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A Review on Immunological Effects of Bacterial Lysate in Upper Respiratory tract Infection

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ABSTRACT:
Bacterial lysates are immunostimulants clinically used to prevent respiratory tract infections (RTIs). They enhance both innate and adaptive immune responses, demonstrating efficacy in restoring epithelial barrier integrity, activating ILC3 and dendritic cells, and promoting a Th1 response. Additionally, they stimulate the production of specific serum IgG and salivary IgA, providing cross-protection against other pathogens via trained immunity. Clinical studies report a reduction in RTI frequency and severity in patients pretreated with bacterial lysates, alongside a potential protective effect against disease progression in conditions like COPD, without significant side effects.Bacterial lysates (BLs), composed of bacterial antigens, have been utilized for decades to reduce the risk of recurrent respiratory tract infections in both pediatric and adult populations. Recent research has explored their application in allergology, particularly for allergic rhinitis (AR). A systematic review of biomedical databases identified six relevant studies on the use of BLs in AR treatment. The findings indicate that incorporating BLs into standard therapy for seasonal or perennial AR alleviates nasal symptoms and reduces the need for antiallergic medications in both children and adults. Furthermore, BLs demonstrate a favorable safety profile. The analysis reveals that therapeutic effects emerge within 2–6 weeks of treatment initiation and persist for at least three months post-treatment.

Keywords: Respiratory tractinfection, Allergic rhinitis, Bacterial lysates, Immunostimulates, Upper respiratory tract infections.

I. INTRODUCTION:

Respiratory tract infections (RTIs) are defined as infectious diseases affecting the upper or lower respiratory tract. Upper respiratory tract infections (URTIs) encompass conditions such as the common cold, laryngitis, pharyngitis/tonsillitis, acute rhinitis, acute rhinosinusitis, and acute otitis media, while lower respiratory tract infections (LRTIs) include acute bronchitis, bronchiolitis, pneumonia, and tracheitis. RTIs are among the most prevalent infectious diseases worldwide, contributing to millions of deaths annually [1]. Additionally, RTIs are significant comorbidities in chronic respiratory conditions such as chronic obstructive pulmonary disease (COPD), chronic rhinosinusitis, and asthma. In 2019, there were an estimated 17 billion incident cases of URTIs [2] and 489 million cases of LRTIs [3] globally, highlighting their substantial social and economic impact. RTIs also account for a high rate of disability-adjusted life years (DALYs), with a declining trend in children as they age but an increasing trend in adults with advancing age.

The high incidence of infections in early life, particularly among preterm infants, is attributed to immature immune responses during the transitional postnatal period. In contrast, age-related immune dysfunction, including inflammaging and comorbidities, significantly increases the risk of morbidity and mortality from respiratory tract infections (RTIs) in the elderly. Older adults also exhibit reduced vaccine efficacy and impaired innate immune responses, which hinder efficient infection clearance. RTIs have been reported to elevate mortality rates among the elderly by 6–7%.

Regardless of age, chronic respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis are strongly associated with recurrent RTIs,

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exacerbating these conditions. Risk factors for RTIs include active and passive smoking, low serum vitamin D levels, physical inactivity, sudden temperature fluctuations, occupational exposure to physical and chemical hazards, obesity, and Type 2 diabetes.

Immunocompromised individuals—such as those with immunodeficiency, cystic fibrosis, or HIV; patients on corticosteroid therapy; post-transplant and post-splenectomy patients—are particularly vulnerable to RTIs. Additionally, anatomical anomalies, including facial dysmorphic features and nasal polyposis, further increase susceptibility to RTIs.

Bacterial Lysates: Definition and Composition

Bacterial lysates are antigenic preparations derived from inactivated pathogens commonly implicated in respiratory tract infections (RTIs). According to the European Medicines Agency, bacterial lysates are medicinal products composed of lysed bacterial cells, designed to stimulate the immune system to recognize and combat infections.

The lysis of bacterial cells can be achieved through chemical (alkaline) or mechanical methods, although heat and detergents have also been employed. Mechanical disruption is preferred for preserving the antigenic structure, whereas chemical lysis often leads to antigen denaturation. The resulting antigens are then combined in specific proportions to create polyvalent bacterial lysates with broad-spectrum immunostimulatory properties.

Table no.1 The bacterial strains present in the different bacterial lysates

Bacterial Lysate	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	-
Streptococcus viridans	X	**Streptococcus mitis**	X	-
Moraxella catarrhalis	X	X	X	X
Haemophilus influenzae	X	X	X	X
Klebsiella pneumoniae	X	X	X	X
Klebsiella ozaenae	X	-	X	-

Mechanisms of Action of Bacterial Lysates:

Bacterial lysates (BLs) mimic natural microbial exposure, stimulating both innate and adaptive antigen-specific immune responses. Administered orally, intranasally, or sublingually, they activate local mucosal immunity, leveraging the gut–lung axis for systemic immune activation. BLs act as pathogen-associated molecular patterns, activating antigen-presenting cells like macrophages and dendritic cells (DCs) through TLR-2 and TLR-4. This leads to the release of inflammatory cytokines (IL-1, IL-6, TNF-α) and chemokines (IL-8, CCL2, CCL20), enhancing cytotoxicity via CD8 and NK cells.

Activated DCs upregulate MHC II, CD40, and CD83, presenting antigens to T cells and promoting B cell differentiation into plasma cells. This increases antigen-specific IgA and IgG levels, particularly in the respiratory mucosa, offering enhanced microbial protection. BLs induce a Th17/Th1 immune profile, marked by elevated IL-17A and IFN-γ levels.

Additionally, BLs stimulate epithelial cells to secrete antimicrobial peptides and pro-inflammatory cytokines, further enhancing protection. They also exhibit antiviral effects, boosting IgA and IgG production against viruses such as influenza and RSV, while activating NK cells to target infected cells. BLs may establish a "trained immunity" state, enhancing non-specific and adaptive responses.

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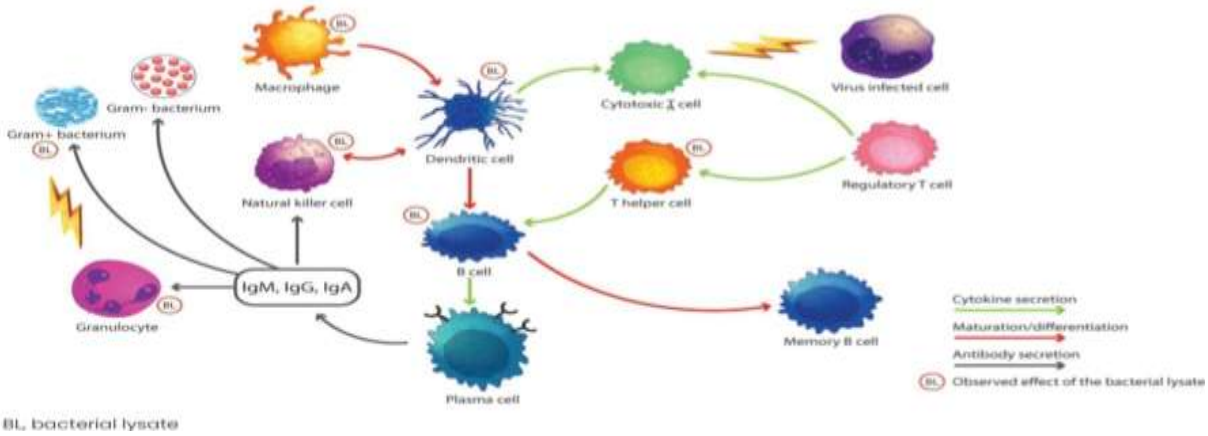
Table no.2: The characteristics of bacterial lysates for use in prevention of respiratory tract infection

DRUG	Bacterial Lysate Preparation Method	Bacterial Content	Formulation	Dosage/dose
Ismigen	Polyvalent, mechanical	48 mld	Sublingual tablets	7 mg for children 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 for 6-12 months, 7 mg for 12 years of age, according to Patient Information Leaflet
Luivac	Polyvalent, chemical	1mld	Tablets	3 mg for 2 years of age, according to Patient Information Leaflet
Ribomunyl	Kleinsiella pneumoniae membrane fraction proteoglycan	Ribosomes/ribosomalRNA: k.pneumoniae3-5p/w str. Pneumoniae3p/w str. Pyogenes3p/w H. influenzae,0.5p/w	Tablets, granules	Tab:0.525mg, granules:0.750mg>2 yrs of age, according to patients information leaflet

Although no direct studies link BLs to bronchus-associated lymphoid tissue (BALT) activation, their systemic immune effects suggest cross-communication within the mucosal immune system, providing broad protective benefits.It would be of interest to investigate the combined effects of bacterial lysates and immune-stimulating molecules such as FLT3 ligand (FLT3L) and macrophage-activating lipopeptide-2 (MALP-2). FLT3L functions as a growth factor for B and T cells by stimulating hematopoietic progenitors and has been shown to increase the number of dendritic cells in nasal-associated lymphoid tissue. MALP-2 enhances macrophage responses, indirectly activates natural killer (NK) cells, and improves antigen presentation by dendritic cells.

Figure no.1:The immune mechanisms affected by bacterial lysates



Bacterial Species and Lysis Methods:

Key pathogens involved in respiratory tract infections include Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans, and Moraxella catarrhalis. However, the use of alkaline lysis in bacterial lysate preparation may

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lead to protein denaturation, reducing the immunogenicity of bacterial antigens and consequently diminishing the immune response.

Polyvalent Mechanical Bacterial Lysate (PMBL) is a lysate derived from a broad spectrum of pathogenic bacteria, including the most common upper and lower respiratory tract pathogens (S. aureus, S. viridans, S. pyogenes, K. pneumoniae, K. ozaenae, H. influenzae serotype B, M. catarrhalis, and S. pneumoniae), produced through mechanical lysis [13]. This method is highly effective, achieving lysis in 80–100% of the bacterial cells, while preserving antigenic integrity and enhancing immunogenicity.

Principle of Bacterial Lysates' Activity:

The enhanced elimination of bacterial pathogens in recurrent respiratory infections is attributed to the activation of the immune system's memory. Bacterial lysates interact with mucosa-associated lymphoid tissue (MALT), which is continuously exposed to pathogenic antigens. MALT comprises gut-associated lymphoid tissue (GALT), bronchus-associated lymphoid tissue (BALT), nasal-associated lymphoid tissue (NALT), and lymphoid tissues of lacrimal, salivary, mammary, and urogenital glands. Its primary function is the production of secretory IgA (sIgA) antibodies, which protect by coating microbial cells, preventing their adhesion, neutralizing toxins, and exerting bacteriostatic effects.

Memory B cells continuously secrete low levels of antibodies, enabling a rapid and robust response upon re-exposure to the same pathogens. Secondary immune responses are more rapid, efficient, and robust than primary responses, requiring lower antigen levels to trigger and producing higher antibody quantities with slower decline rates. The affinity of antibodies in secondary responses is also higher. This enhanced immune readiness can persist for extended periods, but to sustain effectiveness, immunomodulatory agents must be administered periodically.

Safety Profile of Bacterial Lysates:

A systematic review found no statistically significant differences in adverse event incidence between bacterial lysate- and placebo-treated groups. The most commonly reported side effects included rash, vomiting, nausea, abdominal pain, and diarrhea. No serious or life-threatening adverse events were observed, and no association was found between bacterial lysate use and autoimmune diseases. Occasional mild side effects, similar to those seen with vaccines, are attributed to immune system activation, particularly in cases of severe immunosuppression where inactivated pathogens may trigger inflammation.

Limitations of Bacterial Lysate Treatment:

Bacterial lysate therapy has certain limitations, particularly concerning patient age, requiring caution in individuals with immature immune systems. Immunostimulatory treatment should be administered at appropriate intervals to allow for immune system regeneration, as laboratory analyses indicate an initial depletion of peripheral immunocompetent cell reserves during immune-stimulation.

Recommendations for the Use of Bacterial Lysates:

The initiation of immunotherapy with bacterial lysates should be preceded by an evaluation of the immune system's quantitative and functional status, with treatment monitored through clinical assessments and immunodiagnostic tests.Despites favorable outcomes from clinical trials, bacterial lysates are not recommended for use in acute infectious diseases, immunodeficiencies, autoimmune or rheumatic conditions, active tuberculosis, or cardiopulmonary insufficiency.

Here's the information converted into a table format for better readability:

II. CONCLUSION:

Oral immunomodulatory agents available on the Polish market have proven effective in preventing and managing both acute and recurrent upper respiratory tract infections (URTIs) in pediatric and adult populations. Bacterial lysates vary in chemical composition, preparation methods, dosage, administration routes, and age indications for pediatric use. These agents are generally well-tolerated, with only mild adverse effects reported, and their high efficacy, as demonstrated in clinical trials, supports their use across all age groups, particularly during periods of heightened URTI prevalence.Bacterial lysates enhance immune-protection, reduce the frequency and recurrence of respiratory infections in both children and adults, alleviate respiratory symptoms, shorten the duration of infection-related fever, and decrease the need for antibiotic therapy.

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