Poor Functional Status as a Risk Factor for Severe *Clostridium difficile* Infection in Hospitalized Older Adults

Krishna Rao, MD,[*†] *Dejan Micic, MD,*[*] *Elizabeth Chenoweth, MD,*[‡] *Lili Deng, MD, MA,*[*§¶] *Andrzej T. Galecki, MD, PhD,*[*§¶] *Cathrin Ring, MS,*[*†] *Vincent B. Young, MD, PhD,*[*†**] *David M. Aronoff, MD,*[*†**] *and Preeti N. Malani, MD*[*†§††]

OBJECTIVES: To determine the role of impaired functional status as a risk factor for severe *Clostridium difficile* infection (CDI) in older adults.

DESIGN: Prospective cohort study.

SETTING: University of Michigan Health System, a 930-bed tertiary care hospital.

PARTICIPANTS: Hospitalized individuals with CDI aged 50 and older.

MEASUREMENTS: Demographic and clinical characteristics and a composite outcome, CDI severity score: fever (>38°C), acute organ dysfunction, white blood cell count greater than 15,000/μL, lack of response to therapy, intensive care unit admission, need for colectomy, or death from CDI. Preadmission functional status was assessed according to ability to perform activities of daily living (ADLs); participants were assigned to an ADL class (independent, some assistance, full assistance). Secondary outcomes included length of stay, 90-day mortality and readmission, and CDI recurrence.

RESULTS: Ninety hospitalized individuals with CDI were identified (mean age 66.6 ± 10.2); 58 (64.4%) had severe CDI as measured according to a positive severity score. At baseline, 25 (27.8%) required assistance with ADLs. On univariate analysis, ADL class of full assistance was associated with a positive severity score (odds ratio (OR) = 7, 95% confidence interval (CI) = 1.83–26.79, $P = .004$). In a multivariable model including age, ADL class, congestive heart failure, diabetes mellitus, depression, weighted Charlson-Deyo comorbidity score, immunosuppression, prior CDI, and proton pump inhibitor use, an ADL class of full assistance retained its association with a positive severity score (OR = 8.1, 95% CI = 1.24–52.95, $P = .03$). ADL class was not associated with secondary outcomes.

CONCLUSION: In this cohort of hospitalized older adults, impaired functional status was an independent risk factor for severe CDI. **J Am Geriatr Soc 61:1738–1742, 2013.**

Key words: aging; geriatric; infection; *Clostridium difficile*; colitis

In recent years, *Clostridium difficile* infection (CDI) has emerged as a major source of morbidity and mortality in hospitalized older adults.[1–6] The clinical manifestations of CDI vary, ranging from self-limited diarrheal illness to fulminant and even fatal pseudomembranous colitis and toxic megacolon.[7,8] Although toxin production is essential to the pathophysiology of CDI,[9–12] it remains unclear why some individuals experience severe disease. Previous work has identified numerous risk factors for severe CDI, including older age[13] and comorbid conditions.[14–16] In addition to age, the role of poor functional status is increasingly recognized as an important and independent risk factor for poor outcomes in older adults with infection.[17–20]

The relationship between CDI and functional status was explored in a study that demonstrated that impaired functional status, according to lower Barthel scores,[21] was associated with more-severe disease,[22] but Barthel scores were not included in the authors' final multivariate model, because these scores were highly correlated with abbreviated mental test (AMT) scores, and the authors chose to include AMT scores in lieu of the Barthel scores. This prevented any firm conclusions about whether impaired functional status is an independent risk factor for severe CDI.

From the *Department of Internal Medicine, University of Michigan Health System, †Division of Infectious Diseases, University of Michigan Health System, ‡University of Michigan Medical School, §Division of Geriatric and Palliative Medicine, University of Michigan Health System, ¶Department of Biostatistics, University of Michigan Health System, **Department of Microbiology and Immunology, University of Michigan Health System, and ††Geriatric Research, Education and Clinical Center, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan.

Address correspondence to Dr. Krishna Rao, MD, Department of Internal Medicine, Division of Infectious Diseases, 3120 Taubman Center, 1500 E. Medical Center Dr., SPC 5378, Ann Arbor, MI 48109.
E-mail: krirao@med.umich.edu

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Although the identification of risk factors associated with severe CDI has important implications in the management of individuals, the lack of a single consensus definition complicates the concept of severity itself. Investigators must select from a myriad of classification systems published in the literature or devise their own severity definition. One study[23] endorsed a surveillance definition of severe CDI that focuses on outcomes attributable to CDI, including, within 30 days of diagnosis, admission to an intensive care unit (ICU), the need for surgery (such as colectomy), or death. The Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America 2010 clinical practice guidelines[24] recommend using clinical criteria present at the time of diagnosis: leukocytosis (white blood cell (WBC) count ≥15 000 cells/μL), a 1.5-fold rise in serum creatinine, hypotension or shock, ileus, or megacolon. A systematic review[25] identified seven sets of criteria used to measure CDI severity or predict treatment outcomes, using combinations of 17 clinical variables including diarrhea frequency, leukocytosis, fever, hypotension, and renal insufficiency. The current study sought to explore the relationship between functional status and CDI severity, applying a definition that includes individual outcomes and clinical criteria readily available for most hospitalized individuals at the time of diagnosis.

METHODS

Population and Setting

The University of Michigan Health System is a 930-bed tertiary care facility with a comprehensive electronic medical record. Using microbiology records to identify potential subjects, hospitalized adults with diarrhea and a positive *C. difficile* test between October 2010 and May 2012 were prospectively enrolled. Given the interest in the association between impaired functional status and CDI severity, it was decided to limit this analysis to the subset of individuals aged 50 and older. The University of Michigan institutional review board approved this study; all subjects provided written informed consent.

Microbiology

Clostridium difficile testing included the C. DIFF QUIK CHEK COMPLETE test for glutamate dehydrogenase (GDH) and toxins A or B (Techlab, Inc., Blacksburg, VA). All GDH-positive and/toxin-negative stools were analyzed further using the *tcdB* gene using real-time polymerase chain reaction (BD GeneOhm Cdiff Assay, Franklin Lakes, NJ). Positive tests were confirmed according to anaerobic culture as described previously.[26]

Clinical Characteristics

Participant medical records were reviewed, and clinical characteristics of interest were recorded, including immunosuppression (innate or exogenous); acute organ dysfunction (AOD); lack of response to initial CDI therapy (defined as a change in initial therapy or a lack of clinical response within 5 days); and ICU admission, colectomy, or death attributable to CDI within 30 days. The definition for lack of clinical response was based on the Infectious Diseases Society of America clinical practice guidelines,[24] which referenced a previous study[27] and a subsequent study.[6] AOD was defined as acute kidney injury according to the RIFLE criteria (risk, injury, failure, loss, end-stage renal disease),[28] acute respiratory distress syndrome (recorded in the chart or a ration of partial pressure of oxygen in arterial blood to fraction of inspired oxygen <200 and diffuse pulmonary infiltrates with acute onset), new or worse heart failure (recorded in the chart), liver failure (new or worse coagulopathy or hepatic encephalopathy), or shock (systolic blood pressure <90 mmHg or need for pressors or inotropes). Two reviewers (DM, EC) independently abstracted data from participant charts, and a third reviewer (KR) resolved differences.

Data were collected at the time of study enrollment on age, sex, proton pump inhibitor (PPI) use, and temperature and maximum white blood cell (WBC) count within 24 hours of CDI diagnosis. Information on length of stay and 90-day mortality or readmission was obtained from the electronic medical record. CDI recurrence was defined as recurrent diarrhea and repeat positive assay more than 14 days from the original diagnosis.

Upon enrollment, interviews were conducted with the participants or their families to obtain information on comorbid conditions such as chronic kidney disease, congestive heart failure (CHF), diabetes mellitus (DM), and prior CDI and baseline functional status. Ability to perform activities of daily living (ADLs)—bathing, transferring, walking, dressing, grooming, and feeding, independently or with assistance—was asked about. These were assessed at the time of the participant's enrollment (baseline), before the hospitalization, and at the onset of CDI. Overall functional status was characterized as independent (no assistance needed for any ADL), some assistance (assistance needed in 1–5 ADLs), or full assistance (assistance needed in all 6 ADLs). The participant's living arrangements and care needs (living independently at home, living at home with skilled nursing services, or residing in an extended care facility (ECF)) before admission was also asked about. Information about discharge location and need for home care services was obtained from the medical record.

The presence of comorbid illness was also assessed using *International Classification of Diseases, Ninth Revision* (ICD-9) codes as described previously.[29] Weights from the original Charlson Comorbidity Index[30] were assigned to the individual variables in the Deyo modification of the Charlson score to create a weighted Charlson-Deyo comorbidity index. ICD-9 code data and participant enrollment interviews were combined to maximize sensitivity.

Data Analysis

To assess the relationship between diminished functional status and severe CDI, a binary variable called severity score was defined that was true (positive) if any of the following CDI severity markers were present: WBC count greater than 15,000 cells/μL; fever (temperature >38°C); AOD; no initial response to therapy; and ICU admission, colectomy, or death attributable to CDI within 30 days of presentation.

Univariate analysis using simple logistic regression identified risk factors for positive severity score and tested whether ADL class was associated with positive severity score. A two-tailed *P*-value ≤.05 was considered statistically significant. Variables that were significant in univariate analysis and variables that had a priori clinical significance were analyzed using multivariable logistic regression.

The association between ADL class and the secondary outcomes of need for readmission and 90-day mortality was also explored. The association between impaired functional status and CDI recurrence was examined using Kaplan–Meier survival analysis. Chi-square and Fisher exact tests were used to compare proportions for categorical variables. The Student *t*-test was used to compare continuous variables including length of stay. All values are expressed as means ± standard deviations. Crude odds ratios (ORs) and 95% confidence intervals (CI) were calculated. Statistical analysis was conducted using R 2.15.0 (http://www.r-project.org), SAS version 9.3 (SAS Institute, Inc., Cary, NC), and Graphpad Prism 5.04 (Graphpad Software, Inc., La Jolla, CA).

RESULTS

Ninety individuals (mean age 66.6 ± 10.2) met criteria for inclusion in the study. Fifty-two were female (57.8%). Common medical comorbidities were diabetes mellitus (31.1%), CHF (25.6%), depression (24.4%), and immunosuppression (34.4%) (Table 1). CDI had previously been diagnosed in 18 (20%), and 63 (70%) were using PPIs at the time of diagnosis (Table 1).

Sixty-five participants (72.2%) had no impairments in physical function (independent in ADLs); of the remaining 25 participants with poor functional status, eight needed some assistance, and 17 needed full assistance with ADLs (Table 1). Fifty-eight participants (64.4%) had at least one CDI severity marker (positive severity score): most commonly, WBC count greater than 15,000/μL (24), lack of response to initial therapy (22), AOD (14), and ICU admission (5) or death (2) due to CDI (Online Appendix—Figure S1).

Univariate analysis identified several factors associated with severe CDI, including age, history of depression, needing full assistance with ADLs, and ECF residence (Table 2). Needing assistance with each individual ADL was also associated with severe CDI, although an association was not found between an ADL class of some assistance and severe CDI (Table 2).

The final multivariable model for severe CDI included age, ADL class, CHF, DM, depression, weighted Charlson-Deyo comorbidity score, immunosuppression, prior CDI, and PPI use. ECF residence and individual ADLs were excluded from the final model to avoid multicollinearity with ADL class (Table 3). An ADL class of full assistance retained its association with a positive severity score in the presence of these other covariates (OR = 8.1, 95% CI = 1.24–52.98, *P* = .03). There was also an association with age (OR = 1.07, 95% CI = 1.01–1.13, *P* = .03), DM (OR = 0.22, 95% CI = 0.06–0.74, *P* = .01), and depression (OR = 5.04, 95% CI = 1.27–19.97, *P* = .02).

Table 1. Characteristics of Participants Aged 50 and Older with *Clostridium difficile* Infection (CDI) (N = 90)

Characteristic	Value
Age, mean ± standard deviation	66.6 ± 10.2
Female, n (%)	52 (57.8)
ADL class, n (%)	
Independent	65 (72.2)
Some assistance[a]	8 (8.9)
Full assistance[b]	17 (18.9)
Assistance with feeding, n (%)	21 (23.3)
Assistance with walking, n (%)	23 (25.6)
Assistance with moving, n (%)	19 (21.1)
Assistance with dressing, n (%)	22 (24.4)
Assistance with grooming, n (%)	23 (25.6)
Assistance with bathing, n (%)	22 (24.4)
Extended care facility residence, n (%)	15 (16.7)
Proton pump inhibitor use, n (%)	63 (70)
Prior CDI, n (%)	18 (20)
Weighted Charlson-Deyo score, mean ± SD	3.8 ± 2.4
Dementia, n (%)	3 (3.3)
Diabetes mellitus, n (%)	28 (31.1)
Congestive heart failure, n (%)	23 (25.6)
Chronic kidney disease, n (%)	24 (26.7)
Depression, n (%)	22 (24.4)
Cancer, n (%)	50 (55.6)
Stroke, n (%)	23 (25.6)
Immunosuppression, n (%)	31 (34.4)
Outcome, n (%)	
Positive severity score[c]	58 (64.4)
90-day readmission	47 (52.2)
90-day mortality	8 (8.9)

[a]Assistance needed for 1–5 activities of daily living (ADLs).

[b]Assistance needed for all 6 ADLs.

[c]Markers of severe CDI: fever; white blood cell count >15,000 cells/μL; acute organ dysfunction; no response to therapy; or intensive care unit admission, colectomy, or death from CDI within 30 days.

No association was found between ADL class and the secondary outcomes of length of stay, 90-day mortality, or 90-day readmission (data not shown). Kaplan–Meier survival analysis for recurrent CDI comparing participants according to ADL class found greater risk for needing some assistance (hazard ratio (HR) = 2.46, 95% CI = 0.82–7.37, *P* = .11) and full assistance (HR = 1.69, 95% CI = 0.75–3.82, *P* = .20), but these results did not reach significance (Online Appendix—Figure S2).

DISCUSSION

The lack of ability to predict accurately, at the earliest stages of illness, which individuals with CDI will progress to severe disease and experience adverse clinical outcomes remains an important limitation to optimal management. Such knowledge could affect resource allocation and inform early treatment decisions, with the potential to improve outcomes. For example, the decision to use vancomycin, which is recommended for severe CDI (WBC count >15,000 cells/μL or serum creatinine level >1.5 times the premorbid level),[24] in lieu of metronidazole may be appropriate in individuals with greater risk of poor outcomes.

Table 2. Univariate Logistic Regression for Severity Score

Variable	Odds Ratio (95% Confidence Interval) *P*-Value
Age	1.07 (1.02–1.12) .005
Female	0.75 (0.32–1.74) .50
ADL class	
Some assistance[a]	4.50 (0.84–24.04) .08
Full assistance[b]	7.00 (1.83–26.79) .004
Assistance with feeding	5.86 (1.78–19.26) .004
Assistance with walking	5.01 (1.66–15.11) .004
Assistance with moving	7.29 (1.95–27.28) .003
Assistance with dressing	6.43 (1.96–21.05) .002
Assistance with grooming	5.01 (1.66–15.11) .004
Assistance with bathing	4.57 (1.51–13.83) .007
Extended care facility residence	8.27 (1.74–39.25) .008
Proton pump inhibitor use	1.82 (0.73–4.54) .20
Prior CDI	2.24 (0.76–6.61) .15
Weighted Charlson-Deyo score	1.12 (0.94–1.34) .19
Dementia	N/A (N/A) .97
Diabetes mellitus	0.40 (0.16–1.01) .05
Congestive heart failure	1.06 (0.41–2.73) .91
Chronic kidney disease	1.18 (0.46–1.62) .73
Depression	3.38 (1.18–9.68) .02
Cancer	1.56 (0.67–3.59) .30
Stroke	1.06 (0.41–2.73) .91
Immunosuppression	0.69 (0.29–1.66) .41

Markers of severe *Clostridium difficile* infection (CDI): fever; white blood cell count >15,000 cells/μL; acute organ dysfunction; no response to therapy; and intensive care unit admission, colectomy, or death from CDI within 30 days.

[a]Assistance needed for 1–5 activities of daily living (ADLs).

[b]Assistance needed for all 6 ADLs.

N/A = not available.

Table 3. Multiple Logistic Regression for Severity Score

Variable	Odds Ratio (95% Confidence Interval) *P*-Value
Age	1.07 (1.01–1.13) .03
ADL class	
Some assistance[a]	4.54 (0.56–37.07) .16
Full assistance[b]	8.10 (1.24–52.95) .03
Proton pump inhibitor use	3.10 (0.86–11.18) .08
Prior CDI	1.98 (0.43–9.13) .38
Weighted Charlson-Deyo score	1.26 (0.98–1.62) .07
Congestive heart failure	0.26 (0.06–1.13) .07
Diabetes mellitus	0.22 (0.06–0.75) .01
Depression	5.03 (1.27–19.96) .02
Immunosuppression	0.72 (0.24–2.18) .56

Markers of severe *Clostridium difficile* infection (CDI): fever; white blood cell count >15,000 cells/μL; acute organ dysfunction; no response to therapy; and intensive care unit admission, colectomy, or death from CDI within 30 days.

[a]Assistance needed for 1–5 activities of daily living (ADLs).

[b]Assistance needed for all 6 ADLs.

Older adults are at higher risk of poorer outcomes resulting from certain infections,[17–19] in part because of an impaired immune response, and CDI fits within this paradigm.[21] The preceding results suggest that, in addition to age, impaired functional status is an independent predictor of severe CDI, as demonstrated by the final multivariable model, which adjusted for the potential confounding effects of comorbid disease, immunosuppression, and PPI use. Although it was not possible to demonstrate the same connection in participants who needed some assistance, the lack of an association may be because of type II error, because only eight participants fell into this category. There is a critical need for better tools to predict severe CDI; these findings suggest that measurement of functional status may have a role in robust clinical risk prediction algorithms. No greater risk of recurrent disease was found in participants with impaired functional status, but this may also have been because of type II error.

A puzzling result of the present study is that DM appeared to be protective against severe CDI in the final multivariable model. One possible explanation is that impaired neutrophil chemotaxis and antibacterial activities may lead to fewer individuals with diabetes mellitus presenting with fever or leukocytosis,[31] although testing this hypothesis was beyond the scope of the study. Furthermore, a strong body of clinical evidence does not support the classically held dogma that DM is associated with greater susceptibility to infection and poor outcomes from infection.[32] Similar to the unexpected finding, in an analysis of the Nationwide Inpatient Sample, a diagnosis of DM was associated with less mortality from CDI.[33] Also interesting is the strong association between depression and severe CDI observed. Similarly, a previous study found an association between antidepressant use and the risk of developing CDI.[34] Further study is required to explore these intriguing relationships.

A limitation of this work is the lack of validated frailty measures, which may have an effect on the risk of severe disease and other adverse outcomes independent of the contribution from impaired functional status. Similarly, data on impaired cognitive function or delirium during hospitalization were not captured, so it was not possible to account for any contribution from these potential risk factors. Future studies should explore the influence of these factors on the development of severe CDI and clinical outcomes.

In summary, this study offers additional insights into the complex interplay between age, comorbid disease, functional status, and the risk of severe CDI and suggests that impaired functional status is an independent risk factor for development of severe CDI. Future studies could include validation of these findings in a larger cohort of mostly older adults with severe CDI, incorporation of functional status into a broader risk-prediction model with clinical and biochemical predictors of severity, and a prospective trial in which a risk-based clinical algorithm guides treatment decisions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Presence of *Clostridium difficile* infection (CDI) severity markers (fever (>38°C); acute organ dysfunction (AOD); white blood cell count (WBC) in cells/μL; no response to CDI therapy; and outcomes attributable to CDI within 30 days—intensive care unit (ICU) admission, colectomy, and death).

Figure S2. Kaplan–Meier survival curve for *Clostridium difficile* infection (CDI) recurrence. This figure compares the risk of recurrent CDI in participants who were independent in activities of daily living, those who needed some assistance (hazard ratio (HR) = 2.46, 95% confidence interval (CI) = 0.82–7.37, $P = .11$), and those who needed full assistance (HR = 1.69, 95% CI = 0.75–3.82, $P = .20$).

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