

## Proton pump inhibitors as a risk factor for recurrence of *Clostridium-difficile*-associated diarrhea

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### Abstract

**AIM:** To investigate the risk factors for *Clostridium-difficile*-associated diarrhea (CDAD) recurrence, and its relationship with proton pump inhibitors (PPIs).

**METHODS:** Retrospective data of 125 consecutive hospitalized patients diagnosed with CDAD between January 2006 and December 2007 were collected by medical chart review. Collected data included patient characteristics at baseline, underlying medical disease, antibiotic history before receiving a diagnosis of CDAD, duration of hospital stay, severity of CDAD, concurrent

treatment with PPIs, laboratory parameters, response to CDAD therapy, and recurrence of disease within 90 d of successful treatment. Various clinical and laboratory parameters were compared in patients in whom CDAD did or did not recur.

**RESULTS:** Of the 125 patients (mean age,  $67.6 \pm 13.9$  years) that developed CDAD, 98 (78.4%) did not experience recurrence (non-recurrent group) and 27 (21.6%) experienced one or more recurrences (recurrent group). Prior to the development of CDAD, 96% of the 125 patients were prescribed antibiotics, and 56 (44.8%) of the patients received PPIs. Age older than 65 years ( $P = 0.021$ ), feeding *via* nasogastric tube (NGT) ( $P = 0.045$ ), low serum albumin level ( $P = 0.025$ ), and concurrent use of PPIs ( $P = 0.014$ ) were found to be risk factors for CDAD recurrence by univariate analysis. However, sex, length of hospital stay, duration and type of antibiotics used, severity of disease, leukocyte count and C-reactive protein (CRP) were not associated with risk of CDAD recurrence. On multivariate analysis, the important risk factors were advanced age ( $> 65$  years, adjusted OR: 1.32, 95% CI: 1.12-3.87,  $P = 0.031$ ), low serum albumin level ( $< 2.5$  g/dL, adjusted OR: 1.85, 95% CI: 1.35-4.91,  $P = 0.028$ ), and concurrent use of PPIs (adjusted OR: 3.48, 95% CI: 1.64-7.69,  $P = 0.016$ ).

**CONCLUSION:** Advanced age, serum albumin level  $< 2.5$  g/dL, and concomitant use of PPIs were found to be significant risk factors for CDAD recurrence.

**Key words:** *Clostridium difficile*; Diarrhea; Recurrence; Risk factors; Proton pump inhibitors

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## INTRODUCTION

*Clostridium difficile* is a spore-forming Gram-positive anaerobic bacillus and is the most common cause of hospital-acquired diarrhea<sup>[1]</sup>. *C. difficile* infection occurs when a susceptible host ingests spores, which then colonize the large bowel and release endotoxin. Specific antibiotic treatments with metronidazole or vancomycin show high levels of efficacy and reduce morbidity and mortality<sup>[2]</sup>. However, although initial response rates to antibiotic therapy exceed 90%, 10%-30% of patients experience *C. difficile*-associated diarrhea (CDAD) recurrence<sup>[3]</sup>, which increases the cost of medical care, and causes re-hospitalization, complications, and mortality<sup>[4]</sup>. The complications of recurrent CDAD included toxic megacolon, septicemia, and *C. difficile*-associated arthritis. Furthermore, the average length of stay due to admission for recurrent CDAD among outpatients has been reported to be 8.8 d (range, 3-26)<sup>[5,6]</sup>. It has been reported that the elderly, and patients with chronic renal failure, multiple previous CDAD episodes, or a high level of white blood cell count ( $\geq 15 \times 10^9/L$ ), and those that continue to use systemic antibiotics after a diagnosis of CDAD, are at high risk of recurrence<sup>[7,8]</sup>.

Gastric acid inhibits the germination of ingested spores and the survival of *C. difficile*, and recent studies have found that gastric acid suppressive agents, such as PPIs, increase the risk of CDAD development in hospitalized patients<sup>[9,10]</sup>. However, relatively few studies have attempted to determine whether the use of gastric acid suppressive agents is associated with an elevated risk of CDAD recurrence<sup>[11,12]</sup>.

The purpose of this study was to determine the risk factors of CDAD recurrence in hospitalized patients, and to investigate the relation between PPIs use and CDAD recurrence.

## MATERIALS AND METHODS

### Identification of subjects and collection of clinical data

This retrospective study was performed at Seoul National University Boramae Hospital, a 500-bed teaching hospital, between January 1, 2006 and December 31, 2007.

The medical records of all patients diagnosed with CDAD based on typical symptoms, that is, three or more bowel movements per day, abdominal pain, fever, leukocytosis at least 3 d after admission, and a positive ELISA result for *C. difficile* toxins A and B (Wampole TOX A/B Quic Check, Techlab, Blacksburg, VA, USA). The exclusion criteria applied were: age < 18 years, CDAD during the previous 3 mo, failure to complete at least 7 d of antibiotic therapy, a diagnosis of CDAD within 3 d of admission, or the presence of any other cause of diarrhea,

such as, laxative use, the presence of another infectious pathogen, and inflammatory bowel disease.

Medical records included the following information: age; sex; type of underlying disease; duration, number and type of antibiotics prescribed before diagnosis of CDAD; hematological and biochemical parameters; CDAD severity; PPI use; specific therapy used to treat CDAD; time to resolution of CDAD symptoms; and disease recurrence within 90 d of cure. CDAD was considered severe if two or more of the following factors were present: (1) a frequency of stool of > 10/d; (2) fever ( $> 38.3^\circ\text{C}$ ); and (3) a leukocyte count of  $> 15000 \text{ cells/mm}^3$ . PPI use was defined as at least 3 d treatment before the development of CDAD and continuous use thereafter.

In the majority of patients, oral metronidazole for 10-14 d was initially administered. Vancomycin was reserved for those that did not respond to metronidazole or had severe CDAD. The main causes of antibiotic prescription were pneumonia, urinary tract infection, postoperative wound infection, osteomyelitis, and cellulitis. Patients were classified into two groups based on recurrence within 90 d of cure (the recurrent and non-recurrent groups). Patients were regarded as cured when stool frequencies and consistencies were normal for at least three consecutive days. Recurrence was defined as diarrhea recurrence with a positive ELISA result for cytotoxin A, within 90 d after therapy completion, and the complete resolution of signs and symptoms. Patients were monitored for recurrence throughout this 90-d period.

### Statistical analysis

SPSS 12.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Patients were divided into recurrent and non-recurrent groups. Data are presented as mean  $\pm$  SD or percentage frequencies. Student's *t* test,  $\chi^2$  test and Fisher's exact test were used to analyze continuous and categorical variables. Logistic regression analysis was used to determine the effects of continuous variables on recurrence. For all analyses,  $P < 0.05$  was considered significant. This study was approved by the institutional review board of Seoul National University Boramae Hospital.

## RESULTS

A total of 125 patients who received full course therapy for CDAD were included in this study. There were 57 (45.6%) men and 68 (54.4%) women, and mean patient age was 67.6 years (range 35-92). One hundred and twenty (96%) were prescribed antibiotics before CDAD was diagnosed. The most common antibiotics administered were cephalosporins (80.8%), clindamycin (25.6%), penicillin analogues (20%), and quinolones (19.2%). Five patients (4%) did not receive antibiotics prior to diagnosis of CDAD, and 81 (64.8%) were treated with more than one antibiotic. Forty-eight (38.4%) patients had diabetes, 41 (32.8%) had malignant disease, and 17 patients (13.6%) had chronic renal failure. Thirty-five patients (28%) were fed *via* an NGT before diagnosis. Of the

**Table 1** Univariate analysis of risk factors for recurrence of *Clostridium-difficile*-associated diarrhea (mean  $\pm$  SD) *n* (%)

	Recurrence group ( <i>n</i> = 27)	Non-recurrence group ( <i>n</i> = 98)	<i>P</i> value
Age ( $\geq$ 65 yr)	16 (59.3)	31 (31.6)	0.021 <sup>a</sup>
Female	15 (55.6)	53 (54.1)	0.905
Length of hospital stay (d)	36.5 $\pm$ 9.7	32.8 $\pm$ 8.5	0.152
Duration of antibiotics used (d)	13.1 $\pm$ 6.8	12.2 $\pm$ 5.8	0.105
Admission from institution	6 (22.2)	17 (17.4)	0.379
Severe CDAD	13 (48.2)	30 (30.6)	0.156
Comorbidities			
Diabetes mellitus	11 (40.7)	37 (37.8)	0.572
Malignancy	10 (37.1)	31 (31.6)	0.560
Renal failure	5 (18.5)	12 (12.3)	0.215
Active tuberculosis	2 (7.4)	6 (6.1)	0.719
NGT feeding	13 (48.1)	23 (23.5)	0.045 <sup>a</sup>
WBC count, (mean) $\times 10^3/\text{mm}^3$	15.1 $\pm$ 9.7	12.3 $\pm$ 8.1	0.413
WBC count $> 15 \times 10^3/\text{mm}^3$	(44.4)	(40.8)	
Hb (g/dL)	10.9 $\pm$ 1.9	11.4 $\pm$ 1.6	0.279
Serum albumin (g/dL)	2.3 $\pm$ 0.5	3.1 $\pm$ 0.4	0.025 <sup>a</sup>
Serum albumin $< 2.5$ g/dL	(59.3)	(36.7)	
Creatinine (mg/dL)	1.5 $\pm$ 1.4	1.2 $\pm$ 1.6	0.513
C-reactive protein (g/dL)	7.3 $\pm$ 4.8	5.6 $\pm$ 4.5	0.579
Use of PPIs	17 (63.0)	39 (39.8)	0.014 <sup>a</sup>

<sup>a</sup>*P* < 0.05. CDAD: *Clostridium-difficile*-associated diarrhea; WBC: White blood cells; NGT: Nasogastric tube.

125 subjects, 56 (44.8%) received PPIs for  $\geq 3$  d. One hundred and thirteen (90.4%) were initially treated with metronidazole, and 12 (9.6%) with vancomycin.

Of the 125 study subjects, 27 (21.6%) experienced disease recurrence within 90 d after cure, and the remaining 98 (78.4%) did not experience recurrence. The recurrence rate among patients treated with metronidazole was no different from that among patients treated with vancomycin (21.2% *vs* 16.7%). Univariate analysis showed that five parameters were significantly associated with recurrence (Table 1). Patients aged  $\geq 65$  years were found to be more likely to develop recurrence than those  $< 65$  years (59.3% *vs* 31.6%, *P* = 0.021). Patients fed *via* an NGT were also more likely to develop recurrence (48.1% *vs* 23.5%, *P* = 0.045). The mean serum albumin level at the time of CDAD diagnosis was lower in patients with recurrence than in patients without recurrence (2.3  $\pm$  0.5 g/dL *vs* 3.1  $\pm$  0.4 g/dL, *P* = 0.028). Furthermore, significantly more patients in the recurrent group received concurrent PPIs therapy (63.0% *vs* 39.8%, *P* = 0.014). However, sex, length of hospital stay, duration of antibiotics used before diagnosis of CDAD, the presence of diabetes mellitus or renal failure, severity of CDAD, leukocyte count, hemoglobin and CRP levels were not found to be associated with an increased risk of recurrence.

Multivariate analysis showed that age  $> 65$  years (OR: 1.32, 95% CI: 1.12-3.87, *P* = 0.031), serum albumin level of  $< 2.5$  g/dL (OR: 1.85, 95% CI: 1.35-4.91, *P* = 0.028), and concurrent use of PPIs (OR: 3.48, 95% CI: 1.64-7.69, *P* = 0.016) were associated with the risk of recurrence (Table 2).

Table 3 summarizes antibiotic use before CDAD was

**Table 2** Multivariate analysis of risk factors for recurrence of *Clostridium-difficile*-associated diarrhea

Risk factor	Adjusted OR	95% CI	<i>P</i> value
Age ( $\geq 65$ yr)	1.32	1.12-3.87	0.031 <sup>a</sup>
Low serum albumin of $< 2.5$ g/dL	1.85	1.35-4.91	0.028 <sup>a</sup>
Concurrent use of PPI	3.48	1.64-7.69	0.016 <sup>a</sup>
NGT feeding	1.25	0.91-2.65	0.068

<sup>a</sup>*P* < 0.05. NGT: Nasogastric tube; PPI: Proton pump inhibitor.

**Table 3** Comparison of antibiotics used before diagnosis of *Clostridium-difficile*-associated diarrhea between non-recurrent and recurrent group (mean  $\pm$  SD) *n* (%)

Type of antibiotics used	Non-recurrent CDAD ( <i>n</i> = 98)	Recurrent CDAD ( <i>n</i> = 27)	<i>P</i> value
No. of antibiotics used	2.58 $\pm$ 0.9	2.43 $\pm$ 0.8	0.560
No antibiotics	4 (4.1)	1 (3.7)	0.638
1 antibiotics	28 (28.6)	9 (33.3)	0.497
$\geq 2$ antibiotics	64 (65.3)	19 (70.4)	0.435
Penicillin analogue	19 (19.4)	6 (22.2)	0.561
Cephalosporin	79 (80.6)	22 (81.4)	0.613
Clindamycin	26 (26.5)	6 (22.2)	0.265
Quinolone	17 (17.3)	7 (25.9)	0.217
Macrolide	8 (8.2)	2 (7.4)	0.691
Carbapenem	11 (11.2)	5 (18.5)	0.215
Metronidazole	6 (6.1)	2 (7.4)	0.563
Vancomycin	3 (3.1)	1 (3.7)	0.729

CDAD: *Clostridium-difficile*-associated diarrhea.

diagnosed. The mean number of antibiotic types prescribed to patients was not found to be a risk factor for recurrence (2.58 in the recurrent group *vs* 2.43 in the non-recurrent group, *P* = 0.56). Furthermore, the two study groups were similar in terms of exposure to high-risk antibiotics, such as, clindamycin, cephalosporins, or quinolones.

## DISCUSSION

Recurrent CDAD is one of the most difficult problems related to *C. difficile* infection. Despite an initial successful response in more than 90% of patients, CDAD recurs in 15%-30%<sup>[13,14]</sup>. In a previous study of 124 CDAD patients, 24% experienced recurrence<sup>[15]</sup>, which concurs with the 20.8% observed in the present study. Patients treated with metronidazole (21.2%) had a greater tendency to recur than patients treated with vancomycin (16.7%), but this was not significant (*P* = 0.09). Studies have shown that the rates of treatment failure and recurrence are greater for patients treated with initial metronidazole than for patients treated with vancomycin, especially since 2000<sup>[16]</sup>. Because of its low cost and of concerns about vancomycin-resistant enterococci, metronidazole is recommended as first-line therapy. However, our finding that 21% of patients initially treated with metronidazole experienced recurrence suggests that vancomycin might be helpful as a first-line treatment in patients with multiple risk factors for recurrent CDAD. Although the pathogenesis of recur-

rence is poorly understood, several risk factors have been described. The important risk factors were advanced age, longer hospital stay, continued use of antibiotics for the treatment of non-*C. difficile* diarrhea after a first episode of CDAD, inadequate antitoxin antibody response, persistent disruption of colonic flora, and concomitant receipt of antacid medications<sup>[17-19]</sup>.

Several studies have reported that agents that suppress gastric acid secretion, especially PPIs, increase the risk of CDAD development<sup>[20-22]</sup>. According to one study, the adjusted risk ratios for CDAD development for PPIs and H2-receptor antagonist (H2RA) usage are 2.9 (95% CI: 2.4-3.4) and 2.0 (95% CI: 1.6-2.7), respectively. However, another study on the relationship between CDAD development and exposure to acid suppressive therapy in hospitalized patients has revealed an association with PPIs (OR: 3.6, 95% CI: 1.7-8.3) but not with H2RAs. In the present study, we found that PPI use was a significant risk factor of CDAD recurrence, which is in line with previous reports. In one study of 140 CDAD patients treated between 2004 and 2005, those receiving PPIs were found to be 4.17 times more likely to recur, which is greater than the OR found in the present study<sup>[11]</sup>. This result may be due to differences between study populations. In the study conducted by Cadle *et al.*<sup>[11]</sup>, most patients (98.6%) were men and the proportion of patients who received PPIs was greater than in the present study (69% *vs* 55%). In a recent meta-analysis, continued use of non-*C. difficile* antibiotics after a diagnosis of CDAD (OR: 4.23, 95% CI: 2.10-8.55), concomitant receipt of antacid medication (OR: 2.15, 95% CI: 1.13-4.08), and older age (OR: 1.62, 95% CI: 1.11-2.36) were found to be significantly associated with the risk of CDAD recurrence<sup>[12]</sup>. However, in this meta-analysis, PPIs and H2RAs were not differentiated, and thus, their specific effects on CDAD recurrence could not be evaluated.

The mechanisms by which acid suppressive agents increase the risk of CDAD development and recurrence are poorly understood<sup>[23]</sup>. However, although the spores of *C. difficile* are resistant to gastric acid, it has been suggested the survival and germination of *C. difficile* spores are greater at lower acidity, and that higher gastric pH increases vegetative bacteria counts in the small and large intestine<sup>[24]</sup>. Previous studies have found that gastric acid suppression increases stomach and small bowel colonization by bacteria and *C. difficile*<sup>[25,26]</sup>. Alternatively, it is also possible that PPIs directly affect host immune function, and thus, increase susceptibility to CDAD recurrence<sup>[27]</sup>.

In the present study, age was found to be a risk factor for recurrence. A retrospective study of hospitalized patients in Quebec also has shown that patients aged > 65 years have a higher risk of CDAD recurrence after metronidazole and vancomycin therapy<sup>[28]</sup>. The reason why advanced age increases the risk of recurrence may be that these patients have comorbidities and are likely to be administered additional antibiotics for concomitant infections. A low serum albumin level was also found to be a significant risk factor for recurrence in our study. Hypoalbuminemia reflects a poor nutritional status, and may compromise immune response by diminishing

antibody response to *C. difficile*. In one study, patients with recurrent disease were found to have significantly lower levels of IgG to toxin A than patients that did not recur<sup>[29]</sup>. Later increased serum levels of IgM and IgG to toxin A are known to be associated with a substantial reduction in the risk of CDAD recurrence<sup>[16]</sup>.

In contrast to previous reports, we found no relationship between renal failure, leukocytosis, or CDAD severity and recurrence. However, we defined renal failure based on creatinine level alone, rather than on creatinine clearance, and this does not reflect the range of renal failure. With regard to leukocytosis and disease severity, a significant proportion of our study subjects were elderly, due to a failure to increase leukocytes in response to infection in some elderly patients, which may have influenced our results. Previous reports have shown that clindamycin, penicillin and cephalosporin use is an important risk factor for CDAD development, and recently, ciprofloxacin use also has been found to be a significant risk factor for CDAD in hospitalized patients<sup>[30-32]</sup>. In the present study, however, antibiotic use prior to CDAD was similar in our two patient groups, and this suggested that type and number of antibiotics used prior to CDAD might have influenced CDAD development, but not CDAD recurrence.

This study had several limitations that should be considered. First, the study was inherently limited by its retrospective nature, and in particular, stool cultures were not conducted, which prevented our determining whether recurrent CDAD was due to reinfection or relapse. Second, the confidence interval regarding the use of PPIs as a risk factor for recurrent CDAD was relatively large, which was probably due to the small number of patients enrolled in this study. Third, actual compliance to PPIs could not be assessed beyond the prescription data contained in medical charts.

In conclusion, older age (> 65 years) and a low serum albumin level (< 2.5 g/dL) were identified as risk factors for CDAD recurrence. The concomitant use of PPIs further enhanced the risk of recurrence. Of these risk factors, the use of PPIs is modifiable, and thus, it is appropriate to review constantly the necessity for concomitant use of PPIs in patients with CDAD. Prevention of unwarranted PPI therapy may be helpful in reducing the risk of recurrence, and additional larger studies are necessary in order to understand better the relationship between PPI use and CDAD recurrence.

## COMMENTS

### Background

The incidence and severity of *Clostridium-difficile*-associated diarrhea (CDAD) is increasing worldwide due to increased use of antibiotics and the introduction of hypervirulent strains. After successful initial therapy, approximately 10%-30% of patients experience symptomatic recurrence. Recurrence of CDAD causes increasing cost of medical care, re-hospitalization and complications. It is known that older patients, patients with chronic renal failure and multiple episode of previous CDAD are high risk groups for disease recurrence. Recent reports have suggested that the use of proton pump inhibitors (PPIs) is associated with CDAD recurrence in hospitalized patients, although the results appear to be conflicting. The objective of this study was to evaluate the risk factors for CDAD recurrence and to investigate the relationship of PPI use and recurrence of CDAD.

### Research frontiers

Risk factors that are associated with CDAD recurrence and the association between use of PPIs and CDAD recurrence have been hot topics in recent studies. Of the 125 patients that developed CDAD, 98 did not experience recurrence and 27 experienced one or more recurrences. The important risk factors for CDAD recurrence were age > 65 years, low serum albumin level < 2.5 g/dL, and use of PPIs.

### Innovations and breakthroughs

This study showed that advanced age, low serum albumin level and use of PPIs were associated with increased risk of CDAD recurrence.

### Applications

This retrospective analysis of the risk factors for CDAD recurrence imply that avoidance of unwarranted PPI therapy may be helpful in reducing the risk of CDAD recurrence.

### Peer review

This is a timely study extending present knowledge that PPIs are a risk factor for *C. difficile* reinfection.

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