Community-Acquired Methicillin-Resistant *Staphylococcus aureus* in Southern New England Children

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ABSTRACT. *Objective.* **This study was performed to understand the epidemiology of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections in southern New England children.**

Methods. **A retrospective review was conducted of the medical records of children 0 to 18 years old with MRSA isolated by the Rhode Island Hospital microbiology laboratory (Providence, RI) between 1997 and 2001. A case was classified as either health care-associated MRSA (HCA-MRSA) or CA-MRSA based on time of culture and other strict criteria. The spectrum of illness of the HCA-MRSA and CA-MRSA cases was compared, as were the antibiotic-susceptibility patterns of their isolates. Risk factors for CA-MRSA acquisition were identified, and molecular subtyping of selected isolates was performed.**

Results. **Between 1997 and 2001, *S aureus* was isolated from 1063 children. Of these children, 57 had MRSA. During this period, both the absolute number of MRSA cases and the proportion of *S aureus* cases due to MRSA rose more than threefold due to increases in both CA-MRSA and HCA-MRSA infections. Of the 57 MRSA cases, 23 (40%) were CA-MRSA. CA-MRSA patients were more likely to have skin/soft-tissue infections than HCA-MRSA patients (83% vs 38%). Risk factors for acquisition of MRSA including intrafamilial spread, frequent antibiotic exposure, and child-care attendance were identified in 8 of the 23 (35%) CA-MRSA patients. CA-MRSA isolates were more likely to be susceptible to non-β-lactam antibiotics than HCA-MRSA isolates. All isolates were vancomycin susceptible.**

Conclusions. **MRSA accounts for an increasing proportion of all pediatric *S aureus* infections in southern New England. A significant percentage of these cases are due to CA-MRSA. Pediatricians should have heightened suspicion for CA-MRSA in children with presumed *S aureus* infections, especially if they have skin/soft-tissue infections or risk factors for MRSA acquisition. *Pediatrics* 2004;113:e347–e352. URL: http://www.pediatrics.org/cgi/content/full/113/4/e347; *methicillin resistance*, Staphylococcus aureus; *community acquired, New England, children.***

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ABBREVIATIONS. MRSA, methicillin-resistant *Staphylococcus aureus*; CA, community-acquired; HCA, health care-associated; SCC, staphylococcal chromosomal cassette.

Methicillin-resistant *Staphylococcus aureus* (MRSA) was first reported >30 years ago.[1] Within a decade, MRSA was established as an important nosocomial pathogen in both adult and pediatric populations.[2–5] Several risk factors for acquisition of MRSA by both children and adults have been identified: hospitalization in intensive care units, prolonged hospitalization, severe underlying illness, invasive procedures, indwelling devices, and prolonged or recurrent exposure to antibiotics.[6,7]

In the early 1980s, the first reports of community-acquired (CA)-MRSA in adults emerged.[8–10] These isolates were found initially in intravenous drug users or members of other high-risk groups with frequent contact with the health care system. In the late 1980s, the first cases of CA-MRSA in children were reported.[11] Most of these children also had a history of frequent health care contact. Thus, although the infections occurred in a community setting, these MRSA strains are better described as health care-associated (HCA) rather than truly CA.

From the 1990s to the present, CA-MRSA has emerged as a pathogen in adults and children without traditional risk factors for MRSA acquisition.[12–16] More-recent reports have suggested that other risk factors also may exist, such as household contacts with risk factors for MRSA and child-care attendance.[17–19]

Notably, the CA-MRSA isolates described in the past decade differ significantly from previous strains of MRSA in that they have distinct DNA-fingerprinting patterns[20] and lack multidrug resistance.[21] Recent research has demonstrated that these strains have novel resistance and virulence genes. Resistance to β-lactam antibiotics is conveyed by acquisition of a chromosomal *mecA* gene that encodes for a penicillin-binding protein with a low affinity for this antibiotic class. The *mecA* genes are found on mobile genetic elements called staphylococcal chromosomal cassettes (SCC*mec*). CA-MRSA strains have been found to have a novel allelic form of SCC*mec* type IV, thus differing from HCA-MRSA strains that carry types I, II, or III SCC*mec* cassettes. The *mecA* gene of HCA-MRSA strains is flanked by insertion sequence-like elements, acquired through horizontal gene transfer, which act as a trap for additional unrelated antibiotic-resistance genetic determinants leading to

the multidrug resistance seen in these strains. The smaller type IV SCC*mec* cassette found in CA-MRSA does not carry any such multiresistance genes[22,23]; however, these strains can still cause fatal disease.[24]

Additionally, CA-MRSA strains, unlike HCA-MRSA strains, have been found to carry virulence genes encoding a leukocyte-killing toxin called the Panton-Valentine leukocidin determinant. Skin and soft-tissue infections, as well as necrotizing pneumonia, have been associated with Panton-Valentine leukocidin-producing CA-MRSA.[25,26]

There have been no previous studies of CA-MRSA in children in southern New England. The objectives of this retrospective study were to assess and characterize pediatric MRSA infections in southern New England, compare CA-MRSA and HCA-MRSA characteristics, and identify the presence of risk factors in children with CA-MRSA infections.

METHODS

Rhode Island Hospital is a tertiary-care teaching hospital with a 106-bed pediatric division (Hasbro Children's Hospital) located in Providence, Rhode Island. It is the primary pediatric referral center for all of Rhode Island, southeastern Massachusetts, and northern Connecticut. Rhode Island Hospital is part of a local network of hospitals (Rhode Island Hospital, Hasbro Children's Hospital, Bradley Hospital, Miriam Hospital, and Newport Hospital). The microbiology laboratory services the entire network, as well as several pediatric practices in southern New England. A query was submitted to the Rhode Island Hospital microbiology laboratory database requesting identification of all MRSA isolates from patients 0 to 18 years old inclusive between January 1, 1997, and December 31, 2001.

The patients identified had both computerized and paper medical and laboratory records that were reviewed to enable classification of cases. A case of MRSA was considered HCA if any of the following criteria were present: organism isolated >48 hours after admission to the hospital, history of previous MRSA isolation, hospitalization or surgery in the year before the positive MRSA culture, or percutaneous lines or indwelling devices present at the time of culture. A case of MRSA was considered CA if both of the following criteria were met: organism isolated within 48 hours after hospital admission or as an outpatient and no HCA criteria were identified.

Only the initial encounter associated with an MRSA isolate was analyzed for each case even if the patient had MRSA isolated during multiple encounters. Data extracted from the medical records included demographics, insurance type, diagnosis, infection type, culture site, antibiotic susceptibility, initial and subsequent antibiotics administered, surgical procedures, and presence of risk factors for MRSA acquisition. Information on household contacts and previous antibiotic use was not consistently available. A query also was submitted to the hospital's master database, which is linked to all hospitals within the network, to confirm and supplement findings from direct record review. The data requested included demographics, insurance information, network-wide encounter data (ie, date and location of every contact with the hospital network), diagnosis codes, procedure codes, and cost/billing data. The encounter data and cost/billing data identified whether a patient had been hospitalized or had a surgical procedure at any of the hospitals in the network within the year before their initial MRSA infection. A query was also made to the Department of Epidemiology and Infection Control at the hospital to determine whether any MRSA outbreaks had occurred among pediatric patients during the study period.

Isolates were identified as *S aureus* by the microbiology laboratory with standard methods.[27] Methicillin resistance was detected at the time of the initial culture by disk diffusion or by using the Vitek system (BioMérieux, Hazelwood, MO). Isolates initially demonstrating resistance were confirmed by inoculating 10 μL of a 0.5 McFarland standard suspension on oxacillin-screening agar and observing for any growth present. Antibiotic susceptibilities routinely tested by disk diffusion included penicillin, ampicillin/sulbactam, oxacillin, cefazolin, ciprofloxacin, clindamycin, erythromycin, gentamicin, trimethoprim-sulfamethoxazole, and vancomycin. Antibiotic susceptibilities routinely tested by the Vitek system included all of the above as well as ampicillin, nitrofurantoin, rifampin, and tetracycline. Susceptibilities for linezolid and quinupristin-dalfopristin were not routinely performed.

One MRSA isolate from each patient routinely is frozen and stored in the microbiology laboratory. The isolates from 1997 had been discarded before this study, and 1 isolate from 1999 and 2 from 2000 were not found. Overall, 48 of 57 isolates were recovered. Isolates from cases found to represent a family cluster were selected for molecular subtyping by pulsed-field gel electrophoresis with *Sma*I-digested chromosomal DNA. Gels were run at 200 volts for 17 hours in 0.25× Tris-borate-EDTA (TBE) buffer at 14°C with switch times of 5 to 35 seconds. Gels were interpreted by standard criteria.[28]

Categorical variables were compared by using 2-sided Fischer's exact test or Pearson's χ^2, and the increase in the proportion of MRSA by year was tested with a simple least-squares linear regression (Stata 8, Stata Corp, College Station, TX). $P \leq .05$ was considered significant.

This study was approved by the Rhode Island Hospital Institutional Review Board.

RESULTS

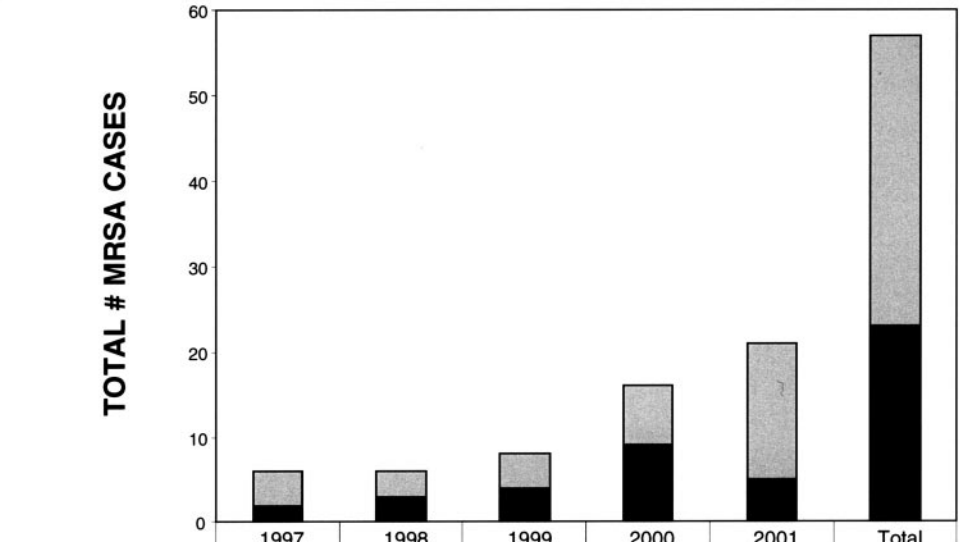
MRSA Epidemiology

Between January 1, 1997, and December 31, 2001, *S aureus* was isolated in 1861 cultures from 1063 children. Of these isolates, 200 were MRSA from 57 children (33 males, 5 weeks to 18.8 years old). All 57 patients had MRSA isolated from at least 1 sterile site, and all had a clinical infection. Nares cultures screening for MRSA are not routinely performed after admission in pediatric patients at our institution, so no information was available about baseline colonization rates. Medical records of the 57 patients were reviewed. Twenty-three patients (40%) met CA-MRSA criteria.

The total number of *S aureus* infections remained relatively constant over the study period (Fig 1); however, the proportion of *S aureus* cases attributable to MRSA steadily increased over the 5 years (2.7%, 3.1%, 4.5%, 6.6%, and 9.3%, respectively). Regressing MRSA percent on year revealed a significant positive relationship, with MRSA increasing by 1.67% per year ($P = .008$; $R^2 = 0.91$). The change we observed was due to increases in both HCA-MRSA and CA-MRSA infections (Fig 1). Of note, there were no hospital outbreaks of MRSA identified in pediatric patients in any of the study years.

Identifiable Risk Factors

Eight (35%) of the 23 CA-MRSA patients had an identifiable risk factor for MRSA acquisition. One child was on prophylactic antibiotics and had received frequent therapeutic courses of antibiotics due to recurrent urinary tract infections. Another child with Crohn's disease was receiving chronic steroid therapy. Two children attended child care, and 4 children were found to be members of an extended family group with MRSA carriers. All the patients from the family group presented with skin/soft-tissue abscesses. Molecular typing of the isolates (Fig 2) from this group showed that all 4 of the children (lanes 3–6) and a young adult family member with a skin abscess (lane 2) had an identical MRSA strain. Two of the patients were a teen mother



	1997	1998	1999	2000	2001	Total
HCA MRSA CASES	4	3	4	7	16	34
CA MRSA CASES	2	3	4	9	5	23
MSSA CASES	217	186	171	227	205	1006

Fig 1. Pediatric MRSA cases: CA versus HCA, 1997–2001.

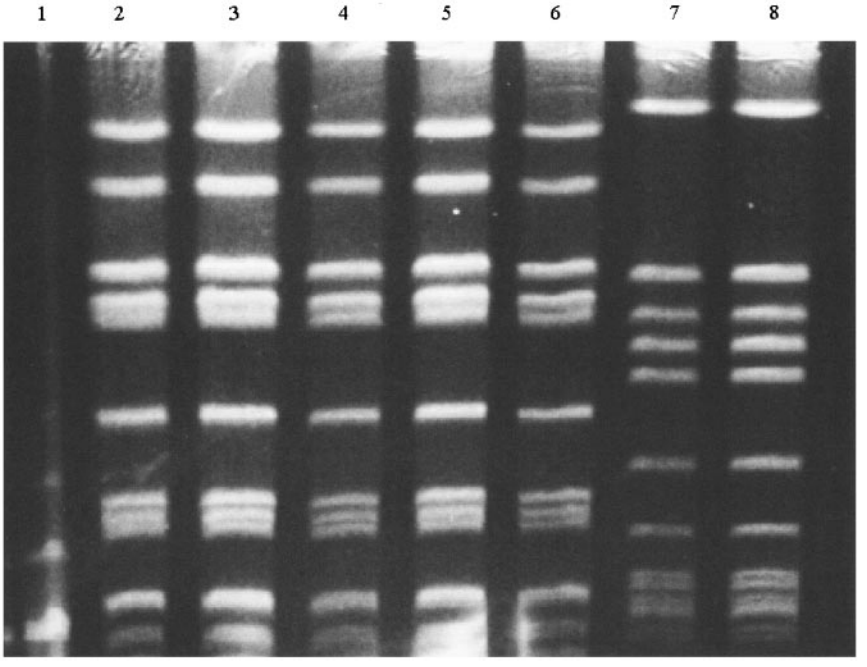


Fig 2. Pulsed-field gel electrophoresis patterns of *Sma*I-digested chromosomal DNA. Lane 1 is NCTC 8325 standard; lane 2, CA-MRSA isolate from adult 1; lane 3, CA-MRSA isolate from child 1 (1.5 year old female); lane 4, CA-MRSA isolate from child 2 (16 year old female); lane 5, CA-MRSA isolate from child 3 (13 year old female); lane 6, CA-MRSA isolate from child 4 (1 year old female, separate household); lanes 7 and 8, HCA-MRSA isolates from adult 2 (sputum and blood samples, nosocomial).

and her child. The third child and the young adult were siblings of the teen mother. These 4 persons resided in the same household. The fourth child was the niece of the 3 siblings; she lived at a separate address. A second adult family member (lanes 7 and 8), who was the grandfather of the teen mother and her siblings, resided separately from the other family members. He acquired MRSA during an extended hospital stay. He was initially believed to be the source patient but turned out to have a completely unrelated, nosocomial strain.

The daughter of the teen mother was the first to present with MRSA infection. The remaining family members presented sequentially with their infections at intervals of ~2 weeks to 1 month. The child who lived at a separate address was the last to acquire her infection and subsequently developed recurrent MRSA infections. This child was seen by the Pediatric Infectious Diseases consultation service. They obtained nares cultures on several members of the extended family, identifying other adults who were asymptomatic MRSA carriers in the different households.

Clinical Characteristics of MRSA Infections

The spectrum of illness differed between patients with CA-MRSA and HCA-MRSA (Table 1). Soft-tissue infections (cellulitis/furunculosis or abscess) ac-

TABLE 1. Spectrum of Illness in CA-MRSA and HCA-MRSA Infections

Category	CA-MRSA (Total $N = 23$) N (%)	HCA-MRSA (Total $N = 34$) N (%)	P Value
Meningitis	0	1 (3)	1.00
Osteomyelitis	0	3 (9)	0.27
Bacteremia	0	3 (9)	0.27
Pneumonia	0	11 (32)	0.002
Urinary tract infection	3 (13)	3 (9)	0.68
Otitis*	1 (4)	0	0.40
Soft tissue	19 (83)	13 (38)	0.001

* Child with persistent ear drainage

counted for 19 (83%) of the 23 CA-MRSA infections vs 13 (38%) of the 34 HCA-MRSA cases ($P = .001$, Fischer's exact test). Illness type did not differ between patients with CA-MRSA with and without identifiable risk factors, with a majority in both groups having soft-tissue infections. The HCA-MRSA isolates were associated with more-invasive infections: 18 (53%) of the 34 HCA-MRSA cases involved meningitis, osteomyelitis, bloodstream infection, or pneumonia compared with 0 of 23 CA-MRSA cases ($P < .0001$, Fischer's exact test).

Antibiotic Susceptibility of MRSA Isolates

Susceptibilities of CA-MRSA and HCA-MRSA isolates, respectively, were 48% and 29% for erythromycin, 67% and 90% for tetracycline, 74% and 53% for clindamycin, 87% and 38% for ciprofloxacin, 100% and 94% for gentamicin, 100% and 91% for trimethoprim-sulfamethoxazole, and 100% and 100% for vancomycin. When looking at individual agents, only ciprofloxacin susceptibility was significantly different between the 2 groups, with greater susceptibility among CA-MRSA isolates ($P < .0001$, Fischer's exact test); however, if the antibiotic data were looked at in aggregate, CA-MRSA isolates were more likely to be susceptible to non-β-lactam agents than HCA-MRSA ($P = .006$, Pearson's χ^2).

Therapy and Outcome of CA-MRSA Infections

Therapeutic interventions received by the 23 CA-MRSA case patients were reviewed. Initial antibiotic choice included ampicillin/sulbactam, nafcillin, cephalexin, cefazolin, cefadroxil, azithromycin, or metronidazole. Notably, none of the 23 patients received an initial antibiotic to which the isolate was susceptible. Eight (35%) of the 23 CA-MRSA patients subsequently received definitive therapy with an agent to which the patient's isolate was susceptible. The therapeutic agents used as definitive therapy were vancomycin, erythromycin, clindamycin, trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin. No patient received tetracycline. All 8 patients also underwent incision and drainage procedures, of which 6 were performed in the operating room. Incision and drainage also was performed on 2 patients who did not receive definitive antibiotic therapy. An additional 7 patients who did not receive definitive antibiotic therapy may have undergone a nonoperative incision and drainage procedure, because they had a wound culture taken from a furuncle or pustule. However, we could not find documentation that incision and drainage was performed. The remaining 6 patients received antibiotic therapy alone but not with agents to which his or her isolate was susceptible.

Definitive outcome data were not available for all CA-MRSA cases. Of the 23 patients, 15 (65%) had severe infections requiring hospital admission. All these patients improved sufficiently to be discharged from the hospital. One patient developed recurring disease despite receiving both vancomycin and intraoperative incision and drainage. Notably, 7 (47%) of the 15 hospitalized patients recovered despite not having received definitive antibiotic therapy.

Of the 23 patients, 8 (35%) were treated as outpatients. None received definitive antibiotic therapy. Three of these patients subsequently relapsed. No patient with CA-MRSA died from his or her infection.

DISCUSSION

Using strict criteria for classification of cases, 40% of our pediatric MRSA infections were due to CA-MRSA. This finding mirrors CA-MRSA rates for adults and children in other regions of the United States,[29–31] as well as in other countries.[32,33]

Similar to other reports[34–36] and in contradistinction to HCA-MRSA cases, CA-MRSA cases predominately manifested as superficial and deep soft-tissue infections, and many of the isolates were susceptible to multiple classes of antibiotics other than β-lactams. These differences reflect coevolution of MRSA in the community setting, with strains unrelated to those that evolved in nosocomial settings[23,35,36]; however, a possible confounder is that HCA-MRSA patients may have had an increased risk of acquiring invasive disease because they were more likely to have undergone an invasive procedure.

Thirty-five percent of our CA-MRSA population had identifiable risk factors for MRSA acquisition. We definitively documented intrafamilial CA-MRSA spread, a potentially important and underrecognized mechanism of transmission in the community only recently described by others.[37] For children presenting with CA skin/soft-tissue infections, there may be some benefit to asking families questions targeted at identifying the previously mentioned risk factors for MRSA acquisition. This practice may help guide initial choice of therapy. A recent report found no difference in exposure to risk factors in children presenting with CA infections caused by methicillin-susceptible or methicillin-resistant staphylococci.[38] Nevertheless, if screening questions reveal that a child 1) has family members who are known to have MRSA colonization or infection, 2) has household contacts who are health care workers,[37] or 3) is immunosuppressed or receives frequent courses of antibiotics, we suggest that a nares culture be obtained at admission to screen for MRSA carriage. Screening cultures also should be obtained from any open wounds.

Clindamycin has become 1 of the first-line agents for the treatment of presumed *S aureus* infections in many parts of the country with high rates of CA-

MRSA[29,31,39,40]; however, erythromycin-resistant MRSA isolates that initially seem susceptible to clindamycin often have rapidly inducible clindamycin resistance[41,42] that may lead to treatment failure. In 1 recent study, 46% of erythromycin-resistant, clindamycin-susceptible pediatric and adult MRSA clinical isolates had inducible clindamycin resistance.[43] Our microbiology laboratory routinely suppresses reports of clindamycin susceptibility if an MRSA isolate is erythromycin resistant. Of note, clindamycin resistance develops much more slowly among erythromycin-susceptible MRSA isolates. Based on the available data, we recommend the following: Clindamycin can be used safely in most circumstances when the MRSA isolate is both erythromycin and clindamycin susceptible. If the initial report from the microbiology laboratory reveals that an MRSA isolate is erythromycin resistant and clindamycin susceptible, then clindamycin should not be used until the microbiology laboratory has used additional methods to exclude inducible clindamycin resistance.[42,43] In all circumstances, appropriate drainage should be used.

Although our CA-MRSA isolates were generally quinolone susceptible, concerns remain about the use of these agents in the pediatric age group. Ciprofloxacin use is associated with the emergence of resistance during therapy and is not recommended. The efficacy and safety of the newer quinolones for treatment of CA-MRSA in children should be investigated.

Most patients with CA-MRSA in our study had a good outcome despite a lack of appropriate initial antimicrobial therapy. This is in sharp contrast to the outcome of patients with infections caused by CA-MRSA strains that carry certain virulence factors, which have been associated with severe, life-threatening infections.[25,36] Pediatricians and other health care providers in our community must have a high index of suspicion for CA-MRSA in children with presumed *S aureus* infections who are critically ill, failing to respond to conventional β-lactam antibiotic therapy, or have relapsing infections. The need for timely and appropriate acquisition of specimens for culture and susceptibilities is paramount. It is hoped that, in the future, rapid tests will become available that reveal the presence or absence of the above-noted virulence factors to help guide a therapeutic plan for children with CA-MRSA infections.

This study has several limitations. The retrospective design increased the chance that patients were misclassified. Because medical records were not always complete and patients were not available for interview, HCA criteria may have been missed. Rhode Island Hospital is a major referral center but not the only source for pediatric care in southeastern New England. Thus, our findings of the number of CA-MRSA versus HCA-MRSA cases may not be reflective of the entire region. Finally, underestimation of the burden MRSA in our population is possible, because nares cultures screening for MRSA are not obtained routinely.

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