

R. Kh. Begaydarova, A. M. Izteleuova, G. M. Omarova, Kh. D. Talipbekova, V. R. Atakishiyeva

ROLE OF ENTEROL (*SACCHAROMYCES BOULARDII*) IN PREVENTION AND TREATMENT OF ANTIBIOTIC-ASSOCIATED DIARRHEA IN CHILDREN

Department of children's infectious diseases of Karaganda state medical university (Karaganda, Kazakhstan)

Among the diversity of the etiological factors of antibiotic-associated diarrhea, the greatest importance is attached to *C. difficile*, a gram-positive aerobic spore-forming bacterium that is resistant to most antibiotics. Probiotics have a good effect in the prevention of antibiotic-associated diarrhea, Enterol (*Saccharomyces boulardii*) is the most successful in the ratio of efficacy.

120 children with diagnosed intestinal infections were under supervision, of whom children under 6 months were 20 (16.7%); from 6 months. up to 1 year - 60 (50,0%), over the year - 40 (33,3%). The syndrome of gastroenteritis was noted in 14 (11.6%) children, in 72 (60.0%) - gastroenterocolitis syndrome, in 30 (25.0%) - enterocolitis. In order to select the optimal treatment regimen and evaluate its clinical effectiveness, Enterol (*Saccharomyces boulardii*) prescribed to children up to 1 packet 1 time per day, children over the age of 1 packet 1-2 times a day. The course of treatment was 5 days. The use of Enterol (*Saccharomyces boulardii*) had a positive effect on the duration of the main clinical symptoms in diarrhea syndrome. The use of Enterol (*Saccharomyces boulardii*) at age dosages for 5 days prevents the development of antibiotic-associated diarrhea in children.

Key words: children, antibiotic-associated diarrhea, *C. difficile*, Enterol, *Saccharomyces boulardii*

Antibiotic-associated diarrhea (AAD) is diarrhea that develops in patients receiving antibiotics or when not identified other reasons that manifested from mild self-limited diarrhea to pseudomembranous inflammation of the intestine.

For the given data of a number of authors: the occurrence of symptoms of antibiotic-associated diarrhea, both during antibiotic treatment and after treatment for 2 months was observed in 5-62% of patients [2, 3, 6, 7]. In children who received antibiotic therapy broad-spectrum, diarrheal syndrome met in more than 11% cases and in some cases 42% [2, 4, 5, 7]. The most common reason for the development of intestinal dysbiosis in children can be the use of antibiotics, which could lead to antibiotic-associated diarrhea that can be linked to the negative impact of waste products of *Clostridium difficile* [1].

Estimates on the prevalence of antibiotic-associated prevalence of diarrhea in children in the scientific literature are presented very poorly, making it impossible to assess the problem. Analysis of scientific literature showed that the prevalence of AAD in children in different countries varies from 6.2% to 80% and is associated with intake of amoxicillin/clavulanate. The risk of AAD increases in children at a younger age [1].

It is therefore apparent the need for continuous improvement of the performances of doctors in different fields about the role of the normal microbiota, etiological factors, leading to its pathological changes, approaches to the correc-

tion of dysbiotic disorders. Clinical studies have shown a preventive effect of several probiotics (*Bifidobacterium lactis*, *Bifidobacterium longum*, *Enterococcus faecium*, *Lactobacillus GG*, *Lactobacillus acidophilus*, *Saccharomyces boulardii*) to prevent the development antibiotic-associated diarrhea [1].

The meta-analysis demonstrates reduced risk of AAD by 53% thanks to the use of *S. boulardii*. This is established in children and adult patients. Included in the review clinical studies have not shown side effects due to the intake of *S. boulardii*. However, the use of probiotics cannot be considered totally devoid of risk in specific groups of patients (with immune deficiency and severe systemic diseases) [8].

The use of *Saccharomyces boulardii* in the clinical studies included 1 117 children demonstrated: reduced risk of diarrhea lasting longer than 4 days, reducing the duration of diarrhea by an average of 1 day, decrease the risk of diarrhea on the third day, decrease the duration of hospitalization [9, 10].

In one of the latest recommendations for probiotics in 2015 in the journal (Journal Clinical Gastroenterology) published the recommendations of the group for the study of probiotics Yale University (Yale/Harvard) on the use of probiotics. That is *Saccharomyces boulardii* has the highest level of recommendations for the prevention and treatment of disorders of the intestines. Thus, prevention of complications from antibiotic therapy for *Saccharomyces boulardii*, in treatment of diarrhea *Saccharomyces boulardii* has

level of evidence A.

Objective of the clinical study was to assess the clinical efficacy of the probiotic Enterol (*Saccharomyces boulardii*) in children with intestinal infections.

MATERIAL AND METHODS

The study included 120 children with enteric infections, from them children till 6 months, there were 20 cases (16.7%); from 6 months to 1 year – 60 (50.0%), over the year – 40 (33.3%) of which were in Regional infectious diseases hospital (RID) of Karaganda city.

Additional laboratory examination of children was carried out using the following methods: General clinical (General analysis of blood, urine, coprogram), biochemical (electrolytes, total protein and protein fractions), culture of feces for pathogenic flora, conducting enzyme immunoassay (EIA) for detection of rotavirus antigen in feces.

The diagnosis of intestinal infection from all the sick children was confirmed bacteriologically. Allocated coproculture *Ps. Aerogenosa* was in 1 (0.8%), *Salmonella Enteritidis* – 2 (1.7%), *Proteus Vulgaris* – 3 (2.5%), *Enterobacter cloacae* – 7 (5.8%), *Citrobacter diversus* – 7 (5.8%), *Klebsiella iarrhea* – 8 (6.7%), *Morganella Morganii* – 9 (7.5%), *Proteus Mirabilis* – 10 (8.3%), *Citrobacter former* – 12 (10%), acute enteric infection unspecified etiology in 61 (50.8%). Detection of rotavirus antigen in the feces was in 12 (10%) of the studied patients.

Syndrome of gastroenteritis was in 14 (11.6%) patient, 72 (60.0%) and 30 (25.0%) had enterocolitis. Signs of dehydration were not expressed in 39 (32.5%) examined children. Exsiccosis of the I degree was in 78 (65.0%) patients, of the II degree – in 3(2.5%).

Pathogenetically based basic therapy included infusion therapy with glucose – salt solutions. Fluid were appointed with the purpose of rehydration was calculated in the volume of physiological needs and pathological losses. To select the optimal plan of treatment and evaluation of its clinical effectiveness Enterol (*Saccharomyces boulardii*) were administered to children under the age of 1 year by 1 sachet 1 times a day, and over 1 year by 1 sachet 1-2 times a day. The course of treatment was 5 days.

Have observed patients in the dynamics were evaluated the severity and duration of main clinical symptoms of the disease such as intoxication, the temperature reaction, vomiting, diarrheal syndrome.

Statistical processing of the results of the clinical study. Statistical analysis was performed

using the program STATISTICA.

N-number of patients, p% – percentage, t – Student's test, p-level – statistical significance 95%, CI – from and to the percent within the 95% CI.

If p is less than ($\leq 0,05$) that the received changes are statistically significant, if more ($\geq 0,05$) that the received changes are statistically insignificant.

RESULTS AND DISCUSSION

Results and discussion: At admission all studied sick children was expressed intoxicating syndrome: fever, intoxication, loss of appetite, drowsiness, lethargy, hypodynamia. Dyspeptic syndrome was manifested by vomiting, flatulence, rumbling stomach, loose stools. However, the frequency of occurrence of clinical symptoms has been mixed. Appetite were absent or reduced in 116 (96.7%), is safed in 4(3.3%), thirst was expressed in 81(67.5%), was absent in 39(32,5 per cent), or repeated vomiting after every drink and food were observed in 52(43,3%), vomiting was observed in 68(56,7%) of patients.

Table 1 presents the results of clinical symptoms in the studied patients at admission to the hospital.

One of the manifestations of the syndrome of dehydration was sunken eyeballs – in 81 (67,5%) children, condition of skin folds, which goes back immediately – in 39 (32,5%), less than in 2 seconds – in 78 (65,0%), more than in 2 seconds – in 3 (2,5%).

Visible mucous membranes were dry in 81 (67.5%), wet in 39 (32.5%), tongue dry, the saliva viscid, 81 (6,5%), wet in 39 (32.5%). In palpation iarrhe swollen and painful, 112 (93,3%), soft and painless in 8 (6.7%), thin stool with pathological impurities in 109 (90.8%), porridge-like stool without pathological impurities in 11 (9.2%).

Interpretation of complete blood cell count revealed inflammatory changes in 115 (95.8%) of sick children. In scotoscopy mucus was detected in 120 (100%), the leukocyte count to 20 in the field of view in 56 (46.7%), more than 20 in 64 (53,3%), indicating that the invasive nature of the diarrhea syndrome in the studied patients. The data presented in table 2.

According to the results of the study after treatment was shown only in 1 (08%) of the 120 children's appetite was reduced, 119 (99.2%) recovered fully. Symptoms of toxicosis and dehydration completely arrested all 120 surveyed children (vomiting, thirst, sunken eyeballs, skin fold, visible mucous membranes, tongue). Thin stool with pathological impurities was observed only in

Table 1 – Characteristics of clinical symptoms in the studied patients before treatment

Clinical symptoms	BEFORE TREATMENT			
	n	p%	95%ДИ	95%ДИ
<i>Appetite</i>				
is absent or reduce	116	96,7	93,5	99,9
saved	4	3,3	0,1	6,5
<i>Thirst</i>				
severe	81	67,5	59,1	75,9
is absent	39	32,5	24,1	40,9
<i>Vomiting</i>				
repeated or after each meal drink and food	52	43,3	34,5	52,2
is absent	68	56,7	47,8	65,5
<i>Eyeballs</i>				
sunken eyes	81	67,5	59,1	75,9
no sunken eyes	39	32,5	24,1	40,9
<i>Skin fold</i>				
goes back immediately	39	32,5	24,1	40,9
less than 2 second	78	65,0	56,5	73,5
more than 2 seconds	3	2,5	0,0	5,3
<i>Visible mucous membranes</i>				
are dry	81	67,5	59,1	75,9
are moist	39	32,5	24,1	40,9
<i>Tongue</i>				
is dry, saliva viscid	81	67,5	59,1	75,9
is moist	39	32,5	24,1	40,9
<i>Abdominal palpation</i>				
swollen and painful	112	93,3	88,9	97,8
soft and painless	8	6,7	2,2	11,1
<i>The nature of the stool</i>				
Thin stool with pathological impurities	109	90,8	85,7	96,0
porridge-like stool, without pathological impurities	11	9,2	4,0	14,3

Table 2 – Characteristics of additional laboratory data in the studied patients before treatment

<i>Complete blood cell count</i>				
inflammatory changes	115	95,8	92,3	99,4
no inflammatory changes	5	4,2	0,6	7,7
<i>Scatocopy</i>				
mucus	120	100,0	100,0	100,0
the leukocyte count to 20 in the field/vision	56	46,7	37,7	55,6
more than 20 in the field/vision	64	53,3	44,4	62,3

2 (1.7%) patients. By the end of treatment these adverse phenomena in children disappeared.

Bloating in the form of flatulence was before treatment in 112 (93.3%) children, and after treatment the abdomen was soft, painless in all examined children. Table 3 presents the results of clinical symptoms in the studied patients after treatment.

Interpretation of the complete blood cell count revealed a positive dynamics in 110 (91.7%) and only 10(8.3%) of children were retained inflammatory changes. In scotoscopy mucus and leukocytes to 20 per field of view were detected only in 2 (1%). The data presented in table 4.

Table 3 – Dynamics of clinical symptoms in the studied patients after treatment

Clinical symptom	After treatment					t	p-level
	n	p%	m2	95%CI	95%CI		
Appetite							
is absent or reduce	1	0,8	0,7	0,0	2,5	52,174	0,000
saved	119	99,2	0,7	97,5	100,8	52,174	0,000
Thirst							
severe	0	0,0	0,0	0,0	0,0	15,787	0,000
is absent	100	83,3	11,6	76,7	90,0	9,303	0,000
Vomiting							
repeated or after each meal drink and food	0	0,0	0,0	0,0	0,0	9,579	0,000
is absent	120	100,0	0,0	100,0	100,0	9,579	0,000
Eyeballs							
sunken eyes	0	0,0	0,0	0,0	0,0	15,787	0,000
no sunken eyes	120	100,0	0,0	100,0	100,0	15,787	0,000
Skin fold							
goes back immediately	120	100,0	0,0	100,0	100,0	15,787	0,000
less than 2 second	0	0,0	0,0	0,0	0,0	14,928	0,000
more than 2 seconds	0	0,0	0,0	0,0	0,0	1,754	0,083
Visible mucous membranes							
are dry	0	0,0	0,0	0,0	0,0	15,787	0,000
are moist	120	100,0	0,0	100,0	100,0	15,787	0,000
Tongue							
is dry, saliva viscid	0	0,0	0,0	0,0	0,0	15,787	0,000
is moist	120	100,0	0,0	100,0	100,0	15,787	0,000
Abdominal palpation							
swollen and painful	0	0,0	0,0	0,0	0,0	40,988	0,000
soft and painless	120	100,0	0,0	100,0	100,0	40,988	0,000
The nature of the stool							
Thin stool with pathological impurities	2	1,7	1,4	0,0	4,0	30,942	0,000
porridge-like stool, without pathological impurities	118	98,3	1,4	96,0	100,6	30,942	0,000

Table 4 – Characteristics of additional laboratory data in the studied patients after treatment.

Complete blood cell count							
inflammatory changes	10	8,3	6,4	3,4	13,3	28,104	0,000
no inflammatory changes	110	91,7	6,4	86,7	96,6	28,104	0,000
Scatocopy							
mucus	2	1,7	1,4	0,0	4,0	84,143	0,000
the leukocyte count to 20 in the field/vision	2	1,7	1,4	0,0	4,0	9,571	0,000
more than 20 in the field/vision	0	0,0	0,0	0,0	0,0	11,711	0,000

Thus, the analysis of the clinical course of intestinal infections in children in this study showed that inclusion in complex therapy of Enterol (*Saccharomyces boulardii*) reduced the duration of the main manifestations of the disease, improved overall health and well-being in the form of reduced weakness, almost all patients have improved appetite, normalized nature of the stool. The use of Enterol (*Saccharomyces boulardii*) had a positive impact on the duration of basic clinical symptoms in the diarrheal syndrome. The use of Enterol (*Saccharomyces boulardii*) in the age dosages within 5 days prevents the development antibiotic-associated diarrhea in children.

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Р. Х. Бегайдарова, А. М. Изтелеуова Г. М. Омарова, Х. Т. Талипбекова, В. Р. Атакишиева

БАЛАЛАРДАҒЫ АНТИБИОТИКПЕН АССОЦИАЦИЯЛАНҒАН ДИАРЕЯЛАРДЫҒЫ ЕМІ МЕН АЛДЫН АЛУДА ЭНТЕРОЛДЫҒЫ (SACCHAROMYCES BOULARDII) РӨЛІ

ААД әртүрлі этиологиялық факторларының ішінде ең маңыздысы *C. difficile* – грамоң аэробты спора түзуші, антибиотиктердің көпшілігіне тұрақты бактериялар. ААД алдын алуда пробиотиктер тиімді, оның ішінде тиімділігі бойынша ең сәттісі Энтерол (*Saccharomyces boulardii*) болып табылады, әлемдегі пробиотиктердің ішінде №1. Ішек инфекцияларымен ауырған барлығы 120 бала, олардың ішінде 6 айға дейінгі сәбилердің саны 20 (16,7%); 6 айдан 1 жасқа дейінгі – 60 (50,0%), бір жастан асқандары – 40(33,3%). Гастроэнтерит синдромы 14 (11,6%) балада, 72 (60,0%) – гастроэнтероколит синдромы, ал 30 (25,0%) – энтероколит байқалған. Оптималды емдеу жоспарын таңдау және оның клиникалық тиімділігін бағалау мақсатында Энтерол (*Saccharomyces boulardii*) 1 жасқа дейінгі балаларға 1 пакеттен күніне 1 рет, ал бір жастан асқан балаларға 1 пакеттен күніне 1-2 рет тағайындалды. Емдеу курсы 5 күн. Использование Энтеролды (*Saccharomyces boulardii*) қолдану диарея синдромында негізгі клиникалық симптомдарының ұзақтығына оң әсерін тигізді. Энтеролды (*Saccharomyces boulardii*) балаларға жас шамасына қарай мөлшерлеп 5 күн бергенде антибиотикпен ассоциирленген диареялардың алдын алуға болады.

Кілт сөздер: балалар, антибиотикпен ассоциирленген диарея, *C. difficile*, Энтерол, *Saccharomyces boulardii*

Р. Х. Бегайдарова, А. М. Изтелеуова, Г. М. Омарова, Х. Т. Талипбекова, В. Р. Атакишиева

ЭНТЕРОЛ (SACCHAROMYCES BOULARDII) В ПРОФИЛАКТИКЕ И ЛЕЧЕНИИ АНТИБИОТИК-АССОЦИИРОВАННОЙ ДИАРЕИ У ДЕТЕЙ

Карагандинский государственный медицинский университет (Караганда, Казахстан)

Среди разнообразия этиологических факторов антибиотик-ассоциированной диареи наибольшее значение придается *C. difficile* – грамположительной аэробной спорообразующей бактерии, обладающей устойчивостью к большинству антибиотиков. Хорошим эффектом при профилактике антибиотик-ассоциированной диареи обладают пробиотики, причем наиболее удачными по соотношению эффективности является Энтерол (*Saccharomyces boulardii*).

Под наблюдением находились 120 детей с диагностированными кишечными инфекциями, из них детей до 6 месяцев было 20 (16,7%); от 6 мес. до 1 года – 60 (50,0%), старше года – 40 (33,3%). Синдром гастроэнтерита отмечался у 14 (11,6%) детей, у 72 (60,0%) – синдром гастроэнтероколита, у 30 (25,0%) – энтероколит. С целью выбора оптимальной схемы лечения и оценки ее клинической эффективности Энтерол (*Saccharomyces boulardii*) назначали детям до года по 1 пакетику 1 раз в сут, детям старше года – по 1 пакетику 1-2 раза в сут. Курс лечения составил 5 сут. Использование Энтерола (*Saccharomyces boulardii*) оказало положительное влияние на длительность основных клинических симптомов при диарейном синдроме. Использование Энтерола (*Saccharomyces boulardii*) в возрастных дозировках в течение 5 сут предупреждает развитие антибиотикоассоциированной диареи у детей.

Ключевые слова: дети, антибиотикоассоциированная диарея, *C. difficile*, Энтерол, *Saccharomyces boulardii*