

**SYNERGISM AND ANTAGONISM IN INTESTINAL MICROBIAL
COMMUNITIES IN CLOSED ORGANIZED COLLECTIVES**

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**СИНЕРГИЗМ И АНТАГОНИЗМ В МИКРОБНЫХ СООБЩЕСТВАХ
КИШЕЧНИКА В ОРГАНИЗОВАННЫХ КОЛЛЕКТИВАХ ЗАКРЫТОГО
ТИПА**

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Abstract

Introduction. The gut microbiota represents the largest part of the entire human microbiome. The formation of a stable microbiota begins at childbirth, continuing to change during life influenced by various exogenous and hereditary factors. One of such external cues is presented by closed organized collectives, where different individuals, due to the common way of life and nutrition, undergo a restructuring of the intestinal microbial communities. In addition to microbiota quantitative and qualitative changes, inter-microbial communities may also be altered (synergism, antagonism, mutualism). The aim of the study was to analyze the synergistic and antagonistic relationships between intestinal microbial communities in individuals from closed organized collectives. **Materials and methods.** The study group included 120 male subjects aged 18 to 22 years, who lived within the same closed organized collectives for 9 months. Fecal samples were selected for plating prior to living in closed organized collectives (stage 1), and 9 months afterwards (stage 2). The identified microorganisms were assigned to the permanent, supplementary, or random microbiota group. To assess the relationship between pairs of genera, the Jaccard index was calculated. **Results.** The results of the study showed that the synergistic relationships between members of the permanent microbiota remain stable or increase over time, which generally corresponds to the data on the properties of the obligate microbiota. Positive synergistic relationships with additional microbiota have also been identified, e.g., between *Bifidobacterium spp.* and the order of *Lactobacillales*. The synergy of these genera can effectively support normal gastrointestinal tract functioning. However, antagonistic relationships were also noted, especially between some representatives of the additional and permanent microbiota, such as *Klebsiella spp.* Such data may indicate a negative effect of certain microorganisms on the intestinal microbiota in a limited collective setting. **Conclusion.** Further research in this field may help explain changes in microbial communities in organized collectives and develop strategies for healthy microbiota maintenance therein.

Keywords: Gut microbiota; organized collectives; synergism; antagonism; closed collectives.

Резюме

Введение. Микробиота кишечника составляет наибольшую часть всего микробиома человека. Формирование стабильной микробиоты начинается с родов, продолжая изменяться в течении жизни под действием различных экзогенных и наследственных факторов. Одними из таких внешних факторов является нахождение в закрытых организованных коллективах, где у разных лиц из-за общности быта и питания, происходит перестройка микробных сообществ кишечника. Помимо количественных и качественных изменений микробиоты, происходит и изменения во взаимоотношениях (синергизм, антагонизм, мутуализм) между микробными сообществами. Цель исследования – анализ синергических и антагонистических взаимоотношений микробных сообществ кишечника у лиц в закрытых организованных коллективах. *Материалы и методы.* В группу исследования вошли 120 человек, в возрасте от 18 до 22 лет, мужского пола, проживавшие в пределах одного закрытого организованного коллектива на протяжении 9 месяцев. Отбирался кал для посева до начала пребывания в закрытом коллективе (1 этап), и спустя 9 месяцев после (2 этап). Идентифицированные микроорганизмы были отнесены в группу постоянной, добавочной или случайной микробиоте. Для оценки связи между парами родов был рассчитан коэффициент сходства Жаккара. *Результаты.* Результаты исследования показали, что синергические связи между представителями постоянной микробиоты сохраняют стабильность или усиливаются с течением времени, что в целом соответствует данным о свойствах облигатной микробиоты. Также были выявлены положительные синергические связи с добавочной микробиотой, например между *Bifidobacterium* spp. и порядком *Lactobacillales*. Синергизм данных родов способен эффективно поддерживать нормальное функционирования ЖКТ. Однако были отмечены и антагонистические взаимоотношения, особенно между некоторыми представителями добавочной и постоянной микробиоты, такими как *Klebsiella* spp. Такие данные могут указывать на негативное влияние некоторых микроорганизмов на микробиоту

кишечника в условиях ограниченного коллектива. *Заключение.* Дальнейшие исследования в этой области помогут объяснить изменения микробных сообществ в организованных коллективах и разработать стратегии для поддержания здоровой микробиоты в подобных условиях.

Ключевые слова: Микробиота кишечника; организованные коллективы; синергизм; антагонизм; закрытые коллективы.

1 Introduction

The gut microbiota make up the largest part of the entire human microbiome and play a crucial role in maintaining healthy homeostasis. Colonization of the gastrointestinal tract by microorganisms and formation of a stable microbiota begin with childbirth and continue to change throughout life under the influence of various external (lifestyle, diet, medications, geographical location) and inherited factors [6, 10]. One of these external factors is the presence in closed organized collectives (for example, in military units), where different individuals, due to the common way of life and changing the diet to the same type, undergo a restructuring of intestinal microbial communities [4, 5, 8, 9]. In addition to quantitative and qualitative changes in the microbiota, there are also changes in the relationships between microbial communities. Synregism and antagonism of various microorganisms can both favorably affect the physiology of the gastrointestinal tract, (for example, antagonism of the intestinal microbiota against pathogens forms colonization resistance) and contribute to the development of pathological processes (for example, the exchange of resistance genes, biofilm formation, etc.) [2, 13].

The aim of this study is to analyze the synergistic and antagonistic relationships of intestinal microbial communities in closed organized collectives.

The study group included 120 people aged 18 to 22 years, male, who lived within one closed organized collective for 9 months. Feces were collected from participants for sowing before the start of their stay in a closed collective (stage 1 of the study), and 9 months after (stage 2 of the study). The study was approved by the Bioethics Committee at Samara State Medical University (protocol No. 252 dated 09/07/2022). Collection and transportation of biomaterial for microbiological research was carried out in accordance with Methodological Guidelines 4.2.2039-05 «Technique for collecting and transporting biomaterials to microbiological laboratories». The biomaterial was sowed under anaerobic conditions using a Bactron 300-2 anaerobic station (Sheldon Manufacturing Inc., USA) on an extended range of nutrient media: MacConkey agar (HiMedia, India), Veillonella agar (HiMedia, India), Clostridium agar (Condalab, Spain), Bifidobacterium agar

(HiMedia, India), Anaerobic agar (HiMedia, India), Brucella agar (HiMedia, India), Muller-Hinton agar with 5% sheep blood (HiMedia, India), chromogenic agar (HiMedia, India), Lactobacillus agar (Condalab, Spain), Saburo agar (HiMedia, India). Cultivation was carried out at a temperature of 37 °C for 120 hours. The cultures were identified by MALDI-ToF mass spectrometry using a MicroflexLT instrument (Bruker, Germany). For all identified microorganisms, the coefficient of constancy (C) was calculated, depending on which they were assigned to the group of constant ($C > 50\%$), additional ($25\% < C < 50\%$) or random ($C < 25\%$) microbiota [3]. To assess the relationship between pairs of genera belonging to permanent and additional microorganisms, the Jaccard index (q) was calculated, depending on which relationship was evaluated as antagonism ($q \leq 30\%$), synergy ($q = 30-70\%$) or mutualism ($q \geq 70\%$) [3]. Statistical analysis was carried out using the StatTech v. 4.6.3 program (developer - StatTech LLC, Russia). Categorical data were described using absolute values and percentages. Quantitative indicators with normal distribution were described using arithmetic means (M) and standard deviations (SD), 95% confidence interval limits (95% CI). In the absence of normal distribution, quantitative data were described using the median (Me) and lower and upper quartiles (Q1 – Q3).

As a result of the study, the permanent intestinal microbiota at the first stage included the following microorganisms: *Aspergillus* spp. (52.5%), *Enterococcus* spp. (84.2%), *Escherichia* spp. (100%), *Lactobacillus* spp. (61.7%). At the second stage, it included: *Enterococcus* spp. (85.8%), *Escherichia* spp. (100%), *Klebsiella* spp. (55%), *Lactobacillus* spp. (53.3%), *Staphylococcus* spp. (65%), *Streptococcus* spp. (53.3%).

Pairs were identified to compare the constant gut microbiota. The results of calculating the Jaccard index for pairs of constant microbiota are presented in Table 1.

As a result of the study, the following microorganisms were included in the additional intestinal microbiota at the first stage: *Bacillus* spp. (30%), *Bifidobacterium* spp. (43.3%), *Citrobacter* spp. (32.5%), *Klebsiella* spp. (49.2%),

Lactococcus spp. (25.8%), *Streptococcus* spp. (33.3%). At the second stage, it included: *Aspergillus* spp. (44.2%), *Bifidobacterium* spp. (48.3%), *Citrobacter* spp. (25.8%), *Clostridium* spp. (25%), *Lacticaseibacillus* spp. (40.8%), *Ligilactobacillus* spp. (29.2%), *Limosilactobacillus* spp. (29.2%), *Micrococcus* spp. (35%), *Pseudomonas* spp. (25.8%).

Pairs were identified to compare the additional gut microbiota. The results of calculating the Jaccard index for pairs of additional microbiota are presented in Table 2.

The study revealed both synergistic and antagonistic relationships between representatives of the intestinal microbiota in individuals forming an organized closed-type team.

Pairs of *Aspergillus* spp. + *Escherichia* spp. and *Aspergillus* spp.+ *Enterococcus* spp. at the first stage, they have a high synergistic relationship, but at the 2nd stage of the study, this relationship is suppressed and turns into an antagonistic one. It can be assumed that this is due to the pronounced negative effect of *Aspergillus* spp. A similar situation can be noted in the pair *Aspergillus* spp.+ *Lactobacillus* spp., where synergy has turned into antagonism. For pairs of representatives of the order *Enterobacterales*, 100% synergy can be noted in the 2nd stage of the study in comparison with the 1st. Also worth noting is the *Escherichia* spp pair. + *Enterococcus* spp. with a coefficient of 84.1% at the 1st stage of the study, corresponding to mutualism, followed by an increase in this relationship at the 2nd stage of the study to 85.8%.

Pairs of additional gut microbiota with a high level of synergy were analyzed. Pairs of *Bifidobacterium* spp. + *Lacticaseibacillus* spp. и *Bifidobacterium* spp. + *Ligilactobacillus* spp. at the 1st stage of the study, when forming an organized closed-type team, they are defined as antagonists, but at the 2nd stage of the study, the presented pairs are defined as synergists. A similar behavior can be observed between pairs of *Bifidobacterium* spp. + *Klebsiella* spp., *Bifidobacterium* spp.+ *Streptococcus* spp., *Lacticaseibacillus* spp. + *Limosilactobacillus* spp., *Ligilactobacillus* spp. + *Pseudomonas* spp.

91 A pair of *Bacillus* spp. + *Klebsiella* spp. at the 1st stage of the study, it was
92 defined as synergistic, but at the 2nd stage, the transition of communication in favor
93 of antagonism is noted. A similar situation can be observed between pairs such as
94 *Citrobacter* spp. + *Klebsiella* spp., *Klebsiella* spp. + *Lactococcus* spp.

95 Thus, the results of the study showed that the synergistic relationships
96 between representatives of the permanent microbiota remain stable or increase over
97 time, which generally corresponds to the data on the properties of the obligate
98 microbiota [7, 11]. Positive synergistic relationships with additional microbiota have
99 also been identified, for example between *Bifidobacterium* spp. and the order of
100 *Lactobacillales*. The synergy of these genera can effectively support the normal
101 functioning of the gastrointestinal tract, which is widely used in the production of
102 probiotics [1]. However, antagonistic relationships were also noted, especially
103 between some representatives of the additional and permanent microbiota, such as
104 *Klebsiella* spp. In recent years, the ability to antagonize the latter has been widely
105 discussed in the scientific community [12]. Such data may indicate a negative effect
106 of certain microorganisms on the intestinal microbiota in closed collectives.

107 Additional data are needed to better understand the synergistic and
108 antagonistic relationships between representatives of the gut microbiota. Further
109 research in this area will help explain the dynamics of changes in microbial
110 communities in organized collectives and develop strategies for maintaining a
111 healthy microbiota in such conditions.

ТАБЛИЦЫ

Table 1. The results of calculating the Jaccard index for pairs of constant microbiota.

Pair	Research stage	a*	b**	c***	q**** *	Relationship direction
<i>Aspergillus</i> spp. + <i>Escherichia</i> spp.	Stage 1	63	120	63	52,5	Synergism
	Stage 2	53	120	53	44,1	Synergism
<i>Aspergillus</i> spp. + <i>Enterococcus</i> spp.	Stage 1	63	101	54	49,0	Synergism
	Stage 2	53	103	46	41,8	Synergism
<i>Aspergillus</i> spp. + <i>Lactobacillus</i> spp.	Stage 1	63	74	39	39,8	Synergism
	Stage 2	53	64	25	27,1	Antagonism
<i>Escherichia</i> spp. + <i>Staphylococcus</i> spp.	Stage 1	120	29	29	24,1	Antagonism
	Stage 2	120	78	78	65,0	Synergism
<i>Enterococcus</i> spp. + <i>Staphylococcus</i> spp.	Stage 1	101	29	24	22,6	Antagonism
	Stage 2	103	78	68	60,1	Synergism
<i>Klebsiella</i> spp. + <i>Staphylococcus</i> spp.	Stage 1	59	29	13	17,3	Antagonism
	Stage 2	66	78	42	41,1	Synergism
<i>Lactobacillus</i> spp. +	Stage 1	74	29	16	18,39	Antagonism
	Stage 2	64	78	49	52,69	Synergism

<i>Staphylococcus</i> spp.						
<i>Staphylococcus</i> spp. + <i>Streptococcus</i> spp.	Stage 1	29	40	8	13,11	Antagonism
	Stage 2	78	64	45	46,39	Synergism

* a – the number of subjects from whom the first microorganism was isolated.

** b – the number of subjects from whom the second microorganism was isolated.

*** c – the number of subjects in whom both microorganisms were isolated from the corresponding pair.

**** q – Jaccard index.

Table 2. The results of calculating the Jaccard index for pairs of additional microbiota.

Pair	Research stage	a*	b**	c***	q*** *	Relationship direction
<i>Bacillus</i> spp. + <i>Klebsiella</i> spp.	Stage 1	36	59	18	23,38	Synergism
	Stage 2	20	66	12	16,22	Antagonism
<i>Bifidobacterium</i> spp. + <i>Klebsiella</i> spp.	Stage 1	52	59	22	24,72	Antagonism
	Stage 2	58	66	37	42,53	Synergism
<i>Bifidobacterium</i> spp. + <i>Ligilactobacillus</i> spp.	Stage 1	52	0	0	0,00	Antagonism
	Stage 2	58	35	22	30,99	Synergism
<i>Bifidobacterium</i> spp. + <i>Limosilactobacillus</i> spp.	Stage 1	52	0	0	0,00	Antagonism
	Stage 2	58	35	22	30,99	Synergism
<i>Bifidobacterium</i> spp. + <i>Streptococcus</i> spp.	Stage 1	52	40	18	24,32	Antagonism
	Stage 2	58	64	35	40,23	Synergism
<i>Citrobacter</i> spp. + <i>Klebsiella</i> spp.	Stage 1	39	59	25	34,25	Synergism
	Stage 2	31	66	18	22,78	Antagonism
<i>Klebsiella</i> spp. + <i>Lactococcus</i> spp.	Stage 1	18	31	20	68,97	Synergism
	Stage 2	66	22	18	25,71	Antagonism
<i>Klebsiella</i> spp. + <i>Streptococcus</i> spp.	Stage 1	18	40	24	70,59	Mutualism
	Stage 2	66	64	40	44,44	Synergism

<i>Lacticaseibacillus</i> spp. + <i>Limosilactobacillus</i> spp.	Stage 1	0	0	0	0,0	Antagonism
	Stage 2	49	35	20	31,2	Synergism
<i>Ligilactobacillus</i> spp. + <i>Pseudomonas</i> spp.	Stage 1	0	12	0	0,0	Antagonism
	Stage 2	35	31	16	32,0	Synergism
<i>Aspergillus</i> spp. + <i>Micrococcus</i> spp.	Stage 1	63	25	10	12,8	Antagonism
	Stage 2	53	42	24	33,8	Synergism

* a – the number of subjects from whom the first microorganism was isolated.

** b – the number of subjects from whom the second microorganism was isolated.

*** c – the number of subjects in whom both microorganisms were isolated from the corresponding pair.

**** q – Jaccard index.

ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи

SYNERGISM AND ANTAGONISM IN INTESTINAL MICROBIAL
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СИНЕРГИЗМ И АНТАГОНИЗМ В МИКРОБНЫХ СООБЩЕСТВАХ
КИШЕЧНИКА В ОРГАНИЗОВАННЫХ КОЛЛЕКТИВАХ ЗАКРЫТОГО
ТИПА

Сокращенное название статьи для верхнего колонтитула:

GUT MICROBIOTA IN CLOSED COLLECTIVES

МИКРОБИОТА КИШЕЧНИКА В ЗАКРЫТЫХ КОЛЛЕКТИВАХ

Keywords: Gut microbiota; organized collectives; synergism; antagonism; closed collectives.

Ключевые слова: Микробиота кишечника; организованные коллективы; синергизм; антагонизм; закрытые коллективы.

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