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Immunomodulation options and frequency of respiratory infections in children

Możliwości immunomodulacji a częstość zakażeń dróg oddechowych u dzieci

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Abstract

Frequent respiratory tract infections in the paediatric population are associated mainly with immune system immaturity. A child aged up to 5 years can have up to 8 respiratory infections in a year. Immunomodulation through the elimination of negative environmental factors is of limited efficacy in the paediatric population. For this reason, in certain cases there is a need for pharmacological stimulation of immune response mechanisms in order to limit the number of infections. Modulators include medication, vitamins and trace elements, probiotics and plant formulations. Unfortunately, there are insufficient scientific data which confirm the efficacy of many such agents. Bacterial lysates are an exception: their effects have been confirmed in well-designed studies. Such formulations consist of killed bacterial cells or fragments of their organelles. Bacterial lysates contain antigens of the most common human respiratory pathogens. The efficacy of a bacterial lysate is the resultant of two components: patient-specific (individual immune reactivity) and formulation-specific (composition, dosing regime). To date, no reliable studies comparing the efficacy of different formulations have been conducted. One of the most thoroughly studied products is the one containing OM-85 lyophilisate (BV, Broncho-Vaxom®).

Keywords: immunomodulators, bacterial lyophilisates, probiotics, recurrent respiratory infections

Streszczenie

Częste infekcje dróg oddechowych w populacji pediatrycznej związane są głównie z niedojrzałością układu immunologicznego. Dziecko do 5. roku życia może przeżyć do 8 zakażeń dróg oddechowych w ciągu roku. Modulacja układu immunologicznego poprzez eliminację wpływu negatywnych czynników środowiskowych w populacji pediatrycznej ma ograniczoną skuteczność. Dlatego też w niektórych przypadkach istnieje potrzeba farmakologicznej stymulacji mechanizmów odpowiedzi immunologicznej w celu ograniczenia liczby zakażeń. Modulatorami mogą być środki farmakologiczne, witaminy i mikroelementy, probiotyki, preparaty roślinne. Niestety dane naukowe potwierdzające skuteczność wielu spośród tych preparatów są niewystarczające. Wyjątek stanowią preparaty lizatów bakteryjnych, których efekt działania został potwierdzony w dobrze zaprojektowanych badaniach. Lizaty bakteryjne to zabite komórki bakterii lub fragmenty ich organelli. Zawierają w swoim składzie antygeny drobnoustrojów najczęściej spotykanych w patologii dróg oddechowych u ludzi. Efektywność działania lizatu bakteryjnego jest wypadkową dwóch składowych: osobniczej (indywidualna reaktywność immunologiczna pacjenta) oraz zależnej od preparatu (skład, schemat dawkowania). Nie ma dotychczas wiarygodnych badań porównujących skuteczność poszczególnych preparatów. Jednym z najlepiej przebadanych jest preparat zawierający liofilizat OM-85 (BV, Broncho-Vaxom®).

Słowa kluczowe: immunomodulatory, liofilizaty bakteryjne, probiotyki, nawracające zakażenia układu oddechowego

INTRODUCTION

Frequent respiratory tract infections in the paediatric population are associated mainly with immune system immaturity. Research has confirmed that it is only at 12 years of age that the immune system reaches full maturity in terms of its defensive abilities⁽¹⁾. **Innate immunity** predominates in a newborn, which is its first line of defence against pathogens. It is genetically determined, and thus it is natural and non-specific. The main cells associated with innate immunity are phagocytic cells such as e.g. macrophages, neutrophils and monocytes, and cells of the complement system. The immune response begins very quickly and does not require preactivation. However, unlike acquired immunity, innate immunity does not contribute to immunological memory.

Specific immunity is acquired throughout the whole life, in an active or passive way. Active specific immunity is generated after exposure to an antigen as a result of developing and recovering from a disease (natural immunity), or being vaccinated (artificial immunity). Passive specific immunity involves transferring immune antibodies by the mother to the child with breastmilk (natural immunity) or administering antisera (artificial immunity).

VIRAL RESPIRATORY INFECTIONS IN CHILDREN

Respiratory tract infections are a very important clinical problem in the paediatric population. Such infections account for approximately 50–60% of all non-hospital infections and are the most common cause of fever in infants and younger children⁽²⁾. The vast majority of respiratory infections are of viral origin (70–85%)⁽³⁾. Viruses are most infectious in the autumn and winter (Fig. 1)⁽⁴⁾.

An important problem both for the clinician and the patient is respiratory illness recurrence. It is estimated that in developing countries this problem affects as many as 25% of children under 12 months of age and 18% of children aged 1–4 years⁽⁵⁾. A child aged up to 5 years can have up to 8 respiratory infections in a year⁽⁶⁾. If risk factors are present (Tab. 1), the number of infections can increase to as many as 10–12 a year.

IMPACT OF ENVIRONMENTAL FACTORS ON RECURRENCE OF RESPIRATORY INFECTIONS

Appropriate environmental conditions have a positive influence on child immunity. Factors which compromise immune system function include stress, poor dietary habits, exposure to tobacco smoke, bad sleep hygiene and low physical activity levels.

Cohen et al.⁽⁷⁾ demonstrated that shortened sleep (<7–8 hours) is associated with a nearly three times higher risk of respiratory infection. The impact of physical activity on developing child immunity is also well-documented. In a prospective study of a cohort of 1,028 schoolchildren, Jedrychowski et al.⁽⁸⁾ demonstrated that regular moderate physical exertion significantly reduced the number of respiratory tract infections.

Undernourishment is another factor that compromises immunity; however, it does not have much relevance to European children. On the contrary, it is obesity that is clinically significant in them. Research on obese children demonstrated an increase in the levels of both CD14 monocytes and their activated phenotypes⁽⁹⁾. In adipose tissue, monocytes differentiate into macrophages, which contributes to the development of systemic inflammation. A higher risk of respiratory infections in obese patients is also due to weakened natural killer cells, which are natural cytotoxic cells that fight viral infections.

In the paediatric population, immunomodulation through the elimination of negative environmental factors has limited efficacy. Recurrent infections often lead to bronchial hyperresponsiveness and contribute to the development of allergies. They can also transform into a chronic disease process. For this reason, in certain cases there is a need for pharmacological stimulation of immune response mechanisms in order to limit the number of infections.

IMMUNOMODULATION

Immunomodulation is the action of external agents that causes changes in the immune system. Modulators include medication, vitamins and trace elements, probiotics and plant products. Unfortunately, there are insufficient scientific data which confirm the efficacy of many such agents⁽¹⁰⁾. Bacterial lysates are an exception: their effects have been confirmed in well-designed studies.

Fig. 1. Viral infectious activity depending on season of the year (adapted from: Hendley, 2000⁽⁴⁾)

Fish oil

Fish oil is a mixture of biologically active compounds, the most important of which are polyunsaturated fatty acids and fat-soluble vitamins. For many years, fish oil has been considered to have a positive impact on immune system function. Due to a high docosahexaenoic acid (DHA) content, fish oil can reduce the risk of infection episodes in children^(11,12).

Plant formulations

Coneflower (*Echinacea*) formulations are considered to have immunostimulatory properties. *Echinacea* is one of the best-selling immunity support products. In their pilot study, Zegan et al.⁽¹³⁾ found that products with vitamin C and formulations containing coneflower were the most frequently purchased supplements intended to reduce the number of respiratory infections.

Numerous well-designed studies assessing the efficacy of coneflower formulations as immunostimulants have been conducted^(14,15). Caution is advised when using *Echinacea* as an immunomodulator in children⁽¹⁶⁾. The fact that the content of ingredients in different formulations is not standardised is also an important problem. For this reason, the evaluation of their effects is difficult, which additionally undermines their reliability.

Polysaccharides and peptides isolated from fungi

Beta-glucans are immune system activators extracted from fungi. Their immunostimulatory action focuses on the activation of T-cells and phagocytes⁽¹⁷⁾. Unfortunately, to date, there have been few studies on the immune effects of beta-glucans in humans. In their clinical study, Jesenak et al.⁽¹⁸⁾ observed a statistically significant difference in the number of respiratory infections in children taking beta-glucan formulations compared to those receiving placebo. However, there are studies which do not provide a definitive confirmation of immunomodulatory properties of beta-glucans for chronic stimulation of immunity⁽¹⁹⁾.

Due to a low number of studies and their poor quality, there is no reliable scientific evidence to recommend such formulations to patients with recurrent respiratory tract infections.

Vitamins

Vitamins are essential compounds for normal body function. There is a particularly high interest in vitamin D as an immunostimulator. Through its receptors, vitamin D affects the proliferation, differentiation and function of immune cells. A meta-analysis of clinical studies published in 2013 demonstrated a positive influence of vitamin D supplementation on the reduction of the number of respiratory

tract infections. This effect was observed both in paediatric and adult populations⁽²⁰⁾.

According to current guidelines, all children should receive vitamin D at 400 IU/day (800 IU/day for obese children) as rickets prevention. There are doubts whether such a dose has an immunomodulatory effect as well. In July 2017, a study was published in the "JAMA" journal on the impact of various doses of a vitamin D supplement on the incidence of viral upper respiratory tract infections in small children⁽²¹⁾. The incidence of respiratory infections was analysed in a group that received a high dose of vitamin D (2,000 IU/day) and a group that received a standard dose of 400 IU/day. No statistically significant differences were found between the groups. For this reason, the authors of that study do not recommend the administration of increased doses of vitamin D to reduce the incidence of respiratory tract infections.

Due to a lack of sufficient scientific evidence, currently it is not possible to confirm or deny that vitamin D is useful for the prevention of respiratory tract infections.

Inosine pranobex

Inosine pranobex (isoprinosine) normalises insufficient or defective mechanisms of cell-mediated immunity by activating Th1-type response, leading to the maturation and differentiation of T-cells. Unfortunately, research to date on the efficacy of isoprinosine in the prevention and treatment of recurrent respiratory tract infections in healthy children has not demonstrated any distinct and significant clinical effect⁽²²⁾.

Bacterial lysates

Bacterial lysates (BL) consist of killed bacterial cells or fragments of their organelles. They contain antigens of the most common human respiratory pathogens: *Staphylococcus aureus*, *Streptococcus viridans*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Moraxella catarrhalis* and *Haemophilus influenzae*. The action of antigens primarily involves stimulating the innate immune response, but they can also stimulate the production of specific antibodies.

There are two types of BL mixtures differing by the method with which they are obtained:

- polyvalent chemical bacterial lysates (PCBL), which contain antigen macroparticles with structural damage;
- polyvalent mechanical bacterial lysates (PMBL), which have no chemical contamination. They are characterised by better immunogenicity than PCBL⁽²³⁾.

The action of BL is based on the assumption that upon contact with the intestinal mucosa, bacterial antigens stimulate immune cells, leading to generalised response of defence mechanisms in the whole body. Oral BL formulations that contain specific bacterial antigens are presented by the intestinal lymphatic tissue to lymphocytes,

Risk factors for recurrent respiratory tract infections

Nursery attendance
Atopy
Having siblings of school age
Prematurity
Low birth weight
Limited breastfeeding
Tobacco smoke exposure
Anatomical or functional respiratory tract defect
Gastrointestinal reflux
Male sex
Poor socioeconomic conditions

Tab. 1. Risk factors for increased number of recurrent respiratory tract infections⁽⁶⁾

which results in an increased production of secretory immunoglobulin A (IgA)⁽²⁴⁾. Antibodies generated in this way are directed against bacterial components of the lysate. The antiviral effect of oral vaccines is associated with the mechanism of toll-like receptors (TLR), which play a key role in non-specific immunity. Microbial particles in a BL stimulate the immune system in a non-specific way, which leads to an increased expression of TLR. For this reason, serial stimulation of the immune system with consecutive administrations of the lysate results in an increased activity of phagocytes against viruses as well⁽²⁵⁾. This effect was confirmed in clinical studies. A meta-analysis conducted in 2012 of data from 15 well-designed clinical studies confirms a positive impact of BL on the reduction of the number of respiratory infections both in the paediatric and adult populations⁽²⁶⁾. The efficacy of prevention was higher for higher baseline numbers of infections⁽²⁷⁾. The safety of lysates was also confirmed and the number of adverse reactions over 8–12 months was similar to that in the placebo group.

The efficacy of a BL is the resultant of two components: patient-specific (individual immune reactivity) and formulation-specific (composition, dosing regime). To date, no reliable studies comparing the efficacy of different formulations have been conducted. There are a few types of BL formulations available on the Polish market. One of the most thoroughly studied products is the one containing OM-85 lyophilisate (BV, Broncho-Vaxom®). In a randomised, double-blind, placebo-controlled clinical trial including 232 children with recurrent respiratory infections, a statistically significant reduction of the number of infections was found (by 40% on average) in a group of children taking BV⁽²⁸⁾. Similar results were obtained by Esposito et al.⁽²⁹⁾. In a phase 4 clinical trial that included 288 children aged 1–6 years, a lower number of respiratory infections were observed in children treated with BV compared to those who received placebo.

There are reports that BV not only reduces the number of infections, but can also affect their duration and the need for antibiotic therapy. In a prospective randomised study, Gutiérrez-Tarango and Berber⁽³⁰⁾ demonstrated shortening of the total infection time and reduction of antibiotic use in

children with recurrent respiratory tract infections treated with BV compared to children who received placebo. Paupe⁽³¹⁾ observed that such an effect can persist even after discontinuation of BV. In 39.5% of children who received BV no infection was observed even at 180 days after the BV administration was stopped.

The efficacy of BV in the reduction of respiratory tract infections was also confirmed for children deficient in IgG subclasses⁽³²⁾ and preschool children with wheezing attacks⁽³³⁾. A meta-analysis of data from clinical studies on the paediatric population indicates that children treated with BV had a significantly shorter duration of antibiotic therapy, fever, coughing and wheezing. In addition, increases in IgG, IgA, IgM and T-cell (CD3+, CD4+ and CD8+) levels were observed⁽³⁴⁾.

In summary, these results seem to suggest that bacterial lysates bring significant benefits to children with recurrent respiratory tract infections.

CONCLUSION

A reduction in the number or duration of respiratory tract infections through appropriate prevention improves the quality of life of paediatric patients and their caregivers. Immunostimulation with bacterial lysates is an effective prevention method against respiratory infections. Their safety has been confirmed in multiple studies.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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