

Community-Acquired MRSA Infections in North Carolina Children: Prevalence, Antibiotic Sensitivities, and Risk Factors

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Abstract

Background: The incidence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections in children has increased dramatically over the past decade. CA-MRSA infections are often resistant to standard outpatient antibiotics and present a large burden to the health care system and to afflicted families.

Objectives: Our aims were to characterize the patterns of CA-MRSA resistance to common antibiotics and to identify significant risk factors for CA-MRSA infection in healthy children at a large urban hospital. Additional goals were to discover the prevalence of CA-MRSA in the institution and to observe any notable trends surrounding CA-MRSA infection in the facility.

Methods: We retrospectively analyzed the medical records of patients under 18 years of age in the WakeMed Health and Hospitals system with cultures positive for *Staphylococcus aureus* over a period of seven and a half months in 2006. Cases were classified as community-acquired, and we then analyzed risk factors and examined trends surrounding CA-MRSA infection.

Results: A total of 229 cases of *Staphylococcus aureus* infection were identified over the study period, of which 142 were CA-MRSA, a prevalence of 75.9% (95% CI, 69.5-82.3). Our CA-MRSA isolates were 98.6% sensitive to trimethoprim-sulfamethoxazole, 94.4% sensitive to tetracycline, 90.8% sensitive to clindamycin, and 59.9% sensitive to levofloxacin. Risk factors for CA-MRSA infection included parental employment in a school or daycare, family history of boils or MRSA, and antibiotic use by children in the past six months.

Limitations: Our definition of CA-MRSA is based on retrospective data from patient and family verbal histories in the medical record. We did not perform molecular genotyping of MRSA samples to confirm community-associated strains.

Discussion: CA-MRSA is now the predominant strain of *Staphylococcus aureus* causing childhood infections in this central North Carolina hospital. Thus, standard antibiotic therapy with penicillins or first generation cephalosporins is no longer adequate for most pediatric skin and soft tissue infections in this population. Trimethoprim-sulfamethoxazole and clindamycin both appear as reasonable alternatives for empiric therapy.

Keywords: MRSA; methicillin-resistant; community-acquired; North Carolina

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a commonly encountered pathogen in medical practices around the world. Initially considered an organism acquired strictly in health care settings, community-acquired MRSA (CA-MRSA) strains now afflict patients without previous hospital exposures. Most CA-MRSA outbreaks reported before 1990 occurred in specific populations such as Native Americans, intravenous drug users, and prison inmates, but over the past decade, the prevalence of this organism has risen dramatically in the general population.¹⁻³ Thousands of cases of CA-MRSA infection have been documented, and the

organism has been increasingly blamed for superficial and invasive infections in pediatric patients.⁴⁻⁸ Furthermore, the majority of afflicted children do not have readily identifiable risk factors for MRSA colonization or infection.⁹ While some studies have demonstrated socioeconomic risk factors for MRSA colonization or infection, there remains no definite consensus as to why otherwise healthy children acquire these resistant bacteria.¹⁰⁻¹²

At one pediatric hospital center in Texas, CA-MRSA is now responsible for 76% of all skin and soft tissue infections.¹³ Similar reports of soaring CA-MRSA infection rates in pediatrics have

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been published across the country, and many pediatricians have altered their prescribing practices to address this increasing problem in the outpatient arena. While generally resistant to beta-lactams and cephalosporins, CA-MRSA is usually susceptible to alternative oral medications such as trimethoprim-sulfamethoxazole, clindamycin, and tetracycline. However, even with adequate outpatient antibiotic therapies, many children still require hospitalization, intravenous antibiotics, and surgical drainage of their lesions.

Despite the increasing burden of CA-MRSA on pediatric patients and on the health care system, the exact prevalence of this organism is still not known in many areas of the country. In North Carolina, one study has examined the CA-MRSA prevalence in children, but this was done in an emergent setting and only investigated cutaneous infections.¹⁴ Furthermore, this study did not release the full antibiotic sensitivity panels on their CA-MRSA isolates. For this study, our primary goals were to characterize the pattern of CA-MRSA resistance to commonly used antibiotics and to discover clinically significant risk factors for infection in our pediatric patients. Secondary goals were to calculate the prevalence of this organism in our pediatric center and to observe any notable trends surrounding CA-MRSA infection in otherwise healthy children.

Methods

All patient data for this study was obtained through the WakeMed Health and Hospitals system in Raleigh, North Carolina and the WakeMed Institutional Review Board approved this study. WakeMed is a tertiary care center with 24 pediatric inpatient beds, a pediatric intensive care unit, a level III neonatal intensive care unit, a busy outpatient pediatric clinic, and a dedicated pediatric emergency department with over 40,000 emergency room visits annually. WakeMed receives pediatric referral patients from numerous outside clinics and hospitals throughout central North Carolina and provides advanced subspecialty care in many areas of pediatrics. It is also affiliated with the School of Medicine at the University of North Carolina at Chapel Hill.

We retrospectively analyzed the medical records of patients under 18 years of age with a microbiology culture positive for *Staphylococcus aureus* from January 1, 2006 to August 15, 2006. Patient records were reviewed by a single clinician over a two-month period. Over 98% of the patients resided within a 30 mile radius of the WakeMed Raleigh campus, an area that includes portions of Wake, Johnston, Durham, Harnett, Franklin, Nash, and Granville counties.¹⁵ This grouping of counties included urban, suburban, and rural communities. Positive MRSA samples were obtained from both inpatient and outpatient subjects in a variety of locations including hospital wards, intensive care units, emergency rooms, operating rooms, and pediatric clinics. Susceptibilities were reported using Clinical and Laboratory Standards Institute (formerly NCCLS) breakpoint guidelines.¹⁶ Microbial susceptibilities to ampicillin-sulbactam, cefazolin, clindamycin,

erythromycin, levofloxacin, oxacillin, penicillin G, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin were tested on each isolate. Inducible resistance to clindamycin through a positive D-test was also reported. Linezolid results were not routinely reported by our microbiology laboratory, and oxacillin resistance was considered synonymous with methicillin resistance. Study data were tracked in a Microsoft Access database and then classified as community-acquired based on patient histories, which were available in the medical record. No direct patient or family interviews were conducted. Statistical analysis was performed using SAS software. We compared the prevalence and antibiotic resistance of CA-MRSA isolates against those of community-acquired methicillin-susceptible *Staphylococcus aureus* (CA-MSSA) samples. The main outcome of interest was the prevalence of CA-MRSA. Prevalence ratios and 95% confidence intervals for a priori demographic, patient history, and infection characteristic risk factors were estimated using unadjusted log-prevalence regression. Statistical significance was evaluated at the $\alpha = 0.05$ level.

For the purposes of this study, infections were considered to be community-acquired if: (1) subjects had no hospital admissions one year prior to their *Staphylococcal aureus* culture; (2) subjects had no chronic diseases or major diagnoses other than asthma, mild eczema, or attention-deficit hyperactivity disorder; and (3) the positive culture was from a lesion that was clinically apparent at the time of admission and was the primary reason for admission. We classified cultures obtained from outpatient surgical procedures as community-acquired if they also met these above criteria. Infections were excluded from community-acquired data analysis if any one of the three above criteria were not met, if the sample was from a child in the neonatal intensive care unit, if the subject lived in a long-term care facility, or if the child had a past history of MRSA infection.

Results

A total of 273 *Staphylococcus aureus* cultures were obtained during the study period, of which 98 were methicillin-susceptible and 175 were methicillin-resistant. During the chart review, 12 cases had *Staphylococcus* urine samples with bacterial colony counts lower than 10,000 and were excluded. Eighteen cases had no clinical information related to the *Staphylococcal* culture in the chart and were also excluded. Six patient charts could not be located for review, and another eight charts had incorrect medical record numbers and were not included. Thus, the final number of records reviewed was 229. Of these 229 files, 42 did not meet the study criteria for community-acquired organisms and were not included in the statistical analysis. Ultimately 45 CA-MSSA cases and 142 CA-MRSA cases were integrated into the final statistical analysis.

In the analyzed data, 76% (142 of the 187 total cases) of the community-acquired *Staphylococcus aureus* infections were MRSA (95% CI, 69.5-82.3). Resistance patterns of CA-MRSA

were as follows: 1.4% resistant to trimethoprim-sulfamethoxazole, 5.6% resistant to tetracycline, 9.2% resistant to clindamycin, and 35.2% intermediately resistant to levofloxacin with 4.9% highly resistant to levofloxacin (see Table 1). There were six cases of inducible clindamycin resistance in our study (D-test positive with erythromycin), but these were categorized as clindamycin-resistant for the purpose of data analysis.

Table 1.
Proportion of CA-MRSA and CA-MSSA Isolates Resistant to Other Antibiotics

Antibiotic	CA-MRSA N = 142 n (%)	CA-MSSA N = 45 n (%)
Trimethoprim-Sulfamethoxazole	2 (1.4)	0
Tetracycline	8 (5.6)	1 (2.2)
Clindamycin	13 (9.2)	4 (8.9)
Levofloxacin - Total	57 (40.1)	2 (4.4)
Levofloxacin - Intermediate	50 (35.2)	2 (4.4)
Levofloxacin - High	7 (4.9)	0

Table note: Percentages may not add to 100% due to missing values.

We grouped infection location by body region (head, trunk/extremity, groin/buttock, and non-skin or soft tissue) for analysis. A groin/buttock infection was more likely to contain CA-MRSA than a trunk/extremity infection; however, this predilection was not statistically significant. We also examined the incidence of non-skin or soft tissue infections (NSST), which were defined as positive cultures in blood, cerebrospinal fluid, urine, bone, joint, pharynx, sputum, or lymph nodes. We found nine cases of NSST infection with CA-MRSA and six cases of NSST with CA-MSSA. There were no significant patterns or trends noted in our NSST infections in this small sample.

Within the demographic analysis, CA-MRSA was less prevalent among Latino patients (56.3%) as compared to white patients (76.8%), with an odds ratio (OR) of 0.73 (95% CI, 0.47-1.15). African Americans showed a slightly higher prevalence of CA-MRSA infection (83.5%) as compared to white patients. The OR was 1.09 (95%CI, 0.93-1.27). Patients with parents who worked in schools or daycares were at significantly increased risk of CA-MRSA illness (100%) compared to those with parents working in an office (64.5%), with an OR of 1.55 (95% CI, 1.19-2.01). Children with parents working in health care or medical fields were not at significantly increased risk for MRSA infections (84.6%) as compared to those whose parents worked in offices. The OR

was 1.31 (95% CI, 0.96-1.79). Children with unemployed parents were not found at statistically increased risk of CA-MRSA infection (83.6%) as compared to employed parents (79.2%), with an OR of 1.06 (95% CI, 0.91-1.22). MRSA was more prevalent among Medicaid patients (80.2%); however, this was not significantly more than those with private insurance (73.3%), with an OR of 1.09 (95% CI, 0.92-1.30). All of these data, as well as data for CA-MSSA risk factors, are presented in Table 2.

Additional risk assessment revealed that children who received antibiotics in the six months prior to their positive culture were more likely to be infected with CA-MRSA (31% overall had recent antibiotics; CA-MRSA among those with recent antibiotics was 86.2%, CA-MRSA among those without was 71.3%, with an OR of 1.21 (95% CI, 1.04-1.41). Patients whose family members had a history of MRSA infection or a history of skin boils were also at significantly greater risk of CA-MRSA infection (88.9%) compared to those without (73.8%). The OR was 1.21 (95% CI, 1.02-1.42). Children with personal histories of cellulitis were not at significantly increased risk of CA-MRSA infection. CA-MRSA among those with a positive history was 85.2%, while prevalence among those without was 74.4%, with an OR of 1.15 (95% CI, 0.96-1.37) (see Table 2).

Discussion

Over the past decade, CA-MRSA infection has become a quickly growing problem in pediatric hospitals across the nation. Pediatric institutions from California, Alabama, Rhode Island, Tennessee, Illinois, and Texas have all published articles reporting CA-MRSA infection rates between 20-76% of their overall *Staphylococcal* infection numbers.^{4,5,8,17,18} While our methods and findings are not identical to these previously published reports, our study confirms that CA-MRSA has indeed established itself as the primary cause of skin and soft tissue infections in the children of this North Carolina facility. The CA-MRSA infection rate of 75.9% (95% CI, 69.5-82.3) is one of the highest percentages reported in the pediatric literature over the past several years. The pediatric centers who reported CA-MRSA rates before 2006 have not published subsequent studies with updated prevalence rates. Thus, our high infection prevalence may demonstrate more CA-MRSA in North Carolina than other states, or it may reflect recent increases in CA-MRSA infections across many states. Further investigation is warranted to determine the current prevalence at hospital and community levels from state to state.

These findings suggest that antibiotic treatment with beta-lactam and cephalosporin drugs is no longer appropriate for children with suspected gram-positive infections in this institution, and this may also be true for hospitals with similar populations throughout North Carolina. Alternative antibiotics such as trimethoprim-sulfamethoxazole, clindamycin, or tetracycline are more appropriate empiric choices for skin and soft tissue infections. More serious infections requiring

Table 2.
Risk Factors for CA-MRSA and CA-MSSA Infection

	CA-MRSA N = 142 n (%)	CA-MSSA N = 45 n (%)	PR ^a	95% CI	p-value
Gender^b					
Male (reference)	63 (76.8)	19 (23.2)			
Female	78 (78.0)	22 (22.0)	1.0	0.87-1.19	0.85
Age^c					
0 to 1 years (reference)	20 (69.0)	9 (31.0)			
>1 to 5 years	44 (71.0)	18 (29.0)	1.03	0.77-1.38	0.85
>5 to 13 years	34 (79.1)	9 (20.9)	1.15	0.86-1.53	0.35
>13 to 18 years	39 (83.0)	8 (17.0)	1.2	0.91-1.59	0.19
Ethnicity^c					
White (reference)	53 (76.8)	16 (23.2)			
African American	76 (83.5)	15 (16.5)	1.09	0.93-1.27	0.3
Latino	9 (56.3)	7 (43.8)	0.73	0.47-1.15	0.18
Other	3 (60.0)	2 (40.0)	0.78	0.38-1.62	0.51
Insurance Status^c					
Medicaid (reference)	97 (80.2)	24 (19.8)			
Non-Medicaid	44 (73.3)	16 (26.7)	1.09	0.92-1.3	0.32
Parent Occupation Status^d					
Employed (reference)	84 (79.2)	22 (20.8)			
Unemployed	51 (83.6)	10 (16.4)	1.06	0.91-1.22	0.48
Parent Occupation^d					
Office (reference)	20 (64.5)	11 (35.5)			
School/daycare	17 (100.0)	0	1.55	1.19-2.01	0.005
Medical	22 (84.6)	4 (15.4)	1.31	0.96-1.79	0.09
Unemployed	51 (83.6)	10 (16.4)	1.3	0.98-1.72	0.04
Other ^e	25 (78.1)	7 (21.9)	1.21	0.88-1.67	0.23
Antibiotic Use					
No recent use (reference)	92 (71.3)	37 (28.7)			
Recent use	50 (86.2)	8 (13.8)	1.21	1.04-1.41	0.01
Family History of MRSA or Boils					
No (reference)	118 (73.8)	42 (26.3)			
Yes	24 (88.9)	3 (11.1)	1.21	1.02-1.42	0.02
Personal History of Cellulitis					
No (reference)	119 (74.4)	41 (25.6)			
Yes	23 (85.2)	4 (14.8)	1.15	0.96-1.37	0.14
Location of Infection^b					
Trunk/extremities (reference)	70 (74.5)	24 (25.5)			
Head	16 (66.7)	8 (33.3)	0.9	0.66-1.22	0.48
Groin/buttock	42 (85.7)	7 (14.3)	1.15	0.98-1.36	0.09
Non-skin or soft tissue (NSST)	9 (60.0)	6 (40.0)	0.81	0.52-1.24	0.3

Table note: Numbers that are presented in bold are statistically significant.

a PR = prevalence ratio (95% confidence interval).

b Data missing on 5 patients.

c Data missing on 6 patients.

d Data missing on 20 patients.

e Other occupation includes manufacturing (4), retired (2), self-employed (2), retail (13), and restaurant (11).

hospital admission may necessitate empiric intravenous clindamycin or vancomycin until susceptibilities are determined. Levofloxacin may be another possible outpatient therapy as the number of highly-resistant CA-MRSA cases was small. Yet there was a large percentage of intermediate resistance to levofloxacin, and it remains unclear if customary treatment dosages would overcome this resistance in vivo. We also included six cases of inducible clindamycin resistance (D-test positive) in our analysis, in which we found nearly 10% of all CA-MRSA cases resistant to clindamycin. Since we cannot determine the true in vivo resistance of these D-test positive cases, the actual rate of clindamycin resistance in our community may be closer to 7%. Finally, treatment with linezolid would also likely be adequate therapy for CA-MRSA infection, but our laboratory did not routinely report results with this drug.

Minority ethnicity and lower socioeconomic status have both been demonstrated in previous studies to be risk factors for CA-MRSA infection.¹⁰⁻¹² While our data did show a trend toward increased risk among African American patients as compared to white patients, we did not find employment status or other demographic factors to be significant risk factors for CA-MRSA. We did find that CA-MRSA infections were less common among Latino children when compared to non-Latino white children; however, this did not reach statistical significance and is based on a very small number of Latinos in the study population. To our knowledge this trend has not been previously reported, and possible environmental or sociological factors responsible for this decreased infection risk were not readily apparent in our data or in the published literature.

There has been past suspicion that parental occupation may play a role in a child's risk for CA-MRSA infection, yet no studies have conclusively proven this theory. We did find that children with parents working in schools or daycares were at significantly increased risk of CA-MRSA illness as compared to those who worked in an office. This likely stems from subclinical colonization of the parent at work, with transmission to the child at home. Conversely, it is possible that children with parents working in schools or daycares are themselves more likely to be enrolled in school or daycare, and direct exposure in those settings could also explain their increased risk. Past studies examining the rates of CA-MRSA colonization in children attending daycare centers have shown significant disease burdens that often mirror increasing MRSA rates in the general community.^{19,20} One might surmise that a child of a parent working in the health care field would also be at higher risk for CA-MRSA infection, yet an elevated prevalence in this group as compared to those who work in an office was not a significant finding in this study. Data on parental occupation was not obtained for 21 subjects. Therefore, power was lost to detect these expected differences assuming that the missing data was absent at random.

In our study, CA-MRSA was more common in soft tissue infections of the groin/buttock region, but this trend did not reach statistical significance. One possible explanation for this increased groin/buttock prevalence is that primary care

physicians may be more likely to refer most groin lesions to a pediatric surgeon for incision and drainage in the hospital setting. There may be other unrecognized reasons influencing groin/buttock area CA-MRSA infections, but at present there are no published reports addressing these risk factors.

Finally, several well-regarded risk factors for CA-MRSA infection were examined in our analysis. MRSA was more prevalent among children with personal histories of cellulitis, children with household exposure to others with past MRSA infection or skin boils, and children with a history of recent antibiotic use. The prevalence of MRSA was increased significantly for the latter two factors. Our finding that patients who received antibiotics in the previous six months were more likely to be infected with CA-MRSA than those who had not suggests that the overuse of outpatient antibiotics may be playing a large role in the acquisition of this resistant organism. In the majority of subjects, the reason for this recent antibiotic use was unknown. Data on household exposures and past history of cellulitis was gathered only if there was mention of these risk factors in the chart review. Many charts were missing this information and therefore were classified as negative. Thus, there could be a larger proportion of subjects with these significant risk factors who were not evident through our retrospective data collection. Although we were able to see a significant positive association of family history of boils or MRSA with MRSA infection, it is likely that if the misclassification was nondifferential, the results of these factors may be an underestimate of the true value.

Limitations

The major limitation of this study is our definition of CA-MRSA cases based solely on retrospective data from patient and family verbal histories in the medical record. Several other hospitals operate in the immediate area, and verbal history alone may have omitted recent patient admissions to these facilities, which would have changed the subject's classification to non-community-acquired for our study. We did not conduct genotyping of MRSA cultures, which would have provided better categorization of samples as community-acquired in origin. Without genotyping, infections in children with past MRSA were considered hospital-associated and removed from our data analysis. Despite the loss of sample size, we feel that being stringent in our definition of the study population was warranted to insure the integrity of our conclusions. Overall, we believe that our definition of community-acquired infection includes all the necessary criteria to adequately analyze our data. Moreover, we feel our criteria are similar to those used in recent published studies addressing CA-MRSA prevalence.^{4,5,8,10,16}

Another possible limitation is that the majority of patients were referred to the emergency department by their primary physicians. Thus, referral bias may have led us to overestimate the prevalence of CA-MRSA in the larger population. It is also possible that our data includes some misclassification error as the medical record review was performed by only one

individual. Finally, missing parental occupation and insurance coverage data may have affected some of our conclusions on CA-MRSA risk factors by decreasing the sample size and the precision of our estimates.

Our study demonstrates that the incidence of CA-MRSA among children in this North Carolina facility is extremely high and that CA-MRSA has become the predominant strain of *Staphylococcus aureus* causing clinically significant pediatric infections. Coming from urban, suburban, and rural surrounding counties, this population appears representative of children across North Carolina. However, MRSA data from other pediatric centers throughout the state is needed in order to

broadly apply our findings and conclusions. This research indicates that empiric antibiotic therapy with penicillins or cephalosporins is no longer adequate for skin and soft tissue infections in this institution and that this may be very relevant to similar sites treating children in North Carolina. Trimethoprim-sulfamethoxazole, tetracycline, and clindamycin appear to be reasonable alternatives for empiric therapy in suspected CA-MRSA infections. Children with parents employed in schools or daycares or those who received recent antibiotics are at greater risk of CA-MRSA infection, as are children with household exposures to family members with histories of MRSA infections or skin boils. **NCMJ**

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