

Efficacy of nasal *Staphylococcus aureus* eradication by topical nasal mupirocin in patients with perennial allergic rhinitis

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Background: *Staphylococcus aureus* (SA) colonization is frequent in patients with perennial allergic rhinitis (PAR). Mupirocin has well-recognized antistaphylococcal activity, and its nasal formulation is approved for the eradication of SA nasal colonization.

Objective: To investigate the frequency of SA nasal carriage, its possible influence on AR severity, and nasal mupirocin's role on AR clinical severity.

Methods: Sixty patients, aged 5 to 60 years, with AR were included, and 55 healthy individuals served as a control group. Nasal smear specimens were drawn from both nares. A skin prick test to inhalational allergens and a score-graded clinical evaluation of AR were performed. Carriers of SA were treated with topical nasal mupirocin.

Results: The SA carrier (SAC) state was found in 23 (38%) of the patients with AR and in 8 (15%) of the healthy controls ($P = .004$). Comparing SACs with AR SA noncarriers, nasal symptom scores (SSs) tended to be higher in the SAC group (mean [SD], 11.09 [2.16] vs 8.86 [1.43]; $P < .005$). Treatment with topical nasal mupirocin diminished the SAC state to 10% ($P = .009$) but did not change AR clinical severity, as assessed by the SS.

Conclusions: In patients with PAR, the SAC state is more prevalent compared with the healthy population. Topical nasal mupirocin reduces the SAC state but fails to clinically improve PAR, as assessed by the SS.

Ann Allergy Asthma Immunol. 2008;100:608–611.

INTRODUCTION

The nasal mucosa is the primary reservoir of *Staphylococcus aureus* (SA) in humans. Approximately 14% to 30% of healthy adults asymptomatically carry SA in the nose. The SA carrier (SAC) state is, however, an important risk factor for subsequent SA infections.^{1,2}

The prevalence of the SAC state in patients with perennial allergic rhinitis (PAR) is higher than that seen in the healthy population,³ and nasal carriage of SA may aggravate PAR.⁴ Furthermore, nasal SA has been shown to actively modulate the disease by promoting local IgE production.⁵ The SAC state does not seem to correlate with the severity of symptoms or the extent of the disease in those with chronic rhinosinusitis.⁶

Mupirocin is a potent, locally active, antistaphylococcal antibiotic. Its nasal ointment, applied twice daily for 5 consecutive days, has demonstrated 91% efficacy in eliminating nasal staphylococcus immediately after therapy, 87% efficacy after 4 weeks, and 48% efficacy after 6 months.⁷

The aims of this study were to examine the prevalence of the SAC state in Israeli patients with PAR and to evaluate the effect of nasal topical mupirocin on the clinical course of PAR in SACs.

METHODS

Study Population and General Study Design

This was a case-controlled, open-labeled, interventional study. Patients were included if they were older than 5 years, had a history of at least 12 months of symptoms consistent with PAR, and had PAR confirmed by a positive skin prick test result to house dust mite allergen. Exclusion criteria included seasonal allergic rhinitis, participation in immunotherapy, any active infectious disease, and/or antibiotic treatment during the month before study recruitment; any ongoing treatment with aspirin, nonsteroidal anti-inflammatory drugs, or steroids; or other serious chronic illness.

Sixty patients, aged 5 to 60 years, fulfilling study criteria and attending the Allergy and Clinical Immunology Unit at Barzilai Medical Center during the recruitment period were included in the PAR group. The recruitment period was tailored to the peak house dust mite "season" in Israel, September to February. Fifty-five consecutive patients, aged 5 to 57 years and without a history of AR, attending the outpatient orthopedic clinic for various traumatic injuries served as our control group. All participants were allowed to continue receiving their medications throughout the study, but initiation of new medications and changes in doses and/or

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Disclosures: Authors have nothing to disclose.

Received for publication June 26, 2007; Received in revised form November 3, 2007; Accepted for publication November 5, 2007.

Table 1. Baseline Characteristics^a

Characteristic	PAR group (n = 60)	Control group (n = 55)	P value
Age, y ^b	38.3 (14.9)	36.9 (17.4)	.73
Male sex	38 (63)	32 (58)	.87
Current smoker	7 (12)	8 (15)	.91
Has PAR	60 (100)	0	<.001
Has asthma	17 (28)	0	<.001
SA carrier	23 (38)	8 (15)	.004
Sensitization to house dust mites	60 (100)	7 (13)	<.001
Skin test index for house dust mites, biological units ^{b,c}	1.23 (0.54)	0.81 (0.65)	.02
PAR symptom score at baseline ^{b,d}	9.97 (2.16)	2.51 (1.33)	<.001

Abbreviations: PAR, perennial allergic rhinitis; SA, *Staphylococcus aureus*.

^a Data are given as number (percentage) of each group unless otherwise indicated.

^b Data are given as mean (SD).

^c The quotient of the diameter of the allergen-induced wheal divided by the diameter of the histamine-induced wheal.

^d The score ranges from 0 to 33, with higher scores indicating a greater severity of symptoms.

frequency, except where mandated by the study protocol, were disallowed.

The study was approved by the hospital ethics committee and all adult participants, and, where appropriate, parents or guardians signed a detailed informed consent form.

PAR Symptom Score Evaluation

The PAR symptom score (SS) at baseline and after 5 weeks was obtained for all patients. Antihistamine use was discontinued at least 3 days before, and nasal spray use was discontinued 2 weeks before, PAR SS assessments. At baseline, the patients fulfilled a standardized SS questionnaire.⁸ Individual allergic symptoms of eyes (itching, redness, tears, and swelling), nose (sneezing, blockage, and rhinorrhea), and chest (exercise intolerance, wheezing, tightness, and breathlessness) were noted on a scale of 0 to 3 (0 indicated no symptoms and 1, 2, and 3 indicated mild, moderate, and severe symptoms, respectively). For each patient, the total individual SS was calculated at baseline and at the 5-week visit.

Skin Prick Test

Skin prick tests were performed in duplicate on the volar forearms. *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, mixed feather, grass, and tree pollens, *Alternaria*, and positive (histamine) and negative (glycerol diluent) controls were applied using commercial extracts (ALK-Abelló A/S, Hørsholm, Denmark). The immediate re-

sponses were recorded after 15 minutes. The skin prick test result was considered positive if the measured wheal diameter was at least 3 mm greater than that of the negative control.

Identifying Carriers of SA

A specimen for nasal culture was obtained by rotating a sterile swab 4 times in the anterior nares (Transwab; Medical Wire and Equipment Co Ltd, Corsham, England). The swabs were sent within 6 hours to the central microbiological laboratory at Barzilai Medical Center and were processed on the same day. The swab was plated on Columbia blood agar plate medium (Becton-Dickinson, Etten-Leur, the Netherlands) and submerged in phenol red mannitol broth. The plates were read after 1 and 2 days of incubation, and the broths were read after 3 days of incubation at 35°C. Broths with a color change from red to orange-yellow were subcultured on blood agar plates. Identification of SA was based on colony features, Gram stain, a positive catalase test result, and the latex agglutination test result (Staphaurex Plus; Murex, Dartford, England).

Treatment and Follow-up

Patients from the PAR group self-administered 2% mupirocin nasal ointment (SmithKline Beecham, Rijswijk, the Netherlands) twice daily for 5 days, according to the manufacturer's instructions. Nasal cultures were taken just before and 5 weeks after mupirocin administration. The SS questionnaires were also completed at the same time.

Table 2. Topical Nasal Mupirocin's Efficacy on the Nasal SA Carriage Rate and PAR Total Symptom Score in the 60 Patients With PAR^a

Characteristic	At baseline	At 5 wk	P value
Positive nasal culture result for SA ^b	23 (38)	6 (10)	.009
PAR symptom score			
In SA carriers	11.09 (2.16)	10.72 (2.31)	.29
In SA noncarriers	8.86 (1.43)	8.59 (1.84)	.67

Abbreviations: PAR, perennial allergic rhinitis; SA, *Staphylococcus aureus*.

^a Data are given as mean (SD) unless otherwise indicated.

^b Data are given as number (percentage) of patients.

Table 3. Nasal SA Carriage Rate and PAR Total Symptom Score in the 55 Healthy Control Subjects^a

Characteristic	At baseline	At 5 wk	P value
Positive nasal culture result for SA ^b	8 (15)	9 (16)	.84
PAR symptom score			
In SA carriers	3.27 (1.54)	3.52 (1.71)	.93
In SA noncarriers	3.62 (1.83)	3.39 (1.92)	.96

Abbreviations: PAR, perennial allergic rhinitis; SA, *Staphylococcus aureus*.

^a Data are given as mean (SD) unless otherwise indicated.

^b Data are given as number (percentage) of patients.

Statistical Analysis

Intention-to-treat analysis was performed with the data of all 60 patients with PAR. The effectiveness of nasal mupirocin was estimated with the use of unpaired *t* tests assessing the mean difference between the baseline and the 5-week SSs.

RESULTS

The demographic characteristics of the PAR study group and the control group are presented in Table 1. They are matched for sex, age, and smoking status. Among the 60 patients who constituted the study group, 5 were withdrawn during the study because of noncompliance.

Nasal culture results were positive for SA (SAC state) in 23 of the patients with PAR but only in 8 of the controls ($P < .005$) (Table 1).

At baseline, the mean (SD) PAR SS was higher in SACs than in noncarriers ($P < .005$). Five weeks after nasal mupirocin treatment, 17 (74%) of the initial 23 SACs had negative nasal culture results. However, the mean (SD) PAR SS remained unchanged in the whole group of SACs and SA noncarriers (Table 2). A subanalysis in the SAC group comparing patients who have undergone SA eradication⁹ with patients remaining positive for the SAC state showed no significant ($P = .48$) differences in individual or global SS.

In the control group, neither SAC state nor PAR SS was changed at 5 weeks (Table 3).

DISCUSSION

Our study aimed to establish the prevalence of the SAC state in Israeli patients with PAR, compared with a group of age-matched healthy controls, and to evaluate the efficacy of nasal mupirocin ointment in the amelioration of PAR SS after SA eradication.

The SAC rate among patients with PAR compared with healthy subjects was addressed in previous studies.^{10,11} An ongoing controversy exists on this subject. One research group did not find higher SA nasal carriage in children¹² or adults¹³ with PAR compared with age-matched healthy controls, whereas in other studies,^{4,6,14} the frequency of SA nasal carriage in those with PAR was significantly higher. Our study seems to support most previously published data, show-

ing an SAC prevalence of 38% in those with PAR compared with 15% in the control group.

In general, the anterior nares are considered the most common site of SA colonization in humans, and prevalence rates were measured in many early studies.^{15,16} Carriage rates of 30% to 40% have been estimated based on limited samples, although some studies^{9,15} suggested rates well more than 40% in healthy persons outside the hospital setting. More recent data,^{1,17} however, have suggested lower SAC rates. Our results also show only a 15% SAC state in the healthy population. The differences in SA colonization rates measured in the various studies may be explained by the quality of sampling, culture techniques, and the populations studied.

Our patients with PAR had an SAC rate of 38%, significantly more than in the control group. One possible explanation for the higher SA carriage is recurrent nostril itching and frequent nose picking in patients with PAR. Other possible explanations for the phenomenon have been previously propounded, with changes in the availability of nutrients, such as glucose in the extravasated nasal discharge, influencing the number and strength of bacterial colonization.

The SA in the nasal mucosa of patients with PAR may be a purely accidental bystander or, as previously imputed, it may play a significant role in the pathophysiological features of PAR by several mechanisms: by promoting local IgE production⁶; by staphylococcal enterotoxin-induced specific IgE and total IgE formation, increased inflammatory markers, and clinical expression of the disease¹⁸; or by SA superantigen stimulation of lymphocyte proliferation and allergic inflammation.¹⁹ The SA enterotoxins are known potential modifiers of allergic diseases,²⁰ but the actual importance of their presence in those with chronic allergic inflammation of PAR is not known.

In an experimental model of BALB/c mice, nasal exposure to SA enterotoxins enhanced susceptibility to PAR, although by itself it did not induce the disease.²¹ Our clinical study does not, in fact, support a cause-effect relationship between the presence of the SAC state and the severity of symptomatic PAR in patients allergic to dust mite.

A well-powered, cross-sectional, open-labeled, intervention study, such as ours, should be able to identify a clinically relevant outcome change, if the intervention studied indeed affects the measured outcome variable. The negative results can be interpreted as follows: either SA is an "innocent bystander" in allergen-induced PAR or the clinical effect is too small to be measured in this relatively small study.

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