Prognostic factors of severity of invasive community-acquired *Staphylococcus aureus* infections in children

Soraya Araya, M.D.[a], Fernando Galeano, M.D.[a], Sara Amarilla, M.D.[a], Nicolás González, M.D.[a], Silvio Apodaca, M.D.[a], Dolores Lovera, M.D.[a], and Antonio Arbo, M.D., MSc[a,b]

ABSTRACT

Objective: To describe the clinical characteristics of invasive *Staphylococcus aureus* infections in children and identify the prognostic factors of severity and mortality.

Materials and methods: Observational study in patients < 16 years old hospitalized between 2010 and 2015 due to invasive *S. aureus* infections at the Instituto de Medicina Tropical, in Asunción, Paraguay. Patients were distributed based on whether or not they required admission to the intensive care unit, and clinical, laboratory, and evolutionary outcome measures were compared.

Results: Out of the 107 included patients, 50 (47 %) developed bacteremia; 50 (47 %), pneumonia; and 21 (19 %), multifocal disease. Among the patients who were admitted to the intensive care unit (41 %), prior antibiotic use ($p < 0.05$), the presence of bacteremia ($p = 0.01$), the presence of comorbidities ($p < 0.05$), and multifocal disease ($p < 0.01$) were more frequent. The overall mortality rate was 15 %. The mortality-associated risk factors were the presence, at the time of admission, of hypotension ($p < 0.01$), multifocal disease ($p < 0.01$), bacteremia ($p < 0.01$), leukopenia ($p < 0.01$), severe anemia ($p < 0.01$), and metabolic acidosis ($p < 0.01$), among others.

Conclusions: The prognostic factors of severity included prior antibiotic use, bacteremia, the presence of comorbidities, and presentation with multifocal disease. Mortality was significant; associated risk factors included the presence, at the time of admission, of hypotension, multifocal disease, leukopenia, severe anemia, and metabolic acidosis.

Key words: Staphylococcus aureus, *invasive staphylococcal infections, children, risk factors.*

http://dx.doi.org/10.5546/aap.2019.eng.381

To cite: Araya S, Galeano F, Amarilla S, González N, et al. Prognostic factors of severity of invasive community-acquired *Staphylococcus aureus* infections in children. *Arch Argent Pediatr* 2019;117(6):381-387.

a. Instituto de Medicina Tropical.
b. Universidad Nacional de Asunción, Paraguay.

E-mail address:
Antonio Arbo, M.D.: antonioarbo@hotmail.com

Funding:
None.

Conflict of interest:
None.

Received: 11-29-2018
Accepted: 6-2-2019

INTRODUCTION

In the past two decades, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections have emerged worldwide.[1-3] In Latin America, the first cases of community-acquired (CA) MRSA infections were reported in Uruguay in 2001;[4] after this, several countries,[5-8] including Paraguay,[9] have reported that the prevalence of methicillin resistance ranges from 25 % to 70 %.[10]

Taking into account the severity associated with community-acquired *S. aureus* infections,[11] in this new setting of antimicrobial susceptibility, it is especially relevant to identify the factors inherent to the host and bacteria, which may be considered prognostic factors of severity at the time of patient hospitalization. Although several studies have assessed these factors in the adult population, the information in this regard in the pediatric population is limited. Therefore, the objective of this study was to describe the clinical characteristics of invasive *Staphylococcus aureus* infections in children and identify the prognostic factors of severity and mortality.

MATERIALS AND METHODS

Study population and design

This was a descriptive, retrospective, and cross-sectional study carried out at the Instituto de Medicina Tropical, in Asunción, Paraguay, the leading national referral facility for infectious diseases. Patients younger than 16 years, diagnosed upon discharge with invasive *S. aureus* infection and hospitalized between 2010 and 2015 were included.

Invasive *S. aureus* infection was defined as the presence of an

infection with concomitant isolation of *S. aureus* in usually sterile sites, including blood, pleural fluid, cerebrospinal fluid, joint fluid, bone, pericardial fluid, peritoneal fluid or other internal body site. Cases of infections limited to the skin and soft tissue were excluded, unless they were associated with a systemic inflammatory response syndrome. Patients who were transferred from other facilities, who had an incomplete medical record in terms of study outcome measures, and who had *S. aureus* isolation in samples collected after 48 hours of hospitalization were excluded.

Data were collected in a standardized sheet. The following outcome measures were included: clinical, demographic (sex, age, comorbidity), type of infection (multiple sources, pneumonia, osteomyelitis, myocarditis, meningitis, endocarditis), laboratory (white blood cells [WBC], hemoglobin, platelets, hypoalbuminemia, bacteremia, etc.), microbiological (susceptibility pattern), and evolutionary (need for admission to the intensive care unit [ICU], assisted mechanical ventilation [AMV], presence of kidney or liver failure). The microbiological characteristics of *S. aureus* and antimicrobial sensitivity were established using the Vitek® automated identification system (BioMérieux).

Patients with hypotension, respiratory insufficiency (oxygen saturation [SaO_2] < 90 % on room air or a fraction of inspired oxygen [FiO_2] > 50 % required to maintain SaO_2 at 92 % or higher), poor respiratory dynamics (accessory muscle use, nasal flaring, respiratory rate > 2 standard deviations [SDs] for age) or a consciousness disorder required admission to the ICU.

Statistical analysis

After the general analysis, patients were stratified based on whether or not they had been admitted to the ICU and on their status upon discharge (dead or alive). The different demographic, clinical, and laboratory outcome measures, and their association with the severity of invasive *S. aureus* infections were analyzed in relation to ICU admission and mortality. Comparative analyses were done using Student's *t* test for parametric outcome measures and the χ^2 test to compare proportions. To analyze risk factors, the odds ratio (OR) and the corresponding 95 % confidence interval (CI) were estimated.

Ethics

The study was approved by the Institutional Ethics Committee. Given the study's retrospective, secondary source nature, no informed consent was requested, and investigators ensured the anonymity of participating patients.

RESULTS

General characteristics

During the study period, 418 patients were hospitalized with *S. aureus* isolation in a sterile site in the first 48 hours of admission. Of them, 107 (26 %) had invasive infections. The patients' mean age was 75 ± 56 months, with a slight prevalence of male sex (58 % versus 42 %). More infections were observed in children older than 5 years (n = 50) compared to those younger than 2 years (n = 20) and to the 2-5 year-old group (n = 37) ($p < 0.05$).

Invasive infections corresponded to pneumonia (n = 50), osteomyelitis (n = 30), multifocal disease (n = 21; in 2 cases, with endocarditis), meningitis (n = 4), and primary endocarditis (n = 2). Bacteremia was confirmed in 50/107 patients (47 %), which corresponded to 20 % of those with pneumonia (n = 10), 30 % of those with osteomyelitis (n = 9), 100 % of those with multifocal disease (n = 21), the 2 cases of primary endocarditis, and the 4 cases of meningitis.

Comorbidities were observed in 34 patients (32 %); atopy (n = 11, 10 %) and nutritional disorders (malnutrition [n = 7] and obesity [n = 4]) were the most common ones. Other causes of comorbidity included asthma (n = 4), corticosteroid use (n = 4), and human immunodeficiency virus (HIV) infection (n = 4). In addition, 44 % of patients had received antibiotics prior to hospitalization. Most patients had leukocytosis at the time of admission (X ± SD: 16 200 ± 5505/mm^3), and moderate to severe anemia was observed in 40 cases (37 %). The overall mortality rate was 15 % (*Table 1*).

Characteristics of patients with methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* infections

Out of 107 *S. aureus* isolations, 42 (39 %) were resistant to oxacillin (MRSA). Methicillin-sensitive *S. aureus* (MSSA) infections predominated among patients younger than 5 years (69 %), whereas MRSA infections were more common among those older than 5 years (70 %) ($p < 0.001$). Whereas 83 % of MRSA infections were observed

in male patients, only 42 % of MSSA infections corresponded to male patients ($p < 0.001$) (*Table 2*). The frequency of comorbidities ($p = 0.02$), as well as pneumonia ($p = 0.04$), bacteremia ($p = 0.01$), and multifocal disease ($p = 0.02$), was higher among patients with MRSA infections (*Table 2*). Although no differences were observed in mortality between MRSA and MSSA infections, admission to the ICU was significantly higher among the patients with MRSA infections (60 % versus 29 %, $p = 0.01$) (*Table 2*).

Admission to the intensive care unit

A total of 44 patients (41 %) were admitted to the ICU (*Table 3*). When comparing those who were admitted to the ICU and those who did not require such admission (n = 63), no difference was observed in the mean age of patients in both groups (72 ± 61 months old versus 75.4 ± 57 months, $p > 0.5$); however, male sex predominated among those who required it (54.5 % versus 31.7 %) ($p < 0.05$). Antibiotic use prior to hospitalization ($p < 0.001$) and the

Table 1. *Clinical and demographic characteristics of patients with invasive community-acquired* Staphylococcus aureus *infections*

Outcome measure	Number	Percentage (%)
Patients	107	100
Mean age (years) (mean ± SD)	6.25 ± 4.7	
< 2 years old	20	18.7
2-5 years old	37	34.6
> 5 years old	50	46.7
Male/female	62/45	58/42
Bacteremia	50	47
Pneumonia	50*	47
Multifocal disease	21	19.6
Osteomyelitis	30	28
Endocarditis	4	3.7
Myocarditis	8	7.5
Meningitis	4	3.7
Admission to the ICU	44	41
AMV	27	25
Deaths	16	15

* Empyema: 11 patients.
SD: standard deviation; ICU: intensive care unit; AMV: assisted mechanical ventilation.

TABLE 2. *Characteristics of patients with methicillin-resistant and methicillin-sensitive* Staphylococcus aureus *infections*

Outcome measure (number)	MRSA infections N = 42 n (%)	MSSA infections N = 65 n (%)	*p* value
Age group			
≤ 5 years old	12 (29)	45 (69)	< 0.0001
> 5 years old	30 (71)	20 (31)	< 0.0001
Male sex	35 (83)	27 (42)	< 0.0001
Female sex	7 (17)	38 (58)	< 0.0001
Comorbidity	21 (50)	13 (20)	0.02
Pneumonia (n = 50)*	25 (60)	25 (38)	0.04
Osteomyelitis (n = 30)*	16 (38)	14 (22)	0.07
Bacteremia (n = 50)*	26 (62)	24 (37)	0.01
Endocarditis (n = 4)*	3 (7)	1 (1.5)	0.29
Multifocal disease (n = 21)*	13 (31)	8 (12)	0.02
Admission to the ICU (n = 44)	25 (60)	19 (29)	0.002
Deaths (n = 16)	6 (14)	10 (15)	0.5

* Some patients had more than one condition.
ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus* aureus infection;
MSSA: methicillin-sensitive *Staphylococcus aureus* infection.

presence of comorbidities ($p < 0.01$) were more common among the patients admitted to the ICU. When comparing the types of invasive *S. aureus* infection, the presence of pneumonia (30/44 versus 20/63, $p < 0.001$) and multifocal disease (18/44 versus 3/63, $p < 0.001$) predominated among patients admitted to the ICU (*Table 3*). Likewise, the presence of bacteremia ($p = 0.01$) was clearly higher among those admitted to the ICU (*Table 3*). When comparing the length of stay, it was longer among the patients admitted to the ICU versus those that did not require it (20 ± 19 days versus 13 ± 15 days, $p < 0.05$). Lastly, mortality was significantly higher among the patients admitted to the ICU ($p < 0.001$) (*Table 3*).

The analysis of lab test characteristics showed that the presence of a WBC count < 5000/mm^3 ($p = 0.02$), severe anemia < 7 g/dL ($p = 0.03$), and thrombocytopenia < 100 000/mm^3 ($p = 0.02$) were more common among the patients admitted to the ICU (*Table 4*). Also, a higher number of patients admitted to the ICU showed elevated transaminases > 3 times the normal value ($p < 0.01$), metabolic acidosis ($p < 0.01$), and hypoalbuminemia < 3.5 g/dL ($p < 0.001$) (*Table 4*). The frequency of methicillin resistance was significantly higher among the patients who required admission to the ICU ($p < 0.01$) (*Table 4*).

The outcome measures associated with mortality were the presence, at the time of

TABLE 3. *Prognostic factors of severity in patients with invasive community-acquired* Staphylococcus aureus *infections*

Clinical outcome measures	Admission to the ICU N = 44 n (%)	Admission to the general ward N = 63 n (%)	*p* value	Odds ratio (95 % CI)
Mean age (months) (mean ± SD)	72 ± 61	75.4 ± 57	> 0.5	
Male sex	24 (54.5)	20 (31.7)	< 0.05	2.58 (1.16-5.71)
Prior antibiotic use	33 (74)	14 (22)	< 0.001	10.50 (4.24-25.94)
Comorbidity	22 (50)	12 (19)	< 0.01	4.25 (1.79-10.07)
Multifocal disease	18 (41)	3 (4.7)	< 0.001	13.84 (3.75-51.11)
Pneumonia	30 (68)	20 (31.7)	< 0.001	4.60 (2.01-10.53)
Osteomyelitis	10 (23)	20 (31.7)	0.30	0.63 (0.26-1.52)
Endocarditis	2 (4.5)	2 (3)	0.71	1.45 (0.19-10.72)
Meningitis	4 (9)	0 (0)	< 0.1	14.11 (0.73-269.13)
Hypotension	26 (59)	1 (1.6)	< 0.001	89.55 (11.35-706.25)
Bacteremia	27 (61)	23 (36.5)	0.01	2.76 (1.24-6.11)
Deaths	14 (32)	2 (3.1)	< 0.001	14.23 (3.03-66.70)

ICU: intensive care unit; SD: standard deviation; CI: confidence interval.

TABLE 4. *Laboratory prognostic factors of severity in patients with invasive community-acquired* Staphylococcus aureus *infections*

Laboratory outcome measures	Admitted to the ICU N = 44 n (%)	Admitted to the general ward N = 63 n (%)	p value	Odds ratio (95 % CI)
WBC count/mm^3 (X ± SD)	16 185 ± 9210	16 232 ± 5505	0.5	
WBC > 15 000/mm^3	27 (61.4)	29 (46)	0.10	1.86 (0.85-4.07)
WBC < 5000/mm^3	7 (15.9)	0 (0)	0.02	25.40 (1.41-457.52)
Mean Hb (g/dL)	9.6 + 2.6	11 + 1.9	> 0.1	
Hb < 7 g/dL	6 (13.6)	0 (0)	0.03	21.44 (1.17-391.33)
Platelet count/mm^3 (X ± SD)	267 667 ± 180 494	318 376 ± 218 296	> 0.1	
Platelets < 100 000/mm^3	7 (15.9)	0 (0)	0.02	25.40 (1.41-457.52)
GOT or GPT > 3 times the normal value	14 (31.8)	5 (7.9)	< 0.01	5.41 (1.78-16.46)
Prothrombin time < 60 %	10 (22.7)	2 (3.2)	< 0.01	8-97 (1.85-43.33)
Bicarbonate < 15 mEq/L	11 (25)	1 (1.6)	< 0.01	20.66 (2.55-167.13)
pH ≤ 7.2	14 (31.8)	0 (0)	< 0.01	60.37 (3.48-1046.00)
Low albumin (< 3.5 g/dL)	18 (40.9)	2 (3.1)	< 0.001	21.11 (4.56-97.64)
Antibiotic sensitivity				
Methicillin resistance	25 (57%)	17 (27)	< 0.01	3.56 (1.57-8.04)
TMP-SMX resistance	5 (11.4)	2 (3.2)	> 0.1	3.91 (0.72-21.15)
Clindamycin resistance	3 (6.8)	1 (1.6)	> 0.1	4.53 (0.45-45.12)

WBC: white blood cells; Hb: hemoglobin; ICU: intensive care unit; CI: confidence interval; SD: standard deviation; TMP-SMX: thrimethoprim-sulfamethoxazole; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase.

admission, of hypotension (OR: 15.20; 95 % CI: 4.31-53.57; $p < 0.001$), bacteremia (OR: 6.32; 95 % CI: 1.68-23.75; $p < 0.01$), pneumonia (OR: 12.16; 95 % CI: 3.50-42.19; $p < 0.01$), and a diagnosis of multifocal disease (OR: 42.50; 95 % CI: 10.45-172.71; $p < 0.01$) (*Table 5*). In relation to lab test information at the time of admission, the presence of a WBC count < 5000 / mm^3 (OR: 20.22; 95 % CI: 3.49-117.03; $p < 0.001$), severe anemia (hemoglobin < 7 g / dL) (OR: 40.90; 95 % CI: 4.37-382.92; $p < 0.01$), metabolic acidosis (OR: 40.90; 95 % CI: 4.37-382.92; $p < 0.01$), and *S. aureus* isolation with clindamycin resistance (OR: 20.76; 95 % CI: 2.00-214.90; $p = 0.01$) were identified as risk factors associated with mortality. The presence of methicillin resistance was not associated with a higher mortality (*Table 5*).

DISCUSSION

In this study, all patients with invasive *S. aureus* infections hospitalized in a referral facility for infectious diseases in Paraguay in a 5-year period were analyzed. Invasive *S. aureus* infections were observed mostly in schoolchildren (50 % of cases), and this is similar to what has been reported in other *S. aureus* bacteremia series conducted in our region, such as in Argentina or Uruguay.[5-7] The fact that the skin is usually the source of *S. aureus* infections and that schoolchildren are more prone to suffer wounds or minor traumas on the skin may partially explain such observation. However, in other series, especially those carried out in the United States of America (USA)[12,13] or Asia,[14] community-acquired *S. aureus* infections were mainly observed in children younger than 3 years.

Although 32 % of patients had a comorbidity which was, in general, of unmarked severity, like atopy or malnutrition, most patients with invasive *S. aureus* infections were immunocompetent. This is different from other series done both in the USA and Europe.[12,15,16]

Forty percent of *S. aureus* causing invasive infections in this series was methicillin-resistant. These findings demonstrate that the growing epidemics of methicillin-resistant *S. aureus*, which has been reported in different countries in both the Northern and Southern hemispheres, has not escaped our country, thus anticipating the increase in resistance to be seen in the next years.

Our series shows the severity of invasive *S. aureus* infections. Admission to the ICU was required in 41 % of cases. Although no differences were observed in the mean age between the patients who required admission to the ICU and those who did not, more male patients required it. It is known that sex has a major impact on the outcomes of a series of infectious diseases.[17] The presence of comorbidities was a factor associated with admission to the ICU, which is not surprising because the integrity of the immune system is critical in the response of the host to the infection.[18] In addition, the frequency of prior antibiotic use was higher among the patients who were admitted to the ICU. This may have affected the delay in the visit to the doctor's office for those who were receiving treatment and may have had an impact on the severity of the condition. This has already been observed in cases of community-acquired pneumonia.[19]

The presence of bacteremia ($p = 0.01$), pneumonia ($p < 0.01$), and clinical presentation with multifocal disease ($p < 0.01$) correlated to the admission to the ICU. These findings are not surprising because the presence of a microorganism in the blood is usually accompanied by cytokine activation, which leads to a systemic inflammatory response syndrome.[20] The severity of *S. aureus* pneumonia has been widely documented and, in our series, this has been confirmed because 68 % of patients admitted to the ICU had pneumonia. In the study by M. A. Carrillo-Márquez et al.,[21] 58 %

TABLE 5. *Mortality-associated prognostic factors in patients with invasive* Staphylococcus aureus *infections*

Outcome measure	Total	Deaths N = 16 n (%)	Survivors N = 91 n (%)	*p* value	Odds ratio (95 % CI)
Hypotension	27	12 (75.0)	15 (16.5)	< 0.001	15.20 (4.31-53.57)
Bacteremia	50	13 (81.2)	37 (40.6)	< 0.01	6.32 (1.68-23.75)
Pneumonia	30	12 (75.0)	18 (19.8)	< 0.01	12.16 (3.50-42.19)
Multifocal disease	18	12 (75.0)	6 (6.6)	< 0.001	42.50 (10.45-172.71)
Leukopenia	7	5 (31.2)	2 (2.2)	< 0.001	20.22 (3.49-117.03)
Severe anemia (Hb < 7)	6	5 (31.2)	1 (1.1)	< 0.01	40.90 (4.37-382.92)
Metabolic acidosis (bic < 15)	14	8 (50.0)	6 (6.6)	< 0.001	14.16 (3.92-51.10)
Methicillin resistance	42	6 (37.5)	36 (39.5)	0.87	0.91 (0.30-2.74)
Clindamycin resistance	4	3 (18.7)	1 (1.1)	0.01	20.76 (2.00-214.90)

Hb: hemoglobin; CI: confidence interval.

of pneumonia cases required admission to the ICU. The incidence of metastatic sources in *S. aureus* bacteremias ranges from 15 % to 68 % in different studies and accounts for a marker of severity.[16,22,23]

Among the patients admitted to the ICU, MRSA was isolated in 57 %, which was a significantly higher proportion than among those who did not require admission to the ICU ($p < 0.01$). MRSA infections were more severe (higher frequency of pneumonia, bacteremia, and multifocal disease) (*Table 2*), which may explain the higher frequency of admission to the ICU.

Our study has allowed us to identify laboratory outcome measures associated with a greater severity in the setting of staphylococcal infections. In this regard, the presence, at the time of admission, of leukopenia ($< 5000/mm^3$) ($p = 0.02$), severe anemia < 7 g/dL ($p = 0.03$), and thrombocytopenia < 100 000/mm^3 ($p = 0.02$) were significantly more common in the patients admitted to the ICU. Such associations had already been reported by other authors.[24-27]

The mortality rate due to invasive *S. aureus* infections in our study was significant (15 %). Although it was similar to that observed in other studies,[28] mortality may be higher than 48 %.[11] However, other studies have reported a much lower mortality rate. Thus, in the study conducted in Argentina by G. Pérez et al.,[7] the mortality rate was 6 %; in the study done in Europe by M. Gijón et al.,[15] 2 %; in the study by D. Engelman et al.[22] or in the one by McMullan et al.,[29] in Australia, between 2 % and 4 %; and in the study by J. S. Gerber et al.,[12] in the USA, 1 %. The high mortality rate observed in our series may be partially explained by the severity of cases hospitalized in this referral facility.

In this study, several mortality-associated risk factors were identified, both clinical (presence, at the time of admission, of hypotension, pneumonia, multifocal disease) and laboratory (bacteremia, leukopenia, severe anemia, and metabolic acidosis). Some of these have already been reported in other studies.[15,23,30]

Our study poses several limitations. Since the inclusion criterion was *S. aureus* isolation, there is a potential bias that cultures were collected in patients who appeared to have a more severe condition at the emergency department. Besides, since the Instituto de Medicina Tropical is a referral hospital for infectious diseases, our population possibly accounts for the most severe cases observed in the community. Therefore, our results may not be fully extrapolated to the population of a general hospital.

Future multicenter studies are required to more clearly elucidate risk factors and define the most effective treatment regimens aimed at reducing the morbidity and mortality in invasive *S. aureus* infections.

CONCLUSION

Our results demonstrate the severity of invasive community-acquired *S. aureus* infections. This study has allowed us to identify the relevant clinical and laboratory risk factors for both infection severity and mortality. ■

REFERENCES

1. DeLeo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated meticillin-resistant *Staphylococcus aureus*. *Lancet*. 2010; 375(9725):1557-68.
2. Kaplan S. Community-acquired methicillin resistant *Staphylococcus aureu* sinfections in children. *Semin Pediatr Infect Dis*. 2006; 17(3):113-9.
3. Deurenberg RH, Vink C, Kalenic S, Friedrich AW, et al. The molecular evolution of methicillin-resistant *Staphylococcus aureus*. *Clin Microbiol Infect*. 2007; 13(3):222-35.
4. Galiana Villar A. Infección por *Staphylococcus aureus* meticilino-resistente adquirido en la comunidad. *Arch Pediatr Urug*. 2003; 74(1):26-9.
5. Pardo L, Vola M, Macedo-Viñas M, Machado V, et al. Community-associated methicillin-resistant *Staphylococcus aureus*in children treated in Uruguay. *J Infect Dev Ctries*. 2013; 7(1):10-6.
6. Paganini H, DelaLatta MP, Muller Opet B, Ezcurra G, et al. Estudiomulticéntrico 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. Pérez G, Martiren S, Reijtman V, Romero R, et al. Bacteriemia por *Staphylococcus aureus* adquirido en la comunidad en niños: estudio de cohorte 2010-2014. *Arch Argent Pediatr.* 2016; 114(6):508-13.
8. Acuña M, Benadof D, Jadue C, Homarzábal JC, et al. *Staphylococcus aureus* resistente a meticilina asociado a la comunidad (SARM-AC): comunicación de los primeros cuatro casos pediátricos descritos en Hospital de Niños Roberto del Río. *Rev Chil Infectol*. 2015; 32(3):350-6.
9. Irala Ledezma J, Sanabria G. Progresión de la resistencia a la oxacilina de *Staphylococcus aureus* aislados entre 2011-2013 en un hospital de referencia de Asunción-Paraguay. *Rev Inst Med Trop (Paraguay)*. 2017; 12(1):5-9.
10. Jones RN, Guzman-Blanco M, Gales AC, Gallegos B, et al. Susceptibility rates in Latin American nations: report from a regional resistance surveillance program (2011). *Braz J Infect Dis*. 2013; 17(6):672-81.
11. Tong SY, Davis JS, Eichenberger E, Holland TL, et al. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev*. 2015; 28(3):603-61.
12. Gerber JS, Coffin SE, Smathers SA, Zaoutis TE. Trends in the incidence of methicillin-resistant *Staphylococcus aureus* infection in children's hospitals in the United States. *Clin Infect Dis*. 2009; 49(1):65-71.
13. Kumarachandran G, Johnson JK, Shirley D-A, Graffunder E, et al. Predictors of adverse outcomes in children with

Staphylococcus aureus bacteremia. *J Pediatr Pharmacol Ther*. 2017; 22(3):218-26.
14. Qiao Y, Ning X, Chen Q, Zhao R, et al. Clinical and molecular characteristics of invasive community-acquired *Staphylococcus aureus* infections in Chinese children. *BMC Infect Dis*. 2014; 14:582.
15. Gijón M, Bellusci M, Petraitiene B, Noguera-Julian A, et al. Factors Associated with Severity in invasive community-acquired *Staphylococcus aureus* infections in children: a prospective European multi-center study. *Clin Microbiol Infect.* 2016; 22(7):643.e1-6.
16. Le J, Dam Q, Tran T, Nguyen A, et al. Epidemiology and hospital readmission associated with complications of *Staphylococcus aureus* bacteremia in pediatrics over a 25-year period. *Epidemiol Infect.* 2017; 145(12):2631-9.
17. Muenchhoff M, Goulde PJR. Sex differences in pediatric infectious diseases. *J Infect Dis*. 2014; 209(Suppl 3):S120-6.
18. Boyd JH, Russell JA, Fjell CD. The meta-genome of sepsis: host genetics, pathogens and the acute immune response. *J Innate Immun.* 2014; 6(3):272-83.
19. Emery DP, Milne T, Gilchrist CA, Gibbons MJ, et al. The impact of primary care on emergency department presentation and hospital admission with pneumonia: a case-control study. *NPJ Prim Care Respir Med.* 2015; 25:14113.
20. Bosmann M, Ward PA. The inflammatory response in sepsis. *Trends Immunol.* 2013; 34)3):129-36.
21. Carrillo-Marquez MA, Hulten KG, Hammerman W, Lamberth L, et al. *Staphylococcus aureus* pneumonia in children in the era of community-acquired methicillin-resistance at Texas Children's Hospital. *Pediatr Infect Dis J.* 2011; 30(7):545-50.
22. Engelman D, Hofer A, Davis JS, Carapetis JR, et al. Invasive *Staphylococcus aureus* Infections in Children in Tropical Northern Australia. *J Pediat Infect Dis Soc.* 2014; 3(4):304-11.
23. Miles F, Voss L, Segedin E, Anderson BJ. Review of *Staphylococcus aureus* infections requiring admission to a paediatric intensive care unit. *Arch Dis Child.* 2005; 90(12):1274-8.
24. Gillet Y, Vanhems P, Lina G, Bes M, et al. Factors predicting mortality in necrotizing community-acquired pneumonia caused by *Staphylococcus aureus* containing Panton-Valentine leukocidin. *Clin Infect Dis.* 2007; 45(3):315-21.
25. Khanafer N, Sicot N, Vanhems P, Dumitrescu O, et al. Severe leukopenia in *Staphylococcus aureus* necrotizing, community-acquired pneumonia: risk factors and impact on survival. *BMC Infect Dis*. 2013; 13:359.
26. Muady GF, Bitterman H, Laor A, Vardi M, et al. Hemoglobin levels and blood transfusion in patients with sepsis in Internal Medicine Departments. *BMC Infect Dis*. 2016; 16(1):569.
27. 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.
28. Gonzalez BE, Martinez-Aguilar G, Hulten KG, Hammerman WA, et al. Severe staphylococcal sepsis in adolescents in the era of community-acquired methicillin-resistant *Staphylococcus aureus*. *Pediatrics.* 2005; 115(3):642-8.
29. McMullan BJ, Bowen A, Blyth CC, Van Hal S, et al. Epidemiology and mortality of *Staphylococcus aureus* bacteremia in Australian and New Zealand children. *JAMA Pediatr*. 2016; 170(10):979-86.
30. Bassetti M, Trecarichi EM, Mesini A, Spanu T, et al. Risk factors and mortality of healthcare-associated and community-acquired *Staphylococcus aureus* bacteraemia. *Clin Microbiol Infect*. 2012; 8(9):862-9.