REVIEW ARTICLE

Practical Approach for the Diagnosis, Prevention, and Management of Recurrent Upper Respiratory Tract Infection in Children: Report from an Expert Closed-group Discussion

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Abstract

Respiratory tract infections (RTIs) are one of the most common infections in childhood. Due to the weaning of maternal immunity during the first year of life and relative immaturity of the immune system, children in the age group of 6 months to 6 years are predisposed to RTIs. Several guidelines are available from western countries on the diagnosis and management of RRTIs. However, owing to the economic, nutritional, environmental, geographic, and social diversity of India, the practical approach to RRTIs, especially, the recurrent URTIs, is likely to differ warranting the need for local guidelines. This expert consensus offers a practical guide for the diagnosis, prevention, and management of recurrent URTIs in pediatric outpatient settings in India.

Keywords: Children, Cough, Levosalbutamol, Pediatrics, Respiratory tract infections.

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Introduction

Respiratory tract infections (RTIs) are one of the most common infections in childhood. Due to the weaning of maternal immunity during the first year of life and relative immaturity of the immune system, children in the age group of 6 months to 6 years are predisposed to RTIs.[1,2] Children might suffer from several annual bouts of uncomplicated RTIs; however, one needs to draw attention to those children, who suffer from unusual yet recurrent or long-lasting infections.[1] Recurrent RTIs (RRTIs) in children pose a challenge to a pediatrician in terms of diagnosis, treatment, and prevention.[3]

The prevalence of recurrent upper RTIs (URTIs) has not been reported globally; however, few cohort studies have tried to estimate the prevalence of recurrent URTIs. A prospective, observational birth cohort study [Steps to the Healthy Development and Well-being of Children (STEPS)] followed 1,089 children from birth to 2 years of age to track RTIs using a daily symptom diary. Recurrent RTIs, defined as the occurrence of >98 respiratory illness days per year, were reported in 10% of the study cohort. Of the children with RRTI, 60% were diagnosed with at least 3 episodes of acute otitis media, 73% received at least 3 antibiotic treatments, and 21% were hospitalized for an acute RTI. By the age of 2 years, 12% of the children with RRTI were diagnosed with asthma.[1]

A longitudinal cohort study assessed all children born in Nijmegen, the Netherlands, between September 1982 and September 1983, repeatedly from 2 to 21 years of age with questionnaires related to URTIs, use of antibiotics, ear-nose-throat (ENT) operations, and known risk factors for URTIs. Of 693 children, 161 (23%) suffered from relapsing recurrent URTIs between 0 years and 21 years of age, and 7 children (1%) suffered from persistent recurrent URTIs throughout 21 years. Among 166 children with recurrent URTIs (between 8 years and 21 years), 140 children (84%) had recurrent URTIs before the age of 8 years.[4]

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A cross-sectional survey from India, involving 2,158 school children between the age group of 5 years and 15 years, reported 78 children with chronic suppurative otitis media (CSOM). Among them, 31.58% had a history of recurrent URTI.[5]

Several guidelines are available from western countries on the diagnosis and management of RRTIs. However, owing to the economic, nutritional, environmental, geographic, and social diversity of India, the practical approach to RRTIs, especially, the recurrent URTIs, is likely to differ warranting the need for local guidelines. Instead of this, an expert consensus meeting was

held to develop a practical guide for the diagnosis, prevention, and management of recurrent URTIs in the pediatric outpatient settings in India.

Materials and Methods

A total of seven meetings were convened between August 31, 2020, and September 5, 2020, to discuss a practical approach to RRTIs in children in India. An expert group comprising leading pediatricians from across India deliberated on different aspects related to RRIs. Owing to the prevailing coronavirus disease 2019 (COVID-19) pandemic, the meetings were convened on a virtual online platform. To facilitate the discussion, a qualitative question-and-answer-based format was used. A literature review was carried out in the PubMed Database to identify relevant articles between January 2001 and October 2020 using keywords "respiratory tract infections", "recurrent respiratory tract infections", "respiratory infections", "expert consensus", "recurrent infections, "India", "children", "upper respiratory tract infections", "common cold", "pharyngitis", "rhinosinusitis", "otitis media", "immunostimulants in respiratory infections", immunostimulant", "antibiotics", "viral infections", "guidelines", and "nonspecific immunomodulators". The articles were circulated among the expert panel members before the board meeting to guide the discussion. The key highlights of the Expert Panel Discussion for each of these topics have been summarized in this manuscript.

Results and Discussion

Definition of Recurrent Upper Respiratory Tract Infections

Experts' Opinion

Recurrent URTIs involve three and more episodes of infection in 6 months or 6–8 episodes of established acute infections in a year.

There is no universal consensus on the definition of recurrent childhood RTIs. According to the Indian expert consensus in 2017, three or more episodes of respiratory tract illness or >15 days of symptoms in past 3 months are considered RRTIs.[2] Children are categorized into having RRTI, if preschool children, up to 3 years of age, report eight or more episodes of airway infections per year and children older than 3 years of age present with 6 or more episodes of infections per year, in the absence of any underlying pathological condition. Within the purview of URTIs, three episodes of otitis media in 6 months or four episodes of otitis media in a year; >5 episodes of infectious allergic rhinitis per year, and >3 episodes of pharyngitis or tonsillitis within a year are regarded as a recurrent infection.[6]

Age of Occurrence of Recurrent Upper Respiratory Tract Infections

Children <6 months of age are protected from infections by maternal antibodies and children aged 6 or more would have developed a mature immune system to fight infections.[2,7] Hence, by the design of nature, children between 6 months and 6 years of age are vulnerable to RRTIs as their immune system is still maturing.[2,8]

Experts agreed that nearly 50–60% of children aged <15 years present with RTIs. Nearly 30–50% of them had recurrent episodes. The majority of the infections are of mixed type, viral, and bacterial. The prevalence of otitis media has decreased by 5–10% in India.

Symptoms of RRTI

In general, the symptoms of RTIs include at least one of the following: runny nose, nasal congestion, sore throat, cough, earache, wheezing, and/or shortness of breath lasting at least 2–3 days or more. The majority of RTIs affecting the upper respiratory tract present as common cold, tonsillitis, pharyngitis, laryngitis, rhinosinusitis, and otitis media.[6]

Experts' Opinion

- Recurrent URTIs were reported in children aged between 6 months and 6 years. However, it is quite common in preschool children.
- In urban cities, children aged <4 years are more frequently affected by recurrent URTIs because of early exposure to day-care centers.
- In children aged <2 years, recurrent URTIs are largely attributed to bottle feeding.

According to the experts, recurrent URTIs are characterized by similar or varying symptoms at each presentation/occurrence. However, in clinical practice, most children present with similar recurrent symptoms such as fever, runny nose, sneezing, or enlarged tonsils, with the predominant reason being exposure to similar risk factors.

Risk Factors for Recurrent URTIs

Experts' Opinion

Nearly 60–70% of patients show up with similar symptoms of URTIs, while 30–40% may present with variable symptoms of URTIs or LRTIs.

The risk factors associated with RRTIs are immune-related or nonimmune-related (Table 1), and some of the risk factors modulate the immune system and hence influence the course of RRIs.[2,9,10]

There is an association between some risk factors and acute RTIs. In a study, multiple logistic regression analysis showed that 5–9 vs 10–14 years age group, family history of allergic disorder, family history of asthma, presence of smoke outlet in kitchen, and absence of windows in sleeping room increased the odds of suffering from acute RTIs.[11]

In the last two decades, nutritional deficiencies, especially of vitamins A and D, have contributed to recurrent URTIs. Allergy and allergens significantly contribute to recurrent URTIs as precursors to infection. Allergic cough and cold manifest with secondary infectious complications.

Experts' Opinion

- Nearly 60–70% of patients show up with similar symptoms of URTI, while 30–40% may present.
- Risk factors for recurrent URTIs are:
  - Bottle feeding
  - Failure to vaccinate children with pneumococcal vaccine (especially under the age of 2 years)
  - Exposure to smoking in the family
  - Early socialization at day-care centers
  - Recurrent environmental factors such as pollution and allergens
  - Parenteral atopy
  - Nutritionally acquired immunodeficiency
  - Educational status of mothers
  - School-going siblings, pets
  - Airborne irritants (mosquito repellents, incense burning, and talcum powder)
  - Milk (unpasteurized)
  - Low immunity with variable symptoms of URTIs or lower RTIs.

Table 1: Risk factors associated with recurrent respiratory tract infections

Immunological	*Non-immunological*
• Atopy and allergies	• Ciliary defects
• B-cell and T-cell deficiency	• Ineffective clearance of mucus
• Phagocytic defects	• Airway obstruction
• Defect in NK cell activity	• Chronic infections
• Complement deficiency	• Cardiovascular abnormalities
	• Food allergies/micronutrient deficiency
	• Social (schooling, daycare visits)
	• Environmental (indoor or outdoor pollution, poor ventilation at home/school, pets)

Red Flags for Recurrent Upper Respiratory Tract Infections

A comprehensive guideline is lacking concerning clinical features that should alert clinicians toward further examination for RRTIs.[12] Based on personal experience, experts pointed out various red flags for recurrent URTIs. Physicians should be on the lookout for the red flags listed in Table 2. These red flags could help either in the prevention or warrant immediate hospitalization.

Consequences of Recurrent Upper Respiratory Tract Infections

Recurrent RTIs have been associated with school/work absenteeism, negative impact on the quality of life, economic burden, frequent medical visits, antibiotic overuse, bacterial resistance, and decline in lung function.[6,9]

Diagnostic Approach to Recurrent Upper Respiratory Tract Infections

Personal and family history and physical examination is the routine evaluation strategy. It is unusual to find an underlying cause in a thriving child with RRI. In the event of a family history of immunodeficiency, early immunologic evaluation is warranted.[13] A generalized approach to diagnosis includes ENT examination, chest X-ray, blood work-up, and culture test.[9,13] in addition, virologic test and immune profiling can be done on a case-to-case basis.[9,13]

In clinical practice, it is rather difficult to diagnose recurrent URTIs. Hence, the steps outlined in Figure 1 can be considered as a referral for diagnosing recurrent URTIs.

Experts' Opinion
Recurrent URTIs are associated with several consequences, such as loss of appetite, failure to thrive, school absenteeism, poor scholastic performance, loss of sleep for patients and parents, parents' absenteeism from work, the financial burden on parents, and behavioral disorders. Hence, early diagnosis and prompt treatment are warranted.

Experts provided criteria for differentiating the severity of infections (Table 3).

Table 2: Red flags for recurrent respiratory tract infections

Red flags for prevention of recurrent upper respiratory tract infections	
• Failure to thrive (growth chart affected, decline in growth parameter by two centiles, no age-appropriate weight gain)	• Early morning sore throat, cough, or vomiting
• Reduced physical activity (children not playing as usual)	• Cardiac system anomaly
• Vitamin D deficiency	• Silent cardiac conditions
• Not able to sleep (sleep disturbance or snoring)	• Gastroesophageal reflux disease
• Low-birth-weight infant being fed cow's milk	• Family history of atopy
• Preterm birth	• Allergy: Atopic dermatitis or eczema, Allergic rhinitis or Asthma
• Excessive crying	• Primary and secondary immunodeficiency related to nutritional deficiency
• In children of any age, snoring at night, keeping the mouth open, dry mouth or lips when awake in the morning, or dental abnormalities due to constant mouth breathing.	• Disabled children (Down's syndrome, children always in prone position)
• Behavioral changes (violent behavior, using bad words, and irritable)	• Congenital disease (cystic fibrosis, Down's syndrome, fistulas)
• Consanguineous marriage	• Comorbidities
• Unusual behavior/irritability	• Frothy stools (fat intolerance)
Red flags for immediate hospitalization	
• Toxic looking children	• The disease persists for >7 days with other systemic problems
• High-grade fever	• Reduced intake of food or feeding difficulties
• Respiratory rate: >30 breaths per minute	• Need for intravenous antibiotics
• Chest retraction	• Inability to speak
• Irritability	• Drooling
• Constant vomiting	• Difficulty in swallowing
• Dehydration	• Stridor
• Cyanosis	

Management of Recurrent Upper Respiratory Tract Infections

Recurrent RTIs in children present as a clinical challenge for treating physicians in terms of treatment.[6] The primary management goal was to offer symptomatic treatment starting with antipyretics for controlling fever. Since viral infections are self-limiting, symptomatic treatment has to be provided for 3 days before considering the administration of antibiotics. Other treatments, including antibiotics, antihistamines, and cough therapy, must be offered on the basis of clinical presentation and thorough workup.

Step 1: Evaluation of patient and family history	Step 2: Evaluation of patient for current illness and past illness	Step 3: Evaluation of underlying disease condition	Step 4: Laboratory and other investigations	Step 5: Refer to ENT specialist and allergist/ immunologist
• History of allergies in patients and family (atopy or skin symptom) • Age • age at the time of onset of the first episode • Number of recurrent episodes in the past • Factors like preterm birth, use of ventilator, etc • Vaccination status • Sleep disturbance or disorder	• Patient history of allergy • Family history of allergy • Vaccination status • Failure to thrive • Nutritonal status (growth chat [is growth affected?]) • Check for primary and secondary immunodeficiency • Anatomical problems (nasal foreign body, adenoids) • Severity of infection • Infection presentation (usual of atypical) • Halitosis • Presence of foreign body • Thorough examination of ears, nose and throat • Immunodefciency in upper respiratory infection is suspected if there are >8 otitis episodes/year >2 sinusitis year • Immunodefeciency • Tuberculosis • Human immunodefi-cency infection	• Cardiac evaluation for congenital disease (mid ventricular septal defect (VSDs) fistula • GERD • Cystic fibrosis • Comorbidities • Urinary tract infections • Congenital disease (Down's syndrome) • Cillary dyskinesias	• Hemogram peripheral smear test • X-ray • Throat swab • In patients with underlying urinary • Tract infections, ultrasound for obstruction, post-and pre-void volume, and renal parenchyma • C-reactive protein • Allergen test • Genetic analysis, only if absolutely required	• Immunoglobulin (ig)-GAME screening: total level may be within normal: however as specific igE may be higher against a particular allergen • Complete blood count with CD4/CD8 ratio and other CD+ panel test' (optional: not routinely recommeded unles ther is an indication for primary or secondary immunodeficiency
SPUR (severe, persistent unusual recurrent infections),	• SPUR (severe, persistent unusual and recurrent infections), functional immunodeficiency, and predisposing factors. • Lmghopenia (<200 cell per mm, neutropenia; unabating fever dospite antibiotic therapy, deep-seated abscess, recurrent candidiasis and family history of immunodeficiency		• Only when the patient presents with recurrent URTIs without fever or secondary infection with fever, and is aged above 1 year of age; or there is family history of allergy	

Fig. 1: Diagnostic approach to recurrent upper respiratory tract infections

Treating Cough During Upper Respiratory Tract Infections

Symptomatic treatment options for cough include antitussives, mucolytic agents, expectorants, and bronchodilators. The Central Drugs Standard Control Organization approved levosalbutamol and terbutaline-based cough formulation for symptomatic relief of bronchospasm in bronchial asthma and chronic bronchitis.[14]

A cross-sectional survey analyzing the trends in cough treatment found that 78 and 76% of children received first-generation sedative antihistamines and second-generation non-sedative antihistamines; 62% received mucolytics; 63% were prescribed expectorants (63%); 50% were prescribed antibiotics; 3% received corticosteroids (nasal spray); 12% received nutritional supplements. Antitussives, including dextromethorphan and codeine, were prescribed for up to 6 days.[15]

A survey reported that a significant proportion of caregivers/patients preferred levosalbutamol-based bronchodilatory cough formulation (92%) over salbutamol-based bronchodilatory cough formulation (51%) for cough management.[16] According to a cross-sectional cohort study, bronchodilatory cough formulations significantly improved the cough severity by 72% in those with a chronic condition and 76% in those with an acute condition.[16]

Table 3: Criteria for the severity of infections

Mild:	Symptomatic presentations that are manageable at home (mild cold, fever, and cough)
Moderate:	High-grade fever, cough, and cold, requiring antibiotics; takes 4–5 days for recovery
Severe:	Sudden high-grade fever; loss of appetite, dehydration requiring intravenous drips, and altered sensorium generally require hospitalization

Kiran et al. conducted a phase IV clinical trial to test the efficacy and safety for the combination of levosalbutamol (bronchodilator), ambroxol hydrochloride (mucolytic agent), and guaifenesin (expectorant) in the treatment of productive cough associated with bronchospasm in conditions, such as bronchitis and bronchial asthma as well as all conditions associated with tenacious mucus,

wheezing, and chest congestion. The study showed that a combination of levosalbutamol, ambroxol, and guaifenesin could reduce the severity of cough by 43 and 85% on day 3 and day 5, respectively.[17]

Kiran et al. conducted another study to determine the efficacy and safety of a fixed-dose combination, containing terbutaline, ambroxol, and guaiphenesin, for the treatment of productive cough in children aged above 2 years. A majority of patients had >80% reduction in their mean cough severity score at the final visit (day 5) with respect to all the parameters. Terbutaline-based cough formulation could reduce the severity of cough by 47.72 and 86.78% on day 3 and day 5, respectively.[18]

The course of cough management treatment depends on the type, severity, and duration of cough; and age of children. Steam inhalation is advisable, and it is recommended to make the child sleep in a reclining position (30° elevation). Bronchodilators are prescribed from 2 years onward. Although there is not much difference between levosalbutamol and terbutaline syrup, levosalbutamol is preferred as first-line in patients <5 years and terbutaline in older patients (above 6 years) and in patients who did not respond to levosalbutamol. Levosalbutamol nebulization can also be considered as a treatment option. Some children might respond better to a terbutaline-based syrup after they are switched from levosalbutamol, because of the downregulation of beta-2 adrenergic receptors. A metered-dose inhaler with spacer is another option. It delivers the drug that is sufficient to have a therapeutic effect and, at the same time, prevents substantial side effects due to minimum dose delivery. Cough suppressants are not recommended; however, dextromethorphan is preferred in case of loss of sleep and vomiting and discomfort due to cough. Noscapine is used in a small section of patients with whooping cough. As the drug is extremely bitter, patient compliance is very low.

Experts' Opinion

- Levosalbutamol can be considered as first-line in patients <5 years of age.
- Terbutaline was preferred in older patients (above 6 years) and in patients who did not respond to levosalbutamol
- Age-wise use of medications for cough and cold:
  - Infant aged <6 months: Bronchodilator with mucolytic
  - Infants <3 years: Levosalbutamol
  - Older age group: Bronchodilator with mucolytic and expectorant
  - Adults (>18 years): Terbutaline

Ambroxol is a mucolytic agent that is known to promote surfactant synthesis and has a high potential for an anaphylactic reaction. Ambroxol is used for noisy breathing. Theophylline has a narrow therapeutic index and is usually avoided.

Antibiotics

Antibiotic use in childhood URTIs remains debatable as >90% of the infections carry a viral etiology. Moreover, over prescription of antibiotics could lead to antibiotic resistance. In certain scenarios, such as severe acute rhinosinusitis lasting >10 days and severe acute otitis media, antibiotics are warranted.[19]

Amoxicillin or amoxicillin/clavulanate remains the first-line therapy for URTIs.[20] Macrolides like azithromycin in addition to their antibacterial activity, are also effective against several respiratory viruses. Macrolides enhance the immune response by promoting the production of immunoglobulins and exert anti-inflammatory effects by regulating inflammatory responses and attenuating the production of anti-inflammatory cytokines.[21,22]

Evidence shows that azithromycin can combat viral infections through various mechanisms. It interferes with the internalization process during the early phase of viral invasion and targets newly synthesized progeny viruses.[23]

Antibiotics should be started immediately, if the bacterial origin is confirmed on initial presentation (some red flags: purulent pharyngitis-confirmed bacterial infections; toxic presentation; high-grade fever, purulent discharge, a tendency toward lower RTIs, no improvement in children; increased C-reactive protein levels). The choice of antibiotics should be based on the infecting organism, the resistance pattern of the organism, the child's immune status, the toxic state of the child, the monetary status of the patients, reliability of follow-up, and age. The first choice of antibiotic is amoxicillin or amoxiclav. Cephalosporins or other penicillins may also be considered. Antibiotics are initiated in the case of otitis media and sore throat (classical strep throat: bilateral jugulodigastric lymph nodes, tender cervical adenopathy, glaring red tonsils oozing pus, odynophagia, high-grade fever, and stomach upset). Amoxicillin is preferred for group A streptococcal infection, while azithromycin for *Arcanobacterium haemolyticum*. In the case of ear infections (purulent discharge), bactericidal antibiotics should be given based on immune status. High-end antibiotics can be administered to a non-immunocompetent child. The use of antibiotics must be stalled and postponed in case of an immunocompetent child or has eustachian tube dysfunction. In the current COVID-19 scenario, macrolides (azithromycin) are preferred.

If the child is older and has a recurrent wheezer, then azithromycin or clarithromycin can be considered. Clarithromycin, unlike azithromycin, has a high potential for drug–drug interactions. Macrolides are given to school-going children with wheezing. Azithromycin is beneficial because it affects cytokines and also has anti-viral and anti-inflammatory effects. Administering macrolides to infants aged <3 months could be associated with an increased risk of pyloric stenosis.

Experts' Opinion

- No antibiotics should be given until three days from the onset of infection if these are believed to be of viral origin.
- If no improvement is seen within three days of onset of infection, antibiotics can be initiated.
- Age-wise preference of antibiotics:
  - 0–3 years: Penicillin (if not allergic to penicillin)
  - >5 years: Macrolides

If the patient has taken amoxicillin in the previous three weeks, then amoxiclav should be given because of the generation of beta-lactamase. Alternatively, cefpodoxime can be used, as it has fewer effects on the oral microbiome as compared to amoxicillin. From the perspective of patient compliance, azithromycin would be preferred over amoxiclav.[24] In acute recurrent URTIs, azithromycin can be given for 3 days at a dose of 10–12 mg/kg body weight.[25] Macrolides (azithromycin) are given for 7–10 days in case of pertussis.[26]

Prevalence of Superinfections and Co-infections

More than 50% of patients with viral infections develop a bacterial infection in due course of time. About 10–15% have ear problems after viral infection.

Age of presentation:
- Children aged <6 months: Otitis media occurs after viral infection.
- Older children: Sinusitis and rhinitis occur after viral infection.

Prevention of Recurrent Respiratory Tract Infections

Recurrent URTIs have a significant negative impact on the quality of life of children as well as their caregivers. Recurrence of infections, especially viral infections, can induce immune dysfunction and set off a vicious cycle of RRTIs complicated by bacterial superinfections, exacerbation of cough, and increased risk of asthma development.

Thus, it is necessary to adopt a multi-faceted management strategy for RRTIs to:[6]
- Reduce the clinical burden of infection.
- Interrupt the vicious cycle of viral and bacterial mucosal colonization.
- Reduce inflammation.
- Correct the defective immune response.

Preventive Strategies in Recurrent Upper Respiratory Tract Infections

Preventive measures include parental education and awareness; active immunization; alternative strategies for prevention of RTI—non-specific immunostimulation/immunomodulation.[1]

Education and Awareness About Prevention of Recurrent Respiratory Tract Infections

Patient, family, and public involvement is key to the prevention of infections. Raising awareness among parents of the modifiable risk factors for RRTIs can play a large role in the prevention of recurrence of infections. Parents, in particular, mothers, should be educated on the benefits of breastfeeding. A child's exposure to passive smoking and indoor/outdoor pollution are some of the risk factors within parental control. Furthermore, it is important to inform parents that surgical approaches (including tonsillectomy and adenoidectomy) might not be the appropriate solution for reducing RRTIs in the majority of children, as they may confer only modest benefits that need to be weighed against the risks and potential complications.[6]

Experts' Opinion
- Awareness among the general public can be created through social media and health awareness camps.
- Special focus on the prevention of overuse of antibiotics is worthwhile to stem the rising antibiotic resistance.
- Healthcare professionals should be supported by patient education materials on the management and prevention of recurrent URTIs and parent-counseling materials.

Active Immunizations

The ultimate goal of vaccination is to provide effective, active immunization against a specific pathogen. There are vaccines for common influenza viruses, measles, pertussis (*Bordetella pertussis*), the potentially invasive bacteria *Haemophilus influenzae* type b, and many serotypes of *Streptococcus pneumoniae*. These vaccines are widely used for the prevention of these diseases.[6,27]

Optimizing the use of influenza, pneumococcal, pertussis, and measles vaccines is mandatory to reduce the acute RTI burden.[24] Routine influenza vaccination is recommended for anyone older than 6 months of age who is without contraindications.[6]

Experts' Opinion
- Vegetarians have a vitamin deficiency and hence must be supplemented in the event of a deficiency.
- Multivitamins and minerals are advised for children who are fussy eaters.
- Vitamin D deficiency is common in *burkha*-clad girls or kids not exposed to adequate sunlight.
- There is no role for zinc in preventing RRTIs. Overconsumption of zinc can cause copper deficiency.

Multivitamin Supplements

The use of multivitamins for the prevention of RTIs has been contentious. A Cochrane review found that vitamin C supplementation was not effective in reducing the incidence of colds in the normal population.[28] However, there are evidence supporting the role of multivitamins (vitamins A, B6, B12, C, D, E, and folate); trace elements (zinc, iron, selenium, magnesium, and copper); and omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid, in modulating the immune system. Inadequate intake and status of these nutrients can lead to a decrease in the body's resistance to infections and consequently increase the disease burden.[29] Zhang et al. found that the serum levels of vitamins A, D, and E were low in children with RRTI. Low serum levels of vitamins A, D, and E were associated with RRTIs in these children.[30]

Experts' Opinion
- Routine vaccination must be offered to children as specified by the Indian Academy of Pediatrics.

Immunostimulants

The frequency of RTIs remains high despite antibiotic use and vaccination. Immune deficiency can be attributed to the immaturity of the immune system in children and immunosenescence in the elderly.[31]

There is no significant alteration in the immune system in children with RRTIs.[10] However, studies have reported several transient alterations in the immune system and its function among children suffering from RRTIs.[2,9,10] The immune-related changes could be a consequence of viral infection. Children with RRTIs might experience viral infection-induced immune depression, which could promote the recurrence of RTIs.[10] Several viral infections may alter cytokine responses or phagocytosis. There are reports of low levels of IgA, IgM, and IgG subclasses and a decrease in the number of CD4+, CD8+, CD19+, and natural killer cells.[2,10]

Immunostimulants are a heterogeneous group of compounds that act non-specifically on the immune system. Immunostimulants can induce the activation of the immune system, either upregulating it or by promoting the activity of one of its components.[31] Thus, immunostimulants can help in improving the clinical outcomes in children. Immunostimulants can be used to correct the deviated immune system, as well as reduce the need for repeated antibiotic therapy.[32,33]

The rationale for the use of orally administered immunostimulants for the prevention of respiratory conditions stems from the gut–lung immune axis, which invokes innate and adaptive immunity.[34] Five immunostimulants, namely OM-85, pidotimod, ribomunyl, LW50020, and polyvalent mechanical bacterial lysate, have been studied in children with RTIs. A meta-analysis assessed

the safety and efficacy of immunostimulants vs. placebo in children to prevent acute RTIs. This meta-analysis showed that immunostimulants reduced the incidence of acute RTIs by 40% on average in susceptible children.[35]

Experts' Opinion
- Experts recommend the use of immunostimulants and immunobiotics for preventing RRTIs.

Immunobiotics, such as the probiotic lactic acid bacteria strains, have a beneficial effect through their immunomodulatory activity. Immunobiotics stimulate mucosal immunity and offer protection to other mucosal sites besides the gut. Evidence supports the use of oral immunobiotics as it increases resistance against respiratory viral infections.[36]

Conclusion

Recurrent URTIs are indeed a significant concern in children. Recurrent URTIs involve three and more episodes of infection in 6 months or 6–8 episodes of established acute infections in a year. At the time of presentation, it is important for doctors to identify the key red flags for recurrent URTIs. Even before diagnosing the condition, the child must be offered symptomatic treatment. Diagnosis includes meticulous evaluation of patients as outlined in the article. Antibiotics, antihistamines, and cough therapy are offered based on the clinical presentation and thorough workup. Levosalbutamol-base cough syrup is preferred in younger children, while terbutaline is preferred in older children. No antibiotics should be administered until 3 days from the onset of infection unless any of the red flags are noted. Amoxicillin, amoxiclav, cephalosporins, penicillin, and macrolides are used for URTIs. Azithromycin is preferred to amoxicillin when compliance is an issue. Immunostimulants and immunobiotics can be used for preventing RTIs.

Clinical Significance

Frequent RRTIs in children are among the most common causes of preschool and school absences, visits to physicians, and hospitalization. For treating physicians, RRTIs pose a significant diagnostic and therapeutic challenge. Several guidelines are available from western countries on the diagnosis and management of RRTIs. However, owing to the economic, nutritional, environmental, geographic, and social diversity of India, the practical approach to RRTIs is likely to differ warranting the need for local guidelines. This document provides expert opinions on various aspects of RRTI to assist physicians with the uniform approach in diagnosing and treating RRTIs in India. This practical approach could reduce diagnostic errors and the rate of antibiotic prescription in children with RRTIs in India. The management of RRTIs is more preventive than curative. Preventive strategies are moving to the forefront as part of a holistic effort to curtail the incidence of RRTIs and limit their sequelae in children. In this article, we have provided expert opinions on various preventive strategies that could improve the immune response and minimize disease recurrence in children.

Authors' Contributions

All authors have contributed equally towards the development of the manuscript.

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