Original Article

Community-associated methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections in a pediatric hospital in Argentina

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Abstract

Introduction: Methicillin-resistant *Staphylococcus aureus* (MRSA) emerged at the Pediatric Hospital of Misiones Province, north Argentina, in 2003 as a cause of community-acquired (CA) infections, mostly associated with skin and soft tissue infections (SSTIs). This study aimed to assess the microbiological, epidemiological, and clinical features of CA-MRSA SSTIs treated at the hospital.

Methodology: From 2003 through 2006, a longitudinal study on CA-MRSA SSTIs was conducted. Clinical, bacteriological, and molecular data were collected and analyzed by multiple correspondences and cluster analysis (MCCA).

Results: A total of 138 children were enrolled; 55.8% of the children required hospitalization. The main clinical presentation was abscesses (51%). Antibiotic therapy in the previous six months was registered in 41% of the patients, and 72% of the patients had relatives with similar symptoms. Resistance to non-β-lactam antibiotics was found in less than 12% of patients. All 44 isolates carried staphylococcal cassette chromosome*mec* (SCC*mec*) type IV, and 30/44 had Panton-Valentine leucocidin (PVL) coding genes. Six pulsed-field gel electrophoresis (PFGE) patterns were detected from 17 isolates. MCCA hierarchic classification resulted in four distinctive patient classes (new variable). No relationship could be observed regarding the PVL detection, as PVL (+) isolates were detected in all classes; the same lack of significance was observed concerning the distribution of resistance to non-β-lactam antibiotics.

Conclusions: This study increases the understanding and knowledge about CA-MRSA skin and soft tissue infections in pediatric patients. Continuous efforts should be made to control this significant public health problem.

Key words: CA-MRSA; skin infections; children; epidemiology.

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a cause of infection among otherwise healthy children and adults in the community. Skin and softtissue infections (SSTIs) are frequent, and children area population particularly affected [1,2].

Even if the majority of community-associated MRSA (CA-MRSA) isolates are susceptible to a number of non-β-lactam antimicrobial agents, resistance patterns change in different locations [3].

CA-MRSA strains harbour SCC*mec* type IV or V, differing from the classical hospital-acquired (HA) MRSA strains that carry SCC*mec* type I, II, or III. Additionally, several studies have described that Panton-Valentine leukocidin (PVL), together with SCC*mec* type IV or V and a specific genetic background, is a genetic marker for CA-MRSA [4]. The contribution of this toxin to the virulence of *S. aureus* has been highly discussed, although necrotizing skin and softtissue infections as well as necrotizing pneumonia have been shown to be epidemiologically associated with PVL-producing strains [5-7].

MRSA emerged at the Provincial Pediatric Hospital of Posadas in Misiones Province, Argentina (PPHM) in 2003 as a cause of community-acquired infections, even replacing methicillin-sensitive *S. aureus* (38% in 2003 to 58% in 2006) and was associated with SSTIs and invasive infections. This proportion was maintained to 2010 when we observed that a 60% of *S. aureus* isolated were MRSA (M. von Specht, unpublished results).

In this study we aimed to assess the microbiological, epidemiological, and clinical features of skin and soft tissue infections caused by CA-MRSA at PPHM.

Methodology

Setting

The PPHM is a 120-bed tertiary care hospital and Reference Center for the region. This public hospital receives patients from other areas of Misiones as well as from northern Corrientes province (Argentina), southern Paraguay, and a few patients from southern Brazil.

From January 2003 to December 2006, all consecutive single patient isolates (n = 138) identified as CA-MRSA that were recovered from patients between 1 month and 14 years of age diagnosed with SSTI were included.

CA-MRSA infection was defined as culture-confirmed MRSA infection in a patient without risk factors for hospital-acquired MRSA during the previous year, who acquired the infection outside hospital settings or within 72 hours of admission, according to CDC criteria [1, 8].

Clinical and socio-economic data from each patient were collected from medical records and from interviews with the patient guardians. Previous antibiotic therapy was defined as receiving antibiotics immediately prior treatment (patient treated at the time of sampling) or receiving antibiotics as pre-treatment for any other infection in the previous six months. The nutritional valuation was made according to Waterlow criteria [9].

The study was reviewed and approved by the Institutional Review Board; informed consent was not required.

Microbiological studies

Staphylococcal strains were isolated on 5% sheep's blood agar plates (Columbia agar base, Britania, Buenos Aires, Argentina) and identified on the basis of conventional diagnostic procedures. Antimicrobial susceptibility testing was performed by the disk diffusion method in accordance with the Clinical and Laboratory Standards Institute guidelines [10]. The antibiotics tested included oxacillin, cefoxitin, ciprofloxacin, gentamicin, rifampin, minociclin, trimethoprim/sulfamethoxazole, chloramphenicol, erythromycin, and clindamycin (Britania, Buenos Aires, Argentina). *S. aureus* ATCC 25923 and 43300 were used as control strains.

Molecular characterization

Detection of the *mecA* and PVL coding genes was performed ona randomly selected group of 44 available isolates, after extraction of genomic DNA as previously described [5,11-13]. SCC*mec* typing was performed by a multiplex PCR method described elsewhere [14].

Genotyping was conducted by pulsed-field gel electrophoresis (PFGE) with *Sma*I as previously described [15] to a randomly selected group of 17 isolates. Comparison of the PFGE fingerprints was performed by the unweighted pair group method with arithmetic mean (UPGMA) clustering analysis, applying the Dice correlation coefficient [16].

Statistical analysis

The variables and their modalities are shown in Table 1.

Categorical data were compared by the Chi-square (χ^2) test with Epi Info (TM) 3.5 software from CDC Atlanta US (http://wwwn.cdc.gov/epiinfo/html/downloads.htm). P values of <0.05 were considered statistically significant.

To identify the socio-demographic and clinical characteristics ofthe study population, factorial multiple correspondence analysis (FMCA) [17,18] was performed, followed by a cluster analysis [19,20]. The intervening variables were type of injury, age, sex, family partners with identical symptoms, nutritional status, infections, and anatomic location of the lesions; these were active variables. Illustrative variables were length of stay, no resistance to β-lactam antibiotics, and presence of PVL genes.

Ward's [21,22] method was used for the hierarchical classification into groups. Efficiency of the differences between inertia and stability of the group numbers in different classes was compared. FAMC and cluster analysis wasperformed using SPAD 4.0 software (Centre International de Statistique et d'Informatique Appliquées, CISIA-CERESTA 1987-1999, Montreuil, France).

Finally, associations between typologies and resistance profiles were examined.

Results

A total of 138 children with CA-MRSA SSTIs were enrolled. The median age was 3 years (range, 1 month to 14 years), and 39.6% of children were younger than 2 years of age. Seventy-seven patients required hospitalization due to the severity of the infection.

Table 1. Factorial analysis of multiple correspondences. Variable and modality labels.

Variable	Categories	Category labels
Age group	Infants: 0.1-1.9 years	Infants
	Preschool 2-4 years	Preschool
	Schoolchildren1: 5-8 years	School1
	Schoolchildren2: 9-14 years	School2
Gender	Male	Male
	Female	Female
Nutritional status	Eutrophic	Eutrophic
	Underweight	Underweight
	Undernutrition grade 1	Undernutrition 1
	Undernutrition grade 2	Undernutrition 2
Length of stay	Outpatient	LOS=0
	< 3 days	LOS(1-<3)
	3-4 days	LOS (3-4)
	5-6 days	LOS (5-6)
	>6 days	LOS (>6)
Family members with identical symptoms	None	Cohab (0)
	One	Cohab (1)
	Two or more	Cohab (2+)
Clinical presentation	Impetigo	Impetigo
	Cellulitis	Cellulitis
	Abscess	Abscess
	Pyoderma	Pyoderma
	Other: infected wound	Other:inf wound
Anatomical location	Arms	Arms
	Face/neck	Face
	Scalp	Scalp
	Generalized infection	Generalized inf
	Groin, buttocks, or perineum	Groin/buttocks/per
	Lower limbs	Lower limbs
	Trunk	Trunk
Co-infections	Scabies	Scabies
	Mycoses	Mycoses
	No co infection	No coinf
	Group A β-hemolytic streptococcus	SBHGA
	Chickenpox	Chickenpox
	No data	Coin no data

Table 2.CA-MRSA skin andsoft tissue infections.Characteristics of patients by inpatient or outpatient status. Provincial Pediatric Hospital of Misiones, 2003–2006.

Characteristic		Admitted N=77 (55.8%)	Outpatient N=61 (44.2%)	Total	*p*
Age group	Infants	37 (48%)	17 (27.8%)	54	0.01
	Preschool/Schoolchildren	40 (52%)	44 (72.2%)	84	
Gender	Male	38 (49.4%)	36 (59%)	74	0.25
	Female	39 (50.6%)	25 (41%)	64	
Nutritional status	Undernutrition	9 (11.7%)[1]	11(18.0%)[1a]	20	0.1
	Eutrophic	47 (61%)	27(44.3%)	74	
	ND	21 (27.3%)	23(37.7%)	44	
Family members with identical symptoms	None	14 (53.8%)	12(46.2%)	26	0.2
	One or more	26 (38.2%)	42(61.8 %)	68	
	ND	37 (84%)	7(16%)	44	
Immediately prior antibiotic treatment	Yes	27 (35.1%)	24(39.3%)	61	0.04
	No	26 (33.8%)	9(14.8%)	35	
	ND	24 (31.2%)	28(45.9%)	52	
Six-month prior antibiotic treatment[6]	Yes	23 (29.8%)	18 (29.5%)	41[6]	0.41
	No	36 (46.7%)	23 (37.7%)	59	
	ND	18 (22.4%)	20 (32.8%)	38	
Anatomical location[7]	Scalp	3 (30%)	7(70%)	10	0.048
	Arms[2]	7 (46.7%)	8 (53.3%)	15	
	Generalized infection[3]	12 (54.5%)	10 (45.5%)	22	
	Face/neck	8 (47.1%)	9 (52.9%)	17	
	Lower limbs	19 (73.1%)	7(26.9%)	26	
	Trunk[4]	10 (52.6%)	9(47.4%)	19	
	Groin, buttocks, or perineum	13 (86.7%)	2 (13.3%)	15	
	ND	5 (35.7)	9 (64.3%)	14	
Clinical presentation	Impetigo	8 (21.1%)	30 (78.9%)	38	0.001
	Cellulitis	16 (100%)	0	16	
	Abscess	45 (643%)	25 (35.7%)	70	
	Pyoderma	6 (66.7%)	3(33.3%)	9	
	Infected wound	2 (40%)	3 (60%)	5	

[1]Underweight: three patients; undernutrition grade 1: four patients; undernutrition grade 2: two patients; [1a]All underweight patients; [2]Arms and hands; [3]Head, neck, trunk and extremities; [4]Back and abdomen; [5]Immediately prior antibiotic treatment: patients treated at the time of sampling; [6]Amoxicillin (26 patients); cephalexin (13 patients); azitromicyn (2 patients); [7]For the variables' anatomical location and clinical presentation, row profiles were considered.

Table 3.CA-MRSA skin and soft tissue infections.Relationship between the lengths of stay and the classes of patients.

	Outpatients N (%)	LOS(1–<3) N (%)	LOS(3–<4) N (%)	LOS(4–<6) N (%)	LOS(6+) N (%)	Total N
Class 1	3 (9.68)	6 (19.35)	8 (25.81)	9 (29.03)	5 (16.13)	31
Class 2	9 (39.13)	2 (8.70)	6 (26.09)	2 (8.70)	4 (17.39)	23
Class 3	16 (84.21)	1 (5.26)	1 (5.26)	0	1 (5.26)	19
Class 4	10(47.62)	4 (19.05)	3 (14.29)	1 (4.76)	3 (14.29)	21
Total	38 (40.43)	13 (13.83)	18 (19.15)	12 (12.77)	13 (13.83)	94

LOS: length of stay in days
p = 0.001

Among them, the median length of hospitalization was 4 days (range, 1 to 22 days). Although all patients survived, some of them had serious complications, including the need for hospitalization in the intensive care unit in two cases.

Demographic and clinical characteristics of children and their distribution according to the need to be admitted to the hospital are shown in Table 2.

Hospitalization was more common among younger children (infants) compared to the rest of the age groups ($p < 0.05$), while patients in the older age groups (preschool and school children) were more frequently treated as outpatients ($p < 0.05$)

Out of 138 patients, 46% were female. A higher percentage of these patients required hospitalization (61%, $p < 0.05$) compared to male patients (54%). From the group of children in which nutritional status was evaluated (n = 94), 20 had some degree of malnutrition (21%), and hospitalization was required in 9 of them (45%). However 47/74 eutrophic patients were admitted ($p = 0.1$, Table2). None were receiving immunosuppressive therapy.

In 51 of the 86 patients from whom data were obtained, immediately prior antibiotic treatment with first-generation cephalosporins was recorded.

Data of antibiotic therapy for any infection in the previous six months were obtained for 100 patients; 41 of them had received antibiotics (amoxicillin, 63% and cephalexin, 32%;Table 2).

Regarding the infection source, 68/94 children had close contact with at least one relative with similar symptoms. The distribution of this variable among hospitalized patients or outpatients was not statistically significant (Table 2).

The main clinical presentations were abscesses, followed by impetigo and cellulitis (Table 2). All cellulitis cases (16) and 64% of the abscesses required hospitalization. On the other hand, 78% of the impetigo cases were treatedas outpatients ($p < 0.05$).

The majority of the infections were located on the lower limbs or spread across the head, neck, trunk, and extremities (Table 2). Most children with infections of the lower limbs (19/26) and buttocks, perineum,or groin (13/15) required hospitalization ($p < 0.05$).

Concurrent *Streptococcus pyogenes* infections were observed in 17 patients with impetigo. Three of them required hospitalization. In terms of other skin conditions, five children had scabies, three had mycosis, and four had chickenpox in both groups (hospitalized or ambulatory).

Antimicrobial susceptibility

All the MRSA isolates (n = 138) were susceptible to trimethoprim/sulfamethoxazole and minocycline.

Resistance to non β-lactam antibiotics was low: erythromycin (11%), gentamicin (9%), rifampicin 6.2%), ciprofloxacin (2.3%), clindamycin (2.3%), and chloramphenicol (2.2%). The main pattern (only resistant to β-lactam antibiotics) was present in 111isolates (80%), followed by resistance to erythromycin (5%), rifampicin (4%), and gentamicin(3%). Other minor resistance patterns were also detected (8%).

Resistance pattern distribution among age groups, clinical diagnosis, previous antibiotic treatment, or infection site was not statistically significant.

Molecular characterization

Molecular analysis was performed on a total of 44 available isolates. Panton-Valentine leukocidin (PVL) geneswere detected in 30 (62%). Staphylococcal cassette chromosome *mec* (SCC*mec*) type IV was detected in 44/44 isolates.

Six PFGE patterns were found; isolates with indistinguishable patterns were grouped in the same pulsotype and coded with capital letters (A–G). The two major groups were Type A (n = 7) and Type G (n = 4). PVL genes were carried by 6/7 isolates of pulsotypeA, 4/5 of pulsotype G, and 3/3 of pulsotype B. Pulsotypes C, E, and F were PVL (-), with one isolate each.

Patients' characteristics

Although a total of 138 isolates and patients were initially considered, the 94 with complete clinical or epidemiological data were used to perform the FAMC.

Overall inertia (variance) of the data matrix in these FACM was 3.29. The first three factors accounted for 26% of the total variance. Factor 1 (F1) and factor 2 (F2) are displayed in the main plane. For more clarity to show labels, the same figure is shown in three parts (Figures 1A, B, C).

The following factors contributed to factor 1 on the positive side: impetigo, patients without affected cohabiting family members, low weight, lesion in face, and injuries with co-infection by *Streptococcus pyogenes* (SBHGA). On the negative side, factors included cellulitis, malnutrition, and injuries located in lower limbs (Figure 1A).

Factors contributing to form the positive side of factor 2 were younger age, scabies, chickenpox, and injuries in groin, buttocks, or perineum. On the negative side, factors included two cohabitants, cases

with no data about co-infection and lesions in the trunk.

Illustrative variables can be seen projected on the main plane (Figure 1B). F1 displays the opposition of the children requiring hospitalization on the left side of the origin, to those that could be treated as outpatients on the positive side, near RA 2+. No resistance patterns (RA0) are projected in the origin, near PVL NR.

In the main plane, right area, medical conditions requiring more complex treatments are projected close to (related to) the first of these groups. In this regard, cellulitis and abscesses correspond with patients requiring hospitalization, and with patients who had abscesses in their legs, groin, buttocks, perineum, and trunk.

As an infection of lesser compromise, not requiring hospitalization, impetigo (related to low weight and no family members with identical symptoms) is projected to the right side of the origin. Age groups are separated along the second axis. A relationship was found between the youngest age (infant) and widespread skin lesions, in which treatment could be performed without requiring hospitalization.

The dendrogram and hierarchic classification resulted in four distinctive classes of patients (Figure 1C).

Class 1 included children requiring hospitalization with cellulitis, having cohabiting family members with symptoms, and having infections localized in legs, groin, buttocks, and perineum (n = 31).

Class 2 included children with two or more cohabitants with similar symptoms, and children with infections localized in the trunk and arms(n = 23).

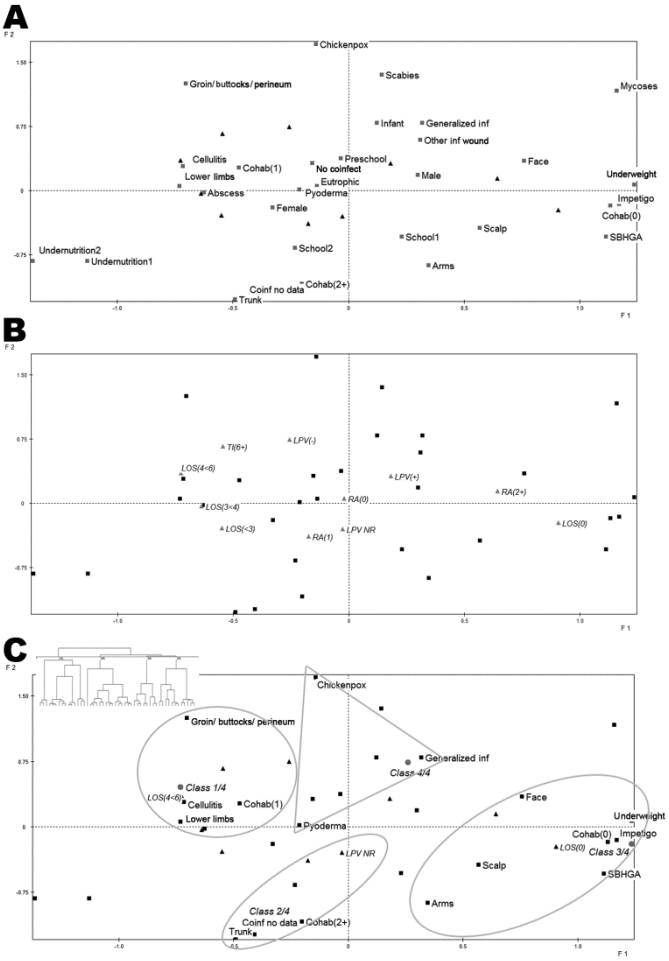
Class 3 included patients treated as low-weight outpatients diagnosed with primary impetigo, patients co-infected with β-hemolytic *Streptococcus*, and patients with infections localized in head and neck who had no affected cohabiting family members (n = 19).

Class 4 included children with pyoderma, generalized infection, and chickenpox (n = 21).

This typology was considered a new variable. Differences in the length of hospital stay distribution among the classes were statistically significant ($p < 0.05$), as patients in class 1 required longer hospital stays compared to all the other classes (Table3).

Although a limited number of isolates were genotyped, no significant statistical association could be observed between detection of the PVL coding genes and the classes defined in this study. The same lack of significance was observed concerning the distribution of resistance to non-β-lactam antibiotics.

Figure 1.CA-MRSA Skin and soft tissue infections. First factorial biplot. Illustrative variable: Length of Stay. Provincial Pediatric Hospital, 2003-2006. References; ■active variables, ▲illustrative variables.



Discussion

CA-MRSA is recognized to cause a variety of infections in previously healthy children [1,23-29]. Purulent SSTIs caused by CA-MRSA are the most frequent clinical manifestations [2,30].

Over the past decade, CA-MRSA infection has become a quickly growing problem in pediatric hospitals [29,31]. As there is no definite consensus about why otherwise healthy children acquire these resistant bacteria, we decided to evaluate the clinical and microbiological characteristics of CA-MRSA isolates recovered from 138 consecutive patients with SSTIs. Considering that many patients suffering from SSTIs are not microbiologically diagnosed, our results represent only a fraction of these infections treated at the hospital.

In our study, the largest age group included patients up to two years of age (54 children), although no statistically significant differences were observed with respect to the other age groups. This finding is in agreement with other studies, in which the median age is similar to our series [32-34], that concluded that age was not a significant predictor for MRSA skin and soft tissue infections [30]. However, others noted a higher incidence of MRSA among children younger than two years of age [34].

The admission requirement observed in this study (56%) is markedly higher than that reported by other researchers. Inadult patients with SSTIs due to CA-MRSA, the reported frequency is variable, ranging from 16% to 44% [2]. In children, Lee *et al.* found that only 4% of patients required hospitalization for further treatment [35]. Such observed variations could reflect some clinical determinants, such as depth and/or extent of lesions [34] as well as treatment failures or a very young age [30].

While we found that a greater number of patients under two years of age were admitted (Table 2), similar to what other authors found [30], we observed that the number of hospitalizations could be higher for extrinsic reasons to the infectious process (*e.g.*, derivation from remote health centers, families with little potential for monitoring, etc.); these patients, in an urban setting near the hospital, might have been treated as outpatients. The predominance of male gender among patients suffering from MRSA infections has been documented, particularly among invasive infections by CA-MRSA, but not among SSTIs [34,36-38]. However, results obtained by Chen *et al*. indicated that gender could not be considered a SSTI MRSA predictor [30]. In our work, both genders were almost equally represented (Table 2).

The fact that most of the children were receiving antibiotic treatment with first-generation cephalosporins, inappropriate for MRSA, shows the lack of knowledge of the treating physicians at the time about MRSA emergence in the community.

Several studies suggested that frequent exposure to antimicrobial agents can facilitate the acquisition of MRSA [39-41], especially multiple antibiotics treatments in the previous year [42], which was also concluded in a meta-analysis conducted in 2008 [43].

However, other studies arrived at the opposite conclusion, that there was no difference between the acquisition of MRSA and non-MRSA [34,44,45]. Data about antibiotic therapy in the previous six months showed the frequent use of β-lactam antibiotics, which may have contributed to the selection of CA-MRSA.

Direct contact with infected patients or colonized subjects is implicated in the transmission of CA-MRSA infection, and intrafamily spread of CA-MRSA is frequent and most certainly accounts for an increasing number of cases [2]. In this study, most patients reported family members with identical symptoms (Table 2).

Abscesses and cellulitis have been described as the most common CA-MRSA skin and soft tissue infections [2, 36]. Similarly, subcutaneous abscesses were the most frequent diagnoses in our series, particularly those located in lower limbs, as also described by other authors [2,30,44,46].

The associated resistance to erythromycin (11%) is similar to other patient series [29,34,47], but is significantly lower than those reported by other authors [30,33].

Several antibiotics, including clindamycin and trimethoprim-sulfamethoxazole, have been proposed for the treatment of suspected CA-MRSA skin infections in outpatient settings [48-50]. In this study, resistance to clindamycin was lower than that described by other Argentine authors [44]; this could be due to a decrease in the use of this drug by that time, and also to differences in the population under study. However, our rate of resistance was similar to those reported in other countries (3%) [30]. All strains were sensitive to trimethoprim/sulfamethoxazole, so these antibiotics could be considered first-line options for empirical treatment at our center.

In the present study, the MRSA isolates that were molecularly evaluated (44) were found to exhibit typical phenotypic molecular features associated with community-acquired MRSA [51], including resistance profile, the presence of SCC*mec* IV in 100% of isolates, and the presence of PVL coding genes in the majority of the isolates. Our data have practical value in the assessment of predisposing factors, and represent a contribution to the optimal management of *S. aureus* SSTI. Patients with greater compromise were grouped in class 1, whose infections were the most invasive of the series and required more effort and length of treatment; most of these infections were located in the legs, groin, buttocks, and perineum (Table 3). Similar relationships were observed by other authors [52,53].

The other classes were consistent, and included patients with lower clinical compromise. Thus, the class 2 patients (infections on the trunk and arms with two or more cohabiting family members with similar symptoms) could probably be treated as outpatients. In this situation, the physician could also consider

studying and eventually treating the household members who had similar symptoms.

In contrast, for those patients grouped in class 3, it is important to consider the possible therapeutic failure in the choice of TMS for empirical therapy due to *Streptococcuspyogenes*co-infection [54].

Finally, class 4 included patients with superficial widespread infections, the lowest clinical compromise that represents the wide range of skin and soft tissue infections caused by CA-MRSA, as described by several authors [55,56].

Limitations of this study include: missing data for some variables, which led us to define the category as *unknown*; a limited number of isolates available for molecular studies; and our retrospective design, which makes our results predisposed to potential biases of studies of similar design.

Conclusions

Despite the limitations described, this study increases our understanding and knowledge about CA-MRSA skin and soft tissue infections in pediatric patients. Further studies on the role of antibiotics in treating CA-MRSA cutaneous infections and surveillance for more invasive infections are needed. Surveillance is considered to be the main resource to achieve information and implement actions. Continuous efforts should be made to control this significant public health problem.

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