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Preventing Surgical-Site Infections in Nasal Carriers of *Staphylococcus aureus*

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ABSTRACT

BACKGROUND

Nasal carriers of *Staphylococcus aureus* are at increased risk for health care–associated infections with this organism. Decolonization of nasal and extranasal sites on hospital admission may reduce this risk.

METHODS

In a randomized, double-blind, placebo-controlled, multicenter trial, we assessed whether rapid identification of *S. aureus* nasal carriers by means of a real-time polymerase-chain-reaction (PCR) assay, followed by treatment with mupirocin nasal ointment and chlorhexidine soap, reduces the risk of hospital-associated *S. aureus* infection.

RESULTS

From October 2005 through June 2007, a total of 6771 patients were screened on admission. A total of 1270 nasal swabs from 1251 patients were positive for *S. aureus*. We enrolled 917 of these patients in the intention-to-treat analysis, of whom 808 (88.1%) underwent a surgical procedure. All the *S. aureus* strains identified on PCR assay were susceptible to methicillin and mupirocin. The rate of *S. aureus* infection was 3.4% (17 of 504 patients) in the mupirocin–chlorhexidine group, as compared with 7.7% (32 of 413 patients) in the placebo group (relative risk of infection, 0.42; 95% confidence interval [CI], 0.23 to 0.75). The effect of mupirocin–chlorhexidine treatment was most pronounced for deep surgical-site infections (relative risk, 0.21; 95% CI, 0.07 to 0.62). There was no significant difference in all-cause in-hospital mortality between the two groups. The time to the onset of nosocomial infection was shorter in the placebo group than in the mupirocin–chlorhexidine group (P=0.005).

CONCLUSIONS

The number of surgical-site *S. aureus* infections acquired in the hospital can be reduced by rapid screening and decolonizing of nasal carriers of *S. aureus* on admission. (Current Controlled Trials number, ISRCTN56186788.)

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Nasal carriers of high numbers of *Staphylococcus aureus* organisms have a risk of health care–associated infection with this microorganism that is three to six times the risk among noncarriers and low-level carriers.[1-3] More than 80% of health care–associated *S. aureus* infections are endogenous.[4-6]

Intranasal application of mupirocin has been shown to be effective for the decolonization of this microbe and the prevention of invasive *S. aureus* infections in patients receiving long-term dialysis treatment.[7-10] However, in other nonsurgical patients, mupirocin had no effect on the rate of health care–associated *S. aureus* infections.[11] Mupirocin nasal ointment was reported to be effective in preventing surgical-site infections in surgical patients, but this study used a historical control group.[12] Two randomized, controlled trials failed to show a reduction in rates of surgical-site infection in orthopedic and general-surgery populations, although a subgroup analysis in one of these studies suggested that intranasal mupirocin may be effective in preventing health care–associated *S. aureus* infections in carriers of this organism.[13,14]

Several explanations have been offered for these failures. In some studies, failure of decolonization may have been due to the timing of treatment. If decolonization is started only after the results of screening cultures become available, health care–associated infections may already be incubating and may therefore be difficult to prevent. With the development of rapid screening tests for *S. aureus*, the carrier status can be assessed within hours after admission.[15-17] Another explanation could be that nasal carriers of *S. aureus* are also colonized at extranasal sites.[18] It is unlikely that nasal application of mupirocin will directly affect these sites. However, decolonization of the skin can be achieved by washing with disinfecting soap, such as chlorhexidine gluconate products.[19]

We conducted a randomized, double-blind, placebo-controlled, multicenter clinical trial in which we rapidly identified nasal carriers of *S. aureus* by real-time polymerase-chain-reaction (PCR) assay on admission. In *S. aureus* carriers only, we assessed whether decolonization of the nostrils with mupirocin ointment and of the skin with chlorhexidine gluconate soap could prevent hospital-associated infections with *S. aureus*.

METHODS

STUDY DESIGN

The study was a randomized, double-blind, placebo-controlled clinical trial, conducted at three university hospitals and two general hospitals in the Netherlands. From October 2005 through June 2007, we screened patients who were admitted to the departments of surgery and internal medicine, where the risk for *S. aureus* infection is high. The primary outcome of the trial was the cumulative incidence of hospital-associated *S. aureus* infections. Secondary outcome measures included all-cause in-hospital mortality, duration of hospitalization, and time from admission to the onset of health care–associated *S. aureus* infections. The institutional ethics committee at each center approved the protocol. Oral informed consent was obtained at the time of screening. Once a patient was randomly assigned to decolonization with either mupirocin–chlorhexidine or placebo, written informed consent was obtained. The manufacturers of the products provided the trial medications and placebo at no cost but did not influence the study design, data collection, analysis, writing, or decision to submit the results for publication.

INCLUSION AND EXCLUSION CRITERIA

Patients were screened by trained nursing staff for nasal carriage of *S. aureus* either immediately on admission or during the week before admission, with decolonization therapy begun at the time of admission. The inclusion criterion for screening was the expectation that a patient would remain hospitalized for at least 4 days in one of the participating departments (internal medicine, cardiothoracic surgery, vascular surgery, orthopedics, gastrointestinal surgery, or general surgery). The exclusion criterion for screening was an age of less than 18 years. Inclusion criteria for randomization were nasal carriage of *S. aureus* as determined by real-time PCR and the ability to start the intervention within 24 hours after the patient's admission to a participating ward. The expected duration of hospitalization was estimated again immediately before randomization and had to be at least 4 days. Exclusion criteria for randomization were the presence of active infection with *S. aureus* at the time of randomization, known allergy to mupirocin or chlorhexidine, pregnancy, breast-feeding,

use of mupirocin in the preceding 4 weeks, and the presence of a nasal foreign body.

RANDOMIZATION

Patients were randomly assigned in a 1:1 ratio to either active treatment with mupirocin ointment 2% (Bactroban, GlaxoSmithKline) in combination with chlorhexidine gluconate soap, 40 mg per milliliter (Hibiscrub, Mölnlycke), or placebo ointment in combination with placebo soap. Placebo soap and ointment were identical to the active treatment except for the active ingredients. A single list of random numbers with a permuted-block design was generated by an independent statistician and distributed to all participating centers.

ENROLLMENT AND FOLLOW-UP

Patients were asked to participate by a member of the trial team. Immediately after providing written informed consent, the patient was assigned to either the active treatment or the placebo according to the randomization list, and the first dose of nasal ointment was applied. Nasal ointment was applied twice daily, and the soap was used daily for a total-body wash. The duration of the study treatment was 5 days, irrespective of the timing of any interventions. Patients who were still hospitalized after 3 weeks and those still hospitalized after 6 weeks received a second and third course of the same trial medication, respectively.

The follow-up period for *S. aureus* infection was the first 6 weeks after discharge. We defined the time to infection as the time from randomization to the onset of infection. Data were censored when follow-up for *S. aureus* infection ended or at the time of death. Time periods for the end points of length of hospital stay and mortality were measured from the primary admission until 6 weeks after discharge from the primary admission. If a patient was readmitted to the hospital within 6 weeks after discharge from the primary admission, the number of hospital days during the subsequent admission were included in the calculation of length of stay.

Patients were monitored for hospital-acquired *S. aureus* infection by means of microbiologic cultures. Attending physicians were encouraged to obtain culture samples if infection was suspected. If a culture grew *S. aureus*, the patient's medical record was reviewed to distinguish infection from colonization and to determine whether the infection was health care–associated according to criteria established by the Centers for Disease Control and Prevention.[20] The results of all clinical cultures performed during the follow-up period were also documented. In surgical patients, standard presurgical prophylactic antimicrobial therapy was given according to the local hospital guidelines.

MICROBIOLOGIC RESULTS

To screen patients for *S. aureus* carriage, a dry, sterile rayon swab (Becton Dickinson) was rotated four times in each nostril. The swab was placed in 100 μl of saline and centrifuged. Part of the sample was processed for real-time PCR, and part was inoculated onto a blood agar plate, to allow nasal and infecting strains to be compared in order to determine whether an infection was endogenous or exogenous. Culture results were not used to assess eligibility for randomization. Cultured strains were genotyped by means of pulsed-field gel electrophoresis to compare them on a clonal level, and results were evaluated according to standard criteria.[21] Further details on the microbiologic testing are included in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STATISTICAL ANALYSIS

On the basis of previous studies, the estimated cumulative incidence of health care–associated *S. aureus* infections in carriers of *S. aureus* is 6%. We originally planned to enroll 1800 subjects for randomization to achieve a power of 80% with a two-tailed type I error rate of 0.05 and a reduction of 50% in health care–associated *S. aureus* infections. After 860 patients had been enrolled, a perceived change in the cumulative incidence of serious *S. aureus* infections was reported in one of the participating centers. On request, the institutional ethics committee at each center approved a sequential analysis of the accumulated data set by an independent statistician. Analysis of the data from the first 400 patients showed that the upper boundary was crossed; thus, there was sufficient evidence to conclude that the difference in outcomes between the two study groups was significant. At the time of the sequential analysis, additional patients had already undergone ran-

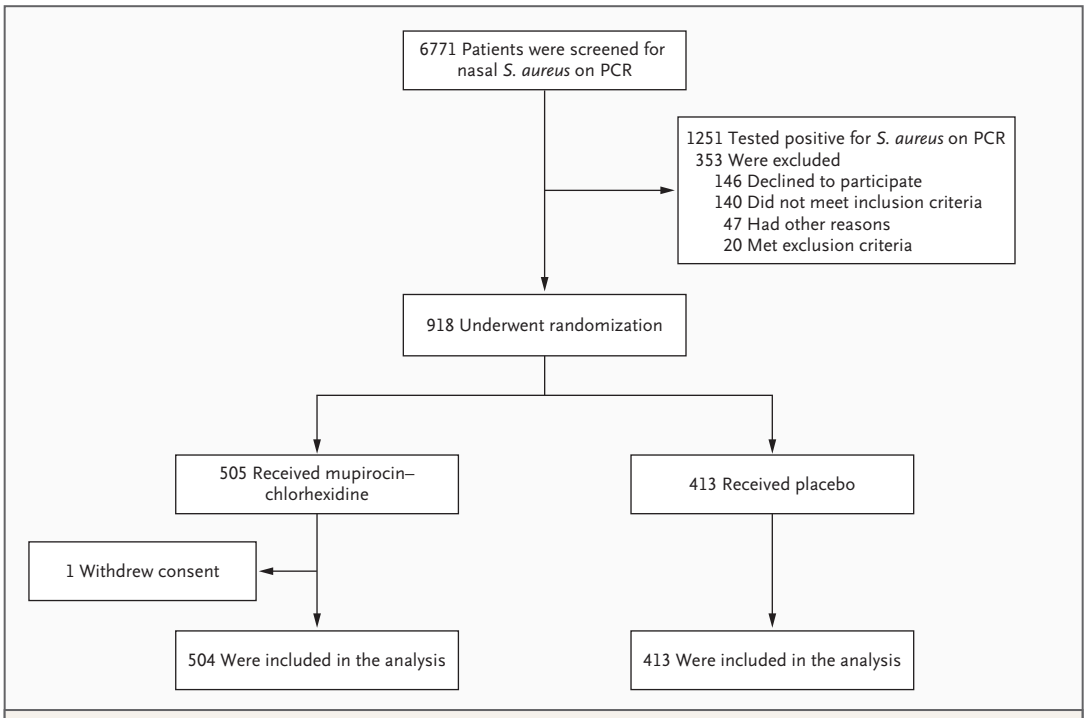

Figure 1. Study Enrollment and Randomization.

Of the 918 patients who underwent randomization, 1 was inadvertently assigned to treatment with mupirocin–chlorhexidine despite a nasal swab that was negative for *Staphylococcus aureus* on polymerase-chain-reaction (PCR) assay.

domization, and the data for these patients were added to the final analysis. The analysis was stratified according to center and was based on the intention-to-treat principle.

RESULTS

STUDY POPULATION

In total, 6771 patients were screened for the presence of *S. aureus* in the nasal passages. Results were positive for *S. aureus* on real-time PCR in 1270 samples (18.8%) obtained from 1251 patients. Of the 918 patients who underwent randomization, 1 withdrew consent and was excluded from the analysis (Fig. 1). Six patients in the mupirocin–chlorhexidine group and 11 patients in the placebo group received a second or third course of treatment. Table 1 shows the baseline characteristics of the patients.

STUDY OUTCOMES

Figure 2 shows the results of the sequential analysis of the cumulative data. The data cross the upper boundary, indicating that there is sufficient evidence that the difference in outcome between the two treatment groups is significant (P=0.008). (A detailed description of this analysis is available in the Supplementary Appendix.)

The cumulative incidence of health care–associated *S. aureus* infection was significantly lower in the mupirocin–chlorhexidine group than in the placebo group (Table 2). Among the 917 patients who underwent randomization, 49 had hospital-acquired *S. aureus* infections: 17 (3.4%) in the mupirocin–chlorhexidine group and 32 (7.7%) in the placebo group (relative risk with mupirocin–chlorhexidine, 0.42; 95% confidence interval [CI], 0.23 to 0.75). In the sequential analysis we corrected for the imbalance between the groups with respect to the proportion of immunocompromised patients, but this did not affect the outcome. The number of patients who would need to be screened and the number of *S. aureus* carriers who would need to be treated to prevent one hospital-acquired *S. aureus* infection were 250 and 23, respectively.

Logistic-regression analysis showed no significant difference in the primary outcome between surgical and nonsurgical patients. The number of nonsurgical patients was small (109 of the 917 patients included in the analysis [11.9%]). Out-

Table 1. Baseline Characteristics of the 917 Study Patients.

Characteristic	Mupirocin–Chlorhexidine (N=504)	Placebo (N=413)	P Value
Mean (±SD) age — yr	61.8±13.9	62.8±13.3	0.25
Male sex — no. (%)	331 (65.7)	251 (60.8)	0.13
Hospital service — no. (%)			
Surgery	441 (87.5)	367 (88.9)	0.53
Internal medicine	63 (12.5)	46 (11.1)	0.53
Admission during month before current admission — no./total no. (%)	86/503 (17.1)	67/411 (16.3)	0.76
McCabe score at admission*			
Median	1	1	
Interquartile range	1–2	1–2	
Underlying disorder — no./total no. (%)			
Diabetes mellitus type 1 or 2	112/503 (22.3)	71/412 (17.2)	0.06
Disorder requiring continuous ambulatory peritoneal dialysis	7/504 (1.4)	4/413 (1.0)	0.57
Renal insufficiency	24/504 (4.8)	23/413 (5.6)	0.57
Immunodeficiency†	19/504 (3.8)	31/413 (7.5)	0.01
Liver-function disorder	25/504 (5.0)	22/413 (5.3)	0.80
Malignant condition	63/504 (12.5)	46/413 (11.2)	0.54
Skin disease	52/501 (10.4)	58/408 (14.2)	0.08
Antibiotic therapy — no./total no. (%)			
At time of admission	17/504 (3.4)	16/413 (3.9)	0.69
During month before admission	41/500 (8.2)	28/408 (6.9)	0.46

* We used the McCabe score, as modified by Doern et al.,[22] to classify the severity of the underlying disease as follows: 1, nonfatal; 2, possibly fatal; 3, ultimately fatal; and 4, rapidly fatal.
† Details concerning the definition of immunodeficiency are available in the Methods section of the Supplementary Appendix.

comes for the surgical and nonsurgical patients are presented separately in Table A in the Supplementary Appendix. Deep surgical-site infections were most frequent (Table 2). Among the surgical patients, this type of infection occurred significantly less frequently in the 441 patients in the mupirocin–chlorhexidine group than in the 367 patients in the placebo group (4 infections [0.9%] vs. 16 [4.4%]; relative risk, 0.21; 95% CI, 0.07 to 0.62).

Of the 49 strains causing infection, 47 were available for molecular typing to determine whether the infection had an endogenous or exogenous source. The results of molecular typing are shown in Table 2.

The time to infection with *S. aureus* was significantly shorter in the placebo group than in the mupirocin–chlorhexidine group (P=0.005 by the log-rank test). Figure 3 shows the cumulative hazard of hospital-acquired *S. aureus* infection in both study groups.

The mean duration of hospitalization was significantly shorter in the mupirocin–chlorhexidine group than in the placebo group (crude estimate, 12.2 vs. 14.0 days; P=0.04). Crude estimates of the median duration of hospitalization were 9 days in the mupirocin–chlorhexidine group and 10 days in the placebo group (P=0.08). All-cause in-hospital mortality did not differ significantly between the groups (2.6% in the mupirocin–chlorhexidine group and 3.1% in the placebo group; relative risk with mupirocin–chlorhexidine, 0.82; 95% CI, 0.37 to 1.78). Of the 13 patients in the mupirocin–chlorhexidine group who died, 1 had a hospital-acquired *S. aureus* infection. Of the 13 patients in the placebo group who died, 3 had a hospital-

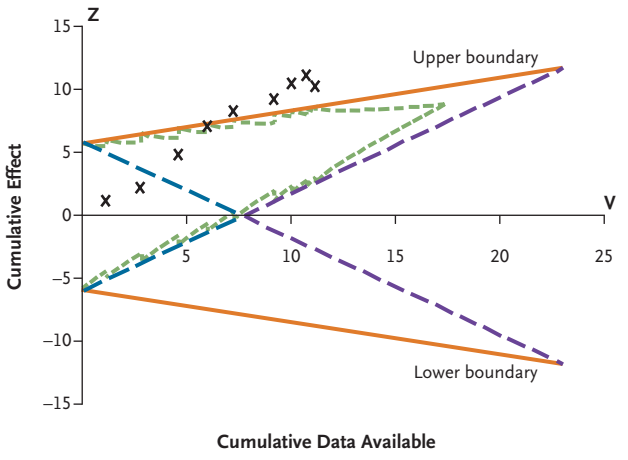

Figure 2. Results of Group Sequential Analysis.

This analysis was conducted as a double-triangular test, in which the horizontal axis (V) represents the cumulative amount of information available and the vertical axis (Z) represents the cumulative effect size. Each point (X) represents a group of 100 patients. Assumptions regarding certain variables determine the boundaries of the test (shown in orange). If the upper boundary is crossed, the intervention can be said to have a beneficial effect; if the lower boundary is crossed, the placebo is more beneficial. If one of the purple dashed lines is crossed, there is no significant difference between the intervention and the placebo. The blue dashed lines are part of the purple boundaries for futility (i.e., equivalence between placebo and intervention); if both blue inner boundaries are crossed, futility would be concluded. The green dashed lines are boundaries that act as a continuity correction. Z represents the difference between the number of infections observed and the number theoretically expected. V represents the variance of Z under the null hypothesis (i.e., no difference between intervention and placebo). In this case, mupirocin–chlorhexidine significantly reduced the cumulative incidence of hospital-acquired *S. aureus* infection (P=0.008).

acquired *S. aureus* infection. These three patients had undergone cardiothoracic surgery, whereas none of the patients in the mupirocin–chlorhexidine group who underwent cardiothoracic surgery died.

MICROBIOLOGIC RESULTS

We screened 6771 swabs obtained from 6496 patients to identify nasal carriers of *S. aureus*. The real-time PCR was positive for 1270 samples (18.8%). In 1143 (90%) of these samples, *S. aureus* was also cultured. All *S. aureus* strains that caused hospital-acquired infections were susceptible to methicillin and mupirocin. The number of cultured microorganisms and the distribution of species other than *S. aureus* did not differ significantly between the mupirocin–chlorhexidine group and the placebo group.

ADVERSE REACTIONS

All reported adverse reactions were due to local irritation of the nose or skin and resolved after the study treatment was discontinued. (Details are available in Table C in the Supplementary Appendix.)

DISCUSSION

This study shows that rapid detection of *S. aureus* nasal carriage followed by immediate decolonization of nasal and extranasal sites with mupirocin nasal ointment and chlorhexidine gluconate soap significantly reduced the risk of hospital-acquired *S. aureus* infections in patients at risk. This intervention also significantly reduced the mean hospital stay by almost 2 days.

In a recent meta-analysis of clinical trials that assessed the effect of nasal mupirocin treatment in surgical patients who were *S. aureus* carriers, the eradication of *S. aureus* reduced the rate of hospital-associated infection with this pathogen by an estimated 45%, but the authors concluded that final proof would be needed from a prospective, randomized clinical trial.[23] A pooled analysis of eight studies showed that intranasal mupirocin application was associated with a significant reduction in the infection rate.[24] The results of our trial provide solid evidence of the preventive effect of *S. aureus* decolonization and a good estimate of the size of this effect: the risk of hospital-associated *S. aureus* infections was reduced by nearly 60%.

Our study differs from previous prospective, randomized trials in several respects. First, nasal carriage of *S. aureus* was detected rapidly by means of real-time PCR at the time of hospital admission. We believe that the rapidity of this assay contributed significantly to the outcome, since it allows targeted decolonization treatment to be initiated within 24 hours of admission — that is, before patients have been exposed to risk factors for health care–associated *S. aureus* infections. A second important factor in reducing risk was the decontamination of both the nasal passages and the skin. It is well known that nasal carriers are likely to have extranasal sites that are contaminated with the same strain and that carriers are at increased risk for endogenous *S. aureus* infections.[18,25,26] We suggest that the use of chlorhexidine for simultaneous elimination of *S. aureus* from extranasal sites is needed to achieve the level

of prophylaxis observed in this trial. Although this additional precaution might not lead to complete eradication of the organism, bacterial loads would probably be sufficiently reduced to prevent infection.[27] Third, in our study, treatment was continued for 5 days even when surgery was performed during the course of treatment. Also, these treatments were repeated 3 and 6 weeks after admission for patients who were still in the hospital.

A modification in the study design was necessary because of a perceived change in the overall cumulative incidence of *S. aureus* infections. Since an independent statistician designed and analyzed the data with no foreknowledge, the switch to a sequential design probably did not influence the outcomes of the study.

No significant difference in the cumulative incidence of hospital-associated *S. aureus* infections was found between surgical and nonsurgical patients. However, the reduction in these infections that was achieved with this intervention was most evident among the surgical patients (see Table A in the Supplementary Appendix). For such patients, screening and decolonization of carriers provide a clear benefit. Since the proportion of nonsurgical patients in this trial was only 11.9%, and the cumulative incidence of *S. aureus* infections was only 2.2% in the nonsurgical patients who received placebo, inferences about nonsurgical patients are difficult to make. Further research involving larger cohorts at risk is required to assess the benefit of this strategy among nonsurgical patients.

Since mortality was defined in this study as all-cause mortality, excess mortality due to *S. aureus* infections had to be very high to result in significant differences between the study groups. Of the 26 patients who died, 4 had a hospital-associated *S. aureus* infection; 3 of these 4 patients received placebo and underwent cardiothoracic surgery. In contrast, none of the patients who received mupirocin–chlorhexidine and underwent cardiothoracic surgery died. A total of 6 nonsurgical patients in the mupirocin–chlorhexidine group died versus 1 in the placebo group, but none of these deaths were associated with *S. aureus* infections. However, since the numbers are small and the subgroups were not predefined, these data should be interpreted with caution.

Mupirocin and chlorhexidine are considered to be relatively safe. However, since *S. aureus* strains can become resistant to mupirocin, we recommend restricting the use of this agent to known carriers who are at risk for infection.[28] For screening purposes, priority should be given to tests with high specificity, thus limiting the number of false positive results and the unnecessary use of mupirocin and chlorhexidine. The prevalence of methicillin-resistant *S. aureus* carriage in the Netherlands is only 0.03%.[29] Although this trial was designed to identify and eradicate both methicillin-sensitive and methicillin-resistant *S. aureus*, we did not encounter the latter. Biologically speaking, however, it is plausible that this strategy would also be effective in carriers of methicillin-resistant strains of *S. aureus* that are susceptible to mupirocin. Since carriage patterns may be different for the methicillin-resistant strains, throat swabs in combination with nasal swabs can be considered for identifying carriers of *S. aureus*.[30,31]

The intervention we describe did not protect patients from all hospital-acquired *S. aureus* infections. As we anticipated, it had no or limited effect on exogenous infections. Our intention was to prevent infections with endogenous strains by

Table 2. Relative Risk of Hospital-Acquired *Staphylococcus aureus* Infection and Characteristics of Infections (Intention-to-Treat Analysis).

Variable	Mupirocin–Chlorhexidine (N=504)	Placebo (N=413)	Relative Risk (95% CI)*
	no. (%)		
S. aureus infection	17 (3.4)	32 (7.7)	0.42 (0.23–0.75)
Source of infection†			
Endogenous	12 (2.4)	25 (6.1)	0.39 (0.20–0.77)
Exogenous	4 (0.8)	6 (1.5)	0.55 (0.16–1.92)
Unknown	1 (0.2)	1 (0.2)	
Localization of infection			
Deep surgical site‡	4 (0.9)	16 (4.4)	0.21 (0.07–0.62)
Superficial surgical site‡	7 (1.6)	13 (3.5)	0.45 (0.18–1.11)
Lower respiratory tract	2 (0.4)	2 (0.5)	0.82 (0.12–5.78)
Urinary tract	1 (0.2)	0	
Bacteremia	1 (0.2)	1 (0.2)	
Soft tissue	2 (0.4)	0	

* Relative risks are for *S. aureus* infection in the mupirocin–chlorhexidine group.
† The source of the *S. aureus* infections was determined by comparing nasal strains with strains isolated from the infection site by pulsed-field gel electrophoresis.
‡ Data are for surgical patients only: 441 in the mupirocin–chlorhexidine group and 367 in the placebo group.

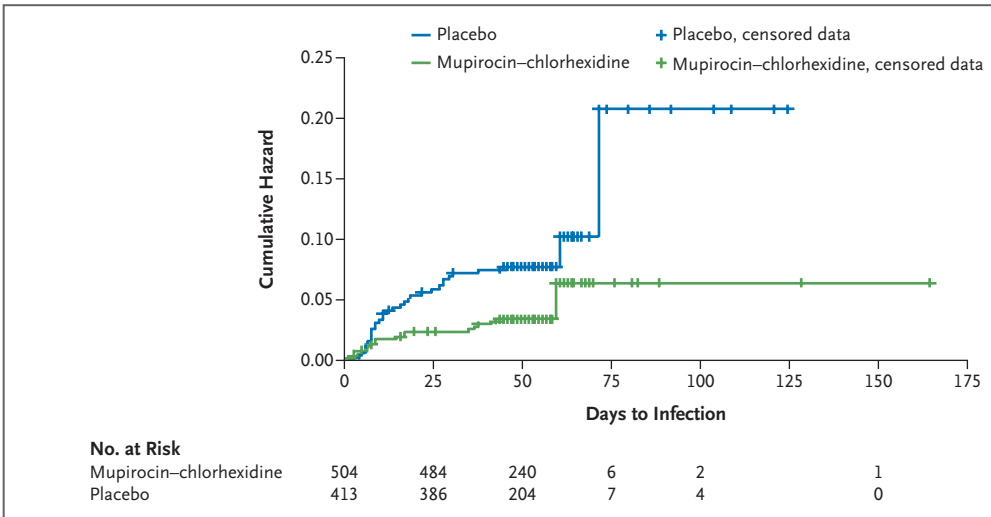

Figure 3. Kaplan–Meier Curves Showing Cumulative Hazard of Hospital-Acquired *Staphylococcus aureus* Infection in the Study Groups.

Data were censored at the end of the follow-up period or at the time of death.

eradicating these strains from nasal and extranasal sites. However, in some of the patients who received mupirocin and chlorhexidine, endogenous infections developed, and it is unclear why treatment failed in these patients. More insight into the pathogenesis of endogenous infections would allow preventive strategies to be further enhanced. Also, addressing the problem of cross-infection from exogenous sources of *S. aureus* remains a challenge.

In conclusion, hospital-acquired infections with *S. aureus*, especially among surgical patients, can be prevented by rapid screening of patients to identify those who are nasal carriers and initiation of decolonization treatment in confirmed carriers immediately after admission.

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