ORIGINAL INVESTIGATION

Associations Between Initial Antimicrobial Therapy and Medical Outcomes for Hospitalized Elderly Patients With Pneumonia

Patrick P. Gleason, PharmD; Thomas P. Meehan, MD, MPH; Jonathan M. Fine, MD; Deron H. Galusha, MS; Michael J. Fine, MD, MSc

Background: Although medical practice guidelines exist, there have been no large-scale studies assessing the relationship between initial antimicrobial therapy and medical outcomes for patients hospitalized with pneumonia.

Objective: To determine the associations between initial antimicrobial therapy and 30-day mortality for these patients.

Methods: Hospital records for 12 945 Medicare inpatients (≥65 years of age) with pneumonia were reviewed. Associations between initial antimicrobial regimens and 30-day mortality were assessed with Cox proportional hazards models, adjusting for baseline differences in patient characteristics, illness severity, and processes of care. Comparisons were made with patients treated with a non-pseudomonal third-generation cephalosporin alone (the reference group).

Results: Initial treatment with a second-generation cephalosporin plus macrolide (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.52-0.96), a non-pseudomonal third-generation cephalosporin plus macrolide (HR, 0.74; 95% CI, 0.60-0.92), or a fluoroquinolone alone (HR, 0.64; 95% CI, 0.43-0.94) was independently associated with lower 30-day mortality. Adjusted mortality among patients initially treated with these 3 regimens became significantly lower than that in the reference group beginning 2, 3, and 7 days, respectively, after hospital admission. Use of a β-lactam/β-lactamase inhibitor plus macrolide (HR, 1.77; 95% CI, 1.28-2.46) and an aminoglycoside plus another agent (HR, 1.21; 95% CI, 1.02-1.43) were associated with an increased 30-day mortality.

Conclusions: In this study of primarily community-dwelling elderly patients hospitalized with pneumonia, 3 initial empiric antimicrobial regimens were independently associated with a lower 30-day mortality. The more widespread use of these antimicrobial regimens is likely to improve the medical outcomes for elderly patients with pneumonia.

Arch Intern Med. 1999;159:2562-2572

From the Department of Pharmaceutical Care and Health Systems, College of Pharmacy, University of Minnesota, Minneapolis (Dr Gleason); Qualidigm (formally known as the Connecticut Peer Review Organization), Middletown, Conn (Drs Meehan and J. M. Fine and Mr Galusha); Section of Pulmonary and Critical Care Medicine, Norwalk Hospital, Norwalk, Conn (Dr J. M. Fine); and Division of General Internal Medicine, Department of Medicine, and Center for Research on Health Care, University of Pittsburgh, Pittsburgh, Pa (Dr M. J. Fine).

EACH YEAR in the United States approximately 4 million adults develop pneumonia, of whom more than 1 million patients are hospitalized.[1-4] In 1993, in-hospital mortality for pneumonia among patients older than 65 years was 10.7 deaths per 100 discharges, and in that year alone $3.5 billion was spent on inpatient care of Medicare patients with this illness.[5] Because of the substantial mortality of pneumonia, particularly among the elderly, it is essential that initial antimicrobial therapy have activity against the causative organism(s). Unfortunately, the causative organism(s) are often unknown at the time antimicrobial therapy is initiated; bacteriological culture results and other microbiological studies are positive in less than 50% of hospitalized patients, even in carefully conducted prospective studies of pneumonia etiology.[6-9]

Wide variations in antimicrobial prescribing practices exist for the treatment of community-acquired pneumonia.[10-13] To reduce this variation and improve the appropriateness of antimicrobial therapy, the Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) have published guidelines for empirical antimicrobial therapy for this

See also pages 2511 and 2576

illness.[14,15] However, these guidelines were derived from a limited number of clinical studies of pneumonia etiology and have not been validated in clinical practice.[14-16] Consequently, even the authors of these guidelines have advocated caution in their clinical adoption until the implications for patient outcomes are better understood.[16]

PATIENTS AND METHODS

STUDY POPULATION

The Medicare Quality Indicator System is a Health Care Financing Administration–sponsored standardized data collection system developed to assess quality of care for hospitalized patients with specific clinical conditions. The Medicare Quality Indicator System pneumonia module, a national, community-based, retrospective study of pneumonia care in adults aged 65 years and older who were community-dwelling or admitted from an LCF, was initiated in March 1994.[19]

SAMPLE SELECTION

Sample selection has been described in detail previously.[19] Briefly, from October 1, 1994, through September 30, 1995, potential pneumonia cases were identified by the Health Care Financing Administration from the Medicare National Claims History File if they had a principal discharge diagnosis of pneumonia according to *International Classification of Diseases, Ninth Edition, Clinical Modification*[20] (*ICD-9-CM*) codes, or if they had a principal discharge diagnosis of respiratory failure and a secondary diagnosis of pneumonia. With the use of a random selection procedure, 26 000 discharges (500 from each state, the District of Columbia, and Puerto Rico) were selected from approximately 650 000 nonfederal, acute care hospital discharges with pneumonia.

After potential cases were identified, data were extracted from the medical records to confirm the diagnosis of pneumonia and to apply exclusion criteria. Of the 26 000 potential cases, medical records were obtained from 25 561 (98.3%). Case confirmation required that the patient have an *ICD-9-CM* code for pneumonia,[21] that a clinician document an initial working diagnosis of pneumonia, and that a chest x-ray examination performed within the first 48 hours after hospital presentation be reported as consistent with pneumonia. Patients were excluded if they were younger than 65 years, had experienced acute care hospitalization within the previous 10 days, were infected with the human immunodeficiency virus, had the acquired immunodeficiency syndrome, had a history of organ transplantation (heart, lung, liver, kidney, or bone marrow), had been exposed to chemotherapy or immunosuppressive therapy within the previous 2 months, had been transferred from another acute care facility, or had died or been discharged on the date of hospitalization. Patients in whom we could not document delivery of antimicrobial therapy within 48 hours after hospitalization (n = 483), patients whose residence was unknown (n = 68), patients whose 30-day mortality could not be verified (n = 33), and patients with missing information on the exact time of antimicrobial administration or the exact time of blood culture performance (n = 874) were not included in these analyses. For patients with more than 1 pneumonia hospitalization during the study period (n = 113), only the initial episode of pneumonia was included.

DATA COLLECTION

Hospitals were asked to provide copies of the medical records of potential cases. Trained medical record abstractors collected the data from the medical records by means of an electronic data collection instrument. Abstracted data were merged with hospital claims data provided by the Health Care Financing Administration. Reliability testing indicated moderate to excellent interabstractor agreement, with κ statistics ranging from 0.48 to 0.95 for pneumonia confirmation and exclusion criteria, clinical characteristics, antimicrobial therapy before hospitalization, timing of initial antimicrobial therapy, and performance of blood cultures within 24 hours of hospitalization.[19]

DATA ELEMENTS

Five categories of variables were used in this study: (1) case confirmation and exclusion criteria (listed previously), (2) patient characteristics, (3) processes of care, (4) antimicrobial agents prescribed, and (5) medical outcomes. Patient characteristics included demographic characteristics (age, sex, and coming from an LCF), comorbid illnesses (cerebrovascular disease, congestive heart failure, and neoplastic disease excluding skin cancer, liver disease, and renal disease), physical examination findings (abnormal mental status, temperature, heart rate, respiratory rate, systolic blood pressure), and laboratory or radiographic results (arterial pH, serum urea nitrogen level, sodium level, glucose level, hematocrit, PaO_2, and pleural effusion). For purposes of this study, an LCF consisted of a skilled nursing home or a long-term or intermediate care facility.

Each patient's risk of 30-day mortality was assessed by means of a validated pneumonia-specific mortality risk index with demonstrated accuracy and discrimination among Medicare patients with pneumonia.[19,22] Patients were assigned to 1 of 4 severity categories (risk classes II-V) based on the presence of the 3 demographic characteristics, 5 comorbid illnesses, 5 physical examination abnormalities, and 7 laboratory or radiographic findings listed above. The physical examination and laboratory values used were the first recorded findings in the initial 24 hours of hospitalization. All other patient characteristics were taken from abstracted data elements except liver disease and neoplastic disease, which were derived from a combination of abstracted data elements and coded secondary *ICD-9-CM* diagnoses, and renal disease, which was assessed from secondary diagnosis codes.

Process of care variables included hospital arrival date and time, blood culture collection date and time, and initial antimicrobial administration date and time. Initial intensive care unit (ICU) admission was defined as ICU treatment with the following procedures documented within 24

Continued on next page

To better understand current prescribing practices and to assess associations between empirical antimicrobial therapy and patient outcomes, we designed a study with the following aims: (1) to describe the initial antimicrobial regimens most frequently prescribed for all hospitalized patients, including the subsets of community-dwelling patients and those admitted from long-term care facilities (LCFs), and (2) to assess the associations between initial antimicrobial regimens, 30-day mortality, and other relevant medical outcomes. Our primary hypothesis was that initial antimicrobial therapy, which includes coverage for "atypical" in addition to "typical" bac-

hours of arriving at the hospital: insertion of an endotracheal tube, respiratory tract intubation, continuous positive airway pressure mechanical ventilation, pulmonary artery catheterization or monitoring, cardiac output determination by thermodilution, or central venous catheter monitoring. Use of all antimicrobial agents was assessed from abstracted data. For each antimicrobial agent prescribed, the date and time of the first dose were recorded; however, the route of administration and discontinuation date were not recorded. The initial antimicrobial regimen was defined as all antimicrobial agents used during the first 48 hours after arrival at the hospital.

The cause of pneumonia was defined by the presence of *ICD-9-CM* diagnosis codes for *Streptococcus pneumoniae*, gram-negative bacilli (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*), *Haemophilus influenzae*, staphylococcal species (*Staphylococcus aureus*, *Staphylococcus epidermidis*), viral pneumonia, fungal pneumonia, *Pneumocystis carinii*, aspiration pneumonia, miscellaneous organisms, and unknown etiology.[21] High-risk pneumonia etiology was defined as gram-negative rod, staphylococcal species, or aspiration pneumonia.[17,23]

Outcome variables were the date of hospital discharge, date of subsequent hospitalization if applicable, and date of death. Mortality data were obtained from the Medicare Enrollment Database, and rehospitalization was assessed by means of Medicare part A claims. Mortality was defined as death within 30 days from the date of the index hospitalization. Length of stay (LOS) was defined as the discharge date minus the admission date. Rehospitalization was defined as any hospitalization within 30 days from the discharge date of the index hospitalization. Assessments of hospital (LOS) and rehospitalization were limited to patients surviving the index hospitalization for pneumonia who were not directly transferred to another acute care hospital.

METHODS OF ANALYSIS

Associations between patient outcomes (ie, mortality, rehospitalization, and LOS) and initial antimicrobial regimens that accounted for greater than 1% of all initial regimens were assessed in all patients and in 2 patient subsets. These 2 patient subsets consisted of patients who were (1) community-dwelling (n = 9751) and (2) LCF-dwelling (n = 3194). Associations between patient outcomes and initial antimicrobial regimens were also assessed by stratification according to severity risk classes. Because of the small number of patients in risk class II (n = 1189), patients in risk classes II and III were combined (n = 4099).

For categorical data, proportions were compared by means of the Pearson χ^2 test. For each antimicrobial regimen, testing for trends in frequency of antimicrobial regimen use by severity risk class was performed with the Mantel-Haenszel χ^2 test for trend. For continuous data (eg, LOS), we calculated medians with interquartile ranges and means with SDs. All LOS analyses were performed with the log transformation of the actual LOS as the dependent variable.

The independent associations between initial antimicrobial regimens and 30-day mortality were assessed by Cox proportional hazards models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for each initial antimicrobial regimen, adjusting for the following independent variables: antimicrobial therapy before hospitalization, 4 baseline pneumonia severity risk classes, arrival from an LCF, initiation of antimicrobial therapy within 8 hours of hospital arrival, performance of blood cultures within 24 hours of hospital arrival, region of enrollment within the United States, ICU treatment on day 1 of hospitalization, change in antimicrobial therapy after the initial 48 hours of hospitalization, and high-risk pneumonia etiology. With the exception of previous antimicrobial therapy and region of enrollment, all of these patient characteristics and process measures have previously been shown to have a significant association with short-term mortality in patients with pneumonia.[19] Significant 2-way interactions between ICU treatment and high-risk etiology, ICU treatment and risk class, and coming from an LCF and high-risk etiology were identified and used as independent variables in the Cox proportional hazards models. The reference category used for initial antimicrobial regimen was therapy with a non-pseudomonal third-generation cephalosporin only (ie, ceftriaxone, cefotaxime, or ceftizoxime), an initial regimen recommended by the ATS and the IDSA guidelines for hospitalized patients with moderate to severe pneumonia.[15,16]

Log-log survival plots were constructed to assess the proportionality assumption underlying the Cox models.[24] The results of all Cox models were confirmed by logistic regression, indicating that our results were insensitive to modeling technique.[25]

To further assess the association between initial antimicrobial regimen and 30-day mortality, 2 separate Cox models were performed in community-dwelling patients (n = 9751) and patients admitted from an LCF (n = 3194). In addition, 3 separate Cox models were performed in patients in risk classes II and III (n = 4099), patients in risk class IV (n = 5711), and patients in risk class V (n = 3135). All of the previously described independent variables used in the overall Cox model were used in these analyses. We varied our definition of initial empirical antimicrobial therapy, specifying it as antimicrobial therapy in the first 8 hours and 24 hours of hospital admission to ensure that our results were insensitive to the time threshold used. We also excluded the 171 patients who died within 48 hours of hospital admission, since initial antibiotic therapy is unlikely to have influenced their mortality.

To assess the independent associations between initial antimicrobial regimens and other medical outcomes (ie, LOS and 30-day rehospitalization), linear regression analysis was used when the dependent variable was LOS and Cox modeling was used when the dependent variable was rehospitalization. All independent variables used in the Cox models for mortality were used in these analyses.

terial pathogens, would be associated with lower 30-day mortality. We made an explicit decision to separately assess the impact of initial antimicrobial therapy on medical outcomes among patients admitted from the community and from LCFs caused by differences in sociodemographic factors, comorbidity, illness severity, and pneumonia etiology across these patient subsets.[6,17,18]

RESULTS

The study population was composed of 12 945 eligible patients: 9751 (75.3%) community-dwelling and 3194 (24.7%) admitted from an LCF. Study patients had a mean (±SD) age of 79.4 ± 8.1 years; 84.4% were white, and 50.7% were female (**Table 1**). The majority of patients (58.1%)

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	Community Dwelling (n = 9751)	Long-term Care Facility Dwelling* (n = 3194)	Total Study Cohort (N = 12 945)
Demographics			
Age, mean, y†	78.1	83.5	79.4
Race, % white	84.3	84.9	84.4
Sex, % female†	48.5	57.2	50.7
Comorbid illness, %			
Congestive heart failure†	25.3	34.6	27.6
Coronary artery disease†	25.5	30.4	26.7
Cerebrovascular disease†	15.8	35.1	20.6
Neoplastic disease†	9.3	6.8	8.7
Chronic renal disease†	2.9	4.6	3.3
Chronic liver disease	0.9	0.7	0.8
Physical examination findings, %			
Altered mental status†	9.4	47.7	18.9
Respiratory rate ≥30/min†	23.2	33.9	25.9
Pulse ≥125 beats/min†	10.1	11.4	10.4
Systolic blood pressure <90 mm Hg†	2.4	6.0	3.3
Temperature <35°C or ≥40°C†	1.6	2.2	1.8
Laboratory and radiographic results, %			
Serum urea nitrogen >10.7 mmol/L (>30 mg/dL)†	19.5	42.2	25.1
Glucose ≥13.9 mmol/L (≥250 mg/dL)†	7.3	9.5	7.8
Hematocrit <0.30†	6.3	10.1	7.2
Sodium <130 mmol/L	5.4	5.2	5.3
Pa_{O_2} <60 mm Hg†	22.0	19.4	21.4
Arterial pH <7.35†	6.9	9.8	7.6
Pleural effusion	19.1	19.4	19.2
Antimicrobial therapy, %			
Previous antimicrobial therapy†	24.4	34.0	26.8
Antimicrobial therapy initiated ≤8 h	80.9	80.4	80.8
Blood cultures within 24 h of hospital arrival, %†	65.7	71.1	67.1
Intensive care unit treatment, day 1 of admission, %	2.6	2.8	2.7
Severity of illness risk classification, %‡			
Risk class II†	11.5	0.3	8.7
Risk class III†	28.7	5.4	22.9
Risk class IV†	44.7	42.4	44.1
Risk class V†	15.1	52.0	24.2
Pneumonia etiology, %			
Streptococcus pneumoniae†	7.5	3.9	6.6
Haemophilus influenzae†	4.7	2.5	4.1
Staphyloccocal species†	2.8	6.0	3.6
Pseudomonas aeruginosa	3.3	3.8	3.4
Klebsiella pneumoniae	1.9	2.3	2.0
Other†§	3.7	2.5	3.4
Aspiration pneumonia†	5.9	22.9	10.1
Unknown†	63.0	52.8	60.5

**Admission from a long-term care facility consisted of residence at a skilled nursing home, intermediate care, or long-term care facility before hospitalization. All other patients were defined as community dwelling.*

†Statistically significant differences (P<.05) between patient subsets (ie, community dwelling and long-term care facility dwelling) were identified by the χ^2 test with the exception of age, where an unpaired t *test was used.*

‡Risk class was determined according to the methods of Fine et al.[22] There were no risk class I patients, who by definition are all younger than 50 years.

§Other microbiological etiology included viral pneumonia (n = 93), fungal pneumonia (n = 53), Pneumocystis carinii *(n = 2), and pneumonia due to other unspecified organisms (n = 263).*

had at least 1 comorbid illness, and 68.3% were in the 2 highest severity risk classes (IV and V) at initial examination. The most frequently coded bacteriological pathogens were *S pneumoniae* (6.6%), and *H influenzae* (4.1%); 10.1% of patients were coded as having aspiration pneumonia and 60.5%, an unknown pneumonia etiology.

In comparison with community-dwelling patients, patients admitted from an LCF were older and had a higher prevalence of the most prevalent comorbid illnesses and a substantially higher prevalence of altered mental status, vital sign abnormalities, laboratory abnormalities, and high-risk etiology. More than 94% of all patients admitted from an LCF were in risk classes IV and V.

INITIAL ANTIMICROBIAL REGIMENS

The 3 most commonly used initial antimicrobial regimens were a non-pseudomonal third-generation cephalosporin only (ceftriaxone, cefotaxime, ceftizoxime) in 26.5%, a second-generation cephalosporin only (cefuroxime) in 12.3%, and a non-pseudomonal third-gen-

Table 2. Use of Initial Antimicrobial Regimens and 30-Day Mortality by Admission Source*

Initial Antimicrobial Regimens†	Prevalence of Antimicrobial Regimen, %			30-d Mortality, % (95% CI)		
	Community Dwelling (n = 9751)	LCF Dwelling‡ (n = 3194)	Total Study Cohort (N = 12 945)	Community Dwelling (n = 9751)	LCF Dwelling‡ (n = 3194)	Total Study Cohort (N = 12 945)
First-generation cephalosporin only§	3.7	2.4	3.3	9.8 (6.9-13.3)	19.7 (11.4-30.4)	11.6 (8.7-14.9)
Second-generation cephalosporin only§	13.5	8.7	12.3	9.3 (7.7-10.9)	23.5 (18.6-28.9)	11.7 (10.1-13.4)
Pseudomonal third-generation cephalosporin only§	1.6	2.2	1.7	10.6 (6.2-16.6)	29.0 (18.6-41.1)	16.4 (11.7-21.9)
Non-pseudomonal third-generation cephalosporins only (reference group)§	25.6	29.2	26.5	10.7 (9.5-11.9)	26.2 (23.4-29.1)	14.9 (13.7-16.1)
Ceftriaxone§	17.8	20.1	18.4	9.8 (8.4-11.2)	27.3 (23.8-30.8)	14.5 (13.1-15.9)
Cefotaxime§	6.6	7.7	6.9	12.9 (10.4-15.7)	24.5 (19.2-30.3)	16.1 (13.7-18.7)
Ceftizoxime	1.0	0.9	0.9	10.8 (5.3-18.8)	20.7 (8.0-39.7)	13.1 (7.7-20.4)
β-Lactam/β-lactamase inhibitors only§	6.7	9.8	7.5	14.1 (11.4-16.9)	27.7 (22.8-33.0)	18.5 (16.0-21.0)
Ampicillin/sulbactam§	3.9	5.4	4.3	13.4 (10.1-17.2)	22.0 (16.0-28.8)	16.1 (13.1-19.3)
Ticarcillin/clavulanate§	2.4	3.8	2.8	14.5 (10.2-19.6)	33.9 (25.5-43.0)	21.1 (16.9-25.6)
Piperacillin/tazobactam§	0.3	0.6	0.4	15.2 (5.1-31.8)	36.8 (16.2-61.6)	23.1 (12.5-36.8)
Macrolides only§	2.2	0.8	1.8	8.6 (5.2-13.2)	20.0 (6.8-40.7)	9.8 (6.3-14.3)
Erythromycin§	1.1	0.6	1.0	10.8 (5.7-18.1)	11.1 (1.4-34.7)	10.9 (6.1-17.5)
Clarithromycin§	0.7	0.1	0.6	4.3 (0.9-12.0)	25.0 (0.6-80.5)	5.4 (1.5-13.2)
Azithromycin	0.2	0.1	0.2	14.3 (3.0-36.3)	50.0 (1.3-98.7)	17.4 (5.0-38.7)
Second-generation cephalosporin plus macrolide§	5.0	1.7	4.2	7.8 (5.6-10.5)	13.0 (5.4-24.9)	8.4 (6.2-11.0)
Non-pseudomonal third-generation cephalosporins plus macrolide§	10.2	4.6	8.8	6.8 (5.3-8.6)	24.3 (17.6-32.0)	9.1 (7.5-10.9)
Ceftriaxone + macrolide§	7.0	3.2	6.1	7.2 (5.3-9.3)	18.8 (11.7-27.8)	8.7 (6.8-10.8)
Cefotaxime + macrolide§	2.5	1.1	2.2	6.5 (3.8-10.8)	40.0 (23.8-57.8)	10.7 (7.3-14.9)
Ceftizoxime + macrolide	0.5	0.3	0.4	4.3 (0.5-14.5)	37.5 (8.5-75.5)	9.1 (3.0-19.9)
β-Lactam/β-lactamase inhibitors plus macrolide§	1.6	0.8	1.4	17.8 (12.0-24.7)	50.0 (29.1-70.8)	22.2 (16.2-29.0)
Ampicillin/sulbactam + macrolide§	0.9	0.3	0.8	14.8 (8.1-23.9)	40.0 (12.1-73.7)	17.4 (10.4-26.3)
Ticarcillin/clavulanate + macrolide	0.6	0.3	0.5	24.1 (13.4-37.6)	60.0 (26.2-87.8)	29.7 (18.9-42.4)
Piperacillin/tazobactam + macrolide	0.1	0.1	0.1	10.0 (0.3-44.5)	33.0 (0.8-90.5)	15.4 (1.9-45.4)
Fluoroquinolones only§	1.7	2.7	2.0	7.1 (3.7-12.0)	17.4 (10.1-27.1)	10.6 (7.1-14.9)
Ciprofloxacin§	1.2	2.1	1.4	6.7 (2.9-12.8)	15.2 (7.5-26.1)	9.7 (5.9-14.9)
Ofloxacin	0.5	0.6	0.5	7.8 (2.2-18.8)	21.1 (6.1-45.5)	11.4 (5.1-21.2)
Aminoglycosides plus any other antimicrobial agent(s)§	5.3	10.1	6.5	18.2 (14.9-21.7)	33.1 (28.0-38.5)	24.0 (21.0-26.9)
All other regimens§‖	23.1	27.1	24.1	13.6 (12.2-15.1)	30.7 (27.6-33.8)	18.4 (17.0-19.7)
Total	NA	NA	NA	11.2 (10.0-11.9)	27.5 (26.5-29.1)	15.3 (14.6-15.9)

*CI indicates confidence interval; LCF, long-term care facility; and NA, not applicable. Percentages for the individual antimicrobial agents within antimicrobial regimens may not sum to the total category percentage because of rounding error.

†The specific antimicrobial agents associated with these regimens were cefazolin for first-generation cephalosporin only; cefuroxime for second-generation cephalosporin only; ceftazidime for pseudomonal third-generation cephalosporin only; erythromycin, clarithromycin, or azithromycin for macrolides; and gentamicin, tobramycin, or amikacin for aminoglycosides.

‡LCF denotes admission from a long-term care facility. Admission from an LCF consisted of residence at a skilled nursing home, intermediate care facility, or LCF before hospitalization. All other patients were defined as community dwelling.

§Statistically significant differences ($P<.05$) between the 2 patient subsets (ie, community dwelling and LCF dwelling) for comparisons of frequency of use of intial antimicrobial regimens by means of the χ^2 test.

‖The "all other regimens" category comprised a total of 851 unique antimicrobial regimens. The most frequent regimens were ceftriaxone plus cefuroxime (n = 97), imipenem/cilastatin only (n = 87), and cefotetan only (n = 67).

eration cephalosporin (as above) plus a macrolide in 8.8% (**Table 2**). Significant differences in the prevalence of use of virtually all initial antimicrobial regimens existed across the 2 patient subsets ($P<.05$). Initial therapy with a non-pseudomonal third-generation cephalosporin only, a β-lactam/β-lactamase inhibitor only, a fluoroquinolone only, or an aminoglycoside plus another agent was more common among patients admitted from an LCF. Significant differences in the choice of initial antimicrobial regimens existed between the northeastern, southern, midwestern, and western regions of the country (defined by the US Census Bureau) for 10 of the 12 initial regimens.[26] The absolute differences in use were minimal with the exception of the northeastern region, where more second-generation cephalosporins alone or in combination with a macrolide were used and fewer non-pseudomonal third-generation cephalosporins alone or in combination with a macrolide than the other 3 regions (data not shown).

Associations between initial antimicrobial regimen and baseline severity of illness existed for 8 of the 12 commonly prescribed regimens (**Table 3**). Treatment with a first- or second-generation cephalosporin only, a macrolide only, and a second- or non-pseudomonal third-generation cephalosporin plus a macrolide occurred less frequently with increasing illness severity. Treatment with a β-lactam/β-lactamase inhibitor only, an aminoglycoside plus any other antimicrobial agent, and the other antimicrobial agent category occurred more frequently with increasing severity of illness at hospital arrival.

Table 3. Use of Initial Antimicrobial Regimens and 30-Day Mortality by Severity Risk Class*

Initial Antimicrobial Regimens†	Prevalence of Antimicrobial Regimen, %			30-d Mortality, % (95% CI)		
	Risk Classes II/III (n = 4099)	Risk Class IV (n = 5711)	Risk Class V (n = 3135)	Risk Classes II/III (n = 4099)	Risk Class IV (n = 5711)	Risk Class V (n = 3135)
First-generation cephalosporin only‡	4.1	3.3	2.5	3.6 (1.3-7.7)	12.1 (7.8-17.6)	27.3 (17.7-38.6)
Second-generation cephalosporin only‡	13.4	13.0	9.6	3.6 (2.2-5.6)	10.3 (8.2-12.8)	29.8 (24.7-35.3)
Pseudomonal third-generation cephalosporin only	1.4	2.0	1.5	3.4 (0.4-11.7)	14.2 (8.3-22.0)	37.5 (24.0-52.6)
Non-pseudomonal third-generation cephalosporins only (reference group)	26.4	26.6	26.4	3.3 (2.3-4.6)	12.4 (10.8-14.2)	34.7 (31.5-38.1)
β-Lactam/β-lactamase inhibitors only‡	5.9	7.8	9.1	2.9 (1.2-5.9)	15.3 (12.1-19.0)	36.6 (31.0-42.5)
Macrolides only‡	2.9	1.7	0.6	3.4 (0.9-8.4)	15.2 (8.7-23.7)	22.2 (6.4-47.6)
Second-generation cephalosporin plus macrolide‡	5.4	4.1	2.6	2.2 (0.7-5.2)	10.2 (6.6-14.8)	19.8 (11.7-30.1)
Non-pseudomonal third-generation cephalosporins plus macrolide‡	10.4	9.2	6.0	1.2 (0.4-2.7)	8.5 (6.3-11.2)	28.6 (22.2-35.6)
β-Lactam/β-lactamase inhibitors plus macrolide	1.6	1.3	1.2	6.0 (1.6-14.6)	29.2 (19.0-41.1)	37.8 (22.5-55.2)
Fluoroquinolones only	2.2	1.9	1.8	4.4 (1.2-10.8)	9.4 (4.6-16.5)	22.8 (12.7-35.8)
Aminoglycosides plus any other antimicrobial agent(s)‡	4.1	6.0	10.4	6.5 (3.3-11.4)	19.6 (15.6-24.3)	37.5 (32.3-43.0)
All other regimens‡§	22.2	23.1	28.4	3.5 (2.4-4.9)	15.9 (14.0-18.0)	37.2 (34.0-40.5)
Total mortality for all regimens	NA	NA	NA	3.3 (2.8-3.9)	13.4 (12.5-14.3)	34.3 (32.6-35.9)

*CI indicates confidence interval; NA, not applicable. Risk classes were determined according to the methods of Fine et al.[22] There were no risk class I patients, who by definition, are all younger than 50 years.

†The specific antimicrobial agents associated with these regimens were cefazolin for first-generation cephalosporin only; cefuroxime for second-generation cephalosporin only; ceftazidime for pseudomonal third-generation cephalosporin only; ceftriaxone, cefotaxime, or ceftizoxime for non-pseudomonal third-generation cephalosporins; ampicillin/sulbactam, ticarcillin/clavulanate, or piperacillin/tazobactam for β-lactam/β-lactamase inhibitors; erythromycin, clarithromycin, or azithromycin for macrolides; ciprofloxacin or ofloxacin for fluoroquinolones; and gentamicin, tobramycin, or amikacin for aminoglycosides.

‡$P<.05$ for comparisons of frequency of use of initial antimicrobial regimens by risk class were calculated by the χ^2 test for trend.

§The "all other regimens" category comprised a total of 851 unique antimicrobial regimens. The most frequent regimens were ceftriaxone plus cefuroxime (n = 97), imipenem/cilastatin only (n = 87), and cefotetan only (n = 67).

ASSOCIATIONS BETWEEN INITIAL ANTIMICROBIAL REGIMENS AND MORTALITY

Thirty-day mortality was 15.3% (95% CI, 14.6%-15.9%) in the entire study population, ranging from 11.2% (95% CI, 10.6%-11.9%) in community-dwelling patients to 27.5% (95% CI, 26.0%-29.1%) among patients admitted from an LCF (Table 2). Mortality ranged from 8.9% for patients who initially received a second-generation cephalosporin plus a macrolide to 24.0% for those who received a β-lactam/β-lactamase inhibitor plus a macrolide. Higher 30-day mortality rates were observed among patients admitted from an LCF for all of the initial antimicrobial regimens, with significantly higher rates observed for 8 regimens.

Increasing risk class was strongly associated with increased 30-day mortality, as follows: class II and III, 3.3% (95% CI, 2.8%-3.9%); class IV, 13.4% (95% CI, 12.5%-14.3%); and class V, 34.3% (95% CI, 32.6%-35.9%) ($P<.001$, χ^2 for trend) (Table 3). With the exception of initial therapy with a fluoroquinolone only in risk classes II and III, the point estimates for 30-day mortality stratified by severity class for fluoroquinolones only, second-generation cephalosporins plus macrolide, and non-pseudomonal third-generation cephalosporins plus macrolide were consistently lower than the reference category (ie, non-pseudomonal third-generation cephalosporins only), while the stratified point estimates for 30-day mortality for β-lactam/β-lacatamase inhibitors plus macrolide and aminoglycosides plus any other agent were consistently higher than the reference category.

Five initial antimicrobial regimens were identified as having an independent association with 30-day mortality (**Table 4**). Use of a second-generation cephalosporin plus a macrolide (HR, 0.71; 95% CI, 0.52-0.96), a non-pseudomonal third-generation cephalosporin plus a macrolide (HR, 0.74; 95% CI, 0.60-0.92), or a fluoroquinolone only (HR, 0.64; 95% CI, 0.43-0.94) were independently associated with a lower 30-day mortality. Use of a β-lactamase inhibitor plus a macrolide (HR, 1.77; 95% CI, 1.28-2.46) and an aminoglycoside plus another agent (HR, 1.21; 95% CI, 1.02-1.43) were independently associated with a higher 30-day mortality.

The adjusted mortality associated with initial treatment with a non-pseudomonal third-generation cephalosporin plus a macrolide ($P<.05$), a second-generation cephalosporin plus a macrolide ($P<.05$), or a fluoroquinolone only ($P<.05$) was significantly lower than the mortality in the reference group on days 2, 3, and 7 after hospitalization, respectively, and remained lower throughout the 30-day follow-up period (**Figure**). In contrast, the adjusted mortality for initial treatment with an aminoglycoside plus any other agent ($P<.05$) or a β-lactam/β-lactamase inhibitor plus a macrolide ($P<.05$) was significantly higher than the mortality in the reference group on days 4 and 7, respectively, and continued to exceed the mortality in the reference group during the remaining time of the 30-day follow-up.

Table 4. Independent Associations Between Initial Antimicrobial Regimens and 30-Day Mortality Among the Total Study Cohort and Stratified by Source of Admission

Initial Antimicrobial Regimens†	Adjusted Hazard Ratio (95% CI)*		
	Total Study Cohort (N = 12 945)	Community Dwelling (n = 9751)	LCF Dwelling‡ (n = 3194)
First-generation cephalosporin only	0.92 (0.69-1.23)	0.99 (0.70-1.41)	0.79 (0.47-1.34)
Second-generation cephalosporin only	0.89 (0.75-1.05)	0.88 (0.71-1.10)	0.90 (0.68-1.19)
Pseudomonal third-generation cephalosporin only	1.12 (0.80-1.57)	0.87 (0.52-1.44)	1.43 (0.91-2.27)
Non-pseudomonal third-generation cephalosporins only	Reference group	Reference group	Reference group
β-Lactam/β-lactamase inhibitors only	1.07 (0.91-1.28)	1.09 (0.86-1.38)	1.07 (0.84-1.37)
Macrolides only	1.06 (0.69-1.61)	1.07 (0.66-1.73)	1.06 (0.44-2.58)
Second-generation cephalosporin plus macrolide	0.71 (0.52-0.96)	0.78 (0.56-1.10)	0.49 (0.23-1.04)
Non-pseudomonal third-generation cephalosporins plus macrolide	0.74 (0.60-0.92)	0.66 (0.51-0.86)	0.95 (0.67-1.34)
β-Lactam/β-lactamase inhibitors plus macrolide	1.77 (1.28-2.46)	1.61 (1.08-2.39)	2.24 (1.24-4.04)
Fluoroquinolones only	0.64 (0.43-0.94)	0.64 (0.36-1.14)	0.64 (0.38-1.09)
Aminoglycosides plus any other antimicrobial agent(s)	1.21 (1.02-1.43)	1.29 (1.02-1.65)	1.16 (0.92-1.46)
All other regimens	1.12 (0.99-1.27)	1.11 (0.94-1.31)	1.14 (0.96-1.36)

**The hazard ratios shown are the hazards of dying within 30 days of hospitalization among patients who received the antimicrobial regimen listed compared with patients who received a non-pseudomonal third-generation cephalosporin only (ie, ceftriaxone, cefotaxime, or ceftizoxime). All hazard ratios were adjusted for severity risk class, admission from community or LCF (for the overall model), previous antimicrobial use, region of enrollment, intensive care unit treatment on day 1 of hospitalization, performance of blood cultures within 24 hours of hospitalization, initiation of antimicrobial therapy within 8 hours of hospitalization, high-risk pneumonia etiology (gram-negative rod, staphylococcal species, or aspiration pneumonia), and change in antimicrobial therapy after 48 hours of hospitalization. CI indicates confidence interval.*

†The specific antimicrobial agents associated with these regimens were cefazolin for first-generation cephalosporin only; cefuroxime for second-generation cephalosporin only; ceftazidime for pseudomonal third-generation cephalosporin only; ceftriaxone, cefotaxime, or ceftizoxime for non-pseudomonal third-generation cephalosporins; ampicillin/sulbactam, ticarcillin/clavulanate, or piperacillin/tazobactam for β-lactam/β-lactamase inhibitors; erythromycin, clarithromycin, or azithromycin for macrolides; ciprofloxacin or ofloxacin for fluoroquinolones; and gentamicin, tobramycin, or amikacin for aminoglycosides.

‡LCF denotes admission from a long-term care facility. Admission from an LCF consisted of residence at a skilled nursing home, intermediate care facility, or LCF before hospitalization. All other patients were defined as community dwelling.

Two separate Cox models were performed in community-dwelling patients and patients admitted from an LCF (Table 4). The HRs for 30-day mortality were very similar in these 2 subsets and in the overall study population, with the exception of non-pseudomonal third-generation cephalosporins plus a macrolide. This initial regimen had an HR of 0.66 (95% CI, 0.51-0.86) for community-dwelling patients and an HR of 0.95 (95% CI, 0.67-1.34) for patients admitted from an LCF. Treatment with a second-generation cephalosporin plus a macrolide and a fluoroquinolone only was associated with a lower 30-day mortality in both models (not statistically significant). Treatment with a β-lactam/β-lactamase inhibitor plus a macrolide was independently associated with higher 30-day mortality in both models, while treatment with an aminoglycoside plus another agent was associated with a significantly higher (HR, 1.29; 95% CI, 1.02-1.65) 30-day mortality among community-dwelling patients and a nonsignificantly higher mortality among patients admitted from an LCF.

Separate Cox models of 30-day mortality performed for patients in severity risk classes II-III, IV, and V were consistent with the findings from the model performed in the total study population. Although few of the associations between initial antimicrobial regimen and mortality were statistically significant because of the relatively small number of patients within cells, the point estimates for the HRs derived in these risk class–specific models had a similar direction and magnitude of effect as those derived from the model in the total study population.

IMPACT OF THE DEFINITION OF INITIAL ANTIMICROBIAL THERAPY ON 30-DAY MORTALITY

Modifications in antimicrobial therapy were observed in 8117 patients (62.7%) after the first 8 hours of hospital admission, 5985 (46.2%) after the first 24 hours, and 4760 (36.8%) after the first 48 hours. From 8 to 48 hours after hospital admission, there was a 38% to 14% absolute decrease in the use of single-agent antimicrobial regimens and a 45% to 74% increase in the use of combination regimens.

Our findings of the association between initial antimicrobial regimen and 30-day mortality were insensitive to our definition of the initial regimen. A model that used an 8-hour post–hospital admission threshold to define initial antimicrobial therapy identified a significantly lower 30-day mortality among patients treated with a non-pseudomonal third-generation cephalosporin plus a macrolide (HR, 0.73; 95% CI, 0.55-0.97) and an independent association with higher 30-day mortality among patients treated with a β-lactam/β-lactamase inhibitor plus a macrolide (HR, 1.65; 95% CI, 1.04-2.61) and the "all other antimicrobial regimens" category (HR, 1.24; 95% CI, 1.07-1.43). The HRs for 30-day mortality associated with a second-generation cephalosporin plus a macrolide (HR, 0.77; 95% CI, 0.51-1.15), a fluoroquinolone only (HR, 0.81; 95% CI, 0.56-1.19), and an aminoglycoside plus any other agent (HR, 1.11; 95% CI, 0.90-1.38) were consistent with

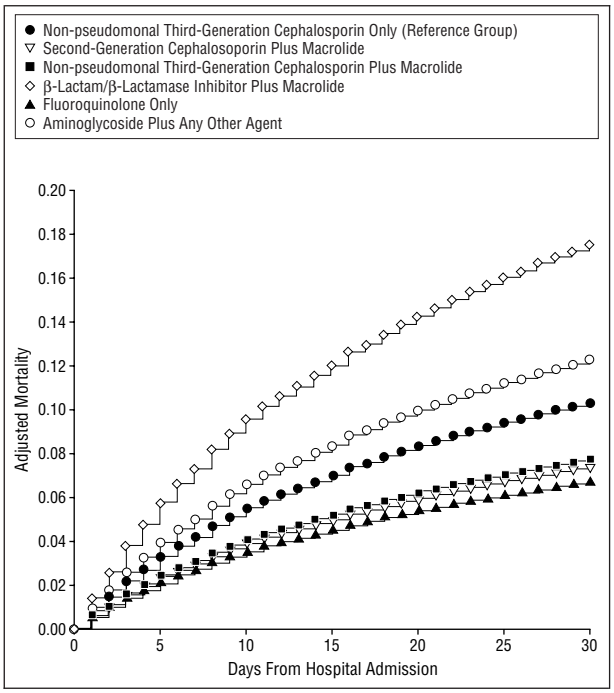
the corresponding HRs estimated when the 48-hour definition of initial therapy was used (although not statistically significant). The HRs observed with a 24-hour threshold used to define initial therapy were nearly identical to those estimated with the 8-hour definition (data not shown).

Our findings were also insensitive to the exclusion of the 171 patients who died within the first 2 days of hospitalization. As in the original model, 30-day mortality was significantly lower with initial treatment with a non-pseudomonal third-generation cephalosporin plus a macrolide (HR, 0.80; 95% CI, 0.64-0.99) and a fluoroquinolone only (HR, 0.64; 95% CI, 0.43-0.97) and significantly higher with a β-lactam/β-lactamase inhibitor plus a macrolide (HR, 1.81; 95% CI, 1.29-2.55) and an aminoglycoside plus another agent (HR, 1.27; 95% CI, 1.07-1.51). The HR for treatment with a second-generation cephalosporin plus a macrolide was consistent with the results of the original model (although not statistically significant), while the "all other antimicrobial regimens" category was associated with a significantly higher 30-day mortality in these analyses (data not shown).

ASSOCIATIONS BETWEEN INITIAL ANTIMICROBIAL REGIMENS AND OTHER MEDICAL OUTCOMES

Among the 11 432 patients discharged alive from the index hospitalization and not transferred to another acute care hospital, the median LOS (interquartile range) was 7 (5 to 10) days, ranging from 7 (5 to 9) days among community-dwelling patients to 8 (6 to 11) days among patients admitted from an LCF. The 30-day rehospitalization rate was 15.9% (95% CI, 15.3%-16.6%), ranging from 15.5% (95% CI, 14.8%-16.3%) in community-dwelling patients to 17.2% (95% CI, 15.8%-18.7%) in patients admitted from an LCF.

Initial therapy with a pseudomonal third-generation cephalosporin alone, a β-lactam/β-lactamase inhibitor alone, a β-lactam/β-lactamase inhibitor plus a macrolide, an aminoglycoside plus another agent, and the "other" category of antimicrobial agents were all independently associated with a longer LOS for the index hospitalization; no regimen was associated with a significantly shorter LOS. Initial therapy with an aminoglycoside plus another agent was associated with an increased rehospitalization rate within 30 days after discharge from the index hospitalization; no regimen was independently associated with decreased rehospitalization.



Adjusted mortality within 30 days of hospital admission for the 5 antimicrobial regimens with an independent association with 30-day mortality based on a Cox model for mortality in the overall study population (N = 12 945). The Cox model adjusted for severity risk class, admission from a community or a long-term care facility, previous antimicrobial use, region of enrollment, intensive care unit treatment on day 1 of hospitalization, performance of blood cultures within 24 hours of hospitalization, initiation of antimicrobial therapy within 8 hours of hospitalization, high-risk pneumonia etiology (gram-negative rod, staphylococcal species, or aspiration pneumonia), and change in antimicrobial therapy after 48 hours of hospitalization.

COMMENT

This national study of antimicrobial therapy for elderly patients hospitalized with pneumonia demonstrated that initial therapy with a non-pseudomonal third-generation cephalosporin plus a macrolide, a second-generation cephalosporin plus a macrolide, or a fluoroquinolone alone was associated with 26%, 29%, and 36% lower 30-day mortality, respectively. Yet, only 15.0% of all patients received 1 of these 3 initial regimens. An additional 7.9% were treated with a β-lactam/β-lactamase inhibitor plus a macrolide or an aminoglycoside plus another agent, which had mortality rates 77% and 21% higher than the reference group, respectively. These findings suggest that opportunities exist to dramatically improve the quality of care for hospitalized elderly patients with pneumonia by modifying existing initial antimicrobial prescribing practices.

The 3 initial antimicrobial regimens associated with a decreased mortality in the overall study population were also associated with a 22% to 36% lower mortality among community-dwelling patients and a 5% to 51% lower mortality among patients admitted from an LCF. In the 75.3% of the entire population who were community-dwelling before hospitalization, only initial therapy with a non-pseudomonal third-generation cephalosporin plus a macrolide was independently associated with a lower 30-day mortality despite trends toward lower mortality in community-dwelling patients treated with a second-generation cephalosporin plus a macrolide or a fluoroquinolone alone. The associations between initial antimicrobial therapy and mortality among LCF-dwelling patients were very similar to the associations in the overall study population, with the exception of non-pseudomonal third-generation cephalosporins plus macrolide. We believe the lack of statistically significant associations between initial antimicrobial regimens and 30-day mortality in these 2 subsets of patients was caused by smaller sample sizes reducing statistical power rather than systematic differences in these associations. Alternatively, initial antimicrobial therapy may not influence

short-term mortality among patients with severe disease or with a greater prevalence of comorbid illnesses such as those admitted from LCFs.[27,28] This alternative explanation is not supported by our findings that treatment with a second- or non-pseudomonal third-generation cephalosporin plus a macrolide was associated with an improved survival beginning within 2 to 3 days after hospital admission and persisting throughout the 30-day follow-up period.

OUR FINDINGS confirm our hypothesis that initial antimicrobial regimens with activity against the most common "typical" bacterial pathogens (eg, *S pneumoniae* and *H influenzae*) and "atypical" pathogens (eg, *Legionella* species, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Coxiella burnetti*) are associated with a decreased 30-day mortality. These findings are supported by recent studies of pneumonia etiology, which showed a high prevalence of "atypical" pathogens especially among hospitalized elderly.[9] The prevalence of atypical pneumonia resulting in hospitalization is as high as 44%, with *M pneumoniae* accounting for 33% and *C pneumoniae,* 9%.[9,29-31] Moreover, contrary to the historical belief that atypical pathogens are associated with a universally favorable prognosis, a recent study demonstrated that *C pneumoniae* was responsible for deadly outbreaks of pneumonia among nursing home residents.[32]

The finding of an association between use of fluoroquinolones alone (ie, ciprofloxacin or ofloxacin) and lower 30-day mortality is surprising given reported in vitro resistance of *S pneumoniae* to ciprofloxacin and ofloxacin, ranging from to 3% to 32%.[33-35] However, reported in vitro resistance of *S pneumoniae* to fluoroquinolones may be attributed to minimum inhibitory concentrations that overlap susceptibility break points and not to in vivo drug resistance.[36] Our findings may underestimate the actual survival benefit of this class of antimicrobial agents given that many of the newer fluoroquinolones (eg, levofloxacin, gatifloxacin, and gemifloxacin) have greater activity against *S pneumoniae* and *S aureus*, in addition to providing excellent coverage of the atypical bacterial pathogens. However, the potential survival advantage associated with this class of antimicrobial agents must be balanced with the problem of increased bacterial resistance that could result if fluoroquinolones are used widely to treat this common illness.[37] Although many difficult-to-treat pathogens, such as *S aureus* and *P aeruginosa*, were exquisitely sensitive to this class of agents when first introduced, within 5 years of introduction, drug resistance began to develop.[38-40] Therefore, judicious use of fluoroquinolones for treatment of pneumonia is strongly recommended.

Our finding of a 77% higher 30-day mortality among patients initially treated with a β-lactam/β-lactamase inhibitor plus a macrolide, an association that remained statistically significant among community- and LCF-dwelling patients, raises concerns for use of this regimen. Although one potential explanation of this finding is that patients treated with a β-lactam/β-lactamase inhibitor plus a macrolide differed from those treated with other initial antimicrobial regimens, patients treated with this initial regimen were not systematically more severely ill at the time of hospital arrival. In fact, with the exception of a slightly higher rate of ICU treatment within 24 hours of hospital arrival (6.3% vs 2.6% for all other regimens), these patients had significantly lower rates of coming from an LCF, less cerebrovascular disease, less altered mental status at hospital arrival, and a significantly greater proportion in the 2 lowest severity risk classes (II and III) at hospital arrival. Another possible explanation for this positive association with mortality is that this regimen was used more often for patients with a presumptive diagnosis of aspiration pneumonia. However, higher use of this regimen was not demonstrated among patients with an *ICD-9-CM* diagnosis code for aspiration pneumonia. Alternatively, the increased mortality associated with this initial regimen may be explained by deterioration of patients' conditions because of the β-lactam/β-lactamase inhibitors' lack of activity against penicillin-resistant *S pneumoniae* and ampicillin/sulbactam's limited activity against gram-negative Enterobacteriaceae (eg, *K pneumoniae*).[41,42] Moreover, it is possible that unrecognized pathogens with differing susceptibility patterns to second- or non-pseudomonal third-generation cephalosporins plus a macrolide compared with β-lactam/β-lactamase inhibitors plus a macrolide exist. Unfortunately, our data cannot be used to either support or refute the latter 2 hypotheses.

One puzzling question raised by this study is why initial therapy with β-lactam/β-lactamase inhibitors alone was not associated with an increased 30-day mortality, while the same class of agents in combination with a macrolide was independently associated with an increased 30-day mortality. A likely explanation for this observation is that patients treated with a β-lactam/β-lactamase inhibitor alone during the 48 hours after admission had an adequate clinical response to initial therapy, while patients with a suboptimal clinical response had a macrolide added to their initial therapy. Among the 1069 patients receiving a β-lactam/β-lactamase inhibitor alone at 24 hours, 132 (12.3%) had a second antimicrobial agent added between 24 and 48 hours after admission. Of the 132 patients who had a second agent added to initial therapy, the 30-day mortality was 30.3%, compared with 18.5% among those continuing to receive a β-lactam/β-lactamase inhibitor alone.

Overall, these findings are likely to be useful for the refinement of medical practice guidelines for the treatment of pneumonia. The recently released IDSA guidelines and ATS guidelines originally published in 1993 were developed with the use of consensus opinion of an expert panel without a large body of empirical evidence to support their clinical recommendations.[15,16] Both the IDSA and ATS guidelines recommend use of a second-generation cephalosporin alone, a non-pseudomonal third-generation cephalosporin alone, or agents from either of these drug classes plus a macrolide as appropriate initial therapy for non–severely ill patients. The IDSA guidelines also recommend use of fluoroquinolones with good *S pneumoniae* activity or azithromycin as appropriate initial therapy for non–severely ill hospitalized pa-

tients. The ATS guidelines recommend use of a β-lactam/β-lactamase inhibitor alone or in combination with a macrolide for this group of patients. Our findings support the recommendations in the IDSA and ATS guidelines for use of a second-generation cephalosporin plus a macrolide, or a non-pseudomonal third-generation cephalosporin plus a macrolide. Our findings also support the IDSA recommendations for use of a fluoroquinolone alone. In contrast, our findings do not support the use of a β-lactam/β-lactamase inhibitor alone or in combination with a macrolide as initial therapy. Firm conclusions about the use of azithromycin alone cannot be made on the basis of our results because of the small number of patients treated with this newer macrolide.

The present study has limitations that warrant further discussion. First, our study was observational in design, and therefore, antimicrobial treatment selection biases were possible. However, we controlled for potential confounding by comorbid disease and illness severity by using a widely validated pneumonia-specific severity model.[22] Second, antimicrobial route of administration, dose, and discontinuation date were not recorded. Consequently, it is possible that antimicrobial therapy was modified during the initial 48 hours of treatment after the patient received only a single dose of an initial agent. Patients treated in this manner would not have received the full benefit of their initial antimicrobial regimen. However, blood and sputum cultures generally require 48 hours for results to be reported, and if an organism is identified, therapy is generally streamlined, not broadened.[43] In addition, study findings on the association between initial antimicrobial regimen and 30-day mortality were insensitive to using either an 8- or a 24-hour posthospitalization threshold to define initial therapy. Third, our definition of initial antimicrobial therapy that consisted of all agents prescribed within 48 hours of hospital arrival does not reflect the influence of subsequent changes in therapy on patient outcomes. Nevertheless, only 36.8% of patients had such a change in therapy after 48 hours, and the results of analyses that considered such changes were nearly identical to the primary results of this study. Fourth, no microbiological culture or sensitivity data were available in this study. As a result, it was not possible to definitively correlate the associations between antimicrobial therapy, microbiological etiology, antimicrobial sensitivity, and patient outcomes. Fifth, "do not resuscitate" orders were not systematically recorded; patients with such orders may have received less aggressive antimicrobial treatment in accordance with patient and family wishes. Finally, because of the small number of patients having an ICU procedure coded as occurring within 1 day of hospital arrival, it was difficult to assess differences in medical outcomes with the 12 separate antimicrobial regimens among patients initially treated in an ICU.

In summary, this study of primarily community-dwelling patients demonstrated that initial antimicrobial regimens with a second-generation cephalosporin plus a macrolide, a non-pseudomonal third-generation cephalosporin plus a macrolide, or a fluoroquinolone alone were associated with lower 30-day mortality among all patients hospitalized with pneumonia. The observed higher mortality associated with 3 initial regimens coupled with the wide variation in the use of all initial antimicrobial regimens suggests that potential opportunities exist to reduce the mortality and thereby improve the quality of care for elderly patients with pneumonia. Although these findings are likely to influence medical practice guidelines designed to improve physician prescribing practices, future randomized controlled trials are warranted to confirm these findings before they are adopted in clinical practice.

Accepted for publication April 27, 1999.

Dr M. J. Fine was supported as a Robert Wood Johnson Generalist Physician Faculty Scholar. Dr J. M. Fine was supported in part by a grant from the Polly Annenberg Levee Charitable Trust, Washington, DC. The analyses on which this publication is based were performed under contract 500-96-P549, entitled "Utilization and Quality Control Peer Review Organization for the State of Connecticut," sponsored by the Health Care Financing Administration, Department of Health and Human Services, Washington.

The content of this publication does not necessarily reflect the views or policies of the US Department of Health and Human Services, nor does the 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 represented. This article is a direct result of the Health Care Quality Improvement Program initiated by the Health Care Financing Administration, which has encouraged identification of quality improvement projects derived from analysis of patterns of care, and therefore required no special funding on the part of this contractor. Ideas and contributions to the authors concerning experience in engaging with issues presented are welcomed.

Reprints: Michael J. Fine, MD, MSc, Department of Medicine, Montefiore Hospital, Room 824 East, 200 Lothrop St, Pittsburgh, PA 15261 (e-mail: mjf1+@pitt.edu).

REFERENCES

1. Garibaldi RA. Epidemiology of community-acquired respiratory tract infections in adults: incidence, etiology, and impact. *Am J Med.* 1985;78:32-37.
2. Adams PF, Marano MA. Current estimates from the National Health Interview Survey, 1994. *Vital Health Stat 10.* 1995;No. 199:95.
3. LaForce FM. Community-acquired lower respiratory tract infections: prevention and cost-control strategies. *Am J Med.* 1985;78:52-57.
4. Graves EJ, Gillum BS. *1994 Summary: National Hospital Discharge Survey.* Hyattsville, Md: National Center for Health Statistics; 1996. Advance Data From Vital and Health Statistics, No. 278.
5. Health Care Financing Administration. *1995 Data Compendium.* Baltimore, Md: US Dept of Health and Human Services, Health Care Financing Administration; 1995:75. HCFA No. 03364.
6. Marrie TJ, Durant H, Yates L. Community-acquired pneumonia requiring hospitalization: 5-year prospective study. *Rev Infect Dis.* 1989;11:586-599.
7. Fang GD, Fine MJ, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implication for therapy: a prospective multicenter study of 359 cases. *Medicine.* 1990;69:307-316.
8. Bates JH, Campbell GD, Barron AL, et al. Microbial etiology of acute pneumonia in hospitalized patients. *Chest.* 1992;101:1005-1012.
9. Marston BJ, Plouffe JF, File TM, et al, for the Community-Based Pneumonia Incidence Study Group. Incidence of community-acquired pneumonia requiring hospitalization: results of a population-based active surveillance study in Ohio. *Arch Intern Med.* 1997;157:1709-1718.

10. Gilbert K, Gleason PP, Singer DE, et al. Variations in antimicrobial use and costs in more than 2000 patients with community-acquired pneumonia. *Am J Med*. 1998;104:17-27.
11. Grasela TH, Welage LS, Walawaander CA, et al. A nationwide survey of antibiotic prescribing patterns and clinical outcomes in patients with bacterial pneumonia. *DICP*. 1990;24:1220-1225.
12. Kappstein I, Daschner FD. Antimicrobial usage in community-acquired pneumonia: results of a survey in 288 departments of internal medicine in German hospitals. *Infection*. 1991;19:301-304.
13. Guglielmo L, Leone R, Moretti U, Conforti A, Spolaor A, Velo G. Antibiotic prescribing patterns in Italian hospital inpatients with pneumonia, chronic obstructive pulmonary disease, and urinary tract infections. *Ann Pharmacother*. 1993; 27:18-22.
14. Niederman MS, Bass JB, Campbell GD, et al. American Thoracic Society guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis*. 1993;148:1418-1426.
15. Bartlett JG, Breiman RF, Mandell LA, File TM Jr. Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis*. 1998;26:811-838.
16. Fein AM, Niederman MS. Guidelines for the initial management of community-acquired pneumonia: savory recipe or cookbook for disaster? *Am J Respir Crit Care Med*. 1995;152:1149-1153.
17. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. *JAMA*. 1996;275:134-141.
18. Leroy O, Santre C, Beuscart C, et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. *Intensive Care Med*. 1995;21:24-31.
19. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA*. 1997;278:2080-2084.
20. *International Classification of Diseases, Ninth Revision, Clinical Modification*. Washington, DC: Public Health Service, US Dept of Health and Human Services; 1988.
21. Fine MJ, Singer DE, Hanusa BH, Lave JR, Kapoor WN. Validation of a pneumonia prognostic index using the Medisgroups comparative hospital database. *Am J Med*. 1993;94:153-159.
22. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify patients with community-acquired pneumonia at low risk for mortality and other adverse medical outcomes. *N Engl J Med*. 1997;336:243-250.
23. Fine MJ, Orloff JJ, Arisumi D, et al. Prognosis of patients hospitalized with community-acquired pneumonia. *Am J Med*. 1990;88:1N-8N.
24. Cantor AB. *Extending SAS Survival Analysis Techniques for Medical Research*. Cary, NC: SAS Institute Inc; 1997:208.
25. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons Inc; 1989.
26. *A Guide to State and Local Census Geography*. Washington, DC: Bureau of the Census Economic and Statistics Administration, US Dept of Commerce; 1993.
27. Torres A, Serra-Batlles J, Ferrer A, et al. Severe community-acquired pneumonia: epidemiology and prognostic factors. *Am Rev Respir Dis*. 1991;144:312-318.
28. Hook EW, Horton CA, Schaberg DR. Failure of intensive care unit support to influence mortality from pneumococcal bacteremia. *JAMA*. 1983;249:1055-1057.
29. Stephenson J. Studies suggest a darker side of "benign" microbes. *JAMA*. 1997; 278:2051-2052.
30. Taylor-Robinson D. Infections due to species of Mycoplasma and Ureaplasma: an update. *Clin Infect Dis*. 1996;23:671-684.
31. Hammerschlag MR. Antimicrobial susceptibility and therapy of infections caused by *Chlamydia pneumoniae*. *Antimicrob Agents Chemother*. 1994;38:1873-1878.
32. Troy CJ, Peeling RW, Ellis AG, et al. *Chlamydia pneumoniae* as a new source of infectious outbreaks in nursing homes [published correction appears in *JAMA*. 1997;278:118]. *JAMA*. 1997;277:1214-1218.
33. Plouffe JF, Breiman RF, Facklam RR, for the Franklin County Pneumonia Study Group. Bacteremia with *Streptococcus pneumoniae*: implications for therapy and prevention. *JAMA*. 1996;275:194-198.
34. Jones RN. Fluoroquinolone (Lomefloxacin) International Surveillance Trial: a report of 30 months of monitoring in vitro activity. *Am J Med*. 1992;92(suppl 4A): 52-57.
35. Goldstein FW, Acar JF. Epidemiology of quinolone resistance: Europe and North and South America. *Drugs*. 1995;49(suppl 2):36-42.
36. Hoban DJ, Jones RN. The North American component (the United States and Canada) of an international comparative MIC trial monitoring ofloxacin resistance. *Diagn Microbiol Infect Dis*. 1993;17:157-161.
37. Coronado VG, Edwards JR, Culver DH, Gaynes RP. Ciprofloxacin resistance among *Pseudomonas aeruginosa* and *Staphylococcus aureus* in the United States: National Nosocomial Infections Surveillance (NNIS) System. *Infect Control Hosp Epidemiol*. 1995;16:71-75.
38. Prosser BLT, Beskid G. Multicenter in vitro comparative study of fluoroquinolones against 25,129 gram-positive and gram-negative clinical isolates. *Diagn Microbiol Infect Dis*. 1995;21:33-45.
39. Acar JF, Goldstein FW. Trends in bacterial resistance to fluoroquinolones. *Clin Infect Dis*. 1997;24(suppl 1):S67-S73.
40. Butler JC, Hofmann J, Cetron MS, et al. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centers for Disease Control and Prevention's Pneumococcal Sentinel Surveillance System. *J Infect Dis*. 1996;174:986-993.
41. Johnson DM, Doern GV, Haugen TA, Hindler J, Washington JA, Jones RN. Comparative activity of twelve beta-lactam drugs tested against penicillin-resistant *Streptococcus pneumoniae* from five medical centers. *Diagn Microbiol Infect Dis*. 1996;25:137-141.
42. Doern GV, Brueggemann A, Holley HP Jr, Rauch AM. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: results of a 30-center national surveillance study. *Antimicrob Agents Chemother*. 1996;40:1208-1213.
43. Bartlett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med*. 1995; 333:1618-1624.