Risk Factors Associated With Complications and Mortality in Patients With *Clostridium difficile* Infection

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**Background.** *Clostridium difficile* infection (CDI) has increased in frequency and severity over the past decade. An understanding of the modifiable risk factors for disease severity has considerable clinical applicability.

**Methods.** We performed a retrospective case review of 485 cases in patients aged 1–99 years at the Naval Medical Center San Diego from November 2004 through December 2008. We compared potential risk factors for association with complications (megacolon, surgery, intensive care unit stay, and death) or mortality alone with use of univariable and multivariable logistic regression modeling.

**Results.** Forty-seven patients (9.8%) developed ≥1 complication, and 23 (4.7%) died. We found independent associations between complications and acid suppression (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.2–4.79), admission for CDI (OR, 4.14; 95% CI, 2.17–7.92), older age (≥80 years; OR, 3.14; 95% CI, 1.46–6.73), and corticosteroid use (OR, 2.09; 95% CI, 1.01–4.35). Age ≥80 years (OR, 5.51; 95% CI, 2.25–13.49) and acid suppression (OR, 4.74; 95% CI, 1.57–14.37) were associated with increased odds of death.

**Conclusions.** Data published elsewhere have suggested that acid suppression therapy is a risk factor for CDI acquisition and relapse. These findings suggest an additional role in increased severity of disease, including mortality, and merit further study.

*Clostridium difficile* infection (CDI) is the cause of more deaths in the United States than all other intestinal infections combined and is the most frequent cause of diarrhea acquired in a hospital setting [1]. Recent surveys by the Centers for Disease Control and Prevention (CDC) of New Jersey hospitals found that the incidence of *C. difficile* has increased by nearly 2-fold, from 370 cases/100,000 admissions in 2000 to 770 cases/100,000 admissions in 2004 [2, 3].

The evidence for acid suppression playing a role in acquisition and relapse of CDI is slowly building [4, 5].

Recent studies have raised concerns about the potential risks of excessive use of acid suppression, particularly proton-pump inhibitors [6]. Acid suppression is of great interest as a modifiable risk factor, because the relatively straightforward intervention of withholding acid suppression could have an impact on the progression of CDI and clinical outcomes. We present the results of a retrospective case review that investigated various potential risk factors, including acid suppression, on the development of complications and/or death in patients with CDI.

**METHODS**

**Study Population**

The population consisted of active-duty military personnel, their dependent children and spouses, and military retirees seeking care at the Naval Medical Center San Diego (NMCS) or the outlying clinics that use NMCS’s laboratory services. NMCS is a military medical center serving a population of almost half...
a million eligible patients in San Diego County and referrals from overseas. A case patient was defined as a patient who had clinical findings consistent with CDI (fever, diarrhea, and/or leukocytosis) and a stool specimen positive for the C. difficile toxin from 15 November 2004 through 15 November 2008. This study was approved by the institutional review boards of NMCSD and San Diego State University.

Data Collection Procedures and Data Collected
All cases were identified using a laboratory database query. Patient demographic characteristics and clinical data were collected by examination of the electronic and written inpatient and outpatient medical records. All prior medications recorded referred to the 90 days preceding diagnosis of CDI and were obtained by examination of electronic medical (Armed Forces Health Longitudinal Technology Application) and pharmacy (Pharmacy Data Transfer System) records held at NMCSD.

Statistical Analysis
The study database was created using EpiInfo, version 9.0, developed by the CDC, and analysis was performed using SAS, version 9.1 (SAS Institute). Unless otherwise stated, all tests were performed at a significance level of \( \alpha = 0.05 \).

Frequency distributions were examined for variability and percentage of missing data. Case patients were excluded if they had missing information on medical history and prior medication use or if the date of positive C. difficile toxin assay was missing. Only patients aged \( \geq 1 \) year were included in the analysis. Univariable analysis was performed using logistic regression to assess the individual, unadjusted relationship between complications and mortality associated with CDI and each variable. Age was recorded as a continuous variable during data collection and was initially examined as a categorical variable according to the age categories shown in Table 1, with adults aged 18–64 years as the reference group. Only the older persons category had a significant association with complications or mortality (data not shown); therefore, age was treated as a dichotomous variable. After univariable analyses, a logistic regression model was fitted to assess the adjusted relationship of the variables to CDI-associated mortality with and without other complications (defined as intensive care unit admission, surgery, and megacolon). An \( \alpha \) value of 0.15 was used as the cutoff for initial inclusion in the multiple regression models. Final logistic regression models were obtained by removing nonsignificant variables from the expanded model one by one until only significant variables remained. The PROC REG procedure was used to assess potential collinearity by examining tolerance levels. All tolerance levels were \( >0.10 \) (no evidence of collinearity).

### RESULTS

Table 1 shows the basic demographic characteristics, significant medical history, exposure to medications (including antibiotics), and outcome in the 485 patients with CDI in our retrospective cohort. Table 2 shows the results of univariable analysis of association between possible risk factors, demographic characteristics, and complications. Age \( \geq 80 \) years, admission for CDI, corticosteroid use \( >5 \) mg per day, and acid suppression were significantly associated with complications, including mortality (n = 47). Associations with mortality alone (n = 23) were similar, but the association with admission for CDI was not present.
Patients with acid suppression had nearly 3 times the odds of complication (odds ratio [OR], 2.86; 95% confidence interval [CI], 1.49–5.49; \( P \leq .002 \)). Corticosteroid use was associated with double the odds of complications (OR, 2.31; 95% CI, 1.17–4.54; \( P = .015 \)). No statistically significant association was found between complications and sex, antibiotic use, hospitalization in the previous year, or history of bowel surgery. Both prescription acid suppression (OR, 5.6; 95% CI, 1.88–16.72; \( P = .002 \)) and age \( \geq 80 \) years (OR, 7.91; 95% CI, 3.31–18.89; \( P < .001 \)) were significantly associated with mortality alone in univariable analysis.

In the multivariable full logistic regression model, the following variables were not significantly associated with complications: sex, prior antibiotic use, prior bowel surgery, and hospitalization in the previous year. As shown in Table 3, the final reduced model for complications, including mortality, contains only 4 independently significant variables (acid suppression, age \( \geq 80 \) years, admission for CDI, and corticosteroid use). The reduced model for mortality alone indicates that the only independently significant associations with death are age \( \geq 80 \) years (OR, 5.51; 95% CI, 2.25–13.49; \( P < .001 \)) and prescription acid suppression use (OR, 4.74; 95% CI, 1.57–14.36; \( P = .006 \)) (Table 3).

**DISCUSSION**

In this study of patients \( \geq 1 \) year of age who received a diagnosis of CDI at the NMCS from November 2004 through December 2008, 47 patients (10%) had the aforementioned complications. We discovered independent associations between acid suppression, admission for CDI, increased age (\( \geq 80 \) years), corticosteroid use, and complications. Acid suppression and age \( \geq 80 \) years were independently associated with mortality. The overall case-fatality rate in this series was 5%.

Fulminant CDI often results in the need for surgical intervention within a few days after development of illness and

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**Table 2. Univariable Analyses of Associations Between Individual Demographic Characteristics and Known Risk Modifiers and Complications, Including Mortality, or Mortality Alone Among Patients Aged \( \geq 1 \) Year Who Received a Diagnosis of *Clostridium difficile* Infection at Naval Medical Center San Diego From November 2004 Through December 2008 (n = 485)**

<table>
<thead>
<tr>
<th>Variable (no. for all complications, mortality alone)</th>
<th>Association with complications, including mortality</th>
<th>Association with mortality alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age ( \geq 80 ) years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (14, 10)</td>
<td>4.20</td>
<td>2.11–8.35</td>
</tr>
<tr>
<td>No (33, 13)</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (23, 9)</td>
<td>0.93</td>
<td>.51–1.69</td>
</tr>
<tr>
<td>Male (24, 14)</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Admitted for CDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (27, 10)</td>
<td>4.17</td>
<td>2.23–7.80</td>
</tr>
<tr>
<td>No (19, 13)</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (14, 6)</td>
<td>2.31</td>
<td>1.17–4.54</td>
</tr>
<tr>
<td>No (33, 45)</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Prior antibiotic use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (40, 20)</td>
<td>1.80</td>
<td>.78–4.14</td>
</tr>
<tr>
<td>No (7, 3)</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Prior acid suppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (33, 19)</td>
<td>2.86</td>
<td>1.49–5.49</td>
</tr>
<tr>
<td>No (14, 4)</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Prior bowel surgeries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (4, 2)</td>
<td>0.77</td>
<td>.27–2.25</td>
</tr>
<tr>
<td>No (43, 21)</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Hospitalization (in previous year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (20, 12)</td>
<td>1.33</td>
<td>.70–2.52</td>
</tr>
<tr>
<td>No (22, 11)</td>
<td>1.00</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, *Clostridium difficile* infection; CI, confidence interval; OR, odds ratio.

* Significant differences (\( P < .05 \)).

b Reference value.
has mortality rates as high as 50% in some populations \[7, 8\]. In severe cases of CDI, hypotension, multi-organ failure, peritonitis, toxic megacolon, and/or intestinal perforation may occur \[9, 10\].

A retrospective survey of \textit{C. difficile} outcomes in inpatients in 58 acute care hospitals in New Jersey during 2000–2004 showed a mean complication rate of 0.4%, mean crude mortality of 1%, and mean recurrence rate of 1.3%, with rates of complications and mortality increasing significantly during 2000–2004 \[3\]. All estimates of Tan et al \[3\] are considerably lower than our study’s findings, although relying on survey data from participating hospitals may have led to underidentification of CDI, depending on each hospital’s definition method and testing protocols for \textit{C. difficile}. The CDC’s 2008 report on community-acquired \textit{C. difficile} infection in Connecticut (data collected from all 32 participating Connecticut hospitals) in 2006 also revealed lower rates of complications (7% of community-acquired cases involved intensive care unit admission, megacolon, and surgery or death), compared with the finding of 10% in our study; however, the difference could be explained by the trend of increased severity of cases, which has been documented in several studies \[1, 11\].

Several studies specifically address risk factors for severe outcome of CDI \[3, 12\]. In a case-control study involving patients with \textit{C. difficile} infection who developed fulminant \textit{C. difficile} colitis, Greenstein et al \[8\] found that leukocytosis, recent surgery, inflammatory bowel disease, and history of treatment with intravenous immunoglobulin were independently associated with development of fulminant disease.

The potential association of acid suppression to exacerbation or prolongation of CDI has been explored by many researchers, because of the biological plausibility of failure to inactivate the vegetative form of \textit{C. difficile} in gastric environments that are less acidic. Unnecessary and off-label use of prescription acid suppressors, particularly proton-pump inhibitors, possibly leading to serious negative health outcomes, such as loss in bone density, pneumonia, and \textit{C. difficile} infection, is reported in the May 2010 issue of \textit{Archives of Internal Medicine} \[6\].

McFarland et al \[13\], in 2007, and Dial et al \[14\], in 2005, found a positive association between acid suppression medication use and community-acquired \textit{C. difficile} infection. In 2007, Peled et al \[15\] surmised that watery diarrhea present in patients taking proton-pump inhibitors or histamine-2 receptor antagonists could be ascribed to CDI. During the same year, a meta-analysis of 12 studies found a strong positive association between proton-pump inhibitor use and CDI and a weaker, but still significant, association with histamine-2 receptor antagonists \[16\].

Although the role of acid-suppressive agents in complications and mortality associated with CDI has not been studied in detail, Hardt et al \[17\] found an association approaching significance between acid suppression therapy and severe CDI, although their definition of severe CDI was based on shock index status at initial diagnosis rather than an outcome of complications, as in our study. Their definition of severe CDI gave a rate of 22% of inpatients with CDI having severe disease, compared with this study’s rate of 18% of inpatients (and 0% of outpatients) developing complications related to CDI. The author’s major finding was a correlation between the Charlson comorbidity score and their definition of severe CDI, with severe CDI also being associated with >30-day mortality and longer hospital stays.

Nachnani et al \[18\] showed that use of proton-pump inhibitors appeared to be an independent risk factor for an increased length of hospital stay among patients with \textit{C. difficile} infection. Howell et al \[4\] found a dose-response relationship between acid-suppression therapy and incidence of nosocomial \textit{C. difficile} infection.

Our results have produced findings in line with those found in previous studies. Fourteen percent of patients who had been receiving acid-suppression therapy and were receiving treatment for CDI had further complications (OR, 2.4), compared with those not receiving acid suppression.

It may be expected that patients who receive a diagnosis of hospital-associated \textit{C. difficile} should have more severe outcomes; however, the opposite was observed in our study.
Admission diagnosis of CDI had the strongest and statistically most significant association in the multivariable model, with >4-fold increased odds of complications (OR, 4.14; 95% CI, 2.17–7.92; \( P < .001 \)). The association with mortality alone, however, was not significant. Less than half (43%) of the patients with fatal cases were admitted with a primary diagnosis of CDI, although this is a higher proportion than observed by Siemann et al [19]. The cause for increased severity in patients with an admission for CDI is not well researched, Barbut et al found that a binary toxin-producing strain of \textit{C. difficile} was more likely to be community acquired and was associated with longer duration of diarrhea. More research is necessary to provide evidence for the possible mechanisms of increased severity of outcome associated with community-acquired CDI [20].

Although age \( >65 \) years is generally considered to be the threshold for increased risk of CDI [10], no statistically significant association was found between age \( \geq 65 \) years and severe outcome of CDI. In this population, persons aged \( \geq 80 \) years had significantly higher odds of severe outcome [12, 21]. Although few studies specifically address the course of CDI in older patients, the literature contains reports of increased mortality associated with CDI among patients aged \( >80 \) years.

In a recent review of 27 studies spanning 30 years, Karas et al [22] calculated a 5.99% overall 90-day mortality rate, with mortality being highest in the oldest age group (13.5% among persons aged \( >80 \) years, compared with our finding of 17.2% among patients aged \( \geq 80 \) years); the authors raise the concern that this increased mortality is not only associated with CDI, but also with comorbid conditions common in older persons. The independent association between age and increased mortality found in our analysis might indicate that aging of the immune system, not comorbidities, could be responsible for the increase in mortality associated with CDI among individuals aged \( \geq 80 \) years.

Our study has several limitations, most of which are related directly to the retrospective design. Documentation of over-the-counter medications is likely to be incomplete, leading to an underestimate of probiotic and over-the-counter acid suppression use. In addition, data for patients seen or admitted at civilian hospitals were not available using our database. Confirmation of actual use of acid suppression was not possible, because pharmacy records of medications prescribed were used as a surrogate. Finally, the definition of CDI uses an enzyme-linked immunoabsorbent assay for toxin rather than recently commercialized molecular techniques [21].

In our study of 485 patients aged \( \geq 1 \) year who had CDI, admission for CDI (vs developing CDI while in the hospital), age \( \geq 80 \) years, and prior use of acid suppression were independently associated with complications, including mortality; mortality alone was associated only with the latter 2 risk factors. In light of our findings and the work of Nachmani et al [4] and Howell et al [18], discontinuation of acid-suppressive medication should be considered after a diagnosis of CDI is made or is strongly suspected, unless otherwise contraindicated (eg, in patients with active peptic ulcer disease). Additional prospective studies using molecular diagnostics to confirm CDI (now the standard at most facilities) should be undertaken to confirm this finding with use of the most stringent methods [21].

### Notes

**Acknowledgments.** We thank Dr David Rockabrand, Dr Mark Simons, and Mr Bob Redublo, for their kind assistance with the laboratory query, and Ms Wayne MacAllister, for her assistance with editing and preparation of this manuscript.

**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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