# Methicillin-resistant *Staphylococcus aureus* Decolonization in Neonates and Children

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*Staphylococcus aureus* is a leading pathogen of nosocomial infections in neonates, children and adolescents. In addition to skin and soft-tissue infections (SSTI) and surgical-site infections, invasive infections may occur (bloodstream, osteomyelitis, septic arthritis, device-associated infections such as ventilator-associated pneumonia). Colonization with *S. aureus* increases the risk of *S. aureus* wound infection after cardiac surgery (sternotomy). *S. aureus* may cause community-acquired pneumonia in children.

Once colonized, some neonatal and pediatric patient populations face an increased risk of subsequent methicillin-resistant *S. aureus* (MRSA) infection, mainly those with underlying severe skin diseases, those who need recurrent antibiotic treatments, intensive care,[1] medical devices (catheters, drains and mechanical ventilation) and surgical interventions, children who are immunocompromised or depend on long-term medical care caused by severe neurodevelopmental impairment.

## *S. AUREUS* AND HEALTH CARE–ASSOCIATED MRSA

Ten to 25% of previously colonized high-risk children develop an MRSA infection. However, it is important to emphasize that methicillin-sensitive *S. aureus* (MSSA) causes the great majority of *S. aureus* nosocomial infection. Notwithstanding, health care–associated methicillin-resistant *S. aureus* (HA-MRSA) has been increasingly detected as nosocomial pathogen in neonatal and pediatric patients. Methicillin-resistance *per se* does not seem to be an independent risk factor for increased mortality in patients who timely receive adequate antimicrobial treatment. Infants with MRSA infection (compared with MSSA infection) had a longer median duration of bacteremia (4.5 vs. 1 day; $P < 0.01$), but no difference in length of hospital stay, mortality or neurodevelopmental impairment. In invasive *S. aureus* infection in neonates (bacteremia or meningitis), mortality was high with both MRSA (26%) and MSSA (24%). In a surveillance study of 76 children, who were identified as MRSA colonized during their pediatric intensive care unit admission, the incidence of subsequent MRSA infection was 10% in the year after discharge.

The backbone of treatment in invasive MRSA infections in neonates and in children remains vancomycin. Prolonged treatment may induce adverse events such as nephrotoxicity and rarely ototoxicity. Guided by *in vitro* sensitivity, clindamycin, rifampicin, cotrimoxazole or fosfomycin are used in combination with vancomycin.

## COMMUNITY-ACQUIRED MRSA

In parallel to the rise of HA-MRSA, some countries faced a dramatic increase in SSTI caused by community-acquired CA-MRSA strains. These infections affected individuals with none of the previously known risk factors. Meanwhile, epidemic CA-MRSA clones expressing the Panton-Valentine leukocidin (PVL) virulence factor, such as the MRSA pulsed-field gel electrophoresis type USA 300 (SCC*mec* type IV), are detected in more than 50% of all *S. aureus* SSTIs in some regions of the United States. Subsequently, CA-MRSA has caused nosocomial outbreaks, for example, in neonatal intensive care units (NICUs) and nurseries in many countries.[2,3] Not only CA-MRSA but also some MSSA isolates can harbor the genes encoding PVL; interestingly, these MSSA isolates are related to recurrent SSTI in children and their close family contacts too.

## COLONIZATION, HOUSEHOLD TRANSMISSION AND ENVIRONMENTAL CONTAMINATION

*S. aureus* colonizes the anterior nares, throat, axillae, groins, intestine, chronic

Accepted for publication March 7, 2018.
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A.S. is the second chairperson of the German Commission for Hospital Hygiene and Infection Prevention (KRINKO), affiliated at the Robert Koch Institute, Berlin. A.S. has received research grants from Schuelke & Mayr (Nordersted, Germany) for the *in vitro* evaluation of Octeniderm for disinfection of needleless connectors. A.M. and T.D.: no conflict of interest to declare.
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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/18/3706-0612
DOI: 10.1097/INF.0000000000001982

The ESPID Reports and Reviews of *Pediatric Infectious Disease Journal* series topics, authors and contents are chosen and approved independently by the Editorial Board of ESPID.

wounds and skin entry sites of medical devices. *S. aureus* contaminates hands of patients and caregivers, hand contact surfaces, fomites and clothes/linen, bath towels and toys and is capable to persist on inanimate surfaces for weeks or months. A recent Canadian study investigated household MRSA transmission and calculated an equal risk for HA-MRSA compared with CA-MRSA (39% vs. 40%). In 1 study, including index children with MRSA SSTI (median age, 3.0 years), MRSA was recovered from environmental household surfaces in 46%, most frequently from the participant's bed linens (18%), television remote control (16%) and bathroom hand towel (15%). In addition, companion animals/pets living in the same household were colonized (dogs 12%, cats 7%).[4] Companion animals can transiently harbor the same MRSA strain as their close human contacts.

Taken together, *S. aureus* is easily transmitted from patient to patient in health care facilities but also within families and household members. Colonization of close contact individuals aids in recurrent colonization and subsequent infection in children after decolonization. As such, information and education on hygiene measures play a critical role in decreasing the risk of transmission and recurrent infection.

In most otherwise healthy children without chronic skin lesions or other risk factors, MRSA-colonization will subside after 6 months.[5] In a prospective surveillance study of index patients with CA-MRSA SSTI, only 20% remained colonized at 6 months. Patients with severe comorbidities, immunosuppression or other risk factors stay colonized for much longer periods without decolonization.

## MRSA DECOLONIZATION

The risk of subsequent infection in otherwise healthy neonates, infants and children colonized with HA-MRSA is low. This led to a consensus among most pediatric infectious disease specialists to offer HA-MRSA decolonization only to children (and there close household contacts) under certain circumstances (eg, severely immunocompromised household member with cancer chemotherapy). At least 1 cycle of MRSA decolonization should be offered to neonates and children colonized with PVL-positive CA-MRSA or with risk factors for HA-MRSA disease.

MRSA decolonization refers to a 5–7 day course of nasal mupirocin ointment plus external antiseptic whole body washings with a liquid soap or wash cloths containing antiseptics. In school age children, antiseptic mouthwashes (gargles) may be added to reach mucosal MRSA decolonization.

Decolonization aims at eradicating colonization to prevent MRSA infection or its recurrence. In health care settings, decolonization tries to reduce the risk of nosocomial transmission and can be performed during systemic antimicrobial therapy in children with MRSA infection. In most children without invasive devices (mechanical ventilation, nasogastric or percutaneous nutrition tubes and tracheostoma), this approach will be effective.

Recommended decolonization schedules show great variability concerning the choice of nasal ointments and antiseptic agents,[6] how often per day patients have to perform whole body washings and how many days a decolonization cycle comprises. In neonates and children, no ideal strategy referring to the results of prospectively randomized controlled studies is available, in particular, in terms of long-term efficacy after 6–12 months.

Mainly during outbreak management, nasal mupirocin ointment has been extensively used in neonatal and pediatric intensive care settings for MRSA decolonization, with acceptable efficacy (>70%). Though the use of mupirocin is off-label in small infants, many neonatologists recommend its use for this particular indication. Some reports point at difficulties concerning successful decolonization in premature infants and in general, the reported effectiveness of MRSA decolonization appears to be lower in this patient population (0–50%). This may be because of gastrointestinal MRSA colonization or a higher risk of external recolonization. In neonatal and pediatric intensive care, parents of MRSA positive patients should be tested and decolonized if MRSA positive to avoid recolonization of the patient.

The use of nasal mupirocin alone is probably not effective in preventing nosocomial MRSA transmission; also some studies in neonates report favorable long-term results for mupirocin concerning this off-label indication.

In contrast to the United States and some other countries (Canada, Australia and New Zealand), where chlorhexidine (CHX) is used for antisepsis and whole body washings in NICU, the use of CHX is not recommended for NICU patients in Germany. This debate continues[7] mainly for 2 reasons. Systemic absorption of CHX has been detected in children, who underwent daily bathing with 2% CHX-gluconate–impregnated cloths and in neonates after using CHX for local skin antisepsis. It is unknown whether systemic CHX exposure poses premature infants at an increased risk of long-term detrimental outcomes. Skin tolerability of CHX (> 0.5%) in extremely low–birth-weight infants is another aspect according to case reports and observations from controlled studies, which documented skin irritation (up to burn-like lesions), in particular, during the first week of life after dermal CHX exposure.[7] Sankar et al did not detect significant adverse effects after single skin cleansing with 0.25% CHX in neonates, but at this concentration, CHX was as effective as normal saline concerning subsequent skin colonization. Some neonatologists restrict the use of CHX washings to infants older than 30 days or those greater than 36 weeks of gestation. Unfortunately, the NICU subpopulation with the most vulnerable skin faces the greatest risk of MRSA infection.

Referring to an orphan drug approval by the European Medical Agency, octenidine dihydrochloride 0.1% is used as an alternative antiseptic for MRSA decolonization. Its antimicrobial spectrum is equivalent to CHX, and no systemic absorption has been documented. Octenidine shows good activity against epidemic MRSA strains and displays an antiseptic remanence effect on human skin. Buehrer et al evaluated the tolerability of an octenidine 0.1%/phenoxyethanol 2% preparation in 25 infants < 27 weeks' gestation. The antiseptic was well tolerated, but phenoxyethanol was readily absorbed by the newborn's skin and underwent metabolism to 2-phenoxyacetic acid, eliminated in urine. The current German recommendation suggests to use 0.1% octenidine without phenoxyethanol for antisepsis in premature neonates with a birth weight below 1500 g (Very low birth weight). Adverse skin reactions to 0.1% octenidine, such as erythema or blistering, may appear in VLBW infants during the first 2 weeks of life. Octenidine nose gel in combination with octenidine 0.1% washings was not effective for sustained decolonization during a NICU MRSA outbreak.

Polyhexanide (ie, 0.5%) was also used for MRSA decolonization in neonates, but the most effective and tolerable concentration is unknown and a randomized study of MRSA decolonization in adults questions efficacy. During a CA-MRSA USA300 outbreak in a pediatric hospital, Kairet et al implemented an MRSA search and destroy policy in affected families. The outbreak management team decided to use a commercially available antiseptic soap containing 4% undecylenamidopropyltrimonium methosulphate and 2% phenoxyethanol in neonates and children under 5 years of age in addition to nasal mupirocin. In 10 of 11 children, decolonization was successful without adverse skin reactions. Recent studies expand the concept of search, isolate and decolonize to premature infants colonized with MSSA.[8] This is a reasonable approach, keeping in mind that most invasive infections are caused by MSSA. The latest study

protocol published by Milstone et al plans to investigate screening and decolonization of colonized parents because parental colonization may serve as an important reservoir for infant colonization.

There is no role for oral antibiotics during decolonization in patients without infection. Because of missing controlled studies, it remains controversial whether children in whom the first decolonization was not successful should receive targeted antibiotic treatment (eg, cotrimoxazole with or without rifampicin during subsequent decolonization cycles). The addition of oral vancomycin to mupirocin and antiseptic washings to eradicate intestinal MRSA colonization did not result in better outcomes in NICU patients but was considered as important component of the decolonization bundle during a pediatric intensive care unit outbreak.

## ADDITIONAL ASPECTS IN OUTPATIENTS

The role of household decontamination and decolonization of all family members is still a matter of debate and requires further study.[9,10] The Infectious Diseases Society of America guideline recommends the use of household bleach bath in selected patients with recurrent SSTIs. In a randomized outpatient study, the effectiveness of MRSA decolonization mainly in CA-MRSA positive children was 48% in controls; 56% for mupirocin only ($P = 0.40$ vs. controls); 54% for mupirocin/CHX ($P = 0.51$); and 71% for mupirocin/bleach ($P = 0.02$)[9]; another study found approximately 20% of index cases still colonized after 6 months.

To reduce the financial burden of the family, we do not recommend general MRSA testing of all family members but encourage all close contact family members to join the decolonization schedule of the index patient and emphasize the role of environmental decontamination (in particular hand contact surfaces, often touched fomites and toys) with hospital grade ready to use disinfectant wipes. To follow the complete 5-day decolonization schedule is complex and elaborate. This may impede the decolonization effectiveness in household settings. Handouts describing all necessary items in detail including a checklist ("daily goals") make it easier to follow the schedule. More than half of the SSTI patients (CA-MRSA) will develop recurrent infections, in 90% because of persistent colonization with the same isolate. Information concerning MRSA prevention and decolonization should be included in discharge instructions for patients undergoing abscess incision and drainage in pediatric emergency departments.

## MUPIROCIN RESISTANCE AND REDUCED SUSCEPTIBILITY TO CHX

There is an increasing body of evidence, that broadening the indication for mupirocin and CHX whole body washings may foster the selection of (high-level) mupirocin-resistant *S. aureus* isolates and MRSA isolates with genetically determined reduced susceptibility to CHX (eg, *qac*A/B mutations). High-level mupirocin resistance (minimal inhibitory concentration; MIC ≥ 512 mg/L; *mup*A [IleS2] gene) may be circulating among both CA- and HA-MRSA backgrounds. It is not known whether reduced CHX susceptibility alters the rates of successful MRSA decolonization in MRSA isolates without high-level mupirocin resistance. The highest *in vitro* MIC in *S. aureus* isolates with reduced susceptibility (16 mg/L) is still far below the concentrations of antiseptic preparations (eg, 2% CHX refers to 20.000 mg/L). According to recent studies, both seem to be rare in NICUs, and the overall prevalence of these isolates is still low. Some reports from tertiary care children hospitals, pediatric oncology and pediatric dermatology at least argue for enhanced vigilance and regional molecular surveillance concerning their prevalence.

Mupirocin should only be used for decolonization of MSSA/MRSA–positive patients and not for external treatment of superficial skin infections. CHX should not be a regular component of hand disinfecting agents. Some MRSA isolates harbor genes encoding efflux pumps for CHX and other antiseptics and related antibiotic resistance genes in addition to mecA (fluoroquinolones, mupirocin, fusidine acid, amikacin). Perhaps this epidemiologic association is the greatest reason to worry.

## CONCLUSION

There still remain many open questions concerning the best approach and schedule for MRSA decolonization in neonates and children. Prospective randomized studies including the evaluation of long-term effectiveness to elucidate whether the protocol used results in long-term clearance of MRSA carriage are warranted in children with risk factors for HA-MRSA infection and children who are infected or colonized with PVL-positive CA-MRSA.

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