Severe *Staphylococcus aureus* infection in three pediatric intensive care units. Analysis of cases of necrotizing pneumonia

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ABSTRACT

Staphylococcus aureus frequently affects human beings. Among clinical manifestations, necrotizing pneumonia is associated with a high mortality rate. Our objective is to describe the progress of severe *Staphylococcus aureus* infections in three intensive care units and analyze cases of necrotizing pneumonia in the period ranging from January 2011 to March 2013. Forty-three patients were studied, 76.7% had a community-acquired infection, and 31 had community-acquired methicillin-resistant *Staphylococcus aureus*.

The main reason for admission was respiratory failure. Bacteremia was confirmed in 55.8% of cases. Mechanical ventilation was required in 86% of admitted patients, while 27 patients developed septic shock. The length of stay in the intensive care unit was 13 (5-25) days, and the mortality rate was 14%. Necrotizing pneumonia was observed in 51% of cases.

Conclusion. A high rate of community-acquired infection was identified. Necrotizing pneumonia was associated with a worse clinical course.

Key words: Staphylococcus aureus, *community-acquired, necrotizing pneumonia.*

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INTRODUCTION

Staphylococcus aureus (SA) is one of the major pathogens that affects human beings. It causes a wide range of infections, from mild types that involve the skin, to severe forms, such as bacteremia and sepsis.[1]

In Argentina, Paganini's studies have described the growing trend in infections caused by community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA).[2-4]

Among clinical manifestations of SA infection, the most feared condition is necrotizing pneumonia (NP), a syndrome characterized by respiratory insufficiency and rapid development of septic shock, in the context of fever, hemoptysis, leukopenia, multifocal consolidation, cavitary lesions and pleural effusion,[5] associated with a high mortality rate (56-63%).[6]

SA virulence factors include the production of a toxin called Panton-Valentine leukocidin (PVL).[7]

OBJECTIVE

To describe the clinical and evolutionary characteristics of children with severe SA infections in three intensive care units.

METHODS

Retrospective (from January 1st, 2011 to February 29th, 2012) and prospective (from March 1st, 2012 to March 31st, 2013) study approved by the Ethics Committee. All patients admitted to the pediatric intensive care units (PICU) of Hospital Pedro de Elizalde (HNPE), Hospital Del Niño de San Justo (HNSJ) and Hospital Santísima Trinidad (HNST) were registered, excluding those readmitted to the PICU because of non-infection complications. Medical records were reviewed and patients were followed by some of the three main authors; conflicts were solved by consensus.

Blood cultures were performed using the Bact-alert system, and antibiotic sensitivity was analyzed as per the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Age, weight, Pediatric Index of Mortality 2 (PIM2) score and disease history were registered. The onset of the infectious process was attributed to the initial focus of infection, objectively confirmed by clinical and/or microbiological tests. The reason for admission to the PICU was classified into respiratory failure (respiratory

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insufficiency and/or poor ventilation), postoperative or hemodynamic failure.

As far as SA, hospital-acquired or community acquired outcome measures were recorded;[8] MRSA or methicillin-sensitive *Staphylococcus aureus* (MSSA), site where the microorganism was collected, prior antibiotic therapy, antibiogram, delay in providing an adequate treatment as per the antibiogram (in hours), and metastatic localization, defined as an infection not adjacent to the initial focus.[9]

In relation to the clinical course while in the PICU, the following outcome measures were registered: mechanical ventilation (MV) and days off MV up to 28 days post-admission, acute respiratory distress syndrome (ARDS),[10] high frequency oscillatory ventilation (HFOV), septic shock, hematological changes, hepatic dysfunction and/or renal involvement,[11] adrenaline requirement >0.25 mcg/kg/min as a consequence of a low cardiac output, Pediatric Logistic Organ Dysfunction (PELOD) score. In addition, the presence of an air leak (radiologic evidence of interstitial emphysema, pneumothorax, pneumomediastinum and/or subcutaneous emphysema), chronic lung disease (supplemental O_2 requirement 30 days after the initiation of MV), and the need for surgery and type of surgery were analyzed.

Finally, cases of NP, their clinical and evolutionary characteristics, their association as a predictor of a worse course, length of stay in the PICU, and mortality were analyzed.

Statistical analysis

The STATA 9.0 software was used; values were expressed as means and standard deviations, or as medians and interquartile range, and analyzed with the Student's t test and the Wilcoxon rank-sum test, respectively. The Chi-square test was used to compare dichotomous outcome measures. A value of $p < 0.05$ was considered significant.

The power of the sample for the analysis of NP cases was retrospectively estimated.

RESULTS

During the study period, 50 patients were admitted to the PICU with a diagnosis of severe SA infection or related complications; seven patients were considered readmissions and therefore, were excluded. Forty-three patients were analyzed *(Table 1)*. Of them, 76.7% (33) had a community-acquired infection; 31 were cases of CA-MRSA. Only one patient out of them had a concomitant chronic disease. Ten patients had a hospital-acquired infection *(Table 2)*; this group included six patients with previous diseases. The main reason for admission to the PICU was respiratory failure, and the initial focus of infection was pulmonary involvement (51%); bacteremia was confirmed in 55.8% of cases (24 patients).

Antibiograms showed that 81.4% of patients (35) had MRSA, with a minimum inhibitory concentration of 1.17 (obtained only in the HNPE). A 20 hour delay was observed in the initiation of an adequate antibiotic therapy as per the antibiogram (10 patients).

Metastatic localization was verified in 10 patients (23%).

During the course of their condition, 86% (37) of admitted patients required invasive MV; of them, 26 patients (70%) developed ARDS and 9 required HFOV. Septic shock was objectively confirmed in 27 patients (63%), and the maximum PELOD score was 18.64 ± 28.3.

Thirty-three surgeries were performed on 25 patients *(Table 3)*. The length of stay in the PICU was 13 (5-25) days, with an overall mortality due to SA infection of 14% *(Tables 1, 2* and *3)*.

NP as clinically defined was observed in 51% of admitted patients (20 due to CA-MRSA and 2 due to CA-MSSA). Below are the main characteristics of NP present in the following percentages: air leak: 54.5% (12 patients), empyema: 50% (11 patients), airway bleeding: 41% (9 patients), leukopenia: 36.6% (8 patients), prodromal flu symptoms: 32% (7 patients), and viral co-infection: 13.6% (3 patients).

In order to make an objective assessment of a worse course in patients who developed NP, the group with NP was compared to the group without NP *(Table 4)*.

The analysis showed that patients in the group that developed NP had worse clinical conditions at the time of admission (PIM2) and a worse clinical course, shown by fewer days off MV up to 28 days post-admission, a higher rate of ARDS, and HFOV requirement, a higher rate of lower cardiac output, a higher rate of multiple organ involvement (PELOD), and a longer length of stay in the PICU. These differences were statistically significant. The power of our sample to detect these differences, considering a two-tailed α level, was 77%.

TABLE 1. *Main characteristics of the 43 patients*

Outcome measure	**N (%) - X ± SD - Me/IQR**
Age (months)	22/6-72
Male gender	26 (60.5%)
Body weight (kg)	18.7 ± 15.1
PIM2 (%)	7.6 ± 11.7
Diagnostic categories/initial focus	
- Pulmonary	22 (51%)
- Muscle SCT	13 (32.5%)
- Osteoarticular	4 (7%)
- VAP	2 (4.7%)
- Meningeal	1 (2.3%)
- CVL	1 (2.3%)
- Underlying chronic disease	7 (16.3%)
Diagnostic categories/reason for admission	
- Respiratory failure	22 (51.2%)
- Hemodynamic failure	16 (37.2%)
- Postoperative period	5 (11.6%)
Outcome measures related to *Staphylococcus aureus*	
Community-acquired infection	33 (76.7%)
MRSA	35 (81.4%)
Antibiogram/resistance	
1. Vancomycin	0
2. Clindamycin	2 (4.7%)
3. Rifampicin	1 (2.4%)
4. Trimethoprim-sulfamethoxazole	1 (2.4%)
5. Gentamicin	1 (2.4%)
Bacteria collection	
1. Blood culture	24 (55.8%)
2. Pleural fluid	15 (35%)
3. Tracheal aspirate	3 (7%)
4. Muscle SCT	3 (7%)
5. CVL	3 (7%)
6. Joint fluid	2 (5%)
7. More than one site	9 (20%)
8. Others	3 (7%)
Prior antibiotic therapy	13 (30%)
Metastatic localization	10 (23%)
Outcome measures related to the clinical course in the PICU	
MV	37 (86%)
Days of MV	7/1-16
Days off MV up to 28 days post-admission	17/4-24
ARDS HFOV	26 (63%)
HFOV	9 (21%)
Air leak syndrome	14 (32.5%)
Chronic lung disease	9 (21%)

Necrotizing pneumonia	22 (51%)
Septic shock	27 (63%)
Organ involvement	
– Blood	16 (37.2%)
– Kidneys	16 (37.2%)
– Liver	8 (18.6%)
– PELOD	18.64 + 28.3
Adrenaline >0.25 mcg/kg/min	20 (46.5%)
Length of stay in PICU	13/5-25
Mortality	6 (14%)

N (%): number (%); X ± SD: mean ± standard deviation; Me/IQR: median/interquartile range.

PIM2: Pediatric Index of Mortality 2; SCT: subcutaneous cell tissue; VAP: ventilator-associated pneumonia;

CVL: central venous line; MRSA: methicillin-resistant *Staphylococcus aureus*; MV: mechanical ventilation; HFOV: high frequency oscillatory ventilation; ARDS: acute respiratory distress syndrome;

PELOD: Pediatric Logistic Organ Dysfunction.

TABLE 2. *Typing and source of Staphylococcus aureus infection as per the hospital*

Hospitals	CA-MRSA	CA-MSSA	HA-MRSA	HA-MSSA	Total
Pedro de Elizalde	15	0	1	2	18
Niños de San Justo	14	1	0	0	15
Niños de La Santísima Trinidad	2	1	3	4	10
Totales	31	2	4	6	43

SA: *Staphylococcus aureus*; MR: methicillin-resistant; MS: methicillin-sensitive; CA: community-acquired; HA: hospital-acquired.

TABLE 3. *Surgeries: 33 procedures performed on 25 patients*

Surgery	Patients
Pleural drainage	14
Pleural debridement	6
Decortication	2
Osteoarticular drainage	4
Muscle debridement	5
Pericardial drainage	1
Closure of bronchial-pleural fistula	1

DISCUSSION

MRSA has been identified as a major burden on public health. In Argentina, Paganini's works[2-4] describe a growing rate of CA-MRSA infections.

No reports have been found in the local literature regarding the course of severe SA infections in PICUs, and very few were found in the international bibliography.[12-14] For this reason, this study is highly relevant, specially for including three sites located in three different geographic areas.

In our study, 76.7% of patients had community-acquired infection, a similar rate to that reported in a multicenter study conducted in Argentina.[3] Unlike that study, the rate of CA-MSSA was 6%.

The main reason for admission to the PICU was respiratory failure, and the primary source for infection was pulmonary-related; this is also described in the studies by Cabeza, et al.,[12] and by Miles, et al.[14] In our series, a high percentage of patients required invasive mechanical ventilation (86%) and hemodynamic support; similar rates were reported in studies conducted in other PICUs.[12-14].

As per the bibliography, mortality rates in the PICUs vary: 27% in Creel's study[13] and 14% in our series.

It is worth noting that in Cabeza's and Miles' papers, the rate of MRSA infection was 12% and 14%, respectively, while in our study was 81.4%.

TABLE 4. *Comparison: necrotizing pneumonia group vs. non-necrotizing pneumonia group*

Outcome measures	Necrotizing pneumonia	Non necrotizing pneumonia	P < 0.05
Nº	22	21	
Age (months)	50.68 ± 52.90	51.33 ± 61.34	0.970
Weight (kg)	18.82 ± 14.08	18.55 ± 16.59	0.954
PIM 2 (%)	10.36 ± 11.47	4.42 ± 6.38	0.044
MV (days)	19	18	0.698
Days off MV up to 28 days	10.82 + 10.20	19.09 ± 9.41	0.022
ARDS	18	8	0.002
HFOV	9	0	0.001
Adrenaline >0.25 mcg/kg/min	14	6	0.015
Maximum PELOD score	26.80 ± 32.02	9.19 ± 21.3	0.031
Surgical drainage	15	10	0.223
Length of stay in PICU (days)	20.23 ± 13.38	11.1 ± 9.21	0.024
Mortality	4	2	0.623

P: pneumonia; PIM2: Pediatric Index of Mortality 2; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome; HFOV: high frequency oscillatory ventilation; PELOD: Pediatric Logistic Organ Dysfunction.

In relation to NP, mortality was 18%, much lower than the 56% reported in Gillet's series.[15]

The main limitation of this study is the scarce number of cases, rendering multivariate analysis impossible. Likewise, it is not possible to generalize results obtained because this was a convenience sample.

Given the increased incidence of CA-SA infection and the torpid evolution of NP, we believe that doctors working in a critical care area should be highly suspicious and follow the guidelines in order to act fast and effectively.

CONCLUSION

A high proportion of community-acquired infection was identified; a high percentage of admitted patients required mechanical ventilation and hemodynamic support. Necrotizing pneumonia was associated with a worse clinical course.■

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