

Community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia in a children's hospital. Our ten-year experience

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ABSTRACT

Introduction. Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections have increased in recent years. CA-MRSA necrotizing pneumonia and empyema are now more common in children.

Objectives. To determine the prevalence of CA-MRSA pneumonia and its clinical and epidemiological characteristics compared to *Streptococcus pneumoniae* (SP) pneumonia in the same population.

Material and methods. Descriptive, observational, cross-sectional study of patients hospitalized due to CA-MRSA pneumonia at Hospital de Niños Víctor J. Vilela (period: January 2008-December 2017).

Results. Out of 54 *Staphylococcus aureus* pneumonia cases, 46 (85 %) corresponded to CA-MRSA. The rate of CA-MRSA pneumonia ranged from 4.9/10 000 (2008) to 10/10 000 hospital discharges (2017). Sepsis/septic shock was observed in 41 %; empyema, in 96 %; pneumothorax, in 35 %; 90 % of cases required pleural drainage and 55 %, surgical debridement. Also, 65 % of patients were admitted to the intensive care unit (ICU); half of them required assisted mechanical ventilation. Two patients died. Strain resistance: 17 %, gentamicin; 13 %, erythromycin; and 11 %, clindamycin. Compared to SP pneumonia, CA-MRSA pneumonia showed a higher risk for sepsis (95 % confidence interval; relative risk: 7.38; 3.32-16.38) and admission to the ICU (RR: 4.29; 2.70-6.83). No patient died due to SP pneumonia.

Conclusions. The prevalence of CA-MRSA pneumonia doubled in the past decade. Compared to SP pneumonia, CA-MRSA pneumonia was more commonly accompanied by sepsis and septic shock, admission to the ICU, and ventilatory support requirement.

Key words: *Staphylococcal pneumonia, methicillin-resistant Staphylococcus aureus; cross-sectional studies; children's hospitals.*

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INTRODUCTION

The worldwide increase in *Staphylococcus aureus* (SA) infections has been mainly related to community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA).¹⁻³ These strains have a type IV or V staphylococcal cassette chromosome *mec* (SCC*mec*). This is a mobile genetic element that carries the central determinant for beta-lactam resistance encoded by the *mecA* gene, which confers resistance to beta-lactam antibiotics and may also lead to accompanying resistance to other antibiotic groups, such as macrolides and aminoglycosides.⁴⁻⁶ In general, they have an exotoxin called Panton-Valentine leukocidin (PVL), which has been associated with invasiveness, necrosis, and a poor prognosis.^{7,8}

CA-MRSA infections usually present as skin and soft tissue infections. However, in recent years, invasive infections have increased, including complicated pneumonia, arthritis, and osteomyelitis.^{9,10} Complicated pneumonia (CP) is defined as that accompanied by pleural effusion, empyema, necrotizing pneumonia or pneumonia with abscess formation.¹¹

Staphylococcal pneumonia used to be an uncommon condition in pediatrics; however, it has become increasingly frequent and has an important morbidity and mortality.¹² The primary objective of this study was to assess the prevalence of CA-MRSA pneumonia in the pediatric population of our hospital and its clinical and epidemiological characteristics. A secondary objective was to compare it to the prevalence

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and characteristics of *Streptococcus pneumoniae* (SP) pneumonia recorded in the same population during the study period.

MATERIAL AND METHODS

This was a descriptive, prospective, cross-sectional study in children and adolescents with a microbiologically documented diagnosis of CA-MRSA pneumonia assessed at Hospital de Niños Víctor J. Vilela between January 2008 and December 2017. Exclusion criteria were patients who, in the six months prior to study inclusion, had been hospitalized (at least, 24 hours), had visited a health care center or been in contact with health care staff, had received antibiotics or had a history of MRSA isolation. In addition, patients with comorbidities at the time of admission, such as immunosuppression, diabetes, corticosteroid therapy, etc. were excluded. Patients who did not have all data of analyzed outcome measures available were not excluded, but this was clarified in each case. Infection was defined as community-acquired when SA growth was isolated in at least one culture from a sterile site in outpatients or in the first 48 hours of hospitalization.

In relation to microbiological diagnosis, the culture sample was obtained from sterile sites (pleura, joint, surgical material, blood cultures, etc.). SA was isolated and typified using conventional automated microbiological tests based on the working protocols currently in place at the hospital's Microbiology Laboratory. Methicillin sensitivity was determined using the disk-diffusion method with a cefoxitin 30-microgram (μg) disk; a halo smaller than 20 millimeters (mm) was defined as methicillin resistance. Resistance to rifampicin (5 μg), gentamicin (10 μg), trimethoprim-sulfamethoxazole (25 μg), erythromycin (15 μg), clindamycin (2 μg), and ceftaroline (5 μg) was also determined, based on international standards. Antibigrams, were interpreted according to the standards of the Clinical and Laboratory Standards Institute (CLSI, 2016).¹³ Inducible clindamycin resistance was identified placing the clindamycin disk at 25 mm from the erythromycin disk in the antibiogram (D test). The minimum inhibitory concentration (MIC) of vancomycin was established by microdilution or the agar dilution method with E-test strips.

The following data were collected in a specially-designed form: sex, age, clinical presentation, medical and/or surgical treatment, antibiotic sensitivity of the isolated

microorganism, length of stay, admission to the intensive care unit (ICU), initiation of assisted mechanical ventilation (AMV), and number of deaths.

Data were analyzed in an overall manner. The SAS 9.2 software was used for statistical analyses. Categorical outcome measures were described as number and percentage. The relative risk (RR) and 95 % confidence interval (CI) were also calculated for primary outcomes. Continuous outcome measures were described as median and range.

The study protocol was authorized by the Ethics Committee of the Secretariat of Public Health of the Municipality of Rosario and approved by the Teaching and Research Committee of Hospital de Niños Víctor J. Vilela. No written informed consent was requested for data use. Before including a child in the study, a member of the research team described the study objectives and descriptive nature to the parents or legal guardians and noted that participation would not affect the child's clinical management or treatment indication. The research team warranted data anonymity and confidentiality.

RESULTS

During the study period, 54 patients with SA pneumonia were eligible. Eight patients, were excluded because they met an exclusion criterion, and 46 were included and analyzed (85 %). The annual rate of CA-MRSA pneumonia in relation to hospital discharges ranged from 4.9/10 000 (2008) to 10.1/10 000 (2017) (*Table 1, Figure 1*). The average age of the 46 patients with CA-MRSA pneumonia was 44 months (median: 27.5 months). Out of all patients, 24 (52 %) were females. The average number of people sharing the household with patients was 4.5 (range: 2-8). A history of infections or an active infection at the time of diagnosis in a family member was confirmed, including impetigo, cellulitis, furunculosis or recurrent furunculosis in 37.5 % of cases (*Table 2*).

In relation to clinical manifestations, 41 % had sepsis or septic shock. The chest X-ray of 22/46 (48 %) patients showed a pattern compatible with necrotizing pneumonia or pneumonia with abscess formation, and 21/46 (46 %), with consolidated or lobar pneumonia. Complications included empyema in 96 % (41/46) and pneumothorax in 35 % (16/46). Skin manifestations were observed in 12 patients (26 %): 6 had scarlatiniform rash and 6, cellulitis.

A pleural drainage tube was required in

89 % of patients; 1 tube: 19 patients; 2 tubes: 14 patients; and 3 or more tubes: 8 patients. The average length of tube placement was 16 days (range: 1-63 days). Surgical debridement was performed in more than half of patients (25/46); in general, it was a single procedure (75 %).

The total length of stay ranged from 1 to 77 days; the median value was 24 days. Blood cultures were positive in 10/46 patients (22 %). Almost 90 % of pleural fluid cultures from 42 samples were positive; pleural biopsy cultures were positive in 7/11 patients (63 %). Skin and soft tissue cultures were positive in 5/6 patients; joint fluid cultures, in 2/3; and pericardial fluid cultures, in 2/4.

The antibiogram showed that 17 % of strains were resistant to gentamicin; 13 %, to erythromycin; 11 %, to clindamycin; and 2 %, to trimethoprim-sulfamethoxazole. No resistance to teicoplanin, vancomycin, minocycline or

linezolid was observed. Sensitivity to ceftaroline was tested in 17 strains; 1 of these (5.7 %) showed intermediate sensitivity. The MIC of vancomycin was established in 45 samples; in approximately 90 % of strains, it was $\leq 1 \mu\text{g/mL}$ (Table 3).

In relation to clinical course, 30/46 patients (65 %) were admitted to the pediatric intensive care unit (PICU). In this subgroup, age ranged from 1 to 132 months, with a median of 23 months. In average, these patients stayed at the PICU for 9 days (maximum: 52 days). Half of patients admitted to the PICU (15/30) required AMV, for an average of 11.4 days. Two patients (4.34 %) in this group died from sepsis and septic shock.

DISCUSSION

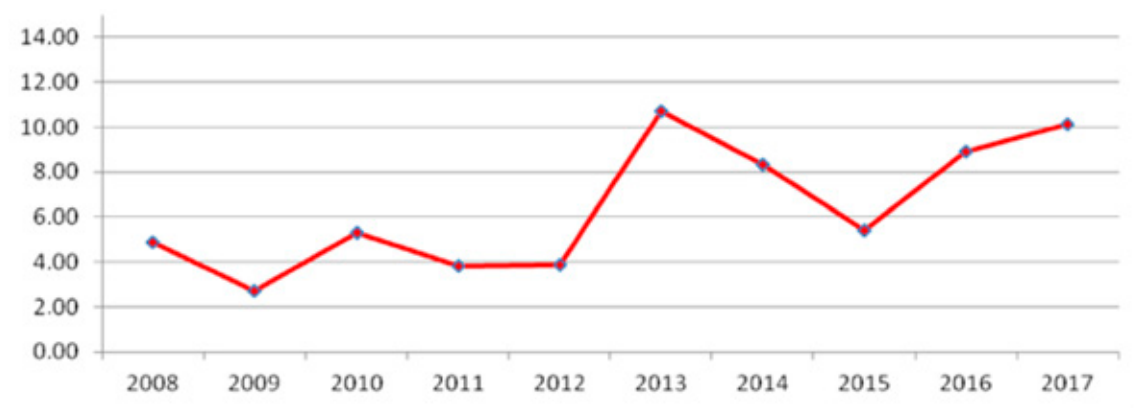
In recent years, the increase in CA-MRSA infections has led to a 3-4-fold increase in medical consultations due to this type of condition;

TABLE 1. Annual rate of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia in relation to hospital discharges. Hospital de Niños Víctor J. Vilela, Rosario. 2008-2017 period

Year	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Discharges	8162	7323	7555	7816	7773	6519	7243	7380	6740	6949
CA-MRSA pneumonia	4	2	4	3	3	7	6	4	6	7
Rate per 10000	4.9	2.7	5.3	3.8	3.9	10.7	8.3	5.4	8.9	10.1

CA-MRSA: community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia.

FIGURE 1. Annual rate of staphylococcal pneumonia per 10 000 discharges. Hospital de Niños Víctor J. Vilela. 2008-2017 period



When CA-MRSA pneumonia was compared to SP pneumonia, the number of the latter decreased and the former increased (Figure 2) during the study period. Compared to SP pneumonia, patients with CA-MRSA pneumonia had a 7-fold higher risk for sepsis or septic shock, had 4 times more chances of developing necrotizing pneumonia or pneumonia with abscess formation, had 2 times more chances of having empyema, were 4 times more likely to be admitted to the PICU, and had a 5-fold higher chance of requiring AMV (Table 4). Also, unlike CA-MRSA pneumonia, no deaths were recorded in the SP pneumonia group.

observed infections have been mild, like skin and soft tissue infections, or invasive and severe, such as sepsis, septic shock, bacteremia, osteoarticular infections, and complicated pneumonia.^{14,15} In a previous 10-year experience at our hospital, community-acquired SA infections were observed to increase approximately threefold, with an average 73 % of CA-MRSA infections.

In this study, CA-MRSA pneumonia or empyema accounted for one of the main clinical presentations and the third leading presentation after skin and soft tissue infections and osteoarticular infections.^{16,17} In turn, other international publications have pointed out an increased incidence of CA-MRSA pneumonia, especially in the form of complicated pneumonia^{11,12,18} and mainly during the flu or influenza season.¹⁹ Such aspect was not analyzed in our study.

During the study period, the prevalence rate of CA-MRSA pneumonia doubled in relation to hospital discharges; and such increase was mainly related to CA-MRSA, which accounts for 85 % of strains. Studies conducted in Argentina in

2012-2014 described the clones circulating in the pediatric population; the most common one was ST5-IV-PVL⁺.^{20,21} The average age of patients was close to 4 years; however, the median age was 27.5 months, similar to what has been reported by other authors.^{18,22}

Different authors demonstrated that the socioeconomic level of the affected population may have an impact on the development of these infections, so this is an aspect related to poverty and overcrowding, as well as the biological

TABLE 3. Minimum inhibitory concentrations of vancomycin in community-acquired methicillin-resistant *Staphylococcus aureus* isolated strains. Hospital de Niños Víctor J. Vilela, Rosario. 2008-2017 period

MIC (µg/mL)	Number	Percentage
0.5	19	42
0.75	1	2
1	20	44
1.5	5	11

MIC: minimum inhibitory concentration.

TABLE 2. Clinical and epidemiological characteristics of children with community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia (n = 46) and pneumococcal pneumonia (n = 118). Hospital de Niños Víctor J. Vilela, Rosario. 2008-2017 period

OUTCOME MEASURES	CA-MRSA n = 46	%	<i>S. pneumoniae</i> n = 125	%
FEMALE	24	52.2	56	45
AGE (MONTHS OLD)				
Average	44		30	
Range	1-152		1-168	
Median	27.5		25	
CLINICAL PRESENTATION*				
Consolidated pneumonia	21	45.65	104	83.2
Necrotizing pneumonia or pneumonia with abscess formation	22	47.8	12	9.6
Sepsis/septic shock	19	41.30	7	5.6
Pneumothorax	16	34.78	1	0.8
Pleural empyema	44	95.6	52	41.6
Skin manifestations	12	26	0	0
COURSE				
Admission to the PICU	30	65.2	19	15.2
Age of patients at the PICU ¹	37.7 (1-132)		31.2 (1-119)	
Average length of stay at the PICU ²	9.4 (1-52)		6.2 (1-22)	
AMV	15	32.6	7	5.6
Average days of AMV ²	11.4 (1-43)		7.7 (1-22)	
Pleural drainage tubes	41	89.13	48	38.4
Surgical debridement	25	54.3	14	11.2

* The same patient had more than one clinical presentation.

¹ Expressed in months and range.

² Expressed in days and range.

CA-MRSA: community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia;

PICU: pediatric intensive care unit; AMV: assisted mechanical ventilation.

factors of the host.^{22,23} In this study, although the population's socioeconomic status was not considered, the number of household members was analyzed, which was, in average, equivalent to more than 4 people per household. It was also observed that almost 40 % of cases had a family member with a history of infection or an active infection at the time of diagnosis. Such infection transmission phenomenon, once described in contact sports and prisoners,³ in our population may be related to poverty, overcrowding conditions, and personal hygiene issues.

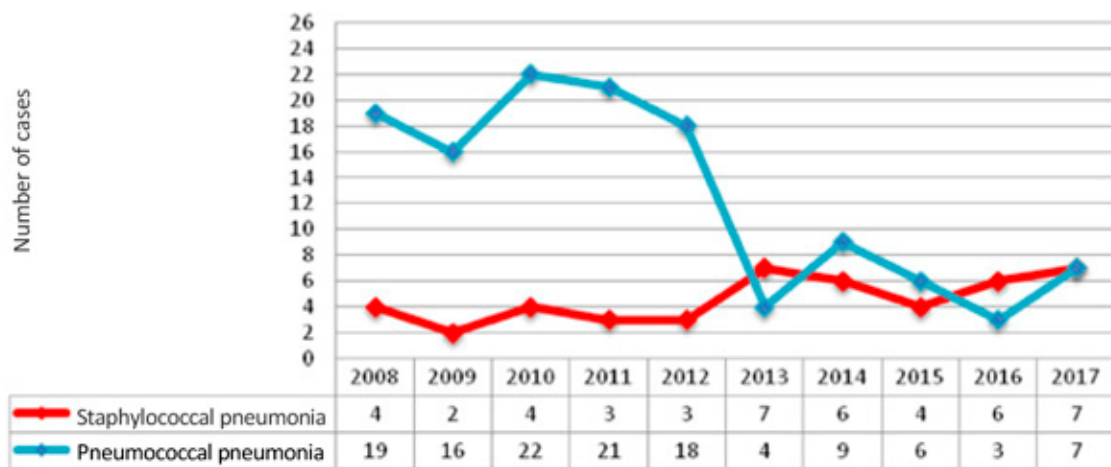
Approximately 40 % of patients had a clinical course with sepsis or septic shock; 2 patients died due to this condition. Such acute course, including complicated pneumonia accompanied by systemic involvement, PICU admission, and AMV requirement, has been reported by other authors at similar rates.^{18,24} Different publications have proposed a correlation between the presence of necrotizing pneumonia, pneumonia with abscess formation or empyema and a SA virulence factor known as PVL.^{25,26} PVL is a cytotoxin that causes white blood cell lysis and tissue necrosis, which undoubtedly enables SA to produce abscesses. PVL was found in both methicillin-sensitive *S. aureus* (MSSA) and MRSA, so methicillin resistance is not considered a predictor of severity.²⁷ A meta-analysis published in recent years supported the association between PVL and skin and soft tissue lesions and disregarded the relation between PVL and invasive infections.²⁸

Almost half of patients showed radiological characteristics of necrotizing pneumonia or pneumonia with abscess formation. Most likely, the necrotizing feature of CA-MRSA pneumonia, together with AMV requirement, is a combination that results in the onset of pneumothorax during clinical course.

Microorganism isolation was high, close to 90 % in pleural fluid culture and over 20 % in blood culture. These values are similar to those published by other authors.¹⁸ Such situation leads us to reflect on the importance of obtaining culture samples, especially a diagnostic pleural tap, before indicating an antibiotic therapy. Clindamycin resistance was lower than that mentioned in other publications,²⁴ while trimethoprim-sulfamethoxazole resistance was very low. Resistance to teicoplanin, vancomycin, minocycline, linezolid or ceftaroline was not confirmed, so these antibiotics should be taken into consideration for the treatment of these infections.²⁹

When comparing pneumococcal to staphylococcal pneumonia, both with microorganism isolation, a reduction in pneumococcal pneumonia was observed in the first place, together with an increase in staphylococcal pneumonia. Without a doubt, such observation is related to the introduction of the 13-valent pneumococcal vaccine to our immunization schedule in 2011. A similar behavior was reported by other authors.^{1,30}

FIGURE 2. Number of staphylococcal and pneumococcal pneumonia cases per year. Hospital de Niños Víctor J. Vilela. 2008-2017 period



Staphylococcal pneumonia was observed in almost half of sepsis or septic shock cases and, more commonly, in the form of necrotizing pneumonia or empyema, which more frequently required PICU admission, AMV, surgical debridement, and pleural drainage tube placement. It is worth noting that CA-MRSA pneumonia showed a 40-fold higher risk for complications due to pneumothorax, thus making evident its necrotizing characteristics and the procedures required for its management.^{8,18,19,24}

In relation to the limitations of our study, it is worth noting that it was conducted at a referral children's hospital; therefore, findings should be extrapolated to other hospital care settings with caution. In addition, given the fact that the diagnosis of bacterial pneumonia without effusion is difficult because only 10-20 % of blood cultures are positive, microorganism isolation in the absence of empyema or pleural effusion is usually low. The scarce number of deaths prevented us from assessing the impact of this infection on mortality.

One of the strengths of this study is its prospective nature for a planned data collection, which, among other contributions to the local context, allowed us to confirm the increased prevalence of CA-MRSA pneumonia in the past decade and outline the presentation characteristics that define its clinical treatment and management.

CONCLUSIONS

Out of all community-acquired SA pneumonia cases, 85 % corresponded to CA-MRSA. The annual rate of CA-MRSA pneumonia increased from 4.9/10 000 to 10.1/10 000 discharges in the past 10 years. Compared to SP pneumonia, CA-MRSA

pneumonia was more commonly accompanied by sepsis or septic shock, necrosis, and empyema, and required five times more surgical drainage, admission to the PICU, and AMV. ■

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TABLE 4. Comparison of clinical presentation and course of staphylococcal and pneumococcal pneumonia. Hospital de Niños Víctor J. Vilela, Rosario. 2008-2017 period

	MRSA (46)	<i>S. pneumoniae</i> (125)	RR (95 % CI)
Septic shock or sepsis	19	7	7.38 (3.32-16.38)
Pleuropulmonary suppuration	44	52	2.30 (1.85-2.86)
Necrotizing pneumonia or pneumonia with abscess formation	22	12	4.98 (2.69-9.23)
Pneumothorax	16	1	43.48 (5.93-318.65)
Surgery	25	14	4.85 (2.77-8.50)
Tubes	41	48	2.14 (1.70-2.70)
PICU	30	19	4.29 (2.70-6.83)
AMV	15	7	5.82 (2.54-13.37)

MRSA: methicillin-resistant *Staphylococcus aureus*; RR: relative risk; CI: confidence interval; PICU: pediatric intensive care unit; AMV: assisted mechanical ventilation.

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