Epidemiology and Infection

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The effect of concomitant use of systemic antibiotics in patients with *Clostridium difficile* infection receiving metronidazole therapy

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Original Paper

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Cite this article: Jin SJ, Seo KH, Wi YM (2018). The effect of concomitant use of systemic antibiotics in patients with *Clostridium difficile* infection receiving metronidazole therapy. *Epidemiology and Infection* **146**, 558–564. https://doi.org/10.1017/S0950268818000390

Received: 9 November 2017
Revised: 30 January 2018
Accepted: 5 February 2018
First published online: 1 March 2018

Key words:
Clostridium difficile infection; concomitant antibiotics; metronidazole; treatment failure

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Abstract

Management of *Clostridium difficile* infection (CDI) involves discontinuation of the offending antibiotic agent as soon as possible. However, the ongoing infection does not allow discontinuation of the offending antibiotic. We aimed to retrospectively investigate the predictors of treatment failure and impact of the concomitant use of systemic antibiotics in patients receiving metronidazole therapy. This study was conducted among patients hospitalised at a second care academic hospital from January 2013 to December 2014. Eligible patients were identified by reviewing stool toxin enzyme immunoassay results for *C. difficile*. Diarrhoea was defined as the passage of at least three loose or watery stools within 24 h. Among 314 patients with CDI receiving metronidazole therapy, 62 (19.7%) showed treatment failure and 105 (33.4%) received concomitant antibiotics. Underlying dialysis, fever >38.3 °C, low median serum albumin levels and concomitant use of antibiotics were independent predictors of treatment failure in patients with CDI receiving metronidazole therapy. The concomitant use of antibiotics increased the rates of treatment failure and 30-day mortality in patients receiving metronidazole therapy. These results suggest that metronidazole should be used in mild cases of CDI only after discontinuation of the offending antibiotics.

Introduction

Clostridium difficile infection (CDI) is one of the most important healthcare-associated infections with high morbidity and mortality as well as healthcare costs (annually 8 billion dollars in the USA and 30 billion euros in Europe) [1]. The costs of CDI in Korea also increased sharply, from US$2.4 million in 2008 to US$15.8 million in 2011 [2]. Metronidazole and vancomycin have been the mainstays of antibiotic treatment for CDI over the last 30 years. Clinical practice guidelines suggest that treatment should be chosen based on infection severity, with metronidazole being used for mild or moderate CDI and vancomycin for severe CDI [3–5]. Factors associated with metronidazole failure include age older than 60 years, fever, hypoalbuminemia, peripheral leucocytosis, ICU stay and abnormal abdominal computed tomography (CT) imaging findings [6–8]. Bauer *et al.* investigated the prognostic markers for severe CDI using the database of two randomised controlled trials and found that both leucocytosis and renal failure on the day of diagnosis were useful predictors of a complicated course of CDI [9]. Other studies showed that age, ongoing treatment with systemic antibiotics, leukocyte count, albumin and serum creatinine can predict the risk of severe CDI [10, 11]. Recently, strain type has been suggested as an additional cause of excess morbidity, disease severity and high recurrence rates of CDI [12]. Accurate prediction of metronidazole failure, preferably early in the course of the disease, could shorten hospital stay and possibly reduce morbidity and mortality.

Since the administration of antibiotics is the most important causative factor of CDI, its initial management involves discontinuation of the offending antibiotic agent as soon as possible [3–5]. However, the severity of the primary infection simply does not allow discontinuation of the antibiotic. Three previous small-scale studies showed that discontinuation of clindamycin successfully resolved the active symptoms of CDI [11, 13, 14]. A recent study investigated the effects of concomitant antibiotics on the response to fidaxomicin or vancomycin [15]. Failure to stop the offending antibiotics is associated with decreased clinical cure rate and CDI recurrence [15].

Therefore, we performed a retrospective study of patients who received metronidazole for the treatment of CDI over a 2-year period to investigate the predictors of treatment failure and the impact of the concomitant use of systemic antibiotics in these patients.

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Methods

Study population and design

A retrospective cohort study was conducted among patients hospitalised at Samsung Changwon Hospital, a second care academic hospital, from January 2013 to December 2014. Eligible patients were identified by reviewing stool toxin enzyme immunoassay (EIA) results for *C. difficile* (Premier Toxins A&B, Meridian Bioscience) during the study period. Only patients who received metronidazole for ⩾3 days were included to evaluate the effect of metronidazole. The following information was collected: demographic characteristics, ward of acquisition, underlying comorbidities, recent medical history within 30 days of diagnosis of CDI, clinical presentations, laboratory parameters obtained 2 days before or 1 day after the diagnosis of CDI, concurrent infection and concomitant medication. To determine the severity of illness, McCabe classification was used for all patients [16]. The study was approved by the institutional review board of Samsung Changwon Hospital. Informed consent was waived due to the observational retrospective nature of the study.

Definition

Diarrhoea was defined as the passage of at least three loose or watery stools within 24 h. CDI was defined as positive stool toxin EIA result in patients with diarrhoea. Treatment success was defined as the resolution of diarrhoea (⩽3 unformed stools for 48 h), improved parameters of disease severity (clinical, laboratory, radiological) and no new signs of severe disease development. Treatment failure was defined as an increase in diarrhoea or increased abdominal discomfort for more than 48 h, development of symptomatic ileus or toxic megacolon, persistent fever or recurrence of diarrhoea attributed to CDI while taking medication. A change in therapy was defined as a failure. Treatment response was checked daily and evaluated after at least 3 days. Concomitant use of antibiotics was regarded as the use of antibacterial agents for more than half of metronidazole's treatment duration. Concomitant antibiotics were further classified by the risk of contributing to the incidence or progression of CDI (high-risk, medium-risk and low-risk antibiotics) as previously described [15]. Carbapenem, second-, third- or fourth-generation cephalosporin, fluoroquinolone, lincosamide, pivampicillin or temocillin were classified as high-risk antibiotics. Penicillin, penicillin combination, first-generation cephalosporin, macrolide, monobactam or streptogramin were classified as medium-risk antibiotics. All other systemic antibiotics were classified as low-risk antibiotics. Topical antibiotics and antifungal and antiviral agents with no antibacterial activity were not considered as concomitant antibiotics. Recurrence was defined as the reappearance of symptoms of CDI within 8 weeks after the onset of a previous episode; the presence of *C. difficile* toxin A, B or both in stool; and the need for retreatment.

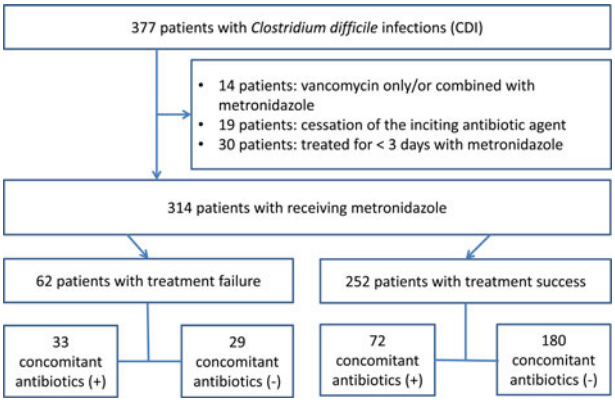

Fig. 1. Flowchart of study.

Statistical analyses

Discrete data were presented as frequencies and percentages and continuous variables were summarised as the mean ± S.D. or as the median and interquartile range according to the distribution. Clinical, laboratory and therapeutic characteristics were compared between subgroups of treatment success and treatment failure using the χ^2 test, Fisher's exact test, two-sample *t*-test or Mann–Whitney *U*-test as appropriate. To identify the predictors of treatment failure, a multivariate logistic regression model was used to control for the effects of confounding variables. When the distribution of the continuous data was skewed, the log transformations of data were applied for univariate analyses. Variables with a *P*-value <0.05 in univariate analyses were candidates for multivariate analysis. All analyses were conducted with SPSS for Windows v.18.0 (SPSS Inc., Chicago, IL).

Results

A total of 377 patients with CDI were identified during the study period, of which 314 were enrolled in the study. Sixty-three patients were excluded from the analysis for the following reasons: patients receiving vancomycin only or combined with metronidazole ($n = 14$), cessation of the offending antibiotic agents ($n = 19$) and patients receiving metronidazole therapy <3 days ($n = 30$). Among the 314 patients with CDI receiving metronidazole therapy, 62 (19.7%) patients showed treatment failure. Thirty-three (53.2%) patients received concomitant antibiotics among the treatment failure group, while 72 (28.6%) patients received concomitant antibiotics among the treatment success group (Fig. 1).

Comparison of characteristics between the treatment failure and treatment success groups

Among a total of 314 patients, patients aged ⩾65 were 62.21%. The most prevalent underlying disease was cerebrovascular diseases (43.6%), followed by diabetes (22.6%) and solid tumours (19.7%). A total of 276 (87.9%) patients had previous histories of antibiotic exposure within 30 days. Moreover, among 105 (33.4%) patients received concomitant antibiotics, 77 (73.3%) patients were treated with concomitant antibiotics with diagnoses of definitive infections. A total of 28 (26.7%) patients did not show any evidence of infection to needing concomitant antibiotics. Among patients receiving concomitant antibiotics ($n = 105$), 67.6% ($n = 71$) received high-risk antibiotics contributing to symptomatic CDI (Table 1).

Clinical and laboratory characteristics of patients with treatment failure were compared with those of treatment success. Concomitant use of antibiotics had a significant effect on treatment failure (53.2% *vs.* 28.6%; $P < 0.001$). Underlying dialysis (19.4% *vs.* 6.0%; $P = 0.001$) and chronic renal failure without receiving dialysis (25.8% *vs.* 13.5%; $P = 0.018$), ultimate fatal underlying diseases (41.9% *vs.* 27.4%; $P = 0.025$) and indwelling

https://doi.org/10.1017/S0950268818000390 Published online by Cambridge University Press

Table 1. Characteristics between the treatment failure and treatment success groups following metronidazole treatment

	Total ($n = 314$)	Treatment failure ($n = 62$)	Treatment success ($n = 252$)	*P*-value
Age ⩾65 year	195 (62.1)	42 (67.7)	153 (60.7)	0.307
Male	161 (51.3)	31 (50.0)	130 (51.6)	0.823
ICU	63 (20.1)	15 (24.2)	48 (19.0)	0.365
Category of admission				0.960
Community associated	14 (4.5)	3 (4.8)	11 (4.4)	
Community-onset healthcare associated	54 (17.2)	10 (16.1)	44 (17.5)	
Hospital onset	246 (78.3)	49 (79.0)	197 (78.2)	
Underlying diseases				
Diabetes	71 (22.6)	18 (29.0)	53 (21.0)	0.177
Dialysis	27 (8.6)	12 (19.4)	15 (6.0)	0.001
Chronic renal failure without dialysis	50 (15.9)	16 (25.8)	34 (13.5)	0.018
Solid tumour	62 (19.7)	13 (21.0)	49 (19.4)	0.787
Cerebrovascular diseases	137 (43.6)	32 (51.6)	105 (41.7)	0.157
Liver cirrhosis	20 (6.4)	3 (4.8)	17 (6.7)	0.775
Cardiovascular diseases	39 (12.4)	7 (11.3)	32 (12.7)	0.763
Chronic lung diseases	55 (17.5)	13 (21.0)	42 (16.7)	0.425
Ultimate fatal underlying diseases	95 (30.3)	26 (41.9)	69 (27.4)	0.025
Charlson's score, median (IQR)	3 (1–4)	3 (1–4.25)	2 (1–4)	0.143
Previous medical history within 1 month				
Immunosuppressant use	61 (19.4)	12 (19.4)	49 (19.4)	0.987
Operation	109 (34.7)	16 (25.8)	93 (36.9)	0.100
Diarrhoea	96 (30.6)	22 (35.5)	74 (29.4)	0.349
Antibiotic exposure	276 (87.9)	56 (90.3)	220 (87.3)	0.514
Extended spectrum cephalosporin	157 (50.0)	32 (51.6)	125 (49.6)	0.777
Quinolones	84 (26.8)	17 (27.4)	67 (26.6)	0.895
β-lactam/β-lactamases	81 (25.8)	17 (27.4)	64 (25.4)	0.744
Tube feeding	81 (25.8)	18 (29.0)	63 (25.0)	0.516
Indwelling catheter				
Central venous catheterisation	54 (17.2)	16 (25.8)	38 (15.1)	0.045
Urinary catheter	127 (40.4)	30 (48.4)	97 (38.5)	0.155
Leven tube	95 (30.3)	22 (35.5)	73 (29.0)	0.317
Signs at diagnosis				
Fever >38.3° C	109 (34.7)	32 (51.6)	77 (30.6)	0.002
Shock	28 (8.9)	10 (16.1)	18 (7.1)	0.026
Laboratory finding				
WBC/μl, median (IQR)	10 100 (6500–14 650)	11 150 (7775–16 000)	9800 (6500–14 250)	0.117
Serum albumin (g/dl, mean ± S.D.)	2.58 ± 0.64	2.30 ± 0.56	2.65 ± 0.63	<0.001
CRP (mmol/l, median) (IQR)	41.1 (16.0–83.1)	44.6 (17.6–143.9)	40.8 (16.2–81.4)	0.115
Acute renal failure	33 (10.5)	9 (14.5)	24 (9.5)	0.251
Concurrent systemic infection	77 (24.5)	23 (37.1)	54 (21.4)	0.010
Concomitant antibiotics	105 (33.4)	33 (53.2)	72 (28.6)	<0.001
Concomitant gastrointestinal medication				
PPI	85 (27.1)	24 (38.7)	77 (30.6)	0.698
Probiotics	56 (17.8)	20 (32.3)	76 (30.2)	0.144

ICU, intensive care unit; IQR, interquartile range; S.D., standard deviation; CRP, C-reactive protein; PPI, proton pump inhibitor.
Data are *n* (%) unless otherwise stated.

https://doi.org/10.1017/S0950268818000390 Published online by Cambridge University Press

Table 2. Univariable and multivariable logistic regression analysis for independent risk factors for treatment failure in patients treated with metronidazole

	OR (95% CI)	*P*-value	Adjusted OR (95% CI)[a]	*P*-value
Age ⩾65 year	1.36 (0.75–2.45)	0.308		
Male	0.94 (0.54–1.64)	0.823		
ICU	1.36 (0.70–2.63)	0.366		
Category of admission				
Community associated		0.960		
Community-onset healthcare associated	0.91 (0.43–1.94)	0.815		
Hospital onset	1.10 (0.30–4.08)	0.891		
Underlying diseases				
Diabetes	1.54 (0.82–2.87)	0.179		
Dialysis	3.79 (1.67–8.59)	0.001	**3.82 (1.03–14.1)**	**0.045**
Chronic renal failure without dialysis	2.23 (1.14–4.38)	0.020	0.83 (0.28–2.47)	0.827
Solid tumour	1.10 (0.55–2.18)	0.787		
Cerebrovascular diseases	1.49 (0.86–2.61)	0.159		
Liver cirrhosis	0.70 (0.20–2.48)	0.583		
Cardiovascular diseases	0.88 (0.37–2.09)	0.763		
Chronic lung diseases	1.33 (0.66–2.66)	0.426		
Ultimate fatal underlying diseases	1.92 (1.08–3.41)	0.027	1.03 (0.49–2.18)	0.938
Charlson's score	1.07 (0.95–1.21)	0.251		
Previous medical history within 1 month				
Immunosuppressant use	0.99 (0.49–2.01)	0.987		
Operation	0.60 (0.32–1.10)	0.102		
Diarrhoea	1.32 (0.74–2.38)	0.350		
Antibiotic exposure	1.36 (0.54–3.41)	0.515		
Extended spectrum cephalosporin	1.08 (0.62–1.89)	0.777		
Quinolones	1.04 (0.56–1.95)	0.895		
β-lactam/β-lactamases	1.10 (0.59–2.08)	0.744		
Tube feeding	1.23 (0.66–2.28)	0.516		
Indwelling catheter				
Central venous catheterisation	1.96 (1.01–3.81)	0.048	1.09 (0.51–2.34)	0.824
Urinary catheter	1.50 (0.86–2.62)	0.156		
Leven tube	1.35 (0.75–2.43)	0.318		
Signs at diagnosis				
Fever >38.3 °C	2.42 (1.38–4.27)	0.002	**2.24 (1.21–4.17)**	**0.011**
Shock	2.50 (1.09–5.73)	0.030	1.45 (0.56–3.80)	0.448
Laboratory finding				
WBC	*2.21 (0.72–6.84)	0.168		
Serum albumin	0.39 (0.24–0.63)	<0.001	**0.54 (0.31–0.94)**	**0.028**
CRP	*1.57 (0.89–2.77)	0.120		
Acute renal failure	1.61 (0.71–3.67)	0.254		
Concurrent systemic infection	2.16 (1.19–3.93)	0.011	0.79 (0.36–1.77)	0.572
Concomitant antibiotics	3.32 (1.83–6.05)	<0.001	**3.22 (1.50–6.92)**	**0.003**

(*Continued*)

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Table 2. (*Continued.*)

	OR (95% CI)	*P*-value	Adjusted OR (95% CI)[a]	*P*-value
Concomitant GI medication				
PPI	1.44 (0.81–2.56)	0.220		
Probiotics	1.10 (0.61–2.00)	0.748		

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; CRP, C-reactive protein.
*The log transformation of data was applied.
[a]Variables with a *P*-value of <0.05 in the univariate analyses were included in the subsequent multivariate regression model.
Hosmer and Lemeshow test, $\chi^2 = 3.263$, $P = 0.917$.

central venous catheter (25.8% *vs.* 15.1%; $P = 0.045$) also significantly affected treatment failure. Other factors also included fever >38.3 °C (51.6% *vs.* 30.6%; $P = 0.002$) and presentation with septic shock (16.1% *vs.* 7.1%; $P = 0.026$). Regarding serological testing, low median serum albumin levels (2.30 *vs.* 2.65 g/dl; $P < 0.001$) had significant influences on treatment failure.

Predictors of treatment failure in CDI patients receiving metronidazole therapy

Multivariate analysis of potential risk factors associated with treatment failure is shown in Table 2. Variables with a *P*-value <0.05 in the univariate analysis were included in the subsequent multivariate analysis. A logistic regression model revealed that underlying dialysis (odds ratio (OR) 3.82, 95% confidence interval (CI) 1.03–14.10; $P = 0.045$)), fever >38.3 °C (OR 2.24, 95% CI 1.21–4.17; $P = 0.011$), low median serum albumin levels (OR 0.54, 95% CI 0.31–0.94; $P = 0.028$) and concomitant use of antibiotics (OR 3.22, 95% CI 1.50–6.92; $P = 0.003$) were independent predictors of treatment failure in patients with CDI receiving metronidazole therapy.

Outcomes of the concomitant antibiotic group

In the concomitant antibiotic group, treatment failure (31.4% *vs.* 13.9%; $P < 0.001$) and 30-day mortality (15.2% *vs.* 6.5%, $P = 0.015$) were more prevalent than those in the non-concomitant antibiotic group (Table 3). Although there was no difference between the two groups for recurrent CDI, there was a significant difference between the two groups if 12 patients from the non-concomitant antibiotic group receiving antibiotic treatment during the follow-up period were included to the concomitant antibiotic group (30.0% *vs.* 11.9%; $P < 0.001$).

Table 4 summarises the outcomes of the concomitant antibiotic group by the risk of contributing to the incidence or progression of CDI. The rates of treatment failure, 30-day mortality and recurrent CDI were compared for patients receiving high-risk, medium-risk or low-risk antibiotics and those receiving no concomitant antibiotics. Only the concomitant use of high-risk antibiotics increased the rates of treatment failure (OR 3.59, 95% CI 1.93–6.68; $P < 0.001$) and 30-day mortality (OR 2.84, 95% CI 1.21–6.69; $P = 0.017$) when compared with the non-concomitant use of antibiotics. The concomitant use of high-risk antibiotics had no significant effect on recurrence, but there was a significant influence on recurrence if 12 patients from the non-concomitant antibiotic group receiving high-risk antibiotic treatments during the follow-up period were included to the concomitant antibiotic group (OR 3.83, 95% CI 1.96–7.47; $P < 0.001$).

Discussion

This retrospective study showed that the treatment failure rate of patients with CDI receiving metronidazole treatment was 19.7%. Predictors of treatment failure were underlying dialysis, fever >38.3 °C, low median serum albumin levels, and concomitant antibiotics in patients with CDI receiving metronidazole treatment. A total of 33.4% of patients received concomitant antibiotics, of which 26.7% did not show any evidence of infection to needing concomitant antibiotics. The concomitant use of high-risk antibiotics increased the rates of treatment failure and 30-day mortality.

CDI still remains an important cause of morbidity and mortality in healthcare-associated infections [17]. Treatment strategies

Table 3. Outcomes of concomitant use of antibiotics during metronidazole treatment in patients with *Clostridium difficile* infections

	Concomitant antibiotics (*n* = 105)	Non-concomitant antibiotics (*n* = 209)	*P*-value
Outcome			
Treatment failure	33 (31.4)	29 (13.9)	<0.001
30-day all-cause mortality	15/99 (15.2)	13/201 (6.5)	0.015
Recurrent CDI	18/88 (20.5)	33/189 (17.5)	0.549
*Recurrent CDI including patients receiving newly antibiotic treatments during the follow-up period	30/100 (30.0)	21/177 (11.9)	<0.001

CDI, *Clostridium difficile* infection.
Data are *n* (%) unless otherwise stated.
*Twelve patients from the non-concomitant antibiotics group received antibiotic treatments during the follow-up period.

https://doi.org/10.1017/S0950268818000390 Published online by Cambridge University Press

Table 4. Effect of concomitant use of antibiotics on outcomes by risk of contributing to the incidence or progression of CDI

Treatment failure	OR (95% CI)	*P*-value
Non-concomitant antibiotics	1	
High-risk[a]	3.59 (1.93–6.68)	<0.001
Medium-risk[b]	1.48 (0.52–4.23)	0.466
Low-risk[c]	2.07 (0.40–10.75)	0.387
30-day mortality		
Non-concomitant antibiotics	1	
High-risk[a]	2.84 (1.21–6.69)	0.017
Medium-risk[b]	1.97 (0.52–7.46)	0.317
Low-risk[c]	2.41 (0.27–21.54)	0.431
Recurrent CDI		
Non-concomitant antibiotics	1	
High-risk[a]	1.21 (0.58–2.52)	0.617
Medium-risk[b]	1.00 (0.32–3.12)	0.993
Low-risk[c]	2.36 (0.42–43.45)	0.332
*Recurrent CDI including patients receiving new antibiotics during the follow-up period		
Non-concomitant antibiotics	1	
High-risk[a]	3.83 (1.96–7.47)	<0.001
Medium-risk[b]	1.61 (0.50–5.21)	0.427
Low-risk[c]	3.83 (0.66–22.24)	0.135

OR, odds ratio; CI, confidence interval; CDI, *Clostridium difficile* infection.
[a]High-risk antibiotic: carbapenem, second-, third- or fourth-generation cephalosporin, fluoroquinolone, lincosamide, pivampicillin or temocillin.
[b]Medium-risk antibiotic: penicillin, penicillin combination, first-generation cephalosporin, macrolide, monobactam or streptogramin.
[c]Low-risk antibiotic: all other systemic antibiotics.
*Twelve patients from the non-concomitant antibiotics group received high-risk antibiotic treatments during the follow-up period.

should be based on disease severity and risk of recurrence [3–5]. For mild to moderate CDI, oral metronidazole remains the preferred therapy [3–5]. However, a wide variety of risk factors for severe CDI have been suggested in the literature, which makes it difficult to set a rigid clinical prediction [3–5, 18, 19]. Guidelines [3–5] defined severe CDI as an episode with significant systemic toxin effects and shock, resulting in the need for ICU admission and colectomy or death. Therefore, one or more of the following clinical markers can be present: marked leucocytosis (leucocyte count $>15 \times 10^9$/l), serum albumin of <3 g/dl, an increase in serum creatinine level of at least 1.5 times the premorbid level and severe underlying disease and/or immunodeficiency. In accordance with the guidelines' suggestions, we found that fever >38.3 °C and low median serum albumin levels were associated with poor clinical outcome among patients with CDI receiving metronidazole therapy. These observations are a cause for concern as they indicate the poor adherence to clinical practice guidelines among healthcare providers. Previous studies suggested that adherence to the treatment guidelines was associated with a reduction in complications and mortality [20, 21]. Patients whose physicians followed the guidelines had a significant reduction in mortality (5.4% *vs.* 21.8%, $P = 0.0012$) [20]. The findings from the above study and our research suggest that closer adherence to treatment guidelines may lead to better patient outcomes. Underlying dialysis was also a predictor of poor outcome among patients with CDI receiving metronidazole therapy, similar to that in previous studies, showing that patients with chronic kidney diseases undergoing long-term dialysis have longer treatment periods [22] and higher in-hospital morbidity [23]. However, data on patients with chronic kidney disease and outcomes of CDI have generated inconsistent results. Therefore, guidelines have recognised only acute kidney injury as a marker of severe CDI [3–5].

Guidelines recommended that any offending antimicrobial agent should be discontinued, if possible. A previous study [15] showed that the use of concomitant antibiotics with CDI treatment was associated with a low initial response to CDI therapy and an extended time to resolution of diarrhoea. In the study, among 999 patients, 192 (19.2%) received concomitant antibiotics concurrently with vancomycin or fidaxomicin (days 1–10). In the absence of concomitant antibiotics, initial treatment failure was equivalent in both fidaxomicin and vancomycin (7.3% *vs.* 7.2%, $P = 5.80$). However, when patients received concomitant antibiotics with the study drug, those receiving vancomycin showed significantly higher treatment failure than those receiving fidaxomicin (20.6% *vs.* 10.0%, $P = 0.04$). In the present study, among the 377 patients with CDI receiving metronidazole therapy, a total of 33.4% received concomitant antibiotics. Initial treatment failure was noted in 13.9% of patients who did not receive concomitant antibiotics compared with 31.4% of those who received concomitant antibiotics concurrently with metronidazole. Compared with the previous study, patients receiving metronidazole therapy showed higher treatment failure rates both with and without concomitant antibiotics than those receiving vancomycin or fidaxomicin [24]. Metronidazole has been recommended as the preferred treatment for mild or moderate CDIs, in part because of its low cost and reduced vancomycin-resistant enterococci (VRE) selection risk (2–4). However, CDI leads to increased VRE colonisation and/or VRE-related complications [25]. Data also suggest that the prevalence of VRE is the same in both vancomycin- and metronidazole-treated CDI patients [26]. In addition, a recent systematic literature review indicated that metronidazole was cost-effective in only one of five economic evaluations when the analysis was restricted to data published in full manuscripts only [27]. In light of consistent observational evidence that showed a lower clinical success rate and vague cost-effectiveness for metronidazole *vs.* vancomycin [21, 24, 27], it may be reasonable to consider vancomycin for mild-to-moderate CDI. Intriguingly, among patients receiving concomitant antibiotics, 26.7% did not show any evidence of infection to need the concomitant use of antibiotics. Therefore, exposure to antibiotics other than those intended for CDI should be avoided unless absolutely indicated. The significance of these observations cannot be overemphasised because the concurrent use of antibiotics is associated with increased treatment failure and mortality in patients with CDI receiving metronidazole therapy.

There was no significant relationship between concomitant antibiotic use during CDI treatment and recurrent CDI. However, concomitant antibiotic use was significantly associated with recurrent CDI if non-CDI antibiotic use both during and after CDI treatment was defined as the concomitant group. Non-CDI antibiotic use occurred after completion of CDI therapy in 12 patients. These 12 patients had more severe underlying diseases and longer hospital stays (data not shown). Consistent with this finding, a previous retrospective review of 246 patients

https://doi.org/10.1017/S0950268818000390 Published online by Cambridge University Press

showed an independent association of non-CDI antimicrobial use with recurrence but only when non-CDI antimicrobials were given after CDI therapy was completed [28].

The present study has some limitations. First, it was retrospective in design and observational. Thus, there is a risk of unmeasured confounding effects. Second, we did not investigate the strain type. The strain type has been suggested as an additional cause of excess morbidity, disease severity and higher recurrence rates of CDI [12]. However, hypervirulent strains of ribotype 027 were not common in Korean hospitals; ribotypes 018, 017 and 014/020 of *C. difficile* were the most prevalent in Korea [29]. Third, EIA demonstrated suboptimal sensitivity compared with the gold-standard cytotoxicity assay, which may have resulted in missing a substantial number of cases.

In conclusion, underlying dialysis, fever >38.3 °C, low median serum albumin levels and concomitant use of antibiotics were found to be independent predictors of treatment failure in patients with CDI receiving metronidazole treatment. Given the increasing recognition of the lack of response to treatment using metronidazole, the risk factors identified in this study may assist in predicting which patients will benefit from initial treatment with metronidazole and help to choose alternatives for those who will not. These results also suggest that careful investigation about the need for concomitant antibiotics is required, especially in patients receiving high-risk concomitant antibiotics.

Conflict of interest. None.

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https://doi.org/10.1017/S0950268818000390 Published online by Cambridge University Press