Epidemiology of Community-Onset Staphylococcus aureus Infections in Pediatric Patients: An Experience at Children’s Hospital at Central Illinois

Kanokporn Mongkolrattanothai¹, MD, Jean Aldag², PhD, Peggy Mankin¹, BS, MA, Barry Gray¹, MD.

From the ¹Department of Pediatrics, Division of Pediatric Infectious Diseases, ²Department of Internal Medicine, University of Illinois College of Medicine at Peoria and Children’s Hospital of Illinois at OSF Saint Francis Medical Center, Peoria, IL

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Address for correspondence: Kanokporn Mongkolrattanothai, M.D., Department of Pediatrics, 530 NE Glen Oak Avenue, Peoria, IL 61637.

Email: kmongkol@uic.edu

Tel: 309-655-4242

Fax: 309-655-2565
**Background:** The nation-wide concern over methicillin-resistant *Staphylococcus aureus* (MRSA) has prompted many clinicians to use anti-MRSA antimicrobial agents when approaching patients with suspected staphylococcal infections.

**Objective:** To characterize the epidemiology of community-onset *S. aureus* (CO-SA) infections in hospitalized children to assist local clinicians in providing appropriate empiric antimicrobial therapy.

**Methods:** From January 2005- June 2008, children (0-18 years old) admitted to the Children’s Hospital of Illinois with CO-SA infections were identified by a computer-assisted laboratory-based surveillance and medical record review.

**Results:** Of 199 patients with CO-SA infections, 67 (33.7%) had invasive infections, and 132 (66.3%) had skin and soft tissue infections (SSTIs). Among patients with invasive infections, *S. aureus* isolates were more likely to be susceptible to methicillin (MSSA 62.7% vs MRSA 37.3%), whereas patients with SSTIs, *S. aureus* isolates were more likely to be resistant to methicillin (MRSA 64.4% vs MSSA 35.6%). Bacteremia and musculoskeletal infections were the most common invasive infections caused by both MSSA and MRSA. Pneumonia with empyema was more likely to be caused by MRSA (*P* = 0.02). The majority (~90%) of MRSA isolates were non-multidrug resistance, even in the presence of healthcare-associated risk factors.

**Conclusions:** Epidemiological data at the local level is important for antimicrobial decision-making. MSSA remains an important pathogen causing invasive CO-SA infections among hospitalized children. Because up to 25% of MSSA circulating in our area are clindamycin-resistant, nafcillin (or oxacillin) in combination with anti-MRSA
antimicrobial agents should be instituted in patients with suspected invasive staphylococcal infections until antimicrobial susceptibility is known.
Introduction

Infections caused by community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) have been increasing reported worldwide. Such isolates differ from healthcare-associated MRSA (HA-MRSA) by a distinct antimicrobial susceptibility pattern, usually being susceptible to non-β-lactam antimicrobial agents and having different genetic backgrounds as determined by SCCmec elements, multilocus sequence types (MLST), and pulsed-field gel electrophoresis [1-4]. Many studies suggest that CA-MRSA have replaced their methicillin-susceptible counterparts as the major cause of skin and soft tissue infections and other invasive diseases [5-9]. These findings have important clinical implications for the selection of antimicrobial agents. In areas where CA-MRSA is common, antimicrobial agents that are active against CA-MRSA should be advocated for empiric treatment of patients with potential *S. aureus* infections, until the culture and susceptibility results are available [5, 8-10].

Knowledge of the antimicrobial susceptibility patterns at the local level is essential for selecting appropriate empiric therapy of the wide variety of *S. aureus* infections. At the Children’s Hospital of Illinois (CHOI), we have observed significant numbers of patients with community-onset infections caused not only by MRSA but also by MSSA. We thus needed a better understanding of the epidemiology of community-onset *S. aureus* (CO-SA) infections in children admitted to our institution.
Methods.

Setting. Children’s Hospital of Illinois at OSF Saint Francis Medical Center has 127 inpatient beds and about 5000 admissions annually. It serves as the academic, tertiary care referral center for the central region of Illinois.

Study design. A database of laboratory records from the OSF System Laboratory at St. Francis Medical Center was used to identify pediatric patients 18 years of age or younger who were hospitalized from January 1, 2005 through June 30, 2008 and had microbiologic specimens that yielded *S. aureus*. For each case of *S. aureus* isolated from clinical specimens, the relevant medical information was examined, including diagnosis, onset of infection, infection sites, demographics (age, gender), underlying illnesses, risk factors for healthcare-associated infections, and isolate antimicrobial susceptibility. The study was approved by the Peoria Institutional Review Board.

Community-onset *S. aureus* infection inclusion and exclusion criteria. Patients were included in the study if (a) their isolates were recovered within 48 hours of admission based on the criteria established by the Centers for Disease Control and Prevention (CDC, Atlanta) or if (b) their isolates were obtained after 48 hours of admission but patients had clinical evidence of community-onset diseases. Patients were excluded if they had positive culture results but no signs of infection, if a diagnosis of MRSA infection was made on the basis of positive MRSA screening cultures (nose, axilla, perineum, or rectum), or if the diagnosis of staphylococcal pneumonia was based solely on the isolation of *S. aureus* from a tracheal aspirate or sputum. Patients with orbital or otogenic infections were excluded if the *S. aureus* isolates were recovered from the swabs of the eye or ear drainage only.
**Definitions.** A case of invasive infection was defined by 1 or more of the following conditions: bacteremia, endocarditis, pneumonia, lymphadenitis, septic arthritis, osteomyelitis, or an illness in which *S. aureus* was isolated from normally sterile body fluids. Infections involving only the superficial layers of the skin, such as impetigo, abscess, or cellulitis were regarded as uncomplicated skin and soft tissue infections (SSTIs). For individuals with multiple hospital admissions for SSTIs during a single year, data were obtained from the first hospitalization. Risk factors for healthcare-associated infections included hospitalization or surgery in the preceding 12 months, the presence of an indwelling catheter or a percutaneous device, or frequent exposure to a healthcare facility related to an underlying condition. A hospital birth without any postnatal complications was not considered a risk factor.

**Antimicrobial susceptibility testing.** An automated system (Vitek 2; bioMérieux) was used to determine the antimicrobial susceptibility profile of *S. aureus* isolates in accordance with the recommendations of the Clinical and Laboratory Standards Institute. For isolates that tested resistant to erythromycin but susceptible to clindamycin, a D-test was performed to detect inducible resistance to clindamycin. However, the results of D-test among MRSA isolates were not routinely documented in the computerized records until year 2007. Thus, among MRSA, multidrug resistance (MDR) was used and defined as resistance to three or more non-β-lactam antimicrobial agents (ciprofloxacin or gatifloxacin, clindamycin, erythromycin, gentamicin, tetracycline, trimethoprim-sulfamethoxazole, rifampin, vancomycin).
Statistical analyses. Differences in variables between groups were calculated by chi-square test or Fisher’s exact test, as appropriate. *P* < 0.05 was considered statistically significant.

Results

We identified 212 hospitalized pediatric patients whose *S. aureus* infections were considered community-onset. Thirteen patients were excluded, including 4 patients who did not have clinical evidence of infections; 3 had *S. aureus* recovered from blood specimens; 1 had *S. aureus* recovered from the gall bladder after undergoing elective cholecystectomy; and 9 had invasive diseases but whose infections could not be definitely proved to be caused by *S. aureus* (3 with orbital cellulitis, 2 with otomastoiditis, and 1 each with pneumonia, retropharyngeal abscess, staphylococcal scalded skin syndrome, and fasciitis of the chest wall).

Of the remaining 199 patients, 67 (33.7%) had invasive infections and 132 (66.3%) had SSTIs. These two groups were significantly different (*P* < 0.01) with regard to the proportion of MSSA and MRSA isolates (Table 1). Patients with invasive infections, *S. aureus* isolates were more likely to be susceptible to methicillin [MSSA 42/67 (62.7%) vs MRSA 25/67 (37.3%)]. In patients with SSTIs, *S. aureus* isolates were more likely to be resistant to methicillin [MSSA 47/132 (35.6%) vs MRSA 85/132 (64.4%)]. The semi-annual distribution of cases is shown in Figure 1. Overall, the number of community-onset infections caused by MRSA increased yearly, but the increase was mainly due to SSTIs.
Demographic and clinical manifestations of patients are summarized in Table 1. There was a significant age group difference ($P < 0.01$) between patients with MSSA and MRSA infections. MSSA infections were common in young children (4-59 mo) and teenagers (11-18 y), whereas MRSA infections occurred more often in young children (4-59 mo). Bacteremia and musculoskeletal infections were the most common invasive infections caused by \textit{S. aureus}, regardless of its methicillin susceptibility. Fourteen patients (9 MSSA and 5 MRSA) had \textit{S. aureus} bacteremia complicated with one or more site of infection. Among patients who had invasive infections, pneumonia complicated with empyema was more likely to be caused by MRSA ($P = 0.02$), although there were only 9 patients with pneumonia in this study. In addition, among patients with invasive infections, only 29 patients had a documented history whether or not they had prior MRSA skin infections or contact with MRSA infected persons or family members before the onset of the illness. Such history was found in 67% (12/18) of patients with invasive MRSA infections, and in only 9% (1/11) of patients with invasive MSSA infections ($P < 0.01$). The most commonly affected sites of SSTIs were perineum and buttocks (45%), especially in the 4-59 mo age group.

Exposure to healthcare-associated risk factors was not significantly different between MSSA and MRSA groups ($P = 0.57$). In the subgroup of patients who had no documented healthcare-associated risk factors, bacteremia (n=9) and musculoskeletal (n=9) infections remained the common invasive infections caused by MSSA, whereas pneumonia complicated with pleural empyema (n=7) was the most common invasive infection caused by MRSA.
Clindamycin resistance (constitutive and inducible resistance) was observed 15% (13 of 89) of MSSA. However, the proportion of MSSA resistant to clindamycin was 21% (10 of 47) among isolates causing SSTIs, but was not significantly different (7%, 3 of 42) among isolates causing invasive infections ($P = 0.08$). Resistance patterns of MRSA isolates from patients with and without healthcare-associated risk factors are shown in Table 2. The majority of MRSA isolates were non-MDR (88% vs 92% in patients with and without healthcare-associated risk factors, respectively). Only 10 MRSA isolates were MDR, of which 4 were in patients who had healthcare-associated risk factors. There were no significant differences in healthcare-associated risk-factors among patients who had invasive infections or SSTIs caused by non-MDR ($P = 0.16$) or MDR MRSA ($P = 0.52$). In our population, presence of risk factors for healthcare-associated infections was not associated with MDR MRSA infections ($P = 0.76$).

**Discussion**

The epidemiology of methicillin resistance continues to perplex clinicians, with designations of “community-associated MRSA (CA-MRSA)”, “healthcare-associated MRSA (HA-MRSA)”, “community-onset HA-MRSA”, and “hospital-onset CA-MRSA”. Additionally, the migration of CA-MRSA into the healthcare setting has further blurred the distinction between CA- and HA-MRSA. Regardless of isolate characteristics, clinicians always face dilemmas in determining empirical therapy for community-onset infections in patients with potential *S. aureus* infections in order to optimize the outcome and minimize the risk of treatment failure.
Our data highlight important regional differences in the epidemiology of CO-SA infections. At CHOI, the percentages of *S. aureus* causing SSTIs that are methicillin-resistant have increased yearly and accounted for 70-75% in year 2007-2008. This finding was not unexpected or different from other regions of the United States. Nevertheless, the important finding of this study was that MSSA remains a common pathogen causing invasive CO-SA infections, especially bacteremia and musculoskeletal infections. McCaskill et al. reported the increase of invasive infections caused by CA-MSSA, of which 35% of isolates were related to USA300, the predominant clone of CA-MRSA [11]. It is plausible that some USA300 strains may have lost their SCCmec elements, thereby becoming MSSA, or alternatively, the ancestor of CA-MRSA USA300 was from an MSSA clone acquired its resistance before spreading in the community [10].

The majority of MRSA isolates from hospitalized children, including individuals with healthcare-associated risk factors, were non-MDR — a characteristic commonly observed in molecularly defined “CA-MRSA” isolates. In this study, presence of healthcare-associated risk factors was neither associated with multidrug-resistant MRSA infections nor reliably predictive of the susceptibility to methicillin in *S. aureus* isolates causing CO-SA infections. The use of healthcare-associated risk factors in exclusion criteria in studies of CA-MRSA epidemiology may have underestimated the CA-MRSA burden. Conversely, infections in patients who have healthcare-associated risk factors are diverse and, therefore, they are at increased risk for *S. aureus* infection not only by MRSA, but by MSSA as well.

Recognition of the emergence of CA-MRSA infections in the community has prompted the recommendation that patients with suspected *S. aureus* infections should
receive antibiotics that are active against CA-MRSA where the prevalence of CA-MRSA is increasing. Clindamycin is one of the antimicrobial agents commonly used against CA-MRSA because of its clinical efficacy. However, the important issue, regardless of methicillin susceptibility, is the risk of clinical failure during therapy if the isolate exhibits inducible clindamycin resistance [12, 13]. It is also difficult to define a threshold for prevalence of clindamycin resistance at which clindamycin might be no longer a reasonable option for empiric therapy, balanced against the potential for unacceptable risk of treatment failure. However, as suggested by Kaplan, in regions where the proportion of CA-MRSA isolates resistant to clindamycin exceeds 10-15%, clindamycin should not be used for empiric treatment of suspected staphylococcal infections [14].

The findings of our study led to a reevaluation of the optimal empiric antibiotic therapy in our area. Based on laboratory surveillance for antimicrobial resistance among *S. aureus*, the percentage of clindamycin resistance in MSSA isolates circulating in our area from 2005 to 2008 has been stable at 20-25% (data not shown). Therefore, clindamycin should be used cautiously for the empiric treatment of invasive MSSA infection. Because of the high morbidity and mortality associated with MSSA bacteremia, it is prudent for us to administer nafcillin in combination with another antimicrobial agent active against MRSA until susceptibility results are known. In contrast, the vast majority of community-onset MRSA isolates were non-MDR and were susceptible to clindamycin (≥ 95%). Clindamycin is the recommended empirical anti-staphylococcal therapy for hospitalized pediatric patients with clinical syndromes likely caused by CA-MRSA, such as cutaneous abscesses or complicated pneumonia with empyema. Its use avoids unnecessary exposure to vancomycin. In addition, the
penetration of vancomycin into lung tissue and pulmonary lining fluid has been reported to be relatively low [15, 16] and may limit the effectiveness of vancomycin in the therapy of MRSA pneumonia. Moreover, clindamycin inhibits toxin synthesis [17, 18] including Panton-Valentine leukocidin, a toxin which is associated with suppurative skin and soft tissue infections and necrotizing pneumonia [19-21]. It also may be responsible for the increased virulence in some CA-MRSA isolates [1, 22], although the relevance of PVL in this context remains unclear. It must be noted here that clindamycin should not be used as solely as an anti-MRSA therapy in a critically ill patient, is not appropriate for the treatment of endocarditis and its penetration into the CSF is not adequate for treating meningitis. Finally it remains important to utilize surgical drainage whenever appropriate, both to obtain clinical cultures at the infected site and to expedite the resolution of the infection.

There are limitations to our study. Strict inclusion and exclusion criteria were used, thus possibly underestimating the true prevalence of CO-SA infections among hospitalized children. Information about other potentially important risk factors were not always documented in medical records, particularly the prior history of MRSA skin infections or a history of MRSA skin infections among family members. Nevertheless, the findings from our study revealed important data to consider in patient management.

Conclusions

We have described the characteristics of CO-SA infections among hospitalized children in Central Illinois. We found that MRSA is increasing as a cause of skin and soft tissue infections, but that MSSA remains a common cause of invasive CO-SA infections.
Because up to 25% of MSSA circulating in our area are clindamycin-resistant, nafcillin (or oxacillin) in combination with anti-MRSA antimicrobial agents should be instituted in patients with suspected invasive staphylococcal infections until antimicrobial susceptibility is known. Local surveillance antimicrobial resistance data remain an essential instrument to be integrated into the approach to antimicrobial decision-making.

**Competing interests**

We declare that we have no conflict of interest.

**Authors’ contributions**

KM, PM and BG conceived and designed the study. KM wrote the first draft of the paper and other coauthors contributed to the final draft. KM was responsible for conducting the study and managing the data. KM and JA conducted the statistical analyses and the interpretation of data. Others participated in data analysis and data interpretation. All authors read and approved the final manuscript.

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References


Figure Legend

Figure 1. Number of cases of community-onset *S. aureus* infections among hospitalized pediatric patients during the study period.
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Additional files provided with this submission:

Additional file 1: table.doc, 43K
http://www.biomedcentral.com/imedia/2291018352536240/supp1.doc