A .gov website belongs to an official government organization in the United States. A lock ( ) or https:// means you've safely connected to the .gov website. Share sensitive information only on official, secure websites. Evidence Summaries from the Recommendations for Prevention and Control of Infections in NICU Patients: S. aureus (2020) guideline. Key Question 1. What are effective strategies for preventing S. aureus transmission from colonized or infected NICU patients to other patients, and do these strategies differ between MRSA and MSSA or in the setting of an outbreak? Key Question 2. If active surveillance is conducted, which anatomic sampling sites and laboratory assays most effectively identify S. aureus colonization in NICU patients? To address these questions, studies were considered that examined interventions for the prevention of transmission of S. aureus, including methicillin-resistant S. aureus (MRSA) or methicillin-sensitive S. aureus (MSSA), from colonized or infected NICU patients to other patients. The search strategy predominantly identified studies describing multiple infection prevention and control strategies implemented simultaneously or sequentially. In multi-intervention studies, it is not possible to distinguish the effectiveness of individual interventions, and it is likely that a combination of interventions led to any reported reductions in healthcare-associated transmission of S. aureus. The interventions described in these studies include core infection prevention and control strategies, institution of preemptive Contact Precautions, changes in hand hygiene protocols, use of polymerase chain reaction (PCR) compared to conventional culture for testing, active surveillance testing, and decolonization of NICU patients. The benefits weighed in evaluating the evidence included the outcomes of reduction in S. aureus infection, colonization, and transmission (a composite measure including both infection and colonization), attributable mortality, and length of stay. Harms included the outcomes of antimicrobial resistance and product-related adverse events. The outcome deemed critical to decision-making was reduction in S. aureus infections. For the purposes of this analysis, healthcare-associated transmission within the NICU is

suggested by an increase in cases of S. aureus colonization or infection as determined by cultures obtained for clinical indications or surveillance purposes. The evidence for these questions consisted of 20 observational studies.[2–9,11,17,23,32,38,52–58] The findings of the evidence review and the grades for all critical and important outcomes are provided in the Appendix. (Appendix Section 3.) The search identified 12 observational studies [2–5,7,8,11,32,54–56,58] that implemented multiple infection prevention and control strategies simultaneously to prevent and control S. aureus transmission. Nine studies[3–8,32,55,56] implemented multi-intervention strategies to prevent MRSA: 2 in the outbreak setting,[3,6] and 7 in the non-outbreak setting.[4,5,7,8,32,55,56] One study[54] implemented multi-intervention strategies to prevent MSSA in the non-outbreak setting, and 2 non-outbreak studies[2,58] implemented these strategies to reduce S. aureus transmission. For the purposes of this analysis, multi-intervention infection prevention and control strategies included a combination of the following interventions: All studies retrieved in this analysis implemented a combination of some or all of these interventions. The independent effect of each of these interventions cannot be determined due to the concurrent implementation of the measures. The optimal combination of infection prevention and control strategies could not be determined because all studies implemented different combinations of infection prevention and control strategies in both the endemic and outbreak settings and reported heterogeneous outcome measures. It is notable that all 7 studies[2,8,10,32,54–56] that reported a reduction in S. aureus, MRSA, or MSSA infections included the intervention of infant decolonization. In these studies, infant decolonization was frequently implemented after other infection prevention and control strategies were not successful in controlling transmission. The added implementation of Contact Precautions for MRSA, versus Standard Precautions alone for MSSA, is the primary difference in the infection prevention and control strategies implemented between studies. The evidence suggests a benefit to implementing multiple infection

prevention and control strategies to reduce S. aureus transmission. This conclusion is based on overall reductions in S. aureus infections[2,8,10,32,54,56] and the composite outcome of transmission, which included both infected and colonized infants.[6] The benefit of implementing multi-intervention strategies to reduce S. aureus colonization as a sole outcome measure could not be determined due to inconsistency in results across studies[4,5,32,55]; however, the results of one study[4] suggesting no benefit in the endemic setting were likely confounded by the emergence of an outbreak strain. The overall quality of this evidence was rated as low. The harms data reported in these studies was limited. One study[7] reported no difference in unadjusted length of stay and attributable mortality. (Appendix Section 3.A.1.a., Table 11) Three studies[3,6,8] suggest a benefit to implementing multi-intervention strategies to reduce MRSA transmission. However, the evidence suggests mixed results regarding the benefit of implementing multi-intervention strategies to reduce MRSA infections and colonization.[4,5,7,8,32,56,58] It is notable that 2 of the 3 studies reporting the outcome of MRSA transmission were conducted in the outbreak setting, and both of these studies[3,6] reported a reduction of transmission. Again, data were limited on harms, and only one study[7] reported no change in unadjusted length of stay and attributable mortality. A reduction in MRSA transmission was seen in 2 studies[3,6] conducted in the outbreak setting. The combination of interventions implemented in the outbreak and non-outbreak setting were similar. (Appendix Section 3.A.1.a., Table 12) Multi-intervention strategy data are limited for MSSA, with only one study[54] suggesting a reduction in MSSA bacteremia following the implementation of multiple infection prevention and control strategies. No harm outcomes were reported for this comparison. (Appendix Section 3.A.1.a., Table 13) Recommendations on strategies considered foundational to infection prevention and control across healthcare settings can be found in the Core Infection Prevention and Control Practices for Safe Healthcare Delivery in All Settings – Recommendations of the HICPAC (2017) document.[1] In the

setting of endemic MRSA, there is limited evidence of benefit to implementing preemptive Contact Precautions for outborn infants until their colonization status is confirmed as negative. A decrease in MRSA transmission rate was observed after implementation of preemptive Contact Precautions; however, this evidence consisted of one study[52] which also reported a 25% increase in hand hygiene compliance during the intervention period, likely confounding the results. This study did not report adjusted morbidity or attributable mortality. (Appendix Section 3.A.1.b., Table 14) Evidence from one study[53] suggests benefit to implementing a new hand hygiene protocol which incorporated multiple policy changes, including implementing universal glove use and changing the cleansing agent from a chlorhexidine hand wash to a chlorhexidine-alcohol hand rub. This study[53] found a decrease in the incidence of MRSA septicemia with the institution of this new hand hygiene protocol. No changes in either mean length of stay or infection-related mortality were associated with the implementation of the interventions associated with this policy. (Appendix Section 3.A.1.c., Table 15) Active surveillance testing of NICU patients to identify newly-colonized infants to guide implementation of infection prevention and control measures, such as Contact Precautions or decolonization, has been shown to be of benefit in the context of an outbreak, increased incidence of infection, or ongoing healthcare-associated transmission.[2,4,5,8–11,58] Observational studies report decreased incidence of infection and colonization. In most studies, the anterior nares were sampled; the umbilicus, rectum, axilla, and groin were also sampled. (Appendix Section 3.A.1.d.) The evidence retrieved suggests that implementation of active surveillance testing to guide implementation of infection control strategies results in a reduction in S. aureus infection[2,4,7–11] and transmission.[3,6] The evidence of benefit was inconsistent for the outcome of S. aureus colonization.[2,4,5,58] The quality of evidence for these outcomes was rated as low. (Appendix Section 3.A.1.d., Table 16) There was evidence of reduction in MRSA transmission after using active surveillance

testing to guide implementation of multiple infection prevention and control strategies. Two of the 3 studies[3,6] reporting this outcome were conducted in the outbreak setting. The evidence suggests no reduction in MRSA infections with the implementation of active surveillance testing. Two studies reported the outcome of MRSA colonization, and the results were inconsistent.[4,58] (Appendix Section 3.A.1.d., Table 17) Two non-outbreak studies[9,11] employed active surveillance to guide the implementation of infection prevention and control measures to prevent MSSA. One study[9] implemented decolonization of MSSA-colonized infants, and the other study[11] provided decolonization to very low birthweight infants with central venous or peripheral catheters. Both reported reductions in composite MSSA infections[9] or MSSA bloodstream infection (BSI) and pneumonia.[11] (Appendix Section 3.A.1.d., Table 18) Thirteen studies reported varying frequencies of active surveillance testing to detect S. aureus colonization in NICU infants. In these studies, active surveillance testing was performed: One study[32] implemented routine surveillance on a monthly basis, and one tested all intubated patients weekly and added admission screening for "increased burden."[58] The interventions implemented for patients following results of surveillance cultures also varied among the studies, which affects the interpretability of the results. (Appendix Section 3.A.1.e.) Five studies found a reduction in S. aureus infection from implementing active surveillance testing on admission and weekly thereafter. Two of these studies[2,17] conducted admission screening for all infants, and 3 conducted admission screening for outborn infants only.[8–10] One non-outbreak study[7] implementing active surveillance testing on admission and weekly for all infants found no reduction in MRSA infections. The choice of the optimal target population for conducting active surveillance testing can be guided by epidemiology in the facility and unit. (Appendix Section 3.A.1.e., Tables 19 – 22) The interpretability of the impact of conducting weekly surveillance testing is limited due to inconsistent results in the outcomes of infection and colonization across studies.[4,11,58] These

studies were conducted in the non-outbreak setting; however, one study4 saw reductions in MRSA colonization that were not sustained during a period of overcrowding and the introduction of a new MRSA strain. One outbreak study3 suggested a benefit to implementing admission screening for all infants in the outbreak setting. (Appendix Section 3.A.1.e., Tables 21 – 25) To address this question, studies providing test characteristics for the detection of S. aureus were critically reviewed. The available data on detection of S. aureus examined the characteristics of tests and the choice of anatomical sites for sampling for active surveillance testing for S. aureus. Laboratory methods available to detect S. aureus colonization included culture-based methods and molecular testing methods. The evidence consists of one diagnostic study examining S. aureus colonization[19] and 5 diagnostic studies examining MRSA colonization.[18,20–22,57] (Appendix Section 3.A.1.f. – 3.A.1.g.) One diagnostic study19 compared assays to detect S. aureus and reported higher sensitivity and negative predictive value for real-time PCR than for culture-based methods using broth enrichment techniques. Results for specificity and positive predictive value to detect S. aureus were the same for PCR and culture. In this study, culture-based methods were used as the reference standard upon which the results were calculated. While this study conducted susceptibility testing, results were reported in aggregate for S. aureus, and not for MRSA or MSSA. (Appendix Section 3.A.1.f., Table 26) Evidence from 2 diagnostic studies[18,20] suggests high sensitivity, specificity, and negative predictive value of PCR for detecting MRSA. However, evidence from both studies suggested that the positive predictive value of PCR was low. In the study finding a positive predictive value of 41%,[18] 7 PCR-positive results were negative on culture: 5 of the 7 cultured positive for MSSA via nasal swabs. In these studies, culture-based methods were used as the reference standard upon which the results were calculated. (Appendix Section 3.A.1.f., Table 27) One observational outbreak study[38] found a benefit to changing from culture-based testing methods to real-time PCR testing to analyze active surveillance

samples during an MRSA outbreak. This study reported a decrease in both the MRSA infection rate and the MRSA transmission rate. This study also reported moderate compliance with hand hygiene protocols and Contact Precautions and did not assess any adverse events. (Appendix Section 3.A.1.f., Table 28) IMPLEMENTATION CONSIDERATIONS Although PCR may have higher sensitivity, multiple considerations influence which test a facility may use to screen for S. aureus colonization. These include, but are not limited to, outbreak identification; turnaround time; performance characteristics of the test; use in clinical management; the number of specimens combined with the capabilities of the laboratory providing the service; and resource utilization. Depending on laboratory capacity, molecular diagnostic testing methods such as PCR may be more useful in circumstances such as identifying an outbreak when there may be an increased volume of cultures to process and a faster turnaround time is needed. However, culture-based methods provide the benefit of lower cost and the ability to assess pathogen susceptibility patterns to guide patient treatment, and to assess genetic relatedness of other strains for outbreak detection. Either PCR or culture-based methods are acceptable, and facilities and providers can balance these situation-specific needs to select the assay that best benefits their NICU patients. Evidence from 3 diagnostic studies[21,22,57] demonstrated that swabs taken from the nares had higher sensitivity and negative predictive value for MRSA than swabs taken from the umbilical and rectal areas. While one study[22] concluded that nasal cultures are sufficient to detect MRSA in the majority of colonized neonates, another study[21] suggested that sampling from 2 sites would increase sensitivity. (Appendix Section 3.A.1.g., Table 29) The literature search did not reveal studies that provided test characteristics for the detection of MSSA; data on the appropriate target populations; or the ideal timing or frequency for active surveillance testing for S. aureus. The literature search did not reveal studies examining the optimal anatomical site for detection of S. aureus or MSSA. IMPLEMENTATION CONSIDERATIONS The available evidence suggests

that the nares samples will yield high sensitivity when screening NICU patients for MRSA and that other sites can be sampled to optimize sensitivity of screening strategy. Although evidence on performance of various biologic samples for detecting MSSA and S. aureus is not available, it is likely that evidence for MRSA applies due to biologic similarities. In general, testing and sampling strategies that apply to MRSA also apply to MSSA; however, future research may provide greater insight into this issue. Eliminating the carrier state was associated with decreases in infections and colonization in the NICU when there was evidence of ongoing healthcare-associated transmission and when there was increased incidence of infection.[9–11,18] No studies retrieved by this literature search examined these interventions as a stand-alone strategy in outbreak settings. In 5 studies,[9–11,17,23] all colonized infants received decolonization. Two of these studies[9,10] were conducted in the same facility at different time periods and found this strategy was associated with reductions in S. aureus infections. One study[10] observed reductions in infections, but not reductions in colonization of other NICU patients. One study[11] that provided prophylactic decolonization and chlorhexidine bathing only to very low birthweight (VLBW) infants with central venous and peripheral venous catheters found reductions in S. aureus infections in all infants in the NICU. Two studies[9,10] that provided all NICU patients mupirocin decolonization, regardless of colonization status, found reductions in S. aureus infections in all NICU patients. (Appendix Section 3.A.1.h.) The literature search did not retrieve studies that compared different decolonization strategies or regimens in NICU patients. Four studies[9–11,23] examined the implementation of decolonization of colonized infants, and all found reductions in S. aureus infections. Two of these studies[9,10] were performed in a single center NICU population and examined the impact of infant decolonization on MSSA[9] and on S. aureus as a whole.[10] One study[23] found no difference in MRSA colonization between the group that was decolonized and the group that was not decolonized. The fourth study[11] found reductions in MSSA-attributable

infections after implementing surveillance and decolonization of only MSSA-colonized infants with IVs. All of these studies were conducted in non-outbreak settings. (Appendix Section 3.A.1.h., Tables 30 – 32) Two studies[11,17] examined prophylactic use of decolonization agents. One[11] targeted VLBW infants with central and peripheral lines with intranasal decolonization and chlorhexidine bathing, and one[17] decolonized all infants in the NICU every 5 weeks with intranasal mupirocin. Both found a reduction in S. aureus infections; however, the prophylactic decolonization regimens and choice of agents were too dissimilar to determine the optimal prophylactic strategy. (Appendix Section 3.A.1.h., Table 33) Decolonization regimens varied across the studies and included intranasal mupirocin[17]; mupirocin ointment applied to the nares and umbilicus[23] or to the nares, umbilicus, eroded skin, and wounds[2]; intranasal mupirocin with chlorhexidine bathing for select patients[9,10]; and intranasal mupirocin and octenidin washes.[11] Octenidin is not approved by the US Food & Drug Administration (FDA) for use in US healthcare settings. All studies suggested reductions in S. aureus infection and transmission. (Appendix Section 3.A.1.h., Tables 30 – 33) Two studies[11,23] examined adverse events associated with the decolonization protocols, and found none. Safety concerns exist, however, for the 2 most commonly utilized decolonizing agents. The FDA has not determined the safety and effectiveness for intranasal mupirocin in children younger than 12 years of age. Specifically, the FDA-approved drug label states that pharmacokinetic data in neonates and premature infants suggests that significant systemic absorption can occur following intranasal administration of mupirocin. Additionally, chlorhexidine bathing products may be used "with care" in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns in these patients. (Appendix Section 3.A.1.h., Tables 30 – 33) Four studies[2,9,17,23] examined S. aureus isolates for increased antimicrobial resistance to the decolonizing agent during the study period. Two studies[9,23] examined resistance after the implementation of targeted decolonization of colonized

infants and found no increase in resistance associated with targeted decolonization. Two studies[2,17] examined resistance after the implementation of a universal decolonization strategy that prophylactically decolonized all NICU infants. One study[2] reported no resistance, and the other[17] reported a small increase in mupirocin resistance associated with universal decolonization. The studies that reported mupirocin resistance evaluated the development of resistance over shorter periods of time. There is greater concern regarding the evolution of harms, such as resistance to the decolonizing agent, if it is applied broadly to an entire population in a unit. (Appendix Section 3.A.1.h., Tables 30 – 33) There are concerns that decolonization can have farther-reaching effects than resistance and can alter the microbiome of NICU patients. One study reported that while the authors could not exclude the possibility of pathogen replacement, they found no changes in either the central line-associated bloodstream infection (CLABSI) rate or the pathogen distribution contributing to CLABSIs among infants who were decolonized with mupirocin.[17] (Appendix Section 3.A.1.h., Tables 30 – 33) Key Question 3. What are the risk factors and risk indicators for S. aureus infection in NICU patients, and do they differ between MRSA and MSSA or in the setting of an outbreak? Key Question 4. What are the risk factors and risk indicators for S. aureus colonization in NICU patients, and do they differ between MRSA and MSSA or the setting of an outbreak? The evidence retrieved for non-modifiable risk factors and risk indicators consists of 29 observational studies. Many of the studies reported differences in the presence of these characteristics between S. aureus-positive and S. aureus-negative infants; however, these results were not statistically significant. Additionally, many possible risk factors and risk indicators were assessed in only one study, which precludes drawing conclusions as to their importance. Several studies reported composite outcomes of colonization or infection rather than reporting colonization and infection rates separately, which hinders the ability to assess the association of risk factors and risk indicators with each specific outcome. A summary of

the evidence on risk factors and risk indicators analyzed in at least 2 studies follows. The findings of the evidence review and the summary of potential risk factors and risk indicators across studies are provided in the Appendix (Appendix Section 3.B.) Lower birthweight[2,33,60–62] and younger gestational age[2,33,60] were reported to be significantly associated with S. aureus and MRSA infection in NICU patients. An association was reported between prior colonization and S. aureus infection,[2,23] while sex[2,61–63] was not associated with S. aureus infection; one of these studies[62] analyzed a composite outcome that included colonization. Inconsistent results across studies suggest an unclear association between race[60,62] and multiple gestation[33,60] for S. aureus and MRSA infection. Data were limited to formulate any conclusions regarding risk factors and risk indicators for MSSA infection; however, 3 studies[26,30,64] compared risk factors and risk indicators for MRSA and MSSA infection. These studies found a significantly higher incidence of MSSA infections in older infants; however, gestational age was not different between these infants, suggesting that a longer length of stay may affect an infant's likelihood of acquiring MSSA infections when compared with MRSA infections. Only one study[33] examined risk factors and risk indicators for MRSA infections in the outbreak setting, which was insufficient to formulate conclusions regarding the differences between risk factors and risk indicators for infection between the endemic and the outbreak settings. (Appendix Section 3.B.1., Tables 42 – 45) Multiple gestation[33,60,65] and administration of antibacterial therapy[65,66] were significantly associated with MRSA colonization. It is notable that administration of antibacterial therapy is a potentially modifiable risk factor to prevent MRSA colonization; however, infants in the NICU are severely ill, and administration of these antibiotics is necessary and likely unavoidable. The literature search did not retrieve any studies demonstrating the optimal duration of antibiotic therapy to prevent MRSA colonization; thus, no recommendation can be formulated to guide practitioners on the duration of systemic antibacterial therapy that may prevent

MRSA colonization. (Appendix Section 3.B.1.b., Table 46) As with MRSA infection, lower birthweight was associated with MRSA colonization[21,23,33,38,41,60,62,65,67]; it should be noted that 3 of these studies[38,62,67] analyzed composite outcomes that included infection. Age at NICU admission,[21,23,62,65,68] delivery method,[4,45,66,68,69] gender,[21,23,41,45,60,62,66–74] race,[62,67–69,73,74] maternal age,[68,69] malformation,[4,65] the presence of a central venous catheter or endotracheal intubation,[63,66,68,70] and occurrence of surgical procedures[66,68] were not associated with MRSA colonization. Due to conflicting results across studies, there was unclear association between MRSA colonization status and gestational age,[4,21,23,33,41,45,60,65,66,68–71,74] inborn status,[4,21,23,41,45,60,65,66,74,75] Apgar score,[4,65,69,70] retinopathy of prematurity,[68,71] length of NICU stay,[65,66,73] and healthcare personnel hand hygiene[68,76] compliance. Lower birthweight[33,38,67] is the only risk factor found in the literature for MRSA colonization in the outbreak setting. This association may be confounded because 2 of these studies[38,67] analyzed composite outcomes that included infection. (Appendix Section 3.B.1.b., Table 46 – 52) No risk factors or risk indicators for MSSA colonization in NICU patients were found in the literature. Younger gestational age,[77,78] birthweight,[68,78] delivery method,[68,77] gender,[68,78] healthcare personnel hand hygiene compliance,[68,77] presence of central venous catheter,[20,74] and occurrence of surgical procedure[63,64] were not associated with MSSA colonization in the available evidence. There was an unclear association between Apgar score[77,78] and MSSA colonization due to conflicting results across studies. Data were limited to confer any difference in risk factors and risk indicators for MSSA colonization status between the endemic and outbreak settings. (Appendix Section 3.B.1.c., Table 53 – 58). Additional studies would elucidate modifiable risk factors and risk indicators for S. aureus transmission and infection to test novel interventions to prevent S. aureus disease. CDC provides information on infection control and clinical safety to help reduce

the risk of infections among healthcare workers, patients, and visitors. Languages Language Assistance Languages Language Assistance

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