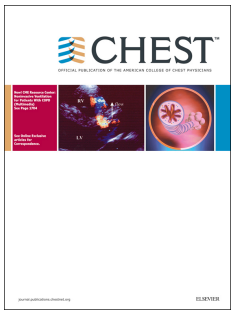
Accepted Manuscript



Community-Acquired Pneumonia due to *Multidrug and non-Multidrug resistant Pseudomonas aeruginosa*

Catia Cillóniz, PhD, Albert Gabarrús, MSc, Miquel Ferrer, MD, Jorge Puig de la Bellacasa, MD, Mariano Rinaudo, Josep Mensa, MD, Michael S. Niederman, MD, Antoni Torres, MD

PII: S0012-3692(16)47572-0

DOI: 10.1016/j.chest.2016.03.042

Reference: CHEST 408

To appear in: *CHEST*

Received Date: 15 January 2016

Revised Date: 22 March 2016

Accepted Date: 25 March 2016

Please cite this article as: Cillóniz C, Gabarrús A, Ferrer M, Puig de la Bellacasa J, Rinaudo M, Mensa J, Niederman MS, Torres A, Community-Acquired Pneumonia due to *Multidrug and non-Multidrug resistant Pseudomonas aeruginosa*, *CHEST* (2016), doi: 10.1016/j.chest.2016.03.042.

Community-Acquired Pneumonia due to *Multidrug and non-Multidrug resistant Pseudomonas aeruginosa*

Catia Cillóniz, PhD[1]; Albert Gabarrús, MSc[1]; Miquel Ferrer, MD[1]; Jorge Puig de la Bellacasa, MD[2]; Mariano Rinaudo[1]; Josep Mensa, MD[3]; Michael S. Niederman, MD[4]; Antoni Torres, MD[1]

[1] Department 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] Department of Microbiology, Hospital Clinic, Barcelona, Spain.

[3] Department of Infectious Disease, Hospital Clinic, Barcelona, Spain

[4] Division of Pulmonary and Critical Care Medicine, Weill Cornell Medical College

Running Head*: Pseudomonas aeruginosa* CAP

Word count of the body of the manuscript: 2,930

Funding: The study was funded by Ciber de Enfermedades Respiratorias (CibeRes CB06/06/0028). 2009 Support to Research Groups of Catalonia 911.

Conflicts of interest: We declare no conflicts of interest.

Corresponding author:

Antoni Torres, MD

Department of Pneumology, Hospital Clinic of Barcelona, Spain

c/ Villarroel 170, 08036 Barcelona, Spain

Email: atorres@clinic.ub.es

Abbreviations list

Community-acquired pneumonia (CAP)

Multidrug-resistant (MDR)

(AIDS)

Extensively drug-resistant (XDR)

Pandrug-resistant (PDR)

Tracheobronchial aspirates (TBAS)

Bronchoalveolar lavage (BAL)

Polymerase chain reaction (PCR)

Pneumonia Severe Index (PSI)

Consciousness, Urea, Respiratory rate, Blood pressure, 65 years old (CURB-65)

Confidence intervals (CIs)

Receiver operating characteristic (ROC)

Mean (SD)

Interquartile range (IQR)

Chronic obstructive pulmonary disease (COPD)

Intensive Care Unit (ICU)

Length of stay (LOS)

ABSTRACT

Background: *Pseudomonas aeruginosa* is not a frequent pathogen in Community Acquired Pneumonia (CAP). However, in patients with severe CAP, *P. aeruginosa* can be the etiology in 1.8% to 8.3% of patients, with a case-fatality rate of 50% to 100%. We describe the prevalence, clinical characteristics, outcomes and risk factors associated with CAP due to multidrug and non-multidrug resistant *P. aeruginosa.*

Methods: Prospective observational study of 2023 consecutive adult CAP patients with definitive etiology.

Results: *P. aeruginosa* was found in 77 (4%) of the 2023 cases with microbial etiology. In 22 (32%) of the 68 cases of *P. aeruginosa* with antibiogram data, the isolates were multidrug-resistant (MDR). Inappropriate therapy was present in 49 (64%) cases of *P. aeruginosa* CAP, including 17/22 (77%) cases of MDR *P. aeruginosa* CAP. Male sex, chronic respiratory disease, C-reactive protein <12.35 mg/dL, and PSI risk class IV – V were independently associated with *P. aeruginosa* CAP. Prior antibiotic treatment was more frequent in MDR *P. aeruginosa* CAP compared with non-MDR *P. aeruginosa* (58% *vs.* 29%, p=0.029), and was the only risk factor associated with CAP due to MDR *P. aeruginosa*. In the multivariate analysis, age ≥65 years, CAP due to *P. aeruginosa*, chronic liver disease, neurologic disease, nursing-home, criteria of ARDS, acute renal failure, ICU admission, and inappropriate empiric treatment were the factors associated with 30-day mortality.

Conclusions: *P. aeruginosa* is an individual risk factor associated with mortality in CAP. The risk factors described can help clinicians to suspect *P. aeruginosa* and MDR *P. aeruginosa.*

INTRODUCTION

Pseudomonas aeruginosa is not a frequent pathogen in community-acquired pneumonia (CAP)[1-4]. Several studies have reported that *P. aeruginosa* was the cause in 1.8% to 8.3% of patients with severe CAP requiring intensive care unit (ICU) admission, with a case-fatality rate of 50% to 100%[5-9]. Since antibiotic treatment for *P. aeruginosa* is completely different from the standard treatment to cover common pathogens in CAP (*Streptococcus pneumoniae*, *Legionella pneumophila,* and atypical bacteria), current guidelines for severe CAP stratify therapy recommendations on the basis of Pseudomonal risk factors. However, since those guidelines were published, highly resistant forms of this pathogen have emerged, and for these patients, treatment is even more difficult. Many years ago, our group published a study[10] on *P. aeruginosa* in CAP. In that study, the prevalence of *P. aeruginosa* was 6.9% and mortality was 28%. Currently, the prevalence of multidrug-resistant (MDR) P. *aeruginosa* is well known in nosocomial pneumonia, but its prevalence in CAP is not well described, and this is now an important organism because of its potential impact on empiric-therapy choices. Knowledge of the associated risk factors for both MDR and non-MDR *P. aeruginosa* could prompt early recognition and diagnosis, and adequate initial antimicrobial therapy, considering the increasingly common population of patients with MDR Pseudomonal CAP.

Therefore, we have studied the prevalence, risk factors, and outcomes for *P. aeruginosa* in a non-immunosuppressed population with CAP. We also investigated the rates, risk factors, and outcomes of MDR *P. aeruginosa*.

METHODS

Study Design and Patients

We performed an observational cohort study of consecutive patients admitted to Hospital Clinic, Barcelona, Spain, between January 1999 and December 2014 with a diagnosis of community-acquired pneumonia. The exclusion criteria were: a) patients without a positive microbiologic diagnosis, b) severe immunosuppression (AIDS, chemotherapy, immunosuppressive drugs [e.g., oral corticosteroid ≥10 mg prednisone or equivalent per day for at least two weeks]), c) health care-associated pneumonia cases, d) active tuberculosis, e) patients with cystic fibrosis, and f) cases with a confirmed alternate diagnosis (additional details are shown in e-Methods in Supplementary Data). We include nursing home patients for the following reasons: 1- In Spain, the definition of nursing-home is very heterogeneous and it is unclear if all these would belong to an HCAP group. 2- In a previous article published by our group in Thorax (Polverino et al[11]) on nursing-home patients, we observed that microbial etiology was not very different compared to CAP. The study was approved by the Ethics Committee of our institution (Register: 2009/5451). Written informed consent was waived due to the non-interventional design.

Data Collection

The following parameters were recorded at admission: age, sex, current smoking, alcohol habits and drug consumption, co-morbidities, antibiotic treatment in the 30 days prior to hospital admission, treatment with corticosteroids (<10 mg prednisone or equivalent and inhaled 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 recorded. We also calculated the pneumonia severity index (PSI) and CURB-65 score[12;13] at admission.

Definitions

Pneumonia was defined as a new pulmonary infiltrate found on the hospital admission chest x-ray, with symptoms and signs of lower respiratory tract infection (e.g., fever, cough, sputum production, pleuritic chest pain) in persons who have not been hospitalized recently and have not had regular exposure to the health care system.

P. aeruginosa pneumonia was defined as pneumonia where *P. aeruginosa* was isolated in blood or in a valid respiratory sample (see Supplementary data).

Prior antibiotic treatment was considered when antibiotics had been taken in the previous month. Appropriateness of empiric antibiotic treatment in all patients was defined according to multidisciplinary guidelines for the management of community acquired pneumonia[14]. Appropriateness of empiric antimicrobial treatment in patients was defined when the isolated pathogens were susceptible in vitro to ≥1 of the antimicrobials administered, except in the case of *P. aeruginosa*. For *P. aeruginosa* infection, initial appropriate empiric treatment required two antibiotics active against the isolated strain [15].

Resistance of *P. aeruginosa* to multiple antibiotics was defined as Multi-drug resistant (MDR), extensively drug-resistant (XDR) or pandrug-resistant (PDR), as described else where[16].

Polymicrobial pneumonia was defined when more than one pathogen was identified as the causative agent

Severe CAP was defined when at least one major or 3 minor criteria of the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines were present[17]. Chronic respiratory disease was defined as treatment for asthma, simple chronic bronchitis or chronic obstructive disease (COPD defined as a documented irreversible airflow obstruction); bronchiectasis or the presence of interstitial lung disorders.

Microbiological Evaluation

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

Sputum (see supplementary data) and blood samples were obtained for bacterial culture before the start of antibiotic therapy in the emergency department. Nasopharyngeal swab for respiratory virus detection was collected when available; urine samples for *Streptococcus pneumoniae* and *Legionella pneumophila* antigen detection were obtained within 24 hours after hospital admission. Blood samples for serology of atypical pathogens and respiratory virus were collected at admission and between the third and sixth week thereafter.

Routine antimicrobial susceptibility testing included the Phoenix system (Becton Dickinson, MD, USA) for *P. aeruginosa* isolated from blood cultures and the disk diffusion method or E-test for *P. aeruginosa* isolated from respiratory samples. Results of susceptibility testing were interpreted according to EUCAST guidelines[18].

Statistical Analysis

We report the number of patients (%) for categorical variables, the median (1st quartile; 3rd quartile) for continuous variables with non-normal distribution, and the mean (SD) for those with normal distribution. Categorical variables were compared using the χ^2 test or the Fisher exact test. Continuous variables were compared using the *t* test or the nonparametric Mann-Whitney test. Univariate and multivariate logistic regression analyses were performed to identify variables associated with the presence of CAP due to *P. aeruginosa* (see supplementary data for the full list of variables); we performed a subgroup analysis for patients with chronic respiratory disease.

Also univariate and multivariate logistic regression analyses were performed to identify variables associated with MDR in patients with *P. aeruginosa*. Variables that showed a significant result in the univariate analysis ($p<0.1$) were included in the corresponding multivariate logistic regression backward stepwise model. Strongly correlated variables were excluded from multivariate analyses. The association with 30-day mortality was also tested by means of univariate and multivariate analysis, and similar inclusion criteria were applied for the logistic regression analysis ($p<0.1$); we performed a subgroup analysis for patients with *P. aeruginosa*. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall fit of the model[19]. Internal validation of the prediction models was conducted using ordinary nonparametric bootstrapping with 1000 bootstrap samples and bias-corrected, accelerated 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curves were constructed for the ability to predict patients with CAP due to *P. aeruginosa*, patients with CAP due to MDR *P. aeruginosa*, and 30-day mortality, using significant variables derived from the respective logistic regression model. All tests were 2-tailed and

significance was set at 0.05. All analyses were performed with IBM SPSS Statistics version 20.0 (Armonk, New York, USA).

RESULTS

Patient Characteristics

A total of 5384 consecutive patients with CAP were enrolled during the study period. The final study population consisted of 2023 patients with an established microbial etiology (Figure 1). There were 1253 (62%) males and the mean (SD) age was 65 (19) years. CAP was due to *P. aeruginosa* in 77 of 2023 cases (4%). Sixty-eight cases of the 77 (88%) had susceptibility data, and 22 (32%) were multidrug resistant (MDR) *P. aeruginosa* and 46 (68%) were non MDR *P. aeruginosa*. We did not find XDR or PDR strains of *P. aeruginosa*.

On average, patients with CAP due to *P. aeruginosa* were older and more frequently males, received prior antibiotics and inhaled corticosteroids more often, had a higher proportion of chronic respiratory disease, especially chronic obstructive pulmonary disease (COPD), and were more likely to have a history of a previous episode of pneumonia, compared to those with other pathogens (Table 1). They also had a more severe clinical presentation (respiratory rate, respiratory failure) at admission, but less fever, less pleuritic pain and lower levels of C-reactive protein. A total of 23% were admitted to the ICU, which is not significantly higher than in other CAP patients. A higher percentage of patients with CAP due to *P. aeruginosa* was in PSI risk class IV-V and CURB-65 class 3-5 than patients with CAP caused by other pathogens. The 30-day mortality rate was significantly higher in patients with CAP due to *P. aeruginosa* (18 % *vs.* 6%, $p<0.001$).

The differences in baseline characteristics between MDR and non-MDR P. aeruginosa CAP are summarized in Table 2. MDR *P. aeruginosa* CAP patients had

received prior antibiotics significantly more often (58% *vs.* 29%, p=0.029) and the rate of pneumonia in the previous year was also higher (46% *vs.* 21%, p=0.034).

Microbiology

In the group of patients with CAP caused by other pathogens, the five most frequent pathogens were *Streptococcus pneumoniae* (862 [44%]), respiratory viruses (302 [16%]), polymicrobial etiology (238 [12%]), *Legionella pneumophila* (121 [6%]) and other atypical bacteria (143 [7%]). *P. aeruginosa* was the eighth most common pathogen overall (e-Table 1).

Susceptibility testing was performed in 68 of the 77 *P. aeruginosa* isolates (88%). Thirty-two isolates (47%) showed in-vitro resistance to ciprofloxacin, 15 (24%) were resistant to piperacillin–tazobactam, 16 (24%) to gentamicin, 14 (24%) to tobramycin, 15 (22%) to ceftazidime, 15 (22%) to imipenem, 15 (22%) to meropenem, 7 (11%) to colistin, and 2 (3%) to amikacin. Twenty-two strains (32%) were classified as MDR *P. aeruginosa.*

Antibiotic Treatment

Data on antibiotic treatment was available in 1965 patients (97%). In general, the most frequent regimens were a combination of a cephalosporin plus a macrolide (700 [36%]), fluoroquinolone monotherapy (417 [21%]), cephalosporin plus fluoroquinolone (392 [20%]), ß-lactam-ß-lactamase inhibitor plus fluoroquinolone (56 [3%]), and cephalosporin monotherapy (54 [3%]).

Compared to other CAP patients, the group with CAP due to *P. aeruginosa* received more often cephalosporin monotherapy (5 [7%] *vs.* 49 [3%], p=0.024), and cephalosporin plus aminoglycosides (8 [11%] *vs.* 18 [1%], p<0.001), and less frequently fluoroquinolone monotherapy (7 [10%] *vs.* 410 [22%], p=0.017). No significant

differences in empiric antibiotic regimens were found between those with MDR and with non-MDR *P. aeruginosa* pneumonia.

The empiric antimicrobial treatment was inadequate in 206 of all cases (13%). In the group with CAP due to *P. aeruginosa*, 49 cases (64%) had inadequate empiric antimicrobial treatment (3 cases were inadequate because only one correct antibiotic was used) compared to the 157 cases (10%) in the group with CAP due to other pathogens (p<0.001). Seventeen of the 22 MDR cases (77%) were treated inadequately compared to the 28 of the 46 non-MDR cases (61%) (p=0.18).

Outcomes

Severe CAP was significantly more frequent in the group of CAP due to *P. aeruginosa* (62% *vs.* 28%, p<0.001) compared with the group of other pathogens, but use of the ICU was similar in both groups. Thirty-day mortality was significantly higher for patients with CAP due to *P. aeruginosa*, compared with the group of other pathogens (18% *vs.* 6%, p<0.001). Length of hospital stay was longer in CAP due to *P. aeruginosa* compared with CAP due to other microorganisms (7 [5; 12] *vs.* 13 [7; 16.5] days, p<0.001) (Table 1). Also, there was a longer median length of hospital stay of the MDR group compared with non-MDR *P. aeruginosa* CAP (14 [12; 21] *vs.* 11 [7; 16] days, p=0.046) (Table 2).

Clinical Factors Associated With CAP Due to *P. aeruginosa*

Several variables were significantly associated with CAP due to *P. aeruginosa* in the univariate logistic regression analyses (Table 3). Of these variables, male sex, chronic respiratory disease, C-reactive protein lower than 12.35 mg/dL, and PSI risk class IV-V were risk factors in the multivariate analysis. Internal validation of the logistic regression model was conducted using bootstrapping with 1000 samples (e-

Table 2). The four variables included in the model demonstrated robust results, with small 95% CIs around the original coefficients. The area under the ROC curve was 0.74 (95% CI 0.68-0.79) for the model predictive of CAP due to *P. aeruginosa*.

In the subgroup of patients with chronic respiratory disease, previous treatment with inhaled corticosteroids was the only variable associated with CAP due to *P. aeruginosa* in the multivariate analysis (e-Table 3). The area under the ROC curve was 0.62 (95% CI 0.52-0.71).

Associations of CAP Due to MDR *P. aeruginosa*

In the subgroup of CAP due to *P. aeruginosa* patients, the only risk factor associated with CAP due to MDR *P. aeruginosa* in the multivariate analysis was prior antibiotic treatment (Table 4). The area under the ROC curve was 0.64 (95% CI 0.49-0.80).

Predictors of 30-Day Mortality

In the multivariate logistic regression analysis, the following factors were independently associated with 30-day mortality: CAP due to *P. aeruginosa*, age ≥65 years, chronic liver disease, neurologic disease, nursing home, acute renal failure, ICU admission, and inappropriate initial empiric treatment (Table 5). The area under the ROC curve was 0.86 (95% CI 0.82-0.90) for the model predictive of 30-day mortality.

In the subgroup of CAP due to *P. aeruginosa* patients, previous treatment with inhaled corticosteroids and acute renal failure were the variables associated with 30-day mortality in the multivariate analysis (e-Table 4). The area under the ROC curve was 0.83 (95% CI 0.72-0.95).

DISCUSSION

The main findings of this study are the following: 1.-The prevalence of CAP due to *P. aeruginosa* in this large series of consecutive patients with CAP was 4% of patients with a defined etiology, and 32% of these patients had MDR *P. aeruginosa.* 2.-We identified several risk factors associated with CAP due to *P. aeruginosa* in general and for CAP due to MRD *P. aeruginosa*. 3.-CAP due to *P. aeruginosa* was associated with a significantly higher rate of inappropriate therapy than CAP due to other pathogens (65% vs. 11%; p<0.001). 4.-CAP due to *P. aeruginosa* was associated with CAP mortality in a multivariate model.

The prevalence of 4% found in our study is higher than other studies, but this was only for patients with an established etiology and for the entire population, the frequency was 1.2%. In another report from Spain,[20] the prevalence was 1.5% in patients with microbial etiology. In a large retrospective study from San Antonio,[21] the prevalence of *P. aeruginosa* was 1.1%.

If we compare the current results with the article from our group published more than 10 years earlier, corresponding to the 1997-1998 period, the prevalence of *P. aeruginosa* CAP was 6.9%[4]. From these figures, it is clear that, at least in our institution, the burden of *P. aeruginosa* in CAP has decreased. An explanation for these differences is the much better ambulatory care, less indiscriminate use of antibiotics, and prevention of pneumonia in the two populations at major risk: COPD and bronchiectasis patients. Furthermore, if we compare current 30-day mortality (18%) with prior data (28%), we can see that 30-day mortality in CAP caused by *P. aeruginosa* has decreased, reflecting changes in management. For the first time in the literature

we provide data and differential characteristics regarding MDR versus non-MDR *Pseudomonas* aeruginosa

Only two studies have investigated risk factors for *P. aeruginosa* CAP in multivariate analyses. We identified four risk factors in the multivariate analysis. In our previous study in 2002,[22] we did not perform a multivariate analysis but we found that *P. aeruginosa* was associated with male sex, previous hospital admission, pulmonary comorbidity and ICU admission. From all this information, it appears that the key factor is chronic respiratory disease. In the absence of chronic respiratory disease, there is probably no need for empiric therapy to cover *P. aeruginosa* in immunocompetent patients.

In addition, we performed a multivariable analysis to determinate risk factors for *P. aeruginosa* in the population with chronic respiratory conditions and found that the use of inhaled corticosteroids was the only risk factor for *P. aeruginosa* pneumonia in this population. Overall, inhaled corticosteroids are a well-defined risk factor for CAP and possibly for a specific pathogen such as *P. aeruginosa.*

An important finding of our study is that that *P. aeruginosa* was MDR in 32% of the isolates with antibiogram data. This has not been previously reported and the only risk factor associated with *P. aeruginosa* MDR was previous antibiotic treatment. A clinical consequence of this finding is to use antibiotics covering MDR *Pseudomonas* when *P. aeruginosa* is suspected and there is prior antibiotic treatment.

The raw mortality of *P. aeruginosa* CAP was 18% in our series, similar to a recent manuscript published in Respirology[23]. *P. aeruginosa* was an independent factor associated with mortality even after adjustment for inadequate antibiotic treatment. In the subpopulation of MDR *P. aeruginosa*, *P. aeruginosa* was not a factor associated

with mortality, suggesting that these resistant strains, although more difficult to treat, may be less virulent[24;25]. Previous inhaled corticosteroids were independently associated with higher mortality (OR, 12.80) in this subpopulation, which contrasts with previous reports that found inhaled corticosteroids to be protective for complications and mortality[26;27].

We published in 1991 a manuscript in which we observed that *Pseudomonas* was associated with higher independently mortality. However, that series included only 5 cases of *Pseudomonas* CAP which makes very difficult to compare with the presented study in which we included 77 cases [5].

Our study has 2 major limitations. First, it is a single-center study in a teaching hospital covering a population of more than half a million persons. This may not apply to other hospitals with different populations. Second, this was a 12-year study, but the standards for diagnosing *P. aeruginosa* CAP have not varied during that period. The major strengths of the study are that it is a very large series of CAP patients and that we studied the resistance patterns of most of the *P. aeruginosa* isolates and found data that may be helpful in guiding empiric therapy of CAP in the current era of drug-resistant *P. aeruginosa*.

Conclusions

In summary, we found that, while not common, *Pseudomonas aeruginosa* was a cause of CAP and one that is often treated inappropriately (64% of patients). Some 32% of cases are have multidrug resistant, and these patients need to be identified because we found that 77% received inappropriate empiric therapy. Compared to other forms of CAP, patients with *P. aeruginosa* had severe disease more commonly (62% vs. 28%). In this series, as in others, inappropriate empiric antibiotic therapy was

a mortality risk for all patients with CAP, so identification of patients requiring special therapy, such as those with *P. aeruginosa*, is essential to assure correct therapy choices. Those most at risk for *P. aeruginosa* were patients with chronic respiratory disease, particularly those receiving inhaled corticosteroids, although patients receiving high dose systemic corticosteroids were excluded from this analysis. Although this organism is uncommon, awareness of it is important because the presence of *P. aeruginosa* was an independent predictor for mortality among patients with CAP.

Acknowledgments

Guarantor: Dr. Torres is the guarantor of the entire manuscript and is responsible for the content of the manuscript, including the data collected and its analysis.

Author contributors: C.C. is the main author of the paper; she reviewed the study data, edited the main body of the manuscript, contributed to supervising the collection of clinical, radiological and microbiological data, and approved the final manuscript. M.N. contributed to the design of the project, analysis and interpretation of the results, and editing of the final manuscript. A.G. performed the statistical analysis of the study. M.F., M..R. and J.M. contributed to the design of the project, and contributed to and approved the final study. J.P. supervised the collection of microbiological data and approved the final manuscript. A.T. led the study group, contributed to the design of the project, and contributed to and approved the final study; he is the guarantor of the entire manuscript.

Conflicts of interest: The authors state that they have no conflicts of interest

Funding: The study was funded by Ciber de Enfermedades Respiratorias (CibeRes CB06/06/0028). 2009 Support to Research Groups of Catalonia 911.

Reference List

1. **Cilloniz, C., S. Ewig, E. Polverino, M. A. Marcos, C. Esquinas, A. Gabarrus, J. Mensa, and A. Torres. 2011. Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax* 66:340-346.**

2. **Ruiz, L. A., A. Gomez, C. Jaca, L. Martinez, B. Gomez, and R. Zalacain. 2010. Bacteraemic community-acquired pneumonia due to Gram-negative bacteria: incidence, clinical presentation and factors associated with severity during hospital stay. *Infection* 38:453-458.**

3. **von Baum, H., T. Welte, R. Marre, N. Suttorp, and S. Ewig. 2010. Community-acquired pneumonia through Enterobacteriaceae and Pseudomonas aeruginosa: Diagnosis, incidence and predictors. *Eur.Respir.J.* 35:598-605.**

4. **Arancibia, F., T. T. Bauer, A. Torres, F. Sanchez, J. Mensa, A. Maldonado, M. J. Rodriguez, and S. Ewig. 1999. Community-acquired Pneumonia caused by Gram-negative bacteria: Incidence and risk and prognosis. *Eur Respir J* (In press)**

5. **Torres, A., B. J. Serra, A. Ferrer, P. Jimenez, R. Celis, E. Cobo, and R. R. Rodriguez. 1991. Severe community-acquired pneumonia. Epidemiology and prognostic factors. *Am Rev Respir Dis* 144:312-318.**

6. **Cilloniz, C., E. Polverino, S. Ewig, S. Aliberti, A. Gabarrus, R. Menendez, J. Mensa, F. Blasi, and A. Torres. 2013. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. *Chest* 144:999-1007.**

7. **Rello, J., M. Bodi, D. Mariscal, M. Navarro, E. Diaz, M. Gallego, and J. Valles. 2003. Microbiological testing and outcome of patients with severe community-acquired pneumonia. *Chest* 123:174-180.**

8. **Paganin, F., F. Lilienthal, A. Bourdin, N. Lugagne, F. Tixier, R. Genin, and J. L. Yvin. 2004. Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. *Eur.Respir J* 24:779-785.**

9. **Yoshimoto, A., H. Nakamura, M. Fujimura, and S. Nakao. 2005. Severe community-acquired pneumonia in an intensive care unit: risk factors for mortality. *Intern.Med.* 44:710-716.**

10. **Arancibia, F., T. T. Bauer, S. Ewig, J. Mensa, J. Gonzalez, M. S. Niederman, and A. Torres. 2002. Community-acquired pneumonia due to gram-negative bacteria and pseudomonas aeruginosa: incidence, risk, and prognosis. *Arch.Intern.Med.* 162:1849-1858.**

11. **Polverino, E., P. Dambrava, C. Cilloniz, V. Balasso, M. A. Marcos, C. Esquinas, J. Mensa, S. Ewig, and A. Torres. 2010. Nursing home-acquired pneumonia: a 10 year single-centre experience. *Thorax* 65:354-359.**

12. **Fine, M. J., T. E. Auble, D. M. Yealy, B. H. Hanusa, L. A. Weissfeld, D. E. Singer, C. M. Coley, T. J. Marrie, and W. N. Kapoor. 1997. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 336:243-250.**

13. **Lim, W. S., M. M. van der Eerden, R. Laing, W. G. Boersma, N. Karalus, G. I. Town, S. A. Lewis, and J. T. Macfarlane. 2003. Defining community**

acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 58:377-382.

14. **Torres, A., J. Barberan, M. Falguera, R. Menendez, J. Molina, P. Olaechea, and A. Rodriguez. 2013. [Multidisciplinary guidelines for the management of community-acquired pneumonia]. *Med.Clin.(Barc.)* 140:223.**

15. **Mandell, L. A., R. G. Wunderink, A. Anzueto, J. G. Bartlett, G. D. Campbell, N. C. Dean, S. F. Dowell, T. M. File, Jr., D. M. Musher, M. S. Niederman, A. Torres, and C. G. Whitney. 2007. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect.Dis.* 44 Suppl 2:S27-S72.**

16. **Magiorakos, A. P., A. Srinivasan, R. B. Carey, Y. Carmeli, M. E. Falagas, C. G. Giske, S. Harbarth, J. F. Hindler, G. Kahlmeter, B. Olsson-Liljequist, D. L. Paterson, L. B. Rice, J. Stelling, M. J. Struelens, A. Vatopoulos, J. T. Weber, and D. L. Monnet. 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin.Microbiol.Infect.* 18:268-281.**

17. **Mandell, L. A., R. G. Wunderink, A. Anzueto, J. G. Bartlett, G. D. Campbell, N. C. Dean, S. F. Dowell, T. M. File, Jr., D. M. Musher, M. S. Niederman, A. Torres, and C. G. Whitney. 2007. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect.Dis.* 44 Suppl 2:S27-S72.**

18. **European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. 2015. Ref Type: Data File**

19. **Hosmer, D. and S. Lemeshow. 1989. Applied logistic regression Wiley, New York.**

20. **Falguera, M., J. Carratala, A. Ruiz-Gonzalez, C. Garcia-Vidal, I. Gazquez, J. Dorca, F. Gudiol, and J. M. Porcel. 2009. Risk factors and outcome of community-acquired pneumonia due to Gram-negative bacilli. *Respirology.* 14:105-111.**

21. **Sibila, O., E. Laserna, D. J. Maselli, J. F. Fernandez, E. M. Mortensen, A. Anzueto, G. Waterer, and M. I. Restrepo. 2015. Risk factors and antibiotic therapy in P. aeruginosa community-acquired pneumonia. *Respirology.* 20:660-666.**

22. **Arancibia, F., T. T. Bauer, S. Ewig, J. Mensa, J. Gonzalez, M. S. Niederman, and A. Torres. 2002. Community-acquired pneumonia due to gram-negative bacteria and pseudomonas aeruginosa: incidence, risk, and prognosis. *Arch.Intern.Med.* 162:1849-1858.**

23. **Sibila, O., E. Laserna, D. J. Maselli, J. F. Fernandez, E. M. Mortensen, A. Anzueto, G. Waterer, and M. I. Restrepo. 2015. Risk factors and antibiotic therapy in P. aeruginosa community-acquired pneumonia. *Respirology.* 20:660-666.**

24. **Pena, C., S. Gomez-Zorrilla, I. Oriol, F. Tubau, M. A. Dominguez, M. Pujol, and J. Ariza. 2013. Impact of multidrug resistance on Pseudomonas**

aeruginosa ventilator-associated pneumonia outcome: predictors of early and crude mortality. *Eur.J.Clin.Microbiol.Infect.Dis.* 32:413-420.

25. Linares, J. F., J. A. Lopez, E. Camafeita, J. P. Albar, F. Rojo, and J. L. Martinez. 2005. Overexpression of the multidrug efflux pumps MexCD-OprJ and MexEF-OprN is associated with a reduction of type III secretion in Pseudomonas aeruginosa. *J.Bacteriol.* 187:1384-1391.

26. Chen, D., M. I. Restrepo, M. J. Fine, M. J. Pugh, A. Anzueto, M. L. Metersky, B. Nakashima, C. Good, and E. M. Mortensen. 2011. Observational Study of Inhaled Corticosteroids on Outcomes for COPD Patients with Pneumonia. *Am J Respir Crit Care Med.* 184:312-316.

27. Sellares, J., A. Lopez-Giraldo, C. Lucena, C. Cilloniz, R. Amaro, E. Polverino, M. Ferrer, R. Menendez, J. Mensa, and A. Torres. 2013. Influence of previous use of inhaled corticoids on the development of pleural effusion in community-acquired pneumonia. *Am J Respir Crit Care Med* 187:1241-1248.

Figures Legend

Figure 1: Flow diagram of the selected population

Table 1. Clinical and Epidemiological Characteristics of CAP and CAP Caused by *P. aeruginosa*

	Other Pathogens (n = 1,946)	*P. aeruginosa* (n = 77)	P Value
Demographic			
Age (years), mean (SD)	65.2 (18.8)	71.4 (14.6)	**0.008**
Male gender, No. (%)	1,187 (61.3)	65 (84.4)	**<0.001**
Current smoker, No. (%)	549 (28.4)	16 (21.9)	0.22
Current alcohol consumer, No. (%)	307 (15.9)	17 (23.3)	0.094
Previous antibiotic, No. (%)	400 (21.5)	24 (34.3)	**0.012**
Influenza vaccine, No. (%)	630 (39.7)	26 (45.6)	0.37
Pneumococcal vaccine, No. (%)	247 (15.6)	12 (21.1)	0.27
Inhaled corticosteroid, No. (%)	360 (18.8)	33 (44.6)	**<0.001**
Systemic corticosteroid, No. (%)	88 (5.0)	3 (4.9)	0.97
Comorbidities, No. (%)*	1,251 (64.3)	64 (83.1)	**0.001**
Chronic respiratory disease	826 (43.3)	51 (68.0)	**<0.001**
Chronic bronchitis	165 (8.7)	4 (5.3)	0.31
Bronchiectasis	55 (2.9)	5 (6.7)	0.061
COPD	341 (17.9)	29 (38.7)	**<0.001**
Asthma	94 (4.9)	2 (2.7)	0.37
Other	171 (9.0)	11 (14.7)	0.094
Chronic cardiovascular disease	255 (13.2)	13 (17.3)	0.31
Diabetes mellitus	350 (18.2)	14 (18.7)	0.93
Neurological disease	283 (15.0)	15 (20.5)	0.19
Chronic renal disease	116 (6.0)	7 (9.3)	0.24
Chronic liver disease	96 (5.0)	5 (6.6)	0.54
Previous episode of pneumonia, No. (%)	268 (14.3)	21 (28.0)	**0.001**
Nursing-home, No. (%)	103 (5.4)	5 (6.7)	0.62
Clinical findings			
Cough, No. (%)	1,551 (81.0)	61 (81.3)	0.95
Purulent sputum, No. (%)	1,145 (61.2)	52 (72.2)	0.060

	Other Pathogens (n = 1,946)	*P. aeruginosa* (n = 77)	P Value
Dyspnea, No. (%)	1,308 (68.7)	59 (78.7)	0.067
Pleuritic pain, No. (%)	808 (42.6)	21 (27.6)	**0.010**
Fever, No. (%)	1,618 (84.3)	56 (73.7)	**0.013**
Altered mental status, No. (%)	332 (17.2)	19 (25.3)	0.069
Respiratory rate (breaths/min), median (1st quartile; 3rd quartile)	24 (20; 32)	28 (24; 32)	**0.005**
Respiratory rate ≥30 breaths/min, No. (%)	553 (31.4)	31 (44.9)	**0.018**
Heart rate (beats/min), median (1st quartile; 3rd quartile)	100 (86; 112)	100 (80; 112)	0.58
Heart rate ≥100 beats/min, No. (%)	958 (51.5)	38 (52.1)	0.93
Laboratory findings			
Creatinine (md/dL), median (1st quartile; 3rd quartile)	1.1 (0.9; 1.5)	1.1 (0.8; 1.6)	0.90
Creatinine ≥1.5 md/dL, No. (%)	473 (24.6)	23 (30.3)	0.27
C-reactive protein (mg/dL), median (1st quartile; 3rd quartile)	20.4 (10.4; 29.3)	15.6 (7.7; 26.2)	**0.033**
C-reactive protein ≥12.35 mg/dL, No. (%)[#]	1,081 (70.2)	32 (54.2)	**0.009**
White blood cell count ($\times 10^9$/L), median (1st quartile; 3rd quartile)	13.1 (8.8; 18.3)	14.2 (9.8; 20.6)	0.28
White blood cell count ≥10×10^9/L, No. (%)	1,314 (68.7)	56 (74.7)	0.28
PaO_2/FIO_2 ratio, median (1st quartile; 3rd quartile)	281 (238; 324)	255 (203; 291)	**0.002**
PaO_2/FIO_2 ratio <250, No. (%)	444 (31.6)	29 (49.2)	**0.005**
CURB-65 risk class 3-5, No. (%)	344 (18.7)	24 (32.9)	**0.003**
PSI risk class IV-V, No. (%)	977 (50.5)	54 (72.0)	**<0.001**
ICU admission, No. (%)	378 (19.4)	18 (23.4)	0.38
Mechanical ventilation, No (%)[$]			0.17
Not ventilated	1,517 (89.4)	52 (89.7)	0.96
Non-invasive	68 (4.5)	0 (0)	0.12

	Other Pathogens (n = 1,946)	***P. aeruginosa* (n = 77)**	**P Value**
Invasive	111 (6.5)	6 (10.3)	0.25
Severe CAP, No (%)	410 (27.8)	31 (60.8)	**<0.001**
Length of hospital stay (days), median (1st quartile; 3rd quartile)	7.0 (5.0; 12.0)	13.0 (7.0; 16.5)	**<0.001**
30-day mortality, No. (%)	107 (5.5)	14 (18.2)	**<0.001**
Appropriate empiric treatment, No. (%)	1,393 (89.9)	28 (36.4)	**<0.001**

Abbreviations: CAP indicates community acquired pneumonia; COPD, chronic obstructive respiratory disease; CURB-65, consciousness, urea, respiratory rate, blood pressure, 65; ICU, intensive care unit; PSI, pneumonia severity index.

Percentages calculated on non-missing data.

*May have more than 1 comorbid condition.

[#]Optimal cut-off value using ROC curves.

[$]Patients who received initially non-invasive ventilation but needed subsequently intubation were included in the invasive mechanical ventilation group.

Table 2. Clinical and Epidemiological Characteristics of MDR and non-MDR *P. aeruginosa* CAP

	MDR *P. aeruginosa* (n = 22)	Non-MDR *P. aeruginosa* (n = 46)	P Value
Demographic			
Age (years), mean (SD)	72.7 (15.6)	71.1 (13.6)	0.45
Male gender, No. (%)	20 (90.9)	36 (78.3)	0.20
Current smoker, No. (%)	3 (14.3)	11 (25.6)	0.31
Current alcohol consumer, No. (%)	5 (23.8)	11 (25.6)	0.88
Previous antibiotic, No. (%)	11 (57.9)	12 (28.6)	**0.029**
Influenza vaccine, No. (%)	9 (52.9)	14 (43.8)	0.54
Pneumococcal vaccine, No. (%)	3 (17.6)	8 (25.0)	0.56
Inhaled corticosteroid, No. (%)	12 (57.1)	19 (43.2)	0.29
Systemic corticosteroid, No. (%)	0	3 (8.6)	0.20
Comorbidities, No. (%)*	20 (90.9)	37 (80.4)	0.27
Chronic respiratory disease	17 (77.3)	28 (63.6)	0.26
Chronic bronchitis	1 (4.5)	2 (4.5)	>0.99
Bronchiectasis	0	4 (9.1)	0.29
COPD	9 (40.9)	18 (40.9)	>0.99
Asthma	1 (4.5)	1 (2.3)	>0.99
Chronic cardiovascular disease	6 (27.3)	7 (15.9)	0.27
Diabetes mellitus	4 (19.0)	10 (22.2)	0.77
Neurological disease	4 (19.0)	7 (16.3)	0.78
Chronic renal disease	3 (13.6)	3 (6.8)	0.36
Chronic liver disease	2 (9.1)	3 (6.7)	0.72
Previous episode of pneumonia, No. (%)	10 (45.5)	9 (20.5)	**0.034**
Nursing-home, No. (%)	2 (9.1)	2 (4.5)	0.47
CURB-65 risk class 3-5, No. (%)	8 (38.1)	13 (30.2)	0.53
PSI risk class IV-V, No. (%)	17 (77.3)	31 (70.5)	0.56
ICU admission, No. (%)	6 (27.3)	11 (23.9)	0.77

	MDR *P. aeruginosa* (n = 22)	**Non-MDR *P. aeruginosa* (n = 46)**	**P Value**
Mechanical ventilation, No. (%)[#]			0.69
Not ventilated	11 (84.6)	32 (88.9)	0.69
Non-invasive	0	0	-
Invasive	2 (15.4)	4 (11.1)	0.69
Severe CAP, No.	9 (75.0)	18 (58.1)	0.30
Length of hospital stay (days), median (1st quartile; 3rd quartile)	14.0 (12.0; 21.0)	11.0 (7.0; 16.0)	**0.046**
30-day mortality, No. (%)	5 (22.7)	8 (17.4)	0.60
Appropriate empiric treatment, No. (%)	5 (22.7)	18 (39.1)	0.18

Abbreviations: MDR indicates multidrug resistant; CAP, community acquired pneumonia; COPD, chronic obstructive respiratory disease; CURB-65, consciousness, urea, respiratory rate, blood pressure, 65; ICU, intensive care unit; PSI, pneumonia severity index.

Percentages calculated on non-missing data.

*May have more than 1 comorbid condition.

[#]Patients who received initially non-invasive ventilation but needed subsequently intubation were included in the invasive mechanical ventilation group.

Table 3. Significant Univariate and Multivariate Logistic Regression Analyses of Associations of CAP Due to *P. aeruginosa*

Variable	Univariate			Multivariate*		
	OR	95% CI	P Value	OR	95% CI	P Value
Age ≥65 years	2.61	1.49-4.56	0.001	-	-	-
Male gender	3.42	1.84-6.38	<0.001	3.71	1.65-8.35	0.002
Current smoker	1.45	0.72-2.93	0.30	-	-	-
Inhaled corticosteroids	3.47	2.16-5.56	<0.001	-	-	-
Prior antibiotic treatment	1.90	1.15-3.15	0.013	-	-	-
Previous episode of pneumonia	2.33	1.39-3.92	0.001	-	-	-
Chronic respiratory disease	2.78	1.70-4.56	<0.001	2.26	1.25-4.10	0.007
C-reactive protein <12.35 mg/dL[#]	1.99	1.18-3.36	0.010	1.91	1.08-3.38	0.027
PSI risk class IV-V	2.52	1.51-4.21	<0.001	1.85	1.00-3.41	0.049

Abbreviations: CI indicates confidence interval; OR, odds ratio; PSI, pneumonia severity index.

*Hosmer-Lemeshow goodness-of-fit test, p=0.57.

[#]Optimal cut-off value to predict *P. aeruginosa* using ROC curves.

Table 4. Significant Univariate and Multivariate Logistic Regression Analyses of Associations of CAP Due to MDR *P. aeruginosa*

Variable	Univariate			Multivariate*		
	OR	95% CI	P Value	OR	95% CI	P Value
Prior antibiotic treatment	3.44	1.11-10.64	0.032	3.32	1.07-10.31	0.038
Previous episode of pneumonia	3.24	1.06-9.87	0.039	-	-	-
White blood cell count $<10 \times 10^9$/L	3.66	1.13-11.82	0.030	-	-	-

Abbreviations: MDR indicates multidrug resistant CI, confidence interval; OR, odds ratio.
*Hosmer-Lemeshow goodness-of-fit test, not applicable.

Table 5. Significant Univariate and Multivariate Logistic Regression Analyses of Predictors of 30-Day Mortality

Variable	Univariate			Multivariate*		
	OR	95% CI	P Value	OR	95% CI	P Value
CAP due to *P. aeruginosa*	3.78	2.05-6.97	<0.001	2.39	1.02-5.59	0.045
Age ≥65 years	4.15	2.49-6.90	<0.001	2.62	1.32-5.19	0.006
Current smoker	0.50	030-0.82	0.006	-	-	-
Inhaled corticosteroids	1.47	0.96-2.25	0.077	-	-	-
Chronic cardiovascular disease	2.12	1.36-3.31	0.001	-	-	-
Chronic renal disease	2.01	1.09-3.69	0.024	-	-	-
Chronic liver disease	2.50	1.35-4.63	0.003	4.17	1.89-9.21	<0.001
Neurological disease	3.47	2.32-5.20	<0.001	3.68	2.05-6.64	<0.001
Nursing home	3.67	2.13-6.34	<0.001	3.69	1.51-8.99	0.004
PSI risk class IV-V	6.75	3.96-11.52	<0.001	-	-	-
Creatinine ≥1.5 mg/dL	4.64	3.17-6.79	<0.001	-	-	-
Multilobar infiltration	1.93	1.32-2.84	0.001	-	-	-
Acute respiratory distress syndrome	4.68	2.56-8.56	<0.001	-	-	-
Acute renal failure	5.57	3.76-8.27	<0.001	4.22	2.48-7.20	<0.001
Septic shock	6.46	4.19-9.97	<0.001	-	-	-
ICU admission	3.54	2.43-5.17	<0.001	5.27	3.05-9.12	<0.001
Mechanical ventilation[#]			<0.001			-
Not ventilated	1	-	-	-	-	-
Non-invasive	5.67	2.64-12.22	<0.001	-	-	-
Invasive	19.09	11.63-31.32	<0.001	-	-	-
Appropriate empiric treatment	0.29	0.18-0.46	<0.001	0.40	0.22-0.76	0.005

Abbreviations: CI indicates confidence interval; ICU, intensive care unit; OR, odds ratio; PSI, pneumonia severity index.

*Hosmer-Lemeshow goodness-of-fit test, p=0.064.

[#]The p-value corresponds to differences between the three groups (not ventilated, non-invasive or invasive).

Figure 1