



# Bacteriophagic Therapy: An Alternative to Antibacterial Therapy in Acute Tonsillitis

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## Abstract

**Background:** To study the effects of bacteriophage therapy on acute tonsillitis in children and adolescents in an outpatient setting.

**Materials and methods:** A total of 128 children aged 3 to 14 years with acute tonsillitis were examined. General clinical characteristics, pharyngoscopy findings, and bacteriological results from a tonsil smear were collected. Bacteriophage therapy was carried out using a liquid complex pyobacteriophage (pyobacteriophage complex liquid - PCL).

**Results:** The main pathogens of acute tonsillitis in children were Staphylococcus aureus and Streptococcus pyogenes (from 24.2% to 42.2%). Bacteriophage therapy was associated with decreases in swelling in the tonsils and general intoxication signs after 2-3 days of treatment. In the blood, the level of leukocytes in 85.07% of the patients returned to normal on the 4th day of the disease.

**Conclusion:** The main predictor of the development of acute tonsillitis in children was viral infection (75.8%), which contributed to increased colonization of the tonsils by pathogenic bacteria, mainly Staphylococcus aureus and Streptococcus pyogenes. The use of bacteriophage therapy for the conservative treatment of acute tonsillitis in children improved their condition 1.4 times faster than standard therapy during the acute period of the disease.

**Keywords:** Acute Tonsillitis; Children; Tonsils; Bacterium; Bacteriophage

**Abbreviations:** PCR: Polymerase Chain Reaction; PCL: Pyobacteriophage Complex Liquid; TLRs: Toll-Like Receptors; NLRs: NOD-Like Receptors; GABHS: Group a Beta-Haemolytic Streptococcus.

## Introduction

The problem of reducing the effectiveness of antibiotic therapy has become one of the topical issues in modern

medicine. The increase in bacterial resistance to drugs has led to an increase in the incidence of complications of many infectious diseases [1,2]. In particular, due to the high spread of coronavirus infection (COVID-19 or SARS-CoV-2) among children, the use of antibiotics to prevent bacterial complications is one of the leading problems in pediatrics [3]. At the same time, one of the clinical manifestations is acute tonsillitis of viral etiology with the addition of a bacterial infection.

Challenges in the treatment and prevention of acute respiratory infections in children of various ages, as well as the development of complications, has always been a pressing issue in modern pediatrics [4,5]. The main causative agents of acute tonsillitis are viruses; subsequently, bacteria can colonize the tonsils. According to Vetrova AD (2014), in children under 4 years of age, the viral etiology prevails in the pathogenesis of the disease and, starting at the age of 4, *Streptococcus pyogenes* prevails, which is the leading cause of acute tonsillitis in children up to 18 years of age. Among these bacteria,  $\beta$ -hemolytic group A streptococcus remains the most significant aetiological agent of acute tonsillitis [6], although other bacteria play a crucial role in the course of the disease [6,7]. Bacterial flora is a major contributor to the chronicity of many childhood diseases [8,9]. However, the role of bacterial flora and their effects on the clinical course of acute tonsillitis in pediatric patients remains unknown in modern pediatric otolaryngology.

### The Purpose of the Study

To study the feasibility of conducting bacteriophage therapy in children and adolescents with acute tonsillitis in an outpatient setting.

### Methods

#### Study Design

We examined 128 children aged 3 to 14 years with clinically diagnosed acute tonsillitis. The children were from families with contact with COVID-19 patients. The clinical study was conducted in an outpatient, setting in collaboration with the clinic of the Tashkent Pediatric Medical Institute. Before the study, written permission for study participation was obtained from the parents or guardians of the children.

Criteria: Inclusion Criteria:

- Children from 3 to 14 years old;
- Children with sore throat;
- Children diagnosed with acute tonsillitis;
- Children diagnosed with acute respiratory infection (rhinitis, sinusitis, nasopharyngitis);
- Children with the opportunity to visit the outpatient clinic;
- Children with the ability to receive inhalation therapy;
- Children from parents (or guardians) who have given written permission to conduct clinical and laboratory research.

Exclusion Criteria

- Children under 3 years old and over 14 years old;
- Children receiving hospital treatment;
- Children with acute respiratory tract diseases (bronchitis, pneumonia, pleurisy);

- Children with chronic respiratory tract diseases (bronchitis, pneumonia);
- Children who are allergic to antibiotics;
- Children with cancer, immunological and hematological diseases;
- Children with severe psychological illnesses (schizophrenia, mental retardation, etc.);
- Children with cancer, immunological and hematological diseases;
- Children with tuberculosis.

### Laboratory Research Methods

All examined children underwent a general clinical examination and pharyngoscopy. Additionally, all the patients had tonsil smears collected for bacteriological examination (bacteriological culture) according to standard methods. Nasopharyngeal swabs were also conducted for viral lesion examination by a standard method-PCR (Polymerase chain reaction).

### Bacteriophage Therapy

Comprehensive outpatient treatment was based on standard clinical guidelines, and symptomatic treatment was performed. On the first day of diagnosis, patients were prescribed complex antibacterial therapy on the basis of possible causative agents. Subsequently, antibiotic therapy was adjusted based on the results of the bacteriological examinations. A total of 67 patients received bacteriophage therapy using a liquid complex of pyobacteriophages (pyobacteriophage complex liquid-PCL). PCL was administered via nebulizer inhalation to irrigate the mucous membranes of the tonsils. In total, 5 ml of PCL was inhaled for up to 10 minutes once every 5 days.

The drug causes lysis of specific bacteria including *Staphylococcus*, *Enterococcus*, *Streptococcus*, enteropathogenic *Escherichia coli*, *Proteus vulgaris*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. The drug is recommended for use for diseases of the ear, throat, nose, respiratory tract and lungs; inflammation of the sinuses and middle ear; tonsillitis; pharyngitis; laryngitis; tracheitis; bronchitis; pneumonia, pleurisy; and other inflammatory diseases. The choice of this drug was based on bacteriological studies.

### Ethical Review

Before the trials, written permission was obtained from the children's parents or guardians. All documentation was recorded in the study log. The Ethics Committee of the Ministry of Health of the Republic of Uzbekistan approved the conduct of this clinical and laboratory study among children in an

outpatient setting (protocol no. 1/10-1484 of 27.02.2021). Research register on the site <https://register.clinicaltrials.gov/> ID:NCT04682964. Information of informed consent from the patients is included in the patient's documentation (child's outpatient card form 112/a), with the informed consent from the children's parents or guardians.

### Statistical Analyses

Statistical analysis was carried out based on the obtained results. All analyses were conducted using a statistical program based on Excel 2013 (Microsoft Office 2013). The program is flexible, with a capacity suitable for all kinds of statistical calculations used in biomedicine. Comparisons between groups were performed using the average population per year over the study period. In all the analyses,  $P \leq 0.05$  was considered significant.

## Results

### Clinical Manifestations of the Disease

The problem of acute tonsillitis always remains relevant in the field of family medicine and pediatrics. Despite the diligence of doctors, the number of patients is increasing from year to year, especially problem has become urgent against the backdrop of a pandemic. At the same time, we noted changes in the clinical picture of the disease in children.

According to our observations, odynophagia was noted in 71.88% (n= 92 of 128) of the patients, swelling and redness of the tonsils in 92.19% (n=118 of 128) of the patients, the occurrence of tonsil exudates in 46.09% (n= 59 of 128) of the patients, cervical lymphadenopathy in 84.38% (n= 108 of 128) of the patients and fever over 38 °C in 83.59% (n=107 of 128) of the patients. Over the course of our study, depending on the stage and appearance of the tonsils, we determined the following types of acute tonsillitis: catarrhal tonsillitis in 65.63% (n=84 of 128) of the children, follicular tonsillitis in 22.66% (n= 29 of 128) of the children and lacunar tonsillitis in 11.72% (n=15 of 128) of the children. Clinical and laboratory studies noted pronounced leukocytosis with neutrophilia associated with an increased ESR.

### Results of Virological and Bacterial Studies

According to our results, a predictor of the development of acute tonsillitis in children is viral infection (acute respiratory disease), which occurred in 75.8% (n= 97 out of 128) of the children. The presence of viral infection was confirmed during viral analysis of nasopharyngeal swabs. Of these, 8 (8,2%) children were identified as carriers of COVID-19, with no other clinical symptoms of the disease. In the presence of clinical symptoms of COVID-19, children

were sent for further research and treatment in specialized medical institutions, and were not included in the study group. In children, mainly laboratory was identified: adenovirus – 9.3% (n = 9 out of 97), RS virus 7.2% (n= 7 out of 97), human metapneumovirus 4.1% (n= 4 out of 97) and influenza virus 2.1% (n= 2 out of 97).

All patients underwent bacteriological examination. Analyses of joint bacterial and viral infection in the pathogenesis of acute tonsillitis showed that the following bacteria were most often observed in patients: *Staphylococcus aureus* (42.2%), *Streptococcus pneumoniae* (32.0%), *Haemophilus influenzae* (24.2%), *Haemophilus parainfluenzae* (18.8%), *Streptococcus anginosus* (10.9%), *Moraxella catarrhalis* (9.4%), *Streptococcus dysgalactiae* ssp. *equisimilis* (8.6%) and *Streptococcus agalactiae* (3.1%); these bacteria were most frequently associated with joint colonization. According to the results of the study, *Staphylococcus aureus*, *Streptococcus pyogenes* and *Haemophilus influenzae*, with different relative proportions, were the predominant species colonizing patients with acute tonsillitis, and *Streptococcus* was the dominant co-colonizer (51.5%). In approximately one-fifth of the patients, *Staphylococcus aureus* was the only pathogenic agent.

### Results of Treatment

Based on the aim of this study, all patients were divided into 2 mutually comparable groups. The 1st group included patients who received standard treatment (47.66%, n= 61). The 2nd group included patients received standard treatment with bacteriophage therapy (52.34%, n= 67). The treatment of children with acute tonsillitis was based on the generally accepted clinical recommendations and comprised mostly symptomatic treatment. Patients were prescribed complex antibacterial therapy on the basis of the possible causative agent in the early stage after diagnosis. Subsequently, antibiotic therapy was adjusted on the basis of the results of the bacteriological examination. Since most pathogenic microorganisms that cause acute tonsillitis in children are beta-lactamase-producing organisms, high-dose therapy with amoxicillin preparations was the first-choice treatment. Comprehensive treatment was administered by an otolaryngologist under strict monitoring.

Patients in group 2 were prescribed standard treatment together with PLC, and the positive results of treatment were noted. Five millilitres of inhaled PLC was administered on the first day of the disease. During treatment, a decrease in tonsil swelling after 2-3 days of treatment and a decrease in general intoxication symptoms were noted. The blood level of leukocytes in 57 (85.07%) patients had returned to normal by day 4. In 37 (60.66%) patients in group 1, the leukocyte level returned to normal on the 4th day of treatment.

## Discussion

### Features of Clinical Manifestation of Acute Tonsillitis in Children

Acute tonsillitis (according to ICD-10: J03.0 - J03.9) is one of the most common otolaryngological pathological processes in childhood and adolescence, with a number of English synonyms, including severe tonsillitis and true tonsillitis. Given the many variables, diverse assessments are needed to evaluate the levels of evidence of various approaches to the treatment of acute tonsillitis [10]. If this need is satisfied, it can be expected that in the coming years, therapeutic approaches will be of great importance [11]. Tonsils play a role in the immune system and immune defence by presenting antigens; they contain T lymphocytes, macrophages and germinal centres of B-lymphocytes [12]. They are the first and most accessible location of the lymphoid tissue system (MALT) associated with the human mucosa [6,11]. The main phase of acquired immunity lasts up to 6 years, and the tonsils are physiologically hyperplastic at this time. Then, involution occurs, which mainly manifests as regression for 12 years [7,10].

As our study showed, among these ambulatory conditions, the catarrhal form of acute tonsillitis was diagnosed in 65.63% (n= 84) of the children, follicular tonsillitis was diagnosed in 22.66% (n= 29) of the children, and lacunar tonsillitis was diagnosed in 11.72% (n= 15) of the children, indicating the predominance of the catarrhal form of acute tonsillitis among outpatients. In a clinical trial, 71.88% (n= 92) of patients were diagnosed with odynophagia. Some authors believe that odynophagia within 24-48 hours should be considered part of the prodromal symptoms of viral infection of the upper respiratory tract, unless the criteria of "acute tonsillitis" are met [10,11].

During the clinical examinations of patients, an increase in swelling in the pharyngeal tonsils (adenoids) was noted. Pharyngeal tonsil hyperplasia developed from the reaction centres of the lymphatic tissue. The role of the oropharyngeal microbiota in the development of inflammatory processes is undeniable, especially during a pandemic. Noted «... The microbiota and immune system have communication through several distinct mechanisms and stages. At first the microbiota induces alpha-defensin, secretory IgA and some other AMPs (antimicrobial peptides), thereby they affect innate lymphoid cells, but mainly they affect innate and adaptive immune system via influencing epithelial or macrophage cell receptors such as Toll-like receptors (TLRs) or NOD-like receptors (NLRs)...» [13]. At the same time, the authors assert the antiviral action of microbes, which is still a study area.

As our study showed, the main pathogens of acute tonsillitis in children were *Staphylococcus aureus*, *Streptococcus pyogenes* and *Haemophilus influenzae* (from 24.2% to 42.2%). Joint colonization with *Moraxella catarrhalis* appeared to increase the risk of acute tonsillitis. It should be noted that the invasion of *Staphylococcus aureus* is influenced by a variety of virulence factors, especially adhesins or so-called "microbial surface components" that recognize adhesive matrix molecules. Against this background, staphylococcal adhesion to host cells is often mediated by binding to bridging matrix molecules, which are also linked to host cells through specific receptors [14]. In the bacterial group, the presence of *Candida sp.* was detected in 16.4% (n= 21) of patients, indicating the role of mixed infection in the development of acute tonsillitis in children. According to a study by Belov BS (2018), the main causative agent of acute tonsillitis in children is group a beta-haemolytic streptococcus (GABHS), which should be considered when developing a treatment strategy [14].

### Bacteriophage Therapy

All viral diseases in children cause suppression of immunity, with the subsequent addition of a bacterial infection. Considering the causative agent COVID-19 is a viral pathogen, it causes depression of the immune system in children [15]. When the immune system decreases, pathogenic bacterial flora activated. Therefore, children with coronavirus infection (COVID-19 or SARS-CoV-2) carriage should receive bacteriophage prophylaxis to prevent severe lung disease, but this question remains open. In recent years, there has been an increase in interest in the use of bacteriophages in medical practice. There are many published studies indicating the effectiveness of the use of bacteriophages for the treatment of respiratory diseases [16,17]. Criscuolo E, et al. [4] noted that the mechanism of action of a phage involves integration into a bacterial cell and subsequent interaction with its genome, resulting in a lysogenic or lytic effect that is determined by the nature of the bacteriophage.

According to our observations, multifactorial development occurs when occult infection occurs due to inflammatory processes and tissue hyperplasia, contributing to further inflammation. Thus, in these patients, viruses elicited immune and inflammatory responses in the upper respiratory tract, and bacterial super infection led to the development of acute tonsillitis. A similar opinion is shared by Wittebole X, et al. [17], who noted that the advantage of therapeutic bacteriophages is their high specificity for certain microorganisms, good compatibility with other drugs, and minimal association with adverse events as well as the absence of allergic reactions [17].

During treatment, the fastest improvement in the disease course occurred in the second group treated with bacteriophage therapy. Compared with that in the first group, clinical improvement in the condition of patients occurred 1.4 times faster in children who received bacteriophage therapy. Based on the obtained results, it can be concluded that the use of bacteriophages in the treatment of children with acute tonsillitis in an outpatient setting has a good therapeutic effect, and the use of bacteriophage therapy in pediatrics can be considered as an alternative therapy in the prevention of severe complications of respiratory infections.

### Study Limitations

As can be seen from the results of this study, there are limitations to the use of inhalant bacteriophage therapy. First, this method requires access to a nebulizer, which limits its use at home. A nebulizer is mainly available in polyclinics, and families who do not have this device are forced to visit polyclinics. Secondly, bacteriophages require special storage in a refrigerator and medical personnel should be trained in the storage and use of bacteriophages. Third, there must be access to the acquisition of bacteriophages. In remote areas of residence of patients, there may be a lack of drugs. All of the above limitations can be solved by the management of the medical institution.

### Conclusion

The main predictor of the development of acute tonsillitis in children was viral infection (75.8%), which increased the colonization of tonsils by pathogenic bacterial flora. Moreover, in 66.4% of the cases, joint colonization by several bacterial species, mainly *Staphylococcus aureus* and *Streptococcus pyogenes*, was observed, with different relative proportions. The use of bacteriophage therapy in the conservative treatment of acute tonsillitis in children can improve the condition 1.4 times faster than standard therapy during the acute period of the disease.

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