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Recurrent Respiratory Infections in Children – Definition, Diagnostic Approach, Treatment and Prevention

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1. Introduction

Paediatric respiratory tract infections are one of the most common reasons for physician visits and hospitalisation, and are associated with significant morbidity and mortality. Respiratory infections are common and frequent diseases and present one of the major complaints in children and adolescents. The role of physicians and other healthcare providers has expanded from merely treating disease to implementing measures aimed at health maintenance and disease prevention (Bellanti, 1997). Respiratory infections (RI), mainly involving the upper airways, are common in children and their recurrence constitutes a demanding challenge for the paediatricians. There are many children suffering from so-called recurrent respiratory infections (RRI). The child with recurrent respiratory infections presents a difficult diagnostic challenge. It is necessary to discriminate between those with simply-managed cause for their symptoms such as recurrent viral infections or asthma, from the children with more serious underlying pathology such as bronchiectasis or immune dysfunction. Many different disorders present this way, including cystic fibrosis, various immunodeficiency syndromes, congenital anomalies of respiratory tract, but in some children lung damage could follow a single severe pneumonia or can be the consequence of the inhalation of food or foreign body (Couriel, 2002). According to the epidemiological studies it was estimated that around 6% of the children younger than 6 years of age present RRI. In developed countries, up to 25% of children aged < 1 year and 18% of children aged 1-4 years experience RRI (Bellanti, 1997). Moreover, ENT infections represent the most frequent pathologies in children aged from 6 months to 6 years. Although the etiologic agents responsible for RRI are not always readily identifiable, viral agents are typically the main cause. The real task for the paediatricians is to discriminate the normal children with high respiratory infections frequency related to an augmented exposure to environmental risk factors from the children affected by other underlying pathological conditions (immunological or not), predisposing to infectious respiratory

diseases (de Martino & Ballotti, 1981). Usually, the children with RRI are not affected by severe alterations and RRI represent essentially the consequence of an increased exposure to infectious agents due to environmental factors during the first years of life (Arden et al., 2006).

In the clinical practice, most of the children suffer from the recurrent infections of the upper airways, but in approximately 10-30%, the lower tract is also affected. There are two peaks of the incidence of RRI (Couriel, 2002):

- 6-12 months of age → after consumption of the maternal passively transferred immunoglobulins with concomitant postponed synthesis of own antibodies,
- the involvement of the child in to the group of children at nursery or school.

Upper respiratory infections are common but are unlikely to indicate an underlying medical condition when they occur in isolation (Wood, 2009). When evaluating the patients with recurrent infections, it is reasonable to use acronym **SPUR** (**s**evere, **p**ersistent, **u**nusual, **r**ecurrent) to prompt appropriate investigations for underlying causes. Children with RRI have the course of the airway infections (feature, severity and duration) similar to those presented by children with "normal" incidence of respiratory infections. The frequency of RI in children with RRI shows typical seasonality with the highest rate during autumn and winter (Arden et al., 2006). Typically, these children are not affected by the recurrent infections of the other systems (gastrointestinal tract, central nervous system, uro-genital tract or skin). While most children with recurrent infection have a normal immunity, it is important to recognize the child with an underlying primary immunodeficiency and investigate and treat appropriately and not over-investigate normal children (Slatter & Gennery, 2008).

RRI are a common problem mainly in preschool age, usually due to the presence of unfavourable environmental conditions, including early socialization, as well as the immaturity and inexperience of the immune system (Dellepiante et al., 2009). In infancy and early childhood the immune system encounters antigens for the first time, mounting immune responses and acquiring memory. Young children mix with other children in families or nursery and are exposed to many pathogens and therefore there are more vulnerable to infection and recurrent infections are common (Slatter & Gennery, 2008). Many of the children are simply having the repeated viral upper respiratory tract infections that are a normal part of growing up. In others, the symptoms are the first manifestations of asthma. If there is a history of persistent or recurrent pneumonia with or without chronic sputum production, it is indicating more severe pathology (Couriel, 2002). RRI initially occur as a viral respiratory tract infection, but bacterial growth is demonstrated in 60% of patients with symptoms of an upper respiratory tract infection of at least 10 days duration (Kowalska et al., 2003; Salami et al., 2008). The children with prolonged or recurrent respiratory illnesses most often have a series of infections rather than persistent infection with one virus strain (Jartti et al., 2008). Some children experience considerable morbidity as a result of RRI and receive repeated courses of antibacterials that are not effective against viral infectious agents and can increase bacterial resistance (Bousquet & Fiocchi, 2006).

2. Recurrent respiratory infections – definition

Definition of RRI is problematic and clear consensus does not exist. In case of otitis media, a reference standard for occurrence is three episodes within 6 months or four episodes within 12 months. Recurrent infectious rhinitis is usually defined as more than five episodes per year and recurrent pharyngitis or tonsillitis more than three episodes within 12 months

(Bellanti, 1997; Graham, 1990; Teele et al., 1989). Every definition of RRI is arbitrary and too generic and restrictive. Rather then defining if a child has recurrent infections with an objective numeric evaluation, it is better to know (Don et al., 2007):

- if the child generally feels good,
- if there are conditions that could be diagnosed and treated as a true disease,
- if the findings on the history and physical examination are suggestive of an immunodeficiency.

It is evident, that only a few appropriate tests are enough helpful to discriminate between a "well-being" child and a patient with immune dysfunction (Woroniecka & Ballow, 2000).
It has been proposed that to diagnose RRI at least one of the following criteria has to be present (Gruppo di Studio di Immunologia della Societá Italiana di Pediatria, 1988):

- ≥ 6 respiratory infections per annum,
- ≥ 1 respiratory infections per month involving the upper airways from September to April,
- ≥ 3 respiratory infections per annum involving the lower airways.

3. "Physiological" respiratory morbidity

Most children with RRI do not have any serious underlying immunological or non-immunological pathology, it is possible to talk about "physiologic" respiratory in children. It means that certain number of respiratory infections can be considered as physiological due to the development of immature immune system in these children. The normal frequency of the respiratory tract is six to eight episodes during the autumn and winter in infancy (in children aged 1-5 years) and two to four episodes in older children (aged 6-12 years). Even the higher frequency of respiratory infections can be a source of great worry of the parents or paediatricians, most of the children with RRI are practically not ill and we are not able to detect any serious underlying illness or disturbance of immune system (de Vries, 2001).

4. Immunology of recurrent respiratory infections

The recurrent respiratory infections in infants and children are among the most common causes of counselling and admission to the hospital. They are responsible for significant morbidity measured by school days lost. Many factors can play an important role in the genesis of the episodes of RRI that can act alone or together. In some children, it is possible to detect also transient or permanent immune system deficiencies (Bellanti, 1997). It should be pointed, that a true immunodeficiency is rare and the first cause of RRI is the childhood itself (Wheeler, 1996), because both humoral and phagocytic immunity reach their best efficacy during the first fifth or sixth years of age (Wheeler & Steiner, 1992; Yang & Hill, 1991). Typically, children with RRI are usually not affected by severe alterations of the immune system functions. The majority of these children do not have recognised immunodeficiencies, but some may have low levels of some laboratory parameters, usually of immunoglobulin isotypes or rarely other immunological parameters such as phagocytosis. Some of the observed immunological alterations are of questionable significance and not convincingly related to an increased susceptibility to respiratory infections (Litzman et al., 1999). Most children with RRI do not have an immunodeficiency. If they do, this is often due to an antibody deficiency. Finocchi et al. (2002) evaluated humoral immune defects in apparently 67 non-atopic patients with recurrent infections and in 55% a humoral defect was diagnosed.

According to the literature, several alterations in immune system and its function have been observed among children suffering from RRI (Atkinson et al., 2004; Bossuyt et al., 2007; Day et al., 2004; de Martino & Ballotti, 2007; Don et al., 2007; Finocchi et al., 2002; Gomi et al., 2004; Ianni et al., 2001; Kvestad et al., 2006; Li Volti et al., 2003; Ottenhoff et al., 2002; Pryjma et al., 1999):

- defects of Fcγ receptor IIIa (CD16) on natural killer cells,
- defect of interleukin receptor-associate kinase 4 (IRAK4),
- reduction in IL-12 production,
- polymorphisms in genes *CCR2*, *CCR5* and mannose-binding lectin gene,
- mutations in TLR-4 encoding sequences,
- defective removal of the apoptotic neutrophils by alveolar macrophages,
- pathologic phagocytosis and production of reactive oxygen intermediates from polymorphonuclear cells,
- decrease neutrophil chemotaxis,
- mild decrease in the number of $CD4^+$, $CD8^+$, $CD19^+$ and NK-cells,
- alterations in the cytokine production by lymphocytes (↑ IL-4, ↑ IL-10, ↓ IFN-γ, ↓ IL-2),
- decreases IgM, IgA, IgG subclasses, mannose-binding lectin, L-ficolin,
- defects in the production post-infectious specific antibodies.

The children with estimated diagnosis of RRI usually have no significant alteration of the immune system and its functions. Coexistence of two or more partial mild immune deteriorations in children with RRI, which was observed by several authors, confirms the secondary post-infective nature of these changes (Bossuyt et al., 2007). It is probable, that all the observed non-specific deteriorations of immunity are rather the consequence of repeated viral infections than the predisposing factor leading to RRI. Various infections (especially viral) can influence immune reaction, cytokine responses and phagocytosis. The combination of RRI and viral infection can lead to the deeper virus-induced immune dysfunction which can favour the recurrence of further respiratory infections (de Martino & Ballotti, 2007; Li Volti et al., 2003).

5. Recurrent respiratory infections as a warning sign of primary immunodeficiencies

Primary immunodeficiencies (PID) are generally the results of genetic defects that interfere with a component of the immune system. In general, these disorders are rare with some exceptions such as selective IgA deficiency or mannose-binding lectin deficiency. The most frequent PID are usually asymptomatic or have only mild clinical symptoms.

An underlying immunodeficiency is more likely when some of the following "warning" symptoms or signs occur (Champi et al., 2002; Slatter & Gennery, 2008):

- eight or more new ear infections (otitis media) within 12 months,
- two or more serious sinus infections within 12 months,
- two or more episodes of pneumonia within 12 months,
- two or more invasive infections in the history (meningitis, cellulitis, osteomyelitis, septicaemia),
- failure of an infant to gain weight or grow normally ± chronic diarrhoea,
- recurrent deep skin or organ abscesses,
- persistent superficial candidiasis after age 1 year,
- two or more months on antibiotics with little or no effect,

- need for intravenous antibiotics to clear infections,
- a family history of primary immunodeficiency.

A pattern of recurrent or persistent infection is the major manifestation of primary immunodeficiencies. While most children with RRI have normal immunity, it is essential to recognise the child with underlying PID and investigate and treat appropriately. Prompt, accurate diagnosis of PID helps to direct the most appropriate treatment, predict prognosis and facilitate genetic counselling for the family.

6. Risk factors for recurrent respiratory infections

The increased prevalence of RRI in younger children could be attributed to the several factors (de Martino & Ballotti, 2007):

- increased exposure to infectious agents during the first years of life, especially when the child is attending a group of children at preschool- or school facilities,
- general immaturity of the immune system of younger children,
- social and environmental factors e.g. day-care attendance, family size, air pollution, parental smoking, home dampness.

To the risk factors contributing to the increased frequency of respiratory infections in children with RRI belong (Ballow, 2008; Bellanti, 1997; Bloomberg, 2011; Bousquet & Fiocchi, 2007; de Martino & Ballotti, 2007, Don et al., 2007; Karmaus et al., 2008; Wheeler, 1996):

- day-care attendance,
- early socialization,
- large family size, overcrowding,
- positive family history on atopic diseases,
- school-aged siblings,
- praematurity,
- low bodyweight infants,
- reduction of breast-feeding,
- climate and environmental factors (indoor and outdoor pollutions exposure),
- home dampness,
- pets at home (especially cats and dogs),
- parental smoking and smoking in pregnancy,
- anatomic or functional alterations of the upper or lower airways,
- allergy/atopy,
- gastroesophageal reflux,
- male gender,
- poor socio-economic conditions with malnutrition,
- intense training and physical stress,
- missed vaccination.

6.1 Day-care attendance

Comparing the children in day-care centres with those cared at home, the first one have substantially higher risk of acute respiratory infections. Approximately 70% of the children with RRI attend day-care centres and about 75% of them start to suffer from RRI during their first year at child-care facilities (Celedon et al., 1999). Early enrolment can although on one side accelerate the acquisition of immunological experiences, but on the other hand this

requires the cost on the disease because of the naivety of the immune system. The younger the child, the greater risk of developing of symptomatic infection and therefore the postponed enrolment of children at day-care centres may prevent this excess risk of acute respiratory illness (de Martino & Balloti, 2007; Kamper-Jorgensen et al., 2006). It is known, that children attending day care outside home are more likely to have infections than children in home care. Early recurrent infections in early life are associated with asthma and reduced lung functions (Shaheen et al., 1994), although it has also been suggested that such infections may have a protective effect on later asthma (Cookson & Moffatt, 1997). It was confirmed that also the number of the children in collective have influence on the incidence of RRI (Marbury et al., 1997).

6.2 Indoor pollution and climate

It was showed that dose-response relation between the number of cigarettes smoked in the home and RI in children exists (Jaakkola et al., 2006; Stick, 2006). Maternal smoking during the pregnancy can influence the development of the immune system of the infants (Noakes et al., 2006). Passive smoking, allergic inflammation and predisposing anatomic variants play an important role in RRI (Arrieta et al., 2004). The exposure to home dampness and moulds (especially early in life), increased the risk of the development of atopic diseases and common respiratory infections.

6.3 Outdoor pollutions

It has been observed the relation between the outdoor pollutions (e.g. SO_2, NO_2) and the augmented respiratory symptoms, reduced expiratory flow rates, incidence of chronic cough or the increased risk of hospitalization due to respiratory infections (Colley, 1975; Chauhan & Johnston, 2003).

6.4 Physical stress

The association between increased psychical and physical stress and the frequency of respiratory infections was suggested by several studies. Highly trained athletes present a higher risk of RRI incidence. During the extreme physical stress several deterioration in the immune system have been reported (e.g. transitory decrease in serum IgA levels, reduction of phagocytosis, decrease of NK-cells) (Bergendiova et al., 2011; Nieman et al., 2002; Tiollier et al., 2005) and also possible prevention of these changes with some immunomodulators such as beta-glucans has been achieved (Bergendiova et al., 2011). It was also observed, that infants attending swimming pool during the first year of life have higher frequency of RRI and otitis media (Nystad et al., 2003).

6.5 Positive family history on atopic diseases

Positive family history on atopic and allergic respiratory diseases is significantly associated with increased risk of recurrent wheezing in children (Chong & Neto, 2010). On the other hand, the recurrent respiratory infections do not protect these children from the development of the atopic diseases of the airways (Balemans et al., 2006; Ciprandi et al., 2006). The children of parents with atopy have higher risk of respiratory tract infections (Nystad et al., 2003).

6.6 Atopy

Non-recognised allergy could lead to the similar clinical picture as RRI or could make the airways more susceptible to the infectious agents, esp. viruses. The relation between atopy

and RRI has been evaluated in several studies, but the results were inconclusive. It was documented, that atopy is a frequent condition among the children with RRI and it is likely that atopy is a favouring factor for RRI (Dellepiante et al., 2009). Atopy affects 15-20% of children and causes chronic inflammation of the airways that can mimic recurrent of chronic upper respiratory infections. Atopy can also facilitate the adherence of pathogens to the respiratory epithelium and thus promote infections (Ballow, 2008). Allergic children have more numerous and severe respiratory infections than non-allergic children (Ciprandi et al., 2006).

7. Diagnostic approach to the child with recurrent respiratory infections

The assessment of the children with RRI is demanding: it requires close attention to the history and examination, and in the selected cases, extensive investigations. Early and accurate diagnosis is essential to ensure that optimal treatment is given and to minimize the risk of progressive or irreversible lung damage. The challenge for the physicians is to distinguish between the child with self-limiting or minor problems and the child with serious, perhaps progressive lung disease. The most common and frequent symptoms of recurrent respiratory infections is chronic cough.

Diagnostic algorithm should be aimed on the exclusion of the underlying severe illness. The diagnosis of RRI is very probable if:

- milder respiratory infection with the similar characteristics as the respiratory infections in children with normal respiratory "morbidity" (severity, duration, absence of complications, good response to the conventional symptomatic therapy and empirical antibiotic therapy),
- the absence of severe and invasive systemic infections,
- absence of failure to thrive,
- negative family history for immune disorders.

To the diagnostic algorithm of RRI belongs the investigation of the possible causes of chronic cough, such as allergy, asthma, α1-antitrypsin deficiency, primary or secondary ciliary dyskinesias, congenital anomalies, gastroesophageal reflux (GER), recurrent pulmonary aspiration of post-nasal drip syndrome (the most frequent cause of chronic cough in children) (de Martino & Ballotti, 2007). The recurrence of the infections in the same specific site should be aimed the attention to the possible congenital developmental anomalies of the respiratory tract or the presence of foreign aspirated body. Recurrent or chronic infections can be associated with anatomic defects that characteristically involve one organ system (Panigada et al., 2009). Foreign body should be considered when the infections are chronic and localized to one anatomical sire, e.g. one ear canal or one nostril. Recurrent symptoms in small children accompanied by malabsorption or nasal polyps should be re-evaluated for possible cystic fibrosis (CF), also despite negative neonatal screening. The incidence of CF is in some countries more common when compared with an incidence of PID. Therefore, the combination of above mentioned symptoms is indication to perform sweat test with the following genetic analysis. RRI can be also the sign of repeated aspiration of gastric content in GER, swallow dysfunction, under-diagnosed bronchial asthma or immotile cilia syndrome (Vaughan & Katkin, 2002). Recurrent otitis media is associated with Eustachian tube dysfunction secondary to atopy (Ghezzi et al., 2011). GER is usually associated with asthma symptoms, but sometimes can be confused with bronchitis or lead to aspiration and recurrent pneumonias. GER can be also factor involved in the

pathogenesis of recurrent otitis media and sinusitis. Children who develop recurrent pneumonia from aspiration in association with GER tend to be younger than 2 years of age. Children who have a history of nocturnal cough or wheeze with exercise or protracted coughing after upper respiratory illnesses should undergo spirometry and assessment of bronchodilator responsiveness (Panitch et al., 2005). Recurrent sino-pulmonary infections with *situs viscerum inversus* may indicate immotile cilia syndrome (primary ciliary dyskinesia, Kartagener syndrome) (Ballow, 2008; Skeik & Jabr, 2011).

The evaluation of the frequency of respiratory infections is usually less important, that the assessment of other characteristics of RRI such as:

- the course of the infections,
- alteration of the general health status,
- duration,
- accompanying fever,
- possible complications,
- response to the standard symptomatic therapy,
- response to the empiric antibiotic treatment,
- causal isolated pathogen.

The diagnostic algorithm for children with RRI contains (de Vries, 2001; Slatter & Gennery, 2008):

- ENT examination with exclusion of adenoidal hypertrophy,
- chest X-ray,
- determination of specific IgE or the performance of skin prick test with common inhalant and food allergens,
- measurement of total IgE levels in serum,
- determination of the levels of IgG, IgA and IgM in serum,
- blood cell count together with absolute count of lymphocytes, neutrophil and eosinophil granulocytes,
- bacteriological cultivation and serological tests,
- viral serological tests,
- in selected patients:
  - levels of IgG-subclasses,
  - production of specific post-vaccination antibodies against *Streptococcus pneumoniae, Haemophilus influenzae type b,* tetanus and diphtheria toxoids taken 4 weeks after vaccination of not previously exposed to vaccine antigens,
  - levels of C3 and C4 components of complement, mannose-binding lectin and functional tests of complement system (CH_{50}, AP_{50}).

8. Treatment and prevention of recurrent respiratory infections

The children with RRI represent a great challenge for the paediatricians, from both therapeutic and preventive standpoints. It is necessary to determine whether these RRI are because of host-derived factors or are the result of increased environmental exposure. Host derived factors may be non-immunological and immunological (related to host immunodeficiency.

In recent years, following the increase in the incidence of antibiotic resistance, interest in preventive treatment has intensified. Such treatment should contribute to the prevention of

RRI, thus reducing the usage and excessive consumption of antibiotics (Marseglia et al., 2007). A diagnosis of viral infection does not justify prescription of antibiotics.
Recent approach in the prevention of RRI includes the encouragement of breastfeeding, the use of intravenous or subcutaneous immunoglobulins and respiratory syncytial virus immune globulin, as well as methods of stimulating immunity, such as bacterial lysates or various nature-based products (Bellanti, 1997).

8.1 Bacterial extracts (lysates)

Since the 1970s, when using of bacteria-derived immune modulators started, several products were developed and their using becomes very popular around the world. Currently more than 8 million patients are treated with bacterial extracts every year and approximately 150 million patients have been treated since their licensing (Bousquet & Fiocchi, 2006).
Bacterial extracts are made from different bacterial species most frequent responsible for recurrent respiratory or urinary tract infections. The most often included species are: *Staphylococcus aureus, Streptococcus viridans, Streptococcus pneumoniae, Streptococcus pyogenes, Klebsiella pneumoniae, Klebsiella ozenae, Moraxella catarrhalis, Hemophilus influenzae.* Bacterial extracts are usually administered orally, although subcutaneous or intranasal forms were tested sooner (Braido et al., 2007; Matricardi et al., 2003).
Bacterial immune modulators could be divided into two-generation preparations:

1. First generation products are bacterial extracts containing killed bacteria or their lysate.
2. Second generation products contain the most immunogenic components of bacteria (e.g. ribosomes, proteoglycans).

Bacterial extracts stimulate both non-specific and specific immunity mechanisms through naturally evoked immune response. The intrusion of pathogen in the human body leads first to non-specific response and consequently to specific response for the epitopes of the pathogen. Bacteria recognition and response takes place in mucosal associated lymphoid tissue (MALT). Typically bacterial extracts are administered orally and absorbed in the intestine, triggering Payer's patches in gut associated lymphoid tissue (GALT). M-cells in Payer's patches are responsible to bacterial recognition. Toll-like receptors (TLR) and other receptors recognize components common to a range of bacteria (e.g. lipopolysaccharide, peptidoglycan, lipoteichoic acid, lipoarabinomannan, un-methylated DNA with CpG motif and bacterial lipoproteins), so-called pathogen-associated molecular patterns (PAMPs). Interactions between PAMPs and TLR result in the activation of dendritic cells, macrophages, NK cells with cytokines and chemokines production, activation of phagocytosis and early pathogens destruction. Enhanced innate immune response also stimulates adaptive immune response. Antigen-specific T and B cells are generated in the Payer's patches as well as a considerable number of lymphoblasts, mostly IgA+ precursors of the IgA producing plasmocytes. Lymphocytes and lymphoblasts maturate in mesenteric lymph node and subsequently migrate into mucosal associated lymphoid tissue in different organs. The protective effect of bacteria-derived immune modulators is particularly related to memory cells and antigen-defined induction of immunoglobulin synthesis, mostly IgA, with quick and specific immune response after future contact with the same antigen (Braido et al., 2007; Del-Rio-Navarro et al., 2006; Rozy & Chorostowska-Wynimko, 2008).
In vitro studies showed that the action of OM-85 BV is mediated, at least in part, by the activation of TLR2 and TLR4 (Alyanakian et al., 2006). Proteoglycans from cell membrane of

Klebsiella pneumoniae strain has been described as a potential TLR-2 inducer (Bellanti et al., 2003). Bacterial extracts enhance natural killer cells activity, increase production of proinflamatory cytokines, increase the expression of adhesion molecules in phagocytes, inhibit serum induced IL-12 expression in peripheral blood lymphocytes (Rozy & Chorostowska-Wynimko, 2008; Matricardi et al., 2003). Bacterial extracts up-regulated oxidative metabolism, superoxide anion and nitric oxide production (Manuel et al., 1989). Bacterial immune modulators induce maturation of dendritic cells; enhanced expression of CD83, CD86 and HLA II molecules - markers of dendritic cells maturation has been observed following bacterial extracts application. Dendritic cells might be important for preferential triggering of T_H1 response (Boccaccio et al, 2002; Zelle-Rieser et al., 2001). In newborn animals bacterial extracts increase IFN-γ and decrease IL-4 productions, which contribute to preferential development of the T_H1 immunity (Bowman & Holt, 2001).

Various clinical trials with children, both young (< 6 yrs) as well as school children, have demonstrated positive effect of bacterial extracts mostly on frequency, duration of the infection episodes and less antibiotic requirements. Recently, reduction of rate and duration of wheezing attacks and improvement of atopic dermatitis after treatment with bacterial extracts in children has been described (Brunetti et al., 2005; Razi et al., 2010). On the other hand, some studies have not demonstrated preventive effect of bacterial immunotherapy (Saracho-Weber et al., 2001; Vautel et al., 1993).

Findings from different clinical trials have been evaluated and summarized with some review and meta-analysis. However, due to heterogeneity and often the poor quality of the trials, the results should be interpreted with caution. Cochrane meta-analysis from 2008 evaluated the effect of all used immune modulators to acute respiratory tract infections in children. 34 placebo-controlled trials were included (24 with bacterial extracts). This review showed that immunostimulants reduce the incidence of acute respiratory infections in children, by 40% on average. The subgroup analysis of bacterial extracts studies produced similar results, with lower heterogeneity (Del-Rio-Navarro et al., 2006). In review performed by Braido et al. (2007) both in children and adults protective effect of bacterial extracts was found such as general reduction of infection rates, reduction of their duration, beneficial effect on symptoms, and reduction of the use of antibiotics. Bousquet & Fiocchi (2006) review demonstrated that ribosomal immunotherapy reduces number, duration, and severity of infectious episodes, reduce antibacterial use and the likelihood of consequent development of bacterial resistance. Other favorable results included a reduction in antibacterial treatments, shorter duration of recurrent episodes, reduced need for other medications, smaller number of lost school days or parent absenteeism from work, less fever, and reduced hearing loss (Bousquet & Fiocchi, 2006). In other review the effect of OM-85 BV to acute respiratory infections in children were examined. 13 included trials were of low or moderate quality. There was a trend for fewer and shorter infections and a reduction of antibiotic use in group treated by bacterial extract versus placebo, but with weak evidence (Steuer- Stey et al., 2007). Recently, other meta-analysis with OM-85 BV has been published. This meta-analysis includes 8 randomized controlled trials and shows significant decrease of recurrent respiratory tract infections frequency. The effect seems to be greater in patients at increased risk of RRI (Schaad, 2010).

Safety and tolerance of bacterial extracts in all paediatric trials were good. Adverse events occurred occasionally and were mild and transitory with rapid resolution. The majority of adverse events were gastrointestinal or cutaneous findings. Reported adverse effects included eczema, urticaria, diarrhoea, abdominal pain, headache, rhinitis, and cough. No

serious adverse events in relation with bacterial extracts treatment have been reported in the literature (Del-Rio-Navarro et al., 2006; Olivieri et al., 2009; Schaad, 2010). No casual association between bacterial extracts and autoimmunity disease has been reported in literature (Olivieri et al., 2009).

8.2 Biologically active polysaccharides (glucans)

Metabolites and components of fungi have been used in medicine for many centuries in order to exploit the properties of several of their active compounds. Many of these substances naturally contained in fungi have demonstrable effects on different components of the immune system. The most important groups of these immunomodulating substances include: polysaccharides (glucans in particular), polysaccharide peptides, polysaccharide proteins and proteins. The main mechanism is their mitogenic and activating effect on different populations of immunocompetent cells, such as hemopoietic stem cells, lymphocytes, macrophages, dendritic cells and NK cells, and subsequent production of several cytokines with complex effects. Besides typical immune system cells, glucans also have demonstrable effects on other cell populations, such as fibroblasts, keratinocytes, or other connective tissue cells. This is why many clinical and experimental studies have focused on the effects of these substances on the prevention and treatment of acute and recurring infectious diseases, congenital and acquired immune disorders, oncologic, autoimmune and allergic diseases (Lull et al., 2005; Vetvicka & Vetvickova, 2009).

Glucans are polysaccharides of natural origin, naturally appearing in fungi, plants and some bacteria. In fungi, they represent the main component of cell walls, and are composed of glucose molecules bound with two types of bonds: β-(1→3) in the main linear chain and β-(1→6), which binds side chains of variable length to the main polysaccharide chain. Immunomodulating effects of various extracts from fungi have been known for a long time, but recently, the attention has been focused mainly on glucans, which occur in nature as a typical structural element of fungal cell walls. They represent a large group of natural substances with immunomodulating effects, and the structure and mechanism of action of many of them have been described in detail. Particular glucans differ in the intensity of their immunostimulating/immunomodulating effect. Imunoglucan – pleuran (*Pleurotus ostreatus*, Oyster mushroom), Schizophyllan (*Schizophyllum commune*, Split gill) and Lentinan (*Lentinus edodes*, Shiitake mushroom) are considered the most effective ones (Lull et al., 2005).

There are several possible mechanisms of action of glucans on the immune system. The activation of human immune system is enhanced through a system of receptors that are able to recognize the so called molecular patterns of microorganism pathogenicity (PAMPs, *pathogen-associated molecular patterns*). Receptors able to identify these PAMPs include mostly those that are involved in recognizing extracellular pathogens – Toll-like receptors and C-type lectin receptors. On the other hand, the activation of these receptors triggers a cascade of inflammatory response associated with subsequent release of many cytokines, chemokines and other soluble factors that lead to the activation of several populations of immunocompetent cells of both specific and non-specific part of the immune system, and the development of antigen-specific immunity (Vetvicka & Vetvickova, 2009). The ability of glucans to activate various components of the immune system and thus modulate the immune response depends on the length of their chain, level of branching, as well as on their tertiary structure (Bohn & Bemiller, 1995). The ability of glucans to modulate the immune response has many potential applications in both clinical and experimental medicine in order to provide an effective defence against negative influences from both

external (e.g. microorganisms) and internal environment (e.g. tumour or damaged cells). Many studies focused on the effects of parenterally administered glucans, although the research has confirmed that they are also active and effective when administered orally (Hong et al., 2004). Among all the glucan receptors (dectin-1, Toll-like receptors, complement receptor 3, so called scavenger receptors, lactosylceramide, etc.), the most important is dectin-1, which is a primary receptor for glucans at least on the surface of leukocytes and plays an essential role in immunomodulation mediated through glucans (Brown & Gordon, 2003; Chen & Seviour, 2007). Whether particular glucans show immunostimulating or immunosuppressive effects in different phases of the immune response depends on the dosage, method of application, frequency of administration, as well as on the overall state of the organism' immune system.

Glucans act on the immune system on many levels. Among all the known mechanisms, the following should be highlighted in particular (Chen & Seviour, 2007; Kodama et al., 2002; Lehne et al., 2006; Lesourd, 1997; Wasser, 2002):

- ↑ metabolic and functional activity of immunocompetent cells (specific and non-specific immunity),
- ↑ proliferation and differentiation of both T and B lymphocytes,
- ↑ content of secretory IgA antibodies in saliva, thus increasing local defence of mucous membranes,
- ↑ phagocytosis → ↑ effectiveness of immune response to both endogenous and exogenous stimulus,
- ↑ bactericidal activity of monocytes and neutrophils,
- they activate complement cascade through both classic and alternative pathways with subsequent formation of many compounds with direct or indirect immunomodulating effect,
- stimulating effect on NK cells → ↑ defence against intracellular viral, bacterial and parasitic infections,
- ↑ phenotypic and functional maturation of dendritic cells (DC), they potentiate the stimulating effect of DC on the proliferation of T lymphocytes and increase the expression of several differentiating marks on the surface of DC (e.g. MHC I, MHC II, CD-86, CD-80, etc.) → more effective presentation of foreign antigens,
- ↑ release and activity of many enzymes (such as lysozyme, elastase, collagenase, nitric oxide synthase), complement components, cytokines (IL-1β, IL-10, IL-12, IL-18, TNF-α, IFN-γ, GM-CSF), other signal molecules (nitric oxide and other nitro-compounds) → proliferation of immunocompetent cells, their migration, ↑ bactericidal and cytocidal effect,
- they have a regulatory effect on the differentiation of T_H1/T_H2 lymphocytes → ↑ Th1 immune response → ↑ IL-10, IL-2, IL-18 → reduction of the symptoms of allergic diseases and prevention of the development of atopy,
- ↑ T_H1 cytokine response with simultaneous suppression of Th2 response → potential use in diseases and states associated with Th1 response insufficiency (e.g. type II diabetes mellitus, ageing), as well as in diseases with inadequate stimulation of T_H2 response (e.g. allergic diseases).

One of the most important indications of glucans application in children are recurring infections of upper and lower respiratory tract, primary and secondary immunodeficiencies of different etiology, as well as repeated administration of antibiotics. Semberova et al. (2009) observed a significant decrease in the volume of adenoid vegetation in children after 40-days treatment using a product containing glucan.

The effect of imunoglucan (Imunoglukan P4H® syrup) on the course and frequency of recurrent infections of upper respiratory tract has shown also multi-centric study. A positive response to the treatment, i.e. ≥50% reduction of the frequency of recurrent respiratory infections, was observed in 153 children (71.2%). The average annual incidence of respiratory infections in children with a positive response to the syrup was 3.6 and was significantly lower compared to that in unresponsive patients (3.6 vs. 8.9, $p<0.001$). The therapy did not show statistically significant effect on the frequency of febrile episodes, need for antibiotics or duration of infection. No adverse effects of Imunoglukan P4H® were reported, with the therapy being very well tolerated. This study proved the therapeutic and preventive effects of biologically active polysaccharides on the frequency of recurrent respiratory infections in children (Jesenak et al., 2010).

8.3 Systemic enzyme therapy

A therapeutic method consisting of a systemic peroral administration of special combined mixtures of enzymes has been gradually developed since the middle of the 20th century. This method was named systemic enzyme therapy (SET). Initially, SET was applied only empirically. Currently, there are a number of relevant data about a biological availability of active substances, their complex activities as well about their favourable clinical effects in many inflammatory diseases (Honzikova et al., 2004). Originally, an empirical treatment of mainly inflammatory diseases due to the many controlled clinical studies was changed to a method which optimizes and modulates several immune functions disrupted in many pathological states. SET is predestinate to using in many indications by their targeted intervention into regulatory and biochemical pathways. The basic pharmacological effects of SET include anti-oedematous, fibrinolytic, anti-inflammatory and immunomodulatory activities (Biziulevicius, 1998; Kleine, 1998). Enzymes bind to the blood antiproteases after resorption through the mucosa of gastrointestinal tract and then they are distributed to sites of inflammation where they modulate and restore the imbalance in immune responses. They are involved in the activation as non-specific as specific immunity mechanisms (Biziulevicius, 1998; Desser et al., 2001; Douwe, 2005; Manhart et al., 2002; Targoni et al., 1999; Zavadova et al., 1995; Zavadova & Desser, 1997). Enzyme therapy can change the expression of adhesion molecules and receptors on the surface of T lymphocytes, reduce the activation of many populations of immunocompetent cells and they increase the activation threshold of autoaggressive T-lymphocytes in the mechanism of specific immunity (Biziulevicius, 1998; Desser et al., 2001; Douwe, 2005; Lauer et al., 2001; Manhart et al., 2002; Targoni et al., 1999; Zavadova et al., 1995; Zavadova & Desser, 1997). Generally, we can say that SET is involved in the regulation of both acute and chronic inflammatory processes, as well as in the activation of individual components of the immune system.

Many respiratory disease of infectious or allergic etiology became an important indication for the using of SET. SET has only additional importance in the case of allergic diseases and it normalizes disrupted functions of immune system. SET appears to be a good adjuvant treatment of atopic dermatitis and asthma. SET reduces the number of febrile states, helps to reach a compensation of disease and reduces the dose of inhaled corticosteroids in asthmatic patients. Many studies have demonstrated the effect of SET in recurrent respiratory infections. The Czech post-multicenter study compared the effect of SET (preparation Wobenzym ®) and the bacterial immunomodulators (BIM) on the course and recurrence of respiratory infections in a cohort of 468 children aged 3-18 years. In both groups, there was a statistically significant decrease in the average number of respiratory tract inflammation

(by 59% in SET and 32% for BIM) and the average number of related antibiotic treatments (68% in SET and 35% for BIM). The positive results achieved by the administration of SET can be explained by favourable immunomodulatory effects of these preparations (Honzikova et al., 2004). Similar effects were also observed other authors (Helms and Miller, 2006; Lanchava et al., 2005; Zavadova et al., 1995). Interesting finding was also the observed improvement in spirometric lung function indices following the application of SET in children with recurrent obstructive bronchitis (Lanchava et al., 2005). SET administration is also effective in the treatment of acute or chronic sinusitis, tonsillitis, acute and recurrent laryngitis and chronic secretory otitis media (Vegh & Vegh, 2009). In patients with elevated IgE, the application of SET can result in the decline or even normalization of their levels.

8.4 Isoprinosine

Isoprinosine (inosiplex, inosine pranobex) is a synthetic immunomodulating agent with pluripotent effects on the immune system. It possesses T-lymphocyte and phagocyte function enhancing immuno-modulating effect similar to those of another synthetic drug, levamisole. Isoprinosine was developed as an anti-viral agent, but in reality, the action of Isoprinosine in viral infections has been attributed to immunomodulatory rather than direct anti-viral effects. *In vitro*, Isoprinosine enhances T-lymphocyte function, stimulates NK cell activity, macrophages and neutrophils. It increases IL-1, IL-2 and interferon gamma production and up-regulates interleukin-2 receptor expression. The data on the effect of this agent on the frequency a re-occurrence of RRI are conflicting. The study of Litzman et al. (1999) does not support the continued use of Isoprinosine in the prevention of RRI in children with normal immune systems. The use of Isoprinosine in the patients with mild but clearly defined immunodeficiencies is probably effective (Litzman et al., 1999).

8.5 Transfer factors

Transfer factors (TFs) present a complex of low-molecular biologically active substances with possible effect of normalization of the disturbances in humoral and cellular immunity. Transfer factors are small proteins that "transfer" the ability to express cell-mediated immunity from immune donors to non-immune recipients. We developed a process for purifying specific transfer factors to apparent homogeneity. This allowed us to separate individual transfer factors from mixtures containing several transfer factors and to demonstrate the antigen-specificity of transfer factors (Kirkpatrick, 2000). The treatment with TFs is an active immunotherapy, which is based on the application of the substance with the capacity to influence the reactivity of the organism to different immunogenic impulses. TFs act as an antigen-dependent, antigen-specific micromolecular polypeptide cytokine. There are two possible sources of TFs: the extract from the peripheral bovine or human leucocytes. The mechanism of TFs action consists from the influence of both specific and non-specific immunity (Barnet et al., 1996; Bystron et al., 1996).

Several studies have demonstrated the effect of TFs in the treatment and prevention of recurrent respiratory or urinary infections in children and also in adults (Anttila et al., 1977; Grohn, 1977; Jose & Ford, 1976). TFs can be used also in the prevention of recurrent herpetic infections, in different secondary immunodeficiencies (especially of cellular immunity) or as a complementary therapy of psoriasis vulgaris, atopic eczema, sepsis or chronic fatigue syndrome. It is also possible to apply Tfs in the cases without confirmed immunodeficiency (Jones et al., 1981; Meduri et al., 1996; Pizza et al., 1996).

8.6 Thymus hormones

On the market there are available preparations containing extract of thymus from different animals. These products are generally recommended as a dietary supplement to restore and strengthen the immune system. They are polypeptide complexes: peptides and signalling factors designed to optimize intercellular communication between cells of the immune system and for maturation, proliferation and activation of T-lymphocytes. Extracts of thymus contain complex mixture of peptides with a stimulating effect on T-lymphocytes and they are called thymus hormones. They have immuno-normalizing effect, so do not affect normal immune function, but reduced functions return to the normal state. Among the indications of using of these products are included acute, chronic and recurrent respiratory infections. They are non-toxic, with minimum side effects. This preparations are contraindicated for pregnant and breastfeeding women and patients taking immunosuppressants. Nowadays their production is stopped and it is tested the production of synthetic analogs (Ambrogi et al., 1983; de Mattia et al., 1993; Longo et al., 1988).

8.7 Vitamins and minerals

Vitamins and minerals are necessary for normal immune system function. Low levels of vitamins and minerals, caused mainly by malnutrition, lead - besides other complications - to increase of infection rate. It is questionable if prophylactic treatments in "healthy" subjects can influence frequency and duration of respiratory tract infections.

Numerous studies have evaluated effect of vitamin C supplementation to prevention of respiratory tract infections with various results. Preventive treatment with vitamin C reduced cold duration and severity of symptoms (Douglas et al., 2004).

Several trials and meta-analysis have examined prophylactic use of zinc for respiratory tract infections with mixed results (Aggarwal et al., 2007; Mathew, 2010). In some children studies decrease incidence of upper or lower respiratory infections has been observed (McElroy & Miller, 2002; Roth et al., 2008).

Also clinical trials examining effect of routine vitamin A supplementation to prevention and treatment of respiratory infections have yielded contradictory results; no significant effect in children has been observed (Roth et al., 2008).

8.8 Prebiotics, probiotics & nucleotides

Breastfeeding is associated with a significant decrease incidence of respiratory infections. Breast milk contains variety of substance with antimicrobial, anti-inflammatory and immunomodulatory activity. High concentration of oligosaccharides in breast milk induces accurate colonization of infant neonatal tract, predominantly with *Bifidobacteria* and *Lactobacili.* Healthy gut flora protect against infection via a number of mechanisms including competitive inhibition of epithelial binding by enteropathogenic bacteria and effects on tight junctions. Accurate colonization plays also important role in the development of mucosal and systemic immune system, and tolerance to non-pathogenic antigens (Jones et al., 2010).

Nonhuman milk oligosaccharides - prebiotics, such as small-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides are used to substitute these functions in formula-fed infants. Supplementation with neutral oligosaccharides leads to optimalized colonization like in breast-feeding infants, but the clinical outcomes are not conclusive yet. Reduced incidence of atopic diseases has been described (Arslanoglu et al., 2008; Moro et al. 2006). Some studies confirmed positive effect of oligosaccharides supplementations in infant formula to incidence of respiratory infections (Arslanoglu et al., 2007).

Breast milk is also rich in nucleotides with immunomodulatory activity. Beneficial effect of nucleotides supplementations in formula-fed infants on various components of the immune system has been reported. Nucleotides added to infant formula augment infantile NK-cell activity and humoral response and my have limited protection against diarrhoea (Jones et al. 2007, Pickering et. al, 1998).

Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (FAO/WHO). The most common bacteria in this group include *Bifidobacteria* and *Lactobacili*. Use of probiotics early in life could favour correct maturation of the immune system, and reduce development of allergy. Effects of probiotics include competitive inhibition with pathogenic bacteria, immunomodulation of local immunity (maintains gut wall integrity) and systemic immunity (enhances non-specific and specific response) (Singh & Das, 2010). The most documented efficacy of probiotics is in the treatment and prevention of infectious and antibiotic-associated diarrhoea. Probiotics are generally regarded as safe, but caution must be given in immunocompromised patients. Only a limited number of trials have evaluated the potential effect of probiotics in reducing the risk respiratory tract infections with inconsistent results. Studies differed in the probiotic strains evaluated, indications for use, dosing or study design. Review of 14 performed trials showed, that probiotics may have a beneficial effect on the severity and duration of symptoms, but do not appear to reduce the incidence of RRI (Vouloumanou et al., 2009).

8.9 *Echinacea* extracts

Non-prescriptional natural therapeutics are used widely and their popularity continue to increase, including children's treatment. Usually these products are well tolerated and believed to be safe, but the true safety is often unknown. Usually there are limited data about efficacy, mechanism of action, active components, and potential drugs – herbal interactions. Well-controlled trials with reliable data about different products are often missing.

Echinacea extracts are one of the most frequent used herbal preparations, especially in North America. Traditionally these herbs were used by indigenous peoples for the treatment of many illnesses (colds and other respiratory diseases, wound healing, candidiasis). Nowadays *Echinacea* extracts are predominantly used for treating and preventing respiratory tract infections, mainly common cold and influenza.

The photochemical composition of *Echinacea* preparations may differ widely both between and within species. *Echinacea* products contain variable amounts of ingredients with pharmacological activity, such as polysaccharides, flavorous, chicory acid glycosides, essential oils, oxyacetylene and alkyl amides (Gunning, 1999). The biological activities of *Echinacea* appear to be the result of a combined action of its components rather that of one single group.

Several studies have shown *in vitro* and *in vivo* effects on immunological parameters, but until now the clear immunomodulatory mechanism has not been identified. *Echinacea* appears to affect mainly non-specific immune response. Macrophage activation, enhanced neutrophil phagocytosis and cytokine expression has been reported (Melchart et al., 1995; Synching et al., 2006). Stimulation of the cannabin receptor (CB2) by alamedas present in *Echinacea* could also play a role in immunomodulatory activity (Rudner et al., 2006). Bactericidal effect against some of the bacteria (*Streptococcus pyogenes, Homophiles influenzae, Legion Ella pneumophilla*) and direct antiviral effects have been also described (Fusco et al., 2010; Sharma et al., 2010).

Many clinical trials with different *Echinacea* preparations have been conducted with variable results on reduction, duration and severity of symptoms associated with respiratory infection. Majority of studies have been performed in adults for assessment the effect of *Echinacea* extracts in the treatment of acute infection, mainly common cold. Some studies have reported decrease frequency, duration and severity of respiratory tract infection, but some did not find any positive effect of *Echinacea* treatment (Barrett et al., 2010; Goel et al., 2004; Melchart et al., 1998; O´Neil et al., 2008; Sperber et al., 2004). In children's study was found no effect on duration of illness or severity of symptoms. Treatment with *Echinacea* was associated with increased risk of rash compared with placebo group (Taylor et al., 2003). In other study treatment with extract of *Echinacea*, vitamin C and propolis reduced significantly number and duration of illness episodes in children when compared with placebo treated group (Cohen et al., 2004). Several meta-analysis were performed with great heterogeneity of trials and results suggest that *Echinacea* extracts might have beneficial effect in the early treatment of common colds, but the there was insufficient evidence to suggest an effect on prevention (Gilles et al., 2000; Linde et al., 2006; Shah et al., 2007). On the other hand, in other meta-analysis *Echinacea* extracts were effective in prevention of the common cold after clinical inoculation (Schoop et al., 2006).
Echinacea products apart from allergic reactions and increased incidence of rash are reported to be generally safe (Mullins, 1998; Mullins & Heddle, 2002). *Echinacea* preparation should not be used by patients with allergy to other members of the Asteraceae family due to possible cross-reactivity. *Echinacea* extracts should be avoided by patients with progressive immune diseases, on treatment with corticosteroids and immunosuppressants. *Echinacea* should not be taken orally for more than 8 weeks because of the potential for decreased immune response after a long-term application (Gunning, 1999).

8.10 Ginseng

Ginseng is composed of a number of different species, which belong to the same plant family, the Araliaceae. Korean, Japanese and American ginseng belong to the genus Panax, whereas Siberian ginseng is of the genus Eleutherococcus (Vohra et al., 2008). Polysaccharide and oligosaccharide fractions are responsible for the immunomodulating effects of North American ginseng (Panax quinquefolium L., Fam. Araliaceae), glykosides called eleutherosides for effects of Siberian ginseng (Mc Elhaney et al., 2004; Roxas et al., 2007).
Ginseng products *in vitro* induce the production of INF-γ, TNF-α, IL-1, IL-2, IL-6, stimulate natural killer cell activity, increase phagocytosis. B-cell proliferation in the spleen with increased circulating immunoglobulin G levels has also been demonstrated (Jie et al., 1984; Kim et al., 1990; Wang et al., 2001). Subjects who took extract of Siberian ginseng for one months have had a significant increase in total lymphocyte, T helper, T suppressor, natural killer and B lymphocyte cells counts compared to placebo. *In vitro* liquid extract of the Siberian ginseng root inhibits replication of RNA viruses (Glatthaar-Saalmuller et al., 2001). Extracts appear to have cytotoxic effects on a wide range of tumour cell lines.
Clinical studies performed mainly in adults showed variable results (Mc Elhaney et al., 2004; Preddy et al., 2005). In the reviews of 5 trials with North American ginseng there was insufficient evidence to conclude that ginseng reduces the incidence or severity of common colds. It appears to be effective in shortening the duration of cold or acute respiratory infections (Seida et al., 2009). In one trial with Siberian Ginseng decrease frequency of respiratory infections in children was observed (Vohra et al., 2008).

8.11 Astralagus

Astralagus membranaceus is rich in polysaccharides, flavonoids, multiple trace minerals and amino acids, all of them contribute to Astragalus's complex immunomodulatory properties. Astralagus demonstrated activation and proliferation of immune cells, particularly $CD8^+$ and $CD4^+$ T lymphocytes compared to placebo. In one trial with small number of children treatment with Astralagus extract reduced incidence of respiratory tract infections (Roxas & Jurenka, 2007).

8.12 Viscum album

Viscum album extracts were shown to have immunomodulatory functions, especially on NK cell functions (Braedel-Ruoff, 2010). *Viscum album* is widely used in complementary medicine for the treatment of cancer. The effects on frequency of recurrent respiratory infections were examined in one trial in children living in areas exposed to the radioactive fallout from Chernobyl. Preparations were effective in reducing frequency of infections and reducing clinical symptoms (Chernyshov et al., 2000).

8.13 Propolis

Propolis, the bee's product, has highly variable composition, depending on geographic location, plant species and the season of collection. Biological activity is mainly due to flavonoids, terpens, caffeic, ferulis and cumaric acids and esters. Anti-microbial and anti-inflammatory properties of propolis documented in some *in vitro* studies may be useful for prevention of upper respiratory tract infections (de Vecchi & Drago, 2007). In children with recurrent acute otitis media suspension of propolis and zinc significantly reduce the risk of new acute otitis media episodes (Marchisio et al., 2010). Because of pollen containing in propolis suspension there is a risk of allergic reactions and sensitisation and preventive treatment with propolis should not be recommended in general for children.

8.14 Other natural products

Different natural products declare to have immunomodulating properties or be assigned to treatment and prevention of acute respiratory disease (e.g. elderberry, garlic, larch arabinogalactans - polysaccharides from *Larix occidentalis*, olive leaf extracts, tea tree oil, colostrum). Until now insufficient number of trials with these preparations have been done, frequently only *in vitro* studies, or with small number of participants (rarely with children) and questionable quality, so it is difficult to make any conclusions regarding use of these preparations in prevention of acute respiratory tract infections.

9. Follow-up and education

When a diagnosis of RRI has been formulated, parents or care-givers should be reassured about the benign and transient nature of this condition. Accurate environmental prophylaxis and regimen changes are crucial. When RRI diagnosis has been formulated, removal of environmental risk factors (e.g. precocious day-care attendance, reducing the smoking in the household) must first be suggested. In some cases, the postponed enrolment of children at day-care centres could be the solution for the prevention and decrease number of RRI. Optimal day-care centres enrol only a limited number of children, have large clean rooms with a good ventilation to guarantee the removal of the air suspended microbial agents and are located in modern buildings in areas with less air pollution (de Martino & Ballotti, 2007;

Uhari et al., 1999). Prophylactic antibiotic treatment is neither indicated nor useful, even could interfere with normal development of the mucosal microflora and immune system functions. In the selected children, adenoidectomy and tonsillectomy should be recommended according to the validated guidelines (Frohna, 2005). Children with RRI are "immunologically normal" and therefore intensive impacts into the developing immune system can be harmful and contra-productive.

10. Conclusion

Respiratory diseases belong to the most frequent and common disorders in clinical praxis of every paediatrician. Recurrent viral infections are part of the growing up process of any child. Especially in children we can observe some which suffer from recurrent upper or lower respiratory tract infections. In general, a thriving child with recurrent respiratory infections does not suffer from a serious underlying disease. Most of the children do not have an immunodeficiency, but if they do, this often concerns an antibody deficiency. It there positive history for immunodeficiency, detailed immunological investigation is mandatory. In other children, immunological examination should be performed after the exclusion of other, more frequent causes of RRI such as gastroesophageal reflux, allergy or ENT focal infection (adenoidal hypertrophy). Treatment and prevention of these infections has its own rules and should consist of early, aimed antibiotic therapy acute attacks of infection, long and appropriate reconvalescence, elimination of all possible focuses and origins of infection and complete examination of the child's immunostatus. There are several possibilities of immunomodulating therapy. Many clinical and experimental trials have confirmed their efficacy and pharmacological safety. The prescription and application of each immunomodulation agent should be performed in correct manner only in indicated cases with individual approach to each child taking into account all the rules of immunomodulation therapy.

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12. References

Adams, E.L., Rice, P.J., Graves, B., Ensley, H.E., Yu, H., Brown, G.D., Gordon, S., Monteiro, M.A., Papp-Szabo, E., Lowman, D.W., Power, T.D., Wempe, M.F., & Williams. D.L. (2008). Differential high affinity interaction of Dectin-1 with natural or synthetic glucans is dependent upon primary structure and is influenced by polymer chain length and side chain branching. *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 325, No. 1, (April 2008), pp. 115-123.

Aggarwal, R., Sentz, J., & Miller, M.A. (2007). Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. *Pediatrics,* Vol. 119, No. 6, (June, 2007), pp. 1120-1130.

Akramiene, D., Kondrotas, A., Didziapetriene, J., & Kevelaitis, E. (2007). Effects of β-glucans on the immune system. *Medicina (Kaunas)*, Vol. 43, No. 8, pp. 597-606.

Alyanakian, M.A., Grela, F., Aumeunier, A., Chiavaroli, C., Gouarin, C., Bardel, E., Normier, G., Chatenoud, L., Thieblemont, N., & Bach, J.F. (2006). Transforming growth factor-{beta} and natural killer T-cells are involved in the protective effect of a bacterial extract on type 1 diabetes. *Diabetes,* Vol. 55, No. 1, (January, 2006), pp. 179–185.

Ambrogi, F., Petrini, M., Caracciolo, F., Azzara, A., & Carulli, G. (1983). Effect of thymostimulin on human lymphocytes adenosine deaminase and purine nucleotide phosphorylase activities: physiological and therapeutic effects. *Advances in Experimental Medicine and Biology*, Vol. 166, pp. 101-104.

Antilla, R., Grohn, P., & Krohn, K. (1977). Transfer factor and cellular response in urinary infections in children. *Acta Paediatrics Scandinavica*, Vol. 66, No. 2, (March 1977), pp. 219-224.

Arden, K.E., McErlean, P., Nissen, M.D., Sloots, T.P., & Mackay, I.M. (2006). Frequent detection of human rhinoviruses, paramyxoviruses, coronaviruses and bocavirus during acute respiratory tract infections. *Journal of Medical Virology*, Vol. 78, No. 9, (September 2006), pp. 1232-1240.

Arrieta, A., & Singh, J. (2004). Management of recurrent and persistent acute otitis media: new option with familiar antibiotics. *Pediatric Infectious Diseases Journal*, Vol. 23, Suppl. 2, (February 2004), pp. 115-124.

Arslanoglu, S., Moro, G.E., & Boehm, G. (2007). Early supplementation of prebiotic oligosaccharides protects formula fed infants against infections during the first 6 months of life. *The Journal of Nutrition,* Vol.137, No. 11, (November 2007), pp. 2420-2424.

Arslanoglu, S., Moro, G.E., Schmitt, J., Tandoi, L., Rizzardi, S., & Boehm, G. (2008). Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *The Journal of Nutrition*, Vol. 138, No. 6, (June 2008), pp. 1091-1095.

Atkinson, A.P. M., Cedzynski, M., Szemraj, J., Swierzko, A. St., Bak-Romaniszyn, L., Banasik, M., Zeman, K., Matsushita, M., Turner, M.L., & Kilpatrick, D.C. (2004). L-ficolin in children with recurrent respiratory infections. *Clinical and Experimental Immunology*, Vol. 138, No. 3, (December 2004), pp. 517-520.

Balemans, W.A., Rovers, M.M., Schildern, A.G., Sanders, E.A., Kimpen, J.L., Zielhuis, G.A., & Ent, C.K. (2006). Recurrent childhood upper respiratory tract infections do not reduce the risk of adult atopic disease. *Clinical & Experimental Allergy*, Vol. 36, No. 2, (February 2006), pp. 198-203.

Ballow, M. (2008). Approach to the patient with recurrent infections. *Clinical Review in Allergy and Immunology*, Vol. 34, No. 2, (April 2008), pp. 129-140.

Barnet, K., Vacek, A., Cech, K., & Pekarek, J. (1996). The effect of DLE-fractions on GM-progenitors on haemopoetic stem cells in vitro. *Biotherapy*, Vol. 9, No. 1-3, pp. 171-174.

Barrett, B., Brown, R., Rakel, D., Mundt, M., Bone, K., Phyto, D., Barlow, S., & Ewers, T. (2010). Echinacea for Treating the Common Cold. A Randomized Trial. *Annals of International Medicine,* Vol. 153, No. 12, (December, 2010), pp. 769-777.

Bellanti, J., Olivieri, D., & Serrano E. (2003). Ribosomal immunostimulation: assessment of studies evaluating its clinical relevance in the prevention of upper and lower respiratory tract infections in children and adults. *BioDrugs,* Vol. 17, No. 5, pp. 355–367.

Bellanti, J.A. (1997). Recurrent respiratory tract infection in paediatric patients. *Drugs*, Vol. 54, Suppl. 1., pp. 1-4.

Bergendiova, K., Tibenska, E., & Majtan, J. (2011). Pleuran (β-glucan from *Pleurotonus ostreatus*) supplementation, cellular response and respiratory tract infections in athletes. *European Journal of Applied Physiology*,

Bhave, S.Y. (2001). Approach to recurrent respiratory infections. *Indian Journal of Pediatrics*, Vol. 68, Suppl. 2, (April 2001), pp. 26-32.

Biziulevicius, G.A. (2006). Where do the immunostimulatory effects of oral proteolytic enzymes (‚systemic enzyme therapy') come from? Microbial proteolysis as a possible starting point. *Medical Hypotheses*, Vol. 67, No. 6, (July 2006), pp. 1386-1388.

Bloomberg, G.R. (2011). The influence of environment, as represented by diet and air pollution, upon incidence and prevalence of wheezing illnesses in young children. *Current Opinion in Allergy and Clinical Immunology,* Vol. 11, No. 2, (April 2011), pp. 144-149.

Boccaccio, C., Jacod, S., Kaiser, A., Boyer, A., Abastado, J.P., & Nardin, A. (2002). Identification of a clinical-grade maturation factor for dendritic cells. *Journal of Immunotherapy,* Vol. 25, No. 1, (January-February 2002), pp. 88-96.

Bohn, J.A., & BeMiller, J.N. (1995). (1 → 3)-beta-D-glucans as biological response modifiers: a review of structure-functional activity relationships. *Carbohydrate Polymers*, Vol. 28, pp. 3-14.

Bossuyt, X., Moens, L., Van Hoeyveld, E., Jeurissen, A., Bogaert, G., Sauer, K., Proesmans, M., Raes, M., & De Boeck, K. (2007). Coexistence of (partial) immune defects and risk of recurrent respiratory infections. *Clinical Chemistry*, Vol. 53, No. 1, (January 2007), pp. 124-130.

Bousquet, J., & Fiocchi, A. (2006). Prevention of recurrent respiratory tract infections in children using a ribosomal immunotherapeutic agent. A clinical review. *Pediatric Drugs*, Vol. 8, No. 4, (December 2006), pp. 235-243.

Bowman, L.M., & Holt, P.G. (2001). Selective enhancement of systemic Th1 immunity in immunologically immature rats with an orally administered bacterial extract. *Infection and Immun*ity, Vol. 69, No. 6, (Jun 2001), pp. 3719–3727.

Braedel-Ruoff, S. (2010). Immunomodulatory effects of Viscum album extracts on natural killer cells: review of clinical trials. *Forsch Komplementmedicine,* Vol. 17, No. 2, (April, 2010), pp. 63-73.

Braido, F., Tarantini, F., Ghiglione, V., Meliolli, G., & Canonica, G.W. (2007). Bacterial lysate in the prevention of acute exacerbation of COPD and in respiratory recurrent infections. *International Journal of Chronic Obstructive Pulmonary Disease,* Vol. 2, No. 3, (September 2007), pp. 335–345.

Brown, G.D. (2006). Dectin-1: a signalling non-TLR pattern-recognition receptor. *Nature Reviews Immunology,* Vol. 6, No. 1, (January 2006), pp. 33-43.

Brown, G.D., & Gordon, S. (2003). Fungal beta-glucans and mammalian immunity. *Immunity*, Vol. 19, No. 3, (September 2003), pp. 311-315.

Brown, G.D., & Gordon, S. (2005). Immune recognition of fungal β-glucans. *Cellular Microbiology*, Vol. 7, No. 4, (April 2005), pp. 471-479.

Brunetti, L., Francavilla, R., Tesse, R., Fiermonte, P., Dambra, P., Massagli, M., Loria, M.P., & Armenio, L. (2005). Effects of oral bacterial immunotherapy in children with atopic eczema/dermatitis syndrome: A pilot study. *BioDrugs*, Vol. 19, No. 6, (2005), pp. 393-399.

Bystron, J., Cech, K., Pekarek, J., & Jilkova, J. (1996). Effect of anti-herpes specific transfer factor. *Biotherapy*, Vol. 9, pp. 73-75.

Celedon, J.C., Litonjua, A.A., Weiss, S.T., & Gold, D.R. (1999). Day care attendance in the first year of life and illness of the upper and lower respiratory tract in children with a familial history of atopy. *Pediatrics*, Vol. 104, No. 3, (September 1999), pp. 495-500.

Champi, C. (2002). Primary immunodeficiency disorders in children: prompt diagnosis can lead to lifesaving treatment. *Journal of Pediatrics Health Care*, Vol. 16, No. 1, (January-February 2002), pp. 16-21.

Chauhan, A.J., & Johnston, S.L. (2003). Air pollution and infection in respiratory illness. *British Medical Bulletin,* Vol. 68, No. 1, (December 2003), pp. 95-112.

Chen, J., & Seviour, R. (2007). Medicinal importance of fungal beta-(1 → 3), (1 → 6)-glucans. *Mycological Research*, Vol. 111, No. 6, (June 2007), pp. 635-652.

Chernyshov, V.P., Heusser, P., Omelcheno, L.I., Chernyshova, L.I., Vodyanik, M.A., Vykhovanets, E.V., Galazyuk, L.V., Pochinok, T.V., Gaiday, N.V., Gumenyuk, M.E., Chong Neto, H.J., Rossario, N., Solé, D. & Mallol, J. (2010). Associated factors for recurrent wheezing in infancy. *Allergy*, Vol. 65, No. 3, (March 2010), pp. 406-407.

Ciprandi, G., Tosca, M.A., & Fasce, L. (2006). Allergic children have more numerous and severe respiratory infections than non-allergic children. *Pediatric Allergy and Immunology*, Vol. 17, No. 5, (August 2006), pp. 389-391.

Cohen, H.A., Varsano, I., Kahan, E., Sarrell, E.M., & Uziel, Y. (2004). Effectiveness of an herbal preparation containing echinacea, propolis, and vitamin C in preventing respiratory tract infections in children: a randomized, double-blind, placebo-controlled multi-center study. *Archives of Pediatrics and Adolescent Medicine,* Vol. 158, No. 3, (March, 2004), pp 217-221.

Colley, J.R. (1975). Air pollution and respiratory disease in children and young adults. *Community Health (Bristol)*, Vol. 7, No. 1, (July-August 1975), pp. 28-31.

Cookson, W.O.C.M., & Moffatt, M.F. (1997). Asthma: an epidemic in the absence of infections? *Science*, Vol. 275, No. 5296, (January 1997), pp. 41-42.

Couriel, J. (2002). Assessment of the child with recurrent chest infections. *British Medical Bulletin*, Vol. 61, No. 1, (March 2002), pp. 115-132.

Day, N., Tangisinmankong, N., Ochs, H., Rucker, R., Picard, C., Casanova, J.L., Haraguchi, S., & Good, R. (2004). Interleukin receptor-associated kinase (IRAK-4) deficiency associated with bacterial infections and failure to sustain antibody response. *Journal of Pediatrics*, Vol. 144, No. 4, (April 2004), pp. 524-526.

de Martino, M., & Balloti, S. (2007). The child with recurrent respiratory infections: normal or not? *Pediatric Allergy and Immunology*, Vol. 18, Suppl. 18, (November 2007), pp. 13-18, ISSN 0905-6157.

de Martino, M., Galli, L., & Vierucci, A. (1989). The child with recurrent respiratory infections. In: *Pathogenesis and Control of Viral Infections,* Aiuti F., eds., pp. 225-231, Raven Press, ISBN-13: 9780881675085, New York.

de Martino, M., Rossi, M.E., Muccioli, A.T., & Vierucci, A. (1984). T lymphocytes in children with recurrent respiratory infections: effect of the use of thymostimulin on the alterations of T-cell subsets. *International Journal of Tissue Reactions*, Vol. 6, No. 3, pp. 223-228.

de Mattia, D., Decandia, P., Ferrante, P., Pace, D., Martire, B., Ciccarelli, M., Caradonna, L., Ribaud, M.R., Jirillo, E., & Schettini, F. (1993). Effectiveness of thymostimulin and study of lymphocyte-dependent antibacterial activity in children with recurrent respiratory infections. *Immunopharmacology and Immunotoxicology*, Vol. 15, No. 4, (August 1993), pp. 447-459.

de Vecchi, E., & Drago, L. (2007). Propolis antimicrobial activity: what's new? *Le infezioni in Medicina,* Vol. 15, No. 1, (March, 2007), pp.7-15.

de Vries, E. (2001). Immunological investigations in children with recurrent respiratory infections. *Paediatric Respiratory Reviews*, Vol. 2, No. 1, (March 2001), pp. 32-36.

Dellepiane, R.M., Pavesi, P., Patria, M.F., Laicini, E., Di Landro, G., & Pietrogrande, M.C. (2009). Atopy in preschool Italian children with recurrent respiratory infections. *La Pediatrica Medica e Chirurgica*, Vol. 31, No. 4, (July-August 2009), pp. 161-164.

Del-Rio-Navarro, B.E., Espinosa-Rosales, F.J., Flenady, V., & Sienra-Monge, J.J.L. (2006). Immunostimulants for preventing respiratory tract infection in children. *Cochrane Database of Systematic Reviews,* Vol. 18, No. 4, (October 2006), CD004974.

Desser, L., Holomanova, D., Zavadova, E., Pavelka, K., Mohr, T., & Herbacek, I. (2001). Oral therapy with proteolytic enzymes decreases excessive TGF-β levels in human blood. *Cancer Chemother Pharmacol*, 47, 2001. s. 10-15.

Don, M., Fasoli, L., Gregorutti, V., Pisa, F., Valent, F., Prodan, M., & Canciani, M. (2007). Recurrent respiratory infections and phagocytosis in childhood. *Pediatrics International*, Vol. 49, No. 1, (February 2007), pp. 40-47.

Engwerda, C.R., Andrew, D., Ladhams, A., & Mynott, T.L. (2001). Bromelain modulates T cell and B cell immune responses *in vitro* and *in vivo*. *Cellular Immunology*, Vol. 210, No. 1, (May 2001), pp. 66-75.

Finocchi, A., Angelini, F., Chini, L., Di Cesare, S., Cancrini, C., Rossi, P., &Moschese, V.(2002). Evaluation of the relevance of humoral immunodeficiencies in a pediatric population affected by recurrent infections. *Pediatric Allergy and Immunology*, Vol. 13, No. 6, (December 2002), pp. 443-447.

Frohna, J.G. (2005). Effectiveness of adenotonsillectomy in children with mild symptoms of throat infections of adenotonsillar hypertrophy: open, randomized controlled trial. *Journal of Pediatrics*, Vol. 146, No. 3, (March 2005), pp. 435-436.

Fusco, D., Liub, X., Savagec, C., Taurb, Y., Xiaoe, W., Kennellye, E., Yuanf, J., Cassilethg, B., Salvatorea, M., & Papanicolaoub, G.A. (2010). *Echinacea purpurea* aerial extract alters course of influenza infection in mice. *Vaccine*, Vol. 28, No. 23, (May, 2010), pp. 3956–3962.

Ghezzi, M., Silvestri, M., Guida, E., Pistorio, A., Sacco, O., Mattioli, G., Jasonni, V. & Rossi, G.A. (2011). Acid and weakly acid gastroesophageal refluxes and type of respiratory symptoms in children. *Respiratory Medicine*, ahead of print.

Giles, J.T., Palat, C.T.III, Chien, S.H., Chang, Z.G., & Kennedy, D.T. (2000). Evaluation of Echinacea for treatment of the common cold. *Pharmacotherapy,* Vol. 20, No. 6, (June, 2000), pp.690-697.

Ginseng C.A. Meyer in the mouse. *Agents and Actions*, Vol. 15, No. 3-4, (October, 1984), pp. 386–391.

Glatthaar-Saalmuller, B., Sacher F., & Esperester A. (2001). Antiviral activity of an extract derived from roots of *Eleutherococcus senticosus*. *Antiviral Research,* Vol. 50, No. 3, (June, 2001), pp. 223-228.

Goel, V., Lovlin, R., Barton, R., Lyon, M.R., Bauer, R., Lee, T.D., & Basu, T.K. (2004). Efficacy of a standardized echinacea preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Pharmacy and Ther*apeutics, Vol. 29, No. 1, (February, 2004), pp. 75-83.

Gomi, K., Tokue, Y., Kobayashi, T., Takahashi, H., Watanabe, A., Fujita, T., & Nukiwa, T. (2004). Mannose-binding lectin gene polymorphism is a modulating factor in repeated respiratory infections. *Chest*, Vol. 126, No. 1, (July 2004), pp. 95-99.

Graham, M.H. (1990). The epidemiology of acute respiratory infections in children and adults: a global perspective. *Epidemiologic Reviews*, Vol. 12, No. 1, pp. 149-178.

Grohn, P. (1977). Transfer factor in chronic and recurrent respiratory tract infections in children. *Acta Paediatrica Scandinavica*, Vol. 66, No. 2, (March 1977), pp. 211-217.

Gruppo di Studio di Immunologia della Società Italiana di Pediatria. (1988). Le infezioni ricorrenti nel bambino: definizione ed approccio diagnostico. *Rivista di Immunolgia ed Allergologia Pediatrica*, Vol. 2, pp. 127-134.

Gunning, K. (1999). Echinacea in the treatment and prevention of upper respiratory tract infections. *The Western Journal of Medicine,* Vol. 171, No. 3, (September, 1999), pp. 198-200.

Helms, S., & Miller, A.L. (2006). Natural treatment of chronic rhinosinusitis. *Alternative Medicine Review*, Vol. 11, No. 3, (September 2006), pp. 196-207.

Hong, F., Yan, J., Baran, J.T., Allendorf, D.J., Hansen, R.D., Ostroff, G.R., Xing, P.X., Cheung, N.K., & Ross, G.D. (2004). Mechanism by which orally administered beta-1,3-glucans enhance the tumoricidal activity of antitumor Monoclonal antibodies in murine tumor models. *Journal of Immunology*, Vol. 173, No. 2, (July 2004), pp.797-806.

Honzikova, M. (2004). Systémová enzymoterapie v komplexní léčbě recidivujících zánětů dýchacích cest u dětí – postregistrační retrospektivní multicentrické hodnocení. *Česko-slovenská Pediatrie*, Vol. 59, pp. 513-521.

Ianni, A., Majore, S., Arzani, D., Carboni, I., Corbo, G.M., & Romano-Spica, V. (2001). CCR2 and CCR5 gene polymorphisms in children with recurrent respiratory infections. *Respiratory Medicine*, Vol. 95, No. 5, (May 2001), pp. 430-432.

Jaakkola, J.J., Kosheleva, A.A., Katsnelson, B.A., Kuzmin, S.V., Privalova, K.I., & Spengler, J.D. (2006). Prenatal and postnatal tobacco smoke exposure and respiratory health in Russian children. *Respiratory Research*, Vol. 7, No. 48, (March 2006), pp. 1-9.

Jartti, T., Lee, W.M., Pappas, T., Evans, M., Lemanske, R.F., & Gern, J.E. (2008). Serial viral infections in infants with recurrent respiratory illnesses. *European Respiratory Journal*, Vol. 32, No. 2, (August 2008), pp. 314-320.

Jesenak, M., Sanislo, L., Kuniakova, R., Rennerova, Z., Buchanec, J., & Banovcin, P. (2010). Imunoglukan P4H® in the prevention of recurrent respiratory infections in childhood. *Cesko-Slovenska Pediatrie*, Vol. 65, No. 11, pp. 639-647.

Jones, K.D.J., Berkley, J.A., & Warner, J.O. (2010). Perinatal nutrition and immunity to infection. *Pediatric Allergy and Immunology,* Vol. 21, No. 4p1, (Jun 2010), pp.564–576.

Jones, J.F., Minnich, L.L., Jeter, W.S., Pritchett, R.F., Fulginiti, V.A., & Wedgwood, R.J. (1981). Treatment of childhood Epstein-Barr virus/cytomegalovirus infection with oral bovine transfer factor. *Lancet*, Vol. 2, No. 8238, (July 1981), pp. 122-124.

Jose, D.G., & Ford, G.W. (1976). Therapy with parent´s lymphocyte transfer factor in children with infection and malnutrition. *Lancet*, Vol. 1, No. 7954, (February 1976), pp. 263-266.

Kamper-Jorgensen, M., Wohlfahrt, J., Simonsen, J., Gronbaek, M., & Benn, C.S. (2006). Population-based study of the impact of childcare attendance on hospitalizations for acute respiratory infections. *Pediatrics*, Vol. 118, No. 4, (October 2006), pp. 1439-1446.

Karmaus, W., Dobai, A.L., Ogbuanu, I., Arshard, S.H., Matthews, S., & Ewart, S. (2008). Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children. *Journal of Asthma*, Vol. 45, No. 8, (October 2008), pp. 688-695.

Kirkpatrick, C.H. (2000). Transfer factors: identification of conserved sequences in transfer factor molecules. *Molecular Medicine*, Vol. 6, No. 4, pp. 332-341.

Kodama, N., Komuta, K., Sakai, N., & Nanba, H. (2002). Effects of D-fraction, a polysaccharide from Grifola frondosa on tumor growth involve activation of NK cells. *Biological & Pharmaceutical Bulletin*, Vol. 25, No. 12, (December 2002), pp. 1647-1650.

Kowalska, M., Kowalska, H., Zawadzka-Glos, L., Debska, M., Szerszen, E., Chmielik, M., & Wasik, M. (2003). Dysfunction of peripheral blood granulocyte oxidative metabolism in children with recurrent upper respiratory tract infections. *International Journal of Pediatric Otorhinolaryngology*, Vol. 67, No. 4, (April 2003), pp. 365-371.

Kvestad, E., Kvaerner, K.J., Roysamb, E., Tambs, K., Harris, J.R., & Magnus, P. (2006). Recurrent otitis media and tonsillitis: common disease predisposition. *International Journal of Pediatric Otorhinolaryngology*, Vol. 70, No. 9, (September 2006), pp. 1561-1568.

Lanchava, N., Nemsadze, K., Chkhaidze, I., Kandelaki, E., & Nareklishvili, N. (2005). Wobenzym in treatment of recurrent obstructive bronchitis in children. *Georgian Medical News*, Vol. 127, (October 2005), pp. 50-53.

Lehne, G., Haneberg, B., Gaustad, P., Johansen, P.W., Preus, H., & Abrahamsen, T.G. (2006). Oral administration of a new soluble branched beta-1,3-D-glucan is well tolerated and can lead to increased salivary concentrations of immunoglobulin A in healthy volunteers. *Clinical and Experimental Immunology*, Vol. 143, No. 1, (January 2006), pp. 65-69.

Lesourd, B.M. (1997). Nutrition and immunity in the elderly: modification of immune responses with nutritional treatments. *The American Journal of Clinical Nutrition*, Vol. 66, No. 2, (August 1997), pp. 478S-484S.

Li Volti, G., Malaponte, G., Bevelacqua, V., Messina, A., Bianca, S., Mazzarino, M.C., & Li Volti, S. (2003). Persistent high plasma levels of interleukin 18 and 4 in children with recurrent infections of the upper respiratory tract. *Transplantation Proceeding*, Vol. 35, No. 8, (December 2003), pp. 2911-2915.

Linde, K., Barrett, B., Wölkart, K., Bauer, R., & Melchart, D. (2006). Echinacea for preventing and treating the common cold. *Cochrane Database of Systematic Reviews*, Vol. 1, No. CD000530, (January, 2006).

Litzman, J., Lokaj, J., Krejčí, M., Pešák, S., & Morgan, G. (1999). Isoprinosine does not protect against frequent respiratory tract infections in childhood. *European Journal of Pediatrics*, Vol. 158, No. 1, (January 1999), pp. 32-37.

Longo, F., Lepore, L., Agosti, E., & Panizon, F. (1988). Evaluation of the effectiveness of thymomodulin in children with recurrent respiratory infections. *Pediatria Medica a Chirgica*, Vol. 10, No. 6, (December 1988), pp. 603-607.

Lull, C., Wichers, J., & Savelkoul, H.F. (2005). Antiinflammatory and immunomodulating properties of fungal metabolites. *Mediators of Inflammation*, Vol. 2005, No. 2, (June 2005), pp. 63-80.

Malaponte, G., Bevelacqua, V., Li Volti, G., Petrina, M., Nicotra, G., Sapuppo, V., Li Volti, S., Travali, S., & Mazzarino, M.C. (2004). Soluble adhesion molecules and cytokines in children affected by recurrent infections of the upper respiratory tract. *Pediatric Research*, Vol. 55, No. 4, (April 2004), pp. 666-673.

Manhart, N., Akomeah, R., Bergmeister, H., Spittler, A., Ploner, M., & Roth, E. (2002). Administration of proteolytic enzymes bromelain and trypsin diminish the number of CD4+ cells and the interferon-gamma response in Peyer´s patches and spleen in endotoxemic balb/c mice. *Cellular Immunology*, Vol. 215, No. 2, (February 2002), pp. 113-119.

Marbury, M.C., Maldonado, G., & Waller, L. (1997). Lower respiratory illness, recurrent wheezing and day care attendance. *American Journal of Respiratory Critical Care Medicine*, Vol. 155, No. 1, (January 1997), pp. 156-161.

Marchisio, P., Esposito, S., Bianchini, S., Desantis, C., Galeone, C., Nazzari, E., Pignataro L., & Principi, N. (2010). Effectiveness of a propolis and zinc solution in preventing acute otitis media in children with a history of recurrent acute otitis media. *International Journal of Immunopathology and Pharmacology,* Vol. 23, No. 2, (April-June, 2010), pp. 567-575.

Marseglia, G.L., Tosca, M., Cirillo, I., Licari, A., Leone, M., Larseglia, A., Castellazzin, A.M., & Ciprandi, G. (2007). Efficacy of *Bacillus clausii* spores in the prevention of recurrent respiratory infections in children: a pilot study. *Therapeutics and Clinical Risk Management*, Vol. 3, No. 1, (March 2007), pp. 13-17.

Mathew, J.L. (2010). Zinc Supplementation for Prevention or Treatment of Childhood Pneumonia: A Systematic Review of Randomized Controlled Trials. *Indian Pediatrics,* Vol. 47, No. 1, (January, 2010), pp. 61-66.

Matricardi, P.M., Bjorksten, B., Bonini, S., Bousquet, J., Djukanovic, R., Dreborg, S., Gereda, J., Malling, H.J., Popov, T., Raz, E., Renz, H., & Wold, A. for EAACI Task Force 7. (2003). Microbial products in allergy prevention and therapy. *Allergy,* Vol. 58, No. 6, (June, 2003), pp. 461-471.

Mauel, J., Van Pham, T., Kreis, B., & Bauer J. (1989). Stimulation by a bacterial extract (Broncho-Vaxom) of the metabolic and functional activities of murine macrophages. *International Journal of Immunopharmacol*ogy, Vol. 11, No. 6, pp. 637–645.

McElroy, B.H., & Miller, S.P. (2002). Effectiveness of zinc gluconate glycine lozenges (Cold-Eeze) against the common cold in school-aged subjects: a retrospective chart review. *American Journal of Therapeutics,* Vol. 9, No. 6, (November-December, 2002), pp. 472-475.

Meduri, R., Campos, E., Scorolli, L., De Vinci, C., Pizza, G., & Viza, D. (1996). Efficacy of transfer factor in treating patients with recurrent ocular herpes infections. *Biotherapy*, Vol. 9, No. 1-3, pp. 61-66.

Melchart, D., Linde, K., Worku F, Sarkady, L., Holzmann, M., Jurcic, K., & Wagner, H. (1995). Results of five randomized studies on the immunomodulatory activity of preparations of Echinacea. *Journal of Alternative and Complementary Med*icine, Vol. 1, No. 2, (Summer, 1995), pp. 145-160.

Melchart, D., Walther, E., Linde, K., Brandmaier, R., & Lersch, Ch. (1998). Echinacea root extracts for prevention of upper respiratory tract infections. *Archives of Family Medicine,* Vol. 7, No. 6, (November-December, 1998), pp.541-545.

Moro, G., Arslanoglu, S., Stahl, B., Jelinek, J., Wahn, U., Boehm, G. (2006). A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Archives of Disease in Childhood*, Vol. 91, No. 10, (October 2006), pp. 814-819.

Mullins, R.J. (1998). Echinacea associated anaphylaxis. *The Medical Journal of Australia,* Vol. 168, No. 4, (February,1998), pp. 170-171.

Mullins, R.J., & Heddle, R. (2002). Adverse reactions associated with echinacea: the Australian experience. *Annals of Allergy, Asthma and Immunology*, Vol. 88, No. 1, (January, 2002), pp. 42-51.

Nieman, D.C., Henson, D.A., Fagoaga, O.R., Utter, A.C., Vinci, D.M., Davis, J.M., & Nehlsen-Cannarella, S.L. (2002). Change in salivary IgA following a competitive marathon race. *Internal Journal of Sports Medicine*, Vol. 23, No. 1, (January 2002), pp. 69-75.

Noakes, P.S., Hale, J., Thomas, R., Lane, C., Devadason, S.G., & Prescott, S.L. (2006). Maternal smoking is associated with impaired neonatal toll-like-receptor-mediated immune responses. *European Respiratory Journal*, Vol. 28, No. 4, (October 2006), pp. 721-729.

Nystad, W., Nja, F., Magnus, P., & Nafstad, P. (2003). Baby swimming increases the risk of recurrent respiratory tract infections and otitis media. *Acta Paediatrica*, Vol. 92, No. 8, (August 2003), pp. 905-909.

Nystad, W., Skrondal, A., & Magnus, P. (1999). Day care attendance, recurrent respiratory tract infections and asthma. *International Journal of Epidemiology*, Vol. 28, No. 5, (October 1999), pp. 882-887.

O´Neil, J., Hughes, S., Lourie, A., & Zweifler, J. (2008). Effects of Echinacea on the frequency of upper respiratory tract symptoms: a randomized, double-blind, placebo-controlled trial. *Annals of Allergy, Asthma and Immunology*, Vol. 100, No. 4, (April, 2008), pp. 384-388.

Olinder-Nielsen, A.M., Granert, C., Forsberg, P., Friman, V., Vietorisz, A., & Bjorkander, J. (2007). Immunoglobulin prophylaxis in 350 with IgG subclass deficiency and recurrent respiratory tract infections: a long-term follow-up. *Scandinavian Journal of Infectious Diseases*, Vol. 39, No. 1, (January 2007), pp. 44-50.

Olivieri, D., Fiocchi, A., Pregliasco, F., Veehof, S., & Cantoni, V. (2009). Safety and tolerability of ribosome-component immune modulator in adults and children. *Allergy and Asthma Proceedings,* Vol. 30, Suppl. 1, (July-August 2009), pp.S33-S36.

Ottenhoff, T.H., Verreck, F.A., Lichtenauer-Kaligis, E.G., Hoeve, M.A., Sanal, O., & Van Dissel, J.T. (2002). Genetics, cytokines and human infectious disease: lessons from weakly pathogenic mycobacteria and samlonellae. *Nature Genetics*, Vol. 32, No. 1, (September 2002), pp. 97-105.

Panigada, S., Sacco, O., Girosi, D., Toma, P., & Rossi, G.A. (2009). Recurrent severe lower respiratory tract infections in a child with abnormal tracheal morphology. *Pediatric Pulmonology*, Vol. 44, No. 2, (February 2009), pp. 192-194.

Pickering, L.K., Granoff, D.M., Erickson, J.R., Masor, M.L., Cordle, C.T., Schaller, J.P., Winship, T.R., Paule, C.L., & Hilty, M.D. (1998). Modulation of the immune system by human milk and infant formula containing nucleotides. *Pediatrics*, Vol. 101, No. 2, (February 1998), pp. 242-249.

Pizza, G., De Vinci, C., Fornarola, V., Palareti, A., Baricordi, O., & Viza, D. (1996). In vitro studies during long-term oral administration of specific transfer factor. *Biotherapy*, Vol. 9, No. 1-3, pp. 175-185.

Predy, G.N., Goel, V., Lovlin, R., Donner, A., Stitt, L., & Basu, T.K. (2005). Efficacy of an extract of North American ginseng containing poly-furanosyl-pyranosyl-saccharides for preventing upper respiratory tract infections: a randomized controlled trial. *Canadian Medical Association Journal,* Vol. 173, No. 9, (October, 2005), pp.1043-1048.

Pryjma, J., Kaszuba-Zwoinska, J., Pawlik, J., Pogorzelski, A., Lis, G., Baran, J., & Zebrak, J. (1999). Alveolar macrophages of children suffering from recurrent infections of respiratory tract are less efficient in eliminating apoptotic neutrophils. *Pediatric Pulmonology*, Vol. 27, No. 3, (March 1999), pp. 167-173.

Raduner, S., Majewska, A., Chen, J.Z., Xie, X.Q., Hamon, J., Faller, B., Altmann, K.H., & Gertsch, J. (2006). Alkylamides from Echinacea are a new class of cannabinomimetics — Cannabinoid type 2 receptor-dependent and –independent immunomodulatory effects. *Journal of Biological Chemistry*, Vol. 281, No. 20, (May 2006), pp. 14192-14206.

Razi C.H., Harmanci, K., Abaci, A., Őzdemir, O., Hizli, S., Renda, R., & Keskin, F. (2010). The immunostimulant OM-85 BV prevents wheezing attacks in preschool children. *The Journal of Allergy and Clinical Immunology*, Vol. 126, No. 4, (October 2010), pp. 763-769.

Roth, D.E., Caulfield, L.E., Ezzatib, M., & Blacka, R.E. (2008). Acute lower respiratory infections in childhood: opportunities for reducing the global burden through nutritional interventions. *Bulletin of the World Health Organization,* Vol. 86, No. 5, (May, 2008), pp.356–364.

Roxas, M., & Jurenka, J. (2007). Colds and Influenza: A review of diagnosis and conventional, botanical, and nutritional considerations. *Alternative Medicine Review,* Vol. 12, No. 1, (March, 2007), pp.25-48.

Rozy, A., & Chorostowska-Wynimko, J. (2008). Bacterial immunostimulants — mechanism of action and clinical application in respiratory diseases. *Pneumonologia i Alergologia Pol*ska, Vol. 76, No. 5, pp. 353–359.

Salami, A., Dellepiante, M., Crippa, B., Mora, F., Guastini, L., Jankowska, B., & Mora, R. (2008). Sulphurous water inhalations in the prophylaxis of recurrent upper respiratory tract infections. *International Journal of Pediatric Otorhinolaryngology*, Vol. 72, No.11, (November 2008), pp. 1717-1722.

Schaad, U.B. (2010). OM-85 BV, an immunostimulant in pediatric recurrent respiratory tract infections: a systematic review. *World Journal of Pediatrics,* Vol. 6, No. 1, (February 2010), pp. 5-12.

Schoop, R., Klein, P., Suter, A., & Johnston, S.L. (2006). *Echinacea* in the Prevention of Induced Rhinovirus Colds: A Meta-Analysis. *Clinical Therapeutics, Vol.* 28, No. 2, (February, 2006), pp. 174-183.

Seida, J.K., Durec, T., & Kuhle, S. (2009). North American (Panax quinquefolius) and Asian Ginseng (Panax ginseng) Preparations for Prevention of the Common Cold in Healthy Adults: A Systematic Review. *Evidence- Based Complementary and Alternative Medicine,* Vol. 2011, 1-7

Šemberová, J., Paulovičová, E., Jelemenská, A., & Jakubíková, J. (2009). Indukcia TNF-α imunomodulačnou liečbou s obsahom β-glukánu u detských pacientov so zväčšenou nosohltanovou mandlou. *Klinická Imunológia a Alergológia*, Vol. 19, pp.15-17.

Senchina, D.S., Flagel, L.E., Wendel, J.F., & Kohut, M.L. (2006). Phenetic comparison of seven Echinacea species based on immunomodulatory characteristics. *Economic Botany,* Vol. 60, No. 3, (September, 2006), pp. 205-211.

Shah, S.A., Sander, S., White, C.M., Rinaldi, M., & Colemn, C.I. (2007). Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis. *The Lancet Infection Disease,* Vol. 7, No. 7, (July, 2007), pp. 473–480.

Shaheen, S.O., Barker, J.P., Shiell, A.W., Crocker, F.J., Wield, G.A., & Holgate, S.T. (1994). The relationship between pneumonia in early childhood and impaired lung function in late adult life. *American Journal of Respiratory Critical Care Medicine*, Vol. 149, No. 3, (March 1994), pp. 616-619.

Sharma, S.M., Anderson, M., Schoop, S.R., & Hudson, J.B. (2010). Bactericidal and anti-inflammatory properties of a standardized Echinacea extract (Echinaforces): Dual actions against respiratory bacteria. *Phytomedicine,* Vol. 17, No. 8-9, (Jul, 2010), pp. 563–568.

Skeik, N. , & Jabr, F.I. (2011). Kartagener syndrome. *International Journal of Genetic Medicine*, Vol. 4, No. 1, (January 2011). pp. 41-43.

Slatter, M.A. & Gennery, A.R. (2008). Clinical Immunology Review Series: An approach to the patient with recurrent infections in childhood. *Clinical and Experimental Immunology*, Vol. 152, No. 3, (June 2008), pp. 389-396.

Sperber, S.J., Shah, L.P., Gilbert, R.D., Ritchey T.W., & Monto, A.S. (2004). *Echinacea purpurea* for prevention of experimental rhinovirus colds. *Clinical Infection Dis*ease, Vol. 38, No. 10, (May, 2004), pp. 1367-1371.

Steurer-Stey, C., Lagler, L., Straub, D.A., Steurer, J., & Bachmann, L.A. (2007). Oral purified bacterial extracts in acute respiratory tract infections in childhood: a systematic quantitative review. *European Journal of Pediatr*ics, Vol. 166, No. 4, (April 2007), pp. 365–376.

Stick, S. (2006). The effects of in-utero tobacco-toxin exposure on the respiratory system in children. *Current Opinion in Allergy and Clinical Immunology*, Vol. 6, No. 5, (October 2006), pp. 312-316.

Stimpel, M., Proksch, A., Wagner H., & Lohman-Matthes, M.L. (1984). Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fractions from the plant *Echinacea purpurea. Infection and Immun*ity, Vol. 46, No. 3, (December, 1984), pp. 845-849.

Targoni, O.S., Tary-Lehmann, M., & Lehmann, P.V. (1999). Prevention of murine EAE by oral hydrolytic enzyme treatment. *Journal of Autoimmunity*, Vol. 12, No. 3, (May 1999), pp. 191-198.

Taylor, J.A., Weber, W., Standish, L., Quinn, H., Goesling, J., McGann, M., & Calabrese, C. (2003). Efficacy and Safety of Echinacea in Treating Upper Respiratory Tract Infections in Children. A Randomized Controlled Trial. *The Journal of American Medical Association,* Vol. 290, No. 21, (December, 2003), pp. 2824-2830.

Teele, D.W., Klein, J.O., & Rosner, B. (1989). Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *Journal of Infectious Diseases*, Vol. 160, No. 1, (July 1989), pp. 83-94.

Tiollier, E., Gomez-Merino, D., Burnat, P., Jouanin, J.C., Bourrilhon, C., Filaire, E., Guezennec, C.Y., & Chennaoui, M. (2005). Intense training: mucosal immunity and incidence of respiratory infections. *European Journal of Applied Physiology*, Vol. 93, No. 4, (January 2005), pp. 421-428.

Tsoni, S.V., & Brown, G.D. (2008). Beta-Glucans and Dectin-1. *Annals of the New York Academy of Sciences*, Vol. 1143, (November 2008), pp. 45-60.

Tzianabos, A.O. (2000). Polysaccharide immunomodulators as therapeutic agents: structural aspects and biologic function. *Clinical Microbiology Reviews*, Vol. 13, No. 4, (October 2000), pp. 523-533.

Uhari, M., & Mottonen, M. (1999). An open randomized controlled trial of infection prevention in children day-care centers. *Pediatric Infectious Diseases Journal*, Vol. 18, No. 8, (August 1999), pp. 672-677.

Vaughan, D., & Katkin, J.P. (2002). Chronic and recurrent pneumonias in children. *Seminars in Respiratory Infectections*, Vol. 17, No. 1, (March 2002), pp. 72-84.

Vautel, J.M., Cauquil, J., Perruchet, A.M., & Thomas, AM. (1993). Prevention of recurrent ear, nose, and throat infections in young children with Ribomunyl, double-blind, placebo-controlled study. *Current Therapeutic Research, Clinical and Experimental,* Vol. 53, No. 6, (June 1993), pp. 722–729.

Vegh, V., & Vegh, T. (2009). Přehled doplňkové imunomodulace v pediatrii. *Pediatrická prax*, Vol. 10, pp. 28-31.

Vetvicka, V., & Vetvickova, J. (2009). Beta-glucan-indomethacin combination produces no lethal effects. *Biomedical Papers of the Medical Faculty of the University Palacky Olomouc Czech Republic*, Vol. 153, No. 2, (June 2009), pp. 111-116.

Vohra, S., Johnston, B.C., Laycock, K.L., Midodzi, W.K., Dhunnoo, I., Harris E., & Baydala., L. (2008). Safety and Tolerability of North American Ginseng Extract in the Treatment of Pediatric Upper Respiratory Tract Infection: A Phase II Randomized, Controlled Trial of 2 Dosing Schedules. *Pediatrics,* Vol. 122, No. 2, (August, 2008), pp. e402-e410, ISSN: 1098-4275

Vouloumanou, E.K., Makris, G.C., Karageorgopoulos, D.E., & Falagas, M.E. (2009). Probiotics for the prevention of respiratory tract infections: a systematic review. *International Journal of Antimicrobial Agents,* Vol. 34, No. 3, (September 2009), pp.197.e1-10.

Wang, M., Guilbert, L.J., Ling, L., Li, J., Wu, Y., Xu, S., Pang, P., & Shan, J.J. (2001). Immunomodulating activity of CVT-E002, a proprietary extract from North American ginseng (Panax quinquefolium). *The Journal of Pharmacy and Pharmacology,* Vol. 53, No. 11, (November, 2001), pp. 1515–1523.

Wheeler, J.G. (1996). Evaluating the child with recurrent infections. *American Family Physician*, Vol. 54, No. 7, (November 1996), pp. 2276-2282.

Wheeler, J.G., & Steiner, D. (1992). Evaluation of humoral responsiveness in children. *Pediatric Infectious Diseases Journal*, Vol. 11, No. 4, (April 1992), pp. 304-310.

Woroniecka, M., & Ballow, M. (2000). Office evaluation of children with recurrent infection. *Pediatric Clinics of North America*, Vol. 47, No. 6, (December 200), pp. 1211-1224.

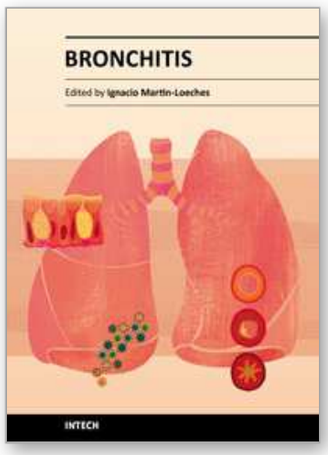
Yang, K.D., & Hill, H.R. (1991). Neutrophil function disorders: pathophysiology, prevention, and therapy. *Journal of Pediatrics*, Vol. 119, No. 3, (September 1992), pp. 343-354.

Zavadova, E., & Desser, L. (1997). Proteolytic enzymes stimulates the cytotoxic activity of human granulocytes in vitro and in vivo. *International Journal of Immunotherapy*, Vol. 13, pp. 147-151.

Zavadova, E., Desser, L., & Mohr, T. (1995). Stimulation of reactive oxygen species production and cytotoxicity in human neutrophils in vitro and after oral administration of a polyenzyme preparation. *Cancer Biotherapy*, Vol. 10, No. 2, (Summer 1995), pp. 147-152.

Zelinsky, G.M., Schaefermeyer, H., & Schaefermeyer, G. (2000). Immunomodulatory and clinical effects of Viscum album (Iscador M and Iscador P) in children with recurrent respiratory infections as a result of the Chernobyl nuclear accident. *American Journal of Therapeutics,* Vol. 7, No. 3, (May, 2000), pp.195-203.

Zelle-Rieser, C., Ramoner, R., Bartsch, G., & Thurnher, M. A. (2001). clinically approved oral vaccine against pneumotropic bacteria induces the terminal maturation of CD83+ immunostimulatory dendritic cells. *Immunology Lett*ers, Vol. 76, No. 1, (February 2001), pp. 63–67.



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Lung parenchyma has been extensively investigated. Nevertheless, the study of bronchial small airways is much less common. In addition, bronchitis represents, in some occasions, an intermediate process that easily explains the damage in the lung parenchyma. The main target of this book is to provide a bronchial small airways original research from different experts in the field.

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