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***Staphylococcus aureus* Nasal Colonization and Subsequent Infection in Intensive Care Unit Patients: Does Methicillin Resistance Matter?**

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Abstract

Objective—*Staphylococcus aureus* is a significant cause of infection in intensive care unit (ICU) patients. Colonization with methicillin-resistant *S. aureus* (MRSA) is a risk factor for subsequent *S. aureus* infection. However, MRSA-colonized patients may have more co-morbidities than methicillin-susceptible *S. aureus* (MSSA)-colonized, or non-colonized patients and therefore more susceptible to infection on that basis.

Design—Prospective cohort study

Setting—A 24-bed surgical ICU (SICU) and 19-bed medical ICU (MICU) of a 1252-bed, academic hospital.

Patients—Patients had nasal swab cultures for *S. aureus* performed upon ICU admission from December 2002 to August 2007

Methods—Patients in the ICU for > 48 hours were examined for an ICU-acquired *S. aureus* infection, defined as development of *S. aureus* infection > 48 hours after ICU admission.

Results—One thousand four hundred thirty-three (27.8%) of 5,161 patients had *S. aureus* colonization at admission [674 (47.0%) with MRSA; 759 (53.0%) with MSSA]. An ICU-acquired *S. aureus* infection developed in 113 (2.2%) patients. 75 (66.4%) of 113 had an infection due to MRSA. Risk factors associated with an ICU-acquired *S. aureus* infection included MRSA

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colonization at admission [adjusted hazard ratio (aHR), 4.70; 95% confidence interval (CI), 3.07–7.21] and MSSA colonization at admission (aHR, 2.47; 95% CI, 1.52–4.01).

Conclusion—ICU patients colonized with *S. aureus* were at greater risk of developing a *S. aureus* infection in the ICU. Even after adjusting for patient-specific risk factors, MRSA-colonized patients were more likely to develop *S. aureus* infection compared to MSSA-colonized or non-colonized patients.

Staphylococcus aureus infection is a common cause of healthcare associated infection worldwide. The proportion of *S. aureus* infection due to methicillin-resistant *S. aureus* (MRSA) strains has been increasing over the past decades. MRSA accounts for more than 60% of *S. aureus* intensive care unit (ICU)-related infections in the U.S.^{1, 2} The prevalence of MRSA infections in U.S. hospitals is approximately 34 cases per 1,000 admissions.³ MRSA carriage is an important predisposing factor for developing MRSA infection. Approximately 15 to 25 % of MRSA-colonized inpatients developed a subsequent MRSA infection during their hospitalization or within 18 months.^{4, 5}

Previous studies reported that MRSA infections were associated with higher morbidity and mortality compared to infections caused by methicillin-susceptible *S. aureus* (MSSA).^{6, 7} Reduced vancomycin susceptibility and emergence of the community associated genotype have complicated the management of MRSA infections.^{8, 9}

Given the significant impact of MRSA infection, earlier identification of high risk patients (i.e., MRSA-colonized patients) is considered essential for reducing the frequency of overall *S. aureus* infection. However, MRSA colonization might be a marker of individuals with substantial co-morbidities compared to individuals with MSSA colonization or without *S. aureus* colonization. Therefore, MRSA-colonized patients may be more susceptible to *S. aureus* infection on the basis of patient risk factors alone.¹⁰ Moreover, previous risk factor studies to examine the role of MRSA colonization and subsequent infection were limited by the sample size or limited patient population.¹¹

The purpose of this study was to determine if MRSA-colonized patients, admitted to medical and surgical ICUs were more likely to develop any *S. aureus* infection in the ICU, compared to patients colonized with methicillin-susceptible *S. aureus* or not colonized with *S. aureus*, independent of predisposing patient risk factors.

METHODS

A prospective cohort study was performed in the 19-bed medical ICU and the 24-bed surgical ICU of Barnes- Jewish Hospital (BJH), a 1,252-bed, academic, tertiary care center in St. Louis, Missouri. The study was conducted between December 2002 and August 2007. This study included a 57-month observation period (2002–2007) in the surgical ICU and a 32-month observation in the medical ICU (2005–2007). An active surveillance program to detect MRSA colonization was implemented in the surgical ICU in December 2002, and then expanded to the medical ICU in January 2005. Nasal cultures for *S. aureus* were performed for all patients admitted to the ICUs. MRSA surveillance cultures were done as part of routine infection control policy in the hospital. Contact precautions were

implemented for ICU patients with MRSA detected by nasal culture or other clinical cultures. Colonized ICU patients did not undergo MRSA decolonization therapy (e.g., mupirocin nasal ointment) and patients at Barnes-Jewish Hospital did not undergo pre-operative MRSA decolonization therapy during the study period.

Demographic and clinical data, including co-morbid conditions and outcomes were obtained for the study population. Skin ulcer was defined as the development of a stage two or greater decubitus ulcer during ICU stay. Nasogastric or Dobhoff tube was defined as a nasoenteric tube. A percutaneous feeding tube was defined as either a gastrostomy, jejunostomy, or gastrojejunostomy tube. All clinical cultures positive for *S. aureus* were evaluated to determine whether or not these positive cultures were associated with ICU-acquired *S. aureus* infection.

National Healthcare Safety Network (NHSN) definitions were used to define ICU-acquired *S. aureus* infections.¹² ICU-acquired *S. aureus* infection was defined as the development of *S. aureus* infection (either MRSA or MSSA) > 48 hours after ICU admission and < 48 hours after ICU discharge. The incidence of *S. aureus* infection was reported per 1,000 ICU-days.¹

Exclusion criteria included patients who were < 18 years old, stayed in the ICU < 48 hours, had a known *S. aureus* infection at ICU admission, or developed *S. aureus* infection during the first 48 hours of their ICU stay.

S. aureus surveillance swab specimens were collected from both anterior nares of each patient, transported and stored at room temperature and inoculated directly onto Mannitol salt agar plates (Becton Dickinson). The Mannitol salt agar plates were incubated at 35 °C and examined for growth after 24–48 hours. Strains that produced yellow colonies on the screening Mannitol salt agar plates were confirmed as *S. aureus* by Gram staining, 3% catalase testing, and coagulase testing with the Staph Latex agglutination assay (LifeSign). Confirmed *S. aureus* isolates were subcultured in Trypase soy broth with 5% sheep blood (Becton Dickinson) and then on oxacillin screening agar containing 6.0 mg/mL of oxacillin (Becton Dickinson) for determining methicillin resistance. Plates were incubated at 35 °C for 18–24 hours and examined for the evidence of growth. Strains showing distinct growth were considered to be methicillin-resistant.

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, IL) and SAS version 9.1.3 (SAS Institute, Cary, NC). Risk factors for time to first infection after ICU admission were assessed using Cox proportional hazards models. Non-infected patients were also censored on 48 hours after discharge from the ICU. Potential risk factors were first assessed in bivariate analysis. The multivariable model was developed in forward, stepwise fashion. Candidate variables were those with $P < .10$ in bivariate analysis. Variables were retained in the model if $P < .05$ or if the variable was a confounder. Two-way interactions were assessed after selection of the main effects. The proportional hazards assumption was assessed via $-\ln(-\ln)$ survival curves, time-dependent covariates, and Shoenfeld residuals^{13, 14}

The dates of initiation and discontinuation were known for central venous catheterization and mechanical ventilation; thus, these variables were first assessed as time-dependent

variables using the counting process approach.¹⁵ Because use of these devices have previously been documented to be associated with MRSA infection,^{16–18} a multivariable model was also constructed and stratified by presence of central venous catheter, mechanical ventilation, and per tube nutrition. The Washington University Institutional Review Board approved this study.

RESULTS

A total of 9,632 patients 18 years old were admitted to the ICUs during the study period. (6,419 in the surgical ICU and 3,213 in the medical ICU) (Figure 1). Nine thousand five hundred and twenty-three (98.9 %) patients had an admission *S. aureus* nasal swab culture. Among the 9,523 patients, 234 had a *S. aureus* infection at ICU admission or within 48 hours of admission. Patients with *S. aureus* infection at admission or within 48 hours of ICU admission and patients who stayed in the ICU 48 hours ($n = 4,128$) were excluded. Of the remaining 5,161 patients, 1,433 (27.8%) had a positive nasal culture for *S. aureus* [674 (47.0%) patients were MRSA-colonized and 759 (53.0%) were MSSA-colonized].

Comparison of patient characteristics based on nasal colonization at ICU admission is shown in Table 1. MRSA-colonized patients were older than either MSSA-colonized or non-colonized patients (median age = 63, 55, and 61 years, respectively). Compared with either MSSA-colonized or non-colonized patients, MRSA-colonized patients were more likely to have multiple co-morbidities including congestive heart failure, malignancy, chronic obstructive pulmonary diseases, diabetes mellitus, systemic corticosteroid use, skin ulcer, and chronic renal insufficiency. MRSA colonized patients were also more likely to have a recent history of multiple drug-resistant organisms and recent exposure to healthcare facilities. Surgical ICU admission was less common in MRSA-colonized patients compared to MSSA-colonized or non-colonized patients.

One hundred and thirteen (2.2%) patients developed a total of 128 ICU-acquired *S. aureus* infections during their ICU stay; 11(9.7%) of 113 patients developed multiple ICU-acquired *S. aureus* infections. MRSA accounted for 66.4% of ICU-acquired *S. aureus* infections. Median time to development of *S. aureus* infection from ICU admission was 7 days. Among 128 ICU-acquired *S. aureus* infections, the most common infection was ventilator-associated pneumonia (39;30.5%). The remaining ICU-acquired *S. aureus* infections were central venous catheter-associated bloodstream infection (19;14.8%), primary bloodstream infection without central venous catheter (16;12.5%), surgical site infection (11;8.6%), hospital acquired pneumonia (without ventilator) (11;8.6%), skin and soft tissue infection (excluding surgical site infection) (9;7.0%), secondary bloodstream infection 7;5.5%), intra-abdominal infection (7;5.5%), musculoskeletal infection (3;2.3%), and other (6;4.7%).

The overall incidence of ICU-acquired *S. aureus* infection was 2.19 per 1,000 ICU-days. All ICU-acquired *S. aureus* infections among MRSA-colonized patients were caused by MRSA. The proportion of infections due to MRSA among MSSA-colonized patients and non-colonized patients were 30.8% and 60.0%, respectively (Table2).

Risk factors independently associated with ICU-acquired *S. aureus* infections were MRSA colonization on admission [adjusted hazard ratio (aHR), 4.70; 95% confidence interval (CI), 3.07–7.21], MSSA colonization on admission (aHR, 2.47; 95% CI, 1.52–4.01), skin ulcer (aHR, 1.68; 95% CI, 1.11–2.54), surgical procedure during the hospitalization (aHR, 1.60; 95% CI, 1.02–2.50), mechanical ventilation during ICU stay (aHR, 1.63; 95% CI, 1.06–2.51) (time dependent variable), and younger age at ICU admission (aHR, 0.99; 95% CI, 0.98–1.00) (Table 3). Stratified multivariate models based on the presence or absence of a central venous catheter, mechanical ventilation, and per tube enteral nutrition were also constructed. Results in stratified models were similar to that in non-stratified model (data not shown)

DISCUSSION

Although previous studies have reported a relationship between nasal colonization status and subsequent *S. aureus* infection, few studies have compared nasal colonization with MSSA or MRSA and the development of ICU-acquired *S. aureus* infection. This study showed that nasal colonization with *S. aureus* was associated with a 2.5 to 4.7-fold increased risk of ICU-acquired *S. aureus* infection compared with non-colonized patients, even after adjusting for underlying patient risk factors.

It remains unclear why MRSA-colonized patients more frequently develop *S. aureus* infection compared with MSSA-colonized patients. While patient co-morbidities, presence of devices, and invasive procedures may facilitate the development of MRSA infections, our analysis controlled for these factors. Potential factors for the increased incidence rate of *S. aureus* infection in MRSA-colonized patients could be the presence of virulent factors and higher bacterial burden at colonized sites.^{19, 20} These factors might be associated with increasing tissue invasiveness and lead to incidence risk of infection. However, the relationship between virulence factors and subsequent incidence of *S. aureus* infection is not completely understood.

The incidence of ICU-acquired *S. aureus* infection in this cohort was 2.3%, which is similar to previous studies of *S. aureus* infection incidence in ICUs (2% to 6%).^{21, 22} The prevalence of MRSA colonization in this cohort was 13.1 %, and the overall prevalence of *S. aureus* colonization at ICU admission was 27.8 %. These findings are slightly higher than previously reported colonization rate in ICU at US hospitals, ranging from 6–9 % for MRSA and 23–24 % for *S. aureus*.^{4, 23, 24} Although the difference in nasal colonization rate between this cohort and previous studies from US hospital are not completely clear, the difference in acquisition rate of nasal swab culture at ICU admission potentially influence the overall colonization rate. Acquisition rate of nasal swab in this cohort was 98.9 %, which was significantly higher than that in previous studies (75–76%).^{4, 23, 24} The large prospective cohort and the high rate of nasal swab culture acquisition over the 4-year study period represent major strengths of this study.

In bivariate risk factor analysis, several risk factors, including hospital admission in the last 12 months, chronic renal failure, and chronic renal failure with hemodialysis surprisingly were protective against ICU-acquired *S. aureus* infection, although these variables were not

statistically significant in multivariate model. After additional analysis, we found that patients with these factors were more likely to have a *S. aureus* infection at or within 48 hours of ICU admission, and therefore be excluded from our study (data not shown).

Several patient-related factors were independently associated with developing an ICU-acquired *S. aureus* infection, including surgical procedure during the ICU stay, the development of skin ulcer, and mechanical ventilation during ICU stay. Surgical patients are at increased risk of developing *S. aureus* infections. Risk factors for *S. aureus* infections in surgical patients include undergoing emergent surgery, clean-contaminated surgery, or prolonged duration of surgery.²⁵ We found the presence of a skin ulcer was associated with developing a subsequent *S. aureus* infection as have others.²⁶ Impairment of skin integrity may result in increased burden of *S. aureus*, leading to subsequent infection. Mechanical ventilation is associated with ventilator associated *S. aureus* pneumonia. MRSA is one of the most common cause of ventilator associated pneumonia.²⁷ Interestingly, older patients had lower risk for developing *S. aureus* infection. Previous studies have variable association between age and *S. aureus* infection in healthcare settings. Some studies reported *S. aureus* infection increased with older age, or showed no association with age.^{4, 5} One study reported that *S. aureus* infection was more commonly seen in younger patients, however the authors concluded that this finding was associated with poor functional status in an age-stratified model.²⁸ A potential explanation for the relationship between age and ICU-acquired *S. aureus* infection in our cohort could be that younger *S. aureus* infected patients in our study tended to have severe traumatic injury (e.g., motor vehicle accident and assault). Trauma patients are at higher risk for *S. aureus* infection.²⁹

Nasal colonization with MRSA at ICU admission was the strongest independent predictor for the development of *S. aureus* infection. These findings support strategies such as decolonization of MRSA-colonized patients in the ICU to try to reduce subsequent *S. aureus* infection in the ICU. Currently, few interventions for reducing MRSA colonization prevalence have been assessed in healthcare settings. The use of intranasal mupirocin ointment, oral antimicrobials, and chlorhexidine bathing, either alone or in combination, may prevent subsequent MRSA infection.^{30–34} However, the ideal strategies to prevent MRSA colonization and infection in healthcare settings remain unclear at this time. Eliminating *S. aureus* colonization may not be easily achieved by antibiotic-based regimens given the emergence of mupirocin resistance, the high rate of re-colonization, and cost and labor issues to implement comprehensive decolonization strategies.^{35, 36}

This study has some limitations. As with any observational study, even after adjusting for known predisposing factors, other unmeasured factors may still cause ICU-acquired *S. aureus* infection. Another limitation was the lack of molecular typing of the *S. aureus* isolates to determine the original sources of infection (i.e., endogenous or exogenous source). However, von Eiff et al. reported a high genotypic correlation between nasal *S. aureus* isolates and subsequent *S. aureus* bloodstream isolates, pointing to the patient's own flora as the primary source of *S. aureus* infection.³⁷ In our cohort, both MRSA- and MSSA-colonized patients tended to develop infection with the same phenotypic strain of *S. aureus* suggesting endogenous sources, however that was less likely to occur among MSSA-colonized individuals. Transmission of MRSA could occur despite use of contact precaution

for known MRSA carriers.¹⁶ It was undetermined whether the source of MRSA infection among non-colonized or MSSA-colonized patients were extra-nasal endogenous source or exogenous source in this cohort. Further studies using molecular typing with a larger sample size may improve our understanding of the relationship between *S. aureus* transmission and acquisition in the ICU. Due to costs and labor constraints, we only obtained anterior nares surveillance culture, which may underestimate the prevalence of *S. aureus*-colonized patients. Nasal swab cultures alone can miss 15% of MRSA carriers.³⁸ Detection of extranasal colonized individual might be important especially community-acquired MRSA genotype strains.³⁹

This study demonstrates that *S. aureus* nasal colonization is independently associated with ICU-acquired *S. aureus* infection and that MRSA-colonized ICU patients are more likely to become infected even after adjusting for patient co-morbidities and ICU process of care. While many issues regarding the detection, eradication, and prevention of *S. aureus* infection remain unresolved, it is necessary to assess the benefits of focused and comprehensive decolonization interventions to reduce the overall rate of *S. aureus* infection in the ICU. Our results suggest developing effective methods of MRSA decolonization and preventing MRSA colonization should be a major component of these strategies.

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Figure 1.

Description of the study population

NOTE. Data are no. (%) of patients. ICU, intensive care unit; SAI, *Staphylococcus aureus* infection; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA; methicillin-susceptible *Staphylococcus aureus*.

Table 1
Comparison of Patients with Colonization Status on Admission to the Intensive Care Units

Variable	MRSA colonization (n = 674)	MSSA colonization (n = 759)	No colonization (n = 3728)	Colonization MRSA vs. MSSA P	Colonization MRSA vs. None P
Patient characteristics					
Age, median, years (range)	63 (18–95)	55 (18–94)	61 (18–97)	<.001	<.001
Female	304 (45.1)	351 (46.2)	1661 (44.6)	.665	.792
White race	444 (65.9)	535 (70.5)	2582 (69.3)	.061	.081
Surgical ICU admission	365 (54.2)	491 (64.7)	2422 (65.0)	<.001	<.001
Any BJH admission in the past 12 months	385 (57.1)	213 (28.1)	1343 (36.0)	<.001	<.001
Location prior to hospital admission					
Home	407 (60.4)	611 (80.5)	2650 (71.1)	Ref. ^a	Ref. ^a
Long term care facility	128 (19.0)	24 (3.2)	237 (6.4)	<.001	<.001
Outside hospital	139 (20.6)	124 (16.3)	841 (22.6)	<.001	.488
Condition present at the time of admission					
Congestive heart failure	154 (22.8)	76 (10.0)	488 (13.1)	<.001	<.001
Chronic obstructive pulmonary disease	197 (29.1)	104 (13.7)	692 (18.6)	<.001	<.001
Malignancy (current diagnosis)	87 (12.9)	97 (12.8)	608 (16.3)	.942	.026
HIV	8 (1.2)	4 (0.5)	34 (0.9)	.171	.499
Diabetes mellitus	264 (39.2)	207 (27.3)	1051 (28.2)	<.001	<.001
Systemic corticosteroid use in past 28 days	150 (22.3)	82 (10.8)	649 (17.4)	<.001	.003
Skin ulcer	146 (21.7)	125 (16.5)	678 (18.2)	.012	.033
Baseline renal function					
Normal renal function	521 (77.3)	684 (90.1)	3098 (83.1)	Ref. ^a	Ref. ^a
CRF	103 (15.3)	56 (7.4)	403 (10.8)	<.001	.098
CRF with hemodialysis	50 (7.4)	19 (2.5)	227 (6.1)	.258	.437
Liver cirrhosis	48 (7.1)	62 (8.2)	261 (7.0)	.457	.910
History of intravenous drug use	13 (1.9)	19 (2.5)	44 (1.2)	.463	.114
Solid organ or bone marrow transplant	21 (3.1)	15 (2.0)	149 (4.0)	.169	.275
Surgical procedure					
< 90 days prior to ICU admission	129 (19.1)	49 (6.5)	548 (14.7)	<.001	.003

Variable	MRSA colonization (n = 674)	MSSA colonization (n = 759)	No colonization (n = 3728)	Colonization MRSA vs. MSSA P	Colonization MRSA vs. None P
During current admission	342 (50.7)	432 (56.9)	2212 (59.3)	.019	<.001
Presence of resistant organism					
MRSA isolated in the past 6 months	137 (20.3)	4 (0.5)	76 (2.0)	<.001	<.001
<i>C. difficile</i> infection in the past 3 months	43 (6.4)	9 (1.2)	90 (2.4)	<.001	<.001
VRE isolated in the past 3 months	74 (11.0)	15 (2.0)	168 (4.5)	<.001	<.001

NOTE.

Data are no. (%) of patients, unless otherwise specified. ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; BJH, Barnes-Jewish Hospital; HIV, human immunodeficiency virus; CRF, chronic renal failure; *C. difficile*, *Clostridium difficile*; VRE, vancomycin-resistant enterococci; Ref, reference category.

^a Obtained from univariate logistic regression analysis.

Table 2
Incidence of ICU-acquired *S. aureus* Infection, by the Nasal Colonization Status on Admission (per 1,000 ICU-days)

Variable (incidence density)	Colonization status at ICU admission			Risk ratio (95%CI) Colonization MRSA vs. MSSA	P	Risk ratio (95%CI) Colonization MRSA vs. None	P
	MRSA (n=674)	MSSA (n=759)	None (n=3728)				
Any ICU-acquired SAI	7.00	4.40	1.71	1.59 (1.00–2.53)	.050	4.10 (2.47–6.78)	<.001
ICU-acquired MSSA infection	0	3.05	0.68	NA*	—	NA*	—
ICU-acquired MRSA infection	7.00	1.35	1.03	5.18 (2.74–9.77)	<.001	6.83(4.00–11.64)	<.001

NOTE.

ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin- susceptible *Staphylococcus aureus*; CI, Confidence interval, SAI; *Staphylococcus aureus* infection.
* The risk ratio and P value were not calculated for MSSA infection because none of the patients colonized with MRSA on admission developed an ICU-acquired MSSA infection.

Table 3

Risk Factors for *S. aureus* Infection in the Intensive Care Units

Characteristics	ICU-acquired <i>S. aureus</i> infection		Crude Hazard Ratio* (95%CI)	P	Adjusted Hazard Ratio† (95%CI)	P
	Yes (n= 113)	No (n=5048)				
Patient characteristics						
Age, median, years (range)	56 (20–94)	60 (18–97)	0.99 (0.98–1.00)	.075	0.99 (0.98–1.00)	.031
Female	45 (39.8)	2271 (45.0)	0.89 (0.61–1.30)	.553		
White race	74 (65.5)	3487 (69.1)	0.78 (0.53–1.15)	.210		
Surgical ICU admission	82 (72.6)	3196 (63.3)	1.18 (0.78–1.78)	.442		
Location prior to hospital admission						
Home	82 (72.6)	3586 (71.0)	Ref.	Ref.		
Long term care facility	5 (4.4)	384 (7.6)	0.62 (0.25–1.53)	.299		
Outside hospital	26 (23.0)	1078 (23.1)	0.95 (0.61–1.47)	.802		
Any BJH admission in the past 12 months	28 (24.8)	1913 (37.9)	0.63 (0.41–0.96)	.033		
Condition present at ICU admission						
Congestive heart failure	10 (8.8)	708 (14.0)	0.65 (0.34–1.25)	.198		
Chronic obstructive pulmonary disease	15 (13.3)	977 (19.4)	0.65 (0.38–1.12)	.119		
Malignancy (current diagnosis)	17 (15.0)	775 (15.4)	1.14 (0.68–1.91)	.618		
Diabetes mellitus	39 (34.5)	1483 (29.4)	1.24 (0.84–1.83)	.273		
Systemic corticosteroid use in past 28 days	20 (17.7)	861 (17.1)	0.98 (0.60–1.59)	.926		
Skin ulcer	58 (51.3)	891 (17.7)	1.98 (1.34–2.93)	<.001	1.68 (1.11–2.54)	.014
Baseline renal function						
Normal renal function	105 (92.9)	4198 (83.2)	Ref.	Ref.		
CRF	7 (6.2)	555 (11.0)	0.53 (0.25–1.13)	.101		
CRF with hemodialysis	1 (0.9)	295 (5.8)	0.16 (0.02–1.12)	.065		
Liver cirrhosis	9 (8.0)	362 (7.2)	1.23 (0.62–2.43)	.556		
History of intravenous drug use	3 (2.7)	73 (1.4)	1.89 (0.60–5.96)	.277		
Surgical procedure						
< 90 days prior to ICU admission	13 (10.6)	714 (14.1)	0.68 (0.38–1.24)	.213		
During hospitalization	86 (76.1)	2900 (57.4)	1.61 (1.04–2.49)	.033	1.60 (1.02–2.50)	.040
ICU related event						

Characteristics	ICU-acquired <i>S. aureus</i> infection		Crude Hazard Ratio* (95%CI)	P	Adjusted Hazard Ratio† (95%CI)	P
	Yes (n= 113)	No (n=5048)				
Central venous catheter present during ICU stay* - time dependent	95 (84.1)	3509 (69.5)	0.77 (0.52–1.15)	.201		
Mechanical ventilation during ICU stay* - time dependent	103 (91.2)	3457 (68.5)	1.96 (1.31–2.92)	.001	1.63 (1.06–2.51)	.026
Enteral nutrition during ICU stay*						
None	27 (23.9)	3295 (65.3)	Ref.	Ref.		
Via naso-enteric feeding tube	60 (53.1)	1311 (26.0)	1.86 (1.14–3.05)	.014		
Via percutaneous feeding tube	11 (9.7)	299 (5.9)	1.80(0.87–3.70)	.112		
Via both	15 (13.3)	143 (2.8)	2.58 (1.30–5.10)	.007		
Presence of resistant organism						
MRSA isolated in the past 6 months	5 (4.4)	212 (4.2)	1.12 (0.46–2.75)	.801		
<i>C. difficile</i> infection in the past 3 months	1 (0.9)	141 (2.8)	0.28 (0.04–2.07)	.217		
VRE isolated in the past 3 months	4 (3.5)	253 (5.0)	0.70 (0.26–1.89)	.479		
Colonization status at ICU admission						
No colonization on admission	50 (44.2)	3678 (72.9)	Ref.	Ref.	Ref.	Ref.
MSSA colonization on admission	26 (23.0)	733 (14.5)	2.58 (1.61–4.15)	<.001	2.47 (1.52–4.01)	<.001
MRSA colonization on admission	37 (32.7)	637 (12.6)	4.37 (2.85–6.68)	<.001	4.70 (3.07–7.21)	<.001

NOTE.

Data are no. (%) of patients, unless otherwise specified. ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; BJH, Barnes-Jewish Hospital; HIV, human immunodeficiency virus; CRF, chronic renal failure; *C. difficile*, *Clostridium difficile*; VRE, vancomycin-resistant enterococci; Ref, reference category.

Variables considered but not retained in the final model were any BJH admission in the past 12 months, CRF with hemodialysis, enteral nutrition during ICU stay (via naso-enteric tube, percutaneous tube, and via both).

* Follow-up days median (range):CVC 6 (2–109), no CVC 3(2–65), $P < .001$; MV 6 (2–109), no MV 3 (2–26), $P < .001$; tube EN 11 (2–109), no tube EN 3 (2–48), $P < .001$

† Stratified multivariate model was also constructed by central venous catheterization, mechanical ventilation and per tube enteral nutrition. Results in stratified model were similar to that in non-stratified model (data not shown).