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Pneumonia: An Arrhythmogenic Disease?

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Abstract

Introduction—Recent studies suggest that there is an increase in cardiovascular disease after pneumonia, however there is little information on cardiac arrhythmias after pneumonia. The aims of this study were to assess the incidence of, and examine risk factors for, cardiac arrhythmias after hospitalization for pneumonia.

Methods—We conducted a national cohort study using Department of Veterans Affairs (VA) administrative data including patients 65 years hospitalized with pneumonia in fiscal years 2002–2007, receiving antibiotics within 48 hours of admission, who did not have a prior diagnosis of a cardiac arrhythmia, and having at least one year of VA care. We included only the first pneumonia-related hospitalization, and follow-up was for the 90 days after admission. Cardiac arrhythmias included atrial fibrillation, ventricular tachycardia/fibrillation, cardiac arrest, and symptomatic bradycardia. We used a multilevel regression model, adjusting for hospital of admission, to examine risk factors for cardiac arrhythmias.

Results—We identified 32,689 patients who met the inclusion criteria. Of these, 3,919 (12%) had a new diagnosis of cardiac arrhythmia within 90-days of admission. Variables significantly associated with increased risk of cardiac arrhythmia included increasing age, history of congestive heart failure, and a need for mechanical ventilation or vasopressors. Beta-blocker use was associated with a decreased incidence of events.

Conclusion—An important number of patients have new cardiac arrhythmia during and post-hospitalization for pneumonia. Additional research is needed to determine if use of cardioprotective medications will improve outcomes for patients hospitalized with pneumonia. At risk patients hospitalized with pneumonia should be monitored for cardiac arrhythmias during the hospitalization.

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INTRODUCTION

More than 1.2 million Americans were hospitalized for pneumonia in 2006, making it the second most common reason for hospitalization in the United States [1]. Pneumonia is also the leading cause of death secondary to infection [2]. The elderly population is particularly susceptible with pneumonia being the seventh leading cause of death in adults 65 years of age [2, 3]. Although pneumonia is one of the leading causes of death and is associated with significant morbidity, there is little information about whether new onset cardiac arrhythmias contribute to this morbidity.

Recent studies suggest that there are a clinically significant number of cardiovascular events following hospital admission for pneumonia [4–8]. These studies have linked respiratory infection with increased risk of cardiovascular events in the short term, from the time of hospital admission to within 15 days of discharge, with the greatest risk occurring during the first week following diagnosis [5–8]. Although the majority of studies have focused on myocardial infarction, Musher et al. [4] found significant occurrences of worsening congestive heart failure and preexisting cardiac arrhythmias at the time of hospital admission for pneumonia.

The majority of previous research has focused on defining the incidence of acute coronary syndromes, and to a lesser extent congestive heart failure, at the time of hospitalization for pneumonia. However, given the likely mechanisms at work, other cardiovascular events such as cardiac arrhythmias, stroke, and myocarditis, may also play an important role in the mortality and morbidity associated with pneumonia. The purpose of this study was to examine the incidence of cardiac arrhythmias within 90 days of admission for pneumonia, utilizing the extensive clinical databases of the Department of Veterans Affairs.

METHODS

For this study, we used data from the administrative databases of the Department of Veterans Affairs (VA) Health Care System. These databases are the repositories of clinical data from more than 150 of the VA hospitals and 850 outpatient clinics [21]. The Institutional Review Boards of the University of Texas Health Science Center at San Antonio and Dallas VA medical center approved this study.

Inclusion and Exclusion Criteria

Subjects included in this study:

- a. Were age 65 or older on the date of admission.
- b. Had at least one VA outpatient clinic visit in the year preceding the index admission.
- c. Received at least one active and filled outpatient medication from a VA pharmacy within 90-days of admission.
- d. Were hospitalized during fiscal years 2002–2007 (Oct 2001–Sep 2007).
- e. Had a previously validated discharge diagnosis of pneumonia/influenza- either a primary ICD-9 codes 480.0–483.99 or 485–487 [22] or a secondary discharge diagnosis of pneumonia with a primary diagnosis of respiratory failure (ICD-9 code 518.81) or sepsis (ICD-9 code 038.xx) [22].
- f. Received at least one dose of antimicrobial therapy within the first 48 hours of admission.

We excluded those subjects with a prior diagnosis of cardiac arrhythmias, so as to examine only incident cardiac arrhythmias. If a subject was admitted more than once during the study period, only the first hospitalization was included.

Data

We used demographic, utilization, and comorbidity data from the National Patient Care Database. Pharmacy data was obtained from the VA Decision Support System National Data Extracts and Pharmacy Benefits Management, and vital status information was obtained from VA's Vital Status File, which incorporates data from veterans' death benefits claims, inpatient deaths, Medicare Vital Status files, and the Social Security Administration death master file. Encrypted patient identifiers linked the information across these databases.

We obtained demographic information (age, sex, race, marital status) from inpatient and outpatient data. Race categories included white, black, Hispanic, and other/unknown. To infer current efforts at smoking use and/or cessation, we identified ICD-9 codes for tobacco use (305.1, V15.82), smoking cessation clinic use, and/or use of medications for the treatment of nicotine dependence (Zyban, nicotine replacement, or varenicline).

We also obtained information on comorbid conditions from inpatient and outpatient administrative data. Alcohol abuse was defined by ICD-9 codes 291, 303, 305.0, and illicit drug use by ICD-9 codes 292, 304, 305 excluding 305.1. We used Charlson's comorbidity methodology to classify other preexisting comorbid conditions, both individually and as a composite score [24,25]. Charlson's comorbidity system includes 19 comorbid conditions, which are classified using ICD-9 codes from prior outpatient and inpatient encounters [26].

Pharmacy data were obtained from the Pharmacy Benefits Management group databases as well as from the DSS NDEs. Subjects were considered a current user of a given medication if they had enough pills to last until the date of hospitalization assuming an 80% compliance rate. To further control for potential confounding by medications, a count of unique drugs in each of the following classes per patient was calculated for drugs refilled/filled within 90 days of presentation: cardiac (excluding statins and beta-blockers), pulmonary and diabetic medications. In addition, dichotomized variables were created to identify those with statin or beta-blocker use within 90-days prior to hospitalization.

Other factors included intensive care unit admission, receipt of invasive mechanical ventilation, and/or vasopressors, all within 48 hours of the admission of interest.

Outcomes

We identified cardiac arrhythmias within 90-days of index admission using ICD9 discharge codes. Cardiac arrhythmias included symptomatic bradycardia and other unspecified arrhythmias (including multifocal atrial tachycardia) (427.8×), atrial fibrillation (427.31–427.32), ventricular fibrillation or tachycardia (427.1, 427.4×), and cardiac arrest (427.5, v12.53).

Statistical Analyses

Statistical significance was defined as a two-tailed p value of ≤ 0.05 . Bivariate statistics were used to test the association of sociodemographic and clinical characteristics with cardiac arrhythmias. Categorical variables were analyzed using the chi-square test and continuous variables were analyzed using Student's t-test.

A generalized linear mixed-effect "multi-level regression" model with the admitting hospital as a random effect was used to examine the association between potential predictors and the

dependent variable of incident cardiac arrhythmia. Covariates included: patient sex, race, Hispanic ethnicity, individual comorbid conditions, tobacco use, alcohol abuse or dependence, medications, use of mechanical ventilation, use of vasopressors, and guideline-concordant antibiotic therapy.

We then performed similar multi-level regression models for the outcomes of 30-day or 90-day mortality with incident cardiac arrhythmia included as a covariate in addition to the covariates discussed above.

All analyses were performed using STATA 10 (StataCorp LP, College Station, Texas).

RESULTS

We identified 32,689 patients who met the inclusion criteria. The mean age was 74.65 (standard deviation (SD) 6.76) years and 32,080 (98%) were men. The majority of the cohort was non-Hispanic white (76%) with black race and Hispanic ethnicity accounting for 12.6% and 7.3%, respectively (Table 1). Approximately, one third (38.2%) of patients were either active smokers or attempting to quit, 4.4% had a history of alcohol abuse, and 1.1% had a history of drug abuse. Overall, 29% of patients were prescribed statins and 28% beta-blockers in the 90 days prior to admission. Patients were prescribed 1.22 (± 1.36) other cardiac medications, 0.3 (± 0.65) diabetes medications, and 1.23 (± 1.94) pulmonary medications in the 90-days prior admission.

In our cohort, 3,919 (12%) patients developed cardiac arrhythmias within 90 days of hospital admission for pneumonia. There were 2,625 (8%) with new onset atrial fibrillation, 1,105 (3.4%) patients with other arrhythmias including significant bradycardia and multifocal atrial tachycardia, 323 (1%) with cardiac arrest, and 105 (0.3%) with ventricular fibrillation or tachycardia. Table 2 shows demographic and comorbid condition data by subsequent diagnosis of arrhythmias. In the univariate analysis, factors significantly associated with arrhythmia diagnosis included white race, other/unknown race, history of myocardial infarction, history of congestive heart failure, and history of peripheral vascular disease. Factors associated with lower risk of arrhythmia diagnosis included being black or Hispanic ethnicity, having a history of dementia, hemiplegia or paraplegia, and malignancy with metastases. In addition, other factors associated with low risk of arrhythmia diagnosis included number of attempts at smoking cessation, and the number of cardiac medications prescribed within 90 days of hospitalization.

Univariate outcomes

The overall average length of stay was 7.86 (SD ± 13.33) days. During their hospital course, 4,353 (13.3%) patients required admission to the intensive care unit, 1,404 (4.3%) required vasopressor support, and 2,105 (6.4%) required mechanical ventilation. Patients who had an arrhythmic event had a significantly higher ($p < 0.01$) 30-day mortality (18.4% vs. 13.1%) and 90-day mortality (31.0% vs. 20.8%). Patients in the arrhythmia group also had significantly higher rates of admission to the intensive care unit (27.3% vs. 11.4%) and required vasopressors (8.4% vs. 3.7%) and mechanical ventilation (12.7% vs. 5.6%) more often than their counterparts.

Multilevel regression models

In the multilevel regression analysis, factors significantly associated with cardiac arrhythmias included age (odds ratio [OR] 1.02, 95% confidence interval [CI] 1.02 – 1.03), being white (OR 1.32, 95% CI 1.08 – 1.60), other/unknown race (OR 1.43, 95% CI 1.13 – 1.83), use of mechanical ventilation (OR 2.15, 95% CI 1.88 – 2.46), use of vasopressors (OR 1.57, 95% CI 1.33 – 1.84), and history of congestive heart failure (OR 1.34, 95% CI

1.22 – 1.46). Factors associated with decreased risk of arrhythmias included history of dementia (OR 0.75, 95% CI 0.63 – 0.89), hemiplegia or paraplegia (OR 0.49, 95% CI 0.33 – 0.70), and use of beta-blockers (OR 0.92, 95% CI 0.85 – 0.99).

When we examined the outcomes of 30-day or 90-day mortality, after adjusting for other potential confounders, incident cardiac arrhythmias were still significantly associated with increased 30-day (OR 1.35 (95% CI 1.21–1.51) and 90day (OR 1.64, 95% CI 1.50–1.79) mortality.

DISCUSSION

The main findings in our study were the occurrence of new-onset cardiac arrhythmias in a large number of patients with pneumonia, and an association between cardiac arrhythmias and an increased severity of illness, as demonstrated by the association with mechanical ventilation and vasopressor use. In addition, incident cardiac arrhythmias are associated with worse 30-day and 90-day mortality in patients hospitalized with pneumonia.

Prior research has demonstrated that a significant proportion of mortality within 90 days of admission for pneumonia is attributable to other comorbid conditions [5–8], and that an important number of cardiovascular events occur during, or soon after, hospitalization for pneumonia. Most of these studies focused on the association between pneumonia and acute coronary syndromes though one study [4] also described a significant occurrence of worsening congestive heart failure and new onset arrhythmias at the time of hospitalization for pneumonia. However, there is little data on the association between pneumonia and cardiac arrhythmias.

Our study found that new onset arrhythmias occur in a significant number of elderly patients with pneumonia. Our rates were higher than those reported in Musher's study (12% vs. 6.8%); however, our study population was larger, our definition of arrhythmias was more inclusive, including symptomatic bradycardias and cardiac arrest, and we included patients with any pneumonia, as opposed to pneumococcal pneumonia alone.

One proposed explanation for the increased risk in cardiovascular arrhythmias around the time of respiratory infection is the increase in serum inflammatory cytokines in serious infections [9–10]. Other possible explanations include disturbed hemodynamic homeostasis, pro-thrombotic conditions, and increased catecholamine release [11]. Additionally, acute infections may have a direct inflammatory effect on coronary arteries, myocardium, and pericardium, as well as direct infection of cardiomyocytes, which may lead to the development of acute arrhythmias [12–20]. Also, acute physiologic or metabolic disturbances associated with pneumonia, such as hypo/hyperthermia, electrolyte abnormalities, and hypoxemia, may provoke arrhythmias.

In our study, factors associated with increased risk of arrhythmias were increased age, congestive heart failure, and septic shock, which clinicians should take into consideration when caring for patients with pneumonia. The development of cardiac arrhythmias was associated with greater severity of illness, as evidenced by increased length of hospital stay, increased rate of ICU admission, more frequent use of vasopressors, and greater need for mechanical ventilation, as well as increased mortality.

Factors associated with decreased risk of arrhythmia included use of beta-blockers prior to admission, which may prevent arrhythmias due to their pharmacologic profiles. Dementia was also associated with a decreased risk of arrhythmias, though we hypothesize that this may be due to low clinical evaluations for arrhythmias in these patients, including a lower likelihood of telemetry monitoring during admission, and not as an actual protective factor.

The major strength of our study is that we have a very large sample size from over 100 hospitals distributed nationwide; however, there are also limitations. Given that the data for this study was taken from the database from a primary study of pneumonia in the elderly, only patients 65 years of age and older were included. In addition, the VA patient population is predominantly male (98%), making the results of this study poorly generalizable to women and younger patients. Since this is an administrative database study, several limitations arose as a result. There is no information on the duration of the arrhythmias and it is difficult to determine whether the arrhythmias contributed directly to the increased mortality. In addition, factors such as concomitant electrolyte abnormalities can not be assessed. In addition, we have insufficient space to examine whether certain antibiotics such as quinolones or macrolides, which are known to have arrhythmogenic qualities. Another limitation was reliance on ICD-9 diagnosis of arrhythmias rather than clinical information, which may lead to underreporting. Additionally, some microorganisms may have a stronger association with arrhythmias [12–13,15–17,20] than others, however that analysis is beyond the scope of the current study; we are currently examining this issue in a different study.

In conclusion, our study demonstrates a significantly increased risk for new-onset cardiac arrhythmias in elderly patients within 90 days of hospital admission for pneumonia. Patients who developed arrhythmias were more likely to be older, had greater severity of illness, and had higher mortality as well as worse long-term outcomes. Further research is needed to better determine the risk of arrhythmias in patients with pneumonia, to assess how long these patients remain at risk for new onset arrhythmias after resolution of the infection, to determine the mechanisms responsible for these events, and to examine potential therapies to minimize these arrhythmias following serious infections such as pneumonia.

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Table 1

Demographics and clinical characteristics by cardiac arrhythmia status

Variable	Cardiac Arrhythmia		P-value
	Yes	No	
	N = 3,919 N (%)	N = 28,770 N (%)	
Demographics			
Age in years, mean (SD) ¹	75.47 (6.6)	74.54 (6.7)	<0.01
Men	3,848 (98.2)	28,232 (98.1)	0.8
Race / Ethnicity			
White	3,118 (79.6)	21,608 (75.1)	<0.01
Black	382 (9.8)	3,725 (13.0)	<0.01
Hispanic	200 (5.1)	2,182 (7.6)	<0.01
Other/unknown	219 (5.6)	1,255 (4.4)	<0.01
Married	2,089 (53.3)	15,242 (53.0)	0.7
Nursing home residence	35 (0.9)	190 (0.7)	0.1
Guideline antibiotic use	3,482 (88.9)	25,737 (89.5)	0.2
Myocardial infarction	231 (5.9)	1,419 (4.9)	0.01
Congestive heart failure	838 (21.4)	4,710 (16.4)	<0.01
Peripheral vascular disease	583 (14.9)	3,896 (13.5)	0.02
Cerebrovascular event	647 (16.5)	4,768 (16.6)	0.9
Dementia	164 (4.2)	1,551 (5.4)	<0.01
Chronic obstructive pulmonary disease	2,015 (51.4)	14,827 (51.5)	0.9
Rheumatoid disease	117 (3.0)	789 (2.7)	0.4
Peptic ulcer disease	112 (2.9)	950 (3.3)	0.1
Cirrhosis	36 (0.9)	252 (0.9)	0.9
Hepatic failure	14 (0.4)	121 (0.4)	0.6
Diabetes mellitus	1,161 (29.6)	8,827 (30.7)	0.2
Diabetes mellitus with complications	350 (8.9)	2,559 (8.9)	0.9
Hemiplegia/paraplegia	32 (0.8)	472 (1.6)	<0.01
Chronic kidney disease	424 (10.8)	2,991 (10.4)	0.4
Malignancy	880 (22.5)	6,897 (24.0)	0.04
Malignancy with metastases	119 (3.0)	1,144 (4.0)	<0.01
Tobacco use/cessation	1,427 (36.4)	11,056 (38.4)	0.02
Alcohol abuse	156 (4.0)	1,278 (4.4)	0.2
Drug abuse	37 (0.9)	328 (1.1)	0.3
Medications			
Number of cardiac ² medications, mean (SD) ¹	1.29 (1.38)	1.21 (1.36)	<0.01
Number of diabetes medications, mean (SD) ¹	0.29 (0.62)	0.31 (0.66)	0.1
Number of pulmonary medications, mean (SD) ¹	1.29 (1.94)	1.29 (1.95)	0.9
Statins	1,124 (28.7)	8,462 (29.4)	0.3
Beta-blockers	1,090 (27.8)	8,224 (28.6)	0.3

¹SD – Standard Deviation,

²excluding statins and beta-blockers

Table 2

Clinical outcomes by arrhythmia status

Outcome	Cardiac Arrhythmia		P-value
	Yes	No	
	N = 3,919 N (%)	N = 28,770 N (%)	
30-day mortality	721 (18.4)	3,763 (13.1)	<0.01
90-day mortality	1,216 (31.0)	5,997 (20.8)	<0.01
ICU admission	1,072 (27.4)	3,281 (11.4)	<0.01
Length of stay (SD ¹)	10.36 (16.0)	7.52 (12.9)	<0.01
Mechanical ventilation	498 (12.7)	1,607 (5.6)	<0.01
Vasopressor use	330 (8.4)	1,074 (3.7)	<0.01

Table 3

Multi-level regression model of factors associated with cardiac arrhythmia diagnosis within 90-days of hospitalization for pneumonia

Variable	Odds Ratio	95% Confidence Interval
Age	1.02	1.02 – 1.03
Male gender	1.13	0.87 – 1.46
Race/ethnicity		
Black	0.93	0.75 – 1.17
White	1.32	1.08 – 1.60
Unknown/other race	1.43	1.13 – 1.83
Nursing home resident	1.44	1.00 – 2.09
Myocardial infarction	1.10	0.94 – 1.28
Congestive heart failure	1.34	1.22 – 1.46
Peripheral vascular disease	1.08	0.98 – 1.19
Cerebrovascular disease	1.04	0.94 – 1.14
Dementia	0.74	0.63 – 0.89
Chronic obstructive pulmonary disease	0.93	0.86 – 1.01
Rheumatologic disease	1.05	0.86 – 1.29
Peptic ulcer disease	0.86	0.70 – 1.05
Cirrhosis	1.20	0.81– 1.76
Hepatic failure	0.78	0.42 – 1.44
Diabetes mellitus	0.95	0.86 – 1.06
Diabetes mellitus with complications	1.02	0.89 – 1.18
Hemiplegia/paraplegia	0.49	0.33 – 0.70
Chronic kidney disease	0.97	0.86 – 1.09
Malignancy	0.98	0.90 – 1.06
Malignancy with metastases	0.81	0.66 – 1.00
Drug abuse	0.96	0.67 – 1.36
Alcohol abuse	0.97	0.81 – 1.15
Smoking use/cessation	0.99	0.92–1.07
Statin	0.96	0.89 – 1.04
Cardiac medications ¹	1.03	1.01 – 1.07
Beta-blockers	0.92	0.85 – 0.99
Diabetes medications	0.98	0.91 – 1.06
Pulmonary medications	1.00	0.98 – 1.02
Use of guideline concordant antibiotics	1.10	0.98 – 1.23
Mechanical ventilation	2.15	1.88 – 2.46
Vasopressor use	1.57	1.33 – 1.84

¹ excluding statins and beta-blockers