

Timing of Antibiotic Administration and Outcomes for Medicare Patients Hospitalized With Community-Acquired Pneumonia

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Background: Pneumonia accounts for more than 600 000 Medicare hospitalizations yearly. Guidelines have recommended antibiotic treatment within 8 hours of arrival at the hospital.

Methods: We performed a retrospective study using medical records from a national random sample of 18 209 Medicare patients older than 65 years who were hospitalized with community-acquired pneumonia from July 1998 through March 1999. Outcomes were severity-adjusted mortality, readmission within 30 days of discharge, and length of stay (LOS).

Results: Among 13 771 (75.6%) patients who had not received outpatient antibiotic agents, antibiotic administration within 4 hours of arrival at the hospital was associated with reduced in-hospital mortality (6.8% vs 7.4%; adjusted odds ratio [AOR], 0.85; 95% confidence interval [CI], 0.74-0.98), mortality within 30 days of admis-

sion (11.6% vs 12.7%; AOR, 0.85; 95% CI, 0.76-0.95), and LOS exceeding the 5-day median (42.1% vs 45.1%; AOR, 0.90; 95% CI, 0.83-0.96). Mean LOS was 0.4 days shorter with antibiotic administration within 4 hours than with later administration. Timing was not associated with readmission. Antibiotic administration within 4 hours of arrival was documented for 60.9% of all patients and for more than 50% of patients regardless of hospital characteristics.

Conclusions: Antibiotic administration within 4 hours of arrival was associated with decreased mortality and LOS among a random sample of older inpatients with community-acquired pneumonia who had not received antibiotics as outpatients. Administration within 4 hours can prevent deaths in the Medicare population, offers cost savings for hospitals, and is feasible for most inpatients.

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PNEUMONIA IS THE SECOND leading reason for hospitalization of Medicare beneficiaries, accounting for over 600 000 fee-for-service admissions each year,¹ and the fifth leading cause of death among Americans older than 65 years.² Timely administration of antibiotic agents to hospitalized patients with pneumonia has been associated with improved survival.³⁻⁵ Until recently, both the Infectious Diseases Society of America⁶ (IDSA) and the American Thoracic Society⁷ (ATS) recommended that the initial dose of an antibiotic be administered to patients with community-acquired pneumonia (CAP) within 8 hours of arrival at the hospital. This recommendation is based largely on the work of Meehan et al,⁵ who examined Medicare CAP hospitalizations that occurred in 1994 and 1995 and found a statistically significant association between improved survival and antibiotic administration within 8 hours. Their primary analysis included patients

regardless of prehospital treatment, but they briefly describe an even stronger association when patients who had received prehospital antibiotics were excluded.

As part of its National Pneumonia Project,⁸ the Centers for Medicare & Medicaid Services (CMS) collected medical record data from over 39 000 pneumonia hospitalizations that occurred during 1998 and 1999. We analyzed these data to explore further the associations between the timing of initial antibiotic administration and mortality, length of stay (LOS), and readmission. In particular, we sought to determine whether administration within periods less than 8 hours after arrival was associated with significantly improved outcomes among patients who had not been treated prior to arrival at the hospital. Such an association in this subpopulation would be clinically important because about three quarters of hospitalized Medicare patients with pneumonia have not received prehospital antibiotic treatment.

SUBJECTS AND SAMPLE SELECTION

The National Pneumonia Project used Medicare fee-for-service hospital claims to identify potential pneumonia hospitalizations. A case was defined by a claim with a principal diagnosis of pneumonia (*International Classification of Disease, Ninth Edition, Clinical Modification*⁹ [ICD-9-CM] codes 480.0-483.8, 485-486, or 487.0) or a principal diagnosis of septicemia or respiratory failure (ICD-9-CM codes 038.XX or 518.81) with a secondary diagnosis of pneumonia. For Medicare programmatic reasons, claims in each state were sampled during one of two 6-month periods: July 1 through December 31, 1998, and September 1, 1998, through March 31, 1999. There were 346 105 cases nationally during these periods. A systematic random sample of up to 850 cases was selected from each state, resulting in an original database with 39 242 cases. Informed consent and institutional review board approval were not required because CMS has statutory access to medical records of Medicare beneficiaries.

DATA COLLECTION

Hospitals sent photocopies of medical records to 1 of 2 clinical data abstraction centers (CDACs). Abstractors used computerized tools with explicit entry criteria to record data elements that included patient characteristics and antibiotic selection and timing. Abstraction was terminated if the patient had no working diagnosis of pneumonia at the time of admission, had been transferred from another acute care hospital, or was admitted for comfort/palliative care only. Inter-CDAC reliability was monitored on a monthly sample of records and averaged 92% overall. Inter-CDAC agreement on administration of antibiotics within 4 hours of arrival was 91% with a κ coefficient of 0.80. We used Medicare enrollment data to detect deaths and Medicare Part A claims to identify readmission. Hospital characteristics were obtained from the American Hospital Association.

EXCLUSION CRITERIA

Exclusion criteria include lack of antibiotic timing data or radiographic evidence of pneumonia in the medical record, patient age younger than 65 years, immunocompromise (receipt of corticosteroids or antineoplastic therapy or history of organ transplantation, leukemia, or lymphoma), lack of antibiotic treatment during the first 36 hours at the hospital, discharge or death on the day of admission, and hospitalization in Puerto Rico or the Virgin Islands. We limited analysis to CAP by excluding cases in which patients had been hospitalized during the 14 days prior to admission. Only the first of a patient's multiple hospitalizations was included.

DATA ANALYSIS

Four outcomes were examined: mortality during hospitalization, mortality during the 30 days following admission, hospital LOS, and readmission within 30 days after discharge. Length of stay was defined as discharge date minus admission date. Unless otherwise noted, the time to diagnostic or therapeutic services was measured from the first time the patient was documented to be in the hospital or emergency department. Geographic regions are those used for the US Census (ie, West, Midwest, South, and Northeast).¹⁰ We calculated the Pneumonia Patient Outcomes Research Team Pneumonia Severity Index (PSI) score for each patient.¹¹ The PSI is validated and uses demographic, comorbidity, physical examination, and labora-

tory data (**Table 1**) to describe the risk of death during the 30 days following admission.

We stratified analyses by history of prehospital antibiotic treatment because it was a strong modifier of the effect of antibiotic timing on outcome. In addition, records rarely documented when prehospital antibiotics were administered, making accurate determination of initial timing impossible. At univariate analysis, differences in characteristics across selected subgroups were assessed using χ^2 tests and odds ratios (ORs) for categorical variables and analysis of variance (ANOVA) for continuous variables. Exact binomial 95% confidence intervals (CIs) were calculated for all reported rates. Multivariate logistic regression was used to produce severity adjusted ORs (AORs) that describe the association between antibiotic timing and each of the 4 clinical outcomes while controlling for potential confounding. These AORs compare outcomes among patients who received initial antibiotic treatment at the hospital within 1- to 12-hour periods following arrival with outcomes among patients whose antibiotics were administered later. The multivariate model included antibiotic timing and factors that were independently associated with outcome in multivariate analysis (the PSI score, admission to a intensive care unit during the first 24 hours, and census region of hospitalization) and factors that were associated with outcome in univariate analysis only or had been reported in previous studies to be associated with outcome (arterial oxygenation assessment,⁵ blood culture within 24 hours of arrival,⁵ initial antibiotic regimen consistent with IDSA or ATS guidelines,^{6,7} and patient ethnicity). Separate multivariate logistic regression analyses were performed for the lower-risk PSI classes (ie, II and III) and the higher-risk classes (ie, IV and V). To assess for effects of clustering by hospital, we repeated multivariate analyses using regression models that used generalized estimating equations and mixed models that included random effect. Specifically, we used PROC GENMOD and %GLIMMIX macro SAS codes (SAS Institute Inc, Cary, NC) with "hospital" in the "REPEATED" and "RANDOM" statements, respectively. These 2 additional techniques produced results essentially identical to those obtained with the standard logistic regression technique, indicating that clustering is not an issue. Therefore, we report results of standard logistic regression. All analyses were completed using SAS statistical software (SAS version 8.2). *P* values are 2 sided. Statistical significance was defined by a 95% CI that excludes 1.0 or *P* < .05. After identifying the lower limit of antibiotic administration times that were significantly associated with 30-day mortality, we compared the characteristics and outcomes of patients who received initial antibiotics within 4 hours of arrival with those of patients whose treatment began later. Although the actual lower limit of significant associations was 3 hours, we chose 4 hours because it is commonly used in quality improvement activities. We examined hospital characteristics to assess whether attaining a 4-hour goal is currently feasible across the full range of facilities.

RESULTS

A total of 18 209 cases remained in the analytic database following sequential application of exclusion criteria. These cases represented 3732 hospitals, with a median of 3 cases (range, 1-122 cases) per hospital. The most common reasons for exclusion from the original database were lack of a working diagnosis of pneumonia at the time of admission, transfer from another acute care hospital, or admission for comfort/palliative care only (*n* = 6531 [16.6%]). Other common reasons were immunocompromise (*n* = 5015 [12.8%]), lack of radiographic evi-

Table 1. Patient Characteristics Stratified by Antibiotic Administration Within 4 Hours of Arrival*

Characteristic	All Patients (N = 13 771)	Antibiotic Within 4 h (n = 8388)	Antibiotic After 4 h (n = 5383)	P Value
Age group, y†				
65-74	27.3 (26.6-28.1)	27.5 (26.5-28.5)	27.0 (25.9-28.3)	.57
75-84	41.8 (41.0-42.7)	41.7 (40.6-42.8)	42.0 (40.7-43.4)	.69
≥85	30.9 (30.1-31.6)	30.8 (29.8-31.8)	30.9 (29.7-32.2)	.91
Female sex†	51.8 (51.0-52.7)	50.4 (49.3-51.5)	54.1 (52.7-55.4)	<.001
Prearrival living setting				
Long-term care/skilled nursing†	20.7 (20.1-21.4)	21.1 (20.3-22.0)	20.1 (19.1-21.2)	.16
Other (primarily home)	79.3 (78.6-79.9)	78.9 (78.0-79.7)	79.9 (78.8-80.9)	.16
Race/ethnicity				
White	87.5 (86.9-88.0)	88.4 (87.7-89.1)	86.0 (85.1-86.9)	<.001
African American	7.1 (6.7-7.6)	6.1 (5.6-6.6)	8.7 (8.0-9.5)	<.001
Other	5.4 (5.0-5.8)	5.5 (5.0-6.0)	5.3 (4.7-5.9)	.58
Census region				
Midwest	23.3 (22.6-24.0)	24.7 (23.7-25.6)	21.2 (20.1-22.3)	<.001
Northeast	18.7 (18.0-19.4)	18.2 (17.3-19.0)	19.5 (18.5-20.6)	.05
South	31.9 (31.2-32.7)	29.6 (28.7-30.6)	35.5 (34.2-36.8)	<.001
West	26.1 (25.3-26.8)	27.5 (26.6-28.5)	23.8 (22.7-25.0)	<.001
Clinical characteristic at admission				
Neoplastic disease†	3.3 (3.0-3.6)	3.1 (2.8-3.5)	3.7 (3.2-4.2)	.07
Liver disease†	1.1 (0.9-1.3)	1.2 (1.0-1.5)	0.9 (0.7-1.2)	.08
Congestive heart failure†	30.9 (30.1-31.7)	30.4 (29.4-31.4)	31.6 (30.4-32.9)	.14
Cerebrovascular disease†	22.7 (22.0-23.4)	22.3 (21.4-23.2)	23.2 (22.1-24.4)	.20
Chronic renal disease†	9.1 (8.7-9.6)	8.5 (7.9-9.1)	10.1 (9.3-10.9)	.001
Altered mental status†	23.7 (23.0-24.4)	23.2 (22.3-24.1)	24.4 (23.2-25.6)	.11
Respiration rate >30/min†	21.0 (20.3-21.7)	23.3 (22.4-24.2)	17.4 (16.4-18.4)	<.001
Systolic blood pressure <90 mm Hg†	3.0 (2.7-3.3)	3.2 (2.8-3.6)	2.8 (2.4-3.3)	.19
Temperature <35°C or >40°C†	2.3 (2.1-2.6)	2.5 (2.2-2.9)	2.0 (1.7-2.4)	.06
Pulse >125/min†	9.4 (8.9-9.9)	10.6 (10.0-11.3)	7.4 (6.7-8.1)	<.001
Arterial pH <7.35†	6.3 (5.9-6.7)	6.2 (5.6-6.7)	6.4 (5.8-7.1)	.49
Serum urea nitrogen >31 mg/dL (11 mmol/L)†	27.8 (27.1-28.6)	27.4 (26.4-28.4)	28.5 (27.3-29.7)	.17
Serum sodium <130 mEq/L†	5.4 (5.1-5.8)	5.4 (4.9-5.9)	5.5 (4.9-6.1)	.80
Glucose >252 mg/dL (14 mmol/L)†	6.8 (6.4-7.3)	7.0 (6.5-7.6)	6.6 (5.9-7.3)	.33
Hematocrit <30%†	7.3 (6.9-7.8)	6.8 (6.3-7.4)	8.2 (7.4-8.9)	.003
Arterial PO ₂ <60 mm Hg or SaO ₂ <90%†	29.6 (28.8-30.4)	31.3 (30.3-32.3)	27.0 (25.8-28.2)	<.001
Pleural effusion†	26.1 (25.4-26.8)	25.7 (24.7-26.6)	26.8 (25.6-28.0)	.15
ICU within 24 h	12.0 (11.5-12.6)	12.1 (11.4-12.8)	11.9 (11.1-12.8)	.81
Risk classification (PSI score)				
Class II	6.8 (6.3-7.2)	6.7 (6.2-7.3)	6.8 (6.1-7.5)	.92
Class III	22.2 (21.5-22.9)	22.2 (21.3-23.1)	22.2 (21.1-23.3)	.96
Class IV	46.8 (46.0-47.7)	46.1 (45.0-47.2)	48.0 (46.7-49.3)	.03
Class V	24.2 (23.5-25.0)	25.0 (24.1-26.0)	23.0 (21.9-24.2)	.008
Selected processes of care				
Oxygenation assessment first 24 h	93.5 (93.1-93.9)	93.7 (93.1-94.2)	93.2 (92.5-93.9)	.29
Blood culture within 24 h	66.7 (65.9-67.5)	69.1 (68.1-70.1)	63.0 (61.7-64.3)	<.001
Use of recommended antibiotics	78.8 (78.1-79.5)	83.2 (82.4-84.0)	71.8 (70.6-73.0)	<.001

Abbreviations: ICU, intensive care unit; PSI, Pneumonia Severity Index.

*Patients without prehospital antibiotic treatment. Data are percentage (95% confidence interval) of patients unless otherwise specified. Patient clinical characteristics are not mutually exclusive. P values are based on pairwise comparisons between the antibiotic timing groups "within 4 h" vs "after 4 h" using χ^2 tests.

†Characteristics represented in the PSI.¹¹

dence of pneumonia (n=3673 [9.4%]), and age younger than 65 years (n=3369 [8.6%]).

PATIENTS WITHOUT PREHOSPITAL ANTIBIOTIC TREATMENT

There was no documentation of prehospital antibiotic treatment in the records of 13 771 (75.6%) patients. They represent the 3463 hospitals described in **Table 2**, with a median of 2 cases per hospital (range, 1-92 cases). Patient demographic and clinical characteristics are described in Table 1. Patients were predominately aged 75

to 84 years (41.8%), female (51.8%), admitted from settings other than nursing homes (79.3%), and white (87.5%). The most common comorbid condition was congestive heart failure (30.9%). At admission, most patients were in PSI risk class IV (46.8%) or V (24.2%), and 12.0% were admitted to an intensive care unit during the first 24 hours. No patient was in class I because all were older than 50 years. Patients who received antibiotics within 4 hours of arrival were less likely than others to be in PSI class IV (46.1% vs 48.0%; $P=.03$) and were more likely than others to be in class V, the highest risk category (25.0% vs 23.0%; $P=.008$).

Table 2. Hospital Characteristics and Antibiotic Administration Within 4 Hours of Arrival*

Hospital Characteristic	No. of Hospitals	No. of Patients	Antibiotic Administered Within 4 h, % (95% CI)	Antibiotic Administered After 4 h, % (95% CI)	P Value
No. of beds					
≥500	227	1378	53.3 (50.7-56.0)	46.7 (44.0-49.3)	Reference
200-499	2192	4925	55.4 (53.9-56.7)	33.8 (32.7-34.9)	.19
<200	937	7192	66.2 (65.1-67.3)	44.6 (43.3-46.1)	<.001
Unknown	107	276	59.8 (53.7-65.6)	40.2 (34.4-46.3)	.05
Ownership					
Not-for-profit	2923	11 953	61.7 (60.9-62.6)	38.3 (37.4-39.1)	Reference
For profit	433	1542	54.7 (52.1-57.2)	45.3 (42.8-47.9)	<.001
Unknown	107	276	59.8 (53.7-65.6)	40.2 (34.4-46.3)	.05
Teaching status					
Nonteaching	2512	9466	63.2 (62.3-64.2)	36.8 (35.8-37.7)	Reference
Teaching	844	4029	55.5 (53.9-57.0)	45.5 (43.0-46.1)	<.001
Unknown	107	276	59.8 (53.7-65.6)	40.2 (34.4-46.3)	.24
Metropolitan area					
Nonmetropolitan	1523	5283	66.9 (65.6-68.2)	33.1 (31.8-34.4)	Reference
<500 000 population	608	3125	56.9 (55.1-58.6)	43.1 (41.4-44.9)	<.001
≥500 000 population	1225	5087	57.2 (55.9-58.6)	42.8 (41.4-44.1)	<.001
Unknown	107	276	59.8 (53.7-65.6)	40.2 (34.4-46.3)	.02

Abbreviation: CI, confidence interval.

*Patients without prehospital antibiotic treatment. P values are based on pairwise comparisons between the reference group and the other hospital characteristic using χ^2 tests.

Table 3. Unadjusted Outcomes Stratified by Time From Arrival to First Antibiotic Administration*

Time to First Dose, h	Patients, No.	In-hospital Mortality, % (95% CI)	30-d Mortality, % (95% CI)	30-d Readmission, % (95% CI)	Median LOS, d (IQR)	LOS Above the Median (5 d), % (95% CI)
0-2	3578	7.4 (6.6-8.3)	12.5 (11.5-13.7)	12.6 (11.5-13.8)	5.0 (3.0-8.0)	43.6 (41.9-45.2)
>2-4	4810	6.3 (5.6-7.0)	10.9 (10.0-11.8)	13.5 (12.5-14.5)	5.0 (3.0-7.0)	41.0 (39.6-42.4)
>4-6	2331	6.9 (6.0-8.1)	11.7 (10.4-13.0)	13.3 (11.9-14.8)	5.0 (3.0-7.0)	42.9 (40.9-45.0)
>6-8	1095	7.2 (5.8-8.9)	13.0 (11.0-15.1)	13.1 (11.1-15.3)	5.0 (3.0-8.0)	46.1 (43.1-49.1)
>8	1957	8.0 (6.9-9.3)	13.8 (12.3-15.5)	15.0 (13.4-16.8)	5.0 (4.0-8.0)	47.2 (45.0-49.5)

Abbreviations: CI, confidence interval; IQR, interquartile range; LOS, length of stay.

*Patients without prehospital antibiotic treatment.

Antibiotics were administered to 26.0% of these patients within 2 hours of arrival, 60.9% within 4 hours, 85.8% within 8 hours, and 92.4% within 12 hours. Initial administration within 4 hours ranged from 53.3% among patients at hospitals with more than 500 beds to 66.2% among those at facilities with fewer than 200 beds ($P<.001$) (Table 2). Patients at smaller, not-for-profit, nonteaching, and nonmetropolitan hospitals generally received antibiotics sooner than did those at other facilities. Overall, antibiotics were administered within 4 hours to more than half of the patients at 71.1% of hospitals. This ranged from 54.9% of hospitals with more than 500 beds to 75.5% of hospitals with fewer than 200 beds. The initial antibiotic regimen was consistent with IDSA or ATS guidelines for 78.8% of patients (Table 1) and was more common among patients with 4-hour antibiotic administration than among those with later administration (83.2% vs 71.8%; $P<.001$).

Overall mortality was 7.0% (95% CI, 6.6%-7.5%) in the hospital and 12.0% (95% CI, 11.5%-12.6%) within 30 days of admission. The median LOS was 5 days with a mean of 6.3 days (95% CI, 6.2-6.3 days). Of patients who were discharged alive, 13.4% (95% CI, 12.8%-14.0%) were readmitted within 30 days following dis-

charge. Crude outcome rates stratified by time to first antibiotic dose are given in **Table 3**. In-hospital and 30-day mortality and LOS generally increased with time to first dose (Table 3), although all 3 outcomes were slightly worse among patients who received initial antibiotic treatment within 2 hours than among those who were first treated from 2 to 4 hours after arrival. The associations between 30-day mortality and increasing times to first antibiotic dose are given in **Table 4**. When compared with later antibiotic treatment, there was significantly reduced 30-day mortality associated with initial antibiotic administration within 3 hours after arrival (AOR, 0.88; 95% CI, 0.79-0.99; $P=.03$) through 8 hours after arrival (AOR, 0.85; 95% CI, 0.73-0.99; $P=.04$).

Table 5 describes severity-adjusted associations between 4-hour antibiotic administration and mortality, LOS, and readmission. They included reduced in-hospital mortality (AOR, 0.85; 95% CI, 0.74-0.98; $P=.03$), reduced mortality within 30 days after admission (AOR, 0.85; 95% CI, 0.76-0.95; $P=.005$), and a lower incidence of LOS exceeding the 5-day median (AOR, 0.90; 95% CI, 0.83-0.96; $P=.003$). In the 2 lower PSI risk classes (ie, II and III), 4-hour antibiotic administration time was associated with reduced 30-day mortality (AOR, 0.62; 95% CI, 0.42-0.93;

Table 4. Antibiotic First-Dose Timing and 30-Day Mortality Rates*

Time of First Antibiotic (Group 1 vs Group 2)	Group 1 Mortality,* % (95% CI)	Group 2 Mortality,* % (95% CI)	Unadjusted		Adjusted†	
			OR (95% CI)	P Value	AOR (95% CI)	P Value
≤1 vs >1 h	12.9 (11.0-15.0)	12.0 (11.4-12.5)	1.09 (0.91-1.31)	.37	0.99 (0.81-1.21)	.91
≤2 vs >2 h	12.5 (11.5-13.7)	11.9 (11.2-12.5)	1.07 (0.95-1.20)	.27	0.94 (0.83-1.06)	.32
≤3 vs >3 h	11.7 (11.0-12.6)	12.3 (11.5-13.0)	0.95 (0.86-1.05)	.33	0.88 (0.79-0.99)	.03
≤4 vs >4 h	11.6 (10.9-12.3)	12.7 (11.8-13.6)	0.90 (0.81-1.00)	.045	0.85 (0.76-0.95)	.005
≤5 vs >5 h	11.6 (11.0-12.3)	13.0 (12.0-14.1)	0.88 (0.79-0.98)	.03	0.86 (0.76-0.97)	.02
≤6 vs >6 h	11.6 (11.0-12.2)	13.5 (12.3-14.8)	0.84 (0.74-0.95)	.004	0.84 (0.73-0.95)	.008
≤7 vs >7 h	11.7 (11.1-12.3)	13.5 (12.2-15.0)	0.85 (0.75-0.97)	.01	0.87 (0.76-1.01)	.06
≤8 vs >8 h	11.7 (11.2-12.3)	13.8 (12.3-15.5)	0.83 (0.72-0.95)	.008	0.85 (0.73-0.99)	.04
≤9 vs >9 h	11.8 (11.2-12.4)	13.8 (12.2-15.6)	0.84 (0.72-0.97)	.02	0.86 (0.73-1.02)	.08
≤10 vs >10 h	11.9 (11.3-12.5)	13.4 (11.7-15.3)	0.87 (0.74-1.02)	.10	0.91 (0.76-1.09)	.33
≤11 vs >11 h	11.9 (11.4-12.5)	13.0 (11.1-15.0)	0.91 (0.76-1.09)	.30	0.93 (0.77-1.13)	.49
≤12 vs >12 h	12.0 (11.4-12.5)	12.8 (10.9-15.0)	0.92 (0.77-1.12)	.41	0.97 (0.79-1.19)	.74

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

*Patients without prehospital antibiotic treatment. Group 1 included patients who received initial antibiotics within the number of hours indicated; group 2 included patients who received initial antibiotics later than the time indicated.

†Using multivariate logistic regression. The model for adjustment included the timing of initial antibiotic, pneumonia severity index, admission to the intensive care unit, census regions of hospitalization, race/ethnicity, and other processes of care (oxygenation assessment, blood culture within 24 hours, and selection of an initial antibiotic consistent with current guidelines).

Table 5. Antibiotic Administration Within 4 Hours of Arrival and Patient Outcomes Stratified by Risk Classes*

Outcome Measures	All Patients, % (95% CI)	Antibiotic Within 4 h, % (95% CI)	Antibiotic After 4 h, % (95% CI)	Unadjusted†		Adjusted‡	
				OR (95% CI)	P Value	AOR (95% CI)	P Value
All patients							
30-d mortality	12.0 (11.5-12.6)	11.6 (10.9-12.3)	12.7 (11.8-13.6)	0.90 (0.81-1.00)	.045	0.85 (0.76-0.95)	.005
In-hospital mortality	7.0 (6.6-7.5)	6.8 (6.3-7.3)	7.4 (6.7-8.1)	0.91 (0.80-1.04)	.17	0.85 (0.74-0.98)	.03
Length of stay >5 d	43.3 (42.5-44.1)	42.1 (41.0-43.2)	45.1 (43.8-46.5)	0.88 (0.82-0.95)	<.001	0.90 (0.83-0.96)	.003
30-d readmission	13.4 (12.8-14.0)	13.1 (12.4-13.9)	13.9 (12.9-14.9)	0.93 (0.84-1.04)	.20	0.95 (0.85-1.06)	.34
PSI risk classes II and III							
30-d mortality	2.6 (2.1-3.1)	2.1 (1.5-2.7)	3.4 (2.6-4.4)	0.60 (0.40-0.89)	.01	0.62 (0.42-0.93)	.02
In-hospital mortality	1.1 (0.8-1.4)	0.9 (0.6-1.4)	1.2 (0.7-1.9)	0.78 (0.42-1.43)	.42	0.77 (0.42-1.44)	.42
Length of stay >5 d	32.8 (31.3-34.3)	31.2 (29.4-33.1)	35.3 (32.9-37.7)	0.83 (0.73-0.95)	.008	0.86 (0.75-0.99)	.03
30-d readmission	10.0 (9.1-11.0)	9.4 (8.3-10.6)	10.9 (9.4-12.6)	0.85 (0.69-1.05)	.12	0.87 (0.70-1.07)	.19
PSI risk classes IV and V							
30-d mortality	15.9 (15.2-16.6)	15.5 (14.6-16.4)	16.5 (15.4-17.7)	0.92 (0.83-1.03)	.16	0.87 (0.78-0.98)	.03
In-hospital mortality	9.5 (8.9-10.0)	9.2 (8.4-9.9)	9.9 (9.0-10.9)	0.92 (0.80-1.05)	.21	0.86 (0.74-1.00)	.04
Length of stay >5 d	47.6 (46.6-48.6)	46.5 (45.3-47.8)	49.2 (47.6-50.8)	0.90 (0.83-0.98)	.01	0.92 (0.84-1.00)	.04
30-d readmission	14.9 (14.2-15.7)	14.7 (13.8-15.7)	15.2 (14.0-16.5)	0.96 (0.85-1.09)	.53	0.99 (0.88-1.12)	.89

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; PSI, Pneumonia Severity Index.

*Patients without prehospital antibiotic treatment.

†Univariate analysis comparing the antibiotic timing subgroups "within 4 h" vs "after 4 h."

‡Multivariate analysis comparing the antibiotic timing subgroups "within 4 h" vs "after 4 h" using logistic regression. The logistic regression model included the timing of initial antibiotic, PSI, admission to the intensive care unit, census regions of hospitalization, race/ethnicity, and other processes of care (oxygenation assessment, blood culture within 24 hours, and initial antibiotic consistent with current guidelines).

$P=.02$) and a lower incidence of LOS greater than the 5-day median (AOR, 0.86; 95% CI, 0.75-0.99; $P=.03$). In PSI classes IV and V, 4-hour administration time was associated with reduced 30-day mortality (AOR, 0.87; 95% CI, 0.78-0.98; $P=.03$), reduced in-hospital mortality (AOR, 0.86; 95% CI, 0.74-1.00; $P=.04$) and a lower incidence of LOS greater than 5 days (AOR, 0.92; 95% CI, 0.84-1.00; $P=.04$). There was no significant association detected among patients in any risk classes between antibiotic administration timing and readmission.

Mean LOS was significantly shorter with 4-hour administration compared with later administration among patients in the 2 lower risk classes (5.1 vs 5.3 days; $P=.04$),

the 2 higher risk classes (6.5 vs 6.9 days; $P<.001$), and all classes combined (6.1 vs 6.5 days; $P<.001$).

PATIENTS WITH PREHOSPITAL ANTIBIOTIC TREATMENT

There were 4438 cases (24.4%) in which patients were documented to have received prehospital antibiotic treatment. These patients were significantly more likely than the others to be female (56.2% vs 51.8%; $P<.001$), from a skilled nursing facility (27.0% vs 20.7%; $P<.001$), white (89.9% vs 87.5%; $P<.001$), hospitalized in the Midwest (25.1% vs 23.3%; $P=.02$), and in PSI class II (7.9% vs 6.8%;

$P = .008$). They were significantly less likely to be African American (5.0% vs 7.1%; $P < .001$), admitted to an intensive care unit (10.4% vs 12.0%; $P = .003$), in PSI class IV (44.5% vs 46.8%; $P = .007$), and to have a blood culture performed within 24 hours of arrival (59.6% vs 66.7%; $P < .001$). These cases represent 2130 hospitals, with a median of 2 cases per hospital.

We did not observe a significant association among these patients between antibiotic administration within 4 hours and 30-day mortality (AOR, 1.18; 95% CI, 0.97-1.45; $P = .10$), in-hospital mortality (AOR, 1.21; 95% CI, 0.93-1.58; $P = .15$), and 30-day readmission (AOR, 0.93; 95% CI, 0.77-1.12; $P = .46$). Administration within 4 hours was associated with a significantly reduced incidence of LOS that exceeded the 5-day median (AOR, 0.84; 95% CI, 0.74-0.95; $P = .005$). The 30-day mortality was significantly higher among pretreated patients whose initial inpatient antibiotics were administered within 8 hours compared with later administration (13.1% vs 9.9%; AOR, 1.38; 95% CI, 1.02-1.87; $P = .04$).

When data from patients who had received prehospital antibiotic treatment were combined with data from patients who had not received such treatment, reduced 30-day mortality was associated with initial antibiotic administration from 3 through 9 hours after arrival, although the association was relatively weak and did not reach statistical significance. Adjusted odds ratios for 30-day mortality ranged from 0.90 (95% CI, 0.81-1.01; $P = .09$) for administration within 6 hours to 0.96 (95% CI, 0.83-1.12; $P = .63$) for administration within 9 hours.

COMMENT

This large population-based study provides additional evidence that timely antibiotic treatment improves outcomes among older patients who are hospitalized because of CAP. It also demonstrates that the benefit of early antibiotic administration may be limited to patients who have not been treated as outpatients, although such patients account for most Medicare CAP admissions. Among the nearly 76% of patients who had not received prehospital treatment, initial antibiotic administration within 4 hours of arrival at the hospital was associated with a 15% reduction in mortality during both the hospitalization and the 30 days following admission. Because almost 40% of such patients did not receive antibiotics within 4 hours, the present study suggests that there is a substantial opportunity to improve survival. It also suggests that timely administration results in shorter hospital LOS.

These findings are consistent with those of several previous studies of pneumonia inpatients. Kahn et al³ observed a 4 percentage point reduction in 30-day mortality among Medicare patients who received antibiotics within 4 hours of admission and appropriate oxygen therapy. McGarvey and Harper⁴ demonstrated that care processes that included antibiotic delivery within 4 hours were associated with lower pneumonia mortality at 2 community hospitals. Meehan et al⁵ examined process-outcome associations over 14,000 randomly selected Medicare inpatients. Regardless of prehospital treatment, they observed significantly lower 30-day mortality among those

who received their first hospital antibiotic treatment within 8 hours of arrival than among those whose antibiotic treatments were delayed (OR, 0.85; 95% CI, 0.75-0.96; $P < .001$). They observed an even stronger association when patients with prehospital treatment were excluded but did not describe that exclusion's effect on associations with times less than 8 hours. It is in the subpopulation of patients without previous treatment, who account for most CAP admissions, that our study provides the most important new information. Meehan et al⁵ also did not describe timing-outcome association among pretreated patients alone. In analyses outside the scope of our report, we examined the Medicare database that was used by those researchers and found the same lack of a favorable timing-mortality association among pretreated patients that is described in the present study. We are unable to explain why earlier antibiotic administration is associated with higher mortality among pretreated patients. This perplexing finding requires further examination. In another study by Dedier et al¹² of 1062 patients with pneumonia who were treated at academic medical centers, no association between antibiotic timing and mortality was detected. That study differed substantially from ours and the study by Meehan et al⁵ in patient selection and characteristics, hospital characteristics, treatment patterns, and number of subjects. Prehospital treatment does not explain the negative findings in the study by Dedier et al¹² because such patients were excluded.

In our study, previously untreated patients who received antibiotic treatment within 4 hours of arrival had a 0.4 day shorter mean LOS and were 10% (95% CI, 4%-17%) less likely than others to have a LOS that exceeded the 5-day median. A similar reduction in LOS was observed among patients who had received prehospital antibiotic treatment. These findings are also consistent with those of previous studies. Rosenstein et al¹³ examined 367 CAP hospitalizations at 15 facilities. Antibiotic administration within 2 hours of registration in the emergency department was associated with a LOS that was on average 0.8 day shorter than among those with later antibiotic treatment. Battleman et al¹⁴ examined 700 pneumonia cases at 7 hospitals and observed that timely antibiotic administration was associated with shorter LOS.

A plausible biological mechanism that explains our main findings rests on 2 concepts. The first is that pneumonia-related death occurs after progression through a sequence of conditions.¹⁵ Pneumonia initiates the sequence by producing acute lung injury that, if severe enough, progresses to a systemic inflammatory response and multiple organ dysfunction. Death occurs if the dysfunction exceeds the patient's physiologic reserves. The second concept is that antibiotics can interrupt this sequence by minimizing lung injury. The later the antibiotic is given, the greater the extent of injury. Up to a point, greater lung injury results in a reversible systemic inflammatory response. Beyond that point, the process is irreversible and death occurs. Whether the progression becomes irreversible depends on the severity of illness and the individual patient's physiologic reserve. Two reports provide additional evidence of the importance of timely intervention with seriously ill patients.

Rivers et al¹⁶ found that early hemodynamic resuscitation for severe sepsis and septic shock (38% of cases due to pneumonia) resulted in improved survival compared with less timely resuscitation treatment. They did not assess the impact of antibiotic timing, and most patients in their study received antibiotics within 6 hours. However, the timing of resuscitation is unlikely to explain our findings fully because we found that timely antibiotic treatment was beneficial to patients in all PSI risk classes. Patients in the lower classes (ie, II and III) were unlikely to have septic shock because age plus the physiological abnormalities of even modest septic shock would place most Medicare patients in PSI class IV or V.¹¹ In another study, Iregui et al¹⁷ observed that intensive care unit patients with ventilator-associated pneumonia were more likely to die if antibiotic treatment was delayed.

Our findings have substantial clinical and financial implications because the number of Medicare CAP hospitalizations is large. Based on our sample, we estimate that about 210 000 Medicare fee-for-service beneficiaries would meet our study's inclusion criteria each year and would not have received prehospital antibiotic treatment. If 85% of those who receive antibiotics more than 4 hours after arrival would actually receive them within that time, their mortality might be reduced from 12.7% to 10.9% (ie, the rate among those patients in the 2- to 4-hour category). Such a mortality rate reduction would decrease the absolute number of deaths in the 30 days following admission by more than 1250. This estimated rate reduction is speculative and could be smaller, but the estimate of 210 000 potentially affected patients is conservative. It does not include non-Medicare patients, Medicare managed care patients, and patients with any of the exclusion characteristics. Even if this crude estimate is too high by a factor of 2 or 3, the opportunity to prevent hundreds of deaths each year is very attractive. Timely antibiotic administration also potentially offers substantial financial benefits for hospitals through shorter hospital stays and lower costs.

Is antibiotic administration within 4 hours feasible in today's hospital environment, where competing priorities place growing demands on health care workers? Our data suggest that it is in most settings, since more than 60% of patients were already receiving antibiotics within 4 hours of hospital arrival at the time of the study. Although 70% of hospitals were able to deliver antibiotics to more than half of the patients within 4 hours of their arrival, our data suggest that the challenge and the opportunity to improve performance are greatest in large metropolitan hospitals. These facilities may face seemingly intractable resource issues, but their performance might be improved through examination of the systems used in smaller hospitals.

Among the strengths of this study are its large sample size and clinical richness. We could retain a substantial number of cases while applying many relevant exclusion criteria and extensive adjustment. We required that pneumonia not only be designated at discharge to be the principal reason for the hospitalization (or a secondary reason with respiratory failure or sepsis as principal reason) but also that it be a radiographically supported working diagnosis at the time of admission. We excluded cases

in which only palliative care was planned or the principal diagnosis was aspiration pneumonitis. Thus, our analytic database likely represented true microbial pneumonia in patients who received aggressive therapy.

Our study has several limitations. As with any retrospective study, there is potential for residual confounding. The PSI is not a perfect risk adjustment tool, but it is validated, pneumonia specific, and state of the art. However, patients who received antibiotics within 2 hours of arrival at hospital were more likely to be in the highest PSI risk class and had crude mortality rates that approximated those of patients in the 6- to 8-hour category. Thus, incomplete severity adjustment would, in part, bias results toward an apparent absence of association between early administration and improved outcomes. A prospective randomized trial of timing has been suggested.¹² While ideal, a study that intentionally delays delivery of the definitive treatment for pneumonia would present substantial ethical challenges. Another potential limitation is the uncertainty that mortality is actually the result of the pneumonic process. A recent study suggests that only 53% of mortality within 90 days of admission is actually related to pneumonia.¹⁸ However, deaths within 30 days of admission were 7.7 times more likely to be pneumonia-related than not. Finally, generalization of our findings to other than older patients with CAP should be done with caution. We excluded younger patients because their Medicare eligibility required disability or conditions that could not be fully described by our data. Additional research is needed on the effect of antibiotic timing on outcomes for younger patients and those who have received prehospital antibiotic treatment. Our inability to demonstrate a favorable timing-mortality association among patients who had received prehospital treatment does not negate the importance of our findings because three quarters of hospitalized patients with CAP have not received such treatment. Our estimate of potential deaths prevented takes this into account.

The results of this study suggest that initial administration of antibiotics within 4 hours of arrival at the hospital is associated with reduced mortality among those patients who have not received antibiotics as outpatients and reduced hospital LOS among all patients. While most Medicare inpatients with pneumonia already receive antibiotics within that time, a substantial proportion do not. Given the growing size of the Medicare population, any additional improvement in administration timing could prevent a substantial number of deaths each year and preserve health care resources.

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