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Review Article

Non-specific immune stimulation in respiratory tract infections. Separating the wheat from the chaff

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SUMMARY

Parents of children suffering from recurrent respiratory infections can be persuaded by advertisements to pressure their family physicians and pediatricians for "immune-stimulating enhancements". However, the evidence base behind these immune stimulants is usually lacking. Often there is no peer-reviewed studies available that support claims made by "immune-booster" supplements.

In this review, we critically analyze most of the marketed immuno-active drugs (including vitamin preparations, dietary supplements, homeopathic remedies, Ecchinacea, bacterial lysates, and probiotics) and identify the necessity to exclude an immunodeficiency in every child suffering from recurrent respiratory tract infections.

INTRODUCTION

Infections, particularly upper respiratory tract infections (RTI) of viral origin, commonly occur in childhood due to an increased risk of exposure, coupled with an immature innate immune system.

The average number of upper and lower respiratory tract infections in healthy children under 5 years of age is 6–8 per year [1]. This number can almost double in those who attend kindergarten or nursery schools. Parents may find this frequency of normal infections difficult to accept, and not surprisingly, often seek vitamins/supplements in an attempt to reduce this natural frequency of infections in early childhood [2]. Understandably, the focus of current research aims to unveil treatments to reduce the number of recurrent RTIs through the stimulation of an innate immune response. Additionally, liberal prescribing of antibiotics and the increasing number of antibiotic-resistant organisms further necessitate an investigation into the issue [3]. We therefore aim in this review to discuss the pathogen defense mechanisms of the respiratory tract, when an immune defect should be considered, and discuss many of the current therapeutic preparations. The selected preparations were assessed by examining systematic reviews, meta-analyses, and randomized controlled trials (RCTs) and are summarized in Table 1.

DEFENSE MECHANISMS IN THE CHILDHOOD RESPIRATORY TRACT

The first line of defense protecting the respiratory tract in children is a mechanical barrier composed of ciliated epithelium, coated with mucous, and supported by classical defense mechanisms including secretory IgA and resident macrophages.

The mucous in adults is enriched with proteins exerting antibacterial (defensins, lysozyme, IgA), immunomodulating (secretoglobins, cytokines), and protective (trefoil proteins, heregulin) functions aiding in infection prevention [4,5]. However, these mechanisms in children develop gradually and are not fully functional until 5–7 years of age [4].

Exemplifying the immaturity of respiratory immune defenses in children is a lower expression of toll-like receptors (primarily TLR2 and TLR4) on epithelial cell membranes compared to the adult [6]. Members of TLR family are located on the epithelial cell surface and recognize pathogen-associated, conserved structures specific to various microorganisms. They activate an inflammatory innate response and engage components of the acquired immune response, providing antimicrobial and antimycotic coverage in the respiratory system. The relative quantitative deficiency of TLR in children reduces the recognition of pathogenic microorganisms and impairs the induction of an early innate immune response [6].

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Table 1
Strategies and measures to prevent respiratory tract infections in children

Intervention		Year (Reference)	Clinical efficacy*
Dietary interventions	Food supplements	–	No data
	Balanced diet	–	No data
	Body weight reduction	2006 [26]	No data
Physical activity	Moderate physical activity	2001 [28]	+
Environmenal tobacco smoke exposure	Avoiding ETS	2009 [30,32]	+
Sleep habits	Regular sleep time	2009 [43]	+
Vaccination	Conjugated pneumococcal vaccine	2009 [44,45]	+
	Seasonal flu vaccine	2007 [46]	+
Herbal remedies	*Ecchinacea*, thuja, aronia, aloe, grapefruit concentrates, traditional Tibetan herbs	[48,49,51]	+/–
Homeopathy	*Calcarea carb*, *Pulsatilla*, *Sulphur*	2005 [53]	–
Fungal derived remedies	Beta-glucan	1999, 2008 [54,55]	–
Vitamins	Vitamin C	2013 [57]	–
	Vitamin D	2013 [59,60]	+/–
Trace elements	Zinc	2011 [62]	+/–
Cod liver oil	Pure cod liver oil	2004 [63]	–
	DHA (decosahexaenoic acid)	2010 [65,66]	+/–
Inosine pranobex		1999 [68]	–
Bacterial lysates	OM-85, D53	2012 [72]	+
	polyvalent mechanical bacterial lysates	2012 [73]	
Probiotics	Selected probiotic strains	2011 [79]	+/–

* Reduction in number RTI.

Mucous concentrations of defensins and collectins are also lower compared to adults [6].

These innate defense mechanisms are supported by a pool of lymphocytes, macrophages, and dendritic cells, forming the bronchus-associated lymphoid tissue (BALT). The BALT has been suggested to play an important role in protecting the respiratory tract during infancy [7]. Both the proliferation and activity of these cells increases rapidly during early development of the immune system as a result of increased exposure to microbes [7,8]. The relatively impaired innate cellular immunity in turn, results from decreased production of pro-inflammatory cytokines, and reduced response of macrophages (chemotaxis, adhesion, migration, and killing) [9].

The mechanisms of humoral immunity in the airways are based on antibodies, whose concentration increases continuously during childhood. The main class of immunoglobulin protecting the upper airways is IgA. The process seems to be intensified in children having attended childcare and during the winter season [10].

Although data is accumulating that the innate and adaptive immune system co-operate to eradicate pathogens, it remains poorly understood whether such responses can be improved by supplements or vitamins. With respect to available literature on the matter, not much has changed in the past 20 years [11].

A CHILD WITH IMMUNE DEFICIENCY

The clinical approach to a child presenting with recurrent RTIs should begin with the exclusion of an underlying primary immunodeficiency as it is the most common presentation manifesting in the majority of these patients [12,13]. The principles of management for primary immune disorders are beyond the scope of this review.

Excluding the diagnoses of immune defects has been thoroughly discussed by Slatter and Gendery [14] and appropriate recommendations for physicians are published by the European Society for Immunodeficiencies (ESID) [15]. Additionally, the Jeffrey Modell Foundation have created a popular model for evaluating risk factors, 'Ten Alarm Signs of Immunodeficiency' (www.info4pi.org) however the model has often been challenged [16].

According to some authors including Subbarayan et al., an immunodeficiency should be suspected based on three findings: (i) a positive family history, (ii) a history of sepsis in the child, (iii) failure to thrive [16,17]. While most children with RTIs have a normal immune system, it is essential to identify early a child with an underlying immunodeficiency. Children suffering from frequent infections, in particular those who present with chronic suppurative wet cough/sinus disease, respiratory infections caused by unusual respiratory pathogens (e.g. fungi), and/or clinical features of bronchiectasis all require a referral to a Paediatric Immunologist to determine whether an immune defect is present. Children who are well in between respiratory infections, where the infections are most likely viral and self-limiting, are on the other hand unlikely to have an immune defect. On the other hand, in children with mild immunodeficiency the symptomatology is often scarce and diagnosis occurs late. Therefore if a Paediatrician is concerned about an immune defect, then a Full Blood Count and IgG/A/M would be suggested as an initial screening test in every doubtful case. The further diagnostic workup should also include an underlying anatomic abnormality, allergic disorder, or congenital diseases manifesting prominently in the respiratory tract (eg. cystic fibrosis), each of which require an appropriate workup and management.

CAN IMMUNITY BE IMPROVED?

There are a range of behavioural factors that can impair the proper functioning of the immune system: inappropriate sleep habits, low levels of physical activity, psychological stress, and poor dietary regimes, among other lifestyle choices. Their influence upon the immune system should not be neglected, and we encourage the physician to actively discuss and optimize them if able to do so.

The influence of diet and obesity

Malnutrition is the most common cause of immunodeficiency in the world [18], but it is a rare reason for frequent infections in European children [19]. There is a lack of data to recommend the use of alternative diets or food supplements to improve immunity in an otherwise healthy child presenting with recurrent RTIs. Dietary guidelines are published by the European Food Information Council (EUFIC), and the American Academy of Nutrition and Dietetics, that emphasize a balanced diet: rich in vegetables, fruits, omega-3 fatty acids, whole-grains, and low in monosaccharides