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Clostridioides difficile infection treatment guidelines adherence and comparison of treatment outcomes of the first, non-severe disease episode between oral metronidazole and vancomycin group: a single tertiary center retrospective study

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Abstract

Background: Management guidelines were established in order to improve disease outcomes of *Clostridioides difficile* infection (CDI); however, recent studies suggest inferiority of oral metronidazole in the treatment of CDI, which brought into question its usefulness even for a first, non-severe CDI. We aimed to explore adherence of the initial CDI therapy to the current ESCMID treatment guidelines and to compare treatment outcomes of the first non-severe CDI episode between oral metronidazole and vancomycin group.

Methods: This retrospective observational study included in-patients of all ages with laboratory confirmed CDI, treated at the University Hospital for Infectious Diseases, Zagreb, Croatia, from 2013 to 2017. Statistical analysis was performed.

Results: Among 1073 hospitalizations due to CDI the mean age was 71.4±17.4 years and females predominated (58.2%). Adherence to the treatment guidelines was found in 655/1073 (61.0%) of patients, being lowest among fulminant CDIs (20.5%). Groups treated initially with oral metronidazole (N=282) and oral vancomycin (N=78) for the first, non-severe CDI episode were comparable by clinical and epidemiological features ($p>0.05$). However, the initial treatment with oral metronidazole had to be changed to another therapy in 64/282 (22.7%) patients, mostly (33/64) due to clinical inefficiency and in 22/64 due to side effects, in comparison to only 2/78 (2.6%) who switched therapy in the vancomycin group.

Conclusions: The low adherence to the treatment guidelines warrants additional education of the clinicians. The high rate of clinical inefficiency and unwanted side effects of oral metronidazole therapy make its usefulness doubtful, even for a first, non-severe CDI.

Keywords: *Clostridioides difficile*, metronidazole, vancomycin, guidelines, adherence

Introduction

Clostridioides difficile has become one of the most important healthcare-associated pathogens in both Europe and United States. Appearance of hypervirulent strains (i.e. BI/NAP1/027) has led to increased incidence, morbidity, mortality and economical impact of the disease.

Management guidelines [1,2] were established in order to reduce morbidity and mortality of *C. difficile* infection (CDI) and their non-observance has been associated with poorer clinical outcomes [3]. The reported overall adherences are low [3-6], often even under 50% of CDI cases, and factors influencing therapeutical decisions being discordant to the guidelines are insufficiently explored.

Although most of the recent studies have shown inferiority of oral metronidazole in comparison to oral vancomycin in treatment of severe/fulminant cases [7,8], clinical validity of its use in the first, non-severe CDI seems to be still an open question.

This study aimed to explore adherence of the administered initial CDI therapy to the current European Society of Clinical Microbiology and Infectious Diseases clinical practice guidelines (ESCMID-CPG) [1], and to compare treatment outcomes of the first, non-severe CDI episodes between oral metronidazole and vancomycin group.

Materials and methods

This retrospective observational study included in-patients of all ages with laboratory confirmed CDI, treated at the University Hospital for Infectious Diseases, Zagreb, Croatia in the period from 2013 to 2017. During 2013, the diagnosis was confirmed by enzyme immunoassay test for detection of A/B toxins from stool samples, while in the period 2014 - 2017 the two-step test was used (screening GDH test confirmed with toxin A/B PCR). Severity of the illness was classified according to Infectious Diseases Society of America/ Society for Healthcare Epidemiology of America clinical practice guidelines (IDSA/SHEA-CPG) formulations; the patients having fever (>38.5 °C), white blood cell count >$15x10^9$/L, and creatinine ≥133 µmol/L [2] were considered to have severe CDI. The observed groups were compared by initial disease severity and comorbidities using ATLAS and McCabe score. Oral metronidazole (500 mg 4 times per day) and oral vancomycin (125 mg 4 times per day) group were compared by following outcome indicators: intensive care unit (ICU) treatment due to CDI (yes/no), all-cause in-hospital mortality rate (%) and need for a change of initial treatment. Symptom progression or stagnation after five days of initial treatment was considered as „clinical inefficiency“. Changing oral vancomycin to the combination of oral vancomycin + intravenous metronidazole was also considered as a „switched therapy“.

Results were analyzed using the SAS (version 9.4, SAS Institute, Cary, North Carolina, USA). Frequencies and percentages, means and standard deviations were calculated. Student t-test, chi-square test, and linear regression method were used. P-value of less than 0.05 was considered as statistically significant.

Results

Overall, there were 1073 treatments due to CDI in an observed period. The mean age was 71.4±17.4 years and majority (58.2%) were female. 23 (2.1%) of the patients were aged 0–17 years, 222 (20.7%) 18–64, 447 (41.7%) 65–79, and 381 (35.5%) ≥80 years. Majority had healthcare-

associated CDI (76.9%), 15.7% had community-associated, and 7.4% had epidemiologically undetermined CDI.

Stratification of the patients by a number of CDI episode, disease severity, and adherence of the intial therapy to the ESCMID-CPG is shown in Table 1.

Adherence to the ESCMID-CPG was found in 655/1073 (61.0%) of patients, and adherence increased with CDI episode number (56.3%, 62.1%, and 85.6% respectively; p=0.214). Adherence to the ESCMID-CPG differed significantly (p<.001) within each number-of-episode group according to the disease severity. Adherence to the guidelines was lowest in the fulminant CDI group (20.5%) whereby it was 21.6% for the first, 15.4% for the second and 25.0% for the ≥ third episode. The overall initial undertreatment was observed in 320/1073 (29.8%) patients; in 9.6% of non-severe, 44.1% of severe and 79.5% of fulminant CDIs.

In-hospital mortality rate decreased with the increase of the disease episode number and it was 11.8%, 8.7% and 5.6% for the first, second and ≥third CDI episode, respectively (p<.001). The need for the ICU admission due to CDI also decreased with the number of the disease episode and it was 2.7%, 0.8% and 0.8% for the first, second and ≥third CDI episode, respectively (p=0.105).

Oral metronidazole and vancomycin groups of patients with first, non-severe CDI episode didn't differ signifficantly regarding mean age, McCabe score, ATLAS score, proportion of healthcare-associated CDIs, need for ICU tretment due to CDI and in-hospital mortality rates (all p>0.05), but the initial treatment with metronidazole had to be changed significantly more often, as it is shown in Table 2.

In patients with first, non-severe CDI initial oral metronidazole treatment was switched to another therapy in 64/282 (22.7%) of patients: in 33/282 (11.7%) due to clinical inefficiency, in 18/282 (6.4%) due to gastrointestinal side effects, in 4/282 (1.4%) due to allergic reaction and in 9/282 (3.2%) due to other/unrecorded reasons. In patients with first, non-severe CDI initial oral vacomycin treatment was switched to another therapy in 2/78 (2.6%) of patients: in one patient due to clinical inefficiency (1.3%) and in other due to gastrointestinal side effects (1.3%). In the group od patients with first, non-severe CDI oral metronidazole treatment was significantly more often clinically inefficient in comparison to oral vancomycin (p=0.005).

Discussion

In comparison to the previous studies, in which adherence of the initial CDI treatment to the treatment guidelines ranged from 40.2 – 54.0% [3-6], in our tertiary care center specialized in infectious diseases the higher, but stil unsatisfactory adherence of 61% has been recorded.

Studies analysing the gudelines adherence reported mostly its decrease with increase of disease severity [4,6], and the adherence as low as 8.5% in a group of severe CDI [4], along with adherence of 16.6% in a group of fulminant CDI has been reported [5]. In a study from USA that analyzed patient factors which indicate provider's nonadherence to an institutional CDI treatment guidelines, bivariate analyses associated 5 factors with nonadherence: older age, ICU admission, duration of antibiotics and mild/moderate and severe infection (all p<.05), and in the logistic regression model, severe infection (p<.001) was independently associated with guideline nonadherence [6], which suggests disregarding of disease-severity criteria while choosing initial CDI therapy.

Our results also indicate outweight of a number-of-disease-episode criteria above disease-severity criteria in decision making process, which has resulted in a high rate of undertreatment, especially in severe (44.1%) and fulminant (79.5%) CDI cases.

The impaired clinical outcomes due to disregard of CDI treatment guidelines, especially among more severe ill patients, have been observed by numerous studies [3,5]. The disease outcomes can be influenced by many predisponing factors existing in a patient, and by clinical burden of the disease *per se*, but the negative clinical impact of the initial undertreatment of CDI infection should also be taken into the consideration. It seems that the rate of unfavorable outcomes could be reduced by familiarization of the attending physicians with the treatment guidelines, and by increased use of CDI severity criteria while making therapeutic decissions.

Recently, a randomized, placebo-controlled trial has shown that oral vancomycin (259 patients) was superior to metronidazole (278 patients); overall clinical success was 81.1 *vs.* 72.7% (p=.02), respectively; however, the significant difference was not confirmed in a subgroup of severe CDIs [9]. Superiority of oral vancomycin *vs.* metronidazole only in a subgroup of severe CDIs has been reported recently in a large meta-analysis which included five randomized controlled trials (risk ratio: 1.19, 95% CI: 1.02-1.39, p=0.03), and in a retrospective, propensity-matched cohort study evaluating 2068 patients treated due to first CDI episode with oral vancomycin matched to 8069 patients in the metronidazole group (adjusted relative risk for all-cause 30-day mortality, 0.79; 95% CI, 0.65 to 0.97; adjusted risk difference, -0.04; 95% CI, -0.07 to -0.01) [7,8]. On the contrary, one retrospective study analysing 168 patients with mild/moderate CDI (NAP1 n = 85, non-NAP1 n = 83) showed higher rate of treatment response in oral vancomycin *vs.* oral metronidazole group (97% vs. 82%, p=0.002*)* [10], as our study did.

The latest (2017) update of IDSA/SHEA-CPG recommend oral vancomycin as a first choice treatment in a first, non-severe CDI episode, while current European ESCMID-CPG (2013) for the same indication recommend metronidazole [1,2]. However, there is an additional recommendation in ESCMID-CPG to prefer the use of oral vancomycin in a tretment of non-severe CDI in a patients with increased risk for recurrent disease (age >65 years, continued use of non-CDI antibiotics after diagnosis of CDI, and/or after CDI treatment, severe underlying disease and/or renal failure, a history of previous CDI, concomitant use of antacid medications) [1], which hugely reduces recommendations for metronidazole use, complicating simultaneously the decision making process and likely decreasing the guidelines adherence. Besides rising resistance of *C. difficile,* common gastrointestinal side-effects, concommitant restriction of alchocol use and, due to its bountifull apsorption in the gut, its increased potential for systemic allergic reactions and rare, but serious, neurotoxicity, in addition to suggested decreased clinical efficacy in a treatment of non-severe CDIs, the place of metronidazole in ESCMID-CPG seems to be questionable. As the strongest argument for metronidazole use in this indication remains its much lower cost in comparison to vancomycin capsules, which can be overbridged by the oral use of much cheaper liquid intravenous vancomycin compositions.

Conclusions

The additional effort should be putted to increase the adherence to the CDI treatment guidelines (i.e. increase of the guidelines practicality, education of the attending clinicians - especially to obey the disease-severity criteria, etc.) which could improve clinical outcomes. The notable rate of

clinical inefficiency and unwanted side effects of oral metronidazole therapy observed in our study confirmes doubtfulness of its use, even for a treatment of first, non-severe CDI.

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Disclosure of interest
The authors report no conflict of interest.

References

[1] Debast SB, Bauer MP, Kuijper EJ, et al. European society of clinical microbiology and infectious diseases: Update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014;20:1–26.

[2] McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:987–94.

[3] Patel I, Wungjiranirun M, Theethira T, et al. Lack of adherence to SHEA-IDSA treatment guidelines for Clostridium difficile infection is associated with increased mortality. J Antimicrob Chemother. 2017;72:574-581.

[4] Kobayashi K, Sekiya N, Ainoda Y, et al. Adherence to clinical practice guidelines for the management of Clostridium difficile infection in Japan: a multicenter retrospective study. Eur J Clin Microbiol Infect Dis. 2017;36:1947–53.

[5] Rodríguez-Martín C, Serrano-Morte A, Sánchez-Muñoz LA, et al. Diferencias entre las recomendaciones y la práctica clínica en la infección por Clostridium difficile. Rev Calid Asist. 2016;31:152–8.

[6] Siehnel JT, Lavigne JE, Rightmier EA, et al. A Retrospective Study of Patient Factors That Indicate Provider Nonadherence to an Institutional Clostridium difficile Treatment Guideline. J Pharm Pract. 2018;31:169–74.

[7] Igarashi Y, Tashiro S, Enoki Y, et al. Oral vancomycin versus metronidazole for the treatment of Clostridioides difficile infection : Meta-analysis of randomized controlled trials. J Infect Chemother. 2018;1–8.

[8] Stevens VW, Nelson RE, Schwab-Daugherty EM, et al. Comparative Effectiveness of Vancomycin and Metronidazole for the Prevention of Recurrence and Death in Patients With Clostridium difficile Infection. JAMA Intern Med. 2017;177:546-553.

[9] Johnson S, Louie TJ, Gerding DN, et al; Polymer Alternative for CDI Treatment (PACT) Investigators. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. Clin Infect Dis 2014;59:345–54.

[10] Siegfried J, Dubrovskaya Y, Flagiello T, et al. Initial Therapy for Mild to Moderate Clostridium difficile Infection Exploring the Role of Oral Metronidazole Versus Vancomycin in 168 Hospitalized Patients. Infect Dis Clin Pract. 2016;24:210–6

Table 1. Initial therapy for *Clostridioides difficile* infection according to the number of episode, severity of illness and adherence to the ESCMID clinical practice guidelines

Number of CDI[†] episode	***Oral metronidazole (N=549)***	***Oral vancomycin (N=479)***	***Metronidazole iv.[§] + oral vancomycin (N=45)***	***Total (N=1073)***
First *(N=695)*				
Non-severe *N (%)*	**282 (77.7)***	78 (21.5)	3 (0.8)	363 (100)
Severe *N (%)*	147 (60.2)	**90 (36.9)***	7 (2.9)	244 (100)
Fulminant *N (%)*	37 (42.0)	32 (36.4)	**19 (21.6)***	88 (100)
Second *(N=253)*				
Non-severe *N(%)*	50 (35.7)	**86 (61.4)***	4 (2.9)	140 (100)
Severe *N (%)*	17 (19.5)	**67 (77.0)***	3 (3.4)	87 (100)
Fulminant *N (%)*	6 (23.1)	16 (61.5)	**4 (15.4)***	26 (100)
≥ Third *(N=125)*				
Non-severe N (%)	5 (7.5)	**61 (91.0)***	1 (1.5)	67 (100)
Severe *N (%)*	4 (8.0)	**44 (88.0)***	2 (4.0)	50 (100)
Fulminant *N (%)*	1 (12.5)	5 (62.5)	**2 (25.0)***	8 (100)
Total *N (%)*	549 (51.2)	479 (44,6)	45 (4,2)	1073 (100)

*initial treatment accordant to the ESCMID guidelines; [†]*Clostridioides difficile* infection; [§]intravenous

Table 2. Comparison of the epidemiological, clinical and outcome parameters among patients with the first non-severe episode of the *Clostridioides difficile* infection treated with oral metronidazole and oral vancomycin

Variables	**Oral metronidazole *(N=282)***	**Oral vancomycin *(N=78)***	**P value**
	mean±SD*	***mean±SD***	
McCabe score	1.3±0.7	1.3±0.6	1.000
ATLAS score	4.1±1.9	4.5±1.9	0.102
Age (years)	66.8±20.9	66.7±20.4	0.970
	N (%)	***N (%)***	
Healthcare-associated CDI	184 (65.2)	59 (75.6)	0.083
ICU treatment due to CDI	1 (0.4)	0	0.577
In-hospital mortality rate	6 (2.1)	1 (1.3)	0.649
Change of initial treatment (yes)	64 (22.7)	2 (2.6)	<.001

*standard deviation