UDC [616.21-022.6-08-059-06-084-085+615.33]-053.2-056.54
DOI: 10.56871/CmN-W.2024.64.58.004

BACTERIAL LYSATE OM-85 IN THE PREVENTION AND TREATMENT OF ACUTE RESPIRATORY INFECTIONS IN FREQUENTLY AND LONG-TERM ILL CHILDREN (LITERATURE REVIEW)

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For citation: Kosenko IM. Bacterial lysate OM-85 in the prevention and treatment of acute respiratory infections in frequently and long-term ill children (literature review). Children's Medicine of the North-West. 2024;12(3):27–37. DOI: https://doi.org/ 10.56871/CmN-W.2024.64.58.004

Received: 10.06.2024 **Revised: 15.07.2024** **Accepted: 10.09.2024**

Abstract. Recurrent respiratory tract infections in frequently and long-term ill children are one of the most pressing and yet unresolved problems of modern pediatrics. Immunostimulants occupy a special place in the treatment of these infections. These medications are designed to neutralize existing disturbances in the immune response during the disease, which is especially important for patients who are often and long-term ill. The use of immunostimulants of microbial origin is one of the promising directions in increasing the effectiveness of the prevention and treatment of acute respiratory infections. Bacterial lysates are the most studied group among them. A review of available scientific publications is devoted to the analysis of the effectiveness and safety of the use of bacterial lysate OM-85 in complex therapy and prevention of acute respiratory tract infections in children. OM-85 is recognized as the most studied immunostimulating agent currently, the effectiveness and safety of which make it a valuable tool for optimizing the treatment of recurrent respiratory infections.

Keywords: *recurrent respiratory infections, frequently and long-term ill children, therapy, bacterial lysate OM-85*

БАКТЕРИАЛЬНЫЙ ЛИЗАТ ОМ-85 В ПРОФИЛАКТИКЕ И ЛЕЧЕНИИ ОСТРЫХ РЕСПИРАТОРНЫХ ИНФЕКЦИЙ У ЧАСТО И ДЛИТЕЛЬНО БОЛЕЮЩИХ ДЕТЕЙ (ОБЗОР ЛИТЕРАТУРЫ)

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Для цитирования: Косенко И.М. Бактериальный лизат ОМ-85 в профилактике и лечении острых респираторных инфекций у часто и длительно болеющих детей (обзор литературы) // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 27–37.
DOI: https://doi.org/10.56871/CmN-W.2024.64.58.004

Поступила: 10.06.2024 **Одобрена: 15.07.2024** **Принята к печати: 10.09.2024**

Резюме. Рецидивирующие инфекции дыхательных путей у часто и длительно болеющих детей — одна из наиболее актуальных и пока не решенных проблем современной педиатрии. Особое место в терапии этих инфекций занимают иммуностимуляторы. Эти лекарственные препараты призваны нивелировать имеющиеся нарушения иммунного ответа при заболевании, что особенно актуально для часто и длительно болеющих пациентов. Одним из перспективных направлений в повышении эффективности профилактики и терапии острых респираторных инфекций является применение иммуностимуляторов микробного происхождения. Среди них наиболее изученная группа — бактериальные лизаты. Обзор имеющихся научных публикаций посвящен анализу эффективности и безопасности применения бактериального лизата ОМ-85 в комплексной терапии и профилактике острых инфекций дыхательных путей у детей. ОМ-85 признан

наиболее изученным в настоящее время иммуностимулирующим средством, эффективность и безопасность которого делают его ценным инструментом для оптимизации лечения рецидивирующих респираторных инфекций.

Ключевые слова: *рецидивирующие респираторные инфекции, часто и длительно болеющие дети, терапия, бактериальный лизат ОМ-85*

The majority of cases of acute respiratory tract infections (ARTI) in childhood are mild and uncomplicated. At the same time, severe disease and serious complications may develop, especially in patients with an unfavourable premorbid background (chronic lung and heart diseases, immunodeficiency, diabetes mellitus, and a number of other conditions) [1]. A special group is children with recurrent ARTI are those in whom the frequency and duration of respiratory infections are increased. Frequently and long-term ill children (FIC) are one of the most pressing and still unresolved problems of modern paediatrics, which has grown into a socially significant problem that worsens the psychological status of the child, reduces the general health of children and leads to "chronic sick leaves" [2]. In 40% of cases, by the age of 7–8 years, chronic pathology develops in FIC, and the risk of chronicity is directly proportional to the increase in frequency of episodes of acute respiratory infections (ARI) during the year [3].

The immune system of the FIC is in a state of extreme tension of immune response processes with impaired intercellular cooperation and insufficient reserve capacity. The result of a long-term, massive antigen impact on child's body and a high-risk factor for development of both local (addition of a bacterial infection) and general (development of immune pathology) complications are pronounced polymorphic changes in the form of combined (96.5%) and isolated (3.5%) defects of T-cell, humoral immunity, and neutrophil granulocyte system, as well as impaired ability of leukocytes to produce interferons [4]. In addition to severe immune disorders, a huge number of selective immunodeficiencies of a transient or permanent nature have been described [5, 6]. Clinical and immunological analysis allows us to state that the identified changes in immune system contribute to frequent recurrence of acute respiratory infections episodes and occurrence of complications [4].

In recent decades, the incidence of allergic diseases has been steadily increasing, including those affecting respiratory tract, which are often associated with recurrent nature of respiratory infections. Symptoms of respiratory atopy can either mimic the symptoms of respiratory infection or cause chronic respiratory tract inflammation and immunodeficiency, which causes frequent infections in children [7, 8].

The recurrent course of respiratory diseases in children is in the vast majority of cases associated with persistent infection [9]. A feature of the modern course of infectious pathology in children is a frequent combination of etiological factors, including viruses, bacteria, fungi and parasitic pathogens. Many infectious agents have the ability to long-term active persistence. These are representatives of the *Herpesviridae* family, "atypical" pathogens from the *Chlamydiaceae* and *Mycoplasmataceae* families [3, 10], and the bacterial flora of the upper respiratory tract [11–13]. The most frequently detected pathogens of persistent infections are representatives of the *Herpesviridae* family (herpes virus type 6, Epstein–Barr virus and cytomegalovirus), beta-haemolytic streptococcus group A, *Staphylococcus aureus* [9]. Moreover, herpes viruses are capable of causing significant disturbances in the immune status of macroorganism, thereby forming a vicious circle: chronic active herpesvirus infection — secondary immunodeficiency, against the background of which frequent acute respiratory tract infections are observed [10–12], and recurrent course of bacterial and parasitic diseases [6, 14, 15].

Without adequate treatment, respiratory infections often take a complicated or chronic course; a mild runny nose can result in severe pneumonia or sinusitis. Acute respiratory infections can also cause exacerbation of chronic diseases such as bronchial asthma, glomerulonephritis, heart diseases, etc. Timely therapy promotes faster recovery and prevents the development of complications. Of course, treatment should be comprehensive and built individually in each specific case [16]. Differentiated etiopathogenetic therapy and immunorehabilitation of FIC depending on the diagnosed persistent infection allows to achieve stable normalization of child`s condition and reduce frequency of antibiotic use [9].

Immunostimulants occupy a special place in the therapy of AID. These drugs are designed to

neutralize existing immune response disorders during the disease, which is especially important for frequently and long-term ill patients. It is assumed that use of drugs in this group will contribute to a more rapid relief of symptoms of respiratory infection, reduce the risk of complications and, accordingly, reduce the need for antibacterial therapy as well [17–19].

Based on the results of the immune status study, targeted selection of adequate immunocorrective therapy is not feasible. At the same time, the effects on the immune system are not indifferent to the body. Immunostimulants have multifaceted effects and are capable of causing unpredictable changes in body with minor effects, changing the balance in the immune system. At the same time, a deficiency or excess of one of the links of the immune system can lead to a violation of the correct response of the immune system. Therefore, it is necessary to use immunotropic drugs, assessing their need in each specific case and prescribing them not instead of, but together with basic therapy. It is necessary to remember that the effect of immunostimulants is of a triggering nature, and the response of the immune system is prolonged in time. The effectiveness of drugs can be judged no earlier than after 1–2 months [20].

Immunocorrective therapy for prevention and complex treatment of acute respiratory infections is indicated for patients [19]:

- with frequent acute and/or recurrent respiratory infections;
- living in ecologically unfavourable conditions and constantly exposed to negative environmental factors;
- with chronic respiratory diseases (chronic tonsillitis, bronchial asthma, rhinosinusitis, etc.);
- who have had a severe respiratory infection;
- from the risk group for development of recurrent respiratory diseases.

Currently, about 100 drugs are available in Russia that, according to the anatomical and therapeutic chemical classification, are classified as immunostimulants; many are intended for treatment and prevention of acute respiratory infections. However, a significant portion of these drugs do not have sufficient evidence base and therefore cannot be recommended for widespread use in respiratory infections in children [17–19].

One of the promising areas in increasing the effectiveness of immunotherapy and immunoprophylaxis of acute respiratory diseases is use of immunostimulants of microbial origin [17]. Among them, the most studied group is bacterial lysates, primarily OM-85.

Bacterial lysates contain components of microbial cells obtained by dissolving (lysing) bacteria — potential pathogens that have lost their viability. They retain the ability to stimulate immunity (innate and adaptive), but are not capable of causing infection (disease) [17, 19]. The production of bacterial lysates begins with fermentation, which ensures growth of the strain. Each bacterial strain is grown separately and inactivated at high temperatures. Destruction (lysis) of the bacterial cell walls is a key stage that allows obtaining different types of bacterial lysates. There are two methods of lysis of bacterial cell walls — mechanical and chemical. Mechanical lysis is carried out by mechanically destroying the cell wall (e.g., using high pressure, ultrasound, crushing the frozen mass, etc.), while chemical lysis is carried out using a chemical substance. After mass cultivation of reference bacterial strains, antigens are obtained either by mechanical or chemical lysis and lyophilization. Currently, there is no convincing data confirming that one or another lysis method (chemical or mechanical) provides an advantage in efficiency [17, 21]. Some authors claim that mechanical destruction may be a better alternative to chemical lysis due to the preservation of antigens. However, no studies have been conducted comparing the biological effects of polyvalent bacterial lysates prepared from the same bacterial cultures but using mechanical or chemical lysis procedures [21]. At the same time, OM-85 obtained by chemical lysis has a more extensive evidence base of efficacy and safety compared to bacterial lysate obtained by mechanical lysis [19].

Bacterial lysate OM-85 in capsule form contains lyophilisate of components of 21 strains of 8 different types of bacteria (*Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans, Moraxella catarrhalis*) in the amount of 3.5 mg (form for children aged 6 months to 12 years) or 7 mg (form for children aged 12 years and adults). According to the instructions for medical use, this drug can be used as part of complex therapy for ARTIs and the prevention of recurrent respiratory tract infections [19, 22].

The effect of bacterial lysate OM-85 on immunological parameters has been well studied in numerous laboratory and clinical studies [18, 19, 23]. OM-85 is a systemically acting drug that enhances the mucosal immune response to both viral and bacterial infections in the respiratory tract by increa-

sing the efficiency of innate and adaptive immunity mechanisms. After oral administration of the drug, its capsule dissolves in stomach, releasing active components — bacterial lysates that pass through the intestinal mucosa into Peyer's patches, resulting in selective activation of dendritic cells, T- and B-lymphocytes, and the release of cytokines. Activated immune cells migrate throughout the body, mainly through the lymphatic system, especially to MALT (mucosal-associated lymphoid tissue) of the respiratory tract. The cellular and molecular mechanisms of OM-85 pharmacological action have been revealed (Table 1) [19, 24]. In particular, it has been established that under action of the drug, there is an increase in the level of interferons and a number of other cytokines in blood serum, which provides an antiviral effect, increases levels of immunoglobulins of classes G, M, A in blood serum, and of secretory immunoglobulin A, which provides an antibacterial effect.

Most studies of the bacterial lysate OM-85 are devoted to its prophylactic use [18, 19, 25, 26]. High prophylactic efficacy of this drug in children has been established in more than 50 clinical studies, the results of which were summarized in systematic reviews and meta-analyses [23, 24, 26–29]. Thus, in 2018, a systematic review with meta-analysis was published [23], which showed that the prophylactic use of the bacterial lysate OM-85 in children with recurrent ARTIs significantly reduces incidence of respiratory infections, reliably reduces the duration of diseases in general and their individual symptoms (fever, cough, wheezing in the lungs); significantly reduces the need for antibacterial drugs.

A number of clinical studies have also been conducted on the use of OM-85 bacterial lysate as part of combination therapy in the acute period of ARDI. Most of the studies were conducted in paediatric patients. In 10 controlled studies, which included a total of about 800 children (patients in the main group received OM-85 bacterial lysate as part of combination therapy, patients in the control group received standard treatment without an immunostimulant), there were differences in design and patient population (age and diseases), but the results obtained are largely the same. In particular, all studies noted a more rapid relief of ARTI symptoms in the main group [29–39]. Several studies also found that the use of an immunostimulant leads to a decrease of antibacterial therapy prescription [33, 34, 37, 38, 40].

In addition to clinical data, most studies analyzed the effect of OM-85 bacterial lysate on immune response parameters. It was found that patients in the main group had a reliable increase in the level of immunoglobulins (primarily IgA and IgG) compared to patients of the control group [30, 32–34, 36, 37, 39, 40]. Some studies showed a positive effect of the drug

Table 1. Characteristics and proposed mechanisms of action of OM-85 [19, adapted from 24]

Таблица 1. Характеристики и предполагаемые механизмы действия OM-85 [19, адаптировано из 24]

Антиген-презентирующие клетки / Antigen presenting cells	Врожденный иммунитет / Innate immunity	Адаптивный иммунитет / Adaptive immunity
• Созревание мезентериальных дендритных клеток (ДК) / Maturation of mesenteric dendritic cells (DCs) • Увеличение продукции цитокинов / Increased cytokine production • Стимуляция противоинфекционной защиты респираторного тракта / Stimulation of anti-infective defense of the respiratory tract	• Высвобождение антимикробных пептидов (β-дефензина и рецептора C1q-компонента комплемента) / Release of antimicrobial peptides (β-defensin and complement component C1q receptor) • Снижение экспрессии ICAM / Decreased expression of ICAM • Цитокиновая активация NK-клеток, моноцитов, фагоцитоза, нейтрофилов / Cytokine activation of NK cells, monocytes, phagocytosis, neutrophils • Активация макрофагов (ИЛ-1β, ИЛ-6, ФНОα) / Activation of macrophages (IL-1β, IL-6, TNFα). • Высвобождение антивирусных цитокинов (ИФНβ) / Release of antiviral cytokines (IFNβ)	• ДК-индуцированная активация Т-лимфоцитов / DC-induced T-lymphocyte activation • Увеличение уровней CD8+, ИЛ-6, ИЛ-10 (про В-клеточных цитокинов), сывороточных и секреторных IgA/IgG / Increased levels of CD8+, IL-6, IL-10 (pro-B-cell cytokines), serum and secretory IgA/IgG • Созревание В-клеток из спленоцитов / Maturation of B cells from splenocytes • Увеличение уровней ИФНγ и IgG2/анти-ИЛ-4 / Increased levels of IFNγ and IgG2/anti-IL-4 • Высвобождение антивирусных цитокинов (ИФНα/ИФНγ) / Release of antiviral cytokines (IFNα/IFNγ)

on other components of the immune system, in particular an increase in the level of interferons [35, 36, 40]. Three studies showed a decrease in the incidence of complications of acute respiratory infections (ARI) against the background of OM-85 use [35, 38–40].

In 7 of the 10 discussed studies, not only therapeutic but also prophylactic effect of OM-85 bacterial lysate was assessed. Patients in the main group, in addition to the course of treatment during the ARI period, received two prophylactic courses of the drug [30–35, 37, 40]. All these studies have shown a significant reduction in the number of recurrent respiratory infections when using the immunostimulant.

In addition, a large clinical study that included 587 children under 12 years of age with recurrent ARTIs deserves attention. It compared the frequency and duration of respiratory infections before and after taking the bacterial lysate OM-85. The drug was administered starting with the next episode of respiratory infection and continued for 10 days (then two more preventive courses were administered according to the standard scheme). Against the background of treatment with the bacterial lysate OM-85 (as part of complex therapy), the average time to improvement (from 6.77 to 3.76 days) and recovery (from 11.86 to 7.36 days) significantly decreased. Follow-up observation showed more than 7-fold reduction in the number of ARTI relapses and a 10-fold reduction in the frequency of antibacterial therapy [41].

Thus, the available scientific data demonstrate high efficiency of using the bacterial lysate OM-85 for therapeutic purposes in children with ARTI. Inclusion of the drug in the composition of complex therapy significantly increases efficiency of therapeutic measures, which allows us to recommend it not only for prevention, but also for treatment of respiratory infections in paediatric practice.

According to the opinion of experts of the All-Russian public organization "Paediatric Respiratory Society", based on the results of evidence-based clinical studies, the bacterial lysate OM-85 can be used in children in the following situations (Table 2) [19]:

- in the initial period of ARTI (as part of complex therapy) — in order to speed up recovery and reduce manifestations of the disease, as well as to prevent development of bacterial complications and, accordingly, reduce the need for antibacterial therapy;
- in complicated respiratory infections (as part of complex therapy, including in combination with antibacterial drugs) — in order to contain further disease progression, increase the effectiveness of antibacterial therapy and reduce the risk of antibiotic-resistant bacterial strains selection;
- during the convalescence period (as part of rehabilitation) — in order to more quickly restore the body, prevent recurrent course of ARTI and chronization of the disease;
- in recurrent ARTI — in order to prevent repeated respiratory infections and progression of chronic respiratory system diseases.

In addition, it is necessary to remember that severe and repeated viral respiratory tract infections, especially in early childhood, are associated with the risk of bronchial asthma developing. The conducted studies, including a meta-analysis and a systematic review [24, 42–46], showed that bacterial lysates are a promising additional tool to the current treatment of wheezing in preschool children and asthma in childhood, they can be considered as a safe and effective additional therapy for dyspnoea in preschool children and in children with recurrent exacerbations of asthma.

In the complex treatment of acute respiratory infections, OM-85 can be used in combination with other drugs, including antiviral and antibacterial ones [22].

To reduce the burden of recurrent respiratory infections, combined use of OM-85 and influenza vaccine was recognized as effective and safe, improving existing prevention strategies [47–49].

Experimental studies have shown that OM-85 *in vitro* reduces the binding of SARS-CoV-2 to bronchial epithelial cells, suppresses the expression of the ACE2 receptor, a key factor in the penetration of SARS-CoV-2 into bronchial cells. OM-85 can reduce binding of the SARS-CoV-2 S protein to epithelial cells by modifying host cell membrane proteins and specific glycosaminoglycans. Thus, OM-85 can be considered as an adjunct to COVID-19 therapy. The data obtained confirm the known antiviral effects of OM-85 on respiratory viruses (including SARS-CoV-2) [50, 51].

In Long-COVID infection, the use of OM-85 is recommended to stimulate mucosal immunity. Its use in the complex treatment of respiratory infection is aimed at reducing the risk of secondary bacterial infection and the need for antibiotics. OM-85 should be recommended as a prophylaxis for recurrent respiratory and secondary bacterial infections [52].

Available data suggest that OM-85 can effectively and safely reduce the risk of new infectious episodes in children with recurrent ARIs, and that repeated annual courses of lysate administration

 ISSN 2221-2582

Table 2. Clinical situations when the use of bacterial lysates is advisable [19]

Таблица 2. Клинические ситуации, когда прием бактериальных лизатов целесообразен [19]

Клиническая ситуация / Clinical situation		Цель назначения / Purpose of appointment
Острая респираторная инфекция (комплексное лечение) / Acute respiratory infection (complex treatment)	В начале заболевания / At the beginning of the disease	• ускорение процессов выздоровления / acceleration of healing processes; • предотвращение развития бактериальных осложнений / prevention of development of bacterial complications; • уменьшение клинических проявлений воспалительного процесса / reduction of clinical manifestations of the inflammatory process; • снижение потребности в антибиотикотерапии / reduction in the need for antibiotic therapy
	При прогрессировании заболевания (вместе с антибиотиками) / As the disease progresses (along with antibiotics)	• ускорение процессов выздоровления / acceleration of healing processes; • повышение эффективности антибактериальной терапии / increasing the effectiveness of antibacterial therapy; • снижение риска сохранения в организме антибиотикорезистентных штаммов бактерий / reducing the risk of antibiotic-resistant bacterial strains remaining in the body; • уменьшение клинических проявлений заболевания / reduction of clinical manifestations of the disease; • ограничение дальнейшей генерализации инфекции, профилактика хронического воспаления / limiting further generalization of infection, preventing chronic inflammation
Реабилитация / Rehabilitation		• ускорение репаративных процессов / acceleration of reparative processes; • профилактика рецидивов и хронизации заболевания / prevention of relapses and chronicity of the disease
Профилактика / Prevention		• стойкая защита слизистой оболочки дыхательных путей от патогенов / persistent protection of the respiratory mucosa from pathogens; • предотвращение повторных острых респираторных инфекций и снижение их тяжести / prevention of recurrent acute respiratory infections and reduction of their severity; • предотвращение обострений и прогрессирования хронических респираторных заболеваний / prevention of exacerbations and progression of chronic respiratory diseases

may be useful for maintaining protection, especially when recurrent ARIs are diagnosed in young children, for whom final maturation of the immune system probably requires a long time [48].

The OM-85 drug has a favourable safety profile, which supports the possibility of its long-term use. Over past 40 years, more than 61 million children have received OM-85 bacterial lysate. According to observations, the drug is well tolerated by children. A meta-analysis of 14 studies (n=1859) and a Cochrane analysis of 9 studies (n=852) showed no significant association between the use of OM-85 in children with recurrent respiratory tract infections and an increased incidence of adverse reactions compared to placebo. Adverse events in children with recurrent respiratory tract infections were reported in 33 of 53 studies included in the meta-analysis, and they did not affect treatment outcomes. In 85% of cases, non-serious adverse events were noted. There were 538 cases of hypersensitivity in children and adults, and 57% of them had skin lesions only [48, 49, 51, 53, 54].

However, the number of studies with a high level of evidence devoted to the therapeutic efficacy of OM-85 bacterial lysate is currently small. In order to form final conclusions about the efficacy of the drug and practical recommendations for its optimal use, it is advisable to conduct well-designed clinical trials with a high level of evidence on a sufficient number of patients, as well as to summarize the results of evidence-based clinical trials in systematic reviews and meta-analyses [40]. Despite this, OM-85 is recognized as the most studied of currently available immunostimulants, which efficacy and safety make it a valuable tool for optimizing treatment of recurrent respiratory infections in both adults and children [47].

The indication for the use of OM-85 is included in numerous clinical guidelines and consensus documents on recurrent respiratory tract infections in children [55–58]. Bacterial lysates are the only agents from the immunostimulant group that are included in the clinical guidelines of the Ministry of Health of the Russian Federation "Acute respiratory tract infection (ARTI)": "For children under 6 months, with recurrent infections of the ENT organs and respiratory tract, the use of other immunostimulants (systemic bacterial lysates) is recommended. The strength of the recommendation is A; the level of evidence is 1" [59].

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

Competing interests. The author declares the absence of obvious and potential conflicts of interest related to the publication of this article.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Автор прочитал и одобрил финальную версию перед публикацией.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Автор заявляет об отсутствии внешнего финансирования при проведении исследования.

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