Combination therapy is associated with better clinical outcomes in hospitalized patients with community-acquired pneumonia (CAP)

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ABSTRACT

Introduction:
Initial antibiotic therapy of hospitalized patients with CAP is empiric with the goal to cover likely etiologies. Beta lactam antibiotics are considered a primary strategy for empiric therapy. Controversy exists regarding the need to add a second agent to the beta lactam, such as a macrolide or a quinolone.
The objective of this study was to compare clinical outcomes of hospitalized patients with CAP treated with beta lactam monotherapy versus patients treated with a beta lactam combined with either a macrolide or a quinolone.

Methods:
This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study database. Patients with monotherapy were compared to patients with combination therapy in regard to in-hospital mortality. A log-binomial regression model was used to adjust for confounding variables.

Results:
A total of 2130 hospitalized patients with CAP were included in the analysis, 458 with monotherapy, and 1,672 with combination therapy. The adjusted Risk Ratio for in-hospital mortality, comparing patients with combination therapy to those with monotherapy was 0.7, P=0.35.

Conclusions:
This study indicates that patients with combination therapy have a 30% decreased risk of in-hospital mortality compared to those treated with monotherapy. The addition of a second antibiotic may improve outcomes by increasing the spectrum of beta lactams to cover for atypical pathogens or by producing an immunomodulatory effect.

INTRODUCTION

Community-acquired pneumonia (CAP) accounts for a high burden of deaths, hospitalizations, and health care costs. The rate of CAP in adults is approximately 5.16 to 6.11 cases per 1,000 persons per year; which increases with age. The mortality rate of CAP ranges from 5.1 percent for combined ambulatory and hospitalized patients to 13.6 percent in hospitalized patients to 36.5 percent in patients admitted to the intensive care unit (ICU)[1]. Treatment of CAP continues to be a challenge in 21st century with more than 100 microbes (bacteria, viruses, fungi, and parasites) that can cause CAP. Moreover, the etiology of CAP varies by geographic region. Current international guidelines for the management of CAP recommend therapy with beta-lactam antibiotics as a primary strategy. However, International medical societies differ in their recommendations. North American guidelines recommend empirical coverage of atypical pathogens with a respiratory fluoroquinolone or with the combination of a macrolide and a β-lactam for all hospitalized patients. European guidelines recommend combination therapy only for more severely ill patients[2].

The need to add a second agent to the beta lactam remains a matter of debate with the lack of trials strictly comparing mono- versus dual therapy strategies in CAP patients.
The addition of a macrolide has potential drawbacks. Macrolides may promote resistance of *Streptococcus pneumoniae* against multiple antibiotic classes. On the other hand, macrolides cover atypical pathogens and might affect favorably the host inflammatory response through an anti-inflammatory effect. Also, addition of quinolones might have synergetic action with beta-lactam . A meta-analysis of randomized trials that compared antibiotic regimens with and without coverage of atypical pathogens did not find superiority in either arm. However, no trial that compared a β-lactam alone with a combination of a β-lactam and a macrolide/ Quinolone was identified.

The aim of the current study is to determine if the addition of a second agent, such as a macrolide or a quinolone will improve the hospital mortality and the clinical outcomes.
Can be moved to the conclusion to explain why the addition of macrolides/quinolones has better outcomes

METHODS

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:

A. New pulmonary infiltrate on imaging (CT scan or chest x-ray) at the time of admission to the hospital.

A. Signs and Symptoms of CAP (at least one of the following)
    A. New or increased cough (per the patient)
    B. Fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F).
    C. Changes in WBC (leukocytosis >11,000 cells/mm^3, left shift > 10% band forms/microliter, or leukopenia < 4,000 cells/mm^3

B. Working diagnosis of CAP at the time of hospital admission with antimicrobial therapy given within 24 hours of admission.

Study groups:

Patients received β-lactam (monotherapy) were compared to patients on β-lactam and a macrolide/Quinolone (combination therapy) in regard to in-hospital mortality.

Statistical analysis

A log-binomial regression model was used to adjust for confounding variables. P-values ≤ 0.05 were considered statistically significant.

RESULTS

- A total of 2,130 hospitalized patients with CAP were included in the analysis, 458 with monotherapy, and 1,672 with combination therapy, shown in Figure 1.
- Patients' characteristics are shown in Table 1.
- The adjusted Risk Ratio for in-hospital mortality, comparing patients with combination therapy to those with monotherapy was 0.7, P=0.35, depicted in Table 3

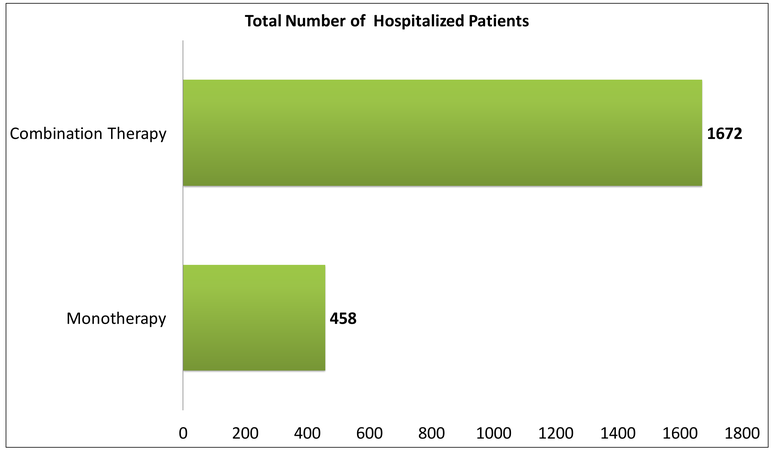

Figure 1 Hospitalized patients antibiotic therapy

RESULTS

Table 1 Patient characteristics

Variable	Mono- Therapy n=458	Combination-therapy n=1672	P-value
Time to Clinical Stability, Median (IQR)	5(5)	4 (6)	0.111
Pleural Effusion, n (%)	94 (21)	400 (24)	0.134
Age, Median (IQR)	71 (32)	70 (28)	0.622
Sex, n (%)	254 (55)	1030 (62)	0.018
Heart rate, Median (IQR)	98.5(26)	99 (27)	0.366
Altered mental Status on Admission, n (%)	79 (17)	234 (14)	0.086
Respiratory Rate, Median (IQR)	24 (9)	24 (9)	0.189
Systolic Blood Pressure, Median (IQR)	120 (34.5)	125 (30)	0.004
Temperature, (Degrees Celsius), Median (IQR)	37.8 (1.6)	37.8 (1.8)	0.195
ICU admission, n (%)	37 (8)	189 (11)	0.049
Congestive Heart Failure, n (%)	85 (19)	299 (18)	0.732
COPD, n (%)	95 (21)	420 (25)	0.056
Diabetes, n (%)	93 (20)	328 (20)	0.741
HIV, n (%)	41 (9)	77 (5)	0.001
Liver Disease, n (%)	32 (7)	83 (5)	0.102
Neoplastic Disease, n (%)	70 (15)	176 (11)	0.006
Chronic Renal Failure, n (%)	62 (14)	169 (10)	0.042
PaO2,Median (IQR)	63 (20)	61 (20)	0.065
PH,Median (IQR)	7.4 (0.1)	7.5 (0.1)	<0.001
Blood Urea Nitrogen, Median (IQR)	32.1(32)	34.4 (34)	0.54
Serum glucose, Median (IQR)	123 (58.8)	121 (52)	0.713
Hematocrit, Median (IQR)	37.8	38.1 (7.1)	0.025
Serum Sodium, Median (IQR)	136 (7)	137 (6)	0.27
Length of Hospital Stay, Median (IQR)	**9 (9)**	**8 (8)**	**0.233**
In Hospital Mortality n (%)	**58 (13)**	**146 (9)**	**0.015**
Pneumonia Severity Index, Median (IQR)	123 (54.8)	117 (55)	0.007
Nursing Home Resident n (%)	42	77 (5)	<0.001

Table 2 Adjusted Risk Ratio

Variable	Risk Ratio	Lower 95% CI	Upper 95% CI	P-value
Intercept	0.003	0	0.066	0
Combination Therapy	0.623	0.456	0.853	0.003
ICU Admission (direct)	3.427	2.505	4.69	0
PSI	1.039	0.998	1.081	0.06

Table 3 Adjusted Risk Ratio of combination vs. monotherapy

Variable	Risk Ratio	Lower 95% CI	Upper 95% CI	P.Value
Combination vs. Monotherapy	0.7	0.57	0.98	0.035
ICU Admission	2.5	1.9	3.31	0
PSI1	1	1.01	1.03	0.001
PSI2	1	0.99	1.01	0.39

CONCLUSIONS

- This study indicates that patients with combination therapy have a 30% decreased risk of in-hospital mortality compared to those treated with monotherapy.
- Our results suggests that better clinical outcome is associated with combination therapy that includes a macrolide/ Quinolone for wide coverage of pathogens in addition to related synergetic actions & immunomodulatory effects.

REFERENCES

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