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One Size Does Not Fit All: Why Universal Decolonization Strategies to Prevent Methicillin-Resistant *Staphylococcus aureus* Colonization and Infection in Adult Intensive Care Units May Be Inappropriate for Neonatal Intensive Care Units

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Healthcare-associated infections (HAIs) are a significant concern for patients and medical institutions due to the morbidity, mortality, and financial burden associated with their occurrence. *Staphylococcus aureus* has been implicated as the most common source of HAIs, with many of those infections due to methicillin-resistant strains.[1] Methicillin-resistant *S. aureus* (MRSA) is a frequent source of infections in the neonatal intensive care unit (NICU). The National Nosocomial Infections Surveillance System found that the incidence of late-onset MRSA infections in NICUs dramatically increased by 308% from 0.7 to 3.1 infections per 10,000 patient-days between 1995 and 2004.[2] Since colonization with MRSA is a strong risk factor for subsequent development of invasive MRSA infection,[3] prevention of MRSA transmission within NICUs is critical. Individual NICUs have adopted various combinations of surveillance, special precautions, and decolonization strategies to minimize the spread of MRSA between patients in an attempt to reduce HAIs. These approaches have had varying rates of success, and an optimal method has not been validated by a rigorous randomized controlled trial.

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Numerous strategies to reduce MRSA colonization and decrease invasive infections have been utilized in adult intensive care units (ICUs). Recently, results from the REDUCE MRSA Trial (Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate Methicillin-Resistant *Staphylococcus aureus*) were published.[4] This large multicenter, randomized controlled trial compared the efficacy of three surveillance and decolonization strategies for reducing MRSA colonization and infection in adult ICUs. The study was a cluster-randomized trial where individual hospital ICUs were randomly assigned to one of three intervention groups: 1) MRSA screening and isolation, 2) targeted decolonization based on results of MRSA screening, and 3) universal decolonization of all admitted patients. Decolonization procedures lasted five days and included daily baths with chlorhexidine cloths and twice daily application of intranasal mupirocin. Proportional hazards models were utilized for analysis. The primary outcome assessed was ICU-attributable MRSA-positive clinical cultures, and secondary outcomes included ICU-attributable blood stream infections caused by MRSA or any pathogen. Universal decolonization was found to be the most effective intervention, associated with a 37% reduction in rates of MRSA-positive clinical cultures and a 44% reduction in bloodstream infections from any pathogen. The large reduction in rates of bacteremia due to any pathogen were likely attributable to the use of chlorhexidine similar to other studies.[5]

In direct response to this report, the Agency for Healthcare Research and Quality (AHRQ), along with the Centers for Disease Control and Prevention, published an enhanced protocol for universal ICU decolonization based on the strategies outlined in the REDUCE MRSA Trial.[6] The protocol includes educational materials, training information, skills assessment tools, and product safety information regarding universal decolonization with chlorhexidine and mupirocin. The protocol is intended to serve as a step-by-step instructional guide for acute care hospitals interested in implementing similar universal decolonization strategies in their own adult ICUs.

Despite the successes reported by the REDUCE MRSA Trial and the publication of the Universal ICU Decolonization protocol by AHRQ, caution should be exercised before similar approaches are universally adopted in all hospital ICUs. In particular, NICUs should be especially vigilant regarding implementation of such interventions, as their unique patient population is very different from adults. The adage “children are not just small adults” is often cited when interventions and policies that have been tested in adult medicine are considered for application in pediatrics. Infants and adults do not necessarily have the same outcomes when treated with the same therapies, and the efficacy and safety of treatments initially tested on adults need to be validated in infants and children prior to widespread utilization. Additionally, a major concern regarding the potential adoption of the decolonization strategies employed by the REDUCE MRSA Trial in NICUs is the potential for adverse events associated with widespread chlorhexidine and mupirocin use, particularly in preterm infants.

Chlorhexidine is a widely used broad-spectrum topical antiseptic agent.[7] The Centers for Disease Control and Prevention recommend its use as a skin cleanser prior to insertion of central venous catheters in children and adults, but do not recommend its use in infants less than 2 months of age due to lack of safety and efficacy data.[8] The Food and Drug

Administration modified drug labeling for 2% chlorhexidine gluconate cloths to include "use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns." [9] Despite these cautions, a national survey of neonatology training program directors revealed that most NICUs use chlorhexidine, most commonly for central venous catheter site preparation and maintenance, but often restrict its administration based on gestational age, chronological age, and/or birth weight.[10] Premature infants could be especially prone to development of adverse events secondary to chlorhexidine exposure due to their underdeveloped and highly permeable skin leading to both local toxicity and systemic absorption, their reduced ability for metabolism and clearance of drugs, and their vulnerable and immature neurologic system.[7]

Chemical burns and severe contact dermatitis have been reported in association with topical application of chlorhexidine in extremely premature infants.[7, 11, 12, 13] Garland et al studied the use of chlorhexidine-gluconate impregnated disks placed under occlusive dressings for prevention of central venous catheter associated infections and found that 15 (15%) of 98 premature neonates with weight less than 1000 grams developed localized contact dermatitis at the site of the dressing.[11] Infants with gestational age <28 weeks and <one week of age were most vulnerable to developing chlorhexidine-associated dermatitis.[11] Although not all studies have observed dermal changes,[14, 15] there have also been reports of premature neonates developing dermatitis in conjunction with bathing with aqueous [12] and alcohol-based [13] chlorhexidine solutions. The mechanism(s) of how chlorhexidine might cause skin irritation in premature infants is unclear. Research is needed to explore the relative risks associated with the type of chlorhexidine, the accompanying vehicle, its application, and exposure length and dose.

Systemic absorption of chlorhexidine by premature neonates and the potential for associated toxicities is another concern. In the 1970s, a related phenol-derivative topical antiseptic agent, hexachlorophene, was widely used for bathing infants to prevent colonization and infection with *S. aureus*. It was later found to be systemically absorbed through the skin, particularly the skin of premature neonates, and was associated with central nervous abnormalities, seizures, and, in some preterm infants, a vacuolar encephalopathy.[16, 17, 18] Several studies have reported detectable blood levels of chlorhexidine in premature infants exposed to topical chlorhexidine.[7, 14, 19, 20, 21] Although no adverse events were reported in any of these cases, chlorhexidine use in this population has been scrutinized. There are no established safe levels of chlorhexidine in the blood and the long-term clinical significance of its systemic absorption is unknown.[7] While the use of chlorhexidine might be beneficial in terms of reducing risk of bacterial infection, it should be used cautiously in premature neonates until more data, especially long-term safety profiles, exist regarding its safety.

Widespread use of universal decolonization strategies employing mupirocin and chlorhexidine in NICUs could lead to the development of antimicrobial resistance. Although there have been conflicting reports,[22] a recent national surveillance study of *S. aureus* in the United States found that high-level mupirocin resistance increased from 2.2% to 3.2% between 2009 and 2011 (P=0.006),[23] a significant and concerning increase. The authors hypothesized that both rates of intranasal mupirocin use and mupirocin-resistant bacteria are likely to increase following widespread adoption of the universal decolonization strategies

utilized in the REDUCE MRSA Trial.[23] Chlorhexidine resistance in strains of *S. aureus* has also been described.[24]

Individual NICUs have adopted many different approaches to attempt to reduce rates of endemic or epidemic MRSA colonization and infection within their unit, with adoption of additional strategies during MRSA outbreaks. These have included varying combinations of enhanced promotion of hand hygiene, strict infection prevention precautions, intermittent and/or longitudinal surveillance screening of patients, parents, or healthcare personnel (HCP), epidemiologic tracking, cohorting of patients and/or HCP, and a variety of decolonization strategies.[25, 26, 27] Decolonization strategies, utilized primarily in NICUs experiencing epidemic MRSA infection, have included chlorhexidine bathing of infants, parents, or HCP, and topical mupirocin administration to patients, parents, and HCP.

The reported success of these differing strategies has been variable in individual NICUs. Universal guidelines for controlling endemic or epidemic MRSA colonization and infection in NICUs are lacking. In 2006, a Chicago-Area Neonatal MRSA Working Group (CANMWG) published a consensus statement with recommendations regarding strategies for controlling MRSA spread in NICUs.[28] Their recommendations included promoting hand hygiene, periodic neonatal surveillance cultures, and cohorting and isolating MRSA-positive infants under contact precautions.[28] They endorsed additional strategies to control MRSA outbreaks, including screening cultures of HCP, environmental cultures, and investigating strain-relatedness of MRSA isolates with molecular analyses. Their recommendations regarding decolonization were less strong. “Mupirocin may be used for decolonization of neonates and/or healthcare workers if deemed necessary by the affected institution (off-label use).” [28] They also advised open communication within NICUs, between regional NICUs, and between the hospital and public health officials in order to facilitate coordination of prevention and eradication efforts.[28]

Many NICUs have adopted their own MRSA control strategies. A recent survey of members of the Society for Healthcare Epidemiology of America (SHEA) regarding their practices for MRSA identification and eradication in the NICU revealed that most respondents (86%) performed surveillance screening for MRSA in neonates.[29] However, there was significant variation in timing of screening, anatomic sites sampled, isolation protocols, and decolonization strategies.[29] Several large NICUs have reported their own individual experiences and outcomes with well-organized, long-term MRSA surveillance programs and/or decolonization procedures.[30, 31, 32]

As MRSA colonization and infection continue to become increasingly common in the NICU, it is imperative that the most effective practices for controlling MRSA are identified and validated. This will not be a simple task. Risk factors for MRSA colonization and infection vary in hospitalized infants. There are temporal and regional differences in MRSA strain types between NICUs. Routes of entry of MRSA into the NICU are variable and pathways of transmission are complex. While colonized infants are the primary endogenous reservoir of MRSA in the NICU, their relatives, fomites, and healthcare providers may also participate in transmission. Variation in NICU organization, structure, and staffing may influence MRSA colonization and invasive infection.

It is time to begin designing a multicenter trial in an effort to discern a clear path forward for patients hospitalized in NICUs, similar to the REDUCE MRSA trial for patients hospitalized in adult ICUs. A randomized controlled trial, not yet underway, will assess safety and efficacy of neonatal decolonization with a 5-day course of mupirocin (NCT01827358). Additional trials are needed to evaluate the efficacy, safety-both short and long-term, and cost effectiveness of education initiatives, surveillance programs, and decolonization strategies, as well as longitudinal trends in colonization, invasive infection, and patterns of antibiotic susceptibility. Neonatologists, infectious disease specialists, pharmacists, nurses, infection preventionists and epidemiologists, and hospital administrators need to join together to determine the best strategy for management of MRSA colonization and infection in the NICU. The babies, the smallest, sickest, and most vulnerable ICU patients in the hospital, deserve it.

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