Original Article

SAGE Open Medicine

SAGE Open Medicine
Volume 13: 1–6

DOI: 10.1177/20503121241309514
journals.sagepub.com/home/smo
Sage

Long-term sublingual bacterial immunotherapy prevents ear, nose and throat infections: A real-life study

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Abstract

Objective: Bacterial extracts have been used for many years to prevent airway infections. Recent findings suggest that immunity can be trained by inducing an immunological memory in both the innate and acquired immune response. This real-life observational study investigated the potential of sublingual bacterial immunotherapy in the prevention of ear, nose, and throat infections.

Methods: Patients received sublingual bacterial immunotherapy for 12 months and were followed for 24 months. The number of ear, nose, and throat infection episodes from the previous year was recorded during the initial visit based on the patient's clinical history. Patients were then followed up with visits every 2 months, and the occurrence of ear, nose, and throat infection episodes was documented at 6, 12, 18, and 24 months after the start of the study.

Results: The results demonstrated a strong potential for preventing ear, nose, and throat infections, with a reduction in the number of episodes by 75.68%, 82.27%, 82.78%, and 89.88% at 6, 12, 18, and 24 months, respectively. No adverse effects related to sublingual bacterial immunotherapy administration were reported.

Conclusion: The results suggested that long-term sublingual bacterial immunotherapy is safe and effectively prevents ear, nose, and throat infections, even after treatment ends.

Keywords

Bacterial extract, immunotherapy, sublingual, infections, prevention, ear infection, nose infection, throat infection, immunological treatment, observational study

Date received: 9 August 2024; accepted: 5 December 2024

Introduction

Recurrent ear, nose, and throat (ENT) infections represent a significant global public health concern. A deficiency in the local immune response of the respiratory mucosa appears to be the primary factor associated with recurrent ENT infections in patients without systemic immune alterations that would indicate a compromised innate or acquired immune response.[1–4]

Recent research has shown that training the innate immune system with bacterial extracts can improve infection clearance and positively influence disease outcomes.[5] For a long time, immunological memory was thought to be exclusive to the adaptive immune response. While immune memory is indeed a defining characteristic of the acquired immune system, the activation of the innate immune system can also lead to enhanced responses to future triggers. Both experimental and clinical studies have demonstrated that exogenous pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMPS) induce trained immunity. As a result, vaccinations can offer broad protection against various pathogens by stimulating innate immune mechanisms in addition to acquired immunity.[6–9]

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Several clinical studies have investigated the efficacy of bacterial extracts immunotherapy in preventing recurrent ENT infections. Despite variations in administration schemes, composition, and delivery routes, these studies consistently report favorable clinical outcomes and excellent safety profiles.[10–18] A meta-analysis on the efficacy and safety of bacterial lysates in chronic obstructive pulmonary disease showed that these lysates can benefit patients by reducing exacerbations and alleviating symptoms.[19] A study[20] with 386 HIV-positive patients receiving bacterial extract immunotherapy also demonstrated a significant reduction in airway infections, leading to a decreased use of antibiotics. In addition, the success of sublingual bacterial immunotherapy (SBI) was noted in a patient with partial IgA immunodeficiency, suggesting that the mechanism of action likely involves stimulation of both innate and acquired immunity.[17]

Current literature indicates that SBI using inactivated whole-cell extracts at high concentrations yields consistent clinical results, effectively preventing recurrent ENT infections.[1,14–17] In particular, high-concentration antigen formulations administered by physicians may enhance immunomodulation. However, most studies have applied bacterial immunotherapy for short, intermittent periods—typically 3–6 months—with limited follow-up. These constraints hinder a comprehensive evaluation of bacterial immunotherapy's long-term effects on immunological memory and ENT infection prevention.

In the present study, we aimed to establish more robust trained immunity and induce immunological memory through both innate and acquired mechanisms. We administered a high-concentration whole-cell bacterial extract immunotherapy continuously for 12 months, followed by an additional 12 months of post-treatment monitoring. Our findings suggest that prolonged use of SBI with a whole-cell bacteria extract with high antigenic concentration can provide long-lasting prevention of ENT infections.

Patients and methods

Study design

This observational cohort study was conducted over 24 months in patients with a clinical history of recurrent ENT infections. All participants, or their legally authorized representative, provided a written informed consent form, and the study was approved by the Research Ethics Committee of the Faculty of Medical and Health Sciences—SUPREMA, Juiz de Fora, MG, Brazil (number 1481788).

Patient selection and evaluation

Outpatients from the Allergy, Asthma, and Clinical Immunology Service of the Monte Sinai Medical Center (Juiz de Fora, MG, Brazil) were enrolled in the study. During each visit, anamnesis and physical examination, including otological and tonsillar ring assessments, were performed. Data on the frequency of ENT infection episodes and antibiotic use were collected. All patients underwent laboratory tests to evaluate immunoglobulin levels (IgG, IgM, IgA, and IgE), complement system activity, and CD3+, CD4+, CD8+, and CD 16/56+ cell counts. In addition, skin prick tests were conducted for the main regional allergens: *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Blomia tropicalis, Lolium multiflorum*, dog dander, and cat dander.

Only patients whose laboratory tests did not suggest a diagnosis of primary immunodeficiencies were included in the study. Before the administration of SBI, antibiotic therapy was the sole treatment used during episodes of ENT infections. No other form of immunotherapy had been previously administered to the patients in the study. Additionally, no other prophylactic treatment was used after the completion of SBI.

The inclusion criteria were as follows: age between 12 and 50 years, a clinical history of recurrent ENT infections with at least four episodes per year, no clinical history of allergic rhinitis or asthma, a negative prick test for aeroallergens, and no evidence of primary immunodeficiencies.

The exclusion criteria were as follows: age under 12 years old and over 50 years old, clinical history of allergic rhinitis or asthma, a positive prick test for aeroallergens, and evidence of primary immunodeficiencies.

The primary outcome investigated was the incidence rate of ENT infections per patient per month. Each occasion where antibiotics were used was recorded as an episode of ENT infection.

Sublingual bacterial immunotherapy

SBI was administered continuously for 12 months, with an additional 12 months of follow-up after the end of treatment. A total of 64 patients received daily sublingual doses of an inactivated whole-cell extract composed of *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Moraxella* (*Branhamella*) *catarrhalis*, *Staphylococcus aureus*, *Haemophilus influenza*, *Streptococcus gordonii* (*S. mitis*), and *Streptococcus pyogenes*. The concentration used was 2×10^9 CFU/ml, with a total monthly dose of 12×10^9 CFU administered over the first 4 months. Subsequently, a dose of 6×10^9 CFU per month was administered for the remaining 8 months, completing the full treatment period.

Outcome

The number of ENT infection episodes from the previous year was recorded during the initial visit based on the patient's clinical history. Patients were then followed up with visits every 2 months, and the occurrence of ENT infection episodes was documented at 6, 12, 18, and 24 months after the start of the study. The total duration of the study was

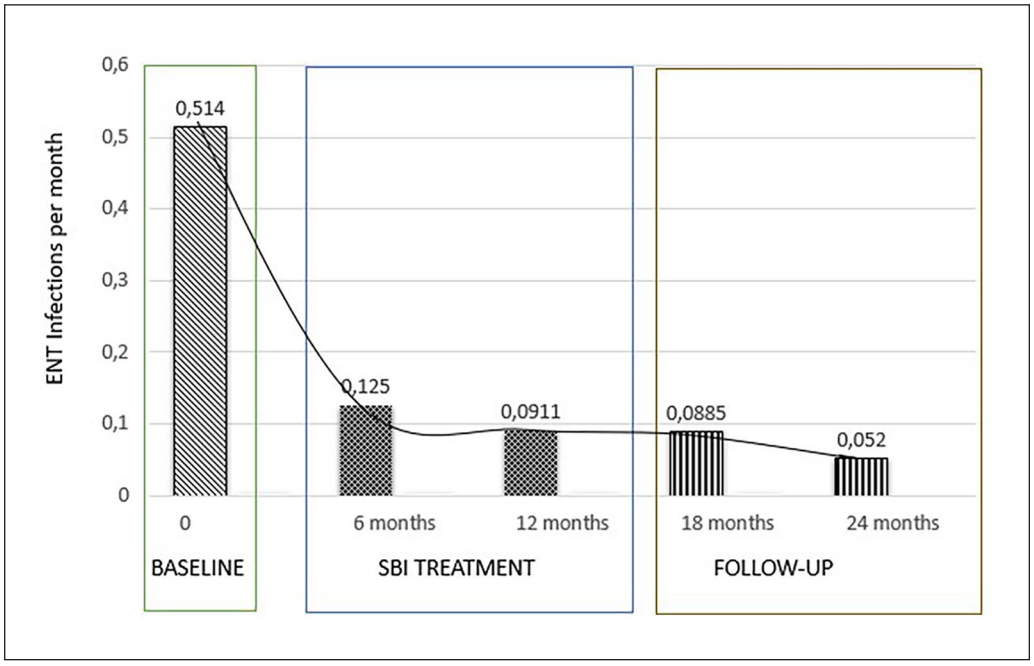

Figure 1. Number of ENT per month. $N = 64$.
ENT: ear/nose/throat; SBI: sublingual immunotherapy.

4 years (2019–2023). Patients or their Legally Authorized Representatives were provided with a short form to document any episode of ENT infections between visits. All episodes were diagnosed and treated accordingly. The safety of SBI administration was assessed by recording any adverse events related to bacterial immunotherapy throughout the study.

Statistical analysis

Statistical analyses were performed using SPSS software (SPSS Institute, Cary, NC, USA). The primary outcome was evaluated by calculating the mean number of ENT infection episodes per patient per month.

Ethics and patient consent

We confirm that guidelines on patient consent have been followed, and any details of informed consent obtained are indicated within the text of the submitted manuscript.

Ethics approval

Ethical approval to report this case was obtained from the Research Ethics Committee of the Faculdade de Ciências Médicas e da Saúde de Juiz de Fora—Suprema (number 1.481.788), in compliance with the Declaration of Helsinki II. Written informed consent was obtained from the legally authorized representative of the subjects and the subjects themselves. The patients had not received any immunotherapy treatment prior to the start of the study. During the study, patients with nose, ear, and throat infections were treated appropriately depending on the diagnosis of viral or bacterial infection.

Results

All patients included in the study were evaluated for potential primary immunodeficiencies. None of the patients showed abnormal levels of immunoglobulin levels (IgG, IgM, IgA, and IgE), complement system activity, or CD3+, CD4+, CD8+, and CD 16/56+ cell counts.

A significant reduction in the number of ENT infection episodes per patient per month was observed throughout the study period. The reduction rates at 6, 12, 18 and 24 months were 75.68%, 82.27%, 82.78%, and 89.88% respectively (Figure 1). Notably, the prevention of ENT infections remained effective even after the completion of SBI treatment. Furthermore, SBI was well tolerated, with no adverse effects related to its administration reported during the study. Table 1 shows the characteristics of the group of patients evaluated.

Discussion

Several studies suggest that SBI with whole-cell bacteria can induce both local and systemic immunity. The administration route is crucial when considering pathogens that infect through mucosal tissues.[21–23] Compared to gastrointestinal administration, the sublingual route induces a superior mucosal immune

Table 1. Frequency distribution and relative percentage of patients who were treated with sublingual bacterial immunotherapy (SBI).

Age	Female		Male		Female and male	
12–18 years	11	17.18%	21	32.81%	32	50%
>18 years	16	25.00%	16	25.00%	32	50%
Total	27	42.18%	37	57.81%	64	100%

response in the airways.[23] Nieto et al.[24] published a study using a bacterial extract with similar characteristics and composition to that used in our study to evaluate the effects of SBI in preventing wheezing in children with asthma. SBI was administered for 6 months, followed by a 12-month observation period. The results demonstrated that SBI effectively prevented and reduced wheezing in asthmatic children. In our present study, 12 consecutive months of SBI were both safe and effective in preventing ENT infections.

Recent advances in understanding trained immunity have rekindled interest in immunostimulation for preventing infectious diseases. The term "trained immunity" was introduced in 2011[6] to describe a functional state of the innate immune response characterized by long-term epigenetic reprogramming of innate immune cells. Although initially observed in circulating monocytes and tissue macrophages, subsequent findings indicate that progenitor cells in the bone marrow can also be trained, a phenomenon referred to as trained central immunity. This concept helps explain the long-term protective effects of vaccines against unrelated infections through innate immune mechanisms.[5–8]

Current evidence suggests that trained immunity, combined with a predominantly Th1-acquired immune response, corresponds to the main mechanisms by which bacterial extracts stimulate the immune system.[21–24] Specific antigen recognition and immunological memory are two hallmark properties of acquired immunity. However, the discovery of trained immunity has shown that innate immunity also possesses a form of immunological memory, resulting in faster and more robust responses upon re-encounter with antigens, that have had previous contact via the skin or mucous membranes. While trained immunity is typically reversible and shorter-lived than classical epitope-specific adaptive immunity, it can last for months to years, with heterologous protection against infections induced by live vaccines extending up to 5 years.[5–9]

Bacterial immunotherapy enhances the availability of PAMPs and DAMPs, via pattern recognition receptors expressed on their surface, which stimulate a secretion of pro-inflammatory cytokines such as interleukin 6, interleukin 1 beta, and tumor necrosis factor-alpha. These cytokines, in turn, promote antigen presentation and activate the acquired immune response. Therefore, bacterial immunotherapy fosters greater interaction between innate and acquired immunity.[7–14,25,26] In this study, we used an extended period of high-concentration SBI to potentiate both trained and acquired immunity responses specific to the main types of bacteria associated with ENT infections. Although we did not directly investigate the immunological mechanism, the significant reduction in ENT episodes suggests that prolonged SBI treatment successfully achieved the objective of potentiating the different effector and memory mechanisms of the immune system.

Most studies use shorter administration periods for bacterial extracts, often considering seasonal patterns of ENT infections. Our study took place in a region of Brazil with little seasonal temperature variation, where the seasonality of ENT infections is less pronounced compared to Europe and the USA. This real-life study included patients aged 12–50 years, selected to avoid potential confounding factors related to immune system development in children or immunosenescence in older adults. A limitation of this study was that power analysis for sample size calculation was not done; however, we included in this study 64 patients who fulfilled very specific inclusion and exclusion criteria.

A notable aspect of our study was the use of long-term SBI to assess its preventive effect throughout the year and the following year. The extended administration period was based on the concepts of trained innate immunity and immunological memory. The results indicated that 12 months of SBI effectively prevented ENT infections during the 12 months post-treatment. Our approach differs from the traditional method of administering bacterial extracts annually during specific seasons. Our findings suggest that long-term SBI can modify the specific immune response to bacteria in a lasting way, similar to allergen-specific immunotherapy. A limitation of the study was the size of the sample. However, qualitatively the sample represents the routine of care in an allergy and immunology clinic when the main complaint is the presence of recurrent nose, ear, and throat infections

Data from the literature indicate that patients with respiratory allergic diseases are more susceptible to ENT infections. However, the patients in our study had no clinical diagnoses of allergic conditions such as rhinitis and asthma and showed no sensitization to aeroallergens. Thus, we eliminated the potential bias of allergic diseases influencing the history of recurrent infections. Our results suggest that SBI primarily acted by establishing effective trained immunity, enabling prolonged immunological memory.

Conclusion

In conclusion, this study demonstrated that 12 months of SBI was safe and effective in preventing ENT infections for a prolonged period, even after the end of treatment. We hope that these findings from a real-life observational study will inspire further double-blind, placebo-controlled randomized clinical trials to explore this novel SBI administration approach.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics committee approval and subject consent

All participants or legally authorized representatives written informed consent form and the research was approved by the Research Ethics Committee (Faculdade de ciências médicas e da saúde de Juiz de Fora – Suprema/number 1.481.788) in compliance with the Declaration of Helsinki II. All participants or their legal guardians signed the consent form authorizing the use of SBI.

Informed consent

Written informed consent was obtained from the legally authorized representative of the subjects and the subjects themselves.

Trial registration

Not applicable.

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