Intensive Care Med (2016) 42:301–302
DOI 10.1007/s00134-015-4139-9

LETTER

Marco Falcone
Alessandro Russo
Alessio Farcomeni
Filippo Pieralli
Vieri Vannucchi
Vincenzo Vullo
Francesco Violi
Mario Venditti

Septic shock from community-onset pneumonia: is there a role for aspirin plus macrolides combination?

Accepted: 3 November 2015
Published online: 19 November 2015

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-015-4139-9) contains supplementary material, which is available to authorized users.

Dear Editor,

Pneumonia occurring in patients living in the community is the most common infection leading to hospitalization in intensive care units and the first cause of death associated with infectious diseases. The mortality rate due to pneumonia has shown little improvement over time despite advances in antimicrobial therapy and improved intensive care medicine, and severe sepsis and septic shock are associated with a mortality rate as high as 50 % [1]. It has been suggested to use agents that interfere with the pathogenesis of sepsis by modulating inflammation and coagulation. From January 2013 to January 2014, we prospectively observed all patients with community-onset pneumonia needing hospitalization at two teaching hospitals in Italy (Policlinico Umberto I, Rome and University Hospital of Careggi, Florence). We performed a post hoc analysis on patients with pneumonia presenting to the emergency department (ED) with septic shock, to evaluate whether any clinical factor or therapeutic intervention is associated with improved survival in this setting of patients.

Adult patients fulfilling criteria for community-acquired pneumonia and healthcare-associated pneumonia were included in the study. Septic shock was defined according to Surviving Sepsis Campaign criteria. The effect of clinical and therapeutics variables on the primary end-point was assessed by means of a logistic regression model. In order to correct for possible bias arising from the observational nature of the experiment, we corrected all relevant effect estimates and p values with the propensity score analysis.

Overall, 188 patients with pneumonia and septic shock were included in the analysis. The 30-day mortality rate was 42.5 %. No difference in the term of median age was detected between survivors and non-survivors. Patients who died had a higher mean sequential organ failure assessment (SOFA) score, presented more frequently with delirium, had a more frequent PaO_2/FiO_2 ratio <300, needed more frequent mechanical ventilation, non-invasive ventilation, and continuous renal replacement therapy. Survivors were more likely to receive macrolide therapy and a combination of aspirin plus a macrolide (see supplementary material). All patients taking aspirin were on chronic aspirin therapy at a dosage of 100 mg/day. At Cox regression analysis SOFA score >3 [hazard ratio (HR) 1.13, 95 % confidence interval (CI) 1.06–1.20, $p < 0.001$], delirium (HR 1.56, 95 %CI 1.14–3.23, $p = 0.01$), and PaO_2/FiO_2 ratio <300 (HR 2.42, 95 % CI 1.28–3.56, $p < 0.001$) were independently associated with death, while receipt of aspirin plus a macrolide (HR 0.24, 95 % CI 0.08–0.79, $p = 0.01$) was associated with survival. This latter finding was confirmed by the propensity score adjusted estimates (see Table 1).

The use of macrolides has been previously associated with lower mortality in patients with severe pneumonia, and the administration of clarithromycin has been associated with restoration of the balance between pro-inflammatory versus anti-inflammatory mediators in patients with Gram-negative sepsis and ventilator-associated pneumonia (VAP). A further double-blind, randomized, multicenter trial found that clarithromycin accelerates resolution of VAP, and favors weaning from mechanical ventilation [2]. As regards to aspirin, a propensity-adjusted analysis by Chen and coworkers revealed that the pre-hospital use of aspirin was associated with a decreased risk of developing an acute respiratory distress syndrome (ARDS) [3]. Furthermore, we recently reported a beneficial activity of aspirin in patients with community-onset pneumonia, with a

Table 1 Effect of aspirin and macrolide therapy alone and in combination after adjustment by propensity score

Population analyzed	Hazard ratio	95 % Confidence interval	p value
Aspirin plus macrolides ($n = 46$)	0.2523	0.078–0.816	0.021
Macrolides (aspirin group, $n = 26$)	0.084	0.016–0.432	0.003
Aspirin (macrolides group, $n = 29$)	0.407	0.064–2.592	0.342

reduction in total 30-day mortality rate (4.9 %) compared to non-aspirin users (23.4 %); aspirin therapy was a factor independently associated with survival at Cox regression analysis [4].

The preliminary data of our study suggest that, in the setting of patients with pneumonia and septic shock, a combination of low-dose aspirin (100 mg/day) plus a macrolide could be associated with improved survival. The benefit may be explained by the anti-inflammatory effect exhibited by these two drugs and by a reduction of acute cardiovascular events associated with aspirin therapy [5].

An important limit of our study is the limited number of patients included, which does not allow further statistical analyses about the specific role of aspirin or macrolide therapy if administered alone. Moreover, the healthy status and the socio-economic status may play a role as confounders in patients taking aspirin, and we did not analyze the possible additive effect of statins or other anti-inflammatory drugs.

Due to the observational methodology of the study, further randomized clinical trials are warranted to support this finding and to evaluate the role of combination therapy with aspirin plus macrolides in patients with severe pneumonia.

Compliance with ethical standards

Conflicts of interest None.

References

1. Restrepo MI, Anzueto A (2009) Severe community-acquired pneumonia. Infect Dis Clin North Am 23:503–520
2. Giamarellos-Bourboulis EJ, Pechère JC, Routsi C, Plachouras D, Kollias S, Raftogiannis M, Zervakis D, Baziaka F, Koronaios A, Antonopoulou A, Markaki V, Koutoukas P, Papadomichelakis E, Tsaganos T, Armaganidis A, Koussoulas V, Kotanidou A, Roussos C, Giamarellou H (2008) Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. Clin Infect Dis 46:1157–1164
3. Chen W, Janz DR, Bastarache JA, May AK, O'Neal HR Jr, Bernard GR, Ware LB (2015) Prehospital aspirin use is associated with reduced risk of acute respiratory distress syndrome in critically ill patients: a propensity-adjusted analysis. Crit Care Med 43:801–807
4. Falcone M, Russo A, Cangemi R et al (2015) Lower mortality rate in elderly patients with community-onset pneumonia on treatment with aspirin. J Am Heart Assoc 4:e001595
5. Cangemi R, Casciaro M, Rossi E, In collaboration with the SIXTUS Study Group et al (2014) Platelet activation is associated with myocardial infarction in patients with pneumonia. J Am Coll Cardiol 64:1917–1925

M. Falcone (✉) · A. Russo · A. Farcomeni · V. Vullo · M. Venditti
Department of Public Health and Infectious Diseases, "Sapienza" University of Rome, Policlinico Umberto I, Viale dell'Università 37, 00161 Rome, Italy
e-mail: marco.falcone@uniroma1.it

F. Pieralli · V. Vannucchi
General and University Hospital of Careggi, Florence, Italy

F. Violi
Department of Internal Medicine and Medical Specialties, "Sapienza" University of Rome, Policlinico Umberto I, Rome, Italy