

NASAL CARRIAGE AS A SOURCE OF STAPHYLOCOCCUS AUREUS BACTEREMIA

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ABSTRACT

Background The consequences of infection with *Staphylococcus aureus* can be severe, so strategies for prevention are important. We examined *S. aureus* isolates from blood and from nasal specimens to determine whether the organisms in the bloodstream originated from the patient's own flora.

Methods In a multicenter study, swabs for culture were obtained from the anterior nares of 219 patients with *S. aureus* bacteremia. A total of 723 isolates were collected and genotyped. In a second study, 1640 *S. aureus* isolates from nasal swabs from 1278 patients were collected over a period of five years and then compared with isolates from the blood of patients who subsequently had *S. aureus* bacteremia.

Results In the multicenter study of *S. aureus* bacteremia, the blood isolates were identical to those from the anterior nares in 180 of 219 patients (82.2 percent). In the second study, 14 of 1278 patients who had nasal colonization with *S. aureus* subsequently had *S. aureus* bacteremia. In 12 of these 14 patients (86 percent), the isolates obtained from the nares were clonally identical to the isolates obtained from blood 1 day to 14 months later.

Conclusions A substantial proportion of cases of *S. aureus* bacteremia appear to be of endogenous origin since they originate from colonies in the nasal mucosa. These results provide support for strategies to prevent systemic *S. aureus* infections by eliminating nasal carriage of *S. aureus*. (N Engl J Med 2001; 344:11-6.)

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STAPHYLOCOCCUS AUREUS is one of the most common causes of both endemic and epidemic infections acquired in hospitals, which result in substantial morbidity and mortality. In U.S. hospitals in the National Nosocomial Infections Surveillance system, *S. aureus* accounted for up to 13 percent of isolates recovered from patients with nosocomial infections from 1979 through 1995, and the percentage has increased in recent years.^{1,2} Community-acquired infections with *S. aureus* are also common.^{2,3} Multidrug-resistant strains of staphylococci have been reported with increasing frequency worldwide, including isolates that are resistant to methicillin, lincosamides, macrolides, aminoglycosides, fluoroquinolones, or combinations of these antibiotics.^{3,4} Because glycopeptides are the main drugs with reliable activity against methicillin-resistant strains of *S. aureus*, the emergence of *S. aureus* strains with intermediate resistance to glycopeptides has aroused

concern about the development of strains resistant to all available antibiotics.⁵ The severe consequences of infection with *S. aureus* heighten the importance of prevention. Colonized patients are the chief source of *S. aureus* in hospitals.^{1,6} Approximately 10 to 40 percent of people tested as outpatients or on admission have nasal carriage of *S. aureus*.^{7,8} Colonizing strains may serve as endogenous reservoirs for overt clinical infections or may spread to other patients. Several studies have shown that elimination of carriage in the anterior nares, the principal reservoirs of *S. aureus*, reduces the incidence of *S. aureus* infections.^{6,9-13} However, previous studies did not systematically investigate the link between *S. aureus* isolated from blood and *S. aureus* isolated from nasal specimens, taken before and after bacteremia was detected, with the use of modern molecular methods. Therefore, we undertook this study to assess the correlation between strains colonizing the anterior nares and strains in the blood of patients with *S. aureus* bacteremia.

METHODS**Study Design**

To investigate the correlation between *S. aureus* isolates from the anterior nares and *S. aureus* isolates from blood, two approaches were used. First, in a multicenter study performed from November 1993 to September 1994, which comprised general and intensive care units of 32 university and community hospitals in Germany, swabs were obtained from the anterior nares of patients with *S. aureus* bacteremia and cultured. As defined by the protocol, the nasal cultures were obtained immediately after the isolation of *S. aureus* from the blood. All isolates, including those from foci of infection as judged on clinical grounds, were sent to one center (the University of Münster) for genotyping. In addition, each patient's physician completed a case-record form. The completed forms were sent to the Biometrics Department of SmithKline Beecham, Munich, for statistical analysis. Information collected in the case-record forms included data that identified the patient (initials, date of birth, and patient identification number); location in the hospital (general ward, specialized ward, or intensive care unit); the dates when blood cultures, nasal swabs, and other clinical specimens that showed growth of *S. aureus* were obtained; and the clinically presumed focus of *S. aureus* bacteremia.

Identification of *S. aureus* was based on conventional criteria (including the coagulase tube test and the API Staph system [ATB32 Staph, BioMérieux, Marcy-l'Étoile, France]). In addition, all isolates of uncertain identity were confirmed as *S. aureus* by testing for the *S. aureus*-specific *nuc* gene by the polymerase chain reaction.¹⁴ If nasal colonization with *S. aureus* was detected, all strains, in-

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*Participants in the study group are listed in the Appendix.

cluding those isolated from presumed foci of infection, were collected and characterized by pulsed-field gel electrophoresis.

In a second study, performed from June 1994 to June 1999, *S. aureus*-positive cultures of swabs from the anterior nares were collected prospectively at a single center in Münster, a 1568-bed tertiary-care hospital with five intensive care units, three of which were for surgical patients. The cultured specimens were obtained over a period of five years from patients in general wards as well as from patients in intensive care units during routine surveillance and were then frozen. These *S. aureus* isolates were also compared by pulsed-field gel electrophoresis with *S. aureus* isolates from the blood of patients in whom bacteremia subsequently developed during the same hospital stay or a later one at the University of Münster.

Pulsed-field gel electrophoresis was performed in one center (the University of Münster), as previously described.¹⁵ Strains isolated from an individual patient were randomly placed on the same gel. They were considered clonally identical if no differences in the band pattern were observed.¹⁶

Whether the isolates were resistant to methicillin was determined on Mueller-Hinton agar (Difco, Augsburg, Germany) supplemented with 2 percent sodium chloride (after incubation for 48 hours at 30°C) and was confirmed by testing for the *mecA* gene by the polymerase chain reaction, as previously described.¹⁷ To test for resistance to methicillin, in general, only one isolate from each patient was studied. If one patient had clonally different strains, the other strains were also tested. The multicenter study was approved by the ethics committee of our institution, and oral informed consent was obtained from all participating patients.

Statistical Analysis

Demographic characteristics were compared with the use of Fisher's exact test (two-tailed) and the Wilcoxon two-sample test. Statistical calculation of the 95 percent confidence intervals for binomial proportions was performed with the SAS statistical program (version 6.12, SAS Institute, Cary, N.C.). The confidence interval for the difference between two proportions was calculated according to the methods of Wallenstein.¹⁸ All reported P values are two-sided.

RESULTS

In this study, pulsed-field gel electrophoresis, an established method of molecular typing, was used to compare colonizing *S. aureus* strains isolated from the anterior nares, strains isolated from the blood in patients with *S. aureus* bacteremia, and strains isolated from the clinically presumed focus of infection. A total of 723 *S. aureus* strains, isolated from 219 patients (mean age, 54.7 years), were included in the multicenter study. Samples were obtained from patients in general care units (55 percent), intensive care units (27 percent), oncology or hematology units (7 percent), and other units (11 percent). Patients were most commonly hospitalized in internal-medicine units (59 percent) and surgical units (21 percent). A total of 219 strains were isolated from the blood, 350 from the anterior nares, and 154 from other clinical specimens. These specimens were obtained primarily from skin, mucous membranes, and soft tissue (48 percent); from short-term or long-term catheters (27 percent); and from the respiratory tract (15 percent).

The most common causes of the *S. aureus* bacteremia, as judged on clinical grounds, were catheter-related infections (in 46 percent of patients); osteomyelitis or skin and soft-tissue infections such as cutaneous

abscesses and cutaneous ulcerations (in 27 percent); and infections of the lower respiratory tract (in 11 percent) (Fig. 1).

Twenty of the 219 patients (9.1 percent) harbored methicillin-resistant strains, of nine different genotypes. Twenty-six methicillin-susceptible strains, obtained from three hospitals in which no methicillin-resistant strains were isolated from blood during the study, were compared with one another; these strains were all clonally different.

For most of the strains, the isolates from the blood were identical to those from the anterior nares of the same patients (180 of 219 [82.2 percent; 95 percent confidence interval, 76.4 to 87.1 percent]), as well as to those from areas other than the nares (94.3 percent); identity was determined according to stringent criteria for the evaluation of the band pattern revealed by pulsed-field gel electrophoresis. These results did not vary significantly according to the time between sample collections in cases in which nasal swabs were obtained after the onset of bacteremia (Table 1).

In the second study, conducted at a single institution, 1640 *S. aureus* strains were isolated from nasal swabs from 1278 patients during a five-year period. In 74 of these patients (5.8 percent), methicillin-resistant strains of 34 different genotypes were isolated from the anterior nares. In 14 of the patients who had nasal colonization, including 1 with a methicillin-resistant strain, *S. aureus* bacteremia subsequently developed. These nine female and five male patients (median age, 35 years; range, 4 to 79) had a broad range of diseases and were hospitalized in nine different units, including general care as well as intensive care units specializing in internal medicine, pediatrics, surgery, neurosurgery, and neurology. There were no significant differences between these 14 patients and the other 258 patients in whom *S. aureus* bacteremia developed at the University of Münster during the five-year period with respect to age (median, 53.5 years; range, 1 to 86) or sex (103 female and 155 male patients). With regard to the proportion with methicillin-resistant strains, the rate of resistance was similar in the patients in whom *S. aureus* had previously been isolated from the anterior nares (1 of 14 patients [7 percent]) and in all other patients with *S. aureus* bacteremia (9 of 258 patients [3.5 percent]). The methicillin-resistant strains isolated from blood represented six different genotypes.

In 12 of the 14 patients who had nasal colonization and in whom *S. aureus* bacteremia subsequently developed (85.7 percent), strains isolated from the anterior nares days or months earlier were clonally identical to the strains later isolated from the blood. In these patients, *S. aureus* isolates from nasal swabs that were clonally identical to the isolates from blood were obtained from six patients within 1 week before the onset of bacteremia, from three additional

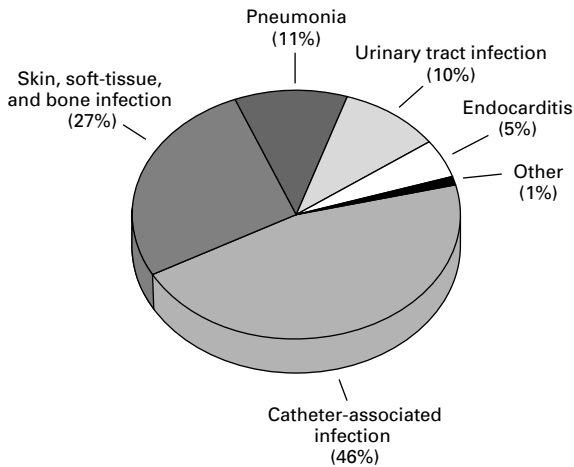


Figure 1. Presumed Causes of the *S. aureus* Bacteremia in 156 Patients, on the Basis of Clinical Evidence.

TABLE 1. DISTRIBUTION OF IDENTICAL AND NONIDENTICAL PAIRS OF *S. AUREUS* ISOLATES STRATIFIED ACCORDING TO THE TIME BETWEEN THE ONSET OF BACTEREMIA AND THE SUBSEQUENT COLLECTION OF NASAL SWABS IN 219 PATIENTS.

TIME BETWEEN BLOOD CULTURE AND NASAL-SWAB CULTURE	NO. OF PATIENTS	CLONAL IDENTITY*
		no. (%)
≤2 Days	99	79 (80)
3–5 Days	98	83 (85)
≥6 Days	22	18 (82)

*These values indicate the numbers of patients with identical strains of *S. aureus* first derived from blood and subsequently derived from the anterior nares, as analyzed by pulsed-field gel electrophoresis. A total of 180 pairs of isolates (82%) were identical.

patients within 1 month before onset, and from three further patients more than 3 months before onset (median time, 6.5 days) (Table 2). Only two patients with *S. aureus* bacteremia had nasal colonization with a clonally different strain of *S. aureus* before the bacteremia developed. Figure 2 shows the results of pulsed-field gel electrophoresis with selected isolates.

The proportion of patients who had nasal colonization by *S. aureus* before clonally identical strains of *S. aureus* were detected in the blood was 85.7 percent (95 percent confidence interval, 57.1 to 98.2 percent). The 95 percent confidence interval for the

TABLE 2. DISTRIBUTION OF IDENTICAL AND NONIDENTICAL PAIRS OF *S. AUREUS* ISOLATES STRATIFIED ACCORDING TO THE TIME BETWEEN THE COLLECTION OF NASAL SWABS AND THE SUBSEQUENT ONSET OF BACTEREMIA IN 14 PATIENTS.

TIME BETWEEN NASAL-SWAB CULTURE AND BLOOD CULTURE	NO. OF PATIENTS	CLONAL IDENTITY*	
		YES	NO
1 Day	4	4	0
2 Days	1	1	0
3 Days	2	1	1
10 Days	1	1	0
2 Weeks	3	2	1
13 Weeks	1	1	0
31 Weeks	1	1	0
60 Weeks	1	1	0

*These values indicate the numbers of patients with identical strains of *S. aureus* first derived from the anterior nares and subsequently derived from blood, as analyzed by pulsed-field gel electrophoresis.

3.5 percentage point difference in this proportion between the two parts of our study (82.2 percent in the first, multicenter study and 85.7 percent in the second, five-year study) was -22.4 to 14.7 percent. Thus, the results of the multicenter study demonstrating that nasal and blood isolates are clonally identical in about 82 percent of patients with *S. aureus* bacteremia were confirmed by the second study, in which about 86 percent of the patients were colonized in the anterior nares by the same clone that was subsequently isolated from the blood. Hence, it can be stated with 95 percent confidence that at least 50 percent of the patients with *S. aureus* bacteremia were first colonized in the anterior nares by an identical strain.

DISCUSSION

The anterior nares are reservoirs for *S. aureus*. Mucin appears to be the critical surface that is colonized in a process involving interactions between staphylococcal protein and mucin carbohydrate.¹⁹ The role of interference by other commensal bacteria, secretory IgA, or specific staphylococcal adhesins is unknown. Three patterns of carriage can be distinguished, although the criteria used to identify these patterns have been inconsistent.^{1,8,20} First, approximately 20 percent of healthy people almost always carry a strain. Second, a large proportion of the population (approximately 60 percent) harbors *S. aureus* intermittently, and the strains change with varying frequency. Third, only a minority of people (approximately 20 percent) almost never carry *S. aureus*.^{1,8,21} Persistent carriage is more common in children than in adults,

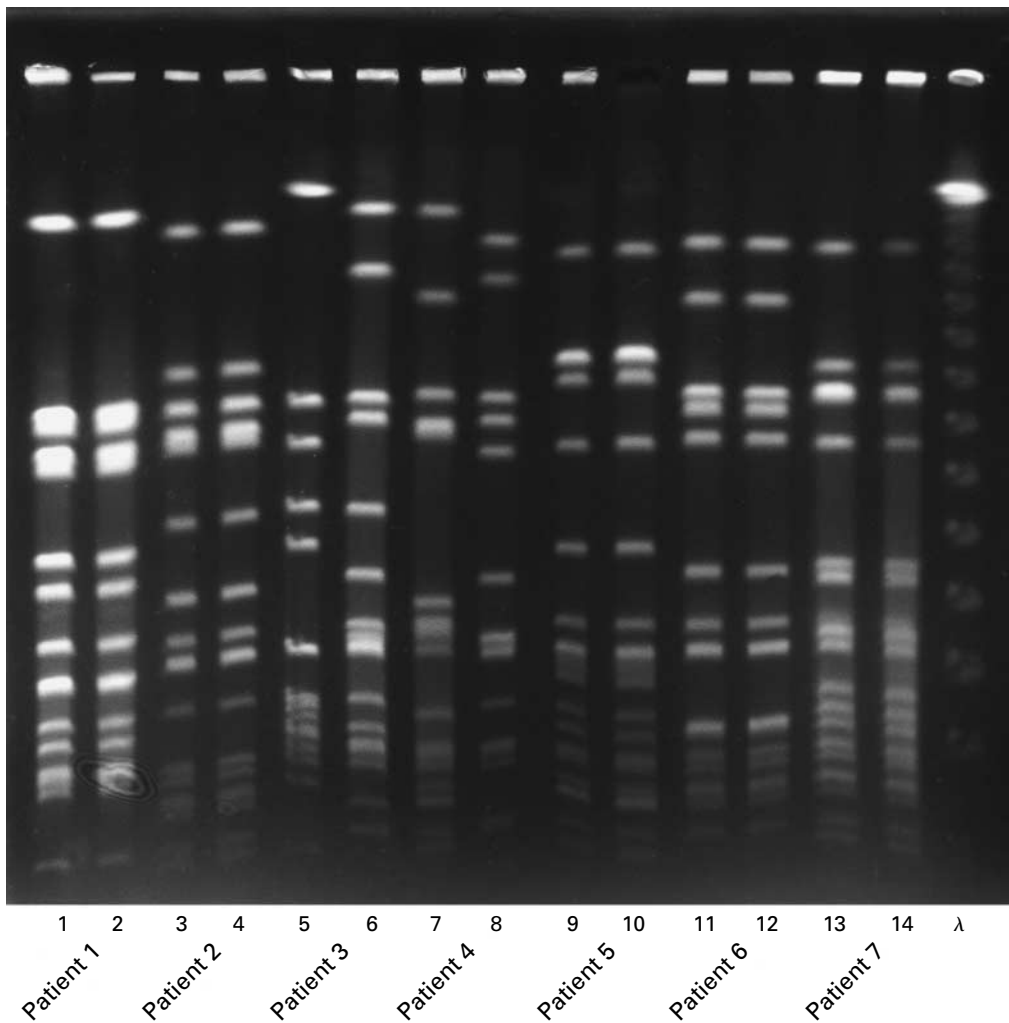


Figure 2. Results of Pulsed-Field Gel Electrophoresis of Selected *S. aureus* Isolates Obtained from Nasal Swabs (Lanes 1, 3, 5, 7, 9, 11, and 13) and Subsequently from the Blood (Lanes 2, 4, 6, 8, 10, 12, and 14) of Seven Patients.

The intervals between sample collections are indicated in parentheses. DNA fragments were separated after digestion with *Sma*I. Lanes 1 and 2 show the results for Patient 1 (1 day); lanes 3 and 4, for Patient 2 (3 days); lanes 5 and 6, for Patient 3 (3 days); lanes 7 and 8, for Patient 4 (2 weeks); lanes 9 and 10, for Patient 5 (2 weeks); lanes 11 and 12, for Patient 6 (31 weeks); and lanes 13 and 14, for Patient 7 (60 weeks). The λ denotes the molecular size marker. In all patients except Patients 3 and 4, nasal and blood isolates were clonally identical.

and the carrier type changes in many people between the ages of 10 and 20 years.²²

Carriage of *S. aureus* in the nose appears to play a key part in the pathogenesis of infection. Nasal carriage has been associated with an increased risk of infection in patients after surgery, in patients receiving continuous ambulatory peritoneal dialysis, and in patients receiving hemodialysis.^{6,7,13,23,24} In a study of the epidemiology of *S. aureus* infections in patients receiving hemodialysis, Ena et al. investigated 12 infections in three patients and reported that 11 of these infections were caused by isolates previously

identified in surveillance studies.²⁵ Luzar reported that 45 percent of the patients she studied were nasal carriers before catheters were inserted. Catheter exit-site infections occurred at a rate of 0.4 episode per patient per year in carriers but less frequently in non-carriers (0.1 episode per patient per year).²⁶ Nasal carriage of *S. aureus* was a risk factor for the development of nosocomial bacteremia during an outbreak of methicillin-resistant *S. aureus* in an intensive care unit, with rates of bacteremia of 38 percent for carriers of methicillin-resistant strains, 9.5 percent for carriers of susceptible strains, and 1.7 percent for noncarriers.²⁷

In several studies, the elimination of nasal carriage reduced the incidence of *S. aureus* infections.^{10,12,13,28} Kluytmans et al. observed a significant reduction in the rate of surgical-wound infection after intervention with mupirocin nasal ointment.⁹ Nasal treatment with mupirocin led to a reduction by a factor of four in the incidence of *S. aureus* bacteremia per patient-year (from 0.097 to 0.024 episode) in carriers receiving hemodialysis.¹¹ When the nares were treated topically to eliminate nasal carriage, *S. aureus* usually disappeared from other areas of the body.²⁹⁻³¹ In patients receiving hemodialysis, 87 percent of those who carried *S. aureus* in their nares and on their hands carried the same strain at both sites.³⁰ Treatment with topical mupirocin, which eliminates nasal carriage, also eliminates hand carriage.²⁹ The proposed mechanism of pathogenesis for a number of endogenous infections is the colonization of the skin from the anterior nares, which causes subsequent infection in patients with areas of impaired skin, such as patients receiving dialysis and patients with intravascular catheters.

Although nasal carriage of *S. aureus* has been suggested as the source of subsequent infections, previous studies were limited to single hospitals^{23-25,27,28,32} or to defined patient groups — such as patients receiving hemodialysis,^{10,12,13,25} patients in intensive care units,^{23,27,32} or patients infected with the human immunodeficiency virus^{24,33} — or they were performed in the setting of an outbreak with methicillin-resistant strains.^{27,32} In addition, in most studies, typing systems of high discriminatory power were not systematically used to show that the strain colonizing the anterior nares was identical to the strain from the focus of infection, the strain from the blood, or both and thus to support the hypothesis that *S. aureus* bacteremia is of endogenous origin.^{7,9-13,24,25,28}

Modern methods of molecular typing, which have high discriminatory power and which differentiate among strains isolated from multiple sources in one patient, are essential to studies of the origin of *S. aureus* bacteremia.^{34,35} We systematically used pulsed-field gel electrophoresis in a large multicenter study to determine whether there was identity between *S. aureus* strains isolated from blood and those isolated from the anterior nares before and after the detection of bacteremia. In the large majority of patients with *S. aureus* bacteremia, the isolate from blood was identical to that from the anterior nares. Strains isolated from blood cultures and from nasal-swab cultures were clonal in 82.2 percent and 85.7 percent of patients, as shown by pulsed-field gel electrophoresis in the two studies. Thus, a substantial proportion of cases of bacteremia may be caused by endogenous strains of *S. aureus*.

In summary, in patients with *S. aureus* bacteremia there is a strong correlation between strains colonizing the anterior nares, strains isolated from foci of infection, and strains isolated from blood, suggest-

ing that *S. aureus* bacteremia may have an endogenous origin. Our results provide evidence that strategies to interrupt transmission of *S. aureus* by the elimination of nasal carriage may prevent systemic *S. aureus* infections.

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APPENDIX

In addition to the authors, the following were participants in the study group: D. Bitter-Suermann, Hannover; W. Ehret, Augsburg; P. Emmerling, Munich; F. Fehrenbach, Berlin; H. Finger, Krefeld; H. Freiesleben, Hamburg; D. Fritsche, Ludwigshafen; H. Hahn, Berlin; J. Heesemann, Munich; U. Hoeffler, Düsseldorf; H.-M. Just, Nuremberg; E. Kühnen, Trier; H. Langmaack, Berlin; R. Laufs, Hamburg; R. Lütticken, Aachen; R. Marre, Ulm; W.A. Müller, Magdeburg; B. Neuhaus, Münster; M. Rölinghoff, Erlangen; G. Ruckdeschel, Munich; J. Sander, Hannover; G. Schroeter, Stuttgart; P. Shah, Frankfurt; W. Sietzen, Hamburg; H.G. Sonntag, Heidelberg; E. Straube, Jena; R. Tauchnitz, Leipzig; U. Ullmann, Kiel; H. Werner, Tübingen; H. Wolf, Regensburg; and P. Wutzler, Erfurt — all in Germany.

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