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Original Article

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Detection and characterization of *Clostridium difficile* infections tracking the trends of *Clostridium difficile* culture

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Abstract

Objectives: In this study, we examined the validity of *Clostridium difficile* culture results as a proxy measure of *Clostridium difficile* infection, and inferred the epidemiologic characteristics of *Clostridium difficile* infection by tracking the trends of *Clostridium difficile* culture results.

Methods: We reviewed the medical records to figure out the actual possibilities of *Clostridium difficile* infection of those with positive or negative results of *Clostridium difficile* culture during the time span from January 2012 to March 2012. We calculated the positive and negative predictive value of *Clostridium difficile* culture results for *Clostridium difficile* infection. Furthermore, epidemiologic characteristics of *Clostridium difficile* infection in a tertiary general hospital in 2012 were analyzed.

Result: The estimated positive predictive value of *Clostridium difficile* culture tests for *Clostridium difficile* infection was 100%, and the estimated negative predictive value was around 94.4~99.3% depending on the cutoff value of possibility of *Clostridium difficile* infection. A total of 622 cases were identified as *Clostridium difficile* infection in a tertiary general hospital in 2012 and there were 4.9 patients with *Clostridium difficile* infection per 1,000 inpatients.

Conclusion: In conclusion, we identified that *Clostridium difficile* culture results can be used as a proxy measure of *Clostridium difficile* infection.

Key words

Clostridium difficile infection, Patient safety indicator, Medical record review.

Ⅰ. Introduction

Clostridium difficile (C. difficile) is a gram positive anaerobic bacterium producing pathogenic toxins A and B [1]. *C. difficile* infection (CDI) is the abnormal proliferation of *C. difficile* in patients' guts following antibiotic treatment. CDI can be regarded as part of antibiotic-associated diarrhea, accounting for 15~20% of antibiotic-associated diarrhea [2]. Symptoms of CDI include diarrhea, abdominal pain, fever, leukocytosis, hypoalbuminemia, and paralytic ileus or toxic megacolon in severe cases [3].

The worldwide incidence of CDI is on the rise, especially in North America [4, 5] as well as its severity [6, 7]. The incidence of CDI in Korea is also rising, and according to a study at a hospital, the number of CDI patients per 10,000 inpatients increased from 1.9 in 1998 to 8.8 in 2007 [8]. Also, according to a study including patient data from 17 hospitals, the incidence of CDI rose with statistical significance from 1.7 cases per 1,000 adult inpatients in 2004 to 2.7 cases in 2008 [9]. Furthermore, the number of deaths due to CDI also rose from 69 in 2008 to 172 in 2011[10]. In addition, 37.5% of the 200 CDI patients were in a severe condition [11]. The economic burden due to *C. difficile* is also continuously increasing, from 7.6 million dollars in 2009 to 10.5 million dollars in 2010 and 15.8 million dollars in 2011[10].

Many studies on the epidemiology of CDI are being published nowadays, but a continuous tracking of such epidemiologic data is necessary [12]. However, since many studies on CDI epidemiology are based on medical record review, which require lots of time and effort, there might be some limitations in conducting studies with more patients and for longer periods of time [8, 9, 11].

This study aims to estimate the scale of CDI using ABLE (Asan BiomedicaL research Environment) by tracking the trends of *C. difficile* culture. Specifically, we aim to examine the validity of *C. difficile* culture results as a proxy measure of CDI, and to infer the epidemiologic characteristics of CDI by tracking the trends of *C. difficile* culture results.

Ⅱ. Methods

Evaluating the validity of Clostridium difficile for CDI

In this study, we mainly used ABLE to collect data. ABLE is a real-time search system with large platform as its core function, developed to anonymize personal identity information so that clinical information of study participants can be used for clinical studies with secondary purposes [13, 14]. ABLE allows researchers to conduct clinical studies and protect personal information of study participants at the same time.

In this study, CDI was defined as any positive outcome in the *C. difficile* culture or stool cytotoxin assay with the presence of antibiotic-associated diarrhea. To estimate CDI using the culture results of *C. difficile*, we first used ABLE to check the culture results of *C. diffi-*

cile at a tertiary general hospital in 2012. All inpatients were included in the study, without limitations on age or department. We reviewed the medical records to figure out the actual possibilities of CDI among those with positive results of *C. difficile* culture during the time span from January 2012 to March 2012 and calculated the positive predictive value of *C. difficile* culture results for CDI. Specifically, we determined the presence of antibiotic-associated diarrhea through medical record review. If a patient had antibiotic-associated diarrhea, we considered the possibility of CDI as high. However, if a patient had diarrhea irrelevant to antibiotics, we regarded the possibility of CDI as low. If there was no record of diarrhea, we assumed that there was no possibility of CDI. Antibiotic-associated diarrhea was defined as diarrhea solely attributable to antibiotic use and diarrhea was defines as more than 3 unformed stools per day for 2 consecutive days or defecating 6 times within 36hours [11]. The criteria for positive growth of *C. difficile* was defined as any growth of the bacteria in stool.

We also chose those with negative results of *C. difficile* growth presenting similar features to CDI positive patients during the same time span in a one-to-one corresponding manner and reviewed their medical records to see if they were CDI positive or not. We used the probit regression model in matching the patients. Patients' sex, age, antibiotics use, and duration of hospitalization were independent variables while the test results of *C. difficile* culture were dependent variables in calculating predicted probability of the positive results of *C. difficile* culture in each patient. Culture negative patients with predicted probability values closest to culture positive patients were chosen in one-to-one correspondence. The chosen patients with negative culture results were reviewed whether they had diarrhea or not, and if their diarrhea is a clinical expression of CDI to calculate the negative predictive value of *C. difficile* culture. One author first reviewed the medical records and the other reconfirmed the results.

Analyzing the epidemiologic characteristics of CDI

Epidemiologic characteristics of CDI in a tertiary general hospital in 2012 were analyzed based on the validity test results of using *C. difficile* culture test outcomes as a proxy measure for CDI. In specific, patients' sex, age, and time period and hospitalization period before CDI as well as antibiotics relatedness were analyzed. Data were processed by Excel, and all analysis such as technical statistical analysis were done with Stata 13.1. This study was reviewed by the Institutional Review Board of Asan Medical Center (S2016-0135-0001).

III. Results

Validity of Clostridium difficile for CDI

There were 136 patients with positive *C. difficile* culture results during the time period from January 2012 to March 2012. A total of 136 patients with negative test results for *C. difficile* culture who had the closest predicted prob-

ability values to positive *C. difficile* culture were also chosen from the same time period using the probit regression analysis. We reviewed the medical records of these 272 patients to see whether they had CDI or not, which is shown in Table 1. All 136 patients who showed positive results for *C. difficile* culture had high probability of CDI based on their medical records. On the other hand, among 136 patients who showed negative results for *C. difficile* culture, 128 had no possibility of CDI, while 7 had low possibility and 1 had high possibility.

Table 1. Validity of *Clostridium difficile* culture for Clostridium difficile infection

		Possibility of *Clostridium difficile* infection based on the chart review			Total
		High	Low	No	
Clostridium difficile culture	Positive	136	0	0	136
	Negative	1	7	128	136
Total		137	7	128	272

Based on such results, the estimated positive predictive value of *C. difficile* culture test for CDI is 100% (95% confidence interval (CI), 97.2–100.0%). The estimated negative predictive value for CDI differs depending on the cut-off point of CDI possibility based on medical records—94.4% (95% CI, 89.3–97.6%) when low possibilities of CDI is regarded as CDI, and 99.3% (95% CI, 96.0–100.0%) when only high possibilities of CDI is regarded as CDI.

Analysis of the epidemiologic characteristics of CDI

There were a total of 622 CDI patients in a tertiary general hospital in 2012 when using the proxy measure of *C. difficile* culture results based on the validity evaluation of CDI estimation (Table 2). This is equivalent to 4.9 CDI patients per 1,000 inpatients. Among them, 350 (56.3%) were male and 272 (43.7%) were female. Average age was 55.1 (standard deviation 22.3, median 61). Those in their 70s took the largest share with 147 (23.6%) patients, followed by 60s (130, 20.9%), and 50s (104, 16.7%). The average hospitalization days before CDI occurrence was 27.0 days (standard deviation 121.4, median 11), most cases fell within the range of 0–9 days (288, 46.3%), followed by 10–19 days (168, 27.0%), and 20–29 days (66, 10.6%). Forty-nine (7.9%) were ICU patients, 493 (79.3%) were in the internal medicine department, and 129 (20.7%) were in the surgical department. Neoplasm, being the primary diagnosis for 293 patients (47.1%), was the leading cause of hospitalization, followed by GI tract diseases (91, 14.6%), and urinary tract diseases (60, 9.6%).

In the case of antibiotics use, the majority of patients (242, 38.9%) were on a single antibiotic (Table 3). A total of 136 (21.9%) were on two antibiotics, 33 (5.3%) on three or more, and 211 (33.9%) did not have any antibiotics. In specific, 189 (30.5%) were on cephalosporins, followed by carbapenems (110, 17.8%) and glycopeptides (107, 17.3%).

Figure 1 shows weekly variation of CDI (Figure 1). There were on average 11.7 CDI patients each week, with standard deviation of 4.4. Thus, more than 20.5 patients in a week can be concluded as an outlier, defined as more than 2 standard deviation away from the average.

Table 2. Characteristics of *Clostridium difficile* infection patients

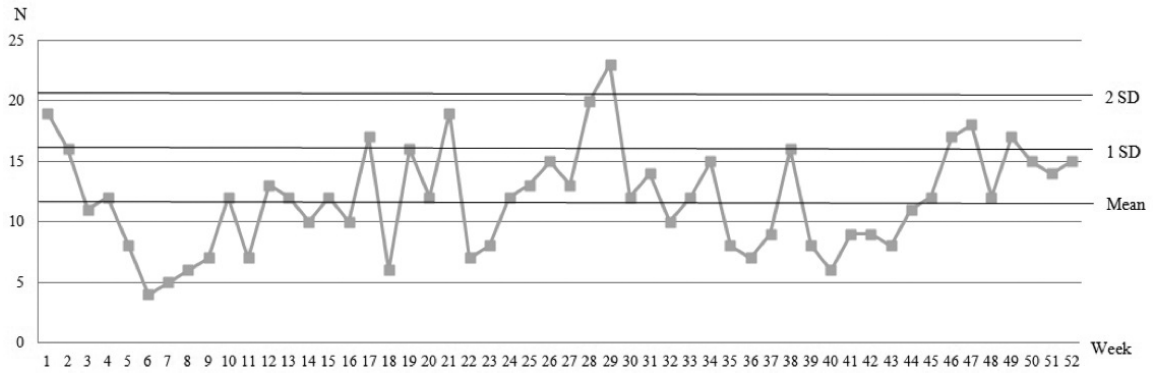
N (%)

Gender	Man	350 (56.3)
	Woman	272 (43.7)
Age group	0-9	35 (5.6)
	10-19	30 (4.8)
	20-29	34 (5.5)
	30-39	41 (6.6)
	40-49	54 (8.7)
	50-59	104 (16.7)
	60-69	130 (20.9)
	70-79	147 (23.6)
	80-	47 (7.6)
Length of stay before *Clostridium difficile* culture positive	0-9	288 (46.3)
	10-19	168 (27.0)
	20-29	66 (10.6)
	30-39	100 (16.1)
Ward	General ward	573 (92.1)
	Intensive care unit	49 (7.9)
Treatment unit	Medical unit	493 (79.3)
	Surgical unit	129 (20.7)
Classification of diagnosis	Neoplasms	293 (47.1)
	Digestive	91 (14.6)
	Genitoruinary	60 (9.6)
	Cardio and cerebrovascular	52 (8.4)
	Respiratory	49 (7.9)
	Endocrine and metabolic	20 (3.2)
	Others	57 (9.2)
Total		622 (100.0)

Table 3. Antibiotic exposure in the *Clostridium difficile* infection patients

N (%)

Combination of antibiotics	No use	211 (33.9)
	One	242 (38.9)
	Two	136 (21.9)
	More than three	33 (5.3)
Classification	Cephalosporins	189 (30.5)
	Carbapenem	110 (17.8)
	Glycopeptides	107 (17.3)
	Penicillin/beta-lactamase inhibitor	103 (16.6)
	Quinolones	76 (12.3)
	Aminoglycosides	6 (1.0)
	Others	28 (4.5)
Total		622 (100.0)



SD, standard deviation

Figure 1. Weekly variation of *Clostridium difficile* infection

Ⅳ. Discussion

In this study, we reviewed the medical records to evaluate the validity of using *C. difficile* culture results as a proxy measure of CDI, and understood the epidemiologic characteristics of CDI using *C. difficile* culture results. The estimated positive predictive value of *C. difficile* culture tests for CDI was 100%, and the estimated negative predictive value was around 94.4~99.3% depending on the cutoff value of the possibility of CDI. Using the *C. difficile* culture results as a proxy measure for CDI, the computed total number of CDI in a tertia-

ry general hospital in 2012 was 622 and there were 4.9 CDI patients per 1,000 inpatients.

Generally, CDI is suspected when high risk patients, such as patients on antibiotics, have three or more events of clinically significant diarrhea or ileus within 24 hours [15]. It is diagnosed through various methods including *C. difficile* toxin assays, *C. difficile* culture tests, or endoscopies. In this study, *C. difficile* culture results were used as primary diagnostic method for CDI. The sensitivity and specificity of *C. difficile* culture results are reported to be 90~100% and 77~100%, respectively [16-18], and they are similar to the results obtained from this study, which estimated sensitivity to be 94.4~99.3% and specificity as 100%.

A total of 622 CDI patients were identified in a tertiary general hospital in 2012 in this study, which is higher than the CDI incidence rate concluded from other studies conducted in Korea. For instance, there were a total of 1,367 CDI patients according to a study including 17 hospitals, which is equivalent to 2.7 CDI per 1,000 adult inpatients [9]. In addition, according to a study using the claims data of Health Insurance Review and Assessment Service, a total of 700 CDI patients in 2008, and 2521 CDI patients in 2011 were identified [10]. Although there are only a handful of data on the epidemiology of CDI, using only the claims data to estimate CDI incidence seems to be underestimating. Furthermore, it is likely that the CDI incidence in Korea is also rising as is the case in Western countries [4, 5]. Thus, it is reasonable to conclude that CDI will become an important issue in patient safety in Korea as well.

Since CDI is recognized as an adverse event caused by antibiotics [19], and can be reduced by minimizing antibiotics use [20], we can put effort to reduce CDI through regular monitoring. Regular monitoring of CDI is important because *C. difficile* can be found anywhere in the hospital and sanitary measures such as isolation of CDI patients are essential. However, this requires a lot of effort since making a clinical decision of whether a patient has diarrhea and ruling out other causes of diarrhea are necessary for the clinical suspicion of CDI. It seems like using only the results of *C. difficile* culture tests in regular monitoring of CDI is meaningful regarding the result of this study that *C. difficile* culture results have high validity to be used as a proxy measure for CDI and that *C. difficile* culture tests are being used as a Global Trigger Tool for adverse events [19].

Antibiotics use, long hospitalization period, age, and comorbidities are among the known risk factors of CDI [15]. In the case of age, the CDI incidence for 65 years or older is reported as 5 times that of 45-64 age group, and 20 times that of 15-45 age group [21]. In this study too, patients older than 60 years comprised 52.1% of the total patient group. In the case of antibiotics, ampicillin, amoxicillin, cephalosporins, clindamycin, and fluoroquinolones are among those known to be highly related to CDI [22]. In this study, 30.5% of all patients were using cephalosporins. Carbapenems,

whose relatedness to CDI is not well known, were used in 17.8% of all patients in this study. Further study clarifying if this is related to the underlying disease or the antibiotic use is required. In addition, it is known that combined use of antibiotics has higher risk to CDI than single use [23]. In this study, one out of four patients was on combined therapy.

In this study, we searched for the comorbidity of CDI patients, which in almost 50% of the cases were cancer. Cancer chemotherapy is also known to be a risk factor of CDI, and it is regarded that the antimicrobial effect or immunosuppressive effect of chemotherapeutic agents are related to CDI [24]. Thus, if a patient receiving cancer chemotherapy develops diarrhea, it is reasonable to suspect CDI primarily. Meanwhile, it is reported that there is seasonal variation in CDI, with higher incidence in winter [25]. However, in this study, which was limited to a single year of 2012, we did not find any results to suspect seasonal variation.

There are two limitations to this study. First, there might have been some limitations in evaluating CDI due to imperfections of medical records. Especially, there were several cases in which CDI was clinically suspected but the test results were incomplete. Such cases might have caused us to underestimate the CDI incidence. Second, there might be some limitations in generalizing the results of this study since it was only based on the data from a single tertiary general hospital. Further studies including multiple centers would be necessary.

In conclusion, we identified that *C. difficile* culture results can be used as a proxy measure of CDI. We expect enhanced patient safety levels by managing CDI regularly and in real-time based on the results of this study.

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