The Controversy of Combination vs Monotherapy in the Treatment of Hospitalized Community-Acquired Pneumonia*

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Background: The majority of community-acquired pneumonia (CAP) patients (about 80%) will be treated as outpatients, because therapy with a single agent will work. For the remaining 20% of patients requiring hospitalization, there is some growing debate regarding the efficacy of different management approaches. For hospitalized patients, monotherapy with a respiratory fluoroquinolone agent seems to be gaining popularity, but dual therapy combining a β-lactam and an advanced macrolide still represents a good choice. Indeed, this regimen was recommended for all of the inpatient categories in the latest Infectious Disease Society of America CAP guidelines in 2003.

Aim: The purpose of this review was to examine the current clinical evidence to support one option or the other by gathering all of the available published literature. We will review the existing controversies in terms of microbiology, immunology, and clinical outcomes comparing dual therapy (ie, with any combination of β-lactams, macrolides, or fluoroquinolones) with monotherapy in the treatment of CAP.

Results: For the vast majority of patients with CAP (ie, outpatients and inpatients on medical wards), the type of antibiotic regimen prescribed does not have any significant impact. For patients with severe pneumonia, for which there is no accepted definition so far, the controversy remains alive. Mortality from pneumococcal pneumonia has been reduced over the last decades, but despite improved medical care, bacteremic pneumococcal pneumonia is still as lethal as ever, probably because of the aging population, the greater number of immunocompromised patients, and the number of patients with frequent comorbid conditions. Worldwide, the increasing rates of resistance of Streptococcus pneumoniae to antibiotics are also a serious concern, and the clinical implications are not always obvious. Although limited in number, the four studies showing the importance of adding a macrolide to a β-lactam regimen for the treatment of bacteremic S pneumoniae pneumonia are retrospective and nonblinded, the findings are consistent, and they point to a trend that has to be explored more thoroughly. Studies published in the last few years suggest that combination therapy may be superior for bacteremic S pneumoniae pneumonia.

Conclusion: In the meantime, for practical purposes, patients hospitalized with a diagnosis of severe CAP may benefit from a dual antibiotic therapy combining a third-generation cephalosporin and a macrolide. For the majority of hospitalized patients with CAP who are not severely ill, fluoroquinolone monotherapy remains an approved, tested, and reliable option. Indeed, the time for more aggressive outpatient fluoroquinolone therapy may reduce the number of patients who are hospitalized with CAP. Independent prospective studies comparing combination therapy with standard monotherapy are urgently required for hospitalized patients with severe CAP.

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Key words: community-acquired pneumonia; single vs dual antibiotic therapy

Abbreviations: CAP = community-acquired pneumonia;
The management of community-acquired pneumonia (CAP) continues to represent a major challenge for physicians. The majority of CAP-infected patients (about 80%) will be treated as outpatients, in which setting most single-therapy regimens will work. For the remaining 20% of patients requiring hospitalization, there is some debate regarding the efficacy of different management approaches. From a wide range of clinical studies, only half of the cases had an etiologic agent identified. *Streptococcus pneumoniae* is the predominant bacterial etiology in this condition, particularly when associated with bacteremia. Marrie reported that about 10% of the admitted patients with CAP have positive blood culture findings, with *S. pneumoniae* representing 60% of these cases. In another review of 12 studies of hospitalized CAP patients, 330 of 2,935 patients (11%) had bacteremia, with *S. pneumoniae* accounting for 67% of the cases. Moreover, *S. pneumoniae* is the most common cause of death in patients with CAP, accounting for about two thirds of all cases. Although the mortality from pneumococcal pneumonia has been reduced over the last decades, bacteremic pneumococcal pneumonia is still as lethal as ever, probably because of, notably, an aging population, a greater number of immunocompromised patients (such as from HIV and chemotherapy), and comorbid conditions (such as COPD or congestive heart failure). Because mostly this condition currently affects patients who have underlying medical problems, it may explain this finding despite the presence of improved medical care.

Not surprisingly, various CAP guidelines have identified this issue as one of the most important issues in their recommendations. Any improvement in the management of bacteremic streptococcal pneumonia will significantly reduce the overall mortality rate of patients with CAP, hence the importance of addressing the dual-therapy issue. Dual therapy can be defined as any combination regimen involving a β-lactam, a macrolide, or a fluoroquinolone; by contrast, monotherapy would be the use of a β-lactam-based regimen or a fluoroquinolone agent alone.

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The In Vitro Paradox

Globally, all surveillance studies continually report increasing *in vitro* resistance to a plethora of antimicrobial agents including penicillin, second-generation cephalosporins, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole. More recently, resistance to fluoroquinolones has also emerged, notably in the elderly population.

However, the “doomsday scenario,” in which large numbers of patients do not respond to therapy while receiving these agents, has not occurred. There have been several anecdotal case reports and some retrospective studies published showing the relationship between *in vitro* resistance and *in vivo* clinical failures, but these remain the exception rather than the rule. Indeed, many primary care physicians report rarely seeing such clinical failures, and yet they are aware of growing antimicrobial resistance. In patients with pneumonia, only those with *S. pneumoniae* with a minimum inhibitory concentration to penicillin of ≥ 2 mg/L may not respond to therapy in significantly greater numbers compared with those patients with susceptible strains. Austrian and Gold showed many years ago that the overall mortality rate for patients with bacteremic pneumococcal pneumonia who were being treated with penicillin was 17% when resistance was not an issue. This suggests that other factors, likely immunologic or genetic, influence the outcome of this infectious condition. The drug-bug relationship alone cannot explain everything.

In Canada and the United States, macrolides remain the recommended first-line therapy for CAP for outpatients without comorbidities. For hospitalized patients, monotherapy with a respiratory fluoroquinolone, especially levofloxacin, has become a popular choice as an empiric therapy notably for hospitalized patients, although high-dose amoxicillin is still the suggested treatment in some European countries. Despite increasing macrolide resistance, significant clinical lack of response with these agents in previously healthy individuals is rarely seen and reported.

With regard to macrolides, efflux-mediated (or *mef*) resistance may rarely lead to clinical lack of response when dealing with infections contained in the respiratory tract, because the respiratory tissue concentrations of these antibiotic agents are tremendously higher than their serum concentrations. Tens of millions of macrolide prescriptions are written every year in North America, yet the number of clinical failures, even if underreported, is very low. Macrolide resistance has been associated with lack of response in cases of bacteremia, but this was fore-
seeable in selected high-risk patients with underlying medical conditions and remains rare.\textsuperscript{15}

Presently in North America, \textit{S} \textit{pneumoniae} resistance to newer respiratory fluoroquinolones (\textit{ie}, moxifloxacin and gemifloxacin) remains at the \textless{} 0.5\% level despite increasing use of this class of agent.\textsuperscript{16} However, the clinical failure of fluoroquinolones in respiratory tract infections has been summarized by Scheld\textsuperscript{17} and, although very rare and anecdotal, becomes a reality in our daily practice. Thus, this article and other publications\textsuperscript{15,17–19} have raised the issue of increasing clinically significant resistance to these classes of antibiotic agents.

It is true that the definition of clinical failure has also not been established, and mortality alone or the occurrence of severe life-threatening conditions such as meningitis while receiving therapy may only represent the tip of the iceberg. A lack of improvement in the condition of a CAP patient after 72 h of treatment may also be considered a clinical failure; however, these cases are not reported or seldom reported. We would suggest that the definition of clinical resistance, rather than strictly relying on National Committee for Clinical Laboratory Standards criteria, should be linked to the inability of an antibiotic agent to reach a concentration high enough at the site of infection to inhibit local bacterial replication and to the need for a second antibiotic prescription 72 h after starting therapy because of the deterioration or nonsignificant improvement of the initial medical condition.

\textbf{Does Antimicrobial Resistance Affect More Than Susceptibility?}

A higher mortality rate for CAP patients has not been reported from countries with high levels of \textit{in vitro} resistance compared with those with lower resistance rates (\textit{eg}, Spain or France vs Sweden or the Netherlands). Prospective international multicenter CAP clinical trials have not shown any significant differences\textsuperscript{30} in the efficacy of mortality between countries, irrespective of the local resistance issues. Therefore, it is important to emphasize that for the majority of CAP, \textit{in vitro} resistance may not have the anticipated impact on the outcome. Resistance levels are always defined in relation to serum concentrations based on National Committee for Clinical Laboratory Standards breakpoints, and they do not make reference to tissue concentrations at the site of infection. Except in cases of associated bacteremia where \textit{in vitro} resistance plays a major role in the outcome,\textsuperscript{5,6} there is some major discrepancy between \textit{in vitro} levels, and resistance and outcomes.

There is some controversy regarding the potential decreased virulence of invasive \textit{S} \textit{pneumoniae} strains. Consistently, large-scale, longitudinal \textit{in vitro} studies\textsuperscript{21,22} have shown lower levels of resistance to penicillin and macrolides among invasive strains compared with isolates from sputum or other nonblood infections. Although not proven, it has been advocated that antimicrobial agent resistance may be associated with a decreased fitness of the resistant organism or an increased energy cost for the bacteria, thus potentially rendering the organism less virulent because of the selection of life support processes over pathogenesis mechanisms.\textsuperscript{23}

Surveillance programs can be criticized on many levels, including a bias toward respiratory tract isolates compared with blood or other systemic isolates. Additionally, the isolates are usually collected from patients presenting at a tertiary care center rather than the primary care setting. The patients in the tertiary or university clinics often have risk factors for antibiotic agent resistance, have chronic underlying diseases, have received numerous antibiotic treatments (\textit{eg}, for COPD), or are immunocompromised patients (\textit{eg}, due to HIV infection and chemotherapy). We may be overestimating resistance levels for first-line practicing physicians.

\textbf{Transatlantic Rift or Same Opinion Expressed Differently?}

North American guidelines are still recommending dual therapy combining a \textit{\beta}-lactam and an advanced macrolide as an alternative. Indeed, this regimen was recommended in seven patient categories in the latest updated Infectious Disease Society of America CAP guidelines.\textsuperscript{24} This combination therapy is still recommended for outpatients with risk factors, nursing home patients, and hospitalized patients, whether they are on a general ward or in the ICU. Despite increasing \textit{in vitro} resistance to macrolides, this class of antibiotic agents still plays a key role in the treatment of CAP.

Some data\textsuperscript{25–28} have suggested that combination therapy may be superior for the treatment of bactereemic \textit{S} \textit{pneumoniae} pneumonia. This group of patients represents only a small fraction of all of the CAP cases, but in terms of mortality it is the most important strata.

Additional support for combination therapy is the enhanced coverage of potentially resistant strains, the appropriate coverage of the organisms implicated in polymicrobial CAP, pneumococci, and atypical organisms, including both \textit{Chlamydia pneumoniae} and \textit{Mycoplasma pneumoniae}. Published data\textsuperscript{20} have suggested that a proportion of bactereemic \textit{S} \textit{pneumoniae} pneumonia patients have concomitant \textit{M} \textit{pneumoniae} or, rarely, Legionella sp infections. However, there is some transatlantic con-
troversy between North American physicians, who support the importance of the atypical organisms, and European doctors, who are yet to be convinced of the benefit of the systematic use of a macrolide. In bacteremic streptococcal pneumonia, at least four retrospective clinical studies have shown a positive impact on mortality.

Aiming Right

Bacteremic S pneumoniae pneumonia is the most common cause of mortality among all of the causes of CAP. Bacteremia, in addition to pneumonia, has been shown to increase the mortality rate. In one study of 108 cases of bacteremic pneumococcal pneumonia, the mortality rate was 24.1%, which is much higher than that for nonbacteremic CAP. A few studies have already demonstrated the importance of initiating the proper antibiotic therapy not only in terms of the antibiotics regimen but also in terms of time. In one study, patients who were given an antibiotic within 8 h after their arrival in the emergency department did better. Gleason et al also demonstrated that in elderly patients, initial antibiotics choices had a key impact on the 30-day survival rate. Patients who were treated with either a combination of a cephalosporin and a macrolide or a fluoroquinolone alone (eg, levofloxacin or ciprofloxacin) did better than those who received monotherapy with a β-lactam, even after adjusting for risk factors, such as age, comorbidity, and others. Therefore, it is crucial for physicians to initiate the right treatment, otherwise the mortality risk increases.

The fact that combination therapy, as defined previously, may be superior to monotherapy in the treatment of patients with severe CAP may be explained by different factors, including a better coverage of atypical microorganisms and the fact that by acting at two different sites in the bacteria (cell wall for β-lactams and the inhibition of protein synthesis for macrolides), this combination targets the microorganism at two different levels. Macrolides have been shown to have some very effective antiinflammatory properties. They are known to reduce the production of interleukin-6 and tumor necrosis factor-α, and erythromycin has been shown to reduce the adherence of S pneumoniae to respiratory epithelial cells. β-Lactams and fluoroquinolones used as bactericidal agents are known to kill and destroy a large number of bacteria in a short amount of time, thus releasing numerous intracellular components responsible for perpetrating the inflammation process.

On the other side, macrolides inhibiting protein synthesis potentially decrease the production of virulence factors. This has been shown in patients with severe group A Streptococcus infections in whom clindamycin, acting as a protein synthesis inhibitor, may add a significant benefit to the global treatment.

The importance of the immune system in cases of S pneumoniae bacteremia has been demonstrated in a pivotal 1964 study in which serum therapy alone significantly decreased the mortality rate compared with a cohort of control subjects with no serum therapy. Therefore, factors other than the simple concept of in vitro activity alone are playing key roles in fighting the infectious process. One study demonstrated the absence of in vitro synergy when combining treatment against S pneumoniae with erythromycin with penicillin or cefotaxime. Therefore, we cannot attribute the observed effect of adding a macrolide in patients with severe CAP to a synergistic action between these two antibiotic agent classes.

What Is the Clinical Data Supporting Combination Therapy?

Waterer et al also have suggested that for treating patients with bacteremic S pneumoniae pneumonia, monotherapy may be suboptimal, irrespective of the therapy given. Patients who were given either a fluoroquinolone (levofloxacin, 55 cases; ciprofloxacin, 1 case) or any β-lactam as a single therapy did poorly when compared with dual effective therapy notably compare with a regimen containing a macrolide. A second study showed a similar trend in Spain, where the addition of a macrolide to a β-lactam regimen decreased the in-hospital mortality rate. In this study of 409 patients with bacteremic pneumococcal pneumonia, not adding a macrolide to a β-lactam in the initial antibiotic regimen resulted in an increased hospital mortality rate. In a logistic regression analysis model, the receipt of empirical macrolide therapy had a protective effect for the patients with an odds ratio of 0.4 (95% confidence interval, 0.17 to 0.92).

In our institution, a similar retrospective study in the outcome of bacteremic S pneumoniae pneumonia in adults showed the same outcome. The mortality rate was significantly higher in the group receiving monotherapy (β-lactam) compared with that in the dual-therapy group (ie, β-lactam plus a macrolide) [11 of 42 patients [26%] vs 4 of 53 patients [7.5%], respectively; p = 0.02]. Patients were comparable in terms of disease severity as the initial pneumonia severity index scores were 113 and 114, respectively. Penicillin nonsusceptibility (ie, strains categorized as intermediate or resistant to penicillin) was not associated with increased mortal-
oney et al37 showed that there was no relationship not have any significant impact on outcomes. Mor-
monery alone in bacteremic pneumococcal pneumonia does mortality rate or the requirement for ICU admission.
many, these conclusions are limited to between the presence of resistant strains and the patients with severe pneumonia for whom the mortality rate is high. The value of these results cannot be extrapolated for the treatment of inpatients with moderate disease, for whom fluoroquinolones still remain an excellent therapy choice.

A few studies12,37 demonstrated that resistance in bacteremic pneumococcal pneumonia does not have any significant impact on outcomes. More-
Only all of the clinical studies comparing newer quinolones with the standard therapeutic reg-
men were designed to show noninferiority or bio-equivalence so as to gain approval from registration agencies, and, therefore, high-risk patients (Fine IV or V categories) were usually excluded from these clinical trials. For example, an outpatient trial38 comparing two fluoroquinolones (gemifloxacin and trovafloxacin) showed response rates of 92.5% and 87.3%, respectively. However, this trial was not designed to evaluate fluoroquinolone efficacy in severe pneumonia.

The capital study published by Marrie et al39 showed a better outcome for treatment with fluoro-
quinolones, but this may have been explained by the study protocol itself. Implementing an active and highly intervention-oriented clinical pathway led to better resource utilization. One study40 has revealed an economic benefit for fluoroquinolone monotherapy over a combination treatment, but the vast majority of cases were not severe CAP. Studies comparing dual therapy with one of the newer respiratory fluoroquinolones with an enhanced activity against S pneumoniae (e.g., moxifloxacin, levofloxa-
cin, and gatifloxacin) in patients with severe CAP are not available yet. There is no clear definition of severe CAP so far, but the presence of pneumococcal bacteremia is certainly something that can be included in this definition. Therefore, severe CAP can be defined as the presence of S pneumoniae bacteremia, the necessity of ventilatory support, or patients with a pneumonia index score classifying them as being in Fine classes 4 or 5. In this scoring system, classes 4 and 5 were linked to a higher mortality rate.38 Although this system was not designed to evaluate severity, it can be used as a good indicator for this purpose. A new rule, designated as CURB-65 and using a 6-point score based on confusion, urea level, respiratory rate, BP, and age, has also been shown to be an excellent indicator for defining the mortality risk.41

Future Challenges

The arrival of a newly conjugated pneumococcal vaccine brings the potential to decrease the number of invasive infections in the future. However, data demonstrating the switch in the community from serotypes contained in the vaccine to new ones have already been reported.

Better and earlier detection methods to rule out the presence of bacteremia at the initial presentation will certainly help. Rapid methods based on DNA detection of S pneumoniae in blood are not far away and will make life easier for clinicians.42 The arrival of a S pneumoniae urinary antigen test may be helpful in the future.43

Although most studies showing the importance of adding a macrolide to a β-lactam regimen for bacteremic S pneumoniae pneumonia are retrospective and nonblinded, the findings are consistent and point to a trend that has to be explored more thoroughly. In the mean time, for practical purposes, patients who are hospitalized with a diagnosis of severe CAP may benefit from a dual antibiotic therapy combining a third-generation cephalosporin and a macrolide. For the majority of patients with CAP who are hospitalized and not severely ill, fluoroquinolone monotherapy remains an approved, tested, cost-effective, and reliable option. Indeed, the time for more aggressive outpatient fluoroqui-

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