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# **Factors Associated with 12 Week Case-Fatality in *Staphylococcus aureus* Bacteraemia, a Prospective Cohort Study**

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And the VIRSTA-AEPEI Study Group.

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## 1 ABSTRACT

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

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

11 **Results.** We enrolled 2091 patients and analysed survival in 1972 (median age:  
12 67.8 years, interquartile range 55.5-78.9; females 692/1972, 35.1%). SAB was  
13 nosocomial or health-care related in 1372/1972 (69.6%) and the primary focus was  
14 unknown in 414/1972 (21.0%) of cases. Week 12 case-fatality rate was 671/1972  
15 (34.0%). Main independent prognostic factors on multivariate analysis were: age  
16 (adjusted odds ratio [OR] by 10-year increment, 1.56; 95% confidence interval  
17 [CI], 1.44–1.69), septic shock (OR, 5.11; CI, 3.84-6.80), metastatic cancer (OR,  
18 4.28; CI, 2.88-6.38) and unknown primary focus (OR, 2.62; CI, 2.02-3.41). In the  
19 1538 patients with methicillin-sensitive *S. aureus* (MSSA) bacteraemia, first-line  
20 empiric antistaphylococcal penicillins (OR, 0.40; CI, 0.17-0.95) and vancomycin  
21 (OR, 0.37; CI, 0.17-0.83), alone or combined with an aminoglycoside, were  
22 associated with better outcome compared to other antibiotics.

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

26 **FULL TEXT**27 **INTRODUCTION**

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

33

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

41

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

48

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

51 **PATIENTS AND METHODS**

52

53 **Study setting.** The observational prospective cohort study VIRSTA was conducted  
54 in 8 tertiary care centres in France, the university hospitals of Besançon, Dijon,  
55 Lyon, Montpellier, Nancy, Nîmes, Paris (Bichat-Claude Bernard) and Rennes.  
56 *Staphylococcus aureus* endocarditis-specific analyses were described elsewhere  
57 [19-21]. Standardized investigation of all cases was encouraged (e.g. follow-up  
58 blood cultures and echocardiography) but was not mandatory.

59

60 **Case identification.** Consecutive patients were included if they had (i) at least one  
61 positive blood culture specimen for *S. aureus* (ii) between April 2009 and October  
62 2011 in a participating hospital. Bacteriology laboratories identified incident  
63 patients and notified the local research team composed of research assistants,  
64 bacteriologists, infectious disease specialists and cardiologists. Exclusion criteria  
65 were (i) positive catheter specimen without SAB, defined as single positive blood  
66 cultures in vascular access device specimens with negative peripheral blood culture  
67 and (ii) age < 18 years, pregnancy and adults under guardianship, for legal reasons.

68

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

74

75 **Data collection.** Standardized electronic case report forms were filled in locally and  
76 compiled by the Centre for Epidemiology and Clinical Evaluation in Nancy.  
77 Clinical data included demographics, comorbidities, initial bacteraemia  
78 characteristics and complications. Treatment data included antibiotics, surgery, and  
79 intensive care. The ethics committee “Comité de Protection des Personnes Sud-  
80 Méditerranée IV” approved this observational study and requested an opt-out  
81 strategy after oral and written information. The VIRSTA study is registered in the  
82 European Clinical Trials Database (EUDRACT) under the number 2008-A00680-  
83 55.

84  
85 **Definitions.** Setting of acquisition was defined as either nosocomial, healthcare-  
86 related or community-acquired [2, 22]. SAB was defined as nosocomial if signs  
87 consistent with bloodstream infection began after 48 hours of hospitalization. Both  
88 healthcare-related and community-acquired SAB patients developed first signs  
89 before 48 hours of hospitalization. Healthcare-related SAB patients either (i)  
90 received intravenous therapy, wound care or specialized nursing care at home  
91 within the thirty days prior to the onset of SAB, (ii) attended a hospital or  
92 haemodialysis clinic or received intravenous therapy within the thirty days before  
93 the onset of SAB, (iii) were hospitalized in an acute care hospital for two or more  
94 days in the ninety days before the onset of SAB or (iv) resided in a nursing home or  
95 long-term care facility. Otherwise, SAB was defined as community-acquired.

96  
97 Primary focus of infection was defined as a unique source for each SAB patient and  
98 was diagnosed by the treating physician. Endocarditis was classified according to  
99 modified Duke criteria into definite, possible or excluded cases by local boards

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

103

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

110

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

117

118 **Statistical analyses.** We used bivariate and multivariate logistic regression to  
119 identify potential prognostic variables, chosen according to previous research. [7-  
120 17] Due to the large number of variables, we performed five separate regression  
121 analyses by groups of variables: demographics and comorbidities (group 1), initial  
122 bacteraemia characteristics (group 2), secondary foci and other complications  
123 (group 3) and sepsis (group 4). Variables were kept for multivariate regression if  
124 the likelihood ratio test showed a p-value <0.20 in bivariate analysis and retained in



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

131

132 **RESULTS**

133

134 **Population description.** Main population characteristics are summarized in Table 1  
135 and in the flowchart (supplementary material). Out of the 2091 included patients,  
136 119 (5.7%) had incomplete follow-up. Patients with incomplete follow-up were  
137 younger, had less comorbidity and were discharged earlier. The remaining 1972  
138 patients were included in the prognostic analysis. Echocardiography was performed  
139 in 1339/1972 patients (67.9%) with at least one transoesophageal echocardiography  
140 in 634/1972 patients (32.1%). Effect of first initiated antibiotic on prognosis was  
141 evaluated on 1896 patients as 76/1972 (3.9%) were excluded because they died on  
142 the day of blood culture sampling or did not receive any antibiotics at all.

143

144 **Prognostic factors.** Among the 1972 patients with complete follow-up, 671 died  
145 before week 12 (case-fatality 34.0%). Bivariate analyses and the reduced logistic  
146 regression model are shown in Table 2. Case-fatality rates according to primary  
147 focus were: unknown primary focus 52.2% (216/414), lungs and pleura 49.6%  
148 (58/117), arterial catheter 31.6% (6/19), peripheral venous catheter 30.1% (41/134),  
149 central venous catheter 29.2% (103/353), skin 28.9% (109/377), urinary system  
150 27.6% (27/98), surgery 26.8% (76/284), arterio-venous fistula 20.9% (9/43) and  
151 injecting drug use 20.9% (7/47).

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

157 of infection (OR, 2.62; CI, 2.02-3.41), primary and secondary pulmonary foci (OR,  
158 2.27; CI, 1.45-3.55 and OR, 2.14; CI, 1.46-3.14, respectively).

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

165

166 ***First line antibiotics description in MSSA patients.*** First line antibiotics in the  
167 1538 patients infected with methicillin-susceptible *Staphylococcus aureus* (MSSA)  
168 with complete follow-up who received antibiotics and survived the first day are  
169 described in Table 3. Oxacillin and cloxacillin were grouped together as  
170 antistaphylococcal penicillins. Neither cefazolin nor daptomycin were used as first-  
171 line treatments. Gentamycin was initiated in 455 out of the 530 patients who  
172 received aminoglycosides as first line therapy (85.8%). First-line antibiotics were  
173 prescribed within 24 hours after the drawing of first positive blood culture in  
174 842/1538 patients (54.8%). Duration of first line antibiotics, patient's  
175 characteristics and case-fatality rates at week 4 and week 12 according to first line  
176 antibiotic are shown in Table 3. Kaplan-Meier survival estimates according to first  
177 line antibiotic are reported in Figure 1.

178

179 ***First line antibiotics description in MRSA patients.*** Similar analyses were done for  
180 the 358 patients infected with MRSA with complete follow-up who received  
181 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

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

216

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

230

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

236

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

244

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

251

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

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

259

260 Our results suggest that using specific antistaphylococcal antibiotics as first-line  
261 treatment is associated with better prognosis in patients infected with MSSA.  
262 Caution is required as indication bias may partially explain our results, but higher  
263 quality evidence from randomized controlled trials is currently missing. Most  
264 cohorts that examined initial SAB antibiotics and their timing did not report an  
265 association with outcome, but could not adjust precisely on baseline severity [13,  
266 16, 17, 28]. Due to higher statistical power in our cohort we could perform detailed  
267 adjustment on prognostic factors and separate specific antistaphylococcal  
268 penicillins from other beta-lactams.

269

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

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

289

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

301



## 302 **TRANSPARENCY DECLARATION**

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316 others have nothing to disclose.

317

## 318 **AUTHORSHIP AND CONTRIBUTION**

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

322

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341

342

343 **FIGURE AND TABLE LEGENDS**

344

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

348

349 Log-rank test  $p < 0.001$ . Case-fatality rates at 12 weeks among these first line  
350 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 <sup>a</sup>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 comorbidities 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).<sup>a</sup>**

364

365 OR: odds-ratio; CI: confidence interval; <sup>a</sup>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. <sup>b</sup>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

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

378

379 IQR: inter-quartile range; ASP were antistaphylococcal penicillins: oxacillin and  
380 cloxacillin; <sup>a</sup> Ceftriaxone or cefotaxim (53%), amoxicillin (28%); <sup>b</sup> Fluoroquinolone  
381 (30%); <sup>c</sup> Ceftriaxone + aminoglycoside (44%); <sup>d</sup> Ceftriaxone + fluoroquinolone  
382 (17%)

383

384

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

388

389 OR: odds-ratio; CI: confidence interval; ASP were antistaphylococcal penicillins:  
390 oxacillin and cloxacillin; <sup>a</sup> Those identified in the multivariate regression model in  
391 table 2, except MRSA (these factors remained associated with outcome when tested  
392 in this MSSA population); A potential interaction between Time to 1<sup>st</sup> antibiotics  
393 initiation and First line antibiotic was not significant by likelihood ratio test,  
394 (p=0.72); <sup>b</sup> 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
<b>Demographics</b>		
Median age	67.8	55.5-78.9
Female gender	692	35.1
<b>Comorbidities<sup>a</sup></b>		
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
<b>Bacteraemia characteristics</b>		
MRSA	374	19.0
Community-acquired	548	27.8
Health care-related (non-nosocomial)	351	17.8
Nosocomial	1021	51.8
<b>Primary focus</b>		
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
<b>Complications</b>		
Endocarditis	286	14.5
Stroke	100	5.1
Heart failure	186	9.4
Pulmonary 2 <sup>ndary</sup> focus	172	8.7
Osteo-articular 2 <sup>ndary</sup> focus	266	13.5
Meningeal 2 <sup>ndary</sup> focus	24	1.2
Cerebral abscess	23	1.2
Severe sepsis (without shock)	303	15.4
Septic shock	376	19.1
<b>Outcome</b>		
Death at 4 weeks	456	23.1
Death at 12 weeks	671	34.0
In-hospital death	524	26.6

<sup>a</sup>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 comorbidities in 192 patients (9.7%)

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

Variable Modality	Frequencies		%	Bivariate analysis		Multivariate model <sup>b</sup>		
	Dead	Exposed		OR	95% CI	OR	95% CI	p (Wald)
<b>Group 1: Demographics and Comorbidities</b>								
<b>Age</b> (By 10-year increment)				1.53	1.43-1.63	1.56	1.44-1.69	<0.001
<b>Gender</b>								
Male	408	1280	31.9	1.00		1.00		
Female	263	692	38.0	1.31	1.08-1.59	1.34	1.06-1.68	0.013
<b>Chronic renal insufficiency</b>								
No	435	1423	30.6	1.00		1.00		
Yes	236	549	43.0	1.71	1.40-2.10	1.46	1.15-1.86	0.002
<b>Chronic heart failure</b>								
No	437	1449	30.2	1.00				
Yes	234	523	44.7	1.88	1.53-2.30			<0.001
<b>Respiratory insufficiency</b>								
No	559	1739	32.1	1.00				
Yes	112	233	48.1	1.95	1.48-2.57			<0.001
<b>Chronic liver disease</b>								
No	569	1693	33.6	1.00		1.00		
Yes	102	279	36.6	1.14	0.87-1.48	1.43	1.04-1.97	0.028
<b>Heart valve disease</b>								
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
<b>Cancer history</b>								
None	434	1395	31.1	1.00		1.00		
Localized Cancer	154	429	35.9	1.24	0.99-1.56	1.17	0.90-1.52	0.246
Metastatic Cancer	83	148	56.1	2.83	2.00-3.99	4.28	2.88-6.38	<0.001
<b>Group 2: Initial Bacteraemia Characteristics</b>								
<b>In vitro susceptibility</b>								
MSSA	510	1598	31.9	1.00		1.00		
MRSA	161	374	43.0	1.61	1.28-2.03	1.33	1.02-1.75	0.039
<b>Setting of acquisition</b>								
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	
<b>Primary focus</b>							1.00
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	1.45-3.55
Unknown focus	216	414	52.2	2.87	2.29-3.59	<0.001	2.02-3.41

### Group 3: Secondary foci and other complications

<b>Endocarditis</b>							
No	558	1686	33.1	1.00			
Yes	113	286	39.5	1.32	1.02-1.70	0.035	
<b>Stroke</b>							
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
<b>Heart Failure</b>							
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
<b>Mycotic Aneurism</b>							
No	656	1943	33.8	1.00			
Yes	15	29	51.7	2.10	1.01-4.38	0.047	
<b>Pulmonary 2<sup>ndary</sup> focus</b>							
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
<b>Osteo-articular 2<sup>ndary</sup> focus</b>							
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; <sup>a</sup>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. <sup>b</sup>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
<b>Monotherapy</b>										
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 <sup>a</sup>	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 <sup>b</sup>	138	9.0	4.5 (2-11)	63.8	24	17.4	19	13.8	37	26.8
<b>BitheraPy</b>										
ASP + aminoglycoside	138	9.0	8 (4-15)	60.9	19	13.7	20	14.5	27	19.6
Other beta-lactam <sup>c</sup> + 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 <sup>d</sup>	333	21.7	4 (2-9)	66.0	55	16.5	66	19.8	107	32.1
<b>Multiple therapy</b>										
Strategy with $\geq 3$ antibiotics	259	16.8	2 (1-4)	64.9	100	38.6	74	28.6	106	40.9
<b>Time to 1<sup>st</sup> antibiotic initiation</b>										
> 24 hours after blood culture collection	696	45.3	4 (2-9)	66.5	101	14.5	130	18.7	211	30.3
$\leq 24$ 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; <sup>a</sup> Ceftriaxone or cefotaxim (53%), amoxicillin (28%); <sup>b</sup> Fluoroquinolone (30%); <sup>c</sup> Ceftriaxone + aminoglycoside (44%); <sup>d</sup> 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 <sup>a</sup>				
	Dead	Treated	OR	CI	OR	CI			
<b>Variable 1: First line antibiotics</b>									
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 $\geq$ 3 antibiotics	106	259	40.9	0.92	0.54-1.55	0.746	0.67	0.35-1.26	0.216
<b>Variable 2: Time to 1<sup>st</sup> antibiotic initiation</b>									
> 24 hours after blood culture collection (Ref.)	211	696	30.3	1.00			1.00		
$\leq$ 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; <sup>a</sup>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 1<sup>st</sup> antibiotics initiation and First line antibiotic was not significant by likelihood ratio test, ( $p=0.72$ ); <sup>b</sup>  $p$  calculated using Wald's test

