Combination antibiotic therapy for community-acquired pneumonia

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Abstract
Community-acquired pneumonia (CAP) is a common and potentially serious illness that is associated with morbidity and mortality. Although medical care has improved during the past decades, it is still potentially lethal. *Streptococcus pneumoniae* is the most frequent microorganism isolated. Treatment includes mandatory antibiotic therapy and organ support as needed. There are several antibiotic therapy regimens that include β-lactams or macrolides or fluoroquinolones alone or in combination. Combination antibiotic therapy achieves a better outcome compared with monotherapy and it should be given in the following subset of patients with CAP: outpatients with comorbidities and previous antibiotic therapy, nursing home patients with CAP, hospitalized patients with severe CAP, bacteremic pneumococcal CAP, presence of shock, and necessity of mechanical ventilation. Better outcome is associated with combination therapy that includes a macrolide for wide coverage of atypical pneumonia, polymicrobial pneumonia, or resistant *Streptococcus pneumoniae*. Macrolides have shown different properties other than antimicrobial activity, such as anti-inflammatory properties. Although this evidence comes from observational, most of them retrospective and nonblinded studies, the findings are consistent. Ideally, a prospective, multicenter, randomized trial should be performed to confirm these findings.

Introduction
Community-acquired pneumonia (CAP) is a common and potentially serious illness that is associated with morbidity and mortality [1]. Only half of the cases had an etiology microorganism identified. Bacteria are the most common identifiable cause; *Streptococcus pneumoniae* is the single most common bacterium responsible. Antibiotic therapy is begun empirically, because the causal organism is not identified in a proportion of patients [1-4]. Approximately 10% of patients hospitalized with CAP are bacteremic [5]. Bacteremic *Streptococcus pneumoniae* pneumonia is the number one cause of mortality, representing up to 70% of all CAP deaths.

Although medical care has improved during the past decades, bacteremic pneumococcal pneumonia is still lethal. Explanations for this situation could be the presence of immune-compromised patients, aging population, or comorbid conditions. But there are more explanations. A severity assessment score based on the PIRO (Predisposition, Insult, Response, and Organ dysfunction) concept was assessed, including comorbidities, age greater than 70 years, multilobar opacities in chest x-ray, shock, severe hypoxemia, acute renal failure, bacteraemia, and acute respiratory distress syndrome. The mean PIRO score was significantly higher in nonsurvivors than in survivors. Furthermore, analysis of variance showed that higher levels of PIRO score were significantly associated with higher mortality, prolonged length of stay in the intensive care unit (ICU), and days of mechanical ventilation. PIRO score for CAP can be used to predict 28-day mortality in CAP patients who require ICU admission [6]. Bacterial load may identify potential candidates for adjunctive therapy, ICU admission, and more aggressive management. High bacterial load appears to be significantly associated with worse outcomes [7].

Treatment of CAP continues to be a challenge in 21st century. Recommendations for CAP therapy are different, depending on whether patients require hospitalization (20%) or are treated as outpatients (80%) [8]. Other issues for treatment recommendations include the emergence of antibiotic resistance among *Streptococcus pneumoniae* and mono versus combination antibiotic therapy. Combination therapy should be defined as the...
combination of two of the following antibiotics: \( \beta \)-lactam, macrolide, or fluoroquinolone. Monotherapy is the use of only one of them.

Antimicrobial therapy remains a controversial issue to treat CAP. Until better diagnostic tests are available in the clinical setting, initial treatment is usually empiric. To recommend mono versus combination therapy, we should differentiate between outpatients with CAP and patients who require hospitalization, hemodynamic support, or mechanical ventilation.

**Ambulatory setting**

In Canada and the United States, macrolides remain the recommended first-line therapy for outpatients with CAP but without comorbidities. Common risk factors for CAP include age greater than 65 years, smoking, alcohol consumption, chronic lung diseases, mechanical obstruction of airways, aspiration of oropharyngeal or gastric contents, pulmonary edema, uremia, and malnutrition [9].

The recommended empirical antibiotics for outpatient therapy of CAP has been published recently in the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) consensus guidelines on the management of community-acquired pneumonia in adults [1]. For previously healthy patients without recent antibiotic therapy within 3 months, a macrolide or doxycycline are recommended. Macrolides remain effective for patients with mild to moderate-severe CAP with no risk factors [10]. For previously healthy patients but with antibiotic therapy within 3 months, guidelines recommend azithromycin or clarithromycin, plus a high-dose amoxicillin (4 g/day) or amoxicillin-clavulanate (4 g/day), or a respiratory fluoroquinolone alone. If there are comorbidities (chronic obstructive pulmonary disease [COPD], diabetes, renal or congestive heart failure, malignancy) but without recent antibiotic therapy, empirical therapy should start with azithromycin or clarithromycin, or a respiratory fluoroquinolone alone. If comorbidities and previous antibiotic therapy within 3 months, azithromycin or clarithromycin should be used, plus high-dose amoxicillin, amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime, or a respiratory fluoroquinolone.

A respiratory fluoroquinolone is one with predictable activity against pneumococcus, such as levofloxacin or moxifloxacin. They are recommended if there is a documented allergy to \( \beta \)-lactams, first-line therapy fails, or against highly resistant pneumococcus prevalence. Anaerobic coverage should be given if loss of consciousness or gingival or esophageal disease. In the nursing home without hospitalization, a respiratory fluoroquinolone or amoxicillin-clavulanate plus a macrolide is recommended as the first-choice [10].

Almost all of the clinical studies comparing newer fluoroquinolones with the standard therapeutic regimen have been designed to reveal noninferiority or bioequivalence. Therefore, high-risk patients were usually excluded from these clinical trials. An outpatient trial that compared two new fluoroquinolones–gemifloxacin and trovafloxacin–showed high response rates of 92.5% and 87.3%, respectively [11]. This trial, like others, was not designed to evaluate fluoroquinolone efficacy in severe pneumonia to gain approval from registration agencies.

**CAP that requires hospitalization**

Two frequent recommended antibiotic regimens for hospitalized patients with CAP are an extended-spectrum \( \beta \)-lactam (an extended-spectrum cephalosporin or \( \beta \)-lactam-\( \beta \)-lactamase inhibitor) with a macrolide or an antipseudomonal quinolone. These regimens have activity against the major causes of CAP, including drug-resistant *Streptococcus pneumoniae* [12-15]. Recent evidence suggests the superiority of combination therapy compared with monotherapy for subset populations, particularly patients with severe CAP, bactereemic pneumococcal CAP, or intubated CAP. Table 1 resumes all of these studies [5,16-29]. Which combination of antibiotics are more effective remains unclear, although many studies had focused on the combination of an extended-spectrum cephalosporin plus a macrolide [17,19-21,23]. Moreover, most of the studies regarding this topic are retrospective or observational, giving apparently weak scientific evidence.

Other studies, however, have refuted the advantages of dual therapy versus monotherapy for CAP [30-33] (Table 2). Burgess et al. [30] enrolled 213 patients treated with a nonpseudomonal third-generation cephalosporin with (116 patients) or without (97 patients) a macrolide; the majority of them (66%) received erythromycin. There were no statistical differences between patients who did or did not receive a macrolide in terms of comorbid illnesses, length of hospital stay (5.2 ± 2.8 vs. 5.2 ± 3.4 days, respectively), length of intravenous antibiotic therapy (4.4 ± 2.5 vs. 4.1 ± 2.3 days, respectively), or mortality (0.9% vs. 3.1%, respectively; \( p = 0.333 \)). This low mortality shows that those patients did not have severe CAP. Data collected prospectively from 340 adult patients hospitalized in five countries with bactereemic pneumococcal CAP and treated with \( \beta \)-lactam ± macrolide were analyzed retrospectively to evaluate the efficacy of this antimicrobial combination. Univariate and multivariate analyses revealed no significant effect on case fatality rate when a macrolide/\( \beta \)-lactam regimen was used as initial therapy. Results were not affected by severity of illness or by excluding patients who died within 2 days of admission [31]. In a
A retrospective study of a cohort of 1,840 adult patients with severe sepsis or septic shock enrolled in two multicenter clinical trials between 1994 and 1999, the subanalysis of 107 patients with pneumococcal sepsis, the case-fatality rate was 20% (5/25) for patients who received antibiotic monotherapy compared with 19.5% (16/82) for patients who received combination therapy (adjusted hazard ratio [HR], 1.1; 95% confidence interval [CI], 0.4-3.1). Similarly, monotherapy did not increase the risk of death (adjusted HR, 1.0; 95% CI, 0.2-4.8) among bacteremic patients (n = 75). However, the latter analysis may have been underpowered (power, 58%) to detect a difference in mortality [32].

Monotherapy with levofloxacin (500 mg every 12 hours) was compared with combination therapy (ofloxacin 200 mg every 12 hours plus cefotaxime 1 g every 8 hours) in a multinational trial of 398 patients with CAP who required ICU admission, but who required neither vasopressors nor mechanical ventilation [33]. In this study, clinical success rates were the same for both regimens (79% vs. 80%). These results were not generalizable to intubated or patients with shock. Although the numbers were small, more patients treated with monotherapy failed a test of cure (7/29 compared with 1/27 in the combination group) [34].

### Table 1 Published studies that favor combination therapy for in-hospital patients with CAP

| Author                  | Year | Cohort                        | Site     | Outcome                                          | Study design          |
|-------------------------|------|-------------------------------|----------|-------------------------------------------------|-----------------------|
| Gleason et al. [16]     | 1999 | Patients aged ≥ 65 years with CAP | Ward     | Lower 30-day mortality with β-lactam plus macrolide | Multicenter, retrospective |
| Dudas et al. [17]       | 2000 | CAP                           | Ward     | Lower mortality with β-lactam plus macrolide and reduced LOS | Multicenter, prospective |
| Waterer et al. [19]     | 2001 | Pneumococcal bacteremia       | Ward     | Lower hospital mortality with combination | Multicenter, retrospective |
| Brown et al. [21]       | 2003 | CAP                           | Ward     | Lower 30-day mortality with combination | Multicenter, retrospective |
| Martínez et al. [20]    | 2003 | Pneumococcal bacteremia       | Ward     | Lower in-hospital mortality with β-lactam plus macrolide | Multicenter, retrospective |
| Baddour et al. [22]     | 2004 | Pneumococcal bacteremia       | Ward     | Lower 14-day mortality with combination | Multicenter, retrospective |
| Weiss et al. [5]        | 2004 | Pneumococcal bacteremia       | Ward     | Lower mortality with combination | Monocenter, retrospective |
| Garcia-Vázquez et al.   | 2005 | CAP                           | Ward     | Lower mortality with β-lactam plus macrolide | Multicenter, prospective |
| Mortensen et al. [24]   | 2006 | CAP                           | Ward     | Lower 30-day mortality with β-lactam plus other than FQ | Multicenter, retrospective |
| Rodriguez et al. [25]   | 2007 | CAP                           | ICU      | Lower 28-day mortality with combination | Multicenter, retrospective |
| Metersky et al. [26]    | 2007 | Pneumococcal bacteremia       | Ward     | Lower 30-day mortality with β-lactam plus macrolide | Multicenter, retrospective |
| Restrepo et al. [27]    | 2009 | Severe sepsis pneumonia       | Ward     | Lower 30- and 90-day mortalities with combination plus macrolide | Multicenter, retrospective |
| Tessmer et al. [28]     | 2009 | CAP                           | Ward     | Lower 14- and 30-day mortalities with β-lactam plus macrolide | Multicenter, retrospective |
| Martin-Löeches et al.   | 2010 | Intubated CAP                 | ICU      | Lower ICU mortality IDSA/ATS combination plus macrolide | Multicenter, prospective |

### Table 2 Trials without significant difference between antibiotic monotherapy and combination therapy for CAP

| Author                  | Year | Cohort                        | Outcome                                      | Study design          |
|-------------------------|------|-------------------------------|----------------------------------------------|-----------------------|
| Burgess and Lewiss [30] | 2000 | Hospitalized CAP without identified microorganism | Nonstatistical differences third-generation cephalosporin ± macrolide | Bicenter, retrospective |
| Dwyer et al. [31]       | 2006 | Bacteremic pneumococcal CAP   | No significant difference in case fatality if initial β-lactam + macrolide | Multicenter, retrospective |
| Harbarth et al. [32]    | 2005 | Pneumococcal sepsis           | Lack of effect of combo therapy               | Multicenter, retrospective |
| Leroy et al. [33]       | 2005 | CAP without vasopressors      | Levofloxacin vs. cefotaxime + ofloxacin      | Multicenter, retrospective |
In overall CAP patients, there are subsets of patients with severe CAP for whom combination therapy is clearly superior compared with monotherapy: severe CAP, bacteremic pneumococcal CAP, CAP with shock, and intubated CAP patients.

Severe CAP
Lodise et al. demonstrated that a combination therapy of a β-lactam plus a macrolide had lower 14-day and 30-day mortality rates than with fluoroquinolone alone (14-day rates: 8.2% vs. 26.8%, \( p = 0.02 \); 30-days rates: 18.4% vs. 36.6%, \( p = 0.05 \)). However, these results were shown in patients with severe CAP, defined as a class V Pneumonia Severity Index (PSI). No differences in mortality between treatment groups were noted for the lower PSI classes. The overall median length of stay (LOS) was significantly longer for the combination therapy group, but no difference in LOS was noted among PSI class V patients [35]. Severe CAP also can be defined as the presence of Streptococcus pneumoniae bacteremia or the necessity for aggressive ICU management due to shock, organ dysfunction, or need for mechanical ventilation.

Bacteremic pneumococcal CAP
Recent observational studies suggest that combination therapy for severe CAP confers a significant benefit for patients, particularly those with bacteremic pneumococcal disease [5,19-22]. This group of patients represents only a small fraction of all of the CAP cases, but in terms of mortality it is highly relevant.

Monotherapy may be suboptimal for patients with severe bacteremic pneumococcal pneumonia. Waterer et al. [19] found in patients with severe bacteremic pneumococcal pneumonia a significantly higher mortality in the single effective therapy group than within the dual effective therapy group (\( p = 0.02 \); odds ratio [OR], 3.0; 95% CI, 1.2-7.6).

Martinez et al. [20] assessed the association between inclusion of a macrolide in a β-lactam-based empirical antibiotic regimen and mortality among patients with bacteremic pneumococcal pneumonia. Multivariate analysis showed four variables to be independently associated with death: shock (\( p < 0.0001 \)), age ≥ 65 years (\( p = 0.02 \)), infections with pathogens that have resistance to both penicillin and erythromycin (\( p = 0.04 \)), and no inclusion of a macrolide in the initial antibiotic regimen (\( p = 0.03 \)). For patients with bacteremic pneumococcal pneumonia, not adding a macrolide to a β-lactam-based initial antibiotic regimen is an independent predictor of in-hospital mortality.

Weiss et al. [5] developed a similar retrospective study on the outcome of bacteremic pneumococcal pneumonia in adults. Data showed the same results. The mortality rate was significantly higher in the group that received monotherapy with a β-lactam compared with that in the combination therapy group with a β-lactam plus a macrolide (26% vs. 7.5%, respectively; \( p = 0.02 \)). Patients were comparable in terms of disease severity using the severity index scores.

Although all of these studies were nonrandomized, retrospective studies, they confirmed the importance of initially adding a macrolide to a β-lactam regimen for the treatment of bacteremic Streptococcus pneumoniae pneumonia. However, these conclusions are limited to patients with severe pneumonia for whom the mortality risk is high. The value of these results cannot be extrapolated for the treatment of inpatients with moderate disease, for which fluoroquinolones still remain an excellent therapy of choice [36].

CAP and shock
An observational study of patients with pneumonia who require ICU care found that patients with CAP and shock who were treated with combination antibiotic therapy (58% with a third-generation cephalosporin plus a macrolide), compared with those treated with monotherapy (42% fluoroquinolone), had a higher 28-day in-ICU survival (HR, 2.69; 95% CI, 1.09-2.6). Survival was not different between combination therapy and monotherapy for ICU patients without shock [25]. As other studies, potential limitations are that it is an observational study and that the CAP severity stratification was not standardized. Although dosing was given according to 2007 IDSA/ATS guidelines [1] to define the appropriateness of empirical treatment, underdosing is a common problem in patients with severe sepsis and multiorgan dysfunction due to a higher volume of distribution [37]. The consequence is finding lower-than-expected plasma drug concentrations. However, if decreased antibiotic clearance occurs, it can lead to drug toxicity. Another limitation could be that by direct extrapolation from the 2007 IDSA/ATS CAP guidelines [1], Pseudomonas infection appears to have been suspected a great deal; more patients were chosen to receive quinolone therapy. It should not be surprising that mortality would be higher in patients suspected of possible Pseudomonas or multidrug resistant pathogens infection [38].

Necessity of ventilator support
The effect on survival of using macrolides or fluoroquinolones in combination therapy in a cohort of intubated patients admitted to the ICU with severe CAP in 27 European ICUs was assessed [29]; 218 consecutive patients who required invasive mechanical ventilation for an admission diagnosis of CAP were recruited prospectively. Monotherapy was given in 19.7% of patients
and combination therapy in 80.3%. Empirical antibiotic therapy was in accordance with the 2007 IDSA/ATS guidelines in 45.9% of patients [1]. Combination was prescribed with macrolides in 46 patients and with fluoroquinolones in 54 patients. In the macrolide group, 89.1% of patients received a third-generation cephalosporin, 4.3% a fourth-generation cephalosporin, and 6.5% received piperacillin-tazobactam. Meanwhile, 40.7% of the fluoroquinolone group received a third-generation cephalosporin as combination therapy, 22.2% received a carbapenem, and 25.9% received piperacillin-tazobactam. Mortality in the ICU was significantly lower for subjects who received a combination therapy with macrolides compared with patients who received quinolones (26.1% vs. 46.3%, p < 0.05). However, when excluding ciprofloxacin, no significant differences were documented. Similar results were obtained with 30-day mortality. In this cohort, a Cox regression analysis adjusted by severity identified that macrolide use was associated with lower mortality (HR, 0.48; 95% CI, 0.23-0.97; p = 0.04) compared with the use of fluoroquinolones. When more severe patients with severe sepsis and septic shock were analyzed, similar results were obtained (HR, 0.44; 95% CI, 0.2-0.95; p = 0.03). Therefore, combination therapy with macrolides should be preferred for invasive mechanically ventilated patients with severe CAP.

Factors for combination therapy
Different factors may explain the superiority of combination therapy compared with monotherapy for the treatment of patients with severe CAP. Combination therapy has a better coverage of atypical microorganisms in polymicrobial CAP, including both *Chlamydia pneumonia* and *Mycoplasma pneumonia*. It has been suggested that a proportion of bacteremic *Streptococcus pneumoniae* pneumonia patients have concomitant *Mycoplasma pneumoniae* or, rarely, *Legionella* sp. infections [39].

Other factor for combination therapy superiority is the fact that combination therapy acts at two different sites in the bacteria: cell wall by β-lactams, and the inhibition of protein synthesis by macrolides. Macrolides, moreover, have been shown to have some very effective anti-inflammatory properties [40]. Macrolides reduce the release of interleukin-8 and tumor necrosis factor-α, and the adherence of *Streptococcus pneumoniae* to respiratory epithelial cells. Moreover, macrolides inhibit protein synthesis, potentially decreasing the production of virulence factors [41]. Other recent studies have suggested that macrolides may have beneficial effects for severe CAP [27] because of their immunomodulatory effects rather than due to their antimicrobial properties [42]. In Berlin at the 24th European Society of Intensive and Critical Care Medicine (ESICM) annual congress, Dr. Restrepo presented a retrospected analysis of the effect of macrolide therapy on 30- and 90-day mortality for patients with severe sepsis that required mechanical ventilation. After multivariable regression analysis, macrolide use in patients with severe sepsis who required intubation was associated with decreased 30-day mortality (31% vs. 53%; OR, 0.49; 95% CI, 0.41-0.6) and 90-day mortality (54% vs. 71%; OR, 0.59; 95% CI, 0.49-0.71) compared with nonmacrolide therapy after adjusting for potential confounders [43]. Confirmatory, randomized, control trials are needed to determine whether macrolide therapy may be protective for septic patients who require mechanical ventilation.

As PIRO approach defends, factors other than the simple concept of in vitro activity alone are playing key roles in bacteremic pneumonia. In fact, a lack of in vitro synergy between erythromycin and cefotaxime combined with penicillin against *Streptococcus pneumoniae* has been published [44]. Therefore, the observed effect of adding a macrolide in patients with severe CAP cannot be attributed to a synergistic action between β-lactams and macrolides [36].

Conclusions
Combination antibiotic therapy achieves a better outcome compared with monotherapy, and it should be given in the following subset of patients with CAP: outpatients with comorbidities and previous antibiotic therapy, nursing home patients with CAP, hospitalized patients with severe CAP, bacteremic pneumococcal CAP, presence of shock, and necessity of mechanical ventilation (Table 3).

At ambulatory setting, if comorbidities and previous antibiotic therapy within 3 months, azithromycin or clarithromycin should be used, plus high-dose amoxicillin, amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime, or a respiratory fluoroquinolone. In previously healthy patients without comorbidities or without previous antibiotic therapy, monotherapy is still the empirical initial recommended therapy. In the nursing home without hospitalization, a respiratory fluoroquinolone or amoxicillin-clavulanate plus a macrolide is recommended as the first choice.

Initial empirical combination therapy of a cephalosporin plus a macrolide for patients with CAP who require hospitalization is associated with decreased mortality and or shorter hospital stay than treatment with a cephalosporin alone. For patients with moderate disease, fluoroquinolones remain an excellent therapy of choice. Although this evidence comes from observational, retrospective, and nonblinded studies, the findings are consistent. For practical purposes, for the majority of patients with CAP in ambulatory settings or hospitalized and not severely ill, fluoroquinolone monotherapy remains an
approved, tested, cost-effective, and reliable option. Otherwise, hospitalized patients with a severe CAP, bacteremia, ICU admission, or need for vasopressors or mechanical ventilation may benefit from a dual antibiotic therapy that combines a third-generation cephalosporin and a macrolide. Ideally, a prospective, randomized trial should be performed to confirm these findings, although severe heterogeneity of patients is a challenge to enroll patients and find differences as several sepsis trials show.

Authors’ contributions
JC wrote the first draft of the manuscript. JR revised the manuscript. Both authors read and approved the final manuscript.

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JR is a well-known expert in critical infectious diseases and chief of Vall d’Hebron Critical Care Department. He has a wide background on pneumonia, either hospital or community-acquired. JC is an attending physician of Vall d’Hebron Critical Care Department.

Competing interests
Jesus Caballero declares that he has no competing interests. Jordi Rello declares that he serves on advisory boards and speakers’ board for Pfizer and Novartis.

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Table 3 Resume of recommendations for monotherapy or combination therapy in CAP

| Ambulatory setting                  | Previously healthy patients | Monotherapy                                      |
|-------------------------------------|-----------------------------|--------------------------------------------------|
|                                     |                             | Combination or respiratory fluoroquinolone       |
| Comorbidities without previous antibiotic therapy | Monotherapy with macrolides or respiratory fluoroquinolone |
| Comorbidities and previous antibiotic therapy | Combination therapy         |

| Nursing home without hospitalization | CAP | Combination therapy |

| Hospitalized CAP | Moderate disease | Monotherapy with respiratory fluoroquinolones or combination therapy |
| Severe CAP       | Combination therapy |
| Bacteremic pneumococcal CAP | Combination therapy |
| CAP and shock    | Combination therapy |
| Ventilation support | Combination therapy |

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