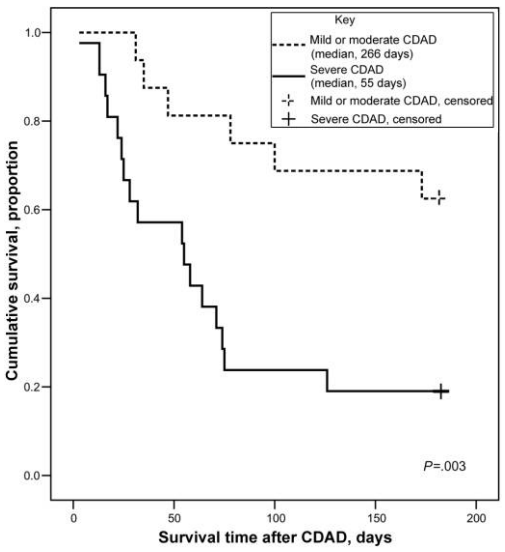


FIGURE. Survival rates 180 days after diagnosis among patients with mild to moderate *Clostridium difficile*–associated disease (CDAD) and patients with severe CDAD.

occurred after onset of CDAD in patients with severe CDAD than in patients with mild or moderate CDAD. Sepsis and bacteremia associated with CDAD have been reported previously[16-20]; however, the association between CDAD and BSI caused by gastrointestinal organisms has not been as well studied. *C. difficile* toxins A and B directly damage colonic mucosa and could thereby lead to BSI.

Most striking is the significant decrease in survival time for those patients who had severe CDAD. This finding has several possible explanations. It is possible that the patients with severe CDAD were initially more ill than patients with mild or moderate CDAD. Although no statistically significant differences were found, prior to CDAD diagnosis, between those patients who developed mild or moderate CDAD and those who developed severe CDAD, assessing severity of illness by retrospective medical record review can be difficult. Alternatively, the increased risk of death may have been the result of the severity of CDAD.

This study has a few limitations. The sample size was small; however, 37 patients with CDAD is a larger sample group than any previously published cohort of CDAD cases in allogeneic transplant recipients. Allogeneic stem cell transplant recipients are highly immunocompromised, and diarrhea is common in these patients.[3,9,10] The symptoms used to evaluate CDAD severity may have been the result of other causes. Potential bias attributable to the ubiquity of CDAD symptoms should have been minimized by limiting the analysis to symptoms experienced within 48 hours before or after CDAD diagnosis. By excluding severe symptoms experienced more than 48 hours before or after diagnosis but potentially truly due to CDAD, any remaining bias should be toward the null hypothesis (ie, more cases mistakenly categorized as mild or moderate).

Despite the small sample size and the complex nature of the study population, this CDAD severity grading system identified patients at high risk for adverse outcomes after CDAD based on presenting symptoms. In addition, an important benefit of this system is the ease with which it can be used. Because both the incidence of CDAD and the size of the immunocompromised population are increasing, a CDAD severity grading system such as the one presented herein may become critical to early identification of patients at high risk for adverse events associated with CDAD. Prospective validation of this system is needed.

## ACKNOWLEDGMENTS

We thank Margaret Olsen, PhD, Jennie Mayfield, BSN, MPH, CIC, and Kristan Augustin, PharmD, for their assistance with this research. We also thank Cherie Hill and Stacy Leimbach for their assistance with data management.

This study was supported by the Centers for Disease Control and Prevention (EpiCenter grant UR8/CCU715087-03).

From the Division of Infectious Diseases (E.R.D., J.S., K.A.R., V.J.F.) and the Division of Oncology (J.F.D., S.M.D.), Washington University School of Medicine, St. Louis, and the University of Missouri—Kansas City School of Dentistry, Kansas City (R.G.), Missouri.

Address reprint requests to Erik R. Dubberke, MD, Division of Infectious Diseases, Washington University School of Medicine, Campus Box 8051, 660 S. Euclid Avenue, St. Louis, MO 63110 (edubberk@im.wustl.edu).

Presented in part: 15th Annual Scientific Meeting of the Society for Healthcare Epidemiology of America, Los Angeles, CA, April 9-12, 2005. Abstract 287.

Received January 19, 2006; accepted May 3, 2006; electronically published January 26, 2007.



## REFERENCES

1. Johnson S, Gerding DN. *Clostridium difficile*–associated diarrhea. *Clin Infect Dis* 1998; 26:1027-1034.
2. Altclas J, Requejo A, Jaimovich G, Milovic V, Feldman L. *Clostridium difficile* infection in patients with neutropenia. *Clin Infect Dis* 2002; 34:723.
3. Avery R, Pohlman B, Adal K, et al. High prevalence of diarrhea but infrequency of documented *Clostridium difficile* in autologous peripheral blood progenitor cell transplant recipients. *Bone Marrow Transplant* 2000; 25:67-69.
4. Bilgrami S, Feingold JM, Dorsky D, et al. Incidence and outcome of *Clostridium difficile* infection following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999; 23:1039-1042.
5. Blot E, Escande MC, Besson D, et al. Outbreak of *Clostridium difficile*–related diarrhoea in an adult oncology unit: risk factors and microbiological characteristics. *J Hosp Infect* 2003; 53:187-192.
6. Chakrabarti S, Lees A, Jones SG, Milligan DW. *Clostridium difficile* infection in allogeneic stem cell transplant recipients is associated with severe graft-versus-host disease and non-relapse mortality. *Bone Marrow Transplant* 2000; 26:871-876.
7. Gorschluter M, Glasmacher A, Hahn C, et al. *Clostridium difficile* infection in patients with neutropenia. *Clin Infect Dis* 2001; 33:786-791.
8. Kavan P, Sochor M, Nyc O, et al. Pseudomembraneous clostridium after

autologous bone marrow transplantation. *Bone Marrow Transplant* 1998; 21:521-523.
9. Tomblyn M, Gordon L, Singhal S, et al. Rarity of toxigenic *Clostridium difficile* infections after hematopoietic stem cell transplantation: implications for symptomatic management of diarrhea. *Bone Marrow Transplant* 2002; 30:517-519.
10. van Kraaij MG, Dekker AW, Verdonck LF, et al. Infectious gastro-enteritis: an uncommon cause of diarrhoea in adult allogeneic and autologous stem cell transplant recipients. *Bone Marrow Transplant* 2000; 26:299-303.
11. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; 34:7-14.
12. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; 16:128-140.
13. National Cancer Institute. Common toxicity criteria v2.0 and common terminology criteria for adverse events v3.0. Available at: http://ctep.cancer.gov/reporting/ctc.html. Accessed September 2003.
14. Kyne L, Merry C, O'Connell B, et al. Factors associated with prolonged symptoms and severe disease due to *Clostridium difficile. Age Ageing* 1999; 28:107-113.
15. Rubin MS, Bodenstein LE, Kent KC. Severe *Clostridium difficile* colitis. *Dis Colon Rectum* 1995; 38:350-354.
16. Siemann M, Koch-Dorfler M, Rabenhorst G. *Clostridium difficile*–associated diseases: the clinical courses of 18 fatal cases. *Intensive Care Med* 2000; 26:416-421.
17. Dobson G, Hickey C, Trinder J. *Clostridium difficile* colitis causing toxic megacolon, severe sepsis and multiple organ dysfunction syndrome. *Intensive Care Med* 2003; 29:1030.
18. Jacobs A, Barnard K, Fishel R, Gradon JD. Extracolonic manifestations of *Clostridium difficile* infections: presentation of 2 cases and review of the literature. *Medicine (Baltimore)* 2001; 80:88-101.
19. Lowenkron SE, Waxner J, Khullar P, et al. *Clostridium difficile* infection as a cause of severe sepsis. *Intensive Care Med* 1996; 22:990-994.
20. Chatila W, Manthous CA. *Clostridium difficile* causing sepsis and an acute abdomen in critically ill patients. *Crit Care Med* 1995; 23:1146-1150.