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Factors Influencing In-hospital Mortality in Community-Acquired Pneumonia*

A Prospective Study of Patients Not Initially Admitted to the ICU

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Purpose: **To determine the factors that predict in-hospital mortality among patients who require hospitalization for the treatment of community-acquired pneumonia (CAP).**
Study design: **Prospective observational study of all patients who were admitted to six hospitals in Edmonton, AL, Canada, with a diagnosis of CAP from November 15, 2000, to November 14, 2002. Pneumonia was defined as two or more respiratory symptoms and signs and an opacity on a chest radiograph as interpreted by the attending physician.**
Results: **A total of 3,043 patients were enrolled in the study, 246 of whom died (8.1%). On multivariate analysis, increasing pneumonia severity score, increasing age, site of care, consultation with a respirologist or infectious diseases physician, and functional status at the time of admission were all independently predictive of mortality. Increasing pneumonia severity risk score, increasing age, site of hospitalization, functional status, and consultation with an infectious diseases physician or a respirologist were independently associated with both early (< 5 days) and late (≥ 5 days) mortality. In contrast, partial or complete use of the pneumonia pathway was associated with decreased early mortality, but had no effect on late mortality. A low lymphocyte count and a high serum potassium level were associated with early but not with late mortality. The type of antibiotic therapy had an effect on late but not on early mortality.**
Conclusions: **Functional status at the time of hospital admission is a powerful predictor of mortality and should be incorporated into any scores or models that are used to predict mortality. While there are some common predictors of early and late in-hospital mortality, early mortality is not affected by the timing or type of antibiotic therapy, whereas late mortality is influenced by the type of antibiotic therapy. Hyperkalemia and lymphopenia are associated with early mortality.** ***(CHEST 2005; 127:1260–1270)***

Key words: functional status; mortality; pneumonia

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; FSA = forward sortation area; HRCT = high-resolution CT; OR = odds ratio

Community-acquired pneumonia (CAP) is a common illness with an incidence rate of approximately 11.6/1,000 adults per year,[1] of which approximately 30% require admission to hospital.[2] The mean age of 43,642 patients hospitalized for treatment of CAP over a 5-year period in Alberta was 65.8 ± 19.7 years (± SD), and the median age was 71 years.[3] The in-hospital mortality rate for patients with CAP is considerable and varies with the population studied. However, in administrative database studies, where large populations are available, the mortality rate ranges from 9.7 to 11%.[3,4]

In the past few years, attention has been paid to processes of care and the impact of these on the outcome of pneumonia. Critical pathways are disease-specific management strategies that define the essential steps of a complex care process.[5] Such pathways were introduced to try to reduce variations in care. We introduced a pneumonia pathway at all six hospitals that provide care for adults in the

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greater Edmonton area. The objective of this study was to determine the factors that influence in-hospital mortality for patients with CAP and whether adherence to the pathway had an effect on mortality.

Materials and Methods

Study Sites

This study involved all six hospitals in the Edmonton area (adult population of 666,505)[6]: two tertiary care hospitals, two hospitals that provided secondary and some tertiary care, and two community hospitals. This study was approved by the Research Ethics Committee at the University of Alberta.

Development of Pneumonia Pathway

A multidisciplinary team developed a comprehensive pathway for the management of CAP.[7] The pathway consisted of an admission guideline,[8] preprinted orders covering routine aspects of care, an algorithm for administration and discontinuation of supplemental oxygen, and antimicrobial therapy (levofloxacin orally or cefuroxime plus azithromycin IV were the options provided), but other options were not prohibited. Reminders to medical staff regarding assessment of vaccination status for pneumococcal and influenza vaccines were provided, and a recommendation for administration of these vaccines, if indicated, was included in the order sheet. In addition, counseling and literature regarding cessation of smoking were made available to those who were tobacco smokers. A three-part discharge algorithm was part of the pathway. Once the patients had achieved physiologic stability,[9] as defined by an oral temperature of $\leq$ 37.5 C for 24 h, a respiratory rate of $\leq$ 24 breaths/min for 24 h, an oxygen saturation of $\geq$ 90% while breathing room air or a return to baseline saturation levels, and ability to eat and drink enough to maintain hydration, functional (get-up-and-go test[10] and an assessment of activities of daily living if the patient failed the get-up-and-go test) and mini-mental status assessments were carried out.[7,10,11] In the get-up-and-go test, the patient is asked to arise from a sitting position and walk 3 m. If this can be done in $\leq$ 20 s, the patient has passed the test. A score $>$ 25/30 on the mini-mental status examination was considered a passing grade. If these test results were satisfactory and comorbid illnesses were stable, the patient was deemed ready for discharge. In general, functional status and mental status assessments were performed only on those patients who were $\geq$ 65 years of age. Functional status premorbid admission was categorized as walking, walking with assistance, and walking with a prosthesis; wheel chair or bed-bound status was also recorded.

Pneumonia Definition

Two or more symptoms or signs of CAP (cough [productive or nonproductive], pleuritic chest pain, shortness of breath, temperature $>$ 38°C, and crackles, or bronchial breathing on auscultation) plus radiographic evidence of pneumonia as interpreted by the emergency department physician or internal medicine consultant. Patients were excluded from the pathway if they required admission to intensive care from the emergency department, were believed to have aspiration pneumonitis (defined as pulmonary opacities in the presence of recent loss of consciousness, vomiting or observation of respiratory distress within 30 min of feeding), tuberculosis, and cystic fibrosis. Pregnant and nursing mothers and immunosuppressed patients ($>$ 10 mg/d prednisone for $>$ 1 month or other immunosuppressive drugs) were also excluded. Those with HIV infection were excluded if the CD_4 count was $<$ 250/μL. During the second year of the study, patients with aspiration pneumonia were included.

Data Collection and Definitions

Adherence to the pathway was classified as complete or partial. If all elements of the pathway were followed, adherence was complete; adherence was incomplete if one or more elements were not followed. The 1996 Canadian census data were used to provide the median household income for each neighborhood area (forward sortation area [FSA]) corresponding to the first three digits of the postal code from the hospitalization records.[12] Two hundred forty-eight unique FSAs were identified in our data, 96.9% of which were within the province of Alberta. The categories of median household income were used as a marker for the socioeconomic status (SES) of the patients. Since some patients had multiple hospitalizations, the analyses were limited to the first hospitalization within the 30-day period. Due to the small number of events, the patients with the prosthesis functional status (n = 11) and no antibiotics administered (n = 46) were also excluded from the analyses. The site identification of each hospital was masked (A–F) to protect the identities of the participating institutions.

Statistical Analysis

The analyses were performed on software (SAS version 8.2; SAS Institute; Cary, NC). Complete case analyses were used throughout. Independent variables with high percentages of missing values were not evaluated in the analysis. Descriptive statistics such as means and proportions were presented, and the differences were tested using F-test or χ^2 test. Univariate analysis was used to exclude predictors that lacked marginal relationship with the all-cause mortality. The predictors with p values $<$ 0.25 in the univariate logistic regression analysis were retained in the multivariate logistic regression model. The risk of death was evaluated using multivariate logistic regression and all factors were evaluated simultaneously, while adjusting for other factors in the model. The predictors selected in the final model were based on both numerical and clinical significance. Odds ratios (ORs) and nominal 95% confidence intervals (CIs) were presented. Both c-statistic and the Hosmer and Lemeshow lack of fit test were used to evaluate the adequacy of the logistic regression models. Hierarchical logistic regression models with predictors added one at a time were also examined to evaluate the possible collinearity among the predictors. No significant collinearity among the factors was observed. Since the comorbidity and medical history of the patients were accounted for during the calculation of the pneumonia severity index, no further adjustment was made. Cox proportional hazard models, which accounted for time from admission to mortality, were also developed. The results from the proportional hazard model were similar to the ones from the multivariate logistic regression model, so they are not presented. A two-sided p value $<$ 0.05 was considered significant for all analyses.

Since adherence to the pneumonia pathway varied among the sites of care, which may have resulted in the imbalances between the covariates, we used the logistic regression model to estimate the propensity of CAP pathway use during hospitalization. The propensity score method[13,14] was chosen because of the following: (1) the CAP pathway was not a randomized intervention, and (2) many factors, as well as their interactions, affected the use of the pathway. The factors selected for the calculation of the propensity score included site, age, nursing home residence,

residence with home care, gender, substance abuse, study year, season at the time of presentation, and median household income. The above variables and their interactions (up to five ways) were evaluated for their associations with CAP pathway used. Site, residence with home care, and their interaction were selected to calculate the estimated propensity score for the pathway use. The estimated propensity score of the CAP pathway was incorporated into the analysis of mortality as a covariate in the model. In addition to the estimated propensity score for the use of CAP pathway, the interaction between site and CAP pathway was also evaluated in the multivariate logistic regression model of mortality. The results from the model with the estimated propensity score (not shown), the model with site by pathway interaction (not shown), and the model with main effects only were very similar; hence, we chose to present the results from main effects only.

Results

During the 2 years of the study (November 15, 2000, to November 14, 2002), there were 3,043 patients with pneumonia (who met criteria for the pathway) admitted to the six Edmonton hospitals (Table 1). In addition, the following patients with a diagnosis of pneumonia were excluded from the study: 704 patients who required admission to an ICU from the emergency department; 352 patients with aspiration pneumonia (first year of the study only—these patients were included in the second year once the pneumonia pathway team had decided on antibiotic therapy for this subset of patients); physician choice (n = 136); palliative care (n = 113); pregnancy (n = 36); immunosuppressed (n = 88); cystic fibrosis (n = 22); WBC count $< 1{,}000$ (n = 19); tuberculosis (n = 11); nosocomial pneumonia (n = 59), bronchiectasis (n = 58); pulmonary fibrosis (n = 78); bronchiolitis obliterans with organizing pneumonia (n = 9); talc lung (n = 2); collagen vascular disease (n = 3); sepsis with no pneumonia (n = 7); exacerbation of COPD (n = 15); diagnosis changed from pneumonia to another diagnosis by attending physician with 48 h of admission (n = 80); HIV infection with CD4 count < 250 (n = 42); and unknown reasons (n = 121).

The admission rate to ICU from the emergency department varied from 0 (this community hospital did not have an ICU, and patients requiring ICU were transferred to one of the other hospitals) to 16%. The rates of admission at the tertiary care hospitals were 11.6% and 16.7%, respectively, and for the secondary care hospitals were 7.8% and 10.2%; for the two community hospitals, rates of admission were 0 and 5.2%, respectively. Admission to an ICU from the ward was uncommon, occurring in only 10 patients, 4 of whom died.

The mean age of the included patients was 69.6 ± 17.7 years; 52.5% were male patients, 47.5% were female patients, and 246 patients (8.1%) died. The site-specific mortality rate ranged from 6 to 13.3%. Table 1 also shows that there were site differences in the mean age, mean pneumonia severity of illness score, mean time from presentation until the first dose of antibiotic, mean length of stay, and median household income. Thirty-one percent were admitted from a nursing home or from a residence where they required some care. Only 60.2% were fully ambulatory; 7.2% required a wheelchair, and 3.4% were bed bound. Three hundred seventy-six patients (12%) had a limitation of care order. One hundred sixty-six patients (5.4%) were taken off the pathway because of increasing severity of the pneumonia; 113 of these were transferred to ICU. Since all of these patients were eligible for the study at the time of hospital admission, they are included in the analysis.

One thousand fifty-one patients had the get-up-and-go test done, and 441 patients (41.9%) failed. Six hundred seventy-six patients had the mini-mental status examination done, and 311 patients (46%) failed.

Table 2 compares selected features of those who survived pneumonia vs those who died. There are a number of instructive observations. Not unexpectedly, there were major differences in mean age, mean pneumonia severity risk score, and mean length of stay between the two groups. Also, the effect of functional status at the time of admission on subsequent mortality was striking. Thus, 4.0%, 11.6%, 20.1%, and 25.2% of those who were walking, walking with assistance, wheelchair, and bedridden, respectively, died. The mean ages for patients in each of these groups were 63.8, 80.0, 73.3, and 74.4 years, respectively. The mean pneumonia severity risk scores for patients in the four functional status categories were 90.6, 117.3, 113.7, and 117.6, respectively. Ten of the 610 patients (1.6%) who passed the get-up-and-go test died, compared with 62 of the 441 patients (14.0%) who failed this test. The group that passed this test was younger (77.3 years vs 81.6 years), had a lower mean risk score (102.2 vs 121.8), and a lower percentage of patients in risk classes IV and V (73% vs 86%). There were major differences in mortality according to the site of hospitalization, with mortality rates ranging from 5.9 to 13.3%. As shown in the multivariate analysis, site of care remained a significant predictor for mortality after simultaneously adjusting for other factors.

The type of antibiotic therapy seemed to influence the mortality rate. The mortality rate for the 1,672 patients who were treated with levofloxacin only was 5.3%, while 5.4% of the 166 patients treated with cefuroxime plus azithromycin died. The mortality rate among the 1,205 patients who received any other antibiotic or antibiotic combination was 12.2%.

Table 1—*Characteristics of Study Population by Site of Care

Characteristics	Site						Total	p Value
	A (n = 426)	B (n = 173)	C (n = 457)	D (n = 1,023)	E (n = 337)	F (n = 627)	(n = 3,043)	
Age, yr	70.9 ± 17.3	71.1 ± 19.3	71.3 ± 16.9	67.8 ± 17.9	71.0 ± 17.4	69.1 ± 17.7	69.6 ± 17.7	0.0011
Risk score	100.9 ± 36.3	93.5 ± 32.9	104.1 ± 34.1	99.1 ± 36.4	102.6 ± 35.2	104.3 ± 32.7	101.2 ± 35.1	0.0009
Hours from presenting to emergency department to administration of the first antibiotics (mean)	9.4 ± 14.8	7.4 ± 12.1	7.2 ± 13.1	9.6 ± 16.6	6.1 ± 7.1	8.6 ± 10.1	8.5 ± 13.6	0.0002
Length of stay	10.2 ± 11.1	10.3 ± 16.4	12.2 ± 15.9	12.3 ± 14.6	7.9 ± 8.6	10.6 ± 13.0	11.0 ± 13.7	< 0.0001
Median household income, thousand	46.2 ± 11.3	46.0 ± 6.0	40.0 ± 11.2	33.1 ± 10.2	47.6 ± 11.2	38.6 ± 12.4	39.4 ± 12.2	< 0.0001
Mortality	28 (6.5)	11 (6.3)	61 (13.3)	75 (7.3)	20 (5.9)	51 (8.1)	246 (8)	0.0005
Aboriginal origin	8 (1.8)	0	19 (4.2)	53 (5.2)	8 (2.4)	25 (3.9)	113 (3.7)	< 0.0001
Nursing home residence	59 (13.8)	17 (9.8)	54 (11.8)	83 (8.1)	36 (10.6)	42 (6.7)	291 (9.6)	0.0009
Residence with home care	79 (18.5)	38 (21.9)	122 (26.6)	202 (19.7)	100 (29.6)	115 (18.3)	656 (21.5)	< 0.0001
Male gender	198 (46.5)	81 (46.8)	234 (51.2)	560 (54.7)	181 (53.7)	344 (54.8)	1,598 (52.5)	0.1523
Ever substance abused	14 (3.3)	4 (0.9)	32 (7)	171 (16.7)	10 (2.9)	60 (9.5)	291 (9.5)	< 0.0001
Passed get-up-and-go test, No.†	76	56	101	151	45	181	610	< 0.0001
Modified mini-mental score < 25, No.†	37	23	43	121	39	48	311	0.0167
Risk class								
1	9 (2.1)	2 (1.2)	5 (1.1)	27 (2.6)	6 (1.8)	11 (1.8)	60 (1.9)	0.0048
2	75 (17.6)	38 (21.9)	71 (15.5)	209 (20.4)	56 (16.6)	88 (14)	537 (17.6)	
3	82 (19.2)	34 (19.6)	77 (16.8)	198 (19.4)	74 (21.9)	115 (18.3)	580 (19.1)	
4	173 (40.6)	80 (46.2)	200 (43.8)	380 (37.1)	121 (35.9)	278 (44.3)	1,232 (40.5)	
5	87 (20.4)	19 (10.9)	104 (22.7)	209 (20.4)	80 (23.7)	135 (21.5)	634 (20.8)	
Age group								
≤ 25	7 (1.6)	5 (2.8)	6 (1.3)	15 (1.5)	9 (2.6)	8 (1.3)	50 (1.6)	0.0045
25–65	110 (25.8)	48 (27.8)	132 (28.9)	356 (34.8)	83 (24.6)	206 (32.8)	935 (30.7)	
≥ 65	309 (72.5)	120 (69.4)	319 (69.8)	652 (63.7)	245 (72.7)	413 (65.8)	2,058 (67.6)	
Study year								
First year	195 (45.8)	89 (51.4)	194 (42.5)	502 (49.1)	136 (40.4)	286 (45.6)	1,402 (46.1)	0.0271
Second year	231 (54.2)	84 (48.6)	263 (57.5)	521 (50.9)	201 (59.6)	341 (54.4)	1641 (53.9)	
Smoking status								
Unknown	66 (15.5)	31 (17.9)	62 (13.5)	100 (9.8)	23 (6.8)	68 (10.8)	350 (11.5)	< 0.0001
Former smoker	152 (35.6)	42 (24.2)	199 (43.5)	319 (31.1)	128 (3.8)	221 (35.2)	1,061 (34.8)	
Nonsmoker	133 (31.2)	63 (36.4)	102 (22.3)	299 (29.2)	108 (32)	196 (31.3)	901 (26.2)	
Current smoker	75 (17.6)	37 (21.3)	94 (20.5)	305 (29.8)	78 (23.1)	142 (22.6)	731 (24)	
Season visited emergency department								
Spring	126 (29.5)	58 (33.5)	145 (31.7)	298 (29.1)	105 (31.1)	189 (30.1)	921 (30.2)	0.8934
Summer	80 (18.7)	32 (18.5)	104 (22.7)	219 (21.4)	66 (19.5)	121 (19.2)	622 (20.3)	
Fall	92 (21.5)	33 (19)	87 (19)	223 (21.7)	64 (18.9)	130 (20.7)	629 (20.6)	
Winter	128 (30)	50 (28.9)	121 (26.5)	283 (27.6)	102 (30.2)	187 (29.8)	871 (28.6)	
1996 FSA median household income, thousand								
Unknown	5 (1.1)	5 (2.8)	8 (1.7)	23 (2.2)	11 (3.3)	12 (1.9)	64 (2.1)	< 0.0001
≤ 25	8 (1.8)	0	16 (3.5)	261 (25.5)	11 (3.3)	49 (7.8)	345 (11.3)	
25 to ≤ 35	69 (16.2)	8 (4.6)	133 (29.1)	246 (24)	15 (4.5)	220 (35)	691 (22.7)	
35 to ≤ 45	97 (22.7)	42 (24.2)	166 (36.3)	377 (36.8)	106 (31.4)	190 (30.3)	978 (32.1)	
45 to ≤ 55	182 (42.7)	113 (65.3)	113 (24.7)	92 (8.9)	69 (20.4)	109 (17.4)	678 (22.2)	
> 55	65 (15.2)	5 (2.8)	21 (4.6)	24 (2.3)	125 (37)	47 (7.4)	287 (9.4)	
Functional status								
Walking without problem	163 (3.8)	102 (58.9)	270 (5.9)	692 (67.6)	218 (64.6)	387 (61.7)	1,832 (60.2)	< 0.0001
Walking with assist	184 (43.1)	52 (11.3)	160 (35)	216 (21.1)	100 (29.6)	177 (28.2)	889 (29.2)	
Wheelchair	15 (3.5)	16 (3.5)	21 (4.6)	104 (10.2)	9 (2.6)	54 (8.6)	219 (7.2)	
Bedridden	64 (15)	3 (1.7)	6 (1.3)	11 (2.9)	10 (1.5)	9 (1.4)	103 (3.4)	
Antibiotic therapy								
Levofloxacin only	299 (70)	87 (50.3)	269 (58.8)	524 (51.2)	155 (45.9)	338 (53.9)	1,672 (54.9)	< 0.0001
Cefuroxime plus azithromycin	13 (3)	19 (10.9)	21 (4.5)	43 (4.2)	53 (15.7)	17 (2.7)	166 (5.5)	
Other antibiotics	114 (27)	67 (38.7)	167 (36.5)	456 (44.5)	129 (38.2)	272 (43.4)	1,205 (39.6)	

*Data are presented as mean ± SD or No. (%) unless otherwise indicated.
†Percentage not calculated because of varying denominator.

Table 2—*Characteristics of Patients by Mortality Status

Characteristics	Mortality		Total (n = 3,043)	
	No (n = 2,797)	Yes (n = 246)		p Value
Age, yr	68.5 ± 17.8	81.2 ± 10.9	69.6 ± 17.7	< 0.0001
Risk score (pneumonia severity index)	98.1 ± 33.7	136.4 ± 30.7	101.2 ± 35.1	< 0.0001
Hours from present to emergency department to administration of the first antibiotics	8.4 ± 13.3	9.1 ± 16.4	8.5 ± 13.6	0.4807
Length of stay, d	10.7 ± 13.3	14.6 ± 16.8	11.0 ± 13.7	< 0.0001
Median household income, thousands	39.3 ± 12.2	40.5 ± 12.4	39.4 ± 12.2	0.1568
Aboriginal origin	112	1 (0.8)	113	0.0167
Nursing home residence	582	74 (11.2)	656	0.0007
Male	1,464	134 (8.3)	1,598	0.7818
Passed get-up-and-go test	600	10 (1.6)	610	< 0.0001
Modified mini-mental score < 25	287	24 (7.7)	311	0.0026
Ever substance abused	276	15 (5.1)	291	0.0539
Risk class				
1	60	0	60	< 0.0001
2	532	5 (0.9)	537	
3	568	12 (2.1)	580	
4	1,152	80 (13.8)	1,232	
5	485	149 (23.5)	634	
Age group, yr				
≤ 25	50	0	50	< 0.0001
25–65	918	17 (1.8)	935	
≥ 65	1,829	229 (11.1)	2,058	
Site				
A	398	28 (6.5)	426	0.0005
B	162	11 (6.3)	173	
C	396	61 (13.3)	457	
D	948	75 (7.3)	1,023	
E	317	20 (5.9)	337	
F	576	51 (8.1)	627	
Study year				
First year	1,300	102 (7.3)	1,402	0.1303
Second year	1,497	144 (8.7)	1,641	
Smoking status				
Unknown	298	52 (14.8)	350	< 0.0001
Former smoker	969	92 (8.7)	1061	
Nonsmoker	830	71 (7.8)	901	
Current smoker	700	31 (4.2)	731	
Season visited emergency department				
Spring	841	80 (8.6)	921	0.5342
Summer	572	50 (8.0)	622	
Fall	574	55 (8.8)	629	
Winter	810	61 (7)	871	
1996 FSA median household income, thousand				
Unknown	60	4 (6.2)	64	0.6232
≤ 25	324	21 (6)	345	
25 to ≤ 35	636	55 (15.9)	691	
35 to ≤ 45	898	80 (8.1)	978	
45 to ≤ 55	615	63 (9.2)	678	
> 55	264	23 (8)	287	
Functional status				
Walking without problem	1,759	73 (3.9)	1,832	< 0.0001
Walking with assist	786	103 (5.6)	889	
Wheelchair	175	44 (20)	219	
Bedridden	77	26 (25)	103	
Antibiotic therapy				
Levofloxacin only	1,583	89 (5.3)	1,672	< 0.0001
Cefuroxime plus azithromycin	157	9 (5.4)	166	
Other antibiotics	1,057	148 (12.3)	1,205	

*Data are presented as mean ± SD, No., or No. (%).

Table 3—*Multivariable Analysis of Factors Predicting Mortality in Patients With CAP*

Effect	Logistic Regression of Mortality*		
	p Value	OR	95% Wald Confidence Limits
Risk score (per additional score)	< 0.001	1.03	1.02–1.03
Age (per additional year)	< 0.001	1.03	1.01–1.04
Functional status walking with assist vs walking without problem	0.020	1.52	1.07–2.17
Functional status wheelchair vs walking without problem	< 0.001	2.92	1.84–4.63
Functional status bedridden vs walking without problem	< 0.001	5.36	2.79–10.26
Site			
A vs E	0.758	0.90	0.45–1.79
B vs E	0.642	1.22	0.53–2.82
C vs E	< 0.001	3.08	1.70–5.56
D vs E	0.338	1.32	0.75–2.34
F vs E	0.118	1.61	0.89–2.92
CAP pathway followed, partially used vs No	0.094	0.70	0.46–1.06
CAP pathway followed, yes vs no	0.059	0.65	0.41–1.02
Antibiotic therapy, levofloxacin only vs other antibiotics	< 0.001	0.46	0.34–0.63
Antibiotic therapy, cefuroxime plus azithromycin vs other antibiotics	0.314	0.68	0.32–1.45
Infectious/respiratory specialists consulted, yes vs no	< 0.001	1.94	1.33–2.84

*c statistic = 0.844, p value for Hosmer and Lemeshow Lack of Fit Test = 0.7587.

It is noteworthy that the time from presentation to the emergency department until the first dose of antibiotic did not influence mortality. In addition to the data provided in Table 1, the mortality rates for the 1,235, 1,078, and 924 patients who received antibiotics within 0 to 4, 4 to 8, and > 8 h after presentation to the emergency department were 9.2%, 8.6%, and 8.7%, respectively. When we removed the patients who received antibiotics prior to presentation to the emergency department from the above data, the numbers of patients were 1,028, 876, and 712, for 0 to 4 h, 4 to 8 h, and > 8 h, respectively; and the corresponding mortality rates were 8.3%, 7.9%, and 8.4%.

One thousand nine hundred seventy-three patients (64.8%) received a single antibiotic for the treatment of their pneumonia. Most of these, 1,838 patients (93%) received levofloxacin only. One hundred eighty-eight patients (6.2%) received cefuroxime and azithromycin only. An additional 628 patients received two antibiotics, 406 patients received three, 121 patients received four, and 77 patients received five or more antibiotics. In most instances, the multiple antibiotics represented sequential therapy.

Five factors were significantly associated with mortality in the multivariate analysis (Table 3): pneumonia severity of illness score, increasing age, site of care, consultation by a respirologist or an infectious diseases physician, and functional status at the time of admission (using a wheelchair or being bedridden at the time of hospital admission was associated with increased mortality). A fifth factor—treatment with levofloxacin only—was protective for mortality. In addition, compliance with the pathway was marginally associated with a reduction in mortality, although the significance was not as strong as the other factors identified above.

Table 4 compares those who died early, within 5 days of hospital admission, to those who died late, ≥ 5 days after admission. Table 5 shows the factors that were associated with early and late mortality by multivariate analysis. Increasing pneumonia severity risk score, increasing age, site of hospitalization, functional status, and consultation with an infectious diseases physician or a respirologist were independently associated with both early and late mortality. In contrast, partial or complete use of the pneumonia pathway were marginally associated with decreased early mortality, but had no effect on late mortality. A low lymphocyte count and a high potassium level were associated with early, but not with late mortality. The type of antibiotic therapy had an effect on late but not on early mortality. Treatment with levofloxacin alone or with cefuroxime plus azithromycin was associated with decreased mortality compared with treatment with other antibiotics. Only one of the patients with a potassium level > 5 mmol/L had chronic renal failure and was receiving dialysis; however, 14 others had creatinine levels > 500 mmol/L indicating acute renal failure.

Discussion

It is evident that there are many factors that contribute to mortality among patients who require hospitalization for treatment of CAP. These can be grouped as patient factors, processes of care factors, physician factors, and other factors. Fine and co-

Table 4—*Comparison of Patients Who Died Within 5 Days of Hospital Admission (Early) vs Those Who Died > 5 Days (Late) Following Admission***

Variables	Time of Death				
	Alive (n = 2,797)	Early Mortality (≤ 5 Days) (n = 100)	Late Mortality (> 5 Days) (n = 146)	Total (n = 3,043)	p Value
Age	68.5 ± 17.8	81.9 ± 9.5	80.7 ± 11.7	69.6 ± 17.7	< 0.0001
Risk score	98.1 ± 33.7	141.7 ± 31.2	132.8 ± 30.0	101.2 ± 35.1	< 0.0001
Hours from time from presenting to emergency department to administration of the first antibiotics, h	8.4 ± 13.3	8.3 ± 13.2	9.6 ± 18.2	8.5 ± 13.6	0.6183
Length of stay, d	10.7 ± 13.3	3.4 ± 1.8	22.2 ± 18.1	11.0 ± 13.7	< 0.0001
Median household income, thousand	39.3 ± 12.2	40.6 ± 11.6	40.4 ± 13.0	39.4 ± 12.2	0.3651
Male gender	1,464	52	82	1,598	0.6647
Risk class					
1	60	0	0	60	< 0.0001
2	532	2 (0.3)	3 (0.5)	537	
3	568	1 (0.2)	11 (1.8)	580	
4	1,152	34 (2.7)	46 (3.7)	1,232	
5	485	63 (9.9)	86 (13.5)	634	
Site					
A	398	13 (3)	15 (3.5)	426	0.0035
B	162	5 (2.8)	6 (3.4)	173	
C	396	28 (6.1)	33 (7.2)	457	
D	948	24 (2.3)	51 (4.9)	1,023	
E	317	10 (2.9)	10 (2.9)	337	
F	576	20 (3.1)	31 (4.9)	627	
Antibiotic therapy					
Levofloxacin only	1,583	38 (2.3)	51 (3)	1,672	< 0.0001
Cefuroxime plus azithromycin	157	6 (3.6)	3 (1.8)	166	
Other	1,057	56 (4.6)	92 (7.6)	1,205	
Lymphocytes < 1.0×10^9/L	1,327	67 (4.5)	78 (5.2)	1,472	0.0003
Creatinine > 125 mmol/L	563	49 (7.5)	39 (5.9)	651	< 0.0001
Potassium, mmol/L					
Unknown	126	3 (2.3)	1 (0.7)	130	< 0.0001
Normal	2,142	65 (2.8)	113 (4.8)	2,320	
< 3.5	368	10 (2.5)	16 (4)	394	
> 5.0	161	22 (11)	16 (8)	199	

*Data are presented as mean ± SD, No., or No. (%).

workers[8] derived a pneumonia severity of illness score based on 20 items that included demographic factors, comorbidity, physical examination findings, and laboratory and radiographic data. Scores ranged from 0 (no points are given for patients ≤ 50 years of age without comorbidity and no physiologic abnormalities) to 250, with higher scores indicating more severe pneumonia. In the original study, patients were grouped into five risk classes for mortality; classes I to III (≤ 90 points) are at low risk for death, while the mortality rate in class IV was 9%, and 27% in class V. Since the mortality for patients in the risk classes I and II in our study was very low and insufficient for estimation, the pneumonia severity was analyzed as a continuous score. Even though age is the major driver in the Fine risk score (one point is given for each year of age for male subjects and 10 points are subtracted from the total age points for female subjects), we found that increasing age still contributed to the risk of mortality over and above that which was accounted for in the severity score. Thus, we carried out additional adjustment for age in the final logistic regression model due to the residual confounding. An additional independent association between age and mortality was observed in both multivariate logistic regression and Cox proportional hazard models.

The pneumonia severity score does not consider other factors that might be important in mortality, namely functional status, site of care, and processes of care. Ethnicity is also an important factor influencing mortality due to pneumonia. Haas et al[15] found that Hispanics and Asian Americans had a lower risk of death from CAP than whites in California. In one study, African-American men admitted to Veterans Affairs hospitals in the United States had lower risk-adjusted mortality for a variety of conditions, including pneumonia.[16] Most of the population of Alberta is white. One hundred thirteen of our patients (3.7%) were Aboriginal Canadians. In an

Table 5—*Multivariate Logistic Regression Analysis of Factors Important in Early (Within 5 Days) and Late (> 5 Days) Mortality*

Effect	Early Mortality		Late Mortality	
	OR	95% CI	OR	95% CI
Risk score (per additional score)	1.024*	1.014–1.033	1.025*	1.018–1.033
Age (per additional year)	1.044*	1.016–1.074	1.028*	1.009–1.047
Site				
A vs E	0.581	0.185–1.817	0.863	0.315–2.361
B vs E	1.594	0.443–5.735	1.089	0.295–9.014
C vs E	3.157*	1.241–8.032	2.924*	1.265–6.758
D vs E	0.672	0.254–1.755	1.533	0.690–3.494
F vs E	1.370	0.523–3.586	1.597	0.689–3.703
Functional status				
Walking with assistance vs walking unassisted	1.810	0.967–3.388	1.229	0.771–1.959
Wheelchair vs walking unassisted	3.313*	1.457–7.533	1.921*	1.037–3.558
Bedridden vs walking unassisted	8.287*	2.877–23.866	3.657*	1.456–9.146
Consult—infectious diseases/respirology	1.965	0.984–3.923	2.468*	1.559–3.905
Pathway partial vs no use	0.453*	0.233–0.882	1.459	0.760–2.873
Pathway completely used	0.443*	0.216–0.909	1.184	0.596–2.354
Levofloxacin vs other	0.643	0.380–1.090	0.433*	0.289–0.647
Cefuroxime/azithromycin vs other	0.976	0.301–3.160	0.223*	0.051–0.975
Lymphocytes < 1 yes vs no	2.047*	1.206–3.477	1.051	0.716–0.975
Potassium > 5.0 vs normal	2.759*	1.411–5.397	0.888	0.950–1.929
Substance abuse yes vs no	2.795*	1.091–7.161		

*Statistically significant.

administrative database study of all persons admitted to hospital with pneumonia in Alberta over a 5-year period, patients of Aboriginal treaty status constituted 7% of the 43,642 comprising the study population.[17] In that study, Aboriginal status was not associated with increased mortality. In the current study, the mortality rate among those of Aboriginal descent was very low at 0.8%. However, these patients were considerably younger than the remainder of the pneumonia population and were more likely to be in risk classes I to III.

A major finding in this study was the contribution of functional status at the time of hospital admission as an independent predictor of mortality. Thus, patients who were in wheelchair or bedridden were 1.4 times and 4 times, respectively, more likely to die compared to patients who walked without problems. Two hundred nineteen persons (7.1%) were using wheelchairs, and 103 persons (3.3%) were bedridden. In a case-control study of 101 patients ≥ 65 years of age with pneumonia, Riquelme et al[18] reported a crude mortality rate of 26%. Bedridden state had a relative risk of 10.75 for mortality.[19] In a study of patients with COPD, Oga et al[20] noted that exercise capacity and health status were significantly predictive of mortality independent of age or airflow limitation. Davis and co-workers[21] studied persons admitted to a tertiary teaching hospital between 1987 and 1992 for cerebrovascular disease or pneumonia. They found that functional status had as much predictive value for in-hospital mortality as laboratory data. Indeed, the requirement for total assistance with bathing was the best single predictor of in-hospital mortality.

In a unique study, Salive et al[19] followed up 6,234 men and 3,035 women ≥ 65 years of age for up to 6 years. Two hundred forty-three men and 160 women died from pneumonia. Limitations in activities of daily living and cognitive impairment were independently associated with a significantly increased risk of pneumonia mortality.

Treatment with levofloxacin only was associated with a major reduction in mortality. Since this was not a randomized clinical trial, it is difficult to conclude that this effect was solely due to the antibiotic. The pathway encouraged levofloxacin use, and the fact that patients treated with levofloxacin only had low mortality could also indicate that physicians seldom change therapy in patients who are responding to treatment; indeed, this is confounding by indication. It also indicates that protocolized care with antibiotics consistent with guidelines[7] leads to lower mortality. Furthermore this observation does not demonstrate the superiority of a quinolone over a cephalosporin/macrolide combination. It is noteworthy, however, that we did not find that administration of antibiotic therapy > 8 h after presentation to the emergency department was associated with increased mortality, as has been described by others.[22,23] Recently, Silber et al[24] were

also unable to show an association between time from arrival at the emergency department to antibiotic therapy, and time to achievement of stability or mortality in patients with CAP. In an illness that typically begins days before the patient presents to the hospital, it seems unusual that a delay of administration of antibiotic therapy of a few hours would be associated with an increased mortality rate. In the absence of data from randomized controlled trials, it is difficult to be sure that this is a real finding, even though as a standard of care timely administration of antibiotic therapy is appropriate. It is important to note that our study and that of Silber et al[24] differed from the two studies[22,23] that found an increased mortality rate if time from arrival to the emergency department to the first dose of antibiotics was prolonged, in that both of these studies dealt with Medicare patients who by definition were all > 65 years of age. It is also noteworthy that Houck et al[23] could not demonstrate such an effect for those who had received antibiotic therapy prior to presentation.

Treatment at hospital C was an independent risk factor for increased mortality in the overall, early, and late mortality models after the adjustment of other factors. Hospital factors such as teaching status, type of ownership, and location have been associated with differences in mortality for a variety of conditions.[25,26] Understaffing of hospitals with nurses has also been associated with increased mortality.[27] In our study, the hospital with a higher mortality rate is one of the three hospitals in Edmonton that does not have medicine house staff. In conjunction with the other hospitals, it is part of a regional health authority under one administration. We did not monitor nurse-staffing patterns as part of our study. Greater physician experience with pneumonia, as indicated by the number of patients treated in hospital with this illness per year, is reflected in a lower mortality rate.[17] Thus, there are at least two factors that may have been different at the hospital with the higher mortality. At the end of the first year of the study, when we noted the higher mortality rate at hospital C, we reviewed all the deaths from pneumonia and noted only one preventable death.

Requirement for consultation by an infectious diseases physician or a respirologist was associated with an increased mortality rate. Consultation was likely because of deterioration or a specific complication, thus indicating a complicated hospital course, *ie*, confounding by indication. The pneumonia severity score only measures severity at the time of hospital admission. An illness is dynamic, and serial measurements of severity of illness are necessary to understand the subsequent course of illness.

One of the most interesting findings in our study is that the risk factors for early and late mortality differed substantially. The type of antibiotic therapy affected only late mortality. Austrian and Gold,[28] in a large study of bacteremic pneumococcal pneumonia in the early 1960s, noted that treatment with penicillin had no effect on mortality for the first 4 days of the illness. Mortensen et al[29] carefully determined the causes of death of the 208 patients (9%) who died within 90 days of enrollment in their study of CAP. Fifty-three percent of the deaths were pneumonia related. Factors predictive of pneumonia-related mortality included hypothermia, altered mental state, increased serum urea nitrogen levels, chronic liver disease, leukopenia, and hypoxemia. Factors predictive of pneumonia-unrelated mortality included dementia, immunosuppressive conditions, active cancer, systolic hypotension, male gender, and multilobar pulmonary infiltrates. Increased age and evidence of aspiration were predictive of both pneumonia-related and -unrelated mortality.

In a study of 157 patients with severe ARDS (severe acute respiratory syndrome), 98% had lymphopenia ($< 1 \times 10^9$/L).[28] Lymphopenia in severe acute respiratory syndrome patients peaked during week 2. We recorded only the lymphocyte count at the time of hospital admission. In our study, 67% of those who died within 5 days of hospital admission were lymphopenic at hospital admission vs 29% of the survivors. For those who died > 5 days after hospital admission, 53.4% were lymphopenic vs 43.8% for the survivors. Clearly, the role of the lymphocyte in pneumonia-related mortality requires further investigation. It should be noted that HIV status did not play a role in lymphopenia predicting mortality. Only 25 HIV-positive patients were in the study, and none died in hospital. Lymphopenia is also a marker for malnutrition. In one study, malnutrition was associated with higher mortality among men (but not women) with pneumonia.[31] Hyperkalemia was an independent predictor of early mortality in our study. In a study of 463 patients with CAP from Chile, 8% of whom died in hospital, hyperkalemia was one of 25 factors associated with mortality.[32] Since a number of our patients had acute renal failure, it is likely that this played a role in the hyperkalemia.

Our study has several strengths. It was prospective, and all patients with a diagnosis of CAP were enrolled. The limitations to our study include the fact that our case definition allowed nonradiologists to diagnose pneumonia on chest radiography. Approximately 25% of the patients had their chest radiographs read as "no pneumonia" by a radiologist. However interobserver and intraobserver variability in the interpretation of chest radiographs of patients with possible pneumonia by radiologists is well

known.[33] Air bronchograms, atelectasis, and COPD are usually not recognized by nonradiologists.[33] Some patients with radiographs read by radiologists as no pneumonia will in fact have pneumonia. In a study[34] in which simultaneously obtained high-resolution CT (HRCT) scans of the chest and chest radiographs were compared in 47 patients presenting with presumed CAP, HRCT identified all 18 cases that were apparent on chest radiography and an additional 8 cases. Thus, 8 of the 26 of the pneumonias (31%) in this study were not identified by chest radiography.[33] In a somewhat similar study[35] performed on 54 hospitalized patients, additional information provided by HRCT resulted in a change in treatment plan in 39% of patients.

In conclusion, we have shown that the following factors are independently associated with mortality among patients with CAP requiring admission to hospital: pneumonia severity score, increasing age, functional status at time of hospital admission, and requirement for consultation with a respirologist or infectious diseases physician. Treatment with levofloxacin only was associated with a decreased risk of mortality. We have also shown that some of the factors associated with early mortality differ from those associated with late mortality.

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