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Original Article

The role of antimicrobial therapy for treatment of uncomplicated skin and soft tissue infections from community-acquired methicillin-resistant *Staphylococcus aureus* in children

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Background and purpose: Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections in skin and soft tissues are increasing in children in Taiwan. This study investigated the outcomes of therapy with or without appropriate antibiotics among children with CA-MRSA skin and soft tissue infections (SSTIs), and analyzed the outcomes of management among children with Panton-Valentine leukocidin (PVL)–positive strains and PVL-negative strains.

Methods: In this retrospective study, data for CA-MRSA SSTIs from 107 children younger than 18 years were analyzed. Worsening infection or other surgical therapy were considered treatment failure. Antimicrobial therapy was considered appropriate if it included at least 1 agent to which the organisms showed in vitro susceptibility.

Results: The rate of successful treatment was 90.7% (97 episodes). Eighty six children (80.4%) underwent incision and drainage as part of their initial therapy. Four of 5 children (80%) treated with an appropriate antibiotic initially were treated successfully, compared with 93 of 102 children (91.2%) who did not receive an appropriate antibiotic agent (p = 0.394; Fisher's exact test). Treatment failed for 5 of the 39 patients (12.8%) with PVL-positive SSTI CA-MRSA compared with only 1 treatment failure among 11 patients (9.1%) with PVL-negative SSTI CA-MRSA (p = 1.0; Fisher's exact test).

Conclusions: The high rate of successful treatment among children with uncomplicated CA-MRSA SSTIs, even when given inappropriate antibiotic therapy, suggests that treatment of these uncomplicated infections without appropriate antibiotic therapy is possible. Incision and drainage may play an important role in the treatment of uncomplicated SSTIs.

Key words: Anti-bacterial agents; Community-acquired infections; Methicillin-resistant *Staphylococcus aureus*; Skin and connective tissue diseases

Introduction

Staphylococcus aureus is the most common organism isolated from skin and soft tissue infections (SSTIs) [1,2], and methicillin-resistant *S. aureus* (MRSA) is a rapidly increasing community-acquired pathogen among the pediatric population [2-5]. These isolates, termed community-acquired MRSA (CA-MRSA), are described and defined by specific epidemiological and molecular criteria [4,6-8]. CA-MRSA possesses a host of virulence factors, chief of which is Panton-Valentine leukocidin (PVL) [9]. CA-MRSA also contributes to severe, and even fatal, infections in the pediatric population [10]. Management of uncomplicated CA-MRSA SSTIs primarily consists of incision and drainage of fluctuant lesions, as recommended by current guidelines [11]. Nonetheless, most physicians believe that treatment with antibiotics is critical to limit the spread of soft tissue infection [12], and most patients expect to receive antibiotics for infections. However, the role of antimicrobial therapy in the

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treatment of CA-MRSA SSTIs in children is not well established [13,14]. This retrospective review of the medical records of children with non-life-threatening CA-MRSA SSTIs was performed to identify the role of ancillary antimicrobial therapy for SSTIs. This study investigated the outcomes of therapy with or without appropriate antibiotics. In addition, the outcomes of management of CA-MRSA SSTIs among children with PVL-positive strains were analyzed and compared with those for patient with PVL-negative strains.

Methods

Case definition and data collection

This retrospective cohort study enrolled all children (age, <18 years) who presented with uncomplicated CA-MRSA SSTIs to the Tri-Service General Hospital (TSGH), Taipei, Taiwan, a 1500-bed tertiary medical center, from January 1, 2004 to June 30, 2007. The medical records were reviewed to classify MRSA infections as CA-MRSA, requiring the isolation of MRSA from a clinical specimen obtained during an outpatient visit, or within 48 h of hospital admission, and with none of the following risk factors for hospital-acquired MRSA (HA-MRSA): previous MRSA infection or colonization, presence of a percutaneous device or indwelling catheter at the time of culture, antimicrobial drug therapy within the 12 months before the date of MRSA isolation, or history of dialysis, surgery, hospital admission, or residence in a long-term care facility within 12 months before MRSA isolation [15]. As nearly all children are born in hospital, MRSA infections in previously healthy infants younger than 12 months who had a routine hospital birth and lacked any other HA-MRSA risk factors were also classified as CA-MRSA cases.

Children with CA-MRSA SSTIs were identified by review of the medical records and the clinical microbiology laboratory records from the computer database of patients at the clinical microbiology laboratory of the TSGH, which included the patients' name, chart number, date and site of the specimen collection, and the susceptibility results to 8 antibiotics: oxacillin, penicillin, clindamycin, erythromycin, gentamicin, trimethoprim-sulfamethoxazole, ciprofloxacin, and vancomycin.

Complicated SSTIs (non-healing skin ulcers, diabetic foot infections, postsurgical wound infections, or processes involving adjacent deep tissue structures, bone, fascia, or tendon sheaths) were excluded. Time zero was defined as the day of the first incision and drainage procedure or the day of the first positive wound culture for a sample obtained from a wound exudate swab, needle aspiration, or skin biopsy.

Treatment failure was defined as documented worsening of signs of infection at least 2 days after time zero, accompanied by 1 or more of the following events: performance of an additional incision and drainage procedure, subsequent hospital admission, occurrence of new culture-proven MRSA SSTI while the patient was receiving antimicrobial therapy, or the persistence of MRSA-positive culture of specimens from the original wound site after the completion of antibiotic therapy [16].

Antimicrobial therapy was considered appropriate if it included at least 1 agent to which the organism showed in vitro susceptibility. Antimicrobial susceptibility and identification of *S. aureus* isolates were performed according to the guidelines of the Clinical and Laboratory Standards Institute [17-19].

Data collected from review of the medical records included age, antibiotic therapy, antibiotic susceptibility, diagnosis, and outcome (treatment success or failure).

Staphylococcal cassette chromosome mectyping and polymerase chain reaction amplification of *lukS-PV* and *lukF-PV*

The CA-MRSA clinical isolates, if available, were collected for staphylococcal cassette chromosome *mec* (SCC*mec*) type determination and PVL gene detection. SCC*mec* typing was performed by polymerase chain reaction using sets of region-specific primers as described previously [20,21]. PCR amplification of the *lukS-PV*, *lukF-PV*, and genes encoding for PVL components was performed as described previously [22].

Statistical analysis

Data collected retrospectively were analyzed using chi-squared and/or Fisher's exact tests by using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 14.0; SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered to be statistically significant.

Results

197 children with SSTIs with culture proven *S. aureus* were identified. Of these, 7 children (3.5%) had HA-

MRSA and 107 (54.3%) had CA-MRSA. The mean age of the 107 children with CA-MRSA included in the study was 6.3 years (range, 3 days to 17 years). Cellulitis was the most common presentation (n = 37), followed by carbuncles (n = 36), abscesses (n = 18), furuncles (n = 7), and impetigo (n = 3). Other clinical conditions included pyoderma (n = 3), felon (n = 2), and preauricular sinus infection (n = 1). Twelve children also had staphylococcal scarlet fever along with cellulitis, carbuncles, abscesses, or furuncles.

The antimicrobial susceptibility data are presented in Table 1. Of the 107 CA-MRSA SSTI isolates, 10.3% (n = 11) were multidrug resistant (resistant to more than 3 non–β-lactam antimicrobials), while 6.5% (n = 7) were susceptible to all of the tested antibiotics except for the β-lactam antibiotics.

Of the 107 children, 86 (80.4%) underwent incision and drainage as part of their initial therapy. Initially, appropriate antimicrobial therapy was administered to 5 children (4.7%), while inappropriate therapy was administered to 102 children (95.3%) before the results of antimicrobial sensitivity testing were known. Four of the 5 children (80.0%) treated with an appropriate antibiotic within 48 h after time zero were treated successfully, compared with 93 of 102 children (91.2%) who did not receive an appropriate antimicrobial agent (p = 0.394; Fisher's exact test). Ten children (9.3%) had treatment failure, of whom 8 (80.0%) needed an additional incision and drainage procedure, and 1 (10.0%) required subsequent hospital admission. One child presented with worsening cellulitis after receiving oxacillin therapy, and a second culture from the original wound site was positive for MRSA. The most frequent inappropriate initial antibiotic therapies given to the children before the culture results were known were intravenous oxacillin (n = 48) and oral cloxacillin (n = 24) [70.6% of children].

Table 1. Resistance rates of community-acquired methicillin-resistant *Staphylococcus aureus* isolates to various antimicrobial agents (n = 107).

Antimicrobial	No. of resistant isolates (%)
Oxacillin	107 (100)
Penicillin	107 (100)
Clindamycin	97 (90.7)
Erythromycin	100 (93.5)
Gentamicin	10 (9.3)
Trimethoprim-sulfamethoxazole	3 (2.8)
Ciprofloxacin	3 (2.8)
Vancomycin	0 (0)

Only 50 of the 107 clinical isolates were available for genotyping analysis. SCC*mec* types IV and V_T were identified in 10 (20%) and 35 (70%) of the isolates, respectively. SCC*mec* type II was identified in only 5 isolates (10%). There was no evidence of any other SCC*mec* type (types I or III). Among the 50 isolates studied, 39 (78%) were PVL-positive. Treatment failed in 5 (12.8%) of the 39 patients with PVL-positive SSTI CA-MRSA compared with only 1 treatment failure (9.1%) for the 11 patients with PVL-negative SSTI CA-MRSA (p = 1.0; Fisher's exact test).

Discussion

CA-MRSA infections have recently increased among pediatric patients in Taiwan [10,23-26]. Despite the increase in the number of children with CA-MRSA SSTIs, most children are treated with a β-lactam antibiotic, which is inactive against CA-MRSA.

In this study, the overall rate of successful treatment was 90.7% (97 of 107 patients). Most uncomplicated CA-MRSA SSTIs resolved regardless of whether or not the children received an antimicrobial agent to which the infecting isolate was susceptible in vitro (termed 'active' antimicrobial therapy), which is similar to the results of several recent non-randomized studies [13,27-29]. It is possible that an agent to which the infecting isolate is not susceptible in vitro could have a clinical impact in vivo, perhaps by eliminating susceptible subpopulations of bacteria and allowing the patient's immune response to overcome the remaining infection [29]. However, Ruhe et al found that adult patients with CA-MRSA SSTIs would benefit from treatment with active antimicrobial therapy [16]. This discrepancy in the findings could be due to differences in the methods and patient population.

In this study, most patients underwent incision and drainage as part of their initial therapy. Most patients who experienced treatment failure required an additional incision and drainage procedure to improve the outcome. In a previous prospective observational study, clinical improvement of CA-MRSA skin and soft tissue abscesses was demonstrated in most patients despite treatment with antibiotics to which the organisms were not susceptible [13]. Recent data have demonstrated that surgical drainage is the primary therapy for SSTIs [14]. Surgical drainage plays a more important role than antibiotics in the treatment of uncomplicated SSTIs.

PVL-positive *S. aureus* strains are associated with virulence, resulting in severe and recurrent SSTIs [22,30-34]. Most of those severe and virulent infections were complicated. However, subgroup analysis of this study showed that 78% of the CA-MRSA causing uncomplicated SSTIs possessed the PVL genes. Nonetheless, the rate of treatment failure was not associated with CA-MRSA having the PVL genes.

In Taiwan, the CA-MRSA isolates from children without risk factors were resistant to multiple antibiotics, including clindamycin (93% to 100%), and erythromycin (94% to 100%), and were significantly more susceptible than HA-MRSA isolates to trimethoprim-sulfamethoxazole [35]. In previous studies conducted by these authors [10] and Fang et al [25], CA-MRSA isolates were also less resistant to gentamicin (11% to 34%) and ciprofloxacin (0%) than nosocomial MRSA. The patients in this study had antibiograms similar to those of the previous studies [10,25]. There are limitations to this study. As the study was retrospective, it raises the possibility of selection, information, and outcome identification biases. Additionally, the number of patients was small. Although the medical records were reviewed in detail, it could not be certain that patients did not receive other treatments outside the hospital.

In conclusion, the increase in infections caused by organisms resistant to many different antibiotics complicates the choice of antibiotics to treat these infections [27]. This study suggests that it may not be necessary to change the traditional empiric first-line antibiotics to achieve better management and outcomes for children with uncomplicated CA-MRSA SSTIs. Incision and drainage should remain the mainstay of therapy for children. The high rate of successful treatment for children with uncomplicated CA-MRSA SSTIs, even with inappropriate antibiotic therapy, suggests that treatment of these uncomplicated infections without appropriate ancillary antibiotics is possible. This report is of 1 hospital's experience of treating children with CA-MRSA SSTIs, but the choice of treatment remains dependent on the condition of individual patients. Large randomized controlled trials of diverse patient populations are needed to resolve the role of ancillary antimicrobial therapy for the treatment of CA-MRSA SSTIs.

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