

Nasal colonization with *Staphylococcus aureus* is not associated with the severity of symptoms or the extent of the disease in chronic rhinosinusitis

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OBJECTIVES: There is an increasing knowledge that the severity of perennial allergic rhinitis is associated with nasal carriage of *Staphylococcus aureus* (*S. aureus*). The aim of this study was to evaluate the rate of bacterial colonization with *S. aureus* in the nose of subjects with and without chronic rhinosinusitis (CRS) and to correlate these findings with the severity of symptoms and the extent of the disease. **STUDY DESIGN AND SETTING:** Open, prospective controlled trial.

METHODS: 190 subjects with CRS and 42 subjects with septal deviation without sinusitis (control subjects) were included in this study. Swabs were taken endoscopically from the middle meatus and bacteria were cultured and identified. Airway symptoms were assessed by subjects in standardized questionnaires and frequencies of respiratory tract infections were noted. The rhinosinusitis extent was graded by CT scan assessment. Analysis of variance, chi-square test, and Pearson's correlation test were applied for statistical analyses.

RESULTS: The *S. aureus* carriage rate was 25.5% in CRS and 31.4% in control subjects. Further facultative pathogens were cultured in 20.6% of subjects with CRS and in 8.5% of controls. 73.8% of *S. aureus* were ampicillin-resistant, multiresistant strains were cultured in 5.8%. Most airway symptoms and the frequencies of respiratory tract infections were significantly higher in the CRS group compared with control subjects. In post hoc comparison between the subgroups with and without *S. aureus* colonization, no significant differences were found between the extent of rhinosinusitis and the severity of airway symptoms.

CONCLUSIONS: Facultative pathogens were detected in more than 40% of CRS patients without acute respiratory tract infections. In contrast to the findings in atopic dermatitis and perennial allergic rhinitis, the colonization rate with *S. aureus* is not increased and *S. aureus* carriage is not a risk factor for the severity or the extent of rhinosinusitis. (Otolaryngol Head Neck Surg 2004;131:200-6.)

Chronic rhinosinusitis (CRS) is one of the most frequent illnesses of humans in the United States and Europe and the prevalence of CRS was reported to be higher than that of arterial hypertension and arthritis.¹ Sinusitis has been understood as inflammation of the sinus mucosa caused by infections, which might be based on impaired ventilation and drainage of the sinuses because of an obstruction of the ostiomeatal complex following viral and/or bacterial infection.^{2,3} Subgroups of CRS, particularly chronic hyperplastic rhinosinusitis with bilateral nasal polyps (CHS/NP), seem to be only partially related to infection, but are stronger associated with eosinophilic inflammatory mechanisms as in aspirin sensitivity, fungal allergy, or asthma.^{2,4,5} The interaction between the nasal microenvironment and the inflammatory mechanisms of CRS and CHS/NP is poorly understood. However, there is increasing evidence that bacterial infections or colonization are as capable of influencing the chronicity or severity of chronic airway disease as asthma or perennial allergic rhinitis.⁶⁻⁸ Shiomori et al showed that patients with perennial allergic rhinitis have a significantly higher rate of nasal carriage of *Staphylococcus aureus* than nonallergic controls.⁸ Furthermore, the nasal symptom scores of the *S. aureus*-positive subjects were significantly higher than those of noncarriers.⁸ The relation between nasal colonization with *S. aureus* and the severity of complaints or the extent of the disease has not been well documented in CRS, although this bacteria is one of the most frequent cultured pathogens in chronic rhinosinusitis.^{3,9-11}

The aim of the study was to evaluate the rate of colonization with potential pathological bacteria, particularly *S. aureus*, in the nose of subjects with and without CRS. Furthermore, the extent of sinusitis, the rate of allergic sensitization, and the severity of airway symptoms were compared between the subgroups with

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and without nasal carriage of *S. aureus* to assess the role of the latter pathogen for chronic rhinosinusitis.

STUDY DESIGN

The study was performed as an open, prospective controlled trial in subjects undergoing nasal surgery in the Department of Otorhinolaryngology–Head and Neck Surgery of the University of Cologne from January 2001 to June 2002.

METHODS

In this study, a total of 232 subjects were included. The diagnosis of CRS was confirmed or excluded by a detailed rhinological history, nasal endoscopy, and CT scans. One hundred and ninety subjects were assigned to the CRS group (mean age, 46.4 ± 14.3 years; 123 males and 67 females) and 42 subjects (with anatomical septal deviation without sinusitis) were assigned to the control group (mean age, 38.4 ± 12.8 years; 29 males and 13 females), respectively.

All subjects also underwent a comprehensive clinical ENT examination including allergy-screening tests [prick tests, total serum IgE levels (UNICAP® system, Pharmacia, Uppsala, Sweden)] and rhinomanometry. Skin prick tests were performed according to the EAACI guidelines for the most relevant inhalant allergens in Germany.¹²

Exclusion criteria were acute infections of the upper respiratory tract and antibiotic pretreatment three weeks before joining the study.

The study was performed according to the “Ethical Principles for Medical Research Involving Human Subjects” (World Medical Association, Helsinki/Edinburgh, 2000). Following oral and written explanation of aims and potential risks of the study, informed written consent was obtained. The study was granted by the Ethics Committee of the University of Cologne.

Microbiological Examinations

Before rhinoscopy was performed with a rigid 4-mm 25° nasal endoscope, the nose was decongested with a topical oxymetazoline spray (0.25%). All nasal swabs were taken by passing a small sterile twisted wire cotton applicator (Transwab® Medical Wire and Equipment, Corsham, Wiltshire, UK) along the middle meatus under direct endoscopic visualization at the patient’s first visit. A contact between the swab and the nasal vestibule was avoided. The swab was then carefully placed in the Transwab® MW 172 PT transport tube for aerobes and anaerobes (Medical Wire and Equipment). After the tube was labeled with the patient’s information, it was immediately transported to the microbiological department for routine culture of bacteria. Samples were incubated at 37° C under aero-

bic and anaerobic conditions on blood agars, MacConkey agars, and chocolate agars. Plates were examined for growth of bacterial colonies after 24 and 48 hours of incubation. The strains were identified by morphological staining and biochemical techniques and reported semiquantitatively for each specimen. If *Staphylococcus* species was detected, coagulase test was performed.

Isolated staphylococci were tested for their resistance against the following antibiotics: penicillin, ampicillin, amoxicillin/clavulanate potassium, oxacillin, cefazolin, cefuroxime, gentamicin, levofloxacin, ciprofloxacin, trimethoprim-sulfamethoxazole, erythromycin, clindamycin, and vancomycin.

Radiological Grading

The extent of rhinosinusitis was graded by using a CT scan assessment (0: no abnormality; 1: partial opacification; 2: total opacification: nasal polyps/ostio-meatal complex (OMC), maxillary~, ethmoidal~, sphenoidal~, frontal sinuses), based on the method described by Lund and Mackay.¹³ In contrast to the original staging system of Lund and Mackay,¹³ we graded the size of the nasal polyps together with the narrowing of the OMC in the middle meatus (0: no opacification; 1: opacification of ostiomeatal complex; 2: total opacification of the ostiomeatal complex and the nasal cavity) and omitted a differentiation between mucosal disease located in the anterior and the posterior ethmoid and an evaluation of anatomic variants, resulting in total scores between 0 and 20.

Evaluation of Airway Symptoms and Frequency of Upper Respiratory Tract Infections

Standardized questionnaires were given to all subjects at their first visit. Questions concerned the major CRS-related symptoms (nasal obstruction, post-nasal drip, headache, hyposmia) and asthmatic complaints.¹⁴ Symptoms were assessed by the subjects on visual analogue scales (VAS) of 0 to 100, where “0” (left end of scale) was no symptom present and “100” the most severe intensity. Furthermore, the frequency of acute viral and bacterial infections of the upper respiratory tract within the last 12 months was noted and allergic symptoms (nasal discharge, sneezing, nose itching) were assessed according to five point ranking scale (0 = never; 1 = once a month, 2 = once a week, 3 = once a day, and 4 = several times a day).

Statistics

SPSS v. 10.0 was used for statistical analyses (Statistical Package for the Social Sciences, SPSS Inc.,

Table 1. Radiological grading of CT scans

Anatomical region	0 no opacification	1 partial opacification	2 total opacification
OMC/nasal polyps right side	50.8	39.6	9.6
OMC/nasal polyps left side	52.4	35.8	11.8
Right maxillary sinus	9.3	51.6	39.1
Left maxillary sinus	12.4	57.8	29.8
Right ethmoidal sinus	24.8	42.2	32.9
Left ethmoidal sinus	24.8	42.9	32.3
Right frontal sinus	44.7	34.8	20.5
Left frontal sinus	47.2	31.1	21.7
Right sphenoidal sinus	47.8	39.8	12.4
Left sphenoidal sinus	54	32.9	13

Modified radiological rhinosinusitis staging system for CT scan assessment according to Lund and Mackay.¹³ Nasal polyps/ostioameatal complex (OMC), maxillary~, ethmoidal~, sphenoidal~, frontal sinuses were graded as 0: no abnormality; 1: partial opacification; 2: total opacification, respectively.

Chicago, IL). Data were expressed as means $\pm$ standard deviation (SD).

Chi-square test was used to compare the rates of carriage of *S. aureus*, the rate of bacterial resistance, and the numbers of subjects with positive skin prick tests in the CRS group and control group, respectively. Pearson's test was applied to analyze correlations between the extent of rhinosinusitis and CRS-related symptoms.

The frequencies of upper respiratory tract infections, the assessments of the severity of airway symptoms and frequency of allergic symptoms were submitted to analyses of variance [between subject factors: airway diagnosis (CRS vs. controls); degrees of freedom corrected according to Greenhouse-Geisser]. ANOVA was then repeated to analyze the influence of the factor "carriage of *S. aureus*" in the subgroups CRS with *S. aureus*, CRS without *S. aureus*, Controls with *S. aureus*, Controls without *S. aureus* on the extent of rhinosinusitis, the severity of airway symptoms, and the rates of respiratory infection, respectively. Bonferroni post hoc analyzes were used for the statistical comparison of more than two groups. A *P*-value of less than 0.05 was regarded statistically significant.

RESULTS

Microbiological Data

Middle meatus secretions were positive for bacteria in 86.4% of swabs cultured from CRS patients and in 83.3% from control subjects. The majority of nasal swabs (CRS group: 58.6%; controls: 60%) revealed a normal flora of the nose (i.e., nonhemolytic streptococci ssp., *Neisseria*, coagulase-negative staphylococci) without *S. aureus*.

S. aureus was isolated from nasal swabs in 45 (25.5%) of the 190 subjects with CRS and in 11 (31.4%) of 42 controls. The rate of nasal carriage of *S.*

aureus was not statistically different between the study groups (chi-square test: *P* = 0.34).

Beside *S. aureus*, the following potential pathogens were cultured in the CRS group: *Streptococcus pneumoniae* 4.2%, *Moraxella catarrhalis* 3.6%, *Haemophilus influenzae* and *Pseudomonas aeruginosa* 3% in each case; *Proteus mirabilis* 2.4%, *Escherichia coli* and *Klebsiella* ssp. 1.8% and *Citrobacter diversus* 0.6%, respectively. In controls, *E. coli* was identified in 5.7% and *P. mirabilis* in 2.9% of cultures.

In the CRS group, 73.8% of *S. aureus* were penicillin/ampicillin-resistant. All other antibiotics tested showed effectiveness against the remaining *S. aureus* strains with the exception of 2 (5.8%) multiresistant pathogens growing from swabs of the CRS group. In controls, 9 (81.1%) of *S. aureus* strains were penicillin/ampicillin-resistant, and only 1 (9.1%) multiresistant strain was detected. There was no statistical difference between bacterial resistance rates in the CRS group and in control subjects, as determined by chi-square test (*P* = 0.77).

Radiological Data

The results of the radiological grading of the total CRS group are condensed in Table 1. Overall, the mucosal disease depicted on computed tomography scans were assessed with an average score of 9.3 ± 4.8 in the CRS group. There was no significant difference between the radiological grading scores in CRS subgroups with (9.3 ± 4.2) or without (9.2 ± 5.0) evidence of *S. aureus* (*F*[1] = 0.185, *P* = 0.67).

CRS-Related Symptoms and Asthmatic Complaints

The assessment of postnasal drip (*F*[1] = 10.234; *P* < 0.002), reduced sense of smell (*F*[1] = 13.370; *P* < 0.001), and asthmatic complaints (*F*[1] = 11.928; *P* <

Table 2. Assessment of symptoms and numbers of upper respiratory tract infections

	CRS group (n ≥ 171)*		Controls (n ≥ 35)*	
	Means	SD	Means	SD
Radiological grading	9.3	4.8	–	
CRS-related symptoms and asthmatic complaints				
Nasal obstruction	59.7	28.2	56.7	26.51
Postnasal drip	55.4‡	29.5	36.6	30.55
Headache	35.7	34.3	29.1	33.28
Reduced sense of smell	46.2‡	36.2	21.8	28.81
Asthmatic complaints*	49.9†	26.6	11.2	15.47
Numbers of airway infections				
Viral rhinitis	3.1‡	4.4	2.33	2.17
Bacterial rhinitis	1.9‡	3.8	0.67	1.89
Acute sinusitis	1.7‡	3.2	0.71	2.46
Allergy symptoms				
Nose itching	1.2	1.6	1.0	1.5
Nasal discharge	1.2	1.6	1.1	1.6
Sneezing	1.0	1.4	0.9	1.3
Total serum IgE	117.5	130.9	104.1	150.9

Symptoms were assessed by the subjects on 100-mm visual analog scales (VAS), where “0” (left end of scale) was no symptom present and “100” (right end of scale) the most severe intensity. Frequency of acute viral rhinitis, bacterial rhinitis and acute sinusitis within the last 12 months.

*Except “asthmatic complaints”: because only 47 subjects of the CRS group and 6 controls were suffering from asthma, only the assessments of asthmatic subpopulation was used for analyses.

† $P < 0.05$.

‡ $P < 0.01$.

0.001) were significantly higher in the CRS group compared to controls (Table 2). Average scores of headache ($F[1] = 1.385; P = 0.51$) and nasal obstruction ($F[1] = 0.00; P = 0.996$) were slightly higher in the CRS group without statistical significance. Pearson’s test revealed significant correlations between the extent of the mucosal disease and the assessment of nasal obstruction ($r_{178} = 0.204, P = 0.01$), postnasal drip ($r_{173} = 0.26, P = 0.01$), and reduced sense of smell ($r_{178} = 0.38, P = 0.001$) in the CRS group (Fig 1).

Post hoc comparison of symptom assessments revealed no significant differences between the subgroups with and without nasal carriage of *S. aureus* (Table 3).

Upper Respiratory Tract Infections

The frequency of viral rhinitis and bacterial infections during the last 12 months were significantly higher in the CRS group compared to controls (all $P < 0.01$, Table 2). No significant differences were found in post hoc comparison between CRS or control subgroups with and without *S. aureus* carriage, respectively (Table 3).

Allergic Sensitization

At least one positive reaction in skin prick test was found in 43.8% of CRS patients and in 38.3% of controls ($P = 0.50$). Post hoc testing revealed statistical significance of differences between total serum IgE levels in the subgroups with allergic sensitization

(CRS: 189.3 ± 165.7 ; controls: 158.9 ± 127.8) and the subgroups without sensitization (CRS: 69.2 ± 71.4 ; controls: 48.6 ± 59.1) ($F[3] = 17.098; P < 0.001$). No significant differences were observed between the frequency of allergic symptoms in the CRS group and the control group.

The numbers of subjects with allergic sensitization were not statistically different in the subgroups with or without nasal *S. aureus* colonization (chi-square test, $P = 0.78$). In the CRS subgroup without *S. aureus*, average assessments of allergic symptoms were nonsignificantly higher than in the subjects with *S. aureus* (Bonferroni’s post hoc comparison: nose itching ($P = 0.47$); nasal discharge ($P = 1$); sneezing ($P = 0.44$)). No significant effects were observed for the factor “nasal carriage of *S. aureus*” concerning total serum IgE levels and the allergy symptoms. Descriptive statistics are summarized in Table 3.

DISCUSSION

Although several studies have previously focused on risk factor analyses in CRS,^{2,15-17} the association between bacterial colonization and chronic rhinosinusitis has not been documented well.⁹ In this study, facultative pathogens were detected in the middle meatus of more than 40% of CRS patients without acute infections of the upper respiratory tract. Although *S. aureus* was the most frequent pathogen in the CRS group, no statistical difference was found in the growth rate in the

VAS

Reduced sense of smell

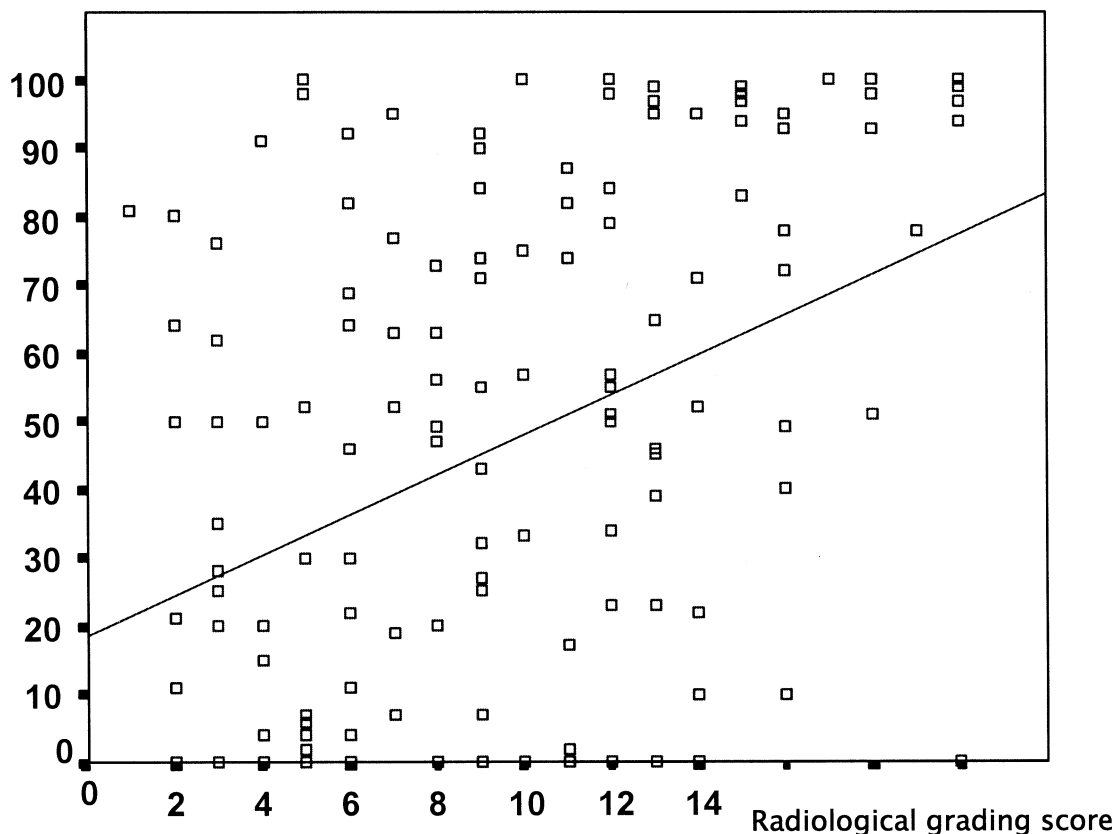


Fig 1. Scatter plot of radiological grading and assessment of reduced sense of smell in the CRS group. Pearson's test revealed a significant correlation between the extent of CRS (graded with the modified radiological staging system according to Lund and Mackay¹³) and subjects assessment of reduced sense of smell ($n = 178$; $r_{178} = 0.38$, $P = 0.001$).

control group. The percentage of *S. aureus* growth in endoscopically taken swabs of the middle meatus have been reported to range from 12% to 36%.^{10,18,19} The culture rates of *S. aureus* observed in this study (CRS: 25.5%; controls: 31.4%) were within the expected range. Araujo et al reported a higher rate of *S. aureus* in controls than in CRS patients,¹⁰ supporting our data. The colonization of *S. aureus* in the nasal cavity varies according to different populations, the mean rate of carriage in the general population is reported to be 37.2% with a range of 19% to 55.1%.²⁰ However, these epidemiological data did not support a close relation between the nasal carriage of *S. aureus* and chronic airway inflammation.

The pathogenic role of *S. aureus* colonization is better confirmed in other chronic inflammatory diseases such as atopic dermatitis. Several studies have reported that the colonization rates of *S. aureus* on the skin are more than 80% in patients with atopic dermatitis compared to 5% to 30% in healthy subjects.^{21,22} *S. aureus*

isolated from the skin of the patients with atopic dermatitis secretes enterotoxins in more than 65%, penetrating the skin and activating different cell populations of the immune system as superantigens.^{21,22} Staphylococcal superantigens induce a polyclonal activation of T cells and promote the generation of antigen-specific IgE antibodies, both mechanisms increase the inflammation in atopic dermatitis.^{21,22} In contrast to atopic dermatitis, our knowledge about mechanisms and interactions between staphylococcal superantigens and airway inflammation is limited. Animal experiments have demonstrated that *Staphylococcus* enterotoxin B promotes the recruitment of several proinflammatory cells and the release of Th2 and proinflammatory cytokines in the airway mucosa, increasing the airway responsiveness.⁷ Bachert et al²² detected in approximately 50% of nasal polyp homogenates specific IgE antibodies against *Staphylococcus* enterotoxins A and/or B, which was linked to a polyclonal IgE formation against inhalant allergens. Furthermore, in *Staph-*

Table 3. Descriptive statistics of clinical data in the CRS group and controls depending on *S. aureus* carriage

	CRS without <i>S. aureus</i> (n ≥ 115)*		CRS with <i>S. aureus</i> (n ≥ 38)*		Controls without <i>S. aureus</i> (n ≥ 25)*		Controls with <i>S. aureus</i> (n ≥ 9)*	
	Means	SD	Means	SD	Means	SD	Means	SD
Radiological grading	9.1	4.9	9.3	4.2	–	–	–	–
CRS-related symptoms and asthmatic complaints								
VAS nasal obstruction	59.1	27.3	53.9	29.5	50.6	26.9	73.7	20.8
VAS headache	37.1	35.8	32.3	31.7	34.7	34.0	17.9	28.1
VAS postnasal drip	50.6	29.4	54.2	26.4	39.4	25.7	35.3	39.1
VAS reduced sense of smell	41.2	34.5	45.2	36.6	14.5	21.8	37.1	37.4
VAS asthma*	43.6	23.7	49.7	36.5	2.3	0.6	21.0	26.9
Frequency of upper respiratory tract infections								
Viral rhinitis	2.9	4.2	3.5	5.0	2.7	2.0	1.4	1.7
Bacterial rhinitis	1.8	3.2	2.0	4.3	0.8	1.6	0.3	0.4
Acute sinusitis	1.7	3.0	1.4	2.3	1.1	3.1	0.2	0.3
Allergy symptoms								
Nose itching	1.4	1.7	0.9	1.4	1.0	1.4	1.3	1.7
Nasal discharge	1.2	1.6	0.9	1.4	1.1	1.5	1.3	1.8
Sneezing	1.0	1.5	0.6	1.1	0.8	1.2	1.4	1.6
Total serum IgE	98.0	115.3	131.0	139.1	82.4	112.5	95.9	84.5

*Because only 47 subjects of the CRS group and 6 controls were suffering from asthma, the total numbers used for statistical analyses were lower for “asthmatic complaints” than for the other symptom assessments.

Staphylococcus enterotoxin-positive polyp samples the eosinophilic inflammation was significantly stronger and these patients more often suffered from asthma and/or aspirin sensitivity.²² Shiomori et al⁸ reported significantly higher rates of nasal *S. aureus* carriage (44%) and superantigen-producing pathogens (22%) in subjects with perennial allergic rhinitis (PAR) compared to a nonallergic population. Peripheral lymphocytes of PAR patients showed significantly higher proliferative responses and released significantly higher levels of Th2 cytokines.⁸ More importantly, the nasal symptom scores of patients with PAR carrying *S. aureus* were significantly higher than that of patients without evidence of *S. aureus*, although there was no significant association between superantigen production and symptom scores.⁸ Berrettini et al⁹ found no correlation between nasal colonization with pathogens in patients with PAR and CRS (most common bacteria was *S. aureus*, carriage rate was 25%) and the extent of rhinosinusitis assessed in the radiological grading system of Lund and Mackay.¹³ In this study, the nasal colonization with *S. aureus* had no significant effect on the severity of CRS-related symptoms, the frequency of allergic symptoms or the extent of rhinosinusitis. Furthermore, no significant effects of *S. aureus* colonization were detected in statistical comparison of airway symptom scores and the radiological grading of subgroups with perennial allergic sensitization or bilateral nasal polyps and CHS/NP in our study population (analyses not shown).

These contradictory results may be caused by methodical differences used for microbiological examinations. The bacterial samples from Shiomori et al⁸ were taken from the nostril and the inferior turbinate. A direct contact to the nasal vestibule was avoided in this study because the nostril is a major resource of *S. aureus* in humans.²⁰

CONCLUSIONS

Facultative pathogens were detected in more than 40% of CRS patients without acute respiratory tract infections. Based on our results, nasal carriage of *S. aureus* occurred at similar rates in patients with CRS and in subjects without sinusitis. The severity of airway symptoms and the extent of rhinosinusitis is not associated with nasal colonization with *S. aureus* in patients with CRS.

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