

Methicillin-susceptible *Staphylococcus aureus* nasal colonization and the risk of subsequent methicillin-resistant *Staphylococcus aureus* infections among hospitalized patients^{☆,☆☆}

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Abstract

Few data exist on the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infections among known methicillin-susceptible *S. aureus* (MSSA) carriers. In a cohort of 2991 hospitalized MSSA carriers, 22 (22%) of 98 *S. aureus* infections that occurred within a subsequent 6-month period were caused by MRSA. Recent fluoroquinolone use was an independent predictor of MRSA infections ($P < .001$).

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Nasal colonization with *Staphylococcus aureus* occurs in up to 40% of patient populations and constitutes a significant risk factor for subsequent infections caused by the same strain (Wertheim et al., 2005). The incidence of subsequent infections is up to 4 times higher among methicillin-resistant *S. aureus* (MRSA) carriers than among methicillin-susceptible *S. aureus* (MSSA) carriers (Safdar and Bradley, 2008). However, few data exist on the rates of and risk factors for the development of MRSA infections among hospitalized individuals already known to be colonized with MSSA.

We performed a retrospective cohort study of all adult patients hospitalized at a tertiary care medical center between September 2007 and May 2010 and whose nasal surveillance cultures grew MSSA. One sterile double swab (Becton Dickinson, Sparks, MD) was used to sample both nares and

was incubated on mannitol salt agar for up to 48 h; further speciation was performed using the Staphaurex coagglutination test (Remel, Lenexa, KS) and a tube coagulase test as indicated. Other body sites were not routinely sampled. Surveillance cultures were obtained <48 h after admission to most wards and all intensive care units. Zero time (ZT) was defined as the day the first nasal swab culture positive for MSSA was obtained. The primary outcome was a subsequent MRSA infection that occurred >24 h and up to 6 months after ZT.

All MSSA carriers with subsequent MRSA infections were compared to all MSSA carriers with subsequent MSSA infections with regard to a variety of demographic and clinical parameters to derive predictors of MRSA infections. In order to validate our results, additional comparisons were performed between all MSSA carriers with subsequent MRSA infections and a randomly selected cohort of MSSA carriers who did not develop any staphylococcal infections within the subsequent 6 months.

Patients from whom MRSA had been isolated prior to the development of a *S. aureus* infection were excluded. Staphylococcal decolonization measures were not performed throughout the observation period. The study was approved by our institutional review board.

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Table 1

Comparison of demographic and clinical characteristics between MSSA carriers with subsequent MRSA infections versus MSSA carriers with subsequent MSSA infections ($n = 98$)

Characteristic	MRSA infection ($n = 22$)	MSSA infection ($n = 76$)	Odds ratio (95% CI)	<i>P</i>
Demographic				
Age, median (range)	62 (32–92)	56 (25–96)		.02
Stay in intensive care unit at ZT	1 (5)	10 (13)	0.31 (0.04–2.60)	>.2
Stay in long-term care facility	5 (23)	5 (7)	4.18 (1.09–16.08)	.04
Hospitalization within the prior year	12 (55)	36 (47)	1.33 (0.51–3.46)	>.2
Underlying comorbidities				
Charlson score, median (range)	2 (1–9)	2 (0–12)		>.2
Current injection drug use	1 (5)	7 (9)	0.47 (0.06–4.04)	>.2
HIV	5 (23)	10 (13)	1.94 (0.59–6.44)	>.2
Diabetes mellitus	8 (36)	26 (34)	1.10 (0.41–2.96)	>.2
Congestive heart failure	2 (9)	9 (12)	0.74 (0.15–3.73)	>.2
Chronic obstructive pulmonary disease/asthma	7 (32)	20 (26)	1.31 (0.47–3.67)	>.2
End-stage liver disease	1 (5)	8 (11)	0.41 (0.05–3.43)	>.2
Current malignancy	4 (18)	8 (11)	1.89 (0.51–6.99)	>.2
End-stage renal disease	1 (5)	8 (11)	0.41 (0.05–3.43)	>.2
Peripheral vascular disease	3 (14)	9 (12)	1.18 (0.29–4.78)	>.2
Invasive devices and procedures				
Central venous catheter	7 (32)	17 (22)	1.62 (0.57–4.61)	>.2
Surgical procedure after ZT	3 (14)	8 (11)	1.34 (0.32–5.56)	>.2
Time to <i>S. aureus</i> infection				
No. of hospitalization days between ZT and <i>S. aureus</i> infection	11 (IQR, 4–19)	7 (IQR, 3–15)		.14
Total no. of days between ZT and <i>S. aureus</i> infection	35 (IQR, 11–84)	19 (IQR, 4–64)		.20
Antibiotic use between ZT and <i>S. aureus</i> infection				
Vancomycin	7 (32)	25 (33)	0.95 (0.34–2.63)	>.2
β -Lactam	15 (68)	37 (49)	2.26 (0.83–6.16)	.11
Fluoroquinolone	15 (68)	19 (25)	6.43 (2.28–18.13)	<.001
Macrolide	5 (23)	7 (9)	2.90 (0.82–10.27)	.13

Data are number (%) of episodes unless otherwise indicated. IQR = Interquartile range.

Bivariate analyses to compare categorical and continuous variables were performed with the Pearson χ^2 , the Fisher exact, and the Mann–Whitney *U* tests as indicated. We present odds ratios rather than relative risks to facilitate comparison to results from multivariate analyses. Logistic unconditional regression models were built to determine independent predictors of subsequent MRSA infections ($P < .05$).

A total of 23,719 nasal surveillance culture samples were collected from 16,104 individual patients during the study period. A total of 3618 samples grew MSSA and a total of 2991 individual MSSA carriers were identified. Of 2991 MSSA carriers, 118 (3.9%) developed a subsequent staphylococcal infection within 6 months after ZT. Twenty patients were excluded due to prior MRSA isolation ($n = 18$) and unavailable medical records ($n = 2$).

The final cohort consisted of 98 (3.3%) patients who developed a *S. aureus* infection at a median of 19 days (interquartile range, 5–83 days) after ZT. The median age of the cohort was 56 years, 56 (57%) were male, and the median Charlson comorbidity score was 2 (Charlson et al., 1987). Infection sites comprised normally sterile ($n = 50$) and nonsterile sites ($n = 48$). Seventy-six (78%) of *S. aureus* infections were caused by MSSA and 22 (22%) were caused by MRSA.

On bivariate analyses, MSSA carriers with subsequent MRSA infections were similar to MSSA carriers with subsequent MSSA infections with regard to a variety of demographic and clinical characteristics (Table 1). Patients

with MRSA infections were more likely to be older, to have previously stayed in a long-term care facility, and to have received a fluoroquinolone between ZT and the event ($P < .05$). In contrast, there was no difference with regard to use of vancomycin, β -lactams, and/or fluoroquinolones within the last 6 months before ZT. Neither the total number of days of hospitalization nor the number of days in an intensive care unit after ZT differed significantly. On logistic regression analyses, receipt of a fluoroquinolone between ZT and the event remained as an independent predictor of a MRSA infection (adjusted OR, 6.43; 95% CI, 2.28–18.13; $P < 0.001$).

MSSA carriers with subsequent MRSA infections were then compared to a randomly selected cohort of MSSA carriers ($n = 114$) who did not develop any *S. aureus* infections within 6 months after ZT (Table 2). Results of bivariate analyses were similar to those obtained from our first comparison. On logistic regression analyses, receipt of a fluoroquinolone between ZT and the event again independently predicted a MRSA infection (adjusted OR, 7.62; 95% CI, 2.67–21.75; $P < 0.001$); HIV infection was also associated with the outcome in previous studies (adjusted OR, 4.41; 95% CI, 1.14–17.08; $P = 0.03$).

Only 22 (0.7%) of 2991 hospitalized MSSA carriers developed MRSA infections within 6 months after determination of their colonization status (in contrast to approx. 7% of 1278 MRSA carriers who developed subsequent MRSA infections; data not shown). Previous fluoroquinolone use

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