CLINICAL INVESTIGATION

Utilizing Pharmacy Records to Assess Antibiotic Prescribing Patterns on the Incidence of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections in Children

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OBJECTIVE To assess the effect of prior antibiotic therapy on the incidence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections in children.
METHODS This was a concurrent and retrospective review of antibiotic records for children < 18 years of age with documented CA-MRSA infection identified between January 1, 2004, and December 31, 2005. Antibiotic records were compared against a control group. The primary outcome was the incidence of CA-MRSA using linear regression as a function of age and prior antibiotic therapy (i.e., 3 months prior to admission). Secondary objectives included a comparison of antibiotic courses and classes and a description of antibiotic susceptibilities in patients with CA-MRSA
RESULTS Data from 26 patients were included. Nine out of 51 patients (18%) with CA-MRSA were included. Another 17 children were enrolled in the control group. The median age was approximately 1.75 years (0.08-14 years) in the CA-MRSA group versus 2.75 years (0.005-15 years) in the control group. A statistical difference was noted in the number of patients with prior antibiotic exposure between the CA-MRSA and control group, 8 (88.9%) versus 6 (35.3%), respectively (P = .01). Antibiotic exposure was found to be a significant independent risk factor (P = .005; 95% CI, 0.167-0.846) for the development of CA-MRSA. The interaction between antibiotic exposure and age < 3 was the most significant predictor of CA-MRSA (P = .019; 95% CI, 0.139-1.40).
CONCLUSIONS Prior antibiotic therapy in patients < 3 years of age was associated with a significant risk of developing CA-MRSA. A comprehensive assessment of CA-MRSA patients should include objective methods of measuring prior antibiotic exposure such as pharmacy records.

KEYWORDS antibiotics, children, community-acquired methicillin-resistant *Staphylococcus aureus*

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INTRODUCTION

Since its initial report in 1968,[1] methicillin-resistant *Staphylococcus aureus* (MRSA) infection has been a growing problem in health care institutions across the United States.

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ABBREVIATIONS CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* CDC, Centers for Disease Control and Prevention; MRSA, methicillin-resistant *Staphylococcus aureus;* HIV, human immunodeficiency virus; PCV-7, pneumococcal conjugate vaccine; TMP/SMX, trimethoprim-sulfamethoxazole

Today, many tertiary care facilities across the

country report that greater than half of the isolates of *Staphylococcus aureus* collected are methicillin resistant.[2] Until recently, many patients with skin and soft tissue infections with *Staphylococcus aureus* isolated from the community were thought to be mainly methicillin susceptible with only a 20% incidence of MRSA isolates noted in ambulatory patients from the 2003 National Nosocomial Infections Surveillance (NNIS) System Report.[2] However, the incidence of infections resulting from community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) in otherwise healthy children is growing at an alarming rate across many regions of the country, including Tennessee, Texas, Minnesota, and Illinois.[3-9] In fact, Kaplan and colleagues[5] reported that over three-fourths of their community-acquired *Staphylococcus aureus* infections were methicillin-resistant.

Many groups have looked specifically at risk factors for CA-MRSA infections in children. Such risk factors include participation in sports activities, history of chronic disease, prior antibiotic therapy, prior hospitalization, patients age of < 3 years, and exposure to the pneumococcal conjugate vaccine (PCV-7).[7,10-14] Another study by Creech et al.[10] noted that children with family members working in a medical facility were at higher risk of contracting CA-MRSA (OR 2.0; 95% CI, 1.03-4.1). Although many different patient characteristics have been suggested, no single risk factor has been recognized as the most important attribute associated with an increased risk of children developing CA-MRSA infections.

Much of the evidence regarding risk factors for colonization and infection with CA-MRSA has been extracted from children and young adults located in disparate geographical locations across the United States. Therefore, it may be difficult to identify specific risk factors in children until further research has been completed. Several investigators have analyzed the impact of previous antibiotic exposure, but these data were primarily collected by obtaining verbal patient and family histories.[4,7,15,16] Potential flaws in this type of data collection include the inability of patients and family members to recall specific information about antibiotics and the inability of researchers to access objective records for specific antimicrobials and the number of antibiotic courses. However, objective measures to access medication history have been documented in the literature. Sherman and colleagues[17] examined adherence to asthma medications using prescription refill histories from community pharmacies. They found that the refill histories had a 92% accuracy at predicting adherence ($r = 0.9$, $P = .0001$). Another group looked at the impact of adherence and viral load response in patients with human immunodeficiency virus (HIV).[18] They found that the pharmacy refill records were a useful tool for quantifying the change in viral load with 80% sensitivity at detecting a 10% non-adherence rate in patients with a viral load greater than 1,000 copies/ml. From these 2 studies, one may note that it could be reasonable to utilize prescription records obtained through community pharmacies to assess disease response rate. Thus, using data obtained by pharmacy records, researchers in the present study sought to ascertain the risk of developing CA-MRSA based on prior antibiotic exposure within 3 months prior to a given time period.

MATERIALS AND METHODS

Study Design

This study was a concurrent and retrospective study conducted at a 117-bed tertiary care children's hospital within a 473-bed, academic medical center. Patient referrals are received from within a 100-mile radius of Lexington, Kentucky. Subjects were included if they were < 18 years of age with a history of CA-MRSA as identified from January 1, 2004, to December 31, 2005, or if they were patients assigned to a control cohort group. Pharmacy records were gathered retrospectively from each subject's pharmacy or pharmacies. Informed consent and assent (i.e., patients > 12 years of age) were obtained upon entry into the study. The study was approved by the University of Kentucky Institutional Review Board.

Patients with CA-MRSA were previously identified through another retrospective and concurrent chart review at our institution analyzing the incidence of CA-MRSA versus community-acquired methicillin-susceptible *Staphylococcus aureus* infections (CA-MSSA) during a 2-year period. In this study, patients

were identified through 2 different methods. First, all isolates of *Staphylococcus aureus* were obtained for patients < 18 years from the clinical microbiology laboratory. To capture patients who may have been transferred from an outside hospital, additional patients were identified utilizing the University HealthSystem Consortium Database (University HealthSystem Consortium, Oak Brook, Illinois). We searched for patients < 18 years of age with potential sites of infections, including skin and soft tissue infections, osteomyelitis, myositis, lymphadenitis, bacteremia, septic arthritis (i.e., diagnostic review codes 020, 091, 126, 238, 242, 248, 277, 278, 279, 417, 683).

We considered the infection community-acquired *Staphylococcus aureus* (CASA) when the patient was admitted to the hospital and/or seen in a primary care clinic with a documented culture with either an oxacillin-resistant or oxacillin-susceptible *Staphylococcus aureus* (CA-MRSA versus CA-MSSA) isolate. This isolate had to have been collected within 48 hours after hospital admission or obtained from a clinic setting if the diagnosis was made on an outpatient basis. Patients were excluded if they had a history of MRSA infection and/or colonization, history of a permanent indwelling catheter or medical device implanted into the skin, and/or history of hospitalization, dialysis, or surgery within the previous year for a condition that fit the Centers for Disease Control and Prevention (CDC) definition for CA-MRSA infection.[19] Additionally, consistent with the methods of Kaplan and colleagues,[5] patients were also excluded if they had frequent visits to a medical facility secondary to a chronic illness (e.g., cystic fibrosis, chronic renal failure, history of malignancy, asthma, chronic skin illness, cerebral palsy).

To control for the high prevalence of antibiotic exposure in pediatric patients, antibiotic profiles were compared between a control group and patients with documented CA-MRSA. The control group was identified January through March 2006 and included patients admitted to the children's hospital with a diagnosis other than a *Staphylococcus aureus* infection; these patients were admitted to the general pediatrics or pediatric surgery services, and/or were seen in a clinic setting. These patients otherwise would have been noted as previously healthy and would have met the exclusion criteria for a documented CA-MRSA infection (i.e., no previous hospitalization, surgery, history of dialysis within the previous year; permanent indwelling catheters, or history of MRSA colonization).

In order to obtain pharmacy records from patients discharged from the hospital, contact information (i.e., telephone numbers) for the parents/guardians in the CA-MRSA group were identified using billing information obtained upon admission. Up to 2 attempts were made (via telephone and/or postal mail) to contact parents and guardians of children who had already been discharged. If no initial contact was made after 2 attempts, patients were considered lost to follow-up. During conversations, patients were provided background information on the study and were asked to provide their mailing address if they were interested in learning more. Interested parties were sent an introductory letter, informed consent form, and assent documents. Parents and guardians were also asked to provide the name of the pharmacy or pharmacies where they may have had a prescription filled within the 3-month timeframe prior to admission to the hospital or clinic visit. Parents and guardians of patients in the control group were asked to sign informed consent and assent documents and to provide pharmacy contact information prior to discharge. The informed consent and assent documents were provided to each subject's pharmacy or pharmacies, serving as a waiver for the Health Insurance Portability and Accountability Act in order to receive permission to access prior prescription records.

Study Endpoints and Data Collection

Baseline demographic and microbiological data were collected by a single investigator (PNJ). Initial assessment included review of patient age at the time of admission to the hospital and/or clinic, gender, and ethnicity. Because a significant association was observed between age and development of CA-MRSA in a number of epidemiologic studies identifying the characteristics of CA-MRSA versus health-care acquired methicillin-resistant *Staphylococcus aureus* (HA-MRSA) and CA-MSSA,[4,5,8,20] we categorized each patient into age ranges, including < 1 year of age, 1–2 years of age, 3–5

years of age, 6–9 years of age, 10–12 years of age, and > 12 years of age to ensure a matched control group to the patients with CA-MRSA. A number of other data were collected, including hospital and intensive care unit length of stay, site of infection, previous hospitalization within 1 year prior to admission, and possible household contacts with CA-MRSA (i.e., yes, no, unknown).

Antibiotic susceptibilities to *Staphylococcus aureus* isolates were performed at the clinical microbiology laboratory at the University of Kentucky, UK HealthCare. Isolates were tested with the Vitek (BioMerieux Vitek Inc., Hazelwood, Missouri) and Microscan systems (Dade International Inc., West Sacramento, California) for specific agents, including clindamycin, erythromycin, oxacillin, penicillin, trimethoprim-sulfamethoxazole (TMP/SMX), linezolid, tetracycline, rifampin, levofloxacin, ciprofloxacin, gentamicin, and vancomycin. For patients with a potential inducible erythromycin methylase gene, a disk diffusion test was performed in accordance to guidelines from the Clinical and Laboratory Standards Institute (CLSI) only at the clinician's discretion to determine susceptibility to clindamycin.[21] For patients who may have had documented cultures from an outside facility, an attempt was made to record the antibiotic susceptibility data as above.

Additional information was obtained from patients in addition to demographic and microbiologic data. The primary diagnoses for admission to the hospital and/or clinic visit were recorded. This diagnosis was grouped into a number of categories, including surgical admissions, an admission related to an infectious etiology other than a *Staphylococcus aureus* infection, and an admission related to other possible etiologies not defined prior to data collection.

Based on information provided by the parents and guardians, we contacted each pharmacy where the patient may have had a prescription filled. The pharmacies were asked to search their records for an antimicrobial agent that was dispensed within a 3-month time frame prior to the patient's admission to the hospital or visit to the clinic. The medication name, dose, dosage form, and duration of therapy were noted. The specific number of prior antibiotics and the number of classes were also recorded for each patient.

The primary end point was the development of CA-MRSA as a function of prior antibiotic exposure and age. Previous antibiotic exposure was defined as documented use of a number of antimicrobial agents, including macrolides, lincosamides (i.e., clindamycin), cephalosporins, other β-lactam antibiotics (i.e., penicillin, amoxicillin, amoxicillin/clavulanic acid), fluroquinolones, linezolid, and TMP/SMX. To control for the high prevalence of antibiotic prescribing patterns in pediatric patients, categorical ages were included in the analysis.

Several secondary outcomes were assessed. The number of antibiotic courses and antibiotic classes received within the 3-month time frame prior to admission to the hospital or clinic visit were compared between the CA-MRSA and control group. The designation of antibiotic class was derived using each drug's chemical structure and mechanism of action (i.e., cephalexin grouped as a cephalosporin and not β-lactam antibiotic). Other secondary outcomes included the effect of prior antibiotic exposure on the development of possible resistance patterns in patients with CA-MRSA. These patients were compared to patients without CA-MRSA that were included in the chart review from 2004 to 2005.

Statistical Analysis

Baseline characteristics were compared between the control cohort and the CA-MRSA group. Data were summarized as mean ± standard deviation or median when appropriate. Percentages were used for categorical data. Continuous data were compared using 2-sided difference of means tests. Nominal data were compared using Fisher's exact test. A P-value less than 5% was considered statistically significant. To control for age and prior antibiotic exposure, multiple linear regression was performed (STATA/SE version 8; Statacorp LP, College Station, Texas). A separate regression analysis was performed to correct for heteroscedasticity or uncertainties of the outcome, using the statistical software package for assessment of the dependent variable controlling for confounding factors including categorical age (i.e., < 1 year of age, 1–2 years of age, 3–5 years of age, 6–9 years of age, 10–12 years of age, and >

Table 1. Baseline demographic data of patients included for analysis of prior antibiotic exposure for the CA-MRSA group and control group

	CA-MRSA Group* (n = 9)	Control Group* (n = 17)
Male	4 (44.4)	8 (47)
Female	5 (55.6)	9 (53)
<1 yr	1 (11.1)	4 (23.5)
1-3 yr	4 (44.4)	4 (23.5)
3-5 yr	1 (11.1)	6 (35.3)
6-9 yr	0	2 (11.8)
10-12 yr	2 (22.2)	0
>12-17 yr	1 (11.1)	1 (5.9)
Caucasian	6 (66.7)	17 (100)
African-American	2 (22.2)	0
Hispanic	1 (11.1)	0

**Data presented as number (%).*

12 years of age), prior antibiotic exposure, and the interaction between the two.

RESULTS

Patient Demographics

From 2004 to 2005, 51 patients with documented CA-MRSA infections were identified. From the 2004-2005 observational study, there was a noticeable increase in the number of CA-MRSA infections over the 2-year period, 9/16 (56.3%) in 2004 versus 40/55 (72.7%) in 2005 (P = .340). We attempted contact of all of the patients with CA-MRSA up to 2 times, but 29 (56.8%) were lost to follow-up. Thirteen patients gave verbal consent, but did not return the consent and assent documents that would have enabled access to data from the pharmacy. The remaining 9 patients (17.6%) were included for analysis.

Several clinical characteristics of these patients were noted. Seven of these 9 patients (77.8%) were hospitalized for treatment of their infection. The median length of stay was about 2.5 days (0-9 days). Three of these patients (33.3%) had a family member with documented MRSA. Eight of the patients (88.9%) had skin and soft tissue infections while 1 patient had a case of septic arthritis.

Seventeen patients admitted to the children's hospital from January to March of 2006 were enrolled in the control group. Pharmacy records were obtained from all of these patients. The most common diagnosis for admission was surgical procedure (n = 8). Nine other patients were also incorporated in the analysis, including 6 children (35.3%) with an infectious etiology other than *Staphylococcus aureus*, 1 (5.9%) with a metabolic disorder, and 2 (11.8%) with neurological complications. Due to the high percentage of patients with CA-MRSA who were lost to follow-up, concurrent identification of patients in the control group was terminated following enrollment of the 17th patient.

Baseline demographic data are presented in Table 1. The median age was approximately 1.75 (0.08-14 years) in the CA-MRSA group versus 2.75 (0.005-15 years) in the control group. Approximately 50% of the patients were < 3 years of age. The majority of patients in the trial were Caucasian, 23 (88.5%).

There was a statistical difference in the number of patients with prior antibiotic exposure between the CA-MRSA group and control group, 8 (88.9%) versus 6 (35.3%), respectively (P = .01) (Table 2). The median number of antibiotic courses was approximately 0.06 (0–3 courses) in the control group and 1.0 (0–3 courses) in the CA-MRSA group. β-lactam antibiotics comprised the majority of antimicrobials prescribed in this cohort of patients (Table 3). However, a number of agents were also prescribed, including TMP/SMX and clindamycin, which have efficacy against CA-MRSA.

Antibiotic susceptibilities were evaluated for those with CA-MRSA. Overall, the CA-MRSA isolates that were available were 100% susceptible to a number of agents, including tetracycline, levofloxacin, vancomycin, linezolid, and rifampin. Although 1 patient had an isolate

Table 2. Description of prior antibiotic therapy within the 3 months prior to hospital admission or clinic visit for CA-MRSA group and control group

	CA-MRSA Group (n = 9)*	Control Group (n = 17)*	P-Value
Prior antibiotic exposure	8 (88.9%)	6 (35.3%)	.01
Number of antibiotic courses†	1.3 ± 0.87	0.59 ± 1.0	.06
Number of antibiotic classes†	1.2 ± 0.67	0.59 ± 1.0	.07

** Data presented as number (%).*
† Mean ± SD

that was resistant to TMP/SMX (11.1%), the patient did not have a prescription for TMP/SMX within the 3-month time frame prior to the development of CA-MRSA infection.

Multiple Linear Regression Analyses

Prior antibiotic exposure, within the 3-month time period, was found to be a significant predictor of the development of CA-MRSA (P = .005; 95% C, 0.167-0.846) (Table 4). Because approximately 50% of our patients were < 3 years of age and since younger patients have a greater risk for developing CA-MRSA, the regression analysis reflected (or included) only these patients. Correcting for heteroscedasticity, a separate regression analysis was performed to examine the development of CA-MRSA controlling for age < 3 years of age, prior antibiotic exposure, and the interaction between age and previous antibiotics. The interaction proved to be the strongest predictor of the development of CA-MRSA (P = .019; 95% CI, 0.139-1.4) (Table 5). Antibiotic exposure increased the probability of resistance by 50.6%, and age < 3 years increased the probability of resistance by 22%. The combination of age < 3 years and prior antibiotic exposure increased the probability of resistance by 75%.

DISCUSSION

Following the original report by Levine and colleagues[22] in 1982, a number of investigators have evaluated the incidence of CA-MRSA across the U.S. These infections have been associated with a number of significant complications, including bone and joint infections, renal failure, deep vein thrombosis, and the Waterhouse-Friderichsen syndrome characterized by petechial rash, coagulopathy, and cardiovascular collapse.[23,24] Perhaps the most distressing characteristic noted in a majority of the reports is the lack of a clear description of risk factors important for the development of these serious CA-MRSA infections. Due to the retrospective nature of this study, we were only able to adequately assess antibiotic exposure, age, history of household contact with MRSA exposure, and race. Only 3 patients with CA-MRSA were noted to have a family member with a history of a MRSA skin and soft tissue infection. This is consistent with the findings of Niami et al.[8] who found that only 4% patients in their cohort had a history of CA-MRSA exposure from a family member. Several groups have noted a disparity in these types of infections among African-American and Hispanic populations compared with other groups.[5,23] Kaplan and colleagues[5] found a significant difference in the number of African-American children with CA-MRSA versus CA-MSSA, 39.3% versus 27.1%, respectively (P < .000001). Due to the small number of patients included for analysis, we cannot comment on any perceived racial disparities in our patient population.

Our data suggest that previous antibiotic exposure (i.e., within a 3-month period) places children at higher risk for developing CA-MRSA infections. Our findings are similar to those reported by Hidron et al.[14] in an adolescent/adult population. The researchers performed a surveillance study that tracked patients after admission to the hospital; they looked at risk factors for nasal colonization with MRSA and found several groups at risk, including hospitalization within the previous 12 months (OR 4.01; 95% CI, 1.97-8.15), human immunodeficiency virus (HIV) negative patients with antibiotic exposure within 3 months prior to hospital admission (OR 2.46; 95% CI, 1.20-5.03), and patients with a clinical diagnosis of skin or soft-tissue infection identified upon admission (OR 3.40; 95% CI,

Table 3. Description of the total number of antibiotic classes that patients received prior to medical visit (n = 8 in the CA-MRSA group and n = 6 in the control group)

	CA-MRSA (n = 12)*	Control (n = 10)*
Penicillin derivates	4 (33.3%)	3 (30%)
Cephalosporins	4 (33.3%)	2 (20%)
Fluroquinolones	1 (8.3%)	0
TMP/SMX	1 (8.3%)	1 (10%)
Lincosamides	2 (16.7%)	0
Macrolides	0	4 (40%)

** Data presented as number (%).*
TMP/SMX = trimethoprim/sulfamethoxazole

1.46-7.90). They concluded that any of these 3 factors could predict 90% of patients colonized with MRSA.

To our knowledge, this is the first study to look specifically at an objective method of identifying antimicrobial therapy in a pediatric population. We attempted to identify the number of antibiotic courses and the specific agents that patients in the control and CA-MRSA groups may have received. The median number of antibiotic courses in the CA-MRSA group versus the control group was 1.0 versus 0.06, respectively. Baggett and colleagues[25] identified risk factors for CA-MRSA in a rural community in Alaska. They noted a significant difference in the median number of antibiotic courses between the CA-MRSA and control group, 4 versus 2, respectively (P = .01). It is important to note that this is difficult to extrapolate to our patient population as Baggett et al. assessed antibiotic therapy 1 year prior to infection. We cannot determine whether we could have found similar results with an additional 9 months of a year of pharmacy data.

Another significant risk factor for CA-MRSA that must not be overlooked relates to the age of the child. Herold et al.[3] looked retrospectively at the number of CA-MRSA infections between 2 different time periods, 1988-1990 and 1993-1995, and found that over 75% of these infections occurred in patients < 3 years of age. During our chart review of 51 patients with CA-MRSA from 2004 to 2005, we also noted that approximately 65% of patients were < 3 years of age. So why are younger patients at a greater risk for CA-MRSA infections? Some have speculated that the pneumococcal conjugate vaccine, PCV-7, recommended for children 2-23 months of age can place young children at risk for CA-MRSA infections.[26] Two recent reports suggest evidence of competition between vaccine-type *Streptococcus pneumoniae* and *Staphylococcus aureus* for patients receiving the PCV-7 vaccine, leading to an increased incidence of *Staphylococcus aureus* colonization in middle ear-fluid and the nasopharyngeal cavity and thus the potential for *Staphylococcus aureus* infections.[27,28] Children ≤ 2 years of age do have a higher incidence of acute otitis media (AOM) and a higher degree of antibiotic exposure to other age groups.[28] If the PCV-7 vaccine promotes *Staphylococcus aureus* colonization, it is unclear whether antibiotic exposure in children ≤ 2 years of age secondary to AOM and other types of infections could lead to the increased rate of CA-MRSA infections that many are observing. Our data suggest that it is both exposure to antibiotic therapy and age that correlate with > 75% probability for developing a CA-MRSA infection rather than the individual factors themselves.

Although the antibiotic susceptibilities for the CA-MRSA patients remained continued with a number of different agents and antibiotic classes, making significant interpretations of this pattern is difficult. The majority of patients with CA-MRSA and documented exposure to CA-MRSA received a β-lactam antibiotic prior to the development of their infections. One patient received the fluoroquinolone levofloxacin prior to the development of infection. Both levofloxacin and ciprofloxacin have been associated with the development of MRSA that indicates the acquisition of the grl*A* mutation.[29] Another patient received an outpatient prescription for TMP/SMX. Though 1 isolate was resistant to TMP/SMX, it was not noted in the patient with previous exposure with this agent.

Table 4. Multiple linear regression analysis for the development of CA-MRSA

Variable	Regression Coefficient	Standard Error	P-Value	95% Confidence Interval
Constant	–0.045			
Antibiotic exposure	0.506	0.164	.005	0.167-0.846
Patients*	–0.221	0.173	.215	–0.137-0.579

Degrees of freedom = 23, $r^2 = 0.476$
** = 3 year of age*

It is difficult to make an assessment of the clindamycin susceptibilities presented in Table 4. At our institution, the confirmatory disk diffusion test is a separate laboratory request from the culture and susceptibility testing and performed only at the request of the clinician. Thus, at this time, it is difficult to identify the exact incidence of CA-MRSA isolates with positive disk diffusion tests for inducible clindamycin resistance. For the 9 patients with CA-MRSA in this cohort, the disk diffusion test was performed on only 1 patient and was negative for inducible resistance. It is interesting to note that this patient did receive clindamycin therapy 3 months prior to the CA-MRSA infection. Another patient in this CA-MRSA cohort received clindamycin therapy after identification of the CA-MRSA infection without the confirmatory disk diffusion testing but had adequate response to this treatment.

Several limitations to our study exist. First, the trial involved a very small number of patients. The analysis here represents data from only one-fifth of the patients with CA-MRSA during the 2-year period, according to hospital or clinic records. With the informed consent and assent requirement, subject recruitment was difficult in the control group and the CA-MRSA group, especially given the primarily retrospective design of the study. Following a lapse of several months in subject recruitment, the study was ended. In light of the small number of patients, we attempted a post-hoc power analysis. As the endpoint is a dummy variable (0 or 1), the power calculation can be based on standard binomial calculations [e.g., assume probability p = 0.5 so the variance is p (1-p)/sample size = 0.25/26] adjusted for the attained r^2 value. Here, we would expect the variance to be almost 50% [e.g., (0.5) (0.25/26) = 0.0048, standard errors = 0.07). Looking at the more standard calculation [e.g., 90% power and 95% confidence implies 1.96 + 1.28 = 3.24 standard errors), we could detect an effect of a difference of 23 percentage points [(3.24) (0.07) = 0.23]. The estimated impact of the interaction is greater than 75% (i.e., 77 percentage points). If the interaction is the same or 50% less than this value, then we have enough power even with our small sample size.

Other limitations exist as well. Approximately 90% of the patients were Caucasian. With this small number of patients and limited racial diversity, it may difficult to apply these results to patients in other geographical regions in the United States. Next, it is worth mentioning that data collected from patients in the control group and CA-MRSA group were collected from 2 different time periods. Prescription records in the CA-MRSA group were largely collected between 2004 and 2005 while prescription records in the control group were collected in 2006. We do not note this to be a significant limitation given that out-patient prescribing practices have not significantly changed in our community during this timeframe. One other limitation is worth highlighting. Despite stratification of enrollment based on age categorization (< 1 year of age, 1–2 years of age, 3–5 years of age, 6–9 years of age, 10–12 years of age, and > 12 years of age), the 2 groups were not evenly matched for age (Table 1). However, the median ages were not statistically different, 2.75 (0.005–15 years) in the control group and 1.75 (0.08–14 years) in the CA-MRSA group. We did note a significant interaction between antibiotic exposures in children < 3 years of age, and there was an equal number of patients greater than and less than 3 years of age. In the study, we did include 2 children less than 1 week of age in the control group. There are now reports of CA-MRSA infections in infants in the neonatal intensive care unit from paternal exposure and health care workers.[30,31] Despite these limitations, we did identify some trends regarding

Table 5. Multiple linear regression analysis for the development of CA-MRSA, correcting for heteroscedasticity

Variable	Regression Coefficient	Standard Error	P-Value	95% Confidence Interval
Constant	0.200			
Antibiotic exposure	0.086	0.269	.753	–0.472–0.643
Patients*	–0.200	0.194	.315	–0.603–0.203
Interaction†	0.771	0.305	.019	0.139–1.40

Degrees of freedom = 22, $r^2 = 0.315$
** = < 3 years of age*
† = Interaction between antibiotic exposure and patients < 3 years of age

prior antibiotic therapy and age as risk factors for the development of CA-MRSA.

CONCLUSIONS

These results suggest that patients with prior antibiotic exposure who are less than 3 years of age have a significant risk for developing CA-MRSA. As other risk factors have been noted, an evaluation of a child with CA-MRSA should include an assessment of household contact with MRSA and daycare exposure. Review of pharmacy records could serve as a potential objective method that pharmacists and other clinicians may consider as part of a thorough medication history to evaluate the likelihood that a patient has been infected with CA-MRSA.

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