Clostridium Difficile Infection in the "Oldest" Old: Clinical Outcomes in Patients Aged 80 and Older

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OBJECTIVES: *Clostridium difficile* infection (CDI) represents a cause of substantial morbidity, particularly for older adults. Although older age is a risk factor for CDI, few studies have specifically focused on clinical outcomes in older adults, particularly the "oldest" old.

DESIGN: Retrospective review.

SETTING: University of Michigan Health System.

PARTICIPANTS: All patients aged 80 and older with a positive cytotoxin assay for *C. difficile* and a clinical course consistent with CDI during 2006.

MEASUREMENTS: Clinical data were recorded, including comorbid conditions and treatment regimens, as well as outcomes, including treatment failure, infection relapse, and 90-day mortality.

RESULTS: Seventy patients aged 80 and older (mean 84.0 ± 4.1) with CDI were identified. Metronidazole was given as initial therapy in 65 (92.8%); 18 of these 65 (27.7%) experienced treatment failure, requiring subsequent use of oral vancomycin. Serious adverse events included three episodes of toxic megacolon, two requiring colectomy. One death was directly attributable to CDI. All-cause mortality was 8.6% at 30 days and 17.1% at 90 days. Higher white blood cell (WBC) counts were independently associated with treatment failure ($P = .02$) and coronary artery disease with 90-day mortality ($P = .02$).

CONCLUSION: In older adults with CDI, treatment failure on metronidazole occurred frequently and was associated with higher WBC count. Larger prospective studies are needed to determine risk factors for treatment failure and relapse in order to develop better paradigms for CDI treatment in older adults. Initial therapy with vancomycin may be appropriate for elderly patients, especially those with elevated WBC counts. **J Am Geriatr Soc 57:659–662, 2009.**

Key words: *Clostridium difficile*; **aging; metronidazole; vancomycin**

In recent years, the incidence and severity of *Clostridium difficile* infection (CDI) have increased. With the emergence of the highly toxigenic strain, BI/NAP1, CDI has emerged as a cause of substantial morbidity and healthcare costs, especially in older adults.[1–3] In recent reports of BI/NAP1 outbreaks, age of 65 and older has been highlighted as an important risk factor for developing CDI, as well as for greater disease severity and higher mortality.[4–6]

The Centers for Disease Control and Prevention (CDC) reports that hospital discharge diagnosis of CDI nearly doubled from 1996 to 2003, increasing from 31 to 61 discharges per 100,000 population.[5] This increase was most notable in older adults; in persons aged 65 and older, rates increased from approximately 150 discharges per 100,000 population in 1996 to 300 discharges per 100,000 population in 2003. In addition to greater incidence and mortality, older adults experience higher rates of treatment failures and disease relapse.[5,6]

Although older age has been repeatedly identified as a risk factor for CDI, few studies have specifically focused on clinical outcomes of CDI in older adults. It was desired to examine the clinical course of CDI in the "oldest" old ($\geq$80), including the rate of important complications, such as need for hospitalization or surgical intervention, and death. Treatment failure and relapse of disease within 90 days of initial treatment were also recorded.

METHODS

Setting and Population

The University of Michigan Health System (UMHS) is a 850-bed tertiary care facility. Using microbiology records, all patients aged 80 and older cared for at the UMHS with a positive enzyme-linked immunosorbent assay for *C. difficile* cytotoxin A or B and a clinical course consistent with CDI from January 1, 2006, to December 31, 2006, were identified. Medical records were reviewed and information of

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interest recorded including demographic data, clinical conditions, and characteristics of CDI. We assessed treatment regimens, complications (including toxic megacolon and need for surgery), pre- and post-hospitalization care requirements, and mortality.

Outcomes of Interest

Specific outcomes of interest were defined as follows failure of initial agent, defined as lack of clinical improvement after 5 days or change in treatment regimen because of lack of clinical response; relapse, defined as any recurrence of CDI within a 90-day period after initial presentation; and death within 90 days of presentation (all-cause mortality). The institutional review boards of the University of Michigan Health System approved this study.

Data Analysis

Univariate analysis using *t*-tests for continuous variables and the chi-square or Fisher exact test for categorical variables identified risk factors for treatment failure, relapse, and death in patients with CDI. A two-tailed $P \leq .05$ was considered statistically significant. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for categorical variables. Crude ORs for continuous variables were obtained using simple logistic regression. Variables that were significant to $P = .20$ and variables that had a priori clinical significance were then analyzed using multivariate logistic regression modeling. All statistical analysis was performed using SAS 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Seventy patient aged 80 and older were identified with CDI (mean age 84.0 ± 4.1, range 80–94). Twenty-nine (41.1%) were male. Common medical comorbidities were coronary artery disease (35.7%), renal insufficiency (27.1%), and diabetes mellitus (18.5%). The mean peak white blood cell (WBC) count was 14.8 ± 8.6 thousand/mm^3 (range 3.6–46.4). Fifty-seven (81.4%) patients received antibiotics, and 41 (58.5%) received proton pump inhibitors during the 30 days before presentation (Table 1).

Initial therapy for CDI consisted of metronidazole in 65 (92.8%), and vancomycin in two (2.9%). Three patients did not receive antimicrobial therapy for CDI treatment. Complications associated with CDI included toxic megacolon in three patients (4.3%), two of whom required colectomy.

Treatment failure prompting a change in CDI therapy occurred in 18 of 65 patients (27.7%), all of whom received initial treatment with metronidazole. All 18 were switched to oral vancomycin. These 18 patients received a median of 7 days of metronidazole before the switch to vancomycin. All 18 had appropriate dosing of metronidazole, generally 500 mg three or four times a day.

Twelve patients (17.1%) experienced disease relapse within 90 days after completion of treatment for CDI. All 12 received initial treatment with metronidazole: four with relapsed disease had experienced treatment failure during their initial presentation, prompting a switch to oral vancomycin.

Table 1. Characteristics for Patients Aged 80 and Older with *Clostridium Difficile*–Associated Diarrhea (N = 70)

Characteristic	Value
Age, mean ± SE	84.0 ± 4.1
Male, n (%)	29 (41.1)
Coronary artery disease, n (%)	25 (35.7)
Congestive heart failure, n (%)	22 (31.4)
Diabetes mellitus, n (%)	13 (18.5)
Renal insufficiency (creatinine clearance < 30 mL/min) , n (%)	19 (27.1)
Colon cancer, n (%)	2 (2.8)
Inflammatory bowel disease, n (%)	2 (2.8)
Peak white blood cell count, K/mm^3, mean ± SE	14.8 ± 8.6
Surgery during previous month, n (%)	11 (15.7)
Antimicrobial use in past 30 days, n (%)	57 (81.4)
Proton pump Inhibitor in past 30 days, n (%)	41 (58.5)
Initial therapy, n (%)*	
Metronidazole	65 (93)
Vancomycin	2 (2.9)
Complications, n (%)	
Toxic megacolon	3 (4.3)
Need for colectomy	2 (2.9)
Relapse	12 (17.1)
Treatment failure	18 (25.7)
Death (within 90 days)	12 (17.1)

*Three patients did not receive antimicrobial therapy for *Clostridium difficile*–associated diarrhea.
SE = standard error.

Twelve patients (17.1%) died within 90 days of initial presentation and diagnosis; one death was directly attributable to CDI. These deaths occurred from 2 to 85 days after the initial diagnosis of CDI (median 33.5 days). Overall, six deaths occurred within 30 days of presentation (8.6%). Neither treatment failure nor disease relapse appeared to be associated with a higher death rate when compared with each other. The death rate for patients experiencing treatment failure was 11.1%; for patients with CDI relapse, it was 8.3%.

Of the 70 patients studied, 31 required 40 admissions with a primary admitting diagnosis of CDI, 15 were treated as outpatients, and 24 developed CDI during hospitalization for another medical or surgical issue. Of the 31 patients admitted for CDI, 25 were community dwelling and independent with activities of daily living before admission; eight of these 25 (32.0%) required discharge to subacute settings because of impaired mobility and functional decline.

Overall, treatment failure occurred in 18 (25.7%) patients. Of the 31 patients admitted primarily for CDI, 11 (35.5%) experienced treatment failure. Fifteen patients were treated on an outpatient basis, with three treatment failures (20%). Of the 24 patients who developed CDI during an admission for another reason, four experienced treatment failure (16.6%). Although the patients admitted with a primary diagnosis of CDI had a higher rate of treatment failure, this difference did not achieve statistical significance (OR = 2.5, 95% CI = 0.84–7.6, $P = .16$).

Univariate analysis identified risk factors associated with outcomes of interest (Table 2). Patients experiencing

Table 2. Univariate Analysis of Patient Characteristics for Treatment Failure, 90-Day Relapse, and 90-Day Mortality

Patient Characteristic	Treatment Failure (n = 18)			90-Day Relapse (n = 12)			Death at 90 Days (n = 12)		
	Mean ± SE	n	OR (95% CI) *P*-Value	Mean ± SE	n	OR (95% CI) *P*-Value	Mean ± SE	n	OR (95% CI) *P*-Value
Age*	86.0 ± 4.4		1.1 (1.0–1.2) .17	85.2 ± 3.9		1.0 (0.9–1.2) .77	85.0 ± 4.7		1.0 (0.9–1.2) .90
Coronary artery disease		5	0.6 (0.2–1.8) .50		3	0.5 (0.1–2.1) .53		8	4.4 (1.2–16.7) .05
Renal insufficiency		6	1.5 (0.5–4.8) .49		2	0.5 (0.1–2.4) .61		3	(0.2–3.6) .99
Peak white blood cell count (thousand/mm^3)	20.0 ± 11.1		1.1 (1.0–1.2) .007	15.2 ± 6.9		(0.9–1.1) .86	16.9 ± 9.8		1.0 (0.9–1.1) .35
Antimicrobial use†		16	2.1 (0.4–10.7) .57		12	7.4 (0.4–133) .13		11	2.9 (0.3–24.5) .58
Proton pump inhibitor use†		13	2.1 (0.6–6.6) .34		6	0.6 (0.2–2.1) .44		10	4.0 (0.8–20.2) .13
Initial therapy									
Metronidazole		18	4.3 (0.2–81.4) .43		12	2.6 (0.1–49.6) .76		11	0.8 (0.1–8.0) .99
Vancomycin		0	0.6 (0.0–11.9) .99		0	0.9 (0.0–20.0) .99		1	5.2 (0.3–89.2) .58
Toxic megacolon		2	6.4 (0.5–75.0) .32		1	2.5 (0.2–30.6) .99		0	0.6 (0.0–13.1) .99
Colectomy required		1	3 (0.2–50.6) .78		0	0.9 (0.0–20.0) .99		0	0.9 (0.0–20.0) .99

* Odds ratio (OR) for age reported for 1-year unit.
† Within 30 days before presentation.
SE = standard error; CI = confidence interval.

treatment failure had a higher peak WBC count than those who responded to initial therapy ($P < .01$). Coronary artery disease was highly associated with 90-day mortality (crude OR = 4.4, $P = .05$). These risk factors remained independently associated with treatment failure and 90-day mortality on multivariate analysis (Table 3).

DISCUSSION

CDI is a serious illness associated with significant morbidity and mortality. In recent years, the incidence of CDI infection has more than doubled.[4] Past investigations have noted that older adults who develop CDI are at high risk of serious adverse effects, including death. It was desired to describe the clinical course of patients aged 80 and older, including identification of possible risk factors for poor outcomes and treatment failure.

These findings suggest that, in the "oldest" elderly patients with CDI, treatment failure on metronidazole occurred frequently (27.7%) and appears to be associated with higher peak WBC count ($P = .01$). The relationship between high WBC count and greater severity of clinical disease is well described; this association was also observed in the initial reports of B1/NAP1 strain outbreaks.[2,6] The nearly 28% rate of metronidazole failure observed in this cohort is consistent with the rate of treatment failure in patients with severe CDI described in two recent prospective studies of CDI treatment.[7,8]

Of previously community-dwelling patients admitted with a primary diagnosis of CDI, 32.0% were discharged to subacute care. Overall death rates were significant, with 17.1% dying within 90 days of CDI diagnosis and one death directly attributable to CDI. If only hospitalized patients are considered (n = 55), the death rate climbs to 21.8%. Adjusted odds of death in patients with coronary artery disease were more than five times as high as patients without coronary artery disease, ($P = .02$).

Limitations of this study include the retrospective design and the small sample size. The overwhelming use of metronidazole as the first line of therapy in these patients makes it impossible to compare the efficacy of metronidazole with that of oral vancomycin. Despite these limitations,

Table 3. Multivariate Analysis of the Association Between Patient Characteristics, Treatment Failure, and 90-Day Mortality in Patients with *Clostridium Difficile*–Associated Diarrhea

	Odds Ratio (95% Confidence Interval) *P*-Value	
	Unadjusted	Adjusted*
Treatment failure		
White blood cell count	1.1 (1.0–1.2) .007	1.1 (1.0–1.2) .02
90-day mortality		
Coronary artery disease	4.4 (1.2–16.7) .05	5.5 (1.3–23) .02
White blood cell count	1.0 (0.9–1.1) .35	1.1 (1.0–1.2) .13

* Based on a multivariable logistic regression adjusting for age, renal insufficiency, serum albumin, coronary artery disease, congestive heart failure, diabetes mellitus.

the 27.7% rate of treatment failure in patients receiving metronidazole is notable and suggests that metronidazole may not be the appropriate initial agent in older adults, particularly those with high WBC counts on presentation or other signs and symptoms of severe CDI. The question of optimal therapy for CDI remains unclear, although it is evolving. Many experts have recommended vancomycin as first-line therapy in older adults, especially for patients with severe disease, characterized by high WBC count, severe abdominal pain, or rising creatinine.[7,9–11] Several clinical studies have demonstrated that oral vancomycin provides higher rates of cure than metronidazole in patients with severe CDI,[7,8] although drug costs remain a major barrier for use of vancomycin as a first line of therapy, particularly in mild or moderate disease, where there is no evidence that vancomycin is superior to treatment with metronidazole.[12]

As the burden of CDI in older adults continues to grow, so does the need to improve understanding of disease in this population. Larger prospective studies are needed to determine risk factors for CDI treatment failure, relapse, and poor outcomes in order to develop better paradigms for CDI treatment for older adults, including how to identify patients who should receive initial therapy with oral vancomycin and patients who may benefit from extended treatment courses or tapered therapy. Efforts to prevent CDI through directed infection control measures and prudent use of antimicrobials remain critical, particularly in the long-term and subacute care settings. Finally, the problem of functional decline associated with the diagnosis of CDI deserves consideration. Although pre- and post-admission functional ability was not formally assessed, a sizable number of patients previously independent in activities of daily living admitted specifically for CDI required subacute care after discharge.

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Conflict of Interest: All authors declare that they have no conflicts of interest.

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