MAJOR ARTICLE

Impact of Combined Low-Level Mupirocin and Genotypic Chlorhexidine Resistance on Persistent Methicillin-Resistant *Staphylococcus aureus* Carriage After Decolonization Therapy: A Case-control Study

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Background. The clinical importance of low-level mupirocin resistance and genotypic chlorhexidine resistance remains unclear. We aimed to determine whether resistance to these agents increases the risk of persistent methicillin-resistant *Staphylococcus aureus* (MRSA) carriage after their use for topical decolonization therapy.

Methods. A nested case-control study was conducted of MRSA carriers who received decolonization therapy from 2001 through 2008. Cases, patients who remained colonized, were matched by year to controls, those in whom MRSA was eradicated (follow-up, 2 years). Baseline MRSA isolates were tested for mupirocin resistance by Etest and chlorhexidine resistance by *qacA/B* polymerase chain reaction. MRSA carriers with high-level mupirocin resistance were excluded. The effect of the primary exposure of interest, low-level mupirocin and genotypic chlorhexidine resistance, was evaluated with multivariate conditional logistic regression analysis.

Results. The 75 case patients and 75 control patients were similar except that those persistently colonized were older ($P = .007$) with longer lengths of hospital stay ($P = .001$). After multivariate analysis, carriage of combined low-level mupirocin and genotypic chlorhexidine resistance before decolonization independently predicted persistent MRSA carriage (odds ratio [OR], 3.4 [95% confidence interval {CI}, 1.5–7.8]). Other risk factors were older age (OR, 1.04 [95% CI, 1.02–1.1]), previous hospitalization (OR, 2.4 [95% CI, 1.1–5.7]), presence of a skin wound (OR, 5.7 [95% CI, 1.8–17.6]), recent antibiotic use (OR, 3.1 [95% CI, 1.3–7.2]), and central venous catheterization (OR, 5.7 [95% CI, 1.4–23.9]).

Conclusions. Combined low-level mupirocin and genotypic chlorhexidine resistance significantly increases the risk of persistent MRSA carriage after decolonization therapy. Institutions with widespread use of these agents should monitor for resistance and loss of clinical effectiveness.

Colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) increases the risk of adverse health outcomes, with 10%–30% of carriers subsequently developing MRSA infection [1, 2]. MRSA carriers also add to the colonization pressure in healthcare facilities, acting as reservoirs for transmission to other patients [3]. MRSA control interventions have therefore included therapies to eradicate colonization, and recent studies have shown that this strategy can be successful [4]. There are concerns, however, regarding the emergence of resistance to agents used for this purpose.

Intranasal mupirocin and chlorhexidine washing are widely used to decolonize MRSA carriers [4]. Increasing resistance to these agents is being reported [5–8]. Low-level mupirocin-resistant MRSA isolates, defined

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by minimum inhibitory concentrations (MICs) between 8 and 256 μg/mL, have mutations in native tRNA synthetase [9, 10]. High-level mupirocin-resistant isolates (MICs ≥ 512 μg/mL) harbor a plasmid-encoded *mupA* gene [9, 10]. Chlorhexidine resistance is associated with plasmid-borne *qacA/B* genes that code for multidrug efflux pumps [11], resulting in at least 2- to 4-fold increases in minimum bactericidal concentrations [12, 13].

Previous studies have concluded that high-level mupirocin resistance is associated with decolonization failure [14–16]. However, the elevated MICs that result in low-level mupirocin resistance and minimum bactericidal concentrations associated with *qacA/B* gene carriage remain well below concentrations achieved in vivo, which suggests that they may be clinically unimportant. Studies evaluating low-level mupirocin resistance have been underpowered to detect a significant association with decolonization failure [14, 15, 17]. A recent report suggested that MRSA strains carrying the *qacA/B* genes may be transmitted more rapidly [13]. Thus, the clinical relevance of low-level mupirocin resistance and genotypic chlorhexidine resistance remains unclear [9, 18].

The University of Geneva Hospitals has been using intranasal mupirocin and chlorhexidine bathing to decolonize MRSA carriers since 1994 [19]. The prevalence of mupirocin resistance in MRSA was noted to steadily increase from 9% in 1999 to 81% in 2008. MIC testing in 2008 showed that >99% of resistant MRSA isolates had low-level mupirocin resistance, and a sample of 12 nonclonal low-level mupirocin-resistant isolates all possessed the V588F point mutation associated with this resistance phenotype [20]. Thus, we aimed to determine whether low-level mupirocin resistance and chlorhexidine resistance are associated with persistent MRSA carriage after decolonization therapy with these agents by conducting a nested case-control study of MRSA carriers admitted to our institution during the period from 2001 through 2008.

METHODS

Study Setting

The University of Geneva Hospitals is a tertiary care center with 1901 beds and 47,706 admissions in 2009. MRSA screening is performed for patients with a history of MRSA carriage or who are hospitalized in the intensive care unit, for contacts of newly identified carriers, and for patients who are about to be transferred to rehabilitation facilities. Universal screening at admission previously occurred hospital-wide from January through August 2003 and in surgical wards from July 2004 through May 2006 [21, 22]. Screening swab samples are collected from the nares, groin, and other clinically indicated sites [19]. MRSA carriers routinely receive decolonization therapy consisting of intranasal mupirocin twice daily for 5 days and chlorhexidine bathing (4% Lifo-Scrub; B. Braun) daily for 7 days. Topical mupirocin is applied intranasally only, and not to skin or catheter exit sites. Systemic antibiotics are not used for decolonization therapy. Patients are rescreened for MRSA daily for 3 days after decolonization treatment, then weekly if they remain MRSA negative. All MRSA isolates from newly identified MRSA carriers were routinely stored at –70°C until June 2005. MRSA strains isolated from sterile sites and strains with unusual phenotypic or genotypic characteristics were stored during the entire study period.

Study Design and Sample Selection

The nested case-control study was conducted between 2001 and 2008. This time period was chosen because of the availability of electronic medical records. Patients with MRSA isolates stored during the study period were eligible for inclusion. Patients were also required to have received at least 3 days of decolonization therapy within 4 weeks after the sampling date of their stored isolate and to have provided at least 1 post-decolonization MRSA screening sample or clinical culture 1–12 months after decolonization therapy.

Patients were excluded if they carried high-level mupirocin-resistant MRSA before decolonization. Patients who had received decolonization therapy within the past 6 months were also excluded, because we were interested in evaluating patients who had not been recently exposed to eradication therapies. Exogenous recolonization, rather than persistent colonization with the same strain, was also an exclusion criterion. This was determined by examining pre- and post-decolonization MRSA isolates for changes in antibiotic sensitivities, staphylococcal cassette chromosome (SCC) *mec* classification, or multiple-locus variable number of tandem repeats analysis (MLVA) pattern.

The primary study outcome was failure of decolonization therapy as documented by at least 1 positive MRSA screening result or clinical culture result 1–12 months after decolonization therapy. This outcome defined the patient as a potential case patient. Control patients were patients who had successfully eradicated their MRSA carriage as strictly defined by at least 6 consecutive negative MRSA swab samples if the last follow-up sample was obtained <2 years after decolonization therapy or only negative MRSA swab samples if the last sample was collected ≥2 years after attempted eradication. Patients were followed up for 2 years. Any positive MRSA culture result (screening or clinical) during the follow-up period made the patient a potential case patient. Successful eradication was the rarer outcome; thus, all eligible control patients were included. One case patient was randomly selected for each control patient and frequency matched by year of decolonization to control for time as a potential confounder.

Microbiological Methods

MRSA screening specimens from individual patients were pooled in the laboratory and inoculated directly and after

overnight enrichment onto MRSA ID plates (bioMérieux). Identification and antibiotic susceptibility testing of MRSA from colonies suggestive of staphylococci were performed using standard methods [21] according to Clinical and Laboratory Standards Institute recommendations [23] and confirmed with multiplex quantitative polymerase chain reaction (PCR) for the genes *femA* and *mecA* [24].

Baseline MRSA isolates, collected prior to decolonization therapy, were screened for mupirocin resistance using a 0.5 McFarland suspension on Mueller-Hinton agar with a 5-μg disk (Becton Dickinson) incubated at 35°C for 18–24 h [25]. Resistance was defined as a zone of inhibition of <14 mm. Resistant isolates underwent MIC determination with Etests (AB Biodisk) [26]. MIC breakpoints were defined as susceptible, ≤4 μg/mL; low-level resistant, 8–256 μg/mL; and high-level resistant, ≥512 μg/mL [9, 10].

Phenotypically mupirocin-resistant isolates underwent *mupA* PCR to detect the gene encoding high-level resistance, and all baseline isolates were tested with an assay for the V588F point mutation, which confers low-level resistance. The presence of the *qacA/B* genes was assessed for all baseline isolates (see Appendix 1 for details of the molecular methods, including primer and probe sequences). SCC *mec* determination was performed for all pre-decolonization and available post-decolonization isolates [27]. Stored isolates from samples that had been collected from patients before and after decolonization therapy were typed by means of MLVA consisting of a multiplex PCR using 10 primer pairs. Representative isolates of all MLVA clusters were selected and subjected to multilocus sequence typing as previously reported [28].

Data Collection

Data regarding demographic characteristics and risk factors for persistent MRSA carriage were collected retrospectively from electronic medical records. Variables included age, sex, admission date, admission department, comorbidities, McCabe score [29], length of stay, hospitalization during the past 2 years, nursing home residency, presence of skin wounds, previous MRSA infection, surgical procedure during hospitalization, receipt of antibiotics during the hospitalization prior to decolonization, and presence of devices during decolonization therapy. The Infection Control Program database was used to obtain prospectively collected decolonization therapy details [19]. MRSA culture and sensitivity results were obtained from the laboratory information system. The study was approved by the hospital institutional review board (approval no. MED 09-057R).

Statistical Analysis

Baseline characteristics were compared with the Student *t* test or Wilcoxon test as appropriate for continuous variables. For differences in proportions, the χ^2 test was used. Odds ratios using Mantel-Haenszel methods matching by year were calculated for risk factors for persistent MRSA carriage. Multivariate conditional logistic regression analysis, group-matched by year, was conducted using variables with $P < .2$ on univariate analysis. Likelihood ratio tests were used with a significance level of $P = .05$ to guide sequential exclusion of covariates from the model. Interaction terms were tested to assess for effect modification. All *P* values were 2-tailed, and a *P* value of ≤0.05 was considered to reveal a statistically significant difference. Results were analyzed using Stata, version 11.0 (StataCorp).

RESULTS

Patient Characteristics and Decolonization Details

A flowchart showing the sample selection process is presented in Figure 1. There were 13,556 MRSA isolates stored from 5094 patients between 2001 and 2008. Of these, 2469 patients (48%) received decolonization therapy for ≥3 days within 1 month after providing the specimen from which their stored isolate originated and were eligible for study inclusion. After exclusions for receipt of decolonization therapy during the past 6 months, inadequate post-decolonization follow-up, contaminated and/or nonviable baseline MRSA isolates, high-level mupirocin resistance, and changes in antibiotic sensitivities, SCC *mec* type, or MLVA pattern after decolonization, a total of 75 control patients were identified and matched to 75 case patients by year of decolonization.

Characteristics of case patients and control patients are shown in Table 1. Those persistently colonized after eradication therapy (case patients) were older than those successfully decolonized (control patients) (median age, 76 vs 68 years; $P = .01$). Case patients also had greater lengths of stay than control patients (median, 49 vs 27 days; $P = .001$). Pre-decolonization MRSA isolates from case patients were more likely to carry SCC *mec* type I ($P = .001$; Table 2), compared with those from controls, in which SCC *mec* type IV was more common ($P = .03$). The median duration of decolonization therapy was 7 days in both groups ($P = .77$). There was no difference in the department where decolonization therapy was administered, number of screening samples collected after decolonization therapy, and time to the last follow-up screening or clinical sample after the end of therapy.

Risk Factors for Persistent MRSA Colonization

Low-level mupirocin resistance was found in MRSA isolates from 49 (64%) of 75 case patients and 26 (35%) of 75 control patients prior to decolonization ($P < .001$; Table 3). Genotypic chlorhexidine resistance was more common than mupirocin resistance, with 68 case patients (91%) and 51 control patients (68%) carrying MRSA with the *qacA/B* genes ($P < .001$). In almost all instances, low-level mupirocin resistance coexisted

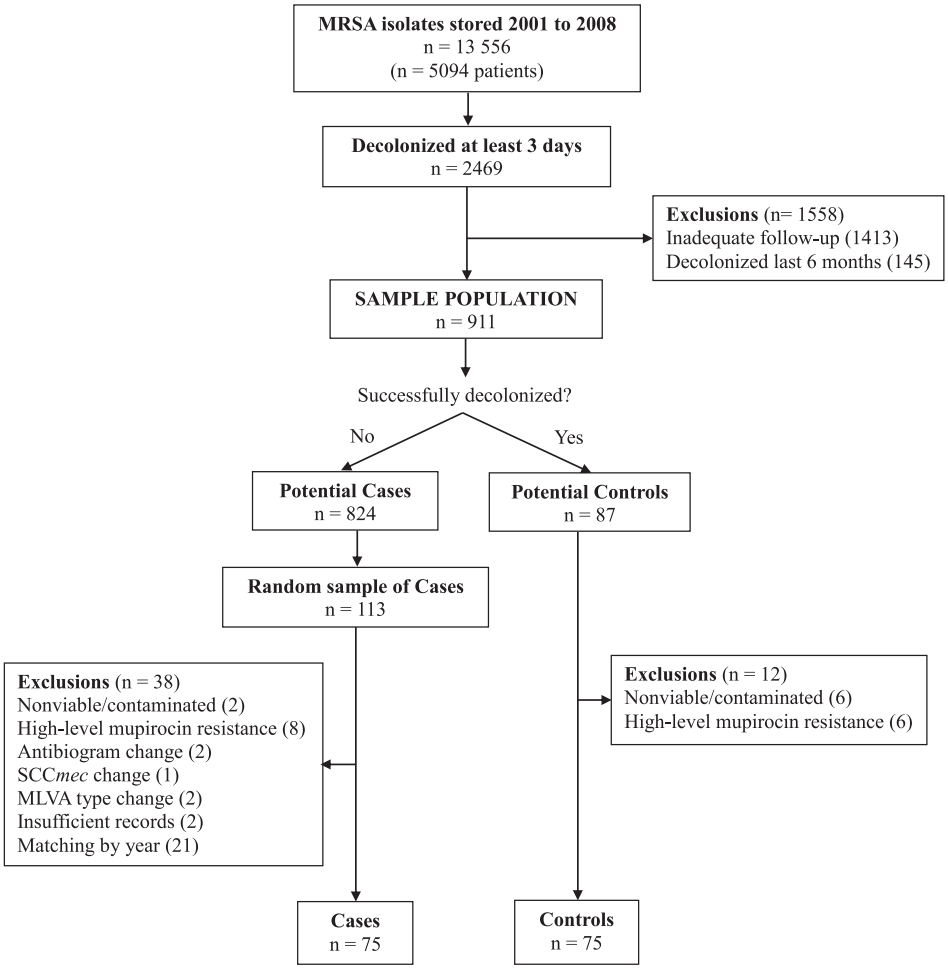

Figure 1. Study population and sample selection for the case-control study.

with genotypic chlorhexidine resistance. Only 1 of the case patients had a baseline MRSA isolate that was resistant to mupirocin and not to chlorhexidine, and there were none among the control patients. Therefore, for further analyses, the combination of resistance to both agents was taken as the exposure of interest.

After multivariate analysis, the presence of both low-level mupirocin resistance and genotypic chlorhexidine resistance at baseline remained strongly associated with persistent MRSA colonization after eradication therapy, with an adjusted odds ratio (aOR) of 3.4 (95% confidence interval [CI], 1.5–7.8; $P = .004$; Table 4). Other independent risk factors for persistent colonization were older age (aOR, 1.04 per 1-year increment [95% CI, 1.02–1.1; $P = .001$), prior hospitalization (aOR, 2.4 [95% CI, 1.1–5.7]; $P = .04$), presence of skin wounds (aOR, 5.7 [95% CI, 1.8–17.6]; $P = .003$), receipt of antibiotics inactive against MRSA (aOR, 3.1 [95% CI, 1.3–7.2]; $P = .01$), and central venous catheterization during decolonization therapy (aOR, 5.7 [95% CI, 1.4–23.9]; $P = .02$). There was no effect modification of SCC *mec* type on the association between combined low-level mupirocin and genotypic chlorhexidine resistance and failure of decolonization.

Genotypic Analyses and Resistance After Decolonization

All low-level mupirocin-resistant isolates contained SCC *mec* type I and the V588F point mutation. Interestingly, the *mupA* gene, usually associated with high-level mupirocin resistance, was present in all low-level resistant isolates with MIC $\geq$ 64 μg/mL. This represented low-level mupirocin-resistant isolates from 12 (24%) of 49 case patients and 2 (8%) of 26 control patients.

Forty-six of 75 case patients had post-decolonization culture isolates stored and available for further evaluation. MLVA typing of pre- and post-decolonization isolate pairs from these patients were identical, consistent with MRSA persistence or relapse rather than exogenous recolonization. Among these 46 case patients, 7 (15%) had mupirocin-sensitive isolates at baseline and developed resistance (5 low-level and 2 high-level resistance) after decolonization. In addition, 3 case patients (7%) had low-level mupirocin-resistant MRSA at baseline and high-level mupirocin-resistant MRSA after decolonization. All 3

Table 1. Clinical Characteristics of Case Patients and Control Patients

Characteristic	Case patients ($n = 75$)	Control patients ($n = 75$)	*P*
Age, median years (IQR)	76 (64–83)	68 (45–81)	.01
Male sex	39 (52)	43 (57)	.51
Admission department			.27
Internal medicine	32 (43)	24 (32)	.18
Surgery	28 (37)	27 (36)	.87
Intensive care	5 (7)	7 (9)	.55
Pediatrics	0 (0)	3 (4)	.08
Other[a]	10 (13)	14 (19)	.37
Comorbidities			
Cardiovascular disease	42 (56)	34 (45)	.19
Chronic pulmonary disease	13 (17)	12 (16)	.83
Chronic renal failure	13 (17)	7 (9)	.15
Requirement of hemodialysis	2 (3)	0 (0)	.16
Diabetes mellitus	13 (17)	12 (16)	.83
Chronic liver disease	9 (12)	10 (13)	.81
Neurological disease	27 (36)	19 (24)	.11
Malignant disease	15 (20)	11 (15)	.39
Autoimmune disease	3 (4)	0 (0)	.08
HIV/AIDS	2 (3)	4 (5)	.41
Intravenous drug use	1 (1)	3 (4)	.31
Chronic skin disease	4 (5)	6 (8)	.51
McCabe score			
1	44 (59)	48 (64)	.50
2	25 (33)	25 (33)	>.99
3	6 (8)	2 (3)	.15
Length of stay, median days (IQR)	49 (23–94)	27 (10–49)	.001

NOTE. Data are no. (%) of patients, unless otherwise specified. HIV, human immunodeficiency virus; IQR, interquartile range.

[a] Includes Dermatology, Psychiatry, Rehabilitation, Intermediate Care, and Outpatient Departments.

case patients were colonized with MRSA carrying both the V588F point mutation and *mupA* gene at baseline.

Induced expression of the *mupA* gene resulting in a high-level resistant phenotype possibly occurred in vivo during decolonization therapy in MRSA strains from the 12 case patients and 2 control patients whose baseline isolates carried this gene. The univariate and multivariate conditional regression analyses were therefore repeated excluding these patients and rematching the remaining case patients and control patients by year (see Appendix 2). After these exclusions, the presence of combined low-level mupirocin and genotypic chlorhexidine resistance remained an independent risk factor for failure of decolonization therapy (aOR, 3.2 [95% CI, 1.3–7.6]; $P = .01$).

DISCUSSION

Controlling MRSA transmission and infection is important in healthcare facilities, and decolonization is often recommended to achieve this goal (strength of evidence, IB–II [30]). However, the results of this study emphasize the need to exercise caution when using this strategy. Our findings demonstrate that carriage of MRSA with both low-level mupirocin resistance and genotypic chlorhexidine resistance is strongly associated with persistent colonization after eradication therapy. Resistance to both these agents was closely linked in our study. Thus, it was difficult to separate the effects of resistance to individual agents. Genotypic chlorhexidine resistance alone did not predict persistent carriage, suggesting that the combination of low-level mupirocin and chlorhexidine resistance may be necessary to result in clinical failure. These agents are often recommended and commonly administered concurrently for MRSA eradication [4, 30, 31]; thus, our findings are likely to have important clinical implications.

Mupirocin resistance has been reported in 65% of MRSA isolates in 1 study [5], but the relative contribution of low- and high-level resistance was not determined. Another study found low-level mupirocin resistance in only 18.6% of their MRSA isolates [32]. Higher rates were found in our institution. In contrast, rates of genotypic chlorhexidine resistance comparable to that seen in our institution have been described previously, in 63% of isolates in Europe [11] and up to 80% of isolates

Table 2. Methicillin-Resistant *Staphylococcus aureus* (MRSA) Culture and Decolonization Details

Characteristic	Case patients ($n = 75$)	Control patients ($n = 75$)	P
Duration of MRSA carriage before decolonization, median days (IQR)	5 (4–6)	5 (4–7)	.27
Patients MRSA positive on the basis of samples collected in month before decolonization			
At screening[a]	66 (88)	64 (85)	.63
At clinical culture[a]	24 (32)	15 (20)	.09
Molecular characteristics of MRSA isolates from samples collected in month before decolonization			
SCC *mec* classification			.03
Type I	67 (89)	50 (67)	.001
Type IV	5 (7)	14 (19)	.03
Other	3 (4)	11 (14)	.03
MLST sequence type			.01
ST228	65 (87)	49 (65)	.002
ST8	5 (7)	8 (11)	.38
ST5	5 (7)	6 (8)	.75
ST22	0 (0)	4 (5)	.04
ST7	0 (0)	3 (4)	.08
Other	0 (0)	5 (7)	.02
Details of decolonization therapy			
Duration, median days (IQR)	7 (7–7)	7 (7–7)	.77
Department of decolonization administration			.25
Internal medicine	19 (25)	23 (31)	.47
Surgery	28 (37)	26 (35)	.73
ICU	4 (5)	1 (1)	.17
Pediatrics	0 (0)	3 (4)	.08
Other[b]	24 (32)	22 (29)	.72
Patients who underwent decolonization therapy during past 12 months	1 (1)	0 (0)	.32
Samples collected ≤2 years after decolonization			
No. of screening samples, median (IQR)	10 (7–16)	9 (6–14)	.36
Time to last follow-up sample, median days (IQR)	234 (107–483)	284 (132–472)	.81

NOTE. Data are no. (%) of patients, unless otherwise specified. ICU, intensive care unit; IQR, interquartile range; MLST, multi-locus sequence typing; SCC, staphylococcal cassette chromosome.

[a] These groups are not mutually exclusive. Patients may have had positive results on both screening and clinical cultures during the month prior to decolonization.

[b] Includes Dermatology, Psychiatry, Rehabilitation, Intermediate Care, and Outpatient Departments.

elsewhere [8]. This is of particular concern in view of increasing chlorhexidine use, not only for MRSA control but also for a variety of other indications [31], as well as reports of possible antibiotic cross-resistance with chlorhexidine [33]. Our high resistance rates are likely due to selection of resistant strains. The V588F mutation, seen in all low-level mupirocin-resistant MRSA in this study, is not associated with substantial fitness costs [34]. In addition, MRSA strains that carry the *qacA/B* genes have the potential for increased transmission when chlorhexidine-based surface antiseptic protocols are used [13]. These factors may explain why resistant strains were able to predominate in our institution where targeted decolonization of MRSA carriers has been routine for more than 15 years.

As far as we are aware, this is the first study demonstrating an association between both low-level mupirocin and genotypic chlorhexidine resistance and persistent MRSA carriage after decolonization therapy. Previous research studying low-level mupirocin resistance has suggested its possible link with persistent MRSA colonization [14, 17]. Because of small patient numbers, these studies were unable to make firm conclusions about the relevance of low-level resistance. In addition, the duration of follow-up was short (≤4 weeks). Other studies have observed relapse 2–12 months after therapy [15, 16, 35, 36]. To ensure that case patients and control patients were classified correctly, we used a strict definition for MRSA eradication and patients were followed up for 2 years. The large sample of patients with resistant MRSA, a long-standing MRSA storage policy, and prospectively collected decolonization data enabled this study to detect a significant association between resistance to agents for eradication therapy and persistent MRSA colonization.

Other independent risk factors for persistent MRSA colonization in this study were older age, previous hospitalization, skin wounds, recent antibiotic use, and central venous catheterization. These factors have been described previously [16, 17, 35, 36] and

Table 3. Risk Factors Associated With Failure of Decolonization-Univariate Analysis

Risk factor	Case patients (n = 75)	Control patients (n = 75)	Crude OR (95% CI)	P
Mupirocin resistance				
Phenotypic resistance				
Low-level resistance[a]	49 (64)	26 (35)	3.4 (1.7–7.1)	<.001
Genotypic resistance				
mupA gene[b]	12/49 (24)	2/26 (8)	5.1 (1.0–25.8)	.03
V588F point mutation	52 (69)	26/73 (36)[c]	4.6 (2.1–9.9)	<.001
Chlorhexidine resistance				
qacA/B genes	68 (91)	51 (68)	10.2 (2.6–40.7)	<.001
Resistance combinations				
Fully sensitive	6 (8)	24 (32)	0.1 (.01–.3)	<.001
Low-level mupirocin resistance only	1 (1)	0 (0)		.32
Genotypic chlorhexidine resistance only	21 (28)	25 (33)	0.7 (0.3–1.6)	.44
Resistance to mupirocin and chlorhexidine	47 (63)	26 (35)	3.2 (1.6–6.5)	.001
Hospitalization during past 2 years	54 (72)	40 (53)	2.3 (1.1–4.6)	.02
Nursing home residence during past 6 months	21 (28)	18 (24)	1.2 (0.6–2.5)	.58
Wound or pressure sore	19 (25)	8 (11)	2.8 (1.1–6.7)	.02
Previous MRSA infection	2 (3)	0 (0)		.16
Surgery during hospitalization	39 (52)	34 (45)	1.3 (0.7–2.5)	.41
Antibiotic use				
MRSA-active antibiotic	19 (25)	18 (24)	1.1 (0.5–2.3)	.85
MRSA-inactive antibiotic	53 (71)	39 (52)	2.2 (1.1–4.3)	.02
Devices present				
Central venous catheter	14 (19)	5 (7)	3.0 (1.1–8.4)	.03
Urinary catheter	21 (28)	8 (11)	3.3 (1.3–8.3)	.01

NOTE. Data are no. (%) of patients, unless otherwise specified. CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.

[a] These patients carried MRSA with low-level mupirocin resistance determined by Etest minimum inhibitory concentrations.

[b] The *mupA* gene polymerase chain reaction was performed in low-level mupirocin-resistant isolates only.

[c] The allelic discrimination assay was indeterminate in MRSA isolates from 2 patients.

may in part reflect reduced ability to effectively administer eradication therapies and endogenous recolonization from extranasal sites where topical therapy may have reduced efficacy, such as wounds or devices. Adherence to and quality of decolonization therapy administration has been associated with success of eradication [37, 38]. This information was not available retrospectively. However, the presence of comorbidities and the department where decolonization was administered were used as proxy measures for this parameter and no difference in these variables was seen between case patients and control patients.

There are limitations to this study. The strict definitions for case patients and control patients resulted in the exclusion of patients who did not provide specimens on multiple occasions after eradication therapy. Thus, there is potential for selection bias from inclusion of patients with multiple comorbidities and frequent healthcare contact. Decolonization success rates are higher among relatively healthy MRSA carriers at our institution, compared with that of our study population [39]. Therefore, the association between resistance and decolonization failure may be underestimated in the current

Table 4. Independent Risk Factors Associated With Failure of Decolonization-Multivariate Analysis

Risk factor	Adjusted OR (95% CI)	P
Combined mupirocin and chlorhexidine resistance	3.4 (1.5–7.8)	.004
Age (per 1-year increment)	1.04 (1.02–1.1)	.001
Prior hospitalization (previous 2 years)	2.4 (1.1–5.7)	.04
Wound or pressure sore	5.7 (1.8–17.6)	.003
Exposure to MRSA-inactive antibiotic	3.1 (1.3–7.2)	.01
Central venous catheterization	5.7 (1.4–23.9)	.02

NOTE. Only risk factors found to be statistically significant on multivariate analysis are shown. CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.

study, in which control patients were more likely to experience a failure of eradication therapy than the general population of MRSA carriers in our facility, including healthy carriers of community-associated MRSA [39]. Misclassification of cases may have occurred as a result of exogenous recolonization. Although we attempted to identify this by means of MLVA typing, we may not have identified all instances of recolonization with the same endemic strain. Information regarding samples processed outside the hospital was unavailable. This may also have caused the misclassification of some patients. However, our institution is the only public hospital for our catchment population; therefore, the majority of patients were likely followed up within our facility for ongoing medical care. In addition, there was no significant difference in follow-up between case patients and control patients in terms of frequency of sampling and time to last post-decolonization sample. Thus, the likelihood of differential misclassification is low. Although there are potential biases in this study, the strength of the effect estimate makes these factors less likely explanations for our findings.

MRSA control is a priority in healthcare facilities, and eradication of carriage can be beneficial for the individual, as well as for patients at risk of MRSA acquisition. However, with any intervention using antimicrobial agents, the risk of emergence of resistance is invariably a potential threat. In this study of MRSA-colonized inpatients, carriage of strains with combined low-level mupirocin and genotypic chlorhexidine resistance significantly increased the risk of persistent MRSA carriage after decolonization therapy. Therefore, widespread use of decolonization therapies should be coupled with procedures to monitor for emergence of resistance. Alternative agents or practices are required in settings where resistance has rendered this MRSA control measure ineffective.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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All other authors: No reported conflicts.

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