MAJOR ARTICLE

Health Care Costs and Mortality Associated with Nosocomial Diarrhea Due to *Clostridium difficile*

Lorraine Kyne,[1] Mary Beth Hamel,[2] Rajashekhar Polavaram,[3] and Ciarán P. Kelly[3]

Divisions of [1]Gerontology, [2]General Internal Medicine and Primary Care, and [3]Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

A total of 271 patients were prospectively followed up to determine whether patients whose hospital stay is complicated by diarrhea due to *Clostridium difficile* experience differences in cost and length of stay and survival rates when compared with patients whose stay is not complicated by *C. difficile*–associated diarrhea. Forty patients (15%) developed nosocomial *C. difficile*–associated diarrhea. These patients incurred adjusted hospital costs of $3669—that is, 54% (95% confidence interval [CI], 17%–103%)—higher than patients whose course was not complicated by *C. difficile*–associated diarrhea. The extra length of stay attributable to *C. difficile*–associated diarrhea was 3.6 days (95% CI, 1.5–6.2). *C. difficile*–associated diarrhea was not associated with excess 3-month or 1-year mortality after adjustment for age, comorbidity, and disease severity. On the basis of the findings of this study, a conservative estimate of the cost of this disease in the United States exceeds $1.1 billion per year.

Clostridium difficile is a major cause of antibiotic-associated diarrhea and colitis [1]. The incidence of infection with this organism is increasing in hospitals worldwide, consequent to the widespread use of broad-spectrum antibiotics [2]. In a recent study, we found that 31% of patients who received antibiotics in acute care medical wards were colonized with *C. difficile*, and 56% of these patients developed *C. difficile*–associated diarrhea (hereafter referred to as "*C. difficile* diarrhea") [3].

Although the clinical and financial impact of nosocomial *C. difficile* infection is believed to be significant, the reported extra costs and extra length of stay attributable to infection with this organism vary widely [4–9]. Similarly, mortality rates associated with *C. difficile* diarrhea in observational and case control studies range from 0.6% to 83% [10–15]. Moreover, the effect of the severity of underlying disease and comorbidity on health care costs or mortality has been poorly defined.

A valid estimate of the financial and clinical burden of diarrhea due to *C. difficile* would help in the evaluation of the potential benefits, in terms of health expenditure and survival, of new therapies or preventative measures to control the disease. By use of a prospective cohort study design, the aim of this study was to determine the association between hospital costs, length of stay, and mortality associated with nosocomial *C. difficile* diarrhea.

METHODS

Patients. Data for this analysis were collected as part of a prospective study of nosocomial acquisition of *C. difficile*. A full description of the primary objectives and

Received 17 July 2001; revised 27 August 2001; electronically published 17 December 2001.

Financial support: National Institutes of Health grants AG00971 (to L.K.) and AG00755 (to M.B.H.); career development award from the Paul Beeson Faculty Scholars in Aging Research Program (to M.B.H.).

Reprints or correspondence: Dr. Lorraine Kyne, Gerontology Div., Rabb 440, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215 (lkyne@caregroup.harvard.edu).

Clinical Infectious Diseases 2002; 34:346–53

1058-4838/2002/3403-0008$03.00

the design of this study has been published elsewhere [3]. In brief, patients who were consecutively admitted to either of 2 general medical wards from 5 January 1998 through 22 May 1998 with infections that required treatment with antibiotics were eligible for enrollment in the study. Patients were excluded if they were not receiving antibiotics. The study was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center, and informed consent was obtained from eligible patients or their health care proxies.

Study protocol. At study entry, we recorded patient age, sex, race, and admission diagnosis. The severity of the primary condition that led to hospitalization was assessed clinically by use of a modified Horn's index and rated as "mild" (1 point), "moderate" (2 points), "severe" (3 points), or "extremely severe" (4 points) [16, 17]. Assessments were made by an experienced geriatrician (L.K.) and by a doctor directly responsible for the care of the patient. Agreement between these raters was excellent ($\kappa > 0.90$). A Charlson comorbidity index, which assesses information on coexistent diseases other than the primary diagnosis, was also obtained [18]. Admitting diagnosis was categorized into 5 categories depending on the body site or system infected, as follows: pulmonary infection (including respiratory tract infections and pneumonia); gastrointestinal infection (including peritonitis, diverticulitis, pancreatitis, ulcerative colitis, and cholangitis); urological infection (including urinary tract infections and pyelonephritis); skin, soft-tissue, or bone infection (including cellulitis and osteomyelitis); and miscellaneous infections (including infections of the CNS and cardiovascular system).

Patients were followed up throughout their hospital stay and assessed for the development of *C. difficile* diarrhea. Stool samples were obtained on the day of admission and every 3 days thereafter; they were tested for the presence of toxigenic *C. difficile* by culture and by tissue culture cytotoxicity (toxin B) testing. "*C. difficile* diarrhea" was defined as antibiotic-associated diarrhea (a change in bowel habit with $\geq$3 unformed bowel movements per day for $\geq$2 days) not attributed to any other cause that occurred in association with a positive stool cytotoxin test result for *C. difficile* [3, 19]. Other infectious causes of diarrhea were excluded by use of the appropriate stool tests. The "time at risk for *C. difficile* diarrhea" was defined as the length of stay before colonization for patients who developed *C. difficile* diarrhea and the total length of stay for patients who did not develop *C. difficile* diarrhea. Patients or their surrogates were interviewed at 90 days after discharge from the hospital. Data on survival beyond this point were obtained by intermittently contacting patients or their surrogates for up to 1 year after discharge.

Cost estimates. Total hospital charges were collected from the hospital's billing system. Hospital costs were estimated by adjusting charges by using the overall Medicare cost-to-charge ratio for our institution. We estimated the mean hospital costs attributable to each case of *C. difficile* diarrhea by taking a weighted average of the total hospital costs for patients admitted with the primary diagnosis of *C. difficile* diarrhea and of the excess hospital costs attributable to *C. difficile* diarrhea for patients hospitalized with infections whose course was complicated by *C. difficile* diarrhea. (Excess costs were estimated from multivariable models, as described in the statistical analysis subsection below.) We calculated the percentage of admissions to our hospital that involved treatment of *C. difficile* diarrhea. We used data from the American Hospital Association to determine the number of admissions to hospitals in the United States each year. On the basis of these estimates, we calculated the total annual hospital costs attributable to the management of *C. difficile* diarrhea by using the following equation: average cost per case of *C. difficile* diarrhea $\times$ percentage of hospitalized patients who required treatment for *C. difficile* diarrhea $\times$ total number of admissions to hospitals in the United States per year.

These estimates only include hospital costs and do not include doctors' costs or the costs of posthospital care of *C. difficile* diarrhea; therefore, they conservatively estimate the actual costs.

Statistical analysis. The primary independent variable was *C. difficile* diarrhea. The outcomes (dependent variables) that we analyzed included estimated hospital costs, total length of hospital stay, and all-cause mortality. We used Wilcoxon rank-sum tests to compare the costs and the length of stay of patients whose hospital stay was complicated by *C. difficile* diarrhea and those whose stay was not complicated by *C. difficile* diarrhea. We analyzed the associations between other potential confounding variables (age, Charlson comorbidity score, disease severity [Horn's index], sex, race, and diagnosis) and costs and length of stay by Spearman correlation coefficients or Kruskal-Wallis tests, as appropriate. Single predictor Cox proportional-hazards regression models were developed for *C. difficile* diarrhea and other baseline characteristics to determine the effect of these variables on the risk of death per unit time (the hazard ratio).

To analyze the independent effect of *C. difficile* diarrhea on hospital costs and length of stay, we used linear regression analyses. Cost and length of stay analyses were based on log-transformed data because of skew in the distribution of these data. In each analysis, we adjusted for age, Charlson comorbidity score, disease severity (Horn's index), sex, race, and diagnosis. Collinearity between variables in each model was assessed by examining the tolerance and variance inflation factor for each independent variable [20]. The normality of each model's residuals was also checked.

Antilogs of the regression coefficients associated with indi-

Table 1. Baseline characteristics of the study cohort of 264 patients.

Characteristic	Value
Age, years	
Mean ± SD	74 ± 16.5
Range	19–101
⩽65	60 (23)
66–84	136 (52)
⩾85	68 (26)
Male sex	106 (40)
White race	226 (86)
Charlson index, median (range)	3 (0–13)
Disease severity[a]	
1	80 (30)
2	96 (36)
3	59 (22)
4	29 (11)
Admitting diagnosis	
Pulmonary infection	116 (44)
Gastrointestinal infection	17 (6)
Infection of skin, soft tissue, or bone	38 (14)
Urinary tract infection	32 (12)
Miscellaneous infections	59 (22)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Horn's index. A score of 1 denotes mild disease severity, 2 denotes moderate disease severity, 3 denotes severe disease severity, and 4 denotes extreme disease severity.

cator variables were used to calculate the adjusted costs and lengths of stay attributable to *C. difficile* diarrhea and to adjustment variables. We used Cox proportional-hazards regression analyses to determine the independent effect of *C. difficile* diarrhea on 1-year mortality and to calculate the adjusted hazard ratio for death while controlling for age, Charlson comorbidity score, disease severity (Horn's index), sex, race, and diagnosis. All analyses were performed with SAS software, version 6.12 (SAS Institute). The α level was set at 0.05. All *P* values were 2-sided.

RESULTS

Patient characteristics. We enrolled 271 patients. Of these, 47 patients (17%) had *C. difficile* diarrhea. For 7 of these patients, the sole reason for hospitalization was for management of *C. difficile* diarrhea. The mean age of these patients (2 women and 5 men) was 72 years (range, 41–90 years). Their median length of hospital stay was 7 days (range, 3–24 days), and the median estimated total cost of their hospitalization was $7400 (range, $2984–$34,860). Two (28.6%) of these 7 patients died within 3 months of discharge. To evaluate the extra costs, length of stay, and mortality associated with *C. difficile* diarrhea that complicated a hospitalization for infection, we excluded these 7 patients from all subsequent analyses.

Demographic and clinical characteristics of the remaining study cohort are shown in table 1. The mean patient age was 74 years; 158 patients (60%) were women, and 88 patients (33%) had severe to extremely severe disease at the time of admission to the hospital.

Cost estimates. In the unadjusted analysis (table 2), estimated hospital costs for patients whose hospital stay was complicated by *C. difficile* diarrhea were twice as high as those for patients whose hospital stay was not complicated by *C. difficile*

Table 2. Univariate analyses of factors associated with hospital costs for 264 patients in the study cohort.

Characteristic	Cost, median US$ (range)	*P*
All patients	6231 (518–188,347)	
Course complicated by *C. difficile* diarrhea		
Yes	12,298 (1761–188,347)	
No	5759 (518–126,680)	.0001
Age, years		
⩽65	7282 (518–188,347)	
66–84	6735 (1867–155,325)	
⩾85	5233 (1745–36,806)	.034
Sex		
Male	6841 (1761–188,347)	
Female	5814 (518–104,411)	.188
Race		
White	5976 (518–188,347)	
Other	7282 (2412–115,663)	.045
Charlson index		
<3	5592 (1761–115,663)	
⩾3	6715 (518–188,347)	.003
Disease severity[a]		
1	4503 (1761–32,354)	
2	5273 (518–18,562)	
3	10,005 (1745–126,680)	
4	29,819 (3129–188,347)	.0001
Admitting diagnosis		
Pulmonary infection	5858 (518–82,669)	
Gastrointestinal infection	10,972 (2412–102,164)	
Infection of skin, soft tissue, or bone	4977 (1867–109,522)	
Urinary tract infection	5657 (1951–74,569)	
Miscellaneous infections	7015 (1745–188,347)	.091

NOTE. *C. difficile, Clostridium difficile.*

[a] Horn's index. A score of 1 denotes mild disease severity, 2 denotes moderate disease severity, 3 denotes severe disease severity, and 4 denotes extreme disease severity.

Table 3. Independent association between *Clostridium difficile* diarrhea and estimated hospital costs, determined by use of a multivariable linear regression model.

Characteristic	Change	*P*
Course complicated by *C. difficile* diarrhea	+3669	.003
Adjustment variables		
Age, per year increase	−36	.09
Male sex	−110	.87
White race	−2052	.07
Charlson index, per point increase	−32	.83
Disease severity[a]		
1	Referent	—
2	+1391	.06
3	+6567	.0001
4	+20,459	.0001
Admitting diagnosis		
Gastrointestinal infection	Referent	—
Pulmonary infection	−1511	.19
Infection of skin, soft tissue, or bone	−2303	.06
Urinary tract infection	−2231	.08
Miscellaneous infections	−789	.55

NOTE. Data are changes in estimated hospital costs (in US$) attributable to each patient characteristic, unless otherwise indicated.

[a] Horn's index. A score of 1 denotes mild disease severity, 2 denotes moderate disease severity, 3 denotes severe disease severity, and 4 denotes extreme disease severity.

diarrhea. Other factors that were associated with significantly higher unadjusted hospital costs included younger age, nonwhite race, higher scores on the Charlson comorbidity index, and increasing severity of underlying disease at admission. Hospital costs did not differ significantly according to sex or admitting diagnosis.

In a multivariable linear regression model (table 3), we found that the independent predictors of increased hospital costs included disease severity and course complicated by *C. difficile* diarrhea. The adjusted estimated hospital cost for a typical patient whose course was complicated by *C. difficile* diarrhea was $10,489. This was $3669 (95% CI, $1126–$7024)—that is, 54% (95% CI, 17%–103%)—higher than the adjusted hospital cost for a typical patient whose course was not complicated by *C. difficile* diarrhea ($6820).

The mean cost per case of *C. difficile* diarrhea was $4657, and 63 (0.7%) of all 9091 persons who were admitted to our institution required treatment of *C. difficile* diarrhea. In 1999, there were 34,180,563 admissions to hospitals in the United States [21]. On the basis of these figures, we estimated that the total annual cost for treating *C. difficile* diarrhea in hospitals in the United States exceeds $1.1 billion.

Length of hospital stay. The median time at risk for patients who developed *C. difficile* diarrhea (6 days; range, 1–36 days) was similar to that for those who did not develop *C. difficile* diarrhea (5 days; range, 3–48 days; $P = .81$). In the unadjusted analysis (table 4), the median total length of hospital stay for patients whose course was complicated by *C. difficile* diarrhea was 7 days longer than that for patients who did not develop *C. difficile* diarrhea. The median length of hospital stay also increased proportionally with the severity of underlying disease at admission.

After adjustment for age, sex, race, comorbidity score, and admitting diagnosis, disease severity and course complicated by *C. difficile* diarrhea were found to be independent predictors of increased length of hospital stay (table 5). The estimated adjusted length of stay for a typical patient whose course was complicated by *C. difficile* diarrhea was 10.2 days. This was 3.6

Table 4. Univariate analyses of factors associated with length of hospital stay (LOS) for 264 patients in the study cohort.

Characteristic	LOS, median days (range)	*P*
All patients	6 (1–56)	
Course complicated by *Clostridium difficile* diarrhea		
Yes	12 (1–56)	
No	5 (3–48)	.0001
Age, years		
≤65	5 (3–56)	
66–84	6 (3–54)	
≥85	5.5 (1–30)	.33
Sex		
Male	6 (1–56)	
Female	5 (3–50)	.19
Race		
White	6 (1–56)	
Other	6 (3–55)	.96
Charlson index		
<3	5 (1–55)	
≥3	6 (3–56)	.06
Disease severity[a]		
1	4 (1–30)	
2	5 (3–28)	
3	9 (3–50)	
4	14 (3–56)	.0001
Admitting diagnosis		
Pulmonary infection	5 (1–36)	
Gastrointestinal infection	8 (4–45)	
Infection of skin, soft tissue, or bone	5 (3–40)	
Urinary tract infection	5 (3–50)	
Miscellaneous infections	7 (3–56)	.17

[a] Horn's index. A score of 1 denotes mild disease severity, 2 denotes moderate disease severity, 3 denotes severe disease severity, and 4 denotes extreme disease severity.

Table 5. Independent association between *Clostridium difficile* diarrhea and length of hospital stay (LOS) in days, determined by use of a multivariable linear regression model.

Characteristic	Change	*P*
Course complicated by *C. difficile* diarrhea	+3.6	.0003
Adjustment variables		
Age, per year increase	0	.14
Male sex	+0.1	.83
White race	−0.1	.93
Charlson index, per point increase	−0.1	.26
Disease severity[a]		
1	Referent	—
2	+1.2	.04
3	+4.6	.0001
4	+7.9	.0001
Admitting diagnosis		
Gastrointestinal infection	Referent	—
Pulmonary infection	−1.4	.16
Infection of skin, soft tissue, or bone	−1.3	.23
Urinary tract infection	−1.7	.13
Miscellaneous infections	−0.8	.48

NOTE. Data are changes in LOS (in days) attributable to each patient characteristic, unless otherwise indicated.

[a] Horn's index. A score of 1 denotes mild disease severity, 2 denotes moderate disease severity, 3 denotes severe disease severity, and 4 denotes extreme disease severity.

days (95% CI, 1.5–6.2)—that is, 55% (95% CI, 23%–94%)—longer than the adjusted length of stay for a typical patient whose course was not complicated by *C. difficile* diarrhea (6.6 days).

Patient mortality. By 3 months after admission, 19 (48%) of 40 patients whose course was complicated by *C. difficile* diarrhea had died, compared with 49 (22%) of 224 patients whose course was not complicated by *C. difficile* diarrhea ($P = .001$). The unadjusted difference in 1-year survival rates for the 2 groups was also significant ($P = .0027$; table 6). Other predictors of death in the unadjusted analysis included higher scores on the Charlson comorbidity index and severe to extremely severe disease severity (table 6).

The results of the Cox proportional hazards regression analysis are shown in table 6. After adjustment for age, race, comorbidity score, disease severity, and other relevant covariates, *C. difficile* diarrhea was not considered to be an independent predictor of death.

DISCUSSION

In this prospective study of 271 patients admitted to the hospital with infection, 40 patients (15%) developed *C. difficile* diarrhea. *C. difficile* diarrhea was associated with an increase in estimated total hospital costs of $3669—that is, a 54% increase (95% CI, 17%–103%)—and an increase in length of hospital stay of 3.6 days—that is, a 55% increase (95% CI, 23%–94%). The crude mortality rate for patients with *C. difficile* diarrhea was higher than that for patients without *C. difficile* diarrhea; this was explained by the increased severity of underlying disease at admission to the hospital for patients with *C. difficile* diarrhea.

The association between the use of health care resources and *C. difficile* diarrhea has been examined by other investigators [4, 6–8, 22]. In an earlier observational study of surgical patients treated in our institution, Kent et al. [22] reported that patients who developed *C. difficile* diarrhea stayed in the hospital almost twice as long as did patients who did not develop *C. difficile* diarrhea. However, in that study, the length of stay was not corrected for confounding variables. In case-control studies performed in Europe and Australia, *C. difficile* diarrhea has also been associated with prolonged hospitalization [5–8, 23]. Up to a 4-fold increase in total length of stay has been reported elsewhere [7]. By use of a prospective case-control study design, Wilcox et al. [8] in the United Kingdom estimated that the increased cost of *C. difficile* infection exceeded £4000 per case; the majority of this extra cost was attributable to the extra days that were spent in the hospital.

Duration of hospital stay is also reported to be a risk factor for *C. difficile* diarrhea [24]. In our study, we found that the length of stay before the onset of *C. difficile* diarrhea was almost identical to the total length of stay for patients who did not develop *C. difficile* diarrhea. Because the time at risk was similar, it seems likely that the excess length of stay that we report is a consequence rather than a cause of *C. difficile* diarrhea.

In the United States, excess health care expenditure attributable to *C. difficile* infection has been poorly defined, but in one retrospective observational study by Kofsky et al. [4], hospital charges associated with the diagnosis and treatment of *C. difficile* diarrhea in a community hospital amounted to $2000 per patient. However, this study involved patients hospitalized >10 years ago; therefore, it may not reflect current practices.

Our study contributes to previous research in this area in several ways. First, we were able to perform detailed adjustment for age, sex, race, admitting diagnosis, severity of underlying disease, and comorbidity. This enabled us to isolate the independent effect of *C. difficile* diarrhea on hospital costs and length of stay. Although some earlier case-control studies have attempted to match by age, sex, or underlying diagnosis, most of these previous studies were not able to incorporate such detailed clinical data on strong predictors of resource use [7, 8, 23]. Second, by use of a prospective cohort study design, we were able to eliminate many potential biases associated with retrospective matched studies. Finally, we analyzed estimated hospital costs rather than hospital charges. Although our method of estimating costs, which involves the cost-to-charge ratio, is subject to unknown bias because of cost shifting, we feel that this method gives a truer estimate of the costs poten-

Table 6. One-year mortality rates associated with *Clostridium difficile* diarrhea.

Characteristic	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Course complicated by *C. difficile* diarrhea	2.13 (1.28–3.54)	0.83 (0.44–1.55)
Age, per year increase	1.01 (0.99–1.03)	1.03 (1.01–1.04)
Male sex	1.52 (0.98–2.36)	0.90 (0.57–1.46)
White race	0.63 (0.36–1.11)	0.52 (0.28–0.96)
Charlson index, per point increase	1.35 (1.25–1.47)	1.29 (1.18–1.42)
Disease severity[a]		
1	Referent	Referent
2	1.64 (0.74–3.65)	1.01 (0.45–2.28)
3	6.64 (3.18–13.87)	3.50 (1.57–7.78)
4	10.58 (4.77–23.48)	9.16 (3.75–22.38)
Admitting diagnosis		
Gastrointestinal infection	Referent	Referent
Pulmonary infection	1.16 (0.41–3.33)	1.42 (0.47–4.28)
Infection of skin, soft tissue, or bone	1.94 (0.65–5.85)	1.01 (0.31–3.24)
Urinary tract infection	2.10 (0.67–6.58)	1.35 (0.41–4.45)
Miscellaneous	2.55 (0.88–7.35)	1.90 (0.64–5.69)

[a] Horn's index. A score of 1 denotes mild disease severity, 2 denotes moderate disease severity, 3 denotes severe disease severity, and 4 denotes extreme disease severity.

tially saved by preventing nosocomial *C. difficile* diarrhea than do estimates based solely on hospital charges [25].

The crude 3-month mortality rate associated with nosocomial *C. difficile* diarrhea (48%) was high in our study population, and it differed significantly from that of patients who did not develop *C. difficile* diarrhea (22%). The 2 groups also differed significantly with regard to 1-year unadjusted survival rates. Higher crude mortality rates have been reported elsewhere in selected populations [11, 12, 14, 15, 26]. In one study of nursing homes residents, Thomas et al. [15] reported a 12-month mortality rate of 83% for patients with *C. difficile* infection; for patients who were not infected, the rate was 50%. In studies that have matched control patients to case patients according to underlying illness, the results concerning mortality attributable to *C. difficile* diarrhea have been conflicting. In 1989, Eriksson and Aronsson [23] reported a 3-fold increase in mortality rate among patients with *C. difficile* diarrhea, as compared with control patients who had been matched by age, sex, and underlying disease. However, more recently, MacGowan et al. [6] reported that the mortality rate for patients with *C. difficile* diarrhea did not differ from that for control patients who were well matched in terms of infective diagnosis, severity of illness, and coexistent diseases.

Severity of illness, whether assessed clinically or by use of rating scales, has been shown to be an important predictor of mortality for a wide variety of conditions [17, 27–29]. We were able to document severity of illness and to record comorbidities for all patients at admission to the hospital. In our cohort, we found that the patients who developed *C. difficile* diarrhea were more likely to be severely to extremely severely ill at admission ($P = .001$). By using survival-analysis methods, we were able to adjust for this important baseline characteristic; consequently, we found that *C. difficile* diarrhea was not an independent predictor of death. Our findings add validity to the observations made by other investigators that mortality associated with *C. difficile* diarrhea is almost always related to underlying disease processes, and that infection with this organism is a general marker of poor outcome [6, 10, 30, 31].

Our study had several limitations. The estimates of hospital costs, length of stay, and survival were obtained by use of data from 1 academic medical center. Although we acknowledge that clinical outcomes and use of health care resources for patients treated at other centers may be different, we believe that our data are relevant to other teaching hospitals in the United States and that they reflect current practices. We limited our study to a cohort of medical patients who were being treated with antibiotics for infections. Because these are the patients at highest risk for *C. difficile* diarrhea, we feel that our results are clinically relevant [1, 3, 32, 33]. Our cost estimates did not include doctors' fees or the cost of treatment of *C. difficile* diarrhea after discharge. In this study, 13 (33%) of the 40 patients with *C. difficile* diarrhea had recurrent diarrhea after discharge, and 46% of those with 1 recurrent episode had an additional recurrence. Because the majority of our patients were elderly and 77% of those with *C. difficile* diarrhea were discharged to nursing homes, it is likely that our results represent underestimations of the true medical costs associated with nosocomial *C. difficile* diarrhea.

Despite these acknowledged limitations, our findings reveal that nosocomial *C. difficile* diarrhea is associated with a significant economic burden. In our institution, we found that the incidence of *C. difficile* diarrhea was 0.7%. This incidence rate is consistent with rates reported from other institutions, which range from 0.05% to 3% [34]. We estimated that the overall annual cost of management of *C. difficile* diarrhea in the United States is likely to exceed $1.1 billion. The increased costs appear to be directly related to the increase in the length of stay. Although the former provides a measure of the direct economic losses attributable to nosocomial *C. difficile* diarrhea, the information on extra days provides an estimate of the opportunity costs associated with the loss of new admissions and their associated diagnostic-related group charges because of beds remaining occupied by patients with *C. difficile* diarrhea [25]. The crude mortality rate associated with *C. difficile* diarrhea is high, but this reflects the general poor health of patients at highest risk of acquiring this disease.

The current approach to management of *C. difficile* diarrhea involves treatment with metronidazole or vancomycin and careful attention to infection control issues. A variety of new, nonantibiotic approaches to prevention and management of *C. difficile* diarrhea have been proposed. These include the use of probiotic agents, such as *Lactobacillus* species or *Saccharomyces boulardii;* the use of toxin-binding and neutralizing agents; and active or passive immunization with a toxoid vaccine or antibody products [35–40]. Our results provide data that may be used in cost-effectiveness studies of potential new therapies. More importantly, our results highlight the potential savings associated with preventing nosocomial *C. difficile* diarrhea and justify the use of additional resources to control this prevalent hospital-acquired infection.

References

1. Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. N Engl J Med **1994**; 330:257–62.
2. Gorbach SL. Antibiotics and *Clostridium difficile.* N Engl J Med **1999**; 341:1690–1.
3. Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. N Engl J Med **2000**; 342:390–7.
4. Kofsky PRL, Reed J, Tolmie M, Ufberg D. *Clostridium difficile*—a common and costly colitis. Dis Colon Rectum **1991**; 34:244–8.
5. MacGowan AP, Brown I, Feeney R, et al. *Clostridium difficile*–associated diarrhoea and length of hospital stay. J Hosp Infect **1995**; 31:241–4.
6. MacGowan AP, Feeney R, Brown I, McCulloch SY, Reeves DS, Lovering AM. Health care resource utilization and antimicrobial use in elderly patients with community-acquired lower respiratory tract infection who develop *Clostridium difficile*–associated diarrhoea. J Antimicrob Chemother **1997**; 39:537–41.
7. Riley TV, Codde JP, Rouse IL. Increased length of hospital stay due to *Clostridium difficile* associated diarrhoea. Lancet **1995**; 345:455–6.
8. Wilcox MH, Cunniffe JG, Trundle C, Redpath C. Financial burden of hospital-acquired *Clostridium difficile* infection. J Hosp Infect **1996**; 34:23–30.
9. Spencer RC. Clinical impact and associated costs of *Clostridium difficile*–associated disease. J Antimicrob Chemother **1998**; 41(Suppl C): 5–12.
10. Olson MM, Shanholtzer CJ, Lee JT Jr, Gerding DN. Ten years of prospective *Clostridium difficile*–associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982–1991. Infect Control Hosp Epidemiol **1994**; 15:371–81.
11. Lesna M, Parham DM. Risk of diarrhoea due to *Clostridium difficile* during cefotaxime treatment; mortality due to *C. difficile* colitis in elderly people has been underestimated. BMJ **1996**; 312:778.
12. Impallomeni M, Galletly NP, Wort SJ, Starr JM, Rogers TR. Increased risk of diarrhoea caused by *Clostridium difficile* in elderly patients receiving cefotaxime. BMJ **1995**; 311:1345–6.
13. Ramaswamy R, Grover H, Corpuz M, Daniels P, Pitchumoni CS. Prognostic criteria in *Clostridium difficile* colitis. Am J Gastroenterol **1996**; 91:460–4.
14. Rubin MS, Bodenstein LE, Kent KC. Severe *Clostridium difficile* colitis. Dis Colon Rectum **1995**; 38:350–4.
15. Thomas DR, Bennett RG, Laughon BE, Greenough WB, Bartlett JG. Postantibiotic colonization with *Clostridium difficile* in nursing home patients. J Am Geriatr Soc **1990**; 38:415–20.
16. Horn SD, Sharkey PD, Bertram DA. Measuring severity of illness: homogeneous case mix groups. Med Care **1983**; 21:14–30.
17. Charlson ME, Sax FL, MacKenzie CR, Fields SD, Braham RL, Douglas RG. Assessing illness severity: does clinical judgment work? J Chronic Dis **1986**; 39:439–52.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
19. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. N Engl J Med **1989**; 320: 204–10.
20. Kleinbaum DG KL, Muller, KE. Applied regression analysis and other multivariable methods. 2nd ed. Belmont, California: Duxbury Press, **1988**.
21. Hospital Statistics 2001: Health Forum. American Hospital Association, **2001**. Available at: http://www.aha.org/resource/statistics.
22. Kent KC, Rubin MS, Wroblewski L, Hanff PA, Silen W. The impact of *Clostridium difficile* on a surgical service: a prospective study of 374 patients. Ann Surg **1998**; 227:296–301.
23. Eriksson S, Aronsson B. Medical implications of nosocomial infection with *Clostridium difficile.* Scand J Infect Dis **1989**; 21:733–4.
24. Bignardi GE. Risk factors for *Clostridium difficile* infection. J Hosp Infect **1998**; 40:1–15.
25. Haley R. Measuring the costs of nosocomial infections: methods for estimating economic burden on the hospital. Am J Med **1991**; 91: 32S–8S.
26. 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**; 26:871–6.
27. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. JAMA **1994**; 271:1598–601.
28. Green J, Wintfeld N, Sharkey P, Passman LJ. The importance of severity of illness in assessing hospital mortality. JAMA **1990**; 263:241–6.
29. Hamel MB, Phillips RS, Teno JM, et al. Seriously ill hospitalized adults: do we spend less on older patients? Support Investigators' Study to Understand Prognoses and Preference for Outcomes and Risks of Treatments. J Am Geriatr Soc **1996**; 44:1043–8.
30. Marts BC, Longo WE, Vernava AM, Kennedy DJ, Daniel GL, Jones I. Patterns and prognosis of *Clostridium difficile* colitis. Dis Colon Rectum **1994**; 37:837–45.
31. Crabtree TD, Pelletier SJ, Gleason TG, Pruett TL, Sawyer RG. Clinical characteristics and antibiotic utilization in surgical patients with *Clostridium difficile*–associated diarrhea. Am Surg **1999**; 65:507–11; discussion on 511–2.

32. McFarland LV, Surawicz CM, Stamm WE. Risk factors for *Clostridium difficile* carriage and *C. difficile*–associated diarrhea in a cohort of hospitalized patients. J Infect Dis **1990**; 162:678–84.
33. Samore MH, DeGirolami PC, Tlucko A, Lichtenberg DA, Melvin ZA, Karchmer AW. *Clostridium difficile* colonization and diarrhea at a tertiary care hospital. Clin Infect Dis **1994**; 18:181–7.
34. Samore MH. Epidemiology of nosocomial *Clostridium difficile* diarrhoea. J Hosp Infect **1999**; 43(Suppl):S183–90.
35. Kyne L, Kelly C. Prospects for a vaccine for *Clostridium difficile*. BioDrugs **1998**; 10:173–81.
36. Gorbach SL, Chang TW, Goldin B. Successful treatment of relapsing *Clostridium difficile* colitis with *Lactobacillus* GG. Lancet **1987**; 2:1519.
37. Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*. Clin Infect Dis **2000**; 31:1012–7.
38. McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. JAMA **1994**; 271: 1913–8.
39. Heerze LD, Kelm MA, Talbot JA, Armstrong GD. Oligosaccharide sequences attached to an inert support (SYNSORB) as potential therapy for antibiotic-associated diarrhea and pseudomembranous colitis. J Infect Dis **1994**; 169:1291–6.
40. Castagliuolo I, LaMont JT, Qiu B, Nikulasson ST, Pothoulakis C. A receptor decoy inhibits the enterotoxic effects of *Clostridium difficile* toxin A in rat ileum. Gastroenterology **1996**; 111:433–8.