Community-acquired *Staphylococcus aureus* bacteremia in children: a cohort study for 2010-2014

Guadalupe Pérez, M.D.,[a] *Soledad Martiren, M.D.,*[a] *Vanesa Reijtman, Biochemist,*[b] *Romina Romero, M.D.,*[b] *Alejandra Mastroianni, B.S.,*[b] *Lidia Casimir, M.D.,*[b] *and Rosa Bologna, M.D.*[a]

ABSTRACT

Introduction. Community-acquired methicillin-resistant *Staphylococcus aureus* infections are a common, serious problem in pediatrics.

Objective. To describe antibiotic resistance in community-acquired *Staphylococcus aureus* (SA) bacteremias. To compare the characteristics of SA bacteremias in terms of methicillin resistance.

Material and methods. Prospective cohort enrolled between January 2010 and December 2014. Inclusion criteria: infants and children between 30 days old and 16 years old hospitalized at the Hospital de Pediatría J. P. Garrahan due to community-acquired infections with SA growth identification in blood cultures. Exclusion criteria: having a history of recent hospitalization, attending a health care facility, living in a closed community, or having a venous catheter. Microbiological, demographic, and clinical characteristics were compared in terms of methicillin susceptibility. Statistical analysis: Stata10.

Results. A total of 208 children were included; boys: 141 (68%). Their median age was 60 months old (interquartile range: 29-130). Thirty-four patients (16%) had an underlying disease. Methicillin-resistant *Staphylococcus aureus* was identified in 136 children (65%). The rate of resistance to clindamycin was 9%. Significant statistical differences were observed in the rate of underlying disease, persistent bacteremia, sepsis at the time of admission, secondary source of infection, admission to the intensive care unit, and surgery requirement. Twelve patients (6%) died; community-acquired methicillin-resistant *Staphylococcus aureus* was identified in all of them.

Conclusions. In the studied cohort, methicillin-resistant *Staphylococcus aureus* was predominant. The rate of resistance to clindamycin was 9%. Community-acquired methicillin-resistant *Staphylococcus aureus* infections prevailed among healthy children. Among patients with methicillin-resistant *Staphylococcus aureus* infections there was a higher rate of persistent bacteremia, admission to the ICU and surgery.

Key words*: community-acquired infections,* Staphylococcus aureus*, methicillin resistance.*

http://dx.doi.org/10.5546/aap.2016.eng.508

a. Department of Epidemiological Control and Infectology. Hospital de Pediatría "Prof. Dr. Juan P. Garrahan". City of Buenos Aires. Argentina.
b. Department of Microbiology. Hospital de Pediatría "Prof. Dr. Juan P. Garrahan". City of Buenos Aires. Argentina.

E-mail address:
Guadalupe Pérez, M.D.: guaperez@hotmail.com

Funding: None.

Conflict of interest:
None.

Received: 1-31-2016
Accepted: 6-14-2016

INTRODUCTION

Staphylococcus aureus (SA) is a universally distributed Gram-positive coccus; its virulence factors determine its persistence, recurrence, and tendency to cause secondary sources of infection. Over the past decades, an increase in SA antibiotic resistance has been recorded worldwide. Since the first reports of community-acquired methicillin-resistant SA (CA-MRSA) infections in South America in 2003,[1] the rate of antibiotic resistance identification has increased.

CA-MRSA infections account for a common reason to seek consultation in pediatrics worldwide. CA-MRSA prevails among children with no underlying conditions or hospitalization history.

In general, it is accompanied by superficial skin and soft tissue infections, which are a common reason for consultation and outpatient antibiotic therapy, but it may cause severe infections that require hospitalization, surgical drainage, or long-term antimicrobial therapy.[3]

CA-MRSA is usually identified in the culture of suppurative lesions; however, it is not uncommon to see bacteremia in children with severe infections. The rate of positive blood cultures among patients with SA infections and no underlying condition is 5%.[4]

It is essential to gain knowledge on community-acquired SA antimicrobial susceptibility, its evolutionary characteristics based on the type of treatment prescribed, and the prognostic factors of children with bacteremia for the treatment of this type of infections.

The objective of this study was to describe the rate of antibiotic resistance and compare the clinical characteristics of patients in terms of methicillin resistance.

MATERIAL AND METHODS

All patients with SA infections and bacteremia were enrolled prospectively, between January 1st, 2010 and December 31st, 2014. Inclusion criteria were age older than 30 days and younger than 16 years, having been hospitalized at the Hospital de Pediatría Prof. Dr. Juan P. Garrahan due to a community-acquired infection with at least one blood culture collected in the first 48 h of hospitalization with SA growth. Patients who were hospitalized for at least 24 h in the past 6 months, attend a health care facility at least on a weekly basis, have a long-term indwelling catheter, or live in closed communities were excluded.

The facility where the study was conducted is a tertiary care hospital with more than 600 beds, 4 intensive care units (ICUs) and a neonatal intensive care unit. Children hospitalized here are referred from the emergency department and walk-in consultations at the outpatient clinic, or are referred by other facilities from across Argentina.

SA was isolated in blood cultures using the automated Bact/Alert 3D system and was then typified using conventional and automated microbiological testing in accordance with the current working protocols established by the Microbiology Laboratory.

Methicillin resistance was determined using the disk-diffusion method with a cefoxitin 30-µg disk. Resistance to rifampicin (5 µg), gentamicin (10 µg), trimethoprim-sulfamethoxazole (25 µg), erythromycin (15 µg), and clindamycin (2 µg) was also determined using, in all cases, disc diffusion antibiograms with Müeller Hinton agar, incubated at 37ºC for 24 h. Antibiograms were interpreted as per the current guidelines recommended by the Clinical & Laboratory Standards Institute (CLSI).[5] Inducible clindamycin resistance was identified by placing the clindamycin disc 25 mm away from the erythromycin disc in the antibiogram. The minimum inhibitory concentration (MIC) of vancomycin was established using the agar dilution method with Etest strips.

The medical history, clinical and evolutionary characteristics of patients were entered into a database. Patients were included in the cohort on the day of hospital admission and remained under follow-up until discharge. The characteristics of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) were compared.

Definitions

Secondary source of infection: any clinical source of infection not present at the time of patient hospitalization and appearing more than 72 h after positive blood culture results.

Duration of bacteremia: days elapsed between the initiation of an adequate antibiotic therapy and the first negative blood culture results.

Empiric treatment: antibiotic therapy prescribed with no information on blood culture results.

Definite treatment: antibiotic therapy prescribed after obtaining the antibiotic susceptibility report from the Microbiology Laboratory.

Persistent bacteremia: positive blood culture results after five days of receiving an adequate antibiotic therapy.

Categorical outcome measures were described in terms of percentage, while continuous outcome measures were described in terms of median and interquartile range (IQR). Continuous outcome measures were analyzed using the t test or the Wilcoxon rank-sum test, depending on their distribution. Categorical outcome measures were compared using the χ^2 test. A value of $p < 0.05$ was considered significant.

The relative risk (RR) and its 95% confidence interval were estimated for each group to measure the strength between the association and the result. The Stata software, version 10.0, was used.

Ethical considerations: at the beginning of follow-up, patients were informed of the study and invited to participate, warranting their data confidentiality and absolute reserve as to patient identity. Parents or legal tutors present during the initial interview were asked to sign an informed consent form. An assent was obtained from children older than 8 years of age. It was explained to patients and their families that the study had a descriptive, analytical nature, with no interventions. The usual treatment measures indicated in each case were not affected by the conduct of this study. The study protocol was approved by the hospital's Institutional Research Committee.

RESULTS

During the study period, 208 patients with CA-SA invasive infection and bacteremia were identified. Boys accounted for 68% (n: 141). Patients' median age was 60 months old (IQR: 29-130). Thirty-four patients (16%) had an underlying disease (*Table 1*).

At hospitalization, a clinical source of infection was observed in 197 patients (96%). The most common sources of infection included infectious osteoarthritis (55%, n: 117), skin and soft tissue infections (34%, n: 71), and pneumonia (15%, n: 32).

MRSA was prevalent. Methicillin resistance was identified in 136 children (65%).

The median duration of bacteremia was 4 days (IQR: 3-5) among patients with MRSA versus 3 days (IQR: 2-5) among those with MSSA.

Clindamycin was used for the empiric treatment of 116 patients (55%). All patients received at least one antibiotic with activity against the microorganism documented in blood cultures.

Definite treatment consisted in clindamycin in 42 children (20%), vancomycin in 98 (46%), and first-generation cephalosporins in 72 (34%).

The median duration of parenteral therapy was 14 days (IQR: 10-24) among patients with MRSA versus 14 days (IQR: 10-14) among those with MSSA; oral treatment lasted 28 days (IQR: 20-60) versus 28 days (IQR: 14-40), respectively.

The median length of stay was 17 days (IQR: 12-30) among children with MRSA and 15 days (IQR: 12-19) among those with MSSA.

The most common secondary source of infection was pneumonia in both groups.

Twelve patients (6%) died because of the infection. MRSA infection was identified in all deceased children.

A bivariate analysis was done to compare the characteristics of patients with MRSA versus MSSA bacteremia; it found statistically significant differences in the rate of underlying disease (11% versus 26%, $p < 0.01$), persistent bacteremia (33% versus 6%, $p = 0.01$), sepsis at the time of hospitalization (33% versus 14%, $p < 0.01$), admission to the ICU (28% versus 12%, $p = 0.01$), and surgery requirement (77% versus 50%, $p < 0.01$).

Eighteen SA isolates (9%) were observed to be clindamycin resistant. Over the study period, the rate of antibiotic resistance remained stable.

Antimicrobial susceptibility is described in *Table 2*.

Among the 18 patients with MRSA and documented clindamycin resistance, 4 (22%) had a history of atopic dermatitis.

DISCUSSION

The prevalence of CA-MRSA infections in children has increased over the past decades until becoming an epidemic. An extensive multicenter study on the epidemiology of MRSA in the pediatric population of Argentina was conducted with participants from the Autonomous City of Buenos Aires, Greater Buenos Aires, Santa Fe, Rosario, Jujuy, Corrientes, Resistencia, and Mar del Plata,[6] and observed a 61% overall prevalence of methicillin resistance. Based on this description, other authors reported on how the rate of methicillin-resistant SA has evolved in Argentina. Corso et al.[7] recorded, in

TABLE 1. *Demographic, clinical and evolutionary characteristics of patients in terms of methicillin resistance (n: 208)*

Characteristic	Total n (%)	MRSA n= 136	MSSA n= 72	*P*
Boys	141 (68)	90 (66)	50 (69)	0.15
Median age (IQR)	60 (29-130)	60 (29-120)	59 (28-159)	0.3
Underlying disease	34 (16)	15 (11)	19 (26)	< 0.01
Duration of bacteremia	4 (3-5)	4 (3-5)	3 (3-5)	0.3
Sepsis	56 (27)	45 (33)	10 (14)	< 0.01
ICU requirement	47 (23)	38 (28)	9 (12)	0.01
Surgery	140 (67)	105 (77)	36 (50)	< 0.01
Secondary source of infection	31 (15)	24 (18)	7 (10)	0.13
Length of parenteral therapy in days	14 (10-21)	14 (10-24)	14 (10-14)	0.6
Length of oral treatment in days	28 (16-60)	28 (20-60)	28 (14-40)	0.4
Length of hospital stay in days	15 (11-26)	17 (12-30)	15 (12-19)	0.4
Death	12 (6)	12 (9)	-	-

MRSA: methicillin-resistant *Staphylococcus aureus*.
MSSA: methicillin-susceptible *Staphylococcus aureus*.
IQR: interquartile range.
ICU: intensive care unit.

a study published in 2014, a 55% overall resistance in SA infections, among both children and adults in Argentina.

Unlike the studies mentioned above, our cohort included only children with community-acquired infections. Patients with hospital-acquired infections and health-care-associated infections were excluded from the study because of the differences in their CA-MRSA epidemiology.[7]

Similar to what has been observed in other published Argentine studies,[6,8] our cohort showed a 65% rate of methicillin resistance.

Community-acquired, invasive SA infections which have been described in other series[7,8] are prevalent among males and school-aged patients. In this cohort, 16% of children had an underlying disease. The presence of an underlying condition in this study was more common among children with a MSSA infection. Other studies also failed to identify risk factors for CA-MRSA acquisition and infection.[9,10]

SA causes cellulitis, abscesses, pyomyositis, and infectious osteoarthritis, and sometimes even pneumonia and pleural empyema.[11,12] In the studied cohort, skin and soft tissue infections and bone and joint infections were also prevalent.

Lung involvement is commonly described in severe infections and may manifest as different clinical presentations, including pleuropulmonary suppuration, necrotizing pneumonia, and bronchopneumonia.[13] In this study, pneumonia was significantly more common in MRSA patients. The increase in MRSA pneumonia has been described worldwide, especially in countries that have introduced the pneumococcal conjugate vaccine.[14]

TABLE 2. *Antimicrobial susceptibility (n: 208)*

Antibiotic	N	%
Methicillin-resistant	108	52
Methicillin- and clindamycin-resistant	12	6
Resistant to methicillin and to at least another antibiotic*	16	8
Methicillin-susceptible	59	28
Methicillin-susceptible, clindamycin-resistant	6	3
Susceptible to methicillin and resistant to at least another antibiotic*	7	3

*Erythromycin, gentamicin, rifamycin, or trimethoprim-sulfamethoxazole

The prognosis of a correctly treated SA bacteremia secondary to a primary clinical source of infection that is drained is usually good. However, the median number of days until the resolution of bacteremia is, according to the literature, 5 days. In this study, the rate of persistent bacteremia was higher among children with MRSA versus MSSA.

The emergence of secondary sources of infection in children with MRSA is probably related to the greater exposure to positive blood cultures, toxin production, and a delay in the initiation of an adequate therapy for children with SA infections.[13,15]

Different studies have attempted to establish a relationship between a worse infection prognosis and SA antibiotic resistance.[16,17] In a study conducted in adults by Wang et al.,[18] no differences were observed in terms of length of stay or mortality at 30 days among patients with MSSA versus MRSA infections.

Some authors suggest that, when assessing patients with severe MRSA infections, those with higher MICs to vancomycin may have a worse prognosis.[19] A meta-analysis published in 2014 comparing the clinical course of patients with MRSA bacteremia failed to demonstrate an association between a MIC of vancomycin below or above 1.5 µg/L and mortality.[20]

In this study, the analysis was not adjusted for severity or delay in definite therapy; however, it is worth noting that all deceased patients were in the MRSA group.

As per the recommendations, severe SA infections should be treated with first-generation cephalosporins, such as cefalotin, if methicillin and vancomycin susceptibility is confirmed for MRSA infections.[21] This would be an optional treatment in regions where resistance to clindamycin is below 15%. In the five-year enrollment period of this cohort, clindamycin resistance was below 9%. In other studies that included hospital-acquired SA infections and health-care-associated SA infections, the rate of clindamycin resistance was higher.[6,8]

The use of clindamycin for the treatment of bacteremia secondary to bone and joint infections has been documented in different studies. Martínez Aguilar et al.[22] reported 53 invasive CA-MRSA infections (including bacteremia, pneumonia, osteomyelitis, and septic arthritis) that were adequately treated with clindamycin and concluded that this drug was effective to treat SA invasive infections. Clindamycin has been

proposed as a useful treatment for toxin-mediated clinical presentations, such as pneumonia and necrotizing fasciitis. However, this is an expert recommendation based on *in vitro* testing and animal models.[23]

The Infectious Diseases Society of America suggest, based on the type of infection, the patient's history and clinical presentation, either vancomycin or clindamycin for CA-MRSA for the treatment of invasive infections.[22] The use of clindamycin is reserved for children with secondary bacteremias but no hemodynamic instability. In our cohort, 21% of children received clindamycin and showed a good clinical course.

In the literature, mortality related to MRSA infection has been reported to range between 0.7%[24] and 1.4%.[11] The lethality rate of MRSA infections is much lower than that described for adults, whose mortality rate reaches 40% among those with severe infections. An adequate initial treatment includes both administering the right antibiotic and draining the suppuration from sources of infection.[25]

In this cohort, children with a history of hospitalization and frequent contact with the hospital were excluded to improve the external validity of findings; however, considering that this research was conducted at a tertiary care hospital, it is not possible to generalize conclusions.

Another limitation of this study is that, given the cohort design characteristics, it is not possible to determine with certainty that the differences observed in the course of patients with MSSA versus MRSA are exclusively the result of antibiotic resistance. Further studies stratified by risk groups are needed to gain additional information.

The main strengths of this study include its prospective nature and duration. Given that patients were enrolled consecutively in the study over a five-year period, had a seasonal change occurred, it would have been recorded.

Another strength of this study is related to the diagnosis of antibiotic resistance because the Microbiology Laboratory determines the susceptibility of all SA isolates using the disc diffusion method and placing erythromycin and clindamycin discs strategically so as to detect inducible clindamycin resistance. In addition, the MIC of vancomycin was established in all cases to detect strains with vancomycin heteroresistance.

The choice of the empiric antibiotic therapy for patients with skin and soft tissue infections who require hospitalization and for those with suspected bacteremia depends on regional methicillin and clindamycin susceptibility patterns.

Based on the results reported by this study and previous studies,[6,7] clindamycin is an option for patients with suspected CA-MRSA infections but no severe sepsis. Vancomycin is reserved for children with severe CA-MRSA infections, persistent bacteremia, and suspected endovascular source. An empiric regimen should be considered as an effective therapy for CA-MRSA in children with severe infections acquired in the community (severe pneumonia requiring admission to the ICU and septic shock).

CONCLUSIONS

Methicillin-resistant SA infections predominated in the studied cohort. The rate of clindamycin resistance remained stable across the five-year period and was below 9%. CA-MRSA infections prevailed among healthy children. Patients with MRSA infections developed persistent bacteremia and required admission to the ICU and surgery more frequently than children with MSSA.

Epidemiological surveillance must continue in order to discover changes in SA antibiotic susceptibility patterns and make recommendations in accordance with local epidemiology. ■

REFERENCES

1. Galiana Villar A. Infección por *Staphylococcus aureus* meticilino resistente adquirido en la comunidad. *Arch Pediatr Urug* 2003;74(1):26-9.
2. Paganini HR. *Staphylococcus aureus*. In: Paganini HR, ed. *Infectología pediátrica*. Buenos Aires: Científica Interamericana; 2007.Págs.955-61.
3. Comité Nacional de Infectología. Infecciones de piel y partes blandas en pediatría: consenso sobre diagnóstico y tratamiento. Parte 2: Celulitis, ectima y ectima gangrenoso, celulitis necrotizantes. Consideraciones finales. *Arch Argent Pediatr* 2014;112(2):183-91.
4. Morin CA, Hadler JL. Population-based incidence and characteristics of community-onset *Staphylococcus aureus* infections with bacteremia in 4 metropolitan Connecticut areas, 1998. *J Infect Dis* 2001;184(8):1029-34.
5. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Five Informational Supplement (M100-S25). Wayne: CLSI; 2015.
6. Paganini H, Della Latta MP, Muller Opet B, Ezcurra G, et al. Estudio multicéntrico sobre las infecciones pediátricas por *Staphylococcus aureus* meticilino-resistente provenientes de la comunidad en la Argentina. *Arch Argent Pediatr* 2008;106(5):397-403.
7. Egea AL, Gagetti P, Lamberghini R, Faccone D, et al. New patterns of methicillin-resistant *Staphylococcus aureus* (MRSA) clones, community-associated MRSA genotypes behave like healthcare-associated MRSA

genotypes within hospitals, Argentina. *Int J Med Microbiol* 2014;304(8):1086-99.
8. Ves Losada JE, Graziano AP, De Abreu M, Blanco M, et al. Infecciones graves por *Staphylococcus aureus:* características clínicas, sensibilidad antibiótica y uso de antimicrobianos. Serie de casos. *Arch Argent Pediatr* 2014;112(4):e152-5.
9. Sattler CA, Mason EO Jr, Kaplan SL. Prospective comparison of risk factors and demographic and clinical characteristics of community-acquired, methicillin-resistant versus methicillin-susceptible *Staphylococcus aureus* infection in children. *Pediatr Infect Dis J* 2002;21(10):910-7.
10. Miller LG, Perdreau-Remington F, Bayer AS, Diep B, et al. Clinical and epidemiologic characteristics cannot distinguish community-associated methicillin-resistant *Staphylococcus aureus* infection from methicillin-susceptible *S. aureus* infection: a prospective investigation. *Clin Infect Dis* 2007;44(4):471-82.
11. Suryati BA, Watson M. *Staphylococcus aureus* bacteraemia in children: a 5-year retrospective review. *J Paediatr Child Health* 2002;38(3):290-4.
12. Denniston S, Riordan FA. *Staphylococcus aureus* bacteraemia in children and neonates: a 10 year retrospective review. *J Infect* 2006;53(6):387-93.
13. Vidal PM, Trindade PA, Garcia TO, Pacheco RL, et al. Differences between "classical" risk factors for infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and risk factors for nosocomial bloodstream infections caused by multiple clones of the staphylococcal cassette chromosome mec type IV MRSA strain. *Infect Control Hosp Epidemiol* 2009;30(2):139-45.
14. Machado K, López A, Pacheco H, Algorta G, et al. Características del empiema paraneumónico luego del inicio de la vacunación antineumocócica: Centro Hospitalario Pereira Rossell, año 2010. *Arch Pediatr Urug* 2014;85(4):212-9.
15. Boucher H, Miller LG, Razonable RR. Serious infections caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2010;51(Suppl 2):S183-97.
16. Al-Nammari SS, Bobak P, Venkatesh R. Methicillin resistant *Staphylococcus aureus* versus methicillin sensitive *Staphylococcus aureus* adult haematogenous septic arthritis. *Arch Orthop Trauma Surg* 2007;127(7):537-42.
17. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, et al. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis* 2003;36(1):53-9.
18. Wang JL, Chen SY, Wang JT, Wu GH, et al. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible S. aureus. *Clin Infect Dis* 2008;46(6):799-806.
19. Jacob JT, Diaz Granados CA. High vancomycin minimum inhibitory concentration and clinical outcomes in adults with methicillin-resistant *Staphylococcus aureus* infections: a meta-analysis. *Int J Infect Dis* 2013;17(2):e93-e100.
20. Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. *JAMA* 2014;312(15):1552-64.
21. Liu C, Bayer A, Cosgrove SE, Daum RS, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011;52(3):285-92.
22. Martinez-Aguilar G, Hammerman WA, Mason EO Jr, Kaplan SL. Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* in children. *Pediatr Infect Dis* J 2003;22(7):593-8.
23. Stevens DL, Ma Y, Salmi DB, McIndoo E, et al. Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*. *J Infect Dis* 2007;195(2):202-11.
24. Asgeirsson H, Gudlaugsson O, Kristinsson KG, Vilbergsson GR, et al. Low mortality of *Staphylococcus aureus* bacteremia in Icelandic children: nationwide study on incidence and outcome. *Pediatr Infect Dis J* 2015;34(2):140-4.
25. López-Cortés LE, Del Toro MD, Gálvez-Acebal J, Bereciartua-Bastarrica E, et al. Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2013;57(9):1225-33.