Cardiovascular events associated with Streptococcus pneumoniae pneumonia versus influenza pneumonia

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ABSTRACT

Introduction: Cardiovascular events have been reported in patients with serious community-acquired pneumonia (CAP) due to the systemic inflammatory response induced by the invading pulmonary pathogen. It is unclear if the etiology of pneumonia can play a role in the frequency of cardiovascular events in these patients. If S. pneumoniae and influenza produce different levels of systemic response, it would be expected that patients with these pathogens would have different rates of cardiovascular events.

Objective: The objective of this study was to compare the incidence of cardiovascular events in hospitalized patients with CAP due to S. pneumoniae versus influenza.

Methods: This was a secondary analysis of the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study database. The following cardiovascular events were collected in hospitalized patients with S. pneumoniae or influenza CAP: 1) Cardiopulmonary edema (CPE), 2) pulmonary embolism (PE), 3) new cardiac arrhythmia (NA), 4) myocardial infarction (MI), 5) worsening of long-term cardiac arrhythmia (LTA), and 6) cerebrovascular accident (CVA).

Results: A total of 1177 hospitalized patients with CAP were included in the study, 912 with S. pneumoniae, and 265 with influenza. Significant differences were found only in CPE (6% vs 3%, respectively, P=0.019).
Conclusions: This study failed to document any clinically significant differences in cardiovascular events in hospitalized patients with S. pneumoniae vs influenza CAP. We speculate that patients with CAP requiring hospitalization have a high severity of disease and a significant level of systemic inflammatory response independent of the etiologic agent leading to equivalent risk for cardiovascular events.

INTRODUCTION

•Cardiovascular events (CVE) have been reported in patients with serious community-acquired pneumonia (CAP) due to the systemic inflammatory response induced by the invading pulmonary pathogen [1,2]. Study findings suggest that being hospitalized for pneumonia, as opposed to other medical illness, heightens the risk of CV events such myocardial infarction(MI), arrhythmia, and/or congestive heart failure [1].
•Patients with influenza pneumonia are at high risk for cardiovascular events. Has been noted that in these patients an increased cardiac stress, hypoxemia, and inflammation may contribute to acute cardiac events [2].
•A previously unrecognized pathogenic mechanism by which Streptococcus pneumoniae causes direct cardiotoxicity is the development of microscopic bacteria-filled lesions within the heart[1,2,6].
•Cardiovascular events are common during the clinical course of pneumonia due to either Streptococcus pneumoniae or Influenza.[3, 4] It is unclear if the etiology of pneumonia can play a role in the frequency of cardiovascular events in these patients. If S. pneumoniae and influenza produce different levels of systemic response, it would be expected that patients with these pathogens would have different rates of cardiovascular events [5].
•The objective of this study was to determine the difference of CVE associated with Streptococcus pneumoniae pneumonia versus influenza pneumonia.

MATERIALS AND METHODS

•**Study Design:** This was a secondary analysis of the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study database. Hospitalized patient with the diagnosis of Community-acquired Pneumonia were included in the analysis.
•**Definition of CAP:** CAP was defined as a new infiltrate on x-ray or CT along with one of the following; 1) Temperature >100F° or <96F°. 2) Cough or shortness of breath. 3) Leukocytosis > 11000 cells/mm3, leukopenia< 4000/mm3 or >10% band forms per microliter.

Definitions for Cardiovascular Events:
•*Cardiopulmonary edema:* New or worsened CHF defined by Framingham criteria.

•*Pulmonary Embolism:*
1. A positive ventilation-perfusion (V/Q) scan
2. A positive pulmonary angiography
3. A positive spiral (helical) CT scanning with intravenous contrast

•*New Cardiac Arrhythmias and Worsening long term Arrhythmias:*
1. Atrial flutter, atrial fibrillation, ventricular tachycardia
2. Atrial fibrillation
3. New-onset or worsening supraventricular arrhythmias and ventricular bigeminy/tachycardia
4. Atrial fibrillation, atrial flutter, supraventricular tachycardia, multifocal atrial tachycardia, ventricular tachycardia, or ventricular fibrillation.

•*Acute Myocardial Infarction (AMI)*:
1. A typical increase and gradual decrease in biochemical markers of myocardial necrosis and ischemic symptoms, development of pathologic Q waves on electrocardiogram, electrocardiogram changes indicative of ischemia, or coronary artery intervention
2. Pathologic findings of AMI
3. ST elevation myocardial infarction (STEMI).

•*Cerebrovascular accidents (CVA)*: The sudden death of some brain cells due to lack of oxygen when the blood flow to the brain is impaired by blockage or rupture of an artery to the brain

RESULTS

•A total of 1,177 hospitalized patients with CAP were included in the study, 912 with S. pneumoniae and 265 with influenza, as depicted in Figure 1.

•Patient characteristics are depicted in Table 1.

•The number of cardiovascular events present in each study group is depicted in Figure 2.

•Significant differences were found only in CPE (6% vs 3%, respectively, P=0.019). Of the 265 patients with Influenza Pneumonia 17(6%) had a cardiopulmonary edema while of the 912 Streptococcus pneumoniae pneumonia patients 13(3%) had a cardiopulmonary edema (p=0.019).

RESULTS

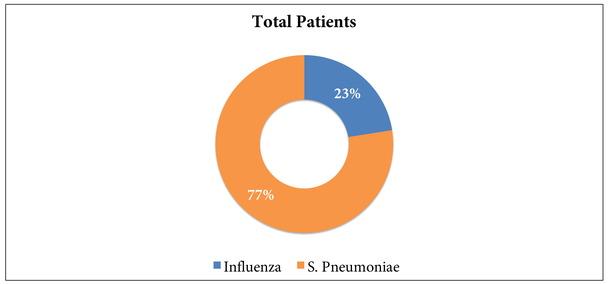

Figure 1. Total Patients Hospitalized with CAP (CAPO International Cohort Study Database)

Table 1. Patient Characteristics Table

Variables	Flu (+) n = 265	PNA (+) n = 912	P-value
Demographics			
Age, Median (IQR)	45 (27)	62 (31)	<0.001
Sex, n (%)	128 (48)	554 (61)	<0.001
Nursing Home, n (%)	3 (1)	45 (5)	0.004
Comorbidities			
Antiplatelet Medications, n (%)	1 (0)	75 (8)	<0.001
HIV, n (%)	4 (2)	144 (16)	<0.001
Liver Disease, n (%)	7 (3)	84 (9)	<0.001
Cancer, n (%)	9 (3)	94 (10)	<0.001
COPD, n (%)	35 (13)	185 (20)	0.009
Cardio-pulmonary Edema, n (%)	17 (6)	13 (3)	0.019
Pulmonary Embolism, n (%)	3 (1)	0 (0)	0.045
CHF, n (%)	20 (8)	103 (11)	0.087
Renal Disease, n (%)	18 (7)	87 (10)	0.18
Cardiac Arrhythmia, n (%)	12 (5)	33 (7)	0.203
Diabetes Mellitus, n (%)	40 (15)	146 (16)	0.774
Acute Myocardial Infarction, n (%)	3 (1)	6 (1)	1
Long-term Arrhythmia, n (%)	6 (2)	11 (2)	1
CVA, n (%)	0 (0)	1 (0)	1
Physical Examination			
Respiratory Rate, Median (IQR)	26 (12)	24 (10)	0.003
Systolic Blood Pressure, Median (IQR)	120 (34.8)	117 (33)	0.005
Temperature, Median (IQR)	37.8 (1.7)	37.8 (2)	0.061
Altered Mental Status, n (%)	39 (15)	148 (16)	0.568
Labs / Radiography			
PAO2 (ABG), Median (IQR)	71.5 (34.5)	61.3 (18.1)	<0.001
Hematocrit, Median (IQR)	39 (7)	37.8 (7.9)	<0.001
BUN, Median (IQR)	23 (23)	30 (31.6)	<0.001
Glucose, Median (IQR)	114 (44)	116 (46)	0.696
Sodium, Median (IQR)	136 (6)	135 (6)	0.045
Ph (ABG), Median (IQR)	7.4 (0.2)	7.4 (0.1)	0.918
Pleural Effusion, n (%)	11 (100)	12 (92)	1
Severity of Disease			
Admitted to ICU, n (%)	119 (45)	210 (29)	<0.001
Pneumonia Severity Index, Median (IQR)	90 (53)	101 (50.2)	0.002

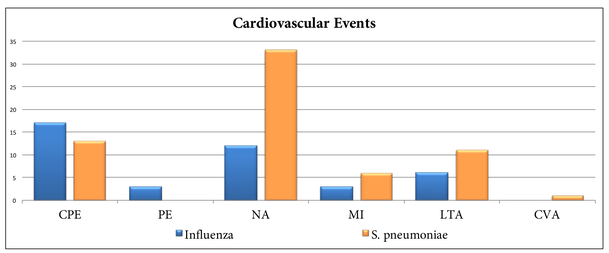

Figure 2. Cardiovascular Events of patients hospitalized with CAP (CAPO International Cohort Study Database)

CONCLUSIONS

- This study failed to document any clinically significant differences in cardiovascular events in hospitalized patients with *S. pneumoniae* versus influenza CAP.
- We speculate that patients with CAP requiring hospitalization have a high severity of disease and a significant level of systemic inflammatory response independent of the etiologic agent leading to equivalent risk for cardiovascular events.
- Another hypothesis that can explain our results is the cardiovascular stress produced by the hypoxemia associated with pneumonia and the tachycardia associated with systemic infection are the primary factors leading to cardiovascular events irrespectively of etiologic agents.
- The hypercoagulability state associated with sepsis may also play a role in the development of ischemia with subsequent development of cardiovascular events.
- Interventions to prevent development of cardiovascular events in patients with pneumonia may significantly increase the clinical outcomes of these patients.

REFERENCES

1. Corrales-Medina VF, musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. Lancet. 2013; 38(9865):496-505.
2. Song BG, Wi YM, Lee YJ, Hong CK, Chun WJ, Oh JH. Clinical features in adults patients with in-hospital cardiovascular events with confirmed 2009 Influenza A (H1N1) virus infection: comparison with those without in-hospital cardiovascular events. J Chin Med Assoc. 2012 Sep; 75(9): 435-41.
3. Loomba RS, Aggarwal S, Shah PH, Arora RR. Influenza vaccination and cardiovascular morbidity and mortality: analysis of 292,383 patients. J Cardiovasc Pharmacol Ther. 2012 Sep; 17 (3):277-83.
4. Warren-Gash C, Hayward AC, Hemingway H, Denaxas S, Thomas SL, Timmis AD, et al. Influenza Infection and risk of acute myocardial infarction in England and Wales: a Caliber self-controlled case series study. J Infect Dis. 2012 Dec 1; 206(11):1652-9.
5. Guan X, Yang W Sun X, Wang L, Ma B, Li H, et al. Association of influenza virus infection and inflammatory Cytokines with acute myocardial infarction. Inflamm Res. 2012 Jun Jun; 61(6):591-8.
6. Brown AO, Mann B, Gao G, Hankins JS, Humann J, Guardina J, et al. (2014) Streptococcus Pneumoniae Translocates into the Myocardium and Forms Unique Microlesions that disrupt Cardiac Function. PLoS Pathog 10(9):e1004383. Doi:10.1371/journal.ppat.1004383