Bacterial infections in neonates following mupirocin-based MRSA decolonization

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Background & Objectives

- Targeted decolonization with mupirocin, a topical antibiotic, has been used to reduce methicillin resistant *Staphylococcus aureus* (MRSA) infections in neonatal intensive care units (NICUs).[1]
- Mupirocin-based decolonization previously has been associated with reduced MRSA infection risk in MRSA carriers.[2]
- *In vitro*, mupirocin is highly active against gram-positive cocci, staphylococci and streptococci, but has poor activity against gram-negative and fungal pathogens.[3-4]
- There is concern that narrow coverage of mupirocin may facilitate colonization and infection with non-covered gram-negative and fungal pathogens.[5]
- **Objective:** Quantify the risk of infection with covered (gram-positive cocci) and non-covered (gram-negative/fungal) organisms associated with mupirocin exposure among NICU MRSA carriers.

Methods

- Retrospective, multi-centered cohort study of neonates admitted to three tertiary care NICUs January 2007-December 2014, during which targeted decolonization was employed for MRSA control.
- Study population includes NICU neonates with MRSA nasal colonization, who were therefore eligible for mupirocin-based decolonization.
- Neonates enter time under observation on date of first MRSA-positive nasal surveillance culture and remain at risk until outcome occurrence or discharge.
- Outcomes:
  1. Novel occurrence of gram-positive cocci (GPC) in sterile site culture. GPC organisms are covered by mupirocin.
  2. Novel occurrence of gram-negative bacilli or fungi (GNB&F) in sterile site culture. GNB&F organisms are not covered by mupirocin.
- Exposure: Mupirocin exposure was obtained from administrative databases and chart review.
- Cox proportional hazards models, accounting for the time-varying nature of mupirocin exposure, were used to examine the association between mupirocin receipt and GPC/GNB&F outcomes.
- Models were adjusted for the occurrence of previous GPC or GNB&F organism (i.e. having a GPC or GNB&F positive clinical culture prior to study entry that is discordant from any observed outcome organisms), calendar year, length of stay prior to study entry, birth weight, gestational age and study site.

Results

- 522 MRSA-colonized neonates were included in the analysis. Person-time under observation was 18,254 and 18,478 patient-days for time to GPC and GNB&F infection, respectively. Incidence rate (IR) of infection was 1.7 per 1000 patient-days for GPC and 1.8 per 1000 patient-days for GNB&F.
- Crude IR of novel GPC infection was significantly decreased among mupirocin-exposed compared to mupirocin-unexposed neonates (IRR 0.38, 95% CI: 0.18-0.82). The adjusted hazard of GPC infection was approximately 60% less among mupirocin-exposed versus mupirocin-unexposed neonates (HR=0.39, 95% CI: 0.17-0.86), controlling for length of stay prior to study entry, calendar year, birth weight, gestational age, study site, and whether a GPC organism had been identified prior to study entry (Table 2).
- Crude IR of novel GNB&F infection was not significantly different among mupirocin-exposed and -unexposed neonates (IRR=1.15, 95% CI: 0.50-2.95). Similarly, the adjusted hazard ratio of GNB&F infection comparing mupirocin-exposed and -unexposed neonates was 1.02 (95% CI: 0.43-2.38), controlling for length of stay prior to study entry, calendar year, birth weight, gestational age, study site, and whether a GNB&F organism had been identified prior to study entry (Table 3).
- In sensitivity analyses, outcomes were restricted to bloodstream infections (BSI) with a novel organism. The hazard of GNB&F BSI was not significantly increased among mupirocin-exposed versus –unexposed neonates (HR=1.13, 95% CI:0.23-5.58). Hazard of GPC BSI was reduced among mupirocin-exposed neonates (HR=0.38, 95% CI: 0.15-0.94).

Table 1. Characteristics of study population

Study Variables by Mupirocin Exposure			
Variable	Received mupirocin during stay n=384	Did not receive mupirocin during stay n=138	p value
GPC infection outcome	20 (5%)	11 (8%)	0.24
GNB&F infection outcome	24 (6%)	8 (6%)	0.85
LOS prior to study entry (days) (median; IQR)	18 (25)	17 (31)	0.21*
Previous GPC positive culture	53 (14%)	25 (18%)	0.22
Previous GNB&F positive culture	43 (11%)	7 (5%)	0.04
Gestational age (weeks) (median;IQR)	30 (9)	32 (10)	0.20*
Birth weight (g) (median;IQR)	1080 (938)	1120 (884)	0.91*
Site			
Site 1	183 (48%)	50 (36%)	
Site 2	127 (33%)	58 (42%)	
Site 3	74 (19%)	30 (21%)	0.13

P values obtained by chi-square test unless otherwise specified, * P value obtained by Kruskal-Wallis test.

Abbreviations: HR, hazard ratio; CI, confidence interval; LOS, length of stay; g, grams; IQR, interquartile range.

Tables 2. & 3. Survival Analyses

Table 2. Time to Infection with Gram Positive Cocci (GPC) Infection

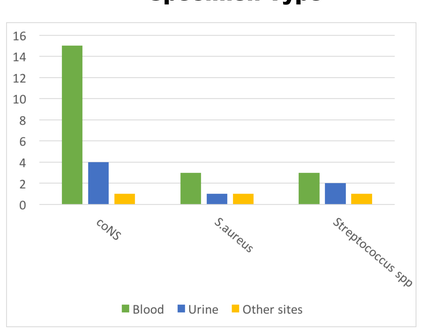
	Unadjusted		Adjusted	
Variable	HR	95% CI	HR	95% CI
Mupirocin treatment	0.43	0.20-0.92	0.39	0.17-0.86
LOS prior to study entry	0.99	0.98-1.01	0.98	0.96-1.00
Year	0.94	0.79-1.11	0.97	0.81-1.16
Previous GPC positive clinical culture	1.40	0.63-3.16	1.33	0.57-3.13
Birth weight (g)	1.00	0.99-1.00	1.00	0.99-1.00
Gestational age (weeks)	0.93	0.85-1.01	0.83	0.70-0.97
Site				
Site 1	1.11	0.44-2.83	1.28	0.46-3.57
Site 2	0.82	0.29-2.37	1.57	0.42-5.89
Site 3 (Ref)	-	-	-	-

Table 3. Time to Gram-Negative Bacilli or Fungi (GNB&F) Infection

	Unadjusted		Adjusted	
Variable	HR	95% CI	HR	95% CI
Mupirocin treatment	1.09	0.47-2.50	1.02	0.43-2.38
LOS prior to study entry	1.00	0.99-1.01	0.99	0.98-1.01
Year	0.97	0.82-1.15	1.02	0.86-1.21
Previous GNB&F positive clinical culture	2.15	0.95-4.86	2.43	0.95-6.22
Birth weight (g)	1.00	0.99-1.00	1.00	0.99-1.00
Gestational age (weeks)	0.94	0.86-1.02	0.91	0.77-1.08
Site				
Site 1	0.76	0.33-1.76	0.80	0.32-2.00
Site 2	0.42	0.15-1.21	0.59	0.15-2.24
Site 3 (Ref)	-	-	-	-

Estimates obtained via Cox Proportional Hazards Regression. Proportionality assumption tested on the basis of Schoenfeld residuals and tests of interaction of primary variables with time. No evidence that the proportional-hazards assumption was violated.

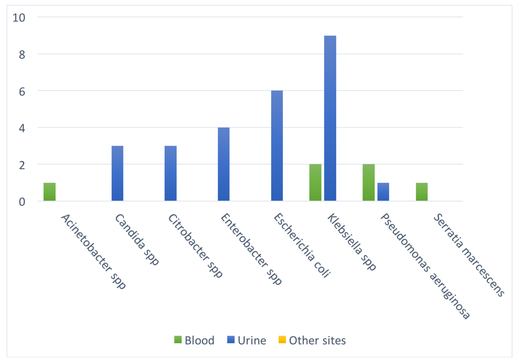
Figure 1. GPC Outcome Organisms by Sterile Specimen Type



Abbreviations: coNS, coagulase negative Staphylococcus spp.; *S.aureus, Staphylococcus aureus*

Other sterile specimen sites include: cerebrospinal fluid, abscess fluid, pleural fluid, bronchoalveolar fluid

Figure 2. GNB&F Outcome Organisms by Sterile Specimen Type



Discussion & Limitations

- Mupirocin-based decolonization appears to be effective in reducing hazard of infections with gram-positive cocci (staphylococci & streptococci), which is consistent with *in vitro* performance of mupirocin.
- Mupirocin exposure was not associated with a significant increase in hazard of infections with gram-negative or fungal organisms.
- Results were consistent when outcomes were limited to bloodstream infections.
- Our data inform clinical outcomes associated with mupirocin treatment, but do not specifically address whether or not dysbiosis is occurring after treatment. We found no evidence that mupirocin-based microbiome disruption, if occurring, increases subsequent risk of GNB&F infection.
- Due to the observational nature of this study, there remains potential for residual confounding.
- NICU patients may represent an epidemiologically distinct patient subgroup due to an underdeveloped microbiome and generally high susceptibility to healthcare-associated infections. Results may not be generalizable to other patient populations.

Future Directions

- Future research is needed to confirm the impact of topical antimicrobials at the level of the microbiome in neonatal populations.
- Further randomized studies are needed to confirm clinical outcomes associated with mupirocin-exposure.

Conclusion

These data suggest that, in MRSA carriers, mupirocin-based decolonization reduces the risk of infection with covered, gram–positive pathogens, but does not appear to increase the risk of infection with non-covered, gram-negative or fungal organisms. This suggests that measurable or clinically-relevant pathogen replacement may not be occurring.

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