Original Investigation

β-Lactam Monotherapy vs β-Lactam–Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia

A Randomized Noninferiority Trial

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IMPORTANCE The clinical benefit of adding a macrolide to a β-lactam for empirical treatment of moderately severe community-acquired pneumonia remains controversial.

OBJECTIVE To test noninferiority of a β-lactam alone compared with a β-lactam and macrolide combination in moderately severe community-acquired pneumonia.

DESIGN, SETTING, AND PARTICIPANTS Open-label, multicenter, noninferiority, randomized trial conducted from January 13, 2009, through January 31, 2013, in 580 immunocompetent adult patients hospitalized in 6 acute care hospitals in Switzerland for moderately severe community-acquired pneumonia. Follow-up extended to 90 days. Outcome assessors were masked to treatment allocation.

INTERVENTIONS Patients were treated with a β-lactam and a macrolide (combination arm) or with a β-lactam alone (monotherapy arm). *Legionella pneumophila* infection was systematically searched and treated by addition of a macrolide to the monotherapy arm.

MAIN OUTCOMES AND MEASURES Proportion of patients not reaching clinical stability (heart rate <100/min, systolic blood pressure >90 mm Hg, temperature <38.0°C, respiratory rate <24/min, and oxygen saturation >90% on room air) at day 7.

RESULTS After 7 days of treatment, 120 of 291 patients (41.2%) in the monotherapy arm vs 97 of 289 (33.6%) in the combination arm had not reached clinical stability (7.6% difference, $P = .07$). The upper limit of the 1-sided 90% CI was 13.0%, exceeding the predefined noninferiority boundary of 8%. Patients infected with atypical pathogens (hazard ratio [HR], 0.33; 95% CI, 0.13-0.85) or with Pneumonia Severity Index (PSI) category IV pneumonia (HR, 0.81; 95% CI, 0.59-1.10) were less likely to reach clinical stability with monotherapy, whereas patients not infected with atypical pathogens (HR, 0.99; 95% CI, 0.80-1.22) or with PSI category I to III pneumonia (HR, 1.06; 95% CI, 0.82-1.36) had equivalent outcomes in the 2 arms. There were more 30-day readmissions in the monotherapy arm (7.9% vs 3.1%, $P = .01$). Mortality, intensive care unit admission, complications, length of stay, and recurrence of pneumonia within 90 days did not differ between the 2 arms.

CONCLUSIONS AND RELEVANCE We did not find noninferiority of β-lactam monotherapy in patients hospitalized for moderately severe community-acquired pneumonia. Patients infected with atypical pathogens or with PSI category IV pneumonia had delayed clinical stability with monotherapy.

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Community-acquired pneumonia accounts for a high burden of deaths, hospitalizations, and health care costs.[1] Optimal coverage of *Streptococcus pneumoniae*, generally with a β-lactam, is advocated for hospitalized patients. However, the need to cover atypical pathogens (eg, *Legionella* species, *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae*) by adding a macrolide to the β-lactam regimen or with fluoroquinolone monotherapy is debated. A meta-analysis[2] found better outcomes in patients treated with the combination of a macrolide with a β-lactam compared with a β-lactam alone. However, confounding can be a problem because patients treated with combination therapy are younger and healthier.[3,4] A meta-analysis[5] of randomized trials that compared antibiotic regimens with and without coverage of atypical pathogens did not find superiority in either arm. However, no trial that compared a β-lactam alone with a combination of a β-lactam and a macrolide was identified. Moreover, clinical success was assessed after completion of the antibiotic treatment, which might preclude the identification of a difference in the speed of resolution of the pneumonia between arms.

Because of this uncertainty, international medical societies differ in their recommendations. North American guidelines recommend empirical coverage of atypical pathogens with a respiratory fluoroquinolone or with the combination of a macrolide and a β-lactam for all hospitalized patients.[6] European guidelines recommend combination therapy only for more severely ill patients.[7]

The addition of a macrolide has potential drawbacks. Macrolide use is associated with possible adverse cardiovascular events[8] and cardiovascular death.[9,10] This association is relevant because pneumonia affects predominantly older people, who are at increased risk of heart disease, and pneumonia itself is a trigger for adverse cardiac events.[11] Macrolides may also promote resistance of *S pneumoniae* against multiple antibiotic classes.[12,13] On the other hand, macrolides cover atypical pathogens and might affect favorably the host inflammatory response through nonantibiotic effects.[14] Consequently, potential advantages of combination therapy should be balanced with a potential increased risk of adverse cardiac events and increased selection of resistant pathogens. We aimed to evaluate whether initial empirical treatment with β-lactam monotherapy was noninferior to the combination of a β-lactam and a macrolide in adult patients hospitalized for moderately severe community-acquired pneumonia.

Methods

Design and Patients

The ethics committees of all participating hospitals and Swissmedic, the Swiss regulatory agency for therapeutic products, approved the study protocol. All patients provided written informed consent. The BICAP DSMB, an independent data safety monitoring board, was informed about the number of severe events in both treatment arms and could stop the trial if judged necessary.

This open-label, noninferiority, randomized trial was conducted in 6 acute care hospitals in Switzerland. We screened consecutive patients who presented to the emergency department with suspected community-acquired pneumonia and who needed hospitalization. Inclusion criteria were an age of 18 years or older, presence of at least 2 clinical findings suggestive of pneumonia, and presence of a new infiltrate on chest radiograph. Main exclusion criteria were severe immunosuppression, recent hospitalization (<14 days), residency in a nursing home, severe pneumonia as defined by the Infectious Diseases Society of America/American Thoracic Society 2007 rule[6] or Pneumonia Severity Index (PSI) category V,[15] and administration of any antibiotic for more than 24 hours before inclusion (eMethods in the Supplement).

Randomization

Randomization was computer generated and stratified by center, with a 1:1 ratio, in randomly alternating blocks of 6, 8, and 10. After informed consent, patients were allocated to the treatment arms by means of consecutive, numbered, sealed, and opaque envelopes.

Intervention

Patients were randomized to initial treatment with a β-lactam alone (monotherapy arm) or a β-lactam and a macrolide (combination arm). The β-lactam could be cefuroxime (1.5 g 3 times a day intravenously) or amoxicillin and clavulanic acid (1.2 g intravenously 4 times a day). The macrolide was clarithromycin, 500 mg twice a day intravenously or orally (eMethods in the Supplement). Urine samples were systematically tested for the presence of *Legionella pneumophila* antigen, and a macrolide was added in the monotherapy arm in case of a positive test result. A change in the assigned treatment was only allowed in the case of clinical deterioration that necessitated admission to the intensive care unit, lack of resolution of fever after 72 hours, or isolation of a resistant pathogen.

Outcomes and Follow-up

The primary outcome was the proportion of patients who did not reach clinical stability at day 7, defined as a heart rate less than 100/min, systolic blood pressure of more than 90 mm Hg, tympanic temperature less than 38.0°C, respiratory rate less than 24/min, and oxygen saturation by pulse oximetry of more than 90% on room air. Vital signs were measured at least twice a day. Time to clinical stability was defined as time elapsed between the first antibiotic dose and the first time all 5 criteria were reached and maintained for a minimum of 24 hours. Time to clinical stability was determined separately after completion of the trial by investigators (N.G. and S.C.) masked to treatment allocation. Discrepancies were resolved by consensus.

Secondary outcomes were 30- and 90-day mortality, transfer to the intensive care unit, length of stay, readmission, recurrence of pneumonia, subsequent introduction of any new antibiotic, and complicated pleural effusion that required chest tube insertion or thoracic surgery. Patients were assessed clinically for 30 days or until hospital discharge. All patients were contacted by telephone at 30 and 90 days. The general practitioner or the hospital was contacted to verify whether a sub-

sequent pneumonia confirmed by chest radiography had occurred. Two investigators (N.G. and S.C.) examined separately the medical records of patients readmitted and determined the cause of readmission. Adverse events, including suspected allergy or toxic effects attributed to the antibiotic treatment, were identified on standard forms.

Diagnostic Tests and Diagnostic Criteria

Two pairs of blood cultures were obtained before administration of antibiotics. A urine sample was collected for detection of the *L pneumophila* antigen. Detection of the *S pneumoniae* antigen in the urine was left to the discretion of the health care professionals. Sputum and pleural fluid were sampled and cultured according to published recommendations.[7] A pharyngeal swab was obtained on the first day of the study and processed for detection of *C pneumoniae* and *M pneumoniae* by polymerase chain reaction. Results of the swab test were not made available to the health care professionals. Diagnostic criteria are available in the eMethods in the Supplement.

Statistical Analysis

Because there is no randomized clinical trial, to our knowledge, that compares antibiotic treatment with a placebo in community-acquired pneumonia, we could not compute the noninferiority margin as a percentage of the effect of the reference treatment over placebo, as generally recommended. We chose the noninferiority margin in reference to unofficial US Food and Drug Administration recommendations for antiinfectious trials that assessed clinical success of a new treatment, which recommend a noninferiority margin of 10%.[16] To be conservative, we computed the sample size with an 8% noninferiority margin.

We assumed a proportion of patients not having reached clinical stability at day 7 of 16% in the combination arm.[17,18] We needed 280 patients per arm to have 90% power with a 1-sided α of .10.[19] Continuous variables are reported as mean (SD) or median (interquartile range [IQR]) and categorical variables as number (percentage). Between-group differences were assessed using the *t* test, Wilcoxon rank sum test, χ^2 test, or Fisher exact test, as appropriate.

The proportions (SEs) of unstable patients at 7 days were measured by the Kaplan-Meier method. Unstable patients who were discharged were censored, and patients who died were considered unstable. We computed the SE on the difference between proportions (se_Δ), calculated as:

$$\sqrt{se_m^2 + se_b^2},$$

where the subscripts *m* and *b* identify the monotherapy and combination therapy arms, and used this value to obtain the upper limit of a 90% CI, which was used to test the noninferiority hypothesis, and a 2-sided 95% CI, which was provided for descriptive purposes. We also tested the null hypothesis of no difference between the proportions using a χ^2 test and reported the corresponding *P* value.

Secondary analyses were prespecified. To perform a global comparison of the 2 study arms, we obtained Kaplan-Meier estimates for the time to clinical stability along with a log-rank test and computed a hazard ratio (HR) from a Cox proportional hazards model. We performed this analysis again with an adjustment for patient age and the PSI score. Three prespecified subgroup analyses were conducted, stratifying on the category of the pathogen identified (atypical or nonatypical, defined as all patients without identification of an atypical pathogen), patient age (<65 or ≥65 years), and PSI (category IV vs I to III). We also performed an additional post hoc analysis, stratifying by the CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≥65 years) score (≥2 vs <2). Strata were compared in a Cox proportional hazards model that included as covariates the treatment, stratification variable, and interaction between the 2 covariates.

Because the Kaplan-Meier survival curves cross during the first week, it follows that the hazards are not strictly proportional. However, we believe that the nonproportionality is not major and that the HR captures a scientifically relevant statistic (ie, the mean HR during the first 7 days). Use of a more complex model (eg, a time-dependent treatment effect with HR[t] a linear function of ln[t] or a stepwise Cox proportional hazards model with a different HR for days 0-3 and days 4-7) would improve fit, but these analyses would not test the prespecified research question, "Is there a general disadvantage (in terms of time to stability during the first week) to using monotherapy in this indication?"

Significance was defined as a 2-tailed $P < .05$. All analyses were performed in the intent-to-treat populations using SPSS statistical software, version 18.0 (SPSS Inc).

Results

From January 13, 2009, through January 31, 2013, we included 602 patients in the study. Twenty-two patients were excluded after randomization (**Figure 1**), leaving a total of 580 patients (291 in the monotherapy arm and 289 in the combination arm). Patients had a median age of 76 years (range, 21-101 years), and 351 (60.5%) had 1 or more comorbidities (median, 1.0; IQR, 0-2). The mean PSI score was 84 (**Table 1**).

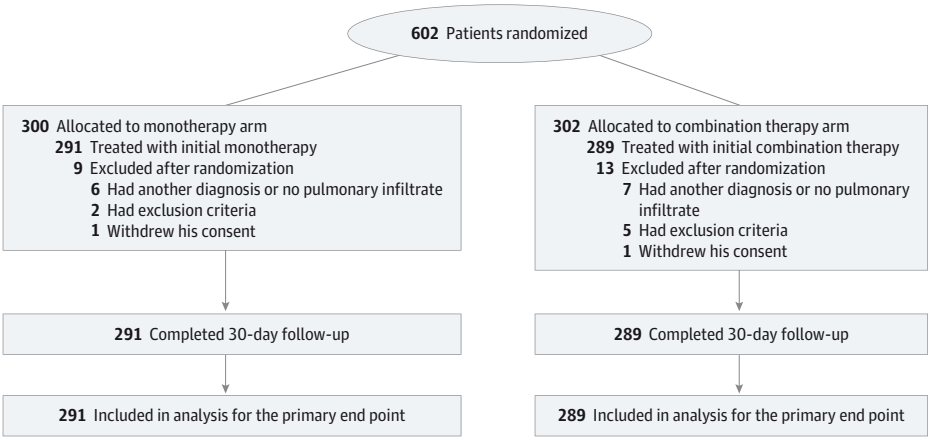
Microbiologic Analysis Results

No imbalance was found between the study arms in the bacteriologic investigations (eTable 1 in the Supplement). A pathogen was identified in 180 patients (31.0%), and 48 (8.3%) had bacteremia. *Streptococcus pneumoniae*, the most common pathogen, was isolated in 43 patients (14.8%) in the monotherapy arm and 45 (15.6%) in the combination arm. *Legionella pneumophila* was identified in 12 patients (4.1%) in the monotherapy arm and 4 (1.4%) in the combination arm. The result of polymerase chain reaction for *M pneumoniae* was positive in 6 patients (2.1%) in the monotherapy arm and 9 (3.1%) in the combination arm (eTable 1 in the Supplement).

Treatment

Twenty-six patients (4.5%) had been treated with oral antibiotics before inclusion in the trial. Patients were treated with antibiotics for a median of 10.0 days (IQR, 8.0-12.0 days) in the monotherapy arm vs 10.0 days (IQR, 7.0-11.0 days) in the com-

Figure 1. Randomization of Patients in the Study



bination arm (P = .41). The β-lactam agent used was amoxicillin-clavulanic acid in 224 patients (77.0%) in the monotherapy arm and 215 patients (74.4%) in the combination arm (P = .48). The remaining 141 patients were treated with cefuroxime.

Initial antibiotic treatment was changed in 39 patients (13.4%) in the monotherapy arm and 46 (15.9%) in the combination arm (P = .39). The reasons for change are listed in eTable 2 in the Supplement. Median time before administration of clarithromycin was 47 hours in the patients with *L pneumophila* infection in the monotherapy arm.

Primary Outcome

After 7 days of treatment, 120 patients (41.2%) in the monotherapy arm had not reached clinical stability compared with 97 (33.6%) in the combination arm (P = .07). The absolute difference was 7.6%, with an upper limit of the 90% CI of 13.0% and a 2-sided 95% CI of −0.8% to 16.0% (**Table 2**). Because 13.0% is above the predefined boundary of 8%, noninferiority of monotherapy could not be demonstrated. In the survival analysis, no significant difference was found between the treatment arms (HR of reaching stability, 0.93; 95% CI, 0.76-1.13), a result that did not change significantly after adjustment for age and PSI category (**Table 3**). On visual inspection of the Kaplan-Meier curves (**Figure 2**), the difference in the proportions of unstable patients peaked on day 7 and persisted until 30 days, although it was globally nonsignificant (P = .44 by the log-rank test). Median time to clinical stability was 5.0 days (IQR, 3.8-6.2 days) in the monotherapy arm and 4.5 days (IQR, 3.9-5.1 days) in the combination arm. Mean time to clinical stability and stabilization of the independent vital parameters is given in eTable 3 in the Supplement.

Table 1. Patient Characteristics at Baseline[a]

Characteristic	Monotherapy (n = 291)	Combination Therapy (n = 289)
Age, median (IQR), y	76 (63-84)	76 (64-83)
Male sex	162 (55.7)	171 (59.2)
Comorbidities, median (IQR)	1 (0-2)	1 (0-2)
Chronic heart failure	64 (22.0)	52 (18.0)
Chronic obstructive pulmonary disease	61 (21.0)	61 (21.1)
Diabetes mellitus	44 (15.1)	52 (18.0)
Chronic renal failure	47 (16.2)	41 (14.2)
PSI score, mean (SD)	84.5 (25.8)	84.2 (24.1)
PSI category		
I	31 (10.7)	23 (8.0)
II	50 (17.2)	55 (19.0)
III	83 (28.5)	98 (33.9)
IV	127 (43.6)	113 (39.1)
CURB-65 score ≥2	155 (53.3)	156 (54.0)
Heart rate, mean (SD), /min	100 (21)	97 (18)
Respiratory rate, mean (SD), /min	24.5 (6.2)	23.6 (5.8)
Temperature, mean (SD), °C	37.9 (1.0)	37.9 (1.0)
Hypoxemia[b]	206 (70.8)	219 (75.8)
Pleural effusion	46 (15.8)	51 (17.6)
White blood cells, mean (SD), /μL	13 400 (6300)	13 600 (6500)

Abbreviations: CURB-65, confusion, urea, respiratory rate, blood pressure, age of 65 years or older; IQR, interquartile range; PSI, Pneumonia Severity Index.

SI conversion factor: To convert white blood cells to $\times 10^9$/L, multiply by 0.001.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Hypoxemia was defined as arterial oxygen saturation less than 92% with room air or the need for supplemental oxygen.

Subgroup Analysis

In the subgroup analysis, the effect of the treatment arm differed significantly for patients with identification of an atypical pathogen (HR of reaching stability, 0.33; 95% CI, 0.13-0.85) and those without (HR, 0.99; 95% CI, 0.80-1.22). Combination therapy was significantly superior for patients with atypical pathogens (Table 3). There was a trend toward better outcome of the combination therapy for patients with more severe pneumonia (Table 3 and eFigure 1 in the Supplement). Patients with PSI category I to III pneumonia had an HR of reaching stability of 1.06 (95% CI, 0.82-1.36) with monotherapy. The corresponding HR was 0.81 (95% CI, 0.59-1.10) for patients with PSI category IV pneumonia (P = .18 for trend). When stratifying on the basis of the CURB-65 score, the HR of

Table 2. Primary and Secondary End Points[a]

End Point	Monotherapy (n = 291)	Combination Therapy (n = 289)	*P* Value
Primary end point			
Patients not reaching clinical stability at day 7[b]	120 (41.2)	97 (33.6)	.07
Secondary end points			
Intensive care unit admission	12 (4.1)	14 (4.8)	.68
Complicated pleural effusion[c]	8 (2.7)	14 (4.8)	.19
Length of stay, median (IQR), d	8 (6-13)	8 (6-12)	.65
Any change in the initial antibiotic treatment	39 (13.4)	46 (15.8)	.39
In-hospital death	8 (2.7)	7 (2.4)	.80
30-Day death	14 (4.8)	10 (3.4)	.42
90-Day death	24 (8.2)	20 (6.9)	.54
30-Day readmission	23 (7.9)	9 (3.1)	.01
90-Day readmission	47 (16.2)	37 (12.7)	.25
New pneumonia within 30 days[d]	10 (3.4)	6 (2.1)	.31

Abbreviation: IQR, interquartile range.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Between-arm difference was 7.6% (1-sided 90% CI, 13.0%; 2-sided 95% CI, −0.8% to 16.0%).

[c] Need for thoracic drainage or surgery.

[d] Pneumonia confirmed by radiography and need for a new antibiotic treatment.

Table 3. Hazard Ratios for Clinical Stability in the Monotherapy Arm vs Combination Arm

Variable	No. of Patients	Hazard Ratio[a] (95% CI)	*P* Value
Unadjusted		0.93 (0.76-1.13)	.46
Adjusted for age and PSI category		0.92 (0.76-1.12)	.41
Stratified			
Atypical	31	0.33 (0.13-0.85)	.02
Nonatypical	549	0.99 (0.80-1.22)	.93
P value for interaction			.03
PSI category IV	240	0.81 (0.59-1.10)	.18
PSI category I-III	340	1.06 (0.82-1.36)	.66
P value for interaction			.18
CURB-65 category 2-5	311	0.80 (0.61-1.06)	.12
CURB-65 category 0-1	269	1.13 (0.85-1.50)	.40
P value for interaction			.09
Age, y			
<65	150	1.09 (0.75-1.59)	.65
≥65	430	0.87 (0.70-1.10)	.25
P value for interaction			.32

Abbreviations: CURB-65, confusion, urea, respiratory rate, blood pressure, age of 65 years or older; PSI, Pneumonia Severity Index.

[a] Reference category is the combination arm.

reaching stability with monotherapy was 1.13 (95% CI, 0.85-1.50) for patients with CURB-65 scores of 0 or 1 and 0.80 (95% CI, 0.61-1.06) for patients with CURB-65 scores of 2 or higher (*P* = .09 for interaction). No interaction was found between age and treatment arm (Table 3).

In a post hoc analysis that excluded all patients with proven infection by an atypical pathogen, the proportion of patients not having reached clinical stability at day 7 was 39.9% in the monotherapy arm and 34.1% in the combination arm (absolute difference, 5.8%; 95% CI, −2.7% to 14.3%; *P* = .15). Mean PSI scores were 86.4 in patients with and 84.2 in patients without a proven atypical pathogen infection (*P* = .64 by analysis of variance).

Secondary Outcomes

No difference was found between the 2 arms in most secondary outcomes (Table 2). However, at 30 days after discharge, more patients in the monotherapy arm had been readmitted (7.9% vs 3.1% in the combination arm, *P* = .01). Of the 23 patients in the monotherapy arm who had been readmitted, 7 (30.4%) had a new episode of pneumonia vs 0 of 9 in the combination arm (*P* = .06). Other causes of readmission or proportion of patients treated for a new episode of pneumonia (in the hospital or as outpatients) did not differ between the treatment arms (Table 2 and eTable 4 in the Supplement).

There was a trend toward more severe events in the monotherapy arm in patients infected with an atypical pathogen, including 3 intensive care unit admissions (all 3 patients were infected with *L pneumophila*) vs none (*P* = .12), respectively and 2 deaths (both patients were infected with *M pneumoniae*) at 30 days vs none (*P* = .21), respectively (eTable 5 in the Supplement).

Safety

Adverse events attributed to the antibiotic treatment were infrequently reported. One patient in the monotherapy arm and 2 patients in the combination arm had acute hepatitis without hepatic failure, and 1 patient in the combination arm had renal failure attributed to acute interstitial nephritis and needed

hemodialysis. Minor allergic reactions were reported in 3 patients in each arm.

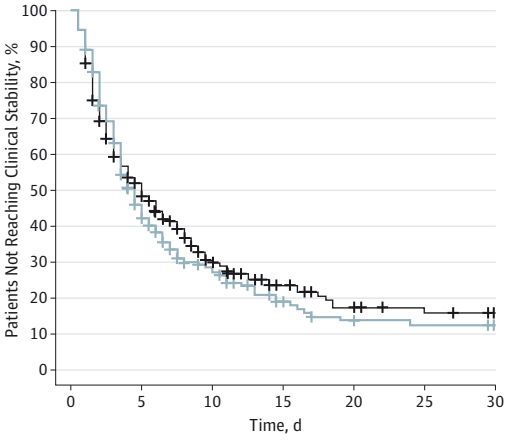
Discussion

We were unable to demonstrate noninferiority of initial empirical treatment with a β-lactam agent alone in hospitalized patients with moderately severe community-acquired pneumonia. There was a nonsignificant trend toward superiority of combination therapy, which could represent a chance finding or true superiority that was not significant because of insufficient power. Although most secondary outcomes did not differ between the 2 treatment arms, patients in the monotherapy arm had more readmissions within 30 days. This finding might also point toward a superiority of combination therapy.

One advantage of the combination therapy is added coverage of atypical pathogens with the macrolide. A Cochrane review[5] included randomized clinical trials that compared treatment regimens with and without atypical coverage. The review did not find a difference in mortality (relative risk [RR], 1.14; 95% CI, 0.84-1.55), but there was a nonsignificant trend toward fewer clinical failures in the atypical arm (RR, 0.93; 95% CI, 0.84-1.04). However, macrolide treatment might also affect favorably the host inflammatory response through nonantibiotic effects.[14,20] Macrolide treatment confers clinical benefits in chronic inflammatory airway conditions, such as bronchiectasis[21] and chronic obstructive pulmonary disease,[22] but this benefit is not established in community-acquired pneumonia. In a recent meta-analysis,[23] macrolide use was associated with a statistically significant mortality reduction (RR, 0.78; 95% CI, 0.64-0.95), an advantage that disappeared when the analysis was restricted to randomized clinical trials (RR, 1.13; 95% CI, 0.65-1.98). A meta-analysis[2] of 16 observational studies comparing β-lactam–macrolide combination with a single β-lactam in more than 42 000 patients with all-cause pneumonia found a lower risk of death in favor of the combination treatment (odds ratio, 0.67; 95% CI, 0.61-0.73). An advantage for combination therapy also has been reported for patients with *S pneumoniae*, although this pathogen is adequately covered by β-lactam drugs.[24,25] This advantage, not present in all studies,[26-28] fueled the hypothesis of an immunomodulatory effect of the macrolide.

In our study, combination therapy was superior in patients with proven infection by an atypical pathogen, despite systematic search for *L pneumophila* infection by urinary antigen testing and subsequent addition of a macrolide in patients undergoing monotherapy. This superiority may be explained by failure to provide timely coverage of the *Legionella* infection. The median time between administration of the β-lactam drug and the addition of clarithromycin was 47 hours for patients with *L pneumophila* infection in the monotherapy arm. This long interval reflects real-life practice, with delays in collecting a urine sample for testing, receiving the results, and prescribing the appropriate antibiotic. These delays may have had repercussions on the concerned patients because 3 of them were transferred to the intensive care unit because of clinical deterioration (eTable 5 in the Supplement). Moreover, sensitivity of the test for *L pneumophila* serotype 1 is only approximately 80%, and other serotypes or species of *Legionella* are inconsistently detected. Finally, the health care professionals were not informed of the result of the swab test for *M pneumoniae* and *C pneumoniae* detection, and lack of initial coverage for these bacteria could also explain the observed difference.

Figure 2. Proportions of Patients Not Reaching Clinical Stability



Black line indicates monotherapy arm; blue line, combination arm. $P = .44$ (log-rank test).

Although clear, this superiority in patients with atypical pathogens does not completely explain the difference in outcomes in the combination arm. First, there was a clear trend toward superiority of the combination therapy for patients with more severe pneumonia (PSI category IV or CURB-65 score of ≥2). This finding is in accordance with observational studies[25,29] that found that higher survival with combination therapy compared with monotherapy was restricted to patients with more severe pneumonia. Because PSI scores did not differ significantly between patients with and without infection with atypical pathogens, better coverage of atypical pathogens is unlikely to explain this differential effect. Second, in an analysis that excluded patients with atypical pathogens, the tendency toward a better outcome in the combination arm persisted (proportion of patients not attaining clinical stability 7 days after treatment, 5.8% compared with 7.6% in the primary analysis). Third, none of the 23 patients readmitted at 30 days in the monotherapy arm had been infected by an atypical pathogen. Better control of the host inflammatory response through a nonantibiotic effect of clarithromycin might have protected patients in the combination arm from adverse events that led to readmission.

Patients enrolled in the trial are representative of patients commonly hospitalized for community-acquired pneumonia, with 25% of patients older than 84 years and a high prevalence of chronic disease. We used strict inclusion criteria. Less than 5% of patients had been treated with oral antibiotics before inclusion, maximizing the effect of the allocated therapy, and adherence to the protocol and follow-up were excellent, with only 3 patients unavailable for follow-up and 85 (14.7%) with a change in treatment allocation (Figure 1

and Table 2). The primary outcome was based on objective physiological measurements, and outcome assessment was masked. Finally, we assessed the outcome at an early time point, in accordance with published recommendations.[30,31]

Our trial was open, and knowledge of treatment arm allocation could have biased clinical decision making. However, we did not observe a difference in the adherence to the assigned treatment between the 2 arms. The study was conducted in Switzerland, and results cannot automatically be generalized to other regions where prevalence of atypical bacteria and resistance of *S pneumoniae* may differ. Specifically, *L pneumophila* causes 93% to 98% of *Legionella* pneumonias in Switzerland, most of them being diagnosed by urinary antigen testing.[32]

A high percentage of patients had not reached clinical stability at 7 days, and the median time to clinical stability was higher than in other trials.[33,34] However, our results were comparable with those of a large international observational study.[35] Several characteristics of our study can explain the longer-than-expected time to clinical stability. We took into account patients dying in the hospital and patients who never reached clinical stability during the acute care stay but were later transferred to a rehabilitation facility by censoring them at 30 days. These patients were excluded from other studies[33,34] that evaluated time to clinical stability. In fact, when we repeated the analysis on the population of patients discharged to their home, we found a median time to clinical stability of 3.5 days (IQR, 3.1-3.9 days), in line with previous studies.[33,34] Finally, despite randomization, a striking imbalance was found in the repartition of *Legionella* between the treatment arms, which could have favored the combination arm.

Conclusions

Our results have important clinical implications. First, the results of this trial indicate that initial empirical treatment with β-lactam monotherapy delays clinical stability for patients infected with atypical pathogens, even when the presence of *Legionella* is systematically searched for with urinary antigen testing. Whether faster introduction of a macrolide in patients with a positive test result would have resulted in better outcomes is hypothetical. Second, patients with higher severity of pneumonia (PSI category IV or CURB-65 score of ≥2) seem also to benefit from combination therapy. Future work might test a strategy of tailoring the initial therapy on the severity of the pneumonia, with combination therapy reserved for patients with PSI category IV or higher pneumonia or a CURB-65 score of 2 or greater.

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Invited Commentary

The Debate on Antibiotic Therapy for Patients Hospitalized for Pneumonia

Where Should We Go From Here?

Jonathan S. Lee, MD; Michael J. Fine, MD, MSc

Although our understanding of pneumonia dates back thousands of years to when symptoms were recognized by Hippocrates, the first typical bacterial pathogen responsible for causing community-acquired pneumonia (CAP), *Streptococcus pneumoniae,* was not isolated until the late 19th century. Another half a century passed before 3 atypical bacteria were discovered as pneumonia pathogens (ie, *Mycoplasma pneumoniae* in 1944, *Legionella* species in 1976, and *Chlamydia pneumoniae* in 1981). Meanwhile, treatment for CAP only became available in the 1940s with the advent of penicillin followed by cephalosporins. Although macrolides were discovered in the 1950s, newer-generation drugs in this class now commonly used to treat CAP (eg, azithromycin and clarithromycin) were approved by the Food and Drug Administration in the early 1990s. Similarly, although discovered in the 1960s, advanced-generation respiratory fluoroquinolones (eg, levofloxacin, moxifloxacin, and gemifloxacin) were approved between 1996 and 2003.

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Contemporary research has added important clinical precepts for the etiology, diagnosis, and clinical presentation of CAP that further inform the antibiotic treatment debate.