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Clinical risk factors for *Clostridium difficile*-associated diseases

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ABSTRACT

Many factors appear to influence the chance of acquiring *Clostridium difficile* (*C. difficile*) infection, and an accurate identification of risk factors could be beneficial in many ways. Thus, in the present study, clinical risk factors for *C. difficile*-associated disease (CDAD) in Korea were identified. A total of 93 patients who met the inclusion criteria and 186 age/gender/ward/admission period-matched control patients were included in this study. Statistically significant associations were found with presence of chronic lung diseases (odds ratio [OR], 3.41; 95% confidence interval [CI], 1.25-9.32; p = 0.017), presence of ileus (OR, 10.05; 95% CI, 2.42-41.80; p = 0.001), presence of intensive care unit (ICU) stay (OR, 9.79; 95% CI, 3.03-31.68; p < 0.001), use of cephalosphorins (OR, 3.30; 95% CI, 1.13-9.62; p = 0.029), history of surgery (OR, 10.89; 95% CI, 3.96-29.92; p < 0.001), and history of long-term care facility stay (OR, 14.90; 95% CI, 4.02-55.26; p < 0.001). Awareness of CDAD is critical to provide appropriate clinical care. Surveillance of the national incidence rate and multicenter studies are needed, and the potential value of a *C. difficile* vaccine should be studied.

Introduction

Clostridium difficile-associated disease (CDAD) has been clearly associated with the use of broad-spectrum antimicrobial agents worldwide. *Clostridium difficile* (*C. difficile*) is a gram-positive, anaerobic, spore-forming bacillus. The clinical manifestations of CDAD range from asymptomatic colonization of the gastrointestinal tract and mild diarrhea to diarrhea with colitis, which can progress to toxic dilatation, sepsis, perforation, and death.[1] Although CDAD may occur during or following the administration of any antimicrobial agent, higher rates are more commonly associated with cephalosporins, ampicillin/amoxicillin, fluoroquinolones, and clindamycin.[1-6] In addition to antimicrobial exposure, other variables that may contribute to CDAD include use of chemotherapeutic agents, severe underlying illness, history of gastrointestinal surgery, advanced patient age, use of enteral tube feedings, and exposure to *C. difficile*.[7-14]

Many factors appear to influence the chance of acquiring *C. difficile* infection, and an accurate identification of risk factors could be beneficial in many ways. However, information about CDAD is scarce in Korea. A full analysis of potential risk factors was warranted. Thus, in this study, the clinical risk factors for CDAD in Korea were identified.

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Methods

The Eulji Medical Center is a 1,030-bed tertiary care teaching hospital. A case patient was defined as any patient who had a positive fecal *C. difficile* toxin (CDT) A by enzyme immunosorbent toxin A assay (CDA 2) result between January 2006 and May 2010. For each case patient, two control patients were randomly selected from a pool of all of the age/gender/ward/admission period-matched patients. The data were gathered by a retrospective chart review, which included patient demographics; comorbidities (cardiovascular diseases, chronic lung diseases, diabetes mellitus, renal failure, or malignancy); presence of ileus or intensive care unit (ICU) stay within 30 days of CDAD diagnosis; use of proton pump inhibitor (PPI), H_2 blocker, cephalosporins, carbapenems, aminoglycosides, macrolides, or quinolones within 30 days of CDAD diagnosis; and history of prior hospitalization, long-term care facility stay, surgery, or previous CDAD within 30 days of diagnosis of CDAD. The laboratory data were collected over a seven-day period spanning four days before and two days after the day of submission of the first *C. difficile*-positive fecal specimen. This interval was chosen to account for variability in the promptness of *C. difficile* testing and initiation of treatment among healthcare providers; max leukocyte count (> 20,000/uL), max serum glucose (> 150 mg/dL), max creatinine level (> 2 mg/dL), alanine aminotranferase levels (> 40 IU/L), and minimum serum albumin level (< 2.5 g/dL).

The data generated were coded, entered, validated and analyzed using the Statistical Package for Social Science (SPSS Inc. – Chicago, USA), version 18.0. Relative risks (RR), both univariate and multivariate together with 95% confidence interval (CI) were calculated. In multivariate analysis, risk factors that had a p-value < 0.05 in univariate analysis were included, as well as other factors that were known to be associated with seroconversion.

Results

A total of 93 patients who met the aforementioned criteria and 186 age/gender/ward/admission period-matched control patients were included in this study. The mean ages of case/control patients were 63.0 ± 16.5 and 62.3 ± 16.9 years, respectively. The gender ratios (M/F) of case/control patients were 37/56 and 74/112, respectively. The incidence rate of CDAD during this study period was 0.2%. Univariate analysis showed that the case patients were more likely than the control patients to have chronic lung diseases (29.0% vs. 9.1%); presence of ileus (14.0% vs. 2.2%); presence of ICU stay (28.0% vs. 3.2%); use of H_2 blocker (63.4% vs. 81.2%); use of cephalosphorins (39.8% vs. 9.1%), aminoglycosides (9.7% vs. 1.6%), and macrolides (11.8% vs. 1.6%); non-use of quinolones (28% vs. 73.7%); history of prior hospitalization (67.7% vs. 46.8%); history of long-term care facility stay (24.7% vs. 2.7%); history of surgery (37.6% vs. 5.4%); history of previous CDAD (10.8% vs. 1.1%); and presence of hypoalbuminemia (17.2% vs. 6.5%) (Table 1). Factors demonstrating an association with CDAD by univariate analyses and other factors that were known to be associated with CDAD were evaluated in a multiple logistic regression model (Table 2). Statistically significant associations were found with the presence of chronic lung diseases (odds ratio [OR], 3.41; 95% CI, 1.25-9.32; p = 0.017), the presence of ileus (OR, 10.05; 95% CI, 2.42-41.80; p = 0.001), the presence of ICU stay (OR, 9.79; 95% CI, 3.03-31.68; p < 0.001), the use of cephalosphorins (OR, 3.30; 95% CI, 1.13-9.62; p = 0.029), the history of surgery (OR, 10.89; 95% CI, 3.96-29.92; p < 0.001), and the history of long-term care facility stay (OR, 14.90; 95% CI, 4.02-55.26; p < 0.001). The use of H_2 blocker showed a protective effect to CDAD (OR, 0.30; 95% CI, 0.13-0.69; p = 0.005). Among surgeries, orthopedic surgery had the greatest risk, followed by neurosurgery and gastrointestinal surgery.

Discussion

C. difficile infection is the most common cause of hospital-acquired diarrhea, accounting for 30% of patients with antibiotic-associated diarrhea, 70% of those with antibiotic-associated colitis, and most cases of pseudomembranous colitis. In addition, healthy adults have been shown to be colonized with *C. difficile*, and outpatient detection rate in specimens has been reported as high as 10.7%.[15,16] Although the incidence rate in Korea was low (0.2-0.7%) compared to the United States (30-50%) or to Europe (40-60%), there was notable recent increase of incidence, which is reasoned as the increased diagnostic approach of CDT assay.[17]

Two likely mechanistic factors increasing the risk of recurrent CDI are an inadequate immune response to *C. difficile* toxins and persistent disruption of the normal colonic flora.[18]

The present study demonstrated that patients with chronic lung disease had higher risk of CDAD. Underlying illness has been hypothesized to decrease host immunity, thereby increasing susceptibility to this disease process. In addition, patients with chronic lung disease often experience higher rates of pneumonia, so they have a higher chance of exposure to antibiotics than healthy adults, rendering chronic lung diseases as a risk factor of CDAD.

Increased antibiotic coverage could lead to further suppression of the normal bowel flora, creating an optimal environment for *C. difficile* to thrive. Interestingly, duration of antibiotic use was not found to be significant. This suggests that broad coverage rather than duration of use contributes to bacterial inhibition in the gut.[19] Cephalospirins had the highest ratio among antibiotics causative of CDI.[17] Although treatment of community-acquired pneumonia (CAP) with newer fluoroquinolones may contribute to selection for *C. difficile*, fluoroquinolones were not associated with increased acquisition rates for *C. difficile*.[20] Many of the fluoroquinolone-associated adverse effects and toxicities occur more frequently in patients with pre-existing risk factors. The risk of developing CDI was higher in patients receiving a combination of a cephalosporin and fluoroquinolone.[21] The present study revealed that only the use of cephalosporins increased CDAD.

It is estimated that 15-20% of patients experience CDI recurrence.[15] Relapse of CDAD is usually caused by the

Table 1 - Univariate analysis of risk factors for *Clostridium difficile*-associated diseases (mean ± SD)

	Case group (n = 93)	Control group (n = 186)	p-value
Age, years	63.0 ± 16.5	62.3 ± 16.9	NS
Gender, M/F	37/56	74/112	NS
Comorbidities			
Cardiovascular diseases	39 (41.9)	76 (40.9)	NS
Chronic lung diseases	27 (29.0)	17 (9.1)	< 0.001
Diabetes mellitus	23 (24.7)	33 (17.7)	NS
Renal failure	9 (9.7)	4 (2.2)	NS
Malignancy	17 (18.3)	20 (10.8)	NS
Presence of			
Ileus	13 (14.0)	4 (2.2)	< 0.001
ICU stay	26 (28.0)	6 (3.2)	< 0.001
Use of			
PPI	14 (15.1)	26 (14.0)	NS
H_2 blocker	59 (63.4)	151 (81.2)	0.002
Cephalosporins	37 (39.8)	17 (9.1)	< 0.001
Carbapenems	13 (14.0)	8 (4.3)	NS
Aminoglycosides	9 (9.7)	3 (1.6)	0.003
Macrolides	11 (11.8)	3 (1.6)	0.001
Quinolones	26 (28.0)	137 (73.7)	< 0.001
History of			
Prior hospitalization	63 (67.7)	87 (46.8)	0.001
Long-term care facility stay	23 (24.7)	5 (2.7)	< 0.001
Operation	35 (37.6)	10 (5.4)	< 0.001
Previous CDAD	10 (10.8)	2 (1.1)	< 0.001
Glucose > 150 mg/dL	18 (19.4)	40 (21.5)	NS
WBC count > 20 x $10^3/mm^3$	10 (10.8)	13 (7.0)	NS
ALT > 40 IU	15 (16.1)	16 (8.6)	NS
Cr > 2.0 mg/dL	7 (7.5)	7 (3.8)	NS
Albumin < 2.5 mg/dL	16 (17.2)	12 (6.5)	0.010

ICU, intensive care unit; PPI, proton pump inhibitor; CDAD, *Clostridium difficile*-associated diarrhea; WBC, white blood cell; ALT, alanine transferase; Cr, creatinine; SD, standard deviation.

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

Risk factor	Adjusted OR	95% CI	p-value
Chronic lung diseases	3.41	1.25-9.32	0.017
Presence of ileus	10.05	2.42-41.80	0.001
Presence of ICU stay	9.79	3.03-31.68	< 0.001
Use of H_2 blocker	0.30	0.13-0.69	0.005
Use of cephalosphorins	3.30	1.13-9.62	0.029
History of operation	10.89	3.96-29.92	< 0.001
History of long-term care facility stay	14.90	4.02-55.26	< 0.001

ICU, intensive care unit; OR, odds ratio.

original strain, and the etiology is multifactorial. Important epidemiologic risk factors include advanced age, continuation of other antibiotics, and prolonged hospital stays.[18] Patients with recent cephalosporin use, CDI on admission, and transfer from another hospital were more likely to fail metronidazole and may benefit from early aggressive therapy. Infection with the epidemic NAP-1 strain was not associated with metronidazole failure in endemic CDI.[22] Continued use of non-*C. difficile* antibiotics after diagnosis of CDI, concomitant prescription of antacid medications, and older age were significantly associated with increased risk of recurrent CDI.[15]

Evidence for the association between *C. difficile* and the use of PPIs is unclear. Whether or not antacids increase the risk of CDI is controversial, with negative and positive reports of antacids as risk factors. In theory, the decreased gastric acid associated with antacid use increases the risk for transit of *C. difficile* vegetative cells and spores to pass beyond the stomach and cause infection. It is thought that PPIs are more important risk factors than other anti-secretory agents.[15] This study, unlike previous reports, did not find PPIs to be a significant factor for CDAD, which is still controversial.

CDAD is also a recognized postoperative complication,[19] especially after total joint arthroplasty (TJA). In hospitalized patients, recent reports have observed a 30% increase in CDAD from 1984-1994 to 1994-2000, and a 3.5% to 15.3% increase in mortality from this complication during the same period.[19] The literature specific to CDAD in orthopedic patients is very limited. In the late 1980s and early 1990s, the discovery of the association between prophylactic antibiotic use and CDAD contributed to the universal recommendation of no more than three doses of prophylactic antibiotics before surgery.[19] The study by Kurd et al. suggests that patients with deteriorated physical status (ASA score, hospital duration), or those who receive more than one antibiotic after surgery are at a higher risk for developing CDAD after TJA.[19] In the present study, the patients who had a history of surgery had higher risk of CDAD. Among the surgeries, orthopedic surgery was the highest, followed by neurosurgery and gastrointestinal surgery. It is reasoned that the high rate of postoperative antibiotics use was the culprit. The most significant risk factor in surgical patients is the routine use of perioperative prophylactic antibiotics. Additionally, it is postulated that the postoperative population is more exposed to highly virulent hospital-acquired strains, and may be more immunosuppressed than typical patients.

Severe CDAD was associated with age > 70 years, maximum leukocyte count > 20,000 cells/mL, minimum albumin level < 2.5 g/dL, maximum creatinine level > 2 mg/dL, small bowel obstruction or ileus, and computed tomography scan showing colorectal inflammation.[23] Hypoalbuminemia and elevated serum urea levels were independently associated with mortality.[24] The present study demonstrated that hypoalbuminemia increased the tendency for CDAD. The organism has evolved over the last eight years to become more virulent and resistant to antimicrobials (NAP1/027 strain), causing a more severe form of the disease that has increased mortality and healthcare costs. The NAP-1 strain (also referred as ribotype 027, toxinotype III, or restriction endocuclease analysis group BI, depending on the typing method used) has since been found to carry certain virulence determinants that could contribute to an increase in disease severity. NAP-1 isolates from Quebec were found to produce 16 and 23 times as much toxin A and toxin B *in vitro*, respectively, as compared with historic non-NAP-1 isolates (toxinotype 0) of *C. difficile*. This increase in toxin production is thought to be due to deletion mutations of the tcd gene in the toxin production. The NAP-1 strain also produces a separate, third toxin named binary toxin, homologous to the iota toxin in *C. perfringens*. However, the role, if any, played by binary toxin in inducing severe CDI is currently unclear.[25] The B1/NAP/027 strain resistance to quinolone is important to the spread of this organism.[17] In Korea, this organism was first found in 2009. In addition, the incidence of tcdA-tcdB+ has increased from under 7% in 2002 to 27.0% in 2005. Therefore, the test should include both toxin A and B.[17]

Current guidelines recommend that the first recurrent episode should be treated with the same agent (i.e. metronidazole or vancomycin) used for the index episode. However, if the first recurrence is characterized as severe, vancomycin should be used. A reasonable strategy for managing a subsequent episode involves tapering followed by pulsed doses of vancomycin. Other potentially effective strategies for recurrent CDI include vancomycin with adjunctive treatments, such as *Saccharomyces boulardii*, rifaximin "chaser" therapy after vancomycin, nitazoxanide, fecal transplantation, and intravenous immunoglobulin. New treatment agents that are active against *C. difficile*, but spare critical components of the normal flora, may decrease the incidence of recurrent CDI.[18]

Rifamycins are now being considered for CDAD therapy based on *in vitro* susceptibility data. Hechat et al. reported rifampin resistance in three of 110 clinical isolates from the United States. The rifampin derivative rifaximin has emerged as an attractive potential therapy for CDAD because of its lack of systemic absorption. The high levels of rifaximin that can be achieved in the gut are an ideal pharmacologic profile for CDAD treatment. The rates of spontaneous rifaximin resistance based on agar dilution have been reported to be $< 10^{-9}$ at drug concentrations that are eight times the rifaximin MIC for *C. difficile*. Successful rifaximin treatment of patients experiencing a CDAD relapse has been reported. Exposure to rifamycins before the development of CDAD was a risk factor for rifampin-resistant CDI. The use of rifaximin may be limited for treatment of CDAD.[26] At the present time, oral bacteria/yeast products do not have a role in the prevention or therapy of CDI. Widespread use of some products may lead to blood stream infection (BSI) in susceptible individuals, and careless use of *S. boulardii* in an intensive care setting may place other patients at risk.[27]

A notable pattern found in the study by Marya et al. was that the regions with the higher incidence of CDAD (Northeast and Midwest) exhibited higher incidence of VRE in at least half of the study period, consistent with the observation that infection with CDAD can facilitate transmission of VRE.[28,29] This positive relationship should be further investigated. The similarity in the geographic distribution of IBD and *C. difficile* colitis could indicate the influence of *C. difficile* colitis in shaping the geographic patterns of IBD. It could also indicate that shared environmental risk factors influence the occurrence of IBD, as well as *C. difficile* colitis.[30] There are several prediction rules. In the RUWA (ratio of white cell count on the day of the positive CDT test to two days previously, urea, white cell count, and albumin on the day of the

positive CDT test) scoring system,[31] which is a novel predictive tool for the identification of patients at high risk for complications from CDI, negative predictive value was high (97.6%). Therefore, there is only a small chance that a severe case will not be identified using the RUWA system. White cell count (WCC) in the first three days is the strongest serum predictor of mortality and should be routinely monitored. A WCC of $20x10^9$/L or greater may be the best cutoff value to identify objectively cases at higher risk of death.[32] Prospective derivation and validation of a clinical prediction rule for recurrent *C. difficile* infection (age, horn index, additional antibiotic use, antitoxin A IgG < 1.29)[33] can be used in the future. In this study, relapse, treatment, mortality, outcome, and the virulence of the NAP strain, which are the limitations of this study, were not investigated. Future studies are expected to cover these subjects.

Effective prevention measures for *C. difficile* infection include contact isolation, antimicrobial stewardship, and proper room cleaning technique. Environmental sampling revealed the presence of spores on faecally contaminated equipment such as commodes and bedpan shells, which persisted after cleaning. Cleaning agents for clinical equipment must have sporicidal activity to prevent cross-transmission. More stringent control measures, including the addition of sodium hypochlorite to cleaning solutions and isolation of patients are required.[34] Diarrhea, when it is the only symptom in hospitalized patient should drive physicians to rethink about the possibility of CDI, especially in elderly patients. The prevalence of asymptomatic *C. difficile* carriage in an Irish continuing care institution for the elderly was 10%, 7% of which were toxin positive. This highlights the importance of increased vigilance for *C. difficile* using microbial and molecular methodology, and identifies patients at increased risk following antibiotic administration.[35] Identifying patients who are at high risk for severe CDAD early in the course of their infection may help clinicians improve outcomes. By studying this disease in different patient populations, researchers may uncover unique risk factors and associations, which may help to shed light on its pathogenesis. This study reveals the importance of evaluating different patient populations aiming for better understanding the pathogenesis of disease. Prudent use of antibiotics and infection control are strategies to prevent CDI in clinical setting. Awareness of CDI is critical to provide appropriate clinical care. The surveillance of the national incidence rate and multicenter studies are needed, and the potential value of a *C. difficile* vaccine should be studied.[36]

Conflict of interest

All authors declare to have no conflict of interest.

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