

# Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies

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## Abstract

**Background:** Antibiotic disruption of the normal intestinal flora is a well-known risk factor for *Clostridium difficile*-associated diarrhea. Reduced gastric acidity has been suggested as a risk factor, and we hypothesized that proton pump inhibitors, because of their potency, may be an independent risk factor for this problem.

**Methods:** For the cohort study we identified from a pharmacy database 1187 inpatients at a Montreal teaching hospital who received antibiotics over a 9-month period beginning in August 2002. We compared patients in this group who had also received a proton pump inhibitor or an H<sub>2</sub> blocker with patients who had not received acid suppressive therapy. Hospital laboratory reports of positive assay results for *C. difficile* toxin were used to ascertain cases in the cohort.

To assess the possibility that proton pump inhibitors were prescribed to patients who were sicker and had other risk factors for *C. difficile* infection, we did a case-control study at a second Montreal teaching hospital. Cases were defined as patients who were positive for *C. difficile* toxin and who had a history of diarrhea ( $n = 94$ ). Control subjects were selected from among patients who had received an antibiotic and were matched to cases by ward, age within 5 years and class of antibiotics ( $n = 94$ ).

**Results:** In the cohort study, *C. difficile* diarrhea developed in 81 (6.8%) of the 1187 patients who received antibiotics while in hospital. In a multivariate analysis, *C. difficile* diarrhea was significantly associated with use of proton pump inhibitors (adjusted odds ratio [OR] 2.1, 95% confidence interval [CI] 1.2–3.5), receipt of 3 or more antibiotics (OR 2.1, 95% CI 1.3–3.4) and admission to a medical ward (OR 4.1, 95% CI 2.3–7.3). In the case-control study *C. difficile* diarrhea was associated with female sex (adjusted OR 2.1, 95% CI 1.1–4.0), prior renal failure (adjusted OR 4.3, 95% CI 1.5–11.9), hospital admission in the 3 months before the index admission (adjusted OR 2.6, 95% CI 1.4–5.2) and use of proton pump inhibitors (adjusted OR 2.7, 95% CI 1.4–5.2).

**Interpretation:** Patients in hospital who received proton pump inhibitors were at increased risk of *C. difficile* diarrhea.

**C**lostridium *difficile* is the most common cause of nosocomial infectious diarrhea in industrialized countries<sup>1</sup> and has been reported to be increasing in frequency and severity,<sup>2,3</sup> with estimated health care costs of over \$1.1 billion in the United States each year.<sup>4</sup> The main cause of this problem is believed to be antibiotic disruption of the normal intestinal flora, resulting in overgrowth of *C. difficile*.<sup>5</sup> Use of proton pump inhibitors has been associated with colonization of the normally sterile upper gastrointestinal tract<sup>6</sup> and can therefore alter gastrointestinal flora. Decreased gastric acidity is a known risk factor for other infectious diarrheal illnesses such as travellers' diarrhea, salmonellosis and cholera,<sup>7</sup> and because the survival of *C. difficile* and its toxin are facilitated by higher gastric pH levels,<sup>8</sup> it may also be a risk factor for *C. difficile* diarrhea. This idea is supported by reports of a possible association between *C. difficile* diarrhea and acid suppressive therapy,<sup>3,4,9–11</sup> and case reports of *C. difficile* diarrhea in patients with pernicious anemia<sup>8</sup> and in patients receiving *Helicobacter pylori* treatment, which combines gastric acid suppressive therapy with antibiotics.<sup>12,13</sup>

Proton pump inhibitors are potent inhibitors of gastric acid production.<sup>14</sup> These drugs have been proven effective in many indications, and as a class these agents had the largest increase in unit sales in North America in 2002. We have observed an increase in the incidence of *C. difficile* diarrhea, coincident with increased use of proton pump inhibitors. To address this possible association, we examined the risk of *C. difficile*-associated diarrhea in hospital patients who were receiving proton pump inhibitors.

## Methods

### Cohort study

We defined the cohort as all patients identified from a pharmacy database who had received antibiotics between Aug. 1, 2002, and Apr. 30, 2003, on the 2 general medical wards and the cardiothoracic surgical ward at the Royal Victoria Hospital, a Montréal teaching hospital. These 3 wards were chosen because they had all experienced significant increases in the incidence of *C. difficile* disease compared with the previous year. Because the patients were

identified from a pharmacy database, the only information available for analysis was on medications, the ward, the total number and type of antibiotics, and the type of acid suppressive therapy (e.g., proton pump inhibitor or H<sub>2</sub> blocker). Cohort patients with *C. difficile* infection were identified by verifying if their names appeared in a registry of patients with a positive toxin assay result, maintained by the hospital's infection control service. Because hospital policy requires the clinical laboratory to report all positive toxin assay results to this registry, we assumed that cohort patients whose names were not in the registry had not had *C. difficile* infection.

### Case-control study

Because the data available from the cohort study was limited and because we wanted to address the possibility that proton pump inhibitors were prescribed to patients who were sicker and had other risk factors for *C. difficile* colitis, we performed a case-control study at a second Montréal teaching hospital (the Sir Mortimer B. Davis Jewish General Hospital) during the same study period. Cases were defined as all consecutive patients on all wards in the hospital who had a history of diarrhea (defined as 2 or more loose bowel movements per day) and a positive *C. difficile* toxin assay result from a stool sample. Because our objective was to study new hospital-acquired cases, we included only patients who had never been diagnosed with *C. difficile* diarrhea previously and whose first positive toxin assay result was reported during or within 1 month after their index hospital admission.

Control subjects were selected from a list obtained from the hospital pharmacy of patients who had been prescribed any antibiotics while in hospital during the study period. To control for other risk factors previously associated with an increased risk of *C. difficile* diarrhea, control subjects were frequency matched to the cases by inpatient ward,<sup>15</sup> age within 5 years, class of antibiotics (in particular quinolones, cephalosporins [first-generation, or second- and third-generation], penicillins, carbapenems and macrolides) and, if possible, number of antibiotics.<sup>16,17</sup> To ensure adequate time of exposure, and equal opportunity for ascertainment, we considered control subjects eligible if they had been in hospital for at least 5 days and had survived at least 30 days from the time of hospital admission.

### Proton pump inhibitor exposure

To be considered exposed, patients had to have received these drugs for at least 3 days before diarrhea developed. For patients who did not have diarrhea, this therapy had to have been prescribed for at least 3 days in hospital. Long-term use was defined as use of these drugs for more than 6 months before the development of *C. difficile* diarrhea.

### Data collection

A standardized form was used to abstract data from the medical records of the cases and control subjects. The following information was collected: age, sex, any institutionalization (defined as long-term residence in a chronic care setting or hospital admission in an acute care setting for more than 2 months), prior hospital admission or antibiotic use in the 3 months before the index hospital admission, diagnosis on admission, and comorbid illnesses, particularly diabetes mellitus, renal failure (defined as a

creatinine level greater than 250 mmol/L), peptic ulcer disease, gastroesophageal reflux disease, cancer and pernicious anemia. Charlson Comorbidity Index scores<sup>18</sup> were calculated for the case and control subjects. Information was collected on all medications taken in the 30 days before the diagnosis of *C. difficile* diarrhea (cases) or during the hospital stay (controls). The indication for acid suppressive therapy was also recorded. Outcomes ascertained included surgical colectomy, relapses, admission to the intensive care unit (ICU), acute renal failure requiring dialysis and death within 30 days after the development of *C. difficile* diarrhea. A relapse was defined as a recurrent episode of diarrhea with a positive *C. difficile* toxin assay result after completion of treatment for *C. difficile* and resolution of diarrhea.

At both hospitals tissue culture cytotoxic assays were performed with diarrheal stool samples using the *C. difficile* Toxin/Antitoxin Kit (TechLab Inc., Blacksburg, Va.).<sup>19</sup>

The studies were approved by the Ethics Review Board of the McGill University Health Centre for the cohort study and by the Jewish General Hospital Ethics Board for the case-control study.

### Data analysis

In the cohort study, the relative risks for the development of *C. difficile* diarrhea in association with the use of proton pump inhibitors, H<sub>2</sub> blockers and antibiotics, taken separately and in various combinations, were estimated along with the corresponding 95% confidence intervals (CIs).<sup>20</sup> Multivariate logistic regression was used to obtain the adjusted odds ratio (OR) of the effect of exposure to proton pump inhibitors after adjustment for the confounders of exposure to 3 or more antibiotics and type of ward.

In the case-control study, characteristics of the case and control subjects were compared and tested for significant differences using a Student *t* test for linear variables and a  $\chi^2$  test for categorical variables. For the primary analysis of risk factors associated with *C. difficile* diarrhea, ORs and 95% CIs of possible risk factors were estimated, and a multivariate logistic regression was performed to adjust for potentially confounding factors. Variables were included in the multivariate model if the univariate analysis showed that they were significantly associated with *C. diarrhea* or showed evidence of a substantial effect; also included were clinical factors associated with *C. difficile* diarrhea in previous studies. We evaluated 2 separate regression models; methicillin-resistant *Staphylococcus aureus* (MRSA) colonization was excluded from the first model because of a concern of detection bias, but this variable was included in the second model.

## Results

### Cohort study

Between Aug. 1, 2002, and Apr. 30, 2003, 1187 patients were prescribed antibiotics while in hospital on 1 of the 3 wards studied. In total, *C. difficile* diarrhea developed in 81 (6.8%) of the patients: 55 (9.3%) of the 591 patients who also received proton pump inhibitors and 26 (4.4%) of the 596 patients who did not receive these drugs. Table 1 shows the incidence of *C. difficile* diarrhea among patients with different ward and antibiotic exposures, including those receiving only 1 antibiotic, and the relative risk associated with proton pump

inhibitor use. For many of the risk factors examined, the relative risk of *C. difficile* diarrhea was higher among the patients who were prescribed proton pump inhibitors than among those who were not prescribed these drugs.

*C. difficile* diarrhea developed in 10.9% of the cohort patients on the medical wards, as compared with 2.9% of those on the surgical ward ( $p < 0.001$ ), and in 12.1% of the patients who received 3 or more antibiotics, as compared with 5.1% of those who received only 1 or 2 different antibiotics ( $p < 0.001$ ). Among the 354 patients exposed to high-risk antibiotics<sup>21</sup> (clindamycin, second- or third-generation cephalosporins, or ampicillin or its analogues), *C. difficile* diarrhea developed in 30 (8.5%), as compared with 51 (6.1%) of the 833 patients given other antibiotics. Patients on the surgical ward were less likely than those on the medical wards to be exposed to 3 or more antibiotics or to high-risk antibiotics (data not shown).

After adjustment in the multivariate analysis for the number of antibiotics received and the ward, *C. difficile* diarrhea remained significantly associated with the use of proton pump inhibitors (OR 2.1, 95% CI 1.2–3.5) but not with the use of H<sub>2</sub> blockers (Table 2).

### Case-control study

Ninety-four patients met the case definition for *C. difficile* diarrhea. As seen in Table 3, the case and control subjects were similar in age, number and type of antibiotics, and Charlson Comorbidity Index scores. However, the cases were more likely than the control subjects to be female, to have had renal failure, to have MRSA colonization

and to have been admitted to hospital in the 3 months before the index admission. The cases had significantly increased morbidity and mortality: 18 required admission to the ICU with fulminant *C. difficile* as the admitting diagnosis, 12 experienced acute renal failure requiring dialysis, 8 had total colectomies, and 21 died within 30 days after the diagnosis of *C. difficile* diarrhea. Of the cases, 60 (64%) were receiving proton pump inhibitors, as compared with 34 (36%) of the control subjects (unadjusted OR 3.1, 95% CI 1.7–5.6). Interestingly, *C. difficile* diarrhea developed in a patient receiving a proton pump inhibitor who was not taking an antibiotic. The cases were also more likely than the control subjects to have had prolonged exposure (> 6 months) to a proton pump inhibitor.

After adjusting for all other significant factors, we found that use of proton pump inhibitors was significantly associated with *C. difficile* diarrhea (Table 4). The association of

**Table 2: Factors associated with *C. difficile* diarrhea in cohort of 1187 patients given antibiotics while in hospital\***

Factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
PPI use (v. no acid suppressive therapy)	2.1 (1.4–3.4)	2.1 (1.2–3.5)
H <sub>2</sub> blocker (v. no acid suppressive therapy)	0.4 (0.1–1.2)	1.1 (0.4–3.4)
≥ 3 antibiotics (v. < 3)	2.4 (1.6–3.6)	2.1 (1.3–3.4)
Medical ward (v. surgical ward)	4.5 (2.6–8.3)	4.1 (2.3–7.3)

Note: OR = odds ratio.  
\*The variable "high-risk antibiotic" (defined in Table 1) was not included in the final model because it was significantly confounded by type of ward.

**Table 1: Relative risk of *Clostridium difficile* diarrhea in relation to use of proton pump inhibitors (PPIs) in cohort of 1187 patients who received antibiotics while in hospital**

Variable	No. of cases of diarrhea/ total no. with risk factor (%)		RR (95% CI)
	Patients taking PPIs	Patients not taking PPIs	
Total no. of cases of <i>C. difficile</i> diarrhea	55/591 (9.3)	26/596 (4.4)	2.1 (1.4–3.4)
Ward			
Surgical	13/287 (4.5)	4/301 (1.3)	3.4 (1.1–10.3)
Medical	42/294 (14.3)	22/295 (7.5)	1.9 (1.2–3.1)
Antibiotic exposure			
1 antibiotic	24/261 (9.2)	10/333 (3.0)	3.1 (1.5–6.3)
2 antibiotics	8/146 (5.5)	3/150 (2.0)	2.8 (0.8–10.3)
≥ 3 antibiotics	23/184 (12.5)	13/113 (11.5)	1.1 (0.6–2.1)
High-risk antibiotic*	16/181 (8.8)	14/173 (8.1)	1.1 (0.6–2.2)
Single-use antibiotic			
Cefazolin	6/54 (11.1)	1/84 (1.2)	9.2 (1.1–74.1)
Any quinolone†	9/47 (19.1)	3/44 (6.8)	2.8 (0.8–9.7)
Vancomycin	3/91 (3.3)	2/103 (1.9)	1.7 (0.3–9.9)
Any second- or third-generation cephalosporin	1/12 (8.3)	1/13 (7.7)	1.1 (0.1–15.5)

Note: RR = relative risk, CI = confidence interval.  
\*Includes ampicillin and its analogues, clindamycin, and second- and third-generation cephalosporins.<sup>21</sup>  
†One patient received gatifloxacin, and the remainder received ciprofloxacin.

MRSA colonization with *C. difficile*, seen in Table 3, may have resulted from detection bias, because all patients with positive *C. difficile* toxin assay results were also routinely screened for MRSA. Therefore, we initially excluded MRSA status from the multivariate model. However, even when we included it, we found that it did not significantly alter the association between proton pump inhibitor use and *C. difficile* diarrhea (Table 4).

Of the 21 patients who had one or more relapses, 19 (90%) were receiving proton pump inhibitors, as compared with 35 (65%) of the 54 cases who did not have a relapse (unadjusted OR 5.2, 95% CI 1.1–24.6). The only other factor associated with relapse in the univariate analysis was diabetes mellitus (unadjusted OR 2.7, 95% CI 0.8–9.2). In the multivariate analysis, after adjustment for the presence of diabetes, use of proton pump inhibitors was the only fac-

**Table 3: Clinical characteristics of hospital patients with *C. difficile* diarrhea and matched control subjects\***

Characteristic	Group; no. (%) of patients†		Unadjusted OR (95% CI)
	Case group n = 94	Control group n = 94	
Age, mean (SD), yr	75.5 (13.4)	73.0 (11.2)	p = 0.17
Female sex	59 (63)	44 (47)	1.9 (1.1–3.4)
Institutionalized‡	15 (16)	10 (11)	1.6 (0.7–3.8)
Time from hospital admission to diagnosis of <i>C. difficile</i> diarrhea, mean (median)	22 (8)	–	–
Length of hospital stay, mean (median)	–	33 (16)	–
Comorbidities			
Renal failure	21 (22)	6 (6)	4.2 (1.6–11.0)
Diabetes mellitus	22 (23)	19 (20)	0.8 (0.4–1.6)
Hypothyroidism	19 (20)	15 (16)	1.3 (0.6–2.8)
Cancer	17 (18)	29 (31)	0.5 (0.2–1.0)
MRSA infection	20 (21)	4 (4)	6.1 (2.0–18.8)
Charlson Comorbidity Index score <sup>18</sup>	2.2 (1.8)	2.1 (1.7)	p = 0.55
Hospital admission in 3 mo before index admission	36 (38)	16 (17)	3.0 (1.5–6.0)
Antibiotic exposure			
No. of antibiotics, mean (SD)	1.9 (1.0)	2.2 (1.2)	p = 0.06
Ampicillin or analogue	5 (5)	7 (7)	0.7 (0.2–2.3)
Clindamycin	3 (3)	1 (1)	3.1 (0.3–30.0)
Any second- or third-generation cephalosporin	9 (9)	7 (7)	1.3 (0.5–3.7)
Any quinolone§	57 (61)	55 (58)	1.1 (0.6–1.9)
High-risk antibiotic	14 (14)	14 (14)	1.0 (0.4–2.2)
No antibiotic	1 (1)	1 (1)	1.0 (0.06–16.2)
1 antibiotic	37 (39)	32 (34)	1.3 (0.7–2.3)
2 antibiotics	28 (30)	25 (27)	1.2 (0.6–2.2)
≥ 3 antibiotics	28 (30)	36 (38)	0.7 (0.4–1.2)
Acid suppressive therapy			
H <sub>2</sub> blocker	1 (1)	4 (4)	0.2 (0.03–2.2)
PPI	60 (64)	34 (36)	3.1 (1.7–5.6)
PPI use > 6 mo	22 (23)	4 (5)	6.9 (2.3–20.8)
Outcome			
Colectomy for severe colitis	8 (9)	–	–
≥ 1 relapses	21 (22)	–	–
Admission to ICU because of <i>C. difficile</i> -associated sepsis	18 (19)	–	–
Acute renal failure requiring dialysis	12 (13)	2 (2)	6.7 (1.5–31.0)
Death¶	21 (22)	12 (14)	2.0 (0.9–4.3)

Note: SD = standard deviation, MRSA = methicillin-resistant *Staphylococcus aureus*, ICU = intensive care unit.

\*Patients were matched by age within 5 years, ward, class of antibiotics and, if possible, number of antibiotics.

†Unless stated otherwise.

‡Long-term residence in a chronic care setting or hospital stay in an acute care setting for more than 2 months.

§Patients received either levofloxacin or ciprofloxacin.

¶Within 30 days after *C. difficile* diagnosis for cases; in the following 30 days for controls.

tor significantly associated with risk of relapse (adjusted OR 5.1, 95% CI 1.1–24.9) (data not shown in tabular form).

## Interpretation

In this hospital-based study, patients with *C. difficile* diarrhea had substantial mortality and morbidity. We found that the use of proton pump inhibitors was independently associated with an increased risk of *C. difficile* diarrhea. We observed this association in the cohort study (which allowed us to adjust for some antibiotic-related confounding) as well as in the case-control study (which took place in another institution and allowed us to also control for other non-antibiotic-related confounding).

Ingestion of *C. difficile* can result in either excretion, asymptomatic colonization of the gut, or disease with diarrhea, colitis or pseudomembranous colitis.<sup>22</sup> The normal stomach acidity is an important host defence against ingested pathogens and provides protection against enteric infections.<sup>7</sup> We hypothesized that the decreased gastric acidity induced by the use of proton pump inhibitors increases the susceptibility of hospital patients to colonization and subsequent infection with *C. difficile*. Significant bacterial overgrowth and even colonization with fecal type bacteria<sup>6</sup> has been demonstrated in the upper gastrointestinal tract of patients receiving acid suppressive therapy,<sup>7</sup> with higher counts in patients taking proton pump inhibitors,<sup>6</sup> presumably because these agents are more effective than H<sub>2</sub> blockers at blocking gastric acid secretion.

An association between acid suppressive therapy and *C. difficile* diarrhea or colitis has been suggested in previous studies.<sup>4,10,11</sup> None of these studies controlled for differences in antibiotic use, nor did they distinguish between different types of acid suppressive therapies. One study found a non-significant association between acid antisecretory therapy and *C. difficile* diarrhea,<sup>4</sup> but the lack of statistical significance may have reflected limited power. A recent, brief report<sup>3</sup> supports our findings of an association between use of proton pump inhibitors and *C. difficile* diarrhea after adjustment for antibiotic exposure and receipt of chemotherapy.

In our case-control study, in addition to other clinical factors, we matched for type and number of antibiotics, because they are the most important known risk factors for *C. difficile* diarrhea.

Decreased gastric acidity has been associated with renal failure<sup>23</sup> and older age,<sup>24</sup> and it may be a factor contributing to the association of *C. difficile* diarrhea with renal failure and older age observed in our study, and in previous reports.<sup>22,25</sup> Use of proton pump inhibitors has been associated with elevated gastrin levels,<sup>26</sup> which have been shown to have trophic effects on the colonic mucosa.<sup>27</sup> Proton pumps have also been described in the colon,<sup>28</sup> but their function is unclear. We have postulated that decreased gastric acidity results in inadequate sterilization of ingested organisms, but other mechanisms are possible. Proton pump inhibitors may also contribute to the disruption of the bowel flora by allowing bacterial colonization of the stomach and upper small intestine;<sup>7</sup> however, it is unclear what effect this might have on colonic flora. Use of proton pump inhibitors may then contribute significantly to outbreaks of *C. difficile* diarrhea by resulting in increased numbers of susceptible hosts as well as possibly increasing the numbers of carriers in the population.

In the cohort study, the effect of proton pump inhibitors on the risk of *C. difficile* diarrhea appeared to be greater among the patients who were taking low-risk antibiotics (e.g., cefazolin) than among those taking high-risk antibiotics. This difference suggests that the use of proton pump inhibitors may be an important effect modifier of antibiotic risk of *C. difficile* infection.

In our study we found many factors that suggest a significant association between the use of proton pump inhibitors and *C. difficile* diarrhea. These include time order (the cases were exposed to proton pump inhibitors before their symptoms developed) and dose response (the association was even stronger among patients with more prolonged exposure to proton pump inhibitors). In addition, our cohort study and our case-control study yielded similar findings despite the fact that they were conducted in different hospitals with different study designs. Furthermore, the proton pump inhibitor used in one hospital was primarily omeprazole, while in the other hospital it was pantoprazole, which suggests a class effect of these drugs. Our findings are also consistent with those from the study by Cunningham and colleagues.<sup>3</sup> The hypothesis is also coherent with reduced gastric acidity being a risk factor for other infectious enteric diseases.

Almost 50% of the patients receiving antibiotics in our cohort study were prescribed proton pump inhibitors, with another 10% receiving H<sub>2</sub> blockers. In the majority of the patients in the case-control study, we could not ascertain from the chart review why the patients were prescribed a proton pump inhibitor. A recent report suggested that acid suppressive therapy is overused in hospital patients and demonstrated that 46% of the patients in whom they determined the prescription unnecessary were still taking the medications 3

**Table 4: Factors associated with *C. difficile* diarrhea in case and control subjects (multivariate logistic regression)**

Characteristic	Adjusted OR (95% CI)	
	Model 1	Model 2
PPI use	2.7 (1.4–5.2)	2.6 (1.3–5.0)
Female sex	2.1 (1.1–4.0)	2.5 (1.2–5.0)
Prior renal failure	4.3 (1.5–11.9)	5.1 (1.7–15.2)
Hospital admission in 3 mo before index admission	2.6 (1.4–5.2)	2.9 (1.4–6.1)
Cancer	0.8 (0.4–1.8)	1.0 (0.4–2.2)
MRSA colonization*	–	7.8 (2.3–26.0)

\*MRSA colonization was excluded initially (model 1) because of a concern of detection bias. The number of antibiotics, exposure to high-risk antibiotics, the Charlson Comorbidity Index score and age were not significant factors and so were dropped from the final model and did not change estimates for PPI exposure.

months after discharge.<sup>29</sup> Although concerns have been raised regarding overuse of proton pump inhibitors, and despite their high cost<sup>30</sup> and the potential risks of prolonged achlorhydria,<sup>14</sup> the use of these drugs has been steadily increasing. Our data suggest that initiatives to curtail inappropriate use of proton pump inhibitors should be considered.

### Limitations

We matched case and control subjects by type of antibiotics; however, this was particularly difficult for patients with longer hospital stays, who may have received several courses of antibiotics. Although the difference was not statistically significant, the control subjects tended on average to have had longer hospital stays and to have received more antibiotics than the cases. We tried to measure and adjust for most of the known risk factors for *C. difficile* diarrhea, but use of proton pump inhibitors may have been associated with some other unidentified risk factor, or with sicker patients who are perhaps more susceptible to *C. difficile* diarrhea. However, the case and control subjects had similar rates of death, Charlson Comorbidity Index scores and mean ages. We did not evaluate tube feeding as a risk factor, as less than 5% of the cases had been fed this way. Although the antitoxin assay is very sensitive, improper handling of the stool specimen may result in inactivation of the toxin.<sup>19</sup> Exclusion of all patients with diarrhea who were negative for *C. difficile* toxin should have decreased the risk of misclassifying the control subjects, but it may have resulted in an underestimate of the incidence.

In conclusion, *C. difficile* diarrhea is associated with increased morbidity and mortality. Among the risk factors identified, the use of proton pump inhibitors may be an important, previously unrecognized and potentially modifiable risk factor for initial occurrence, and relapse. The use of these drugs should be evaluated carefully in hospital patients receiving antibiotics, especially in those with a diagnosis of *C. difficile* diarrhea.

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Contributors: Sandra Dial drafted the manuscript, was responsible for the study concepts and designs and for data analysis and interpretation, and provided statistical expertise. Khalid Alrasadi provided study materials and patients and was responsible for data collection and assembly. Chantal Manoukian provided study materials and patients, and administrative and technical support. Allen Huang provided study materials and administrative and technical support and was responsible for data collection and assembly. Dick Menzies provided statistical expertise and administrative and technical support. All of the authors revised the draft critically for important intellectual content and approved the final version.

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