EDITORIAL

Is *Staphylococcus Aureus* Still a Problem in the Neonatal Intensive Care Unit?

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The study by Jennings et al[1] in this issue of *JAMA Pediatrics* adds to a body of literature indicating that *Staphylococcus aureus* remains one of the major causes of invasive infections in very low-birth-weight (VLBW, birth weight <1500 g) infants.

Related article

In the first decade of the 21st century, adoption of bundles of standard infection prevention practices helped decrease health care–associated infection rates such as central line–associated bloodstream infections in neonatal intensive care units (NICUs). However, after that initial decrease, rates appear to have plateaued in recent years, and declines have not been as clearly identified in freestanding children's hospital NICUs.[2,3] Another recent study examined the effect of maximized infection control measures implemented during COVID on all late-onset infections from 2018 to 2022.[4] In that study, which focused on the NICU's highest-risk group of extremely preterm infants less than 1000 g and less than 29 weeks' gestational age at birth, they did not find a change in *S aureus* infections.[4] The unchanged incidence of *S aureus* invasive infections in NICUs seen in these recent studies, compared to studies from earlier periods of time, highlights a disappointing lack of progress in reducing infection rates due to this pathogen, despite continued prioritization of efforts in NICUs.

Jennings et al[1] examined *S aureus* late-onset infection (>3 days after birth) defined as a positive culture of blood, cerebrospinal fluid, normally sterile body fluid, or abscess. There were 468 201 infants from 315 NICUs between 2016 and 2021 included with an incidence of *S aureus* infection of 0.4% for all NICU admissions, 2.3% for VLBW infants, and 6% for infants less than 750 g. Mortality occurred in *S aureus*–infected infants in 20.3% of infants less than 750 g, 14.3% for VLBW infants, and 5.3% for infants 1500 g or more. The study was able to look closely at timing and mortality, finding that for VLBW infants who died, nearly 90% occurred in the first 7 days after the infection was diagnosed. This yields opportunities for additional research to understand if the burden of mortality is due to bacterial exposure load, antibiotic selection, the neonatal immune system, or other factors related to the adjunctive care in response to sepsis provided to VLBW infants.

A limitation of this study is the lack of delineation of the proportion of methicillin-susceptible *S aureus* (MSSA) and methicillin-resistant *S aureus* (MRSA) and center-level differences in these relative proportions; such data would be useful to better understand the relative burden of these 2 types of bacteria and help drive more informed discussions of whether prevention efforts should be directed broadly against both or, alternatively, be attempted with a more limited scope. To better understand MRSA and MSSA in the NICU, we turned to neonatal studies such as those by Shane et al[5] and Ericson et al[6] showing MSSA causing a greater proportion of infections with similar mortality outcomes as MRSA infections, suggesting that there may be good rationale to target both types of *S aureus* in prevention efforts.

Ericson et al[6] used the same database to look at *S aureus* from 1997 to 2012 in 887 910 infants from 348 NICUs. They reported a 2.2% incidence compared to the 2.3% in VLBW infants in this study. That study had susceptibility information and was able to examine both MSSA and MRSA. Of 3978 infants that had at least 1 invasive *S aureus* infection, 72% were due to MSSA (n = 2868) and 28% due to MRSA (n = 1110). Mortality was similar in infants with invasive MSSA (9.6%) and MRSA infections (11.9%).

In a smaller multicenter study of 8444 VLBW infants, Shane et al[5] examined *S aureus* bacteremia and/or meningitis outcomes. The incidence of *S aureus* infection was 3.7% in VLBW infants, which is higher than the current study, with MSSA occurring in 2.7% (73%) and MRSA in 1% (21%) of patients. Of note, recognizing center-to-center differences, half the centers had no cases of MRSA. Similar to the study by Erikson et al, Shane et al demonstrated that mortality was equally high for MSSA (24%) and MRSA (26%).

Know When to Say No to Vancomycin

With improved recognition of the adverse short- and long-term consequences of unnecessary antibiotic exposure in neonates, antimicrobial stewardship is now an important aspect of NICU care. From the data discussed above, the incidence of MRSA infections has remained low, in that around 1 in 1000 of all NICU admissions and less than 1% of VLBW infants acquire a MRSA infection during their hospitalization. Some centers that in the past always used vancomycin as part of initial empirical therapy for late-onset sepsis evaluations have changed to using nafcillin for Gram-positive coverage except in cases when there has been know colonization (or a previous infection) with MRSA. This approach has been studied without adverse effects on short-term outcomes or mortality.[7-9]

This approach is important for more NICUs to consider adopting as recent studies have found that while MRSA is still susceptible to vancomycin, there is emergence of reduced vancomycin susceptibility that is associated with treatment failure.[10] Continued and repeated exposure of MRSA to vancomycin in infants with colonization may be leading to this reduced susceptibility. In a recent survey, NICUs that use vancomycin for empirical Gram-positive coverage for late-onset sepsis (>3 days after birth) evaluations found some

influencing factors being the presence of a central venous catheter and "critical illness" (which was not specifically defined).[11] While in the past, empirical therapy with vancomycin in patients with MRSA infection may have improved outcomes, this is not the case anymore.[10]

Improvements in blood culture detection have also helped antimicrobial stewardship. New data on time to positivity have shown that MRSA or MSSA can be isolated from blood culture by 24 to 36 hours, allowing for clinicians to change to vancomycin promptly after cultures are sent.[12] Stewardship efforts in patients evaluated for late-onset sepsis in NICUs where the approach continues to include empirical vancomycin for Gram-positive coverage suggest that infants with negative cultures could receive the last dose of vancomycin prior to 36 hours, since that dose will cover the late-onset sepsis evaluation time period through 36 hours or more, by which time blood culture results should be available based on time to positivity data. If antibiotics would be continued, nafcillin could be administered for that Gram-positive coverage.

Decolonization and Prevention

Recognition of the persistent burden of *S aureus* infection in this vulnerable premature infant population has led to targeted quality improvement efforts to mitigate these infections.[13] While hand hygiene and standardized bundles of care of devices remain the cornerstone of infection prevention, NICUs with high rates of MRSA colonization and invasive infections have implemented monthly or weekly surveillance efforts with nasal or rectal screening of colonized infants, to attempt decolonization. But recolonization is quite common in more than half of patients.[14] Some NICUs have extended these efforts to MSSA as well, especially if there is concern for outbreak, or high rates of invasive infections. Other NICUs have demonstrated, in a randomized clinical trial, that nonsterile glove use after hand hygiene with all patient and line contact in high-risk preterm infants decreases Gram-positive infections.[15]

Ongoing research efforts to perform bacterial sequencing to track introduction and transmission of *S aureus* continue to yield insight into transmission dynamics, which in turn can direct prevention efforts in a more guided manner. For example, Milstone et al[16] have shown that a substantial proportion of strains were shared between infants and parents in their single NICU and suggest a role for parental decolonization along with infants. Other studies suggest that health care worker decolonization might be an important adjunctive strategy especially in an outbreak setting.[17] As these measures get adopted in larger numbers of NICUs, it will be important to collect data on the impact of these interventions.

Many unresolved questions remain around the benefits and costs of targeted decolonization strategies to eliminate *S aureus* colonization, and whether this will lead to the intended effect of a decrease in invasive infections, or might in fact lead to development of resistance to antimicrobials, or replacement and infections caused by other bacterial pathogens. The lack of change in the incidence mediated by enhanced infection prevention measures suggests the need for novel strategies to further reduce the incidence and burden of *S aureus* infections. For example, oral care with expressed breast milk and its effect on *S aureus* colonization and infection is an understudied area.[18] Potential research avenues for new interventions could also include approaches to target decolonization of highly pathogenic strains of *S aureus* or populate infant microbiomes with nonpathogenic bacteria.[19]

This study is a strong reminder that *S aureus* infections are a key unsolved issue for NICUs that require further research and iteration of improvement efforts. Future epidemiological studies should measure the presence and nature of surveillance and decolonization efforts as important variables while analyzing trends in rates of *S aureus* infections. It will also be important to assimilate data on antibiotic exposure, especially vancomycin, to understand the impact of changing approaches to antimicrobial use on bacterial resistance and patient outcomes.

ARTICLE INFORMATION

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Published Online: April 14, 2025. doi:10.1001/jamapediatrics.2025.0437

Conflict of Interest Disclosures: None reported.

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