J Antimicrob Chemother
doi:10.1093/jac/dkt016

Journal of Antimicrobial Chemotherapy

Predictive factors for early mortality among patients with methicillin-resistant *Staphylococcus aureus* bacteraemia

O. Gasch[1]*, M. Camoez[1], M. A. Domínguez[1], B. Padilla[2], V. Pintado[3], B. Almirante[4], J. A. Lepe[5], M. Lagarde[6], E. Ruiz de Gopegui[7], J. A. Martínez[8], M. Montejo[9], J. Torre-Cisneros[10], A. Arnáiz[11], M. A. Goenaga[12], N. Benito[13], J. Rodríguez-Baño[14] and M. Pujol[1] on behalf of the REIPI/GEIH Study Groups†

[1]Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain; [2]Hospital Gregorio Marañón, Madrid, Spain; [3]Hospital Universitario Ramón y Cajal, Madrid, Spain; [4]Hospital Universitari Vall d'Hebrón, Barcelona, Spain; [5]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [6]Hospital Universitario 12 de Octubre, Madrid, Spain; [7]Hospital Universitari Son Dureta, Palma de Mallorca, Spain; [8]Hospital Clínic, Barcelona, Spain; [9]Hospital de Cruces, Barakaldo, Spain; [10]Hospital Universitario Reina Sofía, Córdoba, Spain; [11]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [12]Hospital de Donostia, Donostia, Spain; [13]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [14]Hospital Universitario Virgen de Macarena, Sevilla, Spain

*Corresponding author. Infectious Diseases Service, Hospital de Bellvitge, Barcelona, Spain. Tel: +34-932607500; Fax: +34-932607637; E-mail: ogasch@bellvitgehospital.cat
†Members of the REIPI/GEIH Study Groups are listed in the Acknowledgements section.

Received 29 November 2012; returned 17 December 2012; revised 30 December 2012; accepted 8 January 2013

Objectives: A high proportion of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia die within a few days of the onset of infection. However, predictive factors for early mortality (EM) have barely been examined. The aim of this study was to determine the predictive factors for EM in patients with MRSA bacteraemia.

Methods: All episodes of MRSA bacteraemia were prospectively followed in 21 Spanish hospitals from June 2008 to December 2009. Epidemiology, clinical data, therapy and outcome were recorded. All MRSA strains were analysed in a central laboratory. Mortality was defined as death from any cause occurring in the 30 days after the onset of MRSA bacteraemia. EM was defined as patients who died within the first 2 days, and late mortality (LM) for patients who died after this period. Multivariate analyses were performed by using logistic regression models.

Results: A total of 579 episodes were recorded. Mortality was observed in 179 patients (31%): it was early in 49 (8.5%) patients and late in 130 (22.5%). Independent risk factors for EM were [OR (95% CI)] initial Pitt score >3 [3.99 (1.72–3.24)], previous rapid fatal disease [3.67 (1.32–10.24)], source of infection lower respiratory tract or unknown [3.76 (1.31–10.83) and 2.83 (1.11–7.21)], non-nosocomial acquisition [2.59 (1.16–5.77)] and inappropriate initial antibiotic therapy [3.59 (1.63–7.89)]. When predictive factors for EM and LM were compared, inappropriate initial antibiotic therapy was the only distinctive predictor of EM, while endocarditis and lower respiratory tract sources both predicted LM.

Conclusions: In our large cohort of patients several factors were related to EM, but the only distinctive predictor of EM was inappropriate initial antibiotic therapy.

Keywords: MRSA, bloodstream infections, empirical antibiotic therapy

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia is currently a cause of concern in Spain, where the incidence is 7/100 000 patient days and the percentage of methicillin resistance is 30.[1] Mortality among patients with MRSA bacteraemia is close to 30%.[2–4] Predictive factors for mortality have been related to host and microorganism characteristics and the interaction between them, and to therapeutic interventions.[5,6] The impact of host factors on mortality has been extensively analysed; age and comorbidities are the factors identified most frequently.[7] Regarding the interaction between host and MRSA, certain sources of bacteraemia have also been associated with mortality.[8] Some studies have also noted the significance of the setting of acquisition.[9,10] The influence of high MRSA vancomycin MIC on mortality has been widely debated in recent years.

While some studies report worse outcomes in episodes caused by strains with higher vancomycin MICs, even in the susceptible range,[8,11] others do not.[12–16] The impact of distinct MRSA clones on mortality has received little attention.[17,18] Lastly, inappropriate empirical therapy has been described as a predictor of mortality,[19,20] but some studies did not find a significant relationship with poor outcome.[21]

Although a large proportion of deaths occur within the first few days after the onset of *S. aureus* bacteraemia,[2,22] predictors of early mortality (EM) have barely been examined.[23] The objective of this study was to determine distinctive predictors of EM in a large cohort of patients with MRSA bacteraemia.

Patients and methods

Study period and patients

The study was conducted from June 2008 to December 2009 in 21 Spanish hospitals. Four centres had <500 beds, nine had 500–1000 beds and eight had >1000 beds. All consecutive episodes of MRSA bacteraemia observed in adult patients in participating centres were prospectively followed using a standardized protocol. Cases that did not meet the inclusion criteria because of a lack of signs and symptoms consistent with sepsis were excluded. Strains were sent to a central laboratory for further studies.

Study design

Patients with MRSA bacteraemia were classified into three groups according to outcome: (i) patients with EM; (ii) patients with late mortality (LM); and (iii) survivors. With the data, we carried out univariate and multivariate analyses to assess the predictive factors for EM. Then, following the methodology described by Harris *et al*.,[24] two separate analyses were performed: the first compared patients with EM and survivors and the second compared patients with LM and survivors. Variables with statistical significance in the first analysis but not in the second were considered distinctive factors for EM; those that were significant only in the second analysis were considered distinctive predictors of LM.

Definitions

MRSA bacteraemia was defined as the presence of at least one positive blood culture for MRSA in a blood sample from a patient with clinical findings consistent with infection.[25] Comorbidity was measured by the Charlson score,[26] which stratifies the associated diseases on an ordinal scale. Patients were classified into three categories on the McCabe scale,[27] according to their vital prognosis before the MRSA bacteraemia: non-fatal if death was expected within a period of >5 years; ultimately fatal if death was expected between 1 and 5 years; and rapidly fatal if it was expected within the following year. Severity of sepsis in the acute condition was assessed by the Pitt score.[28] According to the Friedman criteria,[29] three acquisition categories were considered: (i) nosocomial bacteraemia if the episode was diagnosed at least 48 h after admission to an ICU or a conventional (non-ICU) hospital ward and if there were no signs or symptoms of infection at admission; (ii) healthcare-related bacteraemia if previous contact with the healthcare system was recorded within the previous 3 months; and (iii) community acquisition if the episode did not fit the previous conditions. The source of the bacteraemia was defined according to the CDC criteria.[30] Bacteraemia from an unknown source (primary) was defined when the origin was uncertain after careful examination of the clinical and microbiological data. Distant extension was diagnosed with the presence of at least one distant infection secondary to blood spread seeding. The initial antibiotic was defined as the antibiotic administered in the first 48 h after the onset of bacteraemia, independently of the microbiological information. Initial antibiotic treatment was considered appropriate if the strain was susceptible to at least one of the antibiotics administered according to the current CLSI breakpoints,[31] with the exception of aminoglycosides, which were considered inappropriate regardless of the susceptibility test results. Source was considered eradicated if the catheter or foreign body was removed, if surgery on the source was carried out or if the bacteraemia source was drained. For outcomes, mortality was defined as in-hospital death from any cause occurring in the 30 days after the onset of MRSA bacteraemia. Mortality was defined as EM for patients who died within the first 2 days and LM for patients who died later.

Susceptibility testing and molecular epidemiology of MRSA isolates

Each hospital identified the strain and performed preliminary susceptibility tests. Isolates were sent to a central reference laboratory. All *S. aureus* were identified by latex agglutination (Pastorex Staph-plus, Bio-Rad Laboratories, Madrid, Spain) and DNase production (DNasE-test Agar, bioMérieux, Marcy l'Étoile, France). Antimicrobial susceptibility of all MRSA isolates was tested by the disc diffusion method according to the CLSI guidelines.[31] The antimicrobial agents tested were penicillin, oxacillin, cefoxitin, erythromycin, clindamycin, gentamicin, tobramycin, ciprofloxacin, rifampicin, trimethoprim/sulfamethoxazole, tetracycline, fosfomycin, vancomycin, teicoplanin, chloramphenicol, daptomycin and linezolid. MICs were determined by the microdilution method in accordance with CLSI criteria by using commercial panels (ESTEN 2009, Sensititre™, Izasa, Barcelona, Spain) read visually. Vancomycin MICs were also determined by Etest (bioMérieux) on Mueller–Hinton agar, using a turbidity equivalent to that of a 0.5 McFarland standard.

PFGE was performed after SmaI restriction of chromosomal DNA.[32] Restriction patterns were interpreted in accordance with criteria published elsewhere.[33] Representative isolates of each PFGE type and subtype were studied to determine the multilocus sequence type (MLST)[34] and the staphylococcal chromosome cassette *mec* (SCC*mec*) type.[35] MLSTs and SCC*mec* types were further inferred for all the strains. The *agr* polymorphism and the presence of genes encoding class S (*lukS-PV*) and class F (*lukF-PV*) proteins for Panton–Valentine leucocidin (PVL) were studied by PCR in all the isolates, following the methodology described elsewhere.[36,37]

Statistical analysis

Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U*-test as appropriate. Qualitative and stratified continuous variables were compared using Fisher's exact test or Pearson's χ^2 test. Relative risks were calculated with 95% CIs in a univariate analysis. The multivariate analyses were performed by using logistic regression models. All the variables with theoretical clinical significance and those that achieved a *P* value <0.10 in the univariate analysis were included in the multivariate analysis and adjusted ORs were calculated with 95% CIs. Analyses were performed using SPSS v15 (Microsoft, USA).

Ethics considerations

The study was approved by the Spanish Network for Research in Infectious Diseases (REIPI) and by the Institutional Review Board at each participating centre. Because no direct patient contact was planned, the requirement for informed consent was waived. The data were de-identified in each centre and only then transferred for analysis.

Results

Overall, 590 episodes of MRSA bacteraemia were recorded. Eleven of them were excluded due to the lack of complete

information. Therefore, 579 episodes were finally included in the analysis. One hundred and seventy-nine patients (31%) died: 49 (8.5%) were defined as EM and 130 (22.5%) as LM. There were 400 (69%) survivors.

Risk factors for EM

The cohort of patients with EM ($n=49$) was compared with the rest ($n=530$). Clinical and microbiological characteristics and therapeutic interventions were included in the univariate and multivariate analyses. Independent risk factors for EM according to logistic regression analysis were rapidly fatal disease (OR 3.67; $P=0.012$), respiratory and unknown sources (OR 3.76; $P=0.014$ and 2.83; $P=0.029$ respectively), non-nosocomial acquisition (OR 2.59; $P=0.021$), Pitt score of ≥3 (OR 3.99; $P=0.001$) and inappropriate initial antibiotic therapy within the first 2 days (OR 3.59; $P=0.001$). No microbiological characteristics, such as *agr* type, clonal complex characterization, PVL or vancomycin MIC, were significantly related to EM (Table 1).

Distinctive predictive factors for EM and LM

Multivariate analysis to identify distinctive predictors for EM and LM are shown in Tables 2 and 3. Survivors and non-survivors were compared. Patients with EM ($n=49$) were more likely to be aged >70 years than survivors (OR 2.77; $P=0.026$), more likely to have

Table 1. Factors independently associated with EM in a logistic regression model of all patients with MRSA bacteraemia

		Early deaths, $n=49$ *n* (%)	Non-early deaths, $n=530$ *n* (%)	Univariate		Multivariate adjusted OR (95% CI)
				OR	*P* value	
Clinical characteristics						
age (years)	>70	33 (67)	283 (54)	1.79	0.07	1.46 (0.66–3.24)
gender	female	15 (31)	179 (34)	0.87	0.65	1.05 (0.48–2.33)
Charlson score	>5	15 (31)	148 (28)	1.13	0.71	
McCabe scale	non-fatal	14 (30)	265 (50)			
	ultimately fatal	20 (43)	192 (37)	1.97	0.06	
	rapidly fatal	13 (28)	69 (13)	3.57	0.02	3.67 (1.32–10.24)
source	skin and soft tissues	4 (8)	77 (15)	1.57	0.48	
	surgical site infection	2 (4)	34 (6)	1.77	0.49	
	catheter	7 (14)	211 (40)			
	endocarditis	1 (2)	16 (3)	1.89	0.57	
	lower respiratory tract	13 (27)	57 (11)	6.88	<0.01	3.76 (1.31–10.83)
	unknown source	17 (35)	77 (15)	6.67	<0.01	2.83 (1.11–7.21)
distant secondary focus		3 (6)	99 (19)	0.28	0.04	
foreign body presence		16 (33)	253 (48)	0.53	0.05	
acquisition	nosocomial	20 (42)	318 (60)			
	non-nosocomial[a]	28 (58)	210 (40)	2.12	0.01	2.59 (1.16–5.77)
Pitt score	>3	24 (49)	92 (18)	4.52	<0.01	3.99 (1.72–9.24)
Microbiological studies						
agr type	I	15 (31)	108 (21)			
	II	32 (67)	386 (77)	0.59	0.12	
	III	1 (2)	10 (2)	0.72	0.76	
PFGE type	12	9 (19)	24 (5)			
	4	1 (2)	47 (9)	0.57	<0.01	
	5	1 (2)	31 (6)	0.09	0.02	
	2	30 (63)	341 (68)	0.24	0.01	
clonal complex	5[b]	32 (67)	385 (78)			
	8	9 (19)	35 (7)	3.09	<0.01	
	22	1 (2)	46 (9)	0.26	0.19	
	other	6 (13)	28 (6)	2.58	0.06	
PVL		1 (2)	14 (3)	0.75	0.78	
vancomycin MIC	≥1.5 mg/L	4 (8)	14 (3)	3.18	0.05	
Initial treatment (<48 h)						
source drainage		6 (12)	199 (38)	0.23	<0.01	
inappropriate initial antibiotic		31 (67)	170 (32)	4.33	<0.01	3.59 (1.63–7.89)

[a]Non-nosocomial acquisition includes healthcare-related and community acquisitions.
[b]Clonal complex 5 (CC5) includes ST125, ST146 and ST228.

Table 2. Associated factors for EM (compared with 30 day survivors); logistic regression model

		Univariate *P* value	Multivariate adjusted OR (95% CI)
Clinical characteristics			
age (years)	>70	0.01	2.77 (1.11–6.89)
gender	female	0.84	
Charlson score	>5	0.39	
McCabe scale	non-fatal		
	ultimately fatal	0.03	
	rapidly fatal	<0.01	10.38 (3.13–34.4)
Pitt score	>3	<0.01	13.36 (4.46–39.9)
acquisition	nosocomial		
	non-nosocomial[a]	0.031	
source	vascular catheter		
	skin and soft tissues	0.51	
	surgical site infection	0.46	
	endocarditis	0.40	
	lower respiratory tract	<0.01	
	unknown	<0.01	5.16 (1.67–15.9)
foreign body presence		0.03	
Microbiological studies			
agr type	I		
	II	0.11	
	III	0.76	
PFGE type	12		
	4	0.06	
	5	0.03	
	2	0.01	
clonal complex	5[b]		
	8	<0.01	
	22	0.17	
	other	0.08	
PVL		0.85	
vancomycin MIC	≥1.5 (mg/L)	0.08	
Initial treatment (<48 h)			
source drainage		<0.01	
inappropriate initial antibiotic		<0.01	3.88 (1.55–9.73)

[a]Non-nosocomial acquisition includes healthcare-related and community acquisitions.
[b]CC5 includes ST125, ST146 and ST228.

rapidly fatal disease (OR 10.38; $P<0.001$), unknown source (OR 5.16; $P=0.004$), a Pitt score ≥3 (OR 13.36; $P<0.001$) and inappropriate initial antibiotic therapy within the first 2 days (OR 3.88; $P=0.004$). Patients with LM ($n=130$) were more likely to be aged >70 years (OR 3.32; $P<0.001$), to have rapidly fatal disease (OR 8.55; $P<0.001$), endocarditis and lower respiratory tract and unknown sources (OR 4.12; $P=0.011$, OR 2.46; $P=0.039$ and OR 3.07; $P=0.003$, respectively) and a Pitt score of ≥3 (OR 6.07; $P<0.001$) than survivors.

A comparison of the two models showed that for patients with EM inappropriate initial antibiotic therapy within the first 2 days was an independent distinctive factor (Figure 1), while endocarditis and lower respiratory tract sources were distinctive factors for LM. Old age, rapidly fatal disease, unknown source and Pitt score were associated with mortality in both groups.

Discussion

More than 20 years since the dissemination of MRSA strains in Spanish hospitals, our knowledge of this microorganism has significantly improved. However, mortality of patients with MRSA bacteraemia remains high, close to 30%.[38] In this large multicentre, prospective study we found that a considerable proportion of all-cause deaths among patients with MRSA bacteraemia occurred in the first 2 days after onset. Inappropriate antibiotic therapy was identified as a distinctive predictor of EM, and endocarditis and lower respiratory tract sources were identified as predictors of LM.

Although this issue has not been specifically studied to date, we infer that about 50% of non-survivors may die within the first 4–9 days after the onset of staphylococcal bacteraemia.[3,39,40] To our knowledge, there are no studies that analyse in detail the

Table 3. Associated factors for LM (compared with 30 day survivors); logistic regression model

		Univariate *P* value	Multivariate adjusted OR (95% CI)
Clinical characteristics			
age (years)	>70	<0.01	3.32 (1.92–5.73)
gender	woman	0.24	
Charlson score	>5	0.01	
McCabe scale	non-fatal		
	ultimately fatal	0.02	
	rapidly fatal	<0.01	8.55 (4.08–17.91)
Pitt score	>3	<0.01	6.07 (3.33–11.07)
acquisition	nosocomial		
	non-nosocomial[a]	0.20	
source	vascular catheter		
	skin and soft tissues	0.23	
	surgical site infection	0.59	
	endocarditis	0.06	4.12 (1.48–11.45)
	lower respiratory tract	0.05	2.46 (1.04–5.79)
	unknown	0.003	3.07 (1.46–6.45)
foreign body presence		0.23	
Microbiological studies			
agr type	I		
	II	0.95	
	III	0.78	
PFGE type	12		
	4	0.53	
	5	0.96	
	2	0.58	
clonal complex	5[b]		
	8	0.55	
	22	0.72	
	other	0.64	
PVL		0.70	
vancomycin MIC	≥1.5 (mg/L)	0.69	
Initial treatment (<48 h)			
source drainage		0.14	
inappropriate initial antibiotic		0.76	

[a]Non-nosocomial acquisition includes healthcare-related and community acquisitions.
[b]CC5 includes ST125, ST146 and ST228.

factors associated with EM. However, a recent population study from the UK found a rate of EM of 11% and reported that the highest risk of death (4.5%) was during the first day of bacteraemia.[23] The absence of clinical, microbiological and treatment data in that study limits the possibility of further analysis regarding the risk factors for EM.

Studies that have examined the relationship between inappropriate empirical therapy and mortality in *S. aureus* and MRSA bacteraemia have yielded conflicting results. Although some studies did not find a significant association,[21,41,42] many others did: Soriano *et al.*[10] identified inappropriate therapy as a predictor of related mortality, with an OR of 2.13, as did Rodríguez-Baño *et al.*[20] in a cohort of healthcare-acquired sepsis due to MRSA (OR 3.0). Marchaim *et al.*[43] identified a delay of 2 days in receiving appropriate antibiotic therapy as a predictor of in-hospital mortality (OR 2.35) and Paul *et al.*[19] reported a significant association with 30 day mortality. Lodise and McKinnon[4] also found an association with 30 day mortality (OR 2.1) and infection-related death (OR 2.2). Lastly, a delay in adequate antibiotic therapy of >44.76 h was identified as an independent predictor of related mortality (OR 3.8) in patients with *S. aureus* bacteraemia.[22] In the study by Lodise and McKinnon,[4] MRSA was an independent predictor of delayed therapy. In our opinion, the identification of inappropriate initial antibiotic therapy as the distinctive predictor of EM supports the hypothesis that the use of 30 day mortality rate may be an excessively crude way of assessing the impact of initial antibiotic therapy.

Our results reinforce the importance of ensuring early administration of adequate antibiotic treatment when MRSA bacteraemia is a diagnostic possibility. As in other studies,[19] a great

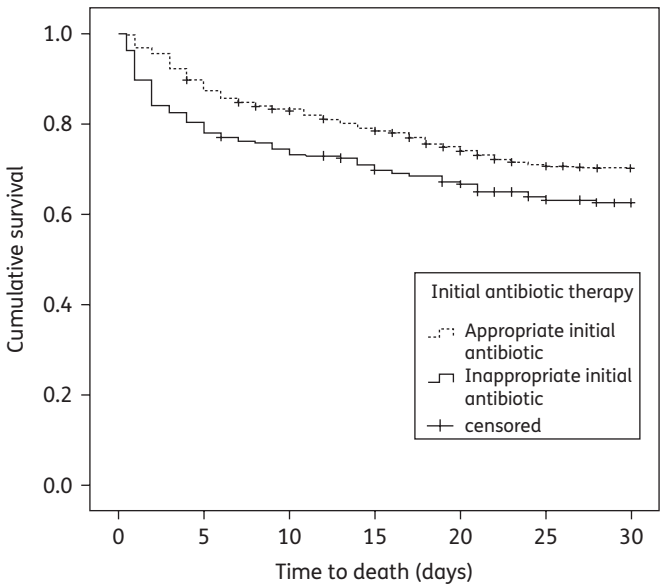

Figure 1. Survival analysis of MRSA bacteraemia episodes according to the administration of appropriate initial antibiotic therapy.

proportion of patients in our series received inappropriate coverage, especially when acquisition was non-nosocomial (data not shown). This is a striking observation since risk factors for MRSA bacteraemia at hospital admission are well established,[44,45] the most significant one being referral from a long-term care facility and prior MRSA colonization. This information should be taken into account to avoid unnecessary delays in the administration of appropriate antibiotic therapy.

Our study has some limitations. First, our definition of appropriate antibiotic therapy is controversial: antibiotics classified as inadequate, such as aminoglycosides, may have some effect on MRSA. Also, glycopeptides were classified as appropriate regardless of serum levels, which were not always assessed in the first 48 h. In contrast, some bacteriostatic antibiotics classified as appropriate would not usually be used as first choice against MRSA bacteraemia, as other authors have previously pointed out.[46,47] Second, differences between centres regarding the clinical management and early suspicion of the infection as well as time until the microbiological identification of susceptibility patterns and the presence of the gene *mecA* may confound the evaluation of antibiotic therapy during the first 2 days.

In summary, our experience suggests that inappropriate antibiotic treatment plays a crucial role in EM among patients with MRSA bacteraemia. Strategies to ensure the adequacy of empirical antibiotic therapy are needed.

Acknowledgements

Writing assistance was provided by the Department of Languages in the Faculty of Medicine of Barcelona University.

Members of the REIPI/GEIH Study Groups

A Jover, F Barcenilla, M Garcia (H Arnau de Vilanova, Lleida, Spain); M Pujol, O Gasch, MªA Domínguez, M Camoez (H Universitari de Bellvitge, Barcelona, Spain); C Dueñas, E Ojeda (H de Burgos, Burgos Spain); JA Martinez, F Marco (H Clínic, Barcelona, Spain); F Chaves, M Lagarde, F López-Medrano (H Universitario 12 de Octubre, Madrid, Spain); JM Montejo, E Bereciartua, JL Hernández (H de Cruces, Barakaldo, Spain); MÁ Von Wichmann, A Goenaga, JM García-Arenzana (H de Donostia, Donostia, Spain); B Padilla, C Padilla, E Cercenado (H General Universitario Gregorio Marañón, Madrid, Spain); G García-Pardo, J Tapiol (H Universitari Joan XXIII, Tarragona, Spain); JP Horcajada, M Montero, M Salvadó (H Universitari del Mar, Barcelona, Spain); A Arnáiz, C Fernandez (H Universitario Marques de Valdecilla, Santander, Spain); E Calbo; M Xercavins (H Universitari Mútua de Terrassa, Terrassa, Spain); A Granados, D Fontanals (H del Parc Taulí, Sabadell, Spain); V Pintado, E Loza (H Universitario Ramon y Cajal, Madrid, Spain); J Torre-Cisneros, R Lara, F Rodríguez-López, M Rodríguez, C Natera (H Universitario Reina Sofía, Córdoba, Spain); JR Blanco, I Olarte (H San Pedro de la Rioja, Logroño, Spain); N Benito, B Mirelis (H de la Santa Creu i Sant Pau, Barcelona, Spain); J Murillas, E Ruiz de Gopegui (H Universitari Son Dureta, Palma de Mallorca, Spain); H Espejo, MªA Morera (H de Terrassa, Terrassa, Spain); J Rodríguez-Baño, E López, A Pascual (H Universitario Virgen Macarena, Sevilla, Spain); C Martín, JA Lepe, J Molina (H Universitario Virgen del Rocio, Sevilla, Spain); R Sordé, B Almirante, N Larrosa (H Universitari Vall d'Hebrón, Barcelona, Spain).

Funding

This study was supported by Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (FIS 08/0335) and co-financed by the European Development Regional Fund 'A way to achieve Europe' ERDF, Spanish Network for Research in Infectious Diseases (REIPI RD06/0008).

O. G. is the recipient of a Río Hortega grant (CM08/228) from the Instituto de Salud Carlos III.

Transparency declarations

B. A. has received funding for research from Pfizer, Novartis, Gilead and MSD, and funds for advisory board membership from Pfizer, Gilead, Novartis, Janssen, Astellas and MSD. N. B. has received funding for speaking, consultancy, advisory board membership and travel from MSD, Pfizer, Gilead, Novartis and AstraZeneca. J. R.-B. has received funding for research from Novartis, has served as speaker for Astellas, Merck, AstraZeneca and Pfizer, and has been a consultant for Roche, Novartis and Janssen. All other authors: none to declare.

References

1 European Centre for Disease Prevention and Control (ECDC). *Annual Epidemiological Report on Communicable Diseases in Europe*. 2010. Stockholm: ECDC. http://www.ecdc.europa.eu/en/eaad/documents/eaad-2011-summary-antimicrobial-resistance-data.pdf (28 December 2012, date last accessed).

2 Benfield T, Espersen F, Frimodt-Moller N *et al*. Increasing incidence but decreasing in-hospital mortality of adult *Staphylococcus aureus* bacteraemia between 1981 and 2000. *Clin Microbiol Infect* 2007; **13**: 257–63.

3 Kaech C, Elzi L, Sendi P *et al*. Course and outcome of *Staphylococcus aureus* bacteraemia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. *Clin Microbiol Infect* 2006; **12**: 345–52.

4 Lodise TP, McKinnon PS. Clinical and economic impact of methicillin resistance in patients with *Staphylococcus aureus* bacteremia. *Diagn Microbiol Infect Dis* 2005; **52**: 113–22.

5 Liao CH, Chen SY, Huang YT *et al*. Outcome of patients with meticillin-resistant *Staphylococcus aureus* bacteraemia at an emergency department of a medical centre in Taiwan. *Int J Antimicrob Agents* 2008; **32**: 326–32.

6 Lin SH, Liao WH, Lai CC *et al*. Risk factors for mortality in patients with persistent methicillin-resistant *Staphylococcus aureus* bacteraemia in a tertiary care hospital in Taiwan. *J Antimicrob Chemother* 2010; **65**: 1792–8.

7 van Hal SJ, Jensen SO, Vaska VL *et al*. Predictors of mortality in *Staphylococcus aureus* bacteremia. *Clin Microbiol Rev* 2012; **25**: 362–86.

8 Soriano A, Marco F, Martinez JA *et al*. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2008; **46**: 193–200.

9 Holmes NE, Turnidge JD, Munckhof WJ *et al*. Antibiotic choice may not explain poorer outcomes in patients with *Staphylococcus aureus* bacteremia and high vancomycin minimum inhibitory concentrations. *J Infect Dis* 2011; **204**: 340–7.

10 Soriano A, Martinez JA, Mensa J *et al*. Pathogenic significance of methicillin resistance for patients with *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2000; **30**: 368–73.

11 Lodise TP, Graves J, Evans A *et al*. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. *Antimicrob Agents Chemother* 2008; **52**: 3315–20.

12 Rojas L, Bunsow E, Munoz P *et al*. Vancomycin MICs do not predict the outcome of methicillin-resistant *Staphylococcus aureus* bloodstream infections in correctly treated patients. *J Antimicrob Chemother* 2012; **67**: 1760–8.

13 van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin Infect Dis* 2012; **54**: 755–71.

14 Pastagia M, Kleinman LC, Lacerda de la Cruz EG *et al*. Predicting risk for death from MRSA bacteremia. *Emerg Infect Dis* 2012; **18**: 1072–80.

15 Albur MS, Bowker K, Weir I *et al*. Factors influencing the clinical outcome of methicillin-resistant *Staphylococcus aureus* bacteraemia. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 295–301.

16 Honda H, Doern CD, Michael-Dunne W Jr *et al*. The impact of vancomycin susceptibility on treatment outcomes among patients with methicillin resistant *Staphylococcus aureus* bacteremia. *BMC Infect Dis* 2011; **11**: 335.

17 Fowler VG Jr, Nelson CL, McIntyre LM *et al*. Potential associations between hematogenous complications and bacterial genotype in *Staphylococcus aureus* infection. *J Infect Dis* 2007; **196**: 738–47.

18 Lalani T, Federspiel JJ, Boucher HW *et al*. Associations between the genotypes of *Staphylococcus aureus* bloodstream isolates and clinical characteristics and outcomes of bacteremic patients. *J Clin Microbiol* 2008; **46**: 2890–6.

19 Paul M, Kariv G, Goldberg E *et al*. Importance of appropriate empirical antibiotic therapy for methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother* 2010; **65**: 2658–65.

20 Rodríguez-Baño J, Millán AB, Domínguez MA *et al*. Impact of inappropriate empirical therapy for sepsis due to health care-associated methicillin-resistant *Staphylococcus aureus*. *J Infect* 2009; **58**: 131–7.

21 Roghmann MC. Predicting methicillin resistance and the effect of inadequate empiric therapy on survival in patients with *Staphylococcus aureus* bacteremia. *Arch Intern Med* 2000; **160**: 1001–4.

22 Lodise TP, McKinnon PS, Swiderski L *et al*. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2003; **36**: 1418–23.

23 Lamagni TL, Potz N, Powell D *et al*. Mortality in patients with meticillin-resistant *Staphylococcus aureus* bacteraemia, England 2004–2005. *J Hosp Infect* 2011; **77**: 16–20.

24 Harris AD, Samore MH, Lipsitch M *et al*. Control-group selection importance in studies of antimicrobial resistance: examples applied to *Pseudomonas aeruginosa*, enterococci, and *Escherichia coli*. *Clin Infect Dis* 2002; **34**: 1558–63.

25 Levy MM, Fink MP, Marshall JC *et al*. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; **31**: 1250–6.

26 Charlson ME, Pompei P, Ales KL *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83.

27 McCabe WR, Jackson GG. Gram-negative bacteremia. Clinical, laboratory and therapeutic observations. *Arch Intern Med* 1962; **110**: 856–64.

28 Chow JW, Yu VL. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. *Int J Antimicrob Agents* 1999; **11**: 7–12.

29 Friedman ND, Kaye KS, Stout JE *et al*. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002; **137**: 791–7.

30 Garner JS, Jarvis WR, Emori TG *et al*. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; **16**: 128–40.

31 Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Seventeenth Informational Supplement M100-S17*. CLSI, Wayne, PA, USA, 2007.

32 Chung M, de Lencastre H, Matthews P *et al*. Molecular typing of methicillin-resistant *Staphylococcus aureus* by pulsed-field gel electrophoresis: comparison of results obtained in a multilaboratory effort using identical protocols and MRSA strains. *Microb Drug Resist* 2000; **6**: 189–98.

33 Tenover FC, Arbeit RD, Goering RV *et al*. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. *J Clin Microbiol* 1995; **33**: 2233–9.

34 Enright MC, Day NP, Davies CE *et al*. Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus*. *J Clin Microbiol* 2000; **38**: 1008–15.

35 Milheirico C, Oliveira DC, de Lencastre H. Update to the multiplex PCR strategy for assignment of mec element types in *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2007; **51**: 3374–7.

36 Shopsin B, Mathema B, Alcabes P *et al*. Prevalence of agr specificity groups among *Staphylococcus aureus* strains colonizing children and their guardians. *J Clin Microbiol* 2003; **41**: 456–9.

37 Lina G, Piemont Y, Godail-Gamot F *et al*. Involvement of Panton-Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. *Clin Infect Dis* 1999; **29**: 1128–32.

38 Gasch O, Ayats J, Angeles DM *et al*. Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection: secular trends over 19 years at a university hospital. *Medicine (Baltimore)* 2011; **90**: 319–27.

39 Cosgrove SE, Sakoulas G, Perencevich EN *et al*. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis* 2003; **36**: 53–9.

40 Mylotte JM, Tayara A. *Staphylococcus aureus* bacteremia: predictors of 30-day mortality in a large cohort. *Clin Infect Dis* 2000; **31**: 1170–4.

41 Fang CT, Shau WY, Hsueh PR *et al*. Early empirical glycopeptide therapy for patients with methicillin-resistant *Staphylococcus aureus* bacteraemia: impact on the outcome. *J Antimicrob Chemother* 2006; **57**: 511–9.

42 Libert M, Elkholti M, Massaut J *et al*. Risk factors for meticillin resistance and outcome of *Staphylococcus aureus* bloodstream infection in a Belgian university hospital. *J Hosp Infect* 2008; **68**: 17–24.

43 Marchaim D, Kaye KS, Fowler VG *et al*. Case-control study to identify factors associated with mortality among patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. *Clin Microbiol Infect* 2010; **16**: 747–52.

44 Manzur A, Vidal M, Pujol M *et al*. Predictive factors of meticillin resistance among patients with *Staphylococcus aureus* bloodstream infections at hospital admission. *J Hosp Infect* 2007; **66**: 135–41.

45 Tacconelli E, Venkataraman L, De Girolami PC *et al*. Methicillin-resistant *Staphylococcus aureus* bacteraemia diagnosed at hospital admission: distinguishing between community-acquired versus healthcare-associated strains. *J Antimicrob Chemother* 2004; **53**: 474–9.

46 McGregor JC, Rich SE, Harris AD *et al*. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. *Clin Infect Dis* 2007; **45**: 329–37.

47 Moellering RC Jr. What is inadequate antibacterial therapy? *Clin Infect Dis* 2009; **49**: 1006–8.