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ABSTRACT

Objectives. *Staphylococcus aureus* bacteraemia (SAB) is a frequent and deadly disease. Given the lack of randomized trial, optimal first-line antibiotic treatment is still debated. Our aim was to identify prognostic factors in SAB patients and to analyse the impact of first line antibiotics.

Methods. The VIRSTA prospective cohort study was conducted in 8 tertiary care centres in France. Consecutive incident adults in whom a blood culture drawn in participating centres grew *S. aureus* between April 2009 and October 2011 were prospectively followed for 12 weeks. Factors associated with 12-week case-fatality were identified by multivariate logistic regression.

Results. We enrolled 2091 patients and analysed survival in 1972 (median age: 67.8 years, interquartile range 55.5-78.9; females 692/1972, 35.1%). SAB was nosocomial or health-care related in 1372/1972 (69.6%) and the primary focus was unknown in 414/1972 (21.0%) of cases. Week 12 case-fatality rate was 671/1972 (34.0%). Main independent prognostic factors on multivariate analysis were: age (adjusted odds ratio [OR] by 10-year increment, 1.56; 95% confidence interval [CI], 1.44–1.69), septic shock (OR, 5.11; CI, 3.84-6.80), metastatic cancer (OR, 4.28; CI, 2.88-6.38) and unknown primary focus (OR, 2.62; CI, 2.02-3.41). In the 1538 patients with methicillin-sensitive *S. aureus* (MSSA) bacteraemia, first-line empiric antistaphylococcal penicillins (OR, 0.40; CI, 0.17-0.95) and vancomycin (OR, 0.37; CI, 0.17-0.83), alone or combined with an aminoglycoside, were associated with better outcome compared to other antibiotics.

Conclusions. There are few modifiable prognostic factors for SAB. Initiating empiric antibiotics with antistaphylococcal penicillins or vancomycin may be associated with better outcome in MSSA bacteraemia.

FULL TEXT

INTRODUCTION

Staphylococcus aureus bacteraemia (SAB) is a frequent infectious disease worldwide, especially in healthcare settings; it is even a suspected negative consequence of medical progress [1-3]. Annual incidences range from approximately 10 to 40 per 100 000 persons [4, 5]. Recent reports indicate an impact of patient- or population-level measures [6].

Case-fatality rates dropped during the 20th century [7] but most recent studies still report 12 weeks case-fatality rates ranging from 18% to 32% [8, 9], especially for community-acquired SAB [5, 10]. Many prognostic factors associated with mortality have been identified [8-17] and have been reviewed in detail [7]. Advanced age and sepsis are the most consistent factors whereas comorbidities, setting of acquisition and treatment (e.g. empirical and definitive antibiotics) are subject to debate.

Adequate treatment requires SAB source control, appropriate intravenous antibiotics and, for some patients, surgery and intensive care, but large areas of uncertainty remain concerning clinical management [18]. No randomized controlled trial has directly evaluated the relative performance of most frequently used empirical antibiotics, like large-spectrum beta-lactams, specific antistaphylococcal penicillins, glycopeptides and aminoglycosides [3].

Our aim was to identify prognostic factors in a large prospective cohort of SAB patients and to analyse the impact of first line antibiotics on case-fatality.

PATIENTS AND METHODS

Study setting. The observational prospective cohort study VIRSTA was conducted in 8 tertiary care centres in France, the university hospitals of Besançon, Dijon, Lyon, Montpellier, Nancy, Nîmes, Paris (Bichat-Claude Bernard) and Rennes. *Staphylococcus aureus* endocarditis-specific analyses were described elsewhere [19-21]. Standardized investigation of all cases was encouraged (e.g. follow-up blood cultures and echocardiography) but was not mandatory.

Case identification. Consecutive patients were included if they had (i) at least one positive blood culture specimen for *S. aureus* (ii) between April 2009 and October 2011 in a participating hospital. Bacteriology laboratories identified incident patients and notified the local research team composed of research assistants, bacteriologists, infectious disease specialists and cardiologists. Exclusion criteria were (i) positive catheter specimen without SAB, defined as single positive blood cultures in vascular access device specimens with negative peripheral blood culture and (ii) age < 18 years, pregnancy and adults under guardianship, for legal reasons.

Endpoint. Twelve-week vital status was compiled from three sources: hospital discharge records, a systematic phone call by a research assistant at week 12 and an enquiry into civil registries in 2013 for patients with unknown outcome at week 12. Follow-up started on the collection day of the first positive blood culture and ended with death or last contact.

Data collection. Standardized electronic case report forms were filled in locally and compiled by the Centre for Epidemiology and Clinical Evaluation in Nancy. Clinical data included demographics, comorbidities, initial bacteraemia characteristics and complications. Treatment data included antibiotics, surgery, and intensive care. The ethics committee "Comité de Protection des Personnes Sud-Méditerranée IV" approved this observational study and requested an opt-out strategy after oral and written information. The VIRSTA study is registered in the European Clinical Trials Database (EUDRACT) under the number 2008-A00680-55.

Definitions. Setting of acquisition was defined as either nosocomial, healthcare-related or community-acquired [2, 22]. SAB was defined as nosocomial if signs consistent with bloodstream infection began after 48 hours of hospitalization. Both healthcare-related and community-acquired SAB patients developed first signs before 48 hours of hospitalization. Healthcare-related SAB patients either (i) received intravenous therapy, wound care or specialized nursing care at home within the thirty days prior to the onset of SAB, (ii) attended a hospital or haemodialysis clinic or received intravenous therapy within the thirty days before the onset of SAB, (iii) were hospitalized in an acute care hospital for two or more days in the ninety days before the onset of SAB or (iv) resided in a nursing home or long-term care facility. Otherwise, SAB was defined as community-acquired.

Primary focus of infection was defined as a unique source for each SAB patient and was diagnosed by the treating physician. Endocarditis was classified according to modified Duke criteria into definite, possible or excluded cases by local boards

involving bacteriologists, infectious disease specialists and cardiologists. Osteo-articular localizations were considered secondary foci (via haematogenous or contiguous spread) unless the primary focus was reported as bone or joint surgery.

Severe sepsis was defined by major organ dysfunction, or blood pressure < 90 mmHg or signs of hypoperfusion (confusion, oliguria, skin mottling, lactate elevation, metabolic acidosis), and septic shock by a severe sepsis requiring the use of vasopressive agents. Laboratory diagnostic procedures and interpretation of in vitro susceptibility were carried out according to the French Society of Microbiology's recommendations (CA-SFM).

Antibiotics. Patients were considered for analysis of antibiotic treatment if they had complete follow-up, received at least one antibiotic for the SAB episode (regardless of timing) and did not die within the first 24 hours following positive blood culture sampling. To prevent survivor treatment selection bias, we took into account first line antibiotics only (i.e. the antibiotics used on the day a patient first received antibiotics for the episode).

Statistical analyses. We used bivariate and multivariate logistic regression to identify potential prognostic variables, chosen according to previous research. [7-17] Due to the large number of variables, we performed five separate regression analyses by groups of variables: demographics and comorbidities (group 1), initial bacteraemia characteristics (group 2), secondary foci and other complications (group 3) and sepsis (group 4). Variables were kept for multivariate regression if the likelihood ratio test showed a p-value <0.20 in bivariate analysis and retained in

the reduced model if p-value was <0.05 after backward stepwise elimination of non-significant variables. In a second step, treatment data (group 5) were described and then used in a new logistic regression with adjustment on the main prognostic variables. Missing data in logistic regression were handled by creating a separate modality labelled “Missing” in the corresponding tables. All statistical analyses were performed with Stata 12.1 (Stata Corp 2011).

RESULTS

Population description. Main population characteristics are summarized in Table 1 and in the flowchart (supplementary material). Out of the 2091 included patients, 119 (5.7%) had incomplete follow-up. Patients with incomplete follow-up were younger, had less comorbidity and were discharged earlier. The remaining 1972 patients were included in the prognostic analysis. Echocardiography was performed in 1339/1972 patients (67.9%) with at least one transoesophageal echocardiography in 634/1972 patients (32.1%). Effect of first initiated antibiotic on prognosis was evaluated on 1896 patients as 76/1972 (3.9%) were excluded because they died on the day of blood culture sampling or did not receive any antibiotics at all.

Prognostic factors. Among the 1972 patients with complete follow-up, 671 died before week 12 (case-fatality 34.0%). Bivariate analyses and the reduced logistic regression model are shown in Table 2. Case-fatality rates according to primary focus were: unknown primary focus 52.2% (216/414), lungs and pleura 49.6% (58/117), arterial catheter 31.6% (6/19), peripheral venous catheter 30.1% (41/134), central venous catheter 29.2% (103/353), skin 28.9% (109/377), urinary system 27.6% (27/98), surgery 26.8% (76/284), arterio-venous fistula 20.9% (9/43) and injecting drug use 20.9% (7/47).

On multivariate analysis, main independent prognostic factors for 12 week case-fatality among background characteristics and SAB characteristics were: age (adjusted odds ratio [OR] by 10-year increment, 1.56; 95% confidence interval [CI], 1.44–1.69), septic shock (OR, 5.11; CI, 3.84-6.80), severe sepsis (OR, 2.44; CI, 1.83-3.30), metastatic cancer (OR, 4.28; CI, 2.88-6.38), unknown primary focus

of infection (OR, 2.62; CI, 2.02-3.41), primary and secondary pulmonary foci (OR, 2.27; CI, 1.45-3.55 and OR, 2.14; CI, 1.46-3.14, respectively).

Female gender was associated with worse outcome (OR, 1.34; CI, 1.06-1.60). After exploratory analyses we found no gender differences in comorbidities, setting of acquisition, MRSA, complications like endocarditis, access to health care and diagnostic procedures (time from 1st symptom to blood culture and from blood culture to treatment, access to cardiac echography), treatments and surgical procedures.

First line antibiotics description in MSSA patients. First line antibiotics in the 1538 patients infected with methicillin-susceptible *Staphylococcus aureus* (MSSA) with complete follow-up who received antibiotics and survived the first day are described in Table 3. Oxacillin and cloxacillin were grouped together as antistaphylococcal penicillins. Neither cefazolin nor daptomycin were used as first-line treatments. Gentamycin was initiated in 455 out of the 530 patients who received aminoglycosides as first line therapy (85.8%). First-line antibiotics were prescribed within 24 hours after the drawing of first positive blood culture in 842/1538 patients (54.8%). Duration of first line antibiotics, patient's characteristics and case-fatality rates at week 4 and week 12 according to first line antibiotic are shown in Table 3. Kaplan-Meier survival estimates according to first line antibiotic are reported in Figure 1.

First line antibiotics description in MRSA patients. Similar analyses were done for the 358 patients infected with MRSA with complete follow-up who received antibiotics and survived the first day. First-line antibiotics were prescribed within

182 24 hours in 181/358 patients (50.6%). Antibiotics were appropriate according to
183 antimicrobial testing in 109/358 patients (30.4%). Due to small numbers in some
184 categories, we were not able to perform regression analyses in MRSA patients.
185
186 ***Association between first-line antibiotics and week 12 case-fatality in MSSA***
187 ***patients.*** Table 4 displays crude ORs of first-line antibiotics effects on outcome and
188 ORs adjusted on previously identified prognostic factors. For these previously
189 identified prognostic factors in the total cohort, the ORs and CIs were nearly
190 identical in the MSSA group and the whole cohort and did not change significantly
191 after adjustment by treatment variables. Antistaphylococcal penicillins and
192 vancomycin prescriptions were associated with better outcome, alone and in
193 association with an aminoglycoside. Time from first positive blood culture
194 sampling to first antibiotic was associated with better survival only after adjusting
195 for main prognostic factors.
196

197 # DISCUSSION

198 In this large prospective multicentre study conducted in 8 tertiary care centres, we
199 showed that case-fatality is still very high in SAB patients and mainly associated
200 with older age, sepsis, metastatic cancer, pulmonary localization (primary and
201 secondary foci) and unknown primary focus. Early initiation of antibiotics and use
202 of specific first line antibiotics including antistaphylococcal penicillins and
203 vancomycin, alone or in combination with an aminoglycoside, were associated with
204 better survival in patients infected with MSSA.
205

Our conclusions may be affected by a referral bias. Since some patients were transferred to tertiary care centres, we may overestimate the case-fatality rate of SAB. Follow-up was incomplete in 119/2091 patients (5.7%) who were younger and had less comorbidities and complications. Therefore one can assume they were less likely to die within 12 weeks. The main strengths of our study were the multicentre recruitment, and the detailed prospective clinical data including antibiotic treatment in a large cohort of patients. We preferred to analyse global case-fatality at week 12 because diagnosis of disease-specific death is subject to interpretation and because longitudinal data suggest a high proportion of deaths attributable to SAB as far as week 12 [14, 23, 24].

Older age and sepsis are major consensual lethal factors [4, 8-17]. Some authors have suggested not adjusting on sepsis because it is too close to outcome [16, 25], but severe sepsis is one of the rare major potentially modifiable factors although its determinants and triggers are insufficiently understood. Metastatic cancer is a major factor as well [12, 15], but prolonging follow-up like in our study leads to measuring some underlying conditions' own contributions to outcome. Unknown primary focus is associated with worse outcome in most reports [10-12, 17]. These patients are older and have more severe disease, but the main explanation of this finding is still unknown. Thorough investigation for primary focus and earlier infectious source control may be ways to reduce case-fatality in patients without identified primary focus. Pulmonary localization is more difficult to diagnose and is also associated with higher case-fatality [8, 10-12, 17]. These patients need close monitoring and intensive care.

Like in most other studies [8, 9, 11, 14, 17], setting of acquisition was not associated with prognosis of SAB in our cohort: community-acquired SAB was associated with unknown primary focus (worse prognosis), whereas patients with nosocomial SAB had more comorbidities (worse prognosis) and more catheter-related primary foci (better prognosis).

Endocarditis was no longer associated with prognosis after adjustment on mycotic aneurism and complications like stroke and heart failure. Since the association of endocarditis with increased mortality was moderate in bivariate analysis and on the contrary lethal complications like stroke and heart failure also occur in non-endocarditis patients, we decided to maintain the latter in the multivariate model. We may thus hypothesize that endocarditis without severe complications does not worsen the prognosis of SAB.

Osteo-articular localizations were associated with a better prognosis, confirming two previous reports [10, 15]. Osteo-articular localizations were considered secondary localizations (except after surgery), and a complication is very unlikely to improve outcome. However, bone and joint infections often have a subacute or chronic evolution and they are associated with lower inoculum and less virulent strains like small colony variants.

In our population, infection with MRSA was associated with older age and comorbidities that act as confounders, leaving only a small specific impact of methicillin resistance after adjustment. Some studies found a small association of methicillin resistance with outcome [9, 26] but most did not [13, 14, 16, 17, 27].

Female gender was associated with worse outcome and has been reported before without a satisfactory explanation [24]. In our cohort it was not mediated by gender differences in baseline characteristics or access to health care.

Our results suggest that using specific antistaphylococcal antibiotics as first-line treatment is associated with better prognosis in patients infected with MSSA. Caution is required as indication bias may partially explain our results, but higher quality evidence from randomized controlled trials is currently missing. Most cohorts that examined initial SAB antibiotics and their timing did not report an association with outcome, but could not adjust precisely on baseline severity [13, 16, 17, 28]. Due to higher statistical power in our cohort we could perform detailed adjustment on prognostic factors and separate specific antistaphylococcal penicillins from other beta-lactams.

We did not find a worse outcome for vancomycin compared to antistaphylococcal penicillins as *first line* antibiotic in MSSA bloodstream infection. Most studies reporting worse outcome for vancomycin in MSSA patients specifically examined definitive treatments in SAB [28]. Our results are in accordance with retrospective cohort data obtained from Veterans Affairs hospitals in the USA [29]. Our data furthermore suggest that other beta-lactams such as amoxicillin/clavulanate or ceftriaxone are less suitable alternatives to antistaphylococcal penicillins like oxacillin when SAB is suspected. Therefore, in case of sepsis of unknown origin when large spectrum beta-lactams are believed necessary and *S. aureus* a possible cause, inclusion of vancomycin in the empiric regimen may be a suitable strategy even if MSSA is responsible for the infection. When *S. aureus* is highly probable

and prevalence of MRSA low, choosing an antistaphylococcal beta-lactam is probably preferable, not least to avoid nephrotoxicity. The association of vancomycin and antistaphylococcal penicillin may also be an efficient empiric therapy when resistance to methicillin is possible [30]. When antimicrobial susceptibility is known, switch from vancomycin to a beta-lactam is mandatory and should be immediate when possible. Adding aminoglycoside to the initial therapy may allow a larger spectrum and activity on other potential microorganisms, without negatively impacting outcome according to our data.

SAB needs urgent attention from clinicians and researchers for prevention as well as for curative treatment, in order to lower its prohibitive case-fatality rate. Reinforcing prevention of SAB associated with medical devices would be a logical first step. Major aspects of SAB management are still uncertain [18], and randomized clinical trials addressing these questions are necessary [31]. A quasi-experimental study has examined the impact of an evidence-based bundle intervention in SAB with promising results [17], but without randomized clinical trials knowledge about optimal antibiotic treatment is unlikely to progress [3]. Quicker procedures to make susceptibility data available at the time of bacteriological diagnosis could be the missing piece to make these trials feasible [32].

TRANSPARENCY DECLARATION

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AUTHORSHIP AND CONTRIBUTION

Designed the experiments: FA XD VLM. Performed the experiments: PB FA FG CC MR CL XD VLM. Analysed the data: PB FA VLM. Wrote the paper: PB FA FG CC MR CL XD VLM.

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FIGURE AND TABLE LEGENDS

Figure 1. Kaplan-Meier survival estimates according to first line antibiotic use in patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteraemia in the VIRSTA study (n=1538)

Log-rank test $p < 0.001$. Case-fatality rates at 12 weeks among these first line antibiotics groups were: 20.0% (7/35) for regimens including an antistaphylococcal

351 penicillin and vancomycin, 23.1% (70/303) for regimens including an
352 antistaphylococcal penicillin, 26.1% (106/406) for regimens including vancomycin
353 and 35.9% (285/794) for any other regimen.
354
355 **Table 1. Characteristics of patients with complete follow-up at 12 weeks in the**
356 **VIRSTA study (n= 1972).**
357
358 [a] No comorbidity was found in 125 patients (6.3%), 1 comorbidity in 286 patients
359 (14.5%), 2 comorbidities in 764 patients (38.4%), 3 comorbidities in 605 patients
360 (30.7%) and at least 4 comorbidties in 192 patients (9.7%)
361
362 **Table 2. Factors associated with week 12 case fatality of *Staphylococcus aureus***
363 **bacteraemia in the VIRSTA study (n=1972).[a]**
364
365 OR: odds-ratio; CI: confidence interval; [a]Main variables not associated with case-
366 fatality in bivariate analyses were diabetes mellitus, peripheral arteriopathy, chronic
367 obstructive pulmonary disease, immunosuppressive therapy, and foci like
368 meningitis and cerebral abscess. [b]For the multivariate logistic regression: events to
369 independent variables ratio is 55.6; age complied with linearity; we analysed only
370 expected interactions (MRSA and treatment variables), results were presented
371 separately (tables 3 and 4); no collinearity was detected;Hosmer-Lemeshaw
372 goodness-of-fit indicated a p-value of 0.618 and area under the curve for receiver
373 operating characteristic was 0.807, which indicated a good fit to the real data.
374

Table 3. First line antibiotics, patients' characteristics and outcome in patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteraemia in the VIRSTA study (n=1538)

IQR: inter-quartile range; ASP were antistaphylococcal penicillins: oxacillin and cloxacillin; [a] Ceftriaxone or cefotaxim (53%), amoxicillin (28%); [b] Fluoroquinolone (30%); [c] Ceftriaxone + aminoglycoside (44%); [d] Ceftriaxone + fluoroquinolone (17%)

Table 4. Association between first line antibiotics and week 12 case-fatality in patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteraemia in the VIRSTA study (n=1538)

OR: odds-ratio; CI: confidence interval; ASP were antistaphylococcal penicillins: oxacillin and cloxacillin; [a] Those identified in the multivariate regression model in table 2, except MRSA (these factors remained associated with outcome when tested in this MSSA population); A potential interaction between Time to 1st antibiotics initiation and First line antibiotic was not significant by likelihood ratio test, (p=0.72); [b] p calculated using Wald's test

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Table 1. Characteristics of patients with complete follow-up at 12 weeks in the VIRSTA study (n= 1972).

Variables	Median or frequency	Inter-quartile range or proportion
Demographics		
Median age	67.8	55.5-78.9
Female gender	692	35.1
Comorbidities[a]		
Diabetes mellitus	551	27.9
Chronic renal insufficiency	549	27.8
Peripheral arteriopathy	352	17.8
Chronic heart failure	523	26.5
Chronic obstructive pulmonary disease	243	12.3
Respiratory insufficiency	233	11.8
Chronic liver disease	279	14.1
Cardiac prosthetic valve	153	7.8
Native valve disease	354	18.0
Localized cancer	429	21.8
Metastatic cancer	148	7.5
Bacteraemia characteristics		
MRSA	374	19.0
Community-acquired	548	27.8
Health care-related (non-nosocomial)	351	17.8
Nosocomial	1021	51.8
Primary focus		
Skin	377	19.1
Urinary system	98	5.0
Lungs and pleura	117	5.9
Surgery	284	14.4
Peripheral venous catheter	134	6.8
Central venous catheter	353	17.9
Arterial catheter	19	1.0
Arterio-venous fistula	43	2.2
Injecting drug use	47	2.4
Other	86	4.4
Unknown	414	21.0
Complications		
Endocarditis	286	14.5
Stroke	100	5.1
Heart failure	186	9.4
Pulmonary 2^{ndary} focus	172	8.7
Osteo-articular 2^{ndary} focus	266	13.5
Meningeal 2^{ndary} focus	24	1.2
Cerebral abscess	23	1.2
Severe sepsis (without shock)	303	15.4
Septic shock	376	19.1
Outcome		
Death at 4 weeks	456	23.1
Death at 12 weeks	671	34.0
In-hospital death	524	26.6

[a] No comorbidity was found in 125 patients (6.3%), 1 comorbidity in 286 patients (14.5%), 2 comorbidities in 764 patients (38.4%), 3 comorbidities in 605 patients (30.7%) and at least 4 comorbidties in 192 patients (9.7%)

Table 2. Factors associated with week 12 case fatality of *Staphylococcus aureus* bacteraemia in the VIRSTA study (n=1972).[a]

Variable	Frequencies			Bivariate analysis			Multivariate model [b]		
Modality	Dead	Exposed	%	OR	95% CI	p (Wald)	OR	95% CI	p (Wald)
Group 1: Demographics and Comorbidities									
Age									
(By 10-year increment)				1.53	1.43-1.63	<0.001	1.56	1.44-1.69	<0.001
Gender									
Male	408	1280	31.9	1.00			1.00		
Female	263	692	38.0	1.31	1.08-1.59	0.006	1.34	1.06-1.68	0.013
Chronic renal insufficiency									
No	435	1423	30.6	1.00			1.00		
Yes	236	549	43.0	1.71	1.40-2.10	<0.001	1.46	1.15-1.86	0.002
Chronic heart failure									
No	437	1449	30.2	1.00					
Yes	234	523	44.7	1.88	1.53-2.30	<0.001			
Respiratory insufficiency									
No	559	1739	32.1	1.00					
Yes	112	233	48.1	1.95	1.48-2.57	<0.001			
Chronic liver disease									
No	569	1693	33.6	1.00			1.00		
Yes	102	279	36.6	1.14	0.87-1.48	0.335	1.43	1.04-1.97	0.028
Heart valve disease									
None	457	1465	31.2	1.00					
Native valve disease	139	354	39.3	1.42	1.12-1.81	0.004			
Prosthetic valve	75	153	49.0	2.12	1.52-2.97	<0.001			
Cancer history									
None	434	1395	31.1	1.00			1.00		
Localized Cancer	154	429	35.9	1.24	0.99-1.56	0.064	1.17	0.90-1.52	0.246
Metastatic Cancer	83	148	56.1	2.83	2.00-3.99	<0.001	4.28	2.88-6.38	<0.001
Group 2: Initial Bacteraemia Characteristics									
In vitro susceptibility									
MSSA	510	1598	31.9	1.00			1.00		
MRSA	161	374	43.0	1.61	1.28-2.03	<0.001	1.33	1.02-1.75	0.039
Setting of acquisition									
Community-acquired	174	548	31.8	1.00					
Health care-related	113	351	32.2	1.02	0.77-1.36	0.890			

Nosocomial	356	1021	34.9	1.15	0.92-1.44	0.214			
Missing	32	59	54.2	2.51	1.41-4.45	0.002			
Primary focus									
Other known focus	397	1441	27.6	1.00			1.00		
Pulmonary focus	58	117	49.6	2.58	1.77-3.78	<0.001	2.27	1.45-3.55	<0.001
Unknown focus	216	414	52.2	2.87	2.29-3.59	<0.001	2.62	2.02-3.41	<0.001
Group 3: Secondary foci and other complications									
Endocarditis									
No	558	1686	33.1	1.00					
Yes	113	286	39.5	1.32	1.02-1.70	0.035			
Stroke									
No	620	1872	33.1	1.00			1.00		
Yes	51	100	51.0	2.10	1.40-3.15	<0.001	1.73	1.05-2.86	0.031
Heart Failure									
No	570	1786	31.9	1.00			1.00		
Yes	101	186	54.3	2.53	1.86-3.43	<0.001	1.76	1.23-2.53	0.002
Mycotic Aneurism									
No	656	1943	33.8	1.00					
Yes	15	29	51.7	2.10	1.01-4.38	0.047			
Pulmonary 2^{ndary} focus									
No	583	1800	32.4	1.00			1.00		
Yes	88	172	51.2	2.19	1.59-3.00	<0.001	2.14	1.46-3.14	<0.001
Osteo-articular 2^{ndary} focus									
No	615	1706	36.0	1.00			1.00		
Yes	56	266	21.1	0.47	0.35-0.65	<0.001	0.55	0.39-0.79	0.001
Group 4: Sepsis									
None	296	1266	23.4	1.00			1.00		
Severe sepsis (without shock)	137	303	45.2	2.70	2.08-3.51	<0.001	2.45	1.83-3.30	<0.001
Septic shock	230	376	61.2	5.16	4.04-6.59	<0.001	5.11	3.84-6.80	<0.001
Missing	8	27	29.6	1.38	0.59-3.18	0.451	1.71	0.68-4.31	0.252

OR: odds-ratio; CI: confidence interval; [a]Main variables not associated with case-fatality in bivariate analyses were diabetes mellitus, peripheral arteriopathy, chronic obstructive pulmonary disease, immunosuppressive therapy, and foci like meningitis and cerebral abscess. [b]For the multivariate logistic regression: events to independent variables ratio is 55.6; age complied with linearity; we did not analyse interactions because none was expected, no collinearity was detected; Hosmer-Lemeshaw goodness-of-fit indicated a p-value of 0.618 and area under the curve for receiver operating characteristic was 0.807, which indicated a good fit to the real data.

Table 3. First line antibiotics, patients' characteristics and outcome in patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteraemia in the VIRSTA study (n=1538)

First line antibiotics				Patients' characteristics			Outcome at 4 weeks		Outcome at 12 weeks	
	Patients treated	= % of MSSA patients	Median duration (IQR) (days)	Median age (years)	Septic shock	= % of treated	Case fatality	= % of treated	Case fatality	= % of treated
Monotherapy										
Antistaphylococcal penicillin (ASP)	80	5.2	9 (4-21)	64.1	10	12.5	12	15.0	17	21.3
Amoxicillin/clav.	127	8.3	3(2-7)	66.5	11	8.7	29	22.8	46	36.2
Other beta-lactam[a]	139	9.0	3 (2-5)	71.9	21	15.1	31	22.3	47	33.8
Vancomycin	92	6.0	2 (1-5)	65.3	11	12.0	11	12.0	20	21.7
Other monotherapy[b]	138	9.0	4.5 (2-11)	63.8	24	17.4	19	13.8	37	26.8
Bitherapy										
ASP + aminoglycoside	138	9.0	8 (4-15)	60.9	19	13.7	20	14.5	27	19.6
Other beta-lactam[c] + aminoglycoside	72	4.7	3 (2-4)	70.1	19	26.4	21	29.2	31	43.1
Vancomycin + aminoglycoside	106	6.9	2 (1-4)	65.2	10	9.4	12	11.3	19	17.9
Vancomycin + beta-lactam	54	3.5	4 (1.5-8)	61.7	7	13.0	5	9.3	11	20.4
Other bitherapy[d]	333	21.7	4 (2-9)	66.0	55	16.5	66	19.8	107	32.1
Multiple therapy										
Strategy with ≥ 3 antibiotics	259	16.8	2 (1-4)	64.9	100	38.6	74	28.6	106	40.9
Time to 1st antibiotic initiation										
> 24 hours after blood culture collection	696	45.3	4 (2-9)	66.5	101	14.5	130	18.7	211	30.3
≤ 24 hours after blood culture collection	842	54.8	3 (2-7)	65.6	186	22.1	170	20.2	257	30.5

IQR: inter-quartile range; ASPs were the antistaphylococcal penicillins: oxacillin and cloxacillin; [a] Ceftriaxone or cefotaxim (53%), amoxicillin (28%); [b] Fluoroquinolone (30%); [c] Ceftriaxone + aminoglycoside (44%); [d] Ceftriaxone + fluoroquinolone (17%)

Table 4. Association between first line antibiotics and week 12 case-fatality in patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteraemia in the VIRSTA study (n=1538)

Group 5: treatment variables		Frequencies			Bivariate analysis			Effect of antibiotics adjusted on other prognostic factors[a]		
		Dead	Treated	%	OR	CI	p[b]	OR	CI	p[b]
Variable 1: First line antibiotics										
Monotherapy	Antistaphylococcal penicillin (ASP)	17	80	21.3	0.36	0.18-0.73	0.004	0.40	0.17-0.95	0.037
	Amoxicillin/clav.	46	127	36.2	0.75	0.42-1.36	0.342	0.85	0.42-1.72	0.650
	Other beta-lactam	47	139	33.8	0.68	0.38-1.21	0.188	0.56	0.28-1.14	0.110
	Vancomycin	20	92	21.7	0.37	0.19-0.73	0.004	0.37	0.17-0.83	0.016
	Other monotherapy	37	139	26.8	0.48	0.27-0.88	0.018	0.50	0.25-1.03	0.059
Bitherapy	ASP+ aminoglycoside	27	138	19.6	0.32	0.17-0.60	<0.001	0.37	0.17-0.78	0.009
	Other beta-lactam + aminoglycoside (Ref.)	31	72	43.1	1.00			1.00		
	Vancomycin + aminoglycoside	19	106	17.9	0.29	0.15-0.57	<0.001	0.33	0.15-0.72	0.006
	Vancomycin + beta-lactam	11	54	20.4	0.34	0.15-0.76	0.009	0.41	0.16-1.02	0.055
	Other bitherapy	107	333	32.1	0.63	0.37-1.05	0.078	0.59	0.32-1.10	0.099
Multiple therapy	Strategy with ≥ 3 antibiotics	106	259	40.9	0.92	0.54-1.55	0.746	0.67	0.35-1.26	0.216
Variable 2: Time to 1st antibiotic initiation										
> 24 hours after blood culture collection (Ref.)		211	696	30.3	1.00			1.00		
≤ 24 hours after blood culture collection		257	842	30.5	1.01	0.81-1.26	0.930	0.71	0.54-0.93	0.015

OR: odds-ratio; CI: confidence interval; ASPs were the antistaphylococcal penicillins oxacillin and cloxacillin; [a] Those identified in the multivariate regression model in table 2, except MRSA (these factors remained associated with outcome when tested in this MSSA population); A potential interaction between Time to 1st antibiotics initiation and First line antibiotic was not significant by likelihood ratio test, (p=0.72); [b] p calculated using Wald's test