Staphylococcus aureus in Patients with Rheumatoid Arthritis Under Conventional and Anti-Tumor Necrosis Factor-α Treatment

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ABSTRACT. ***Objective.*** To compare the prevalence of nasal and oral *Staphylococcus aureus* in patients with rheumatoid arthritis (RA) with the prevalence in controls with other rheumatic diseases, and to determine predictors of *S. aureus* carriage and the influence of treatment with anti-tumor necrosis factor-α (anti-TNF-α) agents.

Methods. Eighty-one patients with RA and 83 other control patients of 2 outpatient rheumatology clinics were cultured for nasal and oral carriage of *S. aureus*. Quantitative nasal cultures for *S. aureus* were performed from swabs of the anterior nares, the posterior pharynx, and the soft palate. Information on medications, medical conditions, and risk factors for *S. aureus* carriage was collected from all participants by a questionnaire and confirmed by chart review.

Results. The *S. aureus* carriage rate (nasal and/or oral colonization) was 34.6% among RA patients and 32.5% among controls (p = 0.87). Being treated with an anti-TNF-α agent plus methotrexate (MTX) was the only independent predictor of *S. aureus* carriage (OR 3.24, 95% CI 1.16–9.05, p = 0.025). The *S. aureus* carriage rate among RA patients treated with an anti-TNF-α agent plus MTX was 60% (9/15) versus 23.1% (3/13) in RA patients treated with an anti-TNF-α agent only (p = 0.049). All *S. aureus* isolates were susceptible to oxacillin.

Conclusion. The *S. aureus* carriage rate among patients with RA was not higher than among controls. Treatment with anti-TNF-α agents was not associated with an increased *S. aureus* carriage rate. However, treatment with an anti-TNF-α agent plus MTX may predispose patients to *S. aureus* carriage. (J Rheumatol 2005;32:2125–9)

Key Indexing Terms:
STAPHYLOCOCCUS AUREUS RHEUMATOID ARTHRITIS CARRIAGE
COLONIZATION ANTI-TUMOR NECROSIS FACTOR-α THERAPY TUMOR NECROSIS FACTOR-α

Patients with rheumatoid arthritis (RA) are at increased risk of developing infections and appear to be particularly susceptible to septic arthritis, osteomyelitis, and skin and soft tissue infections[1], which are mostly caused by *Staphylococcus aureus*. This bacterium is responsible for up to 80% of joint infections in patients with RA[2]. The risk of severe infections may be even higher in RA patients treated with anti-tumor necrosis factor-α (TNF-α) agents[3], which are increasingly used as monotherapy or in combination with methotrexate (MTX)[4]. It has been shown that *S. aureus* and other gram-positive bacteria are potent inducers of TNF-α secretion from macrophages[5], that TNF-α enhances killing of *S. aureus* by neutrophils[6], and that a local increase in TNF levels might improve host defenses against staphylococcal foreign body infections[7]. These observations suggest that inhibition of TNF-α affects the response of the body to colonization and infection with *S. aureus*. Indeed, in a recent study, nasal colonization with *S. aureus* was found in 5 of 8 (63%) RA patients treated with etanercept, but in only 10 of 39 (26%) RA patients treated without anti-TNF-α agents[8].

Nasal *S. aureus* carriage appears to play a key role in the pathogenesis of infection[9,10]. *S. aureus* nasal carriers have a 2- to 12-fold higher risk of *S. aureus* infection than noncarriers[10]. A large multicenter study demonstrated that 82% of patients with *S. aureus* bacteremia carried in their anterior nares the same *S. aureus* strain isolated from the blood, strongly suggesting that most cases of *S. aureus* bacteremia originate from *S. aureus* colonizing the nose[11]. In another study, 14,008 nonbacteremic, nonsurgical patients were screened for nasal *S. aureus* at hospital admission and were monitored for the development of bacteremia. Nosocomial *S. aureus* bacteremia was 3 times more frequent in *S. aureus*

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Dr. Bassetti was supported by grants from the University of Basel (Sonderprogramm zur Förderung des akademischen Nachwuchses) and from the Department of Internal Medicine (VFWAWF), University Hospital Basel, Basel, Switzerland.

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Accepted for publication June 3, 2005.

carriers than in noncarriers[12]. Moreover, the number of nasal *S. aureus* colony-forming units (CFU) influences the risk of subsequent infection in carriers. White obtained quantitative nasal cultures from patients before surgery and found that the incidence of postoperative *S. aureus* infections rose progressively in patients with progressively larger numbers of *S. aureus* in the nose[13]. Heavy nasal *S. aureus* carriers (> 100,000 CFU per swab) had a significantly higher infection rate compared with noncarriers. On the other hand, the elimination of nasal carriage (decolonization) can decrease the rate of nosocomial *S. aureus* infections among *S. aureus* carriers[14]. However, additional studies are necessary to identify patients who would benefit the most from prophylactic decolonization[14].

In the general population, the nasal *S. aureus* carriage rate is about 30%[9], but it is still unknown why an individual carries *S. aureus*. Three other studies reported the prevalence of *S. aureus* colonization among patients with RA and found a significantly higher *S. aureus* nasal carriage rate (50%–56% vs 28%–33%)[15,16] and oral carriage rate (14%–56% vs 4%–24%)[15,17] among patients with RA than among healthy controls.

Our objectives were to compare the prevalence of nasal and oral *S. aureus* carriage in outpatients with RA with the prevalence in outpatients with other rheumatic diseases (controls), and to investigate predictors of *S. aureus* carriage, in particular the influence of treatment with anti-TNF-α agents.

MATERIALS AND METHODS

Patients. The study population consisted of a volunteer sample of outpatients treated at the outpatient rheumatology clinics of the University Department of Rheumatology, Felix Platter-Spital, Basel, and of the Kantonsspital Aarau, Aarau, Switzerland. Both centers provide primary and tertiary care. Consecutive patients attending clinics were asked to participate. There were no exclusion criteria. All subjects with RA were diagnosed by a rheumatologist and met classification criteria for RA established by the American College of Rheumatology[18]. At least one of 2 rheumatologists (PH and TV) either diagnosed RA or confirmed the diagnosis in all patients. Subjects in the control group were patients treated at or referred to the same 2 rheumatology clinics for any disorder other than RA.

Written informed consent according to the Declaration of Helsinki was obtained from each study participant. The study was approved by the Research Ethics Committee of the Cantons Basel-Stadt and Basel-Land, and by the Ethics Committee of the Kantonsspital Aarau.

Risk factors for S. aureus carriage. All participants were interviewed. Information on medications, medical conditions, and risk factors for *S. aureus* carriage[9,19,20] was collected by a structured questionnaire and verified by chart review. The presence or absence of the following risk factors or postulated risk factors for *S. aureus* was systematically recorded: renal insufficiency requiring dialysis, human immunodeficiency virus (HIV) infection, atopic dermatitis, insulin-dependent diabetes mellitus, intravenous drug abuse, and all factors listed in Tables 1 and 2.

Microbiological studies. Specimens were obtained with a sterile polyester fiber-tipped swab moistened with sterile saline from the anterior nares (5 rotations in each anterior nostril), the posterior wall of the pharynx, and the soft palate. Swabs were taken to the laboratory in a transport tube (Transwab® MW170; Medical Wire & Equipment Co., Corsham, UK) and processed within 24 h. Each swab was placed in a tube with phosphate buffered saline (PBS; at the beginning of the study 4 ml, later 2 ml), sonicated for 1 min (35 kHz), and vortexed for 15 s. The PBS was then serially diluted and surface-plated on Columbia sheep blood agar[19]. After incubation at 35°C for 24 h and at room temperature for a further 24 h, colonies with morphology consistent with *S. aureus* were counted and identified by Gram stain, catalase test, and latex agglutination test for the detection of clumping factor, protein A, and capsular polysaccharides of *S. aureus* (Pastorex® Staph-Plus; Bio-Rad, Marnes-la-Coquette, France). Susceptibility testing for oxacillin was performed with oxacillin screening agar plates (6 mg/l) according to National Committee for Clinical Laboratory Standards guidelines[21].

Statistical analysis. Categorical variables were compared using a 2-sided chi-square test or Fisher's exact test, and continuous variables using the t test. *S. aureus* CFU counts among carriers were logarithmically transformed before analysis with parametric tests. Independent predictors of *S. aureus* carriage were determined by multiple stepwise logistic regression analysis. All variables with p value ≤ 0.10 were entered into the model. Statistical analyses were performed using SPSS (v. 10.1.3; SPSS, Chicago, IL, USA).

RESULTS

Study population. Eighty-one patients with RA and 83 patients without RA (controls) were studied. The demographic characteristics of participants and characteristics that could affect the *S. aureus* carriage rate are presented in Table 1. Among the patients with RA, the mean duration of disease was 12 years (SD 9 yrs). No patient had atopic dermatitis, HIV infection, or renal insufficiency requiring dialysis. No intravenous drug user was included. Two patients had insulin-dependent diabetes mellitus; neither was colonized with *S. aureus*.

S. aureus carriage. The *S. aureus* colonization rate of nose, posterior pharynx, and soft palate was similar in RA patients and in controls (Table 1). Overall, 28/81 (34.6%) RA patients and 27/83 (32.5%) controls were *S. aureus* carriers. *S. aureus* was cultured more frequently from the anterior nares than from the oropharynx. The *S. aureus* carriage rate among RA patients treated with an anti-TNF-α agent plus MTX was 60% (9/15) versus 23.1% (3/13) in RA patients treated with an anti-TNF-α agent only (p = 0.049).

Risk factors for S. aureus carriage. Characteristics associated with *S. aureus* carriage are presented in Table 2. The following variables were included in the logistic regression analysis model: age, allergic rhinitis, psoriasis, and combination treatment with an anti-TNF-α agent plus MTX. In this model, the only independent predictor of *S. aureus* carriage was being treated with an anti-TNF-α agent plus MTX (OR 3.24, 95% CI 1.16–9.05, p = 0.025).

Quantitative S. aureus cultures. The highest counts of *S. aureus* CFU were found in the nose. Carriers with RA had similar *S. aureus* counts as carriers without RA. Treatment with an anti-TNF-α agent or with an anti-TNF-α agent plus MTX did not appear to affect *S. aureus* counts (Figure 1).

Susceptibility to oxacillin. All *S. aureus* isolates were susceptible to oxacillin.

Table 1. Characteristics of patients with RA and controls (patients without RA).

Characteristic	RA (%)	Controls (%)	p
No. of patients	81	83	
S. aureus carriage			
S. aureus carriers (nose and/or pharynx and/or palate)	28 (34.6)	27 (32.5)	0.87
Nasal *S. aureus* carriers	26 (32.1)	21 (25.3)	0.39
Pharyngeal *S. aureus* carriers	4 (5)	11 (13.9)	0.06
S. aureus carriage on palate	4 (5)	7 (8.4)	0.54
Demographic characteristics			
Mean age, yrs (± SD)	58 ± 16	56 ± 17	0.28
Women, n	60 (74.1)	44 (53.0)	0.01
Healthcare workers, n	2 (2.5)	6 (7.2)	0.28
Diseases			
Allergic rhinitis	5 (6.2)	9 (10.8)	0.40
Asthma	3 (3.7)	4 (4.8)	1.0
Eczema	1 (1.2)	4 (4.8)	0.37
Psoriasis	5 (6.2)	11 (13.3)	0.19
History of hepatitis B or C, or liver cirrhosis	2 (2.5)	2 (2.4)	1.0
Hospitalizations			
Hospitalization in year preceding the study	27 (33.3)	24 (28.9)	0.54
Medications			
Antibiotics in 6 mo preceding the study	16 (19.8)	15 (18.1)	0.78
Nasal sprays	4 (4.9)	4 (4.8)	1.0
Estrogens (% of women)	14 (23.3)	13 (29.5)	0.48
Anti-TNF-α agents (infliximab, etanercept, adalimumab)	28 (34.6)	3 (3.6)	< 0.001
MTX, PO, SC, or IM	51 (63.0)	14 (16.9)	< 0.001
Anti-TNF-α agents + MTX, PO, SC, or IM	15 (18.5)	2 (2.4)	0.001
Glucocorticoids	48 (59.3)	12 (14.5)	< 0.001
Gold sodium thiomalate IM, ibandronic acid or pamidronate disodium IV	5 (6.2)	11 (13.3)	0.12

Table 2. Characteristics of *S. aureus* carriers (colonization of nose, pharynx, or palate) and noncarriers.

Characteristic	S. aureus Carriers (%)	Noncarriers (%)	p
No. of patients	55	109	
Mean age, yrs (± SD)	54 ± 15	59 ± 16	0.07
Women	38 (69.1)	66 (60.6)	0.31
Healthcare workers	3 (5.5)	5 (4.6)	1.0
Diseases			
RA	28 (50.9)	53 (48.6)	0.87
Allergic rhinitis	8 (14.5)	6 (5.5)	0.07
Asthma	2 (3.6)	5 (4.6)	1.0
Eczema	1 (1.8)	4 (3.7)	0.67
Psoriasis	9 (16.4)	7 (6.4)	0.05
History of hepatitis B or C, or liver cirrhosis	2 (3.6)	2 (1.8)	0.60
Hospitalizations			
Hospitalization in the year preceding the study	21 (38.2)	30 (27.5)	0.16
Medications			
Antibiotics in the 6 mo preceding the study	11 (20.0)	20 (18.4)	0.79
Nasal sprays	3 (5.5)	5 (4.6)	1.0
Estrogens (% of women)	9 (23.4)	18 (27.3)	0.69
Infliximab	8 (14.5)	7 (6.4)	0.15
Etanercept	6 (10.9)	8 (7.3)	0.56
Adalimumab	0	2 (1.8)	0.55
Anti-TNF-α agents (infliximab, etanercept, or adalimumab)	14 (25.5)	17 (15.6)	0.14
MTX, PO	7 (12.7)	14 (12.8)	1.0
MTX, SC or IM	19 (34.5)	25 (22.9)	0.14
MTX, PO, SC, or IM	26 (47.3)	39 (35.8)	0.18
Anti-TNF-α agents + MTX, PO, SC, or IM	10 (18.2)	7 (6.4)	0.03
Glucocorticoids	20 (36.4)	40 (36.7)	1.0
Gold sodium thiomalate IM, Ibandronic acid or pamidronate disodium IV	5 (9.1)	11 (10.1)	0.83

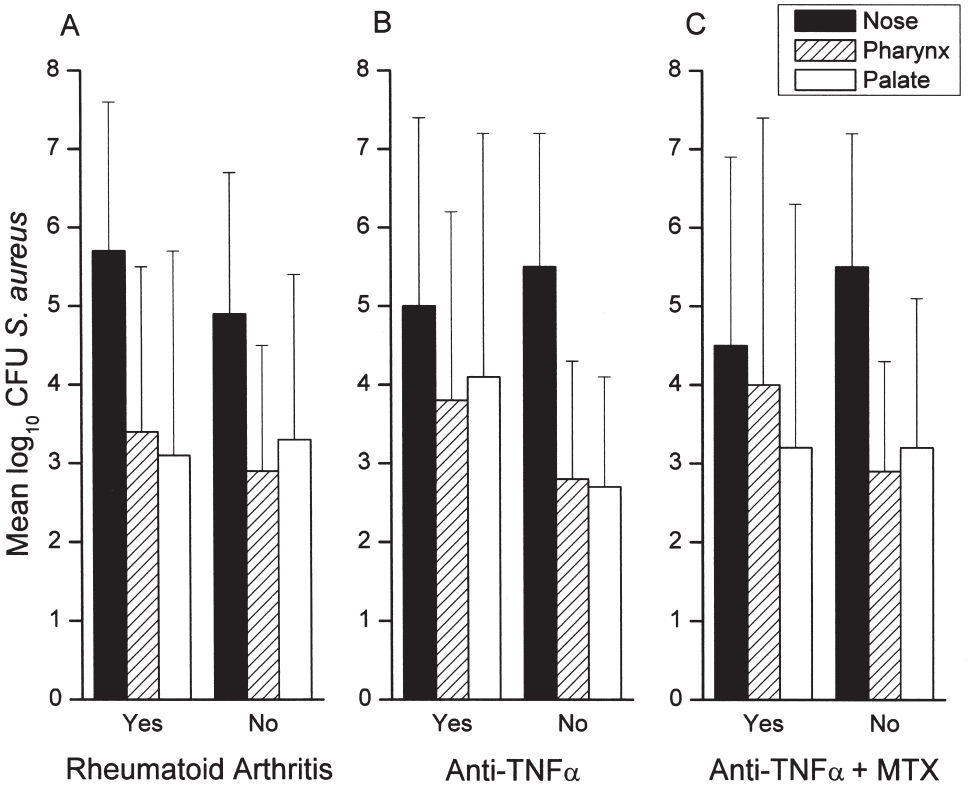

Figure 1. Results of quantitative cultures. Mean $\log_{10}$ ± SD of CFU of *S. aureus* in the nose and posterior pharynx and on the soft palate in *S. aureus* carriers with or without rheumatoid arthritis (A); in *S. aureus* carriers with or without anti-TNF-α therapy (B); and in *S. aureus* carriers with or without therapy with an anti-TNF-α agent and methotrexate (C).

DISCUSSION

The *S. aureus* colonization rate among patients with RA (34.6%) was similar to the colonization rate in patients without RA (32.5%), and also to the mean carriage rate of 37.2% calculated by Kluytmans, *et al* for the general population from 18 published studies involving 13,873 individuals[9]. This indicates that RA does not increase the risk for *S. aureus* colonization. The only independent predictor of *S. aureus* carriage was being treated with an anti-TNF-α agent plus methotrexate.

Three other studies have reported *S. aureus* carriage rates among RA patients. In the study by Jacobson, *et al*[17] cultures were obtained from the posterior wall of the pharynx, saliva, tongue, and gingival crevices. Patients with RA had a significantly higher prevalence of oral *S. aureus* than controls (14% vs 4%). Of 16 RA patients with *S. aureus* identified in at least one of the oral sites, 13 (81%) had *S. aureus* cultured from their posterior pharynx, suggesting that the posterior oropharynx may be the source of oral *S. aureus*, and that colonization of the mucosal surfaces proceeds from the nares (the main reservoir of *S. aureus*) into the oropharynx, and from there to the oral cavity. Jackson, *et al*[15] found that a significantly higher proportion of RA patients were nasally (56%) or orally (56%) colonized with *S. aureus* in comparison to healthy adults (28% and 24%, respectively). Finally, Tabarya and Hoffman[16] found a *S. aureus* nasal carriage rate of 50% among RA patients and 33% among healthy controls.

The increased *S. aureus* carriage rate among RA patients reported in these 3 studies contrasts with our findings. However, important differences in RA patients and/or control subjects included in these studies may explain the different results. In particular, Jacobson, *et al*[17] included only RA patients with longterm (> 6 months) corticosteroid therapy, and Jackson, *et al*[15] only patients "receiving treatment for RA" (treatment was not reported). Moreover, all 3 studies compared RA patients with healthy controls and did not consider other well known risk factors for *S. aureus* carriage[9,19,20] that may have affected colonization rates significantly, such as previous hospitalization, or the presence of psoriasis or allergic rhinitis. Further, quantitative cultures were not performed.

The main limitation of our study is the relatively small number of patients included. In addition, RA patients treated at outpatient rheumatology clinics may be not representative of all patients with RA.

We found that in colonized patients *S. aureus* was cultured more frequently from the nose than from the orophar-

ynx. These findings are in agreement with a recent study reporting a nasal colonization rate of 25.6% among RA patients[8], and with many studies showing that the anterior nares are the ecological niches of *S. aureus* and the most consistent area from which this organism can be isolated[9].

In our study, the only independent predictor of *S. aureus* carriage was being treated with an anti-TNF-α agent plus MTX, suggesting that this combination therapy may predispose to *S. aureus* carriage and therefore increase the risk of *S. aureus* infections. The reasons for this association are unclear. One may speculate that the combined effects of an anti-TNF-α agent and MTX[22] on cytokine production may influence the adhesion of *S. aureus* to nasal epithelial cells and mucosae. On the other hand, the combination therapy consisting of an anti-TNF-α agent plus MTX may have been used in more severe cases of RA. These patients may have particular characteristics, for example, of nasal epithelial cells or of nasal mucin, that are not present in other RA patients and which may favor adhesion of *S. aureus*.

Quantitative cultures in our study showed higher *S. aureus* counts in the nose than in the oropharynx, confirming the predilection of *S. aureus* for the anterior nares. However, the variability of *S. aureus* counts was high, and larger studies are necessary to conclusively address the factors influencing *S. aureus* counts in carriers.

All *S. aureus* isolates in this study were susceptible to oxacillin. This is not surprising, considering the relatively low prevalence of methicillin-resistant *S. aureus* in northwestern Switzerland[23], even among risk groups such as intravenous drug users[20].

The carriage rate of *S. aureus* among patients with RA was not higher than among controls with other rheumatic diseases. However, patients treated with an anti-TNF-α agent plus methotrexate had high colonization rates of *S. aureus* and might have a higher risk of *S. aureus* infections.

ACKNOWLEDGMENT

We thank Margot von Dechend, MD, Department of Rheumatology, Kantonsspital Aarau, for help in the recruitment of patients.

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