

INVESTIGATIVE REPORT

Methicillin-resistant *Staphylococcus aureus* Colonization in Inflammatory versus Non-inflammatory Skin Diseases: Who Should be Screened?

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The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) was prospectively investigated in a dermatology outpatient setting. Swabs were taken from anterior nares, perineum and lesional skin in 229 patients with erosive inflammatory skin diseases ($n=88$), venous leg ulcers ($n=58$) or basal cell carcinoma ($n=83$) and processed by standard methods. The isolated MRSA strains were characterized by pulsed-field gel electrophoresis after digestion with the restriction enzyme *Sma*I. MRSA carriage was detected in 10/88 patients with inflammatory skin diseases, 5/58 with venous leg ulcers and 0/83 with basal cell carcinoma. Most of the MRSA isolates could be identified as either the Rhine-Hessen epidemic strain or local epidemic strains. None of the isolated strains was resistant to vancomycin, gentamicin or mupirocin. MRSA is uncommon in outpatients in our dermatology clinic; however, the presence of chronic ulcers and erosions was significantly associated with MRSA positivity. Therefore, patients with chronic ulcers and erosions should be screened for MRSA colonization to implement infection control measures. **Key words:** venous leg ulcers; inflammatory skin diseases; basal cell carcinoma.

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Staphylococcus aureus is the most important staphylococcal pathogen in bacterial infections of the skin (1). In addition, *S. aureus* and its products (e.g. superantigens) play an important role in inflammatory skin diseases like atopic eczema and psoriasis via immunological pathways (2). A variety of antibiotics is used both systemically (3) and topically (fusidic acid, tetracyclines, gentamicin and mupirocin – the latter for the nares). As a consequence, antibiotic resistance is increasing in dermatology practice (4). More than 90% of *S. aureus* strains are resistant to beta-lactam antibiotics (5), and there are strains that are also resistant to erythromycin, gentamicin, ciprofloxacin and tetracyclines (6). In particular, methicillin-resistant

S. aureus (MRSA) is detected in various dermatological conditions in inpatients and with increasing frequency in outpatients. The proportion of MRSA strains among all cutaneous *S. aureus* isolates from both inpatients and outpatients with a variety of skin infections has been reported to be as high as 41.5% in Japanese patients (7). Moreover, new clonal groups of toxin-producing MRSA have emerged (8). Ewing and co-workers found MRSA in 4.4% of all *S. aureus* strains isolated during surveillance sampling of children treated with flucloxacillin for non-infected atopic eczema (9). The prevalence of fusidic acid- and methicillin-resistant *S. aureus* in children with infected atopic eczema tripled from infancy to school age (10).

During the past 12 years the prevalence of MRSA has increased in German hospitals. Up to 20.7% of all *S. aureus* isolates were resistant to methicillin (11–13). In the early 1990s, the prevalence of MRSA was about 3% in dermatological and in general medical patients in Germany (14, 15). Despite the worldwide increase in MRSA prevalence, only two studies have been published on the surveillance of MRSA in dermatology outpatient clinics so far. Whereas in the year 1986–1987 no MRSA was isolated in a dermatology outpatient clinic (16), Price et al. (17) documented a gradual increase in infections with MRSA from 1.5% of all *S. aureus* in 1988 to 11.9% in 1996 in the same dermatology outpatient facilities.

In the dermatology outpatient clinic of Heidelberg, Germany, 500–1500 specimens per year are taken from patients with visible signs of infection or with a high risk of infection and are routinely screened for potential pathogens. All *S. aureus* isolates are tested for methicillin resistance. Because of an increase in the MRSA isolation rate from 1996 (0.8/100 patients) to 1999 (1.8/100 patients) a prospective study was performed to compare different dermatology outpatient populations concerning the distribution of MRSA carriage and to detect possible risk factors of colonization.

MATERIALS AND METHODS

Population study and sampling

The study was performed in the dermatology outpatient clinic of the Department of Dermatology and Venereology,

University of Heidelberg, Germany, where 100–140 patients are seen each day. Because of a relatively high rate of MRSA detection in 1999 three groups of dermatology outpatients were tested prospectively from 2000 to 2002. From 2000 onwards more sensitive detection methods were applied, which included an enrichment step.

Three groups of outpatients participated in the study: 88 patients with erosive lesions of inflammatory skin diseases (48 female, 40 male, age range 6 months to 84 years), 58 individuals with venous leg ulcers (33 women, 25 men, 22–87 years) and 83 patients suffering from basal cell carcinoma (42 women and 41 men, 27–92 years). Inflammatory diseases included atopic eczema, psoriasis, vasculitis, nummular dermatitis, foot sores, bullous autoimmune diseases, Mb. Hailey-Hailey, irritant and allergic contact dermatitis, acne inversa, folliculitis decalvans and prurigo. Use of topical or systemic antibiotics during the 4 weeks before the clinical visit was an exclusion criterion. Swabs were taken from the anterior nares, perineum and lesional skin by trained nurses or physicians using a commercially available transport medium (Trans-swab, Mast, Rheimfeld, Germany). Anterior nares are known to be a natural reservoir for *S. aureus* and the origin for spread over the entire body, therefore, swabs were taken from the nares first (18). As the detection rate for MRSA is increased up to 93.4% by sampling nose and perineum, we decided to sample these two sites (19), provided that the patient consented. If patients had erosions or ulcers, these were also sampled. Each patient was counted only once, if sequential samples were obtained. Isolates were identified as MRSA or methicillin-susceptible (MSSA) *S. aureus* according to the criteria of the National Committee for Clinical Laboratory Standards (NCCLS). Criteria for infections were as defined by Centers for Disease Control (CDC) guidelines (20). Isolates not associated with infections were classified as colonizing.

Microbiology

All swabs were cultured on Columbia agar (Becton Dickinson, Heidelberg, Germany) and Mannitol salt agar (Becton Dickinson) using standard microbiological procedures. In addition, an enrichment step was performed in thioglycolate broth. *S. aureus* was identified on the basis of colony morphology and a positive slide coagulation test (Staphaurex, bioMérieux, Nürtingen, Germany). If the coagulation test was ambiguous, identification was performed using plasma coagulation to identify free coagulase, decapsulation to identify hyaluronidase and a commercially available micro-identification system (API 32 Staph, bioMérieux). All *S. aureus* isolates were routinely tested for oxacillin resistance by the agar dilution method. This was determined using a Mueller Hinton agar supplemented with 4% (w/v) sodium chloride containing 6 µg/ml oxacillin as recommended by NCCLS (21). Control strains comprised one MRSA (NCTC 10442) and one MSSA (ATCC 25923). Isolates were defined as MRSA by resistance to oxacillin.

Antimicrobial susceptibility testing

Additionally, all available isolates were tested with a different method for susceptibility to the following antibiotics: erythromycin, doxycycline, gentamicin, sulfamethoxazole/trimethoprim, levofloxacin, vancomycin and mupirocin. Mupirocin was included because it is widely used for MRSA eradication in the nares. This was to provide a continuous surveillance concerning the development of mupirocin resistance. Susceptibility testing

was performed by the disc diffusion method according to the NCCLS guidelines (21).

Molecular typing

All available MRSA strains were characterized by pulsed-field gel electrophoresis (PFGE) after digestion with the restriction enzyme *SmaI* as described elsewhere (22). Analysis of *SmaI* macro-restriction profiles was done by visual inspection of the patterns using currently accepted criteria. The isolates were labelled alphabetically from A to F.

Statistics

The following risk factors were abstracted from the medical history and included in the statistical analysis: age, previous antibiotic treatment, number of previous hospitalizations, surgery with general anaesthesia, diabetes mellitus, haemodialysis, pressure sores, intravenous infusion and physiotherapy. A univariate comparison of data was performed using for categorical data the χ^2 or Fisher's exact test as appropriate and for continuous data the Student's t-test (SPSS for Windows, SPSS Inc., Chicago, IL, USA). All tests were two-tailed, and *p* values of <0.05 were considered significant. Multivariate analysis was performed by logistic regression using a conditional forward stepwise method to include variables in the model (SPSS for Windows).

RESULTS

Total *S. aureus* carriage rate

The rate of *S. aureus* carriage (MSSA plus MRSA) in all investigated patients was 74.7% for inflammatory dermatoses, 73.2% for venous leg ulcers and 23.5% for basal cell carcinoma. In 15.4% of *S. aureus*-positive patients with inflammatory dermatoses and 12.2% of patients with venous leg ulcers the strain proved to be MRSA.

In total, 15 of 229 patients were MRSA-positive. This reflected colonization, as none of the patients suffered from an apparent MRSA infection. The proportion of patients with MRSA colonization in outpatients with different skin diseases is summarized in Table I. Patients with inflammatory skin diseases had the highest MRSA carriage rate (10/88). This included only one patient out of 32 with atopic eczema. The MRSA-colonized body sites were anterior nares (10/15), lesional skin (erosion/ulcer) (11/15), throat (2/15), groin (2/15), perineum (2/15) and vagina (1/15).

Risk factors for MRSA carriage in dermatology outpatients

Univariate analysis of risk factors for MRSA carriage among dermatology outpatients revealed two factors that were significantly associated with colonization status: previous history of decubital ulcers as well as the type of skin disease (inflammatory skin diseases with erosive lesions and venous leg ulcers) (Table II). Patients who were diagnosed with basal cell carcinoma

Table I. Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization of dermatology outpatients

Diagnosis	Number of patients	MRSA positivity
Atopic eczema with erosive lesions	32	1 (3.1%)
Other inflammatory skin diseases with erosive lesions	56	9 (16.1%)
Venous leg ulcers	58	5 (8.6%)
Basal cell carcinoma	83	0

had a lower incidence of MRSA carriage than patients with skin lesions due to either inflammatory diseases or venous leg ulcers. In addition patients who had a previous history of pressure sores had an odds ratio of 10.35 to be colonized with MRSA compared with patients without pressure sores. Other risk factors like age, gender, underlying diseases (i.e. diabetes mellitus or dialysis-dependent renal failure), previous antibiotic therapy, previous hospitalization, previous therapy by infusion, previous surgery or physiotherapy were not significantly associated with MRSA carriage. However,

it was interesting to note that nearly 93% of MRSA carriers had been previously hospitalized and 64% had been hospitalized more than three times. A logistic regression model revealed that the type of underlying skin disease and the presence of pressure sores in the past were independently associated with MRSA carriage.

Antibiotic susceptibility profiles

Only 14 of the 15 MRSA isolates were available for further characterization. None of the MRSA strains were resistant to vancomycin, gentamicin or mupirocin. Resistance to sulfamethoxazole/trimethoprim and doxycycline was rare, whereas resistance to levofloxacin and erythromycin was common (Table III). One strain was only resistant to beta-lactam antibiotics and one other was only sensitive to aminoglycosides and glycopeptides. Four patients (3, 4, 7 and 14) had a history of MRSA colonization prior to inclusion in our study, with the first MRSA-positive sample taken while they were hospitalized (Table III). Patients 3, 4 and 14 were

Table II. Statistical evaluation of potential risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) carriage in dermatology outpatients. Significant differences are underlined

	MRSA carriers (n=15)	Non-carriers (n=214)	p value
Age (mean)	56.4	55.0	0.806 (t-test)
Gender (% male)	40.0%	45.8%	0.66 (Pearson's χ^2) OR 1.27 CI ₉₅ 0.43–3.68
Skin disease			<u>0.008 (Pearson's χ^2)</u>
Basal cell carcinoma	0	38.4%	
Inflammatory skin disease	66.7%	36.4%	
Venous leg ulcer	33.3%	24.8%	
Pressure sore	20.0%	2.4%	<u>0.01 (Fisher's exact)</u> OR 10.35 CI ₉₅ 2.21–48.53
Diabetes mellitus	6.7%	11.3%	1.00 (Fisher's exact) OR 0.56 CI ₉₅ 0.07–4.45
Dialysis	0	2.4	1.00 (Fisher's exact)
Previous antibiotic therapy			0.22 (Pearson's χ^2)
None	0	10.3%	
One antibiotic	16.7%	30.4%	
Two or more antibiotics	83.3%	59.3%	
Previous hospitalizations			0.35 (Pearson's χ^2)
None	7.1%	15.4%	
1–3	28.6%	39.9%	
>3	64.3%	44.7%	
Previous infusions			0.35 (Pearson's χ^2)
None	46.7%	49.0%	
One	6.7%	18.9%	
Two or more	46.7%	32.0%	
Previous surgery			0.93 (Pearson's χ^2)
None	40.0%	35.4%	
1–2	33.3%	34.9%	
>2	26.7%	29.7%	
Physiotherapy	46.7%	40.1%	0.40 (Fisher's exact) OR 1.31 CI ₉₅ 0.46–3.74

Table III. Synopsis of antibiotic resistance patterns and molecular typing of methicillin-resistant *Staphylococcus aureus* (MRSA) strains in dermatologic outpatient with or without previous hospitalization

Pat. no.	Hospitalization	History MRSA carriage	Resistant to	PFGE type*
1	Yes	–	O, SMX, LE, E	A
2	Yes	–	O, LE	B
3	Yes	+	O, E	A
4	Yes	+	O, LE, E	C
5	Yes	–	O, LE, E	C
6	Yes	–	O, LE, E	D
7	Yes	+	O, LE, E	A
8	Yes	–	O, LE, E	A
9	No	–	O, E	D
10	Yes	–	O, LE, E	A
11	Yes	–	NA	NA
12	Yes	–	O	E
13	Yes	–	O, LE, D	A
14	Yes	+	O, LE, E	A
15	yes	–	O, SMX, LE, E, D	F

O, oxacillin; SMX, sulfamethoxazole/trimethoprim; LE, levofloxacin; E, erythromycin; D, doxycycline; NA: not available.

*Pulsed-field gel electrophoresis (PFGE) profiles are labelled alphabetically (A–F): A and C represent regional epidemic strains; B, E and F are sporadic strains with unique PFGE profiles.

first shown to be MRSA carriers 11, 3 and 2 weeks, respectively, before enrolment in the study. Patient 7 was shown to be MRSA-positive when hospitalized 2 years before inclusion in our study. All these four patients had been previously hospitalized in the University Hospital of Heidelberg, and three of them (4, 7 and 14) had been on the dermatology ward. The antibiotic resistance profile was identical in isolates from patients 4, 7 and 14.

Characterization of MRSA strains

Molecular typing of the 14 available MRSA isolates revealed six different PFGE profiles (A–F) (Table III). Half of the characterized isolates were identified as the Rhine-Hessen epidemic strain (A), that had previously been characterized by the Robert-Koch-Institute, National Staphylococcal Reference Centre, Germany (23) and which is observed in 50% of MRSA isolates from this region. The strain with PFGE profile D was identified as the northern German epidemic strain. The remaining isolates (B, E and F) were sporadic MRSA strains with unique PFGE profiles, F representing the only strain that was resistant to five different groups of antibiotics (24).

DISCUSSION

In our prospective study of non-hospitalized patients we detected MRSA carriage in 8.6% with venous leg ulcers, 11.4% with inflammatory skin diseases and none

of 83 with basal cell carcinoma. The total *S. aureus* carriage rate (MSSA plus MRSA) detected in the three groups was in agreement with the literature. The carriage rate for basal cell carcinoma patients is relatively low when compared with previous studies on a normal population. However, this rate is within the normal range of nasal carriage rates (19.0–55.1%) reported by Kluytmans et al. (18). Four of fifteen MRSA carriers had a history of MRSA colonization from a previous hospitalization. These four patients most likely had a hospital-acquired MRSA. The other patients (11/15) detected in the course of this study were considered to be colonized with community-acquired MRSA, i.e. present at hospital admission (25). MRSA is predominantly hospital-acquired (26–29), but with increasing outpatient surgery and shorter hospital stays it is increasingly diagnosed in the community (30–36). Most of the strains in our study were identified as either the Rhine-Hessen epidemic strain or local epidemic strains. These results reflect the general epidemiological situation in this region. Nearly all MRSA carriers in our study had been hospitalized, suggesting that most patients had acquired MRSA in hospitals. This is supported by our finding that the outpatient strains were identical with the hospital strains. The prevalence of hospital clones in the community is in concordance with the observations of the National Staphylococcal Reference Centre, which reported the distribution of epidemic MRSA strains (37, 38). According to Friedman and co-workers a differentiation between community-acquired and 'health-care-associated' MRSA would be more accurate when describing MRSA detection in outpatient settings and should be considered in future (39).

In their investigation on a dermatology outpatient population, Price et al. (17) have shown a change in the antibiotic resistance pattern of isolates from 1987 to 1996. Our study revealed that resistance to levofloxacin and erythromycin was common, and resistance to sulfamethoxazole/trimethoprim and doxycycline was rare. None of the MRSA strains was resistant to vancomycin, gentamicin or mupirocin, antibiotics of choice for the treatment of MRSA colonization/infection. The fact that no mupirocin resistance was found is in contrast to an investigation on dermatology inpatients (40). However, those patients suffered from MRSA infection, whereas in our study only MRSA colonization was detected. Mupirocin is not prescribed for the treatment of skin lesions so far but only for eradication of MRSA in the nares. MRSA is defined as non-multi-resistant if resistant to two or fewer classes of antibiotics (41). Accordingly, 10/14 MRSA isolates in our study were multi-resistant. One strain (no. 15) was resistant to more than four different antibiotics. Non-multi-resistant MRSA strains exist and can be mostly isolated from patients with community-acquired

infections (42). The following risk factors favour MRSA colonization: multi-morbidity, intensive care treatment, frequent use of antibiotics, catheters, haemodialysis, hospitalization, multiple antibiotic drug treatment, number of invasive treatments, mechanical ventilation, parenteral alimentation, tracheostoma, decubital ulcers, chiropractice (summarized in ref. 43). Trividic et al. (44) investigated hospitalized dermatology patients and found age, previous hospitalization and chronic wounds (ulcer, foot sores) to be risk factors. In a recent study, the predominant sources of the community acquired MRSA isolates proved to be skin: wounds or abscesses, impetigo and cellulitis. These infections mostly occurred in outpatient settings (45). Over 70% of nursing home residents are hospitalized each year, where they may be exposed to MRSA (46). Our results show that only a previous history of decubital ulcers and the type of skin disease (inflammatory skin diseases with erosive lesions and venous leg ulcers) are significantly associated with MRSA carriage. However, the low number of MRSA carriers in our patient population may have reduced the statistical power to detect other risk factors. On the other hand, increasing numbers of MRSA carriers with no known predisposing risk factors for carriage have been identified (30, 33, 34). The only condition that might specifically predispose to staphylococcal infection or colonization was atopic eczema. However, our study revealed a low rate of MRSA carriage in patients with atopic eczema compared to other reports where an increase in MRSA colonization of non-infected atopic eczema has been observed (9, 10, 47). In contrast to these reports we only included patients with erosive lesions in our study and may, therefore, have missed nasal MRSA colonization. It is also possible that *S. aureus* colonization rates have decreased due to improved treatment of the underlying disease with new immunomodulating drugs and not due to the reduction of bacterial colonization per se (48). MRSA carriage implies consequences for the management of patients in an outpatient clinic. According to the literature, screening should include patients with a positive MRSA history and those who are transferred from departments with definite or probable MRSA occurrence, e.g. burn units, nursing homes or haemodialysis centres. It is important to investigate the antibiotic resistance pattern of each MRSA isolate, as not every MRSA strain is multi-resistant. Unless the data on antimicrobial susceptibility are analysed on a regular basis the tendency towards increased antimicrobial resistance in strains of bacteria frequently found on human skin, as well as a change in the pattern of resistance, might go unnoticed. In addition to clinical and epidemiological considerations, economic aspects have to be taken into account. Increased diagnostic expenses may be compensated by more effective therapy (49). In MRSA

colonization strict disinfection/isolation policies must be followed and the underlying skin disease treated with topical antiseptics and adequate disease management. In contrast, in MRSA infection, eradication is necessary in addition to disinfection measures. In case of severe infections with multi-resistant MRSA, there is still the option to combine effective antibiotics according to the resistance pattern.

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