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Romanian Journal of Rhinology, Volume 8, No. 29, January-March 2018 DOI: 10.2478/rjr-2018-0004

ORIGINAL STUDY

Multicentric study on the efficacy and tolerability of Streptococcus salivarius 24SMB and Streptococcus oralis 89a in respiratory tract infections

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ABSTRACT

BACKGROUND. Bacteriocins are peptides with antimicrobial efficacy produced by certain bacterial species. Probiotics indeed seem a promising method in the prevention of upper respiratory infections and our study would like to contribute to the results available in the literature, in order to underlie their true therapeutic potential role.

MATERIAL AND METHODS. Our multicenter pilot prospective study investigates 366 patients from September 2015 to February 2016. All the patients were treated with a topical device made up of a suspension of two specific bacterial strains: Streptococcus salivarius 24SMB and Streptococcus oralis 89a to be administered as nasal spray. The nasal spray was administered twice daily for 7 days per month for three consecutive months. A questionnaire about the subjective efficacy of the therapy correlated to an improvement of symptoms was also collected from patients.

RESULTS. After one year from the enrolment, a 70.07% reduction in the number of events compared with the number of expected episodes was observed.

CONCLUSION. The aim of our data is to propose a new therapeutic approach to treat the recurrence of upper airway infection and to support an adequate therapy in all cases where the traditional antibiotic therapeutic protocol did not obtain completely efficient results in terms of recurrence.

KEYWORDS: Streptococcus salivarius, Streptococcus oralis, pharyngitis, adenotonsillitis, acute otitis media.

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Received for publication: October 23, 2017 / **Accepted:** November 29, 2017

INTRODUCTION

Microbes in the human body, like in any other living organism, tend to adapt to their environment and also to the associated changes. Commensal microorganisms and their metabolites maintain the stability of their habitat and the health of their host in what is often viewed as a symbiotic system. Inflammation or components of host defence, elicited as a result of the disease condition, create an environment in which certain microbes can or cannot grow and reproduce[1,2]. Whether microbiome changes are a cause or an effect of inflammatory disease remains to be answered for multiple chronic inflammatory conditions associated with disrupted epithelia.

Occupation of vacant upper respiratory tract (URT) niches is the way to provide resistance to colonization: a foreign pathogen has to compete with the commensal flora for adhesion receptors on the mucosal surface as well as nutrients. If the invading pathogen is able to bind surface receptors, it can adhere, replicate and cause disease. Another strategy to compete with invading pathogens is the production of antimicrobial compounds: for example, S. pneumoniae produce hydrogen peroxide, which is bactericidal for S. aureus[3].

Bacteriocins are peptides with antimicrobial efficacy produced by certain bacterial species: S. salivarius presumably inhibits the growth of S. pyogenes by production of bacteriocins[4].

The large surface of the nasal cavity contains niches shaping the ecosystem's habitat, and antibiotic treatment or new invading pathogens can break the balance[5,6].

Preserving biodiversity is paramount in ecological communities: it is possible by the presence of so-called keystone species, the loss of which would result in extinction of many other microorganisms[7].

Through the mechanisms and molecules of the innate immunity[8-10], specifically the expression of different TLRs on the respiratory epithelial cells, commensal bacteria and pathogens orchestrate microbiota diversity. Colonization resistance might be diminished by invading pathogens that induce a low-grade, asymptomatic inflammation, which facilitates invasion by pathogenic bacteria. For example, colonization with Proteobacteria such as non-typeable H. influenzae is accompanied by alterations in the epithelial barrier of the large airways thickness and production of early pro-inflammatory cytokines[11].

On the contrary, commensal strains, such as Prevotella, in lungs with Chronic Obstructive Pulmonary Disease, antagonise pathogens LPS-mediated TLR4-signalling, dampening downstream signaling, thereby contributing to mucosal homeostasis and colonization resistance versus pathogens[12].

In turn, environmental factors such as cigarette smoke can exacerbate the inflammatory response to a bacterial challenge via skewed inflammatory mediator expression[13].

The interplay between innate immunity and mucosal microbial communities makes the healthy microbiome an important component of the epithelial barrier[14].

The most largely studied commensal microorganism of the upper airways has been α-hemolytic Streptococcus, taking into account that its presence in the nasopharynx could interfere with survival and multiplication of pathogens more frequently associated with Acute Otitis Media (AOM) development[15,16].

More recently, Streptococcus salivarius, an α-hemolytic Streptococcus isolated from the pharynx of healthy subjects, has received attention. It is a potential nasopharyngeal probiotic, thanks to its immunomodulatory and anti-inflammatory skills, its production of plasmid-encoded bacteriocins and its good safety profile[17,18]. Recently, Marchisio et al. reported the results of the 1st study in which Streptococcus salivarius 24SMB, with significant activity against AOM pathogens, was intranasally administered in otitis-prone children[19]. Probiotics indeed seem a promising method in the prevention of upper respiratory infections and our study would like to contribute the results available in the literature, in order to underlie their true therapeutic potential role.

The aim of our data is to propose a new therapeutic approach to treat the recurrence of upper airway infection and to support an adequate therapy in all cases where the traditional antibiotic therapeutic protocol did not obtain completely efficient results in terms of recurrence.

MATERIAL AND METHODS

Our multicenter pilot prospective study enrolled 366 patients from September 2015 to February 2016. We investigated 224 children (134 males and 90 females), with a median age of 7.5 years, and 142 adults (78 female and 64 male) aged 18 to 65 years. The patients, after anamnestic data collection and clinical evaluation, reported recurrent upper airway pathology treated with systemic antibiotic therapy by their own family physician. The upper airway recurrent pathology was collected in Table 1.

The exclusion criteria were severe concomitant diseases, or, in case of children, negative consensus from their parents/caregivers. Patients leaving the therapeutic protocol during the first observational period were also excluded. All the patients were treated with a topical device made up of a suspension of two specific bacterial strains: Streptococcus salivarius 24SMB

Table 1
Percentage of upper airway recurrent (UAR) pathologies enrolled and their distribution among adults and children

Adenoiditis & Tonsillitis	Adenoiditis	Acute otitis media	Acute rhinosinusitis
31.15%	13.11% children	14.76%	40.98%
21.20% children		11.20% children	34.95%children
9.95% adults		3.56% adults	6.03% adults

and Streptococcus oralis 89a to be administered as nasal spray. The nasal spray was administered twice daily for 7 days per-month for three consecutive months. All the enrolled patients were treated previously with an antibiotic therapy, as advised by their own general practitioner and started the new intranasal disposable spray only after 10 days of wash out from antibiotic therapy. The treatment was associated with saline nasal irrigations in 40% of patients, in 6% with vasoconstrictor drops and in 6% with oral antihistamines if a concomitant allergic sensitization was present. A questionnaire about the subjective efficacy of the therapy correlated to an improvement of symptoms was also collected from adult patients and from children's parents and/or caregivers.

RESULTS

One year after from the enrolment, a 70.07% reduction in the number of events compared with the number of expected episodes was observed (Figures 1, 2). We want to point out that the number of expected events is a value obtained from the clinical history provided by the patients.

Considering the number of recurrent episodes in specific pathologies, similar results were observed. In fact, one year later, the treatment has proven to be able to reduce the rate of relapses by a single disease of about 70%. The frequency of recurrences was evaluated as the reduction of episodes during the follow-up at 3, 6 and 12 months (Figure 3).

Most of the recurrences (56.10%) occurred in the first months of treatment (October-January) likely due to seasonal reasons, with a progressive decrease over the remaining period: about 26.83% at the 6-month follow-up and 17.07% after 12 months during which the product was not administered (Figure 4).

In our opinion, these data are due not only to seasonal reasons, since the final follow-up was programmed during warm months where the incidence normally decreases, but also to the need of repeated administration to obtain a satisfactory colonization.

This trend was also confirmed analysing the expected episodes for each pathology: in fact, the recurrence percentage in patients affected by adenoiditis was 55.17% during the first 3 months, at 6 months the frequency was reduced to 27.59% and at the final follow-up visit to 17.24%. In rhinosinusitis patients, 75% of recurrences occurred in the first 3 months and 25% at the 6-month follow-up (Figure 3).

Figure 1 Data collected about one year for estimated disease events. One year after from the enrolment, a 70.07% reduction in the number of events compared with the number of expected episodes was observed.

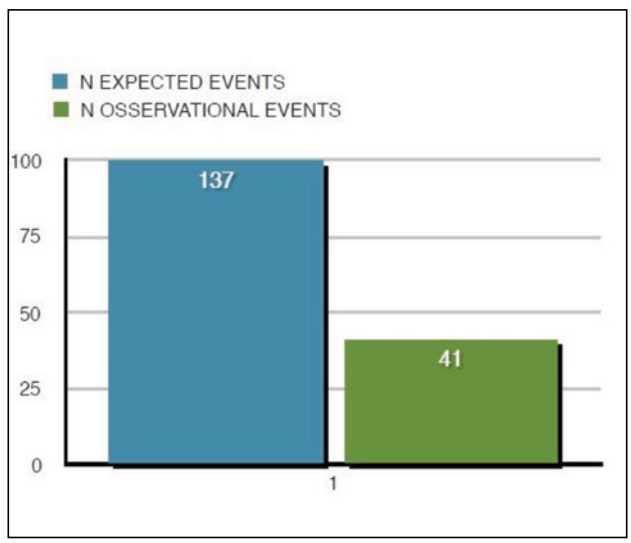

Figure 2 Data collected about one year for estimated disease events. There was a reduction in the number of expected episodes of disease.

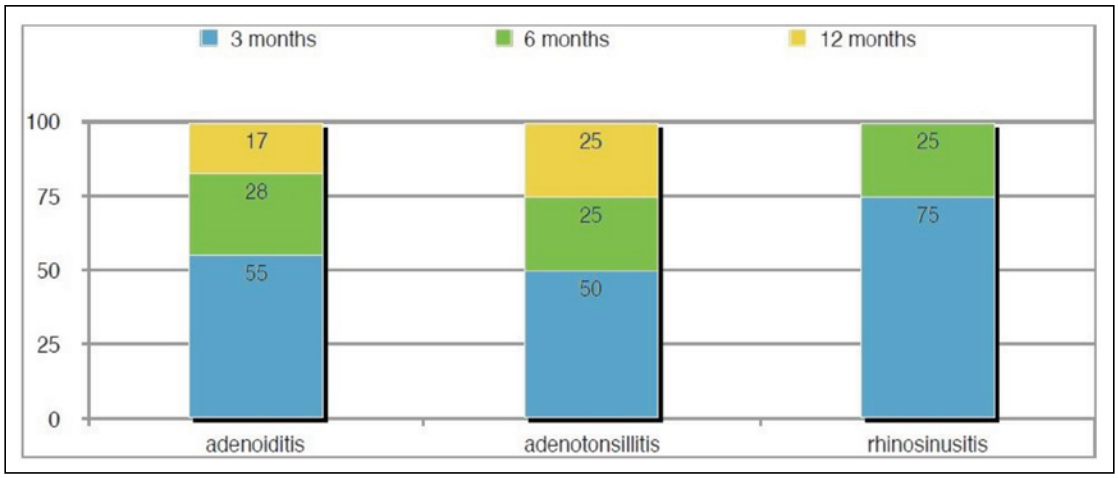

Figure 3 Data collected during the follow-up for each recurrent disease. The frequency of recurrences was evaluated during the follow up at 3, 6 and 12 months and expressed as a percentage.

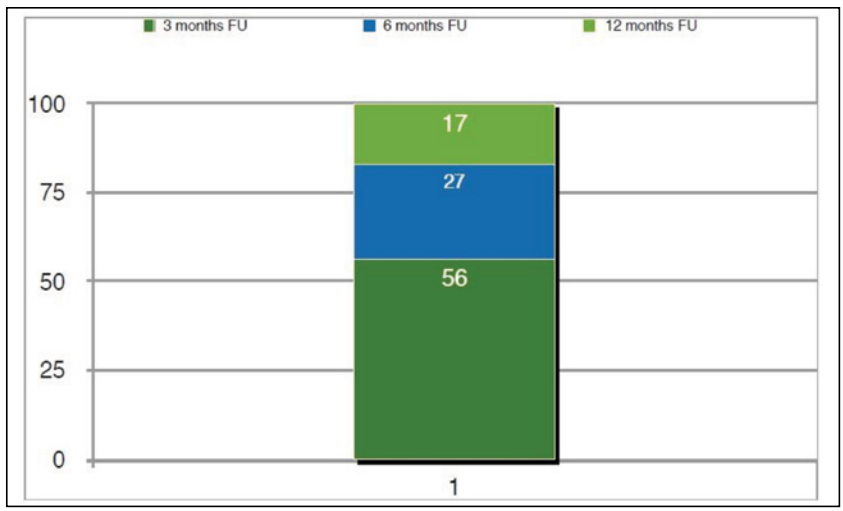

Figure 4 The recurrence rate due to seasonal reason.

The results were confirmed by the subjective judgement on the efficacy of this therapeutic protocol, as 55% of the patients referred a positive change in their symptoms and recurrence rate; 35% had reported doubtful changes and improvement, whereas only 1.63% of enrolled patients referred a negative impact with a worsening of symptoms.

Among symptoms collected from the questionnaire, a significant improvement ($p<0.05$) was observed for nasal obstruction and ear fullness.

DISCUSSIONS

Respiratory infections are the commonest cause of consultation both for GP and ENT doctors worldwide. URTI are also an important cause of reduced school and work loss and increased healthcare expenses[20].

The inflammation of the rhino- and oropharynx with adeno-tonsillar hypertrophy, if neglected or poorly treated, leads to complications in the middle ear and paranasal sinuses. In particular, viral and bacterial infection of the ENT district has been found most frequently in children; in the first three years of life almost all children run into at least one episode of AOM and about a third have three or more episodes. Bacterial infection is also the most frequent cause (80%) of tonsillitis in school children and young adults.

One of the causes of acute otitis media is the impaired ventilation of the middle ear resulting in a tubal obstruction, linked to the inflammation associated to a viral infection of the upper respiratory tract. Viral or allergic inflammation of the nose leads to nasal congestion and ostiomeatal complex obstruction with reduced ventilation of the paranasal sinuses. Such conditions facilitate the ascent of respiratory pathogens (Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis) that colonize the nasopharynx spreading to the tympanic cavity and paranasal sinuses.

Usually, the treatment of these pathologies requires the use of topical/oral anti-inflammatory drugs or antibiotics. It is known that the excessive use of antibiotics, especially in Western Countries, has resulted in the selection of strains resistant to treatment, some of which even in all classes of antibiotics currently available. The increasing difficulty in finding new effective antibiotic molecules directed research interest towards alternative therapeutic approaches, which potentially offer greater specificity and safety, lack of drug interactions and the ability to leverage a complementary mode of action than antibiotics, drastically reducing the risk of development of further resistance. In the upper airways, the commensal flora is able to inhibit growth of potential pathogens in vitro[21].

CONCLUSIONS

ENT diseases involve a significant commitment of care because they require at least a medical examination, prescription of antipyretic medicaments and often antibiotics. In addition to direct costs, URTI involve high indirect costs due to absence from work of at least one parent and a negative impact on life quality of children and their families. Such negative effects are multiplied in the case of recurrent infection.

Therefore, treatment and prevention of ENT diseases in general and of AOM in particular is now a primary focus of paediatric medical care.

The topical application of streptococcal probiotics is a relatively undeveloped field, the first attempts being relatively recent, but it is becoming an attractive approach for both prevention and therapy, especially for paediatric age patients. S. salivarius 24SMB possesses characteristics making this strain suitable for use in bacteriotherapy.

Conflict of interest: The authors have no conflict of interest.

Contribution of authors: All authors have equally contributed to this work.

REFERENCES

1. Hosokawa T, Kikuchi Y, Nikoh N, Shimada M, Fukatsu T. Strict host-symbiont cospeciation and reductive genome evolution in insect gut bacteria. PLoS Biol. [Internet]. 2006;4(10):e337. Available from: http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0040337. https://doi.org/10.1371/journal.pbio.0040337.
2. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, et al. Host-gut microbiota metabolic interactions. Science. 2012;336(6086):1262-7. DOI: 10.1126/science.1223813. Epub 2012 Jun 6.
3. Regev-Yochay G, Trzcinski K, Thompson CM, Malley R, Lipsitch M. Interference between Streptococcus pneumoniae and Staphylococcus aureus: in vitro hydrogen peroxide-mediated killing by Streptococcus pneumoniae. J Bacteriol. 2006;188(13):4996–5001. DOI: 10.1128/JB.00317-06.
4. Dobson A, Cotter PD, Ross RP, Hill C. Bacteriocin production: a probiotic trait? Appl Environ Microbiol. 2012;78(1):1–6. DOI: 10.1128/AEM.05576-11. Epub 2011 Oct 28.
5. Dillon RJ, Vennard CT, Buckling A, Charnley AK. Diversity of locust gut bacteria protects against pathogen invasion. Ecol Lett. 2005;8(12):1291–8. DOI: 10.1111/j.1461-0248.2005.00828.x.
6. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, et al. A core gut microbiome in obese and lean twins. Nature. 2009;457(7228):480–4. DOI: 10.1038/nature07540. Epub 2008 Nov 30.
7. Mills LS, Soule ME, Doak DF. The keystone species concept in ecology and conservation. BioScience. 1993;43(4):219–24.
8. Paine RT. A note on trophic complexity and community stability. The American Naturalist. [Internet]. 1969;103(929):91–3. Available from: http://www.journals.uchicago.edu/doi/abs/10.1086/282586. https://doi.org/10.1086/282586.
9. Schleimer RP, Kato A, Kern R, Kuperman D, Avila PC. Epithelium: at the interface of innate and adaptive immune responses. J Allergy Clin Immunol. 2007;120(6):1279-84. Epub 2007 Oct 18.
10. Avila PC, Schleimer RP. Airway epithelium. In: Kay AB, Kaplan AP, Bousquet J, Holt P. Allergy and allergic diseases. 2nd eds. Oxford: Blackwell Publishing; 2008, p.366-397.
11. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. J Allergy Clin Immunol. 2009;124(1):37-42. DOI: 10.1016/j.jaci.2009.04.045.
12. Larsen JM, Musavian HS, Butt TM, Ingvorsen C, Thysen AH, Brix S. Chronic obstructive pulmonary disease and asthma-associated Proteobacteria, but not commensal Prevotella spp., promote Toll-like receptor 2-independent lung inflammation and pathology. Immunology. 2015;144(2):333–42. DOI: 10.1111/imm.12376.
13. Gaschler GJ, Skrtic M, Zavitz CC, Lindahl M, Onnervik PO, Murphy TF, et al. Bacteria challenge in smoke-exposed mice exacerbates inflammation and skews the inflammatory profile. Am J Respir Crit Care Med. 2009;179(8):666–75. DOI: 10.1164/rccm.200808-1306OC. Epub 2009 Jan 29.
14. Miller SI, Ernst RK, Bader MW. LPS, TLR4 and infectious disease diversity. Nat Rev Microbiol. 2005;3(1):36–46.
15. Tano K, Olofsson C, Grahn-Hakansson E, Holm SE. In vitro inhibition of S. pneumoniae, nontypable H. infuenzae and M. catharralis by alpha-hemolytic streptococci from healthy children. Int J Pediatr Otorhinolaryngol. 1999;47(1):49–56.
16. Roos K, Hakansson EG, Holm S. Effect of recolonisation with "interfering" α steptococci on recurrence of acute and secretory otitis media in children: randomized placebo controlled trial. BMJ. 2001;322(7280):210-2.
17. Santagati M, Scillato M, Patane F, Aiello C, Stefani S. Bacteriocin-producing oral streptococci and inhibition of respiratory pathogens. FEMS Immunol Med Microbiol. 2012;65(1):23–31. DOI: 10.111/j.1574-695X.2012.00928.x. Epub 2012 Feb 3.
18. Santagati M, Scillato M, Muscaridola N, Metoldo V, La Mantia I, Stefani S. Colonization, safety, and tolerability study of the Streptococcus salivarius 24SMBc nasal spray for its application in upper respiratory tract infections. Eur J Clin Microbiol Infect Dis. 2015;34(10):2075–80. DOI: 10.1007/s10096-015-2454-2. Epub 2015 Jul 24.
19. Marchisio P, Santagati M, Scillato M, Baggi E, Fattizzo M, Rosazza C, et al. Streptococcus salivarius 24SMB administered by nasal spray for the prevention of acute otitis media in otitis-prone children. Eur J Clin Microbiol Infect Dis. 2015;34(12):2377–83. DOI: 10.1007/s10096-015-2491-x. Epub 2015 Sep 18.
20. Kung K, Wong CK, Wong SY, Lam A, Chan CK, Griffiths S, et al. Patient presentation and physician management of upper respiratory tract infections: a retrospective review of over 5 million primary clinic consultations in Hong Kong. BMC Fam Pract. 2014;15:95. DOI: 10.1186/1471-2296-15-95.
21. Skovbjerg S, Roos K, Holm SE, Grahn Håkansson E, Nowrouzian F, Ivarsson M, et al. Spray bacteriotherapy decreases middle ear fluid in children with secretory otitis media. Arch Dis Child. 2009;94(2):92-8. DOI: 10.1136/adc.2008.137414. Epub 2008 Aug 19.