

Respiratory infections and immunostimulants in childhood: an update

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From the womb to the adult

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Abstract

Respiratory tract infections are one of the most common childhood illnesses, especially in pre-school children. These infections impose an enormous burden on both the healthcare system (frequent medical consultations and hospitalizations), and on society (parental absenteeism and loss of productivity). Their recurrence still poses a diagnostic challenge in pediatrics due to the difficulty in discriminating between otherwise healthy children and those with more serious underlying pathologies. Moreover, even if viral agents are typically the main cause being responsible of up to 95% of all upper respiratory tract infections, high antibiotic prescription is often reported in clinical practice. It is well known that frequent inappropriate antibiotic use has now led to a significant increase in bacterial resistance. In this context immunostimulants could be a promising preventive approach. Even if the evidence of effectiveness has been debated in the last years, studies focused on one of these compounds (Pidotimod) have recently attempted to better clarify and define its mechanisms of action both *in vitro* and *in vivo* and have provided new evidence of efficacy.

Keywords

Respiratory infections, children, immunostimulants, antibiotic resistance, Pidotimod.

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Introduction

Acute respiratory infections (ARTIs) are one of the most common childhood illnesses and therefore the most common reason for physician visits and hospitalisation in children. The majority of ARTIs involve the upper respiratory tract and viral agents are typically the main cause, being responsible of up to 95% of all upper respiratory tract infections [1]. Several environmental and individual factors contribute to the incidence of ARTIs (**Tab. 1**). During childhood, ARTIs incidence peaks in the first 4 years of life, especially in children attending

day care [1]. Day-care centers constitute a common childhood environment where children are exposed to a larger amount of pathogens, given their closer contact with other children [2]. A tendency toward hyporesponsive immune responses in early life, characterized by both reduced innate and adaptive immune responses, plays an important role in ARTIs recurrence in the first 6 years of life [3].

The majority of children with ARTIs involving the upper airways are otherwise healthy, a minority are affected by an underlying immunological (e.g. primary or secondary immunodeficiency) or non immunological (e.g. cystic fibrosis, anatomical abnormality of the airways, ciliary dyskinesia) disease.

ARTIs impose an enormous burden on both the healthcare system (frequent medical consultations and hospitalizations) and on society (parental absenteeism, loss of productivity) [4]. Up to 20% of medical consultations, emergency room admittances, hospitalizations and prescriptions of pharmacologic treatments are due to these infections, and up to 30% of parental work-days are lost because of their child's respiratory infection [5]. Of note, in the outpatient setting, is

Table 1. Environmental and individual risk factors for ARTIs recurrence [16-22].

Environmental risk factors	Comments
Early socialization, day-care attendance	Children who attend day-care centers have a higher risk of ARTIs compared with children cared at home. Approximately 70% of children with recurrent respiratory infections attend day-care centers, and about 75% of them start with ARTIs during their first year at child-care facilities.
Passive smoking (environmental and/or prenatal)	Direct effect of tobacco smoke on host defence, mainly by reducing the production of oxygen radicals by neutrophils and macrophages, hence suppressing their phagocytic activity.
Indoor and outdoor pollution	Air pollutants cause inflammation of the lung airways and alveoli. Infants and young children are particularly susceptible to these pollutants because of the immaturity of their respiratory defence mechanisms and the anatomy of their airways.
Large family size, overcrowding	Pathogens spread more rapidly, especially in combination with inadequate ventilation and poor sanitation.
Reduction in breastfeeding	Protective effects are due to several factors in human breast milk (ie: lactoferrin has antimicrobial properties, epidermal growth factor induces maturation of the intestinal epithelium, immunoglobulin A and oligosaccharides prevent attachment of pathogens).
Individual risk factors	Comments
Immaturity of the immune system	Both the innate and adaptive arms of the immune system are immature at birth and undergo quite prolonged postnatal maturation.
Atopy	Allergic mucosal inflammation predisposes to upper airway infections as it induces the expression of adhesion molecules such as intercellular adhesion molecule-1 on epithelial cells. Epithelial cells from asthmatic patients show a defective innate immune response that may partially explain the recurrence of respiratory infections.
Post-infective immunosuppression	Viral infections alter cytokine production and macrophage phagocytosis. They induce transiently decreased CD4+ T-lymphocyte numbers, and a switch toward a Th-2 pattern of immune response. Cytokine response and neutrophil chemotaxis are impaired.
Anatomic abnormalities of the respiratory tract: airway caliber, length and position of the Eustachian tube	Recurrent episodes of ARTIs and pneumonia are reported in patients with anatomic abnormalities of the respiratory tract.

that almost half of the antibiotics prescribed are for the treatment of ARTIs, especially in Italy where the antibiotic overuse is extremely common and the prescription rate is significantly higher compared with other European countries [6]. In this scenario, alternative approaches to the most well-studied and known therapies could be useful.

Immunostimulants

Intense investigations over the last decades have been carried out on a new category of biologically active substances called immunostimulants (IS). IS (bacterial lysates and/or synthetic compounds) have been shown to stimulate the immune system such as phagocytosis, complement, T- and B-lymphocytes, secretory IgA and cytokines (**Tab. 2**). IS have been introduced in some countries for the prevention of ARTIs in children. The efficacy of IS in preventing ARTIs is still debated [7]. Some studies reported a reduction of ARTIs following the administration of IS up to 40%, as highlighted by the most recent Cochrane metanalysis [7]. However some bias and confounding factors of these studies were reported such as heterogeneity in studied populations, the variable duration of the interventions and the poor statistical analysis [7].

Table 2. Immunostimulants.

Bacterial immunostimulants	Bacterial lysate
	<ul style="list-style-type: none"> • OM-85 BV • LW 50020 • PMBL
	Components of bacterial cells
	<ul style="list-style-type: none"> • D53 • RU 41740
Syntetic compound	Pidotimod

Pidotimod

At the beginning of 2000s, researches focused on one of these compounds, Pidotimod, have attempted to better clarify and define its mechanisms of action both *in vitro* and *in vivo* [8-11]. Pidotimod (3-L-pyroglutamyl-L-thiazolidine-4-carboxylic acid) is a synthetic dipeptide molecule with immunomodulatory properties. These studies demonstrated that Pidotimod:

a. induces dendritic cells' (DCs) maturation and the releasing of cytokines, enhances natural killer

cell functions, inhibits thymocyte apoptosis, and promotes phagocytosis [8];

- b. up-regulates the expression of HLA-DR and different co-stimulatory molecules [9];
- c. enhances the concentration of salivary IgA directed against some respiratory bacteria [10];
- d. stimulates DCs to release pro-inflammatory molecules, driving T cell proliferation and differentiation towards a Th1 phenotype [8, 10];
- e. modulates airway epithelial cell functions involved in host-virus interactions, possibly through nuclear factor-kappa B activation [11].

In pediatric population, Pidotimod seems to up-regulate a number of genes involved in the activation of innate immune responses and antimicrobial activity in a population of children with Down syndrome. Moreover, when administered with a virosomal influenza vaccination, Pidotimod potentiated the beneficial effect of the immunization, possibly resulting in a greater activity of both innate and adaptive immune responses [12].

More recent studies showed that Pidotimod may prevent respiratory infections in children with an history of recurrent respiratory infections. No severe adverse effect were reported, confirming a good safety profile of this compound [13, 14].

The results of a recent study in healthy children entering day care merit attention [15]. The authors conducted a double-blinded randomized placebo-controlled trial study to assess the efficacy of Pidotimod in a population of 3-year-old healthy children, who just entered kindergarten, enrolled by 17 family pediatricians in Milan and Verona area (Italy). The main outcome was the incidence of respiratory infections and the secondary outcome was the prescription of antibiotics. Children were randomized to receive either Pidotimod 400 mg *per os* or placebo twice daily for the last 10 days of each month from October 2013 to April 2014. The incidence rate ratio for respiratory infections was 0.78 (95% CI 0.53 to 1.15, $p = 0.211$) for Pidotimod vs. placebo. The corresponding risk ratio for antibiotic usage was 0.56 (95% CI 0.27 to 1.16, $p = 0.120$). In this trial, Pidotimod was not statistically superior to placebo for the prevention of ARTIs in a population of healthy children who entered kindergarten. However, Pidotimod showed some potential as a means for reducing antibiotic usage in these children. The reduction in antibiotic use in Pidotimod-treated children seemed to be due to the occurrence of less severe respiratory

infections compared to those experienced in placebo-treated group. Therefore, Pidotimod seems to have immunomodulant properties reducing the severity of ARTIs. Thus, the authors concluded that the administration of Pidotimod could help to reduce antibiotic prescription for ARTIs. Considering the association between unneeded antibiotics and the development of antibiotic resistance, Pidotimod could help to reduce both in the long term.

Conclusions

New and interesting results emerged from recent studies *in vitro* about IS. Moreover, the results obtained in treated patients are also encouraging.

Declaration of interest

The Authors have nothing to declare.

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