Guideline-Concordant Therapy and Reduced Mortality and Length of Stay in Adults With Community-Acquired Pneumonia

Playing by the Rules

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Background: Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide. Clinical practice guidelines for empirical CAP treatment, formulated jointly by the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS), remain controversial and inconsistently applied. We evaluated the impact of guideline-concordant therapy on in-hospital survival and other outcomes using a large database including adults treated for CAP in both community and tertiary care hospitals.

Methods: We evaluated the association between in-hospital survival and guideline-concordant therapy using logistic regression models. Time until discharge from hospital and discontinuation of parenteral therapy were evaluated using survival analysis.

Results: Of 54 619 non–intensive care unit inpatients with CAP hospitalized at 113 community hospitals and tertiary care centers, 35 477 (65%) received initial guideline-concordant therapy. After adjustment for severity of illness and other confounders, guideline-concordant therapy was associated with decreased in-hospital mortality (odds ratio [OR], 0.70; 95% confidence interval [CI], 0.63-0.77), sepsis (OR, 0.83; 95% CI, 0.72-0.96), and renal failure (OR, 0.79; 95% CI, 0.67-0.94), and reduced both length of stay and duration of parenteral therapy by approximately 0.6 days ($P<.001$ for both comparisons). These findings were robust with alternate definitions of "concordance" and were linked to treatment with fluoroquinolone or macrolide agents.

Conclusions: Guideline-concordant therapy for CAP is associated with improved health outcomes and diminished resource use in adults. The mechanisms underlying this finding remain speculative and warrant further study, but our findings nonetheless support compliance with CAP clinical practice guidelines as a benchmark of quality of care.

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COMMUNITY-ACQUIRED PNEUMONIA (CAP) is one of the most common infectious diseases requiring clinician care and affects approximately 1% of adults annually, with 40% to 60% of patients admitted to a hospital[1,2] at a cost of approximately $6000 per admission.[3,4] Pneumonia and influenza are among the most common causes of death in North America.[5,6] Both preventing pneumonia and improving outcomes in individuals with CAP would be associated with tremendous gains in population health and reductions in disease-related costs.

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The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) have released guidelines for the antibiotic treatment of patients with CAP since 1998 and 1993, respectively, including guidelines for both individuals treated in the community and those treated as hospital inpatients.[7] These guidelines, most recently updated in 2007 through a consensus effort by both societies, focus on empirical therapy for individuals with a clinical diagnosis of pneumonia, as even the most aggressive laboratory workup will fail to identify an etiologic pathogen in 30% to 50% of cases.[8-11]

See also pages 1462 and 1515

As has been the case with clinical practice guidelines generally, practice guidelines for CAP have been controversial and are not always followed by treating physicians.[12] While physicians may tailor antimicrobial therapy to address the risk profile, epidemiologic profile, or history of antimicrobial tolerance of a particular patient, the benefits of such a nuanced approach to management remain unclear. Several groups have evaluated the possible clinical benefits associated with adherence to clinical practice guidelines for CAP,[13-16] but some of these studies have been limited by restriction to university-affiliated teaching hospitals, and all have studied relatively modest numbers of patients in circumscribed single geographic regions.

Tenet Healthcare is a large, geographically diverse hospital network providing care in the United States. A Tenet quality-improvement initiative resulted in extensive collection of data on initial antibiotic choice in individuals admitted to 113 Tenet facilities (108 community hospitals and 5 academic tertiary care centers) between 1999 and 2003. Our primary objective was to use these data to assess whether the use of antimicrobial combinations advocated in the 2007 ATS/IDSA guidelines[7] were indeed associated with improvement in patient survival and other clinical outcomes of interest in individuals admitted to non–intensive care settings. We also evaluated such indices of clinical efficiency as time to initiation of oral antimicrobial therapy and length of stay. Secondary objectives included evaluation of adherence to 2001 ATS guidelines (current at the time cohort data were collected)[17] and evaluation of the impact of individual antimicrobial classes on outcomes.

METHODS

STUDY POPULATION

Data collection methods and the demographics of the study population have been described elsewhere.[18] From 1999 to 2003, data were collected from 113 teaching and community hospitals across 15 states, for individuals 18 years or older and diagnosed as having CAP.[18] Diagnoses were captured by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 480.0 to 487.0 after admission to these acute care hospitals. Most hospitals were located in California, Texas, Florida, Louisiana, and elsewhere in the southeastern United States.

Data collection was primarily performed by trained nurse case managers using laptop computers that integrated data input with the ongoing care of their patients. Training of nurses was standardized and overseen by a full-time corporate education director, and collection methods and definitions were standardized across hospitals by the posting of guidelines for clinical abstraction on the Tenet Healthcare's internal Web site. At the end of each month, primary diagnoses of CAP were validated through reconciliation with discharge *ICD-9-CM* codes, which ensured accurate accounting of cases as well correct classification of primary CAP diagnoses.

As these data were collected as part of a systemwide quality-improvement initiative, data sufficient for calculation of Pneumonia Severity Index (PSI) scores were collected,[19] as was vaccination status at the time of admission (used to ensure that individuals received influenza and/or pneumococcal vaccination prior to discharge if appropriate). Subject demographics, medical history, and smoking status were also available. Available health outcomes included mortality, length of stay, duration of parenteral therapy, and such intermediate health outcomes as renal failure, respiratory failure, and development of a "sepsis syndrome" while hospitalized (with these latter outcomes recorded by case managers if the patient had received such a diagnosis from the treating team).

TREATMENT DEFINITIONS

Available data included records of initial antibiotic therapy (up to 3 agents) administered on admission to a hospital (including agents administered to admitted patients still in the emergency department). In our principal analyses, we considered treatment to be concordant with IDSA/ATS guidelines[7] if guideline-recommended regimens for individuals admitted to non–intensive care areas were included in recorded antibiotics (eTable; http://www.archinternmed.com). During the time of data collection (1999-2003), physicians may have been guided by an earlier set of guidelines released in 2001 by the ATS[17]; as such, we also performed a series of sensitivity analyses in which we assessed the impact of therapy concordant with the 2001 ATS guidelines on clinical outcome, as well as the impact of redefining as "nonconcordant" therapeutic regimens that contained recommended agents but also contained other additional agents. We evaluated heterogeneity of effects of concordance, variously defined, on outcome using the meta-analytic Q statistic.[20] Data on route of administration (for drugs that might be given either orally or parenterally) were not available, though the date of transition to an exclusively oral antimicrobial regimen was recorded. Microbiological data and information regarding any follow-up treatment were not available for this analysis.

STATISTICAL ANALYSIS

Characteristics of individuals who received recommended treatment according to 2007 recommendations and individuals who did not receive such treatment were compared using χ^2 tests for categorical variables and unpaired t tests for continuous variables. Univariable odds ratios (ORs) for adverse outcomes in individuals treated with recommended treatment regimens were estimated using logistic regression models; these models were created for the population as a whole, and stratum-specific estimates were also evaluated for each PSI score level. Multivariable models that adjusted for potential confounding factors identified based on an association with treatment status in univariable analyses were created by adding covariates to logistic models in a stepwise fashion and retaining all covariates for which $P \leq .20$. Effect modification was evaluated through creation of multiplicative interaction terms for combinations of covariates (eg, chronic obstructive pulmonary disease and vaccination history) for which there was an a priori expectation of nonindependence. Standard errors were adjusted for clustering in antibiotic use and outcomes by hospital.[21]

We also performed "time-to-event" analyses for 30-day in-hospital survival, for length of hospital stay, and for time from admission to initiation of oral antibiotic therapy through construction of Kaplan-Meier curves, with differences between groups assessed using the log-rank test.[22] We calculated adjusted hazard ratios using multivariable Cox proportional hazards models with confounders evaluated as previously described for logistic regression models; the assumption of proportionality was assessed graphically through the assessment of log-log plots.[22] All statistical analyses were performed using Stata/SE version 9.2 statistical software (StataCorp, College Station, Texas). The study was approved by the research ethics board of the Hospital for Sick Children, Toronto, Ontario, Canada.

Table 1. Characteristics of Individuals Admitted to a Non–Intensive Care Setting for Management of Community-Acquired Pneumonia According to Concordance of Treatment With the 2007 IDSA/ATS Guideline[7a]

Characteristic	No. (%) Guideline Concordant Therapy (n=35 477)	No. (%) Guideline Non-Concordant Therapy (n=19 142)	*P* Value
Age, mean (SD), y	70.8 (17.5)	71.2 (18.0)	.03
Female	19 632 (55.3)	10 252 (53.6)	<.001
PSI level IV or V	27 478 (77.5)	12 627 (66.0)	.03
Current smoker	5344 (15.1)	1828 (9.55)	<.001
Medical history			
Cancer	4986 (14.1)	2815 (14.7)	.04
Chronic obstructive pulmonary disease	10 720 (30.2)	5249 (27.4)	<.001
Congestive heart failure	7534 (21.2)	3882 (20.3)	.93
Diabetes	8566 (24.1)	4380 (22.9)	<.001
Liver disease	726 (2.05)	406 (2.12)	.17
Renal failure	694 (1.96)	446 (2.33)	.006
Stroke	4617 (13.0)	2693 (14.0)	<.001
HIV infection or AIDS	1570 (4.43)	1043 (5.45)	<.001
Current influenza vaccination[b]	4206 (11.90)	1807 (9.45)	<.001
Pneumococcal vaccination[c]	4651 (13.1)	1977 (10.3)	<.001
Hospital region			
Texas	3131 (8.83)	1013 (5.29)	<.001
Florida	7787 (21.9)	4829 (25.2)	<.001

Abbreviations: HIV, human immunodeficiency virus; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; PSI, Pneumonia Severity Index.[19]

[a] Data are presented as number (percentage) unless otherwise specified.

[b] Individuals were considered vaccinated against influenza if hospitalized between November and March and received the current year's influenza vaccine or if hospitalized between April and October and received the prior year's influenza vaccine.[23]

[c] Record of receipt of 23-valent pneumococcal polysaccharide vaccine as described by Fisman et al.[18]

RESULTS

The database included records of 62 918 single admissions of adult individuals (age ≥18 years). Of these, 8299 admissions were to the intensive care unit and were thus omitted, leaving 54 619 records for analysis. The majority (65%) of these individuals received antimicrobial therapy that was concordant with 2007 IDSA/ATS guidelines on hospital admission.[7] The characteristics of the study population according to treatment status are presented in **Table 1**. Individuals receiving guideline-concordant therapy were younger, more likely to be female, had greater severity of illness on admission, and were more likely to have a history of current influenza and pneumococcal vaccination than individuals receiving nonconcordant therapy. We also identified significant differences in the presence of medical comorbidities in individuals according to concordant treatment status; a degree of regional variation in compliance was also identified with concordant therapy observed more commonly in Texas hospitals and less commonly in Florida hospitals than in other geographic locales.

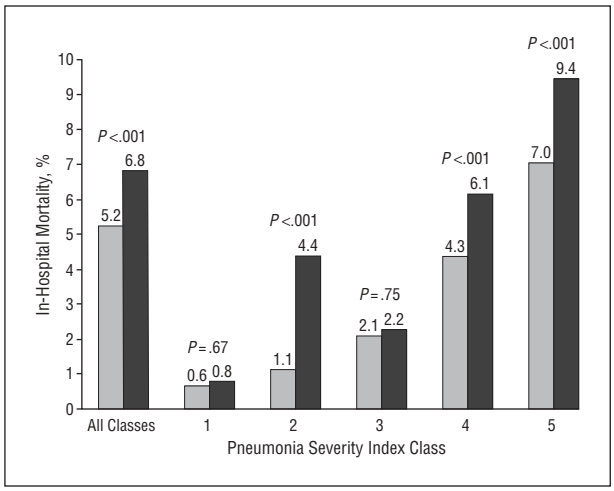

Figure 1. Crude in-hospital mortality and guideline-concordant therapy among individuals admitted for community-acquired pneumonia, stratified by pneumonia severity index. Mortality among those whose treatment is concordant with 2007 Infectious Diseases Society of America/American Thoracic Society guidelines[7] (gray bars) is lower than among those whose treatment is discordant with these guidelines (black bars) at any level of pneumonia severity. Significant differences in likelihood of survival according to concordance status (by χ^2 test) are seen in the population as a whole and in groups where the Pneumonia Severity Index[19] is 2, 4, or 5. Numbers immediately above bars denote percentage of mortality.

In-hospital mortality occurred in 3149 subjects (5.8%). In univariable analyses, individuals receiving therapy concordant with IDSA/ATS guidelines[7] were significantly less likely to die in the hospital than those receiving nonconcordant therapy (crude OR, 0.76; 95% confidence interval [CI], 0.70-0.81). In stratified analyses, a decreased risk of mortality was seen for individuals receiving concordant therapy at all PSI levels, although this effect was not statistically significant in individuals with PSI scores of 1 or 3, and effects exhibited significant heterogeneity (*P* value for multiplicative interaction term, <.001) (**Figure 1**).

The association between receipt of concordant therapy and decreased in-hospital mortality was strengthened after controlling for potential confounding factors in multivariable models (adjusted OR, 0.70; 95% CI, 0.63-0.77) (**Table 2**). Significant protection against mortality was seen in sensitivity analyses using alternate definitions of "concordant therapy," including concordance defined using the 2001 guidelines (adjusted OR, 0.66; 95% CI, 0.60 -73) and reclassification of individuals who received excess antimicrobial agents as having received nonconcordant therapy (adjusted OR, 0.54; 95% CI, 0.47-0.61) (*P*<.001 for all definitions). There was no heterogeneity between estimates derived using the concordance with ATS/IDSA guidelines[7] rather than the 2001 ATS guidelines[17] as the exposure of interest (*Q* statistic, 0.68 on 1 *df*; *P*=.41). However, the effect of concordance was significantly strengthened when individuals receiving excess antimicrobial agents were classified as nonconcordant (*Q* statistic, 9.56 on 1 *df*; *P*=.002).

We also performed univariable and multivariable logistic regression analyses evaluating the association between concordant therapy and intermediate adverse outcomes, including respiratory failure, sepsis syndrome, and renal failure in the hospital. We found no evidence of that guideline-concordant therapy protects against respiratory fail-

Table 2. Effect of Guideline-Concordant Therapy on Mortality and Other Adverse Outcomes in Individuals Hospitalized With Community-Acquired Pneumonia in Multivariable Logistic Regression Models

Characteristic	Odds Ratio (95% Confidence Interval)			
	Death	Respiratory Failure	Sepsis Syndrome	Renal Failure
Received guideline-concordant therapy	0.70 (0.63-0.77)	0.97 (0.85-1.10)	0.83 (0.72-0.96)	0.79 (0.67-0.94)
Smoker	. . .[a]	1.22 (0.97-1.54)	0.82 (0.67-1.00)	0.74 (0.58-0.94)
PSI score	1.41 (1.33-1.49)	1.25 (1.17-1.35)	1.37 (1.28-1.47)	1.33 (1.21-1.47)
HIV infection or AIDS	2.05 (1.76-2.38)	1.58 (1.27-1.96)	1.77 (1.38-2.26)	1.39 (1.07-1.82)
Pneumococcal vaccination[b]	0.53 (0.42-0.68)	0.72 (0.58-0.88)	0.79 (0.62-1.01)	0.48 (0.38-0.61)
Influenza vaccination[c]	0.80 (0.66-0.97)	. . .[a]	0.73 (0.50-1.07)	. . .[a]
Chronic obstructive pulmonary disease	. . .[a]	1.48 (1.30-1.67)	0.77 (0.66-0.89)	0.89 (0.78-1.01)
Diabetes	. . .[a]	1.16 (1.05-1.27)	1.47 (1.29-1.67)	1.88 (1.68-2.11)
Hospitalized in Florida	. . .[a]	0.68 (0.48-0.94)	. . .[a]	. . .[a]
Hospitalized in Texas	1.18 (0.97-1.42)	. . .[a]	1.80 (1.06-3.09)	. . .[a]

Abbreviations: HIV, human immunodeficiency virus; PSI, Pneumonia Severity Index on a 1 to 5 scale.[19]
[a] Missing odds ratio estimates indicate that the covariate was not retained in the final multivariable model owing to $P > .20$.
[b] Record of receipt of 23-valent pneumococcal polysaccharide vaccine as described by Fisman et al.[18]
[c] Individuals were considered vaccinated against influenza if hospitalized between November and March and received the current year's influenza vaccine or if hospitalized between April and October and received the prior year's influenza vaccine.[23]

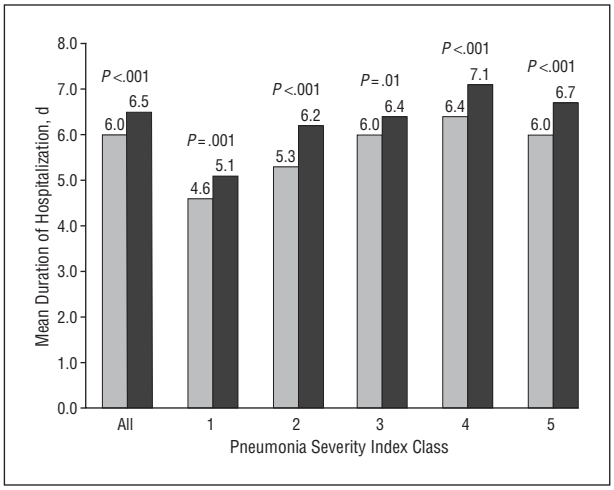

Figure 2. Mean length of hospital stay and guideline-concordant therapy among individuals admitted for community-acquired pneumonia, stratified by the Pneumonia Severity Index.[19] Mean length of stay among those whose treatment is concordant with 2007 Infectious Diseases Society of America/American Thoracic Society guidelines[7] (gray bars) is shorter than among those whose treatment is discordant with these guidelines (black bars) at any level of pneumonia severity, as is median length of stay (not shown). Significant reductions in length of stay according to concordance status (by log-rank test) are seen in the population as a whole and all Pneumonia Severity Index classes.[19] Numbers immediately above bars denote mean length of stay.

Table 3. Effects of Guideline-Concordant Therapy on Rates of Live Discharge and Change to Oral Antibiotics in Multivariable Cox Proportional Hazards Models

Characteristic	Hazard Ratio (95% Confidence Interval)	
	Live Discharge From Hospital	Change to Oral Antibiotic Regimen
Received guideline-concordant therapy	1.12 (1.10-1.14)	1.28 (1.23-1.33)
Smoker	1.10 (1.08-1.13)	1.07 (1.02-1.11)
PSI Score	0.92 (0.91-0.92)	0.98 (0.97-0.99)
HIV infection or AIDS	0.81 (0.78-0.85)	0.94 (0.88-1.01)
Pneumococcal vaccination[a]	1.03 (0.99-1.07)	1.21 (1.14-1.29)
Influenza vaccination[b]	1.09 (1.05-1.13)	1.07 (1.00-1.15)
Chronic obstructive pulmonary disease	0.91 (0.89-0.93)	. . .[c]
Diabetes	0.91 (0.90-0.93)	. . .[c]
Hospitalized in Florida	0.93 (0.91-0.95)	1.16 (1.11-1.21)
Hospitalized in Texas	0.90 (0.87-0.93)	. . .[c]

Abbreviations: HIV, human immunodeficiency virus; PSI, Pneumonia Severity Index on a 1 to 5 scale.[19]
[a] Record of receipt of 23-valent pneumococcal polysaccharide vaccine as described by Fisman et al.[18]
[b] Individuals were considered vaccinated against influenza if hospitalized between November and March and received the current year's influenza vaccine or if hospitalized between April and October and received the prior year's influenza vaccine.[23]
[c] Missing hazard ratio estimates indicate that the covariate was not retained in the final multivariable model owing to $P > .20$. Proportionality of hazards were affirmed via log-log plots.[21]

ure, but concordant therapy was associated with diminished risk of sepsis syndrome and renal failure (Table 2). We found no significant change in the direction or magnitude of these effects in sensitivity analyses using alternate definitions of concordant therapy (data not shown).

Guideline-concordant therapy was also associated with a mean reduction in length of stay of 0.66 days ($P < .001$ by log-rank test); significant decreases in length of stay were observed at all PSI levels (**Figure 2**). In multivariable Cox proportional hazards models, individuals who received guideline-concordant therapy were discharged more rapidly than those not receiving such therapy (adjusted hazard ratio, 1.12, 95% CI, 1.10-1.14) (**Table 3**). Similarly, individuals receiving guideline-concordant therapy were transitioned from parenteral to oral antibiotics, on average, 0.57 days earlier than those receiving nonconcordant therapy (**Figure 3**) ($P < .001$ by log-rank test). In a Cox proportional hazards model adjusting for severity of illness and other potential confounders, the rate of transition to oral antibiotics was 30% more rapid in individuals receiving guideline concordant therapy (adjusted hazard ratio, 1.28; 95% CI, 1.24-1.33). As in logistic regression models, no qualitative difference was seen in observed effects in sensitivity analyses using alternate definitions of guideline-concordant therapy.

We performed a series of exploratory univariable analyses, evaluating the impact of inclusion of individual drug classes on in-hospital survival, adjusting for other (**Figure 4**). A significant reduction in risk of death was seen in individuals whose initial antimicrobial treatment regimens included second- or third-generation cephalosporins, macrolides, and fluoroquinolones compared with other possible antimicrobials. As we unexpectedly identified increased risks of mortality in individuals whose initial therapeutic regimens included such broad-spectrum agents and classes as cefepime, carbapenems, and piperacillin-tazobactam, as well as vancomycin, we evaluated whether individuals receiving these agents might be less likely than others to receive agents providing coverage against *Legionella* species (ie, macrolides and/or fluoroquinolones). We found that receipt of agents with activity against *Legionella* species was less likely, even after adjusting for PSI score, in those who received cefepime (OR, 0.26; 95% CI, 0.23-0.29), carbapenems (OR, 0.32; 95% CI, 0.26-0.38), piperacillin-tazobactam (OR, 0.33; 95% CI, 0.30-0.36), and vancomycin (OR, 0.43; 95% CI, 0.39-0.47).

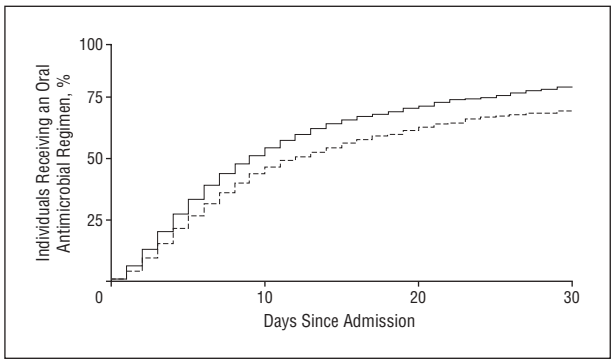

Figure 3. Rate of transition to oral antibiotics and guideline-concordant therapy among individuals admitted for community-acquired pneumonia. The solid black curve represents probability of having transitioned to oral antibiotic therapy by day of hospital stay among those receiving antibiotic treatment concordant with the 2007 Infectious Diseases Society of America/American Thoracic Society treatment guidelines[7]; the dashed curve represents probability among those not receiving guideline concordant therapy. Concordant therapy was associated with a significantly increased rate of transition to oral therapy ($P<.001$ by log-rank test).

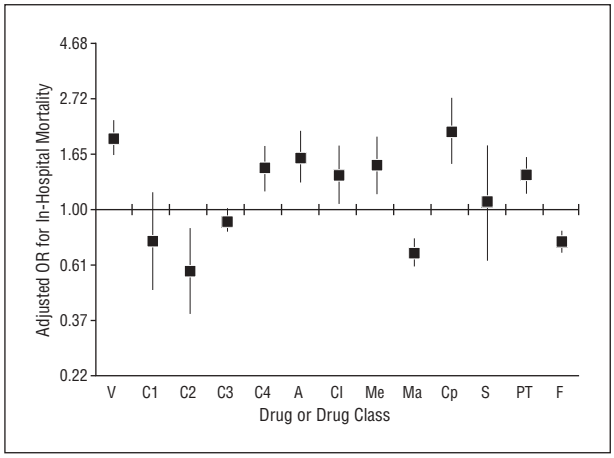

Figure 4. Adjusted odds ratios (ORs) and 95% confidence intervals of death associated with inclusion of individual antimicrobial agents or classes in treatment for community-acquired pneumonia. Inclusion of second- or third-generation cephalosporins (C2 and C3), macrolides (Ma), and fluoroquinolones (F) in treatment regimens is associated with a significant reduction in risk of death. Increased risk of mortality is associated with use of several other classes, including vancomycin (V), aminoglycosides (A), cefepime (C4), clindamycin (Cl), metronidazole (Me), carbapenems (Cp), and piperacillin-tazobactam (PT). Other drugs evaluated include first-generation cephalosporins (C1) and sulfa drugs (S). All estimates generated using logistic regression models that controlled for Pneumonia Severity Index level, smoking status, prior pneumococcal vaccination status, and sex; results are plotted on a log scale for comparability of ORs greater than 1 and less than 1.

COMMENT

Clinical practice guidelines for medicine and related professions have proliferated since the early 1990s,[24] with proponents arguing that guidelines reduce variability in clinical care, strengthen the evidential basis of practice, and limit the inappropriate use of novel drugs and devices.[25] Compliance with practice guidelines has been variable with physicians describing other influences (especially the practice patterns of local opinion leaders) as far more determinative of practice patterns.[25] Clinical practice guidelines for CAP have been subject to criticisms qualitatively similar to those leveled at other guidelines,[26] but these guidelines have also been criticized by some as insufficiently attuned to the dynamic epidemiology of antimicrobial resistance as it might relate to antibiotic choice,[27] and evidence suggests that more experienced clinicians are actually less likely to adhere to CAP clinical practice guidelines.[28]

In this study, however, we found that individuals with CAP severe enough to warrant hospitalization, but not associated with primary admission to an intensive care setting, were significantly more likely to survive hospitalization, avoid complications of pneumonia including sepsis syndrome and renal failure, and have shortened hospital stays and time to transition to oral antibiotic regimens when they received antimicrobial regimens concordant with either the 2001 or 2007 IDSA/ATS consensus guidelines on the management of CAP. A particular strength of this study is the inclusion of patients hospitalized in both community hospitals and academic tertiary care settings in the study population.

A primary concern in any observational assessment of therapeutic efficacy must be the fundamental differences in underlying disease severity in groups receiving different treatments (so-called confounding by indication).[29] For example, the receipt of such antimicrobials as carbapenem agents or cefepime might reflect clinician concern over a sicker patient or a patient more likely to have an antibiotic-resistant organism as the infecting pathogen due to underlying comorbidities (though cefepime has, for instance, been associated with increased mortality when compared with other β-lactam agents in randomized trials[30]). However, our findings persisted and were actually strengthened when we controlled for severity of illness with the well-validated and highly reproducible PSI,[19] suggesting that differences may have indeed been due to treatment assignment rather than underlying patient physiologic conditions. Furthermore, our findings are qualitatively consistent with those of other groups who have evaluated this issue in smaller and more homogeneous populations[15,16,31] and using other study designs[32]; our mix of patients from geographically diverse urban, rural, com-

munity, and teaching hospitals suggests that these effects may have substantial external validity.

Limited evidence to support the primary contribution of antibiotic choice to the effect we observed is derived from our assessment of the effect of inclusion of individual agents or classes in therapeutic regimens: inclusion of a respiratory fluoroquinolone or macrolide agent was associated with a PSI-adjusted reduction in mortality of 20% to 40%, relative to regimens that excluded these classes. This effect is consistent with prevention of mortality and other adverse outcomes due to the treatment of so-called atypical pneumonic pathogens, including *Mycoplasma* species, *Chlamydia pneumoniae*, and *Legionella* species.[33] Furthermore, macrolides have established immunomodulatory effects,[34,35] which could contribute to the observed decrease in mortality in pneumonia patients by reducing airway inflammation.

Of these pathogens, we suspect that *Legionella* species would be most likely to explain the observed effects. *Legionella* species have historically been linked to outbreaks of severe respiratory disease, and there has previously been some controversy as to whether the empirical treatment of legionellosis in individuals hospitalized with CAP not requiring intensive care has received sufficient emphasis.[36] The availability of highly sensitive urine immune fluorescence testing for urinary *Legionella* antigens has revealed *Legionella* species as likely etiological pathogens in up to 4% of individuals seen in outpatient settings,[37] and some investigators suggest that the prevalence of legionellosis among those hospitalized in non–intensive care settings is as high as 6% to 14%.[8,38] The inverse relationship between likelihood of receipt of antimicrobial agents active against atypical pneumonic pathogens and likelihood of receipt of antimicrobials with expanded spectrum activity against important antibiotic-resistant organisms (eg, vancomycin, cefepime, or carbapenems) may indicate that some knowledgeable clinicians focus on emerging risks of antibiotic-resistant pathogens to the detriment of providing coverage for atypical microorganisms.

Although we found the benefits of therapy concordant with IDSA/ATS guidelines to be robust after adjusting for multiple covariates and testing with sensitivity analyses, there are limitations to any observational study that are difficult to overcome without a randomized controlled trial. In the absence of such a trial, analyses such as ours will always be vulnerable to the criticism that individuals receiving guideline-concordant therapy (or their health care providers) are fundamentally different from those receiving discordant therapy in ways that are not captured in our analyses (in other words the results are subject to uncontrolled residual confounding).[39] We do not dismiss this possibility, and indeed it seems plausible to us that individuals receiving guideline-concordant therapy received higher quality care, across multiple dimensions (eg, superior nursing care, ancillary hospital services including early mobilization, care in a more "error-proof" medical system, care in a hospital environment with better infection control practices), compared with those receiving discordant therapy. If this is the case, guideline-concordant therapy would still have value as an important index of high-quality care, whether or not antibiotic choice is actually the causal mechanism underlying the effects we observe. It is also important to note that our database is limited by an absence of data on the microbial cause of pneumonia.[8,38] Incorrect coding of pneumonia diagnosis, which may have resulted in inclusion of individuals without true pneumonia and exclusion of individuals with true pneumonia from our cohort, has been previously noted in database studies of pneumonia.[40] As Grimes and Schulz[41] state, such "non-differential misclassification [ie, noise in the system] tends to obscure real differences," and in the present study, it is likely to result in a bias toward the null.

With regard to the possibility that the effects reported herein are confounded by unobserved factors, it is important to acknowledge the fact that the effects we observed are reasonably large (eg, 20%-30% relative reduction in mortality). As Bross[42] pointed out in a classic article on epidemiological confounding, attribution of strong effects to residual confounding by unmeasured covariates is equivalent to postulating the presence of an important, missed, confounding exposure that has an independent effect on outcome that is even greater in magnitude than the confounded effect. Large confounders are less likely to be overlooked than weaker confounding factors in statistical analyses.[42]

In conclusion, in a large cohort of adults treated for CAP following admission to non–intensive care settings in both community and tertiary care settings, therapy concordant with current IDSA/ATS guidelines was associated with markedly improved health outcomes and reduced resource consumption. Although clinical practice guidelines should never obviate the need to consider carefully the peculiarities of a given clinical scenario, our findings provide an additional support for such guidelines as a high-quality, default path of care for adults sufficiently ill to require non–intensive care unit hospitalization. The widespread availability of administrative databases containing data similar to those contained in our data set should provide other investigators with abundant opportunities to affirm or challenge the findings reported herein. In the interim we argue that compliance with clinical practice guidelines for CAP should be strongly encouraged by those actively engaged in treating this common and still-deadly disease.

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Additional Information: The eTable is available at http://www.archinternmed.com. We dedicate this work to the memory of the late Elias Abrutyn, MD, a valued collaborator, researcher, and teacher.
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