The Management of Recurrent Respiratory Tract Infections in Children

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Abstract
Respiratory tract infections (RTIs) constitute a major healthcare burden in children throughout the world. They tend to be recurrent, often causing multiple episodes of illness within a single year. Immature immune system, the presence of genetic and environmental factors and exposure to pathogens make young children highly susceptible to RTIs. These infections are still treated with antibiotics but the rise in resistant bacterial strains has prompted investigation of novel preventative strategies. One such approach to prevent recurrent RTIs (RRTIs) is the immunostimulant OM-85 that is an extract of eight pathogenic bacteria which has proven safe and effective as prophylaxis of recurrent respiratory infections in children at risk. Increased awareness and use of preventative approaches, including OM-85, are likely to help avoid the complications and co-morbidities of RTIs; and have the potential to significantly reduce the burden of disease and bacterial resistance.

Keywords
Recurrent respiratory tract infections, bacterial infection, virus, lung damage, immune response, immunostimulant, OM-85

Burden of Respiratory Tract Infections in Children
Paediatric respiratory tract infections (RTIs) are associated with significant morbidity and mortality worldwide.\(^6\) In industrialised countries, approximately half of the medical consultations concerning children involve RTIs.\(^2\) Moreover, these are often recurrent infections, occurring numerous times a year.

The epidemiology data of RTIs are variable depending on the specific year and setting studied. In general, mortality rates in children within developed countries are relatively low.\(^4\) In contrast, RTIs in developing countries are not only more prevalent but also more severe, resulting in over 2 million deaths per year.\(^4,5\) A recent report from the United Nations International Children’s Emergency Fund (UNICEF) concluded that over 2 million child deaths could be prevented in the 75 countries with the highest mortality burden if the entire population of children aged less than five years in each of these countries received the same coverage already available to the wealthiest 20 % of people in those countries.\(^6\) From other studies, it was estimated that approximately 6 % of children under the age of six years present with recurrent RTI.\(^1\) In developed countries, up to 25 % of children less than one year and 18 % of those aged 1–4 years experience recurrent RTIs.\(^1\)

The vast majority (80–90 %) of RTIs are caused by viruses including rhinovirus, respiratory syncytial virus (RSV) and influenza. RSV is a common cause of both upper and lower RTIs. The same has been demonstrated for rhinovirus. However, whereas RSV is more common in younger children, rhinovirus strains A and B have been found as a cause of RTIs in both younger and older children.\(^1\) Recent studies have highlighted the burden of influenza in young children.\(^10,11\) While recurrent RTIs often begin as viral infections, bacterial infection is observed in 60 % of patients with symptoms of an upper RTI lasting at least 10 days.\(^8,11\) Bacteria commonly involved in recurrent RTIs include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae* and *Streptococcus pyogenes*.\(^8,14,15\) Bacterial infections of the lung have also been found to play a role in preschool children with recurrent wheeze.\(^16\) In particular, *Mycoplasma pneumoniae*, *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* were the most commonly isolated species in these individuals.

The burden of RTIs extends beyond their incidence and epidemiology data. The diagnosis of recurrent RTIs can be particularly challenging for paediatricians. While many infections involving the upper respiratory tract are easily managed, others are indicative of a more serious underlying pathology such as bronchiectasis or immune dysfunction.\(^1\) Further, differential diagnosis requires the appropriate use of diagnostic tools by physicians. Additional burdens include subsequent morbidity and complications in the child, resultant overuse and misuse of antibiotics, and all associated healthcare as well as indirect societal costs. These will be discussed in greater detail below.

The Child Immune System
The high incidence of respiratory infections in children relative to older adolescent and adult populations can be partially explained by the apparent limitations of their young immune systems. In fact, defects in immune responses are known to correlate with multiple
Respiratory Tract Infections

Table 1: Summary of Environmental and Genetic Risk Factors for the Development of Recurrent Respiratory Tract Infections

<table>
<thead>
<tr>
<th>Environmental risk factors</th>
<th>Genetic risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day care attendance</td>
<td>Positive family history of atopic diseases</td>
</tr>
<tr>
<td>Early socialisation</td>
<td>Prematurity and low bodyweight infants</td>
</tr>
<tr>
<td>Large family size and overcrowding</td>
<td>Anatomic or functional alterations of the airways</td>
</tr>
<tr>
<td>School-aged siblings</td>
<td>Allergy/asthma</td>
</tr>
<tr>
<td>Reduced breastfeeding</td>
<td>Male gender</td>
</tr>
<tr>
<td>Exposure to pollutants (indoor and outdoor)</td>
<td></td>
</tr>
<tr>
<td>Parental smoking and smoking during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Malnutrition and missed vaccination</td>
<td></td>
</tr>
<tr>
<td>Intense training and physical stress</td>
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</tbody>
</table>

Source: Jesenak et al., 2011.

RTIs. It is, however, rare for a child with recurrent RTIs to present with a true immunodeficiency, rather there is likely an immaturity in their immune system due to their young age leading to increased infections; humoral and phagocytic immunity do not reach their optimal protective state until the fifth or sixth year of life. As such, it is important for paediatricians to be able to differentiate between deficiency and immaturity. For the most part, the child has normal immune functions – albeit young and immature – and therefore any symptoms or complications from RTIs will be transient and of limited duration. On the other hand, if a child presents with excessive amounts of infections (e.g. eight or more occurrences of otitis media in 12 months, two or more serious sinus infections within 12 months or several community-acquired pneumonia), there is likely to be an underlying primary immunodeficiency that requires attention. Careful history-taking and examination along with prompt immunologic testing are needed to make an accurate diagnosis and treat these patients appropriately.

Although most affected children do not have immunodeficiencies, some may exhibit lower levels of haematological or immunological parameters such as deficiencies in specific immunoglobulin (Ig) isotypes or, much more rarely, decreased phagocytosis. Other aspects of the immune system that are immature in newborn and young children include T cells, cytotoxic activity, neutrophil production and function, and complement levels.

It is also important to note the possibility that the observed immune defects are the consequences rather than the cause of recurrent RTIs. In particular, viral infections are known to influence immune responses. As such, repeated infections and viral penetration could result in ever deeper virus-induced immune dysfunction, which would in turn favour further respiratory infections, leading to a vicious cycle of recurrent RTIs.

Patient Profile and Risk Factors

Environmental Risk Factors

A number of environmental factors have a well-established effect of increasing the susceptibility of a child to recurrent lung infections. Passive smoking, excessive exposure to pollutants, contact with infectious agents and the absence of breastfeeding have all been reported to increase the risk of infection. Indeed, breast milk contains important nutrients that help enhance the child’s immune response. Furthermore, attendance at crowded day care centres or preschools as well as interactions with siblings and other family members may add to the likelihood of RTIs. Missed or lack of vaccinations and malnutrition are other risk factors for RTIs that are especially prevalent in developing countries.

Genetic Risk Factors

Certain children have a familial predisposition for recurrent and severe respiratory infections. This is often linked to the anatomical, physiological and/or immunological features of the individual. RTIs have been attributed to anatomic or functional alterations of the upper and/or lower airways as well as reduced immunity in the child. A family history of atopic diseases, low bodyweight and male gender have also been reported to contribute to a higher risk of RTIs.

Table 1 lists the key environmental and genetic risk factors associated with the development of recurrent RTIs. Strategies to prevent recurrent RTIs must take into consideration all these patient characteristics and factors that potentially increase the risk for disease. Research has suggested that patients with the greatest risk of recurrent RTIs benefit the most from therapeutic intervention and prevention.

Definition

RTIs include all viral and bacterial infections of the upper or lower airways. These could be relatively benign and easily controlled or potentially more serious diseases such as pneumonia or bronchitis that can cause permanent lung damage. Recurrent RTIs can be defined as at least three RTI episodes per year or fall/winter season for at least two years. However, in terms of more specific definitions of individual types of infections (e.g. otitis media, infectious rhinitis, etc.), there is no clear consensus on a definition of ‘recurrent’, although standard references exist. For otitis media, three episodes within six months or four within 12 months is considered recurrent. In contrast, recurrent infectious rhinitis is frequently defined as greater than five episodes per year. Finally, recurrent pharyngitis or tonsillitis is more than three episodes within 12 months. For the most part, however, definitions tend to be arbitrary and may not necessarily help physicians determine the optimal therapeutic option for individual patients.

Morbidity and Complications

Direct complications from recurrent RTIs include bacterial manifestations such as acute otitis media, sinusitis and bronchitis. Infections of the ear, nose and throat constitute the most common pathologies in children aged six months to six years. Other important consequences include mastoiditis, pneumonia and sepsis. Paediatricians therefore need to diagnose and monitor patients carefully to limit these potentially life-threatening events and manage them appropriately.

In some severe cases, the RTI may be fatal for the child. This risk is especially prevalent in developing countries where child mortality rates are generally higher. In the long-term, recurrent RTIs can cause damage to the lungs and lead to further respiratory problems as well as increased risk of disease in the future. Moreover, RTIs can at times lead to exacerbations of cough and wheeze in children. An association between recurrent RTIs in early life and asthma has been...
Schaad_OM Pharma_A4_2011 02/11/2012 11:19 Page 113

The Management of Recurrent Respiratory Tract Infections in Children

reported and for some children, repeated respiratory infections are the first manifestations of asthma.7

Socioeconomic Burden

Recurrent RTIs are responsible for much socioeconomic burden in the world, causing absenteeism from school for the child and from work for the parents.4,41 Healthcare and medical costs as well as learning delays from missed school days also add to the socioeconomic burden of recurrent RTIs.8

A study of 600 Australian families showed a mean 2.2 respiratory episodes per person per year, the frequency and severity being higher in young children (<2 years).7 The mean episode duration was 6.3 days; 28.7% of these events required a visit to the physician and there was a 23% rate of absenteeism. Another study with healthy children aged 12–71 months during a winter season in Australia demonstrated an average of 0.53 respiratory infectious episodes per child per month.9 The mean duration per episode was 10.4 days and for every 100 episodes there were 46.7 general practitioner visits, 19.7 courses of antibacterial therapies prescribed and 2.2 hospital admissions, all increasing the cost and burden of disease. The average cost of a 100 episodes was AU$241 and approximately 70% of this cost was the carer’s time away from their normal activities in order to care for the child. Non-prescription medications and general practice visits made up only a small proportion of the costs at 5.4% and 5.0%, respectively.6

Antibiotic Overuse and Misuse

Antibacterial resistance in the bacteria that commonly cause or complicate RTIs is a major healthcare concern.4 If it is not adequately addressed, children will continue to encounter stronger, more resistant pathogens in the future. Overuse and misuse of antibiotics are the main factors that perpetuate this issue of resistance. Overuse refers to using antibiotic treatment when it is not necessary or indicated (i.e. for viral infections and non-infectious diseases). Conversely, antibiotic misuse occurs when the therapy is used incorrectly, either the wrong antibiotic is chosen or the dosage and/or duration are not appropriate.

The use of antibiotics is common for the treatment of infections including RTIs. However, as these are often viral infections, antibacterials will likely not be effective in these situations.4,6,10 When a bacterial infection has been properly diagnosed as the cause of disease, antibiotics are the favoured treatment option. However, even with such infections, multiple courses of antibacterial therapies do not cure nor do they prevent subsequent recurrences. Importantly, application of these therapies contributes to the development of antibiotic-resistant strains of bacteria.46–48 Other drivers of resistance include the type of antibiotic used and the high rate of clonal spread.

Considering the prevalence and effects of antibiotic resistance, it becomes important for paediatricians to take care when prescribing and ensure appropriate and responsible use of antibiotics.11 Improved diagnostic techniques that can provide more rapid and reliable identification of causal pathogens in RTI would allow antibiotics to be avoided whenever possible thereby limiting the number of unnecessary courses administered prior to a definitive diagnosis.

Preventive Measures

As a result of the risks and negative impact antibiotic use can have in society, other forms of infection management have been explored. These strategies look to prevent the development of recurrent RTIs in children by reducing the risks of infection.

Parent Education

A key aspect of initiatives to prevent recurrent infections in children is the education of their parents. They need to know what factors increase a child’s risk of recurrent RTIs and work to minimise them. For example, the absence of breastfeeding is a risk factor for infection, suggesting a protective role of mothers’ milk in the infant. Breast milk is rich in nucleotides that have immunomodulatory activity thus enhancing a child’s immune defence. Similarly, nucleotide supplementations to infant formulas augment natural killer cell activity and humoral response.12 By increasing their knowledge of the disease and risk factors, parents can better care for their children and potentially reduce the frequency of RTIs.

Other risk factors must also be limited; a child’s exposure to air pollution, passive smoke and overcrowded day care centres should be reduced as much as possible, and parents can play a major role in avoiding such adverse environments.7 Parents must also remember that children with recurrent infections are still ‘normal’ with regard to their immune response and so any major interferences to their developing immune system, such as surgery (e.g. adenoidectomy and tonsillectomy) or prophylactic antibiotic treatment, may actually be harmful and counter-productive.7

Immunisation

Many vaccines are currently available to prevent various childhood diseases. As such, effective vaccination programmes for children to protect against viruses and bacteria known to cause RTIs will be the ultimate goal. At present, there are vaccines against influenza, measles, S. pneumoniae, B. pertussis and H. influenzae type b, which are relevant to the prevention of the infections due to these infectious agents. However, the availability of these vaccines is low in some areas of the world therefore limiting the effect of this strategy.

Large-scale take-up of vaccination within any population is vital to establish herd immunity and limit exposure of vulnerable children to pathogens. Parents therefore need to understand the importance of immunisations for their children. While these vaccines should be administered wherever available, their role in preventing some recurrent viral infections is limited. In fact, only influenza vaccination can have a direct impact in this setting. As RTIs are mainly due to viruses the roles of bacterial vaccines (pertussis, pneumococcus and H. influenzae b) are limited in avoiding initial episodes even if they can play a relevant role in reducing bacterial complications.

Immunostimulation

As a result of the strong association between recurrent RTIs and inadequacies of the immune system, bacterial immunostimulants have been developed to non-specifically boost the body’s own defences against any invasive pathogens.7–9 Bacterial immunostimulants were first introduced in the 1980s and there are now several licensed formulas that are marketed around the world for the prevention and treatment of bacterial infections of the upper and lower respiratory tract. These include BioStim®, Luivac®, IRS 19®, Ribomunyl® and Broncho-Vaxom® (Broncho-Munal®, Ommunal®, Paxoral® and Vaxoral®).6

Some immunostimulant preparations are bacterial lysates while others contain cellular structures such as ribosomes. The constituents of each
Respiratory Tract Infections

**Figure 1:** Proportion of Children with Recurrent Respiratory Tract Infections Following OM-85 or Placebo

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<tr>
<th></th>
<th>OM-85</th>
<th>Placebo</th>
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<tr>
<td>Percentage of patients in each group with ≥3 respiratory tract infections per six months</td>
<td>32%</td>
<td>58.20%</td>
</tr>
</tbody>
</table>

Source: Schaad, 2010.17

**Figure 2:** Relationship Between Efficacy of OM-85 and Number of Respiratory Tract Infections in the 12 Months Prior to Treatment

<table>
<thead>
<tr>
<th>Number of recurrent RTIs during previous 12 months</th>
<th>Mean difference 95% CI SEM</th>
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<tbody>
<tr>
<td>0</td>
<td>Ref 1</td>
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<tr>
<td>1</td>
<td>Ref 2</td>
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<td>Ref 3</td>
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<td>12</td>
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RTRTs = Respiratory tract infections; SEM = Standard error of the mean.


Mean differences are shown with error bars representing the standard error of the mean.

Source: Schaad, 2010.17

**formulation were chosen according to their highly immunogenic properties. In RTI immunostimulants enhance the immune system, eliciting immune responses both in the respiratory tract and systemically, thereby inducing better protection against infections. This reduces both the frequency and severity of RTIs which in turn decreases the need for antibiotics and any subsequent resistance.**

**Bacterial immunostimulants have shown positive safety data in trials while decreasing the number of RTIs as well as the use of antibiotics and other concomitant medications. Other immunostimulants in the form of herbal extracts and synthetic compounds also exist - such as pidotimod – that may be effective in decreasing the number of recurrent RTIs.** However, compared with bacterial extracts, there is substantially less data available for these treatment options and further research is required.

**OM-85 in the Prevention of Recurrent Respiratory Tract Infection in Children**

OM-85 (Broncho-Vaxom®, Broncho-Munal®, Ommun®al®, Paxoral® and Vaxoral®) is a standardised immunoactive lyophilised extract of 21 bacteria strains coming from eight bacteria species (Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus viridans, Streptococcus pyogenes, Klebsiella pneumoniae ssp. pneumonia, Klebsiella pneumoniae ssp. ozaenae, Staphylococcus aureus, Moraxella catarrhalis) often associated with respiratory infections. Taken orally, it is capable of inducing non-specific innate and adaptive immune responses in an individual. Following intestinal absorption, OM-85 stimulates immune cells in the intestinal mucosa. As a result, OM-85 can raise the overall body defences against infections by shaping the dendritic cell activation into a ‘pre-alert’ phenotype.**

**Efficacy**

The efficacy of OM-85 in children was supported in a recent meta-analysis of eight randomised controlled trials.18 Mean age and number of RTIs were comparable between the OM-85 (n=435) and placebo (n=416) groups at admission. Following treatment, there was a significant decrease in the percentage of children with recurrent RTIs (defined as at least three RTIs in six months) in the OM-85 treatment group relative to the placebo group (32 versus 58.2 %, p<0.001) (see Figure 1). There is also an association between OM-85 efficacy and the number of RTIs in the year prior to treatment indicating that patients with the highest frequency of RTIs benefit the most from treatment (see Figure 2). OM-85 was also shown to significantly reduce the duration of acute RTI, the number of infections, the use of antibiotics and conventional drugs, and the time on treatment compared with placebo.14

Another recent study looked at the effect of OM-85 on wheezing attacks associated with acute RTIs in children over the course of 12 months.33 Wheezing attacks are also a large healthcare concern, responsible for many hospital admissions in young children. OM-85 significantly reduced the number of wheezing attacks (37.9 % cumulative reduction, p<0.001) and the number of RTIs (31.4 % cumulative reduction, p<0.001) relative to placebo in the children studied (n=75).

OM-85 was also shown to improve Ig levels and reduce infections in children with recurrent RTIs and hypogammaglobulinemia.34 This therapy significantly increased IgG and IgA levels post-treatment versus pre-treatment as well as versus placebo, with many reaching normal serum levels for their age.

**Safety**

The safety profile of OM-85 has been evaluated during more than 30 years of post-marketing experience. Adverse events are mostly non-serious and transitory. The most common side effects are headache and nausea, and OM-85 has shown a similar safety profile as placebo. Furthermore, no signs of autoimmunity have been observed in any subjects. A recent study on the effect of OM-85 prophylaxis on autoimmunity in IgA-deficient children found no significant difference between receivers and non-receivers of OM-85 in terms of clinical or laboratory markers for autoimmunity during four years of follow-up.37

Parent education and practical prophylaxis are important in managing recurrent RTIs in children. Parents need to be aware of the options available and how best to use them to benefit their offspring. At present, for preventive treatment, OM-85 is indicated for children as follows: one capsule/sachet (3.5 mg) or 10 drops (11 mg/ml) per day on an empty stomach for 10 consecutive days per month for three consecutive months, ideally before the beginning of the autumn.
Improved understanding by parents will ensure optimal compliance and improved clinical outcomes.

Conclusions

Paediatric recurrent RTIs represent a huge global health burden, resulting in much morbidity and mortality in children. Moreover, they contribute greatly to socioeconomic costs in the form of absenteeism from work of parents as well as visits to the general practitioner. Antibiotic treatments are often prescribed in this population; however, the level of antibiotic resistance around the world. Preventive measures have therefore been almost entirely for the management of this disease and help reduce the risk of developing respiratory infections. At present, many practitioners still fail to employ prevention strategies in children with recurrent RTIs.

Currently there are several immunostimulants approved for use in treating recurrent RTIs and future trends will look to using and developing these more, making them available to a greater number of nations – particularly within developing countries that see higher childhood mortality rates from these diseases. OM-85 is currently the most studied immunostimulant and has the longest post-marketing experience with regards to efficacy and safety.