

Risk factors and predictors of mortality of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in HIV-infected patients

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Objectives: To define the incidence, risk factors and short-term predictors of mortality of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in HIV-infected patients.

Patients and methods: All HIV-infected subjects with *S. aureus* bacteraemia were consecutively enrolled in a case–control study between January 1, 1991 and December 31, 2000 and prospectively followed up.

Results: In the study period, 129 of 419 (31%) HIV-infected patients with bacteraemia had a diagnosis of *S. aureus* bacteraemia. The comparative analysis of incidence of *S. aureus* bacteraemia in the period 1991–96 and 1997–2000 showed a significant decrease ($P < 0.001$). The same trend was observed for MRSA bacteraemia ($P = 0.002$). The analysis of antimicrobial resistance showed that among 129 *S. aureus* strains, 88 (68%) were methicillin susceptible and 41 (32%) were methicillin resistant. The majority of MRSA bacteraemia was hospital acquired (78%). Previous administration of β -lactams ($P < 0.001$), multiple previous hospital admissions ($P < 0.001$) and low numbers of CD4+ peripheral cells ($P < 0.001$) were found to be independent risk factors of methicillin resistance at multivariate analysis. The mortality rate was 34% in the cases and 11% in the controls ($P = 0.002$). Multivariate analysis indicated that a high Acute Physiology and Chronic Health Evaluation (APACHE) III score ($P < 0.001$) and high HIV viraemia ($P = 0.02$), but not methicillin resistance, predicted an increased risk of death in patients with *S. aureus* bacteraemia.

Conclusion: Individual exposure to β -lactams, in association with a history of multiple hospitalizations and low CD4+ cell number, plays a pivotal role as a risk factor for the development of methicillin resistance in HIV-infected patients. Methicillin resistance does not influence the outcome of *S. aureus* bacteraemia when included in a multivariate analysis.

Introduction

Staphylococcus aureus is not only responsible for considerable morbidity and mortality in HIV-infected patients but is also the more commonly isolated agent of bacteraemia in these patients.^{1–8} Several immunological HIV-related alterations and epidemiological risk factors predispose patients with AIDS to bacteraemia. In the past years a favourable effect of highly active antiretroviral therapy (HAART) in reducing the incidence of bacteraemia as well as of several

other opportunistic diseases in HIV-infected subjects has been reported.^{9,10}

Methicillin-resistant *S. aureus* (MRSA) was first described in 1961, and since then it has become a worldwide problem in many areas of medical care, and continuous efforts to control MRSA infections may be justified on an epidemiological, financial and clinical basis.^{11,12} Several studies have indicated that MRSA infections do not influence outcome when major confounders such as age, length of hospital stay, comorbidity, general clinical condition and appropriate treatment are

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considered.^{13–17} In contrast, other studies have suggested that methicillin resistance is independently associated with mortality due to *S. aureus* infections.^{18,19}

Despite several reports describing the incidence and risk factors of bacteraemia in HIV-infected patients, the clinical and epidemiological findings of MRSA bacteraemia have not been, to the best of our knowledge, extensively described.^{20–22} In an attempt to better define the clinical impact of staphylococcal methicillin resistance in HIV-infected subjects, we performed a prospective case–control study investigating the incidence, risk factors and short-term predictors of mortality of MRSA bacteraemia.

Materials and methods

Study setting

The Catholic University hospital is a 1900-bed tertiary care centre with ~65 000 patient admissions each year. The patients came more frequently from central and southern Italy, and to a lesser extent, from northern Italy. The hospital has a 60-bed unit for the admission of HIV-infected patients and a day-hospital for their outpatient care.

Study design

This case–control study used prospectively collected cohort data of bacteraemia in HIV-infected patients.^{4,7,10} In particular, between January 1, 1991 and December 31, 2000, all positive blood cultures processed by the microbiology laboratory were identified through a review of the laboratory computer summary report. All HIV-infected subjects aged >18 years with *S. aureus* bacteraemia were consecutively enrolled in the study and prospectively followed up. The definition of bacteraemia required *S. aureus* blood isolation to be obtained in the presence of fever (body temperature $\geq 38^{\circ}\text{C}$) not attributable to other causes.

In particular, patients who had bacteraemia caused by MRSA strains were designated as cases and patients with methicillin-susceptible *S. aureus* (MSSA) strains were designated as controls.

Patients in whom *S. aureus* was isolated within 48 h from admission were assumed to have a community-acquired infection.

Patients with polymicrobial bacteraemia were excluded from the study.

Parameters evaluated

The following data were obtained: age, gender, HIV risk behaviour, stage of HIV infection, previous manifestations of HIV infection, date of AIDS-defining condition, concurrent opportunistic infections, number of hospital admissions in the previous year, nutritional status (expressed by body weight

and albumin level), previous bacterial infections, corticosteroid therapy, presence and type of central venous catheter (CVC) or of other catheters, surgery, endoscopy, alcoholism, cirrhosis, diabetes, neoplastic disease, chronic renal failure, previous antimicrobial therapy and other medications (if the drug was taken for at least seven of the 30 days preceding the onset of infection), bacteraemia therapy, sensitivity test to antibiotic, vital signs, outcome and cause of death (listed by the attending physicians) and total length of hospitalization. The risk factors were recorded only if present in the 30 days before the development of infection. The revised Acute Physiology and Chronic Health Evaluation (APACHE) was assigned by the APACHE III system.²³

Data collected from the initial laboratory records included: numbers of circulating CD4+ cells (/mm³) and peripheral polymorphonuclear (PMN) cells (/mm³). Data collected also included plasma HIV RNA viraemia (copies/mL), as from September 1996.

Identification of organisms and susceptibility testing

Species identification was performed by the API test ID 32 STAPH (bioMérieux, Marcy l'Étoile, France). Isolates were tested by the broth microdilution method described by the National Committee for Clinical Laboratory Standards (NCCLS) with cation-adjusted Mueller–Hinton broth (Difco Laboratories, Detroit, MI, USA).^{24,25} The antimicrobial agents tested included: ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin, penicillin, teicoplanin, trimethoprim–sulfamethoxazole and vancomycin. In addition, MICs of teicoplanin and vancomycin were determined for each isolate by the Etest (AB Biodisk, Solna, Sweden) in accordance with the manufacturer's instructions. Susceptibility tests were performed by the use of a bacterial inoculum whose turbidity was equivalent to that of a 0.5 McFarland turbidity standard. The suspension was used to inoculate Mueller–Hinton agar plates by swabbing them with a cotton swab. The plates were incubated for 18 h in air at 35°C. The MICs were interpreted as the point of intersection of the inhibition ellipse with the Etest strip edge. The quality control strain of *S. aureus* American Type Culture Collection (ATCC) 29213 and *S. aureus* ATCC 43300 were included with each run. The interpretation of results was performed according to recommendations of the NCCLS.²⁵

Analysis

Quantitative variables were tested for normal distribution and compared by means of Student's two-tailed unpaired *t*-test. Differences in group proportions were assessed using χ^2 and Fisher's exact tests. Potential risk factors for methicillin resistance development were analysed by univariate methods to identify differences in patients who developed and who did not develop methicillin-resistant staphylococcal bacteraemia.

Table 1. Demographic data of patients with MRSA bacteraemia (cases) and MSSA bacteraemia (controls)

	MRSA cases [n = 41 (%)]	MSSA controls [n = 88 (%)]	<i>P</i> ^a	OR (95% CI)
Sex, males/females	25/16	60/28	0.42	0.72 (0.33–1.57)
Mean age ± S.D. (years)	36 ± 9	34 ± 8	0.14	–
HIV risk behaviour				
intravenous drug abuse	32 (78)	45 (51)	0.003	3.39 (1.45–7.94)
homosexual contact	5 (12)	21 (24)	0.12	0.44 (0.15–1.27)
heterosexual contact	4 (10)	22 (25)	0.13	3.56 (0.62–20.41)
Stage of HIV infection				
A	2 (5)	14 (16)	0.07	0.27 (0.05–1.25)
B	4 (10)	21 (24)	0.06	0.34 (0.11–1.08)
C	35 (85)	53 (60)	0.004	3.85 (1.46–10.11)
CD4+ cells/mm ³ (mean ± S.D.)	58 ± 87	228 ± 197	<0.001	–
HIV-RNA ^b copies/mL × 10 ³ (mean ± S.D.)	175 500 ± 204 026	73 000 ± 15 044	0.002	–
PMN cells (mean ± S.D.)	3400 ± 3300	3500 ± 3100	0.8	–

^aSignificance of finding by comparison between cases and controls (two-tailed *P* levels, χ^2 or Fisher's exact test and Student's *t*-test).

^bAvailable for patients from September 1996.

The 95% test-based confidence intervals (95% CI) were used to determine the statistical significance of the odds ratio (OR). Stepwise logistic regression models were used for each factor to adjust for the effects of confounding variables. Two-tailed tests of significance at the *P* ≤ 0.05 level were used to determine statistical significance. Kaplan–Meyer survival curves were used to analyse mortality trends and the results were compared by log-rank analysis. Statistical analysis was performed using the software program Intercooled Stata 6.0 for Windows 98 (Stata Corporation, College Station, TX, USA).

Results

In the study period a diagnosis of bacteraemia was achieved in 419 of 4674 (9%) HIV-infected patients admitted to our ward. In 129 subjects (31%) bacteraemia was due to *S. aureus*.

The patients ranged in age from 22 to 63 years (mean ± S.D., 34 ± 8) and 85 (66%) of them were male. We observed 70 (54%) episodes of community-acquired and 59 (46%) episodes of hospital-acquired *S. aureus* bacteraemia. Table 1 summarizes the characteristics of HIV patients with MRSA and MSSA bacteraemia.

The overall incidence of 129 cases of *S. aureus* bacteraemia was 2.8 episodes/100 person-years (PY). This incidence decreased from 3.7/100 PY in the period 1991–96 to 1.5/100 PY in 1997–2000 (*P* < 0.001). In the above-mentioned periods of time the incidence of MRSA bacteraemia decreased from 1.3 to 0.4 (*P* = 0.002) and the incidence of MSSA bacteraemia decreased from 2.5 to 1.1 (*P* < 0.001). It is of note that HAART became standard for most of our patients beginning in September 1996 when this therapy first became available in

Italy. The temporal trend of *S. aureus* bacteraemia is indicated in Figure 1.

Antimicrobial resistance

The analysis of antimicrobial resistance showed that 25% of *S. aureus* strains were susceptible to all tested drugs. In particular, among 129 *S. aureus* strains, 88 (68%) were methicillin susceptible and among them 39% were penicillin susceptible. Forty-one (32%) were methicillin resistant. The majority of MRSA bacteraemia was hospital acquired (78%). See Table 2 for details regarding multiple antibiotic resistance. Over the study period, none of the *S. aureus* strains was glycopeptide resistant.

Risk factor analysis

Forty-one patients with MRSA bacteraemia and 88 patients with MSSA bacteraemia have been compared. Tables 1 and 3

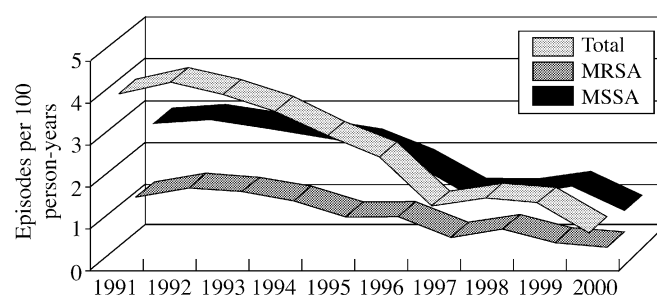


Figure 1. Temporal trend of *S. aureus* bacteraemia (MRSA and MSSA) over the study period.

Table 2. Multiple antibiotic resistance in *S. aureus* isolates causing bacteraemia

Resistance to	<i>S. aureus</i> strains (<i>n</i> = 129)					
	penicillin [<i>n</i> (%)]	methicillin [<i>n</i> (%)]	clindamycin [<i>n</i> (%)]	quinolones [<i>n</i> (%)]	macrolides [<i>n</i> (%)]	TMP-SMX [<i>n</i> (%)]
Penicillin (<i>n</i> = 94)	–	41/94 (44)	50/94 (53)	63/94 (67)	74/94 (79)	83/94 (88)
Methicillin (<i>n</i> = 41)	41/41 (100)	–	25/41 (61)	32/41 (78)	35/41 (85)	30/41 (73)
Clindamycin (<i>n</i> = 50)	50/50 (100)	25/50 (50)	–	49/50 (98)	50/50 (100)	45/50 (90)
Quinolones (<i>n</i> = 63)	63/63 (100)	32/63 (51)	49/63 (77)	–	63/63 (100)	57/63 (90)
Macrolides (<i>n</i> = 74)	74/74 (100)	35/74 (47)	50/74 (67)	62/74 (84)	–	67/74 (90)
TMP-SMX (<i>n</i> = 90)	83/90 (92)	30/90 (33)	45/90 (50)	57/90 (63)	67/90 (74)	–

TMP-SMX, trimethoprim–sulfamethoxazole.

Table 3. Univariate analysis of risk factors for MRSA bacteraemia (cases) and MSSA bacteraemia (controls)

	MRSA [<i>n</i> = 41 (%)]	MSSA [<i>n</i> = 88 (%)]	<i>P</i> ^a	OR (95% CI)
Mean APACHE III score ± S.D.	13.8 ± 7.8	7.2 ± 4.3	<0.001	–
Nosocomial episodes	32 (78)	27 (31)	<0.001	8.03 (3.37–19.12)
Previous pneumonia	6 (15)	15 (17)	0.72	0.83 (0.29–2.33)
Central venous catheterization	9 (22)	14 (16)	0.4	1.48 (0.53–3.98)
Total parenteral nutrition	8 (19)	12 (14)	0.4	1.53 (0.57–4.10)
Previous bacterial infections	23 (56)	26 (29)	0.004	3.04 (1.41–6.56)
Previous antibiotic therapy				
multiple treatment	22 (54)	27 (31)	0.01	2.61 (1.21–5.61)
β-lactams	20 (49)	20 (23)	0.002	3.23 (1.47–7.13)
PCP prophylaxis with TMP-SMX	21 (51)	51 (58)	0.47	0.76 (0.36–1.60)
Previous no. of hospitalizations				
one	12	50	–	
two	10	21	–	
three	12	12	–	
four	5	1	<0.001 ^b	

^aSignificance of finding by comparison between cases and controls (two-tailed *P* levels, χ^2 or Fisher's exact test and Student's *t*-test).

^b χ^2 for trend.

TMP-SMX, trimethoprim–sulfamethoxazole.

summarize the predisposing factors and the clinical conditions among the above-mentioned patients.

Comparison of the cases and controls by univariate analysis indicated remarkable differences in the distribution of known and potential risk factors (see Table 3). Previous administration of β-lactams, intravenous drug abuse (IVDA), multiple previous hospital admissions, nosocomial infection, a high APACHE III score, previous bacterial infections, low (<200/mm³) CD4+ cells and high HIV viraemia were significantly different in the two groups of patients. Moreover, isolation of macrolide- (85% versus 44%; OR = 7.32; 95% CI = 2.79–19.19; *P* < 0.001), clindamycin- (60% versus 28%; OR = 3.93; 95% CI = 1.80–8.58; *P* = 0.004) and quinolone-resistant (78% versus 35%; OR = 6.53; 95% CI = 2.76–15.43;

P < 0.001) strains was significantly more common among the cases than the controls.

The clinical conditions and previous therapeutic regimens most strongly (*P* < 0.2 at univariate analysis) associated with the development of methicillin resistance were further analysed by logistic regression. Previous administration of β-lactams, multiple previous hospital admissions and low CD4+ peripheral cells were found to be independent predictors of methicillin resistance (see Table 4). Stepwise entry of gender and age into the model yielded similar results.

Outcome

The mean (±S.D.) length of total hospitalization was 49 ± 27 for the cases versus 24 ± 16 for the controls (*P* < 0.001). All

Table 4. Logistic regression analysis of predictors for MRSA bacteraemia

Variables	OR	S.E.M.	P value	95% CI
Previous β -lactam use	43.035	40.921	<0.001	6.674–277.477
No. of previous hospitalizations	10.673	5.680	<0.001	3.760–30.290
Low CD4+ cell number	16.731	13.131	<0.001	3.593–77.908

patients received antibiotic therapy that was initially established according to the most likely aetiological agent and later modified, if necessary, when the *in vitro* susceptibility of the *Staphylococcus* became known. In particular, clindamycin or glycopeptides (i.e. teicoplanin or vancomycin) were used to treat MRSA bacteraemia. The mortality rate was 34% in the cases and 11% in the controls ($P = 0.002$), and the OR for death in patients with MRSA bacteraemia was 4.04 (95% CI = 1.60–10.16). Twenty patients suffered endocarditis and nine septic shock. The cumulative 30 days survival trend after the bacteraemic episode was lower for MRSA infections although at a non-statistically significant level ($P = 0.3$).

Univariate analysis identified four prognostic indicators that were significantly associated with an unfavourable outcome of the *S. aureus* bacteraemia: (i) high APACHE III score (mean 18.62 ± 7.33 versus 7.2 ± 3.82 ; $P < 0.0001$); (ii) high HIV viraemia (mean $217\ 893 \pm 213\ 098$ versus $79\ 973 \pm 15\ 539$; $P = 0.004$); (iii) nosocomial infection (OR = 2.88; 95% CI = 1.13–7.33; $P = 0.02$); (iv) methicillin resistance (OR = 4.04; 95% CI = 1.60–10.16; $P = 0.002$). The difference between fatal and non-fatal cases was not statistically significant with respect to age, gender, HIV risk behaviour, CD4 cell number, antiretroviral therapy, risk factors for bacteraemia and antibiotic therapy. Multivariate analysis confirmed that high HIV viraemia (OR = 1.01; 95% CI = 1.00–1.10; $P = 0.02$) and high APACHE III score (OR = 1.36; 95% CI = 1.21–1.53; $P < 0.001$) predicted an increased risk of death in patients with *S. aureus* bacteraemia.

Discussion

MRSA is not only one of the most frequent causes of hospital-acquired infections but it has also recently been associated with some community-acquired infections.^{11,18,26–31} In the present study, we determined the resistance to antimicrobial agents of *S. aureus* causing bacteraemia in a large cohort of HIV-infected patients. In addition, we prospectively identified the risk factors that can favour the emergence of methicillin-resistant infections. Although previous studies have suggested some factors that influence the development of resistance, none of them has investigated and identified the risk factors and the clinical impact of MRSA bacteraemia in HIV-infected patients.

Previous European studies on MRSA indicated an incidence rate ranging from <1% to >30%.^{32,33} Our 10 year prospective study shows that 32% of the *S. aureus* isolates from the blood of HIV-infected patients are methicillin resistant. Interestingly, this incidence remained substantially unchanged (34–36%) from 1991 to 1997 but has reduced to ~20% from 1998 until now. The reduction of the methicillin resistance rate could be an indirect effect of HAART. In fact, HAART has been clearly demonstrated to increase peripheral CD4+ cell count, to decrease plasma HIV RNA viral load and also to reduce the incidence of AIDS-related illness, including bacterial infections, in several open-labelled or controlled studies.^{9,10,34,35} It is possible to hypothesize that the favourable results in terms of reduction of bacteraemia, including MRSA bacteraemia, are largely the consequence of the well known HAART-induced immune restoration. However, besides immune restoration, other cofactors could be responsible for the reduced incidence of MRSA bacteraemia in the HAART era. First, the drop in length of hospitalization reported in HAART-treated subjects and also observed in our patients, is clearly associated with the reduction in nosocomial bacteraemia, most of them caused by MRSA.³⁴ Secondly, whereas HAART causes a drop in bacterial infections, it indirectly reduces antibiotic usage and consequently the possible selection of drug-resistant microorganisms. In addition, the decreased HIV disease progression of HAART-treated HIV-infected patients reduces the incidence of opportunistic infections (including cytomegalovirus retinitis) and severe malabsorption, both conditions often requiring CVC use, another well known staphylococcal bacteraemia risk factor. Notably, we did not observe any statistically significant difference in the percentage of iv drug abuse, an important risk factor for staphylococcal bacteraemia and the most relevant modality of transmission of HIV infection in Italy, over the entire study period. This could explain why *S. aureus* was the most common aetiological agent of bacteraemia in both the pre- and post-HAART period.

None of the *S. aureus* isolates was glycopeptide resistant and, considering the recent growing alarm, the absence of glycopeptide resistance among *S. aureus* is reassuring.^{36–40} Notably, we did not isolate any glycopeptide-resistant *S. aureus* up to October 2001 (data not shown).

As regards the second objective of the study, i.e. to assess risk factors, the results of our logistic regression analysis

clearly indicate that previous antibiotic therapy with β -lactams, low CD4+ cell number and multiple hospital admissions in the previous year were independent predictors for the development of MRSA bacteraemia.

It is important to stress the association of methicillin resistance with the history of multiple hospital admissions and low CD4+ cell number, both indirect indicators of the severity of the patient's underlying disease. However, it is difficult to untangle the interaction of HIV disease severity and more frequent hospitalization with the increased risk of acquiring MRSA, since sicker patients spend more time in hospital and have an increased risk of developing nosocomial infections. In addition, other factors such as misuse or abuse of antimicrobial agents and invasive procedures with disruption of mucocutaneous barriers may all contribute to decrease a patient's resistance to exogenous bacteria and to increase the risk of antibiotic-resistant infection.^{41,42}

Regarding the association between previous β -lactam use and methicillin resistance it is possible to hypothesize that prior use of these drugs, related to the common practice of empirical β -lactam therapy in febrile HIV patients, can induce methicillin resistance. In fact, empirical use of antibiotics has often been reported to predispose to an *in vivo* selection of resistant subclones.^{41,43,44}

It is difficult to define the real incidence of community-acquired MRSA among the population of HIV-infected patients because of their periodic admission to healthcare facilities and the frequent use of antibacterial agents, including trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia prophylaxis. However, as already reported for other community-acquired MRSA isolates, we found a different pattern of antimicrobial resistance in patients with community-acquired MRSA bacteraemia, most of the MRSA isolates being susceptible to multiple antimicrobial agents (i.e. glycopeptides, clindamycin, quinolones or macrolides) and not to β -lactam antibiotics.^{28,45} A different susceptibility pattern was observed for nosocomial MRSA bacteraemia, most of the isolates being susceptible to glycopeptides only. For this reason, it is difficult to consider these MRSA strains as hospital strains that have been transferred into the community. The high rate of IVDA in the Italian HIV-infected patient population could be responsible for the diffusion of the strains of MRSA among our HIV-infected patients. In fact, MRSA have been isolated from the needles used by IVDA who reported, in high number, needle sharing.²⁹ Although MRSA has not been isolated from drugs, aerosol spread from cocaine use could be another interesting possibility.

As regards the outcome of MRSA bacteraemia, an aspect not previously studied through a prospective cohort in HIV-infected patients, we found a significant difference in mortality rate between the cases and the controls with a lower sur-

vival after bacteraemic episode (but not at a statistically significant level) for MRSA bacteraemia.

It is noteworthy that although methicillin resistance was selected as an indicator of unfavourable outcome at univariate analysis, it was not a predictor for mortality in the multivariate analysis, being more a marker of severity of HIV infection. In fact, patients who died of MRSA bacteraemia had concomitant severe HIV-related diseases (with high HIV viraemia) and a high APACHE III score. For this reason, we think that the difference in mortality is likely to reflect the difference in the nature of the underlying diseases and it is probably related to the sub-optimal response to antibiotics, as already described in non-HIV-infected patients with MRSA bacteraemia.¹³⁻¹⁷

In summary, we conclude that individual exposure to β -lactams in association with a history of multiple hospitalizations and low CD4+ cell number plays a pivotal role as a risk factor for the development of methicillin resistance in HIV-infected patients. Based on our statistical evaluation, we are also confident to stress that the antibiotic restriction policy suggested for high-risk patients to prevent and control the spread of MRSA bacteraemia should also include HIV-infected patients.^{45,46}

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