Staphylococcus aureus Bacteremia: Comparison of Two Periods and a Predictive Model of Mortality

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Staphylococcus aureus **is an important pathogen causing bacteremia, primarily affecting hospitalized patients. We studied the epidemiology of *S. aureus* bacteremia, comparing two periods (early and mid 1990s) and developed a predictive model of mortality. A nested case-control was done. All 251 patients over 14 years old with positive blood cultures for *S. aureus* were selected. MRSA (methicillin resistant *S. aureus*) was isolated in 63% of the cases. When comparing the two periods MRSA community-acquired bacteremia increased from 4% to 16% (p=0.01). There was no significant difference in the mortality rate between the two periods (39% and 33%, p=0.40). Intravascular catheters provoked 24% of the cases of bacteremia and were associated with the lowest rate of mortality. In a logistic regression analysis, three variables were associated with death: septic shock, source of bacteraemia and resistance to methicillin. The probability of dying among patients with MRSA and those with methicillin sensitive *S. aureus* bacteraemia ranged from 10% to 90% and from 4% to 76%, respectively, depending on the source of the bacteraemia and the occurrence of septic shock. The MRSA found in Brazil may be a particularly virulent strain.**

Key Words: *Staphylococcus aureus*, bacteremia, mortality.

In recent years, methicillin resistant *Staphylococcus aureus* (MRSA) has emerged as an important pathogen, primarily affecting hospitalized patients, and has become one of the leading causes of nosocomial bacteremia [1-7].

Several studies have indicated no difference in virulence when clinical outcomes in patients with infection due to MRSA were compared with those with methicillin–sensitive *S. aureus* (MSSA) infection. However, other studies indicate that methicillin resistance is a risk factor for a poor outcome in patients with *S. aureus* bacteremia [8-12]

Received on 15 May 2002; revised 12 December 2002.
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This study was supported by INCLEN- International Clinical Epidemiology network.

The Brazilian Journal of Infectious Diseases 2002;6(6):288-297

1413-8670

We compared *S. aureus* bacteremia, during two study periods: 1991-1992 and 1995-1996, and developed a predictive model for mortality.

Material and Methods

Design. The cohort of all adult patients at São Paulo hospital with *S. aureus* bacteremia, during 1990-1991 and 1995-1996 was studied. These two periods were chosen to evaluate the trends of methicillin resistance rate in the hospital and to determine if there were changes in the treatment and evolution of *S. aureus* bacteremia after a more strict antibiotic control policy was implemented at this hospital in 1993. A nested case-control study was done to identify risk factors for mortality. Patients with *S. aureus* bacteremia who died were considered the study cases and the patients with *S. aureus* bacteremia who survived were chosen as controls.

Setting. The study was carried out in the São Paulo Hospital, Brazil, which has a high prevalence rate of

MRSA. It is a 600-bed, university, general public hospital.

Subjects. All patients over 14 years old with a blood culture positive for *S. aureus* were selected. A review of medical records was made to characterize the clinical picture, signs of infection in other sites within 48 hours of the blood culture, drugs used and clinical progress up to the 14th day of bacteraemia. The 14th day after bacteremia was chosen because most deaths related to bacteremia occurred early, normally not later than the second week.

Bacteremia was defined by at least one blood culture positive for *S. aureus*. Patients were grouped, according to clinical manifestation as: (1) Sepsis, (2) Severe sepsis or (3) Septic shock [2]. The clinical manifestation was assessed at the time when the first antibiotic treatment was defined. Nosocomial bacteremia was defined as bacteremia occurring 48 hours or more after hospital admission; bacteremia in patients on hemodialysis or those receiving outpatient intravenous therapy were also defined as nosocomial [13].

Sources of bacteraemia were defined if there was either clinical or bacteriological evidence of infection at another site within 48 hours of the positive blood culture.

The initial antibiotic therapy was considered to be adequate if at least one antibiotic to which the bacterium was sensitive, in vitro, had been used within the first 48 hours after blood culture material collection; corrected whenever the antibiotic used within the first 48 hours had to be replaced by another antibiotic because the microorganism was found to be resistant in vitro; and inadequate when the agent was resistant, in vitro to the antibiotic used within the first 48 hours, and no other antibiotic was used in its place.

Deaths were attributed to bacteremia if they occurred within 14 days of the first positive blood culture and without any other obvious cause.

The Pearson chi-squared test or Fisher's exact test was used to compare proportions. The periods of study were analyzed to determine how they affected mortality, because there were differences in both the proportions of patients with adequate treatment and the principal source of bacteremia between the two periods. Variables showing significant associations in the univariate analysis were further analyzed by logistic regression. The logistic regression model evaluated interactions among treatment, infection source, septic shock and methicillin resistance. The predictive model of mortality was developed using coefficients calculated for each of the variables selected by the logistic regression analysis.

Results

Over 100 patients with *S. aureus* bacteremia were identified during each of the two periods (Table1). Most patients were men 60-years old or under, and most bacteremias were hospital acquired. More than 80% of the patients had one underlying disease.

In a comparison between the two periods, the patients did not differ significantly in terms of age, sex, presence of underlying disease, occurrence of septic shock or frequency of MRSA isolated by blood culture. In the first period, 66% of the strains were MRSA, which was similar to that found in the second period (60%, $p=0.31$). The catheter was considered to be the source of bacteremia in 24% of the patients during the two periods, analyzed together.

The proportion of bacteremias with undetermined source decreased from the earlier to the later period by 24% (95% CI: 12%, 35%; $p<0.01$). The proportion of bacteremias with a respiratory tract source increased by 13% (95% CI: 22%, 30%; $p<0.01$), and bacteremias with other sources increased by 14% (95% CI: -24%, -4%; $p<0.01$). There was an increase in the proportion of community-acquired bacteremia from the first to the second period(from 14% to 28%; $p=0.01$). This increase was largely due to community acquired MRSA bacteremia, which had a frequency of 4% in the first period and 16% in the second ($p<0.01$).

A significantly higher proportion of patients received adequate or corrected treatment in the second than in the first period (69 % and 83%; $p<0.01$). There was an improvement of the treatment for bacteremia by

Table 1. Characteristics of patients with *Staphylococcus aureus* bacteremia

	1991-1992 No. (%)	1995-1996 No. (%)	P	Difference %	CI 95%
Number of cases	136	115			
Age					
<60 years	71%	75%	0.38	4%	15%, 7%
Sex					
Male	62%	61%	0.88	1%	-11%, 13%
Community acquired	14%	28%	0.01	14%	-24%, - 4%
Underlying disease present	85%	86%	0.85	1%	-10%, 8%
Source of bacteremia					
Catheter	26%	23%		3%	-7%, 14%
Respiratory tract	12%	25 %		13%	-22%, -3%
Others	15%	29%		14%	24%, 4%
Undetermined	47%	23%	0.001	24%	12%, 35%
MRSA	66%	60%	0.31	6%	-6%, 18 %
Clinical picture					
Sepsis	60%	50%		10%	-2%, 22%
Severe sepsis	17%	19%		2%	-11%, 8%
Septic shock	22%	30%	0.24	8%	-19%, 26%
Treatment					
Adequate/ corrected	69%	83%	0.01	14%	-24%, 3%
Death	39%	33%	0.40	6%	-6%, 17%

MRSA: methicillin resistant *S. aureus*.

MRSA, with 58% of the patients being treated appropriately in 1991-1992 and 77% in 1995-1996, (p=0.008). There was no significant difference in the mortality rate between the time periods (39% and 33%; p=0.40).

Table 2 shows the statistical association among several clinical variables and death in the two periods. There were no significant differences for any of the variables across time. Therefore the analysis was done considering all patients of each of the two periods together.

The univariate analysis showed that age above sixty years, hospital acquired bacteremia, methicillin resistance, respiratory and undetermined sources of bacteremia, occurrence of septic shock and inadequate treatment were significantly associated with mortality (Table 3). Mortality remained significantly associated with bacteremia by MRSA, source of bacteremia and occurrence of shock septic, when the patients were grouped based on inadequate versus adequate treatment was done (Table 4).

Logistic regression analysis with stepwise backward elimination of variables was applied. At first, the terms of interaction: treatment X methicillin resistance, treatment X septic shock, treatment X source of bacteraemia and methicillin resistance X source were included in the logistic model. The likelihood-ratio test, comparing the model with and without interaction terms, showed no significant difference (p= 0.23).

The logistic regression analysis selected three variables that were significantly associated with death: septic shock, methicillin resistance, and source of bacteremia (Table 5).

Table 2. Association between clinical variables and death by day 14 in cases of *Staphylococcus aureus* bacteremia during each of two periods of study (1991-1992 and 1995-1996)

	First period			Second period		
	Survival	**Death**	**P**	**Survival**	**Death**	**P**
≥60 years	19	22		15	14	
< 60years	64	31	0.02	61	25	0.15
Hospital acquired	67	50		59	24	
Community acquired	16	3	0.02	17	15	0.06
Underlying disease						
Present	70	46		64	35	
Absent	13	7	0.80	12	4	1.00
MRSA	46	44		40	29	
MSSA	37	9	0.01	36	10	0.03
Source of bacteremia						
Catheter	31	4		20	6	
Respiratory tract	6	11		16	13	
Others	14	6		26	7	
Undetermined	32	32	<0.001	14	13	0.05
With Septic shock	8	22		12	23	
Without Septic shock	75	31	<0.001	64	16	<0.001
Inadequate treatment	18	24		9	11	
Adequate treatment	65	29	0.004	76	39	0.02

MRSA: methicillin resistant *S. aureus*; MSSA: methicillin sensitive *S. aureus*.

The predictive model of mortality considering the occurrence of septic shock and source of bacteremia (Table 6) shows that the probability of dying ranged from 10% to 90%, among patients with MRSA bacteremia; and among patients with MSSA bacteremia, the probability of dying varied from 4% to 76%.

Discussion

S. aureus is one of the main agents of hospital acquired bloodstream infection [5,14]. In our study most of the *S. aureus* bacteremias were hospital acquired, and accounted for 86% and 72% of the cases in each of the two periods. The *S. aureus* strains isolated at São Paulo Hospital, had a high frequency of resistance to antibiotics, but these rates were similar in the two study periods (66% and 60%, p=0.31).

Although MRSA is often thought of a nosocomial agent, there are increasing reports of MRSA community acquired infections [15-17]. We observed that 4% of the MRSA bacteremias were community acquired, in the first period, while in the second period the rate increased to 16% (p<0.01). It is known that patients who are colonized by MRSA in the hospital can sustain the infection for 6 to 12 months after discharge. They can serve as a source in the community and be readmitted to the same or another hospital [18]. Some of the MRSA cases that were considered community acquired could in fact have been hospital acquired. Nevertheless, it is important to be aware that an increasingly number of patients already infected with

Table 3. Association between selected clinical factors and risk of death following *Staphylococcus aureus* bacteremia, considering all patients (n=251)

	Survival	Death	P	OR	95%CI
Number	159	92			
<60 years	125	56			
≥60 years	34	36	0.003	0.46	0.25 - 0.84
Hospital-acquired bacteremia	126	74			
Community-acquired bacteremia	33	18	0.82	1.0	0.57 - 2.0
Underlying disease					
Absent	25	11			
Present	134	81	0.41	1.4	0.65 - 2.9
MRSA	86	73			
MSSA	73	19	<0.001	3.3	1.8 - 5.9
Source of bacteremia					
Catheter	51	10		0.6	0.2 - 1.6
Respiratory tract	22	24		3.6	1.3 - 8.6
Undetermined	46	45		3.0	1.3 - 6.8
Others	40	13	<0.001	1.0	-
With septic shock	20	45			
Without septic shock	139	47	<0.001	6.65	3.6 - 12.3
Inadequate treatment	27	35			
Adequate treatment	132	57	<0.001	3.0	1.6 - 5.41

MRSA: methicillin resistant *S. aureus*. MSSA: methicillin resistant *S. aureus*. OR: odds ratio; 95% CI: confidence interval; Others: tegument; surgery infection.

MRSA are being admitted into hospitals for treatment. The intravascular catheter was the source of bacteraemia in 26% and 23% of patients in the two periods of this study and 24% overall. Bacteremia is one of the known complications of infection provoked by intravascular catheters. These data are similar to the situation described by Pittet et al. [19], who analyzed 1090 episodes of primary bacteremia and found 212 cases (19%) associated with vascular catheters, and in 74% of these, the agent was *Staphylococcus* sp.

In our study, , the respiratory tract was considered to be the source of the bacteremia in 12% and 25% of the cases, in the two periods. Similarly, Taylor et al.[20] identified S. aureus in 27% of the nosocomial pneumonia cases that presented a bacteraemia. The patients at high risk of developing nosocomial pneumonia generally have other risk factors for acquiring infections [21,22].

There was an evident improvement, from the first to the second period, in the adequate use of antibiotics in MRSA bacteremia. This might be due to (1) improved physicians knowledge concerning the resistance pattern of the most frequently isolated bacteria in the hospital; (2) a more strict antibiotic control policy adopted by Hospital Sao Paulo after 1993; in that year an infectious disease specialist was responsible for the surveillance of all blood cultures or (3) a decrease in the bacteremia rate from undetermined sources. Thus, the agents involved could be better predicted and an improvement in the initially empirical antibiotic treatment was made possible. Leibovice et al. [23] found inadequate antibiotic treatment to be more frequent among cases with undetermined source bacteremia than those with known source (49% and 35% respectively; p<0.001).

Table 4. Association between selected clinical factors and death after *Staphylococcus aureus* bacteremia, stratified by treatment situation

	Survival	Death	P
Adequate treatment			
First period (94)	69%	31%	
Second period (95)	70%	30%	0.87
MRSA (104)	62%	38%	
MSSA (85)	79%	21%	0.01
Without septic shock (143)	79%	21%	
With septic shock (46)	41%	59%	<0.001
Source of bacteraemia			
Catheter (53)	85%	15%	
Respiratory tract (38)	55%	45%	
Undetermined (54)	57%	43%	
Others (44)	79%	21%	0.001
Inadequate treatment			
First period (42)	57%	43%	
Second period (20)	55%	45%	<0.001
MRSA (55)	38%	62%	
MSSA (7)	86%	14%	0.01
Without septic shock (43)	60%	40%	
With septic shock (19)	5%	95%	<0.001
Source of bacteremia			
Catheter (8)	75%	25%	
Respiratory tract (8)	12%	88%	
Undetermined (37)	40%	60%	
Others (9)	55%	45%	0.05

MRSA: methicillin resistant *S. aureus.* MSSA: methicillin resistant *S. aureus*. Others: tegument; surgery infection.

Mortality within 14 days was chosen as the cutoff, because several authors have suggested that death due to bacteremia occurs early, rarely after the second week. The observed mortality was 39% and 33% in each period (p=0.43), and was associated with source of bacteremia, inadequate treatment, and occurrence of septic shock and methicillin resistance. The source of bacteremia, occurrence of septic shock and methicillin resistance was associated with death, even when adjusted by the treatment received.

The overall mortality rate was 37%, similar to that found by Brum-Buisson, Doyon and Carlet [24], in their study in 24 French hospitals, where the bacteremia mortality rate ranged from 25% to 54%, depending on the clinical presentation.

Mortality due to *S. aureus* bacteremia provoked by catheter contamination is reported to be about 15% [25]. We found a similar percentage (16%) of patients who died from contamination by the vascular catheter. It is believed that bacteremias caused by catheters lead to lower rates of mortality and complications, since they are more easily diagnosed, and more promptly treated. *S. aureus* is therefore more quickly eradicated as the source of infection is removable [26].

Nosocomial pneumonia is associated with an increased death risk, ranging from 20% to 84% [27-

Table 5. Clinical variables found by logistic regression analysis to have a significant association with risk of death by day 14 following *Staphylococcus aureus* bacteremia, considering all 251 patients

Variable	Regression coefficient	SE	P	OR	95% CI
Source of bacteremia					
Catheter	-1.09	0.32	<0.001	0.33	0.17 -0.63
Respiratory tract	0.73	0.29	0.01	2.07	1.27 - 3.37
Undetermined	0.99	0.25	<0.001	2.68	1.63 - 4.41
Others	-	-	-	1.0	-
Septic shock	1.15	0.19	<0.001	3.15	2.16- 4.58
No shock	-	-	-	1.0	-
Methicillin resistance	0.58	0.17	0.002	1.80	1.27 - 2.54
Methicillin susceptibility	-	-	-	1.0	-
1st Period of study	0.63	0.19	0.43		
2nd period of study	-	-	-	1.0	-
Constant	-0.43				

SE: standard error; OR: odds ratio; 95% CI: confidence interval.

Table 6. Predictive model of mortality among patients with *Staphylococcus aureus* bacteremia, considering the coefficient of logistic regression analysis

	Methicillin sensitive *S. aureus* Clinical picture	
	No shock	**Septic shock**
Source of bacteremia		
Catheter	4%	28%
Respiratory tract	20%	71%
Unknown	24%	76%
Others	8%	62%
	Methicillin resistant *S. aureus* Clinical picture	
	No shock	**Septic shock**
Source of bacteremia		
Catheter	10%	53%
Respiratory tract	42%	88%
Unknown	48%	90%
Others	21%	82%

30]. In our study, 52% of the patients with *S. aureus* bacteremia, involving the respiratory tract, died. Rello-Torres et al. [22], also reported a higher mortality rate among patients with MRSA pneumonia, compared with pneumonia caused by sensitive strains (RR =20.72; CI=95%: 2.78 -154.3).

Septic shock is considered to be an important death risk factor among patients with bacteremia [24,29]. The mortality observed by Lundberg et al. [31] among patients who developed septic shock ranged from 39% to 70%. They suggested that delay in the treatment of shock has a significant impact on mortality due to sepsis. In our study, 22/30 of patients with septic shock died. Most patients, even with septic shock, were in hospital wards, and just 9.6% were in Intensive Care Units. Patients in hospital wards may have been treated later and less aggressively, which could explain the observed outcome.

Today there are still doubts about the contribution of methicillin resistance to mortality due to infections caused by *S. aureus*. In our study, patients with MRSA bacteremia had a higher probability of dying compared with patients with MSSA bacteremia (46% and 22%, respectively, OR =3.3, CI=95%: 1.8 - 5.9). Even among those who received adequate treatment, MRSA bacteremia resulted in a higher mortality rate than MSSA bacteremia (38% and 21% respectively, $p<0.01$).

The higher mortality rate among patients with MRSA bacteremia was similar to the results of others author [32]. Romero-Vivas et al.,[11] also observed, in a logistic regression analysis, higher mortality rates among patients with bacteremia caused by methicillin resistant strains, even when considering only the patients who received appropriate treatment (OR = 3.0 CI=95%: 1.44-6.25).

Blot et al. [33] investigated outcomes in critically ill patients with *S. aureus* bacteremia. Logistic regression analysis showed that methicillin resistance and an unfavorable APACHE II score were independent risk factors for death ($p<0.0001$).

Selvey et al. [12] compared nosocomial bacteremia caused by MRSA and MSSA. They found a higher mortality rate among MRSA bacteremia patients (13.8 and 8.2, $p<0.05$).

The risk factors for acquiring MRSA may also influence the evolution of the bacteremia. We were unable to control many confounding factors observed among hospitalized patients. The higher mortality rate observed among the cases of MRSA bacteremia may reflect misclassification of cases, different populations of patients, or types of treatment provided to the patients. On the other hand, the differences could be due to specific microbiological characteristics of the strains isolated in Brazil.

The current geographical variation among the most frequently isolated clones in different locations can partially explain the differences observed in the MRSA infection history. In Brazil, the SP genotype profile, determined by pulsed field gel electrophoresis, is the most common, and it was the most prevalent isolated MRSA clone in our study (86%) [34]. This clone may have specific virulence characteristics that are different from those of other clones.

Higher mortality rates reported for infections with resistant strains have been described in Europe, mainly in the Iberian Peninsula. It has been recently found that the profile found in Brazil is similar to that of isolated strains in Portugal and Spain. This fact reinforces the possibility of differential virulence among the several MRSA strains, and perhaps, that the clone, peculiar to Brazil, Spain and Portugal is more virulent [29,35-37]

Predictive model of mortality. The estimates of death probabilities calculated for each subgroup of patients. suggest a great impact of septic shock on the course of the *S. aureus* bacteremia. The probability of dying is extremely high when shock occurs, except when the catheter is the source. Comparing patients with the same source of infection, and the same clinical presentation, the MRSA bacteremia patients have a higher probability of dying than those with MSSA bacteraemia (10% vs. 4% and 90% vs 76%, respectively).

Conclusion

An increase in MRSA community- acquired bacteraemia was observed when the two periods

(1991-1992 and 1995-1996) were compared. One can estimate the probability of each patient dying by considering the variables simultaneously, these being source of infection, occurrence of septic shock, and susceptibility to methicillin.

Acknowledgements

We are very grateful to Dr. Stephen Walters for his suggestions on the paper.

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