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Factors Affecting the Use of Probiotics during Antibiotic Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To indicate the importance of the use of probiotics and the factors that influence the use of probiotics during antibiotic therapy.
Introduction: Antibiotics are pharmacological agents selectively toxic to bacteria, but non-toxic or acceptably toxic to humans, prescribed and used in the treatment of bacterial infections. The most common gastrointestinal complication during antibiotics use is diarrhea.

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Probiotics are live microorganisms, bacteria and yeasts, which are used in the therapy of numerous conditions, especially in intestinal diseases.
Methods: An anonymous survey of 207 patients from Bosnia and Herzegovina who used antibiotics and probiotics in the period from February 2023 to March 2024.
Results: The results indicate that the use of antibiotics is frequent. About a third of the examined patients used the probiotic occasionally or not at all during the duration of the antibiotic therapy. About two thirds of the patients took the probiotic on their own initiative. A large part of the examined patients is familiar with the purpose of using probiotics. The price of probiotics plays a significant role in the application and length of use of probiotics.
Discussion: Frequent use of antibiotics can increase the likelihood of gastrointestinal side effects, especially diarrhea. The use of probiotics is often shorter than the duration of antibiotic therapy. It's use is often occasional, and on patients initiative, mostly because of the price of probiotics.
Conclusion: The obtained results indicate that it is important to point out the purpose of the use of probiotics in addition to antibiotics to patients, and that a decrease in the price of probiotics would increase the length of use of probiotics.

Keywords: Antibiotic; probiotic; therapy; bacteria.

1. INTRODUCTION

1.1 Antibiotics

Antibiotics are pharmacological agents selectively toxic to bacteria, but non-toxic, or acceptably toxic to humans (Kalenić 2013). There are over 300 types of known antibiotics, but about 40 are used in therapy. Antibiotics are created by lower organisms, most often saprophytic bacteria from the soil or fungi. Synthetic antibiotics (penicillins, cephalosporins) are created by chemical changes in the molecules of biological antibiotics and their superiority over biologicals is that they have a greater antimicrobial spectrum. Each antibiotic has its own spectrum of action. Some act on Gram-positive bacteria (Benzylpenicillin), while others act on Gram-negative bacteria (aminoglycosides). There are also broad - spectrum antibiotics that work on both types of bacteria (chloramphenicol and tetracyclines). Antibiotics as medicines are expected to act on the causative agents of the infection without damaging the cells of the sick host, which is not fully possible for now.

The introduction of antibiotics into clinical use was probably the greatest medical success of the 20th century (Hutchings and Truman 2019). The discovery of penicillin, as the first scientifically proven antibiotic, happened by accident, when in 1928 Alexander Fleming discovered spores of the mold *Penicillium notatum* on the colonies of staphylococci he was researching. Mold caused the death of staphylococcal colonies and was the first evidence of natural antibiotic activity (Lobanovska and Pilla 2017). With that discovery, the golden age of antibiotic development and a new era of modern medicine began. Antibiotics enabled the effective control of infectious diseases and led to the possibility of curing previously deadly diseases and saved the lives of millions of people. Antibiotics can be classified into several large groups based on the following criteria: source, chemical structure, mechanism of action, type of action and spectrum of action (Adzitey 2015).

Based on the source, antibiotics are divided into: natural compounds obtained from microorganisms, semi -synthetic compounds (structurally modified natural compounds) and synthetic compounds. Natural antibiotics (benzylpenicillin, cephalosporins and gentamicin) are highly toxic, while semi-synthetic (ampicillin and amikacin) and synthetic antibiotics (moxifloxacin and norfloxacin) are less toxic and have a greater therapeutic effect (Pancu et al. 2021).

Considering their influence on the growth and survival of bacteria, antibiotics can be divided into bactericidal and bacteriostatic. This division is not strictly defined, considering that bacteriostatic agents can also have a bactericidal effect at high concentrations. Bactericidal compounds cause bacterial cell death while bacteriostatic compounds stop the cellular activity and growth of bacteria without causing cell death. Bactericidal antibiotics include β - lactams, aminoglycosides, glycopeptides, quinolones, streptogramins, lipopeptides and macrolides. Bacteriostatic antibiotics include sulfonamides, tetracyclines, chloramphenicol, oxazolidinones and macrolides (Pancu et al. 2021).

According to the spectrum of action, antibiotics are divided into broad -spectrum and narrow-spectrum antibiotics. Broad- spectrum antibiotics are effective against several types of Gram-positive and Gram-negative bacteria, while narrow- spectrum antibiotics are effective against only one type of pathogen. According to existing experimental evidence, narrow - spectrum antibiotics are preferred over broad-spectrum antibiotics precisely because of the specificity of their action and the lower risk of bacterial resistance to antibiotics (Acar 1997). Based on the chemical structure, antibiotics are divided into: β - lactams, macrolides, tetracyclines, aminoglycosides, sulfonamides and quinolones (Ebimobowei 2016). The structural diversity of antibiotics is directly related to their different mechanisms of action.

Today, we count them among one of the most prescribed medicines (Katzung 2008). In the practice of drug administration, antibiotics take the second place in the frequency of side effects (Souissi et al. 2018).

1.2 Side Effects during Antibiotic Treatment

Antibiotics are prescribed and used in therapy to eliminate pathogenic bacteria that cause a certain disease. However, in addition to therapeutic effects, antibiotics can cause numerous side effects. The most common side effects described during treatment with antibiotics are hypersensitivity, hematological, neurological, gastrointestinal, renal, cardiac, pulmonary and hepatic side effects (Rouveix 2023).

Gastrointestinal side effects are the most common side effects associated with the use of antibiotics. These include:

anorexia, nausea, vomiting, diarrhea, epigastric pain and abdominal cramps. These symptoms are dose-dependent and have been described with all classes of antibiotics. They most often occur with oral preparations. Macrolides are the most difficult to tolerate oral antibiotics (Cunha 2001). Clarithromycin is associated with gastric discomfort and a metallic taste. The symptoms are related either to a direct irritant effect or to the toxic effect of antibiotics. Reducing the harmful effect can be achieved by reducing the dose, treating the symptoms or taking the medicine at the same time with food (Wood 1991). However, food can interfere with the absorption of certain antibiotics such as erythromycin, oleandomycin, or oral penicil lins. Tetracyclines are well tolerated orally with the exception of minocycline and doxycycline, which may cause gastrointestinal reactions if taken on an empty stomach. Therefore, they should always be taken with food (Everts 2013).

Antibiotics, in addition to acting on the pathogenic bacteria for which they are prescribed, destroy and disrupt a large part of the otherwise normal gut microbiome. One of the common gastrointestinal complications of antibiotic use is antibiotic - associated diarrhea, which is thought to be caused by "disrupting the good bacteria" that live inside us. Diarrhea caused by *Clostridium difficile* should be highlighted. It is an irritating diarrhea that occurs due to a change in the balance of the intestinal f lora after the administration of β-lactams. Quinolones, doxycycline, and meropenem can also cause *Clostridium difficile*-related diarrhea. Other diarrheas are most often caused by the use of macrolides, ampicillin, ceftriaxone or trovafloxacin Czepiel et al. 2019, (Mullish and Williams 2018). Antibiotic use is the most important risk factor for *Clostridium difficile* infection.

1.3 Probiotics

Probiotics are products that contain live, precisely defined microorganisms (or are obtained from them), in sufficient numbers, capable of changing the microflora (by implantation or colonization) in a certain part of the human body, and thus exerting beneficial effects on human health (Schrezenmeir and Vrese 2001). They can be a combination of live beneficial bacteria and/or yeasts that naturally live in the body and have multiple roles in maintaining health. Most often, these are lactic acid bacteria of the genus *Bifidobacterium* or *Lactobacillus* and the fungus *Saccharomyces cerevisiae (Saccharomyces boulardii)*, which is most often used in diarrhea caused by the use of antibiotics.

Probiotics are part of the human microbiome, which represents all the microorganisms that inhabit the surface and interior of our body. The microbiome consists of bacteria, fungi, viruses and protozoa. In order for bacterial species to receive the title of probiotics they must be: non-pathogenic, of human origin, resistant to stomach acid and digestive enzymes in order to reach the small and large intestine alive, where they

perform their function. *Lactobacillus* and *Bifidobacterium* species, the yeast *Saccharomyces crerevisiae* and some non-pathogenic *Escherichia coli* and *Bacillus* species are most often mentioned and used as probiotics.

Lactobacillus is a genus of gram-positive, non-sporogenic rod-shaped bacteria in the family *Lactobacillaceae* that are characterized by their ability to produce lactic acid. One of the well-known species of the *Lactobacillus* genus is *Lactobacillus paracasei*, a bacterium that can most often be found in naturally fermented dairy products and is also used as part of therapeutic probiotic preparations. The most important species from this genus are: *Lactobacillus acidophilus*, *Lactobacillus casei, Lactobacillus delbrueckii subsp. bulgaricus, Lactobacillus paracasei, Lactobacillus. reuteri* and *Lactobacillus rhamnosus.*

Bifidobacterium is another large genus of probiotic bacteria. Like *Lactobacillus*, *Bifidobacterium* species are natural inhabitants of the human digestive system and are most abundant in the large intestine. They belong to anaerobic lactic acid bacteria and various factors, such as stress, diet and antibiotic use, significantly affect their number and activity. Unlike *Lactobacillus*, bifidobacteria have the ability to produce short-chain fatty acids, which are known to "feed" intestinal cells and have a positive effect on peristalsis (movement) of the intestine, the work of the heart, brain and kidney muscles, and participate in the metabolism of fats and carbohydrates in liver. *Bifidobacterium longum* is one of the most studied bifidobacteria, and it is used to prevent diarrhea during antibiotic therapy, to reduce the symptoms of lactose intolerance and to reduce blood cholesterol levels. In addition to it, *Bifidobacterium bifidus, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium lactis* and *Bifidobacterium longum* are also important.

1.4 Significance, Action and use of Probiotics

The action of probiotics depends on the genus and species, as well as on the applied dose. It is known that a therapeutic dose of probiotic preparations must contain a certain minimum number of colonies (CFU - number of colony-forming units), whose number should not be below 10^9 to 10^{10} CFU, and for preventive purposes it is recommended to use slightly smaller doses, from 10^6 to 10^9 CFU. Probiotics that are used orally (by mouth) need to pass through the digestive tract alive through the stomach to the intestines where they achieve their effect. And they achieve their effect in several ways: (Kim et al. 2013).

1. **By impacting the epithelial barrier in the intestines:**

- By strengthening tight junctions between cells of the intestinal epithelium (tight junctions)
- By impacting the production of intestinal mucosa

2. **Impacting on pathogenic bacteria:**

- By f ighting for food
- Fighting for the binding site – inhibition of pathogen binding
- Production of bacteriocins - antimicrobial substances

3. **By impacting immunity**

4. **Production of short-chain fatty acids**

Certain live microorganisms can help boost immunity. According to the Recommendations published after the Yale/Harvard workshop, the following species and strains can be used for this purpose: LGG (*Lactobacilus rhamnosus GG*), *Lactobacillus acidophilus, Lactobacillus plantarum, Bifidobacterium lactis and Lactobacillus johnsonii* (Floch et al 2015).

About 70% of the cells that participate in immune responses are found in the intestines. Probiotics affect both innate and acquired immunity.

Probiotics are used in the treatment of numerous conditions. Thus, in bacterial vaginosis, the number of *Lactobacillus* species in the vaginal tract is significantly reduced, and the number of pathogenic bacteria is increased. Bacterial vaginosis is usually treated with the antimicrobial metronidazole vaginally or orally, or clindamycin (an antibiotic) orally. In order to reduce the possibility of the infection returning, it is useful to use a probiotic along with the antibiotic, as wel l as after it (Cribby et al. 2008). Probiotic can be taken orally or in the form of a vaginal tablet (Bastani et al. 2012). The most commonly used species to prevent bacterial vaginosis are *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus gasseri, Lactobacillus reuteri* and *Lactobacillus rhamnosus* (Flochet al. 2015).

The International Scientific Association for Probiotics and Prebiotics recommends the use of probiotics in children for: regurgitation, colic, infectious or diarrhea caused by antibiotics, diarrhea due to *Clostridium difficile*, as a complementary therapy for ulcerative colitis, *Helicobacter pylori*, constipation in intestinal syndrome, nosocomial infections, atopic dermatitis and to preserve oral health. One of the most studied probiotic species in children's colic, *Lactobacillus reuteri*, has shown that it reduces the duration and the intensity of the colic (Chau et al. 2015). The World Allergological Organization recommends the use of probiotics in infants and children with atopic dermatitis (Fiocchi et al. 2015). Pregnant women can use probiotics throughout their pregnancy (Elias et al. 2011).

Comparing the effectiveness of probiotic supplementation with antibiotics, several studies have shown various beneficial therapeutic effects of probiotic bacteria (*Lactobacillus, Bifidobacterium, Saccharomyces*) in many intestinal diseases (Lang 2010, Gao et al. 2010, Fedorak and Madsen 2004, Vuković 2001). The incidence of *Clostridium difficile* infection is lower and dose-dependent with the use of probiotics (Bouza et al. 2006).

Although they are usually used alongside an antibiotic, it is not recommended to take antibiotics with bacterial probiotics at the same time, in order to reduce the effect of the antibiotic on the probiotic bacteria. However, *Saccharomyces boulardii*, the probiotic strain recommended for the prevention of *Clostridium difficile* infection, is a yeast, not a bacterium, and co-administration with an antibiotic does not interfere with its action. There are currently no accepted guidelines on when to take probiotics. Probiotics have a very good safety profile. Some minor side effects that have been reported include thirst, constipation, bloating, nausea, vomiting, stomach pain, rash, and diarrhea. The use of probiotics is not recommended for people who have a severely immunocompromised organism. The use of probiotics along with antibiotic therapy is of great importance for the preservation and maintenance of the human microbiome and for the prevention of gastrointestinal side effects of antibiotic therapy, especially for the prevention of diarrhea caused by antibiotic therapy. Therefore, great attention should be paid to the introduction of probiotic supplementation with antibiotic therapy, as well a s to the selection of an appropriate probiotic, depending on the antibiotic therapy and the condition being treated with the antibiotic.

2. MATERIALS AND METHODS

An examination of the use and factors influencing the use of probiotics during antibiotic therapy was carried out. The instrument used for the examination is an anonymus online survey. The survey was conducted on respondents who used antibiotic therapy and probiotics in the period from February 2023 to March 2024. 207 respondents from the territory of Bosnia and Herzegovina answered questions anonymously, including informations on the age of the patients and their place of residence. The survey consisted of eight questions, including three open-ended questions and five multiple choice questions. Open-ended questions related to the respondent's age, place of residence and frequency of antibiotic use in the last 12 months. Multiple choice questions related to the use of probiotics, the frequency of using probiotics with antibiotic therapy, knowledge of the importance of using probiotics during antibiotic therapy, and the influence of the price of probiotics on the decision to use probiotics. The obtained results were processed statistically. The online survey and graphical representations of the results were created using Google Forms.

3. RESULTS

The age range of the surveyed respondents was from 15 to 78 years. The largest number of respondents, 61.8%, were 31 to 45 years old, 17.9% of respondents were 15 to 30 years old, 12% of respondents were 46 to 60 years old, and 8.3% of respondents were 61 to 78 years old. The average age of the respondents is 35.9 years (Table 1). It is important to note that the majority of patients were from Sarajevo Canton (38.3%) and Tuzla Canton (34.8%), followed by other cantons (19.4%), Republic of Srpska (5.5%) and Brčko District (2%) (Table 2).

Table 1. Respondent's age

Age (years)	15-30	31-45	46-60	61-78
Respondents (%)	17.9%	61.8%	12.0%	8.3%
Average age (years)	35.9			

Table 2. Respondent's residence

Residence	Sarajevo Canton	Tuzla Canton	Republic of Srpska	Brčko District
Respondents (%)	38.3%	34.8%	5.5%	2%

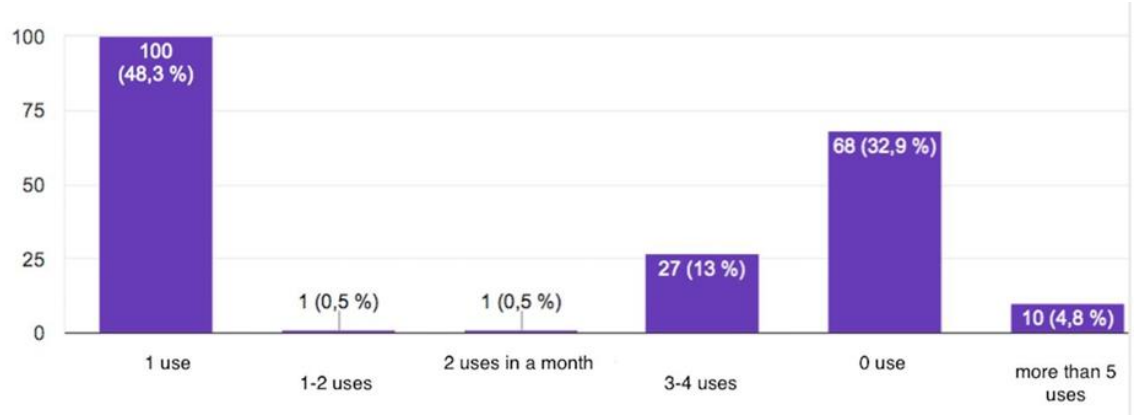

Fig. 1. Answers to the question: "How many times in the last 12 months have you used antibiotic therapy?"

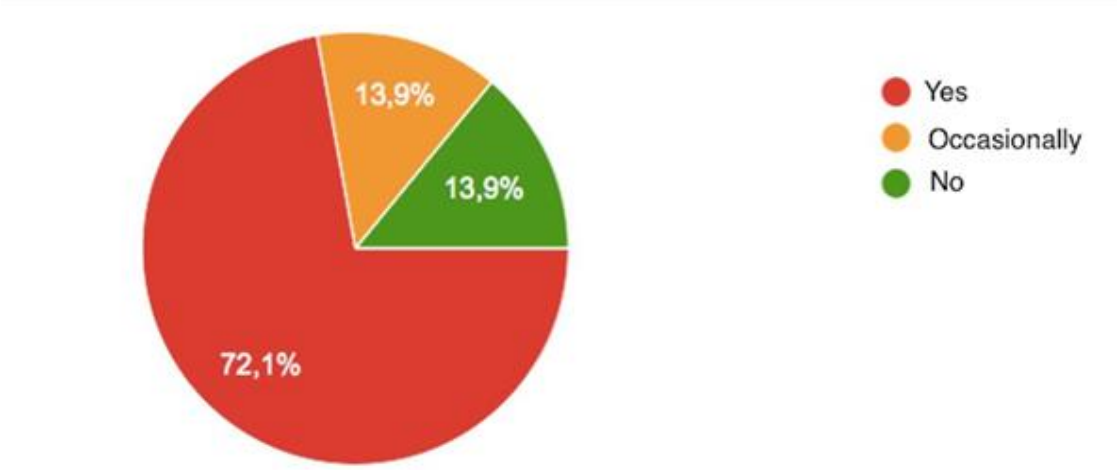

Fig. 2. Answers to the question: "Did you also use a probiotic during antibiotic therapy?"

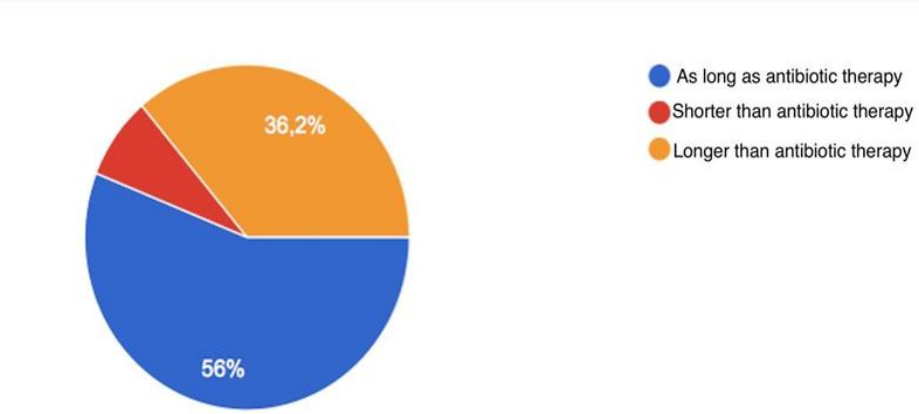

Fig. 3. Answers to the question: "How long do you take probiotics with antibiotic therapy?"

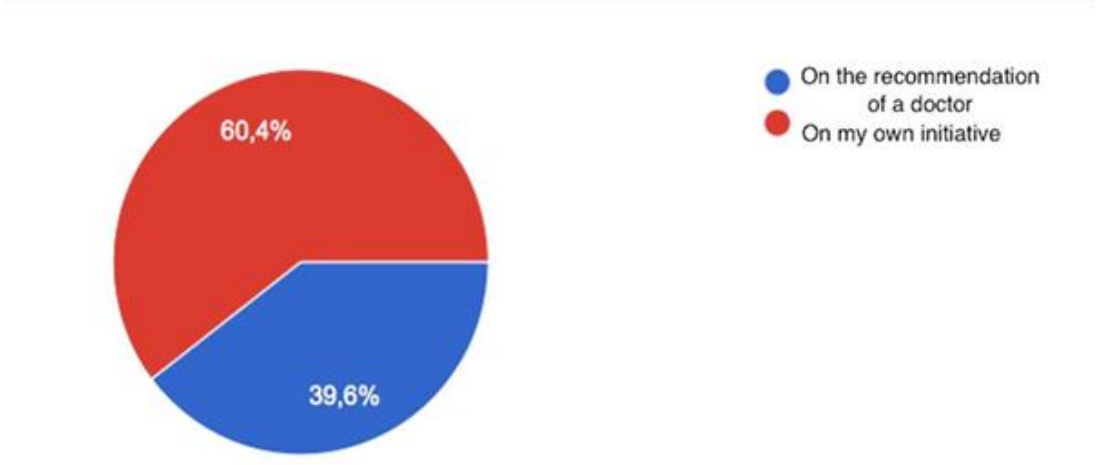

Fig. 4. Answers to the question: "I take probiotics: 1. On the recommendation of a doctor, 2. On my own initiative?"

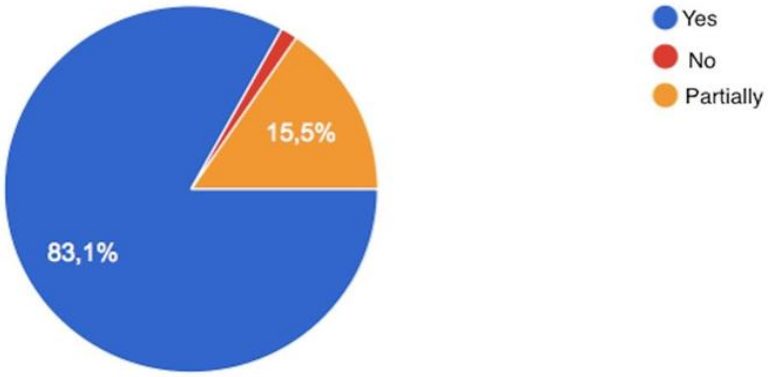

Fig. 5. Answers to the question: "I know the purpose and importance of taking probiotics along with antibiotic therapy?"

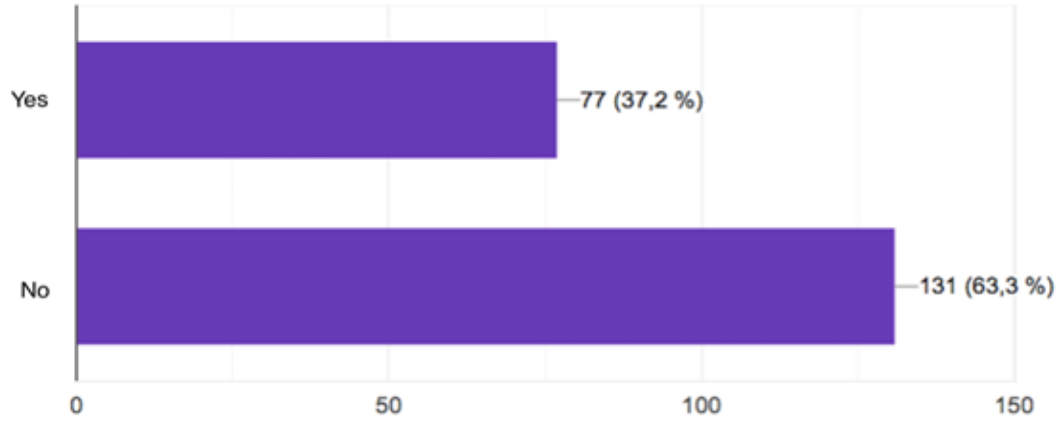

Fig. 6. Answers to the question: "Does the price of probiotics influence your decision on the use and length of use of probiotics with antibiotic therapy?"

According to the answers of respondents to the question about the frequency of antibiotic use (Fig. 1), it is evident that 67% of respondents used some type of antibiotic in the last 12 months. 48.3% of respondents used an antibiotic at least 1 time in the last 12 months, while 13% of them used an antibiotic 3 to 4 times in the last 12 months. 4.8% of respondents used an antibiotic more than 5 times in the last 12 months.

72.1% of respondents who used antibiotic therapy in the last 12 months also used a probiotic during the therapy. 13.9% of respondents claimed that they did not use probiotics with an antibiotic, and 13.9% claimed that they used a probiotic occasionally (Fig. 2).

Regarding the duration of probiotic supplementation with antibiotic therapy (Fig. 3), 56% of the examined respondents claimed that they used the probiotic as long as they used antibiotic, 36.2% used the probiotic longer than the duration of the antibiotic therapy, while 7.7% claimed that they used the probiotic shorter than the duration of the antibiotic therapy.

The last three questions of the survey refer to the examination of factors that influence the use of probiotics and the duration of probiotic supplementation with antibiotic therapy. The obtained results show that 60.4% of the examined respondents used the probiotic on their own initiative, and only 39.6% used the probiotic on the recommendation of a doctor (Fig. 4).

In addition to the above showed results, it was examined how familiar the respondents are with the term probiotics, their importance and purpose of use during antibiotic therapy. The results indicate that the majority of examined respondents, 83.1%, were familiar with the purpose and importance of taking probiotics along with antibiotic therapy. 15.5% of respondents claimed that they are partially aware of the purpose and importance of taking probiotics with antibiotic therapy, and only 1.4% claimed that they are not aware of the purpose and importance of taking probiotics with antibiotic therapy (Fig. 5).

The survey also addressed the issue related to the influence of the price of probiotics on the decision to use probiotis and length of use of probiotics along with antibiotic therapy. 63.3% of examined respondents claimed that the price does not influence their decision on the use and length of use of probiotics with antibiotic therapy, while 37.2% of respondents claimed that the price influences their decision on the use and length of use of probiotics with antibiotic therapy (Fig. 6).

4. DISCUSSION

From the data obtained by this research, we can conclude that the use of antibiotics is very common in all age groups of surveyed respondents and that repeated antibiotic therapy in a period of 12 months is represented by a significant number of respondents, which can increase the probability of gastrointestinal side effects of antibiotic therapy. The obtained results from our research show that a significant number of respondents used probiotics as a supplement to antibiotic therapy, but also that almost one-third of the total number of examined patients did not use probiotics at all in addition to antibiotic therapy or the use of probiotics was occasional. Slightly less than half of the examined patients used a probiotic shorter than the duration of antibiotic therapy or only during antibiotic therapy, which consequently can contribute to the increase in the likelihood of gastrointestinal side effects of antibiotic therapy, especially diarrhea caused by the use of antibiotics. In the literature, similar conclusions are drawn. According to Aberra, relapse of the diarrhea caused by *Clostridium difficile* can be expected in more than 27% of cases (without probiotics) within 3 days to 3 weeks after the end of antibiotics therapy. In a randomized controlled trial, Surawicz observed a significant reduction in the relapse rate of *Clostridium difficile* infection by giving high-dose vancomycin with a probiotic compared to the antibiotic without the probiotic. He also determined that administration of probiotics with low doses of metronidazole or vancomycin was without statistical significance in the occurrence of relapse (Aberra 2024, Bouza et al. 2006). According to McFarland, the use of antibiotics in combination with probiotics has shown promise in reducing the incidence of relapse, especially in cases of *Lactobacillus spp*. and *Saccharomyces boulardii* (McFarland 2009). On the other side, according to the protocol of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), there is insufficient evidence to recommend the addition of probiotics to antibiotic therapy. In support of this, there are new studies that observed the invasive course of the *Clostridium difficile*

infection after the use of *Saccharomyces boulardii* in immunocompromised patients (Hempel et al. 2012, Musher et al. 2005, Gao et al. 2010, Bauer et al. 2009).

Our results support the fact that the examined respondents are highly aware of the importance of taking probiotics along with antibiotic therapy, but also that doctors do not recommend the use of probiotics for a large number of patients who are prescribed antibiotics. Consequently, it can be concluded that recommending probiotic supplementation with antibiotic therapy, choosing the appropriate probiotic and pointing out the importance of it to the patients, by doctors, should be increased. Considering that probiotic preparations are not among the drugs prescribed to patients at the expense of the Health Insurance Institute, and that more than one third of the surveyed patients stated that the price influenced their choice and decision to use probiotics, it can be concluded that the lower price of probiotics could influence an increase in the rate of use of probiotics with antibiotic therapy, as well as an increase in the length of use of probiotics during antibiotic therapy. The research is important because it tries to shed light on the role and importance of probiotics use in addition to antibiotic therapy and also it shows some of the factors that can affect probiotic use. However, more research will be needed to demonstrate the impact of probiotic therapy in preventing side effects of antibiotics, especially gastrointestinal side effects, and to show all the factors that can influence the decision to include probiotics in therapy. The limitation of our study is small sample of patients.

5. CONCLUSION

Probiotics are of great importance in the treatment of numerous conditions, especially as a complementary therapy during antibiotic therapy. Many researches indicated that the use of probiotics together with antibiotics significantly contributes to reducing the likelihood of repeated bacterial vaginal infections, as well as that probiotic cultures have various beneficial therapeutic effects in many intestinal diseases. The incidence of Clostridium difficile infection is significantly reduced when a probiotic is used in therapy along with antibiotics. A survey conducted on patients from the area of Bosnia and Herzegovina who used antibiotic therapy in the last 12 months indicated that the use of antibiotics is common and that additional probiotic therapy is often occasional or not included at all. Using the probiotic on the initiative of the patient s, show that patients are mainly familiar with the purpose and importance of using probiotics. It is also important to pay attention to counseling patients, pointing out the importance of using probiotics in addition to antibiotic therapy and tend to reduce the price of probiotics in order to increase the rate of use and the length of use of probiotics in addition to antibiotics.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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