Master of Medicine

Clinical characteristics and prognostic factors for extraintestinal infection caused by *Clostridioides difficile* : analysis of 60 consecutive cases

Clostridioides difficile 에 의한 장외 감염의 임상적 특징과 치료 결과에 관한 연구

The Graduate School
of the University of Ulsan
Department of Medicine
Hyemin Chung

Clinical characteristics and prognostic factors for extraintestinal infection caused by *Clostridioides difficile* : analysis of 60 consecutive cases

Supervisor: Sang-Ho Choi

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Hyemin Chung

Department of Medicine
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This certifies that the master's thesis of Hyemin Chung is approved

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Committee Chairman Professor Heungsup Sung

Committee Member Professor Sang-Ho Choi

Committee Member Professor Min Jae Kim

Department of Medicine
Seoul, Korea
February 2020

ABSTRACTS

Background: Whereas *Clostridioides difficile* enterocolitis has been well studied, data regarding extraintestinal *C. difficile* infection (ECDI) remain scarce and anecdotal. I investigated characteristics and prognostic factors in patients with ECDI at a large university hospital over a recent 21-year period.

Methods: I conducted a retrospective cohort study of patients at a 2,700-bed tertiary care hospital from January 1997 through December 2018 whose extraintestinal clinical specimen revealed *C. difficile*. Gastrointestinal (GI) disruption was defined as compromised integrity of the GI tract by abdominal surgery, perforation, malignancy, enterocolitis, or bleeding. Patients were divided into 3 groups: group A (GI disruption caused by malignancy, n = 13); group B (GI disruption without malignancy, n = 25); group C (No GI disruption, n = 22). The main outcome was 30-day all-cause mortality.

Results: A total of 60 patients were enrolled, and the incidence of ECDI was 2.53 per 100,000 admissions. Median age was 58 years and 36 (60.0%) of the patients were men. The most common specimens were blood (n=22, 36.7%), followed by peritoneal fluid (n=12, 20.0%), abscess (n=10, 16.7%), and infected tissue (n=9, 15.0%). Six patients (10.0%) had confirmed *C. difficile* enterocolitis, and 36 patients (60.0%) had a polymicrobial infection. *C. difficile* bacteremia was significantly more common in group A (53.8% [7/13]) than groups B (48.0% [12/25]) or C (13.6% [3/22]) (p = 0.02). Thirty-day mortality rates were also significantly higher in group A than groups B or C (69.2% [9/13] vs. 12.0% [3/25] and 18.2% [4/22], respectively; $p < 0.001$). *C. difficile* bacteremia (p = 0.20), polymicrobial infection (p = 0.81), and antimicrobial therapy for *C. difficile* (p = 0.29) were not significantly associated with 30-day mortality. In multivariate analysis, group A (adjusted odds ratio [aOR], 17.32; 95% confidence interval [CI], 2.96-101.21; p = 0.002) and age of > 65 years (aOR, 7.09; 95% CI, 1.31-38.45; p = 0.02) were independent risk factors for 30-day mortality.

Conclusion: ECDI was not commonly associated with *C. difficile* enterocolitis. GI

disruption with malignancy and old age was associated with significantly poorer outcomes.

Keywords: *Clostridioides difficile*, bacteremia, enterocolitis, cancer.

Author: Hyemin Chung

Affiliation: Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine

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INTRODUCTION

Clostridioides difficile is one of the leading causes of nosocomial infection, contributing to estimated 10-25% of antibiotics-associated diarrhea.[1)] It has been recognized that the rate of community-associated *C. difficile* infections (CDIs) has also been rising.[2-5)] CDI can lead to a high mortality rate up to 30%,[6, 7)] and represent a significant economic burden on the global healthcare system.[8, 9)] In South Korea, CDI prevalence and the economic cost was estimated to have increased as 5.06 per 100,000 persons and $15.8 million in 2011, respectively.[10)]

Although *C. difficile* enterocolitis is known to be the predominant presentation type of CDI, it has been reported that *C. difficile* could also cause extraintestinal infections including bacteremia, osteomyelitis, skin and soft tissue infection, visceral abscess, and pyogenic arthritis, which can lead to poor outcomes.[11-22)] Several investigations suggested that most of the extraintestinal *C. difficile* infections (ECDIs) are preceded by gastrointestinal (GI) disruption, either colitis or surgical and anatomical disruption of colon[15, 16, 18)] and more than half of patients with ECDI had serious underlying diseases, most common of which were malignant tumors.[17, 18)] However, those studies were small-sized and the prevalence, clinical characteristics, outcomes of ECDI have not been analyzed adequately yet. Therefore I investigated clinical characteristics and prognostic factors in patients with ECDI, in a tertiary care hospital over a recent 21-year period. Special emphasis was placed on the role of GI disruption or underlying malignant disease.

METHODS

Study design, patient selection, and data collection

I conducted a retrospective cohort study at Asan Medical Center, a 2,700-bed tertiary care hospital in Seoul, Republic of Korea. Using a computerized database of clinical microbiology unit, patients whose extraintestinal site cultures had yielded *C. difficile* from January 1997 through December 2018 were identified. In recurrent or relapse cases, only the first ECDI event was included. Then, I reviewed the electronic medical record of these patients and collected data regarding patients' demographic characteristics, clinical characteristics, and outcomes. The study was approved by the Institutional Review Board of Asan Medical Center (2019-1148).

Definitions and patient categorization

ECDI was defined as the isolation of *C. difficile* from extraintestinal sites such as blood, peritoneal fluid, abscess fluid, pleural fluid, tissue or wound discharge. GI disruption was defined as compromised integrity of the GI tract mucosa by abdominal surgery, perforation, malignancy, enterocolitis or bleeding.[23] Polymicrobial infection was defined as the isolation of more than one organism from the same culture specimen. *C. difficile* enterocolitis was diagnosed when patients with diarrhea had at least one of the following positive tests: *C. difficile* stool culture, toxin enzyme immunoassay, polymerase chain reaction (PCR), or endoscopic findings revealing typical pseudomembrane.[24] PCR was available since October 2015. Place of the acquisition was classified as the following two groups; community-onset infection, or hospital-acquired infection. Then community-onset infection was categorized into community-acquired or healthcare-associated infection, as previously described.[25] Patients who received corticosteroid treatment for more than 2 weeks, cytotoxic chemotherapy or antirejection drugs for more than 1 week were considered to be on immunosuppressive therapy.[26] The severity of the disease was measured on the culture day

by Acute Physiology and Chronic Health Evaluation (APACHE) II Score.[27] The severity of the underlying disease was evaluated by Charlson comorbidity score.[28] Adequate antibiotics for ECDI were defined as oral or intravenous (IV) metronidazole, IV vancomycin or IV teicoplanin according to antimicrobial susceptibility of *C. difficile*.[29, 30] According to the presence or absence of GI disruption and malignancy, patients were categorized into three groups: group A (GI disruption caused by malignancy), group B (GI disruption without malignancy), and group C (No GI disruption). The primary outcome was 30-day all-cause of mortality.

Identification of C. difficile isolates

Conventional anaerobic culture techniques were used to isolate *C. difficile* in extraintestinal sites. Blood samples were processed by the hospital microbiology laboratory using a standard blood culturing system BACTEC FX (Becton-Dickinson, MD, USA). Fluid samples were inoculated into Brucella agar and incubated in an anaerobic chamber or commercial pouch. Tissue specimens were inoculated into enriched thioglycolate broth for the isolation. Then species were identified by gram stain, colony morphology, Vitek ANC card (bioMerieux, Marcy I'Etoile, France), and MALDI-TOF MS (Bruker Daltonik, Bremen, Germany). The toxin test for extraintestinal isolates was not performed. For stool specimen, *C. difficile* toxin was detected using Toxin ELISA (*C. difficile* TOX A/B II™ assay), or PCR (BD MAX Cdiff assay) available from October 2015 according to the manufacturer's protocols.

Statistical analysis

One-way analysis of variance or Kruskal-Wallis test was used to analyze continuous variables, and $\chi 2$ test or Fisher's exact test to categorical variables as appropriate. The survival analysis was performed by the Kaplan-Meier method and compared with the log-rank test. The logistic regression model was used for multivariable analyses to determine

independent risk factors of 30-day mortality. Confounders with a plausible relationship with mortality or with *p*-value of ≤ 0.10 in the univariate analysis were included in the multivariate analysis. The results were expressed as adjusted odds ratio (aOR) with a 95% confidence interval (CI). A *p*-value of < 0.05 was considered statistically significant. SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA), was used for analyses.

RESULTS

The incidence of ECDI

During the 21-year period, *Clostridium* species were isolated from 1,196 extraintestinal cultures. Of these, the most common identified species were *Clostridium perfringens* (n=350, 29.3%), followed by *C. clostridioforme* (n=144, 12.0%), and *C. tertium* (n=90, 7.5%). *C. difficile* were isolated from 83 (6.9%) cases and 340 (28.4%) were not identified to species. The incidence of ECDI was 2.53 cases per 100,000 admissions and the incidence of *C. difficile* bacteremia was 0.79 per 100,000 admissions.

Study population

C. difficile was identified in 83 cultures from 60 patients. Among 60 patients, *C.difficile* were identified from blood (n=22, 36.7%), peritoneal fluid (n=12, 20.0%), abscess fluid (n=10, 16.7%), infected tissue (n=9, 15.0%), surgical excised wound discharge (n=3, 5.0%), pleural fluid (n=3, 5.0%) and bile (n=1, 1.7%). Patients were divided into 3 groups according to GI disruption or malignancy, as defined in the Method section. Among 38 (63.3%) patients who had GI disruption, 13 (21.7%) and 25 (41.7%) patients were classified into group A and group B, respectively. In group B, the most common causes of GI disruption were recent GI operation within 3 months (n=13, 52%) and GI bleeding within 2 weeks (n=7, 28%). The remaining 22 (36.7%) patients without GI disruption were classified as group C (Fig. 1).

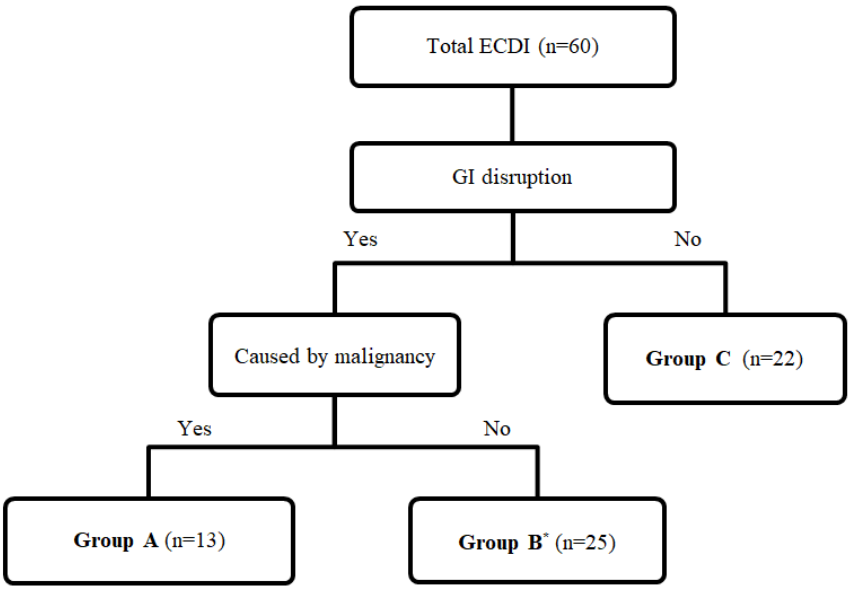

Figure 1. Flow chart of patient disposition. Total 60 patients with extraintestinal *Clostridium difficile* infection (ECDI) were divided into three groups according to the presence or absence of gastrointestinal (GI) disruption and malignancy: group A (GI disruption caused by malignancy), group B (GI disruption without malignancy), group C (no GI disruption).

* Other causes were GI operation within 3 months (n=13, 52%), GI bleeding within 2 weeks (n=7, 28%), bowel perforation or leakage (n=7, 28%), C. difficile enterocolitis (n=3, 12%), and inflammatory bowel disease (n=2, 8.0%). Several patients (n=7, 28%) had one or more causes of GI disruption.

Baseline patient characteristics

The demographic and baseline characteristics of patients are summarized in Table 1. Of all patients, 36 (60.0%) patients were men and the median age was 58 (interquartile range [IQR], 44–69) years. The most common underlying diseases were solid cancer (n=33, 55.0%), diabetes (n=10, 16.7%), and liver cirrhosis (n=8, 13.3%). Forty-seven (78.3%) and 16 (26.7%) patients received antibiotics and proton pump inhibitor (PPI) within 3 months, respectively. Four (6.7%) patients had a recent (≤ 3 months) history of *C. difficile* enterocolitis.

Comparing between the three groups, multiple trauma was identified only in group C (group A, 0% vs. group B, 0% vs. group C, 31.8%; $p < 0.001$). The rate of receiving immunosuppressants within 3 months (46.2% vs. 24.0% vs. 9.1%; $p = 0.04$) and the median Charlson comorbidity index (7.0 vs. 4.0 vs. 1.5; $p = 0.003$) was significantly higher in group A. The proportion of community-onset infection was significantly lower in group B. (53.8% vs. 20.8% vs. 52.2%; $p = 0.047$). There were no differences in the median age between the 3 groups as well as antibiotics exposure, PPI administration, previous *C.difficile* enterocolitis within 3 months ($p > 0.05$ for all).

Table 1. Baseline characteristics of patients with extraintestinal *Clostridioides difficile* infection

Characteristic	Total (n=60)	Group A (n=13)	Group B (n=25)	Group C (n=22)	*p*-value
Male sex	36 (60.0)	7 (53.8)	14 (56.0)	15 (68.2)	0.61
Median age (IQR)	58 (44–69)	58 (44–69)	63 (45–72)	50 (38–64)	0.10
Underlying disease					
Solid cancer	33 (55.0)	13 (100.0)	16 (64.0)	4 (18.2)	<0.001
Hepatocellular carcinoma	7 (11.7)	1 (7.7)	3 (12.0)	3 (60.0)	0.047
Stomach cancer	5 (8.3)	3 (23.1)	2 (8.0)	0	0.44
Bile duct cancer	5 (8.3)	2 (15.4)	3 (12.0)	0	0.58
Colorectal cancer	5 (8.3)	3 (23.1)	1 (4.0)	0	0.25
Pancreas cancer	3 (5.0)	1 (7.7)	2 (8.0)	0	0.68
Gynecologic cancer	3 (5.0)	1 (7.7)	2 (8.0)	0	0.68
Others*	6 (10.0)	2 (15.4)	3 (12.0)	1 (20.0)	0.96
Diabetes mellitus	10 (16.7)	2 (15.4)	3 (12.0)	5 (22.7)	0.61
Liver cirrhosis	8 (13.3)	1 (7.7)	2 (8.0)	5 (22.7)	0.27
End-stage of renal disease on dialysis	6 (10.0)	0	2 (8.0)	4 (18.2)	0.20
Heart failure	3 (5.0)	1 (7.7)	2 (8.0)	0	0.40
Hematologic malignancy	2 (3.3)	1 (7.7)	0	1 (4.5)	0.42
Solid organ transplantation	2 (3.3)	0	1 (4.0)	1 (4.5)	0.75
Inflammatory bowel disease	2 (3.3)	0	2 (8.0)	0	0.24
Underlying condition					
Antibiotics exposure within 3 months	47 (78.3)	8 (61.5)	22 (88.0)	17 (77.3)	0.17
Proton pump inhibitor use within 3 months	16 (26.7)	2 (15.4)	9 (36.0)	5 (22.7)	0.34
Immunosuppressants within 3 months†	14 (23.3)	6 (46.2)	6 (24.0)	2 (9.1)	0.04
Multiple trauma	7 (11.7)	0	0	7 (31.8)	0.001
Previous *C. difficile* enterocolitis within 3 months	4 (6.7)	2 (15.4)	1 (4.0)	1 (4.5)	0.36
Charlson comorbidity index, median (IQR)	4.5 (1.0–7.0)	7.0 (5.5–9.5)	4.0 (0.0–7.0)	1.5 (0.0–6.0)	0.003
Category of acquisition					
Community-onset	24 (40.0)	7 (53.8)	5 (20.8)	12 (52.2)	0.047
Community-acquired	5 (8.3)	0	1 (4.0)	4 (18.2)	0.10
Healthcare-associated	19 (31.7)	7 (53.8)	5 (20.0)	7 (31.8)	0.10
Hospital-acquired	36 (60.0)	6 (46.2)	19 (76.0)	11 (50.0)	0.10

Note. Data are no. (%) of patients, unless otherwise indicated. IQR denotes interquartile range.

* one each was bladder cancer, primary peritoneal carcinomatosis, breast cancer, prostate cancer, lung cancer, and

neuroblastoma.

† Receipt of steroid therapy for >2 weeks or use of chemotherapy or antirejection drugs for > 1 week within 3 months.

Clinical manifestation and laboratory findings

Table 2 demonstrates the clinical manifestation and laboratory findings. The most common site of ECDIs was abdominopelvic infection (n=25, 41.7%) and bacteremia (n=22, 36.7%). Patients with ECDIs initially presented with fever (n=24, 40.0%), followed by abdominal pain (n=21, 35.0%), diarrhea (n=14, 23.3%), and vomiting (n=11, 18.3%). Among patients with diarrhea (n=14), 10 patients underwent *C. difficile* stool test and 6 patients were diagnosed as *C. difficile* enterocolitis. Concomitant microorganisms were identified from 36 (60.0%) patients (Table 3).

When comparing the three groups, bacteremia (group A, 53.8% vs. group B, 48.0% vs. group C, 13.6%; $p = 0.02$), APACHE II Score (13.0 vs. 10.0 vs. 6.0; $p = 0.01$), diarrhea (53.8% vs. 16.0% vs 13.6% ;$p = 0.01$), and confirmed *C. difficile* enterocolitis (23.1% vs. 12.0% vs. 0%; $p = 0.02$) were significantly more common in group A compared with group B or C. Wound infection, pleuropulmonary infection, and peritonsilar abscess was identified only in group C. Other characteristics (fever, abdominal pain, vomiting, white blood cell count, C-reactive protein) were comparable among groups ($p > 0.05$ for all).

Table 2. Clinical manifestation and laboratory findings

Characteristics	Total (n=60)	Group A (n=13)	Group B (n=25)	Group C (n=22)	*p*-value
Site of infection					
Abdominopelvic infection	25 (41.7)	6 (46.2)	13 (52.0)	6 (27.3)	0.21
Bacteremia	22 (36.7)	7 (53.8)	12 (48.0)	3 (13.6)	0.02
Wound infection	8 (13.3)	0	0	8 (36.4)	<0.001
Pleuropulmonary infection	4 (6.7)	0	0	4 (18.2)	0.03
Peritonsilar abscess	1 (1.7)	0	0	1 (4.5)	0.42
Initial manifestation					
Fever (> 38℃)	24 (40.0)	6 (46.2)	12 (48.0)	6 (27.3)	0.31
Abdominal pain	21 (35.0)	6 (46.2)	9 (36.0)	6 (27.3)	0.52
Diarrhea	14 (23.3)	7 (53.8)	4 (16.0)	3 (13.6)	0.01
Vomiting	11 (18.3)	4 (30.8)	5 (20.0)	2 (9.1)	0.27
APACHE II Score, median, (IQR)	9.0 (5.0-13.0)	13.0 (7.5-18.5)	10.0 (6.0-12.0)	6.0 (2.0-10.0)	0.01
Laboratory findings, median (IQR)					
White blood cell (/mm^3)	10,900 (6,700-14,325)	13,700 (5,900-28,950)	10,400 (7,000-12,750)	10,450 (6,625-14,300)	0.46
C-reactive protein (mg/dL)	6.44 (2.47-11.16)	8.91 (4.51-23.01)	7.12 (2.16-12.94)	4.81 (1.83-8.46)	0.08
Polymicrobial infection	36 (60.0)	7 (53.8)	17 (68.0)	12 (54.5)	0.56
Clostridioides difficile* enterocolitis test					
Positive	6/10	3/4	3/4	0/2	0.02

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE denotes Acute Physiology and Chronic Health Evaluation and IQR, interquartile range.

* *C. difficile* stool culture, toxin enzyme immunoassay, polymerase chain reaction, or endoscopy were used.

Table 3. Concomitantly identified pathogens with *Clostridioides difficile*

Group A (n=7/13)	Group B (n=17/25)	Group C (n=12/22)
Bacteroides (4)	*Escherchia coli* (6)	Enterococcus (7)
B. fragilis (2)	Enterococcus (5)	*E. faecalis* (5)
B. caccae (1)	*E. faecium* (3)	*E. avium* (2)
B. capillosus (1)	*E. faecalis* (2)	*Escherchia coli* (3)
Streptococcus (3)	*Staphylococcus aureus* (4)	Staphylococcus (3)
Group C streptococcus (1)	Klebsiella (4)	*S. aureus* (2)
S. schleiferi (1)	*K. oxytoca* (2)	*S. epidermidis* (1)
S. haemolyticus (1)	*K. pneumoniae* (2)	Streptococcus (2)
Escherchia coli (2)	Enterobacter (2)	Group C streptococcus (1)
Enterococcus faecium (2)	Enterobacter spp. (1)	*S. constellatus* (1)
Clostridium perfringens (1)	*E. cloacae* (1)	Bacteroides (2)
Acinetobacter baumannii (1)	Streptococcus (2)	*B. caccae* (1)
Fusobacterium varium (1)	*S. viridans* (1)	*B. distasonis* (1)
Prevotella oris (1)	*S. contellatus* (1)	Bacillus spp. (1)
Sternotrophomonas maltophilia (1)	*Pseudomonas aeruginosa* (2)	*Citrobacter freundii* (1)
Staphylococcus epidermidis (1)	*Peptostreptococcus magnus* (1)	*Klebsiella oxytoca* (1)
	Bacillus spp. (1)	Clostridium spp. (1)
	Parvimonas micra (1)	*Pseudomonas aerugionosa* (1)
	Prevotella oris (1)	*Aeromonas hydrophilia* (1)
	Acinetobacter baumannii (1)	*Provetella oris* (1)
	Candida albicans (1)	Candida, not albicans (1)

Note. Data are presented as the number of patients. More than one pathogen was identified in some patients.

Treatment and outcomes

Adequate antimicrobial therapy for *C. difficile* were administered to 43 (55.0%) patients (Table 4): oral or IV metronidazole was administered to 16 patients (26.7%), IV vancomycin to 10 patients (16.7%), and oral or IV metronidazole plus IV vancomycin to 3 patients (5.0%). Fourteen-day mortality, 30-day mortality, 60-day mortality, and overall mortality were 21.7%, 26.7%, 33.3%, and 58.3%, respectively. All of these rates were significantly higher in group A than group B or C (Table4, Fig.2). The 30-day mortality rates in group A, B, C were 69.2%, 12.0%, 16.7%, respectively ($p < 0.001$).

Table 4. Treatment and outcomes of patients with extraintestinal *Clostridioides difficile* infection

Characteristics	Total (n=60)	Group A (n=13)	Group B (n=25)	Group C (n=22)	*p*-value
Adequate antimicrobial therapy					
Metronidazole (oral, IV)	16 (26.7)	5 (38.5)	11 (44.0)	0	0.002
Vancomycin (IV)	10 (16.7)	0	4 (16.0)	6 (27.3)	0.11
Metronidazole (oral, IV) +Vancomycin (IV)	3 (5.0)	1 (7.7)	1 (4.0)	1 (4.5)	0.88
Teicoplanin (IV)	4 (6.7)	1 (7.7)	1 (4.0)	2 (9.1)	0.78
None*	27 (45.0)	6 (46.2)	8 (32.0)	13 (59.1)	0.18
Outcome					
14-day mortality	13 (21.7)	9 (69.2)	2 (8.0)	2 (9.1)	< 0.001
30-day mortality	16 (26.7)	9 (69.2)	3 (12.0)	4 (18.2)	< 0.001
60-day mortality	20 (33.3)	11 (84.6)	4 (16.0)	5 (22.7)	< 0.001
Overall mortality	35 (58.3)	12 (92.3)	14 (56.0)	9 (40.9)	0.01

NOTE. Data are no. (%) of patients, unless otherwise indicated. IV denotes intravenous.

* It included administration of other antibiotics (23) than metronidazole, vancomycin, teicoplanin, and/or no antibiotics (4).

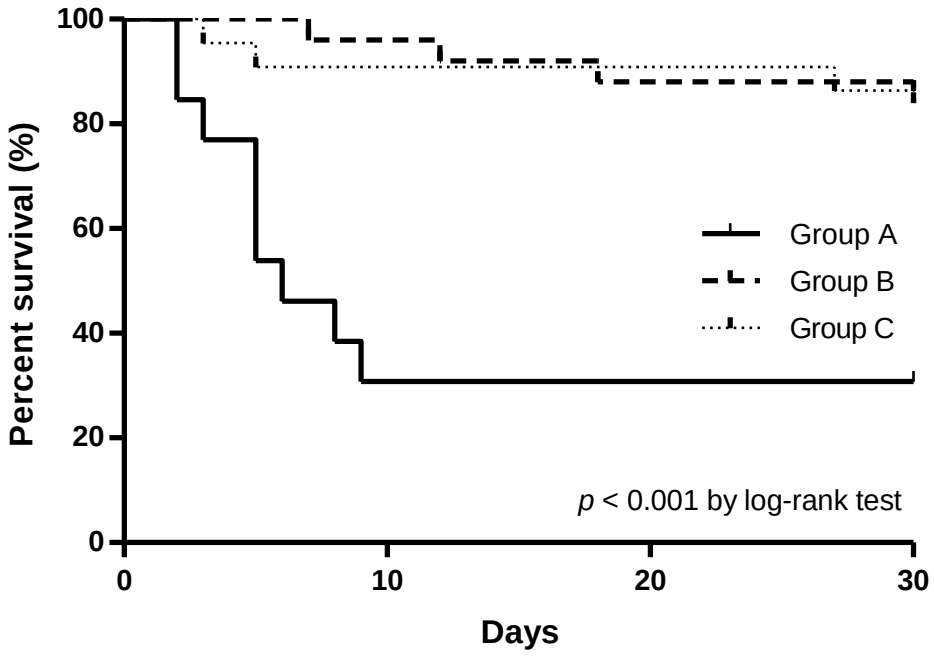

Figure 2. Kaplan-Meier survival curve of patients up to 30 days after culture, stratified for groups A, B, and C.

Thirty-day mortality rate was significantly higher in group A than group B or C (group A, 69.2% vs. group B, 12.0% vs group C, 16.7%; $p < 0.001$).

Predictors for 30-day mortality in patients with ECDI

Univariate analysis of predictors for 30-day mortality of patients with ECDI is presented in Table 5. Age > 65 years (Odds ratio [OR], 3.97; 95% CI, 1.20–13.22; $p = 0.02$), group A (OR, 12.86; 95% CI, 3.09–53.48; $p < 0.001$), and diarrhea (OR, 6.33; 95% CI, 1.72–23.34; $p = 0.006$) were significant risk factor for 30-day mortality. *C. difficile* bacteremia ($p = 0.20$), polymicrobial infection ($p = 0.81$), and adequate antimicrobial therapy for *C. difficile* ($p = 0.29$) were not significantly associated with 30-day mortality. In multivariate analysis, group A (aOR, 17.32; 95% CI, 2.96–101.21; $p = 0.002$) and age > 65 years (aOR, 7.09; 95% CI, 1.31–38.45; $p = 0.02$) were independent risk factors for 30-day mortality.

Table 5. 30-day outcomes of patients with extraintestinal *Clostridioides difficile* infection

Variable	No. of deaths/ No. of episodes (%)	*p*-value	Adjusted Odds Ratio (95% Confidence interval)	*p*-value
Male		0.41		
No	5/24 (20.8)			
Yes	11/36 (30.6)			
Age > 65		0.02	7.09 (1.31–38.45)	0.02
No	6/37 (16.2)			
Yes	10/23 (43.5)			
Diarrhea		0.006		
No	8/46 (17.4)			
Yes	8/14 (50.0)			
Polymicrobial infection		0.81		
No	6/24 (25.0)			
Yes	10/36 (27.8)			
Hospital-acquired infection		0.40		
No	9/24 (37.5)			
Yes	7/36 (19.4)			
Group A		<0.001	17.32 (2.96-101.21)	0.002
No	7/47 (14.9)			
Yes	9/13 (69.2)			
Bacteremia		0.20		
No	8/38 (21.1)			
Yes	8/22 (36.4)			
Adequate antibiotics		0.29		
No	9/27 (33.3)			
Yes	7/33 (21.2)			
Total	16/60 (26.7)			

NOTE. Data are no. (%) of patients, unless otherwise indicated.

DISCUSSION

In this retrospective cohort study, I demonstrated the clinical features and predictors of 30-day mortality for ECDI. ECDI patients commonly had GI discruption and underlying malignancy. ECDI mainly comprised of abdominopelvic infection and bacteremia. Concomitant *C. difficile* enteorocolitis was uncommonly identified. GI disruption caused by malignancy and old age were significant independent risk factors for 30-day mortality.

In review of literature, only few studies reported the incidence of ECID. Two decades ago, an USA group reported the estimated incidence of ECDI as 4 cases per 100,000 admissions,[31] which was higher than that of current study (2.53 cases per 100,000 admissions). This difference may be the results of differences in patient populations and *C. difficile* identification process. In our results, 28.4% of isolated *Clostridium* species were not identified to species level, which may have contributed to underestimate the incidence of ECDI. In contrast, the proportion of *C. difficile* bacteremia over all ECDI (36.7% vs. 6.5–27.5%) and underlying cancer patients (55.0% vs. 11.7–50.0%) were higher in our patients than those of previous studies.[17, 18, 31] With regard to incidence and its influencing factors, it needs further larger scale prospective investigation.

I found that only 10% of ECDI patients had concomitant *C. difficile* enterocolitis. We speculate as follows: first, in the absenes of enterocolitis, *C. difficile* in GI tract can translocate or directly spread to extraintestinal sites through GI disruption. It has been reported that the rate of asymptomatic colonization of C. difficile is substantial, with 7–26% among inpatients in acute care facilities and 50% in an endemic area.[32] In this study, only 14 of 60 patients (23.3%) had diarrhea at the time of ECDI identification. Second, clinicians frequently did not perform *C. difficile* stool test even if patients with ECDI had diarrhea, suggesting that diarrhea was often regarded as one of the manifestations of systemic infections. Even with diarrheal patients, 71.4% patients underwent evaluation for *C. difficile* enterocolitis such as stool test or endoscopy. More cases of concomitant *C. difficile* enterocolitis might have been missed. Third, non-toxigenic type of *C. difficile* isolates might

have been associated with ECDIs. Previous studies showed that 24–30% of *C. difficile* isolates identified from ECDI patients were non-toxigenic phenotype.[21, 33] Patients with non-toxigenic type of *C. difficile* don't have *C. difficile* associated diarrhea.[34]

In accordance with prior ECDI studies,[15-18, 21, 31] the mortality rate of ECDI patient was substantial, with the 30-day mortality of 26.8%. However, contratry to prior reports,[21] adequate antimicrobial therapy for *C. difficile* was not associated with lower mortality rate in this study. I suggest several explanations: first, concomitant polymicrobial infection, which was found in 60% of patients, may have influenced on outcomes. Second, *C. difficile* isolates might be a colonizer. Third, antibiotics other than metronidazole, vancomycin, and teicoplanin can be susceptible to *C. difficile*. For example, Kim et al.,[35] showed that 99.8% of *C. difficile* were susceptible to piperacillin/piperacillin-tazobactam and the sensitivity rates to imipenem, cefotetan, and ampicillin were 75%, 66%, and 58% respectively. Finally, underlying disease, especially malignancy may determine mortalities, not ECDI itself.

It is notable that GI disruption caused by malignancy, and old age are significantly associated with poorer outcomes. Group B and C do not differ significantly in 30-day mortality. It seems to be that the underlying malignancy rather than GI disruption is the important factor for mortality. Five years ago, an Finland group showed that the 1-year mortality rate was significantly correlated with the severity of underlying diseases measured by both Charlson comorbidity score and Horn index.[17] Age and malignancy compose the Charlson comorbidity score. The median Charlson comorbidity index was significantly higher in group A than group B or C. Therefore, the severity of underlying disease, especially old age (>65 years) and malignancy, is associated with mortality.

There are several limitations to this study. First, it is a retrospective study in a single tertiary center which included highly selected patients, limiting the generalization of the results. However, to my knowledge, this study comprises the largest cohort of consecutive ECDIs. Second, there is a lack of information about toxin phenotypes and antimicrobial susceptibility tests of extraintestinal *C. difficile* isolates. Third, residual confounding may still exist although I adjusted for possible confounding factors.

CONCLUSION

In conclusion, ECDIs are uncommonly occurred but associated with high mortality. GI disruption caused by malignancy and old age were significant independent risk factors for 30-day mortality. Further studies are needed to understand its pathogenesis and to improve outcomes.

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국문요약

Clostridioides difficile 에 의한 장외 감염의 임상적 특징과 치료 결과에 관한 연구

정혜민

울산대학교 대학원 의학과

연구 배경: *Clostridioides difficile (C. difficile)* 대장염에 대한 많은 연구는 있으나, *C. difficile* 장외감염에 대한 정보는 적고 일화적이다. 따라서 *C. difficile* 장외감염 환자를 분석하여 이 질환의 특징적인 임상 양상 및 치료 결과 등을 밝히고자 하였다.

연구 방법: 1997년 1월부터 2018년 12월까지 본원에서 시행한 대변 외의 검체에서 *C. difficile* 이 확인된 모든 연령의 환자를 대상으로 후향적 연구를 진행하였다. 이들 환자 중 위장관 손상 (Gastrointestinal disruption)에 따라 그룹을 나누었는데, 위장관 손상이 있는 환자 중 악성종양으로 인한 것일 때를 그룹 A, 그 외 다른 원인으로 인한 것일 때를 그룹 B 로 나누었다. 그 외 위장관 손상이 없는 경우를 그룹 C 로 나누어 이 세 그룹간 임상양상을 비교하였다. 주요 결과는 30일 사망률이었다.

연구 결과: 총 60명의 본 연구에 포함되었으며, *C. difficile* 장외감염의 발생률은 100,000

입원당 2.53 건이었다. 모든 환자를 대상으로 하였을 때 나이 중앙값은 58세였으며 36명 (60%) 이 남성이었다. 가장 흔한 장외 검체는 혈액이었다. 6명 (10%) 는 *C. difficile* 대장염을 앓았으며 36명 (60%) 은 다균감염을 보였다. *C. difficile* 균혈증은 22명으로 group A (53.8%) 와 group B (48.0%) 에서 group C (13.6%) 보다 많았다 (p =0.02). 30일 사망률은 그룹 A 가 그룹 B 나 C 보다 높았다. (69.2% [9/13] vs. 12.0% [3/25] and 16.7% [4/22]; p <0.001). *C. difficile* 균혈증 (p =0.20), 다균 감염 (p =0.81), 그리고 *C. difficile* 에 대한 항생제 투약 (p =0.29) 은 30일 사망률과 관련이 없었다. 다변량 분석에서 그룹 A 와 65세 이상 고령은 30일 사망률의 독립적인 위험인자였다.

연구 결론: *C. difficile* 장외 감염은 드물지만 높은 사망률을 보이며, *C. difficile* 대장염과 동반하는 경우가 드물다. 고령, 그리고 악성 종양으로 인해 위장관 손상이 발생했을 경우에 더 안 좋은 예후를 보인다.

중심 단어: 클로스트리디움 디피실, 균혈증, 장염, 악성종양