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Methicillin-resistant and methicillin-susceptible community-acquired *Staphylococcus aureus* infection among children

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* has emerged as a pathogen associated with community-acquired infections worldwide. We report the spectrum of community-acquired *S. aureus* infections and compare the patients infected with methicillin-susceptible or methicillin-resistant strains among patients aged <20 years. Overall, 90 cases of community-acquired *S. aureus* were detected in an 11-year period. Clinical and microbiological data were registered. Fifty-nine (66%) patients were male and the median age was two years. The majority (87%) of the patients were hospitalized and chronic underlying illnesses were detected in 27 (30%) cases. Overall, 34 (37.8%) patients had skin/soft tissue infections and 56 (62.2%) patients had deep-seated infection. Four (5.1%) patients were transferred to the intensive care unit and two (2.6%) died. Complications were detected in 17 (18.9%) cases, such as pleural effusion (41.2%), osteomyelitis (23.5%), and sepsis (17.6%). Six (6.7%) methicillin-resistant strains were detected. Patients infected with methicillin-susceptible or methicillin-resistant strains had similar baseline characteristics and treatment outcomes. Approximately 93% of the cases received systemic antibiotics, out of which 59 (65.5%) used oxacillin or cefalotin. Both methicillin-susceptible and methicillin-resistant *S. aureus* strains resulted in morbidity and death among children in this setting where methicillin-resistant strains are infrequent.

Introduction

Over the past few decades, infection due to community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has been reported worldwide.[1] CA-MRSA has been observed in many patient groups, and healthy children are also susceptible.[2] Cases of CA-MRSA infection affecting children without established risk factors started emerging in 1990s.[3] Mostly, CA-MRSA infection has been associated not

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only with skin/soft tissue infections (SSTIs), but also with invasive infections, which require aggressive treatment and hospitalization.[4]

The risk of severe disease caused by CA-MRSA is a real concern among researchers. In Minnesota and North Dakota, between 1997 and 1999, four pediatric deaths were associated with CA-MRSA strains.[5] Many institutions have reported their experience with community-acquired *S. aureus* (CA-SA) infection in children. In a previous study conducted in a pediatric center in Northeast Brazil 4.9% of isolated CA-SA strains were resistant to methicillin.[6] Several studies have shown differences between MRSA and methicillin-susceptible *S. aureus* (MSSA) infections even after controlling for confounding variables such as nosocomial infection.[7] A three-year surveillance of CA-SA infections at the Texas Children's Hospital documented a greater percentage of CA-MSSA isolates (8.2%) than CA-MRSA isolates (4.4%) which were collected from patients with invasive infections.[8] Recently, a report of CA-SA pneumonia among hospitalized children in Hawaii revealed the occurrence of pulmonary complications more frequently in MRSA infected patients.[9] The objectives of this investigation were to describe the spectrum of community-acquired disease presented by patients infected with *S. aureus* and to compare the patients infected with MSSA or MRSA strains.

Materials and methods

Design and study population

The Ethics Committee of the university hospital at Federal University of Bahia, Salvador, Brazil, approved this study (approval 53/2005) which was a retrospective cohort conducted in the same hospital. Cultures in which *S. aureus* were isolated from pediatric patients (<20-years-old) between 1994 and 2005 were identified in the Bacteriology Laboratory log-book and the respective medical records were reviewed. CA-MRSA infections were selected by applying the following items, according to the Centers for Disease Control and Prevention (CDC) criteria last updated in December 2, 2010: diagnosis of MRSA in a outpatient setting or by culture within 48 h after admission to the hospital, with no history of MRSA infection or colonization; the patient must not have experienced any of the following conditions during the year before infection: hospitalization, admission to a nursing home, skilled nursing facility, or hospice; dialysis; or surgery. Furthermore, the patient must be without permanent indwelling catheters or medical devices that pass through the skin into the body.[10] *S. aureus* isolates obtained after 48 h of admission from patients with clinical evidence of disease prior to admission were also included.[8] CA-MSSA cases were considered eligible for the study if they met the same criteria of CA-MRSA cases, that is lack of the previously cited healthcare-associated risk factors.[10]

Microbiologic procedures

Cultures were performed manually up to 1999; in 2000, the automatic process was implemented. Both of them were in accordance with standardized procedures previously described.[11] *S. aureus* was identified by routine procedures, including catalase and coagulase tests. Antimicrobial resistance was examined by the disc-diffusion method according to the Clinical and Laboratory Standards Institute.[11] In order to test for resistance to methicillin, a 1 μg oxacillin disc was applied to Mueller-Hinton agar containing 5% sodium chloride and incubated at 35 °C.[12] Additionally, only fluids from which *S. aureus* was the only isolated pathogen were included.

Data collection and analysis

For each case of CA-SA infection, the following medical information was retrieved: demographics (age, gender); diagnosis; infection sites; length of hospitalization, nutritional evaluation, underlying illnesses, treatment; patients' outcomes (stay at a pediatric intensive care unit [ICU], sequela and death). Additional information about healthcare-associated risk factors, as proposed by the CDC in 2010,[10] at the time of *S. aureus* infection, and sequela was collected by a phone call to the patient's families between October 2010 and June 2011, after receiving oral informed consent. Nutritional evaluation was performed by using the software Anthro; malnutrition and severe malnutrition were defined as Z-score for weight-for-age index under −2.00 and −3.00, respectively.[13] Infections were classified as SSTIs, such as abscess, cellulitis, or impetigo, and deep-seated (or invasive) infection which included bacteremia, meningitis, osteomyelitis, pneumonia, septic arthritis, endocarditis or another illness in which *S. aureus* was isolated from normally sterile body fluids. If a patient had both SSTIs and deep-seated infection, the infection was defined as deep-seated.[14]

Statistical methods

Statistical analysis was performed by using SPSS software for Windows version 9.0. Descriptive statistics including distribution, central tendency and dispersion are presented. Two-tailed $p < 0.05$ was considered significant. Comparison of continuous variables was analyzed by using Student t or Mann–Whitney *U*-test, according to the variable distribution. Categorical variables were compared by using Fisher exact test because the expected frequency was <5.

Results

Ninety cases of CA-SA were detected; 59 (66%) patients were male and the median (25th–75th percentile) age was two years (5.4 months–6.2 years). The majority (87%) of the patients were hospitalized. Chronic underlying illnesses were detected in 27 (30%) cases: skin (44.4%), heart (25.9%) respiratory tract (11.1%), and central nervous system (3.7%). Additionally, sickle cell disease, AIDS, prematurity, and trauma were diagnosed (3.7% each). Twelve (13.3%) cases presented malnutrition, out of which two (16.7%) were severely malnourished. Overall, 34 (37.8%) patients had SSTIs (abscess [44.1%], pyodermitis [41.2%], cellulitis [5.9%], conjunctivitis [2.9%], tonsillitis [2.9%], sinusitis [2.9%]) and 56 (62.2%) patients had deep infection (pneumonia [26.8%], arthritis [17.9%], pyodermitis [14.3%],

Table 1 – Comparison of patients with community-acquired methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* infection.

Characteristic	MRSA ($n=6$)	MSSA ($n=84$)	p
Male gender[a]	2 (33.3)	57 (67.9)	0.2
Age			
<2 years[a]	4 (66.7)	41 (48.8)	0.7
Median (25th–75th percentile)	5.4 mo (16d–5.1yr)	26.4 mo (6.5 mo–6.3yr)	0.2
Hospitalization[a]	6 (100)	72 (85.7)	1
Chronic underlying illnesses[a]	4 (66.7)	23 (27.4)	0.06
Skin[a]	1 (16.7)	11 (13.1)	0.6
Heart[a]	1 (16.7)	6 (7.1)	0.4
Respiratory tract[a]	0	3 (3.6)	1
Malnutrition[a]	2 (33.3)	10 (11.9)	0.2
Deep infection[a]	6 (100)	50 (59.5)	0.08
Sterile fluid[a]	5 (83.3)	61 (72.6)	1
Evolution			
Death[a]	1 (16.7)	1 (1.2)	0.1
Intensive care unit[a]	1 (16.7)	3 (4.1)	0.3
Length of hospitalization (days)	16 ± 11	16 ± 12	1
Complications[a]	1 (16.7)	16 (19)	1
Vancomycin use[a]	2 (33.3)	10 (11.9)	0.2

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

[a] Results in *n* (%).

abscess [14.3%], osteomyelitis [8.9%], adenitis [5.4%], sepsis [5.4%], endocarditis [3.6%], cellulitis [1.8%], urinary tract infection [1.8%]). *S. aureus* was recovered from skin lesion (47.1%), skin abscess (41.2%), ocular secretion and nasopharyngeal or oropharyngeal swab (5.9% each) in patients with SSTIs and from blood (71.4%), abscess (10.7%), pleural effusion (5.4%), synovial fluid (5.4%), urine, pericardic effusion, fistula secretion and intra-abdominal lymph node (1.8% each) in patients with deep-seated infections.

Among the 78 hospitalized cases, two (2.6%) died and the median (days) (25th–75th percentile) length of hospitalization for the others was 14 (7–22), range 1–53. All were discharged after improvement. Among the 12 outpatients studied, one (8.3%) was hospitalized for seven days and discharged; all of them also improved. Four (5.1%) patients were transferred to the ICU and their mean stay (days) there was 3.5 (±1.3) days, range (2–5). The mean interval (days) between hospitalization and admission to the ICU was 2.5 (1.3), range (1–4). For the purpose of the analysis presented herein, the outpatient who was hospitalized was added to the group of hospitalized patients. Complications were detected in 17 (18.9%) cases including pleural effusion (41.2%), osteomyelitis (23.5%), sepsis (17.6%), respiratory insufficiency (11.8%), arthritis, cellulitis, fistula, pericarditis, septic shock (5.9% each). Three patients presented more than one complication. None had sequelae and one patient with arthritis was not followed-up after being discharged.

Approximately 93% of the cases had received systemic antibiotics. Initially, 59 (65.5%) patients were treated with oxacillin or cefalotin, to whom aminoglycosides ($n=20$), ceftriaxone ($n=2$), aqueous penicillin G ($n=1$) were also given. Twenty-five cases (28%) used other antibiotic regiments: other penicillins (e.g. aqueous penicillin G, benzathine penicillin or amoxicillin) [13.3%], aminoglycosides [5.6%], trimethoprim-sulfamethoxazole (TMP-SMX) [5.6%], ceftriaxone, vancomycin and a combination of ceftriaxone and aminoglycoside [1.1% each]. Twenty-three (27.4%) children had their first antimicrobial regimen changed to: vancomycin (43.6%) or oxacillin (34.8%), erythromycin (8.7%), TMP-SMX, ceftriaxone and clindamycin (4.3% each). Only one patient had the antibiotic regimen changed for the second time; in this case oxacillin was switched to vancomycin. Six (6.7%) MRSA strains were detected according to the aforementioned microbiologic criteria. Table 1 shows the comparison between the patients with MRSA or MSSA infection. Four patients did not use vancomycin as a therapeutic option, even though MRSA was isolated from their blood. The clinical features of these four cases are summarized in Table 2.

Discussion

In the present study, we did not observe higher morbidity or mortality rates among patients with CA-MRSA infection when they were compared with patients who had CA-MSSA infection. In Korea, MRSA was not found to be significantly associated with higher mortality among adults.[15] However, other studies have described the association between CA-MRSA strains and worse outcomes. A prior report documented the presence of CA-MRSA isolates causing necrotizing pneumonia and severe sepsis.[16] Another investigation demonstrated that CA-MRSA osteomyelitis had a longer duration of hospitalization compared with osteomyelitis caused by CA-MSSA strains in children.[17] Furthermore, it is important to emphasize that CA-MSSA infections are also found to be prevalent among life-threatening staphylococcal infections. This statement is consistent with some published data suggesting that CA-MSSA isolates are more likely than CA-MRSA isolates to be associated with invasive infections.[8] Nevertheless, a recent analysis showed severe clinical course

Table 2 – Patients with community-acquired methicillin-resistant *S. aureus* bacteremia without vancomycin use.

Characteristic	Case I	Case II	Case III	Case IV
Date of admission	8 May 1996	18 September 1996	2 August 2004	10 October 2005
Age	14 days	16 days	36 months	5 months
Gender	Female	Female	Female	Male
Underlying illness	None	Congenital heart disease	Sickle cell disease	None
Diagnosis at presentation	Pneumonia	Pneumonia	Dactylitis	Pyodermitis
Other site of S. aureus isolation	No	No	No	No
Initial antibiotic regimen	Cep & Ami	Pen G & Ami	None	Oxa
Subsequent antibiotic regimen	None	Oxa	None	None
Length of hospitalization (days)	19	12	7	15
Complications	None	None	None	None
Outcome	Resolution	Resolution	Resolution	Resolution
Antimicrobial testing				
Susceptible	Ami, Cip, Tei	Gen, Rif, Tei, TMP-SMX, Van	Ami, Cip, Cli, Ery, Gen, Rif, Tei, Van	Ami, Cip, Ery, Gen, Tei, TMP-SMX, Van
Resistant	Ery, Gen	Ami, Ery	TMP-SMX	–

Ami, amikacin; Cep, cefalotin; Cip, ciprofloxacin; Cli, clindamycin; Ery, erythromycin; Gen, gentamicin; Oxa, oxacillin; Pen G, aqueous penicillin G; Rif, rifampin; Tei, teicoplanin; TMP-SMX, trimethoprim-sulfamethoxazole; Van, vancomycin.

in both CA-MSSA and CA-MRSA pneumonia. Days of oxygen requirement and intubations were similar between MRSA and MSSA infected children.[9] It is increasingly recognized that Panton-Valentine leukocidin-positive *S. aureus* is associated with highly aggressive disease, irrespective of antimicrobial resistance.[18]

Interestingly, we found four bacteremic patients infected with MRSA who improved despite not receiving vancomycin. It is important to state that in spite of the recognized virulent nature of MRSA bacteremia, not all bacteremic patients experience complications.[19] A risk-scoring system was created to estimate the likelihood of developing complications among patients with *S. aureus* bacteremia.[20] Persistent fever at 72 h, positive result of follow-up blood culture at 48–96 h, skin findings of acute systemic infection and community-acquired infection are the individual risk factors included in the score. Except for the *S. aureus* community origin, all other factors were not present among those four bacteremic cases summarized in Table 2. It is useful to classify CA-SA infections as MRSA and MSSA, but this is not necessarily predictive of *S. aureus* virulence.[21]

In this context, one can suspect that several of our MRSA strains were not really resistant to methicillin. However, the disc-diffusion method as outlined by the Clinical and Laboratory Standards Institute (CLSI) was used to detect antimicrobial resistance and methicillin resistance was confirmed by the ability of the isolates to grow on Mueller-Hinton agar supplemented with 5% sodium chloride and 1 μg oxacillin, incubated at 35 °C.[12] The CLSI defines the disc-diffusion test with oxacillin as a reliable method to detect MRSA. Other techniques are also available, such as the cefoxitin disc screen test and the latex agglutination test for PBP2a. When used correctly, all three methods usually can detect MRSA strains accurately.[22,23]

In our analysis, MRSA was isolated from 6 (6.7%) of 90 eligible CA-SA cases. Data reported in other studies showed higher frequency (37%) of CA-MRSA strains.[24] The use of healthcare-associated risk factors in the inclusion criteria in studies of CA-MRSA epidemiology may explain these disparate results. A previous meta-analysis including different CA-MRSA publications documented that the prevalence of MRSA isolates among people without risk factors (genuine CA-MRSA) remains low, which is consistent with our finding.[25] So, it must be emphasized that in some studies found in the literature the majority of those MRSA isolates were not really CA strains.[26] In the present report, we were able to contact patients' families with CA-MRSA to verify any healthcare risk factor that might have been missed in medical records. Thus, we can assure the genuine community origin of isolates enrolled in this investigation according to the updated 2010 CDC definition.[10]

SSTIs are by far the most common clinical manifestations of CA-SA infections in children and adults.[27,28] However, this finding has not been demonstrated in our analysis. SSTIs were responsible for 34 (37.8%) cases of CA-SA infections. The great majority of our patients have experienced invasive infections (62.2%). It is important to note that this investigation was conducted in a tertiary care center and children admitted to our institution might have presented the worse spectrum of disease, which required hospitalization.

The limitations of this study must be emphasized. Firstly, the retrospective design had intrinsic limitations, including incomplete medical charts. This was overcome by telephone contact. Secondly, the number of patients with CA-MRSA infection was small. This finding may have been influenced by the strict criteria used for the classification of CA-SA infection[10] with the purpose of detecting genuine CA-SA infection. Moreover, it is a finding by itself. Thirdly, during the analysis, we did not address additional bacterial characteristics, including clonal types and virulence factors of the strains. This further investigation could add to the understanding of the distinct clinical course and therapeutic response of *S. aureus* strains, especially in invasive infections.[4] Fourthly, recall bias may have occurred because the phone call was performed between October 2010 and July 2011 and the patients had *S. aureus* isolated between 1995 and 2004. But as the phone call searched for sequelae and sequelae are permanent, it is not probable that recall bias have occurred in regard to sequelae. Concerning healthcare-associated risk factors (any

of the following conditions during the year before infection: hospitalization, admission to a nursing home, skilled nursing facility, or hospice; dialysis; or surgery; the patient must be without permanent indwelling catheters or medical devices that pass through the skin into the body) that were also searched for in the previous year to *S. aureus* isolation, they are not usually easy to be forgotten. Therefore, recall bias is unlikely.

In conclusion, this study attempted to describe the characteristics of CA-SA infections among children in a tertiary care center. We found no relevant differences on baseline characteristics or on the outcome of patients infected with CA-MRSA or CA-MSSA strains. In addition, the evidence presented herein supports the occurrence of genuine CA-MRSA in our region. Although it is clinically still significant to classify CA-SA as MSSA and MRSA, the clinicians should be aware of the broad epidemiology of *S. aureus* infections.[29] Both CA-MRSA and CA-MSSA strains may result in life-threatening disease or lethal events.

Conflict of interest

The authors declare no conflicts of interest.

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