



Review Article



Which is the Preferred Regimen for Non-Severe *Clostridioides difficile* Infection in Korea, Vancomycin or Metronidazole?

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ABSTRACT

The emergence of hypervirulent *Clostridioides difficile* strains has decreased the efficacy of metronidazole in the treatment of *C. difficile* infection (CDI). Therefore, revised guidelines no longer recommend the use of metronidazole as a first-line regimen for CDI and restrict its use for non-severe CDI, only when vancomycin and fidaxomicin are unavailable. In Korea, an epidemic caused by a hypervirulent *C. difficile* strain or the emergence of metronidazole resistant *C. difficile* strains have not been reported. This review article aims to compare the treatment outcomes and adverse effects of vancomycin and metronidazole and discuss the validity of the guidelines of various agencies, which restrict the use of metronidazole, for Korean patients. There are no substantial adverse effects of metronidazole, and its clinical outcomes against non-severe CDI are similar to those of vancomycin. Based on these findings, we recommend that the use of metronidazole for the treatment of non-severe CDI is still an appropriate option in Korea.

Keywords: *Clostridioides difficile* infection; Treatment; Metronidazole; Vancomycin

INTRODUCTION

Since the emergence of the hypervirulent strain of *Clostridioides difficile*, *C. difficile* infection (CDI) has been a major healthcare concern. The Center for Disease Control and Prevention (CDC) has listed CDI under an urgent threat of antimicrobial resistance [1].

Several guidelines have been issued to prescribe antibiotics for CDI. According to the 2010 guidelines issued by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA), metronidazole was recommended for the treatment of mild-to-moderate CDI and vancomycin for severe or complicated CDI [2]. In 2017, SHEA-IDSA guidelines were updated [3]. According to these revised guidelines, vancomycin was recommended for initial episodes of CDI, and metronidazole was restricted to an alternative therapy regimen when access to vancomycin and fidaxomicin is limited. The latest guidelines were published in 2021; they consider fidaxomicin as a preferred regimen for the initial and first occurrence CDI, and metronidazole is limited for non-severe CDI when vancomycin and fidaxomicin are unavailable [4].

Conflict of interest

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In 2013, the American College of Gastroenterology (AGC) had recommended metronidazole for mild-to-moderate CDI and vancomycin for severe CDI [5]. However, updated guidelines published in 2021 recommended oral vancomycin or fidaxomicin for the initial episode of non-severe CDI and oral metronidazole for initial non-severe CDI in low-risk patients [6].

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) had recommended the use of metronidazole for non-severe CDI in the 2009 and 2014 guidelines [7, 8]. In the most recent revision in 2021, the ESCMID also recommends avoiding metronidazole use for the treatment of CDI if fidaxomicin or vancomycin are available [9].

Although the use of metronidazole decreased significantly after the change of treatment guidelines, metronidazole for CDI treatment is still prescribed 10 times more than vancomycin [10]. In Korea, metronidazole and vancomycin are being used for the treatment of CDI, and metronidazole is more commonly prescribed than vancomycin [11]. At this point, it is necessary to contemplate the implementation of the revised guidelines in other countries so that proper CDI treatment can be chosen. Recent guidelines have recommended fidaxomicin as an initial therapy; however, it is very costly and unlikely to be imported to Korea. Therefore, more focus has been placed on the use of vancomycin and metronidazole. In this review article, we compared the treatment outcomes and adverse effects of vancomycin and metronidazole and discussed if the guidelines of various agencies, which restrict the use of metronidazole, are valid for Korean patients.

COMPARISON OF TREATMENT OUTCOME BETWEEN METRONIDAZOLE AND VANCOMYCIN

Four meta-analyses, comprising eight studies, have reported results of the comparison between metronidazole and vancomycin treatments. A brief description of these studies is presented in **Table 1** [12-15]. Regardless of the severity of CDI, initial clinical cure rates of vancomycin were found to be superior to those of metronidazole with a risk ratio of 0.91 (95% confidential interval [CI]: 0.84 - 0.98) [12]. Severe CDI showed better clinical and sustained cure rates when treated with vancomycin [14]. However, mild CDI did not show differences in cure rates between metronidazole and vancomycin treatments [12-14]. Recurrence rates and all-cause mortality were similar among patients treated with metronidazole and vancomycin regardless of the disease severity. Moreover, it has been shown that metronidazole for non-severe CDI is not inferior to vancomycin in terms of sustained clinical response and recurrence [16]. Therefore, with respect to clinical outcomes, the use of metronidazole with recommended doses for the treatment of non-severe CDI can be considered as an appropriate disease management strategy.

Table 1. Lists of randomized controlled trials and cohort studies included in the previous meta-analysis of *Clostridioides difficile* infection in adults

Study	Published year	Study period	Area	Daily dose		Conducting meta-analysis
				Vancomycin	Metronidazole	
Teasley	1983	Jan 1982 - Jan 1983	United States	500 mg, 4 times	250 mg, 4 times po	[12, 13, 15]
Wenisch	1996	Jan 1993 - Apr 1995	Austria	500 mg, 3 times	500 mg, 3 times po	[12, 13, 15]
Pépin	2006	Jan 1991 - Jun 2005	Canada	125 mg, 4 times ~ 250 - 500 mg, 3 times	250 mg, 4 times ~ 500 mg, 3 times	[14]
Zar	2007	Oct 1994 - Jun 2002	United States	125 mg, 4 times	250 mg, 4 times po	[12-15]
Schalk	2010	Jan 2003 - Mar 2008	Germany	250 mg, 4 times	400 mg, 3 times po	[14]
Wenisch	2012	Dec 2008 - Mar 2010	Austria	250 mg, 4 times	500 mg, 3 times po	[12]
Le	2012	2006 - 2008	United States	125 mg, 4 times	500 mg, 3 times po or iv	[12, 13]
Johnson	2014	2005 - 2007	United States, Canada, Europe, Australia	125 mg, 4 times	375 mg, 4 times po	[12, 13]

iv, intravenous; po, per Os.

CONSIDERATIONS WHEN CHOOSING METRONIDAZOLE TREATMENT

1. Differences in the parameters of previous studies

Metronidazole was excluded from the list of first-line drugs for CDI and suggested as an alternative because of its higher recurrence rate and lower treatment success rate than those of vancomycin and fidaxomicin [4, 9]. However, there are a few aspects to consider before applying these guidelines in Korea. First, all the studies that reached these conclusions were conducted for different durations. Moreover, they all had used different doses of vancomycin and metronidazole. Four studies had used the recommended doses of metronidazole [17-20], three studies used the recommended doses of vancomycin [18, 20, 21], and the remaining studies used metronidazole and vancomycin at doses lower [21-24] and higher [17, 19, 22-24] than the recommended ones, respectively. Therefore, more data is needed to compare the outcome of the use of the recommended doses of metronidazole with that of vancomycin. Second, most of these studies were conducted in *C. difficile* epidemic areas with hypervirulent strains. Since 2000, the hypervirulent *C. difficile* strain (NAP1/BI/027) has been the dominant strain in Europe and North America [25]. The studies enrolled in the systematic reviews did not consider the virulence of the strains. Infection by the hypervirulent *C. difficile* strains tends to decrease cure rates and increase recurrence rates [26]. Therefore, if analyzed according to the toxinotyping of *C. difficile* strains, the clinical outcomes of treatments may have been different. In Korea, the *tcdA*-positive *tcdB*-positive *C. difficile* strains are the main cause of CDI. In contrast, less than 10.0% of CDIs are caused by hypervirulent strains [11, 27]. In Korea, for the empirical treatment of CDI without toxinotyping results, treatment options for the binary toxin-producing strains are not considered. This is expected to give better outcomes than the studies performed in the epidemic areas of hypervirulent strains.

2. Resistance against metronidazole

Metronidazole has been used in large doses for a long time to treat CDI; therefore, there are high chances of developing resistance to it. However, the resistance rates of *C. difficile* to metronidazole ranged from 0.0% to 18.3%. Approximately 74.5% (41 out of 55) of studies had shown a 0.0% resistance rate [28, 29]. Moreover, the weighted pooled resistance rates of studies conducted before and after 2012 were 2.5%, and 1.7%, respectively. Several studies conducted in Korea also showed a 0.0% resistance rate for metronidazole [30-32]. Only one study had reported a 2.9% metronidazole resistance rate [33]. Therefore, the rate of resistance to metronidazole over time has not yet increased. Therefore, metronidazole should be selected as a treatment choice without any fear of developing resistance.

3. Adverse events

According to the systematic reviews, the frequency of adverse effects of metronidazole treatment of CDI does not differ from that of vancomycin, with a risk ratio of 0.66 (95% CI: 0.25 - 1.77) for metronidazole over vancomycin [13, 15]. The common adverse effects of metronidazole are nausea, abdominal pain, and diarrhea [34]. The irreversible neurotoxicity of metronidazole must be taken into consideration while using it [3]. However, this neurotoxicity is rare and has not been fully elucidated. Incidence of peripheral neuropathy was found to be higher in patients who were administered metronidazole at doses ≥ 42 g for 4 weeks or more. However, in most cases, symptoms improved after discontinuation [35]. Therefore, there is no substantial reason to avoid metronidazole because of its adverse effects.

CONSIDERATIONS WHEN CHOOSING VANCOMYCIN FOR TREATMENT OF CDI

1. Influence on the gut microbiome

The goal of CDI treatment is to eradicate *C. difficile* and restore the distribution of the gut microbiome [36]. To achieve the effective eradication of *C. difficile*, a sufficient amount of the antimicrobial agent must reach the feces. However, high concentrations of antimicrobial agents can disrupt the distribution of the gut microbiota and delay the reconstruction of the normal flora.

Fecal metronidazole concentrations were higher with oral administration than with intravenous administration. Moreover, its concentration was observed to be more in watery stools than in formed stools [37]. It had reached 25 µg/g during the treatment and dropped abruptly at the end of the treatment [38]. Therefore, transient loss of colonization resistance against *C. difficile* recovered after the cessation of metronidazole treatment. This means that the diversity of microbiota can be recovered after metronidazole treatment [39].

In contrast, the fecal concentration of vancomycin reached $\geq 1,000$ mg/L with four oral doses of 125 mg [40]. The vancomycin concentration increased with the dose. Fecal vancomycin levels were lower in patients with ≥ 4 stools per day. Vancomycin was still detected in the feces for >5 days after completion of the treatment [38]. Recovery of species richness and gut microbiome took longer than in the metronidazole group [39, 41]. Therefore, vancomycin affects the gut microbiome more than metronidazole does. Microbiome disruption subsequently results in loss of colonization resistance to *C. difficile* and other pathogenic organisms, including vancomycin-resistant organisms [39].

2. Vancomycin-resistant Enterococcus (VRE)

CDI treatment disrupted the composition of the gut microbiome, rendering it susceptible to VRE and extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) [42, 43]. One study found a preexisting VRE colonization rate of 66.2% in CDI patients [42]. The new detection of VRE colonization after treatment occurred in 15% of the courses of metronidazole and 8.0% of courses of vancomycin. However, the concentrations of VRE significantly decreased after 6 - 10 days of discontinuation of anti-anaerobic antibiotics. After the revised guidelines, vancomycin use increased significantly from ~10.0% in 2006 to ~30.0% in 2016, and the 3-month risk of VRE decreased from 4.8% to 1.2%. Moreover, the impacts of vancomycin and metronidazole on the risk of VRE were similar [44]. Therefore, there is no evidence to avoid the use of vancomycin because of the risk of VRE.

SUMMARY

Clinical guidelines have been revised to limit the use of metronidazole as the first-line therapy for CDI in the United States and Europe. They were mainly issued considering the ineffectiveness of metronidazole on hypervirulent *C. difficile*. In Korea, neither an epidemic caused by a hypervirulent *C. difficile* strain nor an emergence of a metronidazole resistant strain has been reported. Moreover, metronidazole does not have any substantial side effects. Its clinical outcomes on non-severe CDI are similar to those of vancomycin. Therefore, we suggest that the use of metronidazole is still an appropriate therapy to cure non-severe CDI in Korea.

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