SCHOOL OF MEDICINE
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Clinical characteristics and outcomes of patients with Community-Acquired Pneumonia (CAP): real-life versus FDA trials

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ABSTRACT

Introduction: The FDA approval of antibiotics for CAP is based on Phase III clinical trials. For most trials, there is a consistent effect of 90% clinical cure rate for the experimental antibiotic, with a very low rate of mortality in both arms. Since these trials have significant numbers of exclusion criteria, the proportion of CAP patients in FDA trials may not be representative of a "real-life" CAP population.
Objective: The objective of this study was to compare clinical outcomes in hospitalized patients with CAP for a population of patients that would be included in FDA trials versus a population of real-life CAP patients.
Methods: This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) international cohort study. The FDA population was defined via exclusion of patients with the following: cancer, severe renal disease, severe liver disease, nursing home residency, prior antibiotic use in 30 days, and HIV or other immunosuppressive conditions.
Results: A total of 1676 patients were included in the FDA population, and 3,397 in the real life population. In-hospital and 30-day mortality were significantly lower in the FDA population compared to the real life population (6% vs 9%, respectively for in-hospital mortality, P<0.001; 8% vs 12% for 30-day mortality, P=0.002).
Conclusions: This study indicates that FDA populations in clinical trials of CAP have significantly lower mortality than real life populations. Healthcare workers treating patients with CAP should be aware that results of FDA clinical trial may not translate to real life populations of CAP patients.

INTRODUCTION

In the United States, patients with community-acquired pneumonia (CAP) are primarily managed as outpatients, but those admitted to the hospital represent the greatest proportion of economic resources. CAP is one of the leading causes of infectious diseases that require hospitalization [1]. There were 1.3 million hospitalizations for pneumonia in 2005, with 10-20% of patients requiring admission to an intensive care unit [2]. The reported mortality is approximately 12% among all hospitalized CAP patients, escalating over 30% among those admitted to the ICU [3].

Clinical outcomes of hospitalized patients with CAP are closely related to appropriate antimicrobial therapy. With higher rates of multidrug resistant organisms, newer antimicrobials are needed. The FDA process for approval of antibiotics for CAP is based on Phase III clinical trials. Most FDA trials have as exclusion criteria important co-morbidities like cancer, renal disease, liver disease, HIV and immunosuppression, also commonly excluding risk determinants like nursing home residency and prior antibiotics use in 30 days. Since FDA-CAP trials have very significant exclusion criteria, it is unsure if the proportion of CAP patients in these trials could be representative of a "real-life" CAP population. Uncertain increases when some of these FDA-CAP trials show a consistent effect of 90% clinical cure rate, with a very low rate of mortality in both arms, whereas studies with real-life CAP patients show only 67% cure rate.

The objective of this study was to compare clinical outcomes in hospitalized patients with CAP for a population of patients that would be included in FDA trials versus a population of real-life CAP patients.

MATERIALS AND METHODS

Study design and Study population

This was a secondary analysis of patients enrolled in the Community-Acquired Pneumonia Organization (CAPO) international cohort study. Data was collected between 2001 and 2015. In each participating center, non-consecutive medical records of hospitalized patients with the diagnosis of CAP were reviewed. A sample of the data collection form is available at the study website (www.caposite.com). Validation of data quality was performed at the study center before the case was entered in to the CAPO database. Institutional Review Board approval was obtained by each participating center.

Study definitions
CAP: Diagnosis of CAP required the presence of criterion A, B, and C:
New pulmonary infiltrate on imaging (CT scan or chest x-ray) at the time of admission to the hospital.
Signs and Symptoms of CAP (at least one of the following)
New or increased cough (per the patient)
Fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F).
Changes in WBC (leukocytosis >11,000 cells/mm^3, left shift > 10% band forms/microliter, or leukopenia < 4,000 cells/mm^3
Working diagnosis of CAP at the time of hospital admission with antimicrobial therapy given within 24 hours of admission.

Study Groups

FDA-CAP group: defined as the total number of patients hospitalized with CAP who did not have any following comorbidities or characteristics: cancer, severe renal disease, severe liver disease, nursing home residency, prior antibiotic use in 30 days, and HIV or other immunosuppressive conditions.
Real-Life group: defined as the total number of patients hospitalized with CAP available in the database.

Study outcomes

In-hospital mortality: defined as death by any cause during hospitalization.
30-Day mortality: defined as death by any cause during the first 30 days after hospital admission.

Statistical Analyses

Baseline categorical explanatory variables were summarized as frequencies and percentages and differences between both groups of patients were analyzed using a chi-square test or Fisher's exact test when appropriate and warranted. Continuous variables were summarized as frequencies and interquartile range and differences between groups were analyzed by Wilcox-Mann-Whitney test.
TCS and LOS were analyzed with the Kaplan-Meier method, and log-rank tests were applied to evaluate differences between both groups of patients. P-values ≤ 0.05 were considered statistically significant.

RESULTS

- A total of 1676 patients were included in the FDA population, and 3,397 in the real life population.
- Patients' characteristics for both study groups are shown in table 1.
- Mortality rates during hospitalization and at 30 days are shown in table 2.

RESULTS

Table 1. Baseline clinical characteristics and outcomes in FDA-CAP trials and CAPO "Real Life"

Variable	CAPO FDA Population n=1,676	CAPO All n=3,397		P-value
Demographics				
Age , Median (IQR)	68 (31)	67 (31)		0.413
Sex, n (%)	923 (56)	1968 (58)		0.089
Nursing home resident, n (%)	0 (0)	195 (6)		<0.001
History on Admission				
Congestive Heart Failure, n (%)	239 (14)	522 (15)		0.357
COPD, n (%)	372 (22)	760 (23)		1
Diabetes, n (%)	298 (18)	613 (18)		0.907
HIV, n (%)	0 (0)	285 (8)		<0.001
Liver Disease, n (%)	0 (0)	210 (6)		<0.001
Neoplastic Disease, n (%)	0 (0)	374 (11)		<0.001
Renal Disease, n (%)	0 (0)	313 (9)		<0.001
Antibiotics in prior 30 days, n (%)	0 (0)	807 (24)		<0.001
Immunosuppression, n (%)	0 (0)	185 (5)		<0.001
Physical Exam				
Altered mental status on admission, n (%)	202 (12)	476 (14)		0.071
Respiratory Rate, Median (IQR)	22 (10)	22 (10)		0.362
Systolic blood pressure, Median (IQR)	128 (33)	125 (30)		0.003
Temperature (degrees Celsius), Median (IQR)	37.8 (1.7)	37.8 (1.7)		0.031
Heart rate, Median (IQR)	100 (27)	99 (27)		0.957
Lab/Radiography				
pH, Median (IQR)	7.5 (0.1)	7.5 (0.1)		0.222
PaO2, Median (IQR)	62 (19)	62 (19.9)		0.865
Blood Urea Nitrogen, Median (IQR)	31 (30)	32 (32)		0.075
Serum sodium, Median (IQR)	137 (6)	137 (6)		0.411
Serum glucose, Median (IQR)	122 (51)	120 (51)		0.23
Hematocrit, Median (IQR)	39 (6.9)	38 (8)		<0.001
Pleural effusion, n (%)	363 (22)	772 (23)		0.41
Severity of Disease				
ICU admission, n (%)	154 (9)	331 (10)		0.611
Pneumonia Severity Index, Median (IQR)	110 (50)	117 (56)		<0.001

Table 2. In-hospital mortality and Mortality at 30 days in FDA- CAP trial and CAPO "Real life"

Variable	CAPO FDA Population n=1676	CAPO All n=3,397	P-value
In-hospital mortality, n (%)	105 (6)	319 (9)	<0.001
Mortality at 30 days, n (%)	105 (8)	295 (12)	0.002

CONCLUSIONS

- This study indicates that FDA populations in clinical trials of CAP have significantly lower mortality than real life populations. This may have an impact in clinical practice since generalizability of clinical trials is limited by the exclusion of patients who comprise a significant proportion of patients seen in regular practice.
- Healthcare workers treating patients with CAP should be aware that results of FDA clinical trial may not translate to real life populations of CAP patients.

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