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ORIGINAL ARTICLE

Staphylococcus aureus bacteremic pneumonia

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Abstract *Staphylococcus aureus* bacteremic pneumonia is an uncommon cause of hospitalization, with a high mortality rate. However, published reports are scarce and have included a small number of cases. All patients with *S. aureus* bacteremic pneumonia were prospectively collected in our institution from 2000 to 2014, and a retrospective revision was performed to identify risk factors associated with methicillin resistance and to update the mortality of this entity. A total of 98 patients were admitted: 57.1 % were due to methicillin-susceptible *S. aureus* (MSSA) and 42.8 % due to methicillin-resistant *S. aureus* (MRSA). In 40 patients (40.8 %), the infection was community acquired. Thirteen were ventilator-associated pneumonia episodes. The most frequent comorbidities were chronic lung disease (34.7 %), chronic renal failure (31.6 %), diabetes mellitus (29.6 %), and cardiovascular disease (31.6 %). Septic shock was present in 46 patients (46.9 %). The 30-day mortality was 46.9 %. MRSA infections occurred in older patients, more frequently with cardiovascular diseases, and they had received antibiotic treatment in the previous month more often than MSSA-infected patients. Patients with infection due to MSSA presented more frequently with septic shock, but they received more frequently appropriate empirical antibiotic therapy than patients with MRSA pneumonia (96 % vs. 38.1 %), and no differences in mortality were observed between both groups. In conclusion, *S. aureus* bacteremic pneumonia is a severe infection that, nowadays, affects people with comorbidities and the mortality is still high.

Introduction

Staphylococcus aureus pneumonia accounts for <5 % of community-acquired pneumonia (CAP). According to some studies, this percentage increases up to 30–50 % in case of hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), or healthcare-associated pneumonia (HCAP) [1]. CAP due to *S. aureus* has been more frequently described in children with cystic fibrosis, after influenza virus infection, and among intravenous drug users (IVDUs), while nosocomial acquisition was more common in severe patients with a longer length of hospital stay, admitted in burn units, and in patients undergoing intubation and mechanical ventilation [2]. This entity has been associated with a high mortality rate. Watanakunakorn [3] reviewed 44 consecutive patients with community or nosocomially acquired bacteremic *S. aureus* pneumonia from 1980 to 1984, with an overall mortality of 84 %. González et al. [2] reported a 48 % mortality rate among 50 consecutive cases admitted from 1990 to 1995, and the latest case series from DeRyke et al. [4] described 60 cases from 1999 to 2004 with a global mortality rate of 55 %, although, in this series, only nosocomially acquired infections were considered. Therefore, bacteremic *S. aureus* pneumonia is a relatively uncommon infection but it is associated with a high related mortality. In order to improve the outcome, it would be important to periodically review its clinical characteristics and outcomes.

The aim of our study was to retrospectively review the clinical characteristics of patients with bacteremic pneumonia due to *S. aureus* prospectively collected from 2000 to 2014 in

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an 850-bed university hospital and to evaluate the mortality rate throughout the study period.

Materials and methods

The study was conducted in an 850-bed university hospital that serves a population of 500,000 people in Barcelona, Spain. We retrospectively analyzed clinical and microbiological data from all patients with bacteremic pneumonia due to *S. aureus* admitted in our institution from January 2000 to December 2014. A specialist in infectious diseases prospectively collected this information during the admission of patients.

Variables

The following variables were gathered: age, sex, prognosis of the underlying disease, comorbidities, antibiotic or steroids treatment in the previous month, hospitalization, surgery and invasive procedures within the last month, radiological findings, length of hospitalization before the diagnosis of bacteremia in patients in whom the source of infection was nosocomial, presence of septic shock and intensive care unit admission, need for mechanical ventilation, empirical and definitive antibiotic treatment, and 30 day-mortality. Patients were followed up from the diagnosis of bacteremia until 30 days afterwards.

Definitions

Bacteremic pneumonia due to *S. aureus* was considered when the patient had symptoms of lower respiratory tract infection and pulmonary infiltrates on chest X-ray coinciding with the isolation of *S. aureus* in at least one blood culture without any other potential source of bacteremia. The isolation of *S. aureus* in a respiratory sample was not mandatory in order to include the patient in the study. Nosocomial infection was defined when clinical manifestations began 48 h after hospital admission. Healthcare-associated infection was defined when the subject met at least one of the following criteria: recent hospitalization (last 30 days), admission from long-term care facility, being on chronic hemodialysis or intravenous treatment during the previous month. The remaining patients were classified as community acquired. For subsequent analysis, patients with healthcare-associated infection were included in the group of nosocomial acquisition. Underlying diseases were classified according to the McCabe and Jackson modified criteria [5] into rapidly fatal, finally fatal, or non-fatal. Septic shock (at diagnosis or within the first 24 h) was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation [6]. Appropriate empirical therapy was considered when the patient received at least one in vitro active antimicrobial agent within 24 h after obtaining blood cultures, before susceptibility results were available, and the dosage and route of administration were in agreement with the current medical standards. Persistent bacteremia was considered when blood cultures remained positive after ≥24 h of adequate antibiotic treatment. Mortality was defined as death occurring within 30 days of bacteremia onset. Related mortality was considered when the patient died without a definitive infection control.

Microbiological procedures

Blood samples were processed using the BACTEC 9240 system (Becton Dickinson Microbiology Systems), with an incubation period of 5 days. Isolates were identified by standard techniques. Antimicrobial susceptibility testing was performed by a microdilution system (Phoenix system, Becton Dickinson, Franklin Lakes, NJ) or the Etest (AB Biodisk, Solna, Sweden).

Statistical analysis

Categorical variables were compared using Chi-square or Fisher's exact test when necessary and Student's *t*-test or the Mann–Whitney *U*-test for continuous variables. Discrete variables were expressed as counts (percentage) and continuous variables as mean and standard deviation (SD), unless otherwise stated. Backwards logistic regression was used to identify independent risk factors for methicillin-resistant *S. aureus* (MRSA) infection. Variables with a p-value <0.10 in the univariate analysis were entered into the model. The threshold for statistical significance was defined as a two-tailed $p < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 19 (Chicago, IL, USA).

Results

From January 2000 to December 2014, a total of 1750 episodes of *S. aureus* bacteremia were identified (24 % were methicillin resistant) and in 98 patients (5.6 %), pneumonia was the primary source. In 56 cases (57.14 %), *S. aureus* was methicillin susceptible (MSSA) and in 42 (42.85 %), *S. aureus* was methicillin resistant (MRSA). The mean age (SD) of the entire cohort was 65.09 (18.87) years and 68.4 % were males. The clinical characteristics of patients according to the outcome are shown in Table 1. The most common comorbidities were chronic lung disease (34.7 %), chronic renal failure (31.6 %), diabetes mellitus (29.6 %), cardiovascular disease (31.6 %), and solid organ cancer (22.4 %). Finally or rapidly fatal prognosis according to the McCabe and Jackson criteria was present in 51 % of patients. In 40 patients (40.8 %), the infection was community acquired and only 3.1 % were IVDUs. There were 13 VAP episodes, of which six were

Table 1 Baseline characteristics and clinical data of patients included in the study ($N = 98$)

	Alive ($n = 52$)	Dead[a] ($n = 46$)	p-Value
Age (years), mean ± SD	59.77 (19.44)	71.12 (16.41)	0.003
Male gender, *n* (%)	39 (75)	28 (60.9)	0.133
Methicillin-resistant *S. aureus*	21 (40.4)	21 (45.7)	0.599
Origin of pneumonia, *n* (%)			
Community	25 (48.1)	15 (32.6)	0.12
Nosocomial	27 (51.9)	31 (67.4)	
Prognosis of underlying disease, *n* (%)			
Non-fatal	33 (63.5)	16 (34.8)	0.005
Finally or rapidly fatal	19 (36.5)	30 (65.2)	
Comorbidity, *n* (%)			
Diabetes mellitus	17 (32.7)	12 (26.1)	0.475
Chronic lung disease	17 (32.7)	17 (37)	0.658
Chronic renal failure	14 (26.9)	17 (37)	0.286
Liver disease	4 (7.7)	5 (10.9)	0.730
Solid organ cancer	12 (23.1)	10 (21.7)	0.874
Cardiovascular disease[b]	14 (26.9)	17 (37)	0.286
Corticosteroid use[c]	16 (30.8)	18 (39.1)	0.385
Hematological malignancy	5 (9.6)	2 (4.3)	0.442
Bone marrow transplantation	2 (3.8)	0	0.497
Solid organ transplantation	1 (1.9)	1 (2.2)	1
Chronic alcohol intake	6 (11.5)	4 (8.7)	0.746
Intravenous drug users	2 (3.8)	1 (2.2)	1
Human immunodeficiency virus	8 (15.4)	1 (2.2)	0.034
Severe neutropenia (<500 cell/mm^3)	2 (3.8)	3 (6.5)	0.663
No comorbidity, *n* (%)	4 (7.7)	2 (4.3)	0.680
Diagnosis at intensive care unit	6 (11.5)	8 (17.8)	0.383
Undergoing mechanical ventilation	6 (11.5)	7 (15.2)	0.592
Radiological characteristics[d]:			
Pleural effusion	16 (32)	5 (15.6)	0.097
Multilobar pneumonia	12 (24.5)	17 (53.1)	0.009
Necrotizing pneumonia	3 (6)	3 (9.4)	0.674
Persistent bacteremia	5 (9.6)	2 (4.3)	0.442
TTP of blood culture (median, IQR)	17.3 (13.2–22.7)	16.3 (11.6–25)	0.531
Shock	18 (34.6)	28 (60.9)	0.009
Appropriate empirical treatment	38 (73.1)	32 (69.6)	0.701

TTP time to positivity

[a] 30-day mortality

[b] Includes presence of coronary heart disease, cerebrovascular disease, peripheral artery disease, or significant atherosclerosis

[c] ≥20 mg of corticosteroids every day on a regular basis

[d] This information was only available in 56 patients

due to MRSA and seven to MSSA. In 69 patients, a respiratory sample was obtained for culture and 84.1 % of these were positive. Twenty-one patients (21.4 %) had pleural effusion, 29 (29.6 %) multilobar pneumonia, and 6 (6.1 %) necrotizing pneumonia. A total of 46 patients (46.9 %) were in septic shock at diagnosis and 7 (7.1 %) had persistent bacteremia. The 30-day mortality and related mortality were 46.9 % and 38.8 %, respectively. Community-acquired and nosocomial cases were similar, except for the rate of patients with finally and rapidly fatal prognosis of their comorbidity (32.5 % vs. 62.1 %, $p = 0.004$), antibiotic treatment during the prior month (12.5 % vs. 58.6 %, $p < 0.001$), and the methicillin resistance rate, for which they were all more frequent in the nosocomial group (30 % vs. 51.7 %, $p = 0.033$). Mortality was also higher in the nosocomial group but the difference was not statistically significant (37.5 % vs. 53.4 %, $p = 0.12$).

The characteristics of patients with MSSA and MRSA infection are shown in Table 2. MRSA infections occurred in older patients who had more frequently cardiovascular diseases and had received prior antibiotic treatment (particularly beta-lactams and fluoroquinolones) than MSSA infections. In contrast, liver cirrhosis or chronic lung disease were more prevalent in MSSA infections with no statistical significance. Patients with infection due to MSSA presented more frequently septic shock and received appropriate empirical antibiotic therapy in a significantly higher number of cases (96.4 % vs. 38.1 %). A nasal swab for identifying nasal carriers of *S. aureus* was obtained from 46 patients and it was positive in 32 (69.5 %). Among MRSA cases, the prevalence of carriers was higher (75.8 % vs. 53.8 %, $p = 0.146$). Although groups were different in critical variables associated with the outcome, no differences in mortality were observed (44.6 % in MSSA vs. 50 % in MRSA). In the multivariate analysis, previous antibiotic therapy with beta-lactams [odds ratio (OR): 3.79; 95 % confidence interval (CI): 1.28–11.23] or fluoroquinolones (OR: 3.18; 95 % CI: 1.01–10.1), and cardiovascular disease (OR: 3.32; 95 % CI: 1.23–8.69) were the only independent predictors of infection due MRSA.

Discussion

Our results demonstrate that bacteremic *S. aureus* pneumonia is still a severe infection, with a high mortality rate (47 %) that

Table 2 Characteristic of patients with MSSA and MRSA infection

	MSSA ($n = 56$)	MRSA ($n = 42$)	p-Value
Age (years), mean ± SD	59.42 (19.75)	72.66 (14.71)	<0.001
Male gender, *n* (%)	38 (67.9)	29 (69)	0.9
Community acquisition	28 (50)	12 (28.6)	0.06
Non-fatal prognosis	28 (50)	21 (50)	1
Diabetes mellitus	13 (23.2)	16 (38.1)	0.11
Chronic lung disease	16 (28.6)	18 (42.9)	0.14
Chronic renal failure	17 (30.4)	14 (33.3)	0.75
Liver disease	8 (14.3)	1 (2.4)	0.07
Solid organ cancer	15 (26.8)	7 (16.7)	0.23
Cardiovascular disease[a]	11 (19.6)	20 (47.6)	0.003
Human immunodeficiency virus	6 (10.7)	3 (7.1)	0.73
Corticosteroid use[b]	16 (28.6)	18 (42.9)	0.14
Chronic alcohol intake	8 (14.3)	2 (4.8)	0.18
Previous hospitalization (last month)	9 (16.1)	12 (28.6)	0.14
Previous antibiotic treatment	14 (25)	25 (59.5)	0.001
Beta-lactams	7 (12.5)	17 (40.5)	0.001
Fluoroquinolones	6 (10.7)	15 (35.7)	0.003
Diagnosis at intensive care unit	7 (12.7)	7 (16.7)	0.58
Undergoing mechanical ventilation	7 (12.5)	6 (14.3)	0.79
Radiological characteristics			
Pleural effusion	14 (29.2)	7 (20.6)	0.381
Multilobar pneumonia	18 (37.5)	11 (33.3)	0.701
Necrotizing pneumonia	4 (8.3)	2 (5.9)	0.675
TTP of blood culture (median, IQR)	15.9 (11.5–25)	17.55(13.6–22.6)	0.561
Nasal carrier of *S. aureus*[c]	7 (53.8 %)	25 (75.8)	0.146
Appropriate empirical treatment	54 (96.4)	16 (38.1)	<0.001
Shock	32 (57.1)	14 (33.3)	0.02
30-day mortality	25 (44.6)	21 (50)	0.56
Related mortality	21 (37.5)	17 (40.5)	0.76

MSSA methicillin-susceptible *S. aureus*; *MRSA* methicillin-resistant *S. aureus*; *TTP* time to positivity

[a] Includes presence of coronary heart disease, cerebrovascular disease, peripheral artery disease, or significant atherosclerosis

[b] ≥20 mg of corticosteroids every day on a regular basis

[c] Results of nasal swab were available in 13 patients with MSSA infection and in 33 with MRSA infection

is similar to that reported in 1999 [7] and 2005 [4]. For this reason, it is of utmost importance to review the characteristics of patients with this infection in order to start an adequate antibiotic treatment as soon as possible. Interestingly, in our study, 28 (50 %) MSSA and 12 (28.6 %) MRSA episodes were community acquired. This finding is in contrast with previous studies where nosocomial infections represented more than 80 % of cases [2, 7]. The prevalence of community *S. aureus* producing Panton–Valentine leukocidin (PVL) in Spain is low [8, 9] and, according to the characteristics of cases described in Europe, this infection typically affects young people [10–12]. In contrast, the mean age of our cohort was 65 years, suggesting that it was not related to these strains. Influenza infection is a well-known risk factor for staphylococcal pneumonia [13] and 19 patients (47.5 %) from those with community infection were admitted during the influenza season (from December to March in our region). Unfortunately, coinfection with influenza virus or previous symptoms suggesting flu was not collected. On the other hand, our study reflects the great effort to reduce VAP infections that represented only 38.2 % of our nosocomial cases, while in other series, they were more than 75 % [2, 4].

As expected, a large proportion of MRSA cases had comorbidities and had received antibiotics in the previous month (59.5 %), particularly beta-lactams and fluoroquinolones, both well-known risk factors for MRSA infections [14, 15]. In contrast, MSSA pneumonia was associated with a higher prevalence of septic shock (57 % vs. 33 %), suggesting that MSSA is more virulent than MRSA. In a previous article, we described a higher prevalence of septic shock among patients with MRSA bacteremia due to strains with a low vancomycin minimum inhibitory concentration (MIC ≤1 mg/L vs. >1 mg/L) [16]. Other authors studying MSSA bacteremia also observed a higher prevalence of inflammatory response syndrome in patients infected with low vancomycin MIC strains (<1.5 mg/L) (56 % vs. 7 %, $p = 0.005$) and a higher risk of severe sepsis (24 % vs. 7 %, $p > 0.05$), although this had no statistical significance [17]. These findings suggest that resistance is associated with a reduction in virulence. Indeed, genetic changes linked with vancomycin-intermediate *S. aureus* (VISA) and an invertebrate model demonstrated that *S. aureus* strains with reduced susceptibility to vancomycin were attenuated in virulence [18–20]. In line with this, it has been recently demonstrated that the clonal complex (CC) 30 lineage of MRSA, a major cause of hospital-associated sepsis, expresses an allelic variant of the phenol-soluble modulin (virulence factor produced by *S. aureus*) that significantly reduces the cytolytic and the proinflammatory potential (chemotactic activity toward human neutrophils) of these strains [21].

Based on the higher prevalence of septic shock in MSSA than in MRSA cases, it would be reasonable to expect a higher mortality rate among MSSA cases. However, the mortality was similar in both groups (44.6 % vs. 50 %). A potential explanation could be that 96.4 % of patients with MSSA pneumonia received an appropriate empirical treatment in the first 24 h after admission, while it was appropriate in only 38.1 % of patients with MRSA pneumonia. It is well known the impact that this variable has in severe infections [22, 23]. Our results strongly support the Infectious Diseases Society of America (IDSA) guideline of CAP recommending empirically starting treatment for *S. aureus* in critically ill patients and in those with risk factors such as end-stage renal disease, intravenous drug use, prior influenza, and prior antibiotic therapy [24].

There were several limitations in our study, the first being the small sample size. However, due to the low prevalence of this entity, this is one of the largest series that help us to understand the current clinical characteristics of this severe infection. Secondly, the association of the infection with previous influenza syndrome, severity scores (i.e., APACHE II), PVL-producing strains, or vancomycin MIC were not evaluated. Thirdly, a nasal test was performed only in 46 patients and it was positive in 32 (69.6 %) of them. In agreement with previous studies showing sensitivities of nasal positive tests between 70 and 88 % for respiratory infections [25–27], the colonization rate among our MRSA cases was 75 %. Taking into account the recent literature [26, 27], nasal screening for MRSA has a high negative predictive value and it may be useful for de-escalation of empiric therapy in case of negativity.

In conclusion, in our series, bacteremic pneumonia due to *S. aureus* was more prevalent in non-ventilated patients; in 40 % of the cases, they were community acquired and they had a related mortality rate of 38 %. Unfortunately, our study did not find good predictors for MRSA; therefore, taking into account the importance of giving adequate empirical treatment, it is reasonable to cover MRSA while waiting for culture results. Further studies combining antibiotics including new anti-staphylococcal agents are necessary to improve the outcome of this infection.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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