Community-acquired methicillin-resistant *Staphylococcus aureus* infections: hospitalization and case fatality risk in 10 pediatric facilities in Argentina

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ABSTRACT

Introduction. Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections are prevalent both in Argentina and worldwide, and they may have a severe clinical course.
Objectives: To estimate the hospitalization rate and case fatality risk factors of CA-MRSA infection.
Methods. Cross-sectional, analytical study. All patients ≤ 15 years old with community-acquired *Staphylococcus aureus* (CA-SA) infections admitted to 10 pediatric facilities between January 2012 and December 2014 were included.
Results. Out of 1141 patients with CA-SA, 904 (79.2%) had CA-MRSA. The rate of hospitalization of CA-MRSA cases (per 10 000 discharges) among patients < 5 years old was 27.6 in 2012, 35.2 in 2013, and 42.7 in 2014 (p = 0.0002). The 2-4-year-old group was the most affected one: 32.2, 49.4, and 54.4, respectively (p = 0.0057). The clinical presentations included skin and soft tissue infections: 66.2%, pneumonia: 11.5%, sepsis/bacteremia: 8.5%, osteomyelitis: 5.5%, arthritis: 5.2%, psoas abscess: 1.0%, pericarditis/endocarditis: 0.8%, meningitis: 0.6%, and other: 0.7%. In terms of antibiotic resistance, 11.1% had resistance to erythromycin; 8.4%, to gentamicin; and 0.6%, to trimethoprim-sulfamethoxazole. All strains were susceptible to vancomycin. The case fatality rate was 2.2% and associated risk factors were (odds ratio [95% confidence interval]) age ≥ 8 years (2.78, 1.05-7.37), pneumonia (6.37, 2.37-17.09), meningitis (19.53, 2.40-127.87), and sepsis/bacteremia (39.65, 11.94-145.55).
Conclusions. The rate of CA-MRSA infection was high; the rate of hospitalization increased in the 2013-2014 period; the 2-4-year-old group was the most affected one. A higher case fatality risk was observed among patients ≥ 8 years old and those with the clinical presentations of pneumonia, meningitis, and sepsis.

Glossary

CA-MRSA: community-acquired methicillin-resistant *Staphylococcus aureus*
CA-SA: community-acquired *Staphylococcus aureus*
h: hours
HA-MRSA: hospital-acquired methicillin-resistant *Staphylococcus aureus*
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-susceptible *Staphylococcus aureus*
OR: *odds ratio*
PCV13: 13-valent pneumococcal conjugate vaccine
PVL: Panton-Valentine leukocidin
SEL: socio-economic level
SSTI: skin and soft tissue infection
SA: *Staphylococcus aureus*
TMP-SMZ: trimethoprim-sulfamethoxazole

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INTRODUCTION

Staphylococcus aureus (SA) is a widely distributed microorganism in this setting. It colonizes the skin and mucous membranes of 30-50% of healthy children and adults. It may cause a broad range of infections, from mild skin and soft tissue infections (SSTIs) to invasive ones, such as pneumonia, bacteremia, and sepsis.[1]

Years after the introduction of methicillin in 1959, methicillin-resistant SA (MRSA) outbreaks were reported.[2] Initially, MRSA infections occurred in the hospital setting (HA-MRSA) or in association with health care.[3]

In the 1990s, reports started referring to patients colonized by or infected with community-acquired MRSA (CA-MRSA) strains in different areas of the United States and worldwide.[4,5] Outbreaks were documented in communities characterized by over-crowding, prisoners, recruits, children attending daycare centers, contact sport athletes, men who have sex with men, and injection drug users. Initially, they had SSTIs and some patients progressed to invasive disease.[6,7]

In Argentina, Paganini et al. identified SSTIs in a children's hospital around 2004[8] and then reported, in a multicenter study, CA-MRSA rates above 60% in most facilities.[9] Other more recent Argentine studies conducted using different methodologies have reported 55% rates in 66 pediatric and adult health care facilities in November 2009,[10] and a 65% resistance in community-acquired SA (CA-SA) bacteremias.[11]

CA-MRSA strains showed an antibiotic susceptibility pattern different from those acquired in the community. CA-MRSA strains were, in general, multi-drug resistant, whereas CA strains were only resistant to methicillin, variably susceptible to erythromycin/clindamycin, and highly susceptible to trimethoprim-sulfamethoxazole (TMP-SMZ).[4]

Although genes coding for resistance to methicillin in hospital and community strains are the same, the staphylococcal cassette chromosome into which these genes are included is different, thus indicating that community strains do not distribute hospital strains.[12,13] In addition, a cytotoxin called Panton-Valentine leukocidin (PVL) present in CA-MRSA strains and in some methicillin-susceptible SA (MSSA) strains was associated with SSTIs,[4,14] invasiveness, osteomyelitis, necrotizing pneumonia, and poor prognosis.[4,14-18] However, more recently, PVL's role as a virulence determinant has been discussed.[19]

The objectives of this study were to estimate the rate of hospitalization for CA-MRSA infection, describe the patients' clinical, epidemiological, and microbiological characteristics, and analyze case fatality risk factors in selected facilities that represented different regions of Argentina.

POPULATION AND METHODS

Design: Epidemiological, observational, cross-sectional study with prospective data capture.

Study sites: Ten pediatric facilities participated (by region).
a. Northwest: Hospital del Niño Jesús (Tucumán), Hospital de Niños H. Quintana (Jujuy), Hospital de Niños E. Perón (Catamarca).
b. Northeast: Hospital Pediátrico J. Pablo II (Corrientes).
c. Cuyo: Hospital Pediátrico H. Notti (Mendoza).
d. Central Region: Hospital de Niños Víctor J. Vilela (Rosario), Hospital de Niños O. Alassia (Santa Fe).
e. Buenos Aires: Hospital de Niños de San Justo (Buenos Aires), Hospital de Niños P. de Elizalde (Autonomous City of Buenos Aires [CABA]), Hospital de Niños R. Gutiérrez (CABA).

Every site had the human and logistic resources and an adequate infrastructure to cater for hospitalized patients and perform imaging and bacteriological tests.

Inclusion criteria: All patients ≤ 15 years old with CA-SA infection, hospitalized in any of the 10 pediatric facilities between January 2012 and December 2014 were included.

Patients were admitted through the epidemiological surveillance system which is active in hospitalization units. Subsequently, a specially-designed card was completed with the following data: participating site, patient ID code, date of hospitalization, demographic data, clinical and epidemiological outcome measures (age, sex, immunization status, number of household members, number of people rooming together, socio-economic level, underlying diseases, nutritional status, second-hand smoking, prior hospitalizations in the past year, prior antibiotic therapy in the past 3 months, clinical presentations, bacteriological cultures and antibiotic susceptibility, isolation sites, antibiotic therapy, and clinical course [complications and status on discharge]).

In addition, a sheet was used to record the monthly number of CA-SA and CA-MRSA

infections and the total number of hospital discharges.

Definitions

CA-SA infection case: Any patient with SA isolated from a normally sterile site in an outpatient manner, within the first 48 hours (h) of admission to the hospital or after 48 h of hospitalization, but with clear clinical evidence suggesting that the infection was acquired in the community (e.g., a patient without prior hospitalization admitted with osteomyelitis and who had a surgical drainage done 48 h later, where SA developed).[4,20]

CA-MRSA infection case: The same as in case a) with identification of MRSA.

The socio-economic level (SEL) was defined using the Graffar-Méndez Castellanos test[21], and the classification was simplified into high (stratum I), middle (strata II and III), and low (strata IV and V) SEL.

Underlying diseases included conditions that involved the skin (varicella, burn wound, trauma injury, skin disease, perforation, other), chronic pulmonary diseases (chronic obstructive pulmonary disease, cystic fibrosis, emphysema, and asthma), cardiovascular diseases (congenital heart defect, congestive heart failure, cardiomyopathy, hypertensive heart disease, pulmonary hypertension, valvular heart defect, arrhythmia), liver and kidney diseases, metabolic disorders (such as diabetes), neurological or neurodevelopmental disorders (cerebral palsy, seizures, stroke, mental retardation, spinal cord injury or muscle dystrophy), hematological disorders (anemia, functional or anatomical asplenia), chromosomal and genetic disorders, drug- or disease-induced immunosuppression (e.g., human immunodeficiency virus [HIV], cancer or long-term corticosteroid therapy), and complement deficiency.

Nutritional status was diagnosed based on age, weight, and height. The 2013 Guidelines of the Argentine Society of Pediatrics[22] were used to define obesity (Z-score > 2) and malnutrition (Z-score < 2 or a weight for age percentile < 3).

Second-hand smoking (World Health Organization criterion) was defined as the involuntary exposure to environmental tobacco smoke for more than 15 minutes per day, more than once a week.

SA was identified using the conventional methods established in each hospital's bacteriology laboratory. Antibiograms were interpreted according to the currently valid Clinical and Laboratory Standards Institute (CLSI).[23]

Ethical considerations

Information was stored in a restricted access database. Personal data were recorded using an alphanumeric code so that investigators were kept blinded to patient identification.

The study was approved by the Research and Ethics Committee of the corresponding hospitals.

Statistical analysis

Results were expressed as mean ± standard deviation, and the median (range) value was used for the age outcome measure. Categorical outcome measures were described in terms of percentage and analyzed using a χ^2 test with Yates' correction.

Initially, the following potential fatality risk factors were identified: clinical and epidemiological outcome measures and clinical presentations; the measure of association was odds ratio (OR) with a 95% confidence interval (CI).

Finally, a logistic regression was done to establish independent outcome measures; independent outcome measures were included manually if their p value was 0.10 or less in the univariate analysis.

A value of $p < 0.05$ was considered significant.

The annual rate of hospitalization for CA-MRSA infection was estimated by dividing the total number of cases of CA-MRSA infections by the total number of discharges per year and per age group, multiplied by 10 000.

The Epi Info version 7 (CDC, Atlanta) was used to make a descriptive and univariate analysis and to estimate the χ^2 test for the trend of the hospitalization rate. The SPSS Statistics, version 17.0, was used for the multivariate analysis.

RESULTS

Out of a total of 252 050 patients hospitalized in the 10 facilities, 1141 (0.45%) had a CA-SA infection; of these, 904 (79.2%) corresponded to CA-MRSA. *Tables 1 and 2* show the annual rates of hospitalization of patients with CA-SA and CA-MRSA by age group, respectively.

Among the 904 patients with CA-MRSA infection, their mean age was 63.7 months (standard deviation: 55.5); their median age, 44.0 months (range: 1-190); 33.5% were younger than 2 years; and 61.5% were boys. Also, 51.4% had an

immunization card; of these, 90.5% had received the *Haemophilus influenzae* type b vaccine and 66.3% (134/202) of patients < 24 months old had received the 13-valent pneumococcal conjugate vaccine (PCV13). In terms of socio-economic level, 33.1% corresponded to a middle SEL and 65.3%, a low SEL. The number of people sharing the household was recorded in 830 cases and was > 5 in 49.6% of them; likewise, the number of people rooming together was > 3 in 37.2% (294/790). An underlying disease was detected in 35.0% (316/904) of cases (96 had more than one disease), which were the following, by order of frequency: chronic respiratory disease (33.5%), skin disease (20.9%), anemia (19.7%), neurological disease (8.3%), cardiovascular disease (2.9%), genetic disorder (1.7%), renal disease or metabolic disorder (1.5%), liver disease (0.5%), malnutrition (4.3%), obesity (2.6%), immunosuppression (4.1%). Also, 4.2% of patients had a history of prematurity; 19.2%, of second-hand smoking; 14.7%, of prior hospitalizations in the past year; and 7.7%, of prior antibiotic therapy in the past 3 months.

Four patients had mixed infections: 3 had CA-MRSA and *Haemophilus influenzae* type b and 1 had CA-MRSA and group A beta-hemolytic *Streptococcus*.

The clinical presentations are described in *Table 3*; combined presentations were observed in 227 patients.

Among patients with SSTIs, 60.2% (451/749) did not have health care-related predisposing factors (an underlying disease or a history of hospitalization in the past year). In addition, 6 out of the 7 patients with meningitis were previously healthy individuals.

Table 3. *Clinical presentations of patients with community-acquired methicillin-resistant Staphylococcus aureus infections in 10 hospital facilities, Argentina, 2012-2014*

Clinical presentation	N	%
Skin and soft tissue infection*	749	66.2
Pneumonia	130	11.5
Sepsis/bacteremia	97	8.5
Osteomyelitis	65	5.5
Arthritis	92	5.2
Psoas abscess	11	1.0
Pericarditis/endocarditis	9	0.8
Meningitis	7	0.6
Renal abscess	2	0.2
Liver abscess	2	0.2
Peritonitis	2	0.2
Orchiditis	1	0.1
	1131	100.0

* 27 cases of myositis and 4 cases of fasciitis.

TABLE 1. *Hospitalization rates of patients with community-acquired* Staphylococcus aureus *infection by age group in 10 hospital facilities, Argentina, 2012-2014*

Age group	2012			2013			2014			Statistical significance
	Discharges	n	Rate per 10 000	Discharges	n	Rate per 10 000	Discharges	n	Rate per 10 000	*p*
0-23 months old	35 979	112	31.1	32 029	134	41.8	32 787	145	44.2	0.0126
24-59 months old	17 990	77	42.8	15 987	97	60.7	15 447	95	61.5	0.0291
< 5 years old	53 969	189	35.0	48 016	231	48.1	48 234	240	49.8	0.0004
5-15 years old	35 980	128	35.6	32 460	167	51.4	33 391	186	55.7	0.0002

TABLE 2. *Hospitalization rates of patients with community-acquired methicillin-resistant* Staphylococcus aureus *infections by age group in 10 hospital facilities, Argentina, 2012-2014*

Age group	2012			2013			2014			Statistical significance
	Discharges	n	Rate per 10 000	Discharges	n	Rate per 10 000	Discharges	n	Rate per 10 000	*p*
0-23 months old	35 979	91	25.3	32 029	90	28.1	32 787	122	37.2	0.0127
24-59 months old	17 990	58	32.2	15 987	79	49.4	15 447	84	54.4	0.0057
< 5 years old	53 969	149	27.6	48 016	169	35.2	48 234	206	42.7	0.0002
5-15 years old	35 980	99	27.5	32 460	125	38.5	33 391	156	46.7	0.0001

The microbiological diagnosis was done based on 1003 specimens: skin/soft tissue (67.4%), blood (16.8%), pleural fluid (8.0%), joint fluid (4.3%), bone (2.4%), cerebrospinal fluid (CSF) (0.6%), other (0.5%). *Figure 1* describes the antibiotic resistance of CA-MRSA strains.

The overall case fatality rate was 2.2% (20/904) and associated risk factors were age ≥ 8 years and the clinical presentations of pneumonia, meningitis, and sepsis/bacteremia (*Table 4*). The independent predictor of fatality was the clinical manifestation of sepsis/bacteremia (OR: 44.07, 12.07-160.87).

Severe soft tissue infections (fasciitis and myositis) and clinical and epidemiological outcome measures, such as sex, immunization status, socio-economic level, number of people sharing the household, number of people rooming together, underlying disease, prematurity, second-hand smoking, prior hospitalizations in the past year, and prior antibiotic therapy in the past 3 months, were not associated with a higher fatality rate caused by CA-MRSA infection.

DISCUSSION

CA-MRSA infections are prevalent in Argentina and in several other countries worldwide[4,5,8,9] and may have a severe clinical course.[15-18]

At present, it has been recognized that these infections occur in three specific groups: hospital-acquired, community-acquired in patients with health care-related predisposing factors, and community-acquired in patients without predisposing factors.[24,25] This study did not analyze the first group but the two other categories as a whole.

In our study, community-acquired methicillin resistance was almost 80%, higher than that reported in other studies conducted in Argentina and mentioned here. Such increase may be attributed to methodological differences in patient inclusion in the different studies.[8-11]

Likewise, the rate of hospitalization for CA-MRSA infections was observed to increase over the 3 years of the study. Such findings may be explained by a basically ecological phenomenon: nasal colonization by SA may be higher in children who have received the pneumococcal conjugate vaccine, probably due to competence between the vaccine and SA.[26,27] However, in our study, only 66% of patients < 24 months old had completed their PCV13 immunization. In addition, the highest rates of hospitalization for CA-MRSA infection were observed in schoolchildren, who were generally described as the most affected ones[28] and who

TABLE 4. *Risk factors associated with case fatality caused by community-acquired methicillin-resistant* Staphylococcus aureus *infection in 10 hospital facilities, Argentina, 2012-2014*

Risk factor	Case fatality rate		OR (95% CI)
	N	%	
Sepsis/bacteremia	16/97	16.5	39.65 (11.94-145.55)
Meningitis	2/7	28.6	19.53 (2.40-127.87)
Pneumonia	10/130	7.7	6.37 (2.37-17.09)
Age ≥ 8 years old	10/244	4.1	2.78 (1.05-7.37)

OR: odds ratio; CI: confidence interval.

FIGURE 1. *Antibiotic resistance of community-acquired methicillin-resistant* Staphylococcus aureus *strains in 10 hospital facilities, Argentina, 2012-2014*

* It was not possible to obtain data for all tested strains for each antibiotic.
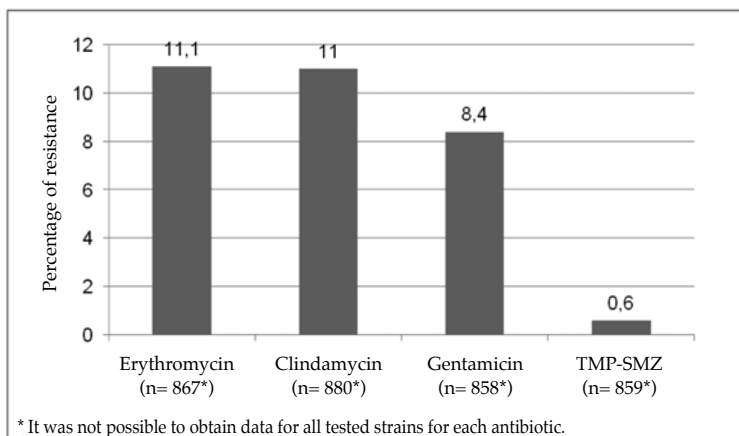
had not received the PCV13 according to the immunization schedule.[29]

A relationship was also described between nasal colonization by SA and amoxicillin/clavulanic acid treatment in the prior 3 months.[30] According to our data, 7.7% of patients had a history of antibiotic therapy in the past 3 months.

CA-MRSA infection occurred mainly among the poorest social strata (65%) and in the population living in over-crowding conditions (50%), as described in the bibliography.[28] Several studies have also described prior colonization by SA in the patient or the people sharing the household in different body surface areas as a risk factor for SA infection,[31] which could be favored in over-crowding conditions.

CA-MRSA infection was observed in 42% of patients with health care-related predisposing factors, such as prior hospitalizations in the past year (15%) and/or an underlying disease (35%). The most common underlying diseases were respiratory conditions, as observed in the general pediatric population, followed by skin diseases, such as varicella, burn injuries, bites, etc. Undoubtedly, skin diseases disrupt the skin barrier and favor SA colonization and infection.[4,31]

Second-hand smoking was observed in almost 20% of patients, so it may be considered a risk factor of the most common underlying disease in the studied population, i.e., respiratory disease.[32]

CA-MRSA infection predominated among healthy children with almost 60% of events, and the most common clinical presentation was SSTI. This was followed by invasive disease, such as pneumonia, sepsis/bacteremia, and osteoarticular infections. Such locations, by order of frequency, are consistent with what has been published by different authors, both at a national and an international level, given that SSTIs account for 60-90% of these infections.[4,20,25] Four patients had mixed infections combined with *Haemophilus influenzae* type b and group A beta-hemolytic *Streptococcus*.

Prior national publications have reported variable antibiotic susceptibility rates for CA-MRSA strains.[8-11,25] In our study, although it included patients with CA-MRSA infection and health care-related predisposing factors, the level of clindamycin and TMP-SMZ susceptibility was acceptable; in addition, all strains were susceptible to vancomycin. These data help to guide pediatricians in the implementation of the initial empirical treatment in the different clinical presentations; clindamycin and TMP-SMZ are still useful antibiotics, especially for the treatment of patients with SSTIs, and vancomycin is reserved for children with severe CA-MRSA infections, such as bacteremia, sepsis, and endocarditis.

The 2% case fatality rate was similar to that reported in the national publications mentioned here. In addition, risk factors associated with fatality, such as age ≥ 8 years and the clinical presentations of sepsis/bacteremia, meningitis, and pneumonia, were similar to those reported in other studies.[4,33-35]

It is worth noting that the presence of predisposing factors, sex, and severe soft tissue infections (fasciitis and myositis) were not associated with a higher case fatality rate.

On the one side, the strength of this study is that of all multicenter studies, i.e., they are as close as possible to the country's reality and include reference hospitals that offer primary, secondary, and tertiary health care services in different regions. On the other side, the weakness inherent to this type of study is that not all regions are represented. And, although facilities work with the same methodology, they are not exempt from institutional differences that may sometimes bias some of the studied outcome measures, especially clinical or microbiological ones.

CONCLUSIONS

The rate of infections caused by CA-MRSA in children was high; the prevalent clinical source was SSTI; and the higher rate of hospitalization was observed among children aged 2-4 years.

Clindamycin resistance was lower than 15%, so it may be used in the case of a suspected infection in children.

The case fatality rate was 2%. Patients ≥ 8 years old and the clinical presentations of pneumonia, meningitis, and sepsis accounted for a higher risk. ■

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