ORIGINAL ARTICLE

Staphylococcus aureus Colonization before Infection Is Not Associated with Mortality among *S. aureus*–Infected Patients: A Meta-analysis

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BACKGROUND AND OBJECTIVE. The literature is conflicted as to whether people colonized with *Staphylococcus aureus* are at an increased risk of mortality. The aim of this meta-analysis was to review and analyze the current literature to determine whether prior history of *S. aureus* colonization is associated with mortality among *S. aureus*–infected patients.

METHODS. The PUBMED databases were searched with keywords related to *S. aureus* colonization and mortality. After reviewing 380 article abstracts and 59 articles in detail, only 7 studies had data on the association between *S. aureus* colonization and mortality among *S. aureus*–infected patients. Crude estimates of study odds ratios (ORs) were calculated on the basis of data from subset analyses. We pooled crude ORs from the 7 studies using a random-effects model. Woolf's test for heterogeneity was assessed.

RESULTS. When all studies were pooled in a random-effects model, no association between *S. aureus* colonization and mortality among *S. aureus*–infected patients was seen (pooled OR, 1.08 [95% confidence interval (CI), 0.32–3.66]; $n = 7$; heterogeneity $P = .05$). When the analyses were restricted to infection-attributable mortality, the association between colonization and mortality among *S. aureus*–infected patients was not statistically significant (pooled OR, 0.42 [95% CI, 0.15–1.21]; $n = 4$; heterogeneity $P = .28$).

CONCLUSIONS. *S. aureus* colonization was not associated with mortality among patients who developed an *S. aureus* infection. Interventions to decolonize *S. aureus* carriers may prevent *S. aureus* infections but may not be sufficient to prevent mortality.

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Approximately 30% of the US population is nasally colonized with *Staphylococcus aureus*.[1] *S. aureus* colonization can lead to self-infection, especially during hospitalizations where medical devices (eg, central venous catheters) often breach the body's natural barriers against bacteria. Consequently, patients colonized with *S. aureus* are more likely to develop *S. aureus* infections compared with patients who are not colonized.[2-5]

Multiple studies have found that patients colonized with *S. aureus* are more likely to die compared with uncolonized patients.[6-9] However, it is unknown whether this is solely due to the increased risk of infection among colonized patients or whether colonization is a risk factor for mortality independent of the increased risk of infection. Patients who are colonized may actually be less likely to die of an *S. aureus* infection for 2 reasons. First, colonized patients who develop an endogenous infection may be immunologically adapted to their *S. aureus* strain and thus have a more adequate immune response compared with uncolonized patients. Second, endogenous strains may be less virulent than exogenous strains; therefore, endogenous infections among colonized patients may lead to less mortality compared with exogenous infections among uncolonized patients.[10] Thus, colonization, while increasing infection risk, may actually be protective against mortality.

If colonization before infection is an independent risk factor for mortality among *S. aureus*–infected patients, clinicians could use prior colonization status to predict patient outcomes and inform prescribing practices. Additionally, decolonizing agents such as mupirocin could be used to prevent patient mortality. Alternatively, if *S. aureus* colonization is protective against mortality among infected patients, decolonization may be discouraged.

The aim of this study was to perform a meta-analysis of all observational studies that assessed the association between *S. aureus* colonization before infection and mortality only among patients infected with *S. aureus*. By limiting the cohort to only *S. aureus*–infected patients, we aim to elucidate the association between *S. aureus* colonization before infection and mortality independent of the association between colo-

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nization and infection. We hypothesized that *S. aureus* colonization before infection would not be a risk factor for all-cause or infection-related mortality among patients infected with *S. aureus*.

METHODS

Literature Search

All observational studies that measured the association between *S. aureus* colonization and mortality were eligible for this meta-analysis. The PUBMED databases were searched for articles published from January 1967 through June 2011 with keywords related to *S. aureus* carriage or colonization and mortality. The reference lists of obtained articles were hand searched. Titles and abstracts from 380 articles were screened to exclude case series or reports, outbreak investigations, review articles, laboratory or animal studies, and intervention studies. If relevance was unclear, the article was reviewed in detail. Figure 1 describes the literature search and review process.

Data Extraction

Three independent reviewers (M.L.S., A.B., J.S.M.) abstracted data for each article, and the standardized abstraction forms were compared for agreement. Inconsistencies in the blinded reviews were re-reviewed 4 times for consensus.

The exposure of interest was *S. aureus* colonization before *S. aureus* infection. The outcome of interest was mortality. Colonization and mortality data were extracted only for the subgroups of patients infected with *S. aureus*. Data that were extracted included (1) study design; (2) where study took place; (3) study period; (4) study population; (5) number of patients with an *S. aureus* infection and type of infection; (6) *S. aureus* colonization status; (7) timing (eg, before infection) and body site of *S. aureus* surveillance culture; (8) methicillin resistance; and (9) outcome data, including the study's definition of mortality (eg, all cause, infection attributable). Study population data collected included descriptions of patient population (eg, neonatal) and patient location (eg, inpatient, outpatient, nursing home).

Among the 59 articles published in English and reviewed in detail, only 7 studies had data on the association between *S. aureus* colonization and mortality among *S. aureus*–infected patients. Only these 7 studies were included in the meta-analysis. The studies not contributing to the meta-analysis were excluded for 2 main reasons: (1) the study did not provide data on the association between colonization and mortality among only *S. aureus*–infected patients; (2) the primary purpose of the study was to assess the impact of decolonization, which is beyond the scope of this study.

Most studies did not report covariate adjusted odds ratios (ORs) or confidence intervals (CIs), since the data of interest were often presented as a subanalysis. Thus, crude estimates were calculated on the basis of the number of *S. aureus*–infected patients who were colonized and died compared with the number of *S. aureus*–infected patients who were not colonized and died. We calculated the natural log of the OR and its variance from reported data.[11] Studies were stratified by their definition of mortality (eg, all cause, infection attributable) and by whether they included all *S. aureus* infections or only methicillin-resistant *S. aureus* (MRSA) infections in their analysis.

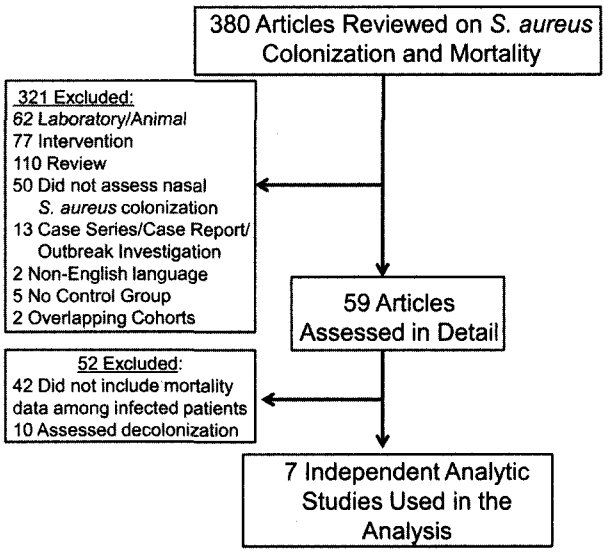


FIGURE 1. Literature search for articles on *Staphylococcus aureus* colonization and mortality among infected patients.

Statistical Analysis

Random-effects models were created in order to determine pooled relative risk estimates (ORs).[11-13] Woolf's test was used to assess heterogeneity.[11,13] Mortality was defined in different ways (ie, all cause or infection attributable) among the studies in the meta-analysis. First, we pooled all studies together to determine an overall pooled association between colonization and any definition of mortality among infected patients. If a study measured both all-cause mortality and infection-attributable mortality, we used all-cause mortality for the overall pooled estimate. We then calculated pooled estimates separately for all-cause mortality and infection-attributable mortality. Studies also varied by whether they included only MRSA infections or all *S. aureus* infections (ie, MRSA and methicillin-susceptible *S. aureus* [MSSA]) in their analyses. Separate pooled estimates were determined for MRSA infections and all *S. aureus* infections.

RESULTS

Overall, 7 studies were included in the meta-analysis.[10,14-19] Of these studies, 4 were from the US, and the other 3 were from the Netherlands, Taiwan, and Belgium. This meta-anal-

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TABLE 1. Study Characteristics and *Staphylococcus aureus* Colonization and Mortality Reported in Individual Studies

Author, publication year	Location	Patient population[a]	When and where colonization detected	Type of *S. aureus* infection	*S. aureus*–infected patients, no.	Infected patients previously colonized, %	Mortality data for MRSA infections only?	Mortality OR (95% CI)[b]	
								Infection attributable	All cause
Wertheim et al 2004[10]	Netherlands	Hospitalized	Nasal colonization at admission before infection	Bacteremia	81	49	No	0.17 (0.05–0.67)	0.25 (0.09–0.68)
Lai et al 2011[14]	Taiwan	Outpatient hemodialysis	Nasal colonization before admission before infection	Bloodstream infection, pneumonia, clinical sepsis, osteomyelitis, intra-abdominal infection	24	25	No	1.75 (0.23–13.31)	10.52 (0.52–214.6)
Nguyen et al 1999[15]	Ann Arbor, MI; Boston, MA; Pittsburgh, PA	Outpatient HIV	Nasal colonization before admission and during current admission before infection	Bacteremia, pneumonia, cutaneous or subcutaneous infections	13	69	No		0.50 (0.05–5.51)
Niclaes et al 1999[16]	Belgium	Nursing home	Nasal, throat, perineum before infection	Not stated	57	7	Yes	4.69 (0.24–91.9)	
Chang et al 1998[17]	Pittsburgh, PA	End-stage renal disease	Nasal colonization measured at admission and during current admission before infection	Bacteremia, sinusitis, pneumonia, infected retroperitoneal hematoma	9	78	No		6.43 (0.23–184.3)
Patel et al 2008[18]	Birmingham, AL	ICU	Nasal and tracheal aspirate colonization measured at admission and during current admission before infection	Late MRSA infection	16	38	Yes		9.00 (0.66–122.8)
Maraqa et al 2011[19]	Jacksonville, FL	NICU	Nasal colonization at admission and during current admission before infection	Bacteremia and pneumonia	27	33	Yes	0.36 (0.07–1.82)	

NOTE. CI, confidence interval; HIV, human immunodeficiency virus; ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*; NICU, neonatal intensive care unit; OR, odds ratio.

[a] All studies used the cohort study design.

[b] Two studies provided data on both all-cause and infection-attributable mortality.

ysis included patient populations from inpatient, outpatient, and nursing home settings. Children and adults were included in these studies. All studies used the cohort study design. These studies were published between 1998 and 2011 (Table 1).

Three studies presented results only among MRSA infections, and 4 studies presented results for all *S. aureus* infections (Table 1). Two studies defined mortality as all-cause mortality, 3 studies defined mortality as infection-attributable mortality, and 2 studies used both definitions.

Table 2 describes the pooled ORs for the association between colonization before infection and mortality among *S. aureus*–infected patients, including stratified analyses for definition of mortality and *S. aureus* infection. When all studies were pooled in a random-effects model, no association between *S. aureus* colonization before infection and mortality among *S. aureus*–infected patients was seen (pooled OR, 1.08 [95% CI, 0.32–3.66]; $n = 7$; heterogeneity $P = .05$). When the meta-analysis was limited to only studies that assessed MRSA, there was no significant association between MRSA colonization and mortality among MRSA-infected patients (pooled OR, 1.29 [95% CI, 0.17–9.97]; $n = 3$; heterogeneity $P = .12$). Similarly, no significant association between *S. aureus* colonization before infection and mortality among *S. aureus*–infected patients was seen when analyses were stratified by definition of mortality.

The forest plot in Figure 2 displays the ORs and 95% CIs for individual studies and the pooled estimates stratified by definition of mortality. When the analyses were restricted to studies that assessed infection-attributable mortality, there was a trend toward a protective effect of *S. aureus* colonization before infection against mortality, although this association was not statistically significant (pooled OR, 0.42 [95% CI, 0.15–1.21]; $n = 4$; heterogeneity $P = .28$). Conversely, when the analyses were restricted to studies that assessed all-cause mortality, *S. aureus* colonization before infection was a nonsignificant risk factor for mortality (pooled OR, 1.74 [95% CI, 0.28–10.73]; $n = 5$; heterogeneity $P = .01$).

The studies that assessed all-cause mortality were significantly heterogeneous ($P = .01$). This may be due to the variation in the proportion of the study populations that were colonized or infected with MRSA compared with MSSA. In 1 study, more than 99% of isolates collected were MSSA.[10] The other studies that assessed all-cause mortality had much higher proportions of patients colonized or infected with MRSA. When that 1 study was removed from the analysis, the other studies were homogeneous (pooled OR, 3.50 [95% CI, 0.75–16.35]; $n = 4$; heterogeneity $P = .30$).

DISCUSSION

In this meta-analysis of 7 cohort studies, we found that *S. aureus* colonization before infection was not associated with mortality among infected patients. The lack of an association between colonization before infection and mortality among *S. aureus*–infected patients is important from a clinical perspective because the topical antibiotic mupirocin is often used to decolonize patients in order to improve outcomes. The literature is currently divided as to whether decolonization of patients at high risk of infections reduces the number of subsequent *S. aureus* infections, and there is little evidence that decolonization prevents mortality.[20-25] If colonization is not associated with mortality, then it cannot be expected that decolonization will prevent mortality. Decolonization is but one tool to prevent *S. aureus* infections, but it cannot replace other effective prevention efforts.

Although a previous meta-analysis found that MRSA-infected patients are more likely to die compared with MSSA-infected patients, this meta-analysis did not see a difference in mortality among infected patients who were MRSA carriers compared with MSSA carriers.[26] No matter whether MRSA or MSSA colonization was assessed, there was still no association between colonization and mortality among infected patients. Therefore, knowledge of MRSA colonization will not predict outcomes among infected patients.

Prior studies have assessed the association between colonization and mortality without acknowledging how this association is modified by *S. aureus* infection.[9,14,16] It is clear that *S. aureus* colonization alone does not cause mortality among uninfected people, since one-third of the US population is colonized.[1] However, *S. aureus* colonization is a risk factor for *S. aureus* infection, and *S. aureus* infection can lead

TABLE 2. Association between *Staphylococcus aureus* Colonization and Mortality among Infected Patients by Definition of Mortality and Type of Infection

			Random-effects model	
Study type	No. of studies	Heterogeneity *P*	OR	95% CI
All studies	7	.05	1.08	0.32–3.66
Infection-attributable mortality	4	.28	0.42	0.15–1.21
All-cause mortality	5	.01	1.74	0.28–10.73
MSSA infections only	4	.05	0.64	0.08–5.06
MRSA infections only	3	.12	1.29	0.17–9.98

NOTE. CI, confidence interval; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; OR, odds ratio.

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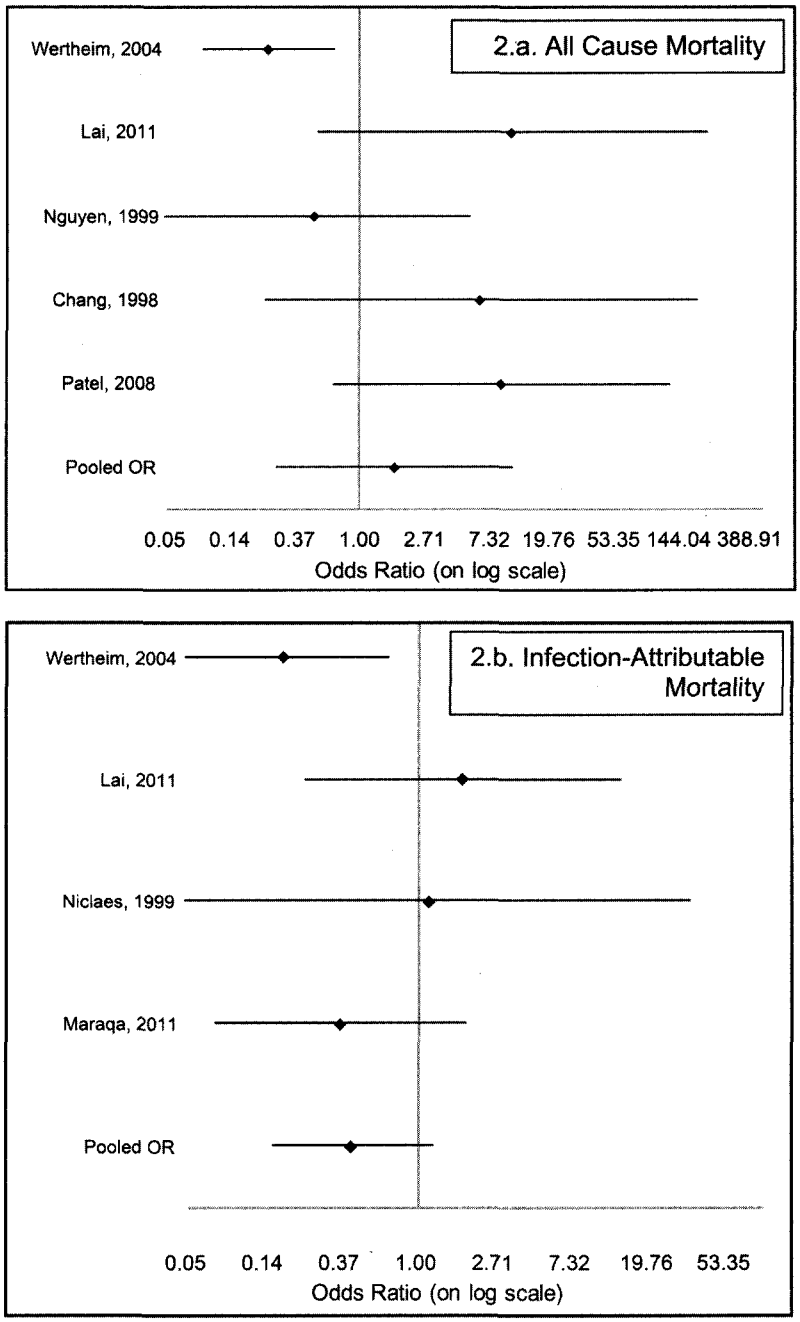


FIGURE 2. Forest plot of measures of effect of the associations between *Staphylococcus aureus* colonization before *S. aureus* infection and mortality among infected patients by definition of mortality. *a*, All-cause mortality. *b*, Infection-attributable mortality.

to mortality.[2-5] Thus, the effect of colonization on mortality is greatly modified by whether a patient is infected with *S. aureus*. Future studies that assess the association between *S. aureus* colonization and mortality must consider this causal pathway and stratify their analyses by *S. aureus* infection.

This meta-analysis is composed of only a few small studies with variable definitions of mortality. Large homogenous studies of *S. aureus*–infected patients are needed to determine the association between *S. aureus* colonization before infection and infection-attributable mortality. Further research should also compare colonizing and noncolonizing *S. aureus* strains to determine whether these strains differ in virulence and immune response.[27-28]

Limitations

This meta-analysis is limited by the small number of studies that have been published and the small sample sizes of the published studies. Another limitation is that the included studies were heterogeneous. The heterogeneity of this meta-

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analysis may be due to the variation in the proportion of MRSA-colonized patients in the study populations or the variety of populations studied, including inpatient, outpatient, and nursing home patients. Furthermore, the studies used different definitions of mortality, including all-cause mortality and infection-attributable mortality. Finally, this meta-analysis was limited by the inclusion of observational studies rather than randomized controlled trials, which are often evaluated in meta-analyses. Therefore, these results are subject to the inherent biases of observational studies. However, the association between colonization and mortality could not be evaluated in a randomized controlled trial.

In conclusion, there is no association between *S. aureus* colonization before infection and mortality among *S. aureus*–infected patients. Interventions to decolonize *S. aureus* carriers may prevent *S. aureus* infections but may not be sufficient to prevent mortality.

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