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ARTICLE

Predictors of mortality in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia: the role of empiric antibiotic therapy

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Abstract The objective of this study was to evaluate prognostic factors and the influence of different empiric antibiotic therapies on outcome and mortality in a cohort of 100 inpatients with bacteraemia (84 cases nosocomial) caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Patients were investigated by means of a standard protocol at a 944-bed hospital in the years 2000–2004. Empiric antibiotic therapies included vancomycin (n=49), teicoplanin (n=20), linezolid (n=17), other antibiotics active in vitro (n=7), and inactive antibiotics (n=7). Overall mortality was 40% (12% among linezolid-treated patients; 46.3% among glycopeptide-treated patients). In bivariate analyses, the following factors were statistically associated with higher mortality: rapidly fatal underlying disease, altered mental status, metabolic acidosis, and acute severe clinical condition at the onset of bacteraemia; development of complications (septic shock, renal failure, and disseminated intravascular coagulopathy); empiric monotherapy with glycopeptides (vs combination therapy with an aminoglycoside); and inadequate empiric treatment. Empiric therapy with linezolid was associated with lower mortality. In multivariate analysis, risk factors associated with higher mortality included acute severity of illness (OR 7.49; 95%CI 1.19–25.3) and altered mental status (OR 4.83; 95%CI 1.22–19.15) at onset, complications (OR 3.42; 95%CI 1.02–17.46), and inappropriate empiric treatment (OR 7.6; 95%CI 1.87–31.14). In multivariate analysis limited to patients who received empiric therapy with either linezolid (n=17) or glycopeptides (n=69), linezolid was associated with greater rates of survival (OR 7.7; 95%CI 1.1–53) and microbiological eradication (OR 11.76; 95%CI 1.46–90.9) but not with fewer complications (OR 0.71; 95%CI 0.16–3.25). In conclusion, the main prognostic factors associated with mortality in patients with MRSA bacteraemia are complications, acute severe clinical condition at onset, and inappropriate empiric treatment. Empiric therapy with linezolid was associated with greater survival and more successful microbiological eradication but did not reduce complications.

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Introduction

Bacteraemia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most challenging problems within the field of infectious diseases, not only because of its increased frequency in recent years but also because of its refractoriness to treatment and its associated high mortality rates [1]. Since 1960, when resistance of *S. aureus* to methicillin was first reported, a notorious and continually increasing increment in the percentage of MRSA isolations, both from the community and from hospitals, has been observed. At present, the percentage of *S. aureus* bacteraemia cases due to MRSA is about 31% in Spanish hospitals, a figure that can increase up to 44% when hospitalised ICU patients are analysed [2, 3]. Mortality related to MRSA bacteraemia can be as high as 60% [4], and the duration of hospitalisation has been reported to be longer in patients with MRSA infections.

Furthermore, as the prevalence of MRSA infections increases, so does the magnitude of the therapeutic problem, since effective treatment options become fewer and fewer. Although the influence of antibiotic treatment during the evolution of MRSA bacteraemia is not well defined [1, 4], some studies have indicated that early administration of an appropriate antibiotic is associated with a better prognosis [5–7].

The aim of the present prospective, observational study was to track the epidemiological and clinical patterns in patients with MRSA bacteraemia in order to detect prognostic factors significantly associated with mortality and to assess the influence of the initial empiric treatment on the evolution of bacteremia.

Patients and methods

Hospital characteristics

The Hospital Universitario Virgen de la Arrixaca in Murcia has 944 beds, 611 of which belong to the general hospital. Its area of care encompasses a population of approximately 450,000 individuals. It is, in addition, a reference hospital in certain specialties such as neurosurgery, burn trauma, cardiovascular surgery, and organ transplantation.

Study period

One hundred inpatients were studied consecutively in a prospective and observational manner. All episodes of bloodstream infection due to methicillin-resistant *S. aureus* bacteraemia during the period from January 2000 to December 2004 were included.

Patients

Data for each patient were collected according to a previously established protocol. Patients admitted to either the paediatric unit or the maternal unit were excluded.

Microbiological investigations

Each episode of possible bacteraemia was evaluated according to the routine protocol followed at our institute. Two blood samples, collected about 15–20 min apart, were drawn. Samples were processed using common microbiological techniques. *S. aureus* was identified by the formation of characteristic colonies of gram-positive cocci on blood agar plates after a 24-h incubation, as well as by positive catalase and positive coagulase in plasma. Sensitivity to cloxacillin was evaluated with the agar dilution reference test, using oxacillin discs of 1 μg/ml.

Definitions and classification of bacteraemia

Bacteraemia was defined as the presence of the microorganism (*S. aureus*) in one or more blood cultures and the existence of clinical signs of infection (temperature >38°C and shivering). Infection was considered to be of community acquisition whenever *S. aureus* was isolated within the first 72 h of hospital admission, provided the patient had not been hospitalised in the previous month. Bacteraemia was considered to be of nosocomial acquisition when a positive blood culture was obtained after the first 72 h of hospitalisation in patients who showed no symptoms or signs of infection at the time of hospital admission. Likewise, when a positive culture was obtained within the first 72 h of hospitalisation in a patient who had been hospitalised during the previous month, infection was understood to be of nosocomial acquisition.

The clinical services to which patients were admitted can be classified into three groups: (a) medical services, comprising internal medicine and medical specialties; (b) high-risk services, including the intensive care unit, the burns unit, haematology, and oncology; and (c) surgical services, comprising general surgery and other surgical specialties.

Bacteraemia was classified using the guidelines of the Centers for Disease Control and Prevention [8]. A focal infection was considered the primary source of bacteraemia when, prior to the onset of bacteraemia, focal symptoms and signs were present or *S. aureus* was isolated from the focus of infection. If bacteraemia could not be associated with a primary focus or if it existed before such a focus appeared, it was considered to be either bacteraemia without a clear focus or primary bacteraemia. An infection was considered to be catheter associated when inflamma-

tory signs were observed at the catheter insertion point or when culture of the catheter tip was positive for *S. aureus*. Pneumonia was diagnosed in those patients with clinical manifestations of lower respiratory tract infection and with radiological evidence of lung infiltrates that could not be explained by any other cause, with or without *S. aureus* isolation in the samples collected by bronchoscopy. The patient was considered to have a urinary tract infection when *S. aureus* was isolated in pure culture in urine, in a quantity exceeding 100,000 colonies/ml.

Patient assessment

Patients were assessed with regard to the prognosis of their underlying disease, according to the criteria of McCabe and Jackson [9]. Their condition was then classified as "rapidly fatal" when death was expected to take place in days or weeks, "ultimately fatal" when death was likely to take place in some months or years, and "nonfatal" when death was not predictable. The severity of the patient's condition at presentation was assessed according to Winston et al. [10], as follows: "critical" when the patient's clinical condition was rapidly deteriorating and the probability of death during the first 24 h was high; "poor" when the clinical condition was deteriorating and death was probable but not imminent; "fair" when the clinical condition was deteriorating but death was not probable; and "good" when the clinical situation did not change during the first 24 h and death was not probable.

Prognostic factors

In order to identify prognostic factors, all clinical and epidemiological characteristics, all complications, and the type of antibiotic treatment were examined in relation to the final evolution of patients, with "recovery" understood to be the disappearance of all active signs and symptoms of infection. Likewise, a "relapse" was defined as the reappearance of signs and symptoms and the isolation of the same microorganism from blood during the first month after an improvement or initial recovery.

When the physician considered the death of the patient to be related to the infection, it was designated as "death related to bacteraemia." If the physician considered that death had occurred after recovery from the infection and was related to the underlying disease or other medical or surgical complications, it was classified as "death not related to bacteraemia."

Treatment

The antibiotic used was considered active when, according to microbiological data, it presented in vitro activity against the *S. aureus* strain isolated. We considered the initial empiric antibiotic to be appropriate when it exhibited in vitro activity against the corresponding *S. aureus* strain isolated, when it was used in a correct dosage, and when its use was not modified after the antibiogram results were obtained. The efficacy of the treatment was considered to be assessable after at least 5 days of administration. Serum levels of vancomycin were not monitored, as these determinations were not available in our hospital at that time for standard clinical care. Vancomycin was administered noncontinuously, i.e. never as a 24-h continuous infusion.

Controls and monitoring

All patients underwent clinical, radiological, microbiological, and laboratory (haemogram, erythrocyte sedimentation rate, biochemistry, and coagulation) examinations during the treatment, at the end of treatment, and 1 month after discharge from the hospital.

Leucocytosis was defined as the presence of more than 12,000 leucocytes/mm^3, leucopenia as less than 1,500 leucocytes/mm^3, and neutropenia as less than 500 leucocytes/mm^3. Likewise, thrombopenia was defined as a platelet count of less than 125,000 cells/μl and thrombocytosis as more than 300,000 platelets/μl. The erythrocyte sedimentation rate was considered high when it exceeded 35 mm/h.

Statistical analyses

Data were analysed using the statistics program SPSS 12.0 (SPSS Software, Chicago, IL, USA). A descriptive study was performed for the clinical and epidemiological characteristics as well as for the prognostic factors of patients with MRSA bacteraemia. The relation or association between pairs of qualitative variables was determined through analyses of contingency tables by means of Pearson's chi-squared test, complemented by an analysis of residues with the aim of determining the directional dependence. In the case of quantitative variables, means have been compared using Student's t test. The difference was considered significant at $p<0.05$. Bivariate and multivariate analyses of the cohort of patients with MRSA bacteraemia were performed in order to detect those factors related to a higher mortality rate. The multivariate analysis comprised a nonconditioned logistic regression, where the death of the patient was taken as the dependent variable and all those variables statistically associated with a higher mortality rate in the bivariate analysis were included as independent variables. We then paid special attention to the influence of the initial empiric antibiotic on patient outcome, comparing glycopeptide-treated patients with linezolid-treated patients.

Results

One hundred patients with MRSA bacteraemia were included in the study, 84 of whom had bacteraemia of nosocomial acquisition. The average period of hospitalisation prior to the development of bacteraemia was 17.8 days (range, 0–150 days). Bacteraemia was monomicrobial in 69% of the patients and polymicrobial in 31%: *Pseudomonas aeruginosa* was isolated in 15 cases, *Escherichia coli* in 10 cases, *Acinetobacter baumannii* in three cases, *Enterobacter cloacae* in two cases, and *Klebsiella pneumoniae* in one case. Epidemiological and clinical characteristics of the patients are summarised in Tables 1 and 2. Ninety-six percent of the patients had an underlying disease (diabetes mellitus in 45%). Predisposing factors for MRSA bacteraemia were present in 93% of the patients, the following being most frequent: presence of vascular catheters (82%), previous use of antibiotics (79%; beta-lactam agents in 57%), presence of urethral catheter (45%), and previous surgery (40%) (Table 1). There was no primary focus evident in 28% of the patients. In those patients in whom a primary focus was found, the presence of venous catheters (40%) and the existence of cutaneous infections (27%) were most common. The importance of the patient's condition at clinical presentation was remarkable, as 59% of patients were assessed as poor or critical upon presentation; and 69% developed complications. Global mortality was 40% (Table 2).

Table 3 summarises the variables that were statistically associated with a higher mortality rate in the bivariate study. In the multivariate analysis, which included all variables related to mortality in the bivariate analysis, four variables were significantly associated with therapeutic failure: an initial clinical condition of critical or poor (OR 5.49; 95%CI 1.19–25.3), an altered level of consciousness at the onset of bacteraemia (OR 4.83; 95%CI 1.22–19.15), the development of complications (OR 3.42; 95%CI 1.02–17.46), and the use of an inappropriate empiric antibiotic (OR 7.6; 95%CI 1.87–31.14) (Table 3).

A subanalysis of patients who received treatment with glycopeptides (n=69) or linezolid (n=17) was performed, and no statistically significant differences were found between the clinical characteristics of the groups (Table 4). Treatment with glycopeptides was significantly associated with higher mortality (46.4% vs 11.8% in linezolid group), with microbiological persistence of bacteraemia (33.3% vs 11.8% in the linezolid group), and with a longer hospitalisation (49 vs 29 days). When the multivariate analysis was performed for this subgroup of patients, empiric treatment with linezolid was associated with higher survival rates (OR 7.7; 95%CI 1.1–53) and a greater rate of microbiological eradication (OR 11.76; 95%CI 1.46–90.9). However, it was not associated with a lower rate of complications (OR 0.71; 95%CI 0.16–3.25).

Table 1 Epidemiological characteristics of the 100 study patients with MRSA bacteraemia

Variable	No. (%)
Sex, no. (%)	
Male	64 (64)
Female	36 (36)
Mean age in years (range)	60 (14–95)
Hospital service, no. (%)	
Medical	51 (51)
Surgical	16 (16)
High risk	33 (33)
Bacteraemia acquisition, no. (%)	
Community	16 (16)
Nosocomial	84 (84)
McCabe score, no. (%)	
I	17 (17)
II	52 (52)
III	31 (31)
Underlying disease, no. (%)	
No	4 (4)
Yes	96 (96)
Diabetes mellitus	45 (45)
Cardiopathy	35 (35)
Chronic renal failure	24 (24)
COPD	19 (19)
Hepatopathy	15 (15)
Neoplasia	16 (16)
Cerebrovascular accident	13 (13)
Predisposing factors, no. (%)	
No	7 (7)
Yes	93 (93)
Vascular catheter	82 (82)
Urethral catheter	45 (45)
Immunosuppression	43 (43)
Previous surgery	40 (40)
Blood transfusion	39 (39)
Trauma	28 (28)
Dialysis	16 (16)
Orotracheal intubation	32 (32)
Decubitus ulcer	31 (31)
ICU stay	33 (33)
Pacemaker	14 (14)
Tracheostomy	11 (11)
Neutropenia	6 (6)
Previous use of antibiotics, no. (%)	
Yes	79 (79)
No	21 (21)

COPD chronic obstructive pulmonary disease

Discussion

Bacteraemia caused by MRSA is a severe infection, usually acquired nosocomially, that occurs in patients with a chronic underlying disease. It is frequently associated with in-dwelling catheters and the previous use of wide-

Table 2 Clinical characteristics of the 100 study patients with MRSA bacteraemia

Variable	No. (%)
Type of bacteraemia	
Monomicrobial	69 (69)
Polymicrobial	31 (31)
Clinical/circulatory manifestations	
ASP <90 mmHg	18 (18)
Altered level of consciousness	40 (40)
Initial clinical condition (Winston et al. [10])	
Critical	18 (18)
Poor	41 (41)
Fair	37 (37)
Good	4 (4)
Primary focus of bacteraemia	
Unclear	28 (28)
Cutaneous	27 (27)
Venous catheter	40 (40)
Other (respiratory and urinary)	5 (5)
Development of complications	
No	31 (31)
Yes[a]	69 (69)
Septic shock	53 (53)
Acute renal failure	47 (47)
Respiratory distress	15 (15)
Disseminated intravascular coagulopathy	10 (10)
Endocarditis	13 (13)
Analytical alterations	
Leucocytosis >12,000/μl	77 (77)
Leucopenia <3,000/μl	10 (10)
Platelet count <125,000/μl	21 (21)
ESR >35 mm/h	83 (83)
pH < 7.20	45 (45)
Empiric antibiotic treatment	
Monotherapy	75 (75)
Combination therapy	25 (25)
Empiric antibiotic treatment	
Appropriate	50 (50)
Not appropriate	50 (50)
Evolution	
Recovery	48 (48)
Relapse	12 (12)
Death	40 (40)

ASP arterial systolic blood pressure, *ESR* erythrocyte sedimentation rate

[a] Some patients presented multiple complications simultaneously

spectrum beta-lactam antibiotics. From a clinical point of view, the frequency of diabetes mellitus as an underlying disease is remarkable. Our clinical and epidemiological findings are similar to those presented in the literature [11], although we found a higher prevalence of polymicrobial bacteraemia (31%).

The most significant clinical/therapeutic finding of our study is that certain prognostic factors were associated with higher mortality in patients with MRSA bacteraemia. As expected, the best predictors of mortality were the severity of the patient's clinical condition at the onset of the disease, the development of complications, and an inadequate initial empiric treatment [4–7, 11, 12]. Other important findings are the higher rates of survival and microbiological eradication observed with linezolid treatment compared with glycopeptide treatment. However, our study must be interpreted in light of its limitations, particularly its nonrandomised design. Another limitation is that vancomycin serum levels were not monitored during treatment, even though such lack of monitoring is standard practice in many hospitals, particularly when antibiotic serum levels cannot be determined. In our patients, vancomycin was administered in a noncontinuous way. Previous studies [13] suggest that the continuous infusion of vancomycin, although still controversial, is associated with a better outcome.

In recent years, there have been reports of therapeutic failures in patients with MRSA bacteraemia caused by strains for which the MIC of vancomycin was >0.5 mg/l. Thus, in a recent study, the rate of recovery in patients with bacteraemia caused by MRSA for which the vancomycin MIC was <0.5 mg/l was about 55.6%, yet it fell to 9.5% when the MIC was 1–2 mg/l [14]. On the other hand, the lower and slower bactericidal activity of vancomycin against MRSA is well known [15]. Recently, cases of patients with serious infections caused by MRSA strains that exhibit a heterogeneous pattern of intermediate resistance to vancomycin have been published. Although the frequency of such strains is variable, depending on the geographical area [16], their prevalence has certainly increased, probably due to the considerable use of vancomycin over a period of many years. Therefore, the development of agents with anti-MRSA activity and with better pharmacodynamic properties and better in vivo activity than glycopeptides is urgent.

Linezolid appears to be a promising antibiotic that has already demonstrated its superiority over glycopeptides in patients with ventilator-associated nosocomial pneumonia caused by MRSA [17]. In our study, as well as in other series of patients with MRSA infections (pneumonia and postsurgical or soft tissue infections) [18, 19], treatment with linezolid was associated with a higher survival rate and greater microbiological eradication than treatment with glycopeptides. This may be related to linezolid's greater in vitro activity, its better pharmacokinetic properties, and its modulatory role in the expression of virulence factors in MRSA strains [20]. Furthermore, due to its high oral bioavailability, which enables the administration of sequential treatment, linezolid offers the advantage of an earlier hospital discharge.

Additional randomised studies that assess the therapeutic effects of different empiric treatments in patients with

Table 3 Prognostic factors significantly associated with mortality in patients with MRSA bacteraemia (bivariate and multivariate analysis)

Prognostic factor	*p* value	OR (95%CI)
Altered level of consciousness	<0.0005	4.83 (1.22–19.15)
Metabolic acidosis	<0.0005	NS
Rapidly fatal underlying disease (McCabe I)	0.001	NS
Antecedents of previous severe infections (sepsis)	<0.045	NS
Severe clinical condition at onset (Winston et al. [10])	<0.0005	5.49 (1.19–25.3)
Development of complications	<0.0005	3.42 (1.02–17.46)
Septic shock	<0.0005	–
Acute renal failure	<0.0005	–
Disseminated intravascular coagulopathy	0.003	–
Inadequate initial empiric treatment	<0.0005	7.6 (1.87–31.14)
Empiric treatment with glycopeptide monotherapy	<0.039	NS
Empiric treatment with vancomycin	<0.0005	NS
Empiric treatment with linezolid[a]	<0.0005	NS

NS nonsignificant
[a] Protective factor, related to lower mortality

MRSA infections are warranted. As such studies are performed over the next few years, it is possible that the therapeutic recommendations for patients with risk factors for MRSA infections will change. Improved therapeutic options will help reduce not only the economic cost of the higher morbidity (longer hospitalisations) and mortality associated with suboptimal treatments, but also the resultant human costs.

Table 4 Epidemiological and clinical characteristics of patients according to treatment group

Variable	Glycopeptide group (*n*=69)	Linezolid group (*n*=17)	*p* value[a]
Sex, no. (%)			
Male	43 (62.3)	12 (70.6)	NS
Female	26 (37.7)	5 (29.4)	NS
Mean age in years (range)	58 (14–90)	66 (15–95)	NS
Hospital service, no. (%)			
Medical	34 (49.3)	10 (58.8)	NS
Surgical	23 (33.3)	5 (29.4)	NS
High-risk	12 (17.4)	2 (11.8)	NS
Bacteraemia acquisition, no. (%)			
Community	10 (14.5)	2 (11.8)	NS
Nosocomial	59 (85.5)	15 (88.2)	NS
McCabe score, no. (%)			
I	15 (21.7)	3 (17.6)	NS
II	33 (47.8)	8 (47)	NS
III	21 (30.4)	6 (35.3)	NS
Underlying disease, no. (%)			
No	3 (4.3)	0	NS
Yes	66 (95.7)	17 (100)	NS
Predisposing factors, no. (%)			
No	1 (1.4)	6 (35.3)	<0.005
Yes	68 (98.5)	11 (64.7)	
Initial clinical condition (Winston et al. [10]), no. (%)			
Critical	13 (18.8)	3 (17.6)	NS
Poor	32 (46.4)	7 (41.2)	NS
Fair	20 (29)	7 (41.2)	NS
Good	4 (5.8)	0	NS
Development of complications, no. (%)			
No	19 (27.5)	10 (58.8)	<0.015
Yes[b]	50 (72.5)	7 (41.2)	<0.015
Microbiological persistence, no. (%)	23 (33.3)	2 (11.8)	<0.001
Death, no. (%)	32 (46.9)	2 (11.8)	<0.001
Mean duration of hospitalisation in days (±SD)	49±41.6	29±18.7	<0.04

[a] Glycopeptide-treated vs. linezolid-treated patients
[b] Some patients presented multiple complications simultaneously

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