Bacteraemia and antibiotic-resistant pathogens in community acquired pneumonia: risk and prognosis

Antoni Torres[1], Catia Cillóniz[1], Miquel Ferrer[1], Albert Gabarrús[1], Eva Polverino[1], Santiago Villegas[2], Francesc Marco[3], Josep Mensa[4], Rosario Menéndez[5] and Michael Niederman[6]

Affiliations: [1]Dept of Pneumology, Institut Clinic del Tórax, Hospital Clinic of Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona (UB) - SGR 911- Ciber de Enfermedades Respiratorias (Ciberes), Barcelona, Spain. [2]Dept de Medicina Crítica y Cuidados Intensivos, Universidad CES, Medellin, Colombia. [3]Microbiology Laboratory (Centre Diagnòstic Biomèdic), Barcelona Centre for International Health Research, Hospital Clínic, Barcelona, Spain. [4]Dept of Infectious Disease, Hospital Clinic of Barcelona, Barcelona, Spain. [5]Dept of Pneumology, Hospital La Fe de Valencia, Valencia, Spain. [6]Dept of Medicine, Winthrop-University Hospital, Mineola, NY, USA.

Correspondence: Antoni Torres, Dept of Pneumology, Hospital Clinic of Barcelona, Spain.
E-mail: atorres@clinic.ub.es

ABSTRACT The sensitivity of blood cultures in the diagnosis of bacteraemia for community-acquired pneumonia is low. Recommendations, by guidelines, to perform blood cultures are discordant. We aimed to determine the incidence, microbial aetiology, risk factors and outcomes of bacteraemic patients with community-acquired pneumonia, including cases with antibiotic-resistant pathogens (ARP).

A prospective, observational study was undertaken on consecutive adult patients admitted to the Hospital Clinic of Barcelona (Barcelona, Spain) with community-acquired pneumonia and blood cultures were obtained.

Of the 2892 patients included, bacteraemia was present in 297 (10%) patients; 30 (10%) of whom had ARP (multidrug-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and an extended spectrum of beta-lactamase producing *Enterobacteriaceae*). In multivariate analyses, pleuritic pain, C-reactive protein $\geqslant$21.6 mg·dL^{-1} and intensive care unit admissions were independently associated with bacteraemia, while prior antibiotic treatment and pneumococcal vaccine were protective factors. The risk factors for ARP bacteraemia were previous antibiotics and C-reactive protein <22.2 mg·dL^{-1}, while pleuritic pain was the only protective factor in the multivariate analysis. Bacteraemia (excluding ARP), appropriate empiric treatment, neurological disease, arterial oxygen tension/inspiratory oxygen fraction <250, pneumonia severity index risk classes IV and V, and intensive care unit admission were independently associated with a 30-day hospital mortality in the multivariate analysis. Inappropriate therapy was more frequent in ARP bacteraemia, compared with other bacteraemias (27% *versus* 3%, respectively, p<0.001).

Antibiotic therapy protected against bacteraemia, but increased specifically the risk of bacteraemia from ARP due to the inappropriate coverage of these pathogens. Identifying patients at risk of ARP bacteraemia would help in deciding appropriate empiric antimicrobial therapy. The results from this study provide evidence concerning community-acquired pneumonia patients in whom blood cultures should not be performed.

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Introduction

Community-acquired pneumonia (CAP) is a disease with high morbidity and mortality, with short-term mortality reaching 14% and long-term mortality reaching 50% within 5 years [1]. CAP with bloodstream infection, continues to be a severe and often life-threatening infection being *Streptococcus pneumoniae* the most common pathogen, and the leading cause of death [2, 3]. The association between bacteraemia and mortality is controversial and has been studied mainly for *S. pneumoniae*. Recent studies did not consistently find an association between pneumococcal bacteraemia and mortality [4]. The reason may be that other factors, such as time to the first dose of antibiotics and discordant therapy, are more important determinants of prognosis [5]. The association between mortality and bacteraemic CAP caused by microorganisms other than *S. pneumoniae* is less well-studied.

While the diagnosis of bacteraemia requires blood cultures, the sensitivity of this test in CAP is low (<20%). Recommendations of guidelines to perform blood cultures are discordant. While the last Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) recommendations limit blood cultures to intensive care unit (ICU) patients [6], the most recent European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases guidelines recommend that they should be performed in all hospitalised CAP patients [7]. METERSKY *et al.* [8] and FALGUERA *et al.* [9] described a set of factors (liver disease, pleuritic pain, tachycardia, tachypnea, systolic hypotension, and absence of prior antibiotic treatment [9], liver disease, recent antibiotic treatment, temperature <35°C or ⩾40°C, blood urea nitrogen ⩾30 mg·dL^{-1}, sodium <130 mmol·L^{-1} and white blood cells (WBC) <5000 mm^{-3} or >20 000 mm^{-3} [8]) potentially useful for clinicians to increase the sensitivity of blood cultures and to decrease costs. To our knowledge these criteria have not been applied in clinical practice. In addition the risk factors for bacteraemia caused by "nonstandard-therapy pathogens" have not been described.

We hypothesised that there are specific populations with a lower or higher risk for bacteraemic CAP and that mortality, attributable to bacteraemia, is different according to the type of microorganism isolated. Our goal was to identify risk factors for bacteraemia so that blood culture sampling could focus on this population. An additional aim was to identify bacteraemia caused by antibiotic-resistant pathogens (ARP) and to determine how risk factors for bacteraemia with these organisms differed from risk factors for all bacteraemias.

Materials and methods

Study design and patients

Prospective observational study carried out at the Hospital Clinic of Barcelona (Barcelona, Spain), including all adult patients admitted with CAP (from January 2000 to January 2012). Pneumonia was defined as the presence of a new infiltrate on a chest radiograph, together with clinical symptoms suggestive of lower respiratory tract infection. Patients coming from nursing home institutions were included. The exclusion criteria, clinical definitions are described in detail in the supplementary material.

Data collection

The following parameters were recorded at admission: age, sex, current smoking, alcohol habits, and drug consumption, comorbidities, antibiotic treatment in the 30 days prior to hospital admission, treatment with corticosteroids, clinical symptoms and features, clinical signs, arterial blood gas measurements, chest radiograph findings, laboratory parameters, diagnostic procedures, empiric antibiotic therapy, ventilator support, pulmonary complications, and other clinical events. The duration of treatment, length of hospital stay, and 30-day in-hospital mortality were noted. We also calculated the pneumonia severity index (PSI) and CURB-65 score (confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) ⩽60 mmHg (diastolic), age ⩾65 years) at admission [10, 11].

Microbiological evaluation

Microbiological examination was performed on sputum, urine, two samples of blood and nasopharyngeal swabs. Pleural fluid, tracheobronchial aspirates and bronchoalveolar lavage (BAL) fluid, when available, were collected for Gram and Ziehl–Neelsen stains and for cultures for bacterial, fungal and mycobacterial pathogens.

Sputum and blood samples were obtained for bacterial culture before starting antibiotic therapy in the emergency department. Nasopharyngeal swab for respiratory virus detection was collected, when available, urine samples for *S. pneumoniae* and *Legionella pneumophila* antigen detection were obtained within 24 h

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of hospital admission. Blood samples for serology of atypical pathogens and respiratory viruses were collected at admission and between the third and sixth week thereafter (supplementary material)

Definitions

Bacteraemic pneumonia was defined as at least one positive blood culture not related to another source of infection or contamination. We considered bacteria contaminants if there was growth of: coagulase-negative *Staphylococcus* spp., α-haemolytic streptococci, *Micrococcus* spp. or *Corynebacterium* spp. in one of the two blood cultures.

ARP bacteraemia was defined when it was caused by one of the following microorganisms: methicillin resistant *Staphylococcus aureus* (MRSA), *Enterobactaeriacea* producing extended spectrum beta-lactamases and multidrug-resistant (penicillins, beta-lactams, macrolides and quinolones) *S. pneumoniae* [12]. *Pseudomonas aeruginosa* cases were also included in this group since it requires a totally different antibiotic treatment.

Appropriateness of empiric antibiotic treatment in all patients was defined according to multidisciplinary guidelines for the management of CAP [13]. Appropriateness of empiric antimicrobial treatment in patients was defined when the isolated pathogens were susceptible *in vitro* to one or more of the antimicrobials administered. For *P. aeruginosa* infection, appropriate treatment required one active antibiotic against the isolated strain [6].

Statistical analysis

We show n (%) for categorical variables and median (interquartile range) for continuous variables with non-normal distribution or mean±SD) for those with normal distribution. Categorical variables were compared using the Chi-square test or Fisher's exact test. Continuous variables were compared using the Student t-test or the nonparametric Mann–Whitney U-test. Univariate and multivariate logistic regression analyses were performed to identify variables predictive of patients with bacteraemic CAP and patients ARP bacteraemia, respectively (dependent variables). Also univariate and multivariate logistic regression analyses were performed to predict 30-day hospital mortality (dependent variable); we also performed a subgroup analysis for patients with bacteraemia. Variables that showed a significant result univariately ($p<0.1$) were included in the corresponding multivariate, logistic regression backward stepwise model (supplementary methods). Variables highly correlated were excluded from multivariate analyses. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the models [14]. Receiver operating characteristic (ROC) curves were constructed for the ability to predict bacteraemia, patients with ARP bacteraemia, and 30-day hospital mortality, using significant variables derived from the respective logistic regression models. The level of significance was set at 0.05 (two-tailed). All analyses were performed with IBM SPSS Statistics 18.0 (Armonk, NY, USA).

Results

Patients' characteristics

Of the 3719 patients with CAP admitted during the observation period, 827 (22%) were excluded for unavailable blood cultures. Clinical characteristics and outcomes comparing patients who received or not

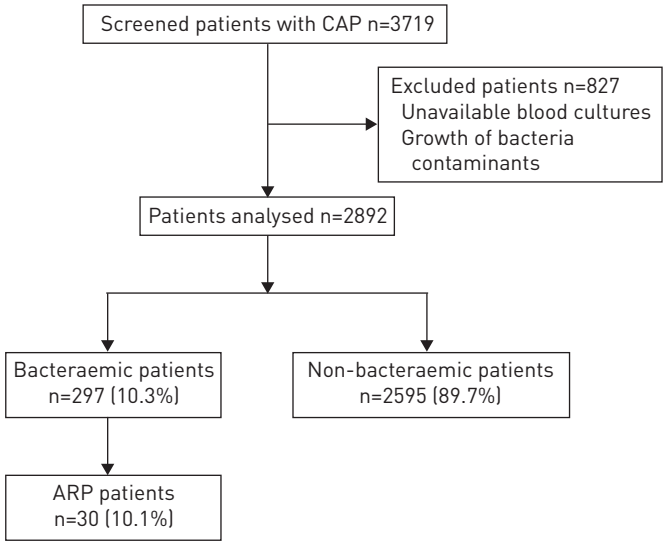

FIGURE 1 Flow diagram of the selected study population.

blood culture are described in table S1. The study population therefore comprised a total of 2892 patients evaluated in the emergency deparment with a diagnosis of CAP (fig. 1).

Altogether, 297 (10%) patients had bacteraemia. On average, patients with bacteraemia were aged <65 years, less frequently males, less often ex-smokers, had less often received prior antibiotics, had a lower rate of pneumococcal vaccination, had a lower incidence of chronic cardiovascular disease, a higher frequency of PSI risk class IV and V, and a CURB-65 risk class 3–5 when compared with non-bacteraemic patients. They also more likely to have creatinine $\geqslant$1.5 mg·dL^{-1}, C-reactive protein $\geqslant$21.6 mg·dL^{-1}, WBC counts $\geqslant 10\times10^{9}$ L^{-1}, oxygen saturation levels <92% and arterial oxygen tension(P_{aO_2})/inspiratory oxygen fraction (F_{iO_2}) <250. Patients with bacteraemia had a significantly longer median length of hospital stay, more frequent admission to the ICU, more need for either invasive or noninvasive mechanical ventilation. On average, patients with bacteraemia were more frequently classified as moderate-to-severe by the Fine score (PSI risk class IV and V). The crude 30-day mortality rate was significantly higher in bacteraemic patients (table 1 and S2).

Of the 297 patients with bacteraemia, 16 (5.4%) were treated as outpatients, 188 (63.3%) were admitted to a ward and 93 (31.3%) were admitted to the ICU. The distribution of bacteraemic patients by site of care, PSI and CURB-65 scores is shown in figures S1, S2 and S3, respectively.

Microbial aetiology and susceptibility

Overall aetiology was established in 1292 (45%) patients (table S3). In bacteraemic patients the main microorganisms isolated were *S. pneumoniae* (n=249, 84%), *S. aureus* (n=16, 5%), *Escherichia coli* (n=9, 3%), and *Haemophilus influenzae* (n=7, 2%). ARP were present in 10% of cases (n=30) (table 2).

TABLE 1 Clinical and epidemiological characteristics of bacteraemic and non-bacteraemic community-acquired pneumonia (CAP) patients

	Bacteraemic CAP	Non-bacteraemic CAP	p-value
Patients n	267	2595	
Demographic			
Age $\geqslant$65 years	156±52.5	1535±59.2	**0.028**
Male	167 (56.2)	1636 (63.0)	**0.022**
Current smoker	83 (28.3)	650 (25.1)	0.24
Current alcohol consumer	48 (16.4)	377 (14.6)	0.43
Previous antibiotic[#]	35 (12.5)	560 (22.4)	**<0.001**
Influenza vaccine	83 (37.4)	958 (43.9)	0.062
Pneumococcal vaccine	22 (10.0)	367 (16.9)	**0.008**
Inhaled corticosteroid	50 (17.2)	462 (18.0)	0.74
Systemic corticosteroid	3 (1.1)	36 (1.5)	0.61
Comorbidities[¶]	185 (62.3)	1643 (63.3)	0.73
Chronic respiratory disease	108 (36.4)	968 (37.3)	0.75
Chronic cardiovascular disease	37 (12.5)	459 (18.8)	**0.024**
Diabetes mellitus	52 (18.2)	417 (16.6)	0.51
Neurological disease	52 (17.7)	438 (17.0)	0.78
Chronic renal disease	16 (5.4)	165 (6.4)	0.52
Chronic liver disease	18 (6.1)	107 (4.1)	0.12
Nursing-home[#]	56 (2.2)	5 (1.7)	0.59
CURB-65 risk class 3–5	76 (25.9)	436 (17.6)	**0.001**
PSI risk class IV and V	166 (55.9)	1261 (48.6)	**0.017**
ICU admission	93 (31.3)	445 (17.1)	**<0.001**
Mechanical ventilation[+]			**0.001**
Not ventilated	255 (85.9)	2390 (92.1)	**<0.001**
Noninvasive	18 (6.1)	92 (3.5)	**0.032**
Invasive	24 (8.1)	113 (4.4)	**0.004**
Length of hospital stay days	9.0 (6.0–13.0)	6.0 (4.0–10.0)	**<0.001**
30-day mortality	33 (11.1)	154 (5.9)	**0.001**
Appropriate empiric treatment	282 (94.9)	2446 (95.2)	0.86

Data are presented as median±SD, n (%) or median (interquartile range), unless otherwise stated. Percentages calculated on non-missing data. CURB-65: confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant$30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) $\leqslant$60 mmHg (diastolic), age $\geqslant$65 years; PSI: pneumonia severity index; ICU: intensive care unit. [#]: variables included in the definition of healthcare associated pneumonia; [¶]: patients could have >1 comorbidity; [+]: patients who initially received noninvasive ventilation but subsequently needed intubation were included in the invasive mechanical ventilation group. Bold indicates statistically significant

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TABLE 2 Pathogens isolated in blood culture from the 297 patients with bacteraemic community acquired pneumonia

Isolate	
Streptococcus pneumoniae	249 (83.8)
S. pneumoniae multiresistant[#]	5 (1.7)
Staphylococcus aureus	16 (5.4)
MRSA[#]	14 (4.7)
MSSA	2 (0.7)
Escherichia coli	9 (3.0)
E. coli beta-lactamase producers[#]	6 (2.0)
Haemophilus influenzae	7 (2.4)
***Enterobacter* sp.**	4 (1.3)
Enterobacter spp. beta-lactamase producers[#]	1 (0.3)
Klebsiella pneumoniae	4 (1.3)
K. pneumoniae beta-lactamase producers[#]	2 (0.7)
Acinetobacter baumannii	2 (0.7)
***Proteus* sp.**	2 (0.7)
Proteus spp. beta-lactamase producers[#]	1 (0.3)
Moraxella catarrhalis	1 (0.3)
***Peptostreptococcus* sp.**	1 (0.3)
***Pseudomonas aeruginosa*[#]**	1 (0.3)
Streptococcus pyogenes	1 (0.3)

Data are presented as n (%). MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-sensitive *S. aureus*. [#]: antibiotic resistant pathogens (n=30).

12 cases (40%) of ARP bacteraemia were admitted to ICU. Complete susceptibility data are described in detail in the supplementary results.

Empiric antibiotic therapy

Initial empiric antibiotic treatment was inappropriate in 15 (5%) of 297 patients with bacteraemic CAP and five patients with inappropriate treatment died (33%). Inappropriate therapy was given to eight of the 30 patients (27%) with ARP bacteraemia *versus* 7 of the 267 with other bacteraemias (3%) ($p<0.001$). Data of complete empiric antibiotic therapy are described in detail in the supplementary results. The pathogens

TABLE 3 Significant univariate and multivariate logistic regression analyses of predictors for bacteraemic community acquired pneumonia

	Univariate		Multivariate[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Pneumococcal vaccine	0.55 (0.35–0.86)	0.009	0.59 (0.35–0.99)	0.047
Influenza vaccine	0.76 (0.57–1.01)	0.062		-
Previous antibiotic	0.49 (0.34–0.71)	<0.001	0.51 (0.32–0.79)	0.003
Pleuritic pain	2.20 (1.71–2.83)	<0.001	2.21 (1.60–3.06)	<0.001
C-reactive protein $\geqslant$21.6 mg·dL^{-1}	2.65 (2.01–3.50)	<0.001	2.36 (1.70–3.27)	<0.001
White blood cell count $\geqslant$10×10^{9}·L^{-1}	1.41 (1.07–1.85)	0.015		-
PSI risk class IV and V	1.34 (1.05–1.71)	0.017		-
CURB-65 risk class 3–5	1.64 (1.24–2.17)	0.001		-
ICU admission	2.20 (1.69–2.87)	<0.001	1.80 (1.27–2.56)	0.001
Mechanical ventilation[¶]		0.002		
Not ventilated	1			
Noninvasive	1.83 (1.09–3.09)	0.023		
Invasive	1.99 (1.26–3.15)	0.003		

PSI: pneumonia severity index; CURB-65: confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant$30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) $\leqslant$60 mmHg (diastolic), age $\geqslant$65 years; ICU: intensive care unit; [#]: Hosmer–Lemeshow goodness-of-fit test, p=0.32; [¶]: the p-value corresponds to differences between the three groups (not ventilated, non-invasive or invasive).

TABLE 4 Probability of bacteraemic CAP

Risk factors	Protective factors			
	Previous antibiotic and pneumococcal vaccine	Previous antibiotic	Pneumococcal vaccine	None
None	1.3	2.2	2.5	4.3
ICU admission	2.3	3.9	4.5	7.4
Plus pleuritic pain	5.0	8.2	9.4	15.1
Plus C-reactive protein ⩾21.6 mg·dL^{-1}	5.3	8.7	10.0	15.9
Plus pleuritic pain and C-reactive protein ⩾21.6 mg·dL^{-1}	11.1	17.5	19.7	29.5
Pleuritic pain	2.8	4.8	5.5	9.0
Plus c-reactive protein ⩾21.6 mg·dL^{-1}	6.5	10.5	12.0	18.9
C-reactive protein ⩾21.6 mg·dL^{-1}	3.0	5.0	5.8	9.5

Data are presented as %. ICU: intensive care unit.

associated with inappropriate treatment were *E. coli* (n=4), *S. aureus* (n=4), *H. influenzae* (n=2), *Klebsiella pneumoniae* (n=2), *S. pneumoniae* (n=1), *Proteus* sp. (n=1) case and *Acinetobacter* (n=1) case (table S4).

Predictors of bacteraemic CAP

Several variables were significantly associated with bacteraemic CAP in the univariate logistic regression analyses (table 3). Among these variables, pleuritic pain, C-reactive protein ⩾21.6 mg·dL^{-1} and ICU admission were risk factors in the multivariate analysis. Alternatively, prior antibiotic treatment and pneumococcal vaccine were protective against the development of bacteraemia in the multivariate analysis. The area under the ROC curve was 0.71 (95% CI 0.68–0.75) for the model predictive of bacteraemia (fig. S4). Predictors from the model were used to calculate the probability of bacteraemia by the following formula. Exp (β)/(1+Exp(β)),where β=−3.111−0.682 (in case of prior antibiotic treatment)−0.533 (in case of pneumococcal vaccine)+0.588 (in case of ICU admission)+0.795 (in case of pleuritic pain)+0.858 (if C-reactive protein ⩾21.6 mg·dL^{-1}). Using this model, the probability of bacteraemia for patients without any of these risk factors and with the two protective factors was 1%, being 30% for patients showing all three risk factors and without any of the protective factors.

The probabilities of bacteraemia for the different combinations of risk and protective factors are shown in tables 4 and 5, and demonstrate that the risk of bacteraemia could be predicted by assessing the number of clinical predictors present. We performed the same analysis excluding cases of ARP bacteraemia and the independent predictors for bacteraemia were the same.

Predictors of patients with ARP bacteraemia

In the subgroup of bacteraemic patients, variables significantly associated with patients having ARP bacteraemia in the univariate logistic regression analyses were previous antibiotic treatment, neurological disease, being in a nursing home, pleuritic pain, C-reactive protein, and CURB-65. Among these variables,

TABLE 5 Recommendation for not performing blood cultures in immunocompetent patients with community-acquired pneumonia (CAP)

Previous antibiotic treatment
Previous pneumococcal vaccination
No intensive care unit admission
Absence of pleuritic pain
C-reactive protein <21.6 mg·dL^{-1}

The risk of having bacteraemia with one, two, three, four or five factors is 19%, 11%, 3%, 2% and 2%, respectively. The risk of having bacteraemia (after excluding previous pneumococcal vaccination) with one, two, three or four factors is 19%, 10%, 4% and 3%, respectively. Previous antibiotic treatment refers to if patients received antibiotics any time during the 2 weeks prior to hospital admission for CAP. Pneumococcal vaccination refers to the 23-valent polysaccharide pneumococcal vaccine (PPV23), if the patient received a vaccine in the last 5 years. Serotypes covered by PPV23 have shifted and now the indicated vaccine is the conjugated 13 valent.

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TABLE 6 Significant univariate and multivariate logistic regression analyses for the prediction of patients with antibiotic-resistant pathogen bacteraemia

	Univariate		Multivariate[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Previous antibiotic	2.55 (1.00–6.50)	0.051	3.70 (1.24–11.03)	0.019
Neurological disease	2.20 (0.94–5.14)	0.067		
Nursing-home[¶]	6.21 (1.00–38.78)	0.051		
Pleuritic pain	0.39 (0.18–0.87)	0.022	0.24 (0.09–0.63)	0.004
C-reactive protein <22.2 mg·dL^{-1}	4.64 (1.86–11.61)	0.001	4.09 (1.55–10.78)	0.004
CURB-65 risk class 3–5	2.07 (0.95–4.53)	0.068		

CURB-65: confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) ⩽60 mmHg (diastolic), age ⩾65 years. [#]: Hosmer–Lemeshow goodness-of-fit test, p=0.70; [¶]: variables included in the definition of healthcare associated pneumonia.

previous antibiotic and C-reactive protein <22.2 mg·dL^{-1} were risk factors in the multivariate analysis, while pleuritic pain was the only protective factor (table 6).

The area under the ROC curve was 0.76 (95% CI 0.66–0.87) for the model predictive of patients with ARP bacteraemia (fig. 2). Predictors from the model were used to calculate the probability of patients with ARP bacteraemia given by the following formula: Exp(β)/(1+Exp(β)), where β=−2.477+1.307 (in case of prior antibiotic treatment)−1.428 (in case of pleuritic pain)+1.408 (if C-reactive protein <22.2 mg·dL^{-1}). Using this model, the probability for ARP bacteraemia for patients without any of these risk factors and with the protective factor was 2%, being 47% for patients showing the two risk factors and without the protective factor.

In addition we performed a multivariate analysis comparing the 30 cases of ARP bacteraemia *versus* total population only CURB-65 risk class 3–5 (OR 2.46, 95% CI 1.15–5.27, p=0.020) and ICU admission (OR 1.99, 95% CI 1.13–5.19, p=0.022) resulted as significant in this analysis. The probability of ARP bacteraemia in patients admitted to the ICU and CURB-65 risk class 3–5 was 3.8%).

Predictors of 30-day hospital mortality

Table 7 shows the crude 30-day hospital mortality in relation to the different microorganisms. The crude mortality of *S. pneumoniae* bacteraemia was 9%, while the mortality of the ARP bacteraemias was at least two-fold higher (23%; *S. aureus* five out of 14 cases, *E. coli* one out of six cases and *K. pneumoniae* one of two cases).

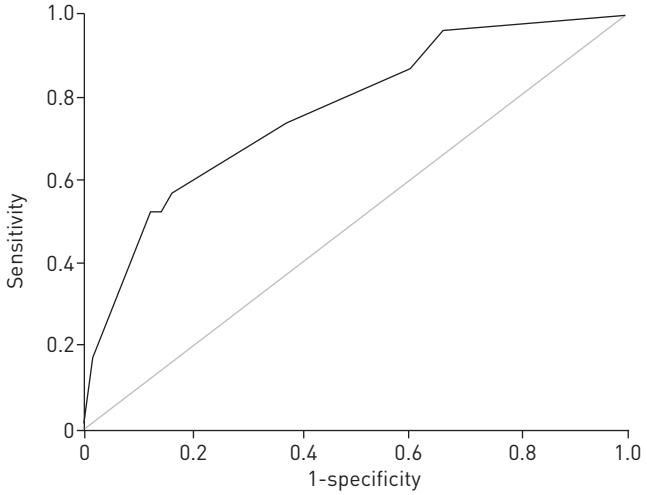

FIGURE 2 Receiver operating characteristic analysis of significant variables derived from the logistic regression model in their capacity to predict patients with bacteraemia caused by antibiotic-resistant pathogens. AUC: area under the curve.

	AUC	SE	95% CI	p-value
Previous antibiotic, pleuritic pain, C-reactive protein <22.2 mg·dL^{-1}	0.76	0.053	0.66–0.87	0.001

TABLE 7 30-day hospital mortality according to microbial aetiology

Streptococcus pneumoniae	23/249 (9.2)
Streptococcus pneumoniae multiresistant[#]	0/5 (0)
Staphylococcus aureus	6/16 (37.5)
MRSA[#]	5/14 (35.7)
MSSA	1/2 (50.0)
Escherichia coli	2/9 (22.2)
Escherichia coli BL producers[#]	1/6 (16.7)
Haemophilus influenzae	1/7 (14.3)
***Enterobacter* sp.**	0/4 (0)
Enterobacter sp. beta-lactamase producers[#]	0/1 (0)
Klebsiella pneumonia	1/4 (25.0)
Klebsiella pneumoniae beta-lactamase producers[#]	1/2 (50.0)
Acinetobacter baumannii	0/2 (0)
***Proteus* sp.**	0/2 (0)
Proteus spp. beta-lactamase producers[#]	0/1 (0)
Moraxella catarrhalis	0/1 (0)
***Peptostreptococcus* sp.**	0/1 (0)
***Pseudomonas aeruginosa*[#]**	0/1 (0)
Streptococcus pyogenes	0/1 (0)
Total	33/297 (11.1)]

Data are presented as n/N (%), where n=number of patients who died and N=total number of patients. MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-sensitive *S. aureus*. [#]: antibiotic-resistant pathogen bacteraemia (7/30 (23.3%)].

The percentage of patients with bacteraemia was higher in non-survivors when compared with survivors (n=33 (18%) *versus* n=264 (10%), respectively, p=0.001). In particular ARP bacteraemia was higher in non-survivors when compared with survivors (n=7 (4%) *versus* n=23 (1%), p<0.001).

In the multivariate logistic regression analysis (table 8), bacteraemia (excluding ARP), neurological disease, P_{aO_2}/F_{IO_2} <250, PSI risk classes IV and V, and ICU admission were risk factors for 30-day hospital mortality, while appropriate empiric treatment was the only protective factor. The area under the ROC curve was 0.80 (95% CI 0.76–0.83) (fig. S5).

In the subgroup of bacteraemic patients, several variables were significantly associated with 30-day hospital mortality in the univariate logistic regression analyses (table S5). The multivariate analysis showed that dyspnoea, PSI risk classes IV and V and ICU admission were risk factors for 30-day hospital mortality while cough and appropriate empiric treatment were protective factors The area under the ROC curve was 0.84 (95% CI 0.78–0.90) for the model predictive of 30-day hospital mortality (fig. S6).

Discussion

The main findings of this study can be summarised as follows. 1) The prevalence of bacteraemia in this large series of consecutive patients with CAP was 10%, of which 5% were not admitted to the hospital. 2) Almost 20% of the cases were due to microorganisms other than *S. pneumonia*. 3) Of particular interest, 10% of bacteraemic cases were caused by ARP. 4) We identified several risk factors to predict bacteraemia in general and ARP bacteraemia, and prior antibiotic therapy was protective against bacteraemia in general but a risk factor for ARP bacteraemia. 5) Bacteraemia (excluding ARP) was a risk factor associated with CAP mortality, while appropriate empiric treatment was a protective factor in a multivariate model. ARP bacteraemia was associated with a significantly higher rate of inappropriate therapy than bacteraemia with other pathogens (27% *versus* 2.6%).

The diagnostic yield of blood cultures was 10% in this series. This prevalence is in the low range of the results reported in the literature [9, 15]. The prevalence of bacteraemia increased according to severity of illness (defined by PSI and CURB-65 scores), and in relation to site of care, with the highest rate being in ICU admitted patients (31%) and only 5% in patients not admitted to the hospital. The factors that may affect the positivity of blood cultures are prior antibiotic treatment, timing to blood culture sampling and accurate microbiological processing [16, 17]. In this study we could only assess the first factor and we found that without previous antibiotic treatment, the prevalence was almost doubled. This was also confirmed when analysing patients according to the probability of bacteraemia (table 4). However, if bacteraemia was present in spite of prior antibiotic therapy, it was more likely to be with ARP. METERSKY *et al.* [8] reported a large retrospective series of CAP patients with bacteraemia, they found that liver disease, vital sign

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TABLE 8 Significant univariate and multivariate logistic regression analyses for the prediction of 30-day hospital mortality in the total population

	Univariate		Multivariate[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Influenza vaccine	1.76 (1.20–2.59)	0.004		
Diabetes mellitus	1.49 (1.03–2.15)	0.034		
Neurological disease	3.48 (2.54–4.77)	<0.001	1.99 (1.33–3.00)	0.001
Cough	0.61 (0.44–0.86)	0.005		
Dyspnoea	3.07 (2.04–4.63)	<0.001		
Pleuritic pain	0.45 (0.32–0.64)	<0.001		
P_{aO_2}/F_{IO_2} <250	5.07 (3.54–7.26)	<0.001	3.21 (2.19–4.71)	<0.001
Nursing-home	5.10 (2.79–9.32)	<0.001		
PSI risk class IV and V	7.74 (5.01–11.91)	<0.001	4.13 (2.46–6.95)	<0.001
CURB-65 risk class 3–5	5.45 (3.98–7.46)	<0.001		
ICU admission	3.16 (2.32–4.31)	<0.001	1.85 (1.26–2.73)	0.002
Mechanical ventilation[¶]		<0.001		
Not ventilated	1			
Noninvasive	3.69 (2.13–6.37)	<0.001		
Invasive	9.86 (6.62–14.70)	<0.001		
Length of hospital stay[+] >7 days	1.19 (1.11–1.29)	<0.001		
Appropriate empiric treatment	0.29 (0.18–0.44)	<0.001	0.28 (0.16–0.50)	<0.001
Bacteraemia[§]		<0.001		0.011
Non-bacteraemic CAP	1			
Non-ARP bacteraemia	1.71 (1.11–2.64)	0.016	1.94 (1.18–3.19)	0.009
ARP bacteraemia	4.82 (2.04–11.42)	<0.001	2.48 (0.82–7.54)	0.11

P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; PSI: pneumonia severity index; CURB-65: confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) ⩽60 mmHg (diastolic), age ⩾65 years; ICU: intensive care unit; CAP: community acquired pneumonia; ARP: antibiotic-resistant pathogens. [#]: Hosmer–Lemeshow goodness-of-fit test, p=0.050; [¶]: the p-value corresponds to differences between the three groups (not ventilated, noninvasive and invasive); [+]: length of hospital stay was treated as a continuous variable and >7 days indicates the increase by 7 days; [§]: the p-value corresponds to the differences between the three groups (non-bacteraemic CAP, non-ARP bacteraemia or ARP bacteraemia).

abnormalities, blood urea nitrogen elevation, sodium abnormalities and WBC elevation were risk factors for bacteraemia in both a derivation and validation cohort. They proposed a score with two categories of risk, low and high. They did not stratify these risks in relation to specific microorganisms.

FALGUERA *et al.* [9] did a similar analysis using a database of prospectively collected data. Chronic liver disease, pleuritic pain and vital sign abnormalities were the predictors of bacteraemia. They also proposed a score, giving one point to each one of the factors and recommended obtaining blood cultures in patients with a score >2. The area under the curve (AUC) of this score was 0.70, but was not adjusted for the different microorganisms. In both studies prior antibiotics were a protective factor [8, 9]. To our knowledge neither of these two scores have been implemented in clinical practice.

In our study we found several risk factors for bacteraemia using multivariate logistic regression analyses, including pleuritic pain, C-reactive protein ⩾21.6 mg dL^{-1} and ICU admission. The AUC for the model was 0.71 (95% CI 0.68–0.75). Interestingly, we found that in the presence of all three risk factors and the absence of the two protective factors, the probability of bacteraemia was 30%. This rule could help to define which patients would benefit from having blood cultures taken and more intensive monitoring [1] and those who would not. Currently, only the last IDSA/ATS [6] guidelines have tried to define which population of CAP patients would benefit from blood cultures, while other guidelines recommend blood samples for all hospitalised patients with CAP [7]. New CAP guidelines should focus on which patients should not undergo blood cultures and our results could help with this specific aspect. By contrast to METERSKY *et al.* [8] and FALGUERA *et al.* [9] we did not find that chronic liver disease was a risk factor for bacteraemia. This can be explained by the fact that not all our patients had liver cirrhosis, which is probably the real risk factor for bacteraemia.

Our results concerning ARP bacteraemia are of interest in the context of an increasing incidence of resistant microorganisms in the community. In our study this problem was of low magnitude since only 30 (10%) patients of the total bacteraemic CAP cases had ARP. In our definition of ARP we included

those microorganisms that cannot be treated with the usual empiric therapy for CAP (MRSA, multidrug-resistant *S. pneumoniae*, *P. aeruginosa*, extended-spectrum beta-lactamase producing (ESBL) *Enterobacteriacea*. We recognise that *P. aeruginosa* is not purely an ARP microorganism but we felt that it would be better to include it in this group since it requires a totally different antibiotic treatment. This is an important group to identify, because these patients had a high frequency of inappropriate empiric therapy, and possibly, by using the risk factor profile that we identified, these patients could be anticipated and treated with appropriate empiric therapy more often. In our study, prior antibiotic treatment, C-reactive protein blood levels and pleuritic pain (protective) were the main predictors of these microorganisms. Nursing homes were not a risk factor for ARP bacteraemia in the multivariate analysis and this can be explained by the heterogeneity of nursing home patients in Spain, which include patients with no risk. The combination of these three factors could be useful to suspect ARP bacteraemia in CAP; the AUC for the model was 0.77 (95% CI 0.66–0.87). In a second multivariate analysis (ARP bacteremic *versus* all population) we found that CURB-65 risk class 3–5 and ICU admission were the only two factors associated with a higher risk of ARP bacteraemia, suggesting that the problem of ARP bacteraemia is restricted to more severe patients.

Interestingly we included in our ARP group multiresistant *S. pneumonia*, since these microorganisms cannot be treated with the standard recommended antibiotics. Recent publications from SHORR *et al.* [18] and ALIBERTI *et al.* [19] have defined risk factors for these types of microorganisms in CAP patients, but not specifically in patients with bacteraemia. In addition they did not include multidrug-resistant *S. pneumoniae*. ALIBERTI *et al.* [20], in a validation study, found that the score from SHORR *et al.* [18] and the score that they proposed had an AUC of 0.79 and 0.71 respectively. We found several factors associated with 30-day hospital mortality in the overall population: bacteraemia, inappropriate empiric treatment, neurological disease, P_{aO_2}/F_{IO_2} <250, PSI risk classes IV and V and ICU admission. Bacteraemia (excluding ARP) was an independent risk factor for mortality, which reinforces the importance of the suspicion and early detection of these patients. However, in multivariate analysis we could not find an independent association between ARP bacteraemia and mortality. This is probably due to the small number of ARP bacteraemia. Alternatively, our data suggest that early and appropriate antibiotic treatment is a key factor for mortality and, in fact, we did find a significantly higher rate of inappropriate empiric therapy with ARP bacteraemia than with other types of bacteraemic CAP (27% *versus* 2.6%).

The major strength of this study is that we provide original data on the burden of ARP bacteraemia in CAP, and define the risk factors associated with these organisms. In addition, and in contrast with previous studies, notably METERSKY [8] and FALGUERA [9], we performed analyses of risk factors and mortality for the group as a whole, as well as for ARP. We also calculated the probability of bacteraemia in the presence or absence of risk factors for each of these two populations. We also provide indications of which population of CAP would not potentially benefit from undergoing blood cultures.

Our study has limitations. First, this is a very specific Spanish population and resistance patterns in our country are different from those in other countries, consequently the findings of our study need to be confirmed in a validation cohort outside of Spain. Second, we did not record the time to the first dose of antibiotic, which is a factor that has been associated with mortality in the most severe CAP patients. Third, a potential limitation is the long period of the study. However, our protocols and microbiological procedures have not substantially changed during these years. Fourth, blood cultures were not performed on all patients and, therefore, could be a potential bias that needs to be taken into consideration.

Finally we do not have data concerning all antibiotic changes that were undertaken once the blood culture results were known. However, in 17 out 30 ARP bacteraemia, initial antibiotic treatment was inadequate and antibiotics were modified according the corresponding antibiogram.

In summary, we have described clinical predictors of bacteraemic CAP and ARP. Importantly, we provide information about CAP patients in whom blood cultures should not be performed (table 5). Mortality in our CAP population was significantly associated with bacteraemia and treatment inadequacy, which was more common with ARP bacteraemia than with other forms of bacteraemia.

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References

1 Ewig S, Torres A. Community-acquired pneumonia as an emergency: time for an aggressive intervention to lower mortality. *Eur Respir J* 2011; 38: 253–260.

2 Niederman MS, Mandell LA, Anzueto A, *et al.* Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001; 163: 1730–1754.

DOI: 10.1183/09031936.00152514

3 Lin SH, Lai CC, Tan CK, *et al.* Outcomes of hospitalized patients with bacteraemic and non-bacteraemic community-acquired pneumonia caused by *Streptococcus pneumoniae*. *Epidemiol Infect* 2011; 139: 1307–1316.
4 Bordon J, Peyrani P, Brock GN, *et al.* The presence of pneumococcal bacteremia does not influence clinical outcomes in patients with community-acquired pneumonia: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort study. *Chest* 2008; 133: 618–624.
5 Garnacho-Montero J, Garcia-Cabrera E, Diaz-Martin A, *et al.* Determinants of outcome in patients with bacteraemic pneumococcal pneumonia: importance of early adequate treatment. *Scand J Infect Dis* 2010; 42: 185–192.
6 Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
7 Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections--full version. *Clin Microbiol Infect* 2011; 17; Suppl. 6, E1–E59.
8 Metersky ML, Ma A, Bratzler DW, *et al.* Predicting bacteremia in patients with community-acquired pneumonia. *Am J Respir Crit Care Med* 2004; 169: 342–347.
9 Falguera M, Trujillano J, Caro S, *et al.* A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. *Clin Infect Dis* 2009; 49: 409–416.
10 Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
11 Lim WS, van der Eerden MM, Laing R, *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58: 377–382.
12 Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis* 2008; 197: 1079–1081.
13 Torres A, Barberan J, Falguera M, *et al.* Guia multidisciplinar para la valoracion pronóstica, diagnostico y Tratamiento de la neumonia adquirida en la comunidad [Multidisciplinary guidelines for the management of community-acquired pneumonia]. *Med Clin (Barc)* 2013; 140: 223.e1–223.e19.
14 Hosmer D, Lemeshow S. *Applied logistic regression*. New York, John Wiley & Sons Inc., 1989.
15 Waterer GW, Wunderink RG. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. *Respir Med* 2001; 95: 78–82.
16 Riedel S, Bourbeau P, Swartz B, *et al.* Timing of specimen collection for blood cultures from febrile patients with bacteremia. *J Clin Microbiol* 2008; 46: 1381–1385.
17 Mylotte JM, Tayara A. Blood cultures: clinical aspects and controversies. *Eur J Clin Microbiol Infect Dis* 2000; 19: 157–163.
18 Shorr AF, Zilberberg MD, Reichley R, *et al.* Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. *Clin Infect Dis* 2012; 54: 193–198.
19 Aliberti S, Di Pasquale M, Zanaboni AM, *et al.* Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clin Infect Dis* 2012; 54: 470–478.
20 Aliberti S, Cilloniz C, Chalmers JD, *et al.* Multidrug-resistant pathogens in hospitalised patients coming from the community with pneumonia: a European perspective. *Thorax* 2013; 68: 997–999.