Original Article

Empiric antibiotic treatment of community-acquired pneumonia in Spanish Intensive Care Units: What has changed over the years?

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ABSTRACT

Background and Objectives: Appropriate empiric antibiotic therapy in patients with severe community-acquired pneumonia (CAP) is crucial in terms of outcome. International guidelines suggest combination therapy (CT) for CAP patients admitted to Intensive Care Units (ICU). However, that type of combination of antibiotics is not clear. This study aims to determine the empiric antibiotic treatment of severe CAP in two periods. Our hypothesis was that macrolide use has decreased in the recent years. **Materials and Methods:** We compared in two prospective similarly designed cohort studies (1) CAP in ICU (2000–2002) and (2) H1N1 SEMICYUC (2009–2011) of critically ill patients with CAP: (a) Rate of CT and (b) use of macrolide or quinolones in each period. Demographic, severity of illness and clinical data were recorded. Chi-square test (categorical variables) and Student's *t*-test (continuous variables) were used. Results are shown as median, standard deviation, odds ratio, and 95% confidence interval. $P < 0.05$ was considered. **Results:** We included 1059 patients, 529 (49.9%) in the first period and 530 (50.1%) in the second period. The severity of illness and mortality rate was not different between periods. In overall, 866 (81.7%) received CT and this therapy was more frequent in the second period (85.3% *vs.* 78.3%, $P < 0.003$). A significant reduction in macrolide use in the second period was observed (26% *vs.* 55%; $P < 0.01$) even in patients with shock. **Conclusions:** Despite published evidence, CT use with quinolones has increased in the last years in Spanish ICUs.

Key words: Combination therapy, community acquired pneumonia, macrolides

INTRODUCTION

Community-acquired pneumonia (CAP) is an important cause of morbidity and increased health care costs[1] and the world's first cause of death of an infectious cause.[2] Mortality rates range from 5% to 20%, but it increased (>50%) when Intensive Care Unit (ICU) admission is needed.

Although controversies remain about the optimal antibiotic treatment in CAP, most of the guidelines recommend that

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Access this article online	
Quick Response Code:	Website: www.caijournal.com
	DOI: 10.4103/2225-6482.184915

How to cite this article: Claverias L, Bodí M, Oviedo AR. Empiric antibiotic treatment of community-acquired pneumonia in Spanish Intensive Care Units: What has changed over the years?. Community Acquir Infect 2016;3:55-60.

antibiotic treatment should be based on the severity of disease at presentation, assessed either on the basis of a prognostic risk score or of the level of care needed.[3] Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) guidelines[4] recommend for the management of CAP in adults admitted to a nonintensive care hospital unit, the use of either a respiratory fluoroquinolone (such as moxifloxacin, gemifloxacin, or levofloxacin) or a β-lactam (preferred agents are cefotaxime, ceftriaxone, or ampicillin) plus a macrolide. These recommendations are mostly based in observational studies that have failed to show differences between both treatments, suggesting that in most nonsevere CAP patients most treatment regimens provide the same results in terms of clinical success rates and survival.

This is different in patients with severe CAP that requires ICU admission. In these cases, the appropriate selection of empiric antibiotic therapy and its prompt initiation are crucial factors in terms of outcome.[5] Adequate antibiotic therapy is defined as the treatment that covers all suspected pathogens, and it is usually started on the basis of epidemiological and clinic considerations as well as local guidelines.[6] Most of the CAP guidelines agree that patients that present with severe CAP and require ICU admission must be treated with combination therapy (CT). Some of them differ in the type of antibiotic that they recommend as the first choice for this CT. Even though there are publications that suggest that there is a benefit in terms of survival when administering CT with a macrolide in patients that require admission to the ICU, IDSA/ATS guidelines, recommend the use of a third generation cephalosporine with a respiratory fluoroquinolone as the first option. However, this recommendation is based on results in no critically ill patients. On the other hand, European guidelines[3] recommend a second to third generation cephalosporine plus a macrolide as the first choice of treatment.

The aim of this study is to determine the empiric treatment of severe CAP in two periods (2000–2002 and 2009–2011). Our hypothesis was that despite the published evidence in recent years, the use of macrolides as empiric treatment of severe CAP has decreased in the recent years.

MATERIALS AND METHODS

This is a secondary analysis of two prospective similarly designed cohort studies of critically ill patients with CAP between December 1, 2000, and February 28, 2002 (CAP in ICU [CAPUCI] study) and 2009–2011 (H1N1 SEMICYUC [Spanish Society of Critical Care] working group database study).

We enrolled immunocompetent subjects if they have the following criteria: (1) ≥15 years of age; (2) documented lower respiratory tract infection symptoms; (3) radiologic confirmation of a pneumonic process at ICU admission or within 48 h of admission to the hospital; and (4) critical illness by requiring invasive mechanical ventilation or because they were judged to be in an unstable condition requiring intensive medical or nursing care.

We excluded: (1) Children <15 years old; (2) immunosuppressed patients defined as any primary immunodeficiency or immunodeficiency secondary to HIV infection, active malignancies, immunodeficiency secondary to radiation treatment or use of cytotoxic drugs, or steroids drugs (daily doses >40 mg of prednisolone or the equivalent for >2 weeks), immunological disease, solid organ transplant, and hematological disease; and (3) any hospital-acquired bacterial pneumonia.

Study design

A detailed description of the H1N1 SEMICYUC working group database study[7] and CAPUCI study[8] patients were given elsewhere. In brief, in CAPUCI study consecutive patients with severe CAP admitted to ICUs in 33 hospitals in Spain were enrolled (2000–2002). The core data of the CAPUCI study included demographic, admission diagnoses, severity of illness at ICU admission, comorbidities, reason for ICU admission, etiological diagnosis, and treatment. Patients with severe chronic illness or disability in whom pneumonia was an expected terminal event were not included in this study. Patients residing in a nursing home and patients with health care-associated pneumonia were not eligible for enrollment in this study. Patients were admitted to the ICU either to undergo mechanical ventilation or because they were judged to be in an unstable condition requiring intensive medical or nursing care. All patients were followed up during their ICU stay.

In the H1N1 SEMICYCU study, consecutive patients with confirmed A (H1N1) pdm09 virus infection that were admitted to the ICU were enrolled. A total of 148 Spanish hospitals participated in this database between 2009 and 2011. Inclusion criteria were: Fever (>38°C); respiratory symptoms consistent with cough, sore throat, myalgia, or influenza-like illness; acute respiratory failure requiring ICU admission; and microbiological confirmation of A(H1N1) pdm09 virus infection. Data were reported by the attending physician reviewing medical charts and radiological and laboratory records. Variables recorded were similar to CAPUCI study, except for the additional specific A(H1N1) pdm09 virus related variables such as antiviral therapies. Additional variables were collected such as onset influenza symptoms, risk factors for severe influenza, time of illness onset to hospital or ICU admission and time to first dose of antiviral delivery. All patients were followed up during their ICU stay. For the purpose of this review, we included only the patients with confirmed bacterial coinfection.

Both studies were approved by the Ethics Committee of the coordinator center, Joan XXIII University Hospital, Tarragona,

Spain. Patient identification remained anonymous, and the informed consent requirement was waived due to the observational nature of both studies.

Statistical analysis

Differences between the two groups were analyzed by means of the Chi-squared test for categorical variables and Student's *t*-test for continuous variables. Results are shown as median with standard deviation, percentage, and odds ratio (OR) with 95% confidence interval (CI). For all analysis, $P < 0.05$ was considered significant. Data were performed using SPSS for windows 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

We included 1059 patients with severe CAP, 529 (49.9%) patients enrolled during the first period and 530 (50.1%) patients in the second period. Characteristics of each group are detailed in Table 1. The population was young and predominantly male. Age, male gender, chronic obstructive pulmonary disease, chronic heart failure, and diabetes mellitus were higher in the first period. In contrast, the need of mechanical ventilation, presence of shock and obesity were more frequents in the second period [Table 1]. The severity of illness assessed by APACHE II score and ICU mortality rate was not different between the groups.

The overall bacterial etiologic diagnostic was obtained in 43.4% ($n = 460$) of patients, 51.6% ($n = 248$) and 40.0% ($n = 212$) in the first and second period, respectively ($P < 0.01$). The most frequents microorganisms isolates were *Streptococcus pneumoniae*, following of *Pseudomonas aeruginosa*, *Haemophilus influnezae*, and methicillin sensitive *Staphylococcus aureus*. *Legionella pneumophila* was more frequent in first period while *Streptococcus pyogenes* and *Aspergillus* spp. were isolated with more frequency in the second period [Table 2].

A total of 866 (81.7%) patients of the two periods received CT. This therapy was more frequent in the last period (85.3% *vs.* 78.3%, $P < 0.003$) respect of first period [Table 1].

Among patients who received CT, 55% ($n = 291$) of them received a macrolide in the first period, while only 26% ($n = 119$) of patients received combination with macrolide in the second period, showing a significant ($P < 0.01$) decrease in the use of a macrolide as an agent of the dual therapy in the second period. When we analyzed the subgroup of patients that presented shock at ICU admission, we observed that these patients were more likely to receive CT during

Table 1: Characteristics of the patients of each period

Variable	Total (*n*=1059)	First Period (*n*=529)	Second Period (*n*=530)	*P* value
Age, mean years (SD)	57.1 (16.3)	59.5 (15.8)	54.5 (15.8)	0.000
Male gender, *n* (%)	725 (68)	380 (71)	345 (65)	0.01
APACHE II score, mean (SD)	18.6 (7.4)	18.9 (7.4)	18.2 (7.4)	0.12
Need for MV, *n* (%)	658 (62)	287 (54)	371 (70)	0.000
Days of MV, median (IQR)	7 (2-12.5)	8 (4-17)	12 (6-22)	0.000
LOS, median (IQR)	10 (5-20)	10 (5-19)	10 (4-20)	1
Presence of shock, *n* (%)	641 (60)	271 (51)	370 (70)	0.000
Comorbidities, *n* (%)				
COPD	324 (30)	196 (37)	128 (24)	0.000
CHF	214 (20)	156 (29)	58 (10)	0.000
DM	207 (19)	121 (23)	86 (16)	0.006
Obesity	216 (20)	79 (15)	137 (26)	0.000
Combination therapy, *n*(%)	866 (81.7)	414 (78.3)	452 (85.3)	0.003
Mortality, *n* (%)	317 (30)	149 (28)	168 (32)	0.2

APACHE II: acute physiology and chronic health evaluation, MV: mechanical ventilation, LOS: length of stay, COPD: chronic obstructive pulmonary disease, CHF: chronic heart failure, DM: diabetes mellitus, SD: standard deviation

Table 2: Most frequent microorganisms isolated in both periods

Microorganisms, *n* (%)	Overall (*n*=460)	First Period (*n*=248)	Second period (*n*=212)	*P* value
Streptococcus pneumoniae	223 (48.4)	126 (50.8)	97 (45.7)	0.2
Legionella pneumophila	25 (5.4)	20 (8.1)	5 (2.3)	0.01
Haemophilus influenza	32 (6.9)	19 (7.7)	13 (6.1)	0.5
Pseudomonas aeruginosa	35 (7.6)	16 (6.5)	19 (8.9)	0.3
MSSA	28 (6.0)	12 (4.8)	16 (7.5)	0.2
MRSA	6 (1.3)	3 (1.2)	3 (1.4)	0.8
Gram negative bacilli	24 (5.2)	13 (5.2)	11 (5.2)	0.9
Streptococcus pyogenes	13 (2.8)	3 (1.2)	10 (4.7)	0.02
Aspergillus spp	11 (2.4)	1 (0.4)	10 (4.7)	0.03
Others	64 (14.0)	36 (14.5)	28 (13.2)	0.6

MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: Methicillin-resistant *S.aureus*

the second period. In contrast, patients with shock were less likely to receive a macrolide as an agent of the CT during the second period [Table 3].

DISCUSSION

The main finding of our study is that over the years we observed greater use of CT in severe CAP. In contrast, we found a significant decrease in the number of ICU patients who receive CT with macrolides in the last period of study.

CT has been suggested to be the best option of treatment in severe CAP patients admitted to the ICU. CAPUCI group study[9] found that in an ICU population of patients with severe CAP, giving CT was associated with significantly higher 28-day adjusted ICU-survival in shock patients. Similar results were obtained by Gattarello *et al*.[10] They performed a multicenter case–control analysis including eighty cases and eighty controls, and found that combined therapy was independently associated with lower risk for ICU mortality in pneumococcal severe CAP (OR 0.36, 95% CI 0.15–0.87; $P < 0.01$). A French study[11] found that ICU patients receiving dual therapy were associated with greater adequacy of initial antibiotic therapy, but differences in 60-day mortality were no statistically significant.

According to the 2007 IDSA/ATS guidelines for CAP, fluoroquinolones are the first option for combination antibiotic therapy in severely ill patients. This might be the reason why we observed a significant increase in its use during the past years in Spanish ICUs, despite the fact that association with macrolides has shown potential benefits in terms of survival. In this way, Restrepo *et al*.[12] found that 30- and 90-day mortality was lower in subjects with severe CAP, who received macrolides (11%) compared with nonmacrolide subjects (29%; $P = 0.001$) despite they found similar rates of ICU admission, need for mechanical ventilation and need for vasopressors. Mortensen *et al*.[13] analyzed 172 CAP patients admitted to the hospital and observed that the overall mortality at 30 days in patients admitted to the ICU (62%) was 19.8%. Interestingly, the 30-day mortality rate for patients who received CT with a β-lactam plus fluoroquinolone was significantly higher (30%) than other guideline-concordant antimicrobial combination ($P = 0.03$). For patients who received a β-lactam with macrolides, 30-day mortality was 17.2% and for other guideline-concordant antibiotic regimes mortality was 11.4%. When stratified by pneumonia severity index risk class, 30-day mortality was 30% (4 of 13) for patients who received a β-lactam with a fluoroquinolone, compared with 7.4% (2 of 27) for other antibiotic combination. After adjustment for potential confounders, this combination was significantly associated with increased 30-day mortality (OR 2.71, 95% CI 1.2–6.1).

In addition, has also been proposed that CT including a macrolide should be used in bacteremic CAP. In this regard, Martínez *et al*. conducted a retrospective study, including bacteremic CAP patients who received monotherapy with a β-lactamic or in combination with another agent.[14] A total of 409 patients were included, and receiving a macrolide as an initial treatment agent was independently associated with lower in-hospital mortality (OR 0.4, 95% CI 0.17–0.92, $P = 0.03$), even when excluding patients who died in the first 48 h. This association was found even when given in combination with a third generation cephalosporine. Along the same line, Metersky *et al*. conducted a retrospective multicenter study including 2209 patients with bacteremic pneumonia admitted to the general ward. They found that treatment with a macrolide but not with a fluoroquinolone was independently associated with lower in-hospital mortality (OR 0.59, 95% CI 0.4–0.8, $P = 0.01$), lower 30-day mortality rate (OR 0.61, 95% CI: 0.4–0.8, $P = 0.007$), and lower ICU readmission (OR 0.59, 95% CI 0.4–0.8, $P = 0.004$). A Brazilian group analyzed differences between two periods after implementing CAP treatment guidelines at a public hospital.[15] In the preimplementation period, CT including a macrolide was given only in 6.3% of the patients, while it was administered to 75% of the population in the postimplementation period. There was a trend to a decrease in mortality in the postimplementation period (35.4% *vs*. 15%), but it did not reach statistical significance, probably due to the low number of cases. In addition, Martin-Loeches *et al*.[16] included 219 ICU patients in the prospective multicentric study, and found that mortality was significantly lower for subjects who received macrolides compared to patients who received quinolones, but this difference was not found when excluding patients who receive ciprofloxacin. A Cox regression analysis adjusted by etiology and severity identified that using a macrolide was associated with lower ICU mortality when compare to quinolone use (hazard ratio 0.48, 95% CI 0.23–0.97, $P = 0.04$). Similarly, the CAP Organization study[17] that analyzed mortality differences in CAP patients in three world regions, found that in the group of patients on the ward, the use of a macrolide (OR 0.53, 95% CI 0.42–0.68, $P < 0.001$) or a fluoroquinolone (OR 0.6, 95% CI 0.46–0.77, $P < 0.001$) were protector for mortality, while in the group of patients admitted to the ICU, just the use macrolides was protector (OR 0.43, 95% CI 0.29–0.64, $P < 0.001$) for mortality. Finally, according to the meta-analysis of Sligl

Table 3: Macrolides use and combination therapy in the subgroup of patients with shock in the two periods

Variable	First period (*n*=270)	Second period (*n*=370)	OR (CI 95%)	*P* value
Combination therapy, *n* (%)	218 (80%)	325 (88)	0.42 (0.26-0.69)	0.000
Macrolide, *n* (%)	143 (53)	81 (22)	3.9 (2.7-5.5)	0.000

OR: odds ratio; CI: confidence interval

et al.,[18] CT with β-lactam plus a macrolide is associated with the highest survival opposed to combination without a macrolide (21% *vs*. 23%, $P = 0.05$).

Despite reported evidence, Spanish ICU physicians have changed their preference to indicate empirical treatment for CAP and CT with quinolone as the first choice of treatment. We are not able to determine the causes that have conditioned the change of attitude of the intensivists respect of macrolide-based on our results. We can only hypothesize that some factors such as the frequent pneumococcal resistance to macrolides, an increase in "*in vitro*" activity against the pneumococci of new fluoroquinolone or even, existence of a commercial promotion for quinolones but not for macrolides, might have contributed to the change observed in the present study.

It is unclear why treatment with CT including a macrolide may contribute to better outcomes in patients with severe sepsis due to CAP. Some of the reasons that have been proposed are (1) antimicrobial synergism; (2) atypical pathogens coverage; and (3) immunomodulatory effect. Antimicrobial synergism is unlikely to be the reason as Gram-positive microorganisms are not the only cause of severe CAP. Indeed, *S. pneumoniae* is frequently resistant to macrolide. It is also unlikely that the reason for this benefit is the coverage of atypical pathogens as *L. pneumophila*. because both macrolides and fluoroquinolones have excellent activity against this pathogen, and the incidence of *L. pneumophila* pneumonia is too low to explain the beneficial effect of macrolides.

Interestingly, in the paper of Restrepo *et al*.,[12] patients that received empirical macrolide therapy were more likely to survive even when evaluating all the cases with documented macrolide-resistant pathogens and patients with cultures positive for a Gram-negative pathogen, suggesting a potential benefit for macrolide treatment not associated to antibiotic coverage. The immunomodulatory effects of macrolides seem to be the reason for its beneficial effects. A recent review on macrolide treatment in CAP[19] explores some mechanisms that have been proposed to explain these effects. Macrolides modulate the expression and release of cytoquines and other neutrophils chemoattractants; they have shown to enhance macrophage function and increase the phagocytosis of apoptotic bronchial ephitelial cells, therefore modulating the recruitment of neutrophils. Macrolides may also suppress the expression of some adherence molecules on neutrophils. All these mechanisms contribute to an attenuation of the inflammatory response that is beneficial not only in severe CAP patients but some chronic respiratory diseases. Another important effect of these agents is that they have shown to disrupt de biofilm formation. Some pathogens often implicated in pneumonia have the ability to form biofilm in the respiratory tract, such *as S. aureus*, *S. pneumoniae*, and *P. aeruginosa*. Although this effect of macrolides has not been demonstrated in CAP patients, it has been observed in patients with cystic fibrosis colonized with *P. aeruginosa*.[20]

We consider that a reason that might explain why not all studies observed a reduced mortality after macrolide administration is because only patients with a high inflammatory response may benefit from it.[21]

Our study has several limitations that should be acknowledged. First, it is a secondary analysis of two databases with more than 7 years of difference between them. However, diagnostic criteria and treatment of CAP have not significantly changed in that period. Second, the last period considered is associated with the emergence of the virus A (H1N1) pdm09. Although the etiology of CAP may be different between periods, the aim of our study was not evaluate the epidemiology of the CAP but to assess the empirical treatment for suspected bacterial infection in patients with CAP admitted at the ICU. Third, because of the descriptive characteristics of the analysis, we are not able to determine the causes associated with our results. Since we can only make a hypothesis, new studies specifically designed to answer this question should be made.

CONCLUSIONS

Despite the fact that the use of CT for CAP patients that require ICU admission has increased in the last years in the Spanish ICUs, there is still approximately a 15% of these patients which received monotherapy. In addition, although there is evidence that suggests that there is a benefit of using a macrolide as an agent of CT, a respiratory fluoroquinolone is the first choice to empiric CAP treatment for Spanish ICU physicians. Based on the above evidence, we advocate the use of macrolides in CT of the severe CAP.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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