Mupirocin for *Staphylococcus aureus* Decolonization of Infants in Neonatal Intensive Care Units

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abstract

BACKGROUND AND OBJECTIVES: *Staphylococcus aureus* (SA) is the second leading cause of late-onset sepsis among infants in the NICU. Because colonization of nasal mucosa and/or skin frequently precedes invasive infection, decolonization strategies, such as mupirocin application, have been attempted to prevent clinical infection, but data supporting this approach in infants are limited. We conducted a phase 2 multicenter, open-label, randomized trial to assess the safety and efficacy of intranasal plus topical mupirocin in eradicating SA colonization in critically ill infants.

METHODS: Between April 2014 and May 2016, infants <24 months old in the NICU at 8 study centers underwent serial screening for nasal SA. Colonized infants who met eligibility criteria were randomly assigned to receive 5 days of mupirocin versus no mupirocin to the intranasal, periumbilical, and perianal areas. Mupirocin effects on primary (day 8) and persistent (day 22) decolonization at all three body sites were assessed.

RESULTS: A total of 155 infants were randomly assigned. Mupirocin was generally well tolerated, but rashes (usually mild and perianal) occurred significantly more often in treated versus untreated infants. Primary decolonization occurred in 62 of 66 (93.9%) treated infants and 3 of 64 (4.7%) control infants ($P < .001$). Twenty-one of 46 (45.7%) treated infants were persistently decolonized compared with 1 of 48 (2.1%) controls ($P < .001$).

CONCLUSIONS: Application of mupirocin to multiple body sites was safe and efficacious in eradicating SA carriage among infants in the NICU; however, after 2 to 3 weeks, many infants who remained hospitalized became recolonized.

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Dr Kotloff conceptualized the study design, oversaw the project, designed the data collection instruments, assisted in the development of the data analysis plan, drafted the initial manuscript, and revised the manuscript; Dr Shirley assisted with the design of the study and the data collection instruments and reviewed and revised the manuscript; Drs Creech and Thomsen directed the laboratory where bacterial isolates were confirmed for identity and tested for susceptibility, assisted with the study design, coordinated and supervised the data collection, and reviewed and edited the manuscript; Mr Oler and Dr Conrad assisted with the design of the data collection instruments and the development of the data analysis plan, conducted statistical

WHAT'S KNOWN ON THIS SUBJECT: *Staphylococcus aureus* is a leading cause of late-onset sepsis among infants in the NICU. Decolonization regimens are used at many centers in an effort to prevent clinical infection, but controlled trials supporting this approach have not been conducted.

WHAT THIS STUDY ADDS: A 5-day course of mupirocin applied to the intranasal, periumbilical, and perianal areas was safe and highly efficacious in eradicating *S aureus* colonization among infants in the NICU, but many who remained hospitalized became recolonized after 2 to 3 weeks.

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Staphylococcus aureus (SA) is a leading cause of late-onset sepsis occurring after the third postnatal day among infants receiving intensive care. The risk of infection increases with decreasing birth weight and gestational age, although term infants are also affected, particularly those undergoing invasive procedures.[1,2] Multicenter surveillance conducted in the United States between 2000 and 2011 revealed SA in 12% of episodes of late-onset sepsis among infants weighing ≤1000 g.[3] Associated mortality has reached 25% among infants weighing ≤1500 g.[4] Interventions to prevent these infections have the potential to improve survival for infants who are critically ill while reducing adverse outcomes, hospital stay, antibiotic use, and health care costs.[5,6]

The observation that SA colonization is a strong predictor of subsequent invasive infection serves as the basis for most available interventions.[7,8] Approaches have included preventing transmission of SA by actively screening and isolating colonized infants[9] and attempting to eradicate SA in infants who have become colonized using nasal and/or topical antimicrobial agents, such as mupirocin and chlorhexidine.[10,11] In most interventions, researchers have targeted methicillin-resistant *S aureus* (MRSA) without concern for methicillin-susceptible *S aureus* (MSSA) because treatment options for MRSA are more limited, and some data suggest that MRSA infections are more severe.[12] In the NICU, morbidity and mortality from MRSA and MSSA appear equivalent.[4]

After a randomized trial among adults revealed that mupirocin and chlorhexidine administration to all ICU admissions was efficacious in preventing nosocomial MRSA infection,[9] guidelines were developed for universal MRSA decolonization of ICU patients.[13] However, uncertainties about the applicability of these results to infants who are critically ill, particularly those who are premature, justify the need for evaluation before widespread implementation in the NICU.[14–16] We conducted a phase 2 multicenter, open-label, randomized trial to assess the safety and efficacy of applying mupirocin to multiple sites (intranasal, periumbilical, and perianal) in eradicating the colonization of both MRSA and MSSA in infants who are critically ill.

METHODS

Participants

The study was performed at NICUs in the United States associated with 6 Vaccine and Treatment Evaluation Units funded by the National Institute of Allergy and Infectious Diseases (see Study Sites Affiliated With the Vaccine Treatment and Evaluation Units in the Supplemental Information). At 1 NICU, nasal swabs were collected to identify SA colonization from all admissions, whereas the other centers performed selective nasal swab screenings of infants <24 months old who had an anticipated NICU stay of >14 days and lacked exclusionary congenital anomalies (Eligibility Criteria section of the Supplemental Information). Swabs were obtained as soon as possible after admission and then weekly thereafter. The median time from admission to the first swab at each site ranged from 0 (day of admission) to 4 days. Infants who tested positive for SA were assessed for eligibility (Eligibility Criteria section of the Supplemental Information) by the study team. At 1 site, infants with birth weights <1000 g who had nasal swabs positive for MRSA were routinely treated with mupirocin and were excluded from participation in this study. Isolation precautions were routine at all centers for infants who were MRSA-positive but not for infants who were MSSA-positive.

Randomization and Interventions

Infants enrolled at each site were stratified into 2 groups according to gestational age, postnatal age, and colonizing strain (MRSA versus MSSA; Fig 1). Age strata were defined as either <28 weeks' gestation and <8 weeks of postnatal life (termed <28 weeks group) or >28 weeks' gestation (termed >28 weeks group). Infants of <28 weeks' gestation but >8 weeks postnatal age were included in the >28 weeks group. The single infant who tested positive for both MRSA and MSSA was categorized as MRSA-positive. Infants were randomly assigned by strata 1:1 to receive either mupirocin (treatment group) or no treatment (control group) by using an online module displaying only individual assignments (The Emmes Corporation, Rockville, MD).

Within 24 hours of randomization, the treatment group began a 5-day course of mupirocin every 8 (±2) hours. Each dose was dispensed by the investigational pharmacy and consisted of mupirocin calcium 2% cream to the periumbilical and perianal areas and mupirocin calcium 2% intranasal ointment to the nares, applied in a standardized fashion by trained clinical nursing staff (Mupirocin Administration section of the Supplemental Information).

Surveillance for Clinical End Points

The study team reviewed the medical record and interviewed the parent or guardian at enrollment to document medical history, demographic characteristics, and clinical findings. Postrandomization clinical data were abstracted from medical records and clinical team interviews.

Nurses administering the study drug recorded pre- and postintervention pain assessment scores, vital signs, apneic events within 3 to 5 minutes after nasal application, and the maximal intervention level initiated for any discomfort or apnea detected.

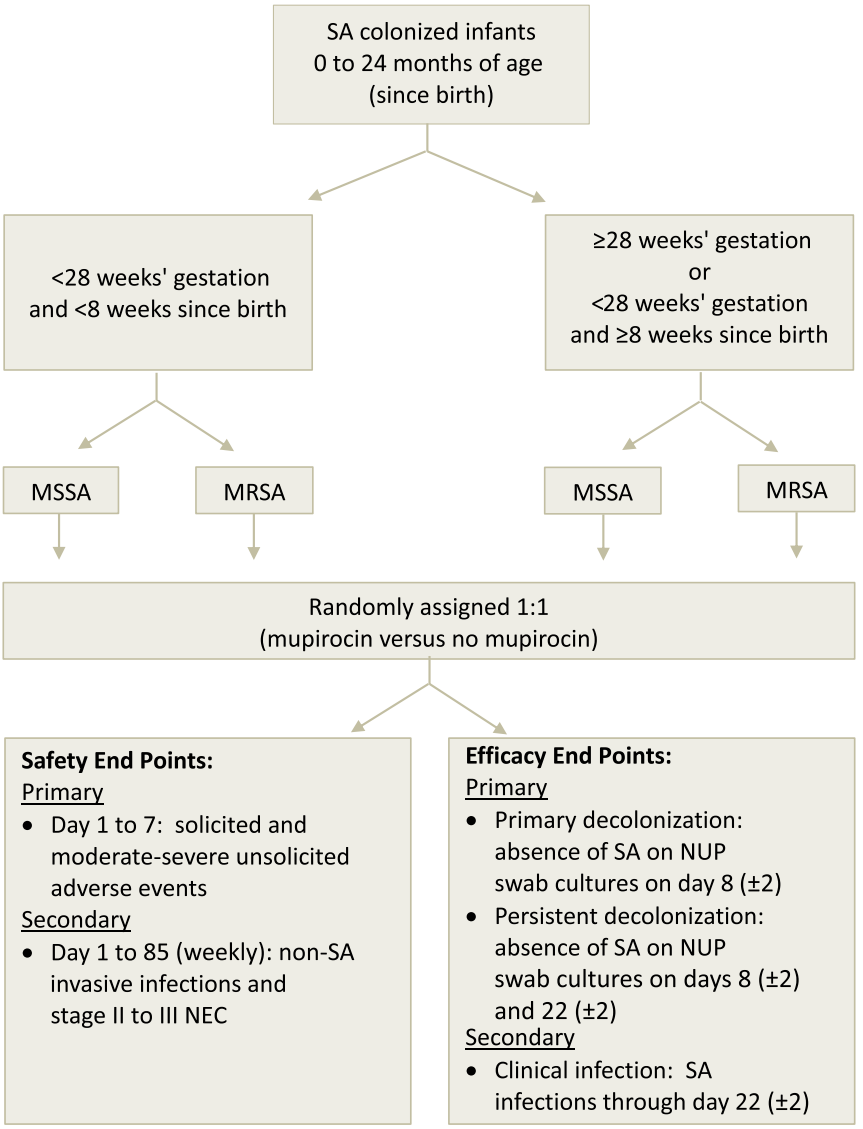

FIGURE 1

Study design. Day 1 began at the time the first dose of mupirocin was administered (treatment group) or at the time of randomization (control group) and ended at 11:59 PM of that same day. Subsequent days for patients and controls coincided with calendar days.

Trained study staff collected nasal, periumbilical, and perianal (NUP) swabs from infants in the treatment and control groups to culture for MSSA and MRSA within 24 hours of randomization (before treatment), every 2 weeks from day 8 to 64 (±2 days), and then on day 85 (±2 days). Conventions for assigning day numbers are described in Fig 1.

Objectives and End Points

The primary objective was to evaluate the safety and clinical acceptability of the mupirocin regimen, defined as the frequency of solicited adverse events (AEs) (fever, rash, nasal mucosal swelling, epistaxis, diarrhea, apnea, bradycardia, pain, and/or desaturations), moderate and severe unsolicited AEs, and serious AEs on days 1 to 7. Study personnel collected and graded events for severity and relationship to mupirocin (Grading of AEs section of the Supplemental Information).

The coprimary objective was to measure the efficacy of mupirocin in eradicating SA colonization. Decolonization was defined as the absence of SA in all NUP cultures. The absence of SA on day 8 ± 2 was considered primary decolonization, whereas the absence of SA on days 8 ± 2 and 22 ± 2 was considered persistent decolonization.

Secondary safety objectives were to assess for associations between mupirocin and non-SA clinical infections or severe necrotizing enterocolitis (NEC) (stages II and III by the Simplified Bell Staging System)[17] during days 1 to 85 or until discharge. These events were considered theoretical undesired outcomes of drug-induced alterations in microbiota. Secondary efficacy objectives were to examine the efficacy of mupirocin in preventing clinical SA infections during days 1 to 22 or until discharge and time until SA decolonization. Clinical SA infection was defined as a culture of SA from a normally sterile body site or from the site of a clinical infection (Definitions of Clinical SA Infections and NEC section of the Supplemental Information).[18] Prevention of clinical SA infection during days 23 to 85 was an exploratory objective.

Laboratory Methods

SA was detected in screening nasal swabs by culture or polymerase chain reaction in each site's laboratory per local practices. By using protocol-defined methods, NUP swabs were cultured directly on BBL CHROMagar SA plates (Becton Dickinson, Sparks, MD) and incubated at 35 to 37°C overnight. Methicillin resistance was determined by either cefoxitin disk diffusion or oxacillin screening agar. SA isolates were cryopreserved at −70°C by using either Microbank or tryptic soy broth with 15% glycerol[19] and shipped to Vanderbilt University Medical Center for mupirocin susceptibility testing using a commercially available

E-test (Biomerieux, Durham, NC). All putative MRSA isolates were confirmed by detection of *mecA*.[20]

Statistical Analysis

The primary and secondary safety analyses and the secondary efficacy analysis were performed by using the intent-to-treat (ITT) cohort, which included all infants enrolled and randomly assigned (Fig 1). The primary efficacy analysis was performed on the modified intent-to-treat (mITT) cohort, which included infants whose NUP swabs obtained within 24 hours of randomization (controls) or within 24 hours before treatment (mupirocin group) were SA-positive at 1 or more body sites. Thus, infants who were spontaneously decolonized between screening and treatment were excluded from analysis. Infants in the mITT analysis of primary (day 8) and persistent (day 22) decolonization were designated to the modified intent-to-treat analysis of decolonization on day 8 (primary decolonization) (mITT-8) and modified intent-to-treat analysis of decolonization on day 22 (persistent decolonization) (mITT-22) cohorts, respectively.

Treatment effects on decolonization were assessed by using Fisher's exact tests and exact 95% confidence intervals (CIs). Multiplicity, including CIs,[21] was controlled by using the Holm method. Stratified analyses of treatment effects on decolonization were performed by using the Mantel-Haenszel test. Time effects (season and year) of colonization incidence during screening were assessed by Poisson regression, controlling for site and allowing for overdispersion. Time-to-event hazard ratios were estimated by using Cox proportional hazards models. For mupirocin efficacy, defined as 1 minus the relative risk (ratio of the proportions of subjects not decolonized, mupirocin-treated over controls), 95% CIs[22,23] were provided. A sample size of 94 infants who were evaluable was chosen a priori to provide 90% power for the primary analysis, assuming a treatment increase of decolonization from a 35% basal rate to 70%.

Safety Oversight and Ethical Approvals

The protocol was approved by each site's institutional review board. Each participant's parent or legal guardian gave informed written consent before the initiation of study activities. A data safety monitoring board provided safety oversight.

RESULTS

Participants

Between April 2014 and May 2016, SA was identified by nasal swabs from 1140 (18%) of 6327 infants, of whom 236 (20%) had MRSA, 902 (79%) had MSSA, 1 (<1%) had both, and 1 (<1%) was not specified; 155 of these infants with positive results (14% with MRSA and 86% with MSSA) were enrolled, randomly assigned, and included in the ITT analysis (Fig 2). The most common reason for the exclusion of 985 infants with SA colonization was ineligibility due to an anticipated NICU stay of <14 days (41.7%). A total of 130 infants were eligible for mITT-8 and 94 were eligible for mITT-22. Most infants who were treated received at least 13 of the 15 required mupirocin doses to both nares (94%) and to the periumbilical (91%) and perianal (90%) areas. Demographic and clinical features of treated and untreated groups at enrollment were comparable, as was the proportion with positive results at each NUP site (Table 1) and the proportion who completed the study.

SA Incidence

The center-specific proportion of infants who were nasally screened and acquired SA after remaining in the NICU for at least 7 days ranged from 11% to 44%, with a corresponding incidence of 6.9 to 15.5 per 1000 hospital days. Statistically significant differences in the incidence of SA colonization were not seen by year of study or season.

Safety and Tolerability

Overall, mupirocin was well tolerated (Fig 3). Rash was the only solicited reaction that was observed significantly more often in infants who were treated (22% vs 5%, odds ratio 5.1; 95% CI 1.5–21.7; P = .004). Most rashes were mild (1 had moderate severity), localized to the perianal area, and attributed to either contact dermatitis or yeast infection. One infant met criteria for severe nasal mucosal swelling (defined as bilateral involvement), with onset on day 7 and a duration of 3 weeks; the swelling was attributed to reflux-induced vomiting and irritation from a nasal cannula. Two infants (3%) experienced severe apnea within 3 to 5 minutes of mupirocin application, and no infant experienced severe pain or discomfort. Non-SA clinical infections occurred in 8% of infants who were treated and 7% of infants who were untreated. No infant in either group experienced severe NEC, or a product-related serious, moderate, or severe AE.

Efficacy

Primary decolonization occurred in significantly more recipients of mupirocin (94%) than controls who were untreated (5%), yielding an overall efficacy of 95% (Table 2). The treatment effect on primary decolonization was statistically significant at all study centers, with success rates reaching 100% at 5 of 7 centers and at least 85% at all centers (Supplemental Tables 8 and 9). Significantly more infants who were treated (46%) than control infants (2%) who had primary decolonization and remained in the NICU were persistently decolonized on day 22, yielding an efficacy of

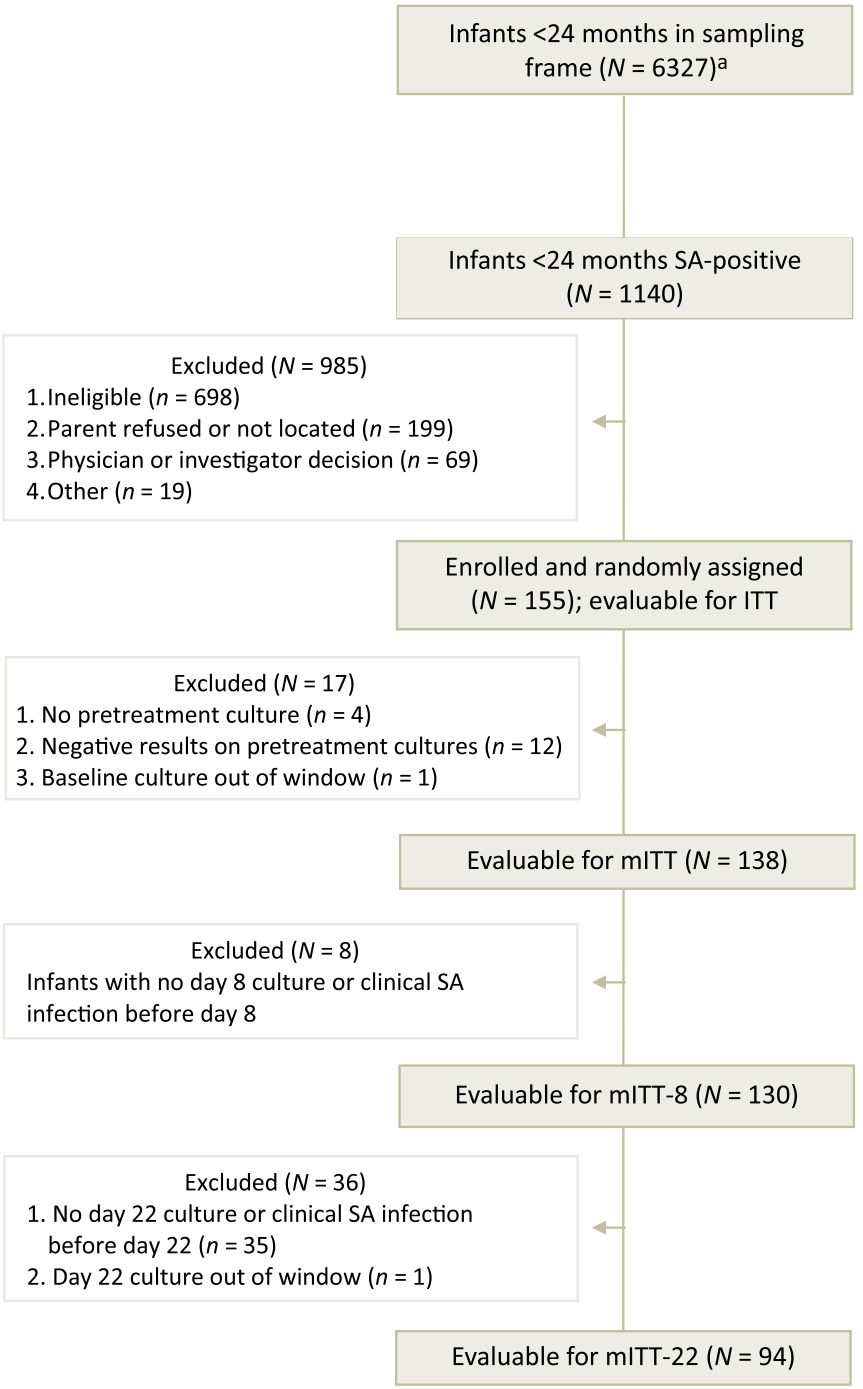

FIGURE 2

Subject enrollment. [a] Nasal swabs were collected from all admissions (universal screening) or from infants <24 months old who had an anticipated NICU stay of >14 days and lacked an exclusionary congenital anomaly (selective screening).

44% (Table 2). The treatment effect on persistent decolonization was statistically significant at the 2 centers with the most participants in the mITT-22 cohort (Supplemental Tables 8 and 9). There were no apparent trends in the success of decolonization according to age strata or a methicillin susceptibility profile. Mupirocin use led to significantly higher frequencies of primary and persistent decolonization at each of the 3 application areas (Table 3).

The emergence of mupirocin resistance in subjects who were treated was not observed. However, the proportion of infants who were colonized with mupirocin-resistant strains at enrollment increased from 0% during the first 14 months of the study to 6% during the final 12 months ($P = .05$). The 4 resistant strains were observed at the center with the most enrollments (not the center administering mupirocin routinely to infants <1000 g at birth who were colonized).

The incidence of clinical infections per 1000 hospital days in infants who were mupirocin-treated versus controls before day 22 was 0.70 (95% CI 0.10–5.00) vs 3.11 episodes (95% CI 1.17–8.29). The mITT analysis of time to clinical infection before day 22 yielded a hazard ratio of 0.23 (95% CI 0.03–2.01; $P = .18$). All clinical infections (with the exception of the 1 treatment failure before day 22) were attributed to MSSA, matched the methicillin susceptibility of the colonizing strain, and manifested as either purulent soft-tissue infection or pneumonia (accompanied by bacteremia in 2 infants).

DISCUSSION

To our knowledge, this is the first multicenter, randomized controlled trial used to assess the efficacy and durability of mupirocin in eradicating SA colonization among infants <24 months of age residing in a NICU. Numerous studies have revealed the value of mupirocin in controlling outbreaks in the NICU, but the impact on endemic SA colonization and its associated risks of SA transmission and progression to clinical infection are less certain.[8,24–26] With this in mind, we managed infants for both primary (day 8) and persistent (day 22) decolonization. We addressed the likelihood that colonization would

TABLE 1 Demographic and Clinical Characteristics at Enrollment by Treatment Group for All Infants Randomly Assigned

	Mupirocin Group (*n* = 80)	Control Group (*n* = 75)
Male sex, *n* (%)	45 (56)	42 (56)
Hispanic ethnicity, *n* (%)	2 (3)	4 (5)
Race, *n* (%)		
Asian American	1 (1)	1 (1)
African American	22 (28)	25 (33)
White	50 (63)	41 (55)
Multiracial	6 (8)	7 (9)
Unknown	1 (1)	1 (1)
Birth wt, *n* (%), g[a]		
<1000	29 (36)	28 (37)
1000–1500	23 (29)	23 (31)
>1500	26 (33)	22 (29)
Gestational age, *n* (%), wk		
<28[b]	21 (26)	21 (28)
28[c]	59 (74)	54 (72)
Postnatal age at enrollment, median (range), wk	4 (0–22)	3 (1–24)
Major comorbidities, *n* (%)[d]		
NEC	4 (5)	1 (1)
Respiratory distress syndrome	60 (75)	56 (75)
Apnea of prematurity	51 (64)	48 (64)
Surgical procedures	16 (20)	14 (19)
With indwelling tubes or catheters, *n* (%)		
Endotracheal tube or tracheostomy	7 (9)	6 (8)
Central vascular access	14 (18)	12 (16)
Orogastric tube	23 (29)	22 (29)
Screening nasal colonizing strain, *n* (%)[e]		
MRSA or MRSA plus MSSA	12 (15)	8 (11)
MSSA	66 (82)	67 (89)
No positive results on baseline culture	2 (3)	0
Pretreatment colonizing site, *n* (%)[f]		
Nasal	72 (90)	66 (88)
Periumbilical	31 (39)	26 (35)
Perianal	33 (41)	18 (24)
No. sites colonized, *n* (%)[g]		
0	5 (6)	7 (9)
1	30 (37)	34 (45)
2	23 (29)	20 (27)
3	20 (25)	12 (16)

Includes all 155 infants evaluable for the ITT analysis.

[a] Four subjects were discharged from the hospital after randomization but before obtaining pretreatment NUP cultures and medical history.

[b] Denotes <28 wk gestation and <8 wk postnatal life.

[c] Denotes ≥28 wk gestation or <28 wk gestation and ≥8 wk of postnatal life.

[d] These categories are not mutually exclusive.

[e] Infants who had a surveillance nasal swab positive for SA were enrolled and randomly assigned.

[f] Positive results on pretreatment NUP cultures were required for infants to be eligible for the mITT analysis.

[g] Cultures were not collected from 2 infants treated with mupirocin and 2 control infants.

be present at multiple anatomic sites by applying mupirocin to multiple body sites rather than supplementing nasal mupirocin with chlorhexidine baths, which have undetermined safety in premature infants.[27] We surveyed participants for unintended consequences that could result from perturbation of the microbiome, such as severe NEC and non-SA clinical infection, and other adverse reactions. Finally, we included infants colonized with both MRSA and MSSA.

Our findings reveal that mupirocin was highly efficacious (85%–100%) in inducing primary SA decolonization, impacting both MRSA and MSSA and extending across study centers, anatomic sites, and gestational age strata. A concomitant trend revealed a reduction in clinical SA infections before day 22, but the results did not achieve statistical significance. An exploratory survival analysis of clinical SA infections suggested that the reduction in SA infections would wane after day 22, which was supported by observations that recolonization occurred in approximately half of infants treated with mupirocin by day 22 and in 70% by day 85. A persistent reservoir of SA likely led to ongoing transmission, which was consistent with the steady incidence of SA acquisition during the 36-month study period.[28] Supplementary strategies that might reduce recolonization include targeted retreatment of patients who have been recolonized and decolonization of caregivers and family members.[29]

Various targeted MRSA decolonization programs for infants in the NICU have been evaluated retrospectively by using historical controls as the comparator.[28,30,31] In some instances, infants who had been recolonized were retreated. Each of these studies revealed a treatment effect; however, the duration of the effect, the impact of retreatment, and the effect of secular changes cannot be fully elucidated when historical controls are used.

A prospective cluster randomized trial of adults in the ICU revealed that a 5-day course of twice-daily intranasal mupirocin plus daily chlorhexidine baths administered to all patients at admission without regard to SA colonization status was superior to targeted decolonization of patients with MRSA colonization or a previous infection.[9] During the 18-month intervention, universal decolonization at admission reduced MRSA-positive clinical culture results by 37% compared with 25% for targeted decolonization, although a significant decrease in MRSA bloodstream infections was not seen. The prompt reduction in the reservoir of SA that resulted from treating all patients without

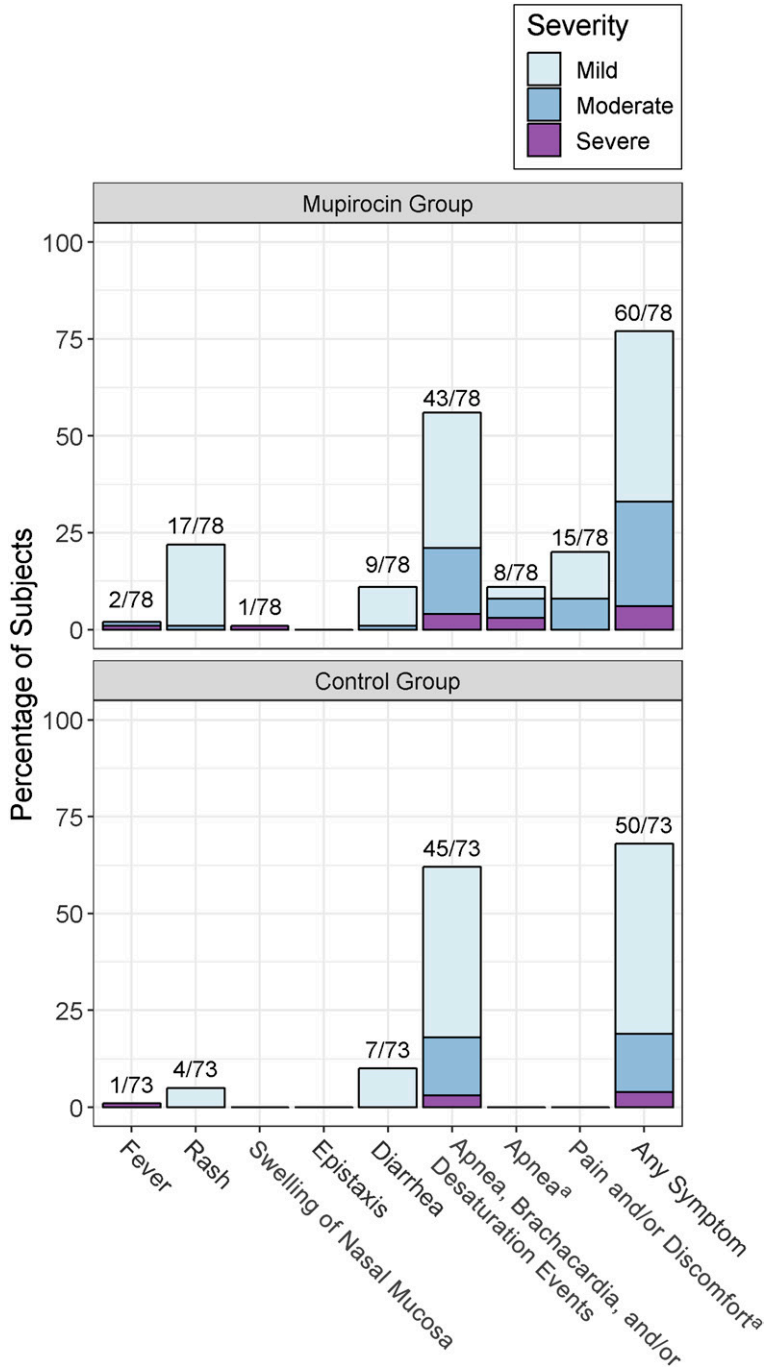

FIGURE 3

Maximum severity of solicited AEs during 1 to 7 days in infants treated with mupirocin and controls, who were not treated. [a] Apnea and pain and/or discomfort were collected within 3 to 5 minutes of mupirocin application but were not collected for controls.

awaiting results of screening tests likely contributed to the superiority of universal decolonization in this trial.[26] Another contributing factor may be the relatively brief duration of hospitalization (median 7 days), thus limiting the risk of recolonization. Universal decolonization was also more effective than targeted decolonization in reducing bloodstream infections from any pathogen, an effect likely mediated by chlorhexidine baths.[32] Whether a universal decolonization regimen would be similarly effective among infants who are critically ill is unknown. A retrospective study evaluated a 7-year program in which mupirocin was applied to the nares, umbilicus, eroded skin, and wounds of all patients in the NICU twice daily throughout hospitalization.[30] The SA colonization rate decreased from 60% at baseline to <5%; however, there were periodic peaks to 20% that were associated with clinical infections.

In our study, we provided careful observations of AEs related to mupirocin use in a controlled, open-label fashion and identified no serious safety concerns. The perianal rashes that appeared to be treatment-related did not lead to systemic complications. The absence of NEC and non-SA clinical infections in our study and elsewhere is also reassuring.[31] Finally, emergence of mupirocin-resistant strains was uncommon in our population, as it has been in other NICU decolonization programs.[8,33] Resistant strains appeared in enrollment swabs at 1 site, but we cannot determine whether the cause was our intervention or the introduction of a resistant strain from an exogenous source. Nonetheless, widespread use of mupirocin could induce resistance and should be considered in decisions regarding programmatic use.[34]

Several limitations of our study are noteworthy. The open-label design could produce reporting bias, particularly for safety parameters (such as rash), because the nurses were instructed to examine infants who were treated for rash before each mupirocin application. Concerns about a possible increased risk of nosocomial infection related to inert topical ointments in premature infants led to the decision not to use a placebo.[35–37] Our study was not statistically powered to assess the secondary and exploratory aims of preventing clinical SA infection, which

TABLE 2 Primary and Persistent SA Decolonization According to Group Assignment and Stratum

Gestational Age	Enrollment Strain[a]	Group	Decolonization, *n* (%)	No Decolonization, *n* (%)	Odds Ratio (95% CI)	*P*	Efficacy, %
Primary decolonization (mITT-8 group; *n* = 66 mupirocin recipients and 64 controls)							
<28 wk[b]	MRSA	Mupirocin	2 (100)	0 (0)	—	.333	100
		Control	0 (0)	2 (100)	—	—	—
≥28 wk[c]	MRSA	Mupirocin	9 (100)	0 (0)	—	<.001	100
		Control	0 (0)	5 (100)	—	—	—
<28 wk[b]	MSSA	Mupirocin	16 (100)	0 (0)	—	<.001	100
		Control	1 (6)	15 (94)	—	—	—
≥28 wk[c]	MSSA	Mupirocin	35 (90)	4 (10)	171 (25–1699)	<.001	89
		Control	2 (5)	39 (95)	—		
Total primary decolonization[d]	All	Mupirocin	62 (94)	4 (6)	288 (58–1433)	<.001	94 (85–98)
		Control	3 (5)	61 (95)	—		—
Persistent decolonization (mITT-22 group, *n* = 46 mupirocin recipients and 48 controls)							
<28 wk	MRSA	Mupirocin	1 (100)	0 (0)	—	.333	100
		Control	0 (0)	2 (100)	—	—	—
≥28 wk	MRSA	Mupirocin	2 (50)	2 (50)	—	.167	50
		Control	0 (0)	5 (100)	—	—	—
<28 wk	MSSA	Mupirocin	7 (47)	8 (53)	—	.006	47
		Control	0 (0)	14 (100)	—	—	—
≥28 wk	MSSA	Mupirocin	11 (42)	15 (58)	19 (2–851)	<.001	40
		Control	1 (4)	26 (96)	—	—	—
Total persistent decolonization[d]	All	Mupirocin	21 (46)	25 (54)	37 (5–284)	<.001	44 (30–59)
		Control	1 (2)	47 (98)	—	—	—

—, not applicable.

[a] Infants colonized with both MRSA and MSSA are listed as MRSA.

[b] Less than 28 wk gestation and <8 wk postnatal age.

[c] Greater than or equal to 28 wk gestation or <28 wk gestation and ≥8 wk of postnatal life.

[d] Mantel-Haenszel χ^2 test.

TABLE 3 Decolonization by Body Area Among 130 Infants Eligible for the mITT-8 and 94 Infants Eligible for the mITT-22

End Point	Anatomic Site[a]	Treatment Group	Primary Decolonization, *n* (%)	No Primary Decolonization, *n* (%)	Odds Ratio (95% CI)	*P*	Efficacy, %
Primary decolonization (mITT-8 group)	Nasal	Mupirocin	62 (95)	3 (5)	420 (70–2997)	<.001	95
		Control	3 (5)	61 (95)	—	—	—
	Umbilical	Mupirocin	27 (100)	0 (0)	—	<.001	100
		Control	7 (27)	19 (73)	—	—	—
	Perianal	Mupirocin	30 (97)	1 (3)	98 (9–4270)	<.001	96
		Control	4 (24)	13 (77)	—	—	—
Persistent decolonization (mITT-22 group)	Nasal	Mupirocin	23 (51)	22 (49)	49 (7–2066)	<.001	50
		Control	1 (2)	47 (98)	—	—	—
	Umbilical	Mupirocin	15 (94)	1 (6)	56 (5–2518)	<.001	92
		Control	4 (21)	15 (79)	—	—	—
	Perianal	Mupirocin	15 (75)	5 (25)	12 (2–138)	.007	69
		Control	2 (20)	8 (80)	—	—	—

—, not applicable.

[a] Each analysis includes only subjects with baseline colonization at the respective anatomic site.

therefore can only be inferred by considering the strong association between colonization and infection. Most importantly, our stringent inclusion and exclusion criteria, screening requirements, and targeted decolonization strategy resulted in only ~14% of all infants who were colonized undergoing randomization, half of whom received mupirocin. The low treatment coverage was largely attributable to the decision to enroll only infants whose length of stay would be ≥14 days from screening to allow sufficient time for treatment and evaluation of primary decolonization.

Our study reveals several drawbacks related to the strategy of screening

infants in the NICU for SA and targeting those with positive results for isolation and decolonization with mupirocin. For one, our observation that the vast majority of infants who are colonized and who develop clinical infection harbor MSSA rather than MRSA suggests that the common focus on infants with MRSA alone is inadequate. Second, although we were not statistically powered to assess the secondary aim of preventing clinical SA infection, our results suggest that a large number of infants (25) would need to receive mupirocin to prevent 1 clinical SA infection. Third, in NICUs where length of stay is prolonged, reacquisition of SA is likely and may be associated with an increased risk of clinical infection. Finally, although mupirocin resistance has been uncommon to date in NICUs with decolonization programs, it has occurred in other inpatient settings.[38,39] Susceptibility patterns should be monitored when consistent use is expected.[34]

CONCLUSIONS

We found that mupirocin was safe and highly efficacious in inducing primary SA decolonization in the NICU, an effect that is expected to translate to the prevention of clinical infection during the 2- to 3-week period after colonization, at which time most SA infections seem to occur.[4,29] With these findings, it is suggested that in NICUs where clinical SA infections are prevalent, mupirocin decolonization might reduce the burden of MRSA and MSSA and prevent clinical infections. However, with the observed recolonization thereafter it is suggested that more effective means for interrupting transmission should be sought.

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ABBREVIATIONS

AE: adverse event
CI: confidence interval
ITT: intent-to-treat
mITT: modified intent-to-treat
mITT-8: modified intent-to-treat analysis of decolonization on day 8 (primary decolonization)
mITT-22: modified intent-to-treat analysis of decolonization on day 22 (persistent decolonization)
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-susceptible *Staphylococcus aureus*
NEC: necrotizing enterocolitis
NUP: nasal, periumbilical, and perianal
SA: *Staphylococcus aureus*

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