
Nasal carriage of *Staphylococcus aureus* and endonasal activity in Wegener's granulomatosis as compared to rheumatoid arthritis and chronic rhinosinusitis with nasal polyps

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ABSTRACT

Objectives. Nasal colonisation with *Staphylococcus aureus* (*S. aureus*) has been implicated in Wegener's granulomatosis (WG) disease activity. In this study, the frequency of nasal colonisation with *S. aureus* in WG was compared to healthy and disease control groups for the first time. Moreover, endonasal activity was correlated to colonisation.

Patients and methods. Nasal carriage of *S. aureus* of a well-defined group of 89 patients with WG was compared to 40 patients with chronic rhinosinusitis with nasal polyps (CRS), 35 patients with rheumatoid arthritis (RA), 50 hospital staff members and 25 subjects without regular hospital contact and correlation analysis of nasal carriage and endonasal activity of WG was performed.

Results. WG patients showed significantly higher rates (72%) of nasal colonisation with *S. aureus* compared to CRS patients (28%) and healthy subjects without regular hospital contact (25%, 95%-CI), but not to RA patients (46%) and hospital staff members (58%).

WG patients with nasal carriage of *S. aureus* had significantly higher endoscopically proven endonasal activity ($p=0.01$), significantly more often first manifestation of WG in the upper respiratory tract ($p=0.02$) and higher relapse-rates ($p=0.052$) than WG patients without such carriage.

Conclusion. Endonasal activity in WG is associated with higher nasal *S. aureus* colonisation rates and subsequent higher relapse rates. The higher frequency of *S. aureus* colonisation could be a consequence of a recently shown mucosal barrier defect in WG and facilitate chronic inflammation and granuloma formation in the upper respiratory tract.

Introduction

One of the most striking features of Wegener's granulomatosis (WG), a potentially organ and/or life-threatening, chronic inflammatory and autoimmune disease of as yet unknown etiology, is its inherent propensity for granulomatous inflammation of the upper and/or lower respiratory tract (1). ENT- and/or lower airway symptoms affect virtually all WG-patients followed over years in large cohorts (2, 3). Further, "grumbling disease" within the respiratory tract related to persistent disease activity is seen in many WG-patients, who are defined as being otherwise in clinical remission (1).

A potential role for respiratory *Staphylococcus (S.) aureus* infection in triggering WG-disease activity was suggested by 2 seminal studies in the mid-1990s (4,5). It was shown that chronic *S. aureus* nasal carriage in patients with persistently or intermittently positive C-ANCA is associated with WG-relapses (4). A later study found that the risk of relapse is highest for tsst-1 superantigen-positive *S. aureus* nasal carriage (6). Treatment with trimethoprim/sulfamethoxazole (T/S) reduces both the annual number of respiratory infections and the incidence of relapses in WG-patients in remission (5). In contrast, colonisation of the nasal mucosa with *S. aureus* has no pathological consequence for the healthy host. However, in immune-compromised patients such as patients on haemodialysis recurrent infections are caused by *S. aureus* nasal carriage and can be prevented by eradication (7).

Abnormal microbial mucosa-invasiveness and composition triggering inflammation and/or autoimmunity has been shown to be an important pathogenic mechanism in chronic inflammatory

diseases associated with barrier dysfunction such as Crohn's disease and autoimmune rheumatic diseases (8, 9). Intriguingly, severely impaired respiratory ciliar function suggestive of barrier dysfunction has been demonstrated in WG recently. A defective mucosal barrier could facilitate mucosal *S. aureus* persistence and/or -invasiveness subsequently triggering chronic inflammation (10).

Furthermore genetic sequences of anti-sense regions complementary to PR-3 are found in *S. aureus* and this complementary PR-3 may lead to PR-3 ANCA formation via anti-idiotypic antibodies in WG (11).

However, previous studies did not correlate *S. aureus* nasal carriage with distinct inflammatory changes of the nasal mucosa. Disease controls in order to cross-check for various influences including immunosuppressive treatment were missing (4-6). Therefore, we analyzed chronic *S. aureus* nasal carriage in a cohort of 89 WG-patients and checked endoscopically for endonasal disease activity. Results were compared to patients with chronic rhinosinusitis with nasal polyps (CRS) or rheumatoid arthritis (RA) and to healthy controls (hospital-staff members versus healthy subjects without regular hospital contact).

Patients and methods

Patient population.

Eighty-nine consecutive patients with WG (age 20–76, mean age 54 years) seeking otorhinolaryngologic care over a period of 2 years were included and followed in this study. Disease controls included 35 patients with RA (age 32–85, mean age 68 years) and 40 with CRS (age 20–83, mean age 49 years). Healthy controls were 50 hospital staff members and 25 healthy subjects without regular hospital contact. The study was performed in accordance with the Helsinki declaration of 1975/83.

Disease definitions

All WG-patients fulfilled the CHC- and ACR-criteria (12, 13). WG was biopsy-proven in 71 of the 89 (80%) patients. Patients were subject to standardised interdisciplinary evaluation as described

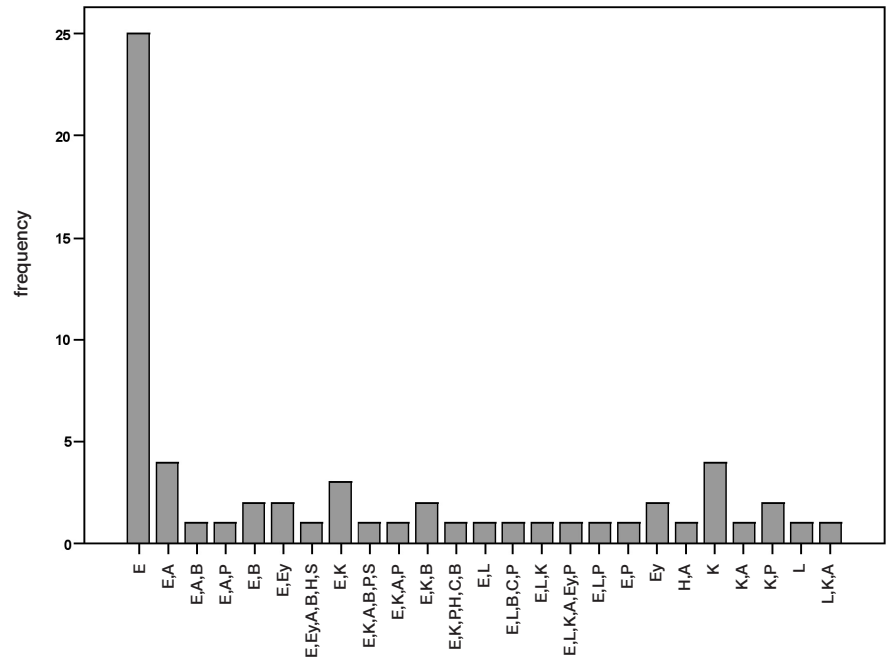


Fig. 1. Distribution of organ involvement by ELK classification for 58 WG patients at t1 (E: ENT, L: Lung, K: Kidney; Ey: Eye; A: Arthritis, S: Skin, C: CNS, H: Heart, P: Peripheral nervous system, M: Muscle, B: Constitutional symptoms)

earlier (3). Organ involvement was described using the ELK classification (14). Disease activity was assessed in accordance with recently published EULAR recommendations (15). Endonasal WG-activity was examined endoscopically and assessed according to the guidelines proposed by Paulsen & Rudert (16). RA was diagnosed according to the revised ACR criteria for RA, CRS according to the criteria of the American Academy of Otolaryngology-Head and Neck Surgery, the American Academy of otolaryngic Allergy, the American Rhinologic Society and the Sinus and Allergy Health Partnership (17, 18).

Clinical manifestations and treatment of patients

Forty-one WG-patients were examined a second time (t2) with a mean of 11 month (minimum 1, maximum 24 month) after the first examination (t1). Patients with WG were categorised to have localised (t1: n=8, 9%; t2: n=3, 7.5%) or generalised (t1: n=81, 91%; t2: n=37, 92.5%) disease and 61 (n=87, 69%) had first manifestation at the upper respiratory tract. The vast majority of 50 (86%) out of 58 patients had involvement of the upper respiratory tract (E, ELK classification (14)) with-

out (n=26, 52%) or with (n=24, 48%) other organ involvement (Fig. 1). Relapse (n=9, 10%), time between first diagnosis (average 27 month, minimum 0 month, maximum 214 month) as well as first manifestation (average 59 month, minimum 1, maximum 228 month) and study entry and paranasal sinus involvement (visualised by MRI, t1: 35 of 64 patients, 39%, t2: 18 of 24 patients, 75%) were documented. MRI findings were classified as paranasal sinus mucosal swelling, inflammation, granuloma formation and fluid level as well as recurrent, increasing or unchanged findings comparing t1 to t2. Signs of systemic inflammation were: mean erythrocyte sedimentation rate (ESR) after the first hour at t1: 35 mm (SD 33) and at t2: 28 mm (SD 29) as well as mean cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) directed against proteinase 3 at t1: 1/119 (SD 268) and at t2: 1/77 (SD 110).

Systemic medication was heterogeneous with patients receiving leflunomide, cyclophosphamide, mycophenolate mofetil, methotrexate, azathioprine, glucocorticoid, adalimumab, infliximab, etanercept, T/S and cyclosporine in different dosages and combinations or no medication.

Microbiological analysis

Nasal carriage of *S. aureus* was investigated by swab cultures of both anterior nares. The swabs were inoculated on 5% sheep-blood agar, Chapman agar and Tarozzi bouillon for 48 h at 37°C. Isolates were identified as *S. aureus* by typical appearance of the colonies, hemolysis, by their ability to coagulate citrate plasma and to cleave DNA and mannitol.

Statistics

Results were analysed using SPSS statistical software for Windows, Release 15.0 (SPSS Inc., Chicago, USA). Normal distribution assumption was checked by Kolmogorov-Smirnov-Test. Associations were evaluated by χ^2 -Test (Fisher's exact test), 95% binominal confidence interval and Mann-Whitney-Test where appropriate and significance was stated in an exploratory meaning for $p < 0.05$.

Results

Nasal carriage of S. aureus in WG is significant higher compared to the healthy population outside the hospital and CRS

Of the 89 WG patients, 64 (72%, 95%-CI: 61%–81%) were carrying nasal *S. aureus*. This is a significant higher rate compared to the healthy population outside the hospital ($n=7$, 28%, 95%-CI: 12%–49%), CRS (10, 25%, 95%-CI: 13%–41%) and also a considerable, but not significant higher rate of nasal carriage of *S. aureus* compared to hospital staff members ($n=29$, 58%, 95%-CI: 43%–72%) and RA (16, 46%, 95%-CI: 29%–63%, Fig. 2).

Endonasal activity in WG

At t1, the patients had endoscopically proved no ($n=43$, 48%), minor ($n=20$, 23%), moderate ($n=23$, 26%) and high ($n=3$, 3%) endonasal activity, and at t2, the patients had no ($n=14$, 16%), minor ($n=8$, 9%), moderate ($n=16$, 18%) and high ($n=1$, 1%) endonasal activity respectively.

Higher relapse rates, endonasal activity and involvement of the ENT tract in WG-patients carrying nasal S. aureus
WG patients with nasal carriage of *S. aureus* showed significant higher endoscopically proven endonasal activity at

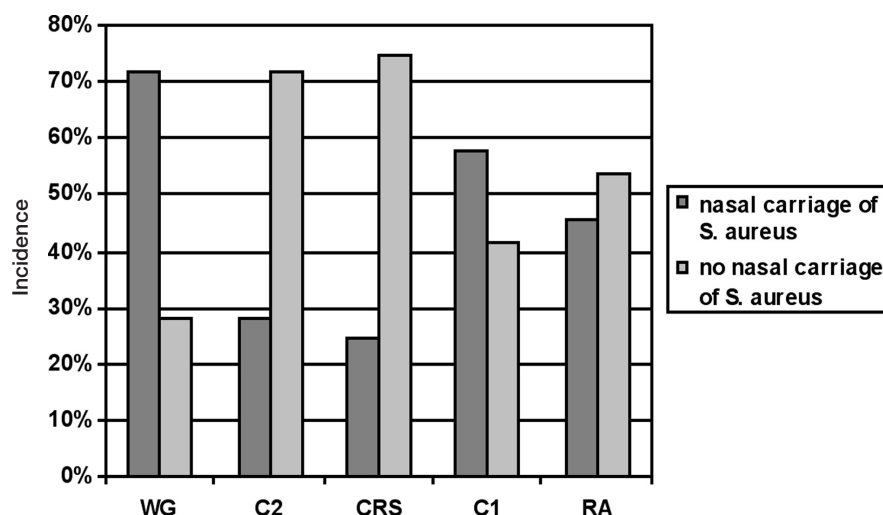


Fig. 2. Incidence of nasal colonisation by *S. aureus* (ncSa) in patients with Wegener's granulomatosis (WG, $n=89$), healthy subjects without regular hospital contact (C2, $n=25$), patients with chronic rhinosinusitis with nasal polyps (CRS, $n=40$), hospital staff members (C1, $n=50$) and patients with rheumatoid arthritis (RA, $n=35$).

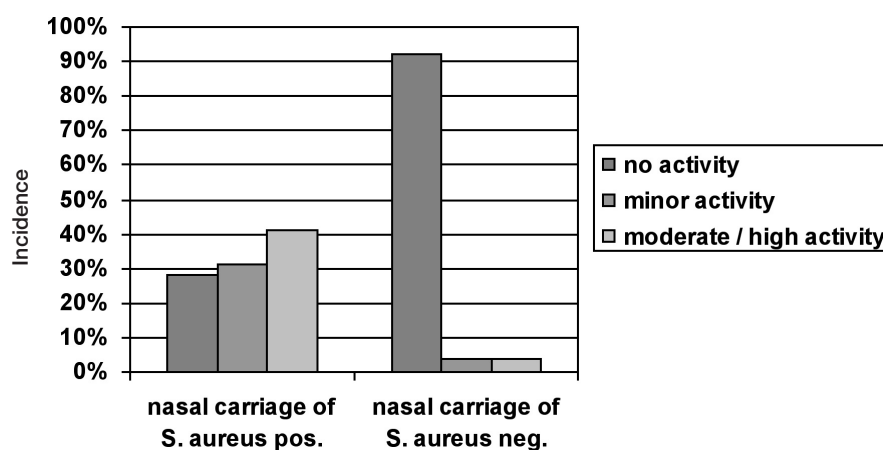


Fig. 3. Incidence of endonasal activity in WG patients with ($n=64$) and without ($n=25$) nasal colonization by *S. aureus* (ncSa) at t1.

t1 ($p=0.01$, Fig. 3) and t2 ($p=0.01$) and significantly more often first manifestation of WG in the upper respiratory tract ($p=0.02$) than those WG patients without nasal carriage of *S. aureus*. Nasal carriage of *S. aureus* was significantly higher in patients with upper respiratory tract involvement in the ELK-classification at t1 and t2 (t1: $p < 0.01$, t2: $p=0.033$) and WG patients had higher relapse rates when carrying nasal *S. aureus* on t1 ($p=0.052$; odds ratio 6.68 (0.36,122.75)) than nasal carriage *S. aureus*-negative patients.

MRI findings correlate with endonasal activity

Sinus involvement detected by MRI correlated significantly with endo-

scopically approved endonasal activity ($p=0.03$) but not with nasal carriage of *S. aureus*. Notably 7 out of 19 patients with minor and 8 out of 36 patients with moderate to high endoscopically approved endonasal activity showed inconspicuous MRI.

Nasal carriage of S. aureus does not correlate with serological activity, ANCA-titre, and treatment with trimethoprim/sulfamethoxazole (T/S) in WG

No statistic correlation was found between nasal carriage of *S. aureus* and signs of systemic inflammation (c-ANCA and ESR), age, generalised or localised disease, time between first manifestation and study entry, time

between first diagnosis and study entry and T/S treatment. Likewise, no correlation between T/S treatment and endonasal activity could be found. Immunosuppressive therapy was too diverse to group patients to be useful for statistical analyses.

Discussion

Case reports and reports on small series suggest a role of chronic nasal carriage and infection with *S. aureus* (especially strains containing the superantigen toxic-shock-syndrome-toxin-1) as risk factors for relapses in WG (4, 6, 19-24). These results could be confirmed in the present study. Another hint for a potential pathophysiologic role of *S. aureus* in WG is the finding of specific adaptive immune system reactions to *S. aureus* in WG patients (25, 26). However, a comparison of nasal colonisation with *S. aureus* in WG and healthy and disease control groups has been missing so far. Moreover, previous studies did not correlate *S. aureus* nasal carriage with distinct inflammatory changes of the nasal mucosa.

In the present study the documented frequencies of nasal *S. aureus* colonisation in the investigated control groups was comparable to that reported in the literature (27-30). In RA, 35% of the patients without and 60% with anti-TNF-alpha agent plus methotrexate medication but only 23% with anti-TNF-alpha agent alone showed nasal carriage of *S. aureus* (31). Other studies could not support higher frequencies of nasal *S. aureus* carrier rates for patients under immunosuppressive therapy (32). On one hand, immunosuppressive therapy might be a risk factor for nasal carriage of *S. aureus*. On the other hand, intensified medical therapy reflects autoimmune disease severity, which could be an independent factor predisposing to higher frequencies of *S. aureus* nasal carriage. The latter seems to be more likely. Immunosuppressive treatment in WG and RA in this cohort was comparable, but medication was too diverse to group for statistical analysis.

In this study, we showed that the frequency of nasal carriage of *S. aureus* is significantly higher in WG compared to CRS. In CRS, a chronic inflamma-

tional disease with nasal mucosa hyperplasia, the barrier dysfunction is obvious by endoscopy (polyps) and a specific immune reaction directed against *S. aureus* was demonstrated in these polyps. Intracellular occurrence of *S. aureus* with the consequence of recurrent infections with unique, patient-specific bacterial clonotypes is present in CRS and a specific role of *S. aureus* in the course of CRS is discussed even though the mechanisms are still unclear (33, 34).

Nasal carriage of *S. aureus* does not necessarily lead to inflammation and/or invasiveness. In fact colonisation of the nasal mucosa with different types of microorganisms (so called commensals) is one prerequisite for protection of this surface against invading pathogens (35). Several patients in the different groups showed endoscopically inconspicuous nasal mucosa but positive nasal swab cultures and nasal carriage of *S. aureus* did not provoke serological signs of inflammation. The significant higher frequency of nasal carriage of *S. aureus* in WG compared to healthy controls without regular hospital contact might be a result of nosocomial colonization in WG, but the obvious higher frequency compared to RA and hospital staff and the procedure of taking the swabs in the first days of admission to the hospital makes such bias unlikely. Taken together the highest carrier rates in all investigated groups in this study seem to be related to WG itself rather than therapy or study protocol effects.

Stegemann *et al.* described an equal distribution of destructive nasal lesions (perforation of the nasal septum and saddle nose deformity) in WG patients with or without nasal carriage of *S. aureus* (4). Such structure defects often constitute damage rather than activity. In this study, precise endoscopic examination for endonasal activity of WG was performed and a significantly higher activity was found in WG patients with nasal carriage of *S. aureus*. Endonasal activity in WG could be detected by MRI, but the frequent false negative results make this investigation redundant especially when considering the simplicity of endoscopy of the nasal cavity.

In WG, the higher frequency of *S. aureus* nasal carriage might be a consequence of impaired mucosal function because of disease activity. This assumption is supported by the statistically significant higher ENT tract involvement in this group. Lately we described a severely impaired ciliar beat frequency of the nasal mucosa in WG compared to RA and healthy controls, which predisposes to a physical barrier dysfunction (10).

Even though antibiotic treatment with trimethoprim/sulfamethoxazole (T/S) is not the first choice for treatment of *S. aureus* infections, T/S is frequently used in WG therapy (36-38), especially to reduce the incidence of relapses in WG in remission (5). This supportive effect is dependent on the disease stage. Patients with localised WG benefit, whereas patients with generalised WG do not (39, 40). Accordingly, nasal carriage of *S. aureus* is independent of T/S therapy. Notable endonasal activity is alike independent of T/S therapy. The mechanism of the positive effect of T/S treatment in WG subgroups still remains unclear and the used dosages are far below any concentrations appropriate for systemic immunomodulatory effects of folic acid (5, 19). It can be speculated that T/S treatment might provoke a shift of nasal microbial colonisation with positive effects to WG independent of the carriage of *S. aureus*.

Conclusion

In WG a significantly higher nasal colonisation rate with *S. aureus* was detected as compared to control groups. Higher endoscopically detected endonasal activity was associated with higher rates of nasal colonisation with *S. aureus*. A higher rate of colonisation correlated with higher relapse rates and endonasal activity, both independent of T/S treatment. The higher frequency of *S. aureus* colonisation could be a consequence of a recently shown mucosal barrier defect in WG.

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