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The need for individual selection of probiotics containing lactobacilli and enterococci to improve efficacy therapy for campylobacteriosis

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Summary

The article highlights the problem of improving the rational therapy of campylobacteriosis. Along with antibiotics there are probiotics in the treatment regimens, which in the form of mono- or complex therapy have advantages because they do not violate intestinal microbiocenosis, but on the contrary, can carry out the correction of dysbiotic conditions. Also as antimicrobials probiotics have different effects on the growth of pathogenic microorganisms.

The review presents the data obtained in the study of the effect on the growth of clinical isolates *of Campylobacter spp.* probiotics in the *in vitro* system. The anticampylobacter activity of *Enterococcus faecium L3*, *Lactobacillus plantarum 8 R-A3*, *Lactobacillus acidophilus* and *Saccharomyces boulardii* probiotic cultures was studied by two-layer agar and drop method. The antagonistic activity of chemically synthesized bacteriocins was also analyzed. High sensitivity *of Campylobacter spp.* to probiotics containing lactobacilli and enterococci and their metabolites (including bacteriocins) was revealed. The strain-specific activity of probiotics and its dependence on their ability to produce bacteriocins was found. The results obtained and the data of other researchers analyzed in the article indicate the need for individual selection of probiotics for the therapy of campylobacteriosis, the advisability of analyzing the bacteriocinogenicity of strains and testing their effect on the growth of clinical isolates.

Keywords: campylobacteriosis, probiotics, bacteriocins, *Enterococcus*, *Lactobacillus*

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The need for individual selection of probiotics containing lactobacilli and enterococci to increase the effectiveness of therapy for campylobacteriosis

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Summary

The article highlights the problem of improving the rational treatment of campylobacteriosis. Probiotics are present in treatment regimens along with antibiotics, which have the advantage that they do not violate intestinal microbiocenosis and provide the ability to correct dysbiotic conditions. As well as antimicrobial agents, probiotics have different effects on the growth of pathogenic microorganisms. *Campylobacter spp.* probiotics in the in vitro system.

The article studies the anticampylobacter activity of probiotic cultures of *Enterococcus faecium L3*, *Lactobacillus plantarum 8 R-A3*, a mixture of *Lactobacillus acidophilus* and *Saccharomyces boulardii* by two-layer agar and droplet method. Analysis of the antagonistic activity of chemically synthesized bacteriocins. The high sensitivity of *Campylobacter spp.* was presented. to probiotics having lactobacilli and enterococci, as well as as their metabolites (including bacteriocins). The strain-specific activity of probiotics and its dependence on their ability to produce bacteriocins were found. The results and data of other researchers indicate the need for individual selection of probiotics for the treatment of campylobacteriosis, the feasibility of analyzing the bacteriocinogenicity of the strains and testing their effect on the growth of clinical isolates.

Keywords: campylobacteriosis, probiotics, bacteriocins, enterococci, lactobacilli

Conflict of interest. Authors declare no conflict of interest.

Campylobacteriosis is one of the most common bacterial intestinal infections worldwide. In Western Europe, Australia and North America, pathogenic Campylobacter is the main cause of acute enterocolitis with hemorrhagic stool manifestations ("bloody diarrhea", hemocolitis) in young children [1]. Campylobacteriosis has spread globally over the past decade, with a dramatic increase in the number of cases in North America, Europe and Australia [1, 2]. In our country, information on the incidence of this infection is collected only in selected medical

The true incidence of campylobacteriosis remains underestimated due to the difficulty of laboratory diagnosis of this infection. The prevalence of campylobacteriosis is largely due to a variety of transmission routes: 90% of all cases of infection arise from eating chicken or other meat products, a little less frequent entry of campylobacter bacteria into the human body occurs through the use of unboiled water, raw milk or by contact with animals [3].

Among the *Campylobacter* species that most commonly cause disease in humans are *C.*

jejuni and *C. coli* [4]. Entry of these microorganisms into the intestine leads to damage of mucosal cells of the digestive tract, triggering local and systemic inflammatory response [3].

Depending on the dose of the pathogen, the state of the digestive tract, and the child's immune response, the infectious process can proceed both as a mild infection with scanty dyspepsia and as a severe form with severe intoxication and diarrheal syndromes [5].

In addition to the "classic" forms of campylobacter, characterized mainly by symptoms of acute gastroenteritis and enterocolitis, the possibility of septicemia, infectious arthritis, Guillain-Barré and Miller-Fisher syndrome has been proved. Particular attention should be paid to data on the frequent development of inflammatory bowel diseases (nonspecific ulcerative colitis, Crohn's disease), as well as functional disorders of the gastrointestinal tract after infection [6.]

The growing incidence of campylobacteriosis, the variety of clinical forms of the disease, and difficulties in timely diagnosis of infection determine the need for a comprehensive study of the peculiarities of this disease.

One of the most pressing problems faced by the practitioner is the choice of a rational therapy regimen for campylobacteriosis. A growing number of publications on the high resistance of the microorganism to a number of antibacterial drugs determine the need for continuous optimization of rational treatment tactics for this infectious disease and the inclusion of new groups of drugs. According to a number of researchers, the use of probiotics can increase the effectiveness of treatment of campylobacteriosis [7]. However, it is worth recognizing that the efficacy of different probiotic strains varies greatly and requires additional study and systematization of the incoming data.

The choice of an optimal treatment regimen for campylobacteriosis depends on the clinical picture of the disease, type of diarrhea, severity of symptoms, local data on the level of campylobacter resistance to drugs, as well as on the features of the patient's premorbid background. Nowadays, according to both Russian clinical guidelines [8] and "guidelines for treatment of acute gastroenteritis" of foreign American [9] and European [10] scientific societies, treatment of campylobacteriosis is based on a combination of etiotropic, pathogenetic and symptomatic therapy.

Pathogenetic treatment includes rehydration and infusion therapy, diet therapy, sorbents, enzyme supplements and probiotics. Symptomatic therapy consists of the use of antipyretics, antispasmodics, and blood-restoring drugs.

The etiotropic antibacterial therapy, which is carried out only in moderate to severe invasive forms of the disease and in immunocompromised cases. Clinical symptoms indicating a severe course of the disease are: blood in the stool, prolonged (more than 3 days) high fever, and prolonged persistence or recurrence of clinical symptoms within one week [5]. Effective therapy is observed when etiotropic treatment is administered in the first days of the disease. The drugs of choice are macrolides (azithromycin), aminoglycosides, chloramphenicol, tetracyclines, and fluoroquinolones. It is worth noting that of all the above groups of drugs, macrolides have proven to be the most effective. Carbapenems and penicillins combined with β-lactamase inhibitors are the reserve drugs for the treatment of severe forms of campylobacteriosis that are resistant to the current therapy.

The efficacy of antibacterial therapy for campylobacteriosis has been reviewed in several large studies. Thus, according to a meta-analysis that included 11 scientific papers, it was shown that antimicrobial therapy reduced the duration of dyspeptic phenomena by an average of 40-48 hours; the number of *Campylobacter spp.* isolated from feces was also reduced. [11].

The duration of etiotropic therapy depends on the form of the disease, so the recommended duration of antibacterial drugs in localized forms is 3-5 days, in generalized forms the duration of treatment is at least 14 days.

However, one of the adverse effects of antibacterial drugs is the development of dysbiotic conditions and the formation of drug resistance. Bacterial strains belonging to the genus *Campylobacter* are becoming increasingly resistant to fluoroquinolones and, to a lesser extent, to macrolides. One of the reasons for resistance to these drugs is their use not only for the treatment of humans, but also in veterinary medicine to reduce contamination of animals and meat products with Campylobacter [1-3, 11]. Compared with resistance to fluoroquinolones, macrolide resistance is much less common in *Campylobacter spp.* Nevertheless, an increase in the prevalence of macrolide-resistant *C. jejuni and C. coli* has been observed in both developed and developing countries [12, 13], which leads to the search for alternative therapies.

One such method is the use of probiotics. However, their efficacy is not always sufficiently effective. It cannot be excluded that this is due to the different anticampylobacter activity of probiotic strains and their metabolites. The results of the study of the effect of probiotic enterococci, lactobacilli, bifidobacteria, and escherichia on the growth of *Campylobacterspp.* are presented in Table 1.

Table 1.

Peculiarities of anti-campylobacter activity of different probiotic strains of Campylobacter in the *in vitro* system [14-20].

No.	Probiotic strain	Effect	Possible mechanism
1.	*Lactobacillus spp.*	Presence of *C. coli* and *C. jejuni* inhibition zones	-
	Bifidobacterium spp..	Presence of *C. coli* and *C. jejuni* inhibition zones	-
	Escherichia coli strain Nissle 1917 (ECN)	The presence of *C. coli* and *C. jejuni*	-
2	*Lactobacillus spp.*	Inhibitory activity t- pH<4.3 against *Campylobacter spp.* (*C. coli* or *C. jejuni*)	a
	Bifidobacterium spp.	No antagonistic effects of- Retrieved from	-
	E. faecium NCIMB	10415No antagonistic effects of- Retrieved from	-
3	*Lactobacillus plantarum* N8, N9, ZL5	Antagonistic activity against *C. jejuni*.	Lowering the pH of the environment due to productionof metabolites such like lactic acid, the synthesis of substances similar to antibiotics.
	Lactobacillus casei ZL4	Reducing adhesion and invasion *C. jejuni* to HT-29 cells. Good tolerance with artificial gastric and small intestinal juices.	
4.	*Lactobacillus plantarum* 0407 and *Bifidobacterium bifidum* Bb12 together with oligofructose and xylo-oligosaccharides	Reduced growth *of C. jejuni*	-
5.	*Lactobacillus acidophilus* ATCC 4356	Reduced growth *of C. jejuni.*	-
6.	*Lactobacilluscrispatus*	. crispatusmost effectively inhibited the growth *of C. jejuni compared* with *L. acidophilus*, *L. gallinarum* and *L. helveticus.*	All probiotic strains produced high levels of lactic acid, which inhib- Biotrophic growth *of C. jejuni* in vitro. When neutralizing the pH of *Lactobacillus spp*. culture supernatants, there was no inhibition of *C. jejuni*
	Lactobacillus acidophilus	Influence on the growth of Campylobacter *L. acidophilus* NCFM, which are pro- bacteriocin lactacin B, which has no activity against Gram-negative organisms, such as *C. jejuni.*	
	Lactobacillus gallinarum	Growth inhibition *of C. jejuni.*	
	Lactobacillus helveticus	Growth inhibition *of C. jejuni.*	
7.	*E.* coli producing colicin	Did not affect the growth of *Campylobacter spp.*	-
	Fifty-six strains *Enterococcus spp.*	Did not affect growth *Campylobacter spp.*	-
	Bacteroides spp.	Did not affect growth *Campylobacter spp.*	-
	Lactobacillus spp.(P93)	Antagonized 10 strains of *Campylobacter spp*.	*Lactobacillus spp.* synthesize organic acids (formic and acetic acids), hydrogen peroxide and bacteriocins.
8.	*Lactobacillus salivarius* SMXD51	Strong activity against four *C. jejuni* (strains: 81-176, NCTC 11168, AC4700, and C94). One- antibacterial activity was not detected against *C. jejuni* strains C97ANSES640, AC4868, AC0858, AC2571, C276, and C1994.	-

Analysis of the literature data showed that probiotic escherichia, bacteroides have low antagonistic activity against *Campylobacter spp*. The exceptions were isolated probiotic strains of bifidobacteria, lactobacilli and enterococci.

This study had two objectives: 1) to develop methods to study the antagonistic anticampylobacter activity of probiotic microorganisms, to evaluate the effectiveness of their action; 2) based on these methods to compare probiotics used in daily practice in our country.

The effect of probiotic strains *Enterococcus faecium* L3 (laminolact, Avena LLC, Russia), *Lactobacillus plantarum* 8 R-A3 (lactobactrin, Microgen), *Lactobacillus acidophilus* mixture (Lekko CJSC, Russia), *Enterococcus faecium* SF68 and *Bifidobacterium bifidum* (company "Ferrosan AS, Denmark) and *Saccharomyces* biocladiin (LABORATRIPE BIOCODEX, France) for the growth of 5 clinical isolates *of Campylobacter spp.*

Table 2.
Growth inhibition *Campylobacter spp.*probiotics.

Designations:
1 - presence of campy growth lobacilli, 0 - no growth. CFU - colony-forming units

Campylobacter strains		C.coli 1			C.coli 2			C. jejuni 1			C. jejuni 2			C.jejuni 3		
Probiotic strains	**Coe/ml**	108	107	106	108	107	106	108	107	106	108	107	106	108	107	106
***Bifidobacterium longum* + *Enterococcus faecium* SF68**	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
***Lactobacillus acidophilus* mixture**	7	1	0	0	0	0	0	1	0	0	0	0	0	1	1	1
	5	1	0	0	0	0	0	1	0	0	0	0	0	1	1	1
***Lactobacillus plantarum* 8R-A3**	7	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Sacharomyces boulardii	7	1	0	0	1	1	0	1	1	1	0	0	0	1	1	1
	5	1	1	0	1	1	0	1	1	1	1	0	0	1	1	1
***Enterocccus faecium* L3**	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Negative control	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Positive control - azithromycin		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Five clinical isolates *of Campylobacter spp.* (two *C. coli* strains and three *C. jejuni* strains) were obtained from the collection of bacterial cultures of the Federal State Research and Clinical Center for Infectious Diseases.

Antagonistic activity was assessed using the two-layer agar method [21]. Probiotic cultures at concentrations of 7 and 5 lg CFU/ml were added to nutrient medium (trypticase-soy agar, Conda Pronadisa, Spain). After solidification, a second layer of the same nutrient medium containing no probiotics was placed on the surface of the lower layer. Then, Campylobacter cultures were seeded on the surface of the upper layer at concentrations of 6, 7 and 8 lg CFU/ml. The minimum amount of probiotic cultures inhibiting *Campylobacter spp.* growth (CFU/ml) was determined.

The total effect of metabolites produced by probiotic cultures on pure cultures of 5 Campylobacter strains is presented in Table 2. As a positive control we used

It was shown that probiotic strains included in laminolact, acipol, lactobacillin, and bifiform exhibited antagonistic activity against *Campylobacter spp.* in concentrations of 5 and 7 lg CFU/ml.

Enterol did not inhibit the growth of all Campylobacter strains when sucrose culture was added to the bottom layer of agar at a concentration of 5 lg CFU/ml, and when indicator cultures were sown at a dose of 6-7 lg CFU/ml. As can be seen from the description of the anti-campylobacter activity of Enterol, to inhibit the growth of Campylobacter under the influence of-

The quantitative ratio of the antagonist to Campylobacter was important, but the metabolites of Saccharomyces (which acted only at a dose of 7 lg CFU/ml) were not.

For the more active lactic acid bacteria cultures, the antagonist dose was also important and had peculiarities for each probiotic. The maximum effect at 5 lg CFU/ml was shown by laminolact and bifiform, which inhibited the indicator cultures at all concentrations. Acipol, regardless of the dose, had no effect on three indicator cultures (*C. coli* 1, *C. jejuni* 1, and *C. jejuni* 3 at 8-7 lg CFU/ml). Lactobacillus was more active, it did not inhibit the reproduction of only *C. jejuni* 3 at 8 lg CFU/ml.

Thus, a strategy for the selection of probiotic agents in the treatment of campylobacteriosis has been developed. The data obtained by other authors were confirmed and supplemented in our experiments. First of all, it concerns high antagonistic activity *of L. plantarum, E. faecium* and *Bifidobacterium bifidum*. The high anticampylo- bacterial activity of lactobacilli may be related to the production of organic acids (in particular, lactic acid), and in the enterococci we studied - additionally to the ability to produce bacteriocins.

All the examples given in this article show that the treatment of campylobacter teriosis requires not only antibiotics but also probiotics. For this purpose, in a practical laboratory, the two-way method can be used.

layer agar or by droplet method, which allow to reveal the antagonistic activity of probiotics. Equally important and promising may be the assessment of bacteriocinogenicity probiotic strains and further development of antibacterial preparations based on already known enterocins with anticampylobacter effect.

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