Annals of Clinical Microbiology www.acm.or.kr

Original Article

Clinical and Microbiological Risk Factors for Community-Associated *Clostridioides difficile* Infections

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지역사회 연관 *Clostridioides difficile* 감염의 임상적, 미생물학적 위험인자

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ABSTRACT

Background: The incidence of community-associated (CA) *Clostridioides difficile* infection (CDI) has increased in Korea. In this study, we evaluated CA-CDI risk factors in terms of clinical features and ribotype considering its region-specific molecular epidemiology.

Methods: A retrospective case-control study was performed on two groups of CDI patients: 127 subjects with CA-CDI and 265 subjects with healthcare-associated (HA)-CDI. Risk factors for CA-CDI were evaluated in terms of clinical and microbiological features such as toxin type and ribotype.

Results: A comparison of the two groups of CDI patients revealed that inflammatory bowel disease, diarrhea, abdominal pain, and fever were more closely associated with CA-CDI. The toxin types and ribotypes of *C. difficile* were similar between the two groups. After adjusting for variables, no risk factors were identified for CA-CDI compared with HA-CDI.

Conclusion: Specific risk factors for CA-CDI were not identified in this study.

Keywords: *Clostridioides difficile* infection, Community-associated, Risk factor

pISSN : 2288-0585
eISSN : 2288-6850

Ann Clin Microbiol 2022 June, 25(2): 53-58
https://doi.org/10.5145/ACM.2022.25.2.3

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Received: March 15, 2022
Revised: April 27, 2022
Accepted: April 27, 2022

INTRODUCTION

Clostridioides difficile causes infectious diarrhea with disease severity ranging from mild to severe [1]. Although the incidence and mortality rate of *C. difficile* infection (CDI) have increased dramatically worldwide since 2003 with the emergence of binary toxin-producing ribotype 027 strains [2], this type is not prevalent in Korea [3]. Although CDI has been regarded as a healthcare-associated (HA) disease entity, the incidence of community-associated (CA) cases has increased since 2011 [4]. This shift was observed in recent epidemiologic data from Korea, showing that CA-CDI accounted for 19.4% of all cases of CDI [3].

In this study, CA-CDI risk factors were evaluated in aspects of not only clinical features, but also ribotypes, considering region-specific molecular epidemiology. A retrospective case-control study was performed to compare patient characteristics, prognosis, and risk factors for CA-CDI.

MATERIALS AND METHODS

Study population and definition

All patients who visited Ilsan Hospital or Gangnam Severance Hospital in 2018 who were diagnosed with CDI based on *C. difficile* culture were included in this study. We only included the first infection during the study period to avoid duplication. This retrospective case-control study was done with two groups: CA-CDI (n = 127) and HA-CDI (n = 265). CA case was defined if the case occurred within 48 hours of hospital admission and the patient had not been admitted to a healthcare facility in previous 12 weeks. Others were regarded as HA cases in this study.

Clinical features were obtained by reviewing electronic medical records. Variables included age, sex, associated disease, history (within 12 weeks) of antimicrobials, history (within 12 weeks) of chemotherapy, history (within 12 weeks) of proton pump inhibitor, sites of acquisition, CDI treatments, history of CDI (within 12 weeks), recurrence after eight weeks, death, toxin type, and ribotype of *C. difficile*.

Molecular study

Toxin production and molecular epidemiology were determined with polymerase chain reaction (PCR)-sequencing as described in a previous study [3]. For toxin A and B genes, primer pairs used were *tcd*A-F and *tcd*A-R for *tcd*A, NK104 and NK105 for *tcd*B, *cdt*A-pos and *cdt*A-rev for *cdt*A, and *cdt*B-pos and *cdt*B-rev for *cdt*B. PCR ribotyping was performed as previously described with primers CD1-CD1445 [3]. A comparison of PCR ribotyping patterns was performed visually with known standards (VPI 10463, UK078, 48489ATCC9689, ATCC43598, and ATCC70057). Ribotype patterns that differed by at least one band were assigned to different types. Multilocus sequence typing (MLST) was performed using a scheme previously described by Griffiths et al. [5], using seven housekeeping genes (*adk, atp*A, *dxr, gly*A, *rec*A, *soda,* and *tpi*). PCR reactions for these seven loci were performed and amplicons were sequenced with forward and reverse primers. DNA sequences were submitted to MLST database (https://pubmlst.org/cdifficile/) to obtain sequence type.

Statistical analysis

A continuous variable such as age was analyzed using the Mann-Whitney U test. Chi-squared test was used for comparative analysis of categorical variables to determine independent risk factors. Odds ratio and 95% confidence interval values were calculated for binomial variables. Variables with *P* values of less than 0.1 in univariate analyses were included in a multivariate logistic regression analysis model to determine independent risk factors. Statistical significance was defined at $P < 0.05$. SPSS 23.0 software (IBM Corp., Armonk, NY, USA) was used for univariate analyses and multivariate analyses. This study was approved by our institutional review board as required by the hospital policy (IRB No. NHIMC-2020-05-015).

RESULTS

Comparison of CA-CDI and HA-CDI

When two groups of CDI were compared, inflammatory bowel disease (6.3% in CA-CDI vs. 0.4% in HA-CDI, $P = 0.0070$), diarrhea (66.1% in CA-CDI vs. 46.0% in HA-CDI, $P = 0.0002$), abdominal pain (22.8% in CA-CDI vs. 10.9% in HA-CDI, $P = 0.0023$), and fever (20.5% in CA-CDI vs. 12.5% in HA-CDI, $P = 0.0394$) occurred more in the CA-CDI group (Table 1).

However, older age (66.9±18.9 years in CA-CDI vs. 72.1±13.5 years in HA-CDI, $P = 0.0064$), cerebrovascular disease (5.5% in CA-CDI vs. 12.8% in HA-CDI, $P = 0.0314$), past history of any antimicrobial use (81.9% in CA-CDI vs. 92.1% in HA-CDI, $P = 0.0036$), inhibitor combination use (9.5% in CA-CDI vs. 22.6% in HA-CDI, $P = 0.0022$), carbapenem use (7.1% in CA-CDI vs. 17.4% in HA-CDI, $P = 0.0080$), fluoroquinolone use (12.6% in CA-CDI vs. 21.9% in HA-CDI, $P = 0.0298$), and teicoplanin use (3.2% in CA-CDI vs. 14.7% in HA-CDI, $P = 0.0019$) were more frequent in the HA-CDI group (Table 1). Toxin types and ribotypes of *C. difficile* were similar to each other between the two groups.

Table 1. Comparison between CA-CDI and HA-CDI groups

Variables	CA-CDI (n = 127)	HA-CDI (n = 265)	*P*-value
Age (yr)	66.9±18.9	72.1±13.5	**0.0064**
Sex, male	51 (40.2)	120 (45.3)	0.3386
Charlson comorbidity index	2.4±2.1	2.7±1.9	0.1109
Associated disease			
Biliary tract disease	3 (2.4)	8 (3.0)	0.7133
Cancer	22 (17.3)	59 (22.3)	0.2593
Pneumonia	18 (14.2)	57 (21.5)	0.0863
Heart failure	5 (3.9)	8 (3.0)	0.6357
Chronic respiratory disease	5 (3.9)	22 (8.3)	0.1185
Chronic renal disease	24 (18.9)	42 (15.9)	0.4508
Diabetes mellitus	23 (18.1)	38 (14.3)	0.3361
Cerebrovascular disease	7 (5.5)	34 (12.8)	**0.0314**
Alcohol disorder	5 (3.9)	4 (1.5)	0.1481
Osteoarthritis	0	4 (1.5)	0.9836
Atherosclerosis	4 (3.2)	9 (3.4)	0.8985
Esophageal disorder	1 (0.8)	8 (3.0)	0.2000
Nutrition deficiency	1 (0.8)	4 (1.5)	0.5580
Inflammatory bowel disease	8 (6.3)	1 (0.4)	**0.0070**
Gastric ulcer	2 (1.6)	10 (3.8)	0.2518
History of antimicrobial use			
Any	104 (81.9)	244 (92.1)	**0.0036**
Penicillin	28 (22.1)	73 (27.6)	0.2448
Narrow-spectrum cephalosporin	12 (9.5)	37 (14.0)	0.2090
Extended-spectrum cephalosporin	31 (24.4)	69 (26.0)	0.7293
Inhibitor-combination	12 (9.5)	60 (22.6)	**0.0022**
Carbapenem	9 (7.1)	46 (17.4)	**0.0080**
Fluoroquinolone	16 (12.6)	58 (21.9)	**0.0298**
Teicoplanin	4 (3.2)	39 (14.7)	**0.0019**
Aminoglycoside	0	5 (1.9)	0.9880

Table 1. Comparison between CA-CDI and HA-CDI groups (continued)

Variables	CA-CDI (n = 127)	HA-CDI (n = 265)	*P*-value
History of PPI use	13 (10.2)	34 (12.8)	0.4603
History of chemotherapy	13 (10.2)	28 (10.6)	0.9209
CDI-associated symptom			
Diarrhea	84 (66.1)	122 (46.0)	**0.0002**
Abdominal pain	29 (22.8)	29 (10.9)	**0.0023**
Fever (> 38°C)	26 (20.5)	33 (12.5)	**0.0394**
Prognosis			
Recovery	112 (88.9)	224 (84.5)	0.2486
Recurrence	4 (3.2)	15 (5.7)	0.2855
ICU admission	3 (2.4)	19 (7.2)	0.0677
Crude mortality	14 (11.0)	44 (16.6)	0.1559
C. difficile toxin			
$A^+B^+CDT^-$	115 (90.6)	232 (87.6)	0.3826
B only	8 (6.3)	22 (8.3)	0.4852
$A^+B^+CDT^+$	4 (3.2)	11 (4.2)	0.6286
Ribotypes of *C. difficile*			
AB24 (ST129)	3 (2.4)	8 (3.0)	0.7133
AB25 (ST102)	5 (3.9)	8 (3.0)	0.6357
Ribotype 001	6 (4.7)	16 (6.0)	0.5979
Ribotype 002	12 (9.5)	17 (6.4)	0.2856
Ribotype 012	8 (6.3)	14 (5.3)	0.6828
Ribotype 014/020	17 (13.4)	43 (16.2)	0.4654
Ribotype 017	5 (3.4)	18 (6.8)	0.2660
Ribotype 018	29 (22.8)	58 (21.9)	0.8318
Ribotype 046	4 (3.2)	18 (6.8)	0.1523
Ribotype 070	3 (2.4)	4 (1.5)	0.5540
Ribotype 106	8 (6.3)	14 (5.3)	0.6828
Others*	27 (21.3)	47 (17.7)	0.4046

Data are presented in number (%) or mean±standard deviation; Bold format indicates statistical significance.

*Others included AB11, AB15, AB21, AB23, AB27, AB30, AB32, AB33, AB37, AB38, AB39, AB43, AB45, AB47, AB59, AB62, AB72, AB84, AB85, AB86, AB89, C29, C3, C31, R020, R023, R027, R078, R081, R087, R088, R103, R137, R159, R161, R163, and R369.

Abbreviations: CDI, *C. difficile* infection; CA, community-associated; HA, healthcare-associated; PPI, proton pump inhibitor; ICU, intensive care unit; CDT, binary toxin; ST, sequence type.

The risk factors of CA-CDI over HA-CDI

After variables such as age, underlying diseases (pneumonia, cerebrovascular disease, inflammatory bowel disease), past antimicrobial use (inhibitor combination, carbapenem, fluoroquinolone, teicoplanin), CDI-related symptoms (diarrhea, abdominal pain, fever), and intensive care unit admission were adjusted for, no risk factor for CA-CDI over HA-CDI was found.

DISCUSSION

Transmission of *C. difficile* could be plausibly sustained by asymptomatically colonized persons in the community or exposure to animal reservoirs [6]. Under-reporting and systematic misclassification might

also underplay the role of community transmission because the potentially long incubation period can make patients display symptoms for the first time in a healthcare facility [7]. According to the present study, the infection should be classified as being acquired prior to admission if symptoms begin within five days of admission. However, we used the commonly recommended two-day cut-off [8].

Although specific risk factors associated with CA-CDI were not found in multivariate analysis, inflammatory bowel disease and CDI-related symptoms (diarrhea, abdominal pain, and fever) were more commonly found in the CA-CDI group. One study has shown that the CDI-CA group tends to be younger and healthier than the HA-CDI group [7]. It has been suggested that those with CDI-CA might be at a higher risk for recurrence than those with HA-CDI [7]. In this study, we could not find a difference in recurrence rate or recovery between the two groups. However, age was younger in the CA-CDI group, consistent with the previous study [7].

The increase of CDI occurring among persons without recent hospitalizations or stays in a long-term care facility could be another challenge to national efforts for reducing CDI with infection prevention and antibiotic stewardship [9]. Great use of outpatient antimicrobials is a well-known contributing factor of CA-CDI [10], but the past antimicrobial use was not a significant risk factor for CA-CDI over HA-CDI after adjustment in this study. The limitation of study is that antimicrobial use was evaluated only according to the electronic medical record findings and deep interview need to be included not to miss the antimicrobial use in other clinics. Although antimicrobial prescription has decreased after the Korean government has implemented a series of healthcare policies, most (72%) of total orders are administered in clinics [11]. Although changing prescribing behaviors can be challenging, we need to force guidelines to optimize antimicrobial therapy in outpatient settings.

요약

배경: 지역사회 관련(community-associated, CA) *Clostridioides difficile* 감염(CDI)이 국내에서 증가하고 있다. 본 연구에서는 CA-CDI의 위험 요인을 임상적 특징과 ribotype을 포함한 지역 특이 분자역학을 고려하여 평가하고자 한다.

방법: 후향적 환자-대조군 연구로 환자군 CA-CDI 127명과 대조군 의료 관련 CDI 265명을 비교하였다. CA-CDI 관련 위험 인자는 임상적 특징과 독소형 및 리보형과 같은 미생물학적인 특성을 포함하여 분석하였다.

결과: 염증성 장질환, 설사, 복통, 발열은 CA-CDI와 더 관련이 있었다. 독소형과 ribotype은 두 그룹 사이에서 서로 유사했다. 변수를 조정한 후에는 CA-CDI와 연관된 의미있는 위험 인자가 없었다.

결론: CA-CDI와 관련된 특정 위험 인자는 본 연구에서 확인되지 않았다.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

ACKNOWLEDGEMENTS

We would like to thank So Ra Yoon (Ph.D., Research Institute of National Health Insurance Ilsan Hospital) for providing help on statistical analyses.

FUNDING

This research was supported by a research grant (2017E4400202) from Korea Centers for Disease Control and Prevention.

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