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Intestinal microbiota in children undergoing surgery for vesicoureteral reflux

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ABSTRACT

BACKGROUND: Vesicoureteral reflux (VUR) is one of the most common congenital anomalies of the urinary system in children. In most cases, urinary tract infection (UTI) serves as a clinical prerequisite for identifying VUR. However, a standardized approach to the diagnosis and management of this patient cohort has not yet been established.

AIM: To study the intestinal microbiota in children with VUR who received antibiotic therapy and antibiotic prophylaxis due to episodes of UTIs.

MATERIALS AND METHODS: The study included 40 children (12 boys and 28 girls) with VUR and chronic UTIs. All children received antibiotic therapy for acute episodes of infection, and, after the diagnosis of VUR, they also received continuous antibiotic prophylaxis. The control groups included 18 healthy boys and 14 healthy girls. Identification of microorganisms isolated from feces was carried out using generally accepted methods.

RESULTS: In the feces of children with VUR, aerobic taxa of microbiota dominate over anaerobic ones. *Klebsiella* spp., *Proteus vulgaris*, and *Pseudomona aeruginosa* appear in the feces of both boys and girls. An increase in the detection rate of most aerobic microorganisms and a decrease in anaerobic taxa were observed compared to healthy controls. In boys with VUR, the maximum (100%) detection rate of microorganisms is more common than in girls.

CONCLUSIONS: Dysbiotic changes were detected in the feces of all children after antibiotic therapy, providing new insights into the effects of the conventional strategy of long-term antibacterial treatment and prevention of UTIs in children with VUR.

Keywords: vesicoureteral reflux; microbiota; microbial diversity; intestine; children.

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Состояние кишечной микробиоты у детей с предстоящим оперативным лечением пузырно-мочеточникового рефлюкса

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АННОТАЦИЯ

Актуальность. Пузырно-мочеточниковый рефлюкс — один из самых частых пороков развития мочевой системы у детей. В большинстве случаев инфекция мочевых путей становится клинической предпосылкой, указывающей на возможное наличие этого порока. Однако единого подхода к диагностике и ведению данной когорты пациентов до сих пор не найдено.

Цель — изучение кишечной микробиоты у детей с пузырно-мочеточниковым рефлюксом, получавших антибиотикотерапию и антибиотикопрофилактику в связи с эпизодами инфекции мочевых путей.

Материалы и методы. В исследование включены 40 детей (12 мальчиков и 28 девочек) с пузырно-мочеточниковым рефлюксом и хроническими инфекциями мочевых путей. Все дети получали антибиотикотерапию по поводу острых эпизодов инфекции, а после выявления пузырно-мочеточникового рефлюкса также непрерывную антибиотикопрофилактику. В контрольные группы вошли 18 здоровых мальчиков и 14 здоровых девочек. Идентификацию выделенных из фекалий микроорганизмов осуществляли общепринятыми методиками.

Результаты. В фекалиях детей с пузырно-мочеточниковым рефлюксом аэробные таксоны микробиоты доминируют над анаэробными. При сравнительном анализе микробиоты установлено присутствие в биотопе *Klebsiella* spp., *Proteus vulgaris*, *Pseudomona aeruginosa*. Характерно повышение частоты обнаружения большинства аэробных и снижение анаэробных таксонов микроорганизмов в сравнении со здоровыми детьми. У мальчиков встречается максимальная (100%) частота обнаружения микроорганизмов, чем у девочек.

Выводы. В фекалиях детей после антибиотикотерапии и антибиотикопрофилактики обнаружены во всех случаях дисбиотические изменения, что открывает новый взгляд на понимание эффектов общепринятой стратегии продолжительного антибактериального лечения и профилактики инфекции мочевых путей у детей с пузырно-мочеточниковым рефлюксом.

Ключевые слова: пузырно-мочеточниковый рефлюкс; микробиота; микробное разнообразие; кишечник; дети.

Как цитировать

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ЭКО•ВЕКТОР

BACKGROUND

Vesicoureteral reflux (VUR) is one of the most common congenital anomalies of the urinary system in children [1]. Its diagnosis by voiding cystourethrography remains a subject of long-standing debate between pediatricians and pediatric urologists [1–4]. The key question is when this diagnostic procedure should be performed: after the first episode of urinary tract infection (UTI), as favored by pediatric urologists, or only in cases of recurrent UTI, as supported by pediatricians. UTIs are essentially the clinical trigger for detecting VUR [5, 6]. UTIs are common in children, and since uncomplicated cases can typically be managed with 7 to 10 days of oral antibiotic therapy (ABT), pediatricians often see no rationale for diagnosing VUR. However, renal and bladder ultrasound is recommended after the first UTI episode, and findings such as pelvicalyceal system dilatation, voiding dysfunction, or atypical clinical course with poor response to antibiotics are clear predictors of VUR [7]. The combination of UTI and VUR is generally considered an indication for long-term antibiotic prophylaxis (ABP). Surgical intervention is recommended for high-grade (III–IV) VUR associated with recurrent episodes of acute pyelonephritis, despite continuous ABP, and progressive upper urinary tract dilatation [5, 8]. Thus, continuous and prolonged ABP is postulated to prevent the need for surgical correction of VUR, even in high-grade cases [1, 2, 6, 9].

However, the adverse effects of ABT in acute UTI and particularly of ABP in recurrent cases are well known. These include the development of antibiotic resistance among uropathogens with all related consequences and, equally concerning, alterations in the microbiota of various organ systems, especially the intestine [10–13]. Even short-term ABP in infants with VUR has been shown to disrupt the intestinal microbiome by increasing the proportion of opportunistic pathogens and reducing beneficial taxa, potentially posing long-term clinical risks [14].

This study aimed to assess the state of the intestinal microbiota in children with VUR who received ABT and ABP due to episodes of UTI.

METHODS

The study included 40 children with VUR and chronic UTI, including 12 boys (group 1) and 28 girls (group 2), aged 28 months [*Q*1, 12; *Q*3, 72.5]. VUR was diagnosed between 1 and 147 months of age: on the right side in 12.5%, on the left in 32.5%, and bilaterally in 55.0% of patients. Active VUR was identified in 17.5% of cases, passive VUR in 5.0%, and combined VUR in 77.5%. All patients underwent surgical treatment with bulking agents (Refluxin, DAM+, and Vantris) at age of 60 months [24; 91]. All children received antibiotic therapy (ABT) for acute UTI episodes, followed by continuous antibiotic prophylaxis (ABP) after VUR diagnosis. Prior to surgery, leukocyturia was detected in 2 patients (5.0%), while asymptomatic bacteriuria was identified in all 40 patients through extended urine culture using 10 to 12 nutrient media types [15].

The control group included 18 healthy boys (group 3) and 14 healthy girls (group 4), aged 60 months [16; 74].

Inclusion criteria for group 1 and group 2: ineffective continuous ABP with recurrent episodes of acute UTI, progressive pelvicalyceal system dilatation, and reflux nephropathy. Exclusion criteria: a history of urinary tract surgery, urinary tract drainage, and voiding or bowel dysfunction. Inclusion criteria for group 3 and group 4: being in the first health status group (healthy child), no history of renal or urinary tract disease or anomalies, and no antibiotic use in the past 3 months.

Fecal samples for bacteriological analysis in children were collected in sterile plastic containers according to para. 6.6.2.7 of MU 4.2.2039–05,[1] and the bacteriological analysis was conducted in accordance with the industry standard.[2] In addition to conventional media, chromogenic media (HiMedia, India) were used: HiCrome Klebsiella Selective Agar Base, HiCrome Candida Differential Agar, HiCrome Enterococci Agar, Streptococcus Selection Agar, Bifidobacterium Agar, MRS Agar, Anaerobic Agar, Shaedler Agar, and Bacteroides Bile Esculinum Agar. Cultures were incubated under aerobic (*t* 37°C for 24–48 h) and anaerobic (AnaeroHiGas Pak, 48–72 h) conditions. Microorganisms were identified using standard microbiological methods. Gram Stains-Kit (a differential Gram staining set, HiMedia) was used to assess morpho-tinctorial characteristics.

Statistical analysis was performed using SPSS version 23. For microorganisms isolated from fecal samples, detection frequency (absolute count and percentage) was calculated. The chi-squared test and Fisher's exact test were used to compare detection frequencies between groups 1 and 2. Because fecal microbial loads were not normally distributed (as confirmed by the Kolmogorov–Smirnov test with Lilliefors correction and the Shapiro–Wilk test), they were expressed as medians (*Me*) and lower and upper quartiles [*Q*1; *Q*3]. The Mann–Whitney U test was used for group comparisons. Statistical significance was defined as $p < 0.01$ and $p < 0.05$.

[1] Methodological Guidelines MU4.2.2039–05. Procedure for Collection and Transportation of Biomaterials to Microbiological Laboratories. Moscow: Federal Center for Hygiene and Epidemiology of Rospotrebnadzor. 2006. P. 43–59.

[2] Industry Standard Patient Management Protocol. Intestinal Dysbiosis (OCT 91500.11.0004–2003). Moscow, 2003.

RESULTS

Table 1 shows the results of fecal microbiota analysis in patients with VUR. A total of 23 microbial taxa were identified: 16 aerobic and 7 anaerobic. Among aerobes, the most stable associates across the studied groups were *Escherichia coli* with typical characteristics (lactose-fermenting, lactose-positive [L^+], and non-hemolytic [Hly^-]) and *Enterococcus* spp. Within the anaerobic microbiota cluster, the predominant taxa were *Lactobacillus* spp., *Bifidobacterium* spp., *Eubacterium* spp., and *Clostridium* spp. Notably, the first two taxa were detected in 100% of fecal samples from the boys. Statistically significant differences in detection frequency were found for three taxa.

Among the boys, the highest detection rate (100%) was observed for three taxa (*E. coli* L^+, Hly^-, *Lactobacillus spp.*, and *Bifidobacterium spp.*), whereas these genera and/or species were only dominant among the girls. Notably, *Klebsiella* spp. were isolated from the feces of one in three boys, and *Staphylococcus aureus* was detected in 41.7%.

The highest fecal colonization levels (CFU/g) among aerobes in children with VUR were observed for *Enterococcus* spp. and *Enterobacterales*, and for *Bifidobacterium* spp., *Eubacterium* spp., and *Bacteroides* spp among anaerobes. The latter taxon showed a significantly higher colonization level in the girls compared with the boys (Table 1).

The comparative analysis of fecal microbiota between the boys with VUR and healthy boys (Table 2) revealed the presence of *Enterobacterales* representatives — *Klebsiella* spp., *P. vulgaris*, and *P. aeruginosa* — *in VUR patients.* The analysis of the detection frequency of various microbial taxa revealed increased levels of the aerobic cluster of microbiota and decreased levels of anaerobic taxa in patient groups compared with healthy individuals. Stable associates across both compared groups included *E. coli* (L^+, Hly^-), *Lactobacillus* spp., and *Bifidobacterium* spp. Statistically significant differences between healthy and affected boys were found for four taxa.

The quantitative analysis of fecal microbiota in the boys with VUR showed oppositely directed changes — some taxa increased; others decreased — compared with similar results in the healthy children. Statistically significant differences were found for seven taxa. Despite the heterogeneous nature of these differences, a pattern was noted: decreased detection of *E. faecalis*, *Eubacterium* spp., and *Bacteroides* spp. was associated with a significant reduction in their quantitative abundance.

Compared with healthy girls, the feces of the girls with VUR showed significantly greater differences in the frequency of detection than in the compared groups of the boys (Table 3). As in the boys, VUR was associated with the microbial taxa not found in healthy individuals: *Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa*, and *E. coli* L^-, Hly^+. Most aerobic and anaerobic taxa exhibited decreased detection frequencies in patients, except for four aerobic taxa: *S. epidermidis, S. aureus, E. faecalis, and E. faecium*.

The quantitative analysis in the girls with VUR showed that decreased detection frequency of *Corynebacterium* spp., *S. saprophyticus*, *Enterococcus* spp., *E. coli* L^+, Hly^-, *Lactobacillus* spp., and *Eubacterium* spp. was accompanied by a significant reduction in their abundance. Conversely, an increased detection frequency of *S. aureus* and *E. faecium* corresponded with a significant rise in their quantitative levels.

Thus, all patients with VUR, regardless of sex, exhibited dysbiotic changes in fecal microbiota compared with healthy children.

DISCUSSION

The intestinal microbiota comprises the community of microorganisms residing in the gastrointestinal tract that maintain symbiotic relationships with the host and perform metabolic, immunological, and neurological functions [14]. Microbial colonization begins at birth, with various taxa identified in meconium [16]. The maturation of intestinal microbiota occurs during the first three years of life [17, 18].

Antibiotic use for various infections in children, including UTIs, alters intestinal microbiota composition, for example, by increasing the abundance of Enterobacteriaceae [19]. In a study of 39 children aged 0 to 3 years, multiple courses of ABT led to reduced microbial diversity and a peak in the abundance of antibiotic resistance genes [20].

Our earlier study on bladder urine microbiota in the children with VUR following multiple ABT courses and ABP for UTIs revealed urinary dysbiosis in 60% of cases [21]. The current study evaluates intestinal microbiota in the same cohort and compares the findings with those in healthy children. All 40 children, both girls and boys, exhibited intestinal dysbiosis. These findings suggest that ABT and ABP more severely affected the intestinal microbiota than the urinary microbiota.

In children with VUR, fecal microbiota demonstrated a broader aerobic spectrum and higher detection frequencies of aerobes, along with reduced detection of anaerobes. *Klebsiella* spp., *P. vulgaris*, and *P. aeruginosa* were detected in feces from both boys and girls following ABT and ABP. Despite persistently high levels of *Lactobacillus* spp. and *Bifidobacterium* spp., there was a marked increase in the frequency of *S. aureus* and *E. faecium*, with concurrent decreases in *Eubacterium* spp., *Bacteroides* spp., *Peptococcus* spp., *Propionibacterium* spp., and the absence of *Prevotella*. A decline in *Bacteroides* spp. and absence of *Prevotella* may be seen as delayed intestinal microbiota maturation compared with the adult microbial profile [22, 23].

Table 1. Fecal microbiota of patients with vesicoureteral reflux

Таблица 1. Микробиота фекалий пациентов с пузырно-мочеточниковым рефлюксом

Microorganisms	Detection frequency, %		*p*	Quantitative bacterial load, log_{10} CFU/mL								*p*
				Group 1 (*n*=12)				Group 2 (*n*=28)				
	Group 1	Group 2		*Me*	Percentile			*Me*	Percentile			
					25	50	75		25	50	75	
Corynebacterium spp.	0	7.1	0.342	–	–	–	–	5.0	5.0	5.0	5.0	–
CNS	41.7	46.4	0.781	2.0	2.0	2.0	4.0	3.0	2.0	3.0	3.5	0.749
Staphylococcus haemolyticus	8.3	0	0.300	5.0	5.0	5.0	5.0	–	–	–	–	–
S. saprophyticus	16.7	7.1	0.358	2.5	2.0	2.5	2.5	4.0	3.0	4.0	4.0	0.221
S. epidermidis	33.3	32.1	0.941	2.5	2.0	2.5	3.0	2.0	2.0	2.0	3.5	0.864
S. lentus	0	10.7	0.238	–	–	–	–	2.0	2.0	2.0	2.0	–
S. aureus	41.7	28.6	0.418	3.0	2.0	3.0	3.0	3.0	3.0	3.0	3.75	0.152
Enterococcus spp.	91.7	92.9	0.896	5.0	4.0	5.0	7.0	6.0	5.0	6.0	7.0	0.348
Enterococcus undif.	25.0	0	0.006*	3.0	2.0	3.0	3.0	–	–	–	–	–
E. faecalis	41.7	75.0	0.043*	4.0	4.0	4.0	5.0	5.0	4.0	5.0	5.5	0.518
E. faecium	58.3	75.0	0.292	6.0	5.0	6.0	8.0	6.0	5.0	6.0	8.0	0.913
Enterobacterales	100.0	96.4	0.507	6.5	6.0	6.5	8.0	7.0	6.0	7.0	7.0	0.899
Escherichia coli L^+, Hly^-	100.0	92.9	0.342	6.5	6.0	6.5	8.0	7.0	6.0	7.0	8.0	0.806
E. coli L^-	8.3	21.4	0.318	7.0	7.0	7.0	7.0	5.5	4.25	5.5	7	0.295
E. coli Hly^+	0	7.1	0.342	–	–	–	–	7.0	7.0	7.0	7.0	–
Klebsiella spp.	33.3	21.4	0.426	6.0	5.0	6.0	7.0	6.5	5.0.	6.5	7.0	0.814
Enterobacter spp.	0	3.8	0.507	–	–	–	–	5.0	5.0	5.0	5.0	–
Proteus vulgaris	8.3	0	0.122	5.0	5.0	5.0	5.0	–	–	–	–	–
Pseudomonas aeruginosa	8.3	10.7	0.818	2.0	2.0	2.0	2.0	3.0	2.0	3.0	3.0	0.317
Bacillus spp.	33.3	14.3	0.168	5.0	2.75	5.0	6.5	4.0	2.25	4.0	6.5	0.765
Lactobacillus spp.	100.0	89.3	0.238	4.0	3.25	4.0	4.0	4.0	4.0	4.0	5.0	0.366
Bifidobacterium spp.	100.0	96.4	–	9.0	8.0	9.0	9.0	8.0	8.0	8.0	9.0	0.296
Propionibacterium spp.	8.3	7.1	0.896	5.0	5.0	5.0	5.0	4.5	2.0	4.5	4.5	1.0
Eubacterium spp.	91.7	75.0	0.227	6.0	3.0	6.0	7.0	6.0	3.0	6.0	7.0	0.609
Bacteroides spp.	41.7	7.1	0.008*	5.0	3.0	5.0	6.0	8.0	7.0	8.0	8.0	0.046*
Peptococcus spp.	41.7	35.7	0.722	5.0	2.5	5.0	7.0	4.0	3.0	4.0	6.25	0.949
Clostridium spp.	83.3	96.4	0.150	5.0	4.75	5.0	6.5	5.0	3.0	5.0	7.0	0.602
Candida albicans	33.3	39.3	0.722	3.0	2.25	3.0	5.25	3.0	2.0	3.0	4.0	0.946

Note. *Me*, median; *p*, nonparametric Mann–Whitney test. *p <0.05.

Примечание. *Me* — медиана; *p* — непараметрический критерий Манна–Уитни. *p <0,05.

Table 2. Comparison of fecal microbiota in healthy boys and boys with vesicoureteral reflux

Таблица 2. Сравнение микробиоты фекалий здоровых мальчиков и пациентов с пузырно-мочеточниковым рефлюксом

Microorganisms	Detection frequency, %		*p*	Quantitative bacterial load, log_{10} CFU/mL								*p*
				Group 3 (*n*=18)				Group 1 (*n*=12)				
	Group 3	Group 1		*Me*	Percentile			*Me*	Percentile			
					25	50	75		25	50	75	
CNS	38.9	41.7	0.879	2.0	2.0	2.0	3.0	2.0	2.0	2.0	4.0	0.628
Staphylococcus haemolyticus	5.5	8.3	0.765	2.0	2.0	2.0	2.0	5.0	5.0	5.0	5.0	0.317
S. saprophyticus	22.2	16.7	0.709	2.0	2.0	2.0	2.8	2.5	2.0	2.5	2.5	0.567
S. epidermidis	22.2	33.3	0.678	2.0	2.0	2.0	3.5	2.5	2.0	2.5	3.0	0.739
S. aureus	5.5	41.7	0.015*	2.0	2.0	2.0	2.0	3.0	2.0	3.0	3.0	0.317
Enterococcus spp.	100.0	91.7	0.213	5.0	5.0	5.0	6.0	5.0	4.0	5.0	7.0	0.981
Enterococcus undif.	22.4	25.0	0.860	5.0	4.3	5.0	5.8	3.0	2.0	3.0	3.0	0.476
E. faecalis	50.0	41.7	0.654	6.0	5.0	6.0	6.5	4.0	4.0	4.0	5.0	0.010*
E. faecium	44.4	58.3	0.456	4.5	4.0	4.5	6.5	6.0	5.0	6.0	8.0	0.059
Enterobacterales	100.0	100.0	–	8.0	7.0	8.0	8.3	6.5	6.0	6.5	8.0	0.048*
Escherichia coli L^+, Hly^-	100.0	100.0	–	8.0	7.0	8.0	8.3	6.5	6.0	6.5	8.0	0.048*
E. coli L^-	0	8.3	0.213	–	–	–	–	7.0	7.0	7.0	7.0	–
Klebsiella spp.	0	33.3	0.009*	–	–	–	–	6.0	5.0	6.0	7.0	–
Proteus vulgaris	0	8.3	0.213	–	–	–	–	5.0	5.0	5.0	5.0	–
Pseudomonas aeruginosa	0	8.3	0.213	–	–	–	–	2.0	2.0	2.0	2.0	–
Bacillus spp.	27.8	33.3	0.745	2.0	2.0	2.0	2.0	5.0	2.75	5.0	6.5	0.028*
Lactobacillus spp.	100.0	100.0	–	6.5	5.0	6.5	7.0	4.0	3.25	4.0	4.0	<0.001*
Bifidobacterium spp.	100.0	100.0	–	9.0	8.0	9.0	9.0	9.0	8.0	9.0	9.0	0.766
Propionibacterium spp.	33.3	8.3	0.113	2.0	2.0	2.0	2.3	5.0	5.0	5.0	5.0	0.041*
Eubacterium spp.	100.0	91.7	0.213	8.0	7.0	8.0	9.0	6.0	3.0	6.0	7.0	0.001*
Bacteroides spp.	72.2	41.7	0.094	8.0	6.5	8.0	9.0	5.0	3.0	5.0	6.0	0.021*
Peptococcus spp.	61.1	41.7	0.296	5.0	4.0	5.0	5.0	5.0	2.5	5.0	7.0	0.725
Peptostreptococcus spp.	44.4	0	0.004*	6.0	4.3	6.0	7.8	–	–	–	–	–
Clostridium spp.	100.0	83.3	0.073	5.0	3.0	5.0	6.3	5.0	4.75	5.0	6.5	0.433
Candida albicans	44.4	33.3	0.009*	2.0	2.0	2.0	4.3	3.0	2.25	3.0	5.25	0.183

Note. *Me*, the median; *p*, the nonparametric Mann–Whitney test. *p <0.05.

Примечание. *Me* — медиана; *p* — непараметрический критерий Манна–Уитни. *p <0,05.

Table 3. Comparison of fecal microbiota in healthy girls and girls with vesicoureteral reflux
Таблица 3. Сравнение микробиоты фекалий здоровых девочек и пациенток с мочеточниковым рефлюксом

Microorganisms	Detection frequency, %		*p*	Quantitative bacterial load, log_{10} CFU/mL								*p*
				Group 4 (*n*=14)				Group 2 (*n*=28)				
	Group 4	Group 2		*Me*	Percentile			*Me*	Percentile			
					25	50	75		25	50	75	
Corynebacterium spp.	21.4	7.1	0.178	4.0	3.0	4.0	4.0	5.0	5.0	5.0	5.0	0.048
CNS	35.7	46.4	0.508	2.0	2.0	2.0	2.5	3.0	2.0	3.0	3.5	0.170
Staphylococcus haemolyticus	7.1	0	0.152	2.0	2.0	2.0	2.0	–	–	–	–	–
S. saprophyticus	28.6	7.1	0.041	2.0	2.0	2.0	2.0	4.0	3.0	4.0	4.0	0.028
S. epidermidis	14.3	32.1	0.215	2.5	2.0	2.5	3.0	2.0	2.0	2.0	3.5	0.896
S. lentus	0	10.7	0.204	–	–	–	–	2.0	2.0	2.0	2.0	–
S. aureus	14.3	28.6	0.306	2	2	2	2	3	3	3	3.75	0.047
Enterococcus spp.	100.0	92.9	0.306	4.5	4.0	4.5	5.3	6.0	5.0	6.0	7.0	0.004
Enterococcus undif.	28.6	0	0.003	4.0	2.5	4.0	5.5	–	–	–	–	–
E. faecalis	50.0	75.0	0.105	5.0	4.0	5.0	6.0	5.0	4.0	5.0	5.5	0.847
E. faecium	35.7	75.0	0.013	4.0	3.0	4.0	5.5	6.0	5.0	6.0	8.0	0.019
Enterobacterales	100.0	96.4	–	8.0	7.8	8.0	8.3	7.0	6.0	7.0	7.0	–
Escherichia coli L^+	100.0	92.9	0.306	8.0	7.8	8.0	8.3	7.0	6.0	7.0	8.0	0.001
E. coli L^-	0	21.4	0.048	–	–	–	–	5.5	4.25	5.5	7	–
E. coli Hly^+	0	7.1	0.306	–	–	–	–	7.0	7.0	7.0	7.0	–
Klebsiella spp.	0	21.4	0.048	–	–	–	–	6.5	5.0.	6.5	7.0	–
Enterobacter spp.	0	3.6	0.474	–	–	–	–	5.0	5.0	5.0	5.0	–
Pseudomonas aeruginosa	0	10.7	0.204	–	–	–	–	3.0	2.0	3.0	3.0	–
Bacillus spp.	35.4	14.3	0.111	3.0	2.0	3.0	4.0	4.0	2.25	4.0	6.5	0.379
Lactobacillus spp.	100.0	89.3	0.204	5.5	5.0	5.5	7.0	4.0	4.0	4.0	5.0	<0.001
Bifidobacterium spp.	100.0	100.0	–	8.5	1.0	8.5	9.0	8.0	8.0	8.0	9.0	0.494
Propionibacterium spp.	28.6	7.1	0.041	3.5	3.0	3.5	4.0	4.5	2.0	4.5	4.5	1.0
Eubacterium spp.	100.0	75.0	0.040	8.0	7.0	8.0	9.0	6.0	3.0	6.0	7.0	<0.001
Bacteroides spp.	64.3	7.1	<0.001	7.0	5.5	7.0	8.5	8.0	7.0	8.0	8.0	0.469
Peptococcus spp.	50.0	35.7	0.374	5.0	4.0	5.0	6.0	4.0	3.0	4.0	6.25	0.765
Peptostreptococcus spp.	14.3	0	0.040	6.0	6.0	6.0	6.0	–	–	–	–	–
Clostridium spp.	100.0	96.4	0.474	5.5	4.0	5.5	7.0	5.0	3.0	5.0	7.0	0.303
Candida albicans	64.3	39.3	0.126	3.0	2.0	3.0	3.0	3.0	2.0	3.0	4.0	0.232

Note. *Me*, the median; *p*, the nonparametric Mann–Whitney test. *p <0.05.
Примечание. *Me* — медиана; *p* — непараметрический критерий Манна–Уитни. *p <0,05.

Our analysis supports that multiple courses of ABT, supplemented by short-term ABP for UTIs in children with VUR, lead to notable changes in intestinal microbiota and delayed microbial maturation. This dysbiosis may compromise intestinal barrier function, potentially explaining the presence of *Klebsiella*, *Proteus*, and *Pseudomonas* spp. in the microbiota. The impact on the risk of infectious complications in VUR surgery still remains to be clarified. However, it is evident that deviations from the eubiotic composition of the intestinal and urinary microbiota can result in metabolic and immunologic disturbances in children [24, 25]. On the other side, prolonged ABP — commonly recommended for up to two years in patients with VUR — may further contribute to clinical consequences, such as obesity, allergies, and other conditions related to intestinal microbiota disruption [26, 27]. In addition, both ABT and ABP are associated with the proliferation of resistance genes in urinary and intestinal microorganisms, facilitating the development of specific virulence factors [28].

The study has certain limitations. The relatively small sample size may affect the magnitude of intergroup differences. Nonetheless, the statistical analysis confirmed significant distinctions between healthy children and those with VUR.

Future research should investigate the post-surgical dynamics of intestinal microbiota and guide strategies for UTI prevention in children with VUR.

CONCLUSION

In children with VUR who received ABT and ABP for UTIs, aerobic microbial taxa were detected more than twice as frequently as anaerobic taxa in fecal samples. All cases exhibited intestinal dysbiosis, characterized by the emergence of *Klebsiella*, *Proteus*, and *Pseudomonas* spp., increased abundance of most aerobic organisms, reduced levels of anaerobes, and dominance of *Escherichia coli*, *Enterococcus*, *Lactobacillus*, and *Bifidobacterium*. These findings enhance our understanding of the impact of prolonged antimicrobial treatment and prophylaxis strategies for UTI management in children with VUR.

ADDITIONAL INFO

Authors' contribution. Ju.L. Naboka, research concept and design, writing the text of the manuscript; V.V. Sizonov, research concept and design, data analysis, editing the text of the manuscript; I.A. Gudima, data analysis; E.M. Kotieva, review of publications; K.T. Jalagonia, performing diagnostic studies; A.I. Anopko, data collection; R.A. Rodina, data collection, patient management; M.I. Kogan, research concept, scientific editing, scientific guidance. The authors have approved the version for publication and have also agreed to be responsible for all aspects of the work, ensuring that the accuracy and integrity of any part of it is properly reviewed and addressed.

Ethics approval. The study protocol was approved by the Ethics Committee of the Rostov State Medical University (protocol No. 2/24 dated 2024 Jan 25).

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Ю.Л. Набока — концепция и дизайн исследования, написание текста статьи; В.В. Сизонов — концепция и дизайн исследования, анализ полученных данных, редактирование текста рукописи; И.А. Гудима — анализ данных; Е.М. Котиева — обзор публикаций; К.Т. Джалагония — выполнение диагностических исследований; А.И. Анопко — сбор данных; Р.А. Родина — сбор данных, ведение пациентов; М.И. Коган — концепция исследования, научное редактирование, научное руководство. Авторы одобрили версию для публикации, а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

Этическая экспертиза. Протокол исследования одобрен этическим комитетом ФГБОУ ВО «Ростовский государственный медицинский университет» Минздрава России (протокол № 2/24 от 25.01.2024).

Согласие на публикацию. Авторы получили письменное информированное добровольное согласие законных представителей пациентов на публикацию персональных данных в научном журнале, включая его электронную версию.

Источники финансирования. Отсутствуют.

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

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