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ORIGINAL RESEARCH

Severity of disease and mortality for hospitalized patients with community-acquired viral pneumonia compared to patients with community-acquired bacterial pneumonia

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Abstract

Background: There exists a large body of literature to help identify, diagnose, treat, and manage community-acquired pneumonia (CAP). Despite this, there is little data that directly compares the clinical syndromes and complications of pure bacterial pneumonia to pure viral pneumonia. Our study compares the clinical presentation, morbidity and mortality of viral vs. bacterial etiologies of CAP.
Methods: This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) international study database. Data was collected concerning patient demographics, physical examination findings, laboratory findings, radiological findings, severity of illness, and clinical outcomes and stratified according to the two study groups, CAVP and CABP. A microbiological diagnosis of CABP was based on the isolation of a bacterium from a respiratory sample, blood culture and/or identification of a urinary antigen for Streptococcus or Legionella; microbiological diagnosis of CAVP was based on polymerase chain reaction or antigen detection from respiratory samples.
Results: Our study included 1,913 patients. Of these, 286 (15.0%) had viral infection, while 1,627 (85.0%) had CAVP. We found that bacterial CAP patients are older, more frequently male, and suffer from a higher proportion of comorbidities when compared to viral CAP patients. Comparison of physical exam findings and laboratory values failed to find a clinically significant difference between bacterial and viral CAP patients. When comparing severity of illness, bacterial CAP patients had greater frequency of PSI ≥ class IV; however, viral CAP patients more frequently needed ICU admission, ventilator support, vasopressor support, and had higher rate of in hospital mortality.
Conclusions: Our study confirms the extreme difficulty differentiating CABP from CAVP using demographics, physical exam, or x-ray findings. We found no major clinical or laboratory findings distinguishing CABP from CAVP. The increased severity of illness of CAVP compared to bacterial etiologies shows that PSI scores may not be an accurate indicator of severity of disease. More studies are needed to identify the best process of care for patients with CAP, including the potential benefits of routine respiratory viral panel testing and empiric antiviral therapy.

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Introduction

Pneumonia is an extremely common, yet exceedingly dangerous condition that makes up 423,000 emergency room visits and is the 8th leading cause of death in the United States, according to the CDC [1]. Inpatient community-acquired pneumonia (CAP) treatment is often empiric and laboratory testing may not result in a definite organism [2]. It has been demonstrated that the microbial etiology of roughly 30%-60% of CAPs treated in the inpatient setting remains unidentified [3-6]. Of those admitted to the hospital, 10-20% of patients are admitted to the ICU [7]. While imaging and prognosticating tools like the CURB-65 and Pneumonia Severity Index assist in the diagnosis and severity assessment of pneumonia, distinguishing between viral and bacterial pneumonia remains a challenge [8].

Bacterial pneumonia is a major cause of pathogen identified CAP. For example, *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia, causing significant morbidity and mortality [7]. Tools like procalcitonin levels are helpful in the diagnosis and management of bacterial pneumonia [9]. On the other hand, viral pneumonia, a significant contributor to the prevalence of CAP, is identified by polymerase chain reaction (PCR) in more than 25% of cases using nasopharyngeal swabs and up to 40% when using lower respiratory tract samples [10]. Tools like rapid antigen testing and real time PCR assist in the diagnosis of several viral pneumonias [11]. Furthermore, morbidity and mortality of bacterial pneumonia after a preceding viral infection increases [12].

There is a large body of literature to help physicians identify, diagnose, treat, and manage CAP. Despite this, there is little data that directly compares the clinical syndromes and complications of bacterial pneumonia to viral pneumonia. Our study aims to compare the clinical presentation, morbidity and mortality of purely viral to purely bacterial etiologies of CAP.

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Methods

Study Design

This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) international study database. This multinational database is coordinated by the University of Louisville School of Medicine, Department of Medicine, Division of Infectious Diseases. Investigators from 130 hospitals across 30 countries perform data collection designed by the University of Louisville. Data is electronically transferred and validated by research associates at the University of Louisville [13].

Subjects

Patients were eligible for inclusion in analysis if they were hospitalized with CAP and a microbiological diagnosis of a viral or bacterial infection was established. Patients were enrolled from 2001 to 2017 and categorized into two groups: those with confirmed bacterial infection and those with confirmed viral infection. Patients without an identified bacterial or viral organism were excluded from the study. Additionally, patients with any coinfection were excluded.

Study Definitions

Community-acquired pneumonia (CAP):

A patient was defined as having CAP when the following 3 criteria were met: 1) presence of a new pulmonary infiltrate on chest radiograph and/or chest computed tomography scan at the time of hospitalization, defined by a board-certified radiologist's reading; 2) at least 1 of the following: a) new cough or increased cough or sputum production, b) fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F), c) changes in leukocyte count (leukocytosis: >11000 cells/μL; left shift: >10% band forms/mL; or leukopenia: <4000 cells/μL); and 3) no alternative diagnosis at the time of hospital discharge that justified the presence of criteria 1 and 2 [14].

Hospitalization with community-acquired bacterial pneumonia (CABP) vs. community-acquired viral pneumonia (CAVP):

A microbiological diagnosis of CABP was based on the isolation of a bacterium from a respiratory sample, blood culture and/or identification of a urinary antigen for Streptococcus or Legionella; microbiological diagnosis of CAVP was based on polymerase chain reaction or antigen detection from respiratory samples.

Coinfection:

A patient was defined as having coinfection if more than one microorganism was identified. All patients with coinfections were excluded from analysis.

Table 1 Most common pathogens isolated in CAVP

Pathogen	n (%)
Influenza H1N1	250 (87)
Influenza H2N2	11 (4)
Rhinovirus	8 (3)
Respiratory Syncytial Viral (A,B)	5 (2)
Parainfluenza Virus (1,2,3)	5 (2)
Adenovirus	4 (1)
Respiratory Syncytial Virus B	1 (0)
Influenza B	1 (0)
Coronavirus NL63	1 (0)

Table 2 Most common pathogens isolated in CABP

Pathogen	n (%)
Streptococcus pneumoniae	858 (53)
Haemophilus influenzae	115 (7)
MSSA	99 (6)
Legionella spp.	95 (6)
MRSA	79 (5)
Pseudomonas aeruginosa	72 (4)
Mycobacterium tuberculosis	61 (4)
Mycoplasma pneumoniae	56 (3)
Klebsiella pneumoniae	50 (3)
Escherichia coli	35 (2)
Moraxella catarrhalis	34 (2)
Chlamydia pneumoniae	18 (1)
Acinetobacter spp.	10 (1)
Nontuberculous mycobacteria	8 (0)
Proteus spp.	8 (0)
Enterobacter spp.	7 (0)
Streptococcus pyogenes	6 (0)
Pseudomonas pseudomallei	4 (0)
Other	12 (1)

Measurements

Data was collected concerning patient demographics, physical examination findings, laboratory findings, radiological findings, severity of illness, and clinical outcomes and stratified according to the two study groups, CAVP and CABP.

Statistical Analysis

Descriptive statistics were performed, with frequencies with percentages as well as medians with interquartile ranges reported for categorical and continuous variables, respectively. Chi-squared tests and Mann-Whitney U-tests were performed to compare categorical and continuous variables. P-values of less than 0.05 were considered statistically significant. R v 3.4.3 was used for all analyses [15].

Results

Our study included 1913 patients. Of these, 286 (15.0%) had CAVP, while 1,627 (85.0%) had CABP. The most common organisms identified for patients CAVP and CABP depicted in **Tables 1 and 2**, respectively.

1. Patient Demographics

Patients with CABP were older (63 [IQR: 31] vs. 48 [IQR: 28] years; P < 0.001) and were more frequently male (64% vs 51%; P <0.001) than patients with CAVP. A higher proportion of co-morbidities, including chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), Human Immunodeficiency Virus (HIV), stroke, and neoplastic diseases were also more commonly found in patients with CABP in comparison to those with CAVP.

2. Physical Examination Findings

Comparison between vitals measurements are shown in **Table 3**. While many variables were statistically significant, the differences between the CABP and CAVP groups were not considered clinically significant.

Table 3 Patient demographics, physical examination findings, laboratory findings, and radiological findings

Variable	CABP	CAVP	
Total study population, n	1627	286	
Demographics			**P-value**
Male sex, n (%)	1033 (64)	145 (51)	<0.001
Age, Median(IQR)*	63 (31)	48 (28)	<0.001
Chronic obstructive pulmonary disease	364 (22)	41 (14)	0.002
Diabetes mellitus	282 (17)	43 (15)	0.393
Current smoker	275 (17)	58 (20)	0.176
Congestive heart failure	227 (14)	27 (9)	0.038
HIV disease	200 (12)	8 (3)	<0.001
Stroke	162 (10)	8 (3)	<0.001
Neoplastic disease	160 (10)	12 (4)	0.002
Renal disease	156 (10)	21 (7)	0.268
Chronic renal failure	130 (8)	22 (8)	>0.999
Home oxygen	30 (4)	4 (1)	0.032
Physical Examination Findings	**Median (IQR)**		**P-value**
Systolic blood pressure (mmHg)	119 (33)	120 (34)	0.01
Heart rate (Beats/Minute)	104 (31)	100 (28)	0.026
Diastolic blood pressure (mmHg)	70 (20)	72.5 (23)	<0.001
Temperature (Degrees Celsius)	37.8 (1.9)	37.8 (1.7)	0.073
Respiratory rate (Breaths/Minute)	24 (8)	26 (12)	<0.001
Laboratory Findings	**Median (IQR)**		**P-value**
Serum sodium (mEq/L)	136 (7.0)	136 (6.0)	0.034
Serum glucose (mg/dl)	117 (50.0)	114 (44.0)	0.3
Hematocrit (percent)	38 (7.8)	39 (6.5)	<0.001
Blood urea nitrogen (mg/dL)	30 (32.0)	22 (21.5)	<0.001
Serum bicarbonate (mEq/L)	23.8 (6.2)	23 (6.0)	0.492
Serum procalcitonin (μg/L)	0.22 (0.94)	0.73 (4.39)	0.026
Radiological Findings	**n (%)**		**P-value**
Diffuse Bilateral, n (%)	20 (1)	9 (3)	0.03
Diffuse Unilateral, n (%)	11 (1)	15 (5)	<0.001
Multilobar Infiltrate, n (%)	857 (53)	166 (58)	0.095

*IQR: Interquartile range

3. Laboratory Findings

Comparison of laboratory values are shown in **Table 3**. Largest difference between the two groups was observed in the blood urea nitrogen (BUN), with bacterial pneumonia having a higher BUN value compared to that found in viral pneumonia (30 [IQR: 32] vs. 22 [IQR: 21.5] mg/dL; P < 0.001). Serum procalcitonin was only enumerated for 18 (6%) patients with CAVP and 118 (7%) patients with CABP; among those patients, serum procalcitonin was significantly higher for CABP compared to CAVP (0.73 [IQR: 4.39] vs. 0.22 [IQR: 0.94] μg/L; p = 0.026). Other differences were clinically or statistically non-significant.

4. Radiological Features

Radiological findings are shown in **Table 3**. On chest radiograph, patients with CAVP had more often diffuse bilateral infiltrate (3% vs 1%; P = 0.03) and unilateral diffuse infiltrate (5% vs 1%; P < 0.001). Multilobar infiltrates were also seen more commonly, though statistically non-significant, in CAVP than CABP (58% vs. 53%, P = 0.095).

5. Severity of Illness

Severity of disease on admission was characterized by frequency of pneumonia severity index (PSI) class IV or greater, need for ICU admission, altered mental status, need for ventilator support, and need for vasopressors, as shown in **Table 4**. There was a greater frequency of PSI ≥ class IV in CABP patients than CAVP patients (38% vs. 30%; P = 0.014). Patients with CAVP more frequently needed intensive care admission (33% vs. 17%; P < 0.001), ventilator support (33% vs. 18%; P <0.001), and vasopressors (20% vs. 9%; P <0.001). Altered mental status was observed to have equal frequency in both groups (15%; P = 0.928).

6. Patient outcomes

Patient outcomes were characterized by time to clinical stability, hospital length of stay, in-hospital mortality, and 30-day mortality, as shown in **Table 4**. Times to clinical stability was not significantly different between CAVP and CABP groups (4 [IQR: 6] vs. 5 [IQR: 5] days); P = 0.276). Lengths of stay were 8 days in both groups. The percentage of in hospital mortality was significantly higher in patients suffering from CAVP compared to CABP (17% vs. 9%; P <0.001); however, mortality at 30 days was not found to be significantly higher (24% vs. 21%; P = 0.345).

Discussion

Using the international CAPO database, we were able to retrospectively evaluate 1,913 patients admitted to the hospital for CAP to compare and contrast the clinical presentation, morbidity, and mortality of CAVP and CABP. Demographically, when compared to viral CAP, we found that bacterial etiologies are more commonly found in males and older patients. Bacterial pneumonia also is more frequent than viral pneumonia in patients with chronic obstructive pulmonary disease, congestive heart failure, human immunodeficiency virus, stroke, neoplastic disease, and those on home oxygen. Physical exam characteristics were found to be clinically non-significant between both groups. Furthermore, the blood urea nitrogen level, a nonspecific marker of plasma volume status, and frequency of PSI scores ≥4 were found to be higher in patients with CABP. However, the overlapping similarity in findings when comparing physical exam, laboratory data, and radiographic findings is in line with the extreme difficulty in diagnosing between bacterial vs. viral pneumonias. This is important to address as CAVP patients were observed to have a greater frequency of overall disease severity when comparing the frequency of need for ICU admission, ventilator support, vasopressor therapy, and mortality.

Table 4 Severity of illness and clinical outcomes

Total Study Population	Bacterial Infection	Viral Infection	
	1627	286	
Severity of Disease on Admission	**Frequency (%)**		**P-value**
Pneumonia severity index risk class IV or V	620 (38)	87 (30)	0.014
Need for intensive care	282 (17)	94 (33)	<0.001
Altered mental status	243 (15)	41 (15)	0.928
Need for ventilatory support	131 (18)	91 (33)	<0.001
Need for vasopressors	65 (9)	55 (20)	<0.001
Outcomes			**P-value**
Time to Clinical Stability, Median (IQR)	5 (5)	4 (6)	0.276
Length of Stay, Median (IQR)	8 (9)	8 (11)	0.195
In-Hospital Mortality, n (%)	148 (9)	50 (17)	<0.001
Mortality at 30 Days, n (%)	248 (21)	47 (24)	0.345

Our findings are both supported and refuted by currently established literature, reiterating the ambiguity between and difficulty in distinguishing the clinical presentation and severity of illness of bacterial vs. viral etiologies of CAP. For example, Johnstone found that viral pneumonias, in comparison to non-viral causes of pneumonia, were found to be more prevalent in older and frailer patients [16]. Other studies have identified a similar age difference between the two groups [6,17]. This is contrary to our finding that CABP patients are older than CAVP patients. Also, patients with COPD, CHF, and cerebrovascular disease were also found to be more commonly affected by viral CAP than bacterial CAP [17]. Similar to our findings, on the other hand, malignancy was observed to be more commonly found in patients with bacterial etiologies than viral [17]. HIV was also observed to be more common in bacterial CAP than viral CAP [18]. Despite these findings, it is important to also note that multiple studies found no significant difference in age or comorbidities between bacterial and viral etiologies of CAP [19-22].

Medical literature also supports our findings that physical exam and laboratory values are often unable to definitively distinguish between bacterial vs. viral pneumonias [17]. We did not find drastic differences between the two groups when comparing physical exam findings. These minor, yet significant differences were seen when comparing respiratory rate, blood pressure, and degree of tachycardia. We found higher BUN levels in patients suffering from CABP compared to CAVP. Higher levels of BUN have been shown to be associated with increased mortality in patients with CAP [23,24], however there were no studies found comparing BUN levels in CAVP vs. CABP. While we observed a significant difference in serum procalcitonin, the large proportion of patients missing those values should cause caution when interpreting these results. Though we observed significant, yet minor differences in serum glucose, hematocrit, and bicarbonate values between CABP and CAVP, Johnstone went on to state, “it seems unlikely that any constellation of symptoms, signs, and routine laboratory findings will ever reliably differentiate between the presence or absence of a virus.16 Furthermore, though there are several studies showing the clinical and laboratory findings of pure bacterial, pure viral, and combined bacterial-viral CAP infections [16,20,25], diagnosing and differentiating purely viral from bacterial CAP remains a problem as the etiology for a significant proportion of CAP remains unknown. It is estimated that 40-60% of CAP remains unidentified [3,26,27]. Caglayan states that bacterial CAP infections resemble combined bacterial-viral CAP in terms of mean age, immune status, leukocyte count, C-reactive protein (CRP) values, hospitalization duration and CURB-65 score [25].

We also evaluated disease severity in the setting of purely viral vs. purely bacterial CAP. CABP more frequently had PSI ≥ class IV, however CAVP significantly showed higher frequencies of ICU admission, intubation, vasopressor support, and in hospital mortality. Though it has been previously demonstrated that PSI ≥ class IV indicates increased disease severity and is strongly associated with ICU admission [28,29], our results show that PSI scores cannot be used to accurately prognosticate viral CAPs. Furthermore, literature suggests that PSI often underestimates the risk of patients with Influenza A H1N1 pneumonia [30,31] and neither PSI nor CURB-65 scores can be used to predict ICU admission or need for mechanical ventilation in influenza patients31. The CDC recommends early antiviral therapy for patients who are suspected of suffering from influenza [32].

There exist limitations to our study. First, this was a retrospective study. Secondly, while the multicenter and international nature of the study increases the strength and generalizability of results, the data collection and other differences in process of care provide an unmeasurable confounding element that may have significant impact on data collection. Also, a large portion of patients included were afflicted by the H1N1 pandemic in 2009, that may explain the increased mortality for CAVP. Patients affected by H1N1 are observed to be younger in age and with fewer comorbidities [33]. Furthermore, pathogens identified from respiratory samples may represent colonization or active infection.

In conclusion, our study confirms the extreme difficulty differentiating CABP from CAVP using demographics, physical exam, or x-ray findings. We found no major clinical or laboratory findings distinguishing CABP from CAVP. The increased severity of illness of CAVP compared to bacterial etiologies shows that PSI scores may not be an accurate indicator of severity of disease. More studies are needed to identify the best process of care for patients with CAP, including the potential benefits of routine respiratory viral panel testing and empiric antiviral therapy.

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Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

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