ORIGINAL INVESTIGATION

Effect of Macrolides as Part of Initial Empiric Therapy on Length of Stay in Patients Hospitalized With Community-Acquired Pneumonia

James E. Stahl, MD; Michael Barza, MD; Jeffrey DesJardin, MD; Rhonda Martin, RN; Mark H. Eckman, MD

Background: The choice of antibiotics to treat community-acquired pneumonia (CAP) is primarily empiric, and the effect of this choice on length of stay (LOS) and mortality is largely unknown.

Objective: To examine the impact of antibiotic choice on these outcomes in general medical patients hospitalized with CAP.

Methods: One hundred patients hospitalized with CAP were prospectively identified. Seventy-six met inclusion criteria and were entered into the study. After hospital discharge, each medical chart was examined by 2 independent physicians who verified the admitting diagnosis and entered the data for antimicrobial regimens, a CAP mortality prediction tool, a social and disposition index, and other health outcomes. Patients were stratified according to the antibiotic received. Simple regression techniques were used to examine the correlation between initial therapy, specifically, ceftriaxone sodium or a macrolide, and LOS and mortality.

Results: Patients who received macrolides within the first 24 hours of admission had a markedly shorter LOS (2.8 days) than those not so treated (5.3 days; $P = .01$). This effect diminished as the interval before administering macrolides increased. Including ceftriaxone as part of the initial therapy did not appear to affect LOS. Patients given a macrolide for initial treatment did not differ significantly from those not treated in terms of mean age, mortality prediction tool score, or Social and Disposition Index score. Eleven of the 12 patients who received macrolides also received a β-lactam antibiotic.

Conclusion: Use of macrolides as part of an initial therapeutic regimen appears to be associated with shorter LOS.

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From the Divisions of Clinical Decision Making (Drs Stahl and Eckman), Informatics and Telemedicine (Drs Stahl and Eckman), Geographic Medicine and Infectious Diseases (Drs Barza and DesJardin), General Medicine (Drs Stahl and Eckman), and Quality Support Services (Ms Martin), Department of Medicine, New England Medical Center and Tupper Research Institute, Tufts University School of Medicine, Boston, Mass.

THERE ARE more than 5 million cases per year of community-acquired pneumonia (CAP) in the United States, resulting in more than 1 million hospital admissions.[1] The estimated annual cost of care is $34.4 billion.[1] The predominant component of the cost of care is the cost of hospitalization, including nursing and hotel costs. In one recent large study[2] in the Midwest, mean hospital length of stay (LOS) was found to be 8.5 days for teaching hospitals; in another multistate study,[3] this was a reported 6.3 days. Such durations are in contrast to a goal of 2 days, which was recently suggested by consultants to the managed care industry.

In most patients with CAP, the causative agents are not identified during the illness. Therefore, patients are commonly treated with empirically chosen antibiotics. The American Thoracic Society has published guidelines[4] for the empiric treatment of CAP, based on the age of the patient and the severity of illness. These guidelines were generated from the recommendations of a consensus panel, and their usefulness has not been prospectively evaluated. The guidelines suggest macrolides as one component of an antimicrobial regimen for hospitalized patients to be used when the clinician suspects that an "atypical" agent (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*) may be the cause of pneumonia.

See also pages 2511 and 2562

We recently conducted a prospective study to determine what factors might explain the variability in LOS for patients with CAP. We examined the correlation between LOS and a series of factors we thought might explain vari-

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PATIENTS AND METHODS

The New England Medical Center is a 300-bed, tertiary care, teaching hospital serving the metropolitan Boston, Mass, area. Patients with CAP admitted between May 1996 and January 1997 were prospectively identified. Shortly after discharge, each patient's medical chart was examined by 2 researchers (J.E.S. and J.D.) to verify that CAP was the primary diagnosis.

Excluded from this study were patients with human immunodeficiency virus, clear evidence of aspiration, those directly admitted to the intensive care unit, and those transferred from another hospital if they had been there for more than 24 hours. Patients admitted for presumed CAP but whose primary reason for hospitalization was determined to be something other than CAP, such as major gastrointestinal bleeding or congestive heart failure, were also excluded. These criteria were intended to ensure that the focus remained on patients in whom CAP was the dominant reason for hospitalization. Patients admitted from nursing homes were included in this study if they met these criteria.

During the study, a guideline for the treatment of CAP was in circulation at the Department of Medicine, New England Medical Center, that recommended ceftriaxone sodium, 1 g once daily, for initial empiric treatment, and suggested adding macrolides if an "atypical" pneumonia was suspected. The guideline was voluntary.

For each patient, data were extracted for several categories of indicators we thought might influence the outcomes, particularly mortality and LOS (**Table 1**). Data were entered into a computer database (Access; Microsoft Corp, Redmond, Wash) and analyzed (JMP software; SAS Corporation, Cary, NC). Statistical associations of dichotomous variables were assessed using the χ^2 test; for continuous variables, the *t* test was used. Simple linear regression and logistic regression were used for multivariate analyses.

ability in LOS, namely, the Pneumonia Severity of Illness Index[5] (a mortality prediction tool), various social factors (Social and Disposition Index [SDI]), and an elevated respiratory rate 48 to 72 hours after admission. We found that only a minority (<35%) of the variability in LOS could be explained by any combination of these factors, consistent with the results of prior studies.[6,7] These results are reported elsewhere (J.E.S., M.H.E., M.B., J.D., and R.M., unpublished data, 1997).

Having determined that less than half of the variability in LOS could be explained by the factors described herein, we decided to examine the impact of the initial choice of antibiotic treatment on LOS. We were particularly interested in the effects of macrolides, because they are active against "atypical" pathogens, and ceftriaxone sodium, because a previous, unpublished study from this institution had shown a somewhat shorter LOS among patients with CAP treated with ceftriaxone as opposed to other agents. In this article, we report our findings on the effect of the antibiotic regimen on the outcomes of patients hospitalized with CAP.

Table 1. Data Extracted for Indicators

Indicator	Components	Scoring System
Severity of illness (mortality prediction tool[7,8])	Age, sex, mental status changes, vital signs, laboratory tests	See Fine et al[7,8] (weighted scores)
Social and Disposition Index	Admission from nursing home, No. of hospital or emergency department visits in previous year, substance abuse, homelessness, anticipated compliance problems	1 Point per item except No. of visits, which received 1 point per visit; range, 0-8 (mean, 2.6) (not weighted)
Clinical course	Respiratory rate >20/min between 48 and 72 h	
Complications of therapy	Intravenous line–related sepsis, pneumothorax after pleurocentesis, *Clostridium difficile*, adverse antibiotic reactions	1 Point per item (not weighted)

RESULTS

Of 100 patients identified, 20 were excluded for not meeting inclusion criteria, misdiagnosis at admission, or missing charts. Four were excluded as extreme outliers because their LOS was greater than 2 SDs from the mean. Average age of the 76 remaining patients was 68.3 years (range, 26-97 years); 43% were male. Each of the following comorbidities was present in 13% to 21% of patients: neoplastic disease, chronic obstructive pulmonary disease, cerebrovascular disease, coronary artery disease, congestive heart failure, and chronic renal insufficiency. Diabetes mellitus was present in 5 patients. Twenty-three patients were admitted from a nursing home, and 4 had a history of substance abuse (alcohol or intravenous drug abuse), homelessness, or anticipated problems with compliance after discharge.

Overall mortality prediction tool[5,8,9] score was 0.17, and average mortality risk class was 4. From the latter value, between 6 and 7 deaths would have been anticipated. In fact, 2 patients died during hospitalization, and 4 others died with pneumonia-related illnesses within 30 days after discharge. Six people were transferred to the intensive care unit during admission. Of the 4 complications that we monitored specifically (Table 1), only *Clostridium difficile* was noted, which occurred in 3 patients.

Sixty-eight patients received a β-lactam antibiotic in the first 24 hours. Ceftriaxone was given to 51 patients, ticarcillin disodium and clavulanic acid to 13, ampicillin sodium and sulbactam sodium to 3, cefuroxime to 2, and imipenem to 1. Twelve patients received a macrolide within the first 24 hours. In 6 patients, the drug was erythromycin, given intravenously; in another 5, clarithromycin was given orally. One patient received both agents. Other agents given to 1 or 2 patients as part of initial therapy were clindamycin, ciprofloxacin, gentamicin sulfate, vancomycin, and doxycycline. Of the 12 patients given a macrolide as part of initial treatment, 11

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Table 2. Effect of Choice of Antibiotic on Outcomes

Outcome	Ceftriaxone Sodium Within First 24 h: Yes (n = 51)	Ceftriaxone Sodium Within First 24 h: No (n = 25)	*P*	Macrolide Within First 24 h: Yes (n = 12)	Macrolide Within First 24 h: No (n = 64)	*P*	Macrolide at Any Time: Yes (n = 27)	Macrolide at Any Time: No (n = 49)	*P*
Length of stay, mean (SD)	4.76 (3.3)	4.96 (3.4)	.8	2.75 (1.8)	5.3 (3.4)	.01	4.6 (3.5)	5.1 (3.3)	.51
Complications, No. (%)	1 (2.0)	2 (8.0)	.18	1 (8.3)	2 (3.1)	.45	1 (3.7)	2 (4.0)	.19
Deaths in hospital, No. (%)	1 (2.0)	1 (4.0)	.61	1 (8.3)	1 (1.6)	.25	1 (3.7)	1 (2.0)	.67
Deaths within 30 d after discharge, No. (%)	2 (4.0)	2 (8.0)	.47	0	4 (6.25)	.23	1 (3.7)	3 (6.1)	.64

Table 3. Comparison of Demographic and Severity of Illness Scores

Variable	Macrolide Within First 24 h (n = 12)	No Macrolide Within First 24 h (n = 64)	*P*	Macrolide at Any Time (n = 27)	No Macrolide at Any Time (n = 49)	*P*
Age, mean, y	67.8	68.5	.91	67.4	69	.73
Male, %	25	45	.18	41	43	.86
Mortality prediction tool score	0.14	0.17	.6	0.15	0.18	.52
Social and Disposition Index score	2.4	3.03	.38	2.1	3.4	.02

Table 4. Microbiologic Agents

Cultured Agents	Macrolides Within First 24 h (n = 12)	No Macrolides Within First 24 h (n = 64)
No. (%) of isolates		
Streptococcus pneumoniae	0	7 (10.9)
Staphylococcus aureus	0	6 (9.4)
Haemophilus influenzae	0	4 (6.3)
Enteric gram negative	1 (8.3)	10 (15.6)
"Atypicals"	0	1 (1.6)
Other	0	2 (3.1)
No. (%) of patients with an identified pathogen†	1 (8.3)	23* (35.9)
No. (%) of patients without identified pathogen	11 (91.7)	41 (64.1)

*χ^2 (Homogeneity across treatment categories) = 3.56; P = .06.
†Three patients had 2 agents cultured, and 2 patients had 3 agents cultured.

also received either ticarcillin–clavulanic acid or ceftriaxone; the last received clarithromycin only.

Mean LOS for all 76 patients was 4.9 days (range, 1-15 days). There was no difference in mean LOS between initial treatments that did and did not include ceftriaxone (**Table 2**). By contrast, there was a striking difference in mean LOS between patients whose initial treatment included a macrolide. Patients who received macrolides within the first 24 hours had a mean LOS of 2.75 days; those who did not had a mean LOS of 5.3 days, ie, about 2-fold longer ($P = .01$). When the data were analyzed on the basis of macrolide therapy within the first 48 hours of admission, the LOS was 4.05 days for patients who received a macrolide vs 5.2 days for those who did not ($P = .19$). There was no significant difference in LOS between patients who received a macrolide at any time during hospitalization and those who never received it (Table 2). Thus, the association of macrolide use with a decreased LOS was statistically significant only if the drug was given in the first 24 hours of admission. There were too few deaths, complications, or readmissions within 30 days to evaluate the impact of early macrolide treatment on these outcomes.

We examined the possibility of significant differences in risk factors between patients who did and did not receive macrolide therapy, which might have independently influenced the LOS. We found no statistically significant differences with regard to age, sex distribution, mortality risk, or social factors between patients who did and did not receive macrolide therapy within the first 24 hours (**Table 3**). There was a trend in the early macrolide group for a lower male-female ratio, but the difference was not statistically significant. Similarly, when patients were segregated according to whether they received a macrolide at any time during hospitalization, there were no differences between the groups in age, sex distribution, or mortality risk. However, patients treated with a macrolide had a lower SDI score, primarily due to a lower rate of admission from a nursing home in the group that received macrolides.

Predictions of LOS from simple univariate and multivariate regression analyses looking at treatment with macrolides within the first 24 hours and admission from a nursing home were not significantly different. The predictive power of early macrolide use (within the first 24 hours) was not significantly affected by adding the variable that denoted admission from a nursing home, as evidenced by a minimal decrease in the β for early macrolide use from 1.27 ($P = .001$) in the univariate model to 1.25 ($P = .01$) in the bivariate model. This did not affect the statistical significance of the model or its correlation with LOS. By itself, admission from a nursing home did not explain a statistically significant amount of the variability in LOS.

We also noted a difference in the incidence of identified pathogens between patients who were and were not given a macrolide. This difference was of borderline significance ($P = .06$) when the groups were stratified by treatment within the first 24 hours (**Table 4**). In both groups, most patients did not have a pathogen identified. In only 1 patient was an "atypical" pneumonia agent

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identified, ie, *M pneumoniae*. A pathogen was identified in 1 (8%) of 12 patients in the early macrolide group, and in 23 (36%) of 64 patients in the group not treated with a macrolide ($P<.06$). Three patients had 2, and 2 patients had 3 identified pathogens. In addition, the mean LOS for the 52 patients with no identified pathogens was significantly shorter than that of the 24 patients with identified pathogens (4.3 vs 6.3 days, $P = .02$).

We examined whether receiving a macrolide early in the admission might be a marker for other factors, which were themselves responsible for shorter LOS. If we controlled for the absence of an identified pathogen (by adding such a variable to the regression model), early use of a macrolide still had significant predictive power on the LOS. The β coefficient for early macrolide use decreased only slightly, from 1.27 ($P = .01$) to 1.15 ($P = .02$).

Finally, in the broader analysis of factors that might affect LOS (J.E.S., M.H.E., M.B., J.D., and R.M., unpublished data, 1997), we found that an elevated maximum respiratory rate measured between 48 and 72 hours of hospitalization predicted a longer LOS. Therefore, we performed a similar analysis in this study. Comparing subjects given and not given a macrolide within the first 24 hours, the mean respiratory rates were 28.8/min vs 26.3/min on day 1 ($P = .3$), 22.9/min and 22.6/min on day 2 ($P = .85$), and 20.4/min vs 22.3/min on day 3 ($P = .16$). Thus, there was no significant difference in respiratory rate at 48 and 72 hours between patients stratified by macrolide use.

COMMENT

The most striking finding in this study is the marked difference in LOS between patients who did and did not receive a macrolide as part of therapy within the first 24 hours of admission. The LOS was about 50% shorter (2.75 vs 5.3 days) for patients who received a macrolide in the first 24 hours. This effect was less evident the longer after admission a macrolide was administered. The lack of a beneficial effect for patients in whom a macrolide was administered after 48 hours is not surprising because the change in treatment presumably reflected concern about a poor response to the initial therapeutic regimen, and such patients would be expected to have a longer LOS.

There were too few events in either group to allow us to evaluate whether early use of a macrolide was associated with fewer deaths or with a lower rate of complications or readmission. The overall predicted mortality in this study, based on the criteria of the Pittsburgh Pneumonia Risk Class scale,[9] was 9% compared with an actual mortality of 7.9%.

We examined the possibility that differences in age, sex distribution, mortality prediction tool score, or SDI score might explain the difference in LOS between patients given or not given a macrolide in the first 24 hours. There was a lower proportion of males and a slightly lower SDI score (primarily because of a smaller proportion admitted from nursing homes) among patients treated with a macrolide within the first 24 hours compared with those not so treated, but the differences were not statistically significant.

More striking was the finding that patients in the "early macrolide" group were more likely to have no pathogen identified as a cause of their CAP than those not given macrolides in the first 24 hours; the difference was of borderline statistical significance ($P = .06$). Furthermore, there was a significantly shorter LOS in patients with no identified pathogen than in those in whom a pathogen was identified. Taken together, these observations raise the possibility that early macrolide treatment may simply be a marker for patients with no pathogen identified, which, in turn, may be a marker for patients with pneumonia caused by an "atypical" or nonbacterial pathogen.

The low overall rate of pathogen identification is not surprising. Even in studies specifically designed to find the causes of CAP, no pathogen has been identified in a high proportion of patients.[10-19] Our study was not designed to investigate the causes of CAP. No special effort was made to identify a pathogen in most patients,[20-25] and the serologic studies that are usually the basis for diagnosis of infection by an "atypical" pathogen were rarely done. Indeed, there was no specified protocol for obtaining cultures or conducting serologic studies in these patients. Therefore, caution must be exerted in interpreting the results of these microbiologic studies. Nevertheless, the lower rate of retrieval of an identified pathogen in the macrolide-treated group in the present study raises the possibility that a higher proportion of these patients than those in the control group was infected by an "atypical" pathogen, such as *M pneumoniae*, *C pneumoniae*, or *L pneumophila*. Recent studies[10-19] suggest that these agents may play a larger role in CAP than was previously thought, either as primary pathogens or as copathogens with ordinary bacteria. Pneumonia caused by an atypical agent might have a shorter LOS—especially when a macrolide is used for treatment—than bacterial pneumonia treated with a β-lactam antibiotic. In that case, the shorter LOS associated with early treatment with a macrolide would be the result of segregation—perhaps unwitting—of a subgroup of patients with infection caused by "atypical" pathogens, rather than a nonspecific effect of macrolides in CAP. The difference in causative agents, rather than the use of the macrolide per se, could explain the difference in LOS.

There are 3 reasons to doubt that the difference between the groups in causative agents is the explanation for our findings. First, physicians would have had to be able to identify patients with infection caused by an "atypical" pathogen at the time of admission in order to assign them preferentially to the macrolide group. Many studies[16,22,25] have shown that clinical and routine laboratory tests have very low predictive power for diagnosing infection by an "atypical" pathogen. Second, the microbiologic studies, as noted herein, were not designed to identify the pathogens in CAP and therefore should be interpreted with great caution. Third, the predictive power of the variable that represents early macrolide use did not decrease significantly when the variable for the unknown pathogen was added to the model predicting LOS.

In addition to a direct antibacterial effect, especially against "atypical" pathogens, there is one other potential effect of macrolides that might explain the finding of a shorter LOS in patients with CAP treated initially with a macrolide, namely, a beneficial immunologic or anti-inflammatory effect. There is some evidence that mac-

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rolides may inhibit interleukin 8 production and may reduce the proinflammatory effects of various bacterial products.[26-31] There is also evidence that macrolides may enhance the production of certain inflammatory mediators such as interleukin 1 and interleukin 6.[26-31] Our data did not allow us to distinguish a role for either of these possibilities.

Other reports suggest a beneficial effect of macrolides for the treatment of CAP. One study[32] of outpatients with CAP found that the use of macrolides was associated with lower rates of mortality and subsequent all-cause hospitalization, although the differences were not statistically significant. In another study,[33] among the factors associated with a significantly lower mortality rate in patients hospitalized for the treatment of CAP was an initial administration of a β-lactam and macrolide combination. A recent study[34] comparing clarithromycin alone with amoxicillin–clavulanic acid alone in the treatment of patients hospitalized for CAP showed no difference between the 2 agents in clinical response, microbiologic response, or LOS, but no specific data were given for LOS. In contrast to these patients, in whom the macrolide was given as sole therapy, in our study, 11 of the 12 patients who received a macrolide within the first 24 hours of admission also received a potent β-lactam agent. It is possible that macrolides are not the most effective antibacterial agents by themselves but play a useful adjunctive role in CAP.

Length of stay is the major determinant of cost for the hospitalized CAP patient. The cost of a typical day in the hospital, with standard nursing care on a medical ward, has been approximated at $640 nationally.[35] Most episodes of CAP never have a specific origin identified and are treated empirically. If the addition of a macrolide to the usual treatment with a β-lactam is able to shorten the LOS substantially, the savings in cost of care could be large. Our findings suggest that a randomized, prospective trial of this hypothesis would be worthwhile.

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Reprints: James E. Stahl, MD, Center for Research on Health Care, University of Pittsburgh Medical Center, 820 E Montefiore University Hospital, Pittsburgh, PA 15213 (e-mail: stahl@genmed.upmc.edu).

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