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EC PHARMACOLOGY AND TOXICOLOGY
Research Article

The Potential of Bacteriophages in the Treatment of Atopic Dermatitis in Children and the Possibility of Controlling Atopic March

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Received: June 11, 2026; **Published:** July 17, 2026

DOI: 10.31080/ECPT.2026.14.00967

Abstract

Rationale: One of the pressing issues in modern pediatrics today is the lack of a tool to manage the AM.

Objective of the Study: To determine the effectiveness of using bacteriophages in patients with AtD and the possibility of interrupting the AM at the AtD stage.

Materials and Methods: A single-center prospective randomized controlled study was conducted from 2019 to 2021. The study included 90 children diagnosed with AtD, divided into two groups. The main group included 53 children, with an average age at initial presentation of 2,87 ± 0,91 months. All patients in the main group underwent stool culture with bacterial identification and antibiotic + bacteriophage susceptibility testing. The presence of associations of *Staphylococcus aureus* with *Klebsiella pneumoniae* or *Klebsiella oxytoca* was an indication for phage therapy (PT). The control group consisted of 37 children diagnosed with AtD, with an average age at initial presentation of 2,89 ± 2,78 months. After stool culture with bacterial identification and antibiotic + bacteriophage susceptibility testing and identification of associations of *Staphylococcus aureus* with *Klebsiella pneumoniae* or *Klebsiella oxytoca*, PT was not performed.

Results: Comparative microbiological analysis of feces did not reveal any differences in the lg CFU/g of *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* associations in children from the study groups. The lg CFU/g level of *Staphylococcus aureus* in children of the main group was 5,85 ± 1,34, *Klebsiella pneumoniae* 5,42 ± 1,31, *Klebsiella oxytoca* 4,11 ± 0,93; in the control group, *Staphylococcus aureus* was 5,22 ± 1,49, U = 1,78, p = 0,0758, *Klebsiella pneumoniae* 5,00 ± 1,56, U = 1,07, p = 0,2856, *Klebsiella oxytoca* 4,00 ± 0,93, U = 0,24, p = 0,8096. The performed physiotherapy in children of the main group allowed achieving a significant clinical effect and substantially reduced the lg CFU/g levels of *Staphylococcus aureus* from 5,85 ± 1,34, *Klebsiella pneumoniae* 5,42 ±

1,31, *Klebsiella oxytoca* 4,11 ± 0,93 to *Staphylococcus aureus* 1,68 ± 1,19, U = 8,87, p = 0,0000, *Klebsiella pneumoniae* 1,84 ± 1,10, U = 7,76, p = 0,0000, *Klebsiella oxytoca* 2,33 ± 1,00, U = 2,92, p = 0,0035. The use of probiotics in children of the control group did not achieve the desired result. The lg CFU/g levels of *Staphylococcus aureus* before use were 5,22 ± 1,49, *Klebsiella pneumoniae* 5,00 ± 1,56, *Klebsiella oxytoca* 4,00 ± 0,93; at the end of the course, *Staphylococcus aureus* was 5,76 ± 1,23, U = 1,42, p = 0,1551, *Klebsiella pneumoniae* 5,41 ± 1,21, U = 1,06, p = 0,2902, *Klebsiella oxytoca* 5,25 ± 1,49, U = 1,63, p = 0,1031.

Conclusion: Phage therapy aimed at decontaminating the excessive growth of the associations of *S. aureus*, *K. pneumoniae*, and *K. oxytoca* is currently one of the promising alternative methods for properly influencing the intestinal biotope of a child in the first weeks, subsequently preventing the development of IgE-mediated hypersensitivity.

Keywords: *Atopic Dermatitis; Atopic March; Gut Microbiota; Bacteriophages; Decontamination*

Abbreviations

AR: Allergic Rhinitis; AM: Atopic March; BA: Bronchial Asthma; IBD: Confirmed Diagnosis; IC: Intestinal Colic; CPM: Conditionally Pathogenic Microflora; PT: Phage Therapy; FCR: Federal Clinical Guidelines

Introduction

The message voiced several years ago by the World Health Organization (WHO) that the current century would be the "age of allergy" has proven to be quite justified. Serious concern is also raised by data from the annual World Health Statistics reports, which confirm that every second person on the planet has some form of allergy [1]. Official data from experts at the Federal State Budgetary Institution "GNC Institute of Immunology" of the FMBA of Russia show that the overall prevalence rate varies depending on the patient's region of residence, ranging from 17,5% to 35%. The prevalence of the most common atopic diseases (AZ) in children includes AtD from 5% to 30,8%, AR from 10% to 24%, and BA from 0,8% to 37,6% [2,3]. The initial manifestation of atopy in children is AtD, which is one of the most common childhood dermatoses. It is a multifactorial, genetically determined inflammatory skin disease characterized by itching, a chronic relapsing course, and age-specific features in the localization and morphology of lesions [4]. In most patients, AtD that appears in the first weeks of life has a moderate to severe course, with a diffuse nature of spread of the primary morphological elements, usually serving as a prologue to AM. Unfortunately, currently, there is no approach to AtD therapy due to the multitude of phenotypes caused by diverse cytokine profiles; at best, symptom control is achieved [5]. AtD therapy is exclusively palliative, which underscores the urgent need to develop measures both of a therapeutic nature and, primarily, preventive [6]. Insufficiently studied mechanisms of AM open up prospects for further research in the field of prediction, as well as the development of strategies for primary and secondary prevention of new, innovative treatment methods. Currently, one of the promising directions that allows explaining the pathogenesis of initial allergic reactions is the understanding of the complex mechanisms of oral tolerance formation [7,8]. At present, there are publications convincingly demonstrating the connection between certain representatives of conditionally pathogenic microflora (CPM) and the development of AtD [9,10]. There are numerous expert opinions indicating the possibility of correctly modeling the dynamic equilibrium of a child's gut symbiotic flora in the first year of life in the formation of immunological tolerance [11-13]. Undoubtedly, the existing paradigm of the dominant role of the genetic component in the development of mechanisms underlying the onset of AtD remains relevant [14]. The leading external environmental factor in AtD and atopy in general is infection, which can quite possibly be managed [15,16].

Formulation of the hypothesis

Daily, long-term work with patients in the field of allergology and immunology has convinced us in understanding the mechanisms of AM formation. What do we mean by this? One of the most common reasons for consulting a pediatrician or an allergist-immunologist is AtD, as the initial nosology of AM. After analyzing the complaints of all patients, not only with AtD, but also AR and BA, we noticed that in all cases, during the first weeks of life, children with a hereditary predisposition to atopy exhibited intestinal dysfunction (ID). Clinically, ID manifested as intestinal colic (IC) of varying intensity, a decrease in the daily number of bowel movements, and the presence

of pathological impurities in the stool (mucus, greenish tinge, blood ranging from streaks to abundant discharge). Routine microbiological examination of the contents of the proximal part of the intestine in infants with a confirmed diagnosis of AtD led to the identification in all patients of associations of *Staphylococcus aureus* and *Klebsiella pneumoniae*, *Klebsiella oxytoca*, significantly exceeding reference values. The detection of UPM (*Staphylococcus aureus* and *Klebsiella pneumoniae*, *Klebsiella oxytoca*) was considered as intestinal dysbiosis, and in accordance with OST 91500.11.0004-2003 'Protocol for the Management of Patients with Intestinal Dysbiosis,' therapy with probiotic preparations was carried out. To date, there has been no alternative to the use of probiotics for correcting dysbiotic disturbances of the intestinal biotope in the first months of life in children with a hereditary predisposition to atopy.

The hypothesis of using bacteriophages for the decontamination of *Staphylococcus aureus* and *Klebsiella pneumoniae*, *Klebsiella oxytoca*, as the main representatives of the gut microbiota capable of initiating the onset of atopic dermatitis, proved to be quite bold and promising. The collegially made decision to use bacteriophages in patients during the first weeks of life with atopic dermatitis led to unexpectedly positive results. Against the background of phage therapy, not only was there a rapid positive dynamic in the disappearance of clinical symptoms of atopic dermatitis, but also a quick decrease in lg CFU/g of *Staphylococcus aureus* and *Klebsiella pneumoniae*, *Klebsiella oxytoca*. Over time, the cautious assumption about the effectiveness of using bacteriophages has grown into a deep conviction that the decision was correct, as confirmed by successful clinical experience. The legitimacy and justification of the phage therapy application method are based on extensive clinical experience.

The implementation in the practical healthcare of the Kemerovo region - Kuzbass of methodological recommendations; 'Early postnatal correction of gut microbiota as the main factor for primary prevention of atopy' (Gladkov S.F., *et al*. 2021), allowing active use of PT for the therapy of AtD, has enabled a multiple reduction in rates of childhood AZ morbidity.

To date, there is no information in the literature about the experience of using PT in the context of AtD therapy, except for isolated publications on the possibilities of local use of bacteriophages in the treatment of secondary infection of AtD elements [21].

Research Objective

To determine the effectiveness of using bacteriophages in patients with AtD and the possibility of discontinuing AM at the AtD stage.

Materials and Methods

In 2006, the Federal State Budgetary Educational Institution of Higher Education "Kemerovo State Medical University" of the Ministry of Health of Russia announced a pilot project for the development and implementation of the program "Primary Prevention of Atopy". The main goal of the project was to develop innovative programs aimed at treating and primarily preventing allergic diseases in children of the Kemerovo region - Kuzbass. All the goals and objectives of the project were achieved, resulting in the development and successful implementation in practical healthcare of original methods for treating and primarily preventing allergic diseases in children, which allow not just alleviating the symptoms of the next exacerbation, but achieving full recovery of the patient.

Analysis of the clinical and anamnesis data of 375 children with a confirmed diagnosis of BA and 1218 patients with AtD conducted at the onset of the study revealed a key pattern. The essence of this pattern was the presence in all patients of colitic syndrome, manifested in the 3rd - 4th week of life by pronounced colic, the presence of pathological impurities in the stool such as mucus, green color, blood, and impaired motor function (reduced frequency of defecation). Detailed assessment of the results of stool culture with bacteria identification and Antibiotic+Bacteriophage susceptibility testing revealed the presence of associations of representatives of the families Micrococcaceae (*Staphylococcus aureus*) and Enterobacteriaceae (*Klebsiella pneumoniae* and *Klebsiella oxytoca*), significantly exceeding the reference range in all observed cases. During the research, a strong conviction emerged that hyper-resistant and aggressive bacterial strains associated with healthcare-associated infections disrupt the process of normoflora coaggregation on intestinal biofilms,

reducing the overall number of *Bifidobacteria*, leading to auto-sensitization and the development of IgE-mediated allergy, i.e. they are the main initiating factor in the development of atopic dermatitis AtD [17]. Being a genetically determined, evolving microecosystem of interactions between obligate, facultative, and transient microflora, the gut microbiota of infants in the first weeks of life requires very delicate methods of intervention [18,19].

The question of addressing the excessive growth of *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* in the absence of a clinical effect from the use of probiotics led to the decision to use bacteriophages. Currently, there is an ongoing process of accumulating scientific and practical experience in the use of bacteriophages as a tool for managing allergen-induced immunopathology [20]. There is already experience with fairly effective topical use of bacteriophages in AtD [21]. However, unfortunately, there is no clinical experience with the use of enteral forms of bacteriophages in the therapy of AtD and atopy in general.

A bacteriophage is a highly advanced biological entity of the biosphere, measuring 100 nm, capable of selectively penetrating a bacterial cell, multiplying there, and causing its destruction, while containing a complex of proteins in its structure for joint replication, completely preventing any effect on other cells, biofilm, or the host's own cells. In addition to its selective lytic action on the cell, phages encode a wide range of highly specific enzymes that break down the exopolysaccharides of the biofilm matrix, which allows for a significant influence on the proper structural organization of the intestinal biotope [22].

Study design

Within the framework of the project, a single-center prospective randomized controlled study was conducted during the period from 2019 to 2021. To confirm the long-term effect of PT, an analysis was conducted on the presence of verified atopic diagnoses in patients of the main and control groups at the age of 6 years (Figure 1).

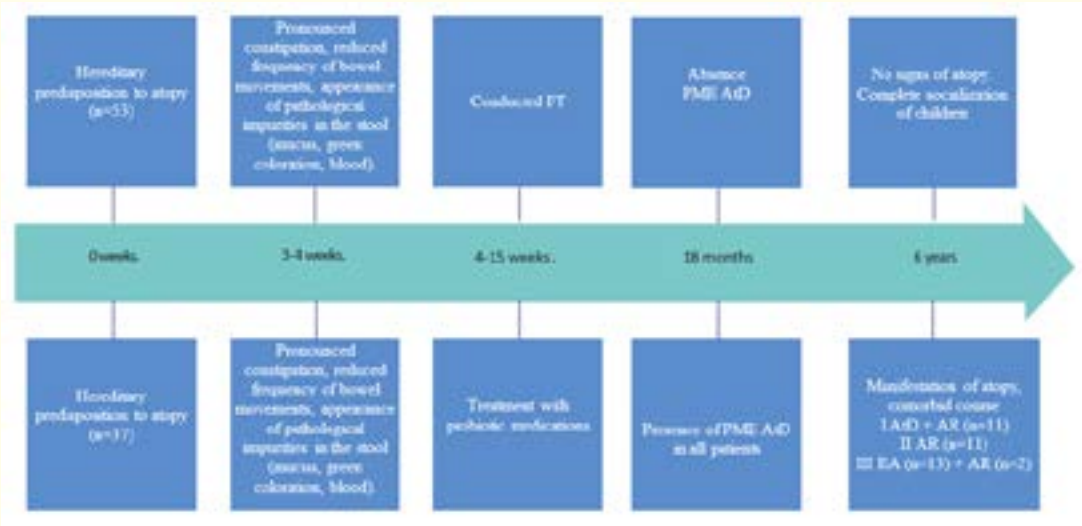

Figure 1: *Study design.*

Inclusion criteria for children in the main study group: Presence of allergies in the parents and/or siblings of the child; age between 1 and 4 months; a verified diagnosis of AtD; absence of clinical and laboratory manifestations of acute or chronic somatic disease; signed informed consent from parents or guardians for participation in the study.

Exclusion criteria from the study: Onset of acute somatic, infectious, neurological, or traumatic disease requiring medication; occurrence of adverse effects (individual intolerance to medications); refusal of participation by the official guardian.

Exclusion criteria for the study: Absence of AZ in the parents and/or siblings of the child; age outside the range of 1 to 4 months; absence of a verified diagnosis of AtD; presence of clinical and laboratory manifestations of acute or chronic somatic disease; absence of signed informed consent from the parents or guardians for participation in the study.

The study included 90 children with a confirmed diagnosis of (IBD), divided into two groups. The main group consisted of 53 children, including 31 boys and 22 girls, who were referred for IBD, with an average age at the time of initial consultation of 2,87 ± 0,91 months. All participants in the main group had a IBD and underwent stool culture with bacterial identification and antibiotic+bacteriophage susceptibility testing. The presence of associations of *Staphylococcus aureus* with *Klebsiella pneumoniae* or *Klebsiella oxytoca* was an indication for conducting phage therapy.

The control group consisted of 37 children, including 23 boys and 14 girls, with a verified diagnosis of AtD, with an average age at the time of initial consultation of 2,89 ± 2,78 months. According to the results of stool culture with bacteria identification and antibiotic+bacteriophage susceptibility testing and the identification of associations of *Staphylococcus aureus* and *Klebsiella pneumoniae*, *Klebsiella oxytoca*, phage therapy was not conducted.

All children in the control group underwent a course of treatment in accordance with the Federal Clinical Guidelines (FCG) for the treatment of AtD (2019). The number of children included in the main group was part of a representative sample from the total number of children (over 30,000) at the time of the study who had received therapeutic and prophylactic phage therapy.

Conditions of the study

The study was conducted at the medical center LLC "Clinic of Allergology and Immunology," Yurg, Russia. The duration of the study was 3 years. The study was conducted as part of the pilot project "Primary Prevention of Atopy" carried out in the Kemerovo region - Kuzbass. The study received approval from the Ethics Committee/IRB of the Federal State Budgetary Educational Institution of Higher Education "Kemerovo State Medical University" of the Ministry of Health of Russia, Kemerovo, Russia, protocol No. 32/k dated 12.12.2007, and protocol No. 356 dated 26.11.2018 for the study, the results of which are presented in the article.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education 'Kemerovo State Medical University' of the Ministry of Health of Russia. Informed voluntary consents for participation in the study were signed by all parents and legal guardians of the children.

The statistical analysis of digital data was carried out using IBM SPSS 23.0 (IBM, USA) and Statistica 6.1 (StatSoft, USA). Missing values were excluded from the analysis. The study group data were presented in absolute numbers and percentages. The statistical processing of the data sets was done by calculating the arithmetic mean (M), standard deviations (σ), and standard errors of the mean (m). To describe the results, we used the median (Me), the 25^{th} and 75^{th} percentiles [Q1 and Q3], and the range (min-max) of values. Nominal data were described with absolute values, percentages, and 95% confidence intervals (95% CI). Pearson's χ^2 test was used to compare frequencies. The Mann-Whitney nonparametric rank test was applied to assess group differences. Differences were considered statistically significant at $p < 0.05$.

Results

The analysis of clinical and laboratory data of the study participants in the main group was carried out by clinic specialists based on patients' medical histories. For the analysis of the corresponding data of the study participants in the control group, a detailed review of outpatient records was conducted.

Extensive clinical experience of the specialists at our clinic indicates the indisputably key role of the mechanism of gut biotope formation in the evolution of immunological tolerance. Excessive expansion of associations of hospital strains of *S. aureus*, *K. pneumoniae*, and *Klebsiella oxytoca* is the main cause of both the onset of AtD and its persistence. Overgrowth of aggressive strains of *S. aureus*, *K. pneumoniae*, and *Klebsiella oxytoca* of hospital origin inevitably leads to the development of colitic syndrome.

According to parents or guardians, all children included in the study experienced the appearance of primary morphological elements (PME) on the skin after the onset of colitic syndrome, which was manifested to varying degrees by changes in stool consistency, longer intervals between bowel movements, changes in stool color, presence of mucus and green coloration in 81,13% of children, and bloody discharge in 20,75% in the main group, while in the control group 86,48% had mucus and green coloration (OR = 0.67 χ^2 = 0.45 95% CI: 0.21 - 2.16 p = 0.575) and 10,81% had blood (OR = 2.16 χ^2 = 1.55 95% CI: 0.63 - 7.41 p = 0.260), respectively.

The debut of colitic syndrome in the main group was recorded at 2,52 ± 0,77 weeks, Me 3,0 [1,0 - 4,0], and in the study group at 2,48 ± 0,80 weeks, Me 2,0 [1,0 - 4,0], respectively, p > 0.05, indicating no significant difference in the timing of onset. Colitic syndrome in all children included in the study always preceded the appearance of the first symptoms of AD. So, in the main group, the appearance of primary morphological elements of AD was recorded at 4,03 ± 0,91 weeks, Me 4,0 [2,0 - 6,0], in the control group at 3,97 ± 0,83 weeks, Me 4,0 [2,0 - 5,0], which also showed no significant difference, p > 0,05.

The presence of colitic syndrome was an absolute indication for performing stool culture with bacteria identification and antibiotic+bacteriophage susceptibility testing. The results of the microbiological examination of stool allowed for the detection of associations of *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* in all children of the studied groups. The titer levels (lg CFU/g) of *Staphylococcus aureus* in children of the main group were 5,85 ± 1,34, *Klebsiella pneumoniae* 5,42 ± 1,31, *Klebsiella oxytoca* 4,11 ± 0,93; in the control group, *Staphylococcus aureus* was 5,22 ± 1,49, U = 1,78, p = 0,0758, *Klebsiella pneumoniae* 5.00 ± 1,56, U = 1,07, p = 0,2856, *Klebsiella oxytoca* 4,00 ± 0,93, U = 0,24, p = 0,8096, respectively, demonstrating no statistically significant differences (Figure 2).

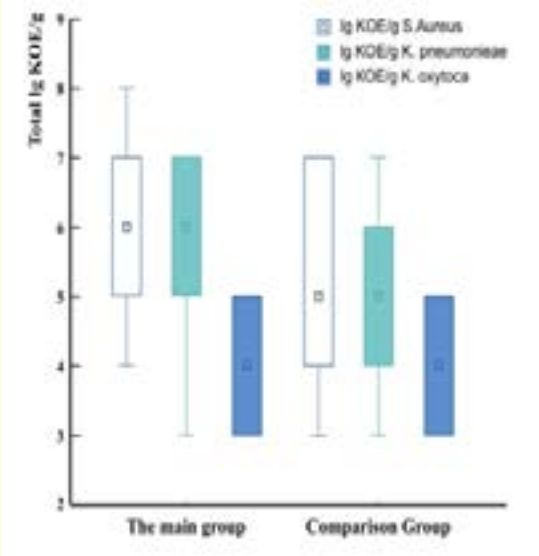

Figure 2: *The level of lg KOE/g in children of the study group at the onset of atopic.*

Description of medical intervention

Based on the results of the conducted stool culture with bacteria identification and antibiotic + bacteriophage susceptibility testing, all infants in the main group underwent three 16-day courses of phage therapy with staphylococcal bacteriophage (Bacteriophagum Staphylococcum) at a dose of 3 ml orally twice a day and 3 ml rectally before bedtime for 8 days. Then, a purified polyvalent *Klebsiella* bacteriophage (*Klebsiella* polyvalent bacteriophage purified) was used in cases associated with *Klebsiella pneumoniae*, and a purified polyvalent Pyo-bacteriophage (Piobacteriophage polyvalent purified) was used in cases associated with *Klebsiella oxytoca* in similar doses, with a 14-day interval. According to our observations, the minimum optimal course of phage therapy should be 48 days with a 28-day break between courses. The possibility of conducting longer courses exists, but in our opinion, no more than 3 courses are sufficient to achieve an adequate prospective clinical effect. Titration of the manufacturer-recommended phage dose, which allowed reducing the single oral dose from 5 ml and rectal dose from 10 ml to 3 ml, was due to the onset of a rapid clinical effect and concerns about the occurrence of adverse effects.

The conducted (PT), in addition to noticeable clinical effects, significantly affected the titer levels of lg CFU/g of associations of *Staphylococcus aureus* and *Klebsiella pneumoniae*, *oxytoca*. The results of the microbiological examination of feces conducted after the PT course revealed a significant dynamic decrease in lg CFU/g levels of associations of *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. Specifically, the titer levels of lg CFU/g of *Staphylococcus aureus* in children of the main group before FT were 5,85 ± 1,34, *Klebsiella pneumoniae* 5,42 ± 1,31, *Klebsiella oxytoca* 4,11 ± 0,93; after PT the levels were *Staphylococcus aureus* 1,68 ± 1,19, U = 8,87, p = 0,0000, *Klebsiella pneumoniae* 1,84 ± 1,10, U = 7,76, p = 0,0000, *Klebsiella oxytoca* 2,33 ± 1,00, U = 2,92, p = 0,0035, respectively (Figure 3).

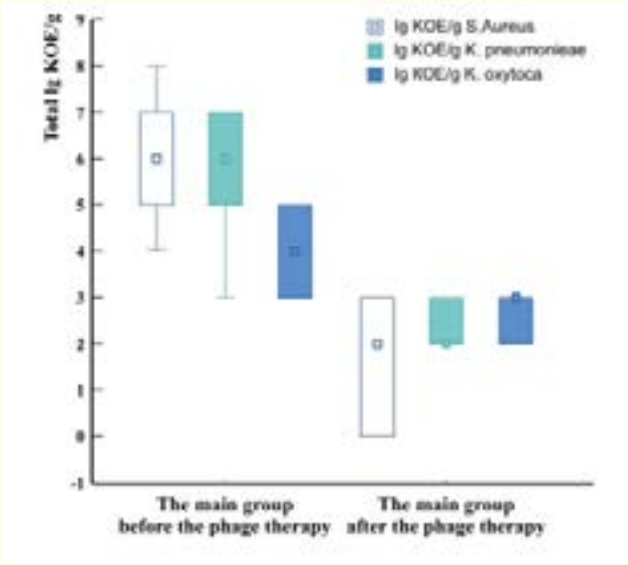

Figure 3: *Dynamics of the level of lg KOE/g against the background of phage therapy.*

As a result of the PT conducted, a significant improvement in clinical symptoms was achieved, manifested by a reduction in intensity and complete disappearance of coughing already by day 2,30 ± 0,69 Me 2,0 [1,0 - 3,0] of treatment. Reduction of pathological inclusions in the stool and normalization of defecation frequency occurred on average by day 3,01 ± 0,63, Me 3,0 [2,0 - 4,0] with objective regression of the skin syndrome observed by day 4,79 ± 0,76 Me 5,0 [3,0 - 6,0] of PT. After the completed PT, all children in the main group aged

5.0 to 5.5 months were successfully introduced to complementary foods in accordance with the 'National Program for Optimizing Infant Feeding in the Russian Federation' (2019). During the introduction of complementary foods, none of the infants showed any signs of atopy. According to follow-up to the present time, children in the main group are fully socialized and will continue to be under the supervision of an allergist-immunologist until they reach 7 years of age.

Analysis of the dynamics of bacteriological examination results of stool in children of the control group revealed an unfavorable trend in the proliferation of *Staphylococcus aureus* and *Klebsiella pneumoniae*, oxytoca, reflected by an increase in lg CFU/g titers. The probiotic correction course conducted to reduce lg CFU/g did not achieve the desired result. Thus, the lg CFU/g titer levels of *Staphylococcus aureus* in children of the group before probiotic correction were 5,22 ± 1,49, *Klebsiella pneumoniae* 5,00 ± 1,56, *Klebsiella oxytoca* 4,00 ± 0,93; after the course, for *Staphylococcus aureus* 5,76 ± 1,23, U = 1,42, p = 0,1551, *Klebsiella pneumoniae* 5,41 ± 1,21, U = 1,06, p = 0,2902, *Klebsiella oxytoca* 5,25 ± 1,49, U = 1,63, p = 0,1031, respectively (Figure 4).

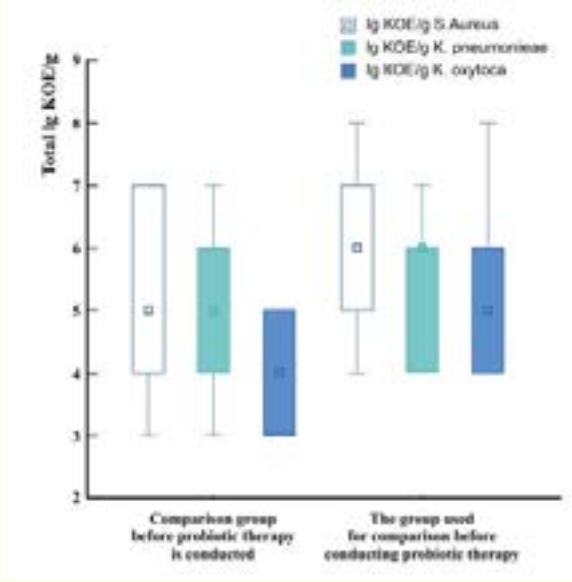

Figure 4: *Dynamics of lg KOE/g after the use of a therapeutic course of probiotics.*

An objective evaluative indicator of the dynamics of AtD progression is the SCORAD index. At the time of initial consultation, the SCORAD index in children of the main group ranged from 12,5 (min) to 34,7 (max) points, with an average of 21,11 ± 7,15. At the first follow-up point corresponding to 18 months, no primary morphological elements of AtD were recorded in any of the patients in the main group. In the control group, at the corresponding time of consultation at the first manifestations of dermatitis, the SCORAD index ranged from 12,5 (min) to 38,9 (max), with an average of 21,37 ± 6,90 points. Accordingly, at the first follow-up point, the SCORAD index in children of the control group ranged from 12,4 (min) to 54,6 (max), with an average of 34,36 ± 8,05 points, indicating the absence of the development of adaptive mechanisms in the body to counter the sensitization component, that is, to stop the formation of an allergic phenotype (Figure 5).

The analysis of the clinical and anamnesis data of patients in the main and control groups, conducted at the second checkpoint corresponding to the patients' 6-year age, convinced us of the long-term effect of PT. At the time of follow-up, all patients in the main group

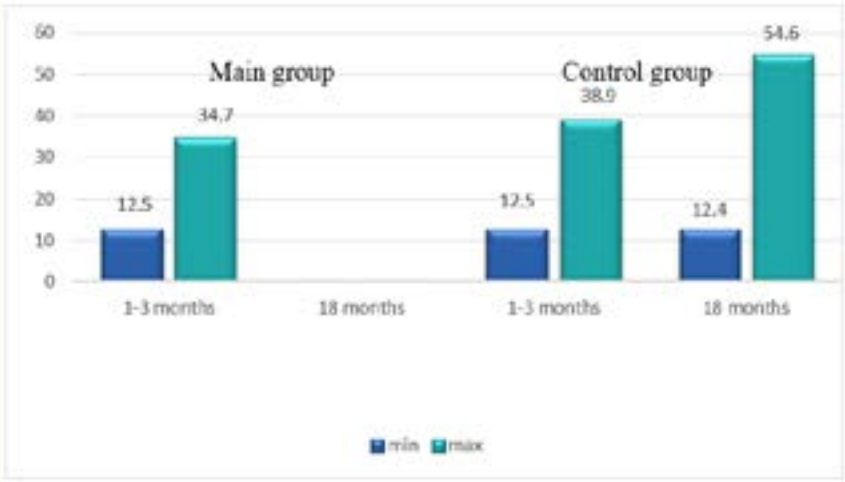

Figure 5: *Dynamics of the SCORAD Index (points) in children in the study groups.*

had no manifestations of atopy, were fully socialized, and most of them attended preschool institutions. In the control group, all children had implemented AM. In 27,02% of children (n = 10), a comorbid course of AtD and seasonal allergic Rhinoconjunctivitis was verified, in 29,7% of children (n = 11) seasonal allergic Rhinoconjunctivitis was verified, and in 43,23% of children (n = 16) a comorbid course of asthma and AR was found, of these, 35,13% of children had asthma (n = 13) and 8,10% had AR (n = 3).

Discussion

Despite numerous studies, the mechanism of microbial colonization in the intestines of infants during the first months of life and methods for correct, controlled influence on the process of healthy microbiota formation remain insufficiently studied. The active practical use of probiotics to achieve an adequate balance of symbiotic intestinal flora in the treatment and prevention of allergic diseases has not had a significant impact on reducing morbidity rates [13]. The growing number of publications demonstrating a link between certain members of the gut microbiota and the development of atopic dermatitis and allergic diseases in general [15], unfortunately, does not provide information on effective ways to influence the gut microbiota through intervention.

In our opinion, one of the key triggering factors for the onset of AM is the generation of an imbalance in the symbiotic microflora due to the active progressive proliferation of *S. aureus* and *K. pneumoniae*, *K. oxytoca*, or their combinations, represented by hospital strains. The escalation of the process by highly resistant, aggressive bacterial strains, associated with healthcare-associated infections, disrupts the coaggregation process of normal flora on intestinal biofilms, leads to autosensitization, and serves as a springboard for the development of AtD.

Currently, the concept of a "window of opportunity," the period required for the formation of the gut microbiome in a child at risk of developing atopy, corresponding to 1000 days, in our opinion, requires a more balanced and differentiated approach. According to our observations, phage modeling of the gut biotope in a child with a hereditary predisposition should be initiated not only at the first clinical manifestations of atopic dermatitis (appearance of primary morphological elements on the skin), but already when there is food allergy, no later than 2 - 3 months of age, meaning that the "window of opportunity" may be significantly shorter than proposed. In the case of delayed application of phage modeling, for example, at 2 years of age, we would have a child who already has a formed atopic phenotype, and our efforts would then be focused solely on alleviating disease symptoms, without any means to influence the atopic march.

I hope that our modest research aimed at further studying the mechanisms of AM control will interest colleagues and serve as a stimulus for studying the processes of forming a 'healthy' gut microbiome in children based on the use of medicinal agents generously provided to us by nature itself, which are bacteriophages.

Conclusion

The innovative method of controlled phage modeling of the gut microbiota in children with AtD, developed, implemented, and actively used in the Kemerovo region - Kuzbass, in addition to the Federal clinical guidelines, allows for successful management of AM. The main principle of the method is phage decontamination of the excessive growth of associations of *S. aureus*, *K. pneumoniae*, and *K. oxytoca*. Today, phage therapy is one of the promising alternative methods for appropriately influencing the gut biotope of a child in the first weeks of life, completely eliminating the possibility of negative impact on the genetically determined evolution of the gut microbiota.

The active use of PT in patients with AtD, based on sufficient clinical experience, allowed the conclusion that there are disruptions in the gut microbiome in children due to the active progressive proliferation of associations of *S. aureus*, *K. pneumoniae*, and *K. oxytoca*, which underlies the mechanism of AM persistence. The presence of intestinal dysfunctions in patients with AtD is an absolute indication for performing Stool Culture with Bacteria Identification and Antibiotic + Bacteriophage Susceptibility Testing to detect associations of *S. aureus*, *K. pneumoniae*, and *K. oxytoca*, followed by PT. Delicate decontamination allows for the most accurate formation of the intestinal microbiome in newborns, taking into account the genetically personalized determinism of the child's microecosystem in the first weeks of life, thereby preventing the development of IgE-mediated hypersensitivity in the future. An addition to the guidelines for the treatment of AtD in early childhood will significantly influence epidemic indicators and achieve meaningful results in the study of complex mechanisms of immune modulation.

Author Contributions

The authors declare that their authorship complies with the international ICMJE criteria. S.F. Gladkov - conceptualization of the idea, hypothesis, and study objectives, development of methods and procedures, verification of results, reproducibility, conducting experiments, data collection, writing the initial draft of the article; N.K. Perevoshchikova - project management and scientific supervision of the project; L.A. Levanova - editing and refinement of the text; N.V. Lyachina - provision of materials and equipment; V.I. Ivanov - creation of software, scripts, algorithms, development of graphs, diagrams, and illustrations. All authors have read and approved the published version of the manuscript.

Originality of Illustrations

The authors confirm that all illustrations presented in the manuscript are original and have not been taken from previously published articles. The authors confirm that Statistica 6.1 software (StatSoft, USA) was used to create all manuscript illustrations. The authors deny the use of artificial intelligence both in writing the manuscript text and in creating the illustrations.

Availability of Data and Materials

The patient archive, clinical and paraclinical data are located in the medical information system 'ARENA', which is designed to create a unified information space in the region's healthcare. The analyzed and generated data of patients included in the study are in the information-statistical system of the LLC Allergy and Immunology Clinic and are not publicly available due to the lack of consent from parents or guardians to share information with third parties, but are available from the author upon reasonable request.

Consent for Publication

All parents and legal guardians of the children have signed informed voluntary consent for voluntary participation in the study.

Conflict of Interest

The authors declare that there are no obvious or potential conflicts of interest related to the conducted study and the publication of this article.

Funding Support

The authors declare that there is no external funding for the research and preparation of the publication.

Use of Artificial Intelligence

In the process of writing the manuscript, the authors declare that no artificial intelligence tools were used.

Acknowledgments

The team of authors sincerely appreciates help of English teacher (Secondary Comprehensive School 64 Penza) Avdonina Ekaterina Alexandrovna for the translation of the manuscript into English and language editing.

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Volume 14 Issue 7 July 2026
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