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FEATURES OF COLONIZATION OF THE MICROFLORA OF THE ORAL CAVITY AND INTESTINES IN PREMATURE INFANTS WITH NECROTIZING ENTEROCOLITIS WHO UNDERWENT SURGICAL TREATMENT

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The microflora of the oral cavity and feces in the first 7 days of life was studied in 20 premature infants with necrotizing enterocolitis undergoing surgical treatment (the main group) and in 20 premature infants without necrotizing enterocolitis (the control group). In 10 % of the children of the main group and in 95 % of the control group, the microflora was normal. In both groups, Bacteroides spp dominated the microflora in 58 %. and the number of other gram-negative aerobic bacteria, including E. coli, gradually increased, while colonization by gram-positive bacteria was slower. Clostridium spp. They were present in only 10 % of the children of the main group. In the first 4 days of birth, the incidence of C. butyricum, C. perfringens, and C. dificile in the main group ranged from 3 to 7 % with a gradual tendency to increase colonies. The colonization pattern of the oral cavity and colon in premature infants with necrotizing enterocolitis differs significantly from newborn premature infants without necrotizing enterocolitis.

Key words: premature newborns, oral microflora, intestinal microflora.

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ОСОБЛИВОСТІ КОЛОНІЗАЦІЇ МІКРОФЛОРИ ПОРОЖНИНИ РОТА І КИШЕЧНИКУ В НЕДОНОШЕНИХ НЕМОВЛЯТ ІЗ НЕКРОТИЧНИМ ЕНТЕРОКОЛІТОМ, ЯКІ ЗАЗНАЛИ ОПЕРАТИВНОГО ЛІКУВАННЯ

Досліджено мікрофлору порожнини рота і калову мікрофлору в перші 7 днів життя у 20 недоношених дітей з некротизуючим ентероколітом, які перебувають на оперативному лікуванні (основна група), і у 20 недоношених дітей, які не страждають на некротизуючий ентероколіт (контрольна група). У 10 % дітей основної групи та у 95 % контрольної групи мікрофлора була нормальною. В обох групах у складі мікрофлори у 58 % переважали Bacteroides spp. і поступово збільшувалася кількість інших грамнегативних аеробних бактерій, у тому числі E. coli, тоді як колонізація грампозитивними бактеріями відбувалася повільніше. Clostridium spp. були присутні тільки у 10 % дітей основної групи. У перші 4 дні народження в основній групі зустрічальність C. butyricum, C. perfringens і C. dificile коливалася від 3 до 7 % із поступовою тенденцією до збільшення колоній. Характер колонізації порожнини рота і товстої кишки в недоношених дітей з некротизуючим ентероколітом істотно відрізняється від новонароджених недоношених дітей, які не страждають на некротизуючий ентероколіт.

Ключові слова: недоношені новонароджені, мікрофлора порожнини рота, мікрофлора кишечнику.

Usually, the gastrointestinal tract, which is sterile during intrauterine life, is colonized within 24 hours after birth. The predominant microflora strains fluctuate during the first 2–3 weeks of life and stabilize in accordance with the diet, usually by the age of 1 month of the child [8].

The gut microbiome influences the development of the immune system and may play an important role in protecting against bacteria and/or their toxins [11, 14]. The data currently obtained indicate that NEC is not the result of the growth of a single pathogen, but rather that the disease is the result of a general disruption of normal colonization patterns in the developing intestine [5, 10].

In premature infants with low body weight, if the intestinal barrier function is damaged, the existing microflora can lead to NEC, sepsis, and systemic inflammatory reaction syndrome [1, 3].

Facultative and aerotolerant bacteria appear first, followed by increasingly severe anaerobes. Symbiotic microbes are the main engine of immune system maturation. Increased hygiene has apparently changed the intestinal flora of infants in the West, which may affect the risk of developing immune-mediated diseases [4, 8].

In the etiopathogenesis of NEC, prematurity is considered the main cause; due to the complete incompleteness of intestinal development, the formation of the normal composition of the microflora is disrupted, which together cause an inflammatory reaction in the wall of the immature intestine [5, 10]. Recently, research aimed at studying the microbial composition of newborns with NEC has expanded rapidly due to the availability of high-throughput DNA-based detection methods instead of culture-based methods. According to the results of experimental studies, NEC was not found without colonization by intestinal microbes; based on this, bacteria were assigned a crucial role in the pathogenesis of NEC [8, 12].

In contrast, premature newborns with low body weight differ in many ways from full-term infants. Premature infants have insufficiently developed humoral and cellular immunity and other protective factors; they experience delayed and often inadequate colonization of the microflora, which leads to increased inflammatory reactions [3, 6, 11].

Bacterial colonization of an infant's oral cavity and colon depends on many factors, including gestational age, birth methods, diet, environment, and exposure to antibiotics. It was found that 6 % of children with intestinal dysbiosis are carriers of enteroaggregative E. coli [11, 13].

In premature infants, an increase in the number of facultative anaerobic microorganisms is detected in the intestines with a simultaneous sharp decrease in obligate microflora. In the early neonatal period, the number of anaerobic flora is represented at a very low level by bacteroids (3.4 %; 4.5 lg CFU/g). The microbiota of the colon in premature infants with very low body weight is characterized by a sharp deficiency of obligate representatives (lactobacilli and functionally significant E. coli [5, 15]). In humans, the following are most often detected in the oral cavity: Str. mutans, Str. salivarius, Str. mitis, saprophytic neisseria, lactobacilli, veillonella, anaerobic streptococci (peptostreptococci), bacteroids, fusobacteria, filamentous bacteria, actinomycetes and anaerobic diphteroids, spirochaetes (saprophytic borrellia, treponema, leptospira) [10, 11].

Studies comparing the microbiota of premature newborns who developed NEC compared to newborns in the control group have shown that NEC leads to unusual types of intestinal microbes and an overall decrease in microbiota diversity [15].

In the literature available to us, there are single sources reflecting the state of the oral microflora in comparison with the microflora of the large intestine in premature newborns with necrotizing enterocolitis [9]. Therefore, the study of the composition of the microflora of the oral cavity and colonizing the large intestine in premature infants is an urgent problem of neonatology.

The purpose of the study was to establish the state of the oral microflora and feces in premature infants with necrotizing enterocolitis.

Materials and methods. A simultaneous study of the composition of the microflora of the oral cavity and colonizing large intestine in premature infants was conducted at the K. Faradzheva Scientific Research Institute of Pediatrics.

Samples for bacteriological examination were taken within 8 hours after the birth of infants and once on the following 2nd, 3rd and 6th days. All samples were processed within 1 hour after collection. Fecal swabs were prepared and fixed for subsequent staining using the Gram method in the Kopeloff modification [2]. Light microscopy results: all smears were compared with the results of seeding to verify the adequacy of nutrient media and incubation methods. All samples were inoculated on horse blood agar (HBA; Columbia Agar Base, Oxoid), MacConkey agar (and mannitol salt agar) and incubated under aerobic conditions at 37 C. Throat swabs were incubated in an atmosphere with 5–10 % carbon dioxide. Faeces were also cultured on various enriched and selective media to isolate anaerobic bacteria. These were blood agar with phenylethyl alcohol and kanamycin-vancomycin-agar with varnished blood (Sutter, Vargo and Finegold, sodium azide blood agar and cycloserine, cefoxitin, egg fructose agar (CCFA;). For fecal culture, meat broth was used, adding 26.5 g / l from Schaedler's broth, vitamin K1 agar and rezazurin according to the instructions. In addition, inoculation was carried out in two more cups containing three antibiotics with agar; in order to detect Campylobacter spp. The cups were kept in a thermostat at temperatures of 42 °C and 25 °C. The number of each microbe species was determined by the number of colonies per 1 g of nutrient medium. The isolated pure cultures were identified by morphological, tinctorial, cultural and biochemical properties according to the determinant of Bergi (1997). The identification of enterobacteria was carried out using microtests to identify microorganisms of the Enterobacteriaceae family. Anaerobic microorganisms were cultured in GasPak microanaerostats in the presence of palladium catalysts and indicator risazurin systems (OXOZD, England). The anaerobes were identified by colonial and cellular morphology, an antibiotic resistance test, a dye resistance test, a biochemical test, and sugar. Biochemical identification of lactobacilli was performed using the API 50 CHL test system. Staphylococci were studied using diagnostic systems: 1) biochemical plates differentiating staphylococci (BPDS); 2) set of Staphytest 16 (PLIVA-Lachema Diagnostika).

The molecular genetic study of the isolated cultures was carried out using PCR. DNA amplification was performed in compliance with the requirements for PCR on a Tertsik programmable thermal cycler using a hot start. A microanaerostat (GasPak, OXOZD, England) was used to cultivate anaerobes. Lactobacilli were identified by the API 50 CHL test system.

To determine the molecular and genetic nature of the obtained microbial cultures, PCR was used, while observing the requirements for the operation of the Tertsik thermal cycler against the background of a "hot start". Anaerobic cups were incubated in anaerobic vessels.

2 groups of newborns were examined: the 1st (main) group included 20 newborns with NEC 2B-ZB stages according to the classification of Walsh and Kliegman (15 boys, 5 girls) with an average gestational age of 30 weeks (range 25–36 weeks) and an average birth weight of 1125 g (range 560–1500 g) who received surgical care. The 2nd (control) group included 20 healthy newborn infants (15 boys, 5 girls).

In the main group, 9 infants received mother's milk, 3 artificial formula, 8 infants received parenteral nutrition; in the control group: 15 newborns received mother's milk and 5 infants received artificial formula.

Light microscopy of the smears was compared with the results of seeding to verify the adequacy of nutrient media and incubation methods. Variables (predictors, confounders, effect modifiers) Bacteroides spp. E. coli, Clostridium spp. ,C. butyricum, C. perfringens and C. dificile .

All data is presented as an average ± standard deviation. Differences between 2 groups (two-way t-test) or 3 groups (single-factor analysis of variance, Tukey multiple comparison criterion) were analyzed using GraphPad Prism version 7. A P value of less than 0.05 was considered significant.

The software package Statsoft Statistica 10 and Microsoft Excel 2016 were used for statistical processing of the research results. The differences between the groups of continuous and ordinal values were determined by nonparametric Mann–Whitney criteria. The indicators of skewness and kurtosis, including quantitative variables for the type of distribution, were checked using Kolmogorov–Smirnov criteria (with the Lilliefors correction), taking into account variables for which the statistical significance in the univariate analysis did not exceed 0.1. To apply variational statistics, the criteria Shapiro –Wilk, Student, Mann–Whitney, Friedman and Wilcoxon were used; coefficients were studied Pearson (r) and Spearman (R).

The study was approved by the local Ethics Committee of the K. Faradzheva Research Institute of Pediatrics (Protocol No. 01–9 dated 01/22/2021). All parents of children gave written consent for their children to participate in the study.

Results of the study and their discussion. Tables 1–2 summarize the types of bacteria isolated from the oral cavity and feces, depending on the age of premature infants at the time of sampling. The most common oral isolate was Strept. salivarius, isolated from a large number of children in the main group from day 1 (56.5 %) to day 6 (73.8–9 %), while Strept. Salivarius was not sown. In the main group, the detection rate of Candida spp. increased progressively: from 13 % on the first day to 47.8 % on the second and 73.9 % on the 3rd and 6th days (Table 1).

Table 1

Identified bacterial flora of the oral cavity of premature newborns

Identified flora	Day 1		Day 2		Day 3		Day 6	
	Main, p., n=23	Control, n=20	Main, p. n=20	Control, n=20	Main p., n=23	Control, n=20	Main, p., n=23	Control, n=20
didn 't give any growth	35 %	85 %	33 %	82 %	30 %	78 %	27 %	74 %
E. coli	10	2	13	3	12	3	13	4
Klebsiella spp.	3	0	3	0	6	0	8	0
Strept. Faecalis	3	0	6	1	10	2	11	2
Strept faecium	0	0	0	0	1	0	0	0
Pseudomonas spp.	5	0	3	0	0	0	0	0
Proteus spp.	2	0	2	0	1	0	1	0
Neiseria spp.	1	0	5	1	8	2	9	2
Group B strept.	6	0	7	0	4	0	3	0
Viridans strept.	6	0	10	0	12	0	14	0
Strept. Salivarius	13	0	17	0	17	0	17	0
Staph. Epidermidis	6	0	13	0	14	0	16	0
Staph. Aureus	0	0	0	0	0	0	1	0
Veillonella spp.	0	0	5	0	6	0	6	1
Bifidobacterium spp.	0	0	3	0	6	1	7	2
Lactobacilli	0	0	1	1	2	1	2	2
Eubacterium spp	3	1	2	0	3	2	3	2
Candida spp.	3	1	17	2	11	3	17	5

Among the control group, Candida spp. was detected in 5 % of infants on day 1, 10 % on day 2, 15 % and 25 % of infants on day 3 and 6, respectively. The next most common microflora was Staphylacoccus epidermeticus, which colonized the oral cavities of newborns with NEC (the main group) in 26 % on the 1st, 56.5 % on the 2nd, 85 % on the 3rd and 95.6 % on the 6th day of examination. Staphylacoccus epidermeticus was not sown among the examined newborns in the control group. Streptococcus viridans in the main group was detected on the first day in 26 % and followed by an increase in samples taken on the 2nd, 3rd and 6th days (43.5 %, 53 % and 60.9 %, respectively). Streptococci in group B were isolated in 6 (26 %) children in the first 24 hours after birth and in 7 (30.4 %), 4 (17.4 %) and 3 (13 %) newborns with NEC on the second, third and sixth days, respectively. At the same time, streptococci were not sown among the children of the control group – group B. In both groups, anaerobic microorganisms were not isolated on the first day, but starting from the third day, they were detected in the main group. The results of microbiological studies of faeces in both groups are shown in Table 2.

Table 2

The revealed bacterial flora of the feces of premature newborns

Identified flora	Day 1		Day 2		Day 3		Day 6	
	Main, n=23	Control, n=20	Main, n=20	Control, n=20	Main, n = 23	Control, n=20	Main, n = 23	Control, n=20
E. coli	18	2	18	3	22	3	22	4
Klebsiella spp.	4	1	8	0	12	2	13	2
Strept. Faecalis	9	2	13	2	19	3	20	2
Strept faecium	2	0	2	0	9	2	12	1
Pseudomonas spp.	1	0	1	0	1	0	2	0
Proteus spp.	1	0	0	0	3	0	3	0
Neiseria spp.	0	0	0	0	2	0	2	0
Group B strept.	7	0	5	0	3	0	3	0
Viridans strept.	4	0	3	0	3	0	3	0
Staph. Epidermidis	7	1	11	1	16	3	17	3
Staph. Aureus	1	0	1	0	2	0	3	0
Bifidobacterium spp.	12	1	20	2	20	3	21	2
Lactobacilli	1		3	1	3	1	3	0
Bacteroides vulgaris	0	0	3	0	12	2	15	3
B. distasonis	0	0	0	0	1	0	1	0
B. ovatus	0	0	0	0	1	0	1	0
Cl. perfringens	4	0	10	2	13	3	11	1
Cl. difficile	0	0	3	1	5	2	5	1
Cl. Butyricum	0	0	5	1	5	0	4	0
Eubacterium spp	0	0	3	1	4	0	4	0
Anaerobic strept.	0	0	1	0	6	1	6	0
Candida spp.	10	2	12	2	12	2	12	2

E. coli was the most common facultative bacterial species isolated from fecal samples of the main group: 78.3 % on days 1 and 2, 95.6 % on days 3 and 100 % on days 6 (Table 2). In contrast, E. Coli was not seeded in all samples taken from the control group of newborns. Strept. faecalis in the main group of newborns was sown in 3.7 % of samples on days 1 and 2 and gradually increased, reaching 39 % on days 4 and 54.5 % on days 6. As can be seen from Table 2. 30.4 % of newborns in the control group had Strept on the first day. faecalis was not detected on day 2 in 47.8 %, on day 3–69.6 % and was not detected in 77.3 % on day 6; 1st and 2nd Strept. Faecalis was not sown among the control group; it was detected in 8.7 % and 4.5 % on days 3 and 6, respectively.

Staph. epidermidis among the main group was detected on day 1 in 30.4 % of the samples; in these infants, Staph. epidermidis was sown on day 2 in 47.8 %, on day 3 in 69.6 % and 77.3 % on day 6. At the same time, among the control group, these indicators did not exceed 5 % on the 1st and 2nd days, 15 % on the 3rd and 6th days.

Colonization of fecal matter by Klebsiella spp. newborns with NEC did not exceed 17.4 % on the first day, gradually increasing to reach 34.8 % on the 3rd day and 52.2 % on the 6th day. Among the control group of newborns, the incidence of Klebsiella spp. Compared with the main group, it was 4.8 and 6 times lower, respectively, on days 1.2, 3 and 6.

Other aerobes isolated in small amounts from several infants were green streptococcus, Proteus, and Neisseria. and Pseudomonas spp. Anaerobes were more common in faeces both qualitatively and quantitatively than aerobes. By the end of the first week of life, 95 % of infants in the main group had been seeded with Bifidobakterii spp.

By the sixth day, about 80 % of the infants of the main group were populated with anaerobes - Bakteroides vulgaris; in infants of the main group.

In infants of the main group, Cl. Perfringens on the 1st day of newborns of the main group was found in 17.4 % of samples, 8.7 % of samples on the 2nd day, 13 % on the 3rd and 4.5 % of samples on the 6th day, Cl. Perfringens was not detected among the control group on the 1st day; On day 2, Cl Perfringens was detected in 8.7 % of the samples, on day 3 in 13.6 %, and on day 6 in only 4.5 % of the samples.

The colonization rate of lactobacilli was low in samples taken over four days in both groups. About 26 % of infants in the main group were colonized with anaerobic streptococci on day 3 and 27.2 % on day 6. Candida spp. in the main group, 43.5 % and 52.2 % were detected in samples taken on subsequent days; in the control group, Candida spp was detected. it did not exceed 8.7 % .

As can be seen from Table 1, in the main group of 20 throat swabs taken, 7 (35 %) premature infants did not grow; all of them received antibiotic therapy; at the same time, among the control group, 17 (85 %) full-term infants did not have microflora in the swabs taken. In the main group, Streptococcus viridans was seeded in 3 (15 %), Staphylococcus epidermidis-in 2 (10 %), E.Coli-in 2 (10 %), Enterobacter

spp. - in 2 (10 %), Strp.pneumonie-in 2 (15 %) and in 1 (5 %) Klebsilla spp. was detected, in 1 (5 %) Pseudomonas spp. In the control group, only 3 infants were seeded with 1(5 %) Staph/epidermidis, E.Coli, and Enterobacter spp.

In 10 % of the children of the main group and in 95 % of the control group, the microflora was normal. In both groups, Bacteroides spp dominated the microflora in 58 %. and the number of other gram-negative aerobic bacteria, including E. coli, gradually increased, while colonization by gram-positive bacteria was slower.

Among the main group of infants, Clostridium spp. no more than 10 % of cases occurred: in this group, the seeding rate of C. butyricum, C. perfringens and C. Dificile in the first 4 days did not exceed 3 %, followed by an increase in colonies to 7 %.

The flora of a premature newborn differs from the mother's flora from birth; in the following days, against the background of placement in a wet cell and the use of parenteral antibiotics in premature infants, the composition and level of microflora differ significantly from the microflora of healthy full-term infants fed with both artificial mixtures and breast milk.

Kobeshavidze N, et all (2019) presented the results of a microbiological study of microbial contamination of the mucous membrane of the respiratory tract of 124 premature newborns: "in the first 72 hours, microbial colonization was detected in only 20.97 % of children, and in 79.03 % the respiratory tract was free of microorganisms. During this period, gram-positive microflora was mainly isolated (92.31 %), among which S. haemolyticus strains were mainly detected, while gram-negative microflora was represented by only 2 (97.69 %) E. coli strains. By the 14th day of life, microbial colonization of the respiratory tract of premature newborns increased almost 3 times. Microbial growth was not detected in 41.94 % of children. During this period, microbial colonization of the pharynx increased 3-fold, and the trachea almost 2-fold, and such genera of microorganisms as Pseudomonas aeruginosae, Stenostophominas maltophylia, Acinetobacter baumanii and Klebsiella pneumonia appeared [6].

The formation of a stable intestinal microbiota in premature infants is delayed compared to full-term infants. Premature babies have an immature gastrointestinal tract and immune system, which predisposes them to infectious diseases. Neonatal microbial dynamics and changes in the early intestinal microbiota may precede and/or predispose to diseases such as necrotizing enterocolitis (NEC), late sepsis, or others. The microflora of the newborn's oral cavity mainly consists of: a) lactobacilli; b) streptococci; c) Neisseria; d) spirochaetes [7].

Multiple studies have shown that the main Clostridium species such as Clostridium perfringens, C. butyricum and C. Neonatale play a crucial role in the etiology of NEC [10]. However, the reported results vary greatly from study to study, and so far no pathogen has been identified as a specific cause of NEC [11].

This flora was mainly gram-negative bacilli, which were easily established in faeces, and to a lesser extent in the throat; the types of microbes considered normal components of the oral flora (Str. Salivarius, viridans streptococci and Neisseria spp.) were reduced or absent [12].

According to our data, the composition of aerobic flora in the feces of both groups was lower in the number of flora species than in the oral cavity. At the same time, the number of populations of detected microflora in the group of premature infants was higher than in the control group.

Mixed populations of E. coli, Klebsiella spp. As well as Bacteroides spp., they were primarily found in faeces; at the same time, the indicated flora resembled a condition that is usually associated with formula feeding rather than breastfeeding. Gram-positive bacteria (aerobic cocci, lactobacilli, and clostridia) have become more common over the years. Although the majority of infants in this study received unprocessed breast milk, especially in the first days of life, the acquisition of lactic acid-producing bacteria in the first 4 days of life was not eliminated. The feeding method significantly affected the composition of colonization by the microflora of the oral cavity and intestines. Parenteral nutrition in the first 4 days of life was associated with delayed colonization in some infants and with a limited variety of colonizing species that were not associated with antibiotic therapy. The effect of parenterally prescribed antibiotics on the developing flora was different. The revealed limited sensitivity of the B. fragilis group to penicillin and aminoglycosides probably explains their rapid spread during the first week of life in most infants. However, antibacterial therapy did not always limit the growth of microflora sensitive to it. For example, E. coli was isolated during the first 11 days of life from one third of infants receiving therapy, despite the fact that all strains, without exception, were sensitive in vitro to aminoglycoside in the treatment regimen. When antibiotics were used, usually by the 4th day after birth, a rapid increase in the diversity of identified bacterial flora species was observed.

The use of antibiotics may partially explain the observed delayed colonization of Clostridiurn spp. before the beginning of the 5th day of life. This colonization pattern differs from that described by other authors by the types of microbes in healthy full-term infants, both breastfed and artificially fed. Full-term infants who are breastfed have a large number of mixed-type clostridium in their faeces; and their number

decreases by the end of 5 days. Full-term infants who are artificially fed after birth also soon develop clostridia and maintain a high level of colonization during the study period. In premature infants in this study, Clostridiurn spp. they appeared in small numbers shortly after birth with feces in only a few infants. In them, C. butyricurn and C. perfringens were more common than C. dificile [10, 11].

Judging by the assessment, there was no evidence of a systemic spread of intestinal flora. This is encouraging, because, as is known, the permeability of the intestinal mucosa in the neonatal period can be increased. On the other hand, in the mucous membrane of the gastrointestinal tract in a premature newborn with a low body weight in the first days of life, the function of effectively concentrating inflammatory cells and performing a bactericidal function is not sufficiently developed. The predominance of gram-negative facultative bacteria and potentially pathogenic organisms such as Escherichia coli, Enterobacter, and Klebsiella and the underrepresentation of obligate anaerobic bacteria, in particular Negativicutes and Clostridia, in the intestines of infants before the development of necrotizing enterocolitis are consistent with the hypothesis that dysbiosis precedes this serious disease [13].

Conclusion

Microbiota analysis of samples from premature newborns requires the use of complex bacteriological methods and requires a lot of time. In addition, the predictive value of the distribution of bacterial species along with the quantification of different strains is still unclear and requires additional research.

The flora of a premature newborn differs from the mother's flora from birth; in the following days, against the background of placement in a wet cell and the use of parenteral antibiotics in premature infants with NEC, the composition and level of microflora differ significantly from the microflora of premature infants not suffering from NEC, fed with both artificial mixtures and breast milk.

Knowing these differences will help interpret the results of bacteriological research and the use of treatment methods for diseases of the gastrointestinal tract in premature infants.

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