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Addressing current challenges in antibiotic treatment of community acquired pneumonia

Antonella Francesca Simonetti

UNIVERSITAT DE BARCELONA

DEPARTAMENT DE CIÈNCIES CLÍNIQUES

FACULTAT DE MEDICINA

ADDRESSING CURRENT CHALLENGES IN ANTIBIOTIC TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA

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Dirigida por:

Jordi Carratalà

Carolina Garcia-Vidal

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El **Dr. Jordi Carratalà,** Profesor titular del Departamento de Ciencias Clínicas de la Facultad de Medicina de la Universidad de Barcelona, y la **Dra. Carolina Garcia-Vidal**, Facultativo Especialista del Servicio de Enfermedades Infecciosas del Hospital Clínic de Barcelona, certifican que la tesis doctoral titulada:

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Para que así conste, firmamos la presente certificación en Barcelona, 05 de Abril 2017.

Dr. Jordi Carratalà

Dra. Carolina Garcia-Vidal

Education is the most powerful weapon, which you can use to change the world.

Nelson Mandela (1918-2013).

Il n'y a rien à craindre de la vie. Il y a tout à comprendre.

(Nothing in life is to be feared, it is only to be understood).

Marie Sklodowska Curie, scientist (1867-1934).

Understanding the science will increase confidence.

David Gilbert, MD, infectious diseases specialist.

Science sans conscience n´est que ruine de l´âme.

(Science without conscience is only the ruin of the soul).

François Rabelais, writer (1494-1553).

Es ist nicht genug, zu wissen, man muss auch anwenden. Es ist nicht genug, zu wollen, man muss auch tun.

(Knowing is not enough; we must apply. Willing is not enough; we must do).

Johann Wolfgang Goethe, writer (1749-1832).

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Impact of pre-hospital antibiotic use on community-acquired pneumonia. Simonetti AF, Viasus D, Garcia-Vidal C, Grillo S, Molero L, Dorca J, Carratalà J. Clin Microbiol Infect. 2014;20:O531-7. Impact factor: 4.575 (1st quartile).

Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia. Simonetti A, Viasus D, Garcia-Vidal C, Adamuz J, Roset A, Manresa F, Dorca J, Gudiol F, Carratalà J. Clin Microbiol Infect. 2012;18:1149-55. Impact factor: 4.575 (1st quartile).

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COMMUNICATIONS

a) <u>SLIDE SESSIONS</u>

- **Características clínicas, etiología y pronóstico de pacientes hospitalizados con neumonía adquirida en la comunidad que habían recibido tratamiento antibiótico previo** . Simonetti A, Viasus D, Garcia-Vidal C, Dorca J, Carratalà J. XVII Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC). Zaragoza 2013. Communication number: 165.
- **Impact of changes in the management of hospitalized patients with community-acquired pneumonia on declining mortality over the last 19 years.** Simonetti AF, Garcia-Vidal C, Viasus D, Cuervo G, Garcia-Somoza D, Gudiol F, Carratalà J. 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 2014.Communication number: L-1913.

b) <u>POSTER SESSIONS</u>

- **Influencia del tratamiento antibiótico precoz en el pronóstico de los pacientes con neumonía adquirida en la comunidad.** Simonetti A, Viasus D, Garcia-Vidal C, Adamuz J, Roset A, Manresa F, Dorca J, Gudiol F, Carratala, J. XIV Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC). Barcelona, 2010. Communication number: 399.
- **Fluoroquinolones and macrolides are equivalent to treat Legionella pneumonia: a propensity score analysis.** Garcia Vidal C, Sanchez I, Simonetti A, Burgos J, Viasus D, Martin M, Falco V, Carratalà J. 23rd European Congress of

Clinical Microbiology and Infectious Diseases (ECCMID). Copenhagen, 2015. Communication number: EP136.

- **Antibiotic de-escalation in hospitalized adults with pneumococcal community-acquired pneumonia.** ECCMID 2015. Simonetti AF, Garcia-Vidal C, Viasus D, Ardanuy C, Dorca J, Carratalà J. 23rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). Copenhagen, 2015. Communication number: EP134
- **Predictors for individual patient antibiotic treatment effect in hospitalized community-acquired pneumonia patients.** 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). Vienna, 2017. Simonetti AF, van Werkhoven CH, Schweitzer VA, Viasus D, Carratalà J, Postma DW, Oosterheert JJ, Bonten MJ.Communication number: 5054

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6.2. Pre-hospital antibiotic use in community-acquired pneumonia

Impact of pre-hospital antibiotic use on community-acquired pneumonia. Simonetti AF, Viasus D, Garcia-Vidal C, Grillo S, Molero L, Dorca J, Carratalà J. Clin Microbiol Infect. 2014;20:O531-7.

6.3. Timing of antibiotic administration in pneumonia

Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia. Simonetti A, Viasus D, Garcia-Vidal C, Adamuz J, Roset A, Manresa F, Dorca J, Gudiol F, Carratalà J. Clin Microbiol Infect. 2012;18:1149-55.

6.4. Antibiotic de-escalation in pneumococcal pneumonia

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6.5. Antibiotic treatment for Legionella pneumonia

Levofloxacin versus azithromycin for treating Legionella pneumonia: a propensity score analysis. Garcia-Vidal C; Sanchez I, Simonetti A, Burgos J, Viasus D, Martin M, Falco V, Carratalà J. Clin Microl Infect. 2017 Mar 3. pii: S1198-743X(17)30127-1. doi: 10.1016/j.cmi.2017.02.030. Article in press.

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1. INTRODUCTION

1.1. Community-acquired pneumonia: the burden of the problem

Community-acquired pneumonia (CAP) is the leading infectious cause of death and the fourth most common cause of global mortality in the world [WHO, 2012]. Most estimates of CAP incidence are obtained from national databases on hospitalized patients, although it is estimated that between 50% and 80% of CAP patients are treated as outpatients [Mandell GL et al. 2000].

The incidence of low respiratory tract infections (LRTI) in Europe in 2002 (25.8 million) was second only to diarrhoeal diseases (205.5 million) and was greater than diabetes mellitus (2.0 million) and all malignant neoplasms combined (2.4 million) [WHO, 2004]. Studies show that the incidence of CAP in Europe varies by country, age and gender. In all studies, the incidence increased sharply with age (0,2-17 cases per 1000 persons/year in patients <45 years, to 10-242 cases per 1000 persons/year in patients ≥ 85 years), and was appreciably higher in men than in women [Welte T et al. 2012].

A recent epidemiological retrospective survey attempted to provide population-based estimates of the burden of hospitalisation for all causes of pneumonia in adults over 50 years of age in Spain during a five-year period (2003–2007). A total of 447,670 hospital discharges for all-cause pneumonia were recorded. The overall annual incidence rate was 6.27 (CI 95%: 6.25–6.29) cases per 1000 in populations greater than or equal to 50 years of age and 10.29 (CI 95%: 10.26–10.33) cases per 1000 in populations greater than or equal to 65 years of age. The incidence of hospitalisation was directly associated with age (CAP: $p < 0.001$; PP: $p < 0.001$),

reaching 23.30 (CI 95%: 23.15–23.44) cases per 1000 patients aged 85 or more for all-cause pneumonia [Gil-Prieto R et al. 2011].

A previous study conducted in Catalunya in 2002-2005 reported similar rates; the incidence of hospitalisation was 10.5 cases per 1000 in populations of patients older than 65 years old [Vila-Corcoles A et al. 2009] and approximately 22 cases per 1000 in populations older than 85 years old [Ochoa-Gondar O et al. 2008].

1.2. Mortality

Mortality in patients hospitalized for CAP ranges from 10% for patients in conventional wards to >30% for those admitted to the intensive care unit (ICU) [Fine MJ et al. 1997; Woodhead M et al. 2006; Welte T et al. 2012]. Interestingly, recent studies based on administrative data have documented a decline in in-hospital mortality over time among this population [Ruhnke GW et al. 2010; Ruhnke GW et al. 2011].

In an extensive review of hospitalized CAP patients among different European countries, reported mortality ranged from <1% to 48% in the different studies. Some variables associated with mortality were: being ≥65 years old, female gender, use of oral corticosteroids, polymicrobial pneumonia, pleural effusion, intensive care unit (ICU) admission, atypical pneumonia, recent hospitalisation, serious underlying disease, acute renal failure, bacteraemic pneumonia, ineffective initial therapy, multilobar involvement, impaired alertness and septic shock [Welte T et al. 2012].

Recent data from Spain reported a total of 75,932 deaths for all-cause pneumonia among the total of patients hospitalized in a 5 year period. The annual death rate was 1.06 (CI 95%: 1.06–1.07) per 1000 population, and the case-fatality rate was 17.0% (CI 95%: 16.9–17.1). The death rate and case-fatality rate increased dramatically with age

($p < 0.001$), reaching their higher values in patients ≥ 85 years old, with an annual rate of 5.51 (CI 95%: 5.44–5.58) deaths per 1000 and a case-fatality rate of 23.6% (CI 95%: 23.4–23.7) [Gil-Prieto R et al. 2011].

A number of studies have documented a wide range of mortality rates for patients with CAP admitted to ICUs, likely due to the considerable heterogeneity of admission policies, compliance with guidelines, and severity of scoring. In one study of 395 patients admitted to a Spanish respiratory ICU in the 1990s the reported mortality rate was 5%, but with rates of mechanical ventilation and septic shock of 9% and 2% respectively [Ruiz M et al. 1999], whereas in a UK study published in 1997 the mortality rate was 58%, with mechanical ventilation and septic shock rates of 96% and 16% respectively [Hirani NA et al. 1997].

The CAPUCI consortium analysed 529 patients admitted to over 30 Spanish ICUs between 2000 and 2002 and found ICU mortality rates of 28% [Bodi et al. 2005]. In a large, more recent prospective study from 17 different countries across Europe on patients with severe CAP admitted to ICUs, the mortality rate at 28 days was 17% [Walden AP et al. 2014].

Similarly, the GenIMS investigators reported 52 deaths of 302 CAP patients admitted to the ICU (17.3%) during their hospital stay [Kellum JA et al. 2007], and in the PORT study, the in-hospital mortality rate in patients admitted to the ICU was 23.3% [Angus DC et al. 2002].

In ICU patients, respiratory failure, diffuse bilateral changes on the chest radiograph (suggesting a diagnosis of acute lung injury/acute respiratory distress

syndrome), the presence of septic shock, and conservative fluid management were independent predictors of mortality in many of the studies realized.

Besides remarkable in-hospital mortality, research from recent years has shown alarming long-term mortality among patients who were discharged as clinically recovered after a CAP episode.

A long-term follow-up study (median 9.2 years) conducted in Finland found that elderly patients treated for CAP in both ambulatory and hospital settings had significantly higher risks of death related to the infection or to cardiovascular diseases for several years after the episode of pneumonia than elderly patients without pneumonia [Koivula I et al. 1999].

A prospective observational cohort compared cause-specific long-term mortality rates for 356 patients who had recovered from CAP with those of the general Dutch population between 2003 and 2007. In patients who had recovered from CAP, cumulative 1-year, 5-year and 7-year mortality rates were 17%, 43% and 53%, respectively, as compared with 4%, 19% and 24% for an age-matched and sex-matched population reference cohort. Overall, patients who had recovered from CAP had significantly higher long-term mortality than matched population controls (rate ratio (RR) 3.6; $p < 0.001$). The causes of long-term mortality were mostly comorbidity related, and significantly different from those in the general population [Bruns AH et al. 2011].

In a recent study performed at our institution, of 1284 patients discharged alive after recovering from a CAP episode, 93 (7.2%) died within one year of leaving hospital, mainly in the first six months (73.1%), and principally for infectious diseases

and acute cardiovascular events. Chronic obstructive pulmonary disease, diabetes mellitus, cancer, dementia, re-hospitalization within 30 days of hospital discharge and living in a nursing home were the factors independently associated with 1-year mortality [Adamuz J et al. 2014].

Little consideration has been given to understanding what contributes to long-term mortality related to a CAP episode. One study found that despite clinical recovery, cytokine concentrations were elevated at hospital discharge and associated with a higher risk of mortality [Yende S et al. 2007]. Moreover, sepsis is associated with alterations in immune response that may explain why many patients die much later with signs of opportunistic infections [Döcke WD et al. 1997]. Therefore, these data suggest residual inflammation or abnormalities in the immune system that persist after hospital discharge might be associated with an increased risk of long-term mortality in CAP patients.

Another explanation for the greater long-term mortality is that pneumonia represents a marker of poor general health. Of note, most risk factors for mortality during long-term follow-up of CAP are not associated with acute illness but are related to comorbidity, and seem to be general measures of frailty. These results emphasize the importance of optimal management of comorbidities in CAP patients.

1.3 Related costs

In Europe, pneumonia costs €10.1 billion annually, with inpatient care accounting for €5.7 billion, outpatient care €0.5 billion and drugs €0.2 billion. The indirect costs of lost workdays amount to €3.6 billion [European Respiratory Society/European Lung Foundation 2003]. The direct and indirect costs of treating CAP were the subject of

several European studies. Analysis of hospital discharge data from the Spanish national surveillance system over a two year period showed that the cost of hospitalisation for CAP in Spain was €114.8 million in 2001 [Monge V et al. 2001]. Another population-based study in Spain estimated that the mean direct costs of treatment of CAP in ambulatory and hospital settings were €196 and €1553, respectively [Bartolome M et al. 2004]. In a prospective study in 22 hospitals in Germany, the median cost of treatment of a hospitalised patient was €1201 [Bauer TT et al. 2005].

The high cost of care for patients with CAP has resulted in the implementation of cost-saving measures, such as reductions in hospital length of stay (LOS), the use of less expensive antibiotics, and stratification of patients by severity of disease to identify those who can be cared for as ambulatory patients.

1.4 Controversies in empirical antibiotic treatment

In an up-to-date review of the antibiotic management in CAP adult patients across Europe, the rate of combination antibiotic therapy ranged from 5.0 to 84.0% of patients. In patients treated with monotherapy, the principal agents used were beta-lactams (range from 5.0 to 87.7%), followed by quinolones (from 2.0 to 46.0%) and macrolides (range from 0.3 to 47.7%). For combination therapy, the most common combinations were beta-lactams plus macrolides (range from 1.7 to 70.0%) or beta-lactams plus quinolones (range from 6.3 to 63.0%). The rate of combination antibiotic therapy was higher in patients in the ICU (84.0 %) and other hospitalised patients (31.8–69.0 %) than in outpatients (5.0– 29.9%) [Torres A et al. 2014].

In recent years, the choice of the best empirical antibiotic treatment in CAP has been the subject of active debate. The IDSA/ATS and Canadian Thoracic Society

guidelines [Mandell LA et al. 2000, Mandell LA et al. 2007] recommend initial selection of β-lactam plus advanced generation macrolides in combination therapy or fluoroquinolone monotherapy for patients with CAP managed outside the hospital ICU setting. On the other side of the Atlantic Ocean, ERS/ECMID and BTS guidelines [Lim WS et al. 2009; Woodhead M et al. 2011] advocate the continued use of beta-lactams as first-line therapy with the addition (if required) of simple macrolides.

The updated European guidelines on LRTI recommend restricting combination treatment to patients with higher risk classes' pneumonia, suggesting that regular coverage of atypical pathogens may not be necessary in non-severe hospitalized patients.

As reported in a recent systematic review, in the majority of older observational studies the β-lactam plus macrolide combination therapy and fluoroquinolone monotherapy are associated with better outcomes in CAP patients than with beta-lactams monotherapy [Lee JS et al. 2016].

Two recent randomized controlled trials demonstrated conflicting results regarding the effectiveness of initial antibiotic regimens. One Swiss trial [Garin N et al. 2014], including 580 in-patients with CAP randomly allocated to receive β-lactam monotherapy or β-lactam plus macrolide combination therapy, did not demonstrate non-inferiority of β-lactam monotherapy in the primary outcome (clinical stability at day 7). Patients in the monotherapy group also had a non-significantly higher 30-day mortality compared with those in the combination therapy group (4.8% vs 3.4%, respectively; P = .42).

The Dutch study [Postma DW et al. 2015] was a pragmatic, cluster randomized non-inferiority trial, in which 2283 patients with clinically suspected CAP admitted outside the ICU setting were randomly allocated in rotating 4-month blocks to receive β-lactam monotherapy, β-lactam plus macrolide, or fluoroquinolone monotherapy. In patients with radiographically confirmed CAP, based on a pre-specified non-inferiority boundary of 3% on 90-day mortality, the trial demonstrated that β-lactam monotherapy was non-inferior to β-lactam plus macrolide combination therapy nor to fluoroquinolone monotherapy.

These conflicting results, together with concerns about selection pressure and the cost of using fluoroquinolones, do not permit definitive recommendations.

1.5 Advances in community-acquired pneumonia management

Our understanding of CAP has improved substantially in recent decades, and as a result we have implemented important changes in CAP management.

In the last 20 years, the introduction of severity-of-illness scores, such as the CURB-65 criteria (confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater) [Lim WS et al. 2003], as well as prognostic models, such as the Pneumonia Severity Index (PSI) [Fine MJ et al. 1997], have helped two generations of doctors in site-of-care decision-making, and are currently recommended for IDSA guidelines as part of the initial evaluation assessment of a patient with CAP [Mandell LA et al. 2007].

At the same time, the emergence of several new diagnostic tests (as well as their broad diffusion worldwide for early aetiological diagnosis of CAP) have significantly enhanced our knowledge of CAP etiology and reduced time to diagnosis. Urinary antigen test for *Streptococcus pneumoniae* and *Legionella pneumophila*

serotype 1, together with multiple PCR for respiratory virus, have lead to a prompter and more precise diagnosis, with the consequence of reduced times to directed antibiotic treatment and better outcomes. A systematic review and meta-analysis of diagnostic techniques for pneumococcal pneumonia found that an aditional 11.4% of pneumococcal pneumonia was diagnosed with urinary antigen beyond conventional techniques [Said MA et al. 2013]. However, some authors have highlighted (with a prospective randomised trial [Falguera M et al. 2010]) that the routine implementation of urine antigen detection tests does not carry substantial benefits for hospitalised CAP patients.

Moreover, the introduction and implementation into critical care of strategies such as non-invasive mechanical ventilation and the improved management of septic patients have played a leading role in the reported better outcomes within the subgroup of severe CAP patients.

Strategies for CAP prevention, such as pneumococcal vaccination and influenza vaccination, have been implemented worldwide in the last few decades, and there are reports of improved outcomes in vaccinated patients [Fisman DN et al.2006; Spaude KA et al. 2007].

The high incidence of CAP and the high burden of morbidity, mortality and their related costs have meant that research into CAP is among the most popular areas of investigation. Nowadays, although there has been important progress in CAP management, there are still controversial points and a great deal of room for improvement. Modern lines of investigations involve the best antibiotic treatment, impact of pre-admission antibiotic use, antibiotic timing, duration of treatment and

antibiotic stewardship, the use of biomarkers to assess CAP severity and/or etiology, the relationship between CAP and cardiac complications, the study of the immune response in CAP and the possible use of immuno-modulators.

Our investigation attempted to focus on some of the current challenges in CAP research. In the next sections, we will detail the rationale for our hypotheses and place our results within the context of current medical knowledge.

2. CURRENT CHALLENGES IN THE MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN ADULT HOSPITALIZED PATIENTS

GENERAL DESCRIPTION AND RATIONALE OF OBJECTIVES

2.1. Declining mortality in patients with community-acquired pneumonia

The current Infectious Diseases Society of America/American Thoracic Society guidelines on the management of CAP in adults state that rates of mortality due to pneumonia have not decreased significantly since penicillin became routinely available [Mandell et al. 2007].

However, our understanding of CAP has improved substantially in recent decades. Helpful tools in site-of-care decision-making such as prognostic severity scores, several new diagnostic tests for early aetiological diagnosis of CAP, and improved management in critical care have been introduced in routine clinical practice. At the same time, the use of new antibiotic agents and new combinations of antibiotics for treating CAP and strategies for its prevention such as pneumococcal vaccination have been implemented. Although some studies have shown the benefit of specific interventions for improving the outcomes of CAP patients [Fishman DN et al. 2006; Frei CR et al. 2006; Spaude KA et al. 2007], the impact of the widespread use of these strategies on mortality has not been extensively measured. Interestingly, recent studies based on administrative data reported falls in inhospital mortality over time among this population [Ruhnke GW et al. 2010; Ruhnke GW et al. 2011]. Nevertheless, clinical studies of the changes over time in CAP management and their impact on 30-day outcomes in patients hospitalized with CAP are lacking.

We aimed to analyse trends of mortality in a large cohort of adult patients with CAP documented over a 20- year period. We analysed factors related with overall mortality and explored changes over time in the characteristics of patients and CAP

management. Finally, we evaluated the relationship between these changes and trends of mortality in CAP patients.

2.2. Pre-hospital antibiotic use in community-acquired pneumonia

Although a large number of patients with CAP require hospitalization, the majority are treated as outpatients [Almirall J et al. 1999; Mandell LA et al. 2007]. However, studies report that around 10% of CAP patients initially treated as outpatients, require subsequent hospitalization [Minogue MF et al. 1998; Niedermann M et al. 2009]. Moreover, the frequency of pre-hospital antibiotic use in hospitalized patients with CAP ranges between 12 and 27% [van de Garde EM et al. 2008; Kruger S et al. 2010].

Recent studies have suggested that outpatient antibiotic treatment for CAP may be associated with increased disease severity and hospital complications, and may affect the predictive value of inflammatory biomarkers [van de Garde EM et al. 2006; Kruger S et al. 2010]. Despite this, however, the few studies published to date have been limited by their exclusive use of database records [Minogue MF et al. 1998; van de Garde EM et al. 2006], retrospective analysis [Mortensen EM et al. 2008] or by the fact that they report the effects of previous antibiotic treatment as a secondary finding [Schaaf B et al. 2007; Kruger S et al. 2010]. Moreover, they do not specify the type of antibiotic used or state whether other confounding factors were considered. Therefore, the information about the influence of pre-hospital antibiotic treatment on the causative organisms, clinical features and outcomes of hospitalized patients with CAP remains limited.

We sought to determine the impact of pre-hospital antibiotic treatment for the same episode of CAP on causative organisms, clinical features and outcomes.

2.3. Timing of antibiotic administration in pneumonia.

The timing of the first dose of antibiotics remains a controversial point in the management of CAP. Although early administration of appropriate treatment has been correlated with a better prognosis in some infections [Pines JM et al. 2008], this relationship is not clear in patients with CAP [Meehan TP et al. 1997; Battleman DS et al. 2002; Silber SH et al. 2003; Houck PM et al. 2004; Metersky ML et al. 2006; Waterer GW et al. 2006; Kanwar M et al. 2007; Welker JA et al. 2008; Yu KT et al. 2008; Bruns AH et al. 2009; Cheng AC et al. 2009]. While some studies do show a lower mortality with early administration of antibiotics [Meehan TP et al. 1997; Battleman DS et al. 2002; Houck PM et al. 2004], other investigators pointed out that the benefit that would be expected with early treatment can be offset by an increased misdiagnosis of CAP, an overuse of antibiotics and misprioritization of patients [Waterer GW et al. 2006; Kanwar M et al. 2007; Welker JA et al. 2008; Pines JM et al. 2009]. Thus, although the 2003 IDSA guidelines recommended early treatment of CAP (≤4 h)[Mandell LA et al. 2003], more recent guidelines do not state a specific time window for delivery of the first antibiotic dose and merely suggest it be given in the emergency department [Mandell LA et al. 2007]. Similar recommendations have been reported in guidelines from other geographical areas [Lim WS et al. 2009; Pines JM et al. 2009].

Healthcare-associated pneumonia has recently been recognized as a new category of respiratory infection that appears to merit a distinct approach to CAP [Kollef MH et al. 2005; Carratala J et al. 2007; Micek ST et al. 2007; Shindo Y et al.

2009]. The available data indicate that patients with Healthcare-associated pneumonia are older, have more comorbidity, are more likely to have pneumonia caused by antibiotic-resistant organisms, and have higher mortality [Kollef MH et al. 2005; Carratala J et al. 2007; Micek ST et al. 2007; Shindo Y et al. 2009]. At present, however, no information is available regarding the effects of the timing of antibiotic administration on outcomes in healthcare-associated pneumonia patients. Thus, the current guidelines for the management of adult patients with healthcare-associated pneumonia do not address this issue [ATS-IDSA guidelines 2005; Abrahamian FM et al. 2008].

Our study in hospitalized patients with community-onset pneumonia was carried out to determine the impact of timing of antibiotic administration on 30-day mortality of patients with CAP and healthcare-associated pneumonia.

2.4. Antibiotic de-escalation in pneumococcal pneumonia

The most common causative bacterial pathogen of CAP is Streptococcus pneumoniae, which also is the most frequent aetiology associated with death in CAP patients [Rosón B et al. 2001; Mandell LA et al. 2007; Garcia-Vidal C et al. 2010; Jain S et al. 2015]. Broad empirical coverage in CAP is recommended by current guidelines to cover the most frequent aetiologies [Mandell LA et al. 2007; Woodhead M et al. 2011]. The same CAP guidelines, otherwise, encourage attempts to broaden, narrow, or completely modify the spectrum of antibiotic therapy on the basis of diagnostic test results. Traditional microbiological investigations in CAP include good-quality sputum and blood cultures. Rapid tests based on urinary detection of pneumococcal and Legionella antigens and nucleic acid amplification techniques, which provide early

diagnosis and allow prompt appropriate antibiotic treatment, are increasingly used today [Johansson N et al. 2010; Sordé R et al. 2011].

In recent years, antibacterial resistance is accelerating at an alarming pace and has led to a global increase in morbidity and mortality [Hawkey PM et al. 2009; Laxminarayan R et al. 2013]. It is recognized that antimicrobial stewardship must be a key component of attempts to reduce costs and adverse drug events and to deal with the threat of antibiotic resistance [Dellit TH et al. 2007; Sordé R et al. 2011]. A variety of strategies may be utilized in stewardship programs to optimize the management of CAP and improve patient outcomes [Bosso JA et al. 2011; Carratalà J et al. 2012]. These include a rational use of antibiotic de-escalation, administering an appropriate pathogen-focused agent or narrowing empirical therapy. In this regard, a recent study reported that de-escalation therapy among bacteraemic patients with CAP, mainly due to S. pneumoniae, non-fermenters and Enterobacteriaceae Gram-negative bacteria, was not associated with an increased risk of 30-day mortality [Carugati M et al. 2015]. However, many aspects are still to be defined, such as the effect of de-escalation therapy on other important CAP clinical outcomes including length of hospital stay, adverse events and readmission rates, and in the case of patients with severe disease.

The aims of our study were to assess the impact of antibiotic de-escalation on clinical outcomes in patients with community-acquired pneumococcal pneumonia. We also specifically evaluated the de-escalation impact in patients classified into high-risk Pneumonia Severity Index classes (IV-V), clinically unstable patients, and those with bacteraemia.

2.5. Antibiotic treatment for Legionella pneumonia

Legionella pneumophila is a common causative agent in both sporadic and epidemic community-acquired pneumonia [Carratalà J et al. 2010]. Recently, important changes in the management of patients with legionella pneumonia, especially in diagnostic methods and treatment options, have improved the poor outcomes traditionally reported for this infection [Mykietiuk A et al. 2005; Viasus D et al. 2013]. The introduction of urine antigen testing for Legionella pneumonia, which profides an early diagnosis, seems to have played a major role in this decreasing mortality; conversely the impact on outcomes of antibiotic choice is less evident.

Although the information available is based mostly on observational studies, levofloxacin appears to be associated with a more rapid resolution of pneumonia symptoms, a shorter time to clinical stability and consequently shorter length of hospital stay than older macrolides [Blázquez Garrido RM et al. 2005; Mykietiuk A et al. 2005; Sabrià M et al. 2005]. However, biases in this comparison cannot be ruled out. For example, patients treated with macrolides were usually hospitalized in the earliest years of most studies, while patients who received levofloxacin were more contemporary and consequently were more frequently diagnosed with the urinary antigen test [Viasus D et al. 2013]. Moreover, there is scarce evidence available for the direct comparison of levofloxacin and azithromycin. Comparing these drugs is justified because azithromycin is more active than old macrolides against intracellular *L. pneumophila* in animal models [Garcia-Vidal C et al. 2006] and because the regimen of betalactams plus azithromycin is the recommended empirical treatment for CAP in the guidelines [Mandell LA et al. 2007].

This study compares the outcomes of a large number of consecutive patients hospitalised with Legionella pneumonia treated with levofloxacin, azithromycin, and old macrolides.

2.6. Clinical predictors for treatment effect in community-acquired pneumonia

For CAP patients admitted to a non–intensive-care-unit, international guidelines recommend either beta-lactam monotherapy, beta-lactam macrolide combination therapy or respiratory fluoroquinolone monotherapy as empiric treatment [Mandell LA et al. 2007; Lim WS et al. 2009; Wiersinga WJ et al. 2012]. However, the necessity for atypical coverage in non-severe CAP patients is uncertain as beneficial effects on mortality were only found in observational studies, but not in randomized controlled trials [Garin N et al. 2014; Postma DW et al. 2015]. Moreover, the use of macrolides and fluoroquinolones has been related to increased risks of antimicrobial resistance and adverse drug effects [Fuller JD et al. 2005; Vanderkooi OG et al. 2005; Malhotra-Kumar S et al. 2007; Ray WA et al. 2012; Mortensen EM et al. 2014]. A limitation of the studies performed so far is that they compared interventions within the whole domain of hospitalized CAP (e.g. at the population level), lacking power for proper subgroup analyses.

Despite important advancements in diagnostic testing, a causative pathogen is not detected in the majority of CAP patients; and if detected there is often a delay of up to 48 hours [Jain S et al. 2015]. Initial antibiotic treatment is therefore almost always empiric. However, CAP is a heterogeneous disease due to heterogeneity in both host and pathogen factors. Therefore, an individualized antibiotic treatment approach might prove beneficial.

The concept of individualized medicine, initially referred to the use of genomics in clinical care, has extended to recognizing the heterogeneity of each individual patient, particularly their risk factors for developing disease or having poor outcomes, and using this to inform treatment decisions. Biomarkers and clinical predictors have been widely studied in CAP in an attempt to predict the microbial etiology [Masiá M et al. 2007; Raeven VM et al. 2016] or clinical outcomes, such as early treatment failure or all cause mortality [Fine MJ et al. 1997; Lim WS et al.2003; 22. Rosón B et al. 2004; Hoogewerf M et al. 2006; Garcia-Vidal C et al. 2008; Kolditz M et al. 2015]. Yet, predictors of pathogens are weak at best, and 1 predictors of all-cause mortality do not inform the treating physician about the necessity to adjust empiric therapy. To pave the way for individualized medicine for CAP, it is necessary to take a step further and assess differences in treatment response based on multiple patient factors.

The objective of this study was to find candidate predictors at individual patient level for effect modification of empiric antibiotic regimens (beta-lactam monotherapy, beta-lactam macrolide combination therapy or respiratory fluoroquinolone) in CAP patients hospitalized to non–intensive-care-unit wards.

3. HYPOTHESES

1. Mortality in community-acquired pneumonia might have decreased in recent years, and there could be certain factors related with this change.

2. Pre-hospital antibiotic treatments could have an impact on the etiology, clinical features and outcomes of patients hospitalized for community-acquired pneumonia.

3. Timing from admission to first dose of antibiotic administration could have an impact on 30-day mortality in patients with pneumonia.

4. Antibiotic de-escalation could be a safe and effective strategy in patients hospitalized with pneumococcal community-acquired pneumonia.

5. Hospitalized patients with community-acquired Legionella pneumonia would have different outcomes depending on the antibiotic treatment administered.

6. There could be differences in response to antibiotic treatment in community-acquired pneumonia based on multiple patient factors.

4. OBJECTIVES

4.1 Changes in clinical characteristics and outcomes over time among hospitalized patients with community-acquired pneumonia

- To analyse trends in mortality within a large cohort of adult patients with community-acquired pneumonia documented over a 20-year period.
- To explore changes over time in the characteristics of patients and community-acquired pneumonia management.
- To identify the factors related to overall mortality.
- To evaluate the relationship between changes in patient characteristics over time and trends in mortality for community-acquired pneumonia patients.

4.2. Impact of pre-hospital antibiotic use on community-acquired pneumonia

- To compare characteristics of patients with community-acquired pneumonia who have received pre-hospital antibiotic treatment for the same episode of CAP with patients who did not receive it.
- To determine, by a propensity score analysis, the impact of pre-hospital antibiotic treatment for the same episode of CAP on causative organisms, clinical features and outcomes.

4.3. Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia.

- To compare patients who received early antibiotic treatment (first antibiotic dose during the first 4 and 8 hours after admission) with those who received late

treatment, both in community-acquired pneumonia or healthcare-associated pneumonia groups.

- To determine the impact of timing of antibiotic administration on 30-day mortality of patients with community-acquired pneumonia or healthcare-associated pneumonia.

4.4 Impact of antibiotic de-escalation on clinical outcomes in pneumococcal pneumonia.

- To describe the frequency and characteristics of antibiotic de-escalation in the first 72 hours from admission in a large cohort of hospitalised patients with pneumococcal community-acquired pneumonia.

- To assess the impact of antibiotic de-escalation on clinical outcomes in patients with community-acquired pneumococcal pneumonia.

- To evaluate the de-escalation impact in patients classified into high-risk pneumonia severity index classes (IV–V), clinically unstable patients and those with bacteraemia.

4.5 Levofloxacin versus azithromycin for treating Legionella pneumonia: a propensity score analysis.

- To compare outcomes of patients hospitalized with Legionella pneumonia in two tertiary hospitals in Barcelona treated with levofloxacin, azithromycin, and old macrolides.

- To assess, by means of a propensity score, whether the choice of levofloxacin vs. azithromycin has an influence on 30-day mortality.

4.6 Predictors for individual patient antibiotic treatment effects on hospitalised community-acquired pneumonia patients.

- To find candidate predictors at the individual patient level for effect modification of empirical antibiotic regimens recommended by guidelines (betalactams monotherapy, beta-lactams plus macrolides, fluoroquinolones) in patients hospitalized with CAP to non-intensive care unit wards.

5. SETTING AND METHODOLOGY

5.1. Setting, patients and studies design

The Hospital Universitari de Bellvitge is a 900 beds university hospital for adult patients that serve a population of approximately 1.5 million of habitants, with more than 26,000 admissions and 100,000 emergency consultations each year. It is accredited as a tertiary centre with all the medical and surgical specialties except paediatrics and obstetrics and is located in Hospitalet de Llobregat, being the referral hospital of the west coast region of the Catalan Health System.

In this hospital since February 1995 there is a prospective survey of all patients diagnosed with community-acquired pneumonia. All patients admitted to the hospital with CAP via the emergency department from 1 February 1995 are prospectively recruited and followed. Patients are seen daily during the hospital stay by one or more of the investigators staff, who recorded clinical, laboratory and microbiological data in a computer-assisted protocol.

Before starting empirical antibiotic therapy, patients undergo a complete clinical history and physical examination. Basic laboratory tests and chest radiography are performed. Two sets of blood samples are obtained and cultured and, when available, a sputum sample was evaluated by Gram staining and culture. Urinary antigen detection tests for Streptococcus pneumoniae and Legionella pneumophila are performed if indicated by the attending physician. Paired serum samples obtained during the acute and convalescent phases of infection (separated by a 3- to 8-week interval) are also obtained for serological studies.

Antibiotic therapy is administered according to the hospital guidelines, which recommended the administration of a β-lactam (ceftriaxone or amoxicillin-clavulanate)

with or without a macrolide (erythromycin or clarithromycin) or a fluoroquinolone with or without a β-lactam.

All patients are prospectively followed up during hospitalization and attended a long-term follow-up visit 1 month after discharge. The 30-day mortality is assessed by a specific search for each patient in the Health-Care Database (SAP) of the Catalan Health Service. The Catalan region provides universal health coverage. All beneficiaries are registered in the SAP, with a unique lifetime personal health number. The data is collected in a protocol and included in a database for analyzes.

The designs of the different studies are described below.

5.1.1. Changes in clinical characteristics and outcomes over time among hospitalized patients with community-acquired pneumonia

This observational study was conducted at Hospital Universitari de Bellvitge, in Barcelona, Spain. All patients admitted to the hospital with CAP via the emergency department from 1 February 1995 through to 31 December 2014 were prospectively recruited and followed. Immunosuppressed patients (those with neutropenia, HIV infection, transplantation or splenectomy, and those receiving immunosuppressants and/or >15 mg/day of prednisone or its equivalent) were excluded. Admission criteria, variables collection, clinical evaluation and follow up of patients with CAP did not change during the study period.

5.1.2. Impact of pre-hospital antibiotic use on community-acquired pneumonia

This observational study was conducted at Hospital Universitari de Bellvitge. All non-severely immunosuppressed patients admitted to the hospital with CAP via the emergency department from 1 January 2003 to 31 December 2012 were prospectively recruited and followed. Immunosuppressed patients (those with neutropenia, HIV infection, transplantation, splenectomy, receiving immunosuppressants and/or >20 mg/day of prednisone or its equivalent) and nursing home residents were excluded.

For the purposes of this study, patients hospitalized with CAP were divided into two groups: patients who had received pre-hospital antibiotic treatment for the same episode of CAP and patients who had not. The use of pre-hospital antibiotics was recorded on admission, and three classes of antibiotic drugs were investigated: b-lactams, macrolides and quinolones.

Early case-fatality rate and overall case-fatality rate were defined as death from any cause within 72 h and 30 days after hospital admission, respectively.

5.1.3. Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia.

The study was performed at Hospital Universitari de Bellvitge. All non-immunocompromised patients hospitalized through the emergency department (ED) with community onset pneumonia between 1 January 2001 and 31 October 2009 were analyzed. Cases were identified at the ED by the attending physicians and/or study investigators. Patients who received pre-hospital antibiotics were excluded.

For the purpose of the present study, patients were divided into two groups: patients with CAP and patients with HCAP. Timing of antibiotic administration was measured in hours and represented the difference between the time of arrival at the ED and the recorded time of initial antibiotic administration by nursing staff. Patients who received the first antibiotic dose within either 4 or 8 h of arrival at the ED (two cut-off points, referred as to 'early treatment') were compared with those who received antibiotics >4 or >8 h after arrival at the ED ('late treatment'). Four and eight hours were chosen as the cut-off points so as to be consistent with previous studies [Meehan TP et al. 1997; Battleman DS et al. 2002; Houck PM et al. 2004; Yu KT et al. 2008]. The primary study outcome was 30-day mortality, defined as death due to any cause in the first 30 days after hospitalization.

5.1.4. Impact of antibiotic de-escalation on clinical outcomes in pneumococcal pneumonia.

This study was conducted at Hospital Universitari de Bellvitge. All adult patients admitted to hospital with community-acquired pneumococcal pneumonia via the emergency department from 1 February 1995 to 31 December 2014 were prospectively followed-up. Patients who died within the first 72 h after hospital admission and those who had already received penicillin, amoxicillin or amoxicillin/clavulanate were excluded.

Community-acquired pneumococcal pneumonia was diagnosed in patients with signs and symptoms of an acute-onset lower respiratory tract infection, a new infiltrate on chest radiograph, and one or more cultures positive for S pneumoniae

obtained from blood, normally sterile fluids or sputum, and/or a positive test for detection of urinary antigen. Only good quality samples of sputum (<10 squamous epithelial cells and >25 leucocytes per field) were accepted for processing. From 2000 onwards, urinary antigen detection using a rapid immunochromatographic assay (Binax Now, Binax, Portland, ME, USA) for S. pneumoniae was also available [Garcia-Vidal C et al. 2010].

Empirical antibiotic treatment was applied according to hospital guidelines, as described above. There was no official hospital policy concerning de-escalation.

For the purposes of this study patients were divided into two groups: those with treatment de-escalation and those without treatment de-escalation within 72 h of hospital admission (henceforth 'de-escalation group' and 'non-de-escalation group'). De-escalation was considered when the initial antimicrobial spectrum was narrowed to penicillin, amoxicillin or amoxicillin/clavulanate within 72 h of hospital admission, by which time the microbiological test results were usually known.

The primary outcome measures were 30 day mortality and LOS. Thirty day mortality was defined as death due to any cause during ≤30 days of hospitalization, and LOS was measured in days from the documented time of admission to the documented time of discharge. Prolonged LOS was defined as an LOS greater than the median (in days). The secondary outcomes were the days of duration of intravenous (iv) antibiotic therapy, the occurrence of adverse events and the subsequent hospital admission. All inpatient antibiotic administration was verified through the paper-based medical administration record.

5.1.5 Levofloxacin versus azithromycin for treating Legionella pneumonia: a propensity score analysis.

This is an observational study performed at Hospital Universitari de Bellvitge and Hospital Universitari Vall d'Hebron, in Barcelona, Spain. These hospitals serve an urban area of 1,800,000 inhabitants. At Bellvitge University Hospital all patients admitted with CAP from January 1st, 2000 through July 31st, 2014 were prospectively followed up during hospitalization. At Hospital Universitari Vall d'Hebron information regarding patients with LP was recorded prospectively from 2000 to 2004 and retrospectively from 2005 to 2014 using microbiologic reports and by discharge diagnosis.

We analysed data from confirmed cases of community-acquired L. pneumophila pneumonia diagnosed with the use of one or more of the following methods: urinary antigen test, isolation of Legionella in sputum, transthoracic needle aspiration specimen, or pleural fluid, and/or a 4-fold increase in the antibody titre using serological methods. Data on epidemiology, demographic characteristics, clinical presentation, diagnosis, antibiotic therapy, and clinical outcome were retrieved from medical records. To reduce measurement error, data quality procedures have been applied (review of protocols and periodic review of the database by descriptive analysis to detect illogical information). The exposure variable was the anti-legionella treatment regimen. For the purpose of the study the first anti-legionella antibiotic administered was considered. This treatment had to be started within the first 48h after admission and administered for at least 5 days. The primary outcome assessed was overall mortality, defined as in hospital 30-day mortality. The secondary outcomes were: time to defervescence, time to achieve clinical stability, length of iv antibiotic

therapy, length of hospital stay, and early mortality, defined as death due to any cause < 48h after hospitalisation. The variables used for the primary outcome related analysis (antibiotic treatment, 30-day mortality and immunosuppression) did not have missing data. Antibiotic therapy was initiated at the emergency department following the hospitals' guidelines, which recommend the use of a beta-lactam (either ceftriaxone sodium 1 g IV once/d or amoxicillin/clavulanate potassium 1 g IV 3 times/d) with or without a macrolide (azithromycin 500mg IV once/d or clarithromycin 500mg IV twice/d); or levofloxacin (500 mg IV once/d). Local guidelines were identical for both centres and they did not change throughout the study period.

5.1.6 Predictors for individual patient antibiotic treatment effect in hospitalised community-acquired pneumonia patients.

This is a post-hoc analysis of three cohorts of hospitalized patients with CAP, two from the Netherlands and one from Spain [Bonten MJM et al. 2015, Postma DF et al 2015, Simonetti AF et al. 2016]. The Dutch cohorts were from two large randomized clinical trials conducted in the Netherlands. All patients hospitalized for CAP from The Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), and all patients included in the Community-Acquired Pneumonia — Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections (CAP-START) were included. CAPiTA, a randomized, placebo-controlled, double-blind trial evaluating pneumococcal vaccination, enrolled 84,496 persons aged ≥65 years between September 15th, 2008, and January 30th, 2010 throughout the Netherlands. Surveillance for suspected pneumonia and invasive pneumococcal disease, including

hospital admissions, was conducted from September 15th, 2008, through August 28th, 2013. From these, patients with clinically suspected CAP hospitalized to a non-ICU ward were included in the current analysis. CAP-START was a cluster-randomized trial comparing three empiric antibiotic treatment strategies (BL, BLM and FQL) in patients with clinically suspected CAP admitted to a non-ICU ward, from February 2011 through August 2013 in seven Dutch hospitals. All patients were followed up to 90 days.

The Spanish (Bellvitge) cohort includes all patients with X-ray confirmed CAP admitted via the emergency department of Bellvitge University Hospital, from February 1st, 1995 through December 31st, 2014. All patients were prospectively followed during hospitalization and attended a long-term follow-up visit. Patients admitted to the ICU within 24 hours of admission were excluded for the current analysis.

All patients included in the current analysis were adults (≥18 years old), hospitalized for at least 24 hours in a non-ICU ward, and were not admitted to the hospital in the previous 14 (the Netherlands) or 10 (Spain) days. The CAPiTA cohort included only patients who were 65 years of age or older. For the purpose of this study, we only analysed patients who received BL, BLM or FQL as empiric antibiotic treatment.

For the purpose of this study, outpatient antibiotic treatment was categorized as beta-lactam monotherapy or antibiotics with atypical coverage.

Data on clinical presentation, laboratory, microbiologic test results, antibiotic use, and clinical outcome were retrieved from medical records. In the absence of notes in clinical records, the following variables were assumed to be absent/negative:

pneumococcal or influenza vaccination, clinical symptoms (cough, purulent sputum, pleuritic chest pain, headache, gastro-intestinal symptoms, chills), confusion, hypotension, tachycardia, positive urinary antigen for S. pneumoniae.

Empiric antibiotic treatment

The preferred empiric antibiotic treatment differed between the cohorts. In the Bellvitge cohort, local hospital guidelines recommended treatment with BL, BLM, or a 4th generation FQL with or without a ß-lactam, depending on CAP severity and clinical suspicion for atypical pathogens.

The empiric antibiotic treatment in the CAPiTA cohort was based on the 2005 Dutch guidelines, which recommended BL for moderate-severe CAP and 4th generation FQL monotherapy, combination therapy of penicillin or amoxicillin with ciprofloxacin, or combination therapy of 2nd or 3rd generation cephalosporin with a macrolide for severe CAP [Shouten JA det al. 2005]. In the CAP-START cohort, during consecutive periods of 4 months, BL, BLM, or FQL was used as the preferred empiric treatment for CAP-patients hospitalized to a non-ICU ward. Deviations from the preferred treatment were allowed at the discretion of the treating physician. Actually received empiric treatment was used for the current analysis.

Outcomes

The primary outcome was all-cause mortality within 30 days after admission. The 30-day mortality was either assessed at a long-term follow-up visit (Bellvitge), from General Practitioner (GP) medical records (Bellvitge, CAPiTA), or from the municipal records database (CAP-START). The secondary outcomes were ICU admission after the first day of hospitalization and length of hospital stay. All outcomes were measured and analyzed at the individual patient level.

Predictors

Through an extensive search in PubMed we selected a list of candidate clinical predictors of treatment effects on CAP. These clinical predictors should be present and known at admission and associated either to specific CAP etiology or to clinical outcome. The predictors chosen for the analysis were the following: age (in years), gender, smoking habit, living in an elderly home, pneumococcal vaccination, influenza vaccination, admission during influenza season, received outpatient antibiotic treatment (with beta-lactams or with atypical coverage), cardiovascular disease, COPD, immunodeficiency (as defined previously), duration of symptoms (in days), cough, purulent sputum, gastrointestinal symptoms, headache, pleuritic chest pain, chills, confusion, fever (temperature>38 °C), hypotension (diastolic blood pressure ≤60 mmHg and/or systolic blood pressure < 90 mmHg), heart rate > 125 bpm, respiratory failure (defined as one of the following: Oxygen saturation < 90 mmHg at ambient air, or pO2 <60 mmHg in arterial gases, or PaO2FiO2 < 300 mmHg), leucocytes count (categorized as: <4000 cells/µL, 4000 – 20000 cells/µL, >20000 cells/µL), serum sodium concentration, bilateral infiltrate on chest X-ray, pleural effusion on chest X-ray, positivity of Streptococcus pneumoniae urinary antigen test, and PSI score.

In addition, the year of admission was included as a confounding variable, categorized in 4 periods of 5 years each, as following: 1995-1999, 2000-2004, 2005-2009, 2010-2014.

5.2. Clinical data and definitions

Community-acquired pneumonia was defined as an acute illness associated with two or more of the following signs and symptoms: new cough with or without sputum production, pleuritic chest pain, dyspnoea, fever or hypothermia, altered breath sounds on auscultation, leukocytosis, and the presence of a new infiltrate on a chest radiograph.

Current smoker was defined as a patient who had smoked more than 10 cigarettes per day for at least one year preceding the study were classified as current smokers. A patient with heavy drinking was defined a patient with a consumption of more than 40g alcohol a day for women (more than 3 standard drinks) and more than 60g a day for men (more than 4 standard drinks).

Influenza and pneumococcal vaccine status was assessed from interviews with the patients or their relatives and from review of hospital and personal health records (vaccination card). Patients were considered to be vaccinated against pneumococcus if any pneumococcal vaccine had been administered in the 5 years before admission, and influenza vaccinated if seasonal influenza vaccine had been administered during the year before admission. In CAPiTA cohort, patients were considered vaccinated against pneumococcus if randomized to receive pneumococcal vaccination at least 14 days before the occurrence of CAP.

A co-morbid condition was defined as the presence of one or more of the following underlying diseases: diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, cerebrovascular disease and dementia. The diagnosis of diabetes mellitus was based on a previous clinical and/or biochemical diagnosis of DM and/or treatment with oral

antidiabetic agents or insulin. Cardiovascular disease was defined as documentation in the medical records of, or treatment for, coronary artery disease, arrhythmia or congestive heart failure, or the presence of valvular heart disease. Chronic obstructive pulmonary disease (COPD) was defined as documentation of COPD in the medical history of the patient records, or the coexistence of chronic and progressive symptoms such as dyspnea, cough and sputum and airflow obstruction diagnosed by spirometry. Chronic kidney disease included pre-existing renal disease with documented abnormal serum creatinine levels outside the pneumonia episode (glomerular filtration rate < 60 ml/min/1.73 m2). Chronic liver disease was defined as a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis. Cerebrovascular disease was defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or computed tomography.

Immunodeficiency was defined as the presence of one or more of the following conditions: terminal renal failure, chemo- or radiotherapy in the past 90-days for solid or hematologic malignancies, use of immunosuppressive drugs, chronic use of corticosteroids (more than 0.5mg/kg/day in the Dutch cohorts, for at least 2 weeks and more than 15mg/day for at least 2 weeks in the Bellvitge cohort), HIV patients with CD4-count < 200, or having received a solid organ or stem cell transplantation.

HCAP included any patient who fulfilled any of the following [Carratalà J et al. 2007]: (i) received any home health care, received intravenous therapy at home, received wound care or specialized nursing care trough a healthcare agency, family or friends, or had self-administered intravenous medical therapy in the 30 days before pneumonia; (ii) attended a hospital or haemodialysis clinic or received intravenous

chemotherapy in the 30 days before pneumonia; (iii) were admitted to an acute care hospital for two or more days in the 90 days before pneumonia; and (iv) currently residing in a nursing home or long-term care facility.

Pre-hospital antibiotic treatment was defined as the oral intake of antibiotic drugs >24 before hospitalization for the same episode of acute disease. Patients were classified as receiving antibiotics if they self-reported prescription of any of these medications or, in Bellvitge's cohorts, by reviewing the prescriptions from their general practitioner at the SAP Healthcare Database of the Catalan Health Service (Institut Català de la Salut).

Respiratory failure was defined as a PaO2/FiO2 ratio less than 300. The diagnosis of septic shock was based on the ACCP/SCCM Consensus Conference Committee [Bone RC et al. 1992]: is defined as sepsis-induced hypotension (systolic blood pressure of less than 90 mmHg), persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction, or the need for vasopressors. Hypoalbuminemia was defined as serum albumin level at hospital admission (within the first 24h) <30 g/L were the independent variables. Patients in risk classes IV or V of the Pneumonia Severity Index (PSI) were considered to be more severely ill [Fine MJ et al. 1997].

Empiric antibiotic treatment was defined as the antibiotic treatment administered in the first calendar day of hospitalization (Dutch cohorts) or prospectively collected as a specific item in the data collection form (Bellvitge cohort), as the first antibiotic regimen administered to the patient after admission. The appropriateness of antibiotic therapy was analyzed for all cases with an aetiological diagnosis. Initial inappropriate therapy was defined as the absence of antimicrobial agents directed at a specific type

of organism or administration of an antibiotic to which the organism was resistant, according to susceptibility test criteria for lower respiratory tract pathogens. Patients with aspiration pneumonia who had not received anaerobic coverage (i.e. amoxicillin-clavulanate) were considered to have received inappropriate empirical antibiotic therapy. For patients with Legionella pneumonia, initial inadequate treatment was considered in patients who did not receive macrolides, levofloxacin or tetracyclines at admission.

Aspiration pneumonia was diagnosed on a clinical and radiological basis in patients who had risk factors such as compromised consciousness, altered gag reflex, dysphagia, severe periodontal disease, putrid sputum, and radiographic evidence of involvement of a dependent pulmonary segment or necrotizing pneumonia [Garcia-Vidal C et al. 2011].

Time to clinical stability was defined as time (days) until stable vital signs will be achieved for at least 24 h, as following: temperature ≤ 37.2°C without antipyretic agents, heart rate/minute ≤ 100, spontaneous respiratory rate ≤ 24 per minute, systolic blood pressure ≥ 90 mmHg without vasopressors support, mental status back to level before CAP, adequate oxygenation on room air of oxygen therapy (PaO2 ≥ 60 mmHg or pulse oximetry ≥ 90%). For patients with chronic hypoxemia or chronic oxygen therapy, PaO2 or pulse oximetry measurement must be back to baseline [Halm EA et al. 1998].

Overall mortality was defined as death from any cause within 30 days after hospital admission.

5.3. Microbiology

Pathogens in blood, pleural effusion, sputum and other samples were investigated using standard microbiological procedures.

Isolation of Legionella was attempted in sputum and other respiratory samples by using selective media (buffered charcoal yeast extract α). The S. pneumoniae antigen in urine was detected by using a rapid immunochromatographic assay (NOW Assay; Binax Inc., Portland, ME, USA). Legionella pneumophila Serogroup 1 antigen in urine was detected by an immunochromatographic method (NOW Legionella Urinary Antigen Test; Binax Inc.) or by ELISA (ELISA-Bartels, Trinity Biotech, Wicklow, Ireland). Both antigens in urine were used routinely from 2000.

Serological methods with enzyme immunoassya (EIA) were used both on admission and 3–4 weeks thereafter, to determine antibodies against the following pathogens: Mycoplasma pneumoniae, Chlamydophila psittacci, Chlamydophila pneumoniae, Coxiella burnetii, L. pneumophila (serogroups 1-6). Real-time PCR were performed to identify influenza A and B viruses from 2009 onwards. Antimicrobial susceptibility was tested by the microdilution method, following the Clinical Laboratory Standard Institute methods and criteria [CLSI 2013]. All microbiological studies were at the discretion of the attending physicians.

5.4. Statistical analysis

Due to substantial differences in the design studies, the statistical methodology is explained separately for each of the articles presented.

5.4.1. Changes in clinical characteristics and outcomes over time among hospitalized patients with community-acquired pneumonia

Data are presented as percentages and numbers, means with SDs, medians and interquartile ranges (IQRs), or proportions and 95% CIs. Accordingly, chi-squared tests for equal proportion, t tests, or the Mann–Whitney U test were used to test differences. To reduce the variability and noise of random in year by year data, we divided the study periods into 5-year blocks, defining 1995–99 as the reference period.

To assess whether 30-day mortality has changed over time, a logistic regression model was used with period of admission as numerical independent variable. Then we multiplied the adjusted ORs for each subsequent period with the observed survival rate for the reference period (1995–99) to obtain risk adjusted survival rates. These rates represent what the survival would be for each 5-year period if the patient case-mix were identical to that of the reference period. Our models adjusted for patients' characteristics and severity of disease that in a univariate analysis were related with 30-day mortality: age, presence of co-morbidity, septic shock at admission, respiratory failure, Gram-negative bacilli aetiology and presence of bacteraemia.

Trends of factors related with demographics, clinical condition, diagnosis, aetiology, treatment and outcome of CAP were analysed using the Mantel–Haenszel test of trend for categorical variables and linear regression for continuous variables. We analysed the impact of initial treatment strategy on mortality, assessing predictors

for overall mortality in the entire study population by using a logistic regression model. Associations are given as ORs with 95% CIs.

In a secondary analysis, we calculated the propensity to receive a fluoroquinolone as empiric antibiotic treatment given the patient's observed pre-treatment characteristics. We limited the analysis from 2000 onwards (year of introduction of fluoroquinolones for CAP in our institution). The propensity score was estimated using a logistic regression model including variables associated with fluoroquinolone use as empiric treatment ($p \leq 0.05$ in the univariate analysis) as: year of admission, patient characteristics (age > 65 years, presence of cancer or dementia) and clinical features (sudden onset, purulent sputum, diarrhoea, headache, arthralgia, multilobar pneumonia or pleural effusion on a chest radiograph, more than 12 000 leucocytes in peripheral blood sample), the fit of which was assessed by the Hosmer–Lemeshow test (p 0.878). Then we carried out a case–control matched analysis on propensity score (1: 1) to reduce the selection bias by factors associated with initial antibiotic therapy.

A value of $p < 0.05$ was considered statistically significant. All reported p values are two-tailed. All statistical calculations were performed using the Statistical Package for the Social Sciences (Version SPSS 15.01s) for Windows.

5.4.2 Impact of pre-hospital antibiotic use on community-acquired pneumonia

Categorical variables were described using counts and percentages from the available data. Continuous variables were expressed as the mean and SD or median and interquartile range for abnormally distributed data (Kolmogorov–Smirnov test). To detect significant differences between study groups, we used the chi-square test or

Fisher's exact test for categorical variables and the Student's t-test or Mann–Whitney U-test for continuous variables, as appropriate.

To evaluate propensity, the probability that a patient had received an antibiotic before hospital admission was assessed with multivariate analysis. The variables included in this multivariate analysis were the ones considered as factors that might influence the decision to give outpatient antibiotic treatment to patients with CAP. This multivariate model was used to create a propensity score for each patient, representing the probability that a patient had received antibiotic treatment during pre-hospital care. We then matched patients who had received antibiotics before hospital admission and patients who had not with an identical propensity score (a precision of five decimal points). This procedure provided two cohorts that were well matched for the confounders measured. The propensity score was used in two ways to correct for baseline disparities between the study groups.

First, the authors compared causative organisms, clinical features and outcomes between the matched patient groups (univariate). Second, the authors conducted a multivariate analysis for intensive care unit admission and 30-day mortality among all patients adjusting for the propensity score within the model. A p value <0.05 was considered statistically significant. Bonferroni correction was used to adjust the significance levels for individual antibiotics ($\alpha = 0.016$). All reported p values are two-tailed. All statistical calculations were performed using the Statistical Package for the Social Sciences (Version SPSS 15.01s) for Windows.

5.4.3 Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia.

Time from arrival at the ED to antibacterial administration was the independent variable. The characteristics of patients who received early treatment were compared with those of the late-treatment group. All proportions were calculated as percentages of the patients with available data. To detect significant differences between groups, we used the chi-square test or Fisher exact test for categorical variables and the Student t-test or Mann–Whitney U-test for continuous variables, as appropriate.

The multivariate logistic regression analysis of factors potentially associated with 30-day mortality included the clinical and significant variables in the univariate analysis and the timing of antibacterial administration and inappropriate empirical antibiotic therapy, regardless of whether the latter were significant or not. We restricted the number of variables included in the multivariable models following the rule of at least five to nine events (deaths) per variable [Vittinghoff E et al. 2007]. The discriminatory power of the logistic model was evaluated by the area under the receiver operating characteristic (ROC) curve and the goodness-of-fit according to the Hosmer–Lemeshow test.

The analyses were performed using SPSS (version 15.0, Chicago, IL, USA). Statistical significance was set at $p < 0.05$. All reported p values are two-tailed.

5.4.4. Impact of antibiotic de-escalation on clinical outcomes in pneumococcal pneumonia.

To detect significant differences in clinical, laboratory and outcomes between de-escalated and non-de-escalated groups, we used the x2 test or Fisher's exact test for

categorical variables, and Student's t-test or the Mann–Whitney U-test for continuous variables, when appropriate.

The multivariate analysis of factors potentially associated with primary and secondary outcomes included all the statistically significant variables in the univariate analysis and other variables with clinical relevance, including the de-escalated group. Model fit was evaluated with the Hosmer – Lemeshow goodness-of-fit test. We used the stepwise logistic regression model of the SPSS software package (SPSS, version 13.5; SPSS, Chicago, IL, USA).

An a priori subgroup analysis was performed in patients classified into high-risk groups according to the PSI (classes IV–V) at admission, in those without clinical instability and in those with bacteraemia.

Moreover, the probability that a patient has been de-escalated was assessed with multivariate analysis including the factors that might influence the decision to de-escalate antibiotic treatment. This multivariate model was used to create a propensity score for each patient. A multivariate analysis for primary and secondary outcomes was performed adjusting for the propensity score within the model.

Statistical significance was established at $\alpha=0.05$. All reported P values are two-tailed.

5.4.5. Levofloxacin versus azithromycin for treating legionella pneumonia: a propensity score analysis.

The Chi-square test or Fisher exact test for categorical variables, and t test or Mann-Whitney U test for continuous variables, (based on Kolmogorov-Smirnov normality test), were used. We analysed the relationship between the anti-legionella antibiotic

administered (levofloxacin vs. azithromycin) and mortality by two different approaches. First, mortality was assessed using logistic regression model that adjust the treatment regimen with the strongest predictor of mortality found in univariate analysis (immunosuppression). In both analysis patients treated with clarithromycin are excluded.

In a second analysis, we estimated the propensity to receive either levofloxacin or azithromycin using a logistic regression model including significant pre-treatment variables (with P values ≤0.025 on univariate analysis). Consequently, we introduced the estimated propensity score as a covariate in a multivariate analysis. Sensitivity analyses were performed by repeating the propensity score approach with 1:1 matching with replacement and a calliper of 0.25, and quintile stratification. Associations were expressed as odds ratios (OR) and 95% confidence intervals (CI). The goodness of fit of the model was evaluated by the Hosmer-Lemeshow test.

All P values reported are 2-tailed. Data were analysed using SPSS statistical software 166 (version 23.0; SPSS Inc, Chicago, Illinois).

5.4.6. Predictors for individual patient antibiotic treatment effect in hospitalised community-acquired pneumonia patients.

Data are presented as percentages and numbers, means with SDs, medians with interquartile ranges (IQRs), or proportions with 95% CIs, as appropriate.

For binary outcomes we used mixed-effects logistic regression models with a random intercept and a random slope for empiric antibiotic treatment for the three different cohorts used. Using these random effects, the model adjusts for dependence of observations within one cohort by allowing the baseline outcome rate and the

effect of antibiotic treatment to differ. Continuous predictors which did not comply with linearity assumptions were either log-transformed (age) or categorized (leukocyte count). Antibiotic treatment was entered in the models as a categorical variable with three values (one for each regimen tested). All models included all the predictors and the confounder as fixed effects.

To identify candidate predictors of treatment effects we applied a two-step approach. First, we estimated for each candidate predictor the interaction effect with antibiotic treatment in separate models, including the fixed effects, random effects, and the single interaction effect. Interaction variables with a two-sided p-value of <0.10 using the Wald test were included in the second step of our analysis.

Then we constructed a mixed-effects model including all selected interactions from the first step and all the afore mentioned fixed and random effects. . P-values of the second-step model were corrected for multiple testing using the Benjamini-Hochberg (BH) method [Benjamini Y, Hochberg Y. 1995]. Two-sided BH adjusted p-values <0.05 were considered statistically significant. Associations are given as ORs with 95% CIs. Effect modifiers for the length of hospital stay (LOS) were tested similarly with mixed-effects linear regression models, after log-transforming length of stay. The exponent of the regression coefficients was interpreted as the effect ratio, e.g. an effect ratio of 2 for factor X implies that a patient with X has a two time longer length of stay compared to a patient without X.

We performed sensitivity analyses including only patients with radiologically confirmed CAP and we performed analyses stratified per cohort. Assumptions of the models were tested visually by plotting residuals. Missing data on smoking habits, pre-hospital antibiotics use, elderly home living, serum sodium concentration, leukocyte

count, and PSI were imputed by multiple imputations (ten imputation datasets), assuming completely at random data missing. Descriptive statistics and multiple imputations were performed using the Statistical Package for the Social Sciences for Windows (Version SPSS 21.0.0.0). Mixed-effects models were performed with R (R Core Team, 2015), and the R-package lme4 (Bates, Maechler, Bolker, Walker 2015).

5.5 Ethical Issues

All the observational studies were conducted in accordance with the Declaration of Helsinki and were approved by the Institutional Review Board and the Ethics Committees of the participating institutions. Informed consent was obtained from patients at the moment of inclusion in the databases, and covered the current analysis.To protect personal privacy identifying information in the electronic database was encrypted for each patient.

6. RESULTS

6.1. Declining mortality among hospitalized patients with community-acquired pneumonia

- Trends of mortality in a large cohort of adult patients with CAP documented over a 20-year period.
- Changes over time in the characteristics of patients and CAP management.
- Factors related with overall mortality.
- The relationship between changes over time in patient characteristics and trends of mortality in CAP patients.

Declining mortality among hospitalized patients with community-acquired pneumonia

A. F. Simonetti[1], C. Garcia-Vidal[1,2], D. Viasus[3], D. García-Somoza[4], J. Dorca[5], F. Gudiol[1,2,6] and J. Carratalà[1,2,6]

1) *Department of Infectious Diseases, Hospital Universitari de Bellvitge—IDIBELL, Barcelona,* 2) *Spanish Network for the Research in Infectious Diseases (REIPI), Madrid, Spain,* 3) *Division of Health Sciences, Faculty of Medicine, Universidad del Norte, and Hospital Universidad del Norte, Barranquilla, Colombia,* 4) *Department of Microbiology, Hospital Universitari de Bellvitge, Barcelona,* 5) *Department of Respiratory Diseases, Hospital Universitari de Bellvitge Barcelona and* 6) *Department of Clinical Sciences, University of Barcelona, Barcelona, Spain*

Abstract

Little information is available on the changes over time in community-acquired pneumonia (CAP) management and their impact on 30-day mortality in hospitalized patients. We performed a prospective, observational study of non-severely immunosuppressed hospitalized adults with CAP from 1995 to 2014. A total of 4558 patients were included. Thirty-day mortality decreased from 9.6% in the first study period (1995–99) to 4.1% in the last period (2010–14); with a progressive downward trend (−0.2% death/year; p for trend = 0.003). Over time, patients were older (p 0.02), had more co-morbidities (p 0.037), more frequently presented severe illness according to the Pneumonia Severity Index (p <0.001) and septic shock (p <0.001), and more often required intensive care unit admission (p <0.001). Combination antibiotic therapy (p <0.001) and fluoroquinolone use (p <0.001) increased. Factors independently associated with 30-day mortality were increasing age (OR 1.04; 95% CI 1.03–1.05), co-morbidities (OR 1.48; 95% CI 1.04–2.11), shock at admission (OR 4.95; 95% CI 3.49–7.00), respiratory failure (OR 1.89; 95% CI 1.42–2.52), bacteraemia (OR 2.16; 95% CI 1.58–2.96), Gram-negative bacilli aetiology (OR 4.79; 95% CI 2.52–9.10) and fluoroquinolone use (OR 0.45; 95% CI 0.29–0.71). When we adjusted for a propensity score to receive fluoroquinolones, the protective effect of fluoroquinolone use was not confirmed. In conclusion, 30-day mortality decreased significantly over time in hospitalized patients with CAP in spite of an upward trend in patient age and other factors associated with poor outcomes. Several changes in the management of CAP and a general improvement in global care over time may have caused the observed outcomes.

Keywords: Antibiotics, community-acquired pneumonia, management, prognosis, time-trends
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Corresponding author: C. Garcia-Vidal, Department of Infectious Diseases, Hospital Universitari de Bellvitge—IDIBELL, Feixa Llarga s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain
E-mail: carolgv75@hotmail.com

Introduction

Community-acquired pneumonia (CAP) is the leading infectious cause of death and the fourth cause of global mortality in the world [1]. Mortality in patients hospitalized for CAP ranged from 10% in patients in conventional wards to >30% in those admitted to the intensive care unit (ICU) [2–4]. The current Infectious Diseases Society of America/American Thoracic Society guidelines on the management of CAP in adults state that rates of mortality due to pneumonia have not decreased significantly since penicillin became routinely available [5]. However, our understanding of CAP has improved substantially in recent decades. Helpful tools in site-of-care decision-making such as prognostic severity scores, several new diagnostic tests for early aetiological diagnosis of CAP, and improved management in critical care have been introduced in routine clinical practice. At the same time, the use of new antibiotic agents and

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new combinations of antibiotics for treating CAP and strategies for its prevention such as pneumococcal vaccination have been implemented.

Although some studies have shown the benefit of specific interventions for improving the outcomes of CAP patients [6–8], the impact of the widespread use of these strategies on mortality has not been extensively measured. Interestingly, recent studies based on administrative data reported falls in in-hospital mortality over time among this population [9,10]. Nevertheless, clinical studies of the changes over time in CAP management and their impact on 30-day outcomes in patients hospitalized with CAP are lacking.

The aim of this study was to analyse trends of mortality in a large cohort of adult patients with CAP documented over a 20-year period. We analysed factors related with overall mortality and explored changes over time in the characteristics of patients and CAP management. Finally, we evaluated the relationship between these changes and trends of mortality in CAP patients.

Material and Methods

Setting, population studied and design

This observational study was conducted at a 700-bed university hospital for adults in Barcelona, Spain. All patients admitted to the hospital with CAP via the emergency department from 1 February 1995 through to 31 December 2014 were prospectively recruited and followed. Immunosuppressed patients (those with neutropenia, HIV infection, transplantation or splenectomy, and those receiving immunosuppressants and/or >15 mg/day of prednisone or its equivalent) were excluded. This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the hospital's ethics committee.

Clinical evaluation and follow-up

Patients were seen daily during the hospital stay by one or more of the investigators, who recorded clinical, laboratory and microbiological data in a computer-assisted protocol. The Pneumonia Severity Index (PSI) was used to stratify patients according to risk [2].

Before starting empirical antibiotic therapy, patients underwent a complete clinical history and physical examination. Basic laboratory tests and chest radiography were performed. Two sets of blood samples were obtained and cultured and, when available, a sputum sample was evaluated by Gram staining and culture. 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 infection (separated by a 3- to 8-week interval) were also obtained for serological studies.

Antibiotic therapy was administered according to the hospital guidelines, which recommended the administration of a β-lactam (ceftriaxone or amoxicillin-clavulanate) with or without a macrolide (erythromycin or clarithromycin) or a fluoroquinolone with or without a β-lactam.

All patients were prospectively followed up during hospitalization and attended a long-term follow-up visit 1 month after discharge. Admission criteria, variables collection, clinical evaluation and follow up of patients with CAP did not change during the study period. The primary outcome (30-day mortality) was assessed by a specific search for each patient in the Health-Care Database (SAP) of the Catalan Health Service. The Catalan region provides universal health coverage. All beneficiaries are registered in the SAP, with a unique lifetime personal health number.

Definitions

Community-acquired pneumonia was defined as an acute illness associated with two or more of the following signs and symptoms: new cough with or without sputum production, pleuritic chest pain, dyspnoea, fever or hypothermia, altered breath sounds on auscultation, leucocytosis, and the presence of a new infiltrate on a chest radiograph.

A co-morbid condition was defined as the presence of one or more of the following underlying diseases: diabetes mellitus, chronic cardiopathy, chronic obstructive pulmonary disease, chronic renal failure, chronic liver disease, cerebral vascular disease and dementia. Initial inappropriate therapy was defined as the absence of antimicrobial agents directed at a specific type of organism or administration of an antibiotic to which the organism was resistant, according to susceptibility test criteria for lower respiratory tract pathogens. Overall mortality was defined as death from any cause within 30 days after hospital admission. Other definitions are described in Appendix 1.

Microbiological studies

Pathogens in blood, pleural effusion, sputum and other samples were investigated using standard microbiological procedures. Isolation of *Legionella* was attempted in sputum and other respiratory samples by using selective media (buffered charcoal yeast extract α). The *S. pneumoniae* antigen in urine was detected by using a rapid immunochromatographic assay (NOW Assay; Binax Inc., Portland, ME, USA). *Legionella pneumophila* Serogroup 1 antigen in urine was detected by an immunochromatographic method (NOW Legionella Urinary Antigen Test; Binax Inc.) or by ELISA (ELISA-Bartels, Trinity

Biotech, Wicklow, Ireland). Both antigens in urine were used routinely from 2000. Serological methods were used both on admission and 3–4 weeks thereafter, to determine antibodies against the following pathogens: *Mycoplasma pneumoniae*, *Chlamydophila psittacci*, *Chlamydophila pneumoniae*, *Coxiella burnetii*, *L. pneumophila*. Real-time PCR were performed to identify influenza A and B viruses from 2009 onwards. Antimicrobial susceptibility was tested by the microdilution method, following the Clinical Laboratory Standard Institute methods and criteria [11].

Statistical analysis

Data are presented as percentages and numbers, means with SDs, medians and interquartile ranges (IQRs), or proportions and 95% CIs. Accordingly, chi-squared tests for equal proportion, *t* tests, or the Mann–Whitney *U* test were used to test differences. To reduce the variability and noise of random in year by year data, we divided the study periods into 5-year blocks, defining 1995–99 as the reference period.

To assess whether 30-day mortality has changed over time, a logistic regression model was used with period of admission as numerical independent variable. Then we multiplied the adjusted ORs for each subsequent period with the observed survival rate for the reference period (1995–99) to obtain risk-adjusted survival rates. These rates represent what the survival would be for each 5-year period if the patient case-mix was identical to that of the reference period. Our models adjusted for patients' characteristics and severity of disease that in a univariate analysis were related with 30-day mortality: age, presence of co-morbidity, septic shock at admission, respiratory failure, Gram-negative bacilli aetiology and presence of bacteraemia.

Trends of factors related with demographics, clinical condition, diagnosis, aetiology, treatment and outcome of CAP were analysed using the Mantel–Haenszel test of trend for categorical variables and linear regression for continuous variables.

We analysed the impact of initial treatment strategy on mortality, assessing predictors for overall mortality in the entire study population by using a logistic regression model. Associations are given as ORs with 95% CIs. In a secondary analysis, we calculated the propensity to receive a fluoroquinolone as empiric antibiotic treatment given the patient's observed pre-treatment characteristics. We limited the analysis from 2000 onwards (year of introduction of fluoroquinolones for CAP in our institution). The propensity score was estimated using a logistic regression model including variables associated with fluoroquinolone use as empiric treatment ($p \leq 0.05$ in the univariate analysis) as: year of admission, patient characteristics (age >65 years, presence of cancer or dementia) and clinical features (sudden onset, purulent sputum, diarrhoea, headache, arthralgia, multilobar pneumonia or pleural effusion on a chest radiograph, more than 12 000 leucocytes in peripheral blood sample), the fit of which was assessed by the Hosmer–Lemeshow test (p 0.878). Then we carried out a case–control matched analysis on propensity score (1: 1) to reduce the selection bias by factors associated with initial antibiotic therapy.

A value of $p < 0.05$ was considered statistically significant. All reported p values are two-tailed. All statistical calculations were performed using the Statistical Package for the Social Sciences (Version SPSS 15.01s) for Windows.

Results

Trends of mortality and main causes of death

A total of 4558 patients were hospitalized with CAP during the study, 47 of whom were lost to follow up. Overall mortality (≤30 days) was 7.3% (330 of 4511 patients); in patients hospitalized in conventional wards mortality was 5.4% (219 of 4063 patients) whereas in patients admitted to the ICU it reached 24.8% (111 of 448 patients).

During the study period, unadjusted rates of 30-day mortality decreased from 9.6% in the first 5 years (1995–99) to 4.1% in the last 5 years (2010–14); with a progressive significant downward trend (−0.2% death/year; *p* for trend 0.003) (Fig. 1).

In a secondary analysis, we adjusted rates of mortality for patient characteristics and severity of disease found to be related with 30-day mortality by univariate analysis: age, presence of co-morbidity, septic shock at admission, respiratory failure, Gram-negative bacilli aetiology and presence of bacteraemia (Table 1). Risk-adjusted rates of mortality decreased in a greater way over the study period (p <0.001).

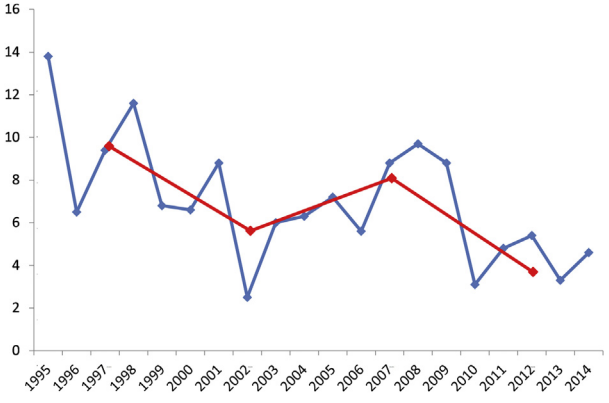

FIG. 1. Trends in 30-day mortality in hospitalized patients with community-acquired pneumonia from 1995 to 2014 (distribution by year and by period).

TABLE 1. Thirty-day mortality per 5-year period

Period	Unadjusted rate (%)	Adjusted rate (%)	Ratio	p value for trend
1995–99	9.6			<0.001
2000–04	5.9	5.1	0.533	
2005–09	8.2	5.6	0.585	
2010–14	4.1	2.8	0.292	

Multivariable analysis adjusted for: β-lactam monotherapy, inadequate empiric treatment.
Rates are adjusted for: age, presence of co-morbidity, septic shock at admission, respiratory failure, Gram-negative bacilli aetiology and presence of bacteraemia.

Acute respiratory failure secondary to pneumonia (n = 168; 51.8%), multiorgan failure associated with septic shock (n = 92; 25.9%) and acute cardiac events related with pneumonia (n = 20; 5.6%) were the most frequent causes of death.

Changes over time in the characteristics of patients and CAP management

Table 2 shows the principal changes in characteristics and management of patients over the study period. Over time, patients were more likely to be older, to present some co-morbidity, and to have received previous pneumococcal and influenza vaccination. Conversely, there were fewer current smokers and alcohol abusers. The percentage of patients with high-risk pneumonia according to PSI, pleural empyema and septic shock at admission increased significantly over time.

Streptococcus pneumoniae caused 33.8% of CAP cases, being the most frequent pathogen. The diagnosis of pneumococcal pneumonia increased significantly mainly due to the introduction of the pneumococcal urine antigen test (routinely available

TABLE 2. Characteristics of 4558 patients with community-acquired pneumonia divided by study period

Variable	1995–99 (n = 1121)	2000–04 (n = 1064)	2005–09 (n = 1634)	2010–14 (n = 739)	p value
Age, years (median, IQR)	69 (57–78)	68 (57–79)	71 (57–80)	71 (55–80)	0.002[a]
Male sex, (%)	69.8	70.4	66.7	65.9	0.02
Current smoker, (%)	28.8	25.5	25.5	24.2	0.02
Heavy drinking, (%)	19.5	14.9	17.9	11.0	<0.001
Influenza vaccine (season), (%)	41.9	48.4	53.7	52.4	<0.001
Pneumococcal vaccine, 5-year, (%)	4.7	18.6	23.0	25.0	<0.001
Underlying disease, (%)	72.4	72.5	77.7	73.7	0.03
COPD	23.8	29.9	27.8	34.1	<0.001
Diabetes mellitus	17.1	18.2	24.5	25.2	<0.001
Cerebral vascular disease	1.5	6.5	12.6	7.3	<0.001
Chronic renal disease	4.0	3.8	10.2	13.0	<0.001
Chronic heart disease	21.1	30.1	22.5	23.0	0.83
Chronic liver disease	6.2	4.3	7.9	7.3	0.02
Dementia	3.4	4.1	6.9	7.0	<0.001
High severity risk PSI classes (IV–V), (%)	55.0	54.6	63.4	60.5	<0.001
Clinical features, (%)					
Respiratory failure	60.5	54.4	59.7	59.7	0.74
Pleural effusion	19.4	16.7	16.0	16.9	0.06
Empyema	2.9	3.0	5.8	4.5	0.002
Bacteraemia	12.9	10.9	15.0	13.1	0.20
Altered mental status	14.3	11.2	16.9	14.3	0.11
Septic shock at admission	3.2	4.6	11.2	11.5	<0.001
Aetiology, (%)					
Streptococcus pneumoniae	23.5	29.5	44.5	31.8	<0.001
Pneumococcal bacteraemia	10.1	8.6	10.9	8.3	0.73
Legionella pneumophila	6.6	7.7	3.9	2.4	<0.001
Haemophilus influenzae	6.2	6.6	3.8	4.7	0.009
Aspiration pneumonia	7.0	6.6	8.1	7.2	0.42
Atypical agents	5.6	4.8	2.9	3.8	0.003
Gram-negative bacilli[b]	1.3	1.5	1.7	2.7	0.04
Virus	1.3	1.1	4.5	6.1	<0.001
Mixed pathogens	3.5	2.4	5.0	5.5	0.002
Unknown aetiology	49.3	43.0	31.9	39.8	<0.001
Treatment, (%)					
Overall β-lactam treatment	85.1	75.1	84.9	85.8	<0.043
Penicillin/Amoxicillin (± clavulanate)	30.3	15.5	18.7	17.3	<0.001
Cephalosporin	53.9	58.4	63.9	64.4	<0.001
β-lactam monotherapy	67.1	47.0	39.3	29.0	<0.001
Fluoroquinolone monotherapy	0.4	20.5	11.1	10.4	<0.001
Overall fluoroquinolone treatment	0.5	44.3	57.3	66.0	<0.001
Overall macrolide treatment	29.7	6.3	0.9	1.1	<0.001
Combination therapy	23.7	29.3	48.6	59.7	<0.001
Combination β-lactam and macrolide	17.2	4.4	0.7	0.8	<0.001
Combination β-lactam and fluoroquinolone	0.1	23.2	43.5	52.9	<0.001
Overall oseltamivir	0	0	4.7	5.5	<0.001
Inadequate empirical antibiotic therapy	4.6	4.2	4.2	2.4	0.04
Timing of antibiotic administration $\leq$ 4h	ND	39.1	37.0	46.0	0.016
Outcomes					
Mechanical ventilation, (%)	4.4	5.3	7.0	6.9	0.003
Non-invasive ventilation, (%)	0	1.3	5.9	10.0	<0.001
ICU admission, (%)	7.3	9.0	11.1	12.0	<0.001
Length of hospital stay, days (median, IQR)	9 (6–12)	8 (6–12)	7 (5–11)	8 (5–12)	0.002[a]
Early mortality (<48 h), (%)	3.2	1.5	2.1	0.7	<0.001
30-day mortality, (%)	9.6	5.9	8.2	4.1	0.002

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; PSI, Pneumonia Severity Index; ICU, intensive care unit.
[a]Kruskas–Wallis test.
[b]Of the 4558 CAP episodes, 83 were due to Gram-negative bacilli. 13 episodes (15.7%) had mixed infection. The Gram-negative bacilli were: *Pseudomonas aeruginosa* (43), *Escherichia coli* (18), *Klebsiella pneumoniae* (13), others Enterobacteraceae (5), *Acinetobacter baumanii* (2), *Stenotrophomonas maltophila* (1). Twelve isolates (14%) were resistant to quinolones. There was no relationship between quinolone resistance and mortality.

from 2000); meanwhile the number of CAP with unknown aetiology decreased. We also observed a significant reduction in rates of diagnosis of *L. pneumophila* and other atypical pathogens as causes of CAP. In contrast, there was a significant increase in CAP due to Gram-negative bacilli. After the introduction of PCR for influenza virus during the 2009 pandemic, we found a substantial increase in viral pneumonia, along with higher rates of mixed infections. The percentage of patients with bacteraemia did not significantly change during the study period. Penicillin resistance of invasive *S. pneumoniae* strains changed from 18.6% in the first period to 8.2% in the last period, while susceptibility to cephalosporins and quinolones did not show major changes. Over time there was an increase in patients requiring ICU admission and patients who underwent invasive and non-invasive mechanical ventilation.

Regarding empirical antibiotic therapy, combination therapy increased, the use of β-lactam monotherapy as well as the use of macrolides fell but there was a huge increase in the use of fluoroquinolones, and initial inappropriate therapy decreased slightly over time. The proportion of patients who received their first antibiotic dose within 4 h from admission increased over time (data available from 2000).

Factors associated with mortality

In a multivariable analysis (Table 3) factors independently associated with 30-day mortality were: increasing age, presence of some co-morbidity, shock at admission, respiratory failure, bacteraemia, Gram-negative bacilli aetiology, and period of admission. Conversely, the use of fluoroquinolones as empiric treatment, either in monotherapy or in combination, was the only factor significantly associated with lower mortality. In a secondary analysis, we calculated the propensity to receive a fluoroquinolone as empiric antibiotic treatment, and performed a case–control matched analysis on propensity score (1: 1 matching with replacement). After applying the propensity score, the protective effect of fluoroquinolone use was not confirmed. (OR 0.317, 95% CI 0.069–1.448; p 0.138).

TABLE 3. Factors independently associated with mortality during the period studied in a multivariable analysis

Variable	OR	95% CI	p value
Year of admission	0.962	0.936–0.989	0.006
Age	1.039	1.029–1.050	<0.001
Presence of co-morbidity	1.481	1.040–2.110	0.02
Shock at admission	4.945	3.494–6.997	<0.001
Respiratory failure	1.890	1.420–2.515	<0.001
Bacteraemia	2.162	1.579–2.960	<0.001
Gram-negative bacilli	4.792	2.523–9.103	<0.001
Fluoroquinolone treatment [a]	0.452	0.289–0.707	0.001

Multivariable analysis adjusted for: β-lactam monotherapy, inadequate empiric treatment.
[a]When a propensity score for receiving fluoroquinolone as empiric treatment was added to the multivariable analysis, fluoroquinolone treatment was not associated with mortality (OR 0.317, 95% CI 0.069–1.448; p 0.138).

Discussion

This observational study of a large prospective cohort of adults hospitalized with CAP found a substantial decrease in 30-day mortality over a period of 20 years, in spite of an upward trend in several factors with negative prognostic influence.

A similar downward trend in mortality due to CAP has been reported in two previous studies [9,10] using US national databases, where mortality due to CAP fell from 8.9% in 1993 to 4.1% in 2005 (p <0.001) in hospitalized patients [9] and from 13.5% in 1987 to 9.7% in 2005 in a population of elderly inpatients and outpatients with CAP [10].

Interestingly, two recent studies have also found reductions in mortality among CAP patients [12,13]. The first study [12], which compared patients with CAP admitted to the ICU in two periods (1995–2000 versus 2005–10), suggests that the decrease in mortality observed may be related to the implementation of a sepsis management bundle derived from the Surviving Sepsis Campaign. Among other interventions, the bundle included the combined use of levofloxacin and a third-generation cephalosporin for the initial empirical antimicrobial regimen. The second study [13], a matched case–control study that compared two periods (2000–02 versus 2008–13) found a 15% decrease in mortality among patients with pneumococcal pneumonia admitted to the ICU. Early antibiotic administration and combination antibiotic therapy were independently associated with better outcomes.

In our cohort, we observed over time some important changes in the management of CAP patients that could have caused the better outcomes observed, including the rise in patients who underwent mechanical (either invasive or non-invasive) ventilation or who were admitted to ICU, and a huge change in empirical antibiotic choice, with an increase in fluoroquinolone use, either alone or in combination with β-lactams.

Several randomized controlled trials have demonstrated a non-inferiority of fluoroquinolone monotherapy when compared with either β-lactams alone or β-lactams plus macrolide regimens in treating patients with CAP [14–18]. Furthermore, fluoroquinolones have also been associated with improvement of other outcomes, such as lower risk of treatment failure, shorter duration of intravenous treatment and hospital stay, a faster clinical improvement and a decrease in the number of admissions of low-risk patients [18–21]. In our cohort the use of fluoroquinolones was the only factor associated with decreased mortality over time in a multivariable analysis. However, after matching patients by means of a propensity score for receiving quinolones, the beneficial effect of fluoroquinolone use on mortality was not confirmed.

In recent years, the possible beneficial effect of combination therapy with β-lactams and macrolides on patient outcomes has been the subject of active debate. Although the use of combination therapy has been linked to better outcomes in some observational studies, especially in patients with severe CAP [22], this benefit has not been found in randomized controlled trials [23,24]. In a large meta-analysis of almost 10 000 critically ill patients with CAP, when broadly guideline-concordant regimens were compared (β-lactams plus macrolides versus β-lactams plus fluoroquinolones), no significant difference in mortality was found [25]. Similarly, we did not observe better outcomes in patients who received the β-lactams plus macrolides regimen.

The strengths of this study include the prospective nature of the cohort, the comprehensive data collection over a period of 20 years, the large number of a wide spectrum of hospitalized patients with CAP and the application of a propensity analysis. There are, however, some limitations that should be acknowledged; the study was conducted at a single centre and the extrapolation of our results to other settings should be done with care.

In summary, 30-day mortality significantly decreased over time in hospitalized CAP patients in spite of an upward trend in patient age and other factors associated with poor outcomes. Several changes in the management of CAP and a general improvement in global care over time may have caused the observed outcomes. In fact, during the past decades mortality has declined for a variety of conditions, including sepsis, myocardial infarction and stroke [26–28], suggesting an overall better clinical management and a general improvement of healthcare systems.

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Author Contributions

AFS, CGV, JC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript. AFS, CGV, DV, DGS, JD, FG and JC contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. Study concept and design: CGV, AFS, JC. Acquisition of the data: AFS, CGV, DV, DGS, JD. Analysis and interpretation of the data: AFS, CGV, DV, FG, and JC. Drafting of the manuscript: CGV, AFS, JC. Critical revision of the manuscript for important intellectual content: DV, DGS, JD, FG, JC. Statistical analysis: CGV, AFS. Study supervision: FG, JC.

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Transparency Declaration

All authors have no conflicts of interest to disclose.

Appendix 1. Definitions

Cerebrovascular disease a clinical diagnosis of stroke or transient ischaemic attack or stroke documented by magnetic resonance imaging or computed tomography.

Chronic cardiopathy chronic heart disease was defined as evidence in records or treatment for coronary artery disease, arrhythmia, or congestive heart failure, or the presence of valvular heart disease.

Chronic liver disease a clinical or histological diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis.

Chronic obstructive pulmonary disease the coexistence of chronic and progressive symptoms such as dyspnoea, cough and sputum and airflow obstruction diagnosed by spirometry.

Chronic renal failure included pre-existing renal disease with documented abnormal serum creatinine levels outside the pneumonia episode (glomerular filtration rate <60 mL/min/1.73 m^2).

Current smoker patients who had smoked more than ten cigarettes per day for at least 1 year preceding the study were classified as current smokers.

Diabetes mellitus diagnosis was based on a previous clinical and/or biochemical diagnosis of diabetes mellitus and/or treatment with oral anti-diabetic agents or insulin.

Heavy drinking consumption of more than 40 g alcohol per day for women (more than three standard drinks) and more than 60 g per day for men (more than four standard drinks).

Influenza and pneumococcal vaccine status assessed from interviews with the patients or their relatives and from reviews of hospital and personal health records (vaccination card). Patients were considered to be pneumococcus-vaccinated if the pneumococcal vaccine had been administered in the 5 years before admission, and influenza-vaccinated if seasonal influenza vaccine had been administered during the year before admission.

Respiratory failure a Pao_2/Fio_2 ratio <300.

Septic shock diagnosis of septic shock was based on a systolic blood pressure of <90 mmHg, and diagnosis of peripheral hypoperfusion on the need for vasopressors.

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6.2. Impact of pre-hospital antibiotic use on community-acquired pneumonia

- Characteristics of patients with CAP who have received pre-hospital antibiotic treatment for the same episode of CAP with patients who did not receive it.

- Impact of pre-hospital antibiotic treatment for the same episode of CAP on causative organisms.

- Impact of pre-hospital antibiotic treatment for the same episode of CAP on prognosis.

Impact of pre-hospital antibiotic use on community-acquired pneumonia

A. F. Simonetti[1], D. Viasus[1,2], C. Garcia-Vidal[1,2], S. Grillo[1], L. Molero[1], J. Dorca[3,4] and J. Carratalà[1,2,4]

1) *Department of Infectious Diseases, Hospital Universitari de Bellvitge – IDIBELL, Barcelona,* 2) *Spanish Network for the Research in Infectious Diseases (REIPI), Madrid,* 3) *Department of Respiratory Medicine, Hospital Universitari de Bellvitge – IDIBELL and* 4) *Department of Clinical Sciences, University of Barcelona, Barcelona, Spain*

Abstract

Information on the influence of pre-hospital antibiotic treatment on the causative organisms, clinical features and outcomes of patients with community-acquired pneumonia (CAP) remains scarce. We performed an observational study of a prospective cohort of non-immunosuppressed adults hospitalized with CAP between 2003 and 2012. Patients were divided into two groups: those who had received pre-hospital antibiotic treatment for the same episode of CAP and those who had not. A propensity score was used to match patients. Of 2179 consecutive episodes of CAP, 376 (17.3%) occurred in patients who had received pre-hospital antibiotic treatment. After propensity score matching, *Legionella pneumophila* was more frequently identified in patients with pre-hospital antibiotic treatment, while *Streptococcus pneumoniae* was less common ($p < 0.001$ and $p < 0.001$, respectively). Bacteraemia was less frequent in pre-treated patients (p 0.01). The frequency of positive sputum culture and the sensitivity and specificity of the pneumococcal urinary antigen test for diagnosing pneumococcal pneumonia were similar in the two groups. Patients with pre-hospital antibiotic treatment were less likely to present fever (p 0.02) or leucocytosis (p 0.001). Conversely, chest X-ray cavitation was more frequent in these patients (p 0.04). No significant differences were found in the frequency of patients classified into high-risk Pneumonia Severity Index classes, in intensive care unit admission, or in 30-day mortality between the groups. In conclusion, *L. pneumophila* occurrence was nearly three times higher in patients who received pre-hospital antibiotics. After a propensity-adjusted analysis, no significant differences were found in prognosis between study groups. Pre-hospital antibiotic use should be considered when choosing aetiological diagnostic tests and empirical antibiotic therapy in patients with CAP.

Keywords: Clinical features, community-acquired pneumonia, aetiology, pre-hospital antibiotic use, prognosis
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Corresponding author: D. Viasus, Department of Infectious Diseases, Hospital Universitari de Bellvitge, Feixa Llarga s/n, L'Hospitalet de Llobregat, Barcelona 08907, Spain
E-mail: dfviasusp@unal.edu.co

Introduction

Although a large number of patients with community-acquired pneumonia (CAP) require hospitalization, the majority are treated as outpatients [1,2]. However, studies report that around 10% of CAP patients initially treated as outpatients require subsequent hospitalization [3,4]. Moreover, the frequency of pre-hospital antibiotic use in hospitalized patients with CAP ranges between 12 and 27% [5,6].

Recent studies have suggested that outpatient antibiotic treatment for CAP may be associated with increased disease severity and hospital complications, and may affect the predictive value of inflammatory biomarkers [6,7]. Despite this, however, the few studies published to date have been limited by their exclusive use of database records [3,7], retrospective analysis [8] or by the fact that they report the effects of previous antibiotic treatment as a secondary finding [6,9]. Moreover, they do not specify the type of antibiotic used or state whether other confounding factors were considered. Therefore, the information about the influence of pre-hospital antibiotic treatment on the causative organisms, clinical

features and outcomes of hospitalized patients with CAP remains limited.

In this study we sought to determine the impact of pre-hospital antibiotic treatment for the same episode of CAP on causative organisms, clinical features and outcomes.

Methods

Setting, patients and study design

This observational study was conducted at a 700-bed teaching hospital for adults in Barcelona, Spain. All non-severely immunosuppressed patients admitted to the hospital with CAP via the emergency department from 1 January 2003 to 31 December 2012 were prospectively recruited and followed. Immunosuppressed patients (those with neutropenia, HIV infection, transplantation, splenectomy, receiving immunosuppressants and/or >20 mg/day of prednisone or its equivalent) and nursing home residents were excluded. The study was approved by the Ethics Committee of the hospital. Written informed consent was obtained from all patients before enrolment.

For the purposes of this study, patients hospitalized with CAP were divided into two groups: patients who had received pre-hospital antibiotic treatment for the same episode of CAP and patients who had not. The use of pre-hospital antibiotics was recorded on admission, and three classes of antibiotic drugs were investigated: β-lactams, macrolides and quinolones.

Follow-up

Patients were seen daily during the hospital stay by one or more of the investigators, who recorded clinical data in a computer-assisted protocol. Data were collected on demographic characteristics, comorbidities, causative organisms, antibiotic susceptibilities, biochemical analysis, empirical antibiotic therapy, and outcomes, including mortality. The Pneumonia Severity Index (PSI) and CURB-65 were used to stratify patients according to risk [10,11].

Definitions

Pre-hospital antibiotic treatment was defined as the oral intake of antibiotic drugs >24 h before hospitalization for the same episode of acute disease. Patients were classified as receiving antibiotics if they self-reported prescription of any of these medications or by reviewing the prescriptions from their general practitioner at the SAP Healthcare Database of the Catalan Health Service (Institut Català de la Salut).

Community-acquired pneumonia was defined as an acute illness associated with two or more of the following signs and symptoms: new cough with or without sputum production, pleuritic chest pain, dyspnoea, fever or hypothermia, altered breath sounds on auscultation, leucocytosis, plus the presence of a new infiltrate on a chest radiograph. Pneumococcal pneumonia was diagnosed as defined elsewhere [12].

The diagnosis of septic shock was based on a systolic blood pressure of <90 mmHg and peripheral hypoperfusion with the need for vasopressors. Time to clinical stability was defined as described elsewhere [13]. Early case-fatality rate and overall case-fatality rate were defined as death from any cause within 72 h and 30 days after hospital admission, respectively. All patients were prospectively followed up during hospitalization. In addition, a long-term follow-up visit took place 1 month after discharge.

Microbiological studies

Pathogens in blood, pleural effusion, sputum and other samples were investigated using standard microbiological procedures. The *Streptococcus pneumoniae* antigen in urine was detected by using a rapid immunochromatographic assay (NOW Assay; Binax Inc., Portland, ME, USA). *Legionella pneumophila* Serogroup 1 antigen in urine was detected by an immunochromatographic method (NOW Legionella Urinary Antigen Test; Binax Inc.) or by ELISA (ELISA-Bartels, Bartels, Trinity Biotech, Wicklow, Ireland). Serological methods were used both on admission and 3–4 weeks thereafter, to determine antibodies against the following pathogens: *Mycoplasma pneumoniae*, *Chlamydophila psittacci*, *Chlamydophila pneumoniae*, *Coxiella burnetii*, *L. pneumophila*, respiratory syncytial virus, parainfluenza virus and influenza A virus [14]. Real-time PCR was performed to identify influenza A (H1N1)pdm09 virus.

Statistical analysis

Categorical variables were described using counts and percentages from the available data. Continuous variables were expressed as the mean and SD or median and interquartile range for abnormally distributed data (Kolmogorov–Smirnov test). To detect significant differences between study groups, we used the chi-square test or Fisher's exact test for categorical variables and the Student's *t*-test or Mann–Whitney *U*-test for continuous variables, as appropriate.

To evaluate propensity, the probability that a patient had received an antibiotic before hospital admission was assessed with multivariate analysis. The variables included in this multivariate analysis were the ones considered as factors that might influence the decision to give outpatient antibiotic treatment to patients with CAP. This multivariate model was used to create a propensity score for each patient, representing the probability that a patient had received antibiotic treatment during pre-hospital care. We then matched patients who had received antibiotics before hospital admission and

patients who had not with an identical propensity score (a precision of five decimal points). This procedure provided two cohorts that were well matched for the confounders measured. The propensity score was used in two ways to correct for baseline disparities between the study groups. First, the authors compared causative organisms, clinical features and outcomes between the matched patient groups (univariate). Second, the authors conducted a multivariate analysis for intensive care unit admission and 30-day mortality among all patients adjusting for the propensity score within the model.

A p value <0.05 was considered statistically significant. Bonferroni correction was used to adjust the significance levels for individual antibiotics ($\alpha = 0.016$). All reported p values are two-tailed. All statistical calculations were performed using the Statistical Package for the Social Sciences (Version SPSS 15.01s) for Windows.

Results

During the study period, 2179 consecutive episodes of CAP in non-immunosuppressed patients were recorded, of which 376 (17.3%) occurred in patients who had received pre-hospital antibiotic treatment. The most common pre-hospital antibiotics administered were β-lactams in 233 (62%) patients, followed by quinolones in 90 (24%) and macrolides in 29 (8%). Fifteen (4%) patients received more than one antibiotic class before hospitalization, three patients (0.8%) received other antibiotics and in six patients (1.6%) the antibiotic class was not registered. The reasons for hospitalization in this group of patients were persistent CAP symptoms despite outpatient treatment in 288 patients, appearance of new CAP symptoms in 91, respiratory failure in 131, hypotension in 14, presence of pleural effusion in 76, and other condition not related to the current CAP episode in 28.

Table 1 shows the demographic features of patients with and without pre-hospital antibiotic treatment. Patients who received pre-hospital antibiotic treatment were younger and less likely to be heavy alcohol consumers. They also had fewer chronic comorbidities, mainly diabetes mellitus and chronic cardiac disease.

An aetiological diagnosis for CAP was more frequently established in patients who had not received antibiotic treatment before hospitalization. Table 2 shows the distribution of causative organisms in the study groups. *Streptococcus pneumoniae* was the most frequent causative organism in patients from both groups. Patients who received pre-hospital antibiotic treatment presented more infections attributable to *L. pneumophila*, mainly patients who had been receiving β-lactams. Conversely, *S. pneumoniae* and *Haemophilus influenzae* were more frequently identified in patients who had not received antibacterial drugs in the outpatient setting. Oral penicillin and erythromycin resistance rates in *S. pneumoniae* were more frequently documented in patients who had received pre-hospital antibiotic treatment. Bacteraemia was less common in pre-treated patients (15.6% versus 4.4%; p <0.001), mainly in those who had received β-lactams (1%; p <0.001).

Regarding clinical features (Table 3), patients with pre-hospital antibiotic treatment were more likely to report cough, headache and arthromyalgias and less likely to present fever at admission. In addition, they also presented lower rates of impaired consciousness, tachypnoea, tachycardia and septic shock. These patients were also less likely to be classified into high-risk PSI and CURB-65 classes. Laboratory data showed that patients in the pre-hospital antibiotic treatment group had less leucocytosis.

TABLE 1. Demographic features in patients with and without pre-hospital antibiotic treatment

	Without pre-hospital antibiotics *n* = 1803 (%)	With pre-hospital antibiotics *n* = 376 (%)	p value	β-Lactams *n* = 233 (%)	Quinolones *n* = 90 (%)	Macrolides *n* = 29 (%)
Age, median (IQR), years	69 (55–78)	64 (51–76)	0.005	62 (48–77)[a]	68 (54.5–75.5)	58 (46–73)
≥65 years old	1104 (61.2)	198 (52.7)	0.002	122 (52.4)[a]	51 (56.7)	13 (44.8)
Male sex	1246 (69.1)	247 (65.7)	0.19	153 (65.7)	61 (67.8)	17 (58.6)
Current Smoker	501 (27.9)	96 (25.6)	0.36	62 (26.7)	18 (20.0)	8 (27.6)
Alcohol abuse	324 (18.0)	52 (13.9)	0.05	31 (13.4)	13 (14.6)	8 (27.6)
Influenza vaccine	872 (52.6)	173 (50.4)	0.47	107 (50.2)	41 (50.0)	13 (50)
Pneumococcal vaccine	375 (23.6)	78 (23.4)	0.94	46 (22.2)	19 (23.8)	6 (24)
Comorbid conditions	1376 (76.4)	265 (70.5)	0.01	165 (70.8)	61 (67.8)	22 (75.9)
COPD	542 (30.1)	106 (28.2)	0.47	59 (25.3)	33 (36.7)	8 (27.6)
Diabetes mellitus	413 (22.9)	65 (17.3)	0.01	40 (17.2)	17 (18.9)	5 (17.2)
Chronic heart disease	414 (23.0)	71 (18.9)	0.08	49 (21.1)	12 (13.3)	5 (17.2)
Chronic renal disease	177 (9.8)	31 (8.2)	0.34	21 (9.0)	7 (7.8)	3 (10.3)
Chronic liver disease	132 (7.3)	23 (6.1)	0.40	9 (3.9)	8 (8.9)	3 (10.3)

COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
Data are number and % unless otherwise indicated.
[a]A p value <0.05 was considered statistically significant. Bonferroni correction was used to adjust the significance levels for individual antibiotics ($\alpha = 0.016$).

TABLE 2. Causative organisms in patients with and without pre-hospital antibiotic treatmenta

	Without pre-hospital antibiotics *n* = 1803 (%)	With pre-hospital antibiotics *n* = 376 (%)	p value	*β*-Lactams *n* = 233 (%)	Quinolones *n* = 90 (%)	Macrolides *n* = 29 (%)
Streptococcus pneumoniae[b]	822 (45.6)	92 (24.5)	<0.0001	41 (17.6)[c]	30 (33.3)	11 (37.9)
Legionella pneumophila	68 (3.8)	34 (9.0)	<0.0001	27 (11.6)[c]	2 (2.2)	4 (13.8)
Haemophilus influenzae[b]	93 (5.2)	10 (2.7)	0.03	4 (1.7)	2 (2.2)	3 (10.3)
Aspiration pneumonia[d]	96 (5.3)	19 (5.1)	0.83	15 (6.4)	4 (4.4)	0 (0)
Gram-negative bacilli	37 (2.1)	9 (2.4)	0.67	4 (1.7)	4 (4.4)	0 (0)
Pseudomonas aeruginosa	26 (1.4)	7 (1.9)	0.54	2 (0.9)	4 (4.4)	0 (0)
Atypical agents[e]	56 (3.1)	14 (3.7)	0.53	13 (5.6)	1 (1.1)	0 (0)
Virus	75 (4.2)	12 (3.2)	0.38	6 (2.6)	3 (3.3)	2 (6.9)
Influenza A (H1N1)pdm09	68 (3.8)	10 (2.7)	0.36	5 (2.1)	2 (2.2)	2 (6.9)
Mixed aetiology[f]	101 (5.6)	7 (1.9)	0.002	3 (1.3)[c]	2 (2.2)	1 (3.4)
No pathogen identified	578 (32.1)	180 (47.9)	<0.0001	120 (51.5)[c]	41 (45.6)[c]	9 (31.0)

Data are number and % unless otherwise indicated.
[a]Sputum cultures were performed in 826 patients (37.9%), blood cultures in 1902 (87.3%), pleural effusion cultures in 158 (7.2%), pneumococcal urinary antigen test in 1882 (86.4%), *L. pneumophila* Serogroup 1 antigen in urine in 1133 (52%) and serology in 546 (25.1%).
[b]Oral penicillin resistance and erythromycin resistance rates were more frequently documented in patients who had received pre-hospital antibiotic treatment (9.8% versus 25%, p 0.04 and 14.8% versus 40%, p 0.008; respectively). Among *H. influenzae* strains, no significant differences in the prevalence of *β*-lactamase production were detected between groups.
[c]Bonferroni correction was used to adjust the significance levels for individual antibiotics ($\alpha = 0.016$).
[d]Aspiration pneumonia was diagnosed on a clinical and radiological basis in patients who had risk factors such as compromised consciousness, altered gag reflex, dysphagia, severe periodontal disease, putrid sputum and radiographic evidence of involvement of a dependent pulmonary segment or necrotizing pneumonia.
[e]*Mycoplasma pneumoniae*, *Chlamydophila psittacci*, *Chlamydophila pneumoniae*, *Coxiella burnetii*.
[f]Mixed aetiology was defined as community-acquired pneumonia due to more than one pathogen.

TABLE 3. Clinical features at admission in patients with and without pre-hospital antibiotic treatment

	Without pre-hospital antibiotics *n* = 1803 (%)	With pre-hospital antibiotics *n* = 376 (%)	p value	*β*-Lactams *n* = 233 (%)	Quinolones *n* = 90 (%)	Macrolides *n* = 29 (%)
Headache	258 (14.3)	84 (22.3)	<0.0001	56 (24.0)[a]	20 (22.2)	4 (13.8)
Arthralgias	383 (21.3)	97 (25.8)	0.05	58 (24.9)	19 (21.1)	9 (31.0)
Cough	1505 (83.7)	340 (90.4)	0.001	208 (89.3)	81 (90.0)	28 (96.6)
Purulent sputum	761 (44.8)	172 (48.3)	0.22	104 (47.9)	40 (46.0)	15 (53.6)
Pleuritic chest pain	768 (42.6)	157 (42.0)	0.81	92 (39.7)	51 (56.7)[a]	7 (25.0)
Fever	774 (43.4)	125 (33.6)	0.001	76 (32.8)[a]	29 (32.6)	10 (37.0)
Tachycardia (heart rate ≥100)	917 (51.2)	151 (40.7)	<0.0001	90 (39.9)[a]	39 (43.3)	13 (46.4)
Tachypnoea (respiratory rate ≥30)	721 (46.4)	116 (37.4)	0.004	64 (33.5)[a]	30 (40.5)	12 (50.0)
Impaired consciousness	251 (13.9)	32 (8.5)	0.004	17 (7.3)[a]	9 (10.0)	3 (10.3)
Septic shock	198 (11.0)	16 (4.3)	<0.0001	8 (3.4)[a]	5 (5.6)	1 (3.4)
Pleural effusion	318 (17.7)	70 (18.6)	0.67	39 (16.7)	22 (24.4)	4 (13.8)
Multilobar pneumonia	563 (31.5)	128 (34.0)	0.32	86 (36.9)	21 (23.3)	11 (37.9)
Chest X-ray cavitation	23 (1.3)	13 (3.5)	0.003	8 (3.4)	4 (4.4)	0 (0)
Leucocytosis (white blood cell ≥12000)	1115 (61.9)	198 (52.7)	0.001	117 (50.2)[a]	56 (62.2)	14 (48.3)
Respiratory failure (PaO_2/FiO_2 <300)	870 (70.2)	167 (66.3)	0.22	109 (67.7)	35 (57.4)	13 (81.3)
PSI high risk classes[b]	1086 (60.3)	177 (47.1)	<0.0001	109 (46.8)[a]	40 (44.4)[a]	16 (55.2)
CURB-65 high risk classes[b]	1088 (63.4)	170 (47)	<0.0001	101 (47)[a]	47 (54)	13 (50)

PSI, pneumonia severity index.
Data are number and % unless otherwise indicated.
[a]A p value <0.05 was considered statistically significant. Bonferroni correction was used to adjust the significance levels for individual antibiotics ($\alpha = 0.016$).
[b]Patients were stratified into the following risk classes according to the PSI score: low risk (≤90 points, classes I, II, and III) and high risk (>90 points, classes IV and V). Patients were stratified into the following risk classes according to their CURB-65 score: low risk (0–1 point) and high risk (>1 point).

As detailed in Table 4, patients with pre-hospital antibiotic treatment were less likely to present complications during hospitalization or to require admission to the intensive care unit. Similarly, patients with pre-hospital antibiotic treatment had a shorter time to clinical stability, although there was no difference in length of hospital stay. There was a non-significant difference in mortality between study groups.

Propensity score analysis

The propensity score was generated using 13 variables (Table 5). With this model, 150 patients in the pre-hospital antibiotic group were matched to 416 patients in the other study group with a precision of five decimal points. *Legionella pneumophila* was more frequent in patients with pre-hospital antibiotic treatment and *S. pneumoniae* was less common

TABLE 4. Outcomes in patients with and without pre-hospital antibiotic treatment

	Without pre-hospital antibiotics *n* = 1803 (%)	With pre-hospital antibiotics *n* = 376 (%)	p value	β-Lactams *n* = 233 (%)	Quinolones *n* = 90 (%)	Macrolides *n* = 29 (%)
In-hospital complications	560 (31.2)	86 (22.9)	0.001	55 (23.6)	21 (23.6)	5 (17.2)
ICU admission	213 (11.9)	24 (6.4)	0.002	16 (6.9)	4 (4.5)	2 (6.8)
MV and/or NIMV	186 (10.5)	19 (5.1)	0.001	13 (5.7)	4 (4.5)	1 (3.6)
Length of intravenous therapy (days), median (IQR)	4 (2–7)	4 (2–7)	0.07	4 (2–7)	4 (2–8)	2.5 (2–4)
Time to clinical stability, median (IQR)	3 (2–6)	3 (2–5)	0.04	4 (2–5)	3 (1–6)	2 (1–4)
Length of hospital stay, median (IQR)	7 (5–11)	7 (5–10.5)	0.54	7 (6–10)	8.5 (5–12)	6 (5–7)[a]
Early case-fatality rate (≤72 h)	22 (1.2)	4 (1.1)	1	3 (1.3)	1 (1.1)	0 (0)
Overall case-fatality rate (≤30 days)	86 (4.8)	21 (5.6)	0.50	11 (4.7)	8 (8.9)	1 (3.4)

ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation; NIMV, non-invasive mechanical ventilation.
Data are number and % unless otherwise indicated.
[a]A p value of <0.05 was considered statistically significant. Bonferroni correction was used to adjust the significance levels for individual antibiotics ($\alpha = 0.016$).

TABLE 5. Logistic regression model for derivation of the propensity score

Variable	Coefficient	OR (95% CI)	p value
Age (>64 years old)	−0.397	0.67 (0.44–1.02)	0.06
Male sex	−0.070	0.93 (0.65–1.33)	0.69
Comorbidities	−0.224	0.79 (0.52–1.21)	0.29
Current smoker	−0.162	0.85 (0.55–1.30)	0.45
Alcohol abuser	−0.161	0.85 (0.52–1.37)	0.50
Seasonal influenza vaccination	0.251	1.28 (0.84–1.94)	0.23
Pneumococcal vaccination	0.010	1.01 (0.66–1.52)	0.96
Purulent sputum	0.093	1.09 (0.79–1.50)	0.56
Altered mental status at admission	−0.348	0.70 (0.38–1.30)	0.29
Septic shock at admission	−1.217	0.29 (0.11–0.74)	0.01
Tachycardia at admission	−0.471	0.62 (0.44–0.87)	0.006
Tachypnoea at admission	−0.331	0.71 (0.51–1.01)	0.05
Respiratory failure (Pao_2/Fio_2 <300) at admission	0.016	1.01 (0.71–1.44)	0.93

(p <0.001 and p <0.001, respectively). Patients with pre-hospital antibiotic treatment presented less fever (p 0.02), leucocytosis (p 0.001) and bacteraemia (p 0.01). The frequency of positive sputum culture was similar in the two groups (97 of 168 (44.2%) versus 19 of 43 (57.7%); p 0.11) as were the sensitivity and specificity of the pneumococcal urinary antigen test used for diagnosing pneumococcal pneumonia (85.2% versus 90.3% and 98.1% versus 99.1%, respectively) or bacteraemic pneumococcal pneumonia (78.5% versus 75% and 92% versus 100%). No significant differences in the *S. pneumoniae* resistance patterns were documented. Conversely, chest X-ray cavitation was more frequent in the pre-hospital antibiotic treatment group (p 0.04). No significant differences were found in the frequency of patients classified into high-risk CAP-specific scores, intensive care unit admission or 30-day mortality between study groups.

When the propensity score was entered into the multivariate models, the pre-hospital antibiotic use was not significantly associated with intensive care unit admission and 30-day mortality (OR 0.74, 95% CI 0.33–1.66 and OR 2.69, 95% CI 0.77–9.08, respectively).

Discussion

The demographic features of patients with pre-hospital antibiotic treatment in our cohort were similar to those previously reported: that is, these patients were significantly younger and had lower rates of comorbidity than the other group. These demographic differences are probably because clinicians reserve in-hospital treatment for older and more compromised patients. In addition, the current CAP severity scores used to assess the need for hospitalization attach great importance to age and the presence of comorbidities. These variables are an obstacle to obtaining valid results unless they and other confounding factors are carefully controlled. Significantly, previous studies have not studied the propensity for prescribing pre-hospital antibiotic therapy.

We compared the clinical picture of CAP at admission in patients who received and who did not receive pre-hospital antibiotic treatment. Although CAP occurs regularly in both groups, with purulent sputum, pleuritic pain and signs of consolidation, the groups present differences with regard to other clinical features. Patients who received pre-hospital antibiotic treatment presented more headache and arthralgias, and less fever at admission. Likewise, regarding radiographic findings, we found that patients with pre-hospital antibiotic treatment more frequently had chest X-ray cavitation. Previous studies offer little information on the clinical presentation of CAP in this context.

Moreover, we observed that patients receiving prior antibiotics were less likely to have fever and leucocytosis. Hence, it is plausible to think that prior use of antibiotics may lead to a blunted inflammatory response at admission. In this regard, in a cohort of CAP patients Krüger *et al.* [6] demonstrated that procalcitonin, C-reactive protein and white blood cell count are not good predictors of mortality in patients who have received pre-hospital antibiotic treatment. This finding suggests caution in interpreting the diagnostic and

predictive values of inflammatory markers in CAP patients with antibiotic treatment prior to hospital admission.

An important finding in our study was the difference in the frequency of causative organisms of CAP between the study groups. The prevalence of *L. pneumophila* was nearly three times higher in patients who received pre-hospital antibiotics, mainly β-lactams. Furthermore, we did not find differences in the proportion of other potentially resistant organisms, such as *Pseudomonas aeruginosa*, between the study groups. As expected, bacteraemia was less frequent in patients pre--treated with antibiotics and we also found a higher proportion of unknown aetiology in this group of patients. Interestingly, the frequency of positive sputum culture was comparable in the two groups. The sensitivity and specificity of the pneumococcal urinary antigen test for diagnosing pneumococcal pneumonia was also similar. Therefore, information on pre-hospital antibiotic treatment should always be recorded because it can guide the choice of aetiological diagnostic tests and the empirical antibiotic therapy to be used in patients with CAP. In fact, the current Infectious Diseases Society of America/American Thoracic Society guidelines provide recommendations for using aetiological evidence in this group of patients [1], although they are still to be validated.

In the propensity analysis, we did not find significant differences in prognosis between study groups. In contrast, Johnson *et al.* [15] found decreased in-hospital mortality associated with antibiotic treatment before hospitalization, while van de Garde *et al.* [7] and Marrie and Wu [16] showed increased in-hospital mortality in this group of patients. However, these studies did not control for confounding factors. Interestingly, we found that patients who required hospitalization after attempted outpatient treatment had a higher mortality rate than is normally expected in the outpatient setting [17].

The strengths of the current study include the prospective nature of the cohort, the large number of hospitalized patients with CAP, and the comprehensive data collection. In addition, this is the first study to perform a widespread analysis of the impact of pre-hospital admission antibiotic use on the clinical presentation and outcomes of CAP. We also performed a propensity analysis to control for confounding factors. Nevertheless, there are some limitations that should be acknowledged. First, the study was conducted at a single Spanish centre and we do not know whether the results can be extrapolated to other settings. Second, this is an observational study and we could not eliminate unmeasured confounders between study groups. Third, we were unable to verify outpatient diagnosis and time of antibiotic administration before hospitalization in all patients. Finally, because of the small sample size of patients who receive individual antibiotics, our data for these groups should be interpreted with caution.

In conclusion, after controlling for confounding factors in a propensity analysis, patients who received pre-hospital antibiotic treatment presented distinct clinical features from those who did not. In addition, the prevalence of *L. pneumophila* was nearly three times higher in patients who received pre-hospital antibiotics, mainly β-lactams. Bacteraemia was less frequent in patients pre-treated with antibiotics. No significant differences were found in the prognosis between study groups. Information about pre-hospital antibiotics use can help to guide the choice of aetiological diagnostic tests and the empirical antibiotic therapy to be used in patients with CAP.

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Author Contributions

DV, AFS, JC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript. Study concept and design: DV, AFS, JC. Acquisition of the data: DV, AFS, CG, SG, LM, JD. Analysis and interpretation of the data: DV, AFS, CG. Drafting of the manuscript DV, AFS, JC. Critical revision of the manuscript for important intellectual content: CG, SG, LM, JD. Statistical analysis: DV, AFS. Study supervision: JC.

Transparency Declaration

All authors have no conflicts of interest to disclose.

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6.3. Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia.

- Comparison of patients who received early antibiotic treatment (first antibiotic dose in the first 4 and 8 hours after admission) with those who received late treatment, both in CAP and HCAP groups.

- Impact of timing of antibiotic administration on 30-day mortality of patients with CAP and HCAP.

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Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia

A. Simonetti[1], D. Viasus[1], C. Garcia-Vidal[1], J. Adamuz[1], A. Roset[1], F. Manresa[2,3], J. Dorca[2,3], F. Gudiol[1,3] and J. Carratalà[1,3]

1) *Infectious Disease,* 2) *Respiratory Medicine Services, Institut d'Investigaciò Biomèdica de Bellvitge (IDIBELL), Hospital Universitari de Bellvitge and* 3) *Department of Clinical Science, Faculty of Medicine, University of Barcelona, Barcelona, Spain*

Abstract

The effects of antibiotic timing on outcomes of patients with community-acquired pneumonia (CAP) are controversial. Moreover, no information is available regarding this issue in healthcare-associated pneumonia (HCAP). We aimed to determine the impact of antibiotic timing on 30-day mortality of patients with CAP and HCAP. Non-immunocompromised adults admitted to hospital through the emergency department (ED) with community-onset pneumonia were prospectively observed from 2001 to 2009. Patients who received prior antibiotics were excluded. Of 1593 patients with pneumonia who were analyzed, 1274 had CAP and 319 HCAP. The mean time from patient arrival at the ED until antibiotic administration was 5.8 h (standard deviation (SD) 3.5) in CAP and 6.1 h (SD 3.8) in HCAP (p 0.30). Mortality was higher in patients with HCAP (5.5% vs. 13.5%; p <0.001). After adjusting for confounding factors in a logistic regression analysis, the antibiotic administration ≤4 h was not associated with decreased 30-day mortality in patients with CAP (odds ratio (OR) 1.12, 95% confidence interval (CI) 0.57–2.21) and in patients with HCAP (OR 0.59, 95% CI 0.19–1.83). Similarly, antibiotic administration ≤8 h was not associated with decreased 30-day mortality in CAP (OR 1.58, 95% CI 0.64–3.88) and HCAP patients (OR 0.59, 95% CI 0.19–1.83). In conclusion, antibiotic administration within 4 or 8 h of arrival at the ED did not improve 30-day survival in hospitalized adults for CAP or HCAP.

Keywords: Antibiotic timing, community-acquired pneumonia, healthcare-associated pneumonia, mortality, risk factors
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Corresponding author: Dr D. Viasus, Service of Infectious Diseases, Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain
E-mail: dfviasusp@unal.edu.co

Introduction

Community-acquired pneumonia (CAP) continues to be an important public health problem worldwide with a mortality rate between 8% and 15% in hospitalized patients [1–3]. In recent years there have been significant changes in the management of CAP due to the availability of new diagnostic tests, the publication of research that helps in selecting the most appropriate initial site of care [4,5], and new recommendations on the duration of antibiotic therapy [6]. Despite these changes, however, mortality in patients with CAP remains high and has barely improved since antimicrobials were first introduced in the 1940s [7].

The timing of the first dose of antibiotics remains a controversial point in the management of CAP. Although early administration of appropriate treatment has been correlated with a better prognosis in some infections [8], this relationship is not clear in patients with CAP [9–19]. While some studies do show a lower mortality with early administration of antibiotics [10,13,15], the benefit that would be expected with early treatment can be offset by an increased misdiagnosis of CAP, an overuse of antibiotics and misprioritization of patients [9,12,17,20]. Thus, although the 2003 IDSA guidelines recommended early treatment of CAP (≤4 h) [21],

more recent guidelines do not state a specific time window for delivery of the first antibiotic dose and merely suggest it be given in the emergency department (ED) [6]. Similar recommendations have been reported in guidelines from other geographical areas [20,22].

Healthcare-associated pneumonia (HCAP) has recently been recognized as a new category of respiratory infection that appears to merit a distinct approach to CAP [23–26]. The available data indicate that patients with HCAP are older, have more comorbidities, are more likely to have pneumonia caused by antibiotic-resistant organisms, and have higher mortality [23–26]. At present, however, no information is available regarding the effects of the timing of antibiotic administration on outcomes in HCAP patients. Thus, the current guidelines for the management of adult patients with HCAP do not address this issue [27,28].

The present prospective study of a large cohort of hospitalized patients with community-onset pneumonia was carried out to determine the impact of timing of antibiotic administration on 30-day mortality of patients with CAP and HCAP.

Materials and Methods

Setting, patients and study design

The study was performed in an 800-bed university hospital for adults in Barcelona, serving an area of 900 000 inhabitants. All non-immunocompromised patients hospitalized through the emergency department (ED) with community-onset pneumonia between 1 January 2001 and 31 October 2009 were analyzed. Cases were identified at the ED by the attending physicians and/or study investigators. Data on all patients were prospectively recorded using a computer-assisted protocol. Patients who received prehospital antibiotics were excluded. The study was approved by the hospital Institutional Review Board and informed consent was obtained from patients.

For the purpose of the present study, patients were divided into two groups: patients with CAP and patients with HCAP. Timing of antibiotic administration was measured in hours and represented the difference between the time of arrival at the ED and the recorded time of initial antibiotic administration by nursing staff. Patients who received the first antibiotic dose within either 4 or 8 h of arrival at the ED (two cut-off points, referred as to 'early treatment') were compared with those who received antibiotics >4 or >8 h after arrival at the ED ('late treatment'). Four and eight hours were chosen as the cut-off points so as to be consistent with previous studies [10,13,15,18].

Clinical assessment and follow-up

At the initial visit and before starting empirical antibiotic therapy, patients underwent a physical examination and a full clinical history was taken. They were then seen daily during their hospital stay by one or more of the investigators. Data were collected on demographic characteristics, comorbidities, causative organisms, antibiotic susceptibilities, biochemical analysis, empirical antibiotic therapy and outcomes, including 30-day mortality.

Two sets of blood samples were obtained and cultured and, when available, a sputum sample was also evaluated by use of Gram staining and culture. Urinary antigen detection tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed if indicated by the attending physician. Paired serum samples during the acute and convalescent phases of infection (separated by a 3–8-week interval) were also obtained for serological studies.

Antibiotic therapy was initiated in the emergency department in accordance with the hospital guidelines, which recommend the administration of a β-lactam (ceftriaxone sodium or amoxicillin/clavulanate potassium) with or without macrolide or levofloxacin. Combination therapy was recommended for patients with clinical suspicion of a Legionella species or an atypical pathogen, or in the absence of a demonstrative finding on sputum Gram stain results. Levofloxacin was recommended for patients with a urine antigen test result that was positive for *L. pneumophila* serogroup 1. Combined amoxicillin/clavulanate was recommended for patients with clinical suspicion of aspiration pneumonia.

Definitions

Pneumonia was defined as an acute illness associated with one or more of the following signs and symptoms: new cough with or without sputum production, pleuritic chest pain, dyspnea, fever or hypothermia, altered breath sounds on auscultation, leukocytosis, and the presence of a new infiltrate on a chest radiograph. HCAP included any patient who fulfilled any of the following [23]: (i) received any home health care, received intravenous therapy at home, received wound care or specialized nursing care through a healthcare agency, family or friends, or had self-administered intravenous medical therapy in the 30 days before pneumonia; (ii) attended a hospital or haemodialysis clinic or received intravenous chemotherapy in the 30 days before pneumonia; (iii) were admitted to an acute care hospital for two or more days in the 90 days before pneumonia; and (iv) currently residing in a nursing home or long-term care facility.

Comorbidity was defined as the presence of one of the following previously diagnosed diseases: chronic lung disease, chronic heart disease, chronic renal disease, chronic liver

disease, chronic cognitive deficit, cerebrovascular disease, malignancy or diabetes mellitus. Patients in risk classes IV or V of the Pneumonia Severity Index (PSI) were considered to be more severely ill [5]. The diagnosis of septic shock was based on the ACCP/SCCM Consensus Conference Committee [29]. Initial inappropriate empirical therapy was defined as the absence of antimicrobial therapy for a specific type of organism or administration of an antibiotic to which the isolated organism was resistant. The appropriateness of antibiotic therapy was analyzed for all cases with an aetiological diagnosis according to susceptibility test criteria. Patients with aspiration pneumonia who had not received anaerobic coverage (i.e. amoxicillin-clavulanate) were considered to have received inappropriate empirical antibiotic therapy. Aspiration pneumonia was diagnosed as described elsewhere [30].

The primary study outcome was 30-day mortality, defined as death due to any cause ≤30 days after hospitalization. Mortality was ascertained by patients follow-up.

Statistical analysis

Time from arrival at the ED to antibacterial administration was the independent variable. The characteristics of patients who received early treatment were compared with those of the late-treatment group. All proportions were calculated as percentages of the patients with available data. To detect significant differences between groups, we used the chi-square test or Fisher exact test for categorical variables and the Student *t*-test or Mann–Whitney *U*-test for continuous variables, as appropriate. The multivariate logistic regression analysis of factors potentially associated with 30-day mortality included the clinical and significant variables in the univariate analysis and the timing of antibacterial administration and inappropriate empirical antibiotic therapy, regardless of whether the latter were significant or not. We restricted the number of variables included in the multivariable models following the rule of at least five to nine events (deaths) per variable [31]. The discriminatory power of the logistic model was evaluated by the area under the receiver operating characteristic (ROC) curve and the goodness-of-fit according to the Hosmer–Lemeshow test. The analyses were performed using SPSS (version 15.0, Chicago, IL, USA). Statistical significance was set at $p < 0.05$. All reported p values are two-tailed.

Results

Of the 1883 non-immunocompromised patients hospitalized with community-onset pneumonia during the study period, we excluded from the analyses those who had received prehospital antibiotics ($n = 290$). The study sample comprised the remaining 1593 patients, of whom 1274 (80%) had CAP and 319 (20%) had HCAP. Overall, the mean time from patient arrival at the ED until administration of the first dose of antibiotics was 5.9 h (standard deviation (SD) 3.6 h). Among study groups, the mean time from patient arrival at the ED until antibiotic administration was 5.8 h (SD 3.5) in CAP and 6.1 h (SD 3.8) in HCAP (p 0.30). Eighty-six patients (27%) in the HCAP group had been admitted to an acute care hospital for 2 or more days in the 90 days before pneumonia; 139 (43.6%) attended a hospital or a haemodialysis clinic or received intravenous chemotherapy in the 30 days before pneumonia; 108 (33.9%) resided in a nursing home or a long-term care facility; and 21 (6.6%) received home healthcare. A total of 113 (7.1%) patients died within 30 days of hospitalization. The baseline characteristics of patients with CAP and HCAP are detailed in Table S1 (see description and table in the supplementary online file).

When comparing patients who received early (≤4 or ≤8 h) antibiotic treatment with those who received late (>4 or >8 h) treatment there were no significant differences in the main demographic characteristics of the CAP and HCAP groups (Tables 1 and S2). Regarding the clinical features at admission, patients receiving early treatment (mainly ≤4 h) had significantly greater illness severity at admission: they were more likely to present altered mental status, septic shock and multilobar infiltrates on chest X-ray. By contrast, there were no differences as regards aetiology. In addition, patients with CAP who were given early treatment (≤4 h) were more likely to require intensive care unit (ICU) admission and they also had higher 30-day mortality.

Table 2 details the factors associated with 30-day mortality in patients with CAP and HCAP, respectively. Advanced age, altered mental status, septic shock, bacteraemia and high-risk PSI classes were more common in patients who died in both pneumonia groups.

After adjustment for age, sex, comorbidities, initial inappropriate empirical therapy and illness severity, the timing of the first dose of antibiotics (4 or 8 h) had no impact on mortality in CAP patients (Table 3). The p-value of the Hosmer–Lemeshow statistic for goodness-of-fit was 0.45.

The multivariate logistic regression analysis for factors associated with 30-day mortality in HCAP patients is shown in Table 4. The timing of antibiotic administration (≤4 and ≤8 h) was not associated with decreased 30-day mortality in patients with HCAP. The p-value of the Hosmer–Lemeshow statistic for goodness-of-fit was 0.28.

TABLE 1. Characteristics of patients hospitalized for CAP and HCAP and classified into early and late treatment groups (≤4 vs. >4 h)

Characteristics	CAP (*n* = 1274)			HCAP (*n* = 319)		
	≤4 h (*n* = 477)	>4 h (*n* = 797)	p	≤4 h (*n* = 116)	>4 h (*n* = 203)	p
Demographic features						
Age (>64 years old)	271 (56.9)	466 (58.5)	0.56	89 (76.7)	155 (76.4)	0.94
Male sex	327 (68.6)	548 (68.8)	0.93	76 (65.5)	125 (61.6)	0.48
Underlying disease	343 (71.9)	584 (73.3)	0.59	112 (96.6)	182 (89.7)	0.02
Current/former smoker	265 (56)	481 (60.6)	0.11	64 (55.7)	105 (52.2)	0.55
Alcohol abuse	82 (17.3)	150 (18.9)	0.47	15 (13)	26 (12.9)	0.97
Seasonal influenza vaccination (<1 year)	210 (49.3)	328 (45.1)	0.17	67 (67.7)	111 (64.9)	0.64
Clinical features at hospital admission						
Altered mental status	69 (14.5)	93 (11.7)	0.14	38 (33)	45 (22.2)	0.03
Septic shock	50 (10.5)	59 (7.4)	0.05	21 (18.3)	22 (10.8)	0.06
Multilobar pneumonia	173 (36.5)	245 (31.1)	0.04	49 (42.2)	64 (32)	0.06
Pleural effusion	77 (16.3)	143 (18)	0.42	14 (12.1)	35 (17.3)	0.21
Bacteraemia	65 (15.1)	99 (13.5)	0.43	12 (12.4)	26 (14.7)	0.59
High-risk PSI classes[a]	277 (58.2)	435 (54.7)	0.22	95 (81.9)	156 (76.8)	0.28
Aetiology						
Streptococcus pneumoniae	209 (43.8)	315 (39.5)	0.13	40 (34.5)	74 (36.5)	0.72
Legionella pneumophila	38 (8.0)	57 (7.2)	0.59	1 (0.9)	7 (3.4)	0.15
Aspiration pneumonia	25 (5.2)	43 (5.4)	0.90	27 (23.3)	28 (13.8)	0.03
Initial antibiotic therapy						
β-lactam monotherapy	191 (40)	331 (41.5)	0.60	61 (52.6)	106 (52.2)	0.94
Levofloxacin monotherapy	78 (16.4)	158 (19.8)	0.12	8 (6.9)	20 (9.9)	0.36
Combination therapy[b]	202 (42.3)	37.5 (.08)		45 (38.8)	76 (37.4)	0.81
Inappropriate antibiotic therapy	18 (5.8)	29 (5.7)	0.99	8 (10.4)	13 (9.8)	0.90
Outcomes						
ICU admission	64 (13.5)	64 (8.1)	0.002	11 (9.5)	12 (5.9)	0.23
30-day mortality	33 (6.9)	37 (4.6)	0.08	20 (17.2)	23 (11.3)	0.13

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; ICU, intensive care unit. Data are presented as *n* (%).
[a]Patients were stratified into the following risk classes according to the PSI score: low risk (≤90 points, classes I, II and III) and high risk (>90 points, classes IV and V).
[b]β-lactam plus levofloxacin.

TABLE 2. Factors associated with 30-day mortality in hospitalized patients with CAP and HCAP: univariate analysis

Characteristics	CAP (*n* = 1274)			HCAP (*n* = 319)		
	Alive (*n* = 1204)	Death (*n* = 70)	p Value	Alive (*n* = 276)	Death (*n* = 43)	p Value
Demographic features						
Age (>64 years old)	679 (56.4)	58 (82.9)	<0.001	203 (73.6)	41 (95.3)	0.002
Male sex	826 (68.6)	49 (70)	0.80	174 (63)	27 (62.8)	0.97
Underlying disease	871 (72.3)	56 (80)	0.16	252 (91.3)	42 (97.7)	0.14
Current/former smoker	711 (59.3)	35 (51.5)	0.20	149 (54.4)	20 (47.6)	0.41
Alcohol abuse	224 (18.6)	8 (11.8)	0.15	39 (14.2)	2 (4.8)	0.08
Seasonal influenza vaccination (<1 year)	519 (46.6)	19 (47.5)	0.91	162 (67.2)	16 (55.2)	0.19
Clinical features at hospital admission						
Altered mental status	138 (11.5)	24 (34.3)	<0.001	59 (21.4)	24 (57.1)	<0.001
Septic shock	85 (7.1)	24 (34.3)	<0.001	32 (11.6)	11 (26.2)	0.01
Multilobar pneumonia	383 (32.1)	35 (51.5)	0.001	93 (34.1)	20 (46.5)	0.11
Pleural effusion	206 (17.2)	14 (20.6)	0.47	45 (16.4)	4 (9.3)	0.23
Bacteraemia	139 (12.6)	25 (37.9)	<0.001	28 (11.7)	10 (28.6)	0.007
High-risk PSI classes[a]	645 (53.7)	67 (95.7)	<0.001	209 (75.7)	42 (97.7)	0.001
Inappropriate antibiotic therapy	40 (5.2)	3 (5.5)	1	18 (10.1)	2 (6.5)	0.74
Timing of antibiotic administration						
≤4 h	444 (36.9)	33 (47.1)	0.08	96 (34.8)	20 (46.5)	0.13
≤8 h	972 (80.7)	58 (82.9)	0.66	213 (77.2)	31 (72.1)	0.46

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; PSI, pneumonia severity index. Data are presented as *n* (%).
[a]Patients were stratified into the following risk classes according to the PSI score: low risk (≤90 points, classes I, II and III) and high risk (>90 points, classes IV and V).

Discussion

This prospective study of a large cohort of non-immunocompromised adult patients hospitalized with community-onset pneumonia shows that antibiotic administration within 4 or 8 h of arrival at the ED did not improve 30-day survival in hospitalized adults for CAP or HCAP.

Our finding that the timing of the first dose of antibiotics (≤4 or ≤8 h) was not associated with 30-day mortality in patients with CAP differs from the results reported by Houck *et al.* [15]. These investigators found that patients who received early treatment (≤4 h) had lower hospital mortality, lower 30-day mortality and a shorter length of hospital stay. However, it should be noted that this was a retrospective study based on an analysis of medical records and discharge

TABLE 3. Factors associated with 30-day mortality in hospitalized patients with CAP: multivariate analysis

Characteristics	Odds ratio	(95% confidence interval)	p value
Age (>64 years old)	4.38	(1.95–9.94)	<0.001
Male sex	0.70	(0.35–1.39)	0.31
Underlying disease	1.01	(0.43–2.37)	0.96
Altered mental status	2.55	(1.31–4.96)	0.005
Septic shock	4.93	(2.44–9.94)	<0.001
Multilobar pneumonia	1.74	(0.91–3.31)	0.08
Bacteraemia	3.13	(1.63–6.03)	<0.001
Inappropriate antibiotic therapy	0.78	(0.16–3.75)	0.76
Early antibacterial treatment (≤8 h)[a]	1.58	(0.64–3.88)	0.31

CAP, community-acquired pneumonia.
[a]Early antibacterial treatment (≤4 h), OR 1.12, 95% CI 0.38–3.33; p 0.82.

TABLE 4. Factors associated with 30-day mortality in hospitalized patients with HCAP: multivariate analysis

Characteristics	Odds ratio	95% confidence interval	p value
Age (>64 years old)	15.0	(1.50–149.3)	0.02
Altered mental status	7.69	(2.79–21.1)	<0.001
Septic shock	1.57	(0.45–5.40)	0.47
Bacteraemia	4.85	(1.54–15.2)	0.007
Inappropriate antibiotic therapy	0.25	(0.02–2.59)	0.25
Early antibacterial treatment (≤8 h)[a]	0.59	(0.19–1.83)	0.36

HCAP, healthcare-associated pneumonia.
[a]Early antibacterial treatment (≤4 h), OR 1.12, 95% CI 0.38–3.33; p 0.72.

diagnoses, with the study population including patients from a long-term care/skilled nursing setting and being limited to patients aged 65 years. Furthermore, they found that patients who received antibiotics in the first 2 h died more frequently than did those with later antibiotic administration, but it disappeared under multivariate analysis. Interestingly, our results similarly show that patients with CAP who received early treatment (mainly ≤4 h) were more likely to require ICU admission and had higher 30-day mortality. However, these patients had more severe clinical features at hospital admission (septic shock and multilobar pneumonia), which indirectly indicates that in the ED context the more serious patients are usually treated as a priority [12,16]. In addition, Dedier *et al.* [32] and Cheng *et al.* [14] observed a strong relationship between pneumonia severity on admission as measured by the PSI, and earlier antibiotic administration. Other studies have also found that lower 30-day mortality [13] and shorter length of hospital stay [10] are associated with antibiotic administration within 8 h of hospital arrival in patients with pneumonia. However, these were also retrospective studies that included patients from a nursing home, and one of them [13] was limited to patients aged 65 years.

Our results are, however, consistent with other published studies [11,18,19]. Moreover, Yu and Wyer [18] conducted a systematic review of 13 observational studies to assess the impact of antibiotic timing on outcomes of patients with CAP. They identified four groups of studies according to their methodological quality (inclusion criteria, prospective or retrospective design, exclusion of patients treated prior to hospital admission and the use of a validated severity score), but reported that evidence from observational studies fails to confirm decreased mortality with early antibiotic administration in stable patients with CAP.

Significantly, previous studies evaluating the effect of delay in the administration of antibiotics in patients with pneumonia have not differentiated between CAP and HCAP [10,13,15]. Thus, no information is available regarding the effects of antibiotic timing on outcomes in patients with HCAP. Therefore, the current guidelines for the management of adult patients with HCAP do not address this point [27,28]. Importantly, we did not find significant differences in the mean time from patient arrival at the ED until antibiotic administration between CAP and HCAP patients. However, our results suggest that early administration of antibiotics (≤4 or ≤8 h) is not associated with a decrease in 30-day mortality in HCAP patients. Interestingly, it was also recently reported that guideline-concordant HCAP antibiotic therapy was not associated with improved 30-day mortality for non-critically-ill HCAP patients in the USA [33].

The strength of our study lies in the prospective collection of data from a large number of patients. In addition, we performed a detailed evaluation of the clinical features of patients with CAP and HCAP according to the time from arrival at the ED to antibiotic administration. Similarly, to our knowledge this is the first study of its kind that includes patients with HCAP. Finally, we controlled for confounding factors related to mortality in our multivariate analysis. However, as the study is observational it is unable to avoid residual confounding. In this regard, we did not control for patients with treatment limitations. In addition, sample size calculation was not performed previous to the study. Similarly, because of the relatively small sample size of patients who died in HCAP patients, our data should be interpreted with caution and need further validation.

In conclusion, antibiotic administration within 4 or 8 h of arrival at the ED did not improve 30-day survival in hospitalized adults for CAP or HCAP.

Transparency Declaration

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics (by study groups) of 1593 patients hospitalized for community-onset pneumonia.

Table S2. Characteristics of patients hospitalized for CAP and HCAP and classified into early and late treatment groups (≤8 hours vs. >8 hours).

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6.4. Impact of antibiotic de-escalation on clinical outcomes in pneumococcal pneumonia.

- Frequency and characteristics of antibiotic de-escalation in hospitalised patients with pneumococcal community-acquired pneumonia.

- Impact of antibiotic de-escalation on clinical outcomes in patients with community acquired pneumococcal pneumonia.

- Impact of antibiotic de-escalation in patients classified into high-risk pneumonia severity index classes (IV–V), clinically unstable patients and those with bacteraemia.

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Impact of antibiotic de-escalation on clinical outcomes in community-acquired pneumococcal pneumonia

Diego Viasus[1]*, Antonella F. Simonetti[2], Carolina Garcia-Vidal[2,3], Jordi Niubó[4,5], Jordi Dorca[5,6] and Jordi Carratalà[2,3,5]

[1]Health Sciences Division, Faculty of Medicine, Hospital Universidad del Norte and Universidad del Norte, Barranquilla, Colombia; [2]Infectious Disease Department, Hospital Universitari de Bellvitge – IDIBELL, Barcelona, Spain; [3]Spanish Network for Research in Infectious Diseases (REIPI), Sevilla, Spain; [4]Microbiology Department, Hospital Universitari de Bellvitge – IDIBELL, Barcelona, Spain; [5]Clinical Science Department, Faculty of Medicine, University of Barcelona, Barcelona, Spain; [6]Respiratory Medicine Department, Hospital Universitari de Bellvitge – IDIBELL, Barcelona, Spain

*Corresponding author. Tel: (+57)-(5)-3509509; E-mail: dviasus@uninorte.edu.co

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Background: Although antibiotic de-escalation is regarded as a measure that reduces selection pressure, adverse drug effects and costs, evidence supporting this practice in community-acquired pneumococcal pneumonia (CAPP) is lacking.

Methods: We carried out a retrospective analysis of prospectively collected data of a cohort of hospitalized adults with CAPP. Pneumococcal aetiology was established in patients with one or more positive cultures for *Streptococcus pneumoniae* obtained from blood, sterile fluids or sputum, and/or a positive urinary antigen test. De-escalation therapy was considered when the initial antibiotic therapy was narrowed to penicillin, amoxicillin or amoxicillin/clavulanate within the first 72 h after admission. The primary outcomes were 30 day mortality and length of hospital stay (LOS). Adjustment for confounders was performed with multivariate and propensity score analyses.

Results: Of 1410 episodes of CAPP, antibiotic de-escalation within the first 72 h after admission was performed in 166 cases. After adjustment, antibiotic de-escalation was not associated with a higher risk of mortality (OR=0.83, 95% CI=0.24–2.81), but it was found to be a protective factor for prolonged LOS (above the median) (OR=0.46, 95% CI=0.30–0.70). Similar results were found in patients classified into high-risk pneumonia severity index classes (IV–V), those with clinical instability and those with bacteraemia. No significant differences were documented in adverse drug reactions or readmission (<30 days).

Conclusions: Antibiotic de-escalation seems to be safe and effective in reducing the duration of LOS, and did not adversely affect outcomes of patients with CAPP, even those with bacteraemia and severe disease, and those who were clinically unstable.

Introduction

Community-acquired pneumonia (CAP) is an important public health problem worldwide. Despite continuing improvements in aetiological diagnosis, effective antibiotic treatment and advances in supportive care, mortality rates in patients with CAP remain high.[1,2] The most common causative bacterial pathogen of CAP is *Streptococcus pneumoniae*, which also is the most frequent aetiology associated with death in CAP patients.[1–4]

Broad empirical coverage in CAP is recommended by current guidelines to cover the most frequent aetiologies.[1,5] The same CAP guidelines encourage attempts to broaden, narrow or completely modify the spectrum of antibiotic therapy on the basis of diagnostic test results. Traditional microbiological investigations in CAP include good-quality sputum and blood cultures. Rapid tests based on urinary detection of pneumococcal and *Legionella* antigens and nucleic acid amplification techniques, which provide early diagnosis and allow prompt appropriate antibiotic treatment, are increasingly used today.[6,7]

In recent years, antibacterial resistance has been accelerating at an alarming pace, leading to a global increase in morbidity and mortality.[8,9] It is recognized that antimicrobial stewardship must be a key component of attempts to reduce costs and adverse drug events and to deal with the threat of antibiotic resistance.[6,10] A variety of strategies may be utilized in stewardship programmes to optimize the management of CAP and improve patient outcomes.[11,12] These include a rational use of antibiotic de-escalation, administering an appropriate pathogen-focused agent or narrowing empirical therapy. In this regard, a recent study reported that de-escalation therapy among bacteraemic

patients with CAP, mainly due to *S. pneumoniae*, non-fermenters and Enterobacteriaceae Gram-negative bacteria, was not associated with an increased risk of 30 day mortality.[13] However, many aspects are still to be defined, such as the effect of de-escalation therapy on other important CAP clinical outcomes including length of hospital stay (LOS), adverse events and readmission rates, and in the case of patients with severe disease.

The aims of our study were to assess the impact of antibiotic de-escalation on clinical outcomes in patients with community-acquired pneumococcal pneumonia (CAPP). We also specifically evaluated the de-escalation impact in patients classified into high-risk pneumonia severity index (PSI) classes (IV–V), clinically unstable patients and those with bacteraemia.

Methods

Study design

This study was conducted at Hospital Universitari de Bellvitge – IDIBELL, a 700 bed public hospital in Barcelona, Spain. All adult patients admitted to hospital with CAPP via the emergency department from 1 February 1995 to 31 December 2014 were prospectively followed-up. Patients who died within the first 72 h after hospital admission and those who had already received penicillin, amoxicillin or amoxicillin/clavulanate were excluded.

At hospital admission, patients underwent a complete clinical history and physical examination. Microbiological studies included two sets of blood cultures and sputum Gram's stain and culture when available. Urinary antigen detection for *S. pneumoniae* was performed if indicated by the attending doctor. Patients were stratified into risk classes by the PSI score, as described elsewhere.[14] They were seen daily during their hospital stay by one or more of the investigators who recorded clinical, laboratory and microbiological data in a computer-assisted protocol.

Empirical antibiotic treatment was applied according to hospital guidelines, which recommend the administration of a β-lactam agent (ceftriaxone or amoxicillin/clavulanate) with or without a macrolide or a fluoroquinolone. Combination treatment was recommended for patients with clinical suspicion of *Legionella* or an atypical pathogen, or in the case of severe pneumonia in the absence of a demonstrative sputum Gram's stain. There was no official hospital policy concerning de-escalation.

Definitions

CAPP was diagnosed as described elsewhere.[4] Briefly, patients with signs and symptoms of acute-onset respiratory tract infection, new infiltrate on chest X-ray, one or more cultures positive for *S. pneumoniae* obtained from blood, normally sterile fluids or sputum, and/or a positive urinary antigen test were diagnosed with CAPP. *S. pneumoniae* was identified using standard microbiology procedures. From 2000 onwards, urinary antigen detection using a rapid immunochromatographic assay (Binax Now, Binax, Portland, ME, USA) for *S. pneumoniae* was also available. Clinical stability was defined when the patient met the following objective criteria: ability to maintain oral intake; stable vital signs (considered as temperature $<37.8^{\circ}$C, respiratory frequency <24 breaths/min, systolic blood pressure 90 mm Hg without vasopressor support); absence of exacerbated major comorbidities (i.e. heart failure, chronic obstructive pulmonary disease) and/or septic metastases, baseline mental status, and adequate oxygenation on room air (PaO_2 60 mm Hg or pulse oximetry 90%). For patients with chronic hypoxemia or receiving chronic oxygen therapy, PaO_2 or pulse oximetry measurement had to be similar to their baseline values.[15]

For the purposes of this study patients were divided into two groups: those with treatment de-escalation and those without treatment de-escalation within 72 h of hospital admission (henceforth 'de-escalation group' and 'non-de-escalation group'). De-escalation was considered when the initial antimicrobial spectrum was narrowed to penicillin, amoxicillin or amoxicillin/clavulanate within 72 h of hospital admission, by which time the microbiological test results were usually known.

The primary outcome measures were 30 day mortality and LOS. Thirty day mortality was defined as death due to any cause during $\leq$30 days of hospitalization, and LOS was measured in days from the documented time of admission to the documented time of discharge. Prolonged LOS was defined as an LOS greater than the median (in days). The secondary outcomes were the days of duration of intravenous (iv) antibiotic therapy, the occurrence of adverse events and the subsequent hospital admission. All inpatient antibiotic administration was verified through the paper-based medical administration record.

Ethics

Written informed consent was considered not necessary for the study, as it was a prospective analysis of our usual everyday work. The data of the patients were anonymized for the purposes of this analysis. Confidential patient information was protected according to national standards. This manuscript has been revised by the Clinical Research Ethics Committee of Bellvitge University Hospital (PR070/16).

Statistical analysis

To detect significant differences in clinical, laboratory and outcomes between de-escalated and non-de-escalated groups, we used the χ^2 test or Fisher's exact test for categorical variables, and Student's *t*-test or the Mann–Whitney *U*-test for continuous variables, when appropriate. The multivariate analysis of factors potentially associated with primary and secondary outcomes included all the statistically significant variables in the univariate analysis and other variables with clinical relevance, including the de-escalated group. Model fit was evaluated with the Hosmer–Lemeshow goodness-of-fit test. We used the stepwise logistic regression model of the SPSS software package (SPSS, version 13.5; SPSS, Chicago, IL, USA). An *a priori* subgroup analysis was performed in patients classified into high-risk groups according to the PSI (classes IV–V) at admission, in those without clinical instability and in those with bacteraemia.

Moreover, the probability that a patient has been de-escalated was assessed with multivariate analysis including the factors that might influence the decision to de-escalate antibiotic treatment. This multivariate model was used to create a propensity score for each patient. A multivariate analysis for primary and secondary outcomes was performed adjusting for the propensity score within the model. Statistical significance was established at $\alpha = 0.05$. All reported *P* values are two-tailed.

Results

Patient characteristics

A total of 1410 consecutive episodes of CAPP were analysed. The microbiological methods used to establish the diagnosis of CAPP were Gram's stain and sputum culture in 472 patients, blood cultures in 410, urinary antigen test in 927, and others (tracheal aspirate, transcutaneous puncture, bronchoscopy) in 59. Diagnosis was made with two or more of these tests in 424 patients. Patients who received initially penicillin, amoxicillin or amoxicillin/clavulanate were excluded ($n = 127$). Inappropriate escalation therapy was given to 62 patients, and 1055 received partial reduction of antimicrobial spectrum (not penicillin, amoxicillin or amoxicillin/clavulanate) or continued high-spectrum antibiotic therapy without changes. The 30 day mortality (excluding patients who died in the first 72 h) was 5.1% (72 patients), the median LOS was 8 days (IQR, 6–12 days) and the median duration of iv antibiotic therapy was 5 days (IQR, 3–8 days).

There were 166 patients in the de-escalation group and 1117 patients in the non-de-escalation group. There was a higher frequency of antibiotic de-escalation within 72 h of hospital admission over the years (from 1.1% in 1995–2000 to 17.8% in 2010–14) and the LOS did not decrease significantly over the time. No significant differences were documented in age, sex or comorbidities between the two study groups (Table 1). Regarding clinical features and laboratory findings, patients in the de-escalated group less frequently had hypotension, tachycardia, multilobar pneumonia on chest X-ray, empyema and bacteraemia. In addition, these patients were less commonly classified into the high-risk PSI groups. Penicillin-resistant *S. pneumoniae* was found in 27 patients, but there were not significant differences between study groups ($P=0.73$).

Effect of antibiotic de-escalation on outcomes

Outcomes by study group are shown in Table 2. In univariate analysis, 30 day mortality, LOS (above the median >8 days) and duration of iv antibiotic therapy (above the median >5 days) were significantly lower in the de-escalation group. Moreover, the number of patients with adverse drug reactions or who required readmission (<30 days) was similar in the two groups. No patient developed *Clostridium difficile*-associated diarrhoea.

After adjustment for confounding factors, antibiotic de-escalation was not associated with a higher risk of mortality in the multivariate analysis (Table 3). Moreover, antibiotic de-escalation was a protective factor for prolonged LOS (Table 4) and prolonged duration of iv antibiotic therapy (Table 5).

Subgroup analysis

Assessment of CAPP severity resulted in 835 patients being classified into high-risk PSI classes. In the univariate analysis, antibiotic de-escalation was not associated with higher risk of mortality (3.1% versus 8.1%; $P=0.08$). It was linked with a lower risk of prolonged LOS (26% versus 55.9%; $P<0.001$) and prolonged duration of iv antibiotic therapy (13.5% versus 54.4%; $P<0.001$).

Table 1. Characteristics of patients by study group

	De-escalation group ($n=166$)	Non-de-escalation group ($n=1117$)	*P*
Demographic data			
age (years), median (IQR)	69 (56–78.5)	69.5 (55–78)	0.83
female sex, *n* (%)	66 (39.8)	411 (36.7)	0.45
current/former smoker, *n* (%)	88 (53.3)	661 (59.1)	0.15
influenza vaccine, within last year, *n* (%)	86 (54.4)	493 (48.7)	0.17
pneumococcal vaccine, within last 5 years, *n* (%)	35 (22.7)	183 (18.6)	0.23
Comorbid conditions, *n* (%)			
chronic pulmonary disease	40 (24.1)	324 (29)	0.23
chronic heart disease	29 (17.5)	233 (20.8)	0.31
diabetes mellitus	34 (20.5)	227 (20.3)	0.95
Clinical features, *n* (%)			
cough	147 (88.6)	976 (87.5)	0.70
tachycardia (≥100 beats/min)	78 (47.3)	609 (57.8)	0.01
tachypnoea (≥24 breaths/min)	109 (79)	839 (83.6)	0.17
impaired consciousness	20 (12.1)	170 (15.2)	0.30
septic shock	11 (6.6)	154 (13.8)	0.01
pleuritic chest pain	83 (50)	593 (53.2)	0.43
empyema	3 (1.8)	76 (6.8)	0.01
Laboratory and radiographic findings, *n* (%)			
leucocytosis (leucocytes $\geq 12\times10^9$/L)	109 (65.7)	716 (64)	0.68
respiratory failure	71 (67)	607 (72.4)	0.24
multilobar pneumonia	32 (19.8)	401 (36.1)	<0.001
pleural effusion			
bacteraemia	37 (22.8)	337 (30.6)	0.07
High-risk PSI classes, *n* (%)	96 (57.8)	739 (66.2)	0.03
ICU admission, *n* (%)	2 (1.2)	167 (14.9)	<0.001
Initial prescribed antibiotics, *n* (%)			
β-lactam	85 (51.8)	534 (47.7)	0.32
β-lactam plus other antibiotic	71 (42.8)	438 (39.1)	0.37
other antibiotic	9 (5.4)	147 (13.1)	0.005
Time to antibiotic de-escalation (days), mean (SD)	2.2 (0.7)	6.6 (0.9)	<0.001
De-escalation to oral antibiotics, *n* (%)	134 (84.8)	750 (72.4)	0.001

Table 2. Crude outcomes stratified by study group

Event	De-escalation group (n=166)	Non-de-escalation group (n=1117)	P
Primary outcomes			
30 day mortality, *n* (%)[a,b]	3 (1.8)	62 (5.5)	0.04
LOS (days), median (IQR)	5 (4–8)	9 (6–13)	<0.001
LOS above the median, *n* (%)[b]	37 (22.3)	561 (50.4)	<0.001
Secondary outcomes			
iv antibiotic therapy (days), median (IQR)	3 (2–3)	5 (4–9)	<0.001
iv antibiotic therapy above the median, *n* (%)[b]	18 (10.8)	545 (49.7)	<0.001
adverse drug reactions, *n* (%)			
phlebitis	10 (6.0)	59 (5.3)	0.69
skin rashes	0 (0)	16 (1.4)	0.24
C. difficile-associated diarrhoea	0 (0)	0 (0)	1
Subsequent hospital admission (<30 days), *n* (%)	4 (2.4)	31 (2.9)	0.74

[a]Patients who died within the first 72 h of hospital admission were excluded.
[b]Similar results were obtained comparing those with treatment de-escalation within 72 h of hospital admission (166 patients) and those without treatment de-escalation (915 patients) for 30 day mortality (1.8% versus 6.7%; P=0.015), LOS above the median (22.3% versus 56.2%; P<0.001) and iv antibiotic therapy above the median (10.8% versus 55.8%; P<0.001).

Table 3. Factors associated with 30 day mortality in hospitalized patients with CAPP: multivariate analysis

	OR	95% CI	P
Age (>65 years old)	2.02	0.90–4.52	0.08
Comorbid condition	1.86	0.68–5.12	0.22
Pneumococcal vaccine, 5 years	0.38	0.13–1.13	0.08
Tachycardia (≥100 beats/min)	1.04	0.52–2.10	0.89
Septic shock	2.63	1.20–5.75	0.01
Multilobar pneumonia	2.13	1.06–4.26	0.03
Bacteraemia	2.19	1.05–4.56	0.03
Antibiotic de-escalation[a]	0.43	0.10–1.83	0.25

[a]If the multivariate logistic regression is performed including patients with treatment de-escalation within 72 h of hospital admission (166 patients) and those without treatment de-escalation (915 patients), the result of antibiotic de-escalation is OR=0.38 (95% CI=0.09–1.65).

Table 4. Factors associated with prolonged LOS (above the median) in hospitalized patients with CAPP: multivariate analysis

	OR	95% CI	P
Age (>65 years old)	1.14	0.80–1.62	0.44
Comorbid condition	0.90	0.63–1.27	0.56
Influenza vaccine, 1 year	0.83	0.60–1.15	0.26
Pneumococcal vaccine, 5 years	1.05	0.73–1.53	0.76
Tachycardia (≥100 beats/min)	1.32	0.99–1.76	0.06
Tachypnoea (≥24 breaths/min)	1.46	0.98–2.16	0.06
Bacteraemia	1.40	1.03–1.90	0.03
Septic shock	2.17	1.39–3.39	0.001
Multilobar pneumonia	2.08	1.56–2.78	<0.001
Empyema	9.96	3.82–25.9	<0.001
Antibiotic de-escalation[a]	0.39	0.25–0.62	<0.001

[a]If the multivariate logistic regression is performed including patients with treatment de-escalation within 72 h of hospital admission (166 patients) and those without treatment de-escalation (915 patients), the result of antibiotic de-escalation is OR=0.33 (95% CI=0.20–0.53).

Data about time from hospital admission to clinical stability were available for 997 patients. Clinical stability was not achieved within 72 h of hospital admission in 559 patients. In this subgroup of patients, in the univariate analysis, antibiotic de-escalation was not associated with a higher risk of mortality compared with non-escalation (1.9% versus 5.4%; P=0.50); however, it was associated with a lower risk of prolonged LOS (40.4% versus 62.2%; P=0.002) and prolonged duration of iv antibiotic therapy (21.2% versus 66.7%; P<0.001).

Bacteraemia was documented in 373 patients. In the univariate analysis, lower frequencies of mortality (0% versus 9.2%; P=0.05), prolonged LOS (18.4% versus 59.2%; P<0.001) and prolonged antibiotic therapy (2.7% versus 55.4%; P<0.001) were found in the de-escalation group compared with the non-de-escalation group.

Antibiotic de-escalation was not associated with a higher risk of mortality in the multivariate analysis performed in each subgroup. Moreover, multivariate analysis showed that antibiotic de-escalation was not a protective factor for prolonged LOS only in the subgroup of patients with clinical instability (P=0.08), and it was a protective factor for prolonged duration of iv antibiotic therapy in all subgroups (data not shown).

Propensity score analysis

The propensity score was generated using eight variables that might influence the decision to de-escalate antibiotic treatment (age, comorbid conditions, tachycardia, septic shock, multilobar pneumonia, empyema, bacteraemia and ICU admission) (Table 6). When the propensity score was entered in the multivariate models, antibiotic de-escalation was not associated with

Table 5. Factors associated with prolonged iv antibiotic therapy (above the median) in hospitalized patients with CAPP: multivariate analysis

	OR	95% CI	*P*
Age (>65 years old)	0.91	0.66–1.26	0.50
Comorbid condition	1.03	0.71–1.49	0.41
Influenza vaccine, 1 year	1.22	0.86–1.91	0.26
Pneumococcal vaccine, 5 years	0.94	0.63–1.41	0.78
Tachycardia (≥100 beats/min)	1.15	0.85–1.57	0.34
Bacteraemia	1.15	0.84–1.57	0.38
Septic shock	2.09	1.29–3.38	<0.001
Multilobar pneumonia	2.31	1.70–3.14	<0.001
Empyema	6.15	2.96–12.73	<0.001
Antibiotic de-escalation[a]	0.16	0.09–0.30	<0.001

[a]If the multivariate logistic regression is performed including patients with treatment de-escalation within 72 h of hospital admission (166 patients) and those without treatment de-escalation (915 patients), the result of antibiotic de-escalation is OR=0.11 (95% CI=0.06–0.20).

Table 6. Logistic regression model for derivation of the propensity score

Variable	Coefficient	OR	95% CI	*P*
Age (>65 years old)	−0.162	0.85	0.57–1.26	0.42
Comorbid conditions	−0.078	0.92	0.59–1.44	0.73
Tachycardia (≥100 beats/min)	−0.248	0.78	0.54–1.12	0.17
Septic shock	−0.135	0.87	0.43–1.76	0.70
Multilobar pneumonia	−0.598	0.55	0.35–0.85	0.007
Empyema	−0.870	0.41	0.12–1.38	0.15
Bacteraemia	−0.203	0.74	0.49–1.13	0.16
ICU admission	−2.299	0.10	0.024–0.42	0.002

a higher risk of mortality (OR=0.83, 95% CI=0.24–2.81; *P*=0.76), but it was a protective factor for prolonged LOS (OR=0.46, 95% CI=0.30–0.70; *P*<0.001) and prolonged duration of iv antibiotic therapy (OR=0.15; 95% CI=0.08–0.26; *P*<0.001).

Discussion

This study offers a comprehensive evaluation of the effects of antibiotic de-escalation within the first 72 h of hospital admission on outcomes in CAPP. The results suggest that de-escalation therapy was not associated with a higher risk of 30 day mortality, but was associated with a shorter LOS and duration of iv antibiotic therapy.

In a recent study, Carugati *et al.*[13] reported that de-escalation therapy among patients with CAP was not associated with an increased risk of 30 day mortality or clinical failure. However, their study evaluated only CAP patients with Gram-positive and Gram-negative bacteraemia, de-escalation therapy was considered within 7 days of hospital admission, and the number of patients with CAPP was low. Other studies have also evaluated the effects of antibiotic de-escalation in infections due to difficult-to-treat Gram-negative bacilli,[16] neutropenia[17] and urinary tract infections.[18] Antibiotic de-escalation was not associated with an increased risk of mortality in all these studies. Similarly, in a recent multicentre non-blinded randomized non-inferiority trial performed in patients requiring ICU admission for severe sepsis, de-escalation therapy was not related to mortality, ICU stay, LOS or duration of mechanical ventilation or vasopressors.[19]

In agreement with a previous study,[13] we found that the non-de-escalation group was characterized by a more severe presentation at admission, as evidenced by higher frequencies of hypotension, tachycardia, multilobar pneumonia on chest X-ray and bacteraemia. In the present study, after adjustment for confounders in multivariate and propensity score analyses, we found that antibiotic de-escalation was not associated with an increased risk of 30 day mortality in patients with CAPP. Evaluating other important clinical outcomes in CAP, our results suggest that antibiotic de-escalation was independently associated with shorter duration of LOS. No significant differences were found regarding adverse drug reactions or readmission (<30 days) between study groups.

In an era of cost containment and resource constraints in many healthcare systems, adequate resource allocation and cost-effective healthcare delivery are of paramount importance.[20] The economic burden associated with CAP remains substantial, and LOS is the most important cost driver of hospitalization.[21] A recent study in the US estimated that reducing the course of a CAP admission by 1 day may represent a saving of $2273–2373.[22] Therefore, our finding of shorter LOS in patients with CAPP who underwent de-escalation therapy may have significant economic implications.

There is a concern about performing antibiotic de-escalation in patients with severe disease or in patients who are not clinically stable. To date, therapy de-escalation has not been assessed in these CAP patients. In the present study, we found antibiotic de-escalation to be safe in patients classified into high-risk PSI classes, and no increase in mortality was observed. Similar results were found if antibiotic de-escalation was performed in patients who remained clinically unstable during the first 72 h after hospital admission. Our results suggest that antibiotic de-escalation also seems to be safe among these subgroups of CAPP patients. However, it is important to note that only 159 patients did not reach clinical stability within 72 h of hospital admission and only 2 patients in the de-escalation group were admitted to the ICU.

In recognition of the fact that antimicrobial resistance results in increased morbidity, mortality and cost of healthcare, a series of guidelines has been published for improving the use of antimicrobial agents in hospitals.[10] A comprehensive evidence-based stewardship programme to combat antimicrobial resistance includes streamlining or de-escalating antimicrobial therapy towards more targeted therapies that decrease antimicrobial exposure and contain cost. The Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the management of CAP in adults recommends antibiotic de-escalation as best medical practice,[1] but the evidence available in support of this recommendation is scarce. Our study shows that antibiotic de-escalation to penicillin, amoxicillin or amoxicillin/clavulanate is safe among patients with CAPP. Significantly, we did not consider de-escalation or narrowing of antibiotic therapy to third-generation cephalosporins to be appropriate. Third-generation cephalosporins are recommended for empirical therapy in CAP or as an alternative antimicrobial in CAPP. However, some data suggest that broad-spectrum cephalosporins have been associated with a higher risk for selection of penicillin-

resistant pneumococci, resistant enterococci and ESBL Enterobacteriaceae.[23]

The strengths of the current study include its prospective design, the large cohort of consecutive hospitalized patients with CAPP and the comprehensive data collection. In addition, we evaluated the impact of antibiotic de-escalation on prognosis and other important clinical outcomes of CAP. Finally, we used multivariate analysis and a propensity score analysis to rule out possible confounding factors in the relation between antibiotic de-escalation and outcomes. However, the present study also has some limitations that should be acknowledged. Caution should be taken in the interpretation of some of our results because the de-escalation group was characterized by a less severe presentation at admission and more frequent de-escalation to an oral antibiotic. The present study was not a randomized trial; as with any observational study, there is potential for residual confounding despite multivariate analysis. Moreover, the study was performed at a single institution and some of the subgroups analysed comprised only a few patients. The number of patients admitted to the ICU who underwent de-escalation therapy was also small. Finally, it is likely that some cases of CAPP were not detected because the urinary antigen tests were not available in the first years of the study.

In conclusion, antibiotic de-escalation within the first 72 h after hospital admission seems to be safe and effective in reducing the duration of LOS, and did not adversely affect outcomes of patients with CAPP, even those with bacteraemia and severe disease, and those who were clinically unstable. Our results suggest that de-escalation strategies should be more widely implemented in the management of hospitalized adults with CAPP.

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Transparency declarations

None to declare.

Author contributions

D. V. and J. C. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. D. V., A. F. S. and C. G.-V. contributed to the study conception and design. J. N. contributed to collecting samples and carrying out experiments. D. V. and A. F. S. contributed to data analysis. D. V., A. F. S. and J. D. contributed to data interpretation. D. V., A. F. S. and J. C. contributed to writing the manuscript. C. G.-V., J. N. and J. D. contributed to revising the manuscript. All authors approved the final version of the manuscript.

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6.5. Levofloxacin versus azithromycin for treating Legionella pneumonia: a propensity score analysis.

- Compare characteristics and outcomes of patients hospitalised with Legionella pneumonia treated with levofloxacin, azithromycin, and old macrolides.

- Impact of antibiotic choice (macrolides vs. quinolones) on outcomes in hospitalised patients with Legionella pneumonia.

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Original article

Levofloxacin versus azithromycin for treating legionella pneumonia: a propensity score analysis

C. Garcia-Vidal [1, 2, *], I. Sanchez-Rodriguez [3], A.F. Simonetti [1], J. Burgos [3], D. Viasus [1, 4], M.T. Martin [3], V. Falco [3], J. Carratalà [1, 2]

[1)] *Hospital Universitari de Bellvitge, IDIBELL (Institut D'investigació Biomèdica de Bellvitge), Universitat de Barcelona, Barcelona, Spain*
[2)] *REIPI (Spanish Network for the Research in Infectious Diseases), Instituto de Salud Carlos III, Madrid, Spain*
[3)] *Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain*
[4)] *Health Science Division, Universidad del Norte and Hospital Universidad del Norte, Barranquilla, Colombia*

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ABSTRACT

Objectives: Concerns have arisen regarding the equivalence of levofloxacin and some macrolides for treating community-acquired legionella pneumonia (LP). We aimed to compare the outcomes of current patients with LP treated with levofloxacin, azithromycin and clarithromycin.
Methods: Observational retrospective multicentre study of consecutive patients with LP requiring hospitalization (2000–2014) conducted in two hospitals. The primary outcome assessed was 30-day mortality. To control for confounding, therapy was assessed by multivariate analysis.
Results: We documented 446 patients with LP, of which 175 were treated with levofloxacin, 177 with azithromycin and 58 with clarithromycin. No significant differences in time to defervescence (2 (interquartile range (IQR) 1–4) versus 2 (IQR 1–3) days; p 0.453), time to achieve clinical stability (3 (2–5) versus 3 (2–5) days; p 0.486), length of intravenous therapy (3 (2–5.25) versus 4 (3–6) days; p 0.058) and length of hospital stay (7 (5–10) versus 6 (5–9) days; p 0.088) were found between patients treated with levofloxacin and those treated with azithromycin. Patients treated with clarithromycin had longer intravenous antibiotic treatment (3 (2–5.25) versus 5 (3–6.25) days; p 0.002) and longer hospital stay (7 (5–10) versus 9 (7–14) days; p 0.043) compared with those treated with levofloxacin. The overall mortality was 4.3% (19 patients). Neither univariate nor multivariate analysis showed a significant association of levofloxacin versus azithromycin on mortality (4 (2.3%) versus 9 (5.1%) deaths; p 0.164). The results did not change after incorporation of the propensity score into the models.
Conclusions: In our study, no significant differences in most outcomes were found between patients treated with levofloxacin and those treated with azithromycin. Due to the small number of deaths, results regarding mortality should be interpreted with caution. **C. Garcia-Vidal, Clin Microbiol Infect 2017;■:1**

Introduction

Legionella pneumophila is a common causative agent in both sporadic and epidemic community-acquired pneumonia (CAP) [1]. Recently, important changes in the management of patients with legionella pneumonia (LP), especially in diagnostic methods and treatment options, have improved the poor outcomes traditionally reported for this infection [2,3]. The introduction of urine antigen testing for LP, which provides an early diagnosis, seems to have played a major role in this decreasing mortality; conversely the impact on outcomes of antibiotic choice is less evident.

Although the information available is based mostly on observational studies, levofloxacin appears to be associated with a more rapid resolution of symptoms, a shorter time to clinical stability and consequently shorter length of hospital stay than older macrolides [3–5]. However, biases in this comparison cannot be ruled out. For example, patients treated with macrolides were usually hospitalized in the earliest years of most studies, whereas patients who received levofloxacin were more contemporary and consequently

* Corresponding author. C. Garcia-Vidal, Infectious Disease Department, Hospital Universitari de Bellvitge; Feixa Llarga s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain.
E-mail address: carolgv75@hotmail.com (C. Garcia-Vidal).

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were more frequently diagnosed with the urinary antigen test [2]. Moreover, there is scarce evidence available for the direct comparison of levofloxacin and azithromycin. Comparing these drugs is justified because azithromycin is more active than old macrolides against intracellular *L. pneumophila* in animal models [6] and because the regimen of β-lactams plus azithromycin is the recommended empirical treatment for CAP in most guidelines [7].

This study compares the outcomes of a large number of consecutive patients hospitalized with LP treated with levofloxacin, azithromycin and old macrolides.

Materials and methods

Setting, patients and study design

This is an observational study performed at Hospital Universitari de Bellvitge and Hospital Universitari Vall d'Hebron, in Barcelona, Spain. These hospitals serve an urban area of 1 800 000 inhabitants. At Bellvitge University Hospital all patients admitted with CAP from 1 January 2000 through to 31 July 2014 were prospectively followed up during hospitalization. At Hospital Universitari Vall d'Hebron information regarding patients with LP was recorded prospectively from 2000 to 2004 and retrospectively from 2005 to 2014 using microbiological reports and by discharge diagnosis. This observational study was approved by the Institutional Review Board in the two hospitals. To protect personal privacy, data were anonymized.

We analysed data from confirmed cases of community-acquired *L. pneumophila* pneumonia diagnosed with the use of one or more of the following methods: urinary antigen test, isolation of *Legionella* in sputum, transthoracic needle aspiration specimen, or pleural fluid, and/or a four-fold increase in the antibody titre using serological methods. Data on epidemiology, demographic characteristics, clinical presentation, diagnosis, antibiotic therapy and clinical outcome were retrieved from medical records. To reduce measurement error, data quality procedures have been applied (review of protocols and periodic review of the database by descriptive analysis to detect illogical information).

The exposure variable was the anti-legionella treatment regimen. For the purpose of the study the first anti-legionella antibiotic administered was considered. This treatment had to be started within the first 48 h after admission and administered for at least 5 days. The primary outcome assessed was overall mortality, defined as in-hospital 30-day mortality. The secondary outcomes were: time to defervescence, time to achieve clinical stability, length of intravenous (i.v.) antibiotic therapy, length of hospital stay and early mortality, defined as death due to any cause <48 h after hospitalization. The variables used for the primary outcome related analysis (antibiotic treatment, 30-day mortality and immunosuppression) did not have missing data.

Antibiotic therapy was initiated at the emergency department following the hospitals' guidelines, which recommend the use of a β-lactam (either ceftriaxone sodium 1 g i.v. once per day or amoxicillin/clavulanate potassium 1 g i.v. thrice per day) with or without a macrolide (azithromycin 500 mg i.v. once per day or clarithromycin 500 mg i.v. twice per day); or levofloxacin (500 mg i.v. once per day). Local guidelines were identical for both centres and they did not change throughout the study period.

Definitions

Pneumonia was defined as an acute illness associated with at least one of the following clinical signs and symptoms, such as: cough with or without sputum production, pleuritic chest pain, dyspnoea, fever or hypothermia, altered breath sounds, leucocytosis, and a new infiltrate on a chest radiograph.

Definitions of tobacco smoking, alcohol abuse and hypoalbuminaemia have been previously described by our group [2]. Time to clinical stability was defined as described elsewhere (normalization of all five vital signs—temperature, heart rate, respiratory rate, systolic blood pressure and oxygen saturation—plus ability to eat and normalization of mental status [2]). Respiratory failure was considered to be present when p_{O_2}/Fi_{O_2} <300. Patients with chronic renal disease and glomerular filtration rate <60 mL/min/1.73 m^2 or the need for chronic dialysis therapy were classified as patients with renal insufficiency. Immunosuppression was considered in patients with chemotherapy, haematological cancer, acquired immune deficiency syndrome, transplantation, corticosteroid use (>15 mg/day of prednisone or equivalent steroid dose for more than 2 weeks), biological therapies or other cause of immunodeficiency. To stratify patients according to risk, we used the Pneumonia Severity Index [8]. Empiric antibiotic treatment was collected as a specific item in the data collection form, defined as the antibiotic received at the emergency room. Initial inadequate treatment was considered in patients with LP who did not receive macrolides, levofloxacin or tetracyclines at admission.

Microbiological studies and aetiological diagnosis

The selective medium buffered charcoal yeast extract-α was used for the isolation of *Legionella* species in biological samples. *Legionella pneumophila* serogroup 1 antigen in urine was detected by an immunochromatographic method (NOW *Legionella* Urinary Antigen Test; Binax Inc.,Portland, ME) or enzyme-linked immunosorbent assay (ELISA-Bartels; Bartels, Trinity Biotech, Wicklow, Ireland). Enzyme immunoassay (EIA) was used to identify antibodies against *L. pneumophila* serogroups 1–6. All microbiological studies were at the discretion of the attending physicians.

Statistical analysis

The χ^2 test or Fisher exact test for categorical variables, and *t* test or Mann–Whitney *U* test for continuous variables (based on Kolmogorov–Smirnov normality test) were used. We analysed the relationship between the anti-legionella antibiotic administered (levofloxacin versus azithromycin) and mortality by two different approaches. First, mortality was assessed using a logistic regression model that adjusts the treatment regimen with the strongest predictor of mortality found in univariate analysis (immunosuppression). In both analyses patients treated with clarithromycin are excluded.

In a second analysis, we estimated the propensity to receive either levofloxacin or azithromycin using a logistic regression model including significant pre-treatment variables (with $p \leq 0.025$ on univariate analysis). Consequently, we introduced the estimated propensity score as a covariate in a multivariate analysis [9,10]. Sensitivity analyses were performed by repeating the propensity score approach with 1 : 1 matching with replacement and a calliper of 0.25, and quintile stratification. Associations were expressed as OR and 95% CI. The goodness-of-fit of the model was evaluated by the Hosmer–Lemeshow test. All p values reported are two-tailed. Data were analysed using SPSS statistical software (version 23.0; SPSS Inc, Chicago, IL, USA).

Results

Patients, clinical characteristics and outcomes

Over the study period we documented 446 patients with LP. The diagnosis was established with at least one of the following: urinary antigen test in 423 cases, seroconversion in 66 cases and

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positive culture in 58 cases. Cases were uniformly distributed during the study period. Data on co-infection were available in 237 patients. Of these, 10 (4.2%) had co-infection, due to: *Chlamydophila pneumoniae* (five patients), *Mycoplasma pneumoniae* (two patients), *Chlamydophila psittacci* (one patient), *Pseudomonas aeruginosa* (one patient), and *Moraxella catharralis* (one patient).

The mean age of patients was 60.9 years (SD 14) and 327 (73.3%) were men. History of alcohol abuse and smoking was present in 98 (22%) and 197 (44.2%) patients, respectively. Two hundred and twenty-six patients (50.7%) had underlying diseases, mostly diabetes mellitus, chronic heart disease, chronic obstructive pulmonary disease and chronic liver disease. One hundred and eighty-five patients (41.5%) were classified into Pneumonia Severity Index score IV–V risk classes. Fig. 1 shows the study flowchart.

Three hundred and thirty-five patients (75.1%) received appropriate initial therapy. Appropriate antibiotic treatment within the first 8 h was administered to 70% of patients. Levofloxacin was given to 175 (39.3%) patients. A dose of 500 mg i.v. once per day was used in almost all cases (98.3%). Macrolides were given to 235 (52.7%) patients; azithromycin to 177 and clarithromycin to 58. Combination therapy with rifampicin was administered to 15 patients (associated with macrolides in 12 and with levofloxacin in three). Fifteen patients were given treatment with both levofloxacin and macrolides, one patient was treated with moxifloxacin and five were on other antibiotics. These patients were excluded from further analyses.

Table 1 shows clinical characteristics and microbiological diagnoses of the study population. Patients treated with levofloxacin were younger, had more history of alcohol abuse and more co-morbid conditions than those treated with azithromycin. Moreover, they had less hypoalbuminaemia but more frequently presented with respiratory failure, multilobar pneumonia, intensive care unit admission, and positive serology or culture results. Patients treated with levofloxacin had less renal failure but more respiratory failure than those treated with clarithromycin. No differences in microbiological methods for diagnosing LP and time to first dose of antibiotics were found between groups. Variables included on the propensity score model were centre of admission, age > 65 years, co-morbid conditions, multilobar pneumonia and intensive care unit admission. Our model showed a very good ability to predict the use of levofloxacin or azithromycin (Hosmer–Lemeshow test p 0.784, area under the receiver operating curve of 0.916; 95% CI 0.885–0.947).The regression model was shown in a supplementary file.

When considering all patients, the median time to defervescence was 2 days (interquartile range (IQR) 1–3.25) and median

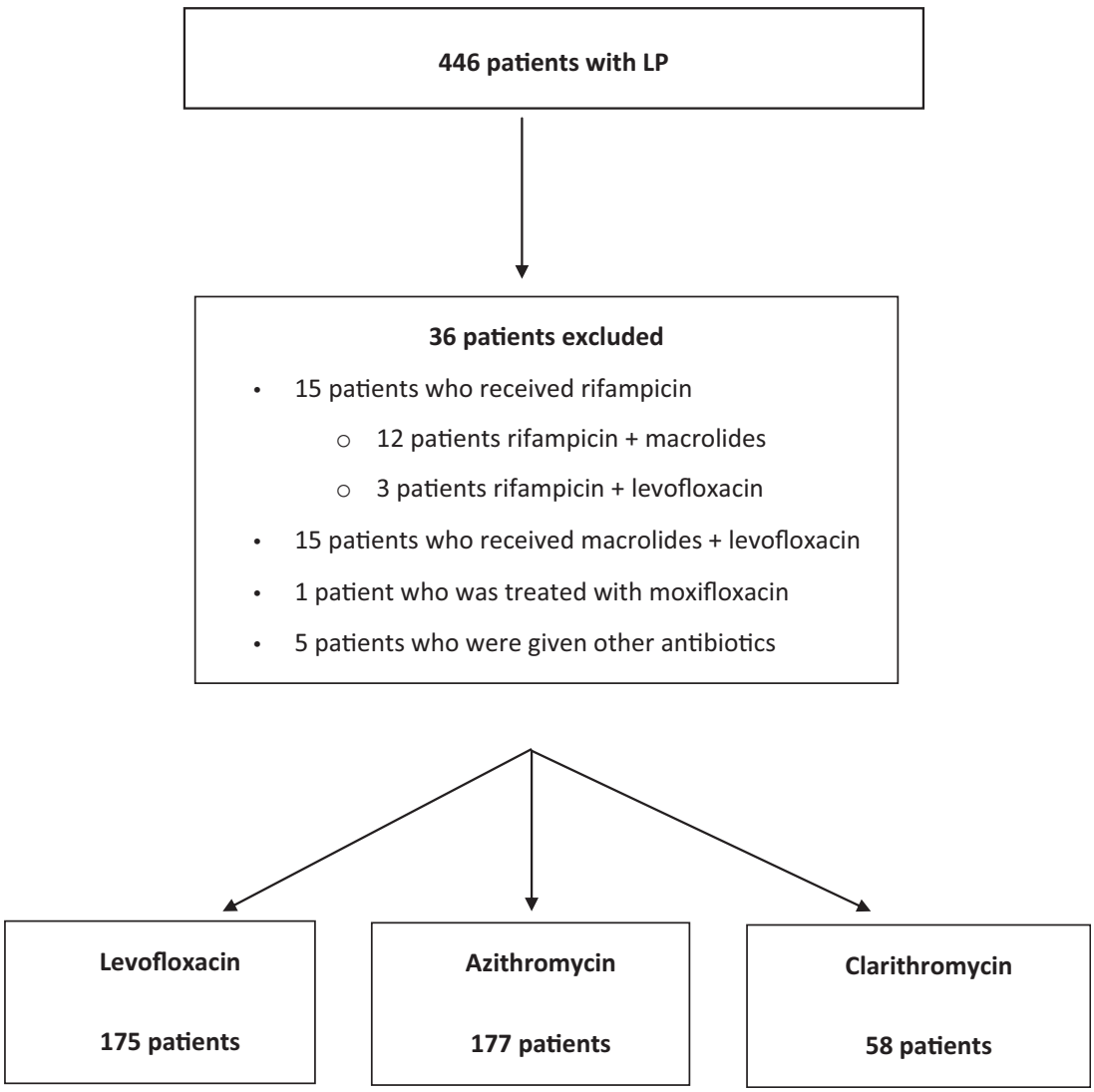

Fig. 1. Study flowchart.

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Table 1
Baseline characteristics of patients with community-acquired legionella pneumonia treated with levofloxacin, azithromycin or clarithromycin

	Levofloxacin ($n = 175$) n (%)	Azithromycin ($n = 177$) n (%)	p-value[a]	Clarithromycin ($n = 58$) n (%)	p-value[b]
Variable					
Male Sex	121 (69.1)	134 (75.7)	0.168	41 (70.7)	0.824
Age, mean (SD) years	59.8 (14.1)	63.3 (13.3)	0.019	58.71 (14.4)	0.598
Age >65 years	68 (38.9)	87 (49.2)	0.052	22 (37.9)	0.900
Hospital Universitari de Bellvitge	134 (76.6)	1 (0.6)	<0.001	49 (84.5)	<0.001
Hospital Universitari Vall d'Hebron	41 (23.4)	176 (99.4)	<0.001	9 (15.5)	<0.001
Time period					
2000–2004	70	55	0.080	58 (100)	<0.001
2005–2009	73	71	0.760	0	<0.001
2010–2014	32	51	0.020	0	<0.001
Alcohol consumption >80 g per day	46 (26.3)	30 (16.9)	0.033	10 (17.2)	0.162
Smoking	82 (46.9)	68 (38.4)	0.109	30 (51.7)	0.520
Co-morbid condition	100 (57.1)	73 (41.2)	0.003	29 (50)	0.343
Immunosuppression	15 (8.6)	27 (15.3)	0.053	8 (13.8)	0.248
Hypoalbuminaemia (<3 g/dL)[c]	58 (42)	54 (56.3)	0.032	5 (55.6)	0.427
Renal insufficiency	18 (10.3)	18 (10.2)	0.971	13 (22.4)	0.018
Respiratory failure (Pao_2/fio_2 <300)[d]	82 (59.9)	85 (48.0)	0.037	23 (44.4)	0.013
Multilobar pneumonia	59 (33.7)	25 (14.1)	<0.001	12 (20.7)	0.055
Pleural effusion	17 (9.7)	10 (5.7)	0.152	2 (3.4)	0.128
High-risk PSI classes[e]	77 (44)	63 (35.6)	0.094	28 (48.3)	0.641
Admission to the intensive care unit	27 (15.4)	12 (6.8)	0.010	8 (13.8)	0.763
Diagnosis					
Positive urinary antigen test	164 (93.7)	174 (98.3)	0.071	54 (91.4)	0.628
Positive Culture or serology	58 (33.1)	23 (13.1)	<0.001	18 (31.0)	0.767

[a] Comparison between levofloxacin and azithromycin.
[b] Comparison between levofloxacin and clarithromycin.
[c] Data available in 271 patients.
[d] Data available in 403 patients.
[e] High-risk Pneumonia Severity Index (PSI) classes were defined as IV and V.

time to achieve clinical stability was 3 days (IQR 2–5). Median length of i.v. therapy and median length of hospital stay were 4 days (IQR 2–6) and 7 days (IQR 5–10) respectively. Early mortality rate was 1.1% (5 of 446 patients), and overall mortality was 4.3% (19 of 446 patients).

Table 2 summarizes the clinical outcomes for patients according to antibiotic treatment. No significant differences were found between outcomes of patients receiving levofloxacin and those treated with azithromycin. Patients treated with clarithromycin had longer i.v. antibiotic treatment and longer hospital stay than those receiving levofloxacin. The results were similar when we analysed only patients with severe CAP (high-risk Pneumonia Severity Index classes).

Table 3 shows univariate and multivariate analysis of predictors for overall mortality. Neither univariate nor multivariate analysis showed any association between levofloxacin versus azithromycin use and mortality. A second-step model with the propensity score to receive levofloxacin in it confirmed this finding (OR 0.461; 95% CI 0.034–6.308; p 0.562). Sensitivity analysis reaffirmed our results (data shown in Supplementary material, Tables S1 to S3).

Discussion

The present multicentre study offers a detailed comparison between antibiotic treatments of community-acquired LP. The main finding is that we were not able to find differences between levofloxacin, primarily at a dose of 500 mg i.v. once per day and azithromycin on 30-day mortality in multivariate analysis. However, mortality was twice as high for azithromycin compared with levofloxacin on univariate analysis.

The efficacy and usefulness of different types of antibiotics against *Legionella* spp. have been evaluated in some experimental studies [6]. In intracellular models of *Legionella* infection, although old macrolides inhibit bacterial growth, it promptly recurs after removal of drugs from the cells [11,12]. Conversely, levofloxacin and azithromycin are more active than old macrolides, and bacterial regrowth is not observed [13–15]. Studies in animal models have confirmed the superiority of levofloxacin and azithromycin over old macrolides [16,17].

Clinical research comparing the utility of levofloxacin and azithromycin in the treatment of LP is scarce [18,19] and no

Table 2
Clinical outcomes for patients with community-acquired legionella pneumonia treated with levofloxacin, azithromycin or clarithromycin

	Levofloxacin ($n = 175$)	Azithromycin ($n = 177$)	p-value[a]	Clarithromycin ($n = 58$)	p-value[b]
Time (days) to defervescence (temp ≤37°C), median (IQR)	2 (1–4)	2 (1–3)	0.453	2 (1–4)	0.432
Time (days) to achieve clinical stability, median (IQR)	3 (2–5)	3 (2–5)	0.486	4 (2–5)	0.761
Length of intravenous antibiotic therapy, median (IQR)	3 (2–5.25)	4 (3–6)	0.058	5 (3–6.25)	0.002
Length of hospital stay, median (IQR)	7 (5–10)	6 (5–9)	0.088	9 (7–14)	0.043
Early mortality, n (%)	1 (0.6)	2 (1.1)	0.569	1 (1.7)	0.410
Overall mortality (30-day), n (%)	4 (2.3)	9 (5.1)	0.164	3 (5.17)	0.264

IQR, interquartile range.
[a] Comparison between levofloxacin and azithromycin.
[b] Comparison between levofloxacin and clarithromycin.

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Table 3
Univariate and multivariate logistic regression analysis of prognostic factors for overall mortality (30 days) in 446 patients with legionella pneumonia (LP)

	Univariate analysis			Multivariate analysis			Multivariate analysis including treatment[a]		
	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age >65 years	1.539	0.613–3.866	0.355						
Male sex	0.981	0.345–2.784	0.971	–	–	–	–	–	–
Alcohol consumption >80 g/day	0.406	0.092–1.787	0.218	–	–	–	–	–	–
Smoking	0.435	0.154–1.230	0.107	–	–	–	–	–	–
Co-morbid condition[b]	3.839	1.254–11.755	0.012	–	–	–	–	–	–
Hypoalbuminaemia (<3 g/dL)	3.116	0.618–15.723	0.148	–	–	–	–	–	–
Renal insufficiency	5.209	1.947–13.935	<0.001						
Immunosuppression	10.185	3.919–26.473	<0.001	9.365	2.947–39.755	<0.001	10.236	3.091–33.900	<0.0001
Respiratory failure (Pao_2/fio_2 < 300)	5.010	1.436–17.474	0.005						
Multilobar pneumonia	1.778	0.682–4.633	0.233	–	–	–	–	–	–
High-risk Pneumonia Severity Index classes	6.172	1.733–21.989	0.002						
<8 h to antibiotic administration[c]	1.349	0.385–4.733	0.639	–	–	–	–	–	–
Azithromycin versus Levofloxacin[d]	2.290	0.692–7.580	0.164	1.811	0.526–6.234	0.346	2.633	0.409–16.97	0.308
Levofloxacin treatment[e]	0.426	0.137–1.330	0.131	–	–	–	–	–	–
Azithromycin treatment	1.667	0.631–4.409	0.298	–	–	–	–	–	–
Clarithromycin treatment[f,g]	1.280	0.359–4.566	0.703				–	–	–

[a] Including in the model the use of levofloxacin compared with azithromycin and the propensity score to receive these treatments.
[b] Co-morbid conditions were not included in the final multivariate analysis due to the inclusion of this variable in the propensity score (PS). If we had included this variable in our selected model, co-morbid conditions would not have been independently associated with mortality (OR 1.015; 95% CI 0.253–4.084) and the variables independently associated with mortality would have been the same.
[c] Comparison between those patients treated with levofloxacin versus azithromycin. Patients treated with other antibiotics active against LP are excluded. The results showed higher probability for mortality with azithromycin.
[d] Less than 8 h from hospital admission to receive optimal treatment for LP.
[e] Patients treated with levofloxacin versus all the other treatments. Patients treated with levofloxacin in combination with other antibiotics active against LP are excluded.
[f] Patients treated with clarithromycin versus all the other treatments. Patients treated with clarithromycin in combination with other antibiotics active against LP are excluded.
[g] Patients treated with azithromycin versus all the other treatments. Patients treated with azithromycin in combination with other antibiotics active against LP are excluded.

randomized trials have been performed. Recently, a retrospective analysis of a cohort of adults hospitalized for LP showed similar results for hospital mortality, development of *C. difficile* colitis, length of hospital stay and cost of the hospitalization for patients treated with either azithromycin or levofloxacin [18]. Of note, patients in that study were identified by an International Classification of Diseases 9th revision clinical modification code from a drug utilization database. A prospective observational study comparing only 43 patients treated with azithromycin with 18 treated with levofloxacin found no differences in days to defervescence, length of hospital stay or mortality [19]. The results of that study are limited by the small sample size. Our observational study, with a large number of consecutive patients recruited from clinical databases, found that patients treated with azithromycin had similar outcomes to those treated with levofloxacin, including time to defervescence, time to achieve clinical stability, length of intravenous therapy and length of hospital stay. Conversely, patients treated with clarithromycin had longer i.v. antibiotic treatment and longer hospital stay compared with those treated with levofloxacin. Of note, both early and overall mortality were twice as high in patients treated with azithromycin compared with levofloxacin in univariate analysis. However, it is important to note that due to the low number of deaths in both groups, results regarding mortality should be interpreted with caution.

Previous observational studies comparing levofloxacin with old macrolides in the treatment of LP have reported that patients treated with levofloxacin might have better outcomes [3–5]. Our study provides additional support for the beneficial effect on length of stay of levofloxacin compared with clarithromycin in a cohort of patients with similar diagnostic methods and similar timing of antibiotic administration.

Early and overall mortality were both low. Recently, a substantial fall in the rate of mortality due to CAP has been documented [20]. Focusing on LP, two studies have reported decreases in the mortality rate in hospitalized patients [2,21]. These authors considered that two factors may play a key role in explaining this falling rate: first, the use of the urinary test, which is more sensitive than culture or serology for LP diagnosis, may have led to the detection of milder forms of legionellosis; second, it is likely that patients diagnosed by the urinary test were administered adequate treatment more quickly.

Finally, we stress that almost all patients in the quinolone group (98.3%) in our study received 500 mg/24 h of levofloxacin. Fluoroquinolones exhibit concentration-dependent antimicrobial activity. For these reasons, some authors have suggested that high doses of levofloxacin (750 mg/24 h or even 500 mg/12 h) may increase killing of the pathogen due to the higher peak concentrations. However, it has been demonstrated that the exposure necessary for favourable outcomes varies according to the bacteria [22,23]. To our knowledge, no studies correlating pharmacodynamic parameters with efficacy in patients with LP treated with quinolones have been performed. Our study did not aim to perform this correlation; nevertheless, we stress the low rates of early (0.6%) and overall (2.3%) mortality in our contemporary cohort of patients with LP treated with 500 mg/24 h of levofloxacin, including more than 15% of patients with intensive care unit admission and more than 45% with a high-risk Pneumonia Severity Index. Although no definitive conclusions can be drawn, this dose appeared to be a good treatment option for our patients with LP.

The strengths of the current study include the large cohort of consecutive hospitalized patients with LP in two hospitals with a long tradition in clinical research on CAP. The clinical data collection was meticulously performed and we applied rigorous criteria for diagnosis of LP. Some limitations of our study should be acknowledged. Taking into account that the study was observational, it is difficult to completely rule out confounding due to unmeasured variables. Ideally, a randomized trial should be performed to compare empirical regimens; however, given the relative rarity of LP, a trial of this kind is unlikely to be feasible or practical [3,11,24]. Finally, we did not monitor the adverse events of the different drugs used for LP treatment; unfortunately, our study was not designed to address these issues.

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In summary, no significant differences in time to defervescence, time to achieve clinical stability, length of intravenous therapy and length of hospital stay were found between patients treated with levofloxacin and those receiving azithromycin. The absence of significant differences in mortality rates between the two treatment groups should be interpreted with caution, due to the small numbers of deaths in our cohort of patients with LP.

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Transparency declaration

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2017.02.030.

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Supplementary file.

Table 4. Propensity score analysis to receive Levofloxacin or Azithromycin

	Multivariate analysis		
	adjusted OR	**95% CI**	***p*-value**
Center of admission	.001	.001-011	<.001
Comorbid conditions	.509	.253-1.024	.058
Multilobar pneumonia	1.668	.577-4.819	.345
ICU admission	.267	.093-.766	.014
Age > 65 years	1.428	.708-2.880	.320

*Results with OR >1 are in favor of Azithromycin

Table 5. Overall mortality (30 days) of 84 patients matched by 1:1 using the propensity score.

	Alive	**Death**
Levofloxacin	40	2
Azithromycin	39	3

P= 1.000

Table 6. Overall mortality (30 days) of 84 patients matched by quintiles using the propensity score.

	Alive	**Death**
Levofloxacin	38	4
Azithromycin	40	2

P=.676

6.6. Predictors for individual patient antibiotic treatment effect in hospitalised community-acquired pneumonia patients.

- Explorative search of candidate predictors at individual patient level for effect modification of empiric antibiotic regimens recommended by guidelines (betalactams monotherapy, beta-lactams plus macrolides, fluoroquinolones) in patients hospitalized with CAP to non-intensive care unit wards.

14-Mar-2017

CLM-17-11340.R1

Predictors for individual patient antibiotic treatment effect in hospitalised community-acquired pneumonia patients

Simonetti, Antonella; van Werkhoven, Cornelis; Schweitzer, Valentijn; Viasus, Diego; Carratalà, Jordi; Postma, DF; Oosterheert, J.J.; Bonten, Marc

Dear Dr. Simonetti,

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ORIGINAL ARTICLE

Predictors for individual patient antibiotic treatment effect in hospitalised community-acquired pneumonia patients

Authors: Antonella F. Simonetti[1], Cornelis H. van Werkhoven[2], Valentijn A. Schweitzer[2], Diego Viasus[3], Jordi Carratalà[1,4], Douwe F. Postma[5], Jan Jelrik Oosterheert[5], Marc J.M. Bonten[6].

Affiliations:

1. Hospital Universitari de Bellvitge, IDIBELL (Institut D'investigació Biomèdica de Bellvitge), Barcelona, Spain.
2. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands.
3. Division of Health Sciences, Faculty of Medicine, Universidad del Norte, and Hospital Universidad del Norte, Barranquilla, Colombia.
4. Department of Clinical Sciences, University of Barcelona, Barcelona, Spain.
5. Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Utrecht, the Netherlands.
6. Departments of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands.

Key Words: Community-acquired pneumonia, antibiotic treatment, clinical predictors, treatment effect, outcomes.

Running head: Predictors for antibiotic effect in CAP hospitalized patients.

Corresponding author: Antonella F. Simonetti, MD, Department of Infectious Diseases, Hospital Universitari de Bellvitge - IDIBELL, Feixa Llarga s/n, 08907, L'Hospitalet de

Llobregat, Barcelona, Spain. Telephone: +34-932607625.e-mail: antonella.f.simonetti@gmail.com

ABSTRACT

OBJECTIVE: Our objective was to identify clinical predictors of antibiotic treatment effects in non-ICU hospitalised CAP patients.

METHODS: Post-hoc analysis of three prospective cohorts (from the Netherlands and Spain) of CAP adult patients admitted to a non-ICU having received either beta-lactam monotherapy (BL), beta-lactam + macrolide (BLM), or fluoroquinolone-based therapy (FQL) as empiric antibiotic treatment. We evaluated candidate clinical predictors of treatment effects in multiple mixed-effects models by including interactions of the predictors with empiric antibiotic choice and using 30-day mortality, ICU admission, and length of hospital stay (LOS) as outcomes.

RESULTS: Among 8,562 patients, empiric treatment was BL in 4,399 (51.4%), FQL in 3,373 (39.4%), and BLM in 790 (9.2%). Older age (interaction OR 1.67, 95% CI 1.23 – 2.29, p-value 0.034) and current smoking (interaction OR 2.36, 95% C.I. 1.34 – 4.17, p-value 0.046) were associated with lower effectiveness of FQL on 30-day mortality. Older age was also associated with lower effectiveness of BLM on LOS (interaction effect ratio 1.14, 95% CI 1.06 – 1.22, p-value 0.008).

CONCLUSIONS: Older age and smoking could influence the response to specific antibiotic regimens. The effect modification of age and smoking should be considered hypothesis generating to be evaluated in future trials.

INTRODUCTION

Community-acquired pneumonia (CAP) is a leading cause of hospitalization and death worldwide [1-3]. Although recent studies described a downward trend in 30-day mortality in hospitalized patients with CAP over the last 20 years [4-5], the reported hospital mortality in these patients remains high, ranging from 4% to 15% [4-7].

For CAP patients admitted to a non–intensive-care-unit (non-ICU), international guidelines recommend either beta-lactam monotherapy (BL), beta-lactam macrolide combination therapy (BLM) or respiratory fluoroquinolone monotherapy (FQL) as empiric treatment [8-10]. However, the necessity for atypical coverage in non-severe CAP patients is uncertain as beneficial effects on mortality were only found in observational studies, but not in randomized controlled trials [11-12]. Moreover, the use of macrolides and fluoroquinolones has been related to increased risks of antimicrobial resistance and adverse drug effects [13-17]. A limitation of the studies performed so far is that they compared interventions within the whole domain of hospitalized CAP (e.g. at the population level), lacking power for proper subgroup analyses.

Despite important advancements in diagnostic testing, a causative pathogen is not detected in the majority of CAP patients; and if detected there is often a delay of up to 48 hours [2]. Initial antibiotic treatment is therefore almost always empiric. However, CAP is a heterogeneous disease due to heterogeneity in both host and pathogen factors. Therefore, an individualized antibiotic treatment approach might prove beneficial.

The concept of individualized medicine, initially referred to the use of genomics in clinical care, has extended to recognizing the heterogeneity of each individual patient, particularly their risk factors for developing disease or having poor outcomes, and using this to inform treatment decisions. Biomarkers and clinical predictors have been widely studied in CAP in an attempt to predict the microbial etiology [18, 19] or clinical outcomes, such as early treatment failure or all-cause mortality [20-25]. Yet, predictors of pathogens are weak at best, and predictors of all-cause mortality do not inform the treating physician about the necessity to adjust empiric therapy. To pave the way for individualized medicine for CAP, it is necessary to take a step further and assess differences in treatment response based on multiple patient factors.

The objective of this study was to find candidate predictors at individual patient level for effect modification of empiric antibiotic regimens (BL, BLM and FQL) in CAP patients hospitalized to non-ICU wards.

PATIENTS AND METHODS

Setting, study population and research design

This is a post-hoc analysis of three cohorts of hospitalized patients with CAP, two from the Netherlands and one from Spain [4, 12, 26]. The Dutch cohorts were from two large randomized clinical trials conducted in the Netherlands. All patients hospitalized for CAP from The Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), and all patients included in the Community-Acquired Pneumonia — Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections (CAP-START) were included.

The Spanish (Bellvitge) cohort includes all patients with X-ray confirmed CAP admitted via the emergency department of Bellvitge University Hospital. **Supplementary table 1** shows the main characteristics of the three cohorts. For the purpose of this study, we only analysed patients who received BL, BLM or FQL as empiric antibiotic treatment.

Data collection

Empiric antibiotic treatment was defined as the antibiotic treatment administered in the first calendar day of hospitalization (Dutch cohorts) or prospectively collected as a specific item in the data collection form (Bellvitge cohort), as the first antibiotic regimen administered to the patient after admission.

Data on clinical presentation, laboratory, microbiologic test results, antibiotic use, and clinical outcome were retrieved from medical records. In the absence of notes in clinical records, the following variables were assumed to be absent/negative: pneumococcal or influenza vaccination, clinical symptoms (cough, purulent sputum,

pleuritic chest pain, headache, gastro-intestinal symptoms, chills), confusion, hypotension, tachycardia, positive urinary antigen for *S. pneumoniae.* Definitions of predictors and empiric antibiotic treatment are explained in the **Supplement**.

All studies were approved by the Institutional Review Board in the participating hospitals and the informed consent covered the current analysis. To protect personal privacy, data were anonymized.

Outcomes

The primary outcome was all-cause mortality within 30 days after admission. The 30-day mortality was either assessed at a long-term follow-up visit (Bellvitge), from General Practitioner (GP) medical records (Bellvitge, CAPiTA), or from the municipal records database (CAP-START). The secondary outcomes were ICU admission after the first day of hospitalization and length of hospital stay. All outcomes were measured and analyzed at the individual patient level.

Predictors

Through an extensive search in PubMed we selected a list of candidate clinical predictors of treatment effects on CAP. These clinical predictors should be present and known at admission and associated either to specific CAP etiology or to clinical outcome.

A complete list of the predictors chosen for the analysis and the correspondent bibliography are shown in the **Supplement**.

In addition, the year of admission was included as a confounding variable, categorized in 4 periods of 5 years each, as following: 1995-1999, 2000-2004, 2005-2009, 2010-2014.

Statistical Analysis

Data are presented as percentages and numbers, means with SDs, medians with interquartile ranges (IQRs), or proportions with 95% CIs, as appropriate.

For binary outcomes we used mixed-effects logistic regression models (see **Supplement** for details). To identify candidate predictors of treatment effects we applied a two-step approach. First, we estimated for each candidate predictor the interaction effect with antibiotic treatment in separate models, including the fixed effects, random effects, and the single interaction effect. Interaction variables with a two-sided p-value of <0.10 using the Wald test were included in the second step of our analysis. There we constructed a mixed-effects model including all selected interactions from the first step and all afore mentioned fixed and random effects. P-values of the second-step model were corrected for multiple testing using the Benjamini-Hochberg (BH) method [28]. Two-sided BH adjusted p-values <0.05 were considered statistically significant. Associations are given as ORs with 95% CIs. Effect modifiers for the length of hospital stay (LOS) were tested similarly with mixed-effects linear regression models, after log-transforming length of stay. The exponent of the regression coefficients was interpreted as the effect ratio, e.g. an effect ratio of 2 for factor X implies that a patient with X has a two time longer length of stay compared to a patient without X.

We performed sensitivity analyses including only patients with radiologically confirmed CAP and we performed analyses stratified per cohort. Assumptions of the models were tested visually by plotting residuals. Missing data on smoking habits (6.6% of missing data), pre-hospital antibiotics use (2.5%), elderly home living (12.4%), serum sodium concentration (12.4%), leukocyte count (0.2%), and PSI (0.1%) were imputed by multiple imputations (ten imputation datasets), assuming data missing at

random. Descriptive statistics and multiple imputations were performed using the Statistical Package for the Social Sciences for Windows (Version SPSS 21.0.0.0). Mixed-effects models were performed with R (R Core Team, 2015), and the R-package lme4 (Bates, Maechler, Bolker, Walker 2015).

RESULTS

A total of 8,562 patients were included: 2,184 (25.5%) from the CAPiTA cohort, 2,154 (25.2%) from the CAP-START cohort and 4,224 (49.3%) from the Bellvitge cohort (**supplementary figure 1**). Patient characteristics are described in **table 1**. A probable or definite microbiological diagnosis was made in 46.3% of patients. The diagnostic work-up by cohorts is described in supplementary **table 2.** The causative pathogens identified per age group are summarized in supplementary **table 3**. The majority of patients received BL as empiric treatment (4,399; 51.4%), followed by FQL (3,373; 39.4%) and BLM (790; 9.2%). The different empirical antibiotics administered in each cohort, either in monotherapy or in combination, are listed in supplementary **table 4**.

Clinical predictors for treatment effect: 30-day mortality

In the first step models, five interactions between a clinical predictor and antibiotic empiric treatment were significant at a p-value of <0.10 for 30-day mortality: age, current smoking, tachycardia at admission (heart rate >125 bpm), confusion at admission, and pleuritic chest pain. In the second step we tested the combination of these five interactions (**table 2**). After correction for multiple testing, the following predictors of treatment effect for 30-day mortality were statistically significant: increasing age with the use of FQL vs. BL (interaction OR 1.67, per unit increase of standardized age, 95% CI 1.23 – 2.29, BH adjusted p-value 0.034) and active smoking with the use of FQL vs. BL (interaction OR 2.36, 95% C.I. 1.34 – 4.17, BH adjusted p-value 0.046).

Clinical predictors for treatment effect: ICU admission

In the first step models, three interactions between clinical predictors and antibiotic empiric treatment were statistically significant at a p-value of <0.10 for ICU admission:

admission during influenza season, having a positive urinary antigen test for *S. pneumoniae*, and leukopenia (leukocyte count less than 4000 cells/μL) or extreme leukocytosis (leukocyte count more than 20000 cells/μL) at admission. In the second step we tested the combination of these three interactions (**table 3**). After correction for multiple testing, the only statistically significant predictor of treatment effect for ICU admission was extreme leukocytosis for the use of BLM vs. BL (interaction OR 4.42, 95% CI 1.83 – 10.66, BH adjusted p-value 0.029).

Clinical predictors for treatment effect: length of hospital stay

In the first step models, 12 interactions between clinical predictors and antibiotic empiric treatment were statistically significant at a p-value of <0.10 for LOS: increasing age, previous outpatient antibiotic treatment with atypical coverage, history of cardiovascular disease, new or worsened coughing, presentation with gastro-intestinal symptoms, headache, duration of symptoms (in days), having a positive urinary antigen test for *S. pneumoniae*, serum sodium concentration, presentation with bilateral infiltrates or pleural fluid on chest X-ray, and PSI score. In the second step we tested the combination of these 12 interactions (**table 4**). After correction for multiple testing, the only statistically significant predictor of treatment effect for LOS was increasing age with the use of BLM vs. BL (interaction effect ratio 1.14 per unit increase of standardized age, 95% CI 1.06-1.22, BH adjusted p-value 0.008).

Sensitivity analyses

Sensitivity analyses of the three final models in patients with radiologically confirmed CAP did not reveal substantial changes in the estimates of interactions (**supplementary table 4**). Subsequently, we performed the analyses in each of the three cohorts separately (**supplementary table 4**). In the 30-day mortality model, the ORs for the

interaction between increasing age and FQL use were consistent in the three cohorts, ranging from 1.62 to 1.75, while the OR for the interaction between being an active smoker and FQL use showed larger variation (1.45 to 3.97) albeit all in the same direction. In the LOS model, the effect size for the interaction between increasing age and BLM treatment ranged from 0.93 to 1.78. In the ICU admission model, the ORs for the interaction of leukocytosis with BLM use showed substantial inter-cohort differences (from 1.58 to 48.91).

Finally, since the analyses yielded similar interaction effect estimates in models without inclusion of confounders, confounding by indication appeared to be limited for the interaction effect (**supplementary table 4**).

Individual predicted treatment effect on 30-day mortality

Focusing on our primary outcome, we refitted the step 2 model, restricted to the significant interaction variables (increasing age and to be a current smoker), to construct a predictive model of 30-day mortality based on the provided antibiotic treatment (**figure 1**). According to this model, in older currently smoking patients empiric treatment with FQL is associated with higher 30-day mortality than empiric treatment with BL. Yet, in young non-smoking patients, FQL empiric treatment was predicted to be associated with lower 30-day mortality. There were no clear effects for BLM vs. BL.

DISCUSSION

In this post-hoc analysis of three prospective cohorts from the Netherlands and Spain we identified age and smoking as candidate clinical predictors for the response to empiric antibiotic treatment, from an individualized patient perspective. In a previous clinical trial comparing BL with BLM [11] authors indicate an interaction effect of PSI high classes classification and monotherapy, with a reduced HR for clinical stability. Conversely, in a recent register-based cohort study comparing narrow vs. broad spectrum beta-lactams therapy in CAP patients, the authors did not find significant interaction effects of clinical variable with antibiotic effectiveness [29].

Our findings suggest that older age and smoking are associated with increased 30-day mortality in patients receiving FQL as empiric treatment, either alone or combined with beta-lactams. In older patients the beneficial effects of atypical coverage could be less than in younger patients partly due to a lower incidence of CAP caused by atypical pathogens, as reported in different series [19, 30, 31] and also observed in our data **(supplementary table 3).** Moreover, adverse effects and toxicity of FQL (among them the QT interval prolongation [32]) could be more pronounced in older patients, possibly due to a decline in renal function and changes in pharmacokinetics [33]. Older age was also related with decreased effectiveness of BLM, with an interaction OR of 1.67. However, presumably due to the lower number of patients with this regimen, the association was not statistically significant.

Yet, the direction of the effect of smoking was unexpected, especially in the light of studies reporting a higher proportion of smokers in *Legionella pneumophila* patients, which should, in contrast to our findings, favour fluoroquinolone-based treatment in smokers [34, 35]. This finding raises new questions about a possible interaction

between smoking and antibiotic effectiveness. To the best of our knowledge, currently there is no mechanism that could explain such an interaction. We can only hypothesize that smoking patients might have malignancies, COPD, or other unexplored characteristics, which were not yet recognized and/or reported in the medical chart, which could interact with fluoroquinolone use in a detrimental way. Still, due to the large variability of the ORs between cohorts, this finding should be interpreted with caution.

Older age was related to an increase in LOS in patients who received BLM as empiric treatment, with an addition of one day on the median LOS of 7 days. As mentioned above, the lower incidence of atypical pathogens in older patients could lead to less beneficial effects of BLM in these patients. Furthermore, this finding could refer to the well described association between macrolide use and cardiac events [15, 16], which more frequently occur in older patients. Unfortunately, our data did not allow testing of this hypothesis. Moreover, we observed that the effect size of the interaction between age and BLM use was highly variable between the three cohorts, raising uncertainty on the generalizability of this finding.

Similarly, the large confidence interval of the OR and the wide range of ORs between the three cohorts for the association between ICU admission and leukocyte count over 20,000 in patients who received BLM prohibit firm conclusions.

Of note, the interaction between PSI score and empiric antibiotic treatment showed no effect on clinical outcome. In current clinical practice, the choice of empiric antibiotic treatment is mainly based on clinical severity criteria, supported by disease severity scores such as the PSI score [8, 10]. Our findings suggest that the PSI score does not predict whether a patient will respond better to one empiric antibiotic

treatment over another, suggesting that we need to re-evaluate how we select empiric antibiotics to treat CAP patients.

The key strengths of this study are the large number of patients from different cohorts allowing us to assess treatment effects in subgroup analyses, the high quality prospective data collection, and the inclusion of all possible relevant clinical predictors in the analysis. This study could serve as a prototype for future research in CAP, being the first study in using the novel approach of identifying predictors for the effect of empiric treatment strategies, instead of looking at predictors for clinical outcome or causative pathogen. One source of weakness in this study is the presence of some important differences between cohorts. In Bellvitge cohort all patient included have a confirmed CAP on chest X-ray, unlike the Dutch cohorts. Whereas radiologically confirmed CAP patients represent a more well-defined disease entity, the Dutch cohorts included all patients that are treated for a clinical diagnosis of CAP, improving generalizability of the results to daily clinical practice. However, a sensitivity analysis which included only X-ray confirmed CAP showed similar results. Furthermore, there is a large variability in the presence of some clinical signs and symptoms between the three cohorts (**table 1**), which is probably due to a lack of uniformity in the collection of clinical data. The possibility of misreporting clinical characteristics could underestimate their modifying effect on treatment and hence influence results. To correct for clustering within the cohorts, we used mixed-effects regression models. In addition, we performed a sensitivity analysis stratified by cohorts to assess the robustness of our findings in each of the cohorts.

Importantly, these are all observational data, and we could not rule out confounding by indication of the different empiric antibiotic treatments used, although

we adjusted for multiple confounders in the multivariate models. Yet, as we focus on the interaction effect of clinical factors with empiric antibiotic treatment, we can postulate that the same bias is present in all the different strata, thus not largely biasing the direction and size of the interaction effect.

Moreover, as we cannot rule out bias on the direct effects of antibiotics, the same interaction effect could either mean benefit for one group, or harm for the other group. For example, we cannot claim that fluoroquinolone-based treatment is harmful in older smoking patients, as our results could be also interpreted the other way round, meaning that they are beneficial in younger and non-smoking patients. Considering this limitation, our results should be considered hypothesis generating and need to be confirmed in a randomized controlled trial designed to estimate these interaction effects.

In conclusion, it is plausible that older age influences the response to specific antibiotic treatment, as we found a relationship with both the use of FQL and increased 30-day mortality and BLM use and LOS in older patients. Current smoking was also associated with a decreased response to FQL. Future trials evaluating antibiotic strategies for CAP could assess the treatment effects in patients of different age categories and smoking status. In addition, further research illuminating the causal mechanism underlying the identified associations needs to be performed.

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Conflict of interest:

The authors declare no conflict of interest.

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Table 1. Principal clinical characteristics and outcomes in each cohort.				
	CAPiTA [26] n=2184(25.5%)	**CAP-START [12] n=2154(25.2%)**	**BELLVIGE [4] n=4224(49.3%)**	**ALL n=8562**
Age, years(IQR)	76.0 (72-82)	70.0 (59-79)	70.5 (58-79)	73.0 (63-80)
Male sex, n(%)	1545 (70.7)	1250 (58.0)	2860 (67.7)	5655 (66.0)
Elderly home, n(%)	81 (4.1)	102 (4.8)	234 (6.9)	417 (5.6)
Current smoker, n(%)	323 (19.0)	441 (21.1)	1037 (24.7)	1801 (22.5)
Influenza season, n(%)	1565 (71.7)	1553 (72.1)	3230 (76.5)	6348 (74.1)
S. pneumoniae vaccination, n(%)	1066 (48.8)	44 (2.0)	710 (16.8)	1820 (21.3)
Influenza virus vaccination, n(%)	1916 (87.7)	1396 (64.8)	2001 (47.4)	5313 (62.1)
Outpatient antibiotic, n(%)	656 (31.0)	639 (30.4)	882 (21.4)	2177 (26.1)
Beta-lactams, n(%)	373 (17.8)	366 (17.7)	538 (13.2)	1277 (15.5)
Atypical coverage, n(%)	296 (14.1)	251 (12.1)	327 (8.0)	874 (10.6)
Comorbidities				
Cerebrovascular disease, n(%)	278 (12.7)	221 (10.3)	343 (8.1)	842 (9.8)
COPD, n(%)	1351 (61.9)	973 (45.2)	1230 (29.1)	3554 (41.5)
Malignancy, n(%)	301 (13.8)	364 (16.9)	414 (9.8)	1079 (12.6)

Cardiovascular, n(%)	909 (41.6)	454 (21.1)	1042 (24.7)	2405 (28.1)
Immunosuppression, n(%)	235 (10.8)	210 (9.7)	337 (8.0)	782 (9.1)
Symptoms days, days (IQR)	3 (1-6)	3(1-7)	3 (2-6)	3 (1-7)
Cough, n(%)	1509 (69.1)	1776 (82.5)	3585 (84.9)	6870 (80.2)
Purulent sputum, n(%)	924 (42.3)	1247 (57.9)	2022 (47.9)	4193 (49.0)
Gastro-intestinal symptoms, n(%)	167 (7.6)	291 (13.5)	635 (15.0)	1093 (12.8)
Pleuritic chest pain, n(%)	225 (10.3)	294 (13.6)	1767 (41.8)	2286 (26.7)
Headache, n(%)	78 (3.6)	99 (4.6)	618 (14.6)	795 (9.3)
Chills, n(%)	320 (14.7)	426 (19.8)	1927 (45.6)	2673 (31.2)
Confusion, n(%)	291 (13.3)	193 (9.0)	586 (13.9)	1070 (12.5)
Fever, n(%)	786 (36.7)	1206 (57.1)	2013 (48.1)	4005 (47.5)
Hypotension, n(%)	343 (15.7)	293 (13.6)	635 (15.0)	1271 (14.8)
Heart rate > 125 bpm, n(%)	202 (9.2)	269 (12.5)	352 (8.3)	823 (9.6)
Respiratory failure, n(%)	528 (24.2)	837 (38.9)	2435 (57.6)	3800 (44.4)
Bilateral infiltrate on chest X ray, n(%)	185 (8.5)	190 (8.8)	627 (14.8)	1002 (11.7)
Pleural fluid on chest X ray, n(%)	206 (9.4)	146 (6.8)	708 (16.8)	1060 (12.4)
Positive urinary antigen	166 (7.6)	197 (9.1)	939 (22.2)	1302 (15.2)

for *S. pneumoniae*, n(%)				
PSI score, points (IQR)	107 (91-125)	86 (66-107)	99 (77-124)	98 (79-120)
PSI class I, n(%)	0	0	184 (4.4)	184 (2.2)
PSI class II, n(%)	34 (1.6)	644 (29,9)	672 (16.0)	1350 (15.8)
PSI class III, n(%)	506 (23.2)	556 (25.8)	859 (20.4)	1921 (22.5)
PSI class IV, n(%)	1228 (56.2)	770 (35.7)	1641 (39,0)	3639 (42.6)
PSI class V, n(%)	416 (19.0)	184 (8.5)	857 (20.3)	1457 (17.0)
Antibiotic empiric treatment				
Beta-lactam monotherapy, n(%)	1493 (68.4)	730 (33.9)	2176 (51.5)	4399 (51.4)
Beta-lactam + Macrolide, n(%)	64 (2.9)	536 (24.9)	190 (4.5)	790 (9.2)
Fluoroquinolone-based, n(%)	627 (28.7)	888 (41.2)	1858 (44.0)	3373 (39.4)
Outcomes				
30-day mortality, n(%)	195 (9.2)	114 (5.3)	261 (6.2)	570 (6.7)
Early mortality, n(%)	55 (2.5)	12 (0.6)	89 (2.1)	156 (1.8)
ICU admission, n(%)	112 (5.1)	41 (1.9)	207 (4.9)	360 (4.2)
Length Of Hospital Stay, days (IQR)	7 (5-11)	6 (4-9)	8 (5-11)	7 (5-10)

IQR: interquartilic range. COPD: chronic obstructive pulmonary disease.

PSI: Pneumonia Severity Index.

FQL based treatment was defined as any regimen including a FQL (FQL in monotherapy or in combination therapy).

Early mortality: mortality for any cause in the first 48 hours from admission.

ICU: Intensive Care Unit.

Table 2. 30-day mortality: difference in response to antibiotic empiric strategy by clinical predictors in the second step mixed-effects logistic regression model.

	Adjusted interaction OR (95% IC)	**BH p-value for interaction**
Age*BLM	1.67 (1.03-2.72)	0.282
Age*FQL	1.67 (1.23-2.29)	0.034
Smoker*BLM	1.10 (0.40-2.99)	>0.999
Smoker*FQL	2.36 (1.34-4.17)	0.046
Heart rate>125 bpm*BLM	0.36(0.11-1.20)	0.487
Heart rate>125 bpm*FQL	1.32 (0.73-2.41)	>0.999
Confusion*BLM	0.73 (0.33-1.60)	>0.999
Confusion*FQL	0.53 (0.32-0.87)	0.123
Pleuritic chest pain*BLM	2.47 (1.01-6.02)	0.282
Pleuritic chest pain*FQL	0.99 (0.53-1.83)	>0.999

FQL: fluoroquinolone-based. BLM: beta-lactam plus macrolide. BH: Benjamini – Hochberg method.

Table 3. Intensive Care Unit admission: difference in response to antibiotic empiric strategy by clinical predictors in the second step mixed-effects logistic regression model.

	Adjusted interaction OR (95% CI)	**BH p-value for interaction**
Influenza season*BLM	0.76 (0.29-1.90)	>0.999
Influenza season*FQL	0.66 (0.37-1.16)	>0.999
S.pneumoniae+Ag*BLM	0.45 (0.09-2.19)	>0.999
S.pneumoniae+Ag*FQL	0.46 (0.25-0.84)	0.117
Leukocyte count <4000 cells/µL*BLM	3.27(0.60-17.83)	>0.999
Leukocyte count <20000 cells/µL *BLM	4.42 (1.83-10.66)	0.029
Leukocyte count <4000 cells/µL *FQL	3.71 (1.34-10.28)	0.117
Leukocyte count <20000 cells/µL *FQL	1.30 (0.69-2.46)	>0.999

FQL: fluoroquinolone-based. BLM: beta-lactam plus macrolide. BH: Benjamini – Hochberg method.

Table 4. Length of Hospital Stay: difference in response to antibiotic empiric strategy by clinical predictors in the second step mixed-effects linear regression model.		
	Adjusted interaction effect ratio (95% CI)	**BH p-value for interaction**
Age*BLM	1.14 (1.06-1.22)	0.008
Age*FQL	1.02 (0.98-1.06)	>0.999
Outpatient atypical coverage*BLM	0.81 (0.69-0.96)	0.213
Outpatient atypical coverage*FQL	0.93 (0.84-1.02)	0.591
History of cardiovascular disease*BLM	1.04 (0.92-1.18)	>0.999
History of cardiovascular disease*FQL	1.02 (0.95-1.09)	>0.999
New or worsened coughing*BLM	0.94 (0.83-1.07)	>0,999
New or worsened coughing*FQL	1.02 (0.95-1.10)	>0.999
Gastro-intestinal symptoms*BLM	0.87 (0.75-1.00)	0.394
Gastro-intestinal symptoms*FQL	0.94 (0.86-1.02)	0.591
Headache*BLM	0.96 (0.77-1.18)	>0.999
Headache*FQL	0.95 (0.86-1.06)	>0.999
S.pneumoniae+ Urinary Antigen*BLM	1.19 (1.01-1.40)	0.375
S.pneumoniae+ Urinary Antigen*FQL	1.11 (1.02-1.20)	0.167
*PSI-score*BLM*	1.00 (1.00-1.00)	>0.999

*PSI-score*FQL*	1.00 (1.00-1.00)	>0.999
Sodium^2*BLM	0.98 (0.93-1.04)	>0.999
Sodium^2*FQL	1.03 (1.00-1.06)	0.519
Number of symptom days*BLM	1.00 (0.99-1.00)	>0.999
Number of symptom days*FQL	1.00 (0.99-1.00)	0.519
Pleural fluid on chest X-ray*BLM	1.02 (0.85-1.22)	>0.999
Pleural fluid on chest X-ray * FQL	1.06 (0.97-1.16)	0.765
Bilateral infiltrate on chest X-ray *BLM	1.01 (0.85-1.19)	>0.999
Bilateral infiltrate on chest X-ray *FQL	1.13 (1.03-1.24)	0.167
FQL: fluoroquinolone-based. BLM: beta-lactam plus macrolide. BH: Benjamini – Hochberg method.		

Figure 1.

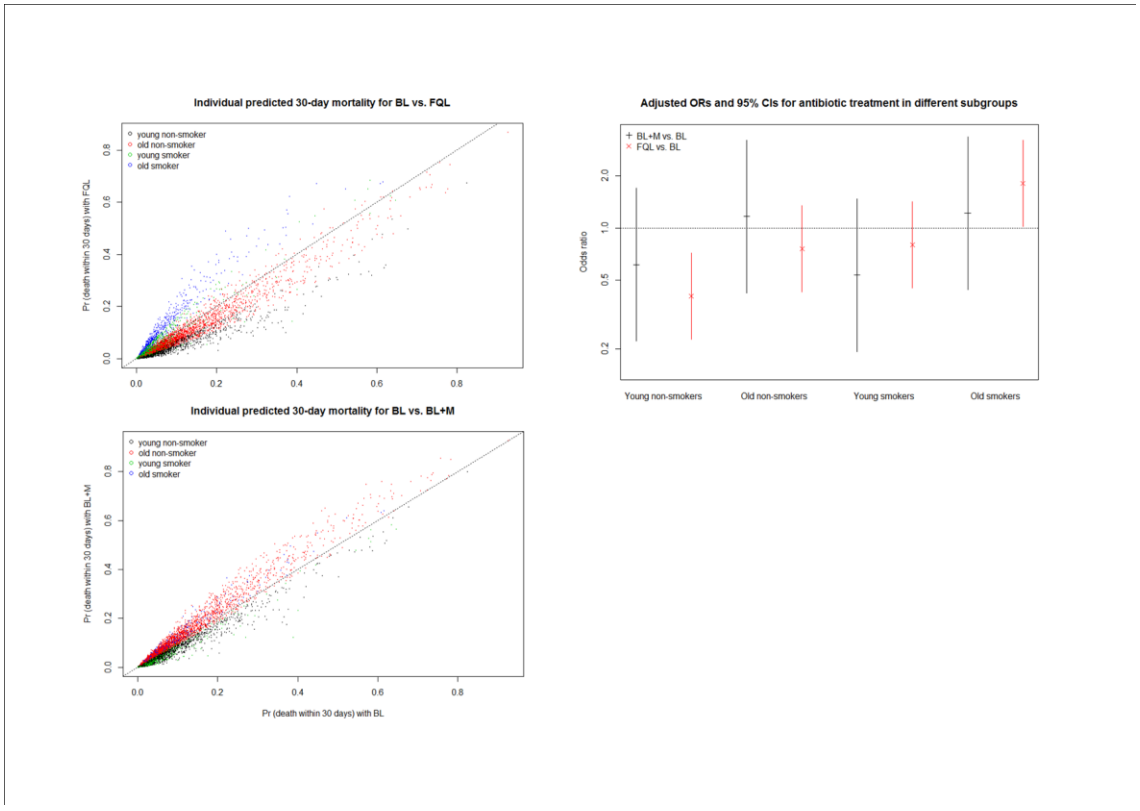
Predicted 30-day mortality at individual patient level.

A. Individual predicted 30-day mortality in a logistic regression model restricted to the significant interaction variables (age and smoke habit), comparing patients who receive BL vs. patients who receive FQL as empiric treatment.

B. Individual predicted 30-day mortality in a logistic regression model restricted to the significant interaction variables (age and smoke habit), comparing patients who receive BL vs. patients who receive BLM as empiric treatment.

C. Adjusted (BH method) Odds Ratio with 95% Confidence Interval for 30-day mortality in different subgroups of patients, divided for their group age and smoke habit.

FQL: fluoroquinolone-based. BLM: beta-lactam plus macrolide. BH: Benjamini – Hochberg method.



Supplement

Clinical predictors.

The predictors chosen for the analysis were the following: age (in years), gender, smoking habit, living in an elderly home, pneumococcal vaccination, influenza vaccination, admission during influenza season (from week 40 up to and including week 20), received outpatient antibiotic treatment (with beta-lactams or with atypical coverage), cardiovascular disease, COPD, immunodeficiency (as defined previously), duration of symptoms (in days), cough, purulent sputum, gastrointestinal symptoms, headache, pleuritic chest pain, chills, confusion, fever (Temperature>38 °C) , hypotension (diastolic blood pressure ≤60 mmHg and/or systolic blood pressure < 90 mmHg), heart rate > 125 bpm, respiratory failure (defined as one of the following: Oxygen saturation < 90 mmHg at ambient air, or pO2 <60 mmHg in arterial gases, or PaO2FiO2 < 300 mmHg), leucocytes count (categorized as: <4000 cells/µL, 4000 – 20000 cells/µL, >20000 cells/µL), serum sodium concentration, bilateral infiltrate on chest X-ray, pleural effusion on chest X-ray, positivity of *Streptococcus pneumoniae* urinary antigen test, and PSI score.

Definitions of clinical predictors

Immunodeficiency was defined as the presence of one or more of the following conditions: terminal renal failure, chemo- or radiotherapy in the past 90-days for solid or hematologic malignancies, use of immunosuppressive drugs, chronic use of corticosteroids (more than 0.5mg/kg/day in the Dutch cohorts, for at least 2 weeks and more than 15mg/day for at least 2 weeks in the Bellvitge cohort), HIV patients with CD4-count < 200, or having received a solid organ or stem cell transplantation.

Cardiovascular disease was defined as documentation in the medical records of, or treatment for, coronary artery disease, arrhythmia or congestive heart failure, or the presence of valvular heart disease. Chronic obstructive pulmonary disease (COPD) was defined as documentation of COPD in the medical history of the patient records.

Influenza and pneumococcal vaccine status was assessed from interviews with the patients or their relatives and from review of hospital and personal health records (vaccination card). Patients were considered to be vaccinated against pneumococcus if any pneumococcal vaccine had been administered in the 5 years before admission, and influenza vaccinated if seasonal influenza vaccine had been administered during the year before admission. In CAPiTA cohort, patients were considered vaccinated against pneumococcus if randomized to receive pneumococcal vaccination at least 14 days before the occurrence of CAP.

Outpatient antibiotic treatment was defined as the oral intake of antibiotics before hospitalization for the same episode of acute respiratory disease. For the purpose of this study, outpatient antibiotic treatment was categorized as beta-lactam monotherapy or antibiotics with atypical coverage.

Empiric antibiotic treatment

The preferred empiric antibiotic treatment differed between the cohorts. In the Bellvitge cohort, local hospital guidelines recommended treatment with BL, BLM, or a 4th generation FQL with or without a ß-lactam, depending on CAP severity and clinical suspicion for atypical pathogens.

The empiric antibiotic treatment in the CAPiTA cohort was based on the 2005 Dutch guidelines, which recommended BL for moderate-severe CAP and 4th generation FQL monotherapy, combination therapy of penicillin or amoxicillin with ciprofloxacin, or combination therapy of 2nd or 3rd generation cephalosporin with a macrolide for severe CAP [27]. In the CAP-START cohort, during consecutive periods of 4 months, BL, BLM, or FQL was used as the preferred empiric treatment for CAP-patients hospitalized to a non-ICU ward. Deviations from the preferred treatment were allowed at the discretion of the treating physician. Actually received empiric treatment was used for the current analysis.

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Statistical analysis: mixed-effect models.

For binary outcomes we used mixed-effects logistic regression models with a random intercept and a random slope for empiric antibiotic treatment for the three different cohorts used. Using these random effects, the model adjusts for dependence of observations within one cohort by allowing the baseline outcome rate and the effect of antibiotic treatment to differ. Continuous predictors which did not comply with linearity assumptions were either log-transformed (age) or categorized (leukocyte count). The PSI-score was added as a continuous variable, however, to avoid redundancy, in every model we included PSI score minus the interaction variables tested in each model. Antibiotic treatment was entered in the models as a categorical variable with three values (one for each regimen tested with BL being the reference value). All models included all the predictors and the confounder as fixed effects.

Supplementary table 1. Main characteristics of the three cohorts.

	CAPiTA	**CAP-START**	**BELLVIGE**
Type of study	Randomized, placebo-controlled, double-blind trial evaluating pneumococcal vaccination.	Cluster-randomized trial comparing three empiric antibiotic treatment strategies.	Observational, prospective cohort.
Patients included in the original cohorts	84,496 persons aged ≥ 65 years, not immunosuppressed.	2283 patients with clinical suspected CAP hospitalised to a non ICU ward.	4890 patients with X-ray confirmed CAP admitted via the emergency department.
Patients considered for the current study	Patients hospitalised with clinically suspected CAP (n=3290).	All patients.	All patients.
Exclusion criteria for the current study	• Hospitalization in the previous 14 days. • ICU admission in the first 24 hours.	• Age < 18 years. • Hospitalization in the previous 14 days. • empiric antibiotic treatment	• Age < 18 years. • Hospitalization in the previous 10 days. • ICU admission in the first 24

	• empiric antibiotic treatment other than BL, BLM or FQL	other than BL, BLM or FQL	hours. • empiric antibiotic treatment other than BL, BLM or FQL
Follow up	Until the end of the study (from 90 days to 5 years).	90 days.	Follow up during hospitalization and long term follow up visit (30 days from discharge).
Period of inclusion	September 15th 2008 - 28th August, 2013	February 2011 - August 2013	February 1995 – December 2014
Location	58 Dutch hospitals	Seven Dutch Hospitals	Bellvitge University Hospital, Barcelona, Spain.

Supplementary table 2. Diagnostic work-up in the three cohorts.

	CAPiTA n=2184(25.5)	**CAP-START n=2154(25.2)**	**BELLVIGE n=4224(49.3)**	**ALL**
Sputum cultures, n (%)	943 (43.2)	976 (45.3)	2478 (58.7)	4397 (51.4)
Blood cultures	1694 (77.6)	160 (76.6)	3809 (90.2)	7153 (83.5)
Legionella urinary antigen test collected	25 (1.1)	1647 (76.5)	1761 (41.7)	3433 (40,1)
Streptococcus pneumoniae urinary antigen test collected	2040 (93.4)	1703 (79.1)	2547 (60.3)	6290 (73.5)
Rx thorax performed	2184 (100)	2154 (100)	4224 (100)	8562 (100)
RX confirmed CAP	1888 (86.4)	1970 (91.5)	4224 (100)	8082 (94.4)
TC scan performed	155 (7.1)	146 (6.8)	NO DATA	-------

Supplementary table 3. Most common etiology of community-acquired pneumonia for age groups.

	<50 years n=991 (11.6%)	**50-75 years n=3761 (43.9%)**	**>75 years n=3810 (44.5%)**	**All n=8562**
Streptococcus pneumonia,n(%)	333 (33.6)	928 (24.7)	829 (21.8)	2090 (24.4)
Other streptococci, n(%)	18 (1.8)	32 (0,9)	27 (0.7)	77 (0.9)
Haemophilus influenzae, n(%)	39 (3.9)	259 (6.9)	196 (5.1)	494 (5.8)
Atypical etiology, n(%)	109 (11.0)	227 (6.0)	100 (2.6)	436 (5.1)
Legionella pneumophila, n(%)	45 (4.5)	128 (3.4)	54 (1.4)	227 (2.7)
Mycoplasma pneumoniae, n(%)	44 (4.4)	28 (0,7)	13 (0.3)	85 (1.0)
Pseudomonas aeruginosa, n(%)	5 (0.5)	61 (1.6)	79 (2.1)	145 (1.7)
Influenza virus[1], n(%)	35 (3.5)	59 (1.6)	17 (0.4)	111 (1.3)
Anaerobics, n(%)	39 (3.9)	84 (2.2)	134 (3.5)	257 (3.0)
Staphylococcus aureus, n(%)	16(1.6)	60 (1.6)	64 (1.7)	140 (1.6)
Moraxella catharralis, n(%)	5 (0.5)	64 (1.7)	45 (1.2)	114 (1.3)
Enterobacteriaceae, n(%)	11 (1.1)	119 (3.2)	149 (3.9)	279 (3.3)
Other Gram-negative bacteria, n(%)	0 (0)	16 (0.4)	7 (0.2)	23 (0.3)
Mixed etiology[2], n(%)	55 (5.5)	222 (5.9)	175 (4.6)	452 (5.3)
Unknown etiology, n(%)	406 (41.0)	1946 (51.7)	2243 (58.9)	4595 (53.7)

1. Influenza virus was routinely tested from 2008-2009 pandemia in Bellvitge cohort.

2. Patients with mixed etiology are also listed in the individual pathogens rows.

Supplementary Table 4. Empiric antibiotics in monotherapy or combination used in the different cohorts.

	CAPiTA **n=2184(25.5)**	**CAP-START** **n=2154(25.1)**	**BELLVIGE** **n=4224(49.3)**	**ALL**
Beta-lactam monotherapy, n (%)	**1493 (68.4)**	**730 (33.9)**	**2176 (51.5)**	**4399 (51.4)**
Penicillin/Amoxicillin	264 (12.1)	202 (9.4)	7 (0.2)	473 (5.5)
Amoxicillin-clavulanic acid	811 (37.1)	338 (15.7)	816 (19.3)	1965 (23.0)
Cephalosporins	401 (18.4)	173 (8.0)	1285 (30.4)	1859 (21.7)
Fucloxacillin	0	1 (0)	0	1 (0)
Piperacillin/tazobactam	12 (0.5)	7 (0.3)	43 (1.0)	62(0.7)
Carbapenems	5 (0.2)	9 (0.4)	25 (0.6)	39 (0.5)
Beta-lactam plus macrolide	**64 (2.9)**	**536 (24.9)**	**190 (4.5)**	**790 (9.2)**
Penicillin/Amoxicillin + Erythromycin	14 (0.6)	141 (6.5)	0	155 (1.8)
Penicillin/Amoxicillin + Clarithromycin	2 (0.1)	45 (2.1)	0	47 (0.5)
Penicillin/Amoxicillin + Azithromycin	1 (0)	12 (0.6)	0	13 (0.2)
Amoxi-clavulanic + Erythromycin	10 (0.5)	12 (0.6)	21 (0.5)	43 (0.5)

Amoxi-clavulanic + Clarithromycin	13 (0.6)	114 (5.3)	13 (0.3)	140 (1.6)
Amoxi-clavulanic + Azithromycin	1 (0)	22 (1.0)	1 (0)	24 (0.3)
Cephalosporins + Erythromycin	16 (0.7)	104 (4.8)	59 (1.4)	179 (2.1)
Cephalosporins + Clarithromycin	5 (0.2)	18 (0.8)	88 (2.1)	111 (1.3)
Cephalosporins + Azithromycin	1 (0)	68 (3.2)	6 (0.1)	75 (0.9)
Fluloxacillin + Erythromycin	1 (0)	0	0	1 (0)
Carbapenems + Clarithromycin	0	0	2 (0)	2 (0)
Fluoroquinolone monotherapy	**174 (8.1)**	**752 (34.4)**	**549 (13.0)**	**1475 (17.2)**
Ciprofloxacin	45 (2.1)	10 (0.5)	9 (0.2)	64 (0.7)
Levofloxacin	10 (0.5)	197 (9.1)	539 (12.8)	746 (8.7)
Moxifloxacin	119 (5.4)	545 (25.3)	1 (0)	665 (7.8)
Beta-lactam plus fluoroquinolone	**453 (21.0)**	**136 (6.2)**	**1309 (31.0)**	**1898 (22.2)**
Penicillin/Amoxicillin + Ciprofloxacin	178 (8.2)	53 (2.5)	0	231 (2.7)
Penicillin/Amoxicillin + Levofloxacin	0	3 (0.1)	0	3 (0)
Penicillin/Amoxicillin + Moxifloxacin	1 (0)	4 (0.2)	0	5 (0.1)

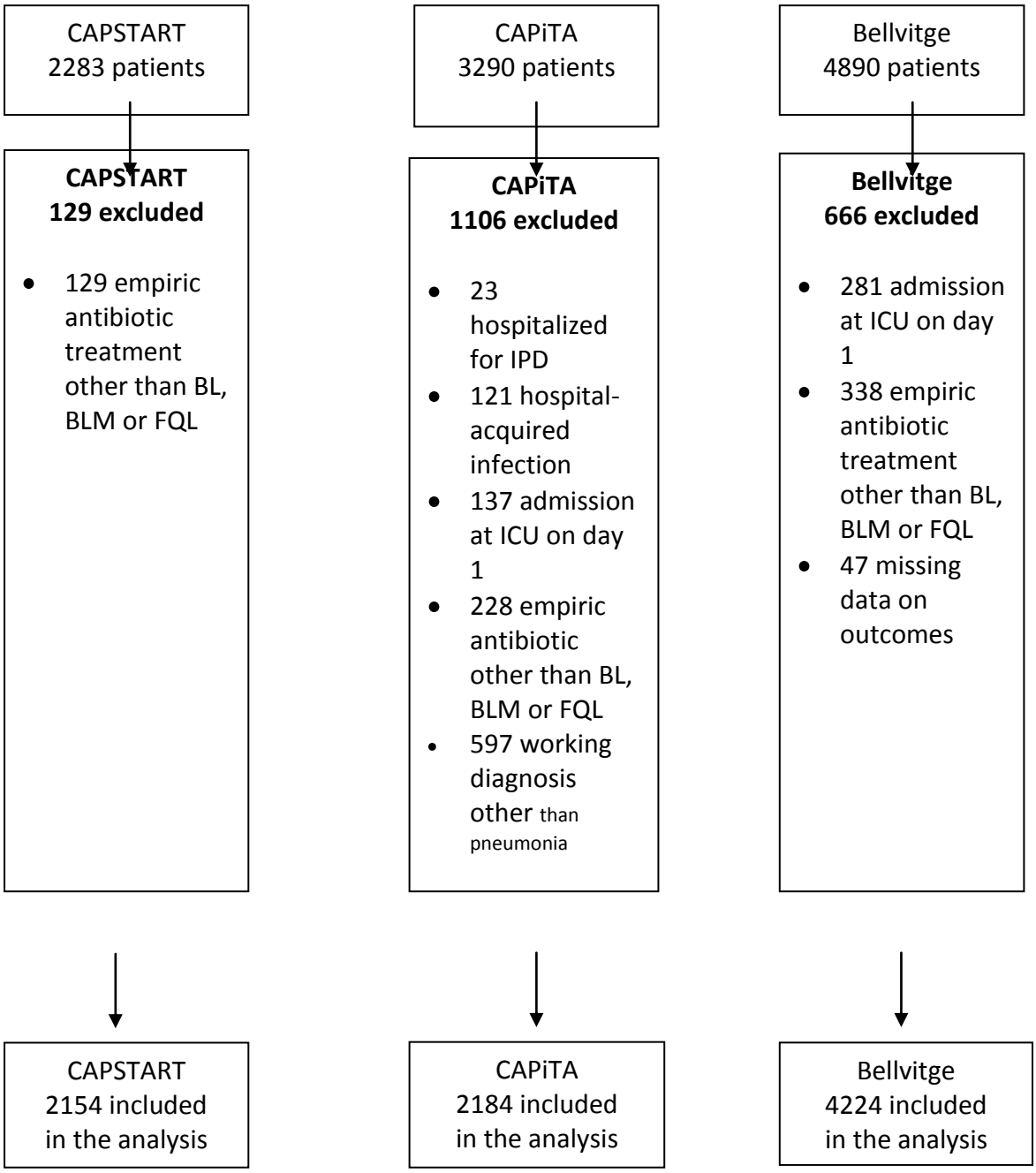
Amoxi-clavulanic + Ciprofloxacin	174 (8.0)	36 (1.7)	0	210 (2.5)
Amoxi-clavulanic + Levofloxacin	3 (0.1)	4 (0.2)	49 (1.2)	56 (0.7)
Amoxi-clavulanic + Moxifloxacin	3 (0.1)	9 (0.4)	0	12 (0.1)
Cephalosporins + Ciprofloxacin	89 (4.1)	19 (0.9)	1 (0)	109 (1.3)
Cephalosporins + Levofloxacin	0	2 (0.1)	1239 (29.3)	1241 (14.5)
Cephalosporins + Moxifloxacin	5 (0.2)	3 (0.1)	0	8 (0.1)
Cloxacillin + Levofloxacin	0	0	1 (0)	1 (0)
Cloxacillin + Moxifloxacin	0	2 (0.1)	0	2 (0)
Piperacillin/Tazobactam + Levofloxacin	0	0	11 (0.3)	11 (0.1)
Carbapenems + Ciprofloxacin	0	1 (0)	1 (0)	2 (0)
Carbapenems + Levofloxacin	0	0	7 (0.2)	7 (0.1)

Supplementary Table 5. Interaction effect estimates from sensitivity analysis with significant clinical predictors from the second step models.

	All patients	Rx Confirmed CAP	CAPiTA	CAP-START	Bellvitge	Without confounders
30-day mortality						
Age*FQL	1.67	1.75	1.62	2.61	1.62	1.60
Smoker*FQL	2.36	2.93	1.77	1.45	3.97	2.12
Intensive Care Unit admission						
Leucocyte count<20000 cells/µL *BLM	4.42	4.37	48.91	1.58	2.44	4.16
Length of Hospital Stay						
Age*BLM	1.13	1.11	1.78	1.07	0.93	1.13
FQL: fluoroquinolone-based. BLM: beta-lactam plus macrolide.						

Supplementary Figure 1.

Flowchart of patients' inclusion.



7. DISCUSSION

Our investigation focused on some of the current challenges in antibiotic treatment of community-acquired pneumonia (CAP).

The first study, an observational analysis of a prospective cohort of adults hospitalized with CAP, found a substantial decrease in 30-day mortality over a period of 20 years, despite an upward trend in several factors with negative prognostic influence. In our cohort, we observed significant changes over time in the management of CAP patients that could have caused the improved outcomes observed, such as an increased number of patients who underwent mechanical ventilation or who were admitted to the ICU, and an increase in fluoroquinolone use, either alone or in combination with β-lactams.

In our cohort, the use of fluoroquinolones was the only factor associated with decreased mortality over time in a multivariable analysis. However, after carefully matching patients by means of a propensity score, the beneficial effect of fluoroquinolone use on mortality was not confirmed. Similarly, we did not observe better outcomes in patients who received the β-lactams plus macrolides regimen. Several changes in the management of CAP and a general improvement in global care over time may have caused the observed outcomes.

In the second study, we analysed the impact of pre-hospital antibiotic treatment on CAP patients. The demographic features of patients with pre-hospital antibiotic treatment in our cohort were similar to those previously reported: these patients were significantly younger and had lower rates of comorbidity than the other group.

Patients who received pre-hospital antibiotic treatment were also less likely to have fever and leukocytosis and, as expected, presented less bacteraemia.

Interestingly, the prevalence of *L. pneumophila* was nearly three times higher in patients who received pre-hospital antibiotics, mainly β-lactams. After controlling for confounding factors in a propensity analysis, we did not find significant differences in prognosis between study groups. Therefore, information on pre-hospital antibiotic treatment should always be considered as it can guide the choice of aetiological diagnostic tests and empirical antibiotic therapy to be used in patients with CAP.

In the study on timing of antibiotic therapy, we found that antibiotic administration within 4 to 8 hours of arrival at the ED did not improve 30-day survival in hospitalized adults for CAP or HCAP.

Our results also show that patients with CAP who received early treatment (mainly ≤4 hours) were more likely to require ICU admission and had higher 30-day mortality. These patients had more severe clinical features at hospital admission, which indirectly indicates that in the ED context, the more serious patients are usually treated as a priority. Importantly, we did not find significant differences in the mean time from patient arrival at the ED until antibiotic administration between CAP and HCAP patients.

In the study on antibiotic de-escalation in patients with community-acquired pneumococcal pneumonia, we found that the non-de-escalation group was characterized by a more severe presentation at admission, as evidenced by higher frequencies of hypotension, tachycardia, multilobar pneumonia on chest X-ray, and bacteraemia. No significant differences were detected regarding adverse drug reactions or readmission (<30 days) between study groups. After adjusting for confounders in multivariate and propensity score analyses, we found that antibiotic de-escalation within the first 72 hours after hospital admission was not associated with

an increased risk of 30-day mortality and was effective in reducing the duration of LOS in patients with pneumococcal pneumonia, even in those patients with bacteraemia and severe disease, and those who were clinically unstable.

We subsequently explored the impact of different antibiotic treatments for Legionella pneumonia in a multicenter study. Our observational study found that patients treated with azithromycin had similar outcomes to those treated with levofloxacin, including time to defervescence, time to achieve clinical stability, length of intravenous therapy and length of hospital stay. Conversely, patients treated with clarithromycin had longer intravenous antibiotic treatment and longer hospital stays compared to those treated with levofloxacin. The main finding is that we were unable to find any difference between levofloxacin and azithromycin on 30-day mortality in multivariate analysis. Of note is that both early and overall mortality were twice as high in patients treated with azithromycin compared to levofloxacin in a univariate analysis. However, it is also important to note that due to the low number of deaths in both groups, results regarding mortality should be interpreted with caution.

Finally, we realised a post-hoc analysis of three prospective cohorts from the Netherlands (where I carried out my international stay) and Spain to analyse predictors for response to empirical antibiotic treatment in hospitalised CAP patients. Our findings suggest that older age and smoking are associated with increased 30-day mortality in patients receiving fluoroquinolones (FQL) as an empirical treatment, either alone or combined with beta-lactams. Older age was also related with decreased effectiveness of beta-lactams plus macrolides (BLM) combination therapy, although the association was not statistically significant. Older age was related to an increase in

LOS in patients who received BLM as empiric treatment, with an addition of one day on the median LOS of 7 days.

Future trials evaluating antibiotic strategies for CAP could assess the treatment effects in patients of different age categories and smoking status. In addition, further research illuminating the causal mechanism underlying the identified associations needs to be performed.

7.1. Declining mortality among hospitalized patients with community-acquired pneumonia.

This observational study of a large prospective cohort of adults hospitalized with CAP found a substantial decrease in 30-day mortality over a period of 20 years, in spite of an upward trend in several factors with negative prognostic influence.

A similar downward trend in mortality due to CAP has been reported in two previous studies [Ruhnke GW et al. 2010; Ruhnke GW et al. 2011] using US national da- tabases, where mortality due to CAP fell from 8.9% in 1993 to 4.1% in 2005 ($p < 0.001$) in hospitalized patients [Ruhnke GW et al. 2010] and from 13.5% in 1987 to 9.7% in 2005 in a population of elderly in- patients and outpatients with CAP [Ruhnke GW et al. 2011].

Interestingly, two recent studies have also found reductions in mortality among CAP patients [Georges H et al. 2013; Gattarello S et al. 2014]. The first study [Georges H et al. 2013], which compared patients with CAP admitted to the ICU in two periods (1995 – 2000 versus 2005 – 10), suggests that the decrease in mortality observed may be related to the implementation of a sepsis management bundle derived from the

Surviving Sepsis Campaign. Among other interventions, the bundle included the combined use of levofloxacin and a third-generation cephalosporin for the initial empirical antimicrobial regimen. The second study [Gattarello S et al. 2014], a matched case–control study that compared two periods (2000–02 versus 2008–13) found a 15% decrease in mortality among patients with pneumococcal pneumonia admitted to the ICU. Early antibiotic administration and combination antibiotic therapy were independently associated with better outcomes.

In our cohort, we observed over time some important changes in the management of CAP patients that could have caused the better outcomes observed, including the rise in patients who underwent mechanical (either invasive or non-invasive) ventilation or who were admitted to ICU, and a huge change in empirical antibiotic choice, with an increase in fluoroquinolone use, either alone or in combination with β-lactams.

Several randomized controlled trials have demonstrated a non-inferiority of fluoroquinolone monotherapy when compared with either β-lactams alone or β-lactams plus macrolide regimens in treating patients with CAP [Frank E et al. 2002; Erard V et al. 2004; Portier H et al. 2005; Dresser LD et al 2011; Postma DF et al. 2015]. Furthermore, fluoroquinolones have also been associated with improvement of other outcomes, such as lower risk of treatment failure, shorter duration of intravenous treatment and hospital stay, a faster clinical improvement and a decrease in the number of admissions of low-risk patients [Marrie TJ et al. 200; Welte T et al. 2005; Carratalà J et al. 2005; Postma DF et al 2015]. In our cohort the use of fluoroquinolones was the only factor associated with decreased mortality over time in a multivariable analysis. However, after matching patients by means of a propensity score for

receiving quinolones, the beneficial effect of fluoroquinolone use on mortality was not confirmed.

In recent years, the possible beneficial effect of combination therapy with β-lactams and macrolides on patient outcomes has been the subject of active debate. Although the use of combination therapy has been linked to better outcomes in some observational studies, especially in patients with severe CAP [Nie W et al. 2014], this benefit has not been found in randomized controlled trials [Asadi L et al. 2012; Garin N et al. 2014]. In a large meta-analysis of almost 10 000 critically ill patients with CAP, when broadly guideline-concordant regimens were compared (β-lactams plus macrolides versus β-lactams plus fluoroquinolones), no significant difference in mortality was found [Sligl WI et al. 2014]. Similarly, we did not observe better outcomes in patients who received the β-lactams plus macrolides regimen.

The strengths of this study include the prospective nature of the cohort, the comprehensive data collection over a period of 20 years, the large number of a wide spectrum of hospitalized patients with CAP and the application of a propensity analysis. There are, however, some limitations that should be acknowledged; the study was conducted at a single centre and the extrapolation of our results to other settings should be done with care.

In summary, 30-day mortality significantly decreased over time in hospitalized CAP patients in spite of an upward trend in patient age and other factors associated with poor outcomes. Several changes in the management of CAP and a general improvement in global care over time may have caused the observed outcomes. In fact, during the past decades mortality has declined for a variety of conditions, including sepsis, myocardial infarction and stroke [Roger VL et al. 2010; Kaukonen KM

et al. 2014; Ma J et al. 2015], suggesting an overall better clinical management and a general improvement of healthcare systems.

7.2. Impact of pre-hospital antibiotic use on community-acquired pneumònia

The demographic features of patients with pre-hospital antibiotic treatment in our cohort were similar to those previously reported: that is, these patients were significantly younger and had lower rates of comorbidity than the other group. These demographic differences are probably because clinicians reserve in-hospital treatment for older and more compromised patients. In addition, the current CAP severity scores used to assess the need for hospitalization attach great importance to age and the presence of comorbidities. These variables are an obstacle to obtaining valid results unless they and other confounding factors are carefully controlled. Significantly, previous reports have not studied the propensity for prescribing pre-hospital antibiotic therapy.

We compared the clinical picture of CAP at admission in patients who received and who did not receive pre-hospital antibiotic treatment. Although CAP occurs regularly in both groups, with purulent sputum, pleuritic pain and signs of consolidation, the groups present differences with regard to other clinical features. Patients who received pre-hospital antibiotic treatment presented more headache and arthralgias, and less fever at admission. Likewise, regarding radiographic findings, we found that patients with pre-hospital antibiotic treatment more frequently had chest X-ray cavitation. Previous studies offer little information on the clinical presentation of CAP in this context.

Moreover, we observed that patients receiving prior antibiotics were less likely to have fever and leucocytosis. Hence, it is plausible to think that prior use of antibiotics may lead to a blunted inflammatory response at admission. In this regard, in a cohort of CAP patients Krüger et al. [Krüger et al. 2010] demonstrated that procalcitonin, C-reactive protein and white blood cell count are not good predictors of mortality in patients who have received pre-hospital antibiotic treatment. This finding suggests caution in interpreting the diagnostic and predictive values of inflammatory markers in CAP patients with antibiotic treatment prior to hospital admission.

An important finding in our study was the difference in the frequency of causative organisms of CAP between the study groups. The prevalence of *L. pneumophila* was nearly three times higher in patients who received pre-hospital antibiotics, mainly β-lactams. Furthermore, we did not find differences in the proportion of other potentially resistant organisms, such as *Pseudomonas aeruginosa*, between the study groups. As expected, bacteraemia was less frequent in patients pre-treated with antibiotics and we also found a higher proportion of unknown aetiology in this group of patients. Interestingly, the frequency of positive sputum culture was comparable in the two groups. The sensitivity and specificity of the pneumococcal urinary antigen test for diagnosing pneumococcal pneumonia was also similar.

Therefore, information on pre-hospital antibiotic treatment should always be recorded because it can guide the choice of aetiological diagnostic tests and the empirical antibiotic therapy to be used in patients with CAP. In fact, the current Infectious Diseases Society of America/American Thoracic Society guidelines provide recommendations for using aetiological evidence in this group of patients [Mandell LA et al. 2007], although they are still to be validated.

In the propensity analysis, we did not find significant differences in prognosis between study groups. In contrast, Johnson et al. [Johnson D et al. 2004] found decreased in-hospital mortality associated with antibiotic treatment before hospitalization, while other investigators [Marrie TJ et al. 2005; van de Garde EM et al 2006] showed increased in-hospital mortality in this group of patients. However, these studies did not control for confounding factors. Interestingly, we found that patients who required hospitalization after attempted outpatient treatment had a higher mortality rate than is normally expected in the outpatient setting [Carratalà et al. 2005].

The strengths of the current study include the prospective nature of the cohort, the large number of hospitalized patients with CAP, and the comprehensive data collection. In addition, this is the first study to perform a widespread analysis of the impact of pre-hospital admission antibiotic use on the clinical presentation and outcomes of CAP. We also performed a propensity analysis to control for confounding factors. Nevertheless, there are some limitations that should be acknowledged. First, the study was conducted at a single Spanish centre and we do not know whether the results can be extrapolated to other settings. Second, this is an observational study and we could not eliminate unmeasured confounders between study groups. Third, we were unable to verify outpatient diagnosis and time of antibiotic administration before hospitalization in all patients. Finally, because of the small sample size of patients who receive individual antibiotics, our data for these groups should be interpreted with caution.

In conclusion, after controlling for confounding factors in a propensity analysis, patients who received pre-hospital antibiotic treatment presented distinct clinical

features from those who did not. In addition, the prevalence of *L. pneumophila* was nearly three times higher in patients who received pre-hospital antibiotics, mainly β-lactams. Bacteraemia was less frequent in patients pre-treated with antibiotics. No significant differences were found in the prognosis between study groups. Information about pre-hospital antibiotics use can help to guide the choice of aetiological diagnostic tests and the empirical antibiotic therapy to be used in patients with CAP.

7.3. Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia

Our prospective study of a large cohort of non-immunocompromised adult patients hospitalized with community-onset pneumonia shows that antibiotic administration within 4 or 8 h of arrival at the ED did not improve 30-day survival in hospitalized adults for CAP or HCAP.

Our finding that the timing of the first dose of antibiotics (≤4 or ≤8h) was not associated with 30-day mortality in patients with CAP differs from the results reported by Houck et al. [Houck PM et a. 2004]. These investigators found that patients who received early treatment (≤ 4 h) had lower hospital mortality, lower 30-day mortality and a shorter length of hospital stay. However, it should be noted that this was a retrospective study based on an analysis of medical records and discharge diagnoses, with the study population including patients from a long-term care/skilled nursing setting and being limited to patients aged 65 years. Furthermore, they found that patients who received antibiotics in the first 2 h died more frequently than did those with later antibiotic administration, but it disappeared under multivariate analysis.

Interestingly, our results similarly show that patients with CAP who received early treatment (mainly ≤ 4 h) were more likely to require ICU admission and had higher 30-day mortality. However, these patients had more severe clinical features at hospital admission (septic shock and multilobar pneumonia), which indirectly indicates that in the ED context the more serious patients are usually treated as a priority [Metrsky ML et al. 2006; Waterer GW et al. 2006]. In addition, other studies [Dedier J et al. 2001; Cheng AC et al. 2009] observed a strong relationship between pneumonia severity on admission as measured by the PSI, and earlier antibiotic administration. Other studies have also found that lower 30-day mortality [Meehan TP et al. 1997] and shorter length of hospital stay [Battleman DS et al. 2002] are associated with antibiotic administration within 8h of hospital arrival in patients with pneumonia. However, these were also retrospective studies that included patients from a nursing home, and one of them [Meehan TP et al. 1997] was limited to patients aged 65 years. A recent review [Lee JS et al. 2016] based on 8 observational studies, all of them reported as low-quality evidence, recommend initiating antibiotic therapy within 4 to 8 hours of hospital arrival in patients with radiographically confirmed community-acquired pneumonia and moderate to severe illness severity at presentation.

Our results are, however, consistent with other published studies [Silber SH et al. 2003; Bruns AH et al. 2009]. Moreover, Yu and Wyer [Yu HT et al. 2008] conducted a systematic review of 13 observational studies to assess the impact of antibiotic timing on outcomes of patients with CAP. They identified four groups of studies according to their methodological quality (inclusion criteria, prospective or retrospective design, exclusion of patients treated prior to hospital admission and the use of a validated

severity score), but reported that evidence from observational studies fails to confirm decreased mortality with early antibiotic administration in stable patients with CAP.

Significantly, previous studies evaluating the effect of delay in the administration of antibiotics in patients with pneumonia have not differentiated between CAP and HCAP [Meehan TP et al. 1997; Battleman DS et al. 2002; Houck PM et al. 2004]. Thus, no information is available regarding the effects of antibiotic timing on outcomes in patients with HCAP. Therefore, the current guidelines for the management of adult patients with HCAP do not address this point [ATS/IDSA 2005; Abrahamian et al. 2005]. Importantly, we did not find significant differences in the mean time from patient arrival at the ED until antibiotic administration between CAP and HCAP patients. However, our results suggest that early administration of antibiotics (≤ 4 or ≤ 8 h) is not associated with a decrease in 30-day mortality in HCAP patients. Interestingly, it was also recently reported that guideline-concordant HCAP antibiotic therapy was not associated with improved 30-day mortality for non-critically-ill HCAP patients in the USA [Attridge RT et al. 2011].

The strength of our study lies in the prospective collection of data from a large number of patients. In addition, we performed a detailed evaluation of the clinical features of patients with CAP and HCAP according to the time from arrival at the ED to antibiotic administration. Similarly, to our knowledge this is the first study of its kind that includes patients with HCAP. Finally, we controlled for confounding factors related to mortality in our multivariate analysis. However, as the study is observational it is unable to avoid residual confounding. In this regard, we did not control for patients with treatment limitations. In addition, sample size calculation was not performed previous to the study. Similarly, because of the relatively small sample size of patients

who died in HCAP patients, our data should be interpreted with caution and need further validation.

In conclusion, antibiotic administration within 4 or 8 h of arrival at the ED did not improve 30-day survival in hospitalized adults for CAP or HCAP.

7.4. Impact of antibiotic de-escalation on clinical outcomes in community-acquired pneumococcal pneumonia

Our study offers a comprehensive evaluation of the effects of antibiotic de-escalation within the first 72 h of hospital admission on outcomes in community-acquired pneumococcal pneumonia (CAPP). The results suggest that de-escalation therapy was not associated with a higher risk of 30 day mortality, but was associated with a shorter Length of Hospital Stay (LOS) and duration of iv antibiotic therapy.

In a recent study, Carugati et al. [Carugati M et al. 2015] reported that de-escalation therapy among patients with CAP was not associated with an increased risk of 30 day mortality or clinical failure. However, their study evaluated only CAP patients with Gram-positive and Gram-negative bacteraemia, de-escalation therapy was considered within 7 days of hospital admission, and the number of patients with CAPP was low. Other studies have also evaluated the effects of antibiotic de-escalation in infections due to difficult-to-treat Gram-negative bacilli [Shime N et al. 2013] neutropenia [Mokart D et al. 2014] and urinary tract infections [Khasawneh FA et al. 2014]. Antibiotic de-escalation was not associated with an increased risk of mortality in all these studies. Similarly, in a recent multicentre non-blinded randomized non-inferiority trial performed in patients requiring Intensive Care Unit (ICU) admission for

severe sepsis, de-escalation therapy was not related to mortality, ICU stay, LOS or duration of mechanical ventilation or vasopressors [Leone M et al. 2014].

In agreement with a previous study [Carugati M et al. 2015], we found that the non-de-escalation group was characterized by a more severe presentation at admission, as evidenced by higher frequencies of hypotension, tachycardia, multilobar pneumonia on chest X-ray and bacteraemia. In the present study, after adjustment for confounders in multivariate and propensity score analyses, we found that antibiotic de-escalation was not associated with an increased risk of 30 day mortality in patients with CAPP. Evaluating other important clinical outcomes in CAP, our results suggest that antibiotic de-escalation was independently associated with shorter duration of LOS. No significant differences were found regarding adverse drug reactions or readmission (<30 days) between study groups.

In an era of cost containment and resource constraints in many healthcare systems, adequate resource allocation and cost-effective healthcare delivery are of paramount importance [Vergis EN et al. 1999]. The economic burden associated with CAP remains substantial, and LOS is the most important cost driver of hospitalization [File TM et al. 2010]. A recent study in the US estimated that reducing the course of a CAP admission by 1 day may represent a saving of $2273–2373 [Kozma CM et al. 2010]. Therefore, our finding of shorter LOS in patients with CAPP who underwent de-escalation therapy may have significant economic implications.

There is a concern about performing antibiotic de-escalation in patients with severe disease or in patients who are not clinically stable. To date, therapy de-escalation has not been assessed in these CAP patients. In the present study, we found antibiotic de-escalation to be safe in patients classified into high-risk PSI classes, and

no increase in mortality was observed. Similar results were found if antibiotic de-escalation was performed in patients who remained clinically unstable during the first 72 h after hos- pital admission. Our results suggest that antibiotic de-escalation also seems to be safe among these subgroups of CAPP patients. However, it is important to note that only 159 patients did not reach clinical stability within 72 h of hospital admission and only 2 patients in the de-escalation group were admitted to the ICU.

In recognition of the fact that antimicrobial resistance results in increased morbidity, mortality and cost of healthcare, a series of guidelines has been published for improving the use of antimicrobial agents in hospitals [Dellit TH et al. 2007]. A comprehensive evidence-based stewardship programme to combat antimicrobial resistance includes streamlining or de-escalating antimicrobial therapy towards more targeted therapies that decrease antimicrobial exposure and contain cost. The Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the management of CAP in adults recommends antibiotic de- escalation as best medical practice []Mandell LA et al. 2007, but the evidence available in support of this recommendation is scarce. Our study shows that antibiotic de-escalation to penicillin, amoxicillin or amoxicillin/clavulanate is safe among patients with CAPP. Significantly, we did not consider de-escalation or narrowing of antibiotic therapy to third-generation cephalosporins to be appropriate. Third- generation cephalosporins are recommended for empirical therapy in CAP or as an alternative antimicrobial in CAPP. However, some data suggest that broad-spectrum cephalosporins have been associated with a higher risk for selection of penicillin- resistant pneumococci, resistant enterococci and ESBL Enterobacteriaceae [Dancer SJ et al. 2001].

The strengths of the current study include its prospective design, the large cohort of consecutive hospitalized patients with CAPP and the comprehensive data collection. In addition, we evaluated the impact of antibiotic de-escalation on prognosis and other important clinical outcomes of CAP. Finally, we used multivariate analysis and a propensity score analysis to rule out possible confounding factors in the relation between antibiotic de-escalation and outcomes. However, the present study also has some limitations that should be acknowledged. Caution should be taken in the interpretation of some of our results because the de-escalation group was characterized by a less severe presentation at admission and more frequent de-escalation to an oral antibiotic. The present study was not a randomized trial; as with any observational study, there is potential for residual confounding despite multivariate analysis. Moreover, the study was performed at a single institution and some of the subgroups analysed comprised only a few patients. The number of patients admitted to the ICU who underwent de-escalation therapy was also small. Finally, it is likely that some cases of CAPP were not detected because the urinary antigen tests were not available in the first years of the study.

In conclusion, antibiotic de-escalation within the first 72 h after hospital admission seems to be safe and effective in reducing the duration of LOS, and did not adversely affect outcomes of patients with CAPP, even those with bacteraemia and severe disease, and those who were clinically unstable. Our results suggest that de-escalation strategies should be more widely implemented in the management of hospitalized adults with CAPP.

7.5. Levofloxacin versus azithromycin for treating legionella pneumonia: a propensity score analysis

The present multicentre study offers a detailed comparison between antibiotic treatments of community-acquired Legionella pneumonia (LP). The main finding is that we were not able to found differences between levofloxacin, primarily at a dose of 500 mg IV once/d, and azithromycin on 30-day mortality in multivariate analysis. However, 2-times higher mortality was found with azithromycin compared to levofloxacin on univariate analysis.

The efficacy and usefulness of different types of antibiotics against *Legionella* spp. have been evaluated in some experimental studies [Garcia-Vidal C et al. 2006]. In intracellular models of *Legionella* infection, although old macrolides inhibit bacterial growth, it promptly recurs after drugs removal from the cells [Edelstein PH 1998; Smith RP et al. 1997]. Conversely, levofloxacin and azithromycin are more active than old macrolides, and bacterial regrowth is not observed [Eldestein PH et al. 1991; Fitzgeorge RB et al. 1993; Eldestein PH 1995]. Studies in animal models have confirmed the superiority of levofloxacin and azithromycin over old macrolides [Saito A et al. 1985; Kitsikawa J et al. 1991].

Clinical research comparing the utility of levofloxacin and azithromycin in the treatment of LP is scarce [Falcó V et al. 2006; Gershengorn H et al. 2015] and no randomized trials have been performed. Recently, a retrospective analysis of a cohort of adults hospitalized for LP showed similar results for hospital mortality, development of *Clostridium difficile* colitis, length of hospital stay and cost of the hospitalization for patients treated with either azithromycin or levofloxacin [Gershengorn H et al. 2015]. Of note, patients in that study were identified by an ICD-9-CM code from a drug

utilization database. A prospective observational study comparing only 43 patients treated with azithromycin with 18 treated with levofloxacin found no differences in days to defervescence, length of hospital stay or mortality [Falcó V et al. 2006]. The results of that study are limited by the small sample size. Our observational study, with a large number of consecutive patients recruited from clinical databases, found that patients treated with azithromycin had similar outcomes than those treated with levofloxacin, including time to defervescence, time to achieve clinical stability, length of intravenous therapy and length of hospital stay. Conversely, patients treated with clarithromycin had longer iv antibiotic treatment and longer hospital stay compared with those treated with levofloxacin. Of note, both early and overall mortality were 2-times higher in patients treated with azithromycin compared to levofloxacin in univariate analysis. However, it is important to note that due to the low number of deaths in both groups, results regarding mortality should be interpreted with caution.

Previous observational studies comparing levofloxacin with old macrolides in the treatment of LP have reported that patients treated with levofloxacin might have better outcomes [Blàzquez Garrido RM et al. 2005; Mykietiuk A et al. 2005; Sabrià M et al. 2005]. Our study provides additional support for the beneficial effect on length of stay of levofloxacin compared with clarithromycin in a cohort of patients with similar diagnostic methods and similar timing of antibiotic administration.

Early and overall mortality were both low. Recently, a substantial fall in the rate of mortality due to CAP has been documented [Simonetti AF et al. 2016]. Focusing on LP, two studies have reported decreases in the mortality rate in hospitalized patients [Benin AL et al. 2002; Viasus D et al. 2013]. These authors considered that two factors may play a key role in explaining this falling rate: first, the use of the urinary test,

which is more sensitive than culture or serology for LP diagnosis, may have led to the detection of milder forms of legionellosis; second, it is likely that patients diagnosed by the urinary test were administered adequate treatment more quickly.

Finally, we stress that almost all patients in the quinolone group (98.3%) in our study received 500mg/24h of levofloxacin. Fluoroquinolones exhibit concentration-dependent antimicrobial activity. For these reasons, some authors have suggested that high doses of levofloxacin (750mg/24h or even 500mg/12h) may increase killing of the pathogen due to the higher peak concentrations. However, it has been demonstrated that the exposure necessary for favourable outcomes varies according to the bacteria [Forrest A et al. 1993; Fields BS et al. 2002]. To our knowledge, no studies correlating pharmacodynamic parameters with efficacy in LP patients treated with quinolones have been performed. Our study did not aim to perform this correlation; nevertheless, we stress the low rates of early (0.6%) and overall mortality (2.3%) in our contemporary cohort of LP patients treated with 500 mg/24h of levofloxacin, including more than 15% of patients with ICU admission and more than 45% with high-risk PSI. Although no definitive conclusions can be drawn, this dose appeared to be a good treatment option for our patients with LP.

The strengths of the current study include the large cohort of consecutive hospitalized patients with LP in two hospitals with a long tradition in clinical research on CAP. The clinical data collection was meticulously performed and we applied rigorous criteria for diagnosis of LP. Some limitations of our study should be acknowledged. Taking into account that the study was observational, it is difficult to completely rule out confounding due to unmeasured variables. Ideally, a randomized trial should be performed to compare empirical regimens; however, given the relative

rarity of LP, a trial of this kind is unlikely to be feasible or practical [Eldestein PH 1998; Fields BS et al. 2002; Mykietiuk A et al. 2005]. Finally, we did not monitor the adverse events of the different drugs used for LP treatment; unfortunately, our study was not designed to address these issues.

In summary, no significant differences in time to defervescence, time to achieve clinical stability, length of intravenous therapy and length of hospital stay were found between patients treated with levofloxacin and those receiving azithromycin. The absence of significant differences in mortality rates between the two treatments groups should be interpreted with caution, due to the small numbers of deaths in our cohort of LP patients.

7.6. Predictors for individual patient antibiotic treatment effect in hospitalised community-acquired pneumonia patients

In this post-hoc analysis of three prospective cohorts from the Netherlands and Spain we identified age and smoking as candidate clinical predictors for the response to empiric antibiotic treatment, from an individualized patient perspective. In a previous clinical trial comparing beta-lactams (BL) with beta-lactams plus macrolides (BLM) [Garin N et al. 2014] authors indicate an interaction effect of PSI high classes classification and monotherapy, with a reduced Hazard Ratio for clinical stability. Conversely, in a recent register-based cohort study comparing narrow vs. broad spectrum beta-lactams therapy in community-acquired pneumonia (CAP) patients, the authors did not find significant interaction effects of clinical variable with antibiotic effectiveness [Rhedin S et al. 2016].

Our findings suggest that older age and smoking are associated with increased 30-day mortality in patients receiving fluoroquinolones (FQL) as empiric treatment, either alone or combined with beta-lactams. In older patients the beneficial effects of atypical coverage could be less than in younger patients partly due to a lower incidence of CAP caused by atypical pathogens, as reported in different series [Klapdor B et al. 2012; Torres A et al. 2014; Raeven VM et al. 2016] and also observed in our data. Moreover, adverse effects and toxicity of FQL (among them the QT interval prolongation [Briasoulis A et al. 2011]) could be more pronounced in older patients, possibly due to a decline in renal function and changes in pharmacokinetics [Stahlmann R et al. 2010]. Older age was also related with decreased effectiveness of BLM, with an interaction OR of 1.67. However, presumably due to the lower number of patients with this regimen, the association was not statistically significant.

Yet, the direction of the effect of smoking was unexpected, especially in the light of studies reporting a higher proportion of smokers in *Legionella pneumophila* patients, which should, in contrast to our findings, favour fluoroquinolone-based treatment in smokers [Férnandez-Sabé N et al. 2003; Almirall J et al. 2014]. This finding raises new questions about a possible interaction between smoking and antibiotic effectiveness. To the best of our knowledge, currently there is no mechanism that could explain such an interaction. We can only hypothesize that smoking patients might have malignancies, COPD, or other unexplored characteristics, which were not yet recognized and/or reported in the medical chart, which could interact with fluoroquinolone use in a detrimental way. Still, due to the large variability of the ORs between cohorts, this finding should be interpreted with caution.

Older age was related to an increase in LOS in patients who received BLM as empiric treatment, with an addition of one day on the median LOS of 7 days. As mentioned above, the lower incidence of atypical pathogens in older patients could lead to less beneficial effects of BLM in these patients. Furthermore, this finding could refer to the well described association between macrolide use and cardiac events [Ray WA et al. 2012; Mortensen EM et al. 2014], which more frequently occur in older patients. Unfortunately, our data did not allow testing of this hypothesis. Moreover, we observed that the effect size of the interaction between age and BLM use was highly variable between the three cohorts, raising uncertainty on the generalizability of this finding.

Similarly, the large confidence interval of the OR and the wide range of ORs between the three cohorts for the association between ICU admission and leukocyte count over 20,000 in patients who received BLM prohibit firm conclusions.

Of note, the interaction between PSI score and empiric antibiotic treatment showed no effect on clinical outcome. In current clinical practice, the choice of empiric antibiotic treatment is mainly based on clinical severity criteria, supported by disease severity scores such as the PSI score [Lim WS et al. 2009; Wiersinga WJ et al. 2012]. Our findings suggest that the PSI score does not predict whether a patient will respond better to one empiric antibiotic treatment over another, suggesting that we need to re-evaluate how we select empiric antibiotics to treat CAP patients.

The key strengths of this study are the large number of patients from different cohorts allowing us to assess treatment effects in subgroup analyses, the high quality prospective data collection, and the inclusion of all possible relevant clinical predictors in the analysis. This study could serve as a prototype for future research in CAP, being

the first study in using the novel approach of identifying predictors for the effect of empiric treatment strategies, instead of looking at predictors for clinical outcome or causative pathogen. One source of weakness in this study is the presence of some important differences between cohorts. In Bellvitge cohort all patient included have a confirmed CAP on chest X-ray, unlike the Dutch cohorts. Whereas radiologically confirmed CAP patients represent a more well-defined disease entity, the Dutch cohorts included all patients that are treated for a clinical diagnosis of CAP, improving generalizability of the results to daily clinical practice. However, a sensitivity analysis which included only X-ray confirmed CAP showed similar results. Furthermore, there is a large variability in the presence of some clinical signs and symptoms between the three cohorts, which is probably due to a lack of uniformity in the collection of clinical data. The possibility of misreporting clinical characteristics could underestimate their modifying effect on treatment and hence influence results. To correct for clustering within the cohorts, we used mixed-effects regression models. In addition, we performed a sensitivity analysis stratified by cohorts to assess the robustness of our findings in each of the cohorts.

Importantly, these are all observational data, and we could not rule out confounding by indication of the different empiric antibiotic treatments used, although we adjusted for multiple confounders in the multivariate models. Yet, as we focus on the interaction effect of clinical factors with empiric antibiotic treatment, we can postulate that the same bias is present in all the different strata, thus not largely biasing the direction and size of the interaction effect.

Moreover, as we cannot rule out bias on the direct effects of antibiotics, the same interaction effect could either mean benefit for one group, or harm for the other

group. For example, we cannot claim that fluoroquinolone-based treatment is harmful in older smoking patients, as our results could be also interpreted the other way round, meaning that they are beneficial in younger and non-smoking patients. Considering this limitation, our results should be considered hypothesis generating and need to be confirmed in a randomized controlled trial designed to estimate these interaction effects.

In conclusion, it is plausible that older age influences the response to specific antibiotic treatment, as we found a relationship with both the use of FQL and increased 30-day mortality and BLM use and LOS in older patients. Current smoking was also associated with a decreased response to FQL. Future trials evaluating antibiotic strategies for CAP could assess the treatment effects in patients of different age categories and smoking status. In addition, further research illuminating the causal mechanism underlying the identified associations needs to be performed.

7.7 Limitations of the studies

In the studies presented, there are some limitations that should be acknowledged.

The studies on declining mortality, impact of pre-hospitalization antibiotic use and timing of antibiotic administration were conducted at a single Spanish center and the extrapolation of our results to other settings should be conducted with caution.

Secondly, all the studies reported are observational, and despite all our efforts to adjust for confounders (either with multivariate analysis, or use of propensity score analysis) we were not able to eliminate unmeasured confounders between study groups.

Regarding specific studies, in the study on pre-hospital antibiotic treatment we were unable to verify outpatient diagnosis and time of antibiotic administration before hospitalization in all patients. Moreover, because of the small sample size of subgroups of patients who received individual antibiotics, our data for these groups should be interpreted with caution.

In the study on timing of antibiotic administration, we did not control for patients with treatment limitations. In addition, sample size calculation was not performed prior to the study. Similarly, because of the relatively small sample size of patients who died in HCAP patients, our data should be interpreted with caution and needs further validation.

In the study on de-escalation in pneumoccocal CAP, caution should be taken in the interpretation of some of our results as the de-escalation group was characterized by a less severe presentation at admission and more frequent de-escalation to an oral antibiotic. The number of patients admitted to the ICU who underwent de-escalation therapy was also small. Finally, it is likely that some cases of pneumococcal CAP were not detected because the urinary antigen tests were not available during the first years of the study.

In the study comparing macrolides with levofloxacin for treating Legionella pneumonia, we did not monitor the adverse events of the different drugs used for LP treatment; unfortunately, our study was not designed to address these issues.

In the study exploring the existence of clinical predictor as a response to different antibiotic treatment strategies in CAP, one source of weakness is the presence of some important differences between cohorts. In Bellvitge cohort, all patients included had a CAP confirmed by chest X-ray, unlike the Dutch cohorts.

Whereas radiologically confirmed CAP patients represent a more well-defined disease entity, the Dutch cohorts included all patients that are treated for a clinical diagnosis of CAP, improving generalizability of the results to daily clinical practice. Furthermore, there is a large variability in the presence of some clinical signs and symptoms between the three cohorts, which is likely due to a lack of uniformity in the collection of clinical data. The possibility of misreporting clinical characteristics could underestimate their modifying effect on treatment and hence influence results. To correct for clustering within the cohorts, we used mixed-effects regression models. In addition, we performed a sensitivity analysis stratified by cohorts to assess the robustness of our findings in each of the cohorts.

Importantly, these are all observational data, and we could not rule out confounding by indication of the different empirical antibiotic treatments used, although we adjusted for multiple confounders in the multivariate models. However, as we have focused on the interaction effect of clinical factors with empirical antibiotic treatment, we can postulate that the same bias is present in all the different strata, thus not greatly biasing the direction and size of the interaction effect. Considering this limitation, our results should be considered as hypothesis generating and in need of confirmation by a randomized controlled trial designed to estimate these interaction effects.

8. CONCLUSIONS

8.1. Declining mortality among hospitalized patients with community-acquired pneumonia

- Thirty-day mortality significantly decreased over time in hospitalized community-acquired pneumonia patients, despite an upward trend in patient age and other factors associated with poor outcomes.
- Several changes in the management of community-acquired pneumonia and a general improvement in global care over time may have caused the observed outcomes.

8.2. Impact of pre-hospital antibiotic use on community-acquired pneumonia

- In our cohort, 17.3% of patients received pre-hospital antibiotic treatment. These patients were younger, with fewer comorbidities, and less frequently presented bacteraemia than those patients who had not received antibiotic before hospitalisation.
- The prevalence of *Legionella pneumophila* was nearly three times higher in patients who received pre-hospital antibiotics, mainly those who received β-lactams.
- Pre-hospital antibiotic use should be considered when choosing aetiological diagnostic tests and empirical antibiotic therapy in patients with community-acquired pneumonia.

8.3. Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia

- Patients receiving early treatment had significantly greater illness severity at admission.

- Antibiotic administration within 4 or 8 hours of arrival at the emergency department did not improve rates of 30-day survival in hospitalized adults for community-acquired pneumonia or healthcare-associated pneumonia.

8.4. Impact of antibiotic de-escalation on clinical outcomes in community-acquired pneumococcal pneumonia

- Antibiotic de-escalation appears to be safe and effective in reducing the duration of hospital stay.
- Antibiotic de-escalation did not adversely affect outcomes of patients with community-acquired pneumococcal penumonia, even those with bacteraemia and severe disease, and those who were clinically unstable at time of de-escalation.
- De-escalation strategies should be more widely implemented in the management of hospitalized adults with community-acquired pneumococcal penumonia.

8.5. Levofloxacin versus azithromycin for treating Legionella pneumonia: a propensity score analysis.

- No significant differences in relevant outcomes were found between patients with Legionella pneumonia treated with levofloxacin and those receiving azithromycin.

8.6. Predictors for individual patient antibiotic treatment effect in hospitalised community-acquired pneumonia patients.

- Older age and smoking could influence the response to specific antibiotic regimens.
- The effect modification of age and smoking should be considered as a hypothesis to be evaluated in future trials.

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10. ANNEXES

10.1 STUDY PROTOCOL

PROTOCOL DE PNEUMÒNIA D'ADQUISICIÓ EN LA COMUNITAT

FILIACIÓ

NºHª		Nº PROTOCOL	
NOM			
COGNOMS			
EDAT			
SEXE		**0=home 1=dona**	
DATA D'INGRÉS			
SERVEI D'INGRÉS INICIAL			
LLIT			

CRITERIS DE GRAVETAT

	0=no 1=si
Edat avançada (>70anys)	
Insuficiència respiratòria (pO2basal<60 ó pO2/Fi02<300 ó Sat O2<90%)	
Pneumònia extensa i/o bilateral	
Shock	
Vessament pleural/empiema	
Patologia de base	
Pneumònia aspirativa o abcés	
Endocarditis o meningitis concomitant	
Sospita de patogen potencialment greu	
No resposta a ATB ambulatoris	
Nº de criteris de gravetat	

PNEUMÒNIA ASSOCIADA AL SISTEMA DE SALUT

	0=no 1=si
Tractament EV en domicili	
Cures de ferides per metge, infermera, familiar o amic	
Auto-administració de medicació EV (durant els 30 dies previs)	
Atenció en un hospital o hemodiàl·lisi (durant els 30 dies previs)	
Hospitalització durant 2 ó més dies (durant els 90 dies previs)	
Residència d'avis o cures cròniques	
Nº de criteris	

MALALTIA DE BASE

	0=no 1=si
MPOC	
DM	
Cardiopatia	
Neoplàsia	
Nefropatia	
Hepatopatia	
AVC	
Demència	
Altres malalties de base 1	
Altres malalties de base 2	
Altres malalties de base 3	
Nº malalties de base	

FUMADOR		**0=no 1=si 2= ex-fumador**
BEBEDOR		
PNEUMÒNIA PRÈVIA (<12 mesos)		
CORTICOIDS SISTÈMICS		
QUIMIOTERÀPIA		
ALTRES IMMUNOSUPRESSORS		
VACUNA GRIP (<1 any)		
VACUNA PNEUMOCOC (<5 anys)		
Any de l'administració		

ANTECEDENTS EPIDEMIOLÒGICS **0=no 1=si**

Ocells		Viatges fora del país	
Altres malalts en l'entorn		Brot *Legionella*	
Altres		Especificar	

ANTIBIÒTICS PREVIS (en els últims 6 mesos abans de la clínica actual) **0=no 1=si**

ATB PREVI 1	
ATB PREVI 2	

ANTIBIÒTICS AMBULATORIS PER AQUEST EPISODI **0=no 1=si**

ATB AMBULATORI 1	
ATB AMBULATORI 2	

Protector gàstric habitual **0=no 1=si**

Especificar	

CLÍNICA

			0=no 1=si
CVA previ		Dolor pleurític	
Inici brusc		Díspnea	
Calfreds		Cefalea	
Dies de clínica		Artromiàlgies	
Tos		Confusió	
Diarrea i/o vòmits		Shock	
Expectoració		Tta vasopresor	
Expectoració purulenta		Cianosis	

Tipus d'expectoració:

□ No purulenta □ Purulenta □ Rovellada □ Hemoptoica □ Fètida

Temperatura		Freqüència cardíaca	
TA sistòlica		Freqüència respiratòria	
TA diastòlica		Semiologia de condensació	

Altres manifestacions:

□ Espenomegàlia □ meningisme □ pericarditis □ otitis □ lesions cutànies

□ rabdomiolisi □ icterícia □ boca sèptica □ crisi comicial □ artritis

EXPLORACIONS COMPLEMENTÀRIES

Leucos		Saturació 02	
% PMN		ALT	
HTC		AST	
PO2/FiO2		Albúmina	
pH		Sodi	
pO2		Creatinina	
pCO2		LDH	

RX tòrax

☐ Segmentària ☐ unilobular ☐ multi-unilateral ☐ multi-bilateral ☐ difusa ☐ intersticial

Vessament pleural	0=no 1=si	
Cavitació		
Dissociació clínico-radiològica		

Punts SAPS (anotar la pitjor puntuació en les primeres 24 hores)

Edat		
FC		
TA sistòlica		
Tº axilar		
FR		
Ventilació o CPAP		
Volum d'orina		
HTC		
Leucos		
Urea		
Glucosa		
Potasi		
Sodi		
Bicarbonat		
Glasgow		

PSI

Edat		Edat en anys (- 10 en dones)	
Residència d'avis		+10	
Malaltia de base	Neoplàsia	+30	
	Hepatopatia	+20	
	ICC	+10	
	AVC	+10	
	Insuficiència renal	+10	
Exploració física	Alteració nivell de consciència	+20	
	FR ≥ 30 per minut	+20	
	TA < 90 mmHg	+20	
	Tº < 35 ó >40ºC	+15	
	FC ≥125 per minut	+10	
Laboratori	pH arterial < 7.35	+30	
	Urea ≥ 11mMol/L	+20	
	Sodi < 130	+20	
	Glucosa ≥ 14mMol/L	+20	
	HTC < 30	+10	
	pO2 < 60	+10	
	Vessament pleural	+10	
		Punts PSI	

Grup PSI

GRUP 2 → ≤70 **GRUP 3** → 71-90 **GRUP 4** → 91-130 **GRUP 5** → >130

Punts CURB-65

Grup CURB-65

Qualsevol de les següents un punt:

□ Confusió □ Urea > 7mmol/l □ FR ≥ 30/min □ PAS <90mmHg o PAD ≤ 60 mmHg □ Edat ≥ 65 anys

GRUP 1 → < 1 **GRUP 2 → 2** **GRUP 3 > 3**

MICROBIOLOGIA

Mostra d'esput **0=**no **1=**si

Gram d'esput

□ no valorable □ DCGP □ DCGPR □ DGPC

□ CBGN □ BGN □ flora mixta □ PMN sols

Cultiu d'esput **0=**negatiu **1=**positiu

Bacteri esput 1

Bacteri esput 2

ZN d'esput **0=**negatiu **1=**positiu

Hemocultiu **0=**negatiu **1=**positiu

Bacteri hemo 1

Bacteri hemo 2

Cultiu pleura **0=**negatiu **1=**positiu

Pus pleura **0=**no **1=**si

pH pleura

Proteïnes pleura

Glucosa pleura

Cèl·lules pleura

% PMN pleura

Gram pleura

□ no valorable □ DCGP □ DCGPR □ DGPC

□ CBGN □ BGN □ flora mixta □ PMN sols

AG pneumo pleura **0=**negatiu **1=**positiu

Bacteri pleura 1

Bacteri pleura 2

Cultiu altra mostra **0=**negatiu **1=**positiu

Tipus mostra □ PTA □ RBCT □ necro

Bacteri altra mostra 1

Bacteri altra mostra 2

Cultiu orina

AG Legionella **0=**negatiu **1=**positiu

AG pneumococ **0=**negatiu **1=**positiu

Serologia **0=**no **1=**si

DX serologia

1ª SEROLOGIA		**2ª SEROLOGIA**	
Data		Data	
Nº serologia		Nº serologia	
Legionella		Legionella	
Febre Q		Febre Q	
Mycoplasma		Mycoplasma	
Clamydia sp M		Clamydia sp M	
Clamydia sp G		Clamydia sp G	
Clamydia psittacci		Clamydia psittacci	
Clamydia pneumoniae		Clamydia pneumoniae	

TRACTAMENT ANTIBIÒTIC

Nº antibiòtics empírics

ATB 1 ATB 2 ATB 3

Hores fins l'inici d'antibiòtic

CANVI DEL TRACTAMENT ANTIBIÒTIC **0=**no **1=**si

Motiu per canvi d'antibiòtic

☐ Empitjorament clínic o radiològic ☐ aïllament de microorganisme resistent ☐ efectes adversos
☐ superinfecció ☐ complicacions ☐ protocols ☐ simplificació

ATB canvi 1		Dia canvi:	
ATB canvi 2		Dia canvi:	
ATB canvi 3		Dia canvi:	

AFEGIR ANTIBIÒTIC **0=**no **1=**si

Motiu per afegir antibiòtic

☐ Empitjorament clínic o radiològic ☐ aïllament de microorganisme resistent ☐ efectes adversos
☐ superinfecció ☐ complicacions ☐ protocols ☐ simplificació

ATB canvi 1		Dia canvi:	
ATB canvi 2		Dia canvi:	
ATB canvi 3		Dia canvi:	

DIES DE TRACTAMENT ANTIBIÒTIC ENDOVENÓS

DIES TOTALS DE TRACTAMENT ANTIBIÒTIC

Tractament empíric adequat **0=**no **1=**si

EVOLUCIÓ

DATA D'ALTA

CONTROL EN CONSULTES EXTERNES — **0=**no **1=**si

Data de consultes externes

Vacuna pneumococ — **0=**no **1=**si

RX consultes externes — **1=**desaparició de l'infiltrat, **2=**sense canvis, **3=**milloria

Dies febre

Dies tos/expectoració

Dies dolor toràcic

Dies fins estabilitat clínica

FR ≤ 24, TAS ≥ 90, Sat 02 ≥ 90%, pO2 ≥ 60, Tº ≤ 37.2ºC, estat mental normal, ingesta normal

COMPLICACIONS — **0=**no **1=**si

Pleurals		Respiratòries	
Empiema		Confusió	
Drenatge pleural		Renals	
Dies de drenatge pleural		Hepàtiques	
Cardíaques		Infecció nosocomial	
Insuficiència cardíaca		Metabòliques	
Arítmies		Shock	
		Sagnat digestiu	

Altres complicacions 1

Altres complicacions 2

Nº complicacions

Comentaris

Recaiguda — **0=**no **1=**si

Efectes adversos — **0=**no **1=**si

☐ Rash ☐ Reacció al·lèrgica ☐ Hepàtiques
☐ Renals ☐ Digestius ☐ Flebitis
☐ Altres efectes adversos

Dia de l'efecte advers

Ingrés a UCI — **0=**no **1=**si

Dies d'ingrés a UCI

Ventilació mecànica — **0=**no **1=**si

VMNI — **0=**no **1=**si

Dies de ventilació mecànica

DIES D'INGRÉS

Mort		**0=**no **1=**si
	Mort ≤ 30 dies	**0=**no **1=**si
Dia mort		

Causa mort			
□ Fracàs respiratori	□ shock	□ FMO	□ sepsis
□ infeció nosocomial	□ TEP	□ status epilèptic	□ hemorràgia digestiva
□ IC/IAM/arrítmia	□ insuficiència renal	□ insuficiència hepàtica	□ cetoacisosi
□ DM	□ endocarditis	□ pancreatitis	□ isquèmia intestinal
□ neoplàsia	□ AVC embòlic	□ mort sobtada	□ fascitis/miositis

DIAGNÒSTIC ETIOLÒGIC

DX definitiu

□ No pneumònia □ DX de probabilitat □ DX de seguretat □ no filiada

DX ETIOLÒGIC

DX etiològic 1		
DX etiològic 2		
DX etiològic 3		
Nº de DX etiològics		
DX si NO pneumònia		

Comentaris

	Día 0	Día 1	Día 2	Día 3	Día 4	Día 5	Día 6
Tª axilar							
TA							
FC							
FR							
Tos							
Expectoració							
Dolor pleural							
ATB							
Efectes adversos							
Altres							

	Día 7	Día 8	Día 9	Día 10	Día 11	Día 12	Día 13
Tª axilar							
TA							
FC							
FR							
Tos							
Expectoració							
Dolor pleural							
ATB							
Efectes adversos							
Altres							

10.2. CERTIFICATE OF FOREIGN ROTATION

To whom it May Concern:

Ons kenmerk MB/EdT
Uw kenmerk
Datum **September 26, 2016**
Betreft certificate of foreign rotation

Divisie Laboratorium en Apotheek

Medische Microbiologie

Prof. Dr. M.J.M. Bonten

Tel: 088 7557676

mbonten@umcutrecht.nl

This is to certify that ***Antonella Francesca Simonetti*** was a visiting Doctoral Fellow in our Department of Microbiology and Infectious Diseases at the University Medical Center (UMC) UMC in Utrecht for three months, from July to September 2016.

During this time period, Dr. Simonetti worked in the area of community-acquired pneumonia. Specifically, she worked on a retrospective analysis of three cohorts of patients admitted with CAP, together with other component of the CAP team, studying for predictors of response to different classes of antibiotic treatment.

Academically, she attended the weekly CAP meeting on Friday morning, the weekly Wednesday meeting with all other PhD and post-doctoral students of the Microbiology and Infectious Diseases department, she attended the Journal Club organized by PhD students and the seminars for PhD students at Julius Centre.
She also prepared an oral presentation about the results of her study and she is now working at the manuscript of this study, that we wish to publish in the next few months.

Met vriendelijke groet,

Marc J.M. Bonten
Professor of Molecular Epidemiology of Infectious Diseases

Bezoekadres:
Heidelberglaan 100
3584 CX Utrecht

Postadres:
Huispostnummer G04.614
Postbus 85500
3508 GA Utrecht

www.umcutrecht.nl

11. SPANISH SUMMARY

(Resumen en castellano)

Nuestro trabajo se ha centrado en algunos de los retos actuales sobre el tratamiento antibiótico en la neumonía adquirida en la comunidad (NAC).

El primer estudio, un análisis observacional de una cohorte prospectiva de adultos hospitalizados con NAC, encontró una disminución sustancial en la mortalidad a 30 días durante un período de 20 años, a pesar de una tendencia al alza en varios factores con influencia pronóstica negativa. En nuestra cohorte observamos a lo largo del tiempo importantes cambios en el manejo de los pacientes de la NAC, como el aumento de los pacientes sometidos a ventilación mecánica o ingresados en la Unidad de Cuidados Intensivos (UCI) y el uso de fluoroquinolonas solas o en combinación con betalactámicos. Estos cambios pudieron ser la causa de la disminución de mortalidad observada.

En nuestra cohorte el uso de fluoroquinolonas fue el único factor asociado con la disminución de la mortalidad en el tiempo en un análisis multivariable. Sin embargo, después de comparar a los pacientes por medio de un *propensity score*, no se confirmó el efecto beneficioso del uso de fluoroquinolonas sobre la mortalidad. Del mismo modo, no se observaron mejores resultados en los pacientes que recibieron el régimen de betalactámicos más macrólidos.

En el segundo estudio analizamos el impacto del tratamiento antibiótico previo al ingreso hospitalario en pacientes con NAC. Las características demográficas de los pacientes con tratamiento antibiótico previo de nuestra cohorte fueron similares a las reportadas en estudios anteriores: estos pacientes eran significativamente más jóvenes y tenían tasas más bajas de comorbilidad. Los pacientes que recibieron tratamiento antibiótico previo fueron menos propensos a tener fiebre y leucocitosis y, como se esperaba, presentaron menos bacteriemia. La prevalencia de *Legionella*

pneumophila fue casi tres veces mayor en pacientes que recibieron antibióticos prehospitalarios, principalmente en los que recibieron betalactámicos. Después de controlar los factores de confusión en un *propensity score*, no encontramos diferencias significativas en el pronóstico entre los grupos de estudio. Por lo tanto, la información sobre el tratamiento antibiótico prehospitalario debe ser siempre registrada porque puede guiar en la elección de las pruebas diagnósticas etiológicas y en la terapia antibiótica empírica que se utilizará en pacientes con CAP.

En el estudio sobre el tiempo hasta la administración de la primera dosis de antibióticos se encontró que la administración de antibióticos dentro de las primeras 4-8 horas de la llegada a Urgencias no mejoró la supervivencia a los 30 días en los adultos hospitalizados para NAC o neumonía relacionada con el ámbito sanitario.

Nuestros resultados también muestran que los pacientes con neumonía que recibieron tratamiento precoz (principalmente ≤ 4 h) tuvieron mayor probabilidad de requerir ingreso en la UCI y presentaron una mayor mortalidad a los 30 días. Estos pacientes tenían características clínicas más graves al ingreso hospitalario, lo que indica indirectamente que en el servicio de Urgencias los pacientes más graves son generalmente tratados con prioridad. Es importante destacar que no encontramos diferencias significativas en el tiempo medio desde la llegada del paciente a Urgencias hasta la administración de antibióticos entre los pacientes con neumonía comunitaria y aquellos con neumonía relacionada con el ámbito sanitario.

En el estudio sobre la desescalada de antibióticos en pacientes con neumonía neumocócica adquirida en la comunidad, se encontró que los pacientes en los cuales no se desescaló el tratamiento presentaron mayor gravedad al ingreso, como lo demuestran mayores frecuencias de hipotensión, taquicardia, neumonía multilobar y

bacteriemia. No se detectaron diferencias significativas en cuanto a reacciones adversas a fármacos o reingresos entre los grupos de estudio. Después del ajuste para los factores de confusión en los análisis multivariados y de *propensity score*, se encontró que la desescalada del tratamiento antibiótico no se asoció con un mayor riesgo de mortalidad a los 30 días y fue eficaz para reducir la duración de la estancia hospitalaria en pacientes con neumonía neumocócica. Los mismos resultados se hallaron en aquellos pacientes con bacteriemia y enfermedad grave, así como aquellos que estaban clínicamente inestables al momento de desescalar.

Posteriormente, en un estudio multicéntrico, exploramos el impacto de diferentes tratamientos antibióticos para la neumonía por Legionella. Nuestro estudio observacional encontró que los pacientes tratados con azitromicina tuvieron resultados similares a los tratados con levofloxacino, incluyendo el tiempo hasta la defervescencia, el tiempo para alcanzar la estabilidad clínica, la duración de la terapia intravenosa y la duración de la estancia hospitalaria. Por el contrario, los pacientes tratados con claritromicina tuvieron un tratamiento antibiótico endovenoso y una estancia hospitalaria más prolongados en comparación con los tratados con levofloxacino. El hallazgo principal es que no pudimos encontrar diferencias entre el tratamiento con levofloxacino o azitromicina en cuanto a la mortalidad a los 30 días en el análisis multivariante. Cabe destacar que tanto la mortalidad precoz como la general fueron 2 veces mayores en los pacientes tratados con azitromicina en comparación con levofloxacino en el análisis univariado. Sin embargo, es importante señalar que, debido al bajo número de muertes en ambos grupos, los resultados con respecto a la mortalidad deben ser interpretados con precaución.

Por último, se realizó un análisis post-hoc de tres cohortes prospectivas de los Países Bajos (donde llevé a cabo mi estancia internacional) y España para analizar los predictores de respuesta a tratamiento antibiótico empírico en pacientes hospitalizados con NAC. Nuestros hallazgos sugieren que la edad avanzada y el tabaquismo se asocian con una mayor mortalidad a los 30 días en pacientes que reciben fluoroquinolonas (FQL) como tratamiento empírico, ya sea solas o combinadas con betalactámicos. La edad avanzada también se relacionó con la disminución de la eficacia del tratamiento combinado de betalactamícos más macrólidos (BLM), aunque la asociación no fue estadísticamente significativa. La edad avanzada se relacionó con una mayor estancia hospitalaria en los pacientes que recibieron BLM como tratamiento empírico, con una adición de un día en la mediana de 7 días de estancia.

Con nuestros hallazgos sugerimos que, en los ensayos futuros que evalúen las estrategias antibióticas para NAC, se podrían evaluar los efectos del tratamiento antibiótico en pacientes de diferentes edades y estado de tabaquismo. Además, es necesario realizar más investigaciones que aclaren el mecanismo causal subyacente a las asociaciones identificadas.

12. ACKNOWLEDGEMENTS

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