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Bacteriotherapy for preventing recurrent upper respiratory infections in children: a real-world experience

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ABSTRACT:

Background: Recurrent upper respiratory infections (RURI) constitute a social problem for both their pharmaco-economic impact and the burden for the family. Bacteriotherapy could be an interesting preventive option.

Objective: The aim of this study was to evaluate the preventive effects of RURI in children.

Design: The study was designed as spontaneous and was conducted in real-life setting. Globally, 80 children (40 males, mean age 5.26 (2.52) years) with RURI were enrolled. Children were treated with *Streptococcus salivarius 24SMB* and *Streptococcus oralis 89a*: nasal spray 2 puffs per nostril twice/day for a week for 3 monthly courses. Number of URI, and school and work absences were evaluated and compared with the past year.

Results: Bacteriotherapy significantly halved the mean number of URI episodes being 5.98 (2.30) in the past year and 2.75 (2.43) after the treatment ($p<0.0001$). Bacteriotherapy also induced an over 35% reduction both in the number of school days and in the number of working days missed per month from 4.50 (2.81) to 2.80 (3.42) and from 2.33 (2.36) to 1.48 (2.16), respectively ($p<0.0001$).

Conclusions: This real-life study provides the first evidence that *Streptococcus salivarius 24SMB* and *Streptococcus oralis 89a* nasal spray could be effective in preventing RURI in children..

KEYWORDS: recurrent upper respiratory infections, bacteriotherapy, *Streptococcus salivarius 24SMB, Streptococcus oralis 89a*, nasal spray, children

INTRODUCTION

Upper respiratory infections (URI) during infancy and childhood are a relevant issue (1,2). As many children suffer from recurrent URI (RURI), it determines a relevant impact on pharmaco-economy and is a burden for both the family and the society (2,3). So, RURI represents a challenge for both the paediatrician and the otolaryngologist.

Many factors may be involved in promoting and/or causing RURI, including early age (for a relative immaturity of the immune system), early attendance at nursery school, air and home pollution, passive smoking, low socio-economic level, and atopy (2). In addition, viral infections may increase the probability of contracting frequent RI because of the high number of circulating viruses and numerous sub-types (3). Usually, viral infections are predominant, but bacterial over-infections may also frequently appear.

In common practice, the diagnosis of URI is usually based on a clinical ground, such as consideration of the clinical history, and the presence of typical signs and symptoms. As punctually pointed out by guidelines, treatment includes anti-inflammatory drugs and antibiotics prescribed on an empiric basis (3,4). On the other hand, anti-inflammatory agents may have relevant side effects, mainly in children. In addition, antibiotic overuse is frequently associated with the outgrowth of multi-resistant microbes. Actually, effective RURI preven-

Tab. I. Demographic and clinical characteristics of studied population (No. 80).

	WHOLE POPULATION (NO. 80)
Age at the beginning of treatment [yrs mean (SD)]	5.26 (2.52)
Preschool aged children (<6 yrs) [(No. (%)]	57 (71.25)
Male-to-female ratio (m/f)*	1.0 (40/40)
Days of treatment [median (LQ-UQ)]	89 (69-92)
[mean (SD)]	88.59 (32.54)
Follow-up duration [median (LQ-UQ)]	122.00 (94.00-156.50)
[mean (SD)]	132.00 (40.90)
Siblings [No. (%)]	44 (55.00)
Exposure to passive smoking [No. (%)]	15 (18.75)
Allergy [No. (%)]	6 (7.50)

Tab. II. Decrease in the number of URI, in the number of school days missed per month and in the number of working days missed per month after treatment with Rinogermina.

		>6 URI EPISODES/YR	<6 URI EPISODES/YR	P VALUE
Number of URI after treatment	Mean (SD)	5.8 (2.2)	2.0 (2.8)	<0.0001
	Median (LQ-UQ)	6.0 (4.5-7.0)	2.0 (1.0-4.0)	
Number of school days missed per month after treatment	Mean (SD)	2.2 (3.6)	1.4 (2.5)	<0.0001
	Median (LQ-UQ)	3.0 (1.5- 4.5)	1.0 (0-3.0)	
Number of working days missed per month after treatment	Mean (SD)	1.5 (1.9)	0.5 (1.6)	<0.0001
	Median (LQ-UQ)	2.0 (0-3.0)	0 (0-1.5)	
		0 (0-1.5)	0.5 (1.6)	

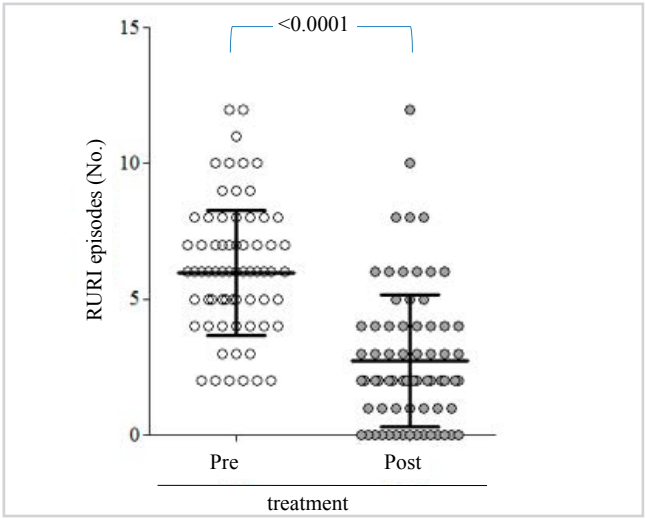

Fig. 1. Number of URI episodes in the past year before and after treatment with Rinogermina. Horizontal bars represent mean values with standard deviation. Each point represents an individual patient.

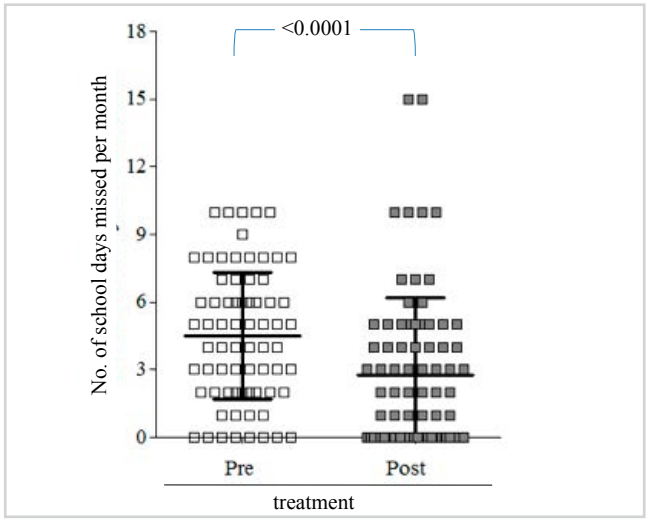

Fig. 2. Number of school days missed per month before and after treatment with Rinogermina. Horizontal bars represent mean values with standard deviation. Each point represents an individual patient.

tion might significantly affect risk of complications, medical costs, and social and family impact. On the other hand, many past attempts of prevention were tried, but they were usually expensive, long-lasting, and seldom fruitless or accompanied by adverse events. Therefore, preventing RURI using alternative ways might represent an interesting and stimulating issue. In this regard, an intriguing topic has been highlighted by the investigation of the upper airways microbiome (5). The physiological nasopharyngeal microbiome does physiologically inhibit the growth of local pathogens. So, it has been hypothesized that the administration of ‚good' bacteria could exert preventive effects on infections as it might wipe out pathogens. Some years ago, it was demonstrated that an α-haemolytic strain, obtained from healthy children (*Streptococcus salivarius 24SMB*), administered by nasal spray, had the capability to reduce the risk of new episodes of acute otitis media (AOM) in otitis-prone children (6). The results were promising, so a further study was successful in demonstrating that *Streptococcus salivarius 24SMB* associated with *Streptococcus oralis89a* administered as nasal spray in children suffering from recurrent AOM was effective in preventing recurrent otitis in a real-life setting (7). However, no clinical study evaluated the capacity of this combined Bacteriotherapy in children with RURI. Therefore, the present real-world study aimed to evaluate the po-

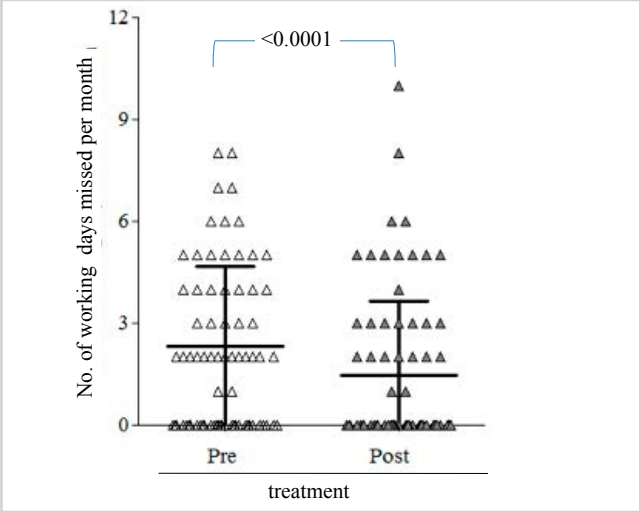

Fig. 3 Number of working days missed per month before and after treatment with Rinogermina. Horizontal bars represent mean values with standard deviation. Each point represents an individual patient.

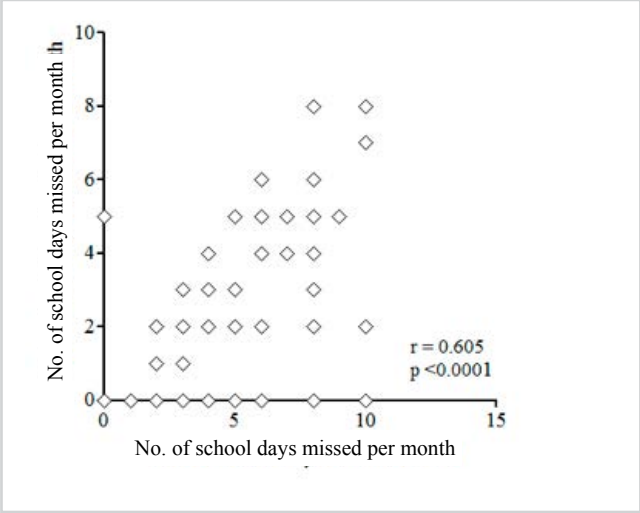

Fig. 5 Correlation between the number of school days missed per month and the number of working days missed per month.

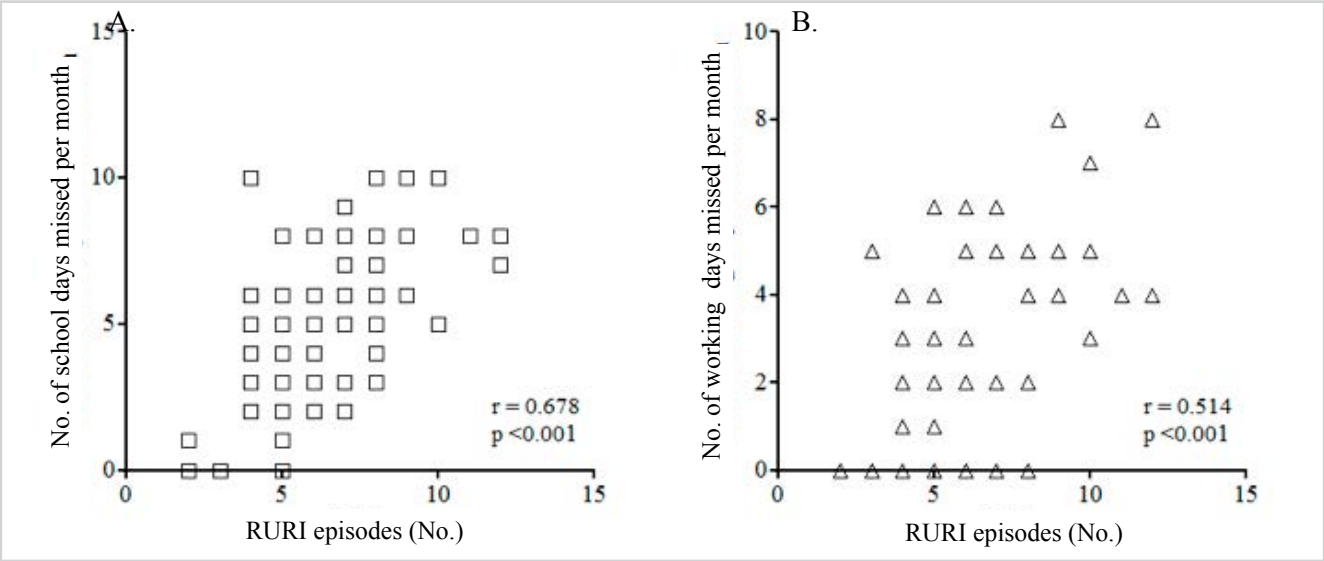

Fig. 4. Correlation between the number of URI episodes and the number of school days missed per month (panel A) or the number of working days missed per month (panel B).

ssible preventive effect of this Bacteriotherapy in a cohort of children suffering from RURI.

MATERIALS AND METHODS

Population and eligibility criteria

Globally, 80 children [40 males, mean age 5.26 (2.52) years] with RURI were enrolled in the study. Inclusion criteria were: i) age ranging between 3 and 14 years, ii) both genders, iii) documented history of RURI in the past year, iv) written informed consent by parents. Exclusion criteria were: i) severe allergic symptoms (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., immunomodulant, homeopathic therapy, or systemic corticosteroids for at least 2 consecutive weeks).

Study design

The current study was designed as retrospective and observational. Children with URI were initially visited by primary care paediatricians who sent them to the otolaryngologists for thorough management. Children were treated with a commercially available class IIa medical device nasal spray containing *Streptococcus salivarius 24SMB* and *Streptococcus oralis 89a* (Rinogermina nasal spray, DMG, Rome, Italy). It was administered in 2 puffs per nostril twice/day for 7 days. The suspension consisted of a minimum of 109 colony forming unit per dose. This course was usually administered for 3 consecutive months. As Bacteriotherapy has a preventive activity, the course usually started in early autumn.

The evaluated parameters were: the number of URI, and the number of days of school or work (for parents) absence in the past. These variables were evaluated in the past year and at follow-up re-evaluation. In addition, siblings' presence, and passive smoking were evaluated.

Safety

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

Study procedures

The investigators diagnosed URI on the basis of the symptoms reported by the parents, as previously defined (8). RI diagnosis was made when at least 2 symptoms or fever (axillary temperature >38°C), in addition to one other symptom, were present for at least 48 hours. The symptoms taken into consideration for this diagnostic purpose were: mucopurulent rhinorrhoea, stuffy or dripping nose or both, sore-throat, cough (dry or productive), otalgia (earache), fever, and mucopurulent secretion. RURI diagnosis was performed based on history, such as patient's recall of symptoms.

The children were examined at study entry, and at follow-up re-evaluation (in the summer). The study started in September 2016 and ended in June 2017.

All assessed parameters were regularly recorded in a daily diary card.

Statistical analysis

Demographic and clinical characteristics are described using means with SDs for normally-distributed continuous data (i.e. age) or medians with lower and upper quartiles for not normally-distributed. Any statistically significant difference in mean values or in median values of each continuous variable (URI number, number of school days or working days missed per month between pre- and posttreatment with Rinogermina or between patients with more or less frequent URI episodes was evaluated with the Wilcoxon signed-rank test or with Mann–Whitney U test, respectively.

Correlations were evaluated with Spearman rank-order correlation coefficient. We labelled the strength of the association as follows: for absolute values of r, 0 to 0.19 is regarded as very weak, 0.2 to 0.39 as weak, 0.40 to 0.59 as moderate, 0.6 to 0.79 as strong, and 0.8 to 1 as a very strong correlation (9).

Statistical significance was set at $p < 0.05$, and the analyses were performed using GraphPad Prism software, GraphPad Software Inc, CA, USA

RESULTS

All treatments were well tolerated and no clinically relevant side effect was observed.

Analysis of the whole population

The present study analysed the reports of 80 outpatients. Demographic and clinical characteristics are reported in Table I.

Bacteriotherapy significantly halved the mean number of URI episodes being 5.98 (2.30) [median: 6 (4.25-7)] in the past year and 2.75 (2.43) [median: 2 (1-4)] after the treatment ($p<0.0001$, Figure 1). Bacteriotherapy also induced an over 35% reduction both in the number of school days and in the number of working days missed per month from 4.50 (2.81) [median: 5.0 (2.0-6.0)] to 2.80 (3.42) [median: 2.0 (0.0 – 5)] and from 2.33 (2.36) [median: 2.0 (0.0-4.75)] to 1.48 (2.16) [median: 0.0 (0.0 – 2.0)], respectively ($p<0.0001$, Figure 2 and 3).

The number of URI episodes strongly correlated with the number of school days missed per month ($r = 0.678$, $p<0.001$, Figure 4A). Similarly, a moderate correlation was detected between the number of URI episodes and the number of working days missed per month ($r = 0.514$, $p<0.001$, Figure 4B). As expected, the number of school days missed per month strongly correlated with the number of working days missed per month ($r = 0.601$, $p<0.0001$, Figure 5).

No correlations were found between changes in the number of URI episodes after Bacteriotherapy and the age at the beginning of treatment (r = 0.076, p = 0.50, not shown).

Moreover, sibling presence and allergy did not affect any result. Passive smoking was significantly associated only with school absence (p=0.02).

Comparison between patients with high or low number of URI episodes in the year preceding treatment

Patients were subdivided in two sub-groups on the basis of the number of URI episodes in the year preceding the study: > 6 or < 6.

The reduction in the number of URI episodes after treatment and in the number of school days or working days missed per month was higher for patients with a high number of URI episodes (i.e. >6 episodes) in the year preceding treatment than in those with a low number of URI episodes (i.e. <6 episodes) in the year preceding treatment (p<0.001, each comparison) as reported in Table II.

DISCUSSION

RURI represents a demanding challenge for both the ENT specialist and the paediatrician. The therapy is suggested by guidelines that limit antibiotic prescription to more demanding infections. However, in the clinical practice, antibiotics are frequently prescribed, ignoring guidelines precepts. In addition, prevention of RURI is even more debated. In this regard, a very recent placebo-controlled study investigated the potential preventive effect of a 12-month treatment with azithromycin (5mg/Kg/d) 3 d/wk in children with RRS (10,11). Actually, azithromycin prophylaxis reduced the number of ARS episodes, the medication score, and respiratory symptoms. However, this preventive proposal is very long-lasting and could easily induce the occurrence of resistance to macrolides. Macrolides resistance is an emerging problem in many European countries, including Italy (12). So, it seems better to consider alternative ways. Bacteriotherapy, such as the use of ‚good' bacteria, may be a promising preventive strategy. In fact, the rationale is based on the demonstration that some non-pathogenic strains may protect from bacterial infections. Indeed, the current study, conducted in a real-life setting, shows that *Streptococcus salivarius 24SMB* and *Streptococcus oralis 89a* nasal spray may be a reliable option in RURI prevention. Off note, no side effects were reported, so the compound was safe and well tolerated by all treated children. The main outcomes of the current study provided evidence that Bacteriotherapy significantly diminished the number of URI and consistently, school and work absences. Notably, Bacteriotherapy was more effective in children with frequent RURI, such as >6/year. This issue underlines the clinical relevance of the present findings.

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 the unmet needs.

In conclusion, the current real-life study demonstrated that *Streptococcus salivarius 24SMB* and *Streptococcus oralis 89a* nasal spray could be effective in preventing RURI in children.

REFERENCES

1. Mansback AI, Brihave P, Casimir G, et al. Clinical aspects of chronic ENT inflammation in children. B. ENT 2012;8 (Suppl 19), 83-101
2. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. Int Forum Allergy Rhinol. 2016;6 Suppl1:S22-209
3. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012 Mar;50(1):1-12
4. Gisselson-Solen M. Acute otitis media in children – current treatment and prevention. Curr Infect Dis Rep 2015;17:22
5. Marchisio P, Nazzari E, Torretta S, Esposito S, Principi N. Medical prevention of recurrent acute otitis media: an updated overview. Expert Rev Anti Infect Ther 2014;12(4):611-20
6. Marchisio P, Santagati M, Scillato M, et al. Streptococcus salivarius24SMB administered by nasal spray for the prevention of acute media otitis in otitis-prone children. Eur J Microbiol Infect Dis 2015;34(4):2377-83
7. La Mantia I, Varricchio A, Ciprandi G. Bacteriotherapy with Streptococcus salivarius 24SMB associated with Streptococcus oralis89a administered as nasal spray for preventing recurrent acute otitis media in children: a real-life clinical experience. Int J Gen Med 2017;10:171-5
8. Ciprandi G, Tosca MA, Fasce L. Allergic children have more numerous and severe respiratory infections than non-allergic children. Ped Allergy Immunol2006;17:389–391
9. Swinscow TDV. Correlation and regression. In: Swinscow TDV, Campbell MJ. eds. Statistics at square one. 9th edn. Southampton: BMJ Publishing Group, 1997:75–84

10. Bakshi SS. Revisiting recurrent acuterhinosinusitis prevention by azithromycin in children. J Allergy Clin Immunol Pract. 2017;5:1802
11. Veskitkul J, Wongkaewpothong P, Thaweethamchareon T, et al. Recurrent Acute Rhinosinusitis Prevention by Azithromycin in Children with Nonallergic Rhinitis. J Allergy ClinImmunolPract. 2017; 20175:1632-1638
12. Stefani S, Mezzatesta M, Oliveri S, Nicolosi VM, Russo G. In vitro study of dactimicin (ST 900) against methicillin-susceptible and -resistant staphylococci. Chemioterapia.1987;6:264-8

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