

Oral bacteriotherapy in children with recurrent respiratory infections: a real-life study

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Abstract. Children with recurrent respiratory infections (RRI) represent a social issue for the economic burden and the familiar negative impact. Bacteriotherapy, such as the administration of “good” bacteria, is a new therapeutic strategy that could be potentially effective in preventing infections. The current study tested the hypothesis of preventing RRI by oral Bacteriotherapy in a real-life setting. This open study was conducted in an outpatient clinic, enrolling 51 children (27 males, mean age 4.8 ± 2.6 years) suffering from RRI. Children were treated with an oral spray, containing *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a (125×10^9 CFU/g), 2 puffs per os once/day for 30 consecutive days; this course was repeated for 3 months. The evaluated parameters were: RI number and school absences reported in the current year; these outcomes were compared with those recorded in the past year. The mean number of RI significantly diminished: from 5.17 (2.30) in the past year to 2.25 (2.43) after the treatment ($p < 0.0001$). The mean number of school absences significantly diminished (from 3.35 to 1.86; $p < 0.0001$). In conclusion, this real-life study suggests that oral Bacteriotherapy with *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a could efficaciously and safely prevent RRI in children. (www.actabiomedica.it)

Key words: recurrent respiratory infections, bacteriotherapy, *Streptococcus salivarius* 24SMB, *Streptococcus oralis*89a, oral spray, children

Introduction

The recurrent respiratory infections (RRI) in children constitute an impressive drawback for the family and a significant burden for the Healthcare Service (1-3). Pediatricians and otolaryngologists are, therefore, engaged to counteract this relevant issue in daily practice.

Many factors may cause the RI recurrence, namely early age (because of the relative immaturity of the immune system), early attendance at nursery school, environmental pollution, passive smoking, low socio-economic level, and allergic disorders (4). Noteworthy, viral infections exert a crucial role as are the most common cause of respiratory infection in childhood (5).

The guidelines state the appropriate use of anti-inflammatory drugs and antibiotics, even though they are really prescribed on an empiric basis in clinical practice and often uselessly (6, 7). Notably, antibiotic overuse/abuse is frequently associated with resistance to many bacteria because multi-resistant microbes are selected by indiscriminate and excessive antibiotic prescriptions. Consequently, to prevent RRI could succeed in reducing antibiotic resistance, complications, medical costs, and the family and social burden. However, many prevention attempts have experimented in the past. Unfortunately, these efforts were frequently expensive, long-lasting, and/or ineffective, and even dangerous. Therefore, to prevent RRI is still an unresolved puzzle.

Respiratory microbioma is currently an intriguing topic that deserves particular attention (8,9). The “normal” nasopharyngeal microbioma counteracts the pathogens. As a consequence, it has been hypothesized that the administration of “good” bacteria (usually saprophytic) could prevent infections contrasting the growth of the pathogens (10). In this regard, it was initially reported that an α -haemolytic strain, obtained from healthy children (*Streptococcus salivarius* 24SMB), and administered as a nasal spray, reduced the recurrence of acute otitis media (AOM) in otitis-prone children (11). A further study showed that *Streptococcus salivarius* 24SMB, associated with *Streptococcus oralis*89a, was effective in preventing recurrent otitis in a real-life setting (12). These findings were confirmed by a study that reported a positive outcome in the prevention of RRI in clinical practice (13).

Recently, this Bacteriotherapy compound has been proposed also as an oral formulation. A first study has been conducted in children with recurrent streptococcal pharyngotonsillitis caused by Group A β -haemolytic *Streptococcus* (14). This study showed that oral spray with *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a significantly reduced the number of streptococcal infections, the use of antibiotics, and the scholar absences.

Therefore, the current study aimed to extend the potential application of this new oral formulation also in children with RRI.

Materials and Methods

The present experience included 51 children (27 males, mean age 4.8 ± 2.6 years) with a history of RRI in the past year. Inclusion criteria were: i) age ranging between 3 and 10 years, ii) both genders, iii) documented RRI in the past year, iv) written informed consent by parents. Exclusion criteria were: i) severe allergic symptoms (such as able to interfere the assessment of treatments), ii) congenital or acquired immunodeficiency, iii) craniofacial abnormalities, iv) sleep apnoea, v) Down syndrome, vi) chronic disease (including metabolic disorders, cystic fibrosis, cancer, etc.), vii) clinically relevant passive smoking, and viii) previous (last 3 months) or current administration of drugs able

to interfere with the study (e.g. immunomodulators, homeopathic therapy, or systemic corticosteroids for at least 2 consecutive weeks).

Study design

The current experience was designed as an open study. Children with RRI were visited by the otolaryngologist for thorough management. Children were treated with a commercially available, class IIa medical device, oral spray containing *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a (Orogermina, DMG, Rome, Italy). It was administered as 2 puffs *per os* once/day for 30 consecutive days. The suspension consisted of a minimum of 125×10^9 CFU/g per bottle. This course was usually administered for 3 consecutive months. As Bacteriotherapy has a preventive activity, the first course usually started in the early autumn.

The number of RI and the number of days of school absence were considered. These variables were evaluated in the past year (T0) and the current year (T1).

Safety

Safety and tolerability were evaluated based on the number and type of adverse events recorded according to the rules of good clinical practice.

Study procedures

RI was diagnosed based on the symptoms reported by the parents, as previously defined (13, 15). The RI diagnosis was made when at least 2 symptoms or fever (axillary temperature $\geq 38^\circ\text{C}$), in addition to one other symptom (see below), were present for at least 48 hours. The considered symptoms were: mucopurulent rhinorrhoea, stuffy or dripping nose or both, sore-throat, cough (dry or productive), otalgia (earache), fever, and mucopurulent secretion. RRI diagnosis was performed on history, such as the patient's recall of symptoms.

The children were examined at study entry, and the follow-up re-evaluation (in the late summer). All assessed parameters were regularly recorded on a daily diary card.

Statistical analysis

Continuous variables were given as median with range and categorical variables as the number of subjects and percentage values. To evaluate the statistical significance of RI episode number and number of school days lost differences, the Wilcoxon test for paired samples was performed and then, the adjustment for multiple testing was done using the Bonferroni method. Differences, with a p-value less than 0.05, were selected as significant and data were acquired and analyzed in the R v3.6.2 software environment.

Results

All the children completed the study without any clinically relevant adverse event.

Bacteriotherapy significantly halved the mean number of RI episodes from a median value of 5 (2-10) in the past year (T0) to 2 (0-5) in the current year (T1) ($p < 0.0001$, Figure 1A).

Bacteriotherapy also reduced (about 35%) both the number of school days missed from 3 (0-10) at T0 to 1 (0-6) at T1 ($p < 0.0001$), Figure 1B).

Discussion

RI guidelines suggest limiting antibiotic prescription to severe and bacterial infections as most of RI are viral. In clinical practice, antibiotics are often prescribed ignoring guidelines precepts. In this regard, preventing RI could reduce antibiotic overuse/abuse and have important socio-economic outcomes. However, this topic is still debated and argued. In this regard, a placebo-controlled study investigated a 12-month treatment with azithromycin (5 mg/Kg/d) 3 days/week in children with recurrent rhinosinusitis (16, 17). This schedule reduced the number of rhinosinusitis, the medication use, and the severity of the symptoms. However, it is obvious that this preventive proposal is yet long-lasting and could induce resistance to macrolides. Macrolides resistance is an emerging problem in many countries (18). Moreover, long-standing antibiotic therapy is frequently associated with adverse events and antibiotic resistance. Instead, the so-called Bacteriotherapy, such as the administration of "good" bacteria, could be a promising way. The rationale is that some non-pathogenic physiological, mainly saprophytic, strains may protect from pathogens ("bad" bacteria) infections. In particular, *Strep-*

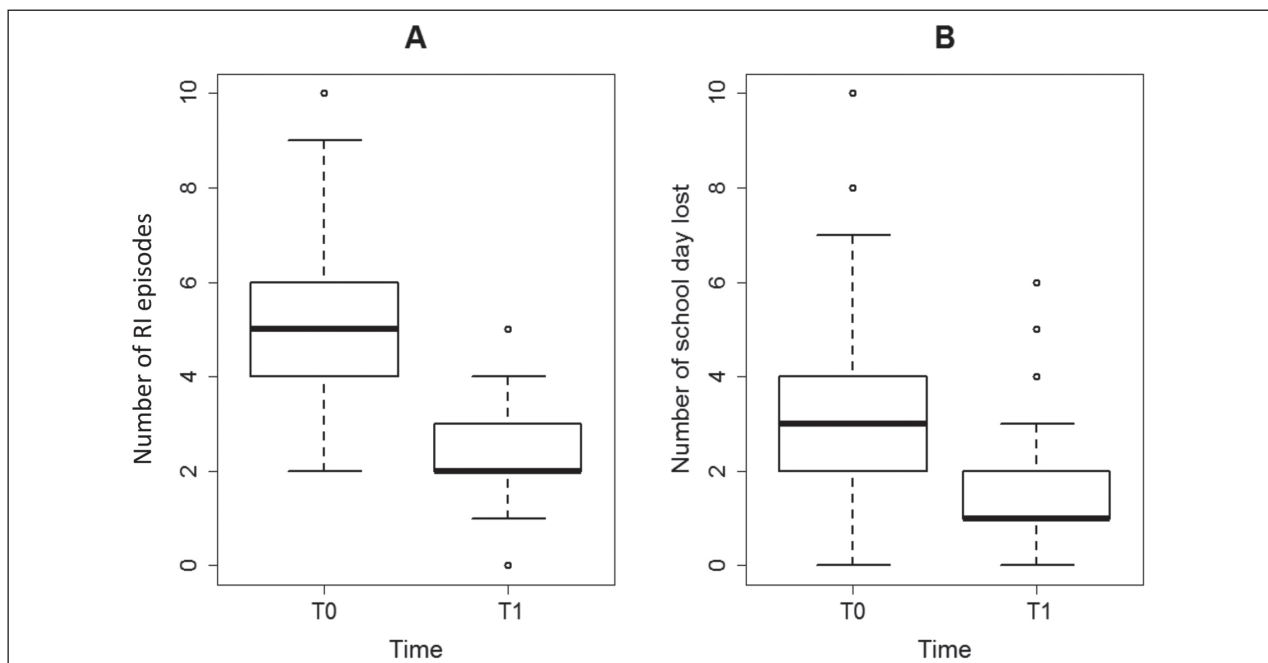


Figure 1. Panel A = number of RI episodes at T0 and T1; Panel B = number of school day lost at T0 and T1

Streptococcus salivarius 24SMB and *Streptococcus oralis*89a turned attention to this topic as some studies provided promising results (10-14).

The current experience real-life reported that *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a oral spray could reliably prevent RI; of note, no side effects were reported, so the compound was safe and well-tolerated by all treated children. Oral Bacteriotherapy significantly diminished RI and consistently school absences. These outcomes confirmed the previous studies (10-14) and may have a relevant spillover in daily practice.

However, this study has some limitations: i) to be an open study, ii) to be without a control-placebo group, iii) to be based only on clinical outcomes without cultural investigations, and iv) data concerning the past year were retrospectively collected by parents' queries. Thus, further studies should be conducted to correctly define unmet needs.

In conclusion, *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a oral spray could efficaciously and safely prevent respiratory infections in children.

Conflict of interest: All the authors, but VD employee of DMG, state that have no conflict of interest concerning the present paper.

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