Prevalence of MRSA Colonization among Neonatal and Pediatric ICU Patients in Chicago

BY

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THESIS
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This thesis is dedicated to my mother, Ella Flowers, without whom it would never have been accomplished.
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<table>
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<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
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<tr>
<td>MRSA</td>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>NICU</td>
<td>Neonate Intensive Care Unit</td>
</tr>
<tr>
<td>PICU</td>
<td>Pediatric Intensive Care Unit</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<td>PPS</td>
<td>Point Prevalence Survey</td>
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SUMMARY

Background: Beginning October 2007, the MRSA Screening and Reporting Act (210 ILCS 83/) mandated active surveillance for all ICU patients in Illinois, with isolation of MRSA-colonized patients. We assessed MRSA colonization prevalence among neonatal (NICU) and pediatric (PICU) patients using a series of point prevalence surveys.

Methods: Chicago hospitals with NICU or PICU patients were recruited for 6 single-day point prevalence surveys (PPSs) approximately 6 months apart from June 2008 to July 2011. After 2011, yearly surveys were obtained in 2012 and 2013. All ICU patients were cultured for MRSA (nose and umbilicus for neonates; nose and groin for pediatric patients) using a single swab for each body site. Hospital-reported admission screen results (i.e. 210 ILCS 83/-mandated) were also obtained. Point prevalence cultures were screened for MRSA using broth enrichment, chromogenic agar, and standard confirmatory methods.

Results: All eligible hospitals (N=10) participated (10 NICUs and 6 PICUs) with 99.6% of NICU and 93% of PICU eligible patients cultured across PPSs. Hospital-reported adherence to admission screens mandated by 210 ILCS 83/ was high (99.6% for NICU and 93.3% for PICU). Overall MRSA prevalence by PPSs in NICUs was 4.2% (89/2101); PICU, 5.7% (36/632). MRSA colonization prevalence declined in NICUs (estimated yearly odds ratio [OR], 0.92, 95% confidence interval [CI] 0.77 to 1.11, P<0.39) but not in PICUs (OR 1.25, 95% CI 1.10 to 1.42, P<0.001).
Conclusion: In the time period following implementation of mandatory active surveillance, we found MRSA colonization in a proportion of NICU and PICU patients, with evidence of ongoing MRSA transmission.
I. INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important healthcare-associated pathogen among critically ill children [1]. MRSA has been well described among patients in neonatal and pediatric intensive care units (NICUs and PICUs), with many single center as well as regional outbreaks reported [2-4]. MRSA-colonized neonates and children are at risk for subsequent invasive disease, leading to significant cost and morbidity [5].

The epidemiology of MRSA, particularly with respect to colonization, is incompletely understood in the critically ill pediatric population. Few studies have surveyed for asymptomatic carriage of MRSA [6-10]. Furthermore, prior epidemiologic studies of MRSA colonization among critically ill children have been primarily single center, some during MRSA outbreak periods, limiting generalizability. Since 2000, the epidemiology of MRSA among hospitalized children has evolved in many geographic regions with the encroachment of community-associated MRSA strains.

In October 2007, Illinois became the first state in the United States to mandate active surveillance of MRSA for patients admitted to intensive care units (MRSA Screening and Reporting Act, 210 ILCS 83/). Following the start of the law, we initiated a series of regional point prevalence surveys (8 surveys over 5 years) to assess the epidemiology of MRSA colonization among NICU and PICU patients across all hospitals, community and academic, in a large metropolitan region (Chicago, IL). We evaluated whether the prevalence of MRSA
colonization would decline during the 3 years following the active surveillance mandate. We also pursued a broader goal of describing the epidemiologic characteristics of MRSA colonization in the neonatal and pediatric ICU populations, including microbiologic characterization of MRSA isolates and assessment of hospital surveillance practice.
II. METHODS

A. Facility and Patient Recruitment

In 2008, we invited acute care hospitals in the city of Chicago with NICUs or PICUs to participate in serial point prevalence surveys for MRSA colonization. Eight serial point prevalence surveys were performed over 5 years (June 21, 2008 to July 9, 2013). All NICU or PICU patients present at the time of the surveillance visit were eligible for participation. Patients who were physically unavailable at the time of the surveillance (e.g., because they were away from their room for testing or procedures) were excluded. Written informed consent was waived for this study. Parents at the bedside, as well as minors, were asked to give verbal assent using a standardized script explaining the rationale of the project.

B. Ethical Review

This project underwent ethical review at the CDC and was determined to be a non-research activity. Thus, it was not subject to a review by the CDC institutional review board. The project was also evaluated independently at each participating healthcare facility and either deemed a public health assessment or human subjects research and approved by local review boards where applicable.
C. **Culture and Data Collection**

On each point prevalence survey day, facilities were provided all standardized culturing and data tracking materials as well as on-site training and coordination. Local hospital staff (primarily infection preventionists, with help from ward nurses if available) as well as one investigator (RL) performed the patient-level specimen collection.

Patients were cultured for MRSA at 2 body sites (nose and umbilicus for neonates; nose and inguinal region for pediatric patients) using a single swab for each body site. A sterile dry rayon swab (BBD BBL Culture Swab, Fisher Scientific, Pittsburg, PA) was placed in one nostril and rotated 3 times such that the entire swab was moistened by the anterior nares. For neonates, a swab specimen from a 3 x 3 cm region in the umbilicus region was collected with a second sterile dry rayon swab. Similarly, for pediatric patients, a swab specimen from a 10 x 10 cm region in the inguinal region was collected with a sterile dry rayon swab. All swabs were transported to the central laboratory in liquid Stuart medium.

At the time of specimen collection, the following patient characteristics were recorded: patient age, ICU length of stay, gender, mechanical ventilation, and contact precautions status.

D. **Laboratory Methods**

All specimens were transported to a central laboratory and processed within 6 hours of collection. Individual nose, groin, or umbilicus swab specimens were cultured into separate tubes
of Tryptic Soy Broth with 6.5% salt (Remel, Lenexa, KS). After overnight incubation, the broth was inoculated onto chromogenic MRSA-Select agar (BioRad, Hercules, CA). After subculture, *Staphylococcus aureus* was confirmed by colonial morphology and standard biochemical techniques. Susceptibility to oxacillin was determined by the cefoxitin disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) recommendations (CLSI M7-A8). All MRSA isolates were subtyped by pulsed-field gel electrophoresis. Community-associated MRSA genotypes were defined as USA300, 400, 1000, or 1100 [11]. Mupirocin resistance (low and high level) was detected using an E-test method. High-level mupirocin resistance was defined as a minimum inhibitory concentration (MIC) ≥512 mcg/mL, low-level mupirocin resistance was defined as an MIC 8-64 mcg/mL, and mupirocin susceptibility was defined as MIC ≤4 mcg/mL [12].

E. **Statistical Analyses**

For bivariable comparisons, we used Fisher’s exact test or Student’s *t* test, as appropriate. Exact binomial methods were used to calculate 95% confidence intervals for proportions. We constructed linear regression models using the generalized estimating equations to model prevalence and incidence trends, accounting for ICU and hospital-level correlation across time. All data were analyzed using SAS software, version 9.2 (SAS Institute, Cary, NC).
III. RESULTS

In total, 10 of 10 eligible hospitals (representing all eligible 10 NICUs and 6 PICUs) voluntarily participated in the point prevalence surveys. The median NICU size was 38.5 beds, ranging from 10 to 88, and the median PICU size was 12 beds, ranging from 7 to 42.

The overall participation rate among eligible NICU patients was high across the survey period, 99.6% (1577/1584); for PICU patients, 93.3% (485/520). Patient demographics are shown in Table I.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>NICU</th>
<th>PICU</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay, median (IQR)</td>
<td>18 (6 – 43)</td>
<td>7 (3 – 20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>1141/2095 (55)</td>
<td>350/633 (55)</td>
<td>0.79</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>19 days (7 – 42)</td>
<td>1.8 years (0.4 - 10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilated (%)</td>
<td>422/2092 (20)</td>
<td>182/631 (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contact isolation (%)</td>
<td>114/2096 (5)</td>
<td>266/632 (42)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

A. Hospital-reported Surveillance for MRSA

All 10 hospitals reported that they complied with the 210 ILCS 83/ legislation by performing active surveillance testing for MRSA colonization.
MRSA screening practice varied among NICUs. Of the 10 NICUs, 9 performed active surveillance for all patients at the time of admission; 1 NICU did not perform admission surveillance but instead performed weekly periodic surveillance for all patients. MRSA screening was performed using nares culture for 9 NICUs, while 1 NICU performed combined nares/axilla/groin culture using a single swab. Polymerase chain reaction (PCR)-based MRSA testing was used in 4 of 10 NICUs, with the remainder using a culture-based detection method. Screening at time points after admission (e.g., weekly, twice a month, or at ICU day 10) was used at some point during the study period for 7 of 10 NICUs, involving 55% (1162/2101) of all NICU patients surveyed.

In comparison, PICU MRSA screening practice was fairly homogeneous. Of the 6 PICUs, all performed active surveillance for MRSA at the time of admission using nasal sampling. One out of 6 PICUs utilized PCR-based MRSA testing. Screening at time points after admission was not routinely performed in any of the PICUs.

We found high rates of compliance with the state law by hospitals across the study period, with 95% of NICU patients and 94% of PICU patients in the study cohort receiving active surveillance testing for MRSA.
The overall admission prevalence of MRSA colonization, as reported by hospitals, was as follows: NICU, 1.5% (95% confidence interval [CI] 1.0 to 2.2%) vs. PICU, 6.9% (95% CI 4.0% to 7.8%). Admission prevalence did not significantly change across the 6 survey periods for any participating NICU or PICU.

B. **Point Prevalence Survey Results**

Of 2101 NICU patients who participated in the surveys, 89 (4.2%) were colonized with MRSA (95% CI 3.4 to 5.1%). The MRSA colonization prevalence among NICU patients remained stable during the study period (Figure 1A; estimated yearly odds ratio 0.92, 95% CI 0.77 to 1.11, P=0.39).

Of 632 PICU patients who participated in the surveys, 36 (5.7%) were colonized with MRSA (95% CI 4.0 to 7.8%). In contrast to the NICU trend, the MRSA colonization prevalence among PICU patients increased significantly over time (Figure 1B; estimated yearly odds ratio 1.25, 95% CI 1.10 to 1.42, P<0.001).
A) NICU

Figure 1. Estimated MRSA colonization prevalence trend for NICU and PICU during the 5 year study period. (NOTE: Each circle represents a survey point at a single ICU. Circles sizes are proportional to the relative number of patients contributing data.)
C. Molecular Epidemiology and Mupirocin Resistance

CA-MRSA genotypes represented 46% (41/89) of MRSA isolates from the NICU, and 36% (13/36) of MRSA isolates from the PICU. During the study period, the proportion of MRSA isolates represented by CA-MRSA genotypes did not change significantly for either the NICU or PICU.

In the NICU, high-level mupirocin resistance was detected in 3% (3/89) of MRSA isolates tested. Among the 36 PICU MRSA isolates tested, 8% (n=3) demonstrated high level resistance, while 3% (n=1) demonstrated low level resistance.

D. Epidemiologic Differences in MRSA Colonization Between NICU and PICU

The epidemiology of MRSA colonization differed in terms of ICU day distribution between NICU and PICU settings (Figure 2). In the NICU, MRSA-colonized neonates were detected only on ICU day ≥2; of the 192 neonates (9% of total sample) surveyed within the first 2 ICU days, none were MRSA-colonized. In contrast, MRSA-colonized PICU patients were found throughout the entire range of ICU days. The median ICU day for MRSA-colonized NICU patients was 29, versus 9 for PICU patients (P<0.001).
E. *Appropriate Contact Precautions in the Setting of Active Surveillance*

Among MRSA-colonized patients identified through the point prevalence surveys, 44% (39/89) in the NICU and 67% (24/36) in the PICU (P=0.03 for difference) were in contact isolation for any reason. Lack of appropriate contact precautions was particularly common for neonates identified by point prevalence survey as being MRSA-colonized during the first 14 days of ICU stay (only 16% [4 of 25] of MRSA-colonized neonates during the first 14 days were in contact precautions, versus 55% [35 of 64] during days >14, P<0.001 for difference, Figure 2).
Figure 2. The distribution of MRSA-colonized patients across ICU days of surveillance.
F. **Impact of Periodic Active Surveillance in NICUs**

In addition to mandated admission screening, 7 of 10 NICUs additionally employed periodic screening strategies (e.g., weekly, twice monthly, or 10 days post-admission) at some point during the 5 year study period, affecting 55% (1162/2101) of participating NICU patients. There was no significant difference in MRSA colonization prevalence during NICU time periods with versus without periodic screening (3.5 vs 5.1% respectively, \( P = 0.08 \)). Furthermore, we did not find a significant difference in rates of appropriate contact precautions during NICU periods with or without periodic screening (42 vs 46%, \( P = 0.83 \)).

G. **Performance Characteristics of Testing Different Body Sites for MRSA**

**Colonization Testing**

We assessed the performance characteristics of testing body sites individually for MRSA carriage (nose and umbilicus for NICU patients; nose and groin for PICU patients) using the reference standard of being MRSA positive in any combination of the two body sites during point prevalence testing. For NICU patients who had MRSA culture results available for both nostrils and umbilicus sites, nasal culturing alone identified 87% (62 of 71) MRSA-positive neonates, while 9 patients (13%) were nasal culture negative and umbilicus culture positive for MRSA (Table II). For PICU patients, nasal culturing alone identified 85% (23 of 27) MRSA-positive PICU patients, while 4 patients (15%) were nasal culture negative and groin culture positive for MRSA.
### TABLE II

PERFORMANCE CHARACTERISTICS OF INDIVIDUAL BODY SITE TESTING FOR MRSA COLONIZATION

<table>
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<tr>
<th></th>
<th>Sensitivity % (95% CI)</th>
<th>Negative predictive value % (95% CI)</th>
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<tr>
<td><strong>NICU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nose only</td>
<td>87 (77 – 94)</td>
<td>99.4 (99 – 100)</td>
</tr>
<tr>
<td>Umbilicus only</td>
<td>55 (43 – 67)</td>
<td>98 (97 – 99)</td>
</tr>
<tr>
<td>Nose + umbilicus (Ref)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>PICU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nose only</td>
<td>85 (66 – 96)</td>
<td>99 (98 – 100)</td>
</tr>
<tr>
<td>Groin only</td>
<td>41 (22 – 61)</td>
<td>97 (95 – 98)</td>
</tr>
<tr>
<td>Nose + groin (Ref)</td>
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</table>

**Note.** Since a positive culture for MRSA was always considered a true positive, specificity and positive predictive value = 100% for all body sites.
IV. DISCUSSION

We studied the epidemiology of MRSA colonization among NICU and PICU patients across a spectrum of community and academic hospitals in the city of Chicago, during the 5 years following mandated active surveillance for MRSA. Using serial point prevalence surveys, we identified MRSA colonization in approximately 1 in 25 NICU patients and 1 in 20 PICU patients, with evidence of on-going ICU acquisition in both unit types. We did not find a decrease in MRSA colonization during the 5 years of surveillance; rather, NICU colonization rates were unchanged, and PICU colonization rates increased over time.

This study assessed MRSA epidemiology during a time period in which community-associated MRSA strain types had already become endemic in the United States [13]. Prior single-center studies among NICU patients, performed over prolonged time periods, have found MRSA colonization rates of 1.3 to 1.8% [7, 14]. Higher MRSA colonization rates of 8.6 to 40% have been reported among other single centers during outbreak settings [8, 10, 15]. Among PICU patients, endemic MRSA colonization rates of 3.6 to 4.3% have been reported [16, 17].

The goal of active surveillance is to identify all MRSA-colonized patients to appropriately apply infection control precautions and prevent patient-to-patient transmission. We found high rates of compliance with active surveillance across all NICUs and PICUs. Yet, we found that among MRSA-colonized patients identified through the point prevalence surveys, over half of those in the NICU and a third of those in the PICU were not in contact precautions.
There are several possible explanations for the deficit in appropriate contact precautions: (1) study testing (we used 2 body sites and used broth enrichment) was modestly more sensitive than that used in most hospitals, (2) lag time between hospital admission test collection and result, (3) lag time between positive test result and contact precautions initiation, or (4) MRSA acquisition.

We were not able to directly assess the impact of routine MRSA active surveillance on MRSA prevalence rates, as all hospitals in our study cohort performed mandated MRSA active surveillance; thus, we did not have a non-intervention control group (either historically or concurrently) as a comparator.

This study provides insight into some important knowledge gaps regarding MRSA active surveillance in the pediatric population [18]. Consistent with prior studies [7, 19], we found MRSA to be uncommon among NICU patients within 2 days of admission; therefore, if facilities choose to perform MRSA active surveillance among NICU patients, they should consider performing surveillance at least one additional time point beyond the first 2 ICU days. It is important to note that we did not detect a significant difference in MRSA prevalence or incidence between NICU time periods with and without periodic surveillance; however, lack of difference may have resulted from confounding, as ICUs choosing to perform period surveillance may have been responding to higher MRSA rates.

Our findings also suggest that screening the anterior nares alone is sufficient to detect MRSA colonization. For both the NICU and the PICU populations, nares screening alone had a negative predictive value of 99%, compared to adding the umbilicus site among NICU patients
or groin site among PICU patients. Other studies have supported the nares as the single best site for screening MRSA colonization among NICU patients [8, 20]. Notably, we did not screen the pharynx among PICU patients; this site has been reported in one study to have higher sensitivity compared to nares for MRSA surveillance [17].

Our MRSA surveillance method included testing at 2 body sites as well as broth enrichment of specimens, making the study method more sensitive than that reported by hospitals, potentially biasing estimates of hospital acquisition rates. With respect to extra-nasal testing, the additional MRSA cases recovered was modest (9 additional neonates and 4 additional pediatric patients over the entire study period) and did not substantially change our estimates for ICU acquisition. Furthermore, the primary colonization prevalence outcome, which relied only point prevalence testing results, was unbiased with respect to testing method.

In summary, in a region with mandated MRSA active surveillance, we found on-going MRSA colonization and acquisition in a proportion of NICU and PICU patients across a large metropolitan city. Our findings highlight differences in MRSA epidemiology between NICU and PICU patients, particularly with respect to admission prevalence and timing of acquisition, which may inform future prevention interventions.
CITED LITERATURE


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ABSTRACTS:


7. Michael Lin, MD, MPH, Rosie Lyles, MD, MHA, Karen Lolans, B.S., Mary Hayden, MD, Alexander Kallen, MD, MPH, Stephen Weber, MD, MSc, Robert Weinstein, MD and William Trick, MD. “Glass half empty or half full? The effectiveness of mandated active surveillance in placing methicillin-resistant Staphylococcus aureus (MRSA)-colonized intensive care unit (ICU) patients in Contact Precautions.” Oral presentation at the 20th Annual Scientific Meeting of the Society for Healthcare Epidemiology of America (SHEA), March 2010, Atlanta, Georgia.


LECTURES/SEMINARS:


5. Lyles, RD, Weinstein, RA, & Vollman, K, “New Evidence-Based Approaches to Preventing Hospital Acquired Infections in the ICU Setting: Emphasis on Resistant Organisms,” Oral
presentation at the National Teaching Institute and Critical Care Exposition, May 2006, Anaheim, CA.