Eur J Clin Microbiol Infect Dis (2017) 36:123–130
DOI 10.1007/s10096-016-2779-5

ORIGINAL ARTICLE

Improved survival among ICU-hospitalized patients with community-acquired pneumonia by unidentified organisms: a multicenter case–control study

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Received: 2 September 2016 / Accepted: 2 September 2016 / Published online: 21 September 2016

Abstract A retrospective analysis from prospectively collected data was conducted in intensive care units (ICUs) at 33 hospitals in Europe comparing the trend in ICU survival among adults with severe community-acquired pneumonia (CAP) due to unknown organisms from 2000 to 2015. The secondary objective was to establish whether changes in antibiotic policies were associated with different outcomes. ICU mortality decreased ($p = 0.02$) from 26.9 % in the first study period (2000–2002) to 15.7 % in the second period (2008–2015). Demographic data and clinical severity at admission were comparable between groups, except for age over 65 years and incidence of cardiomyopathy. Over time, patients received higher rates of combination therapy (94.3 vs. 77.2 %; $p < 0.01$) and early (<3 h) antibiotic delivery (72.9 vs. 50.3 %; $p < 0.01$); likewise, the 2008–2015 group was more likely to receive adequate antibiotic prescription [as defined by the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines] than the 2000–2002 group (70.7 vs. 48.2 %; $p < 0.01$). Multivariate analysis showed an independent association between decreased ICU mortality and early (<3 h) antibiotic administration [odds ratio (OR) 3.48 [1.70–7.15], $p < 0.01$] or adequate antibiotic prescription according to guidelines (OR 2.22 [1.11–4.43], $p = 0.02$). In conclusion, our findings suggest that ICU mortality in severe CAP due to unidentified organisms has decreased in the last 15 years. Several changes in management and better compliance with guidelines over time were associated with increased survival.

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Introduction

Community-acquired pneumonia (CAP) is a major cause of death worldwide and the foremost cause of death due to infectious diseases in western countries [1]. In its most severe forms of presentation, CAP is still associated with high morbidity and mortality, and entails a significant social cost [2]. Despite extensive studies, the management of several aspects of severe CAP remains controversial. For example, optimal antibiotic treatment in severe CAP is still an open issue.

The administration of early antibiotic treatment seems to be associated with better outcomes, both in patients requiring vasopressors [3] and in those who underwent mechanical ventilation [4]. Combination antibiotic therapy has also been associated with a decrease in mortality, although not all studies have reached similar conclusions [5]. Finally, compliance with international guidelines is associated with improved survival [6]. However, even with extensive sampling, the microorganism responsible for CAP is identified in fewer than 50 % of cases [2].

We hypothesized that mortality related to severe CAP without an identified microorganism has decreased in recent years, and that the optimization of management strategies has contributed to this trend. The primary objective of the present study was to compare mortality between two cohorts of patients diagnosed with severe CAP in different time periods and admitted to the intensive care unit (ICU). The secondary objective was to determine whether changes in antibiotic policies were associated with different outcomes.

Materials and methods

This was a secondary analysis of two prospective cohorts. CAPUCI (Community-Acquired Pneumonia en la Unidad de Cuidados Intensivos) I and II are two European, prospective, multicenter studies performed among patients admitted to the ICU for CAP. The CAPUCI I study recorded data from 33 hospitals from 2000 to 2002. Data from CAPUCI I have been reported elsewhere [7]. The CAPUCI II study was a follow-up project endorsed by the European Critical Care Research Network (ECCRN), and data on this study have also been published [8].

Pneumonia was diagnosed when a patient had symptoms of lower respiratory infection plus a new consolidation on chest radiography. Patients diagnosed with healthcare-associated pneumonia or with a no-cardiopulmonary resuscitation indication were not included. Severe CAP was defined as pneumonia that required ICU admission following Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) indications. Patients with severe chronic illness in whom pneumonia was an expected terminal event (do not resuscitate or intubate orders) were not included.

In both CAPUCI cohorts, the following data were recorded: demographic data and clinical presentation, outcome, and antibiotic therapy. Patient management and antibiotic prescription were not standardized and were left to the discretion of the attending physician. In accordance with the IDSA/ATS guidelines, patients were admitted to the ICU either to undergo mechanical ventilation, vasopressors, or because they were with severe hypoxemia/hypotension. These patients were observed until ICU discharge or death. The ethical board of the coordinating center approved the study and it was performed in accordance with the amended Declaration of Helsinki. The need for informed consent was waived because of the observational nature of the studies.

Immune compromise was defined as primary immunodeficiency or immunodeficiency secondary to radiation treatment, use of cytotoxic drugs or steroids (daily doses >20 mg prednisolone or equivalent for >2 weeks), transplantation, or acquired immune deficiency syndrome (AIDS) [9]. Other definitions, such as comorbidities or rapid radiologic spread, have been reported elsewhere [7, 8]. The probability of death was calculated according to the Acute Physiology and Chronic Health Evaluation (APACHE) II [10] score in the CAPUCI I cohort and the Simplified Acute Physiology Score (SAPS) III [11] in the CAPUCI II cohort. Combined therapy was defined as the administration of the same antibiotics (two or more) during 48 h since admission. Early antibiotic administration was defined if the first antibiotic dose was administered within 3 h of hospital admission [12, 13].

Before starting therapy, patients underwent a complete clinical history assessment and physical examination. Basic laboratory tests and chest radiography were performed. Two sets of blood samples were obtained and cultured. When available, a respiratory specimen was evaluated by Gram staining and culture as well. Urinary antigen detection tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed if indicated by the attending physician. Paired serum samples obtained during the acute and convalescent phases of infections were also obtained to determine antibody levels to *Mycoplasma pneumoniae*, *Chlamydophila psittaci*, *Coxiella burnetii*, and *L. pneumophila*. Pathogens in blood, pleural effusion, and respiratory samples were investigated using standard microbiological procedures. Real-time polymerase chain reaction (PCR) was performed to identify influenza A and B viruses from 2009 onwards.

The results are expressed as medians and interquartile ranges for continuous variables or as absolute percentages for categorical variables. Categorical variables were assessed with the chi-square or two-tailed Fisher's exact test, while continuous variables were compared with the Mann–Whitney U test.

A multivariate model was performed to identify the variables associated with changes in mortality. To construct the model, we performed a binary logistic regression using as covariates all variables from the univariate analysis that were associated with changes in ICU mortality with a cutoff of $p < 0.05$; subsequently, to optimize the model and minimize an over-fitting bias, an automatic stepwise backward covariate selection was performed. All data were managed and statistical analyses performed using the SPSS 20 package.

Results

A total of 1145 patients were enrolled, with 237 (44.8 %) episodes with unknown organisms in the baseline period and 236 (38.3 %) in the more recent period. Overall, 140 (12.2 %) patients were excluded due to missing variables during follow up. Figure 1 shows the flow chart for the distribution of patients. After excluding 672 patients with identified organisms, 333 patients were enrolled in the analysis—193 selected from the CAPUCI I database and 140 from CAPUCI II (Table 1). Age above 65 years was documented in 164 (49.25), 195 (58.5 %) underwent intubation, and 145 (43.5 %) received

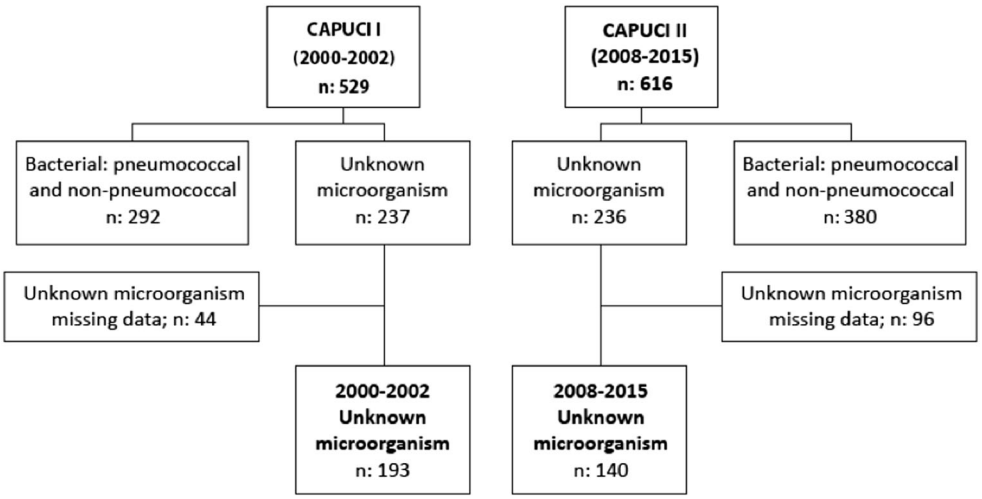

Fig. 1 Flow chart for patient selection

vasoactive agents. Chronic obstructive pulmonary disease (COPD) was documented in 117 (35.1 %). In the 2008–2015 group, 18.6 % of patients received antibiotic therapy before hospital admission, compared with 25.6 % in the 2000–2002 group. The median time from hospital to ICU admission was 1 day.

Compared to the 2008–2015 period, the 2000–2002 group included a higher proportion of individuals aged over 65 years (55.4 vs. 40.7 %; $p = 0.01$) and had a greater incidence of cardiomyopathy (32.6 vs. 18.7 %; $p < 0.01$). The rest of the demographic and clinical variables did not show significant differences between groups. ICU mortality fell from 26.9 % in 2000–2002 to 15.7 % in 2008–2015 ($p = 0.02$). This represents an absolute and relative reduction of 11.2 and 42.7 % over a 15-year period, respectively. Kaplan–Meier survival curves, censored at 45 days, are detailed in Fig. 2.

The 2008–2015 patients presented with a significantly ($p < 0.01$) higher prevalence of combination therapy (94.3

Table 1 Demographic and clinical data at admission, divided by study period

Variable	2008–2015 (n = 140)	2000–2002 (n = 193)	p-Value
Age, years[a]	60.15 (49.0–73.8)	62.4 (54.0–74.0)	0.20
Age over 65 years	**57 (40.7)**	**107 (55.4)**	**0.01**
Gender male	88 (62.9)	138 (71.5)	0.10
Active smoker	52 (37.1)	88 (45.8)	0.12
Alcohol use	24 (17.1)	34 (17.6)	1.00
Diabetes mellitus	33 (24.6)	45 (23.3)	0.79
Cardiomyopathy	**25 (18.7)**	**63 (32.6)**	**<0.01**
Cerebral vascular disease	8 (5.7)	17 (8.8)	0.40
Malignancy	12 (9.0)	15 (7.8)	0.84
Chronic obstructive pulmonary disease	41 (29.3)	76 (39.4)	0.06
Immunosuppression	2 (1.4)	9 (4.7)	0.13
Estimated probability of death[a]	30.5 (12.3–45.5)	34.6 (19.0–46.0)	0.09
ICU length of stay[a]	13.6 (4.0–17.8)	15.4 (5.0–18.0)	0.30
Need for vasopressors	60 (42.9)	85 (44.0)	0.91
Invasive mechanical ventilation	75 (53.6 %)	120 (62.2 %)	0.14
Days of mechanical ventilation[a]	10.7 (3.0–12.0)	12.7 (4.0–16.0)	0.39
Acute kidney injury	50 (37.3)	53 (27.6)	0.07
Rapid radiographic spread	68 (50.7)	78 (40.8)	0.09
Intensive care unit mortality	**22 (15.7)**	**52 (26.9)**	**0.02**

Data are given as: n (%), unless otherwise indicated

[a] Median (interquartile range 25th–75th)

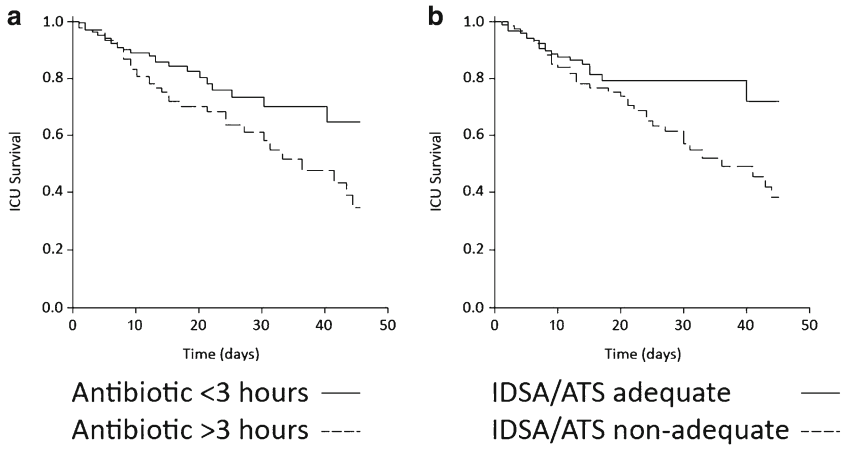

Fig. 2 Kaplan–Meier survival analysis, censored at 45 days. **a** Stratification according to early vs. non-early antibiotic administration. **b** Stratification according to adequate vs. non-adequate Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) indication. Log-rank test $p = 0.03$

vs. 77.2 %), early (<3 h) antibiotic administration (72.9 vs. 50.3 %), and treatment compliant with the 2007 IDSA/ATS guidelines (70.7 vs. 48.2 %) (Table 2). Overall, the use of quinolones doubled in the 2008–2015 cohort. The most frequently prescribed antibiotic patterns were statistically similar in the two groups: a combination of cephalosporin plus a macrolide (36.4 % in the 2008–2015 group vs. 44.0 % in the 2000–2002 group; p-value = 0.18) a combination of a cephalosporin plus a quinolone (32.1 % in the 2008–2015 group vs. 15.5 % in the 2000–2002 group; p-value < 0.01). Treatment against methicillin-resistant *Staphylococcus aureus* was prescribed to 7.1 % of the 2008–2015 group and to 5.2 % of the 2000–2002 group (Table 3).

Univariate analysis was performed to assess differences in ICU mortality between groups; age over 65 years, need for vasopressors, invasive mechanical ventilation, acute kidney injury, rapid radiographic spread, and increase in estimated probability of death were associated ($p < 0.05$) with increased ICU mortality; conversely, treatment compliant with the 2007 IDSA/ATS guidelines and early antibiotic administration were associated with a decreased risk of mortality ($p < 0.01$ in both analyses) (Table 4).

Subsequently, a binary logistic regression model was constructed including all variables from the univariate analysis that were associated with a change in ICU mortality. Thus, multivariate analysis was finally adjusted according to the following variables: age over 65 years, need for vasopressors, invasive mechanical ventilation, acute kidney injury, rapid radiographic spread, treatment compliant with the 2007 IDSA/ATS guidelines, estimated probability of death, and early (<3 h) antibiotic treatment. Finally, the need for invasive mechanical ventilation [odds ratio (OR) 0.24 [0.10–0.62]; p <0.01), acute kidney injury (OR 0.21 [0.10–0.44]; $p < 0.01$), and the estimated probability of death (OR 0.97 [0.95–0.99] per 1 % variation of risk; p <0.01) were associated with a lower probability of survival. Conversely, early (<3 h) antibiotic administration (OR 3.48 [1.70–7.15]; p <0.01) and adherence to 2007 IDSA/ATS guidelines (OR 2.22 [1.11–4.43]; $p = 0.02$) were associated with an increased probability of ICU survival.

Discussion

We report that mortality in ICU CAP with unidentified organisms showed an absolute decrease of around 11 % over the last 15 years and our findings show an association between early (<3 h) and adequate antibiotic administration (according to the 2007 ATS/IDSA guidelines) and survival. This multicenter cohort study is, to the best of our knowledge, the first to

Table 2 Characteristics of antibiotic treatment

Variable	2008–2015 (n = 140)	2000–2002 (n = 193)	p-Value
Previous antibiotic	26 (18.6)	50 (25.6)	0.15
Monotherapy	**8 (5.7)**	**44 (22.8)**	**<0.01**
Combined therapy	**132 (94.3)**	**149 (77.2)**	**<0.01**
Antibiotic initiated 0 to 3 h	**102 (72.9)**	**97 (50.3)**	**<0.01**
Antibiotic initiated 4 to 6 h	**25 (17.9)**	**59 (30.6)**	**0.01**
Antibiotic initiated more than 6 h	**13 (9.3)**	**37 (19.2)**	**0.01**
Adequate treatment according to 2007 IDSA/ATS guidelines	**99 (70.7)**	**93 (48.2)**	**<0.01**

Data are given as: n (%)

IDSA/ATS Infectious Diseases Society of America/American Thoracic Society

Table 3 Most frequent patterns of antibiotic treatment, divided by study period

Variable	All patients (n = 333)	2008–2015 (n = 140)	2000–2002 (n = 193)	p-Value
Cephalosporin plus macrolide	137 (40.8)	51 (36.4)	86 (44.0)	0.18
Ceftriaxone/cefotaxime plus clarithromycin	**81 (24.3)**	**13 (9.3)**	**68 (35.2)**	**<0.01**
Ceftriaxone/cefotaxime plus azithromycin	**37 (11.1)**	**37 (26.4)**	**0 (0)**	**<0.01**
Ceftriaxone/cefotaxime plus erythromycin	**11 (3.0)**	**0 (0)**	**11 (5.2)**	**<0.01**
Cefepime clarithromycin/azithromycin	8 (2.4)	1 (0.7)	7 (3.6)	0.15
Cephalosporin plus quinolone	**75 (22.5)**	**45 (32.1)**	**30 (15.5)**	**<0.01**
Ceftriaxone/cefotaxime plus levofloxacin	**64 (19.2)**	**40 (28.6)**	**24 (12.4)**	**<0.01**
Cefepime/ceftazidime plus levofloxacin	8 (2.4)	5 (3.6)	3 (1.6)	0.29
Cefepime/ceftazidime plus ciprofloxacin	3 (0.9)	0 (0)	3 (1.6)	0.27
Levofloxacin	**21 (6.3)**	**3 (2.1)**	**18 (9.3)**	**0.01**
Quinolone plus penicillin	13 (3.9)	8 (5.7)	5 (2.6)	0.16
Levofloxacin plus piperacillin–tazobactam	**10 (3.0)**	**8 (5.7)**	**2 (1.0)**	**0.02**
Other Q plus other penicillin	3 (0.9)	0 (0)	3 (1.6)	0.27
Levofloxacin plus meropenem/imipenem	12 (3.6)	8 (5.7)	4 (2.1)	0.13
Triple non-MRSA broad-spectrum therapy	11 (3.3)	6 (4.3)	5 (2.6)	0.54
Amoxicillin–clavulanate	11 (3.3)	2 (1.4)	9 (4.7)	0.13
Levofloxacin plus clarithromycin/azithromycin	10 (3.0)	7 (5.0)	3 (1.6)	0.10
Piperacillin–tazobactam	7 (2.1)	2 (1.4)	5 (2.6)	0.70
Cephalosporin	7 (2.1)	2 (1.4)	5 (2.6)	0.70
Ceftriaxone/cefotaxime	6 (1.8)	1 (0.7)	5 (2.6)	0.41
Cefepime	1 (0.3)	1 (0.7)	0 (0)	0.42
Other monotherapy	**11 (3.3)**	**1 (0.7)**	**10 (5.2)**	**0.03**
Other combined therapy	18 (5.4)	5 (3.6)	13 (6.7)	0.23
Overall	333 (100)	140 (100)	193 (100)	
Anti-MRSA therapy	20 (6.0)	10 (7.1)	10 (5.2)	0.49

Data are given as: n (%). p-Values calculated between the 2008-2015 and 2000–2002 groups

MRSA methicillin-resistant *Staphylococcus aureus*

provide information on prognostic factors specifically in patients with ICU CAP with unidentified organisms, and adds knowledge about the large and understudied subgroup of severe CAP due to unidentified organisms.

Optimal prescription practices in patients with severe CAP should be based on early administration of antibiotics in accordance with guidelines [13]. In two previous publications [7, 8], we already showed a decrease in mortality between the two historical cohorts (35 vs. 17 % in non-pneumococcal CAP and 34 vs. 18 % in pneumococcal CAP) and an association between early and combined administration of antibiotics and survival. The association between combined antibiotic treatment and mortality in the subgroup of patients with *L. pneumophila* was further reported in an additional publication [14].

Notably, in contrast to severe pneumonia with an identified etiology [7, 8, 14], we did not find an association between the administration of combined antibiotic therapy and reduced mortality either in the population as a whole or in the subgroup of patients requiring vasopressors (data not shown). A possible explanation for this finding is that a fraction of current patients had non-bacterial pneumonia; moreover, it may be that other diseases that mimic pneumonia (pulmonary edema, pulmonary embolism, acute respiratory distress syndrome, or an acute exacerbation of COPD) were the real cause of respiratory failure rather than CAP. Alternatively, a vast majority of patients received combination therapy, whereas only 52 patients received monotherapy (indeed, only eight in the second cohort), limiting the power of the analysis of this association.

The most striking finding in the present study was the 11 % increase in ICU survival between the two cohorts. There may be several reasons for this trend, all of them attributable to an improvement in the management of critical patients in recent years. In fact, improvements in the management of shock [15], the optimization of mechanical ventilation [16], more insight in

Table 4 Univariate and multivariate analyses to assess variables associated with changes in intensive care unit (ICU) survival

Variable	Survival (n = 259)	No survival (n = 74)	Univariate analysis: p-value	Multivariate analysis: OR (95 % CI); p-value
Age over 65 years	**117 (45.2)**	**47 (63.5)**	**<0.01**	0.87 (0.43–1.76); 0.71
Alcohol use	44 (17.0)	14 (18.9)	0.73	
Active smoker	111 (43.0)	29 (39.2)	0.60	
Diabetes mellitus	59 (23.2)	19 (26.0)	0.64	
Cardiomyopathy	62 (24.4)	26 (35.6)	0.07	
Chronic obstructive pulmonary disease	88 (34.0)	29 (39.2)	0.41	
Immunosuppression	6 (2.3)	5 (6.8)	0.07	
Need for vasopressors	**93 (35.9)**	**52 (70.3)**	**<0.01**	0.89 (0.40–1.96); 0.77
Invasive mechanical ventilation	**128 (49.4)**	**67 (90.5)**	**<0.01**	**0.24 (0.10–0.62); <0.01**
Acute kidney injury	**58 (22.7)**	**45 (63.4)**	**<0.01**	**0.21 (0.10–0.44); <0.01**
Rapid radiographic spread	**105 (41.3)**	**41 (57.7)**	**0.02**	0.58 (0.29–1.16); 0.12
Adequate treatment according to 2007 IDSA/ATS guidelines	**164 (63.3)**	**28 (37.8)**	**<0.01**	**2.22 (1.11–4.43); 0.02**
Estimated probability of death[a]	**26.0 (15.0–42.0)**	**46.0 (26.5–61.0)**	**<0.01**	**0.97 (0.95–0.99); <0.01**
Combined therapy	220 (84.9)	61 (82.4)	0.59	
Antibiotic initiated within 3 h	**166 (64.1)**	**33 (44.6)**	**<0.01**	**3.48 (1.70–7.15); <0.01**

Data are given as: n (%), unless otherwise indicated

IDSA/ATS Infectious Diseases Society of America/American Thoracic Society

[a] Median (interquartile range 25th–75th)

feeding [17], prevention of ICU-related complications [18], and improvements in antibiotic policies [7] have been put forward as factors related with increased survival in ICU patients.

Early administration of the first dose of antibiotic was independently associated with increased survival. Other studies have obtained the same results [19], but never in a population of patients with CAP due to an unidentified organism. International guidelines recommend delivery of the first dose of antibiotic as soon as CAP is diagnosed [13]; likewise, the sepsis survival campaign suggests initiation of antibiotic treatment within an hour of recognition of severe sepsis or septic shock [3]. Although several papers have proposed early antibiotic administration as a quality-of-treatment marker [20], our results suggest that prompt antibiotic delivery should be guaranteed to all patients with CAP.

Another important finding in the present paper is the association between adherence to international guidelines and the increase in survival. Similar results were reported in patients with pneumonia by a confirmed microorganism [7] and non-severe hospitalized adults [21]; however, this issue has not been addressed to date in patients with pneumonia of unknown etiology. This finding confirms the importance of compliance with management guidelines.

The most important limitation of the present study is that no systematic search for virus infection or comprehensive molecular testing for respiratory pathogens was performed. This is because many of the diagnostic techniques at our disposal today were not available during the first study period. This is an important point: among patients receiving prior antibiotics, 78 % had a bacterial pathogen detected by PCR but only 32 % were culture-positive [22]. Jain et al. [23] recently observed that CAP due to an unidentified microorganism might be caused by rhinovirus in a significant proportion of patients. Second, residual confounding due to the retrospective and observational design of the analysis should be mentioned. Moreover, 96 patients were excluded due to missing data about clinical evolution, with an imbalance in the proportion of exclusion between the two cohorts, which may represent a potential source of bias and limit the validity of comparisons. ICU mortality was chosen to identify "direct causes of death", but we ignore the "hidden" mortality, because some patients may be transferred to the floor and not be censored because they die outside the ICU. Another limitation is the lack of data on pneumococcal/influenza vaccination strategies, septic shock resuscitation, and mechanical ventilation setting in both cohorts. Whether these potential differences in strategies represented a bias is unknown. Indeed, several changes in the management of CAP and a general improvement in global care over time may have caused the observed outcomes and early antibiotic administration may be a confounding factor for these variables. Indeed, a scatterplot graph that analyzes mortality with respect to the year/month of admission would be interesting, but it requires a larger cohort and, with the current sample size, was not feasible. Estimated mortality was based on scores validated in different populations and periods,

but it is unlikely that they influenced the multivariate model. Important strengths include the multicenter design, the comprehensive data collection over a period of 15 years, the high quality of the cleaned database, and the high severity-of-illness of patients.

Conclusions

Our findings confirm that, over the past 15 years, survival for community-acquired pneumonia (CAP) in the intensive care unit (ICU) has improved in all subsets, like in sepsis, myocardial infarction, or stroke. Better implementation of the recommendations in the guidelines has been associated with improved survival in a condition that remains a management challenge, being the first cause of sepsis in general ICUs.

Acknowledgments CAPUCI II is a European Critical Care Research Network (ECCRN) project endorsed by the European Society of Intensive Care Medicine (ESICM).

We thank the investigators Consortium "Community-Acquired Pneumonia en la Unidad de Cuidados Intensivos II study" for their dedication.

Compliance with ethical standards

Financial support 2014SGR0218, RED RESPIRA ISCIII (RTIC 03/11), FISS (PI 04/1500), and CIBERES (PCI Pneumonia).

Conflict of interest Dr. Rello served as a consultant for Lasco and Paratek. The remaining authors have no conflicts of interest to declare.

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