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REVIEW ARTICLE

Bacterial lysates in the prevention of respiratory tract infections

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ABSTRACT: Bacterial lysates stimulate the general immunity of the body in a non-specific way. They act on non-specific defense mechanisms, leading to an increase in type A antibody in mucous membranes, phagocytic activity and INF-γ production. They can also stimulate the production of specific antibodies against the bacterial antigens that make up the preparation. The oral immunomodulatory preparations with the best documented clinical efficacy available on the Polish market are Ismigen, Broncho-Vaxom, Ribomunyl and Luivac. They are all lysates of bacterial strains that most often cause respiratory tract infections. In many clinical trials, oral bacterial lysates have been shown to minimize the risk of recurrent respiratory infections in children and adults and reduce the need for antibiotics.

KEYWORDS: bacterial lysates, immunity, prevention, respiratory tract infection

Bacterial lysates constitute a separate category of medicinal products for use in prevention of recurrent upper and lower respiratory tract infections. Children are at particular risk of infections since the complete maturity of the immune system is achieved at the age of about 12. Presented in Figure 1 is an outline of serum IgA, IgM, IgG levels at different developmental stages.

Before that age, the immature immune system is incapable of ensuring an efficient barrier against bacterial pathogens. The highest incidence of diseases related to insufficient number and function of immunocompetent cells is observed at the developmental age when the defense mechanisms have not yet reached full maturity and differentiation, and at the elderly age when they have been already largely depleted.

Environmental factors are also responsible for the risk of infections in children due to the possible exposure and nurseries, kindergartens, and schools. Viruses are the main cause of acute respiratory tract infections; however, the disorders are frequently misdiagnosed as bacterial infections and unnecessarily treated with antibiotics; as a result, the immature immune system of a young patient becomes additionally compromised.

Respiratory system infections develop as a result of imbalance between pathogenic penetration and current efficacy of specific and non-specific defense mechanisms [2].

Recurrent respiratory tract infections are also thought to be caused by environmental changes consisting in increasing air pollution (smog) and second-hand tobacco exposure. Chemical and physical contamination of inhaled air disrupts the structure of mucosal membranes within the respiratory tract, facilitating deeper penetration of pathogens and development of inflammation.

In Poland, the treatment of infections usually consists in administration of an antibiotic; as a result, Poland is one of the countries with the highest per capita antibiotic use. Due to the widespread use of antibiotics, particularly in the outpatient setting where they used to be prescribed without preceding susceptibility tests and, most importantly, at incorrect doses and treatment durations, the efficacy of antibiotic treatment has been greatly reduced and numerous bacterial strains have developed resistance to these drugs [3].

Antibiotics may have an immunodepressive effect as a result of direct interaction with immunocompetent cells or by significant reduction of the exposure of individual immune system elements to particular antigens leading to reduced antigen stimulation, inhibition of the immune response, and delayed maturation of the immune system. Antibiotics adversely affect physiological, non-pathogenic bacterial flora which plays an important role in inhibition of inflammation via interference

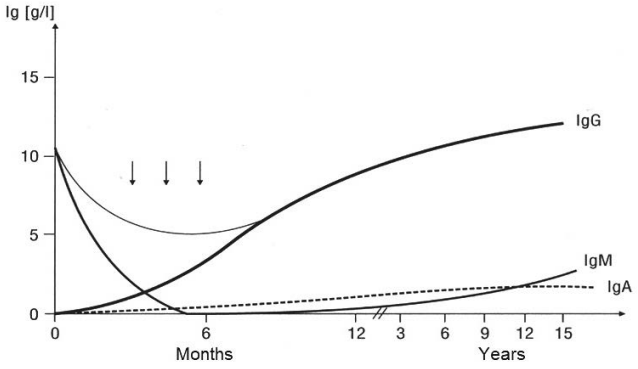

Fig. 1. Outline of serum IgA, IgM, and IgG levels at different developmental stages in children [1].

mechanisms (bacterial interference described the impact of a particular group of bacteria on the growth and proliferation of another group). The efficacy of antibacterial treatment is short in duration, and recurrence cannot be prevented. In order to reduce the incidence of respiratory tract infections in adults and particularly in pediatric patients whose immune systems are not fully developed, prophylaxis and immunomodulatory treatment with products of bacterial origin should be considered to support the system's fight of recurrent infections [4].

Biological material used in immunomodulatory products consists in inactivated (killed) pathogens presenting with antigen molecules required to trigger the immune response or live attenuated pathogens [3, 4].

BACTERIAL LYSATES – DEFINITION, MAIN BACTERIAL SPECIES, AND PROCESSING METHODS

Bacterial lysates, introduced in the 1970s, consist of bacterial cells killed and subjected to mechanical, chemical or enzymatic lysis or of isolated bacterial organelles. Usually, they are mixtures of several bacterial species most frequently responsible for respiratory tract inflammations, including *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Haemophilus influenzae, Diplococcus pneumoniae, and Neisseria catarrhalis* [6–8].

Oral immunomodulatory products for use in the treatment of recurrent respiratory tract infections and containing the aforementioned inactivated pathogen cells are available on the Polish market. Bacterial lysates are particularly recommended when recurrent inflammations are caused by bacterial infections [4].

Tab. I. Composition of bacterial lysates used in the prevention of respiratory tract infections.

	ISMIGEN	LUIVAC	BRONCHO-VAXOM	RIBOMUNYL
Staphylococcus aureus	X	X	X	_
Streptococcus pneumoniae	X type1, 2, 3, 5, 8, 47	X	X	X
Streptococcus pyogenes	X	X	X	X
Streptococcus viridans	X	*Streptococcus mitis*	X	_
Moraxella catarrhalis	X	X	X	_
Haemophilus influenzae	X	X	X	X
Klebsiella pneumoniae	X	X	X	X
Klebsiella ozaenae	X	_	X	_

Lysates are obtained from various inactivated bacterial pathogens. Antigens are obtained from mass cultures of appropriate bacterial strain by means of mechanical cell disruption (polyvalent mechanical bacterial lysate, PMBL) or chemical proteolysis (polyvalent chemical bacterial lysate, PCBL). By activating the immune system, bacterial lysates strengthen the systemic defense to prevent or more effectively combat infections.

Compared to the Ismigen's PBML, polyvalent chemical bacterial lysates (PCBL) are less immunogenic due to protein denaturation occurring in the preparation process leading to reduced immune response following administration. On the other hand, high pressures used in PMBL production lead to elimination of numerous chemical contaminants and the products are characterized by a lower degree of damage to bacterial antigens. Conservation of particular antigens determines the high immunogenic potential, and is markedly important for the significant clinical efficacy of PMBL [9].

Immunomodulation secondary to the administration of a bacterial lysate product depends on the product, i.e. the type and composition of the lysate as well as the method of administration, dose and dosage regimen, patient's individual immune reactivity, natural immunostimulation (recurrent infections) as well as the exposure to pathogenic microbes [4].

Table I lists the qualitative and quantitative compositions of bacterial lysates in terms of bacterial types and species [6–8].

Table II lists the qualitative and quantitative compositions of

Tab. II. Characteristics of bacterial lysates for use in prevention of respiratory tract infections.

DRUG	BACTERIAL LYSATE PREPARATION METHOD	BACTERIAL CONTENT	FORMULATION	DOSAGE AGE/DOSE
Ismigen	Polyvalent, mechanical	48 mld	Sublingual tablets	7 mg: > 3 years of age, once daily for 10 consecutive days each month for 3 months
Broncho-Vaxom	Polyvalent, chemical	3.5 mg; 7 mg	Capsules	3.5 mg: 6 months-12 months, 7 mg: >12 years of age, according to the Patient Information Leaflet
Luivac	Polyvalent, chemical	1 mld	Tablets	3 mg: >2 years of age, according to the Patient Information Leaflet
Ribomunyl	*Klebsiella pneumoniae* membrane fraction proteoglycan	Ribosomes/ribosomal RNA: *Klebsiella pneumoniae* 3.5 parts per weight; *Str. pneumoniae* 3 parts per weight; *Str. pyogenes* 3 parts per weight; *H. influenzae*, 0.5 parts per weight.	Tablets, granules	Tablets: 0.525 mg, granules: 0.750 mg: >2 years of age, according to the Patient Information Leaflet

bacterial lysates in terms of preparation method, formulation, and dosage regimen [5–8].

The dosage of oral immunomodulatory products is very characteristic, as age-adjusted doses are administered at specific time intervals. Immunomodulatory treatment regimens feature long intervals between drug administration periods so as to reduce the risk of excessive burden being placed on the immune system by the pathogens contained within the product [6–8]. Oral immunomodulatory agents were shown to be safe in infants and neonates [10].

THE PRINCIPLE OF BACTERIAL LYSATES' ACTIVITY

The increased efficacy of elimination of bacterial pathogens in recurrent inflammatory tract infections is explained by involvement of the system's immune memory. The mechanism of action of the immunostimulatory products consists in interaction with the mucosa-associated lymphoid tissues (MALT) which are continuously exposed to pathogenic antigens. MALT consists of gut-associated lymphoid tissue (GALT), bronchus-associated lymphoid tissue (BALT), nasal-associated lymphoid tissue (NALT), as well as the lymphoid tissue of lacrimal, mammary, salivary, and urogenital system glands. The main role of the MALT system consists in production of IgA antibodies which, in their secretory form (sIgA) perform the protective function by coating and agglutinating microbial cells, exerting bacteriostatic action, preventing endothelial adhesion and neutralizing toxins [11].

Memory B cells secrete small quantities of antibodies long after inflammation has been resolved so that antibodies are ready for immediate response should the system be penetrated by the same bacterial pathogens again.

Secondary immune response is faster, more efficient and stronger than the primary one. The quantity of antigen required to trigger the secondary response is lower than in the case of the first exposure to the pathogen. The quantities of antibodies produced are also higher, and the reduction of antibody blood levels is much slower. The affinity of individual antibodies to specific antigens is larger than the affinity of antibodies secreted as part of the primary immune response. Once triggered by the immune memory, the increased readiness to protect the system against bacterial pathogens is usually maintained for considerably long periods. To prevent its gradual deactivation, immunomodulatory agents should be administered in a repeatable fashion.

Although bacterial lysates are used in the prevention and treatment of upper and lower respiratory tract infections, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) of 2012 lists chronic rhinosinusitis as the only specific indication (recommendation grade D) [12].

BENEFITS AND EFFICACY OF BACTERIAL LYSATES

The benefits and efficacy of oral immunomodulators (bacterial lysates) in the prevention of recurrent bacterial infections was confirmed in numerous clinical trials. Results of analyzes suggest a significant potential for reduced use of antibiotics in recurrent respiratory tract infections, particularly in pediatric patients. Meta-analysis carried out by Del-Rio-Navarro et al.

[13] showed that compared to placebo, bacterial lysates reduced the incidence of respiratory tract infections by 41.21%. In their systematic review of available literature, Schaad et al. [14] demonstrated that the efficacy of respiratory tract infection prevention was the higher, the higher was the incidence of infections, thus confirming better efficacy of bacterial lysates in patients suffering from more common recurrences. The reduction in the incidence rate was by 35.5% compared to placebo. Gutierrez-Tarango and Berber [15] observed that bacterial lysates not only reduced the incidence of respiratory tract inflammations, but also shortened the durations of the infections (35.23 ± 17.64 vs. 60.75 ± 25.44 days) and reduced the number of antibiotic regimens (2.46 ± 2.08 vs. 4.46 ± 2.08).

In studies by Rosaschino and Cattaneo [16], conducted in a population of pediatric patients aged 10 months to 16 years, sublingual PMBL tablets were shown to statistically significantly reduce the number of upper respiratory tract infection episodes in the course of two consecutive winter seasons, with PMBL Ismigen being administered in the second but not in the first winter season (4.78 and 7.84 episodes, respectively). Increased B cell counts were observed in the sera of children in the PMBL-treated group. The study confirmed the high efficacy as well as good tolerance and safety of PMBL Ismigen.

Meta-analyses regarding the efficacy of bacterial lysates are available mainly for PMBL (Ismigen), OM-85 (Broncho-Vaxom) and D-53 (bacterial ribosomes) preparations. Statistically significant reduction in the incidence of respiratory tract infections was shown in children treated with these medicinal products. As suggested by the authors of the meta-analyses, the lysates may be particularly beneficial in the prevention of bacterial infections and are most efficient in non-immunodeficient patients and children suffering from acute recurring (usually viral) respiratory tract infections [13–16]. Prophylaxis was shown to be less effective in children who were additionally exposed to environmental pollution [17].

Clinical trials demonstrated a significant improvement in test clinical parameters in children with recurrent rhinosinusitis and palatine tonsillitis [18, 19]. The treatment reduced the number of recurrence episodes and the number of antibiotic therapies as well as improved the clinical condition of patients in the course of the infection [18–20]. In children with recurrent palatine tonsillitis, a reduction in the number of patients requiring tonsillectomy was observed [19].

Bacterial lysates were also shown to reduce colonization of airways with the most common Streptococcus species observed within the respiratory tract (S. pneumoniae, pharynx and paranasal sinuses) as well as group B streptococci [21]. In 2012, a meta-analysis was performed on the available clinical trials (35 trials) assessing the immunomodulatory efficacy of non-specific bacterial lysates. The lysates were shown to be highly effective in reducing the incidence of recurring infections by more than 40% [13].

THE MECHANISM OF THE IMMUNOACTIVITY OF BACTERIAL LYSATES

Bacterial lysates are delivered to the system via the oral route (sublingual tablets, tablets, capsules, granules); increased production of secretory IgA occurs as a result of their presentation to the lymphocytes within the GALT for the protection of respiratory mucosa [22]. The specific sublingual administration route facilitates efficient delivery of PMBL to dendritic cells which are abundantly present within the oral mucosa. Following recognition of antigens and expression of specific biomarkers on the surface of the dendritic cells, cells become activated and transported into the cervical lymph nodes and subsequently into the bloodstream [9, 23].

In the cervical lymph nodes, the activated dendritic cells, also referred to as antigen presenting cells (APCs), specifically release pro-inflammatory cytokines which facilitate differentiation of T cells into T helper cells, differentiation of B cells into plasmocytes capable of secreting specific IgA, IgG and IgM and increase in the number of natural killer (NK) cells. Mature immune cells and immunoglobulins are transported from the lymph nodes into the blood. Specific IgA and mature immune cells are then transported to the upper and lower respiratory tract mucosa resulting in salivary immunoglobulin secretion being increased on average by as much 250% [9] to efficiently opsonize living bacteria [9, 24].

Bacterial lysates stimulate non-specific immunity mechanisms via toll-like receptors (TLRs). Bacterial fragment particles efficiently and rapidly activate the non-specific defense mechanisms, including epithelial cells, macrophages, dendritic cells, and mast cells which improve the local immune readiness of the mucosal membranes and increase the cytotoxic activity of phagocytes [25]. In the pediatric population, high susceptibility to respiratory tract infection is due to the low expression of TLRs which increase in number with increased exposure to pathogens as well as with maturation of the immune system.

The use of immunomodulatory agents stimulates non-specific immunity after each administration, manifested by increased expression of TLRs, increased immunocompetence of hosts' APCs, increased activity of phagocytes and better immune response against the pathogens.

Bacterial lysates reduce the frequency, duration, and severity of respiratory tract infections.

THE IMMUNE EFFECT OF BACTERIAL LYSATES

The immune effect of bacterial lysates is achieved by means of activation of non-specific as well as specific immune mechanisms. Activation of non-specific mechanisms (innate immune system) consists in signal being transmitted by TLRs (TLR-2/6, 9, TLR-7/8), an increase in chemotaxis as well as cytotoxic and phage activity of phagocytes (macrophages, dendritic cells, neutrophils), an increase in the activity of NK cells (CCL2, 3), activation of dendritic cells and along with the increase in their antigen presentation ability and increased migration into respiratory tract, increased pro-inflammatory response (IL-1, IL-6, TNF-α), and increased secretion of antiviral cytokines (IFN-α, IFN-γ). Activation of specific mechanisms (acquired immune system) is characterized by increased concentration of IgA and IgG antibodies, increased T cell activity and ability to activate other specific mechanisms (activation of T and B cells), activation of B cells (CCL2, 3, 20, 22, BAFF, IL-6, APRIL) and increased activity of CD4+ CD25+ Foxp3+ regulatory T cells [26].

HYPOTHETICAL MECHANISM OF THE ANTIVIRAL ACTIVITY OF PMBL

Viral infection facilitates bacterial colonization by modifying local defense mechanisms within the respiratory tract and contributing to changes within cellular membranes resulting in easier bacterial cell adhesion. On the other hand, bacteria facilitate viral infections by proteolytic degradation of hemagglutinin. Studies suggest that Ismigen PMBL may exert a beneficial effect on the "vicious circle" of bacteria-virus interactions leading to less virulent infections [9]. Another study demonstrated stimulated maturation of circulating and plasmacytoid dendritic cells involved in the innate immune response and detection of viruses following PMBL administration [27]. Stimulation of a subgroup of natural killer (NK) involved in elimination of virus-infected cells was demonstrated following PMBL stimulation [28].

SAFETY OF BACTERIAL LYSATES

Meta-analysis carried out by Del-Rio-Navarro et al. [13] revealed no statistically significant differences in the incidence of adverse events between bacterial lysate- and placebo-treated groups The most commonly reported adverse effects included rash and vomiting, nausea, abdominal pain, and diarrhea. In their systematic review of available literature, Schaad et al. [14] estimated the incidence of adverse effects to be at the level of 17.7% in the group treated with the immunomodulatory agent and 18.2% in the placebo group, with no direct correlations being observed between lysate administration and symptom development.

No serious life-threatening adverse effects were observed as well as no correlation between the use of bacterial lysates and the incidence of autoimmune diseases [29]. Occasional adverse effects observed in the course of bacterial lysate treatment have also been observed following administration of other drugs exerting beneficial effect on the immune system, i.e. vaccines; such symptoms are usually observed when the immune system is so weak that inflammation is induced within the system by the inactivated pathogen.

LIMITATIONS OF BACTERIAL LYSATE TREATMENT

Immunostimulation with bacterial lysates has certain limitations. Patient's age is of importance here, and therefore caution should be taken when using bacterial lysates in patients with immature immune systems. Immunostimulatory treatment should be delivered at specific intervals required for regeneration of the immune system as a sequence of changes observed in laboratory analyses in the course of immunostimulation suggests initial depletion of "peripheral reserves" of immunocompetent cells. Doe to the antigen-mimicking mechanism of lysate action, bacterial lysates should not be used in the course of or immediately after an infection. Excessive use of bacterial lysates may result in immunosuppression.

When making a decision to start an immunostimulatory treatment it is very important to appropriately select the type of immunostimulating agent, its dose and treatment duration so that the treatment does not result in paradoxical immunosuppression. Each immunotropic treatment should be appropriate for the pathology, patient's age and, most importantly, the competence of the immune system [30].

Each decision to initiate immunotherapy should be preceded by an assessment of quantitative and functional efficacy of the immune system and the treatment should be monitored by clinical assessments and immunodiagnostic tests.

Despite positive opinions from clinical trials, the currently available bacterial lysates should not be recommended in acute infectious diseases, immunodeficiencies, autoimmune diseases, rheumatic diseases, as well as in active tuberculosis and cardiopulmonary insufficiency.

SUMMARY

Oral immunomodulatory products available on the Polish market are efficient in the prevention and treatment of both acute and recurrent upper respiratory tract infections in pediatric and adult patient populations. Bacterial lysates differ in chemical composition, preparation method, dosage and administration method and age of use in pediatric patients. The usually very good tolerance of the drugs with occasional low--degree adverse effects and high efficacy confirmed in clinical trials support the use of bacterial lysates in patients of all ages, particularly in periods of increased respiratory tract infection morbidity rates. Bacterial lysates increase immunoprotection and immunity, reduce the number of respiratory tract infection recurrence and incidence rates in adults and children alike, reduce the intensity of airway-related symptoms, shorten the duration of infection-associated pyrexia, and reduce the number of infections requiring antibiotic treatment. In specific acute bacterial infections of the respiratory tract, however, bacterial lysates should not replace appropriate antibiotic treatment.

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