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ARTICLE

Community-onset bacteraemia of unknown origin: clinical characteristics, epidemiology and outcome

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Abstract Bacteraemia of unknown origin is prevalent and has a high mortality rate. However, there are no recent reports focusing on this issue. From 2005 to 2011, all episodes of community onset bacteraemia of unknown origin (CO-BSI), diagnosed at a 700-bed university hospital were prospectively included. Risk factors for Enterobactericeae resistant to third-generation cephalosporins (3GCR-E), Pseudomonas aeruginosa, *Staphylococcus aureus* and *Enterococcus* spp, and predictors of mortality were assessed by logistic regression. Out of 4,598 consecutive episodes of CO-BSI, 745 (16.2 %) were of unknown origin. Risk factors for *S. aureus* were male gender (OR 2.26; 1.33–3.83), diabetes mellitus (OR 1.71; 1.01–2.91) and intravenous drug addiction (OR 17.24; 1.47–202); for *P. aeruginosa* were male gender (OR 2.19; 1.10–4.37) and health-care associated origin (OR 9.13; 3.23–25.83); for 3GCR-E was recent antibiotic exposure (OR 2.53; 1.47–4.35), while for enterococci, it was recent hospital admission (OR 3.02; 1.64–5.55). Seven and 30-day mortality were 8.1 % and 13.4 %, respectively. Age over 65 years (OR 2.13; 1.28–3.55), an ultimately or rapidly fatal underlying disease (OR 4.15; 2.23–7.60), bone marrow transplantation (OR 4.07; 1.24–13.31), absence of fever (OR 4.45; 2.25–8.81), shock on presentation (OR 10.48; 6.05–18.15) and isolation of *S. aureus* (OR 2.01; 1.00–4.04) were independently associated with mortality. In patients with bacteraemia of unknown origin, a limited number of clinical characteristics may be useful to predict its aetiology and to choose the appropriate empirical treatment. Although no modifiable prognostic factors have been found, management optimization of *S. aureus* should be considered a priority in this setting.

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Introduction

Bloodstream infections (BSI) remain a leading cause of morbidity and mortality [1] and are currently the 11th leading cause of death in the United States [2]. The latest studies on community-onset bacteraemia that encompass health-care-associated (HCA) and community-acquired (CA) bloodstream infections report an overall 30-day mortality of 13.5–20 % [3–5]. Bacteraemia of unknown origin represent between 9 and 22 % of all bacteremic episodes and are associated with increased mortality [4, 5] in comparison to those with a known source.

Appropriate empirical antibiotic treatment has been commonly associated with a better outcome in patients with bloodstream infections [6, 7]. Knowledge of the source of the infection usually helps in the selection of appropriate empirical treatment by narrowing the range of potential aetiological microorganisms.

There is limited data focusing on bacteraemia of unknown origin, despite its high frequency and mortality rate. Our group has been interested in this aspect in recent years [8], but since important changes in epidemiology of resistant microorganisms have been observed, we believe that it is essential to re-evaluate the issue. The objective of our study was to analyze the current clinical and microbiological characteristics and outcome of patients with community-onset bacteraemia of unknown origin with emphasis on predictors of *Enterobactericeae* resistant to third-generation

cephalosporins (3GCR-E), *Pseudomonas aeruginosa, Staphylococcus aureus* and *Enterococcus* spp.

Materials and methods

Study design The study was conducted in a 700-bed university centre that provides specialized and broad medical, surgical, and intensive care for an urban population of 500,000 people. Since 1991 our unit has been prospectively identifying and monitoring all patients with bacteraemia admitted to our hospital. The present report refers to all adult patients (≥18 years old) with community-onset bacteraemia of unknown source recorded from January 2005 to December 2011. The Ethics Committee board of our institution approved the study.

Data collection and definitions

Assessed clinical variables The following data were obtained from all patients: age, gender, comorbidities, McCabe classification of underlying diseases, treatment with antibiotics or steroids in the previous month, recent hospitalization (within the last month), surgery and other invasive procedures, origin of infection (community or health-care related), source of bacteraemia, shock on presentation, need for mechanical ventilation, etiologic microorganisms, empirical antibiotic treatment, appropriateness of empirical therapy, and mortality (evaluated at 7 and 30 days).

Definitions Bacteraemic patients were prospectively followed up by a senior infectious disease specialist who assessed the patient's medical history, physical examination, the results of other microbiological tests and complementary imaging explorations in order to determine the source of infection. An unknown origin was established when no source could be identified.

Community-onset bacteraemia refers to health-care-associated (HCA-BSI) and community-acquired (CA-BSI) bloodstream infections. HCA-BSI were defined as those with a first positive blood culture obtained ≤2 days from admission in patients having at least one of the following characteristics: (1) Being discharged within 30 days from an acute care hospital, (2) Receiving haemodialysis or any kind of intravenous therapy provided by a hospital-dependent facility within 30 days prior to the bloodstream infection, or (3) Residence in a nursing home or long-term care facility. CA-BSI were defined as those with a first positive blood culture obtained ≤2 days from admission and not fulfilling criteria for HCA-BSI.

Prior antibiotic therapy was defined as the use of any antimicrobial agent for ≥3 days during the month prior to the occurrence of the bacteraemic episode. Empirical therapy was considered appropriate when the initial regimen administered within the first 24 h after blood cultures and before knowing the susceptibility testing results was active in vitro against all the subsequent isolated bacteria and the dosage and route of administration were in accordance with the current medical standards.

Microbiological methods During the study period, blood cultures were processed by the BACTEC 9240 system (Becton-Dickinson Microbiology Systems) with an incubation period of 5 days. Isolates were identified by standard techniques. Antimicrobial susceptibility testing was performed by using a microdilution system (Phoenix system [Becton, Dickinson, Franklin Lakes, NJ] or Etest [AB Biodisk, Solna, Sweden]). Current Clinical and Laboratory Standards Institute (CLSI) breakpoints for each year were used to define susceptibility or resistance to these antimicrobial agents, and intermediate susceptibility was considered as resistance.

Statistical analysis Data from different groups of patients were compared using chi-square or Fisher's exact tests for categorical variables and the Student *t* test or Mann-Whitney *U* test for continuous variables. Patient's characteristics or exposures with a *P* value of ≤0.20 in the univariate analysis were subjected to further selection by using a forward stepwise non-conditional logistic procedure, and the criteria for variables to step in and out the model were a P value of 0.05 and 0.10, respectively. To evaluate model calibration, the Hosmer-Lemeshow (H-L) test for goodness of fit was applied. The analysis was done by using the SPSS software (version 18.0; SPSS, Inc., Chicago, IL).

Results

During the study period, out of 4,598 consecutive episodes of community-onset bacteraemia a total of 745 (16.2 %) were of unknown origin. Patient clinical characteristics are shown in Table 1. Almost all (93.6 %) patients had comorbidities with the most frequent being haematological malignancies, solid organ cancer, diabetes mellitus and liver cirrhosis.

Of all isolated organisms, 391 (52.5 %) were Gram-negative bacteria, 357 (47.9 %) Gram-positive, 10 (1.3 %) fungi, and 18 (2.4 %) polymicrobial (Table 2). *E. coli*, *Klebsiella* spp. and *S. aureus* (including methicillin-resistant strains) were equally prevalent in HCA-BSI and CA-BSI. *P. aeruginosa* and coagulase-negative staphylococci were more frequent in HCA-BSI while *Listeria* spp., *Salmonella* spp. and *S. pneumoniae* predominated in CA-BSI. Third-generation cephalosporin resistance in *Enterobacteriaceae* and beta-lactam and ciprofloxacin resistance in

Table 1 Characteristics of patients

Variable	Value
Age, years (SD)	63.8 (17.54)
Gender, male (%)	414 (55.6)
Prognosis of underlying disease (McCabe) ultimately or rapidly fatal	449 (60.3)
Prior hospital admission	203 (27.2)
BSI subcategories	
CA-BSI	340 (45.6)
HCA-BSI	405 (54.4)
Comorbidity	
Hematological neoplasm	223 (29.9)
Solid organ cancer	158 (21.2)
Diabetes mellitus	151 (20.3)
Neutropenia	132 (17.7)
Liver cirrhosis	106 (14.2)
Chronic renal insufficiency	92 (12.3)
Hemodialysis	38 (5.1)
Heart disease	90 (12.1)
Chronic lung disease	66 (8.9)
Neurologic impairment	41 (5.5)
HIV infection	39 (5.2)
SOT	31 (4.2)
HSCT	26 (3.5)
Uropathology	12 (1.6)
Clinical findings on the day of bacteraemia	
Fever	685 (91.9)
Shock	86 (11.5)
Extrinsic risk factors	
Corticosteroids	154 (20.7)
Previous antibiotic therapy (last month)	189 (25.4)
Previous surgery (last month)	14 (1.9)
Indwelling urinary catheter	38 (5.1)
Endovascular catheterization	189 (25.4)
Admission ICU	76 (10.2)
Inappropriate empirical therapy	189 (25.4)
Mortality	
Seven days	60 (8.1)
Thirty days	100 (13.4)

HSCT haematopoietic stem cell transplantation, *SOT* solid-organ transplantation

P. aeruginosa were more frequent in isolates involved in HCA-BSI episodes.

The results of univariate analysis of *S. aureus*, *P. aeruginosa* and 3GCR-E risk factors are shown in Table 3. In regards to *S. aureus*, the multivariate analysis selected male gender (OR 2.26; 1.33–3.83), diabetes mellitus (OR 1.72; 1.01–2.91) and intravenous drug addiction (OR 17.24; 1.47–201.98) as risk factors while neutropenia was protective (OR 0.25; 0.09–0.71). Independent predictors of *P. aeruginosa* were male gender (OR 2.19; 1.10–4.37) and HCA-BSI (OR 9.13; 3.23–25.83). For 3GCR-E, recent antibiotic exposure (OR 2.53; 1.47–4.35) was the only significant predictor, and for enterococci only recent hospital admission (OR 3.02; 1.64–5.55) was selected as an independent risk factor.

The overall 7 and 30-day mortality rate was 8.1 % (60 patients) and 13.4 % (100 patients), respectively. The highest rates of 7- and 30-day mortality by organism were observed among patients with bacteraemia due to *Pseudomonas aeruginosa* (18.2 %, 25 %), *Staphylococcus aureus* (17.9 %, 21.8 %) *and Enterococcus* spp. (4.4 %, 15.6 %). For *P. aeruginosa* and *S. aureus*, mortality was significantly higher than that associated with other microorganisms at both 7 (18.2 % vs 7.4 %, $p=0.019$ and 17.9 % vs 6.9 %, $p=0.001$, respectively) and 30 (25 % vs 12.7 %, $p=0.020$ and 21.8 % vs 12.4 %, $p=0.022$, respectively) days. It is of note that patients with 3GCR-E had the lowest 7-day mortality (1/59, 1.7 %), with a trend towards being significantly lower than that of episodes due to all other microorganisms (59/686, 8.6 %, $p=0.07$) or to Enterobacteriaceae susceptible to third-generation cephalosporins (19/231, 8.2 %, $p=0.08$). Empirical antibiotic treatment was inappropriate in 25.5 % of episodes, particularly in those due to 3GCR-E (42.4 % *vs.* 23.9 % for other episodes, $p=0.002$) and enterococci (53.3 % *vs.* 23.6 % for other episodes, $p<0.001$). Prevalence of inappropriate empirical treatment was not significantly different between survivors and non-survivors (25 % *vs.* 28 %, $p=0.52$). Univariate and multivariate analysis of variables associated with 30-day mortality is shown in Table 4. Age over 65 years, having an ultimately or rapidly fatal underlying disease, bone marrow transplantation, absence of fever, shock on presentation and isolation of *S. aureus* were independently associated with 30-day mortality. The best model predicting 7-day mortality included the above mentioned variables plus isolation of 3GCR-E that entered the model as a protective factor (OR 0.06; 0.01–0.77). No interaction between appropriateness of empirical antibiotic treatment and etiologic microorganisms was found.

Discussion

According to the findings of the present study, an unknown focus of bacteraemia is still prevalent, occurs in patients with comorbidities, is commonly due to resistant or potentially resistant microorganisms and is associated with an appreciable mortality. Without the aid of a clinically apparent source, to assess the predictive features of individual organisms may be particularly

Table 2 Isolated microorganisms and antibiotic susceptibility in community-onset bacteraemia of unknown origin

Microorganisms	Total *n*=745	CA-BSI *n*=340	HCA-BSI *n*=405	*p*
Gram-negative organisms				
Enterobacteriaceae				
E. coli	190 (25.5)	88 (25.9)	102 (25.2)	0.828
Klebsiella spp.	31 (4.2)	15 (4.4)	16 (4.0)	0.754
Salmonella spp.	41 (5.5)	31 (9.1)	10 (2.5)	<0.001
Enterobacter spp.	13 (1.7)	5 (1.5)	8 (2.0)	0.600
Citrobacter spp.	4 (0.5)	2 (0.6)	2 (0.5)	1.000
Morganella spp.	3 (0.4)	3 (0.9)	0	0.095
Proteus spp.	6 (0.8)	5 (1.5)	1 (0.2)	0.098
Providencia spp.	1 (0.1)	1 (0.3)	0	0.456
Serratia spp.	1 (0.1)	1 (0.3)	0	0.456
3GCR-E [a]	59 (7.9)	20 (5.9)	39 (9.6)	0.059
P. aeruginosa	44 (5.9)	4 (1.2)	40 (9.9)	<0.001
P. aeruginosa resistant to ciprofloxacin or ceftazidime or imipenem	7 (0.9)	0	7 (1.7)	0.018
Gram-positive organisms				
Methicillin-sensitive *S. aureus*	64 (8.6)	35 (10.3)	29 (7.2)	0.128
Methicillin-resistance *S. aureus*	14 (1.9)	5 (1.5)	9 (2.2)	0.452
Coagulase-negative staphylococci	83 (11.1)	25 (7.4)	58 (14.3)	0.003
Enterococcus spp.	45 (6.0)	14 (4.1)	31 (7.7)	0.044
S. pneumoniae	43 (5.8)	26 (7.6)	17 (4.2)	0.044
Listeria spp.	29 (3.9)	18 (5.3)	11 (2.7)	0.070
Candida spp.	9 (1.2)	3 (0.9)	6 (1.5)	0.520
Polymicrobial bacteraemia	18 (2.4)	13 (3.8)	5 (1.2)	0.022

[a] *3GCR-E* Enterobacteriaceae resistant to third-generation cephalosporin. The organisms evaluated for third-generation-cephalosporin-resistant rate were *E. coli, Klebsiella spp, Enterobacter (aerogenes, cloacae), Citrobacter spp, Morganella spp, Proteus (penneri, vulgaris), Providencia spp, Serratia spp*

important in order to design strategies aimed to improve empirical antibiotic therapy appropriateness.

The prevalence of bacteraemia of unknown source observed in the present study (16.2 %) agrees with the previously reported range (9–22 %) [3, 9–12]. Furthermore, the observed global distribution of microbial species is quite similar to that of many recent reports on community-onset bacteraemia [3, 10, 13, 14], although these did not specify the distribution of microbial species according to the source. The present study focused on bacteraemia of unknown origin and in comparison with previous studies there was, as expected, a lesser incidence of *S. aureus* and *S. pneumoniae* and a higher of *Listeria spp*. and *Salmonella spp*. In addition, *P. aeruginosa* isolates were almost exclusively observed in HCA-BSI, while *S. pneumoniae* and *Salmonella spp.* were mainly found in CA-BSI.

To our knowledge, only three studies have specifically focused on bacteraemia of unknown origin [8, 11, 12]. Two of them were carried out more than 10 years ago and included both community-onset and hospital-acquired episodes. The more recent study (2003–06) did not include neutropenic patients and was performed in a period when ESBL-producing enterobacteriaceae were still uncommon. In spite of these drawbacks, the global distribution of microbial species does not seem to have changed substantially over time. In the present study, *E. coli* was the most frequent isolated microorganism, either in HCA-BSI or in CA-BSI, followed by coagulase-negative staphylococci (CNS), *Staphylococcus aureus, P. aeruginosa* and *S. pneumoniae*. Not unexpectedly, the main difference with prior studies was that currently 20.3 % of *Enterobacteriaceae* were resistant to third-generation cephalosporins and 17.9 % of *Staphylococcus aureus* were methicillin-resistant.

Our findings confirm the results of previous studies [4, 5] which reported an appreciable mortality rate (12–29.4 %) in patients with bacteraemia of unknown origin. In the present study, fatal outcome was predicted by six factors: age older than 65 years, an ultimately or rapidly fatal prognosis of underlying disease, bone marrow transplant, no fever at admission, presence of shock at admission and *S. aureus* isolation. It is of note that

Table 3 Univariate analysis of predictors of *Enterobacteriaceae resistant* to third-generation cephalosporins (3GCR-E), *Pseudomonas aeruginosa, Staphylococcus aureus* and *Enterococcus spp* bacteraemia in patients with community-onset bacteraemia of unknown origin

Risk factor[a]	*S. aureus*			*P. aeruginosa*			*3GCR-E*			*Enterococcus spp.*		
	No *n*=667	Yes *n*=78	*p*	No *n*=701	Yes *n*=44	*p*	No *n*=686	Yes *n*=59	*p*	No *n*=700	Yes *n*=45	*p*
Gender, male (%)	357 (53.5)	57 (73.1)	**0.001**	382 (54.5)	32 (72.7)	**0.018**	383 (55.8)	31 (52.5)	0.626	392 (56.0)	22 (48.9)	0.352
Prior hospital admission	187 (28.0)	16 (20.5)	0.158	183 (26.1)	20 (45.5)	**0.005**	176 (25.7)	27 (45.8)	**0.001**	180 (25.7)	23 (51.1)	**<0.001**
HCA-BSI	367 (55.0)	38 (48.7)	0.290	365 (52.1)	40 (90.9)	**<0.001**	366 (53.4)	39 (66.1)	0.059	374 (53.4)	31 (68.9)	**0.044**
Comorbidity												
Haematological neoplasm	209 (31.3)	14 (17.9)	**0.015**	202 (28.8)	21 (47.7)	**0.008**	202 (29.4)	21 (35.6)	0.322	212 (30.3)	11 (24.4)	0.407
Diabetes mellitus	127 (19.0)	24 (30.8)	**0.015**	140 (20.0)	11 (25.0)	0.421	140 (20.4)	11 (18.6)	0.746	139 (19.9)	12 (26.7)	0.271
Liver cirrhosis	93 (13.9)	13 (16.7)	0.515	105 (15.0)	1 (2.3)	**0.019**	99 (14.4)	7 (11.9)	0.588	97 (13.9)	9 (20.0)	0.253
Hemodyalisis	31 (4.6)	7 (9.0)	0.105	32 (4.6)	6 (13.6)	**0.020**	34 (5.0)	4 (6.8)	0.532	34 (4.9)	4 (8.9)	0.279
HSCT	26 (3.9)	0	0.099	21 (3.0)	5 (11.4)	**0.015**	23 (3.4)	3 (5.1)	0.452	22 (3.1)	4 (8.9)	0.065
Neutropenia	128 (19.2)	4 (5.1)	**0.002**	116 (16.5)	16 (36.4)	**0.001**	115 (16.8)	17 (28.8)	**0.020**	126 (18.0)	6 (13.3)	0.427
IVDU	1 (0.1)	2 (2.6)	**0.030**	3 (0.4)	0	1.000	3 (0.4)	0	1.000	3 (0.4)	0	1.000
Extrinsic risk factors												
Corticosteroids	143 (21.4)	11 (14.1)	0.130	137 (19.5)	17 (38.6)	**0.002**	143 (20.8)	11 (18.6)	0.689	139 (19.9)	15 (33.3)	**0.030**
Previous antibiotic therapy	174 (26.1)	15 (19.2)	0.188	175 (25.0)	14 (31.8)	0.311	163 (23.8)	26 (44.1)	**0.001**	172 (24.6)	17 (37.8)	**0.048**
Endovascular catheterization	177 (26.5)	12 (15.4)	**0.032**	171 (24.4)	18 (40.9)	**0.015**	167 (24.3)	22 (37.3)	**0.028**	174 (24.9)	15 (33.3)	0.205

3GCR-E Enterobacteriaceae resistant to third-generation cephalosporin, *HSCT* haematopoietic stem cell transplantation, *IVDU* intravenous drug users

Values in bold are considered statistically significant

[a] Prognosis of underlying disease, other comorbidities (solid organ cancer, heart disease, chronic lung disease, neurologic impairment, HIV infection, solid-organ transplantation, uropathology), fever or shock on the day of presentation, previous surgery, and indwelling urinary catheter were not significant ($p>0.05$) for any of the microorganisms analysed

factors associated with 7- and 30-day mortality were the same with the exception of 3GCR-E which was associated with less acute mortality. The latter observation is intriguing, and there is not a satisfactory explanation for it. The possibility of 3GCR-E being less pathogenic than their susceptible counterparts or other microorganisms ensues, but given the current knowledge of the complex relationship between resistance and virulence [15], it seems a rather speculative explanation that should be specifically assessed in further studies. All these prognostic factors have been previously mentioned [16–18] and none of them is potentially modifiable. Contrary to some previous reports [16, 19, 20], we could not find a significant association between 7- and 30-day mortality and inappropriate empirical treatment. This result might reflect recent improvements in microbiological diagnosis allowing an earlier administration of appropriate therapy. In spite of the present findings we believe that improving the management of *S. aureus* bacteraemia is still of crucial importance, which may include the use of empirical antibiotics that are not only "appropriate" by definition but optimal in terms of clinical efficacy.

In this study, we looked for clinical features predictive of infections caused by species that may require a particular therapeutic approach, namely, *S. aureus*, *P. aeruginosa*, 3GCR-E and *Enterococcus spp*. Male gender, diabetes mellitus and intravenous drug addiction were independently associated with *S. aureus*; HCA acquisition and male gender were predictors of *P. aeruginosa*, and for 3GCR-E and *Enterococcus spp.* the only independent risk factor was recent antibiotic therapy (within the last month) and prior hospital admission, respectively. All these clinical characteristics have been previously recognized as potential risk factors for the respective microorganisms [21–26], and may be useful to guide the selection of an appropriate empirical antibiotic regimen.

There is no consensus about the minimum prevalence of a given microorganism that would recommend the coverage for it by the empirical antibiotic regimen. Based on our criteria that empirical antibiotic treatment should be active against all microorganisms with a prevalence of at least 10 % (and

Table 4 Univariate and multivariate analysis of predictors of 30-day mortality in patients with community-onset bacteraemia of unknown focus. Multivariate analysis of variables associated with mortality

Risk factor	Survivors n=645	Exitus n=100	Univariate; odds ratio (95 % CI)	Multivariate; OR (95 % CI)
Age >65 years	328 (50.9)	61 (61)	1.51 (0.98–2.33)	2.13 (1.28–3.55)
Last month hospitalization	168 (26.0)	35 (35)	1.53 (0.98–2.39)	–
HCA-BI	335 (51.9)	70 (70)	2.16 (1.37–3.40)	–
Ultimately or rapidly fatal prognosis of underlying disease	365 (56.6)	84 (84)	4.03 (2.31–7.03)	4.15 (2.24–7.68)
Not underlying disease	46 (7.1)	2 (2)	0.27 (0.06–1.11)	–
Chronic lung disease	63 (9.8)	3 (3)	0.29 (0.09–0.93)	–
Bone marrow transplant	20 (3.1)	6 (6)	1.99 (0.78–5.10)	4.07 (1.24–13.31)
Neutropenia	108 (16.7)	24 (24)	1.57 (0.95–2.60)	–
Corticosteroids treatment	128 (19.8)	26 (26)	1.42 (0.87–2.31)	–
Absence of fever at admission	39 (6.0)	21 (21)	4.13 (2.31–7.38)	4.45 (2.25–8.81)
Admission to ICU	49 (7.6)	27 (27)	4.50 (2.65–7.64)	–
Presence of shock	43 (6.7)	43 (43)	10.56 (6.39–17.46)	10.48 (6.05–18.15)
E. coli	159 (24.7)	31 (31)	1.37 (0.87–2.18)	
S. pneumoniae	41 (6.4)	2 (2)	0.30 (0.07–1.26)	–
P. aeruginosa	33 (5.1)	11 (11)	2.29 (1.12–4.70)	–
S. aureus	61 (9.5)	17 (17)	1.96 (1.09–3.52)	2.01 (1.00–4.04)
S. coagulase negative	76 (11.8)	7 (7)	0.56 (0.25–1.26)	–

probably of ≥5 % in cases of severe sepsis or septic shock), we propose some recommendations. In settings with an overall 6 % prevalence of 3GCR-E, cefotaxime or ceftriaxone may be appropriate for CA-BSI of unknown origin in non-diabetic women without prior antibiotic exposure. In our study, methicillin-sensitive *S. aureus* had 16.1 % prevalence in diabetic women, 10.9 % in men regardless of diabetes, and 66.7 % in intravenous illicit drug users. Hence, it may be advisable to provide empirical coverage against this organism to patients with these characteristics. Whether cefotaxime or ceftriaxone can be considered as an appropriate empiric therapy for methicillin-susceptible *S. aureus* bacteraemia is questionable. In a rabbit model of endocarditis, ceftriaxone 2 g once a day was less effective than cloxacillin [27], and there is some clinical evidence suggesting that for methicillin-sensitive *S. aureus* bacteraemia empiric treatment with a third-generation cephalosporin may be associated with a higher mortality rate than treatment with cloxacillin or cefazolin [28]. This may be due to the less intrinsic activity of ceftriaxone and cefotaxime against *S. aureus* ($MIC_{50–90}$= 4 mg/L) [29] and, therefore, increasing their dose (to at least 2 g of ceftriaxone or 6 g of cefotaxime per day), adding an isoxazolyl-penicillin or using ceftaroline [30], would be appropriate. In our series, MRSA was rare except in diabetic men, in whom a prevalence of 6 % was found. Therefore, empirical coverage for MRSA only for diabetic men with severe sepsis is suggested. In patients with CA-BSI of unknown source recently exposed to antibiotics, a 13 % prevalence of *Enterobacteriaceae* resistant to third-generation cephalosporins is of concern and ertapenem may be the most appropriate choice. In other circumstances (prevalence≈ 5 %), a carbapenem should be only considered for patients with severe sepsis. According to the present data, *P. aeruginosa* is of concern only in patients with HCA infections, particularly in men regardless of recent antibiotic exposure, and coverage against enterococci may be considered for patients with recent hospital admission.

There are some limitations to our study. First, it was conducted in a single, tertiary-care hospital and, therefore, the results may have been influenced by local epidemiological variables and not applicable to other settings. Second, the presence or absence of a "Do Not Attempt Resuscitation" (DNAR) order was not recorded, and this might have limited an effective search for the source of bacteraemia in some patients. Third, our definition of prior antibiotic therapy was limited to the month preceding the BSI episode, and this may have contributed to blur a possible association of previous antibiotic exposure with resistant or potentially-resistant pathogens such as MRSA or *P. aeruginosa*. Last, the sample size is relatively large for a single-centre study but may still be too small to detect differences in outcome and risk factors for specific microorganisms.

In conclusion, a limited number of clinical characteristics may be useful to predict the microorganisms involved in bacteraemia of unknown origin and to choose the appropriate empirical treatment. Given the fact that *S. aureus* is an independent predictor of mortality, management optimization of this microorganism should be considered as a priority.

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Conflict of interest The authors declare that they have no conflict of interest.

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