Epidemic of Community-Acquired Methicillin-Resistant Staphylococcus aureus Infections

A 14-Year Study at Driscoll Children’s Hospital

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Background: Previously we reported the rapid emergence and exponential increase of community-acquired (CA) methicillin-resistant Staphylococcus aureus (MRSA) infections in South Texas children.

Objective: To assess whether changes have occurred in the frequency, types, susceptibility, and treatment of CAMRSA infections at Driscoll Children’s Hospital.

Methods: Data from 1990 through 2001 were collected during 2 previous studies. Data from 2002 through 2003 were collected and compared with data from 1990 through 2001. All S aureus isolates were identified by a computer-assisted search of culture results, and the medical records were reviewed for all patients with MRSA infections.

Results: A total of 1002 MRSA cases were identified from 1990 through 2003 of which 928 (93%) were community-acquired. The number of CAMRSA cases ranged from 0 to 9 per year from 1990 through 1999 and then increased exponentially from 36 in 2000 to 459 in 2003. The most common type of CAMRSA infection in children without (94%) and with (72%) risk factors was cellulitis and abscess. A higher percentage of children with risk factors had invasive CAMRSA infections (26% vs 3%; P<.001). From 2002 through 2003, there was a significant difference in clindamycin susceptibility between CAMRSA isolates from children without and with risk factors and nosocomial isolates (97% and 86% vs 62%; P<.005). A higher percentage of patients admitted for treatment of CAMRSA infections received an empirical intravenous antibiotic to which the organism was susceptible when comparing 2002-2003 with 1990-2000 (96% vs 15%; P<.001). During this 14-year study, all patients recovered, including those with life-threatening CAMRSA infections.

Conclusion: The rapid emergence of CAMRSA as a cause of noninvasive and invasive infections in children, which started occurring in the 1990s, has reached epidemic proportions.

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14-year study period. Data were collected on patient age and sex, inpatient or outpatient treatment, community-acquired or nosocomial infection, presence of risk factors for MRSA infection, types of infections, susceptibility patterns of isolates, antibiotic therapy, requirement of incision and drainage, and mortality. Methicillin-resistant Staphylococcus aureus isolates not associated with disease (acute or chronic infection) were obtained from the noses, considered to be colonization, and excluded. Methicillin-
resistant Staphylococcus aureus isolates associated with disease were obtained by a variety of methods, including collection of spontaneously draining purulent fluid, incision and drainage, bronchoalveolar lavage, and bone aspiration. Duplicate MRSA isolates from the same patient were eliminated unless they represented new infections that were diagnosed and treated during outpatient visits or hospitalizations that were separated by at least 1 month. Methicillin-resistant Staphylococcus aureus isolates from patients with chronic infections or relapses were considered duplicates and excluded.

Methicillin resistance was determined by minimum inhibitory concentration using the VITEK broth culture system (bioMérieux Vitek, Inc, Hazelwood, Mo) and confirmed with the disk diffusion method. Double-disk diffusion tests (D-tests) were not routinely performed to determine inducible clindamycin resistance. Methicillin-resistant Staphylococcus aureus infections were considered to be community-acquired if they did not meet the Centers for Disease Control and Prevention (Atlanta, Ga) 1988 criteria for nosocomial infections. Accordingly, a nosocomial infection was defined as a localized or systemic condition that (1) resulted from adverse reaction to the presence of an infectious agent or its toxin and (2) was not present or incubating at the time of admission to the hospital. Additionally, if the MRSA infection was determined to be community-acquired, the CAMRSA infection was further categorized as occurring either in a patient without risk factors or in a patient with 1 or more risk factors for MRSA infection.

Children were classified as having 1 or more known risk factors for MRSA infection if review of the medical record indicated any of the following: underlying chronic disease, recent hospitalization or surgery (last 6 months), residence in a long-term care facility, presence of an indwelling catheter, child daycare center attendance, intravenous drug abuse, household contact with an identified risk factor, previous antibiotic use (last 6 months), or history of MRSA infections or colonization. The presence or absence of these risk factors was not always noted in the medical record. It was assumed that the risk factor was not present if it was not documented.

Infections were considered to be invasive if they were 1 of the following: bacteremia or sepsis, meningitis, endocarditis, toxic shock syndrome, pneumonia or empyema, bronchitis, osteomyelitis, septic arthritis, bursitis, lymphadenitis, periorbital or orbital cellulitis, mastoiditis, pyelonephritis, cystitis, and deep abscesses involving organs and structures other than the skin and subcutaneous tissues.

Descriptive and inferential statistics were performed with Sigmastat statistical software (SPSS Inc, Chicago, Ill). We used \( \chi^2 \) analysis and the Fisher exact test to compare frequencies between groups. The institutional review board at Driscoll Children’s Hospital approved this research project. Patient or parental informed consent was not required.

### RESULTS

#### EPIDEMIOLOGY

The number of Staphylococcus aureus isolates per year was relatively stable in 1991-2000 (range, 214-330) before precipitously increasing from 402 in 2001 to 830 in 2003 (Figure 1). The increase in Staphylococcus aureus isolates was due mainly to a rise in the number of MRSA isolates per year (range, 8-518), although there also was an increase in the number of methicillin-susceptible Staphylococcus aureus isolates per year (range, 206-312). The percentage of Staphylococcus aureus isolates that were methicillin-resistant gradually rose from 2.9% in 1990 to 10.6% in 1999 and then increased rapidly from 19.0% in 2000 to 62.4% in 2003 (Figure 1).

A total of 1002 cases of MRSA infection were identified in 1990-2003 of which 928 (92.6%) were community-acquired. Patient age and sex were recorded only for the 749 MRSA cases in 2002-2003. The mean age was 7.9 years and 51.3% were boys. The number of MRSA cases per year was stable in 1990-1999, ranging from 1 to 15 cases per year, and then increased exponentially from 43 cases in 2000 to 467 cases in 2003 (Figure 2). This increase was accounted for solely by a rise in the number of CAMRSA infections. The number of nosocomial MRSA infections ranged from 1 to 8 cases per year throughout the 14-year study period. In the final year of this study (2003), 459 (98.3%) of 467 MRSA cases were community-acquired.
During the 14-year study period, 461 (49.7%) of 928 patients with CAMRSA infections were hospitalized for treatment. The number of children with CAMRSA infections (with and without risk factors) that required hospitalization increased from 3.8 cases per 10,000 admissions in 1990-1999 to 57.8 cases per 10,000 admissions in 2000-2001 (P < .001) and then increased further to 277.1 cases per 10,000 admissions in 2002-2003 (P < .001 compared with 2000-2001).

RISK FACTORS AND SPECTRUM OF DISEASE

During this 14-year study period, 826 (89.0%) of 928 children with CAMRSA infections did not have an identified risk factor and 102 (11.0%) did have 1 or more known risk factors. Specific risk factor data were collected for 89 of 102 CAMRSA cases in children with risk factors (all years except 2001). Multiple risk factors were present in 35 (39.3%) of 89 children. The most common risk factors were chronic disease (50.6%), recent hospitalization (46.6%), documented MRSA colonization (30.7%), recent surgery (14.8%), and previous antibiotic use (11.4%).

During the 14-year study period, 873 (94.1%) of 928 children with CAMRSA infections had localized noninvasive infections, which were predominately skin and soft tissue infections (Table 1). Children with risk factors were more likely to have invasive CAMRSA infections than children without risk factors (26.5% vs 3.4%; P < .001) with bronchitis infections in patients who had cystic fibrosis being the most common. However, the percentage of children with risk factors who had invasive infections significantly decreased from 48.0% for the 1990-2001 time period to 18.2% for the 2002-2003 time period (P < .01) as the percentage of them who had cellulitis and abscess increased from 44.0% to 80.5% (P < .01). Conversely, the percentage of children without risk factors who had invasive infections increased slightly from 2.9% for the 1990-2001 time period to 5.4% for the 2002-2003 time period but the difference failed to reach statistical significance (P = .17; power = 0.26). Of the 74 children with nosocomial MRSA infections, 49 (66.2%) had invasive infections, which were mainly lung and bloodstream infections.

ANTIBIOTIC SUSCEPTIBILITY PATTERNS

The antibiotic susceptibility patterns for CAMRSA isolates from children with and without risk factors were similar except that isolates from children without risk factors had a higher susceptibility to clindamycin (97.0% vs 86.3%; P < .001; Table 2). Both differed from nosocomial isolates by demonstrating less susceptibility to erythromycin and greater susceptibility to clindamycin. A couple of changes occurred over time. First, the percentage of CAMRSA isolates from children without risk factors that were susceptible to erythromycin decreased from 19.9% for the 1990-2001 time period to 6.5% for the 2002-2003 time period (P < .05). The erythromycin susceptibility was unchanged for CAMRSA isolates from children with risk factors. Second, the percentage of CAMRSA isolates from children with and without risk factors that were susceptible to clindamycin increased from 68.0% for the 1990-2001 time period to 92.2% for the 2002-2003 time period (P < .05). The clindamycin susceptibility was unchanged for CAMRSA isolates from children without risk factors.

TREATMENT AND CLINICAL OUTCOME

In 2002-2003, data on intravenous antibiotic therapy during admission were available for 347 of 360 inpatients with CAMRSA infections, and data on oral antibiotic therapy on discharge were available for 247 of 360 inpatients. An empirical intravenous antibiotic to which the organism was susceptible was prescribed upon admission for 6 (14.6%) patients with CAMRSA infections, and data on oral antibiotic therapy on discharge were available for 35 of 46 inpatients. An empirical intravenous antibiotic to which the organism was susceptible was prescribed upon admission for 6 (14.6%) of the 74 children with nosocomial MRSA infections, 49 (66.2%) had invasive infections, which were mainly lung and bloodstream infections.

Table 2

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<th>Years</th>
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<tr>
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Figure 2. Number of outpatient and inpatient cases of methicillin-resistant *Staphylococcus aureus* infections. MRSA indicates methicillin-resistant *S. aureus*.
of the 41 inpatients \( (P < .001\) compared with 2002-2003). An intravenous antibiotic to which the organism was susceptible was ultimately prescribed during hospitalization for 26 (63.4%) of the 41 inpatients \( (P = .001\) compared with 2002-2003). The most commonly prescribed empirical antibiotics were nafcillin (48.8%), cefazolin (22.0%), clindamycin (12.2%), cefotaxime (4.9%), and ceftriaxone (4.9%).

An oral antibiotic to which the organism was susceptible was prescribed upon discharge to 23 (65.7%) of the 35 inpatients \( (P = .001\) compared with 2002-2003). The most commonly prescribed discharge antibiotics were clindamycin (42.9%), trimethoprim-sulfamethoxazole (20.0%), cephalexin (8.6%), amoxicillin/clavulanate (8.6%), and cefadroxil (3.7%).

Data on incision and drainage were obtained for 760 patients with CAMRSA cellulitis and abscess (all years except 2001). Of the 760 CAMRSA cellulitis and abscess cases, 372 (48.9%) were treated as inpatients and 388 (51.1%) as outpatients. Incision and drainage was required in 178 (47.8%) of the 372 inpatients compared with 56 (14.4%) of the 388 outpatients \( (P < .001)\). There was no standard used to guide when incision and drainage was performed. This decision was made by individual physicians based on their clinical judgment.

During the 14-year study period, all 928 patients with CAMRSA infections recovered, including those with severe invasive disease. We have not yet reported any deaths due to CAMRSA infections.

### COMMENT

The rapid emergence of CAMRSA infections in South Texas children, which began in the 1990s, has now reached epidemic proportions. During this 14-year study period, we observed a dramatic increase in the number of hospitalizations for CAMRSA infections from less than 10 cases per 10,000 admissions each year during the 1990s...
to 315 cases per 10 000 admissions in 2003. We have not yet seen a leveling off in the number of children with CAMRSA infections or the percentage of S aureus isolates that are methicillin-resistant. Although other investigators have conducted studies of CAMRSA isolates and infections, few have long-term epidemiological data to document changes in antibiotic susceptibility patterns, types of infection, hospitalization rates, and treatment over time. Seal et al reported that the annual number of S aureus isolates increased significantly from 874 in 1986 to 1176 in 2000 and that the annual rate of methicillin resistance in S aureus isolates increased from 13% in 1986 to 28% in 2000 at the University of Chicago Hospitals (Chicago), which were smaller percentage increases than we observed during a similar time period. Herold et al found that the prevalence of CAMRSA infections in children without risk factors who were hospitalized at the University of Chicago Children's Hospital increased from 10 per 100 000 admissions from 1986 through 1990 to 259 per 100 000 admissions from 1993 through 1995. These prevalence rates were similar to the rates we recorded for the 1990-1999 and 2000-2001 time periods, but much less than the rate we documented for the 2002-2003 period (277 per 10 000 admissions).

One of the important findings of our study was that categorizing children with CAMRSA infections into those with or without risk factors is losing any clinical relevance, at least in our area. The antibiotic susceptibility patterns and the spectrums of disease are becoming increasingly similar (predominantly clindamycin-susceptible localized skin and soft tissue infections) while remaining distinctly different from patients with nosocomial MRSA infections (mainly clindamycin-resistant invasive lung and bloodstream infections). We hypothesize that initially many of the CAMRSA infections in children with risk factors were actually of hospital origin whereas now most of the CAMRSA infections in children with risk factors truly are of community origin. In the beginning, most of the children with risk factors had invasive infections whereas now they have mostly localized infections similar to the ones occurring in children without risk factors.

We did see a shift in the physicians’ prescribing pattern during this study. During the 2002-2003 time period, almost all of the inpatients received an empirical intravenous antibiotic to which the organism was susceptible, but during the 1990-2000 time period, very few did. Using empirical antibiotic therapy that provided coverage for MRSA was not the standard of care for typical cellulitis and abscess cases during the 1990s. This change in physicians’ prescribing habits was probably primarily due to us making pediatricians in our area aware of the emergence of CAMRSA as an important pathogen. In 2001, we began presenting our research data and providing new empirical antibiotic therapy recommendations for the outpatient and inpatient settings in a variety of local forums (eg, hospital-sponsored grand rounds and other continuing medical education conferences, Corpus Christi Pediatric Society meetings, pharmaceutical company-sponsored education programs). We have shown in the past that a multifaceted educational approach can influence physicians’ prescribing patterns.

We made the following recommendations to ensure that empirical antibiotic therapy for common pediatric infections provided coverage for CAMRSA. Oral clindamycin or trimethoprim-sulfamethoxazole should be considered for empirical therapy in children with suspected localized CAMRSA infections (cellulitis and abscesses) that are managed on an outpatient basis. Trimethoprim-sulfamethoxazole may be the preferred drug if the rate of inducible clindamycin resistance is high in the community (>15%). There has been wide variation in the rates of inducible clindamycin resistance reported across the country; from 8% of the CAMRSA isolates in Houston, Tex, to 94% of the MRSA isolates in Chicago.24,25 We recently found that 19% of our CAMRSA isolates demonstrate inducible clindamycin resistance.26 Alternatives include oral minocycline, ciprofloxacin, and linezolid with drug selection based on price, convenience of dosing, taste, and local antibiogram data. Performing incision and drainage when an abscess is present was emphasized because it may be more important than drug therapy for resolution of the infection. Lee et al showed that incision and drainage without adjunctive antibiotic therapy was effective management for skin and soft tissue abscesses with a diameter smaller than 5 cm in immunocompetent children, and having a lesion initially larger than 5 cm was a significant predictor of hospitalization.

For children hospitalized with non–life-threatening invasive and noninvasive infections and without a toxic appearance, intravenous clindamycin can be prescribed and has been shown to be effective.23 Additionally, incision and drainage should be performed if an abscess is present. For children who are critically ill and hospitalized with life-threatening invasive infections, intravenous vancomycin or clindamycin with or without gentamicin should be prescribed.29 In fact, it may be prudent to administer vancomycin to children with life-threatening infections until a negative D-test is documented to prevent a possible clindamycin treatment failure. Several treatment failures due to inducible clindamycin resistance have been reported.30,31 Alternatives include intravenous linezolid, quinupristin-dalfopristin, and daptomycin.

The strength of our study is that it provides a long-term perspective on the impact of the emergence and epidemic of CAMRSA on children in a regional community. However, there were several limitations of our retrospective medical-record review study. First, we may have overestimated the number of children without risk factors. We only recorded the presence of risk factors if we found positive documentation to support it. Second, the increase in the number of CAMRSA infections may have been partially due to more aggressive attempts at making a microbiological diagnosis due to the epidemic. However, we recently reported an increase in number of cellulitis and abscess hospitalizations of all causes from 224 per 10 000 admissions in 1990 to 710 per 10 000 admissions in 2004 while the number of cases in which CAMRSA was the cause increased from 0 per 10 000 admissions in 1990 to 360 per 10 000 admissions in 2004.32 Thus, it appears that we are seeing a true increase in the number of infections. Third, we did not have adequate data (eg, initial size of lesion) to compare clinical outcomes between drugs and between medical and surgical therapy. Finally, because we did not...
routinely perform D-tests, we were not able to evaluate if the presence of inducible clindamycin resistance was a factor in outpatient treatment failures. Our main concern for the future is that we may be starting to see an increase in the percentage of children with CAMRSA infections who have invasive disease. Although the percentage of children with risk factors who had invasive infections significantly decreased over time, the percentage of children without risk factors, which accounted for 89% of the CAMRSA infections, increased slightly. Our sample size was not large enough to resolve if there really was a significant increase over time (2.9% to 5.4%), but if this is a trend, it will have a significant impact considering the large and growing number of CAMRSA cases that are occurring in our area and across the United States and the world. The possible increase in invasive disease could be due to specific virulence genes in the staphylococcal cassette chromosome of CAMRSA organisms, such as the Panton-Valentine leukocidin genes, which encode for potent cytotoxins. These have been consistently found in CAMRSA isolates from around the world and are associated with highly lethal necrotizing pneumonia and deep-seated follicular infections. Alternatively, this could be due to ineffective empirical outpatient therapy (eg, a β-lactam antibiotic or clindamycin for D-test–positive CAMRSA).

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REFERENCES