Community-Acquired Methicillin-Resistant Staphylococcus aureus in Children With No Identified Predisposing Risk

Betsy C. Herold, MD; Lilly C. Immergluck, MD; Melinda C. Maranan, MD; Diane S. Lauderdale, PhD; Ryan E. Gaskin; Susan Boyle-Vavra, PhD; Cindy D. Leitch; Robert S. Daum, MD

Context.—Community-acquired methicillin-resistant Staphylococcus aureus (MRSA) infections in children have occurred primarily in individuals with recognized predisposing risks. Community-acquired MRSA infections in the absence of identified risk factors have been reported infrequently.

Objectives.—To determine whether community-acquired MRSA infections in children with no identified predisposing risks are increasing and to define the spectrum of disease associated with MRSA isolation.

Design.—Retrospective review of medical records.


Setting.—The University of Chicago Children’s Hospital.

Main Outcome Measures.—Prevalence of community-acquired MRSA over time, infecting vs colonizing isolates, and risk factors for disease.

Results.—The number of children hospitalized with community-acquired MRSA disease increased from 8 in 1988-1990 to 35 in 1993-1995. Moreover, the prevalence of community-acquired MRSA without identified risk increased from 10 per 100 000 admissions in 1988-1990 to 259 per 100 000 admissions in 1993-1995 (P<.001), and a greater proportion of isolates produced clinical infection. The clinical syndromes associated with MRSA in children without identified risk were similar to those associated with community-acquired methicillin-susceptible S aureus. Notably, 7 (70%) of 10 community-acquired MRSA isolates obtained from children with an identified risk were nonsusceptible to at least 2 drugs, compared with only 6 (24%) of 25 isolates obtained from children without an identified risk (P=.02).

Conclusions.—These findings demonstrate that the prevalence of community-acquired MRSA among children without identified risk factors is increasing.

The epidemiology of MRSA infections is complex. Acquisition of the organism in a hospital or a long-term care facility is well documented in adults and children.

Community-acquired MRSA infections among hospital inpatients, ie, isolates obtained within 72 hours of hospitalization, have been described among adults. The majority of these, however, have occurred in individuals with a recognized predisposing risk factor, such as recent contact with a health care–providing environment or parenteral substance abuse. Community-acquired MRSA infections in the absence of identified risk factors have been reported infrequently.

Thus, we were surprised when we recently observed several community-acquired MRSA infections among children without risk factors hospitalized at a university-based teaching hospital.

INFECTIONS CAUSED BY Staphylococcus aureus resistant to methicillin (MRSA) are increasing in prevalence in adults and children. Although such infections were once concentrated in relatively few large, university-based teaching hospitals, now 97% of such institutions report the presence of MRSA isolates.
clinical observation prompted a retrospective review of available medical records of hospitalized children from whom *S aureus* was isolated from any site between August 1988 and July 1990 (1988-1990) and between August 1993 and July 1995 (1993-1995). We sought to determine whether community-acquired MRSA infections in hospitalized children with no identified predisposing risks were increasing in prevalence and whether the clinical spectrum of disease associated with community-acquired MRSA infection differed from that of community-acquired methicillin-susceptible *S aureus* (MSSA) disease or nosocomially acquired (NA) MRSA disease.

**METHODS**

**Study Design and Facility**

The University of Chicago Children’s Hospital (UCCH) is a 156-bed, tertiary care pediatric facility. The Clinical Microbiology Laboratories maintain records of all *S aureus* isolates from hospitalized patients and the proportion of them resistant to methicillin. With the use of data from the Clinical Microbiology Laboratories, we compiled a list of all *S aureus* isolates (both MSSA and MRSA) for 1993-1995. We then reviewed all available medical records for hospitalized children with 1 or more *S aureus* isolates from any site in the designated interval. For comparison purposes, we also reviewed all available records of hospitalized children from whom MRSA was isolated during a 24-month period 5 years previous (1988-1990). The number of hospital discharges (about 4800 per year), payer mix (about 35% private insurance), age distribution, and average length of stay of children hospitalized at UCCH remained stable from 1988 through 1995.

From the medical records, we sought information regarding age, sex, race/ethnicity, date of admission, site of culture specimen yielding *S aureus*, the date of specimen collection, antimicrobial therapy administered prior to hospitalization, care rendered at another facility, and any underlying medical condition or other relevant family history.

From the information found in the records, isolates were classified as to whether they were acquired in the “community” or “nosocomially” and “infec ting” or “colonizing.” A community-acquired MRSA isolate was defined as one isolated from a specimen obtained within 72 hours of admission. A nosocomially acquired isolate was one isolated from a specimen obtained beyond that time. A “disease-associated” isolate was defined as one responsible for a clinical syndrome (eg, osteomyelitis) as determined from consideration of the site from which *S aureus* was isolated, the physical examination findings, and other relevant clinical evidence. Isolates not associated with disease were said to be colonizing.

Hospitalized children with community-acquired MRSA were classified as “with identified risk” if review of the medical record indicated any of the following: previous hospitalization or antimicrobial therapy within 6 months of the date of MRSA isolation, history of endotracheal intubation, underlying chronic disorder, presence of an indwelling venous or urinary catheter, a history of any surgical procedure, or a notation in the medical record of a household contact with an identified risk factor. All other patients with community-acquired MRSA isolates were classified “without identified risk.”

We describe the epidemiology of community-acquired MRSA among hospitalized children in 4 ways. First, we compared the prevalence of community-acquired MRSA without identified risk in 2 time periods, 1988-1990 and 1993-1995. Second, we compared the proportions of infecting vs colonizing isolates for 1988-1990 and 1993-1995. Third, we compared the clinical spectrum of disease for infecting isolates for 5 1990-1995 groups: community-acquired MRSA with identified risk, community-acquired MRSA without identified risk, nosocomially acquired MRSA, community-acquired MSSA, and nosocomially acquired MSSA. Fourth, for the 3 MRSA groups, we compared proportions of isolates susceptible to other antibiotics. Statistical analysis was performed using Stata Statistical Software 4 (StataCorp, College Station, Tex). Frequency data were compared with a 2-tailed Fisher exact test.

**Laboratory Methods**

Susceptibility testing on *S aureus* isolates was initiated on the Vitek system (BioMerieux Vitek Inc, Hazelwood, Mo) in the Clinical Microbiology Laboratories at the University of Chicago Hospitals. Briefly, the isolate was inoculated onto a gram-positive susceptibility-SA card (SA indicates the combination of drugs available on the card) containing 1% sodium chloride and placed into the Vitek instrument for incubation and reading. An isolate was further evaluated by disk diffusion testing when Vitek testing revealed that it was resistant to methicillin but susceptible to clindamycin and erythromycin. Disk diffusion testing was performed as recommended by the National Committee for Clinical Laboratory Standards. A broth culture suspension of the isolate to be tested was prepared in trypticase soy broth and turbidity adjusted to a 0.5 McFarland standard. The zone sizes were read after 24 hours of incubation in ambient air at 35°C. Isolates were classified as either susceptible or nonsusceptible; the latter classification included isolates with intermediate and resistant zone sizes. Disk diffusion testing was performed for 51% of isolates designated MRSA by Vitek in the 1993-1995 study interval and for 57% of isolates obtained in the 1988-1990 interval. The MRSA isolates were usually tested for susceptibilities to the following additional antibiotics: clindamycin, erythromycin, gentamicin, trimethoprim-sulfamethoxazole, and vancomycin.

The Clinical Microbiology Laboratories retain only isolates from blood for long-term storage. Seven MRSA blood isolates from 1993-1995 were available for further analysis by pulsed-field gel electrophoresis (PFGE) and for presence of the meca gene by polymerase chain reaction (PCR) assay. For PFGE, genomic DNA was prepared using previously described methods and digested with the restriction endonuclease *Smal*. Band patterns were visualized by ethidium bromide staining and UV illumination and compared visually. For the PCR assay, template DNA was obtained from colonies after lysis in achromopeptidase as previously described. Synthetic oligonucleotides used as primers were 5'-CTTGTAGAGTAGACACTCG-3' and 5'-GCTAGCCATTCCTTTATCTTG-3', which correspond to nucleotides from position 1538-1557 and 2049-2069, respectively, of the meca gene sequence.

**RESULTS**

We identified 32 cases of MRSA in 1988-1990 and 56 cases in 1993-1995. Fifty-two (93%) of 56 charts were available from the patients hospitalized in 1993-1995 and all 32 (100%) from those hospitalized in 1988-1990. Of those with available charts, 8 of the 1988-1990 MRSA isolates were community acquired, and 35 of the 1993-1995 isolates were community acquired. Patients with community-acquired isolates in the 2 time periods did not differ significantly with respect to sex or race/ethnicity, but did differ in age distribution (Table 1). When the community-acquired cases were classified by the absence or presence of identified risk factors, only one of the 1988-1990 cases lacked an identified risk factor, whereas 25 of the cases in 1993-1995 lacked an identified risk factor (Table 1). The prevalence of community-acquired MRSA with or without identified risk factors increased from 10 per 100 000 admissions in 1988-1990 to 259 per 100 000 admissions in 1993-1995 (*P* < .001).

©1998 American Medical Association. All rights reserved.
To determine whether the isolation of 1993-1995 community-acquired MRSA was clustered or scattered throughout the 24-month time period, we stratified the isolates by month of isolation. The 35 isolates obtained from children with or without identified risk in 1993-1995 were detected throughout the 2-year period, an observation suggesting that the increase did not represent a mini-outbreak(s).

To compare the proportion of MRSA isolates associated with clinical disease in 1988-1990 and 1993-1995, we classified them as colonizing or disease associated according to relevant clinical features associated with isolation of MRSA. In 1993-1995, 8 (80%) of 10 community-acquired isolates obtained from children with identified risk and 22 (88%) of 25 community-acquired isolates obtained from children without identified risk were associated with a clinical disease. Similarly, 12 (71%) of 17 1993-1995 nosocomially acquired isolates were associated with clinical disease. In contrast, in 1988-1990, only 3 (43%) of 7 community-acquired isolates obtained from children with an identified risk factor and 9 (37.5%) of 24 nosocomially acquired isolates obtained were associated with a clinical illness. Thus, the increase in community-acquired MRSA isolates in 1993-1995 compared with 1988-1990 represents primarily an increase in disease-associated isolates and not increased collection of specimens not associated with disease.

Next we examined the clinical spectrum of disease associated with MRSA and MSSA isolates in 1993-1995 (Table 2). The distribution of clinical syndromes associated with community-acquired MRSA in children with identified risk was similar to that of children with nosocomially acquired MRSA. The clinical spectrum of disease for the community-acquired MRSA without identified risk appears to be different. First, none of the 22 children with community-acquired MRSA isolates without identified risk had bacteremia without a focus of infection, whereas 2 (20%) of 10 children with community-acquired MRSA with identified risk and 4 (33%) of 12 children with nosocomially acquired MRSA had bacteremia without a focus. Second, abscesses were more common among the children with community-acquired MRSA isolates without identified risk compared with the children with community-acquired MRSA with identified risk and children with nosocomially acquired isolates. Abscesses were the diagnosis in 6 (27%) of 22 children with community-acquired isolates without identified risk compared with none of the 10 children with community-acquired isolates with identified risk and only 1 (8%) of 12 children with nosocomially acquired isolates.

To compare the distribution of clinical syndromes associated with MRSA in 1993-1995 with that associated with MSSA for the same time period, we reviewed all available charts from children hospitalized in 1993-1995 from whom MSSA was isolated. The charts of 233 were reviewed, and 268 patients were available. We classified them as community-acquired and nosocomially acquired (145/233 and 88/233, respectively), using the same 72-hour criterion, and identified those that were colonizing or disease associated. Eighty-seven (60%) of 145 community-acquired MSSA isolates and 47 (53%) of 88 nosocomially acquired MSSA isolates were disease associated. The distribution of clinical syndromes associated with community-acquired MSSA was similar to that associated with community-acquired MRSA in children without an identified risk. For example, cellulitis and abscesses predominated among both community-acquired MRSA with or without identified risk and community-acquired MSSA patients, whereas bacteremia without a focus predominated among nosocomially acquired MRSA and nosocomially acquired MSSA (Table 2). Thus, the clinical syndromes associated with S aureus isolation are independent of methicillin susceptibility and relate more closely to the predisposing risks or their absence. A notable exception was in children with cystic fibrosis (CF). In 1988-1990, no patient hospitalized with CF had an MRSA isolate. However, in 1993-1995, 4 (19%) of 21 MRSA isolates were recovered from children with CF hospitalized for acute respiratory infection; 3 of the children had community-acquired infection with identified risk (previous antibiotics and hospitalizations), and 1 had nosocomially acquired MRSA. Notably, 1 child had MRSA isolated from blood. In contrast, no child with CF was hospitalized for a pulmonary exacerbation associated with isolation of MSSA from tracheal secretions or sputum (P=.007).

Several differences were observed among the 1993-1995 groups when the MRSA isolates were compared with respect to susceptibility to other antibiotics. First, the isolates obtained from children with community-acquired MRSA and without identified risk were more likely to be susceptible to other antibiotics compared with isolates obtained from children with community-acquired MRSA with identified risk or with nosocomially acquired MRSA. For example, the number of isolates that were nonsusceptible (intermediate or resistant) to 2 or more additional antibiotics were 6 (24%) of 25 community-acquired MRSA without identified risk; 7 (70%) of 10 community-acquired MRSA with identified risk; and 13 (76%) of 17 nosocomially acquired MRSA. These proportions are not significantly different between the community-acquired MRSA with identified risk and the nosocomially acquired MRSA (P=.53), while they are different between the community-acquired MRSA with identified risk and the community-acquired MRSA without identified risk (P=.02) as well as between the community-acquired MRSA without identified risk and the nosocomially acquired MRSA (P=.001). When we...
examined susceptibility to specific antibiotics, the same pattern was evident (Table 3). For example, only 6 (24%) of 25 community-acquired MRSA isolates obtained from children without identified risk were nonsusceptible to clindamycin compared with 6 (60%) of 10 community-acquired isolates obtained from children with identified risk and 13 (76%) of 17 nosocomially acquired isolates. Similarly, only 1 (7%) of 15 community-acquired MRSA isolates obtained from children without identified risk were nonsusceptible to gentamicin compared with 6 (55%) of 11 nosocomially acquired isolates tested. None of the community-acquired MRSA isolates obtained from children without identified risk were resistant to clindamycin compared with 3 (30%) of 10 community-acquired MRSA isolates obtained from children with identified risk and 5 (29%) of 17 nosocomially acquired MRSA isolates. The nosocomially acquired isolates and the community-acquired isolates obtained from children with identified risk tended to be multiply resistant, whereas the community-acquired MRSA isolates obtained from children without identified risk did not.

A limited sample of 7 MRSA isolates was available to assess for the presence of the meca gene and for evaluation by PFGE. Six were obtained from blood cultures, and 1 was obtained from aspiration of an infected hematoma. Five of the isolates were nosocomially acquired; 2 were community-acquired isolates obtained from children without identified risk. As indicated by the S30–base pair PCR amplimer in all isolates (Figure, left), the meca gene was present in all 7 isolates, an observation suggesting the identical, classical mechanism for methicillin resistance among the isolates. Four distinct patterns were recognized by PFGE among these 7 isolates (Figure, right). The isolates in lanes 1 and 2 appear to be genetically closely related but were obtained from 2 patients hospitalized 6 months apart, on different hospital wards, and on different medical services. Both patients had multiple previous hospitalizations; the Staphylococcus aureus isolates in both cases represented nosocomially acquired bacteremia. The isolate in lane 1 was obtained from a patient who had CF, and the isolate in lane 2 was obtained from a patient who had received a liver transplant. The antibiotic susceptibilities of these 2 isolates, however, were different in that the isolate in lane 1 was resistant to clindamycin, whereas the isolate in lane 2 was not. The isolates in lanes 3 and 4 may be genetically related. These 2 isolates were obtained from patients hospitalized 1 month apart, also on different wards and different medical services. The isolate in lane 3 was obtained from a newborn transferred from another hospital who developed nosocomially acquired bacteremia. The isolate in lane 4 was obtained from a 4-year-old with cerebral palsy as a sequela of neonatal meningitis. She had multiple previous admissions and had received antibiotics for recurrent aspiration pneumonia. Both isolates (lanes 3 and 4) were susceptible only to vancomycin. There were no genetic differences detected for the isolates depicted in lanes 5 and 6. The isolate in lane 5 was obtained from a 14-year-old boy transferred to UCCH for osteomyelitis of the right calcaneus bone. He had no known risk factors for MRSA acquisition. The organism was recovered from blood and pus obtained from aspiration of the bone and was resistant only to methicillin. The isolate in lane 6 was obtained from a 6-year-old boy with pyomyositis of the left gluteus maximus muscle who was hospitalized 6 months later. He too had no known risk factors for MRSA acquisition. His isolate was obtained from aspiration of the gluteal abscess (infected hematoma) with an identical antibiotic susceptibility pattern to the isolate in lane 5. The isolate in lane 7 was distinct. It was obtained from a newborn with nosocomially acquired bacteremia. Although this was a limited sampling, the finding of 4 distinct patterns among the MRSA isolates suggests that a single clone was not responsible for disease at UCCH.

COMMENT

We have found an increase in the prevalence of community-acquired MRSA among hospitalized children in a tertiary care pediatric hospital. Our retrospective chart review of pediatric patients suggests a change in the epidemi-
ology of MRSA. The isolation of MRSA is no longer limited to those patients at risk for nosocomial infection or with other predisposing factors. Several anecdotal reports and abstract reports of community-acquired MRSA infections in both adults and children who had no identified risk factors support our findings.\textsuperscript{24-25} Three recent reports documented that community-acquired or outpatient MRSA infections may be increasing among adults,\textsuperscript{9,17,31} although it was unclear whether the isolates were obtained from patients with identified risk factors. Moreover, a similar increase in community-acquired MRSA in children has been reported from a second university hospital in Chicago.\textsuperscript{32} Together with our findings, these isolated reports support the notion that MRSA infections are no longer confined to patients with previously ascertained risk factors.

This study was a retrospective chart review from a single institution with relatively small sample sizes and few isolates available for molecular studies. To fully define the extent of the problem of MRSA infections in children without identified risk, further population-based studies are warranted. For example, it is uncertain whether the increased prevalence of community-acquired MRSA infection we documented is limited to the children we studied in an inner-city university hospital. While there was no documentation of MRSA risk factors such as intravenous drug abuse among the children or their families, the information we obtained was by retrospective chart review. Thus, it is possible that a community-based study would reveal risk factors not recognized in this study or, possibly, reveal as-yet-unknown risk factors.

We observed a difference in age distribution among children with community-acquired MRSA isolates in the 2 time periods. The increase in community-acquired MRSA among toddlers might be explained, for example, by changes in day care usage or rates of transmission. We also observed an increase in the percentage of MRSA isolates associated with clinical disease in 1993-1995 compared with 1988-1990. The reasons for this are also unclear. These observations underscore the need for further investigation and for population-based studies.

Although our study was not designed to examine the prevalence or importance of MRSA in children with CF, the data indicate that MRSA has emerged as a clinical problem in this patient population. A retrospective review of sputum and throat \textit{S} aureus isolates obtained from 452 patients with CF in 1986 found that \textit{S} aureus was isolated in 212 (47\%) of the patients, but only 14 (3\%) had MRSA.\textsuperscript{23} All the MRSA isolates were considered to be colonizing since none of the patients received treatment for MRSA, and MRSA colonization, per se, did not appear to affect the course of pulmonary disease. The authors of that study warned, however, of the potential for MRSA to become a pathogen in children with CF. No children with CF were hospitalized and treated for pulmonary exacerbations associated with MRSA or MSSA in 1988-1990. However, all 4 children with CF who were hospitalized and treated for pulmonary exacerbations associated with isolation of \textit{S} aureus in 1993-1995 had an MRSA isolate. This observation is of obvious concern and suggests that MRSA may be an important pathogen for children with CF.

The community-acquired MRSA isolates obtained from children without identified risk differed from those obtained from children with identified risk and from nosocomially acquired isolates with respect to their susceptibility to other antibiotics. In the isolates obtained from children without identified risk, resistance was usually limited to methicillin. In contrast, multidrug resistance characterized most nosocomially acquired MRSA strains and most community-acquired MRSA strains isolated from children with identified risk. A similar observation was reported in studies of community-acquired MRSA isolates among adult intravenous drug abusers compared with nosocomially acquired MRSA isolates.\textsuperscript{16,34} Two smaller studies of community-acquired MRSA isolates obtained from children with no identified risk have also found that the isolates tended to be susceptible to non-\beta-lactam antibiotics.\textsuperscript{32,35} Only a few isolates were available for PFGE studies. Notably, the PFGE patterns for the isolates obtained from 2 children without identified risk differed from those obtained from 5 children with nosocomially acquired disease. This result suggests that the community-acquired isolates obtained from children without identified risk may have important differences when contrasted with nosocomially acquired MRSA isolates.

Data regarding antimicrobial susceptibility among our isolates reinforce this notion. Although several mechanisms identified to date have accounted for decreased methicillin susceptibility or actual resistance among \textit{S} aureus clinical isolates, the best-studied mechanism of methicillin resistance in \textit{S} aureus is related to the presence of the \textit{meaA} gene. The \textit{meaA} gene is present in all of the isolates we examined. It encodes a novel penicillin binding protein (PBP) called PBP2\textsuperscript{a} or PBP2\textsuperscript{ac} and is often acquired with a larger DNA fragment called the mec region. Presumably because multiple insertion sequences are present in this mec region, transposons mediating resistance to quinolones, clindamycin, erythromycin, trimethoprim, and gentamicin have been identified in MRSA strains. Thus, MRSA isolates have tended to become multiply resistant.

However, the majority of the community-acquired isolates obtained from our patients without identified risk were not multiply resistant. Notably, we have found a similar phenotype (presence of the \textit{meaA} gene but susceptibility to non-\beta-lactam antibiotics) among a small sampling of MRSA isolates obtained from ambulatory children without predisposing risks in another ongoing study.\textsuperscript{35} Thus, currently, at UCCH, we now consider clindamycin or other alternative therapies for initial antimicrobial treatment for severely ill children, while awaiting identification and susceptibility testing of the infecting bacterium. Because the community-acquired isolates obtained from children without identified risk were usually susceptible to clindamycin, we have not yet encouraged empiric use of vancomycin.

This study was supported in part by a grant from the Blowitz-Ridgeway Foundation and a grant from the Children’s Research Foundation. We are grateful to Robert Arbet, MD, for advice on PFGE, Jihad Zahraa, MD, for assistance in chart retrieval and review, and Karen Goldstein, MD, for critical reading of the manuscript.

References


