Family Medicine & Primary Care Review 2024; 26(2): 155–160, https://doi.org/10.5114/fmpcr.2024.139023

ORIGINAL PAPERS

ISSN 1734-3402, eISSN 2449-8580

An analysis of probiotic use for treatment of *Clostridioides difficile* infections in patients hospitalized at the University Clinical Hospital in Wroclaw, Poland, 2016–2018

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** *Clostridioides difficile* infection is the most common diarrheal disease associated with antibiotic use. Treatment includes fidaxomicin, vancomycin, metronidazole, rifaximin, fecal flora transplants, and bezlotoxumab. There are numerous reports of the potential beneficial effects of using probiotics in *Clostridioides difficile* infection.

Objectives. This study aimed to analyze the effects of the use of probiotics on patients with *Clostridioides difficile* infection who were hospitalized at the University Clinical Hospital in Wroclaw from 2016 to 2018.

Material and methods. The study was conducted by analyzing the medical records of patients treated from 2016 to the end of 2018 at the University Clinical Hospital in Wroclaw. We examined the frequency of use of probiotics in *Clostridioides difficile* infection, differences in the use of probiotics by year of hospitalization, mortality among patients taking probiotics and not receiving this type of treatment, length of hospitalization by probiotic use, and the relationship between the gender of patients and the use of probiotics.

Results. 313 patients were enrolled in the study, out of 319 patients total. Almost half of the patients (45.54%) received no probiotic during hospitalization. The most commonly administered probiotics were preparations containing *Saccharomyces boulardii*, which were received by 24.2% of patients. The use of probiotics did not affect mortality in *Clostridioides difficile* infection. Patients receiving probiotics were hospitalized longer. There was no significant statistical difference in probiotic use by patient gender.

Conclusions. Probiotic use did not reduce the risk of death or shorten the length of hospitalization of patients with *Clostridioides difficile* infection.

Key words: Clostridium infections, therapeutics, probiotics.

Baran MP, Drobnik J, Belovičová M, Moricová Š, Pobrotyn P. An analysis of probiotic use for treatment of *Clostridioides difficile* infections in patients hospitalized at the University Clinical Hospital in Wroclaw, Poland, 2016–2018. *Fam Med Prim Care Rev* 2024; 26(2): 155–160, doi: https://doi.org/10.5114/fmpcr.2024.139023.

Background

Clostridioides difficile infection is the most common diarrheal disease associated with antibiotic use [1], causing up to 25% of post-antibiotic diarrhea [2]. Carriage of this bacterium is found in about 3% of the population [3], though the percentage is much higher in newborns and infants, at around 50–60%. After the first year of life, it decreases to the value found among the rest of the population [4]. Carriage among hospitalized patients is significantly higher at 20–40% [5, 6].

According to the US Centers for Disease Control and Prevention, *Clostridioides difficile* infection can be diagnosed when a patient has diarrhea or toxic megacolon and at least one of the following criteria is met:

- presence of toxin A or B in the stool or detection of a *Clostridioides difficile* strain in the stool by another method,
- finding of pseudomembranous colitis on endoscopic examination or during surgery,
- finding of pseudomembranous colitis on histopathological examination [7].

The course of the disease varies from mild symptoms to severe diarrhea with dehydration, intestinal obstruction, and septic shock. Treatment includes fidaxomicin, vancomycin, metronidazole, rifaximin, fecal flora transplants, and bezlotoxumab [8–10].

One of the main factors in the occurrence of infection is antibiotic therapy, which leads to damage to the physiological flora of the gastrointestinal tract, creating favorable conditions for the growth of the *Clostridioides difficile* bacteria [1].

Probiotics are being sought to restore the intestinal flora and thereby prevent the development of this infection or alleviate its course. According to the World Health Organization's 2002 definition, probiotics are living organisms that, when ad-

ministered in adequate amounts, cause beneficial health effects [11]. There are numerous reports of the potential beneficial effects of using probiotics in *Clostridioides difficile* infection. *Saccharomyces boulardii* has been shown to secrete a protease that degrades toxin A and impedes the binding of the toxin to its receptors on the surface of the small intestine in rats [12]. *Lactobacillus acidophilus* strain LA-5 has been shown to decrease the concentration of toxins produced by *Clostridioides difficile* and to reduce the symptoms of infection in mice [13]. *Bifidobacterium breve* BR3, *Bifidobacterium lactis* LR5, *Lactococcus lactis* SL3, and *Lactobacillus rhamnosus* LR5 strains have been seen to compete with *Clostridioides difficile* in *in vitro* studies, resulting in reduced bacterial viability [14, 15].

Objectives

This study aimed to analyze the effects of the use of probiotics on mortality and length of hospitalization of patients with *Clostridioides difficile* infection who were hospitalized at the University Clinical Hospital in Wroclaw from 2016 to 2018.

Material and methods

The study was conducted by analyzing the medical records of patients treated from 2016 to the end of 2018 at the University Clinical Hospital in Wroclaw. Adult patients with symptoms of *Clostridioides difficile* in whom the infection was confirmed by laboratory methods were qualified to the study. We examined the frequency of use of probiotics in *Clostridioides difficile* infection, differences in the use of probiotics by year of hospitalization, mortality among patients taking probiotics and not receiving this type of treatment, length of hospitalization by probiotic use, and the relationship between the gender of patients and the use of probiotics. Due to the small number of patients treated with Lakcid or treated with more than one probiotic, these cases were excluded from the analysis of differences in the type of probiotic used by year of hospitalization. If the patient was hospitalized at the turn of the year, he or she was counted in the year in which more days of hospitalization had elapsed. Patients for whom it was not possible to determine if they used probiotics or not were excluded from the study.

Statistical analysis

Relationships between the qualitative variables were verified using the chi-square test (along with a post-hoc test based on standardized residuals), and Fisher's exact test was used when some of the categories were low in number. Relationships between quantitative variables and qualitative variables with more than three categories were verified using the Kruskal-Wallis test with Bonferroni's correction and Dunn's test as a post-hoc test for the distribution of the quantitative variable (length of hospitalization), which deviated significantly from the normal distribution. The normality of the distributions was verified using the Kolmogorov-Smirnov test. A *p*-value of 0.01 was taken as the level of significance on account of the small size of the patient group (313, of whom 176 received a probiotic) and to reduce the risk of taking a random result as statistically significant. The analysis was performed using *R* software (https://cran.r-project.org).

Table 1 lists the probiotics used in patients with *Clostridioides difficile* infection hospitalized at the University Clinical Hospital in Wroclaw from 2016 to 2018.

Ethical consideration

Permission to perform the study was issued by the Bioethics Committee of the Medical University of Wroclaw. Opinion Number: KB-611/2018.

Results

Out of 319 patients diagnosed with *Clostridioides difficile* infections while hospitalized at the University Clinical Hospital in Wroclaw between 2016 and 2018, 313 patients were enrolled in the study. Information on whether probiotics were used in the remaining 6 diagnosed patients was not available, so these patients were excluded from the study.

Table 2 shows the frequency of probiotic use in patients with *Clostridioides difficile* infection.

Almost half of the patients (45.54%) received no probiotic during hospitalization. The most commonly administered probiotics were preparations containing *Saccharomyces boulardii* (Enterol/LacidoEnter), which were received by 24.2% of patients. Only 1 in 10 patients (9.87%) was treated with more than one probiotic.

Table 1. Probiotics used in patients with *Clostridioides difficile* infection at the University Clinical Hospital in Wroclaw, 2016–2018

Trade name	Composition
Enterol 250 [16], LacidoEnter [17]	*Saccharomyces boulardii* 250 mg
Lacidofil [18]	2×10^9 CFU *Lactobacillus rhamnosus* R0011, *Lactobacillus helveticus* R0052
Lakcid [19]	2×10^9 CFU *Lactobacillus rhamnosus*
Lakcid forte [19]	10^{10} CFU *Lactobacillus rhamnosus*
Sanprobi IBS [20]	10^{10} CFU *Lactobacillus plantarum* 299v
Trilac plus [21]	7.4×10^8 CFU *Lactobacillus acidophilus* 1×10^8 CFU *Lactobacillus delbrueckii* subsp. bulgaricus 7.6×10^8 CFU *Bifidobacterium lactis* 1.6×10^9 CFU *Lactobacillus rhamnosus* GG (ATCC 53103) 72 mg fructooligosaccharides
Osłonka Gastro [22]	1.64×10^9 CFU *Lactobacillus plantarum* 1.64×10^9 CFU *Streptococcus thermophilus* 409×10^8 CFU *Lactobacillus acidophilus* 410×10^8 CFU *Lactobacillus rhamnosus* 410×10^8 CFU *Bifidobacterium lactis* 246×10^8 CFU *Bifidobacterium breve* 246×10^8 CFU *Bifidobacterium longum* 346.384 mg fructooligosaccharides

Source: authors' work based on bibliographic references [16–22].

Table 3 presents the analysis of the use of probiotics by year of hospitalization.

There were no statistical differences in the use of probiotics by year of hospitalization; this allows us to analyze data from the individual years together and to exclude the year of hospitalization as a factor that might confound later statistical analysis.

Table 4 shows the mortality rate of patients infected with *Clostridioides difficile*, by probiotic use.

Table 5 shows an analysis of the use of specific probiotics by survival in patients with *Clostridioides difficile* infection.

There were no differences in mortality between patients using different probiotics. The use of probiotics did not affect mortality in *Clostridioides difficile* infection.

Table 6 presents probiotic use in relation to duration of hospitalization.

Table 7 shows an analysis of hospitalization duration in patients receiving specific probiotics.

Patients who received several probiotics were hospitalized longer than patients who received Enterol/LacidoEnter, with a median length of hospitalization amounting to 40 days compared to 24 days ($p = 0.005$, $Z = 3.50$).

The use of probiotics did not lead to shorter hospitalizations.

Table 8 shows the relationship of probiotic use to patient gender.

Table 2. Analysis of the frequency of probiotic use in patients with *Clostridioides difficile* infection hospitalized at University Clinical Hospital in Wroclaw between 2016 and 2018

Probiotic	Number of patients	Percentage of patients included in the study
The patient did not receive a probiotic	143	45.54
The patient received a probiotic	170	54.14
Enterol/LacidoEnter	76	24.20
Lacidofil	56	17.83
Lakcid	4	1.27
Lakcid forte	1	0.32
Sanprobi IBS	2	0.64
More than one probiotic	31	9.87

Table 3. Use of probiotics by year of hospitalization in patients with *Clostridioides difficile* infection treated at the University Clinical Hospital in Wroclaw, 2016–2018

Year of hospitalization	2016	2017	2018	*p*
Probiotics (%)				0.212
No probiotic	31 (48.4)	59 (59.0)	53 (47.7)	
Enterol/LacidoEnter	17 (26.6)	21 (21.0)	38 (34.2)	
Lacidofil	16 (25.0)	20 (20.0)	20 (18.0)	

Table 4. Mortality in *Clostridioides difficile* infection by probiotic use among patients treated at the University Clinical Hospital in Wroclaw, 2016–2018

	Number of patients who died	Number of patients who survived	Mortality (%)	*p*
Patients who received a probiotic	38	132	22.35	0.200
Patients who did not receive a probiotic	41	102	28.67	
All patients	79	234	25.24	

Table 5. Analysis of the effect of probiotic use on survival in patients hospitalized with *Clostridioides difficile* infection at the University Clinical Hospital in Wroclaw between 2016 and 2018

Probiotics (%)	Number of patients who died	Number of patients who survived	*p*
No probiotic	41 (51.90)	102 (43.59)	0.446
Enterol/LacidoEnter	17 (21.52)	59 (25.21)	
Lacidofil	13 (16.46)	43 (18.38)	
Lakcid, Lakcid forte, Sanprobi IBS	0 (0.0)	7 (2.99)	
Several probiotics	8 (10.13)	23 (9.83)	

Table 6. Probiotic use among patients hospitalized with *Clostridioides difficile* infection at the University Clinical Hospital in Wroclaw in 2016–2018 by duration of hospitalization

Variable under study	No	Yes	*p*
Probiotics used (median [interquartile range])	22 [22]	29 [29]	**0.002**

Patients receiving probiotics were hospitalized longer.

Table 7. Analysis of hospitalization duration by probiotic used to treat patients with *Clostridioides difficile* infection

	Enterol, LacidoEnter (median [interquartile range])	Lacidofil (median [interquartile range])	Lakcid (median [interquartile range])	Multiple probiotics (median [interquartile range])
Length of hospitalization (median [interquartile range])	24 [26]	27 [36.5]	16 [26]	40 [39]
p	**0.004**			
Dunn's test Values above the main diagonal of the matrix are Z coefficients, while those below the main diagonal are the significance levels of the individual comparisons				
	Enterol, LacidoEnter	Lacidofil	Lakcid	Several probiotics
Enterol, LacidoEnter	–	0.88	-0.46	**3.50**
Lacidofil	1.000	–	-0.84	2.64
Lakcid	1.000	1.000	–	2.22
Several probiotics	**0.005**	0.083	0.267	–

Table 8. Probiotic use by gender of patients with *Clostridioides difficile* infection at the University Clinical Hospital in Wroclaw in 2016–2018

	Men	Women	*p*
Probiotics (%)			0.160
No probiotic	63 (52.1)	80 (51.9)	
Enterol/LacidoEnter	28 (23.1)	48 (31.2)	
Lacidofil	30 (24.8)	26 (16.9)	
Probiotic used (%)	76 (54.7)	94 (54.0)	0.999

There was no significant statistical difference in probiotic use by patient gender.

Discussion

The disruption of the natural bacterial flora of the intestines by antibiotic therapy plays an important role in the pathogenesis of *Clostridioides difficile* infection. It should thus be expected that treatment with bacterial flora will bring therapeutic benefits. There are numerous reports in literature on the use of fecal transplantation in patients with *Clostridioides difficile* infection. Such treatment has generally good results, reduces the risk of recurrence, and reduces mortality [23, 24]. Stool transplantation is recommended in the current 2021 IDSA/SHEA guidelines as a treatment option for second and subsequent recurrences of *Clostridioides difficile* infection [8]. It would therefore be expected that the use of probiotics alone (fecal transplantation being, in fact, the administration of bacterial flora) will bring benefits to the treatment of *Clostridioides difficile* infection. However, literature casts doubt on this hypothesis, and the impact of probiotic use on the course of *Clostridioides difficile* infection remains unclear. There are conflicting reports in literature regarding the benefits of using probiotics in preventing and treating *Clostridioides difficile* infection. The greatest hopes are associated with the *Saccharomyces boulardii* strain. *Saccharomyces boulardii* secretes a protease that degrades toxin A and impedes its binding to receptors on intestinal epithelial cells [12]. A retrospective cohort study by Wombwell et al. (*n* = 8763) showed that administration of *Saccharomyces boulardii* led to a 57% reduction in the risk of in-hospital *Clostridioides difficile* infection: an OR of 0.57 with a CDI rate of 0.66% [25]. As mentioned in the introduction to this paper, beneficial effects of *Lactobacillus* and *Bifidobacterium* in *Clostridioides difficile* infection have been found in animal and *in vitro* studies [13–15]. However, the results of the large randomized controlled clinical trial PLACIDE (*n* = 2941) showed no effect of *Lactobacillus* or *Bifidobacterium* administration on the incidence of CDI [26]. The 2012 meta-analysis by Johnston et al. supports the use of probiotics in preventing *Clostridioides difficile* infection. Their study, which included 3,818 adult patients with this infection, showed that the use of probiotics during antibiotic therapy reduced the risk of *Clostridioides difficile* infection by 66% [27]. However, in another meta-analysis, Pillai and Nelson examined papers evaluating the effects of using probiotics in the treatment of *Clostridioides difficile* infection [28]. In one of the studies examined in the meta-analysis [29], a reduction in the risk of recurrence of *Clostridioides difficile* infection was found, with an odds ratio of 0.59, at a 95% confidence interval of 0.35–0.98, *p* = 0.04. However, no benefits of using probiotics in the treatment of *Clostridioides difficile* infection were found in the other studies examined by those authors [28].

Due to the lack of conclusive data, the 2021 guidelines of the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) for treatment of *Clostridioides difficile* infection lack a recommendation for probiotic use [8]. Analogous guidelines are given by ESCIMID [9]. In addition, it should be mentioned that there are reports of cases of gastrointestinal mycoses caused by the *Saccharomyces boulardii* [30].

Conclusions

The use of probiotics was not a standard element of the treatment of *Clostridioides difficile* infection at the University Clinical Hospital in Wroclaw between 2016 and 2018.

Probiotic use did not reduce the risk of death or shorten the length of hospitalization of patients with *Clostridioides difficile* infection at the University Clinical Hospital in Wroclaw. There is no clinical justification for the use of probiotics in *Clostridioides difficile* infection.

Source of funding: This work was funded from the authors' own resources.
Conflicts of interest: The authors declare no conflicts of interest.

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Figures: 0
References: 30

Received: 28.11.2023
Reviewed: 04.12.2023
Accepted: 18.02.2024

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