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State of the Science Review

Risk factors for methicillin-resistant *Staphylococcus aureus* colonization in the neonatal intensive care unit: A systematic review and meta-analysis

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Context: Methicillin-resistant *Staphylococcus aureus* (MRSA) causes a significant burden of illness in neonatal intensive care units (NICUs) worldwide. Identifying infants colonized with MRSA has become an important infection control strategy to interrupt nosocomial transmission.

Objective: Assess risk factors for MRSA colonization in NICUs via a systematic review and meta-analysis.

Data sources: MEDLINE, Embase, Web of Science, and The Cochrane Library databases were searched from inception through September 2015.

Study selection: Studies reporting risk factors for MRSA colonization using noncolonized controls in subspecialty level III or IV NICUs were included.

Data extraction: Two authors independently extracted data on MRSA colonization risk factors, study design, and MRSA screening methodology.

Results: Eleven articles were included in the systematic review, with 10 articles analyzed via meta-analysis. MRSA colonization was associated with gestational age <32 weeks (odds ratio [OR], 2.67; 95% confidence interval [CI], 1.35-5.27; $P = .01$) and birth weight <1,500 g (OR, 2.63; 95% CI, 1.25-5.55; $P = .01$). Infant sex ($P = .21$), race ($P = .06$), inborn status ($P = .09$), and delivery type ($P = .24$) were not significantly associated with colonization.

Conclusions: Very preterm and very-low birth weight infants were identified as having an increased risk for MRSA colonization on meta-analysis. Multifaceted infection prevention strategies should target these high-risk infants to reduce MRSA colonization rates in NICUs.

Staphylococcus aureus has become an increasingly problematic bacterial pathogen within neonatal intensive care units (NICUs) worldwide. Preterm and critically ill neonates are especially vulnerable to the development of invasive infections because of *S aureus*, and it is now the second most common cause of late-onset sepsis in very-low birth weight (VLBW) neonates.[1,2] Endemic transmission and outbreaks because of antibiotic-resistant *S aureus*, including methicillin-resistant *S aureus* (MRSA), occur frequently in many NICUs.[3-5] Controlling MRSA transmission in NICUs represents a challenging problem because many health care workers, families, and visitors are asymptomatically colonized and unknowingly serve as reservoirs for transmission.[6,7] The ability of *S aureus* to survive for prolonged periods on environmental surfaces further adds to the difficulty in controlling transmission.[8]

The establishment of colonization represents the first step in pathogenesis for most infections caused by *S aureus*.[9] MRSA colonization was associated with a 24.2 times increased risk of infection in a recent meta-analysis involving patients admitted to NICUs and pediatric intensive care units.[10] The use of active surveillance cultures to identify colonized infants and utilization of appropriate isolation precautions represents frequently used infection prevention strategies to interrupt horizontal MRSA transmission.[11] Previous studies have identified a variety of risk factors associated with MRSA colonization and infection: prematurity, younger gestational age, multiple gestation, endotracheal tube intubation, mechanical ventilation, surgery, central venous catheterization, gavage and parenteral feedings, and kangaroo care.[6,10,12] The objective of this study was to

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systematically review the literature on risk factors for MRSA colonization in the NICU and to quantitatively analyze the most commonly reported risk factors via meta-analysis.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines were used in this study.[13] The literature was systematically searched using the following predetermined inclusion criteria: studies evaluating risk factors for MRSA colonization using noncolonized controls as identified via active surveillance cultures; studies occurring in subspecialty level III or IV NICUs; publication in peer-reviewed journals; and English language studies. MRSA colonization was classified as either prevalent (initial MRSA screen positive at admission) or as incident (subsequent MRSA screen positive after a negative initial screen). Studies including MRSA clinical infections or investigating a specific MRSA outbreak were excluded. Abstracts and poster presentations were excluded because of the inability to review study methodology needed to determine if incorporation for quantitative analysis was appropriate. MEDLINE, Embase, Web of Science, and The Cochrane Library databases were searched from inception through September 2015 with the following search terms: *Staphylococcus*, *S. aureus*, methicillin resistant *Staphylococcus aureus*, MRSA, oxacillin resistant *Staphylococcus aureus*, ORSA, neonatal intensive care unit, neonatal, and NICU.

The following data were extracted from studies meeting inclusion criteria by 2 investigators independently (M.W. and J.W.): study design; sample size; method, timing, and frequency of screening for MRSA colonization; demographic and clinical characteristics; and all identified risk factors for MRSA colonization. Risk factors reported in ≥4 studies were included in the meta-analysis to increase the power of the statistical tests performed. Risk factors not included in the meta-analysis were included as part of the systematic review. The quality of observational studies was assessed using the modified Newcastle-Ottawa Scale with scores ≥7 considered high quality and scores of 5-6 considered fair quality.[14,15] Interrater agreement was measured using Cohen κ statistic.

Odds ratios (ORs) were used as the summary measure.[16] If studies reported other measures of effect sizes (ie, relative risks), ORs were calculated from summary data provided in the study.[17] Separate meta-analyses were performed for each exposure variable using the inverse variance method. Summary effect estimates were calculated using a random effects model with Bayesian estimation using Gibbs sampling of between-study variance.[18] Publication bias was assessed using funnel plots, Egger regression test, and Peters regression test.[19] Heterogeneity of study effect sizes was assessed using Cochran Q statistic and Higgins and Thompson I^2 statistic.[20,21] Significant heterogeneity was defined as either a $P < .10$ for Cochran Q statistic or I^2 values >50%.

In exposure variables with significant heterogeneity, meta-regression was performed using the average study gestational age to investigate sources of heterogeneity. Control rate meta-regression was used for the exposure variable gestational age. Effect modification for summary effect estimates was assessed based on study location (United States vs outside United States) and colonization type included in analysis (prevalent vs incident). All analyses were performed using STATA version 14.0 (StataCorp, College Station, TX), SAS version 8.4 (SAS Institute, Cary, NC), and WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, and Imperial College School of Medicine, London, UK).

RESULTS

After removal of duplicates, the search strategy identified 3,191 studies yielding 64 articles for full-text review after screening titles and abstracts (Fig 1). Eleven studies were included in the systematic review, and 10 were included in the meta-analysis (1 study did not include exposure variables reported in ≥4 studies). Basic characteristics of the included studies are listed in Table 1.[22-32] The included studies consisted of 5 retrospective cohorts, 4 prospective cohorts, 1 case-control study, and 1 cross-sectional study. Two

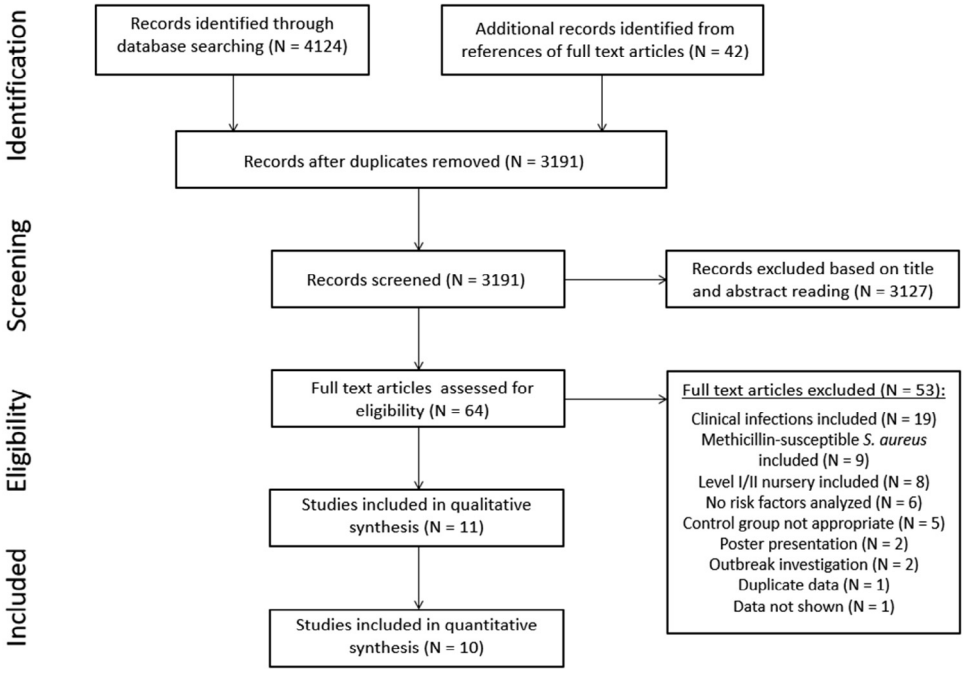

Fig 1. Study selection flow diagram. After screening for eligibility, 11 studies were included in the systematic review and 10 studies were included in the meta-analysis.