Do antiplatelet medications prevent poor clinical outcomes in patients with community-acquired pneumonia (CAP)

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ABSTRACT

Introduction
CAP is characterized by a pro-inflammatory state as well as a pro-coagulant state. Excessive inflammatory and/or coagulatory state may be associated with poor clinical outcomes. A significant number of subjects are prescribed antiplatelet medications and may develop CAP. We hypothesize that these patients may be at a decreased risk for mortality once hospitalized for CAP.
The objective of this study was to compare the risk of mortality in hospitalized patients with CAP on antiplatelet medications versus those not on antiplatelet medications.

Methods
This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study database. Log binomial regression models were used to evaluate the adjusted impact of antiplatelet medications on the risk for 30-day mortality.

Results
A total of 3,337 patients were included in the analysis, 639 receiving antiplatelet medication, and 2,698 without. After adjusting for confounding effects, the risk ratio for 30-day mortality for patients on antiplatelet medication compared to those not on antiplatelet medication 0.55, p<0.001.

Conclusions
This study indicates that hospitalized patients with CAP that were taking antiplatelet medications prior to hospitalization have a 45% decreased risk for mortality at 30 days. Aspirin and other antiplatelet medications decrease coagulation as well as inflammation. Our data suggest that modifying excessive inflammatory and coagulatory responses may be an important intervention to improve outcomes in hospitalized patients with CAP.

INTRODUCTION

Acute pneumonia has important effects on the cardiovascular system. Pneumonia tends to affect individuals who are also at high cardiovascular risk. Results of recent studies show that about a quarter of adults admitted to the hospital with pneumonia develop a major acute cardiac complication**. (1,2)**
It is well established that platelets are integral to hemostasis. Evidence points to an important role ~~for~~ platelets have in inflammation and immunity. Platelet activation contributes to microvascular thrombosis and organ failure in systemic inflammation. (3,4)
CAP is characterized by a pro-inflammatory state as well as a pro-coagulant state. It is considered that an excessive inflammatory and/or coagulatory state may be associated with poor clinical outcomes. Antiplatelet drugs may have a beneficial effect in systemic inflammation and sepsis, and could be a novel therapy option. (5,6) A significant number of subjects that are prescribed antiplatelet medications ~~and~~ may develop CAP. We hypothesize that these patients may be at a decreased risk for mortality once hospitalized for CAP.
The objective of this study was to compare the risk of mortality in hospitalized patients with CAP who are on antiplatelet medications versus those not on antiplatelet medications.

METHODS

Study design and Study population
This was a secondary analysis of patients enrolled in the Community-Acquired Pneumonia Organization (CAPO) international cohort study. Each non-consecutive medical record of hospitalized patients with the diagnosis of CAP from each participating center, 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 into the CAPO database. Institutional Review Board approval was obtained for 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.
B. 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
C. Working diagnosis of CAP at the time of hospital admission with antimicrobial therapy given within 24 hours of admission.

Antiplatelet was defined as use of medications depicted in Figure 1.

Study outcomes
Time to clinical stability *(TCS):* A patient was defined as clinically stable the day that the following four criteria were met: 1) improved cough and shortness of breath, 2) lack of fever for at least 8 hours, 3) improving leukocytosis (decreased at least 10% from the previous day), and 4) tolerating oral intake with adequate gastrointestinal absorption. Patients were evaluated daily within the first 7 days of hospitalization to determine the day when clinical stability was reached.

Statistical Analyses
Baseline categorical explanatory variables were summarized as frequencies and percentages, and differences between both groups of patients were analyzed using a chi-squared test or Fisher's exact test when appropriate and warranted. Continuous variables were summarized as frequencies and interquartile ranges, and differences between groups were analyzed by Wilcoxon-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.

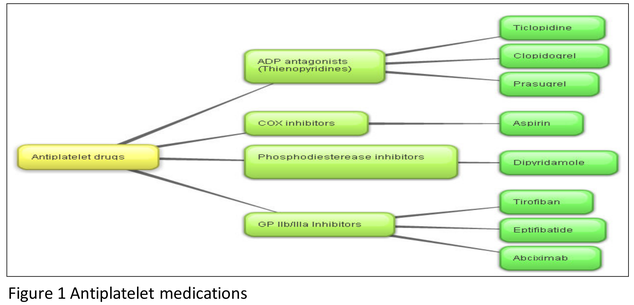

Figure 1 Antiplatelet medications

RESULTS

- A total of 3,337 patients were included in the analysis, 639 receiving antiplatelet medication, and 2,698 without. The study flowchart is shown in Figure 2.
- After adjusting for confounders, antiplatelet medications have a protective effect over those who did not receive antiplatelet medications, lessening the risk of 30 day mortality by 45%, p<0.001 (Table 1).

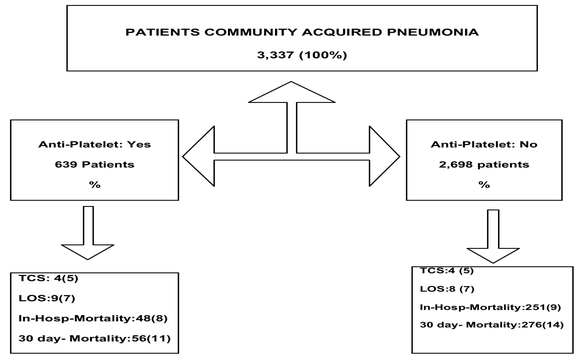

Figure 2 Study flowchart

Table 1 (30 days mortality)

30 Day Mortality				
	Risk Ratio	Lower 95% CI	Upper 95% CI	P-value
Anti-Platelet Meds	0.55	0.42	0.72	< 0.001
ICU Admission	3.4	2.8	4.13	< 0.001
Pneumonia Severity Index	1.02	1.02	1.02	< 0.001

CONCLUSIONS

- This study indicates that hospitalized patients with CAP that were taking antiplatelet medications prior to hospitalization have a 45% decreased risk for mortality at 30 days.
- Aspirin and other antiplatelet medications decrease coagulation as well as inflammation.
- Our data suggest that modifying excessive inflammatory and coagulatory responses may be an important intervention to improve outcomes in hospitalized patients with CAP.
- Our preliminary data can be used to design a prospective randomized study evaluating current standard of care versus current standard of care plus the addition of antiplatelet medication in hospitalized patients with CAP.

REFERENCES

1. Jackson Michael L, Neuzil Kathleen M, Thompson William W, Shay David K, Yu O, Hanson Christi A, Jackson Lisa A. The Burden of Community-Acquired Pneumonia in Seniors: Results of a Population-Based Study.Clinical Infectious Diseases. 2004;39:1642–50. [PubMed]
2. A. Kendall Gross, Steven P. Dunn, David J. Feola, Craig A. Martin, Richard Charnigo Clopidogrel treatment and the incidence and severity of community acquired pneumonia in a cohort study and meta-analysis of antiplatelet therapy in pneumonia and critical illness. Journal of Thrombosis and Thrombolysis. February 2013, Volume 35, Issue 2, pp 147-15
3. Henn V, Slupsky JR, Grafe M, Anagnostopoulos I, Forster R, Muller-Berghaus G, Kroczek RA. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature. 1998;391:591–
4. [PubMed]
4. Evangelista V, Manarini S, Dell'Elba G, Martelli N, Napoleone E, Di Santo A, Savi P, Lorenzet R. Clopidogrel inhibits platelet-leukocyte adhesion and platelet dependent leukocyte activation. Thrombosis and Haemostasis.2005;94:568–77. [PubMed]
5 Siempos II[1], Vardakas KZ, Kopterides P, Falagas ME Adjunctive therapies for community-acquired pneumonia: a systematic review. J Antimicrob Chemother. 2008 Oct;62(4):661-8. doi: 10.1093/jac/dkn283. Epub 2008 Jul 18.
6. Akinosoglou K[1], Alexopoulos D[2]. Use of antiplatelet agents in sepsis: a glimpse into the future. Thromb Res. 2014 Feb;133(2):131-8. doi: 10.1016/j.thromres.2013.07.002. Epub 2013 Oct 6.