CHEST

Original Research

LUNG INFECTION

Antibiotics for Bacteremic Pneumonia*

Improved Outcomes With Macrolides but Not Fluoroquinolones

Mark L. Metersky, MD, FCCP; Allen Ma, PhD; Peter M. Houck, MD; and Dale W. Bratzler, DO, MPH

Background: **The questions of whether the use of antibiotics that are active against atypical organisms is beneficial in the treatment of community-acquired pneumonia and of the potential mechanisms of any beneficial effects remain unresolved. Proposed mechanisms include activity against atypical organisms vs the immunomodulatory effects of these antibiotics. The study of outcomes of a large cohort of patients with bacteremic pneumonia provides a unique opportunity to address these questions by excluding patients with primary atypical infection.**

Methods: **We reviewed data from the charts of 2,209 Medicare patients who were admitted to hospitals across the United States from either home or a nursing facility with bacteremic pneumonia between 1998 and 2001. Patients were stratified according to the type of antibiotic treatment. Multivariate modeling was performed to assess the relationship between the class of antibiotic used and several outcome variables.**

Results: **The initial use of any antibiotic active against atypical organisms was independently associated with a decreased risk of 30-day mortality (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.59 to 0.98; p = 0.03) and hospital admission within 30 days of discharge (OR, 0.67; 95% CI, 0.51 to 0.89; p = 0.02). Further analysis revealed that the benefits of atypical treatment were associated with the use of macrolides, but not the use of fluoroquinolones or tetracyclines, with macrolides conferring lower risks of in-hospital mortality (OR, 0.59; 95% CI, 0.40 to 0.88; p = 0.01), 30-day mortality (OR, 0.61; 95% CI, 0.43 to 0.87; p = 0.007), and hospital readmission within 30 days of discharge (OR, 0.59; 95% CI, 0.42 to 0.85; p = 0.004).**

Conclusions: **Initial antibiotic treatment including a macrolide agent is associated with improved outcomes in Medicare patients hospitalized with bacteremic pneumonia. These results have implications regarding the mechanism by which the use of a macrolide for treatment of pneumonia is associated with improved outcomes.** ***(CHEST 2007; 131:466–473)***

Key words: antibiotics; atypical bacterial forms; bacteremia; outcomes assessment

Abbreviations: CI = confidence interval; OR = odds ratio; PSI = pneumonia severity index; ROC = receiver operating characteristic

At least 1.3 million people are admitted to the hospital with pneumonia each year in the United States,[1] and approximately 10% of these patients will die within 30 days of admission.[2] Many questions remain about the optimum empiric antibiotic treatment of patients with community-acquired pneumonia, as well as the treatment of patients in whom a causative organism is identified. A major area of debate is the role of agents that are active against "atypical" organisms.[3] While several observational studies[4–7] have demonstrated improved outcomes associated with atypical coverage, and pneumonia treatment guidelines recommend such treatment,[8,9] a recent metaanalysis[10] and systematic review of randomized, controlled trials[11] failed to demonstrate an advantage of this practice. Improved outcomes associated with atypical treatment in patients with pneumococcal bacteremia have also been reported,[12,13] but there is poor understanding of the mechanism by which atypical coverage could improve outcomes when an alternative pathogen is identified. Possible mechanisms could include treatment of dual infection with an atypical pathogen such as *Chlamydophila pneumoniae*,[14] the immunomodula-

tory effects of macrolide[15] and fluoroquinolone antibiotics,[16] or the achievement of broader coverage against unusual or resistant pathogens when these antibiotics are used in combination with β-lactam antibiotics.

In order to better understand the effect of atypical antibiotic coverage in patients who are admitted to the hospital with pneumonia, we studied the relationship between the initial antibiotic regimen and several patient outcomes in a large cohort of Medicare beneficiaries who were hospitalized with bacteremic pneumonia. The large size of this cohort provided the unique opportunity to compare the effects of fluoroquinolones and macrolides. Because > 60% of the cases in this cohort were patients who were infected with an organism other than *Streptococcus pneumoniae*, this analysis also provided the opportunity to expand on the observations of prior studies[12,13,17] that were limited to patients with pneumococcal bacteremia.

Materials and Methods

The data analyzed were part of the Medicare National Pneumonia Project, which is a component of the Medicare Quality Improvement Program. Therefore, neither informed consent nor institutional review board approval were required. Eligible patients were fee-for-service Medicare beneficiaries who had been discharged from the hospital between 1998 and 2001 with a principal diagnosis of pneumonia, and those with a principal diagnosis of septicemia or respiratory failure and a secondary diagnosis of pneumonia. Patients included in the study were admitted to the hospital from either home or a nursing facility. The details regarding the selection of the cohort used in this study, the data collection and validation methods have been previously described in detail.[18]

Patients with fungemia and those in whom antibiotic therapy was not initiated within 24 h of arrival to the hospital were excluded. Patients were defined as *bacteremic* if a blood culture drawn within 36 h of presentation to the hospital grew an organism that was not defined as a contaminant (*eg*, coagulase negative staphylococci, Corynebacterium spp other than jeikeium, Clostridium spp, Micrococcus spp, Propionibacterium spp, and Bacillus spp).[18]

Initial atypical antibiotic coverage was defined as the use of any macrolide, fluoroquinolone, or tetracycline agents within 24 h of hospital arrival. For the comparison of these three agents, we included patients who received only one of these agents within 24 h, whether alone or in combination with other antibiotics that are not active against atypical organisms. *Concordant antibiotic therapy* was defined as initial antibiotic therapy including any antibiotic to which the infecting organism was sensitive based on the microbiology report. Because complete sensitivity data were lacking for some patients, and the method of abstraction did not allow us to differentiate between missing data and antibiotic resistance, antibiotic therapy was defined as being either *concordant* or *unable to determine*. *Hospital discharge destination* was defined as either to home or to any other destination.

Summary statistics were calculated for the abstracted data, measures of association including univariate odds ratios (ORs) were obtained, and χ^2 tests were performed. The relationships among patient characteristics, antibiotic therapy, and the following outcomes were determined by univariate analysis: in-hospital mortality; 30-day mortality; hospital length of stay; 30-day hospital readmission rate; and hospital discharge destination. The analysis of hospital discharge destination was performed only on patients who were admitted to the hospital from home.

Multivariable logistic regression analysis was performed using the backward-elimination procedure. If two independent variables were highly correlated, the variable with the largest variance was excluded from the multivariable analysis.[19] After it was determined that there was an association between atypical antibiotic coverage and several patient outcomes, we attempted to determine whether the length of time for which atypical coverage was received correlated with patient outcomes. This was a problematic analysis, due to the interaction between the length of time that a patient survived and the length of time for which a given antibiotic could be received. Stated simply, a patient who died on hospital day 2 could not receive antibiotics for > 2 days, and this factor biased the analysis in favor of longer courses of atypical therapy. This problem was addressed by constructing a series of models in which patients who received specific lengths (in days) of atypical therapy were compared to the group of patients who survived for at least that length of time and had received no atypical therapy. Because this analysis involved the creation of multiple models, no valid statistical test of trend could be performed.[20] However, the results can be interpreted on the basis of face validity.[20]

The goodness of fit of the multivariable models was tested with the Hosmer-Lemeshow test,[21] which revealed adequate fit for all models. Receiver operating characteristic (ROC) curves were constructed by a series of cut points.[22] The area under the ROC curves varied from 0.58 for the 30-day readmission model to 0.78 and 0.77 for in-hospital and 30-day mortality, respectively. All reported p values are based on two-tailed tests. Statistical significance was accepted at $p < 0.05$. Analyses were conducted using a statistical software package (SAS, version 8.0; SAS

*From the Division of Pulmonary and Critical Care Medicine (Dr. Metersky), University of Connecticut School of Medicine, Farmington, CT; Oklahoma Foundation for Medical Quality, Inc (Drs. Ma and Bratzler), Oklahoma City, OK; and the Department of Epidemiology (Dr. Houck), University of Washington School of Public Health and Community Medicine, Seattle, WA.
The analyses on which this publication is based were performed under contract No. 500–02-OK-03, funded by the Centers for Medicare & Medicaid Services, an agency of the US Department of Health and Human Services. The content of this publication does not necessarily reflect the views of the policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government. The authors assume full responsibility for the accuracy and completeness of the ideas presented.
Dr. Metersky has served on an advisory board/speaker's bureau for the following pharmaceutical companies: Aventis; Bayer; Ortho; Oscient; and Pfizer. The other authors of the article have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Manuscript received June 7, 2006; revision accepted August 24, 2006.

Correspondence to: Mark L. Metersky, MD, FCCP, Division of Pulmonary and Critical Care Medicine, University of Connecticut Health Center, 263 Farmington Ave, Farmington, CT 06030-1321; e-mail: Metersky@nso.uchc.edu
DOI: 10.1378/chest.06-1426

Institute; Cary, NC). ROC curve analysis was performed using designated software (AccuROC, version 2.5; AccuROC; Montreal, QC, Canada).

Results

A total of 2,349 episodes of bacteremic pneumonia from two sampling periods (1998 to 1999 and 2000 to 2001) were considered for inclusion in the study. Fifty-three episodes were excluded because of missing data elements, 26 because either an atypical pathogen or fungemia was identified, and 61 because antibiotic therapy was not started within 24 h of admission to the hospital. This left 2,209 cases, 1,140 from the 1998-to-1999 sampling period and 1,069 from the 2000-to-2001 sampling period. Table 1 shows the organisms that were cultured. Table 2 shows the antibiotics that were most commonly used as monotherapy and in combination during the first 24 h of treatment.

Overall, patients from the two time periods were quite similar, although there were small but statistically significant differences with respect to severity of illness, as well as the percentage of patients who received antibiotics within 8 h of hospital arrival and the frequency of atypical antibiotic coverage, both of which were higher in patients from the 2000-to-2001 sampling period. For all further analyses, the two groups of patients were combined. The sampling period for each case was retained as an independent variable in all modeling to prevent temporal trends in patient characteristics or treatment patterns from skewing the study results.

Table 3 demonstrates demographic characteristics, treatment, and selected outcomes of those patients who did and did not receive atypical coverage within 24 h of hospital arrival. Patients who did not receive atypical coverage were no more likely to be admitted to the ICU but were slightly older, and on that basis tended to have a higher pneumonia severity index (PSI). Patients who received atypical treatment were more likely to have received two or more antibiotics and to have received concordant antibiotic therapy during the first 24 h. There was a lower crude 30-day mortality rate among the patients who received atypical therapy, but no statistically significant differences in the other four measured outcomes (*ie*, in-hospital mortality, hospital length of stay, hospital discharge destination, and hospital readmission rate).

Table 1—*Blood Culture Isolates*

Pathogens Isolated	Patients, No. (%)
S pneumoniae	846 (38)
Staphylococcus aureus	314 (14)
Streptococcus spp (other)	314 (14)
Escherichia coli	300 (14)
Other enteric Gram-negative bacilli	197 (9)
Other	238 (11)

Table 2—*Most Common Antibiotics Used as Monotherapy and in Combination Therapy During the First 24 h After Hospital Arrival*

Therapy	Patients, No.
Most common antibiotics used as monotherapy	
Levofloxacin	301
Ceftriaxone	270
Cefotaxime	74
Cefuroxime	56
Ampicillin-sulbactam	28
Other monotherapy	156
Total	885
Most common antibiotic combinations	
Azithromycin/ceftriaxone	170
Ceftriaxone/levofloxacin	98
Ceftriaxone/clarithromycin	43
Azithromycin/cefotaxime	35
Ceftriaxone/erythromycin	32
Cefotaxime/levofloxacin	26
Azithromycin/cefuroxime	26
Clindamycin/levofloxacin	22
Ceftriaxone/gentamicin	18
Levofloxacin/vancomycin	19
Other antibiotic combinations	835
Total	1,324

The multivariable analysis demonstrated that several factors were independently associated with at least one of three outcome measures (Table 4). Neither hospital length of stay nor hospital discharge destination were affected by the type of antibiotic therapy; therefore, no other data are presented relating to these outcomes. The initial receipt of antibiotics that are active against atypical organisms was associated with improved adjusted 30-day mortality rate and 30-day hospital readmission rate. Other factors associated with at least one improved outcome were hospital admission source other than a skilled nursing facility, concordant initial antibiotic treatment, PSI class, and initial monotherapy.

Severity of illness had only a slight effect on the likelihood of a patient receiving more than one antibiotic. Initial treatment with two or more antibiotics was received by 62% of patients in PSI class V, 60% of those in PSI class IV, and 56% of those in PSI classes I to III. The association of single antibiotic coverage with mortality rates was explored further by restricting the analysis to PSI class V patients. For these patients, there was no significant association between single antibiotic treatment and mortality.

When the effect of atypical coverage was stratified according to antibiotic class, only macrolides had a

Table 3—*Univariate Analysis of Selected Patient Characteristics, Processes of Care, and Outcomes Stratified by Receipt of Atypical Antibiotic Coverage

Variable	All Patients (n = 2,209)	Atypical Coverage Within 24 h: Yes (n = 1,408)	Atypical Coverage Within 24 h: No (n = 601)	p Value
Age				
Mean (SD)	76.9 (11.7)	76.4 (11.5)	77.8 (11.9)	0.008
< 65 yr	222 (10.0)	144 (10.2)	78 (9.7)	0.028
65–74 yr	582 (26.3)	384 (27.3)	198 (24.7)	
75–84 yr	746 (33.8)	491 (34.9)	255 (31.8)	
85+ yr	659 (29.8)	389 (27.6)	270 (33.7)	
Gender				
Female	1,099 (49.8)	705 (50.1)	394 (49.2)	0.690
Male	1,110 (50.2)	703 (49.9)	407 (50.8)	
Race				
African-American and Hispanic	235 (10.6)	141 (10.0)	94 (11.7)	0.207
White and other	1,974 (89.4)	1,267 (90.0)	707 (88.3)	
Admitted to hospital from nursing facility				
Yes	542 (24.5)	303 (21.5)	239 (29.8)	< 0.001
No	1,667 (75.5)	1,105 (78.5)	562 (70.2)	
Antibiotic timing				
Antibiotics administered prior to hospital admission	471 (21.3)	306 (21.7)	165 (20.6)	0.270
Antibiotics administered in hospital but prior to blood cultures	1,343 (60.8)	839 (59.6)	504 (62.9)	
Antibiotics after blood cultures	395 (17.9)	263 (18.7)	132 (16.5)	
Antibiotics administered within 8 h				
Yes	2,021 (91.5)	1,313 (93.3)	708 (88.4)	< 0.001
No	188 (8.5)	95 (6.7)	93 (11.6)	
Admitted to ICU within 24 h				
Yes	494 (22.4)	319 (22.7)	175 (21.8)	0.661
No	1,715 (77.6)	1,089 (77.3)	626 (78.2)	
PSI class				
I	20 (0.9)	14 (1.0)	6 (0.7)	0.003
II	110 (5.0)	84 (6.0)	26 (3.2)	
III	299 (13.5)	190 (13.5)	109 (13.6)	
IV	954 (43.2)	628 (44.6)	326 (40.7)	
V	826 (37.4)	492 (34.9)	334 (41.7)	
Concordant antibiotic therapy within 24 h				
Yes	1,000 (45.3)	706 (50.1)	294 (36.7)	< 0.001
Unable to determine	1,209 (54.7)	702 (49.9)	507 (63.3)	
Antibiotics administered within 24 h				
Single	885 (40.1)	363 (25.8)	522 (65.2)	< 0.001
More	1,324 (59.9)	1,045 (74.2)	279 (34.8)	
Sample period				
1998–1999	1,140 (51.6)	629 (44.7)	511 (63.8)	< 0.001
2000–2001	1,069 (48.4)	779 (55.3)	290 (36.2)	
In-Hospital mortality				
Yes	309 (14.0)	184 (13.1)	125 (15.6)	0.098
No	1,900 (86.0)	1,224 (86.9)	676 (84.4)	
30-day mortality				
Yes	416 (18.8)	238 (16.9)	178 (22.2)	0.002
No	1,793 (81.2)	1,170 (83.1)	623 (77.8)	
Hospital Readmission within 30 d of hospital discharge†				
Yes	322 (14.6)	197 (14.0)	125 (15.6)	0.301
No	1,887 (85.4)	1,211 (86.0)	676 (84.4)	
Hospital discharge destination‡				
Home	918 (65.9)	607 (66.3)	311 (65.1)	0.860
Other	475 (34.1)	308 (33.7)	167 (34.9)	
Hospital length of stay†§	8.6 (9.1)	8.7 (9.5)	8.5 (8.3)	0.609

*Values are given as No. (%), unless otherwise indicated.
†Includes only those patients who survived until hospital discharge.
‡Includes only those patients admitted from home.
§Values are given as the mean (SD).

Table 4—*Clinical Characteristics and Outcomes

Variables	In-Hospital Mortality		30-Day Mortality		30-Day Hospital Readmission	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
PSI class I, II, III vs V	0.13 (0.07–0.22)	< 0.001	0.10 (0.06–0.17)	< 0.001	0.94 (0.65–1.35)	0.725
PSI class IV vs V	0.25 (0.19–0.34)	< 0.001	0.27 (0.21–0.35)	< 0.001	1.12 (0.85–1.48)	0.412
Admitted from SNF	1.36 (1.02–1.81)	0.035	1.74 (1.35–2.24)	< 0.001	0.81 (0.60–1.10)	0.172
Admitted to ICU within 24 h	2.58 (1.96–3.40)	< 0.001	1.75 (1.35–2.27)	< 0.001	1.42 (1.08–1.88)	0.014
Initial concordant antibiotic treatment	0.75 (0.57–0.98)	0.037	0.75 (0.59–0.96)	0.021	1.06 (0.83–1.36)	0.648
Initial single antibiotic treatment	0.60 (0.43–0.82)	0.001	0.74 (0.56–0.97)	0.032	0.62 (0.46–0.83)	0.002
Initial atypical antibiotic treatment	0.81 (0.61–1.08)	0.154	0.76 (0.59–0.98)	0.034	0.67 (0.51–0.89)	0.024
Macrolide	0.59 (0.40–0.88)	0.010	0.61 (0.43–0.87)	0.007	0.59 (0.42–0.85)	0.004
Fluoroquinolone	0.94 (0.69–1.28)	0.693	0.82 (0.62–1.07)	0.148	0.82 (0.61–1.09)	0.165
Tetracycline	0.95 (0.25–3.58)	0.939	1.28 (0.42–3.92)	0.670	0.98 (0.32–3.01)	0.968

*SNF = skilled nursing facility.

statistically significant association with any of the outcome measures. Compared to patients who received no atypical coverage, patients treated with a macrolide had a lower adjusted risk of in-hospital mortality (OR, 0.59; 95% confidence interval [CI], 0.40 to 0.88; p = 0.01), 30-day mortality (OR, 0.61; 95% CI, 0.43 to 0.87; p = 0.007), and hospital readmission at 30 days after discharge (OR, 0.591; 95% CI, 0.42 to 0.85; p = 0.004). There were no significant associations between fluoroquinolones or tetracyclines and patient outcomes.

In order to investigate potential confounders, we studied the effect of three additional factors on the association between macrolide use and mortality. In patients who were admitted to the hospital from nursing facilities, a similar trend toward improved in-hospital and 30-day mortality rates was seen in those patients receiving initial treatment including a macrolide, but the differences did not reach statistical significance, perhaps due to the much smaller sample size in this subgroup. Among patients infected with organisms other than *S pneumoniae*, other Streptococcus spp, Haemophilus spp, and *Moraxella catarrhalis* (*ie*, those organisms that are less likely to have susceptibility to macrolides), there were similar trends toward improved in-hospital and 30-day mortality rates with the use of macrolides, although these trends also fell short of reaching statistical significance. Finally, among patients who had received antibiotics prior to hospital admission, there were no trends toward improved mortality rates associated with the use of macrolides after hospital admission.

Analysis of the relationship between mortality and the length of time for which each patient received macrolide therapy (Table 5) revealed that macrolide therapy for ≥ 96 h was associated with a significantly improved 30-day adjusted mortality rate relative to patients who received no atypical coverage. As noted in the "Materials and Methods" section, there is no way to perform a valid statistical test of trend for multiple models[20]; however, an inspection of the data suggests a trend toward improved adjusted mortality rate with longer courses of macrolide therapy.

Discussion

We have demonstrated that several factors are independently associated with improved outcomes in Medicare patients with bacteremic pneumonia. Severity of illness and concordant initial antibiotic therapy were predictive of outcomes. More notewor-

Table 5—*The Relationship Between Duration of Macrolide Treatment and Mortality*

Atypical Coverage Duration	In-Hospital Mortality		30-Day Mortality	
	Adjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
≤ 24 h vs none	0.73 (0.42–1.27)	0.265	0.64 (0.39–1.07)	0.092
25–48 h vs none	0.56 (0.26–1.19)	0.133	0.65 (0.34–1.23)	0.186
49–72 h vs none	0.75 (0.32–1.74)	0.505	0.52 (0.24–1.14)	0.103
73–96 h vs none	0.45 (0.16–1.26)	0.128	0.45 (0.19–1.03)	0.060
> 96 h vs none	0.39 (0.11–1.40)	0.149	0.34 (0.12–0.94)	0.038

thy was the finding that treatment with a macrolide, but not with a fluoroquinolone, was independently associated with lower mortality rates and a lower 30-day hospital readmission rate. In contrast to some studies,[17,23] but not all prior studies,[7,24] monotherapy was also associated with a lower mortality rate, although not for the most severely ill patients.

Several retrospective cohort studies have demonstrated lower mortality[4,5,7] and shorter hospital length of stay[5,6] associated with atypical therapy for patients with community-acquired pneumonia. Since approximately 20% of patients with community-acquired pneumonia have primary infection with an atypical organism and most patients are treated empirically,[8] there is obvious plausibility in the concept that empiric atypical coverage could have a benefit in unselected pneumonia patients. However, a systematic review[3] and a metaanalysis[11] of randomized trials failed to find a benefit from atypical treatment. Consequently, recommendations for empiric atypical coverage[8,9] remain controversial, and many physicians continue to use β-lactam monotherapy.[3,17]

Studies[12,13,25] have also demonstrated lower mortality rates in patients with bacteremic pneumococcal pneumonia who received a macrolide in addition to a β-lactam. It is not clear why macrolide treatment might benefit patients with proven infection due to a nonatypical pathogen. One potential reason is the potential for dual infection with an atypical pathogen such as *C pneumoniae*. Studies employing serologic methods support this possibility,[14] but others[8] have questioned the clinical significance of serologic evidence alone. Both fluoroquinolones and macrolides have excellent activity against the atypical pathogens.[9] Therefore, our finding of improved outcomes associated with macrolides, but not fluoroquinolones, does not support the speculation that coinfection with an atypical pathogen accounts for the improved outcomes seen in patients receiving therapy including a macrolide.

Another possible explanation for a benefit from macrolide therapy is a non-antimicrobial effect. Macrolides are well known to have immunomodulatory effects, and there is ample evidence in patients with cystic fibrosis and diffuse panbronchiolitis that these effects are clinically relevant.[15] While fluoroquinolones may also have immunomodulatory effects, there is little evidence at this time that these effects improve patient outcomes.[16] Macrolides also interfere with quorum sensing and biofilm formation by Pseudomonas spp,[26] but it is not clear whether this effect is relevant to the more common pathogens causing community-acquired pneumonia.

The finding of improved outcomes associated with macrolide antibiotic coverage is reinforced by the apparent trend toward improved outcomes associated with longer courses of macrolide therapy. In essence, we may be seeing a "dose effect" of macrolide therapy, supporting the plausibility of the association being causal.[27] While the magnitude of benefit seen even with short courses of therapy may be more than expected, the long half-life of azithromycin, which is the most commonly used macrolide agent used in these patients, might allow a prolonged effect.

If atypical or macrolide coverage truly improves the outcomes of patients with pneumonia, why have randomized trials failed to show this benefit? One explanation has been noted by Shefet et al,[10] who found an overall mortality rate of 3.7% in the randomized trials included in their systematic review. This is much lower than the 8 to 10% mortality rate generally reported for studies of community-acquired pneumonia[2] and suggests that patients who are recruited into these types of trials are different from patients who are entered into larger scale observational studies.

Several limitations of our study must be acknowledged. It included only Medicare patients, so it may not be representative of all pneumonia patients. This was an observational study, like virtually all of the previous studies of this issue.[12,13,17,23,25] Although we adjusted for severity of illness using well-validated measures, in any retrospective study there is the potential for bias. The finding of lower mortality among patients who received monotherapy raises this concern, as it is contrary to the results of some prior reports. However, it is unlikely that our study was more susceptible to this problem than were prior studies, as we used a very rich database and adjusted for many patient-related factors, including the PSI. Also, in studies[12,13,17,23,25] demonstrating improved outcome with dual therapy, dual therapy often included a macrolide, so it is difficult to separate the effect of dual therapy from the effect of macrolide therapy. Furthermore, we are not the first investigators to note improved outcomes associated with monotherapy. Feldman et al[24] found a shorter hospital length of stay in patients who received azithromycin monotherapy; and Gleason et al[7] demonstrated the lowest pneumonia mortality in Medicare patients receiving monotherapy with a fluoroquinolone. The patients in the population used in these studies and ours were much older than the patients in the studies[12,13,17,23,25] demonstrating improved outcomes with dual therapy. Perhaps these elderly patients are more susceptible to adverse drug effects, which may be more common with the use of more than one antibiotic. For example, *Clostridium difficile* colitis, which is frequently lethal in elderly

patients, is more commonly seen with the use of more than one antibiotic.[28]

There are some unique strengths of this study. Patients were randomly selected from hospitals across the United States, making it a truly representative sample. It is also larger than prior studies[12,13,17,23,25] investigating the effect of antibiotic treatment on patients with bacteremic pneumonia. Thus, the effect of different classes of atypical antibiotics could be compared, providing insight into the mechanism by which atypical therapy might result in improved patient outcomes.

It is difficult to make comprehensive treatment recommendations based on our results. We found that the use of a macrolide in therapy was strongly associated with improved outcomes, but the finding of improved outcomes with monotherapy makes it difficult to recommend the use of a β-lactam with a macrolide over that of monotherapy with a respiratory fluoroquinolone. Although many studies have reported success with macrolide monotherapy,[24,29,30] experts recommend against it for the majority of patients who are hospitalized with community-acquired pneumonia[8,9] However, our results suggest that if combination therapy is going to be used, a macrolide combination may have advantages over a fluoroquinolone combination.

In summary, our results add to the growing body of evidence suggesting that even when an alternative pathogen is identified, treatment including a macrolide results in improved outcomes in patients with pneumonia.[12,13,24,26] Since improved outcomes were not noted with fluoroquinolone therapy, this effect was most likely not related to the treatment of coinfecting atypical organisms. It is difficult to translate our results into specific treatment recommendations, given the finding of improved outcomes associated with monotherapy. Rather, this study demonstrates the profound need for large-scale randomized trials to definitively answer these questions. There are > 100,000 lives lost each year, and the large differences in mortality rates related to the type of antibiotic therapy noted in this and prior studies[12,13,25] demand that we have robust data from randomized trials on which to base antibiotic treatment decisions.

ACKNOWLEDGMENT: The authors wish to thank David Dorsky, MD, and Thomas Meehan, MD, MPH, for kindly reviewing the manuscript.

References

1 Kozak LJ, Owings MF, Hall MJ. National Hospital Discharge Survey: 2002 annual summary with detailed diagnosis and procedure data. Vital Health Stat 13 2005; 158:1–199
2 Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 335:243–250
3 Oosterheert JJ, Bonten MJM, Hak E, et al. How good is the evidence for the recommended empirical antimicrobial treatment of patients hospitalized because of community-acquired pneumonia? A systematic review. J Antimicrob Chemother 2003; 52:555–563
4 Houck PM, MacLehose RF, Niederman MS, et al. Empiric antibiotic therapy and mortality among Medicare pneumonia inpatients in 10 western states: 1993, 1995, and 1997. Chest 2001; 119:1420–1426
5 Brown RB, Iannini P, Gross P, et al. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest 2003; 123:1503–1511
6 Stahl JE, Barza M, DesJardin J, et al. Effect of macrolides as part of initial empiric therapy on length of stay in patients hospitalized with community-acquired pneumonia. Arch Intern Med 1999; 159:2576–2580
7 Gleason PP, Meehan TP, Fine JM, et al. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med 1999; 159:2562–2572
8 American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy and prevention. Am J Respir Crit Care Med 2001; 163:1730–1754
9 Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis 2000; 31:347–382
10 Shefet D, Robenshtok E, Paul M, et al. Empirical atypical coverage for inpatients with community-acquired pneumonia. Arch Intern Med 2005; 165:1992–2000
11 Mills GD, Oehley MR, Arrol B. Effectiveness of β lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. BMJ 2005; 330:456–462
12 Mufson MS, Stanek RJ. Bacteremic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978–1997. Am J Med 1999; 107:34S–43S
13 Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a β-lactam-based empirical antibiotic regimen is associated in lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003; 36:389–395
14 Lieberman D, Schlaeffer F, Boldur I, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. Thorax 1996; 51:179–184
15 Amsden GW. Anti-inflammatory effects of macrolides: an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? J Antimicrob Chemother 2005; 55:10–21
16 Reisbeck B. Immunomodulating activity of quinolones: review. J Chemother 2002; 14:3–12
17 Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004; 170:440–444
18 Metersky ML, Ma A, Bratzler DW, et al. Predicting bacteremia in patients with community-acquired pneumonia. Am J Respir Crit Care Med 2004; 169:342–347
19 Healey JF. Statistics: a tool for social research. Belmont, CA: Wadsworth Publishing Company, 1993
20 Breslow NE, Day NE. Statistical methods in cancer research (vol I): the analysis of case-control studies. Lyon, France:

International Agency for Research on Cancer, LARC Scientific Publications, 1980; 16
21 Hosmer DW, DeLong DM. Applied logistic regression. New York, NY: John Wiley & Sons, 1989
22 Hanley JA, McNeil BJ. The meaning and use of the area under a ROC (ROC) curve. Radiology 1982; 143:29–36
23 Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001; 161:1837–1842
24 Feldman RB, Rhew DC, Wong JY, et al. Azithromycin monotherapy for patients hospitalized with community-acquired pneumonia. Arch Intern Med 2003; 163:1718–1726
25 Weiss K, Low DE, Cortes L, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic *Streptococcus pneumoniae* pneumonia in adults. Can Respir J 2004; 11:589–593
26 Nguyen T, Louie SG, Beringer PM, et al. Potential role of macrolide antibiotics in the management of cystic fibrosis lung disease. Curr Opin Pulm Med 2002; 8:521–528
27 Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965; 58:295–300
28 Moshkowitz M, Ben Baruch E, Kline Z, et al. Clinical manifestations and outcome of pseudomembranous colitis in an elderly population in Israel. Isr Med Assoc J 2004; 6:201–204
29 Vergis EN, Indorf A, File TM Jr, et al. Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients: a prospective, randomized, multicenter trial. Arch Intern Med 2000; 160:1294–1300
30 Lentino JR, Krasnicka B. Association between initial empirical therapy and decreased length of stay among veteran patients hospitalized with community acquired pneumonia. Int J Antimicrob Agents 2002; 19:61–66