Background/Aims: Clostridium difficile infection (CDI) is a common nosocomial infection associated with substantial morbidity, mortality and increased medical care costs. Although most patients initially respond to therapy, with either metronidazole or vancomycin, about 15-20% of patients experience recurrence. The aim of this study was to analyze the risk factors related to recurrent CDI (RCDI). Methods: We retrospectively reviewed data, from patients diagnosed with CDI during admission at a university hospital between January 2000 and December 2006, for comparison with data from RCDI patients. Results: Among a total of 294 CDI patients, 32 (10.8%) had experienced RCDI. Risk factors for RCDI included anemia, congestive heart failure, respiratory infection, time between admission and CDI diagnosis, duration of antibiotic therapy prior to CDI diagnosis, tube feeding, and gastrointestinal endoscopy. Multivariate analysis revealed that tube feeding was associated with recurrence (odds ratio, 3.65; 95% confidence interval, 1.38-9.65; P=0.009). Conclusions: Patients who received tube feeding were at increased risk of RCDI. Targeting these patients for preventive strategies may contribute to a reduction in the incidence of RCDI. (Intest Res 2012;10:176-182)

Key Words: Clostridium difficile; Recurrence; Risk Factors; Enteral Nutrition

INTRODUCTION

Since the use of broad-spectrum antibiotics has recently increased, the frequency of Clostridium difficile (C. difficile) infection (CDI) has risen in the United States and as well as in Korea. Patients who contracted their first episode of CDI, responded well to standard treatment using metronidazole or vancomycin, and the recurrence rate was reported in 15-20%. The recurrence rate in patients who had already experienced recurrence once was as high as 65%. Frequent recurrence has been a problem as it leads to extended hospital stays, increased hospital costs due to rehospitalization and occurrence of complications. However, knowledge about risk factors for recurrent CDI (RCDI) is still lacking, which would guide the understanding the pathogenesis.
We sought out the etiological basis of recurrence by analyzing risk factors for RCDI.

SUBJECTS AND METHODS

1. Definition

CDI was defined as the occurrence of diarrhea (loose or watery stool) three or more times a day and a positive result obtained from the *C. difficile* cytotoxin A assay (VIDAS enzyme-linked immunoassay, bioMérieux, Marcy l’Etoile, France) and other causes of diarrhea (other bacteria found on bacterial culture to cause diarrhea or the use of laxatives) were excluded. Diarrhea that occurred within 48 hours after hospital admission was classified as community-acquired diarrhea, whereas diarrhea that occurred more than 48 hours after hospital admission was classified as a hospital-acquired infection. The date of CDI diagnosis was defined as the day when a positive result was first obtained from the *C. difficile* cytotoxin A assay. Patients were considered to be in the resolution stage when they showed normal consistency and number of times (less than three times a day) for three or more consecutive days. RCDI was defined as diarrhea and a positive stool from the *C. difficile* cytotoxin A assay within 8 weeks after improvement of diarrhea following the first CDI treatment.

2. Materials

We retrospectively analyzed the medical records of patients diagnosed with CDI at a university hospital between January 1, 2000 and December 31, 2006. Cases whose clinical features could not be found in medical records or cases of community acquisitions were excluded.

3. Methods

We investigated patient age, gender, duration of hospital stay, time elapsed from admission date to diagnosis, occurrence of symptoms, and whether or not the patient had been transferred from another hospital. We investigated the underlying diseases, such as cerebrovascular disease, dementia, congestive heart failure, diabetes, renal failure or malignant neoplasm. Symptoms that included diarrhea, fever, abdominal pain and vomiting and laboratory data, such as hematocrit, leukocyte count, serum albumin and creatinine were investigated. We also investigated whether or not gastric antisecretory agents, tube feeding, or gastrointestinal endoscopy had been used until two months before the date of diagnosis, as well as other details on the patient’s history of admission to the intensive care unit, the type of antibiotics used, the duration and indications of antibiotic administration, and whether or not treatment included surgery within preceding 60 days of illness or chemotherapy within preceding 30 days. The method, duration and effectiveness of primary treatment after diagnosis and incidence of recurrence were also investigated. Identical risk factors and treatment response for RCDI patients were investigated during the period between the date of the first CDI diagnosis and the date of diagnosis of recurrence.

4. Statistical Analysis

Continuous variables were displayed as mean±standard deviation and unpaired t-test was performed. Discrete variables were presented as fractions and chi-square test or Fisher’s exact test was carried out. We used multiple logistic regression analysis for variables with *P*-value of 0.1 or below in univariate analysis to identify risk factors for recurrence; the result was described as odds ratio and 95% confidence interval. All *P*-values were regarded as significant when a two-tailed test found that the value was less than 0.05. Data were analyzed using SPSS version 11.5 for Windows (SPSS Inc., Chicago, IL, USA) with statistical testing.

RESULTS

1. Clinical Characteristics

A total of 294 patients were diagnosed with CDI. Among them, 32 patients (10.8%) were diagnosed with RCDI. The average frequency of recurrence in the RCDI patient group was 1.48 (±1.15), while 2 and 3 recurrences were reported in 2 cases, respectively, 4 recurrences in 1 case, and 6 recurrences in 1 case. No annual trend in CDI occurrence rate was found. Among the
CDI patients, RCDI patients represented 1.8% and 2.6% in 2002 and 2003 down from 5.4% and 8.7% in 2000 and 2001, respectively. The RCDI patient ratio spiked up to 26.7% in 2004 and then decreased to 10.7% and 16.0% in 2005 and 2006 (Fig. 1).

The mean age of the RCDI patient group was 64.1 years and the gender ratio of male and female was found to be 1:1.29. Underlying diseases included cerebrovascular diseases in 23 cases (71.9%), malignant tumors in 7 cases (21.9%), diabetes in 6 cases (18.8%) and congestive heart failure in 2 cases (6.3%). Clinical symptoms other than diarrhea included fever in 12 cases (37.5%), hypoalbuminemia was detected in peripheral blood tests in 30 cases (93.8%), and anemia was reported in 25 cases (78.1%) (Table 1). Indications for antibiotic administration included respiratory infection in 18 cases (56.3%), preoperative preventive use in 15 cases (46.9%), and urinary tract infection in 3 cases (9.4%). Combination therapy for primary treatment using culprit antibiotics along with vancomycin or metronidazole administration was reported in 11 cases (34.4%), while oral administration of vancomycin was reported in 9 cases (28.1%), and metronidazole administration in 7 cases (21.9%) (Table 2).

### 2. Risk Factors for Recurrence

The duration of hospital stay and antibiotic admin-

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### Table 1. Clinical and Laboratory Findings between Two Groups

| Characteristics                  | No recurrence (n=262) | Recurrence (n=32) | OR (95% CI) | P-value |
|----------------------------------|-----------------------|-------------------|-------------|---------|
| Age (yr)                         | 61.7±14.4             | 64.1±12.2         | NS          |
| Female sex                       | 121 (46.2)            | 18 (56.3)         | NS          |
| Comorbidities                    |                       |                   |             |         |
| Cerebrovascular accident         | 157 (59.9)            | 23 (71.9)         | NS          |
| Congestive heart failure         | 3 (1.1)               | 2 (6.3)           | 5.75 (0.92–35.83) | 0.035   |
| Diabetes mellitus                | 32 (12.2)             | 6 (18.8)          | NS          |
| Renal failure                    | 31 (11.8)             | 2 (6.3)           | NS          |
| Malignancy                       | 45 (17.2)             | 7 (21.9)          | NS          |
| Clinical manifestations          |                       |                   |             |         |
| Fever (axillary temperature >38°C) | 92 (35.1)             | 12 (37.5)         | NS          |
| Abdominal pain                   | 71 (27.1)             | 6 (18.6)          | NS          |
| Vomiting                         | 17 (6.5)              | 1 (3.1)           | NS          |
| Laboratory findings             |                       |                   |             |         |
| Anemia (Hb<11 g/dL)              | 148 (56.5)            | 25 (78.1)         | 2.75 (1.14–6.58) | 0.019   |
| White blood cell count >10,000/mm³ | 144 (55.0)            | 13 (40.6)         | NS          |
| Serum albumin <3.8 g/dL          | 239 (91.2)            | 30 (93.8)         | NS          |
| Time from admission to CDI diagnosis (day) | 26.8±26.4 | 37.5±30.6       | 1.01 (0.99–1.02) | 0.070   |
| Intensive care unit admission    | 80 (30.5)             | 12 (37.5)         | NS          |

*Values are presented as number of patients (%) or mean±standard deviation.*

CDI, *Clostridium difficile* infection; NS, not significant.
Table 2. Procedures and Treatment between Two Groups before CDI Diagnosis

| Characteristics                          | Group                        | OR (95% CI) | P-value |
|------------------------------------------|------------------------------|-------------|---------|
|                                          | No recurrence (n=262)        |             |         |
|                                          | Recurrence (n=32)            |             |         |
| **Indications for antibiotics treatment**|                              |             |         |
| Respiratory infection                    | 94 (35.9)                    | 18 (56.3)   | 2.29 (1.09-4.83) 0.025 |
| Urinary tract infection                  | 19 (7.3)                     | 3 (9.4)     | NS      |
| Prophylactic therapy for surgical procedures | 148 (56.5)                | 15 (46.9)   | NS      |
| **Types of antibiotic exposure**         |                              |             |         |
| Third generation cephalosporins          | 113 (43.1)                   | 19 (59.4)   | NS      |
| Fluoroquinolones                         | 108 (41.2)                   | 15 (46.9)   | NS      |
| Carbapenems                              | 31 (11.8)                    | 4 (12.5)    | NS      |
| **Total number of antibiotics**          | 2.7±1.4                      | 3.0±1.6     | NS      |
| Duration of antibiotics therapy before CDI diagnosis, (day) | 16.4±11.6                   | 25.3±18.2   | 1.03 (1.01-1.06) 0.001 |
| Acid suppressive therapy*                | 168 (64.1)                   | 21 (65.6)   | NS      |
| Chemotherapy                             | 23 (8.8)                     | 2 (6.3)     | NS      |
| Tube feeding                             | 102 (38.9)                   | 23 (71.9)   | 3.45 (1.65-7.20) 0.000 |
| Gastrointestinal endoscopy†              | 30 (11.5)                    | 8 (25.0)    | 2.24 (1.08-4.63) 0.031 |
| Surgery within 2 months                  | 127 (48.5)                   | 14 (43.8)   | NS      |
| **Initial treatment of CDI**             |                              |             |         |
| Discontinue implicated antibiotics only   | 44 (16.8)                    | 5 (15.6)    | NS      |
| Metronidazole                            | 52 (19.8)                    | 7 (21.9)    | NS      |
| Vancomycin                               | 92 (35.1)                    | 9 (28.1)    | NS      |
| Continue implicated antibiotics with metronidazole or vancomycin | 74 (28.2)                    | 11 (34.4)   | NS      |

Values are presented as number of patients (%) or mean±standard deviation.

*To be considered exposed, patients had to have received these drugs for at least 3 days before diarrhea developed.

†Gastroscopy and/or colonoscopy, excluding sigmoidoscopy for diagnosing pseudomembranous colitis.

CDI, *Clostridium difficile* infection; OR, odds ratio; CI, confidence interval; NS, not significant.

Table 3. Multiple Logistic Regression Analysis about Potential Risk Factors for Recurrent CDI

| Risk factors                           | OR    | (95% CI)    | P-value |
|----------------------------------------|-------|-------------|---------|
| Anemia                                 | 2.48  | (0.96-6.42) | NS      |
| Congestive heart failure               | 0.42  | (0.03-5.12) | NS      |
| Respiratory infection                  | 0.73  | (0.31-1.89) | NS      |
| Time from admission to CDI diagnosis   | 0.99  | (0.97-1.01) | NS      |
| Duration of antibiotics therapy before CDI diagnosis | 1.02  | (0.99-1.05) | NS      |
| Tube feeding                           | 3.65  | (1.38-9.65) | 0.009   |
| Gastrointestinal endoscopy             | 1.58  | (0.48-5.16) | NS      |

CDI, *Clostridium difficile* infection; OR, odds ratio; CI, confidence interval; NS, not significant.

Univariate analysis of clinical characteristics and risk factors in the RCDI group and the non-recurred patient group found that congestive heart failure, anemia, respiratory infection, hospital stay until the first diagnosis of CDI and duration of antibiotic administration, tube feeding and gastrointestinal endoscopy were associated with recurrence. In a multivariate analysis, tube feeding (OR,
3.65; 95% CI, 1.38-9.65; \(P=0.009\) was the only independent risk factor for RCDI (Table 3).

**DISCUSSION**

The mechanism of CDI recurrence is not yet clear, however, it is assumed that recurrent CDI is caused by the proliferation of the *C. difficile* strain after survival or by re-infection with a new strain, rather than drug resistance to metronidazole or vancomycin.\(^{15,16}\) A variety of risk factors have been presented, including old age of 65 or above,\(^{9,17,18}\) female,\(^{7}\) chronic renal failure, leucocyte count of 15,000/mm\(^3\) or over in first occurrence of the disease, community acquisition,\(^{19}\) use of antibiotics for other inflammation following treatment of the first episode of CDI,\(^{7,20,21}\) severe underlying disease, insufficient antibody response to *C. difficile* toxin A,\(^{17}\) use of a gastric antisecretory agent, and residence in a nursing home,\(^{21}\) stool vancomycin-resistant enterococci colonization,\(^{22}\) operation history within 1 month of development of CDI.\(^{23}\) That is, host immunity-related factors, use of antibiotics, and subsequent eradication of normal intestinal flora, preventing germination of *C. difficile* spores that remains after primary infection, and re-infection from the surrounding environment can cause recurrence. In particular, use of gastric antisecretory agents or residence in a nursing facility may presumably explain the oral infection associated with weakening of the gastric acid barrier and re-infection from contaminants in the environments.\(^{24}\) A study conducted by Pépin et al.\(^{24}\) on 463 RCDI patients found that 154 patients (33%) experienced a second recurrence. In their study, duration of hospital stay after the first recurrence was directly proportional to the subsequent recurrence rate, suggesting some probability of re-infection from the surrounding environment. Meanwhile, in a study to compare *C. difficile* strains before and after recurrence using DNA fingerprinting techniques, recurrence from different strains accounted for 48-75%, suggesting that re-infection occurred.\(^{25,26}\) Among annual CDI patients in our study, RCDI patients (RCDI/CDI) sharply increased from 1.8% and 2.6% in 2002 and 2003, respectively, to 26.7% in 2004, and then decreased to 10.7% and 16.0% in 2005 and 2006, showing no constant change in tendency. As patients’ immunity or virulence of strain cannot be changed in the short term and is more likely to show a constant change in tendency, the recurrence may be attributable to other mechanisms, such as re-infection.\(^{27}\) Another explanation for our findings is that increasing prevalence of toxin A-negative/toxin B-positive strains of *C. difficile* is postulated as the cause. Kim et al.\(^{28}\) reported a significant increase in these strains in 2004, these results are in agreement with annual trend of RCDI occurrence rate.

There have been a few studies showing tube feeding as a risk factor for RCDI. A retrospective study reported that 47.9% of the patients who were not responsive to initial metronidazole therapy or showed recurrence (non-responder group) received tube feeding, while 20.9% of the responder group received tube feeding, and the difference was statistically significant.\(^{29}\) Another study demonstrated that 48.1% of the patients who showed recurrence (recurrence group) received tube feeding, while 23.5% of the non-recurrence group also received tube feeding, but that tube feeding was not a risk factor for recurrence in multivariate analysis.\(^{30}\) Our results are different from those of previous studies. The reason for this may be that more patients receiving tube feeding were included in the recurrence and non-recurrence groups of our study.

Multivariate analysis of factors associated with various recurrences found that tube feeding was the only independent risk factor for RCDI. Guenter et al.\(^{31}\) reported that 30% of patients using tube feeding experienced diarrhea and *C. difficile* toxin was detected in half. Similarly, according to a study by Edes et al.\(^{32}\) *C. difficile* was the causative agent of diarrhea, which occurred in approximately 17% of patients who underwent tube feeding. In a prospective study by Bliss et al.\(^{33}\), occurrence rate of CDI was 9 times higher in patients on tube feeding. Tube feeding can be a risk factor for CDI because it can play the role of a carrier that introduces the *C. difficile* strain from contaminants in the surrounding environment. That is, as *C. difficile* can easily be detected on the hands of asymptomatic hospital personnel, it can also be spread from them.\(^{34}\) Manual handling of the tube may lead to contamination of the feed.\(^{35}\) In addition, aseptic manipulation and ready-to-use formula contributed to a reduction in feeding tube contamination\(^{36}\) and prevention of CDI.\(^{37}\) *C. difficile* in par-
ticular is widely distributed in the surrounding environment and its spores can exist up to 5 months in the barren environment while maintaining the virulence and capacity to cause re-infection. Therefore, in the same mechanism of CDI occurrence caused from tube feeding, patients recovered from primary infection can be re-infected from the surrounding environment.

This study has some limitations. First, this study is a retrospective study at a single practice site. Second, we could not be sure that re-infection actually occurred whether by the strain that caused the primary infection or a new strain that caused the recurrent infection. Identification of the strain requires use of the random amplified polymorphic DNAs-based DNA fingerprinting method. Third, we were unable to perform C. difficile cytotoxin B assay. Therefore we cannot evaluate the effect of the toxin A-negative/toxin B-positive C. difficile strains in this study. Fourth, regarding duration of exposure to risk factors, it will be reasonable to compare elapsed time from the date of the first CDI diagnosis to the date of recurrence. However, as many patients in the non-recurrent patient group were discharged from the hospital after their first CDI improved, we were not able to make presumptions regarding their progress. Therefore, we compared and analyzed risk factors prior to the date of the first CDI diagnosis in both groups. In this study, we investigated and compared each risk factor from the date of first CDI diagnosis to the date of recurrence diagnosis in the RCDI patient group, and found no statistically significant difference. These restrictions can be complemented in prospective studies.

In conclusion, our study suggests that tube feeding, rather than various underlying host diseases, or antibiotic administration deserves attention as a risk factor for RCDI and that RCDI can result from re-infection with the C. difficile strain through contaminant in the surrounding environment or from feeding formula. Although, vancomycin pulse therapy, probiotics, immunoglobulin, and C. difficile toxoid vaccine have been proposed for RCDI treatment, further study is needed on the effectiveness of these therapies. Therefore, it may be more efficient to prevent recurrence by minimizing chances for re-infection from contaminant in the environment.

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