

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** (severe, persistent, unusual, recurrent) 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 than 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 (Woroniciecka & 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 Società 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, septicæmia),
- 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. SO₂, NO₂) 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 (Dellepiane et al., 2009). Atopy affects 15-20% of children and causes chronic inflammation of the airways that can mimic recurrent or chronic upper respiratory infections. Atopy can also facilitate the adherence of pathogens to the respiratory epithelium and thus promote infections (Ballou, 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, α 1-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 site, 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) (Ballou, 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 mature 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 (Alyanikian 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 proinflammatory 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 \rightarrow 3) in the main linear chain and β -(1 \rightarrow 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. Immunoglucan – 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's 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-1 β , 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 cytotoxic 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 imunoglukan (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. $\geq 50\%$ 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 optimized 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 may 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, flavonoids, chicory acid glycosides, essential oils, oxycetylene and alkyl amides (Gunning, 1999). The biological activities of *Echinacea* appear to be the result of a combined action of its components rather than 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 cannabinoid 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*, *Legionella 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 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), glycosides 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 month 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 Astragalus

Astragalus membranaceus is rich in polysaccharides, flavonoids, multiple trace minerals and amino acids, all of them contribute to Astragalus's complex immunomodulatory properties. Astragalus 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 Astragalus 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. If there is 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 convalescence, 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

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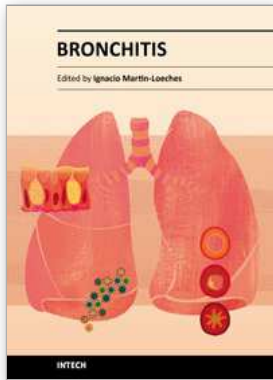
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Lung parenchyma has been extensively investigated. Nevertheless, the study of bronchial small airways is much less common. In addition, bronchitis represents, in some occasions, an intermediate process that easily explains the damage in the lung parenchyma. 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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