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What Is New in Antibiotic Therapy in Community-Acquired Pneumonia? An Evidence-Based Approach Focusing on Combined Therapy

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Abstract Despite all published literature, controversies remain about the optimal antibiotic treatment in community-acquired pneumonia. The most debated issue is whether it is necessary to empirically start one or two antibiotics, i.e. whether or not to cover atypical agents. A review of the literature published from 2005 to present was completed, searching for new insights in antibiotic treatment in community-acquired pneumonia (CAP) focusing on monotherapy versus combined therapy. Forty-one articles were identified enrolling outpatients, and patients admitted to the ward and to the intensive care unit: 11 were meta-analyses, 8 clinical trials and 22 observational—prospective and retrospective—studies. Although controversies remain in the treatment of CAP, the use of combination therapy seems to be associated with a lower mortality in case of severe CAP that requires intensive care unit (ICU) admission, especially when a beta-lactam–macrolide association is delivered. Moreover, combination therapy is associated with better outcomes—although not always with a lower mortality—in cases of non-ICU patients with risk factors for a poor outcome, bacteraemic pneumococcal pneumonia and high suspicion of infection by atypical agents. In this setting, it appears that the best choice of treatment may be a beta-lactam–macrolide regimen.

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Abbreviations

CAP	Community-acquired pneumonia
ICU	intensive care unit
PSI	Pneumonia severity index

Introduction

Community-acquired pneumonia (CAP) is a common and potentially severe disease. In Europe, it is estimated that the annual incidence in younger adults is 1.2 cases per 1000 person-years, increasing up to 14 per 1000 in patients over 65 years old [1].

In Western countries, mortality due to CAP varies widely depending from the severity of the illness: less than 1 % in individuals treated outside the hospital; around 10 % in hospitalised non-intensive care unit (ICU) patients, and up to 20 to 40 % in severe forms, i.e. when ICU admission is required [2, 3•].

In CAP, antibiotic therapy is the cornerstone of treatment; after diagnosis of pneumonia is done, an adequate antimicrobial therapy is always recommended, as it has been associated with better outcomes [4, 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 [4]. Although CAP may be caused by many pathogens, a reduced number of microorganisms are responsible for the majority of cases; classically, they are classified into typical and atypical.

Guidelines for the management of CAP were published [4, 6], and the antibiotic regimens proposed are classified

according with the site of care: outpatients, ward or intensive care unit (ICU).

What Do the Guidelines Recommend?

Outpatients

In outpatients with CAP, the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines recommend administration of a macrolide (azithromycin, clarithromycin or erythromycin) or doxycycline. If a patient received antibiotic therapy within 3 previous months, or presents with some risk factor for a higher mortality for CAP (chronic heart disease, lung or liver disease, diabetes mellitus, alcohol abuse, malignancy, asplenia or hyposplenism, immunocompromised status), the recommended antibiotic regimen is a respiratory fluoroquinolone (moxifloxacin, gemifloxacin or high-dose levofloxacin), or a combination of a beta-lactam (high-dose amoxicillin or amoxicillin–clavulanate, ceftriaxone, cefuroxime or cefpodoxime) with a macrolide. In the same setting, European guidelines recommend the administration of amoxicillin or a tetracycline. If these agents are considered contraindicated or there is a high suspicion of infection by atypical agents, the indication is monotherapy with a macrolide or a respiratory fluoroquinolone. Both American and European guidelines suggest considering the local flora pattern of antibiotic resistance.

Ward

In the case of patients with CAP who require hospitalisation, the IDSA/ATS guidelines suggest administration of a respiratory fluoroquinolone, and a beta-lactam (cefotaxime, ceftriaxone, ampicillin or ertapenem) plus a macrolide or doxycycline if patients have a high risk of pneumonia due to Gram-negative bacilli. As stated in the guidelines, monotherapy with a macrolide should be avoided because of the high rate of macrolide-resistant pneumococci. In the same setting, European guidelines suggest the administration of an aminopenicillin with or without a beta-lactamase inhibitor or a cephalosporin (ceftriaxone or cefotaxime), and to consider the addition of azithromycin or clarithromycin. In the case of high suspicion for *Streptococcus pneumoniae*, as several publications have demonstrated that low-level resistance to penicillin is not associated with worsened outcomes [7], penicillin G plus a macrolide could be an alternative. If those antibiotics are considered inappropriate, a respiratory fluoroquinolone may be an alternative. As stated in the European guidelines, the use of a specific antibiotic pattern should be guided by the severity of the disease (most severe cases should be treated with combined therapy) and based on considerations of allergy, intolerance, previous use of penicillins, macrolides or fluoroquinolones, cost and potential adverse effects.

Intensive Care Unit

According to both the American and the European guidelines, a patient in an ICU setting should be covered for all suspected microorganisms (resistant *Streptococcus pneumoniae* and atypical pathogens) because it was observed in severe CAP that an inadequate antibiotic treatment is associated with an increased mortality [8].

IDSA/ATS guidelines suggest initiating a combination regimen with a beta-lactam (cefotaxime, ceftriaxone or ampicillin–sulbactam) plus either azithromycin or a respiratory fluoroquinolone. Likewise, European guidelines suggest combination therapy in the form of a non-antipseudomonal third-generation cephalosporin (ceftriaxone or cefotaxime) plus either a macrolide (azithromycin or clarithromycin) or a respiratory fluoroquinolone. Both guidelines recommend that if an infection by methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa* is suspected, the antibiotic treatment should empirically cover these microorganisms. Conversely, it was demonstrated that the regular coverage of resistant agents did not decreased mortality [9].

Controversies regarding the optimal antibiotic regimen persist; the most debated issues are whether it is necessary to empirically cover atypical microorganisms, and if it is better to start one antibiotic or two. In the present review, all articles aimed at the study of monotherapy versus combination therapy in CAP were reviewed.

Material and Methods

A review of the literature was performed searching for any recent article about antibiotic treatment in CAP. The search process was performed in PubMed in March 2015; articles in English, performed in adults and published from January 1, 2005 to March 1, 2015, were selected. The search key was “community-acquired pneumonia” plus “antibiotic”.

Of all the studies individuated, the ones that assessed differences in outcomes after the administration of different antibiotic regimens were selected; finally, the articles that compared monotherapy versus combination therapy or compared different patterns of combination therapy were chosen for the present review. Publications on health-care-associated pneumonia and aspiration pneumonia were excluded from the analysis. The items found in the review were then analysed and classified as meta-analysis, clinical trial or observational study.

Those articles that included either outpatients and patients proceeding from the ward were categorized in the present review as outpatients. Likewise, articles enrolling both patients from the ward and ICU patients were categorized in the present review as ward-patients.

Results

The PubMed search obtained 2233 results. The screen resulted in a total of 41 selected articles: 11 meta-analyses, 8 clinical trials and 22 observational—prospective and retrospective—studies.

What Is New in the Literature?

Since 2005, several studies were published assessing monotherapy versus combination therapy in CAP.

Outpatients

Four papers were identified: three meta-analyses and one observational study (Table 1).

The most recent article is a Cochrane meta-analysis published in 2014 by Pakhale et al. [10] that explored changes in mortality by using different antibiotic prescriptions—in monotherapy and combined therapy—in outpatients with CAP: 11 clinical trials were included without observing differences in mortality or in the incidence of adverse effects. A meta-analysis by Skalsky et al. [11] included 16 trials enrolling both outpatients and ward patients exploring whether the administration of a macrolide-based versus fluoroquinolone-based regimen was associated with different outcomes. As a conclusion, no differences were observed in all-cause mortality between the two regimens of antibiotics. Treatment failure and microbiological failure decreased significantly when a fluoroquinolone was administered, and a higher incidence of adverse event and antibiotic discontinuation was associated with macrolide prescription, mainly attributed to digestive complications. Thus, although these finding were not associated with changes in mortality, authors conclude that fluoroquinolones may be superior when compared with macrolides.

Finally, An et al. in 2010 published a meta-analysis [12] comparing outcomes after administration of moxifloxacin versus a beta-lactam-based combination with a macrolide. Seven trials were identified including around 4000 patients. Again, no differences were observed regarding mortality, clinical success and adverse effects rates. Conversely, microbiological failure was significantly lower with moxifloxacin.

One observational study by Ye et al. [13] compared outcome and costs of treatment in outpatients with CAP after administration of levofloxacin (500 or 750 mg) versus macrolides: Although the rate of treatment failure was lower for the levofloxacin group, no differences were observed in term of costs, CAP-related hospitalisations and mortality.

Ward

Twenty-seven articles were identified: 7 meta-analyses (Table 2), 7 clinical trials (Table 3) and 13 observational studies (Table 4).

A Cochrane meta-analysis by Eliakim-Raz et al. [16] explored changes in mortality depending on coverage for atypical agents; 28 clinical trials were included, and no difference in mortality or in the development of adverse effects was observed. Patients who received atypical coverage showed a non-significant trend toward clinical and microbiological resolution. This trend was statistically significant in patients with

Table 1 Published studies in outpatients that assess monotherapy versus combination therapy

Author	Year	Study design	Study population	Objective	Outcomes
Pakhale et al. [10]	2014	Meta-Analysis	11 RCTs	Compare efficacy and safety of different antibiotic regimens in CAP	Same mortality and clinical success rate between different antibiotic regimens
Skalsky et al.[a] [11]	2013	Meta-Analysis	16 RCTs, mostly in outpatients with mild to moderate CAP	Compare outcomes after mono or combined therapy with macrolide or quinolone regimens	No differences in mortality; higher eradication rate with quinolones; macrolides associated with higher adverse effects
An et al. [12]	2010	Meta-Analysis	7 RCTs	Compare efficacy and safety of moxifloxacin monotherapy versus BL regimens	No difference in mortality, clinical resolution or adverse effects; quinolones had higher eradication rate
Ye et al. [13]	2008	Observational	Retrospective, enrolling 7526 patients	Compare treatment failure, safety, outcomes and costs of levofloxacin (500 and 750 mg) versus macrolides	Levofloxacin associated with lower treatment failure, especially in over 65. No differences in hospitalization or costs of treatment

CAP community-acquired pneumonia, *RCT* randomized controlled trial, *BL* beta-lactam

[a] The study includes outpatients and ward patients

Table 2 Published meta-analyses in ward patients that assess monotherapy versus combination therapy

Author	Year	Study population	Objective	Outcomes
Nie et al.[a] [14]	2014	16 observational studies: 4 prospective and 12 retrospectives	Compare mortality after BL monotherapy versus BL–macrolide combination therapy	Mortality was higher in patients receiving monotherapy
Zhang et al. [15]	2013	10 RCTs: 5 compared gemifloxacin with quinolones, and 5 gemifloxacin versus BL and/or macrolides	Compare mortality and efficacy of gemifloxacin versus other approved regimens	Comparable mortality, treatment and microbiological failure rate were observed
Eliakim-Raz et al. [16]	2012	28 RCTs	Compare mortality and adverse effects after empirical coverage or not of atypical agents	Same mortality and adverse effects after coverage or not of atypical agents; in case of *Legionella* infection higher clinical resolution after atypical coverage
Yuan et al. [17]	2012	14 RCTs	Compare outcomes after moxifloxacin monotherapy versus other approved regimens	Same mortality and adverse effects; moxifloxacin was associated with higher eradication rate
Asadi et al. [18]	2012	23 either RCTs and observational studies, including 137,574 patients	Compare outcomes between macrolides versus other approved regimens	Lower mortality with macrolides; same mortality when only RCTs were analysed
Varner et al. [19]	2011	4 bioactivity evaluations, 6 clinical studies and 6 reported cases of combination rifampin use	Compare mortality after addition of rifampicin in *Legionella* pneumonia	Scarce data available; consider rifampicin addition only in severe or refractory pneumonia and presence of risk factors
Vardakas et al. [20]	2008	23 RCTs	Compare outcomes between quinolone versus BL with/without macrolides	Same mortality, although higher success of treatment with quinolones

BL beta-lactam, *RCT* randomized controlled trial

[a] The study includes ward and ICU patients

pneumonia due to *Legionella pneumophila*, still without observing changes in mortality.

Two meta-analyses found a decreased mortality after addition of a macrolide to the treatment; Nie et al. [14] compared a beta-lactam–macrolide regimen versus beta-lactam monotherapy in a meta-analysis that only included observational studies enrolling ward and ICU patients. In the conclusions, combined therapy resulted in a significant decrease of mortality. Likewise, Asadi et al. [18] in a meta-analysis that included 23 studies of in-hospital patients with CAP—either clinical trials or observational studies—observed a significant reduction of mortality in individuals who received a macrolide regimen. Importantly, this trend was not significant when only the clinical trials were analysed, or in patients who received guideline-concordant antibiotics.

Three meta-analyses compared outcomes after administration of a respiratory fluoroquinolone versus a beta-lactam regimen. After comparing oral gemifloxacin with a beta-lactam regimen in mild to moderately severe patients with CAP and bronchial exacerbations, Zhang et al. [15] observed a comparable mortality between the two arms. Gemifloxacin was associated with a higher rate of adverse effects, mostly in form of gastrointestinal complications. Two other meta-analyses in 2008 and 2012 achieved similar conclusions; Vardakas et al. [20] compared the use of monotherapy with fluoroquinolones versus a combination beta-lactam regimen documenting a comparable mortality, although a higher eradication rate after fluoroquinolone administration was observed. Yuan et al. [17] observed a comparable mortality and a higher rate of microbial eradication after administration of moxifloxacin versus a beta-lactam antibiotic regimen.

Finally, a meta-analysis by Varner et al. [19] explored the benefit of the addition of rifampicin to the standard treatment of CAP due to *L. pneumophila*, without observing different outcomes. Authors concluded that rifampicin should not be added to treat CAP due to *Legionella* spp. unless pneumonia is severe or is refractory to the standard treatment.

In the last years, several clinical trials were published assessing outcomes after comparing monotherapy versus combination therapy. In a recent study, Postma et al. [21] did not find differences in mortality after comparing fluoroquinolone monotherapy versus beta-lactam monotherapy versus beta-lactam–macrolide combination in non-ICU hospitalised patients; thus, authors concluded that beta-lactam monotherapy was non-inferior to other regimens. Garin et al. [22] obtained similar conclusions: No differences in mortality, length of stay and ICU admission were observed after administration of a beta-lactam alone versus a beta-lactam–macrolide regimen.

Table 3 Published clinical trials in ward patients that assess monotherapy versus combination therapy

Author	Year	Study population	Objective	Outcomes
Postma et al. [21]	2015	Multicentric, cluster-randomized clinical trial, enrolling 2283 patients	Compare outcomes after BL alone, quinolone alone or BL–macrolide combination	Comparable mortality between different antibiotic regimens
Garin et al. [22]	2014	Non-inferiority, multicentric, randomized clinical trial, in 580 patients	Compare clinical outcomes after BL alone versus BL–macrolide association	Comparable mortality, length of stay and recurrence of pneumonia. Delayed clinical stability after monotherapy in atypical pneumonia and PSI V pneumonias
Lee et al. [23]	2012	Open-label, unicentric, randomized clinical trial, enrolling 40 patients	Compare outcome after high-dose levofloxacin or ceftriaxone plus azithromycin	Levofloxacin 750 mg per day showed same mortality, clinical success and microbiological eradication rate than ceftriaxone plus azithromycin
Torres et al.[a] [24]	2008	Multicentric, randomized, double-blind non-inferiority trial, enrolling 733 patients with PSI score III to V	Compare outcomes after moxifloxacin monotherapy versus ceftriaxone plus levofloxacin	Comparable mortality, adverse effects, clinical success and eradication rate between the 2 arms
Lin et al. [25]	2007	Open-label, randomized, unicentric clinical trial, enrolling 50 patients	Compare outcomes after levofloxacin versus amoxicillin-clavulanate plus clarithromycin	Comparable mortality and clinical success rate were observed
Xu et al. [26]	2006	Unicentric, randomized, open-label clinical trial, enrolling 40 patients	Compare outcomes after moxifloxacin versus cefoperazone plus azithromycin	No differences were observed in terms of mortality, microbiological eradication and adverse effects
Portier et al. [27]	2005	Multicentric, randomized, open-label clinical trial, enrolling 346 patients	Compare outcomes between moxifloxacin versus amoxicillin-clavulanate plus roxithromycin in CAP with risk factors	No differences in mortality, eradication rate or adverse effects

BL beta-lactam, *RCT* randomized controlled trial, *CAP* community-acquired pneumonia, *PSI* pneumonia severity index

[a] The study includes ward and ICU patients

Patients with a pneumonia severity index (PSI) score of IV or V and patients infected by atypical microorganisms presented delayed clinical stability with monotherapy. Other studies documented similar conclusions; a comparable mortality and adverse effect rates, and a higher eradication rate in the fluoroquinolone group were observed by Lee et al. [23] after comparing high-dose levofloxacin versus ceftriaxone plus azithromycin. No differences in mortality or an increased eradication rate in the fluoroquinolone arm were found when comparing a fluoroquinolone versus a beta-lactam plus a macrolide [25–27]. One clinical trial by Torres et al. [24] did not observe differences in mortality after comparing moxifloxacin monotherapy with ceftriaxone plus levofloxacin in a cohort of CAP patients including 10 % with severe pneumonia (PSI score IV or V).

Thirteen observational studies were identified. Several studies, either prospective or retrospective, compared fluoroquinolone monotherapy with a beta-lactam monotherapy regimen. Asadi et al. [28] did not find a difference in mortality after comparing fluoroquinolone monotherapy with a beta-lactam–macrolide regimen, in ward and ICU patients. When comparing high-dose levofloxacin with ceftriaxone plus azithromycin, a similar mortality was observed, but a decrease in costs of treatment was documented after fluoroquinolone administration [30, 33–35, 38, 39].

A decreased mortality was observed after the administration of a beta-lactam–macrolide combination when compared with beta-lactam monotherapy [29, 32, 40]. In the paper by Rodrigo et al., these conclusions were not observed in the mildest forms of CAP. On the other hand, in patients with severe CAP with pneumococcal bacteraemia, a difference in mortality was not found between the administration of a beta-lactam plus a macrolide and monotherapy with a beta-lactam [37].

Two observational studies explored changes in mortality after the addition of a macrolide. Restrepo et al. [31] found that patients with CAP and severe sepsis had a decreased mortality when a macrolide was added. Metersky et al. [36] achieved the same conclusions in patients with bacteraemic CAP admitted to the ward or in the ICU.

Intensive Care Unit

Ten studies were identified: one meta-analysis, one clinical trial and eight observational studies (Table 5).

In 2014, Sligl et al. [41] published a meta-analysis exploring outcomes after administration of combined therapy with a macrolide regimen versus monotherapy or combined therapy without a macrolide; 28 observational studies enrolling critically ill patients with CAP were included, accounting for nearly 10,000 patients. As a conclusion, mortality was lower in

Table 4 Observational studies published in ward patients that assess monotherapy versus combination therapy

Author	Year	Study population	Objective	Outcomes
Asadi et al.[a] [28]	2013	Multicentric, retrospective, enrolling 3203 patients, 63 % of which with PSI score IV/V	Compare outcomes after BL–macrolide versus quinolone	No differences in mortality between different regimens
Rodrigo et al.[a] [29]	2013	Multicentric, retrospective, enrolling 5240 patients	Compare mortality after BL–macrolide versus BL alone in CAP depending from severity	Higher mortality in moderate and severe CAP while comparable mortality was observed in milder forms
Frei et al. [30]	2009	Multicentric, retrospective enrolling 495 patients	Compare length of stay and antibiotic duration after administration of high dose levofloxacin versus ceftriaxone plus azithromycin	Lower length of stay and length of treatment were observed after high dose levofloxacin
Restrepo et al.[a] [31]	2009	Multicentric, retrospective, enrolling 237 patients	Explore changes in mortality after addition of a macrolide in CAP with severe sepsis	Lower mortality when a macrolide was added
Bratzler et al. [32][a]	2008	Multicentric, retrospective, enrolling 27,330 patients	Compare mortality after 3rd generation cephalosporin versus quinolone or a BL–macrolide regimen	Higher mortality after BL alone with respect to the administration of a quinolone alone or a BL–macrolide combination
Bhavnani et al. [33]	2008	Multicentric, prospective study	Explore cost-effectiveness of oral gemifloxacin compared with ceftriaxone with/without macrolide	Comparable mortality with different regimens; lower costs with quinolone therapy
Lloyd et al.[a] [34]	2008	Multicentric, retrospective, enrolling 738 patients	Explore costs after moxifloxacin versus ceftriaxone plus levofloxacin	Lower costs after moxifloxacin administration; comparable treatment success rate
Lodise et al.[a] [35]	2007	Multicentric, retrospective study enrolling 515 patients	Compare outcomes after BL–macrolide versus quinolone administration	Lower mortality after combination therapy in PSI V; no difference in mortality in PSI lower than V
Metersky et al.[a] [36]	2007	Multicentric, retrospective, enrolling 2209 patients with bacteraemic CAP	Explore if atypical coverage was associated with different outcomes	Lower mortality after atypical coverage; further decrease in mortality if coverage was with a macrolide-based regimen
Dwyer et al.[a] [37]	2006	Prospective, multicentric study enrolling 340 patients with bacteraemic pneumococcal CAP	Compare outcomes after BL monotherapy compared with BL–macrolide regimen	No differences in mortality after BL alone versus BL plus macrolide
Welte et al. [38]	2005	Multicentric, randomized non-blinded clinical trial enrolling 317 patients	Compare outcomes after moxifloxacin versus ceftriaxone with/without erythromycin administration	Same mortality with a faster clinical improvement after moxifloxacin administration
Querol-Ribelles et al. [39]	2005	Prospective, unicentric, enrolling 459 patients	Compare outcomes after levofloxacin monotherapy versus ceftriaxone plus clarithromycin	Lower mortality after levofloxacin administration; no difference in terms of length stay
Garcia Vazquez et al. [40]	2005	Prospective, multicentric study enrolling 1391 patients	Assessing changes in outcomes after administration of a BL–macrolide regimen versus a BL alone	Lower mortality after combined therapy in all severity pneumonias

BL beta-lactam, *PSI* pneumonia severity index, *CAP* community-acquired pneumonia

[a] The study includes ward and ICU patients

patients who received combination therapy with a macrolide, when compared with that in those who received monotherapy or combination therapy without a macrolide.

Leroy et al. [42] performed a clinical trial enrolling 398 critical patients without shock or a requirement for mechanical ventilation and compared levofloxacin with ceftriaxone plus ofloxacin; no differences in mortality, clinical resolution and adverse event rate were observed.

Five observational studies obtained similar results. Our group of research in pneumonia, in a case-control analysis published in 2014 [3], observed an increased survival after combination therapy; this association was found in the main

Table 5 Published studies in ICU patients that assess monotherapy versus combined therapy

Author	Year	Study design	Study population	Objective	Outcomes
Sligl et al. [41]	2014	Meta-analysis	Twenty eight observational studies, without clinical trials, enrolling 9850 patients	Compare outcomes after macrolide-containing regimen versus non-macrolide regimens	Combined therapy with a macrolide regimen was associated with lower mortality
Leroy et al. [42]	2005	Clinical trial	Multicentric, randomized, open-label clinical trial, enrolling 398 patients without shock or mechanical ventilation	Explore outcomes after levofloxacin monotherapy versus cefotaxime plus ofloxacin	Comparable mortality, clinical resolution and adverse effects rate after administration of either monotherapy or combined therapy
Gattarello et al. [3•]	2014	Observational	Multicentre, case-control analysis of a prospective data compared with an historic cohort, enrolling 80 patients	Compare mortality after monotherapy versus combined therapy	Combined therapy was associated with improved survival in patients with shock, under mechanical ventilation, and without shock neither mechanical ventilation
Adrie et al. [43]	2013	Observational	Multicentre, retrospective study enrolling 956 patients	Compare mortality and resistance development after combined versus monotherapy	Combined therapy improved survival in patients with shock; combined therapy increased probability of adequate treatment; no resistance development was observed in combination therapy
Rello et al. [44]	2012	Observational	Multicentric, retrospective enrolling 1989 patients over 65 years	Compare mortality after BL–macrolide versus BL–quinolone	No differences in mortality; higher length of stay after BL–quinolone administration
Rello et al. [45]	2012	Observational	Multicentre, retrospective, enrolling 25 patients with severe sporadic *Legionella* pneumonia	Compare mortality in *Legionella* pneumonia	Lower mortality after combination therapy in patients with shock
Martin-Loeches et al. [46]	2010	Observational	Multicentre, prospective study enrolling 218 patients	Explore changes in mortality after macrolide addition in intubated patients with CAP	Lower mortality in patients that received macrolide-based combination therapy
Rodriguez et al. [47]	2007	Observational	Multicentre, prospective study enrolling 529 patients	Compare mortality after combination therapy or monotherapy administration	Lower mortality in patients with shock after combination therapy administration
Harbarth et al. [48]	2005	Observational	Multicentre, retrospective analysis of 1840 patients with pneumococcal CAP and severe sepsis/septic shock	Compare mortality after monotherapy versus combined therapy	No differences in mortality after monotherapy or combination therapy
Mortensen et al. [49]	2005	Observational	Multicentric, retrospective study enrolling 172 patients with severe CAP	Compare mortality after BL–quinolone versus other guidelines-concordant antibiotic regimens	Higher mortality when BL plus quinolone versus other guidelines-concordant regimens

BL beta-lactam, *CAP* community-acquired pneumonia, *RCT* randomized controlled trial

cohort and in all analysed subgroups: patients with shock or a need for mechanical ventilation, and critically ill patients without shock or a need for mechanical ventilation. Adrie et al. [43] documented a decreased mortality after combination therapy; interestingly, this association was stronger in patients with shock or with pneumococcal infection. Rello et al. documented the same trend [45] in patients with severe CAP by *L. pneumophila* and shock, Rodriguez et al. [47] in patients with severe CAP with shock and Martin-Loeches et al. [46] in intubated patients with CAP.

Only one study published by Harbarht in 2005 [48] documented a comparable mortality between monotherapy and combination therapy in patients with CAP and severe sepsis or shock.

Finally, two studies explored outcomes after administration of a beta-lactam–macrolide regimen compared with a beta-lactam–fluoroquinolone regimen; Mortensen et al. [49] found a lower mortality after administration of the macrolide-based regimen in a cohort of 172 critical patients with severe CAP. Conversely, Wilson et al. [44] did not find differences in

mortality in elderly patients with CAP. It was noteworthy that a higher length of stay was documented in the beta-lactam–fluoroquinolone group.

Discussion

In the present article, we reviewed the available literature regarding monotherapy versus combined therapy in CAP. Although recent publications have not resolved all the remaining controversies, a majority of the meta-analyses and the observational studies support combination therapy with macrolide therapy, but the outcomes measured in clinical trials did not favour either arm.

In summary, outpatients with CAP without risk factors for a poor clinical outcome did not benefit from combined therapy; hence, monotherapy with either a macrolide, a fluoroquinolone or a beta-lactam may be proposed as no differences in mortality were observed by any specific antibiotic class. This controversy reflects the differences between the European and American guidelines. In fact, unlike the American guidelines, the European guidelines do not recommend empiric atypical coverage as a first-line treatment.

On one side, fluoroquinolone administration appears to be associated with a higher eradication rate, a lower treatment failure and possibly less cost of treatment; however, concerns about an increased resistance rate after fluoroquinolone administration have been raised [50]. In the case of a social environment with high rates of pulmonary tuberculosis, the empiric use of a fluoroquinolone could actually mask pulmonary tuberculosis delaying its diagnosis [51]. Thus, antibiotic prescription should be done considering local epidemiological data, i.e. the most frequent aetiologies of CAP and the local resistance pattern.

In the case of outpatients with CAP and with risk factors for poor clinical evolution, there is evidence supporting atypical coverage, although no differences in mortality were observed, and there was a decreased cost of treatment because of reduced treatment failures and secondary hospital admissions. Although the American guidelines recommend a fluoroquinolone or a beta-lactam plus a macrolide equally, some authors advocate the use of a beta-lactam plus macrolide combination. A decision should be guided by local guidelines based on epidemiological data.

In case of a hospitalised non-ICU patient, contrasting conclusions do not allow supporting the administration of monotherapy rather than combination therapy. As a general indication, in case of a mild to moderate pneumonia without risk factors for a poor clinical evolution, the use of a beta-lactam or a fluoroquinolone in monotherapy is probably the best choice. Conversely, in case of moderate to severe CAP with PSI score of IV or V, bacteraemia due to *Streptococcus pneumoniae*, the presence of risk factors for a poor outcome, or a high suspicion of atypical pneumonia, the use of beta-lactam monotherapy is probably not enough. Again, because of the current lack of evidence, the use of a fluoroquinolone monotherapy rather than a beta-lactam and macrolide association should be based on local epidemiological considerations. It is noteworthy that levofloxacin 750 mg per day is more effective than standard dose (500 mg), without an increase of adverse effects [22].

Finally, in case of severe CAP and ICU admission, stronger evidence for promoting the use of combined therapy was published. In fact, a meta-analysis and several observational studies documented an increased survival after dual antibiotic administration. This statement seems to be conclusive in patients with septic shock, although it was not always confirmed in the rest of ICU patients. However, despite the contrasting results in ICU patients without shock and because of the high mortality of severe CAP, it seems safer to administer combination therapy to all ICU patients with CAP. Furthermore, according with the meta-analysis of Sligl et al., the combination regimen associated with the highest survival appears to be a beta-lactam plus a macrolide as opposed to without a macrolide.

The main argument to justify combination therapy in mild to moderate pneumonia is the coverage of atypical agents; although contrasting results were obtained regarding mortality, it appears that in certain subgroups (i.e. the presence of risk factors for a poor outcome or bacteraemic pneumococcal pneumonia), atypical coverage is likely beneficial in terms of cost of treatment, eradication rate and clinical resolution. Alternatively, in case of severe CAP, the use of combined therapy is almost always associated with a decreased mortality; in fact, it was observed that the lack of atypical coverage in atypical pneumonia was associated with an increased mortality [52]; moreover, the association between macrolide use and a reduced mortality may be explainable by the antiinflammatory effects attributed to macrolides [41, 46]. In fact, severe CAP is often associated with sepsis or septic shock, and macrolide administration may decrease the inflammatory reaction. 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. However, this is a hypothesis and should be confirmed with a well-designed randomised controlled trial.

The use of combined therapy aroused concerns about the development of antibiotic resistance. In the present review, only one study [43] explored this issue, without differences in the development of new bacterial resistances after either monotherapy or combination therapy. Follow-up studies exploring microbial resistance after monotherapy or combination therapy would be beneficial.

Conclusions

Although many controversies remain in the optimal treatment of CAP, the use of combined therapy seems to be associated with an improved mortality in cases of severe CAP that requires ICU admission, especially when a beta-lactam–macrolide is prescribed. Moreover, it appears that combination therapy may be associated with better outcomes in cases of outpatient or ward hospitalised patients with risk factors for a poor outcome, with bacteraemic pneumococcal pneumonia and with a high suspicion of infection by atypical agents. In this setting, it appears that the best choice of treatment may be a beta-lactam–macrolide regimen.

In the next years, forthcoming challenges will be to better identify the subgroups of patients that are benefited by combination therapy, and to study the impact of monotherapy and combination therapy in the emergence of new antimicrobial resistances.

Compliance with Ethics Guidelines

Conflict of Interest Simone Gattarello has no relevant disclosures to report.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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