The impact of adjuvant atorvastatin therapy on community-acquired pneumonia outcome: a prospective study of clinical and inflammatory responses in relation to mortality reduction

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Introduction In treatment of pneumonia, new drugs besides antibiotics are investigated; especially statins with their anti-inflammatory, immunomodulatory, and antioxidant effects.

Objective The aim was to determine whether or not adjuvant atorvastatin could improve 30-day mortality, and clinical and inflammatory outcomes of community-acquired pneumonia (CAP).

Patients and methods This is a prospective study, in which 47 CAP patients were randomized into: statin naive, *n*=23 (received antibiotics according to guidelines) and statin users, *n*=24 (received antibiotics according to guidelines +atorvastatin 40 mg daily for 30 days). Total leukocytic count and C-reactive protein (CRP) were measured, pneumonia severity index was estimated on the first day and on the seventh day, and length of hospital stay and mortality were also recorded.

Results Statin users showed statistically significant reduction of CRP (*P*=0.049) and significantly shorter hospital stay (*P*<0.001). No statistically significant difference on comparing both groups as regard the reduction magnitude of total leukocytic count (*P*=0.406), pneumonia severity index (*P*=0.325), and mortality (*P*=0.489).

Conclusion Incorporating atorvastatin therapy with antibiotics compared to antibiotics alone in the treatment of CAP showed significantly lower CRP levels, shorter hospital stay, but no impact on mortality reduction.

Egypt J Bronchol 2019 13:249–257

Egyptian Journal of Bronchology 2019 13:249–257

Keywords: atorvastatin, inflammatory markers, pneumonia

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Received 6 June 2017 **Accepted** 14 August 2018

Introduction

Although pneumonia is one of the oldest well-described diseases, and despite the revolutionary impact of antibiotics on pneumonia-related mortality and morbidity, lower respiratory tract infection LRTI (including pneumonia) remain among the top 3 killers worldwide, and one of the top 10 killers in Egypt [1,2].

Since the 1950s to the 20th century, only a few antibiotics have been added to the treatment of arsenal of infections, without any new drug class other than antibiotics being added in the last 70 years [3].

That is why; the use of anti-inflammatory drugs as adjuvant therapy with antibiotics is taking a reasonable share of research in the field of sepsis and inflammatory diseases; the agents used so far include corticosteroids, statins, macrolides, angiotensin converting enzyme inhibitors, and toll-like receptor antagonists [3].

Statins with their powerful anti-inflammatory, immunomodulatory, and antioxidant properties make them candidate members to be used in the management of sepsis and different types of infections including pneumonia [4].

Aim

The aim was to evaluate whether or not adjuvant atorvastatin could improve the outcomes of community-acquired pneumonia (CAP) as regards 30-day mortality (primary outcome), the change from baseline in total leukocytic count (TLC) and C-reactive protein (CRP), and pneumonia severity index (PSI) after 7 days of treatment, as well as length of hospital stay (secondary outcomes).

Patients and methods

Study population

This 1 : 1 randomized, prospective, interventional trial was conducted in Ain Shams University hospitals form October 2013 to October 2016.

Ethical approval was granted by the ethical committee of scientific research, Ain Shams University, Faculty of Medicine. Informed written consent was obtained

 DOI: 10.4103/ejb.ejb_50_17

from all patients or their next of kin prior to enrollment.

Patients were included in the study if they had CAP, with PSI greater than 70 'class III or more', defined as evidence of acute respiratory illness, and radiographic findings consistent with pneumonia developing either in the outpatient setting or within 48 h of admission.

Patients were excluded if allergic to statins, or had treatment with one or more doses of a statin within 30 days prior to admission, had history of ileal bypass, baseline aspartate transaminase (AST) and/or alanine transaminase (ALT) more than three times the upper limits of normal (ULN), baseline creatine phosphokinase (CPK) more than 3 times the ULN, increased CPK (over five times the upper limit) during hospitalization, or if already receiving potentially interacting drugs: ketoconazole, itraconazole, cyclosporine, niacin, verapamil, gemfiborzil, and ezetimibe.

Study protocol and intervention

Eligible patients were randomized to either: 'statin naive patients' (N=23), who received empirical antibiotics initially according to the guidelines of the Egyptian Scientific Society of Bronchology 2012 and then tailored according to the culture and sensitivity results; or the interventional group: 'statin users' (N=24) received empirical antibiotics initially according to the guidelines of the Egyptian Scientific Society of Bronchology 2012 and then tailored according to the culture and sensitivity results, plus atorvastatin 40 mg/day starting the day of diagnosis and till the end of 30-day follow-up period. Informed written consent was obtained from all patients or their next of kin prior to enrollment.

On admission, the following laboratory and imaging investigation were performed for all participants: complete blood count (CBC), CRP, urea, creatinine, AST, ALT, CPK, oxygen saturation or arterial blood gases whenever needed, random blood glucose, sputum culture and sensitivity, chest computerized tomography (whenever needed), and calculation of PSI (Table 1) [5]. CBC, CRP, CPK, PSI were repeated on the seventh day. Length of hospital stay and mortality after 30 days of diagnosis were also recorded (Fig. 1).

Study outcomes

The primary outcome was 30-day mortality. However, the change from baseline in TLC, CRP, and PSI after 7 days of treatment, as well as length of hospital stay were the secondary outcomes.

Table 1 Pneumonia severity index

Characteristics	Points assigned
Demographic factor	
Age (years)	
Men	10
Women	
Nursing home resident	+10
Coexisting illnesses	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical examination findings	
Altered mental status	+20
Respiratory rate >30/min	+20
Systolic blood pressure <90 mmHg	+20
Temperature <35°C or ≥40°C	+15
Pulse ≥125/min	+10
Laboratory and radiographic findings	
Arterial pH <7.35	+30
Blood urea nitrogen ≥30 mg/dl	+20
Sodium <130 mmol/l	+20
Glucose ≥250 mg/dl	+10
Hematocrit <30%	+10
Partial pressure of arterial oxygen <60 mmHg or oxygen saturation <90%	+10
Pleural effusion	+10

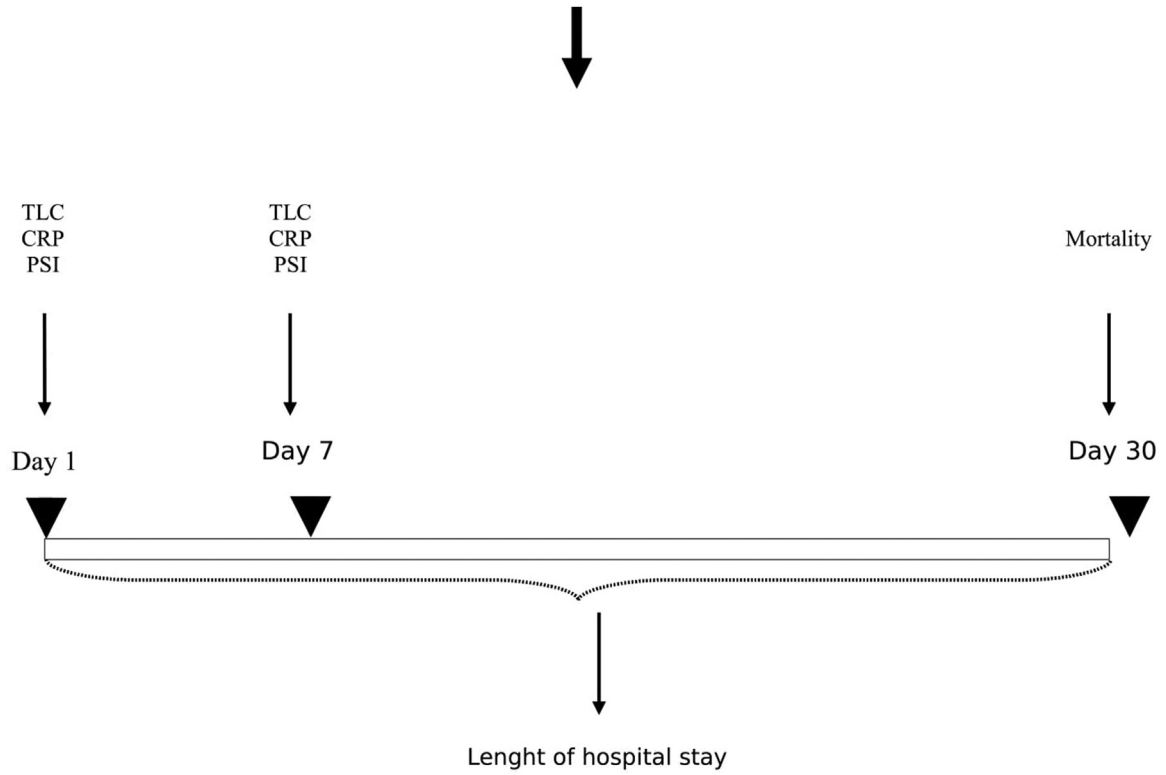
Class I: <50), class II: 51–70, class III: 71–90, class IV: 91–130, class V: >130 [5].

Statistical analysis

Baseline characteristics were analyzed using Student's t test (for continuous variables) and χ^2-test or Fisher's exact test (for categorical variables).

Normality and homogeneity of variances were done using Shapiro–Wilk test and Levene's test, respectively. Two-way mixed-design analysis of variance was applied for repeated measures analysis (TLC, CRP, and PSI), where treatment×time interactions were tested by using Pillai's trace. In these analyses, the treatments (antibiotics +atorvastatin vs. antibiotics alone) were regarded as between-subject factors, and time with 2 timepoints (baseline and 7 days of the intervention) was considered a within-subject factor. To identify within-group differences (before and after 7 days of intervention), we used paired-samples t tests. Length of hospital stay comparison was performed applying Mann–Whitney U-test. Precise mortality analysis with univariate and multivariate logistic regression was not possible because of small numbers.

Figure 1



Study chart.

Results

Among 53 patients enrolled in the study, three patients had PSI less than 70, two patients had baseline CPK level more than three times the ULN, and one patient had baseline AST and ALT more than three times the ULN; all of them were excluded, leaving 47 patients for the analysis (Fig. 2).

Baseline characteristics

The demographics and baseline characteristics of the entire study population are presented in Table 1, where there was no statistically significant difference as regards age, sex or comorbidities (apart from chronic kidney disease that was almost significant), and baseline TLC, CRP, and PSI between statin users and statin naive patients (Table 2).

Outcomes

Reduction in TLC was statistically significant ($P<0.001$) from day 1 to day 7, but not significantly ($P=0.921$) different between the two treatment groups, with no significant interaction ($P=0.406$) between time and treatment type; which means TLC was reduced from day 1 to day 7 with antibiotics independent of atorvastatin inclusion in the treatment (Table 3).

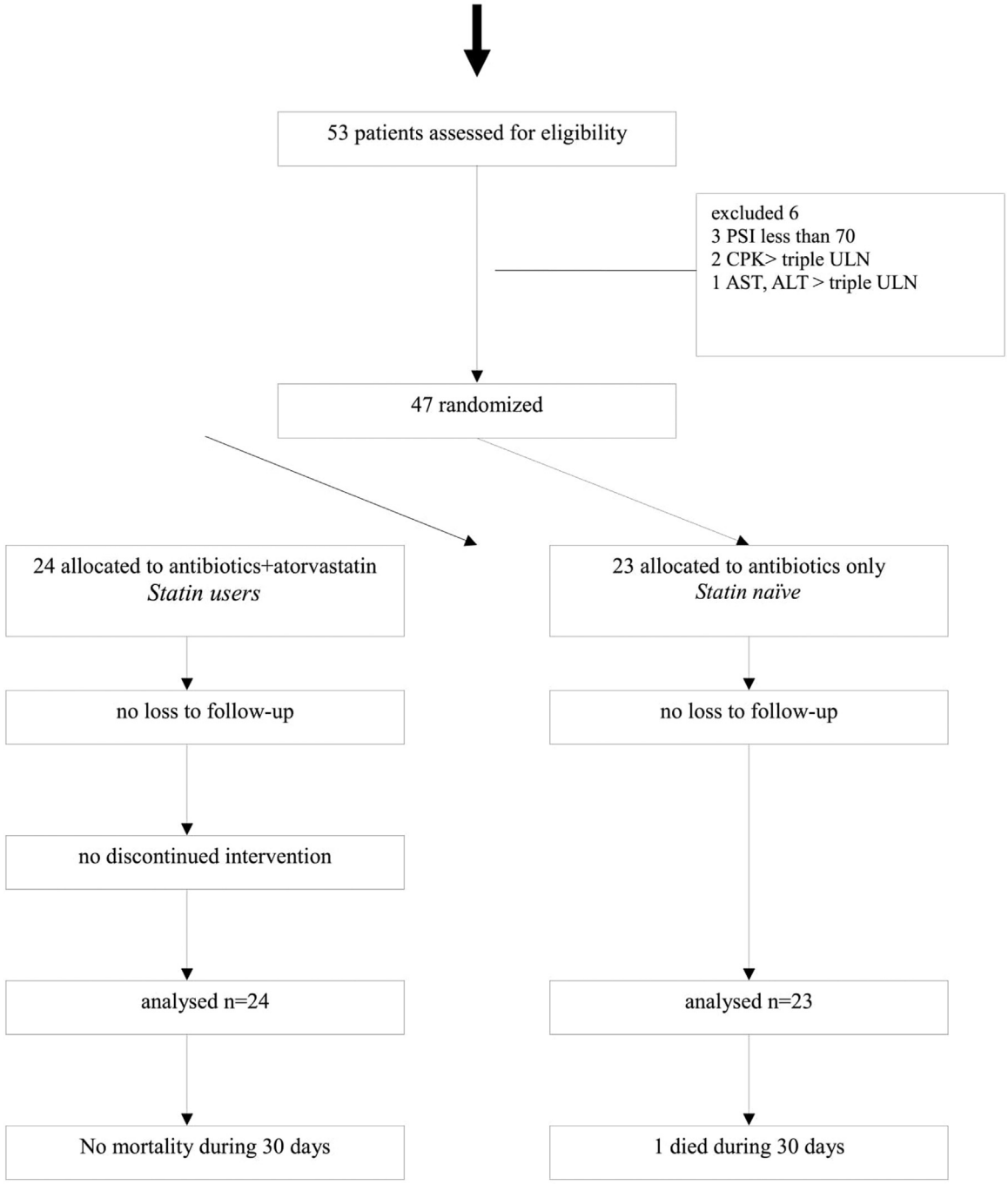
When two-way mixed-design analysis of variance was applied in case of CRP (Table 3), it revealed that CRP was reduced significantly ($P<0.001$) over time, with no statistically significant difference ($P=0.145$) between the treatment groups, but significant interaction ($P=0.049$) between time and treatment type; which means that atorvastatin inclusion in the treatment of pneumonia resulted in significantly lower CRP levels (Fig. 3).

In case of PSI, it was also reduced significantly (Table 3; $P<0.001$) from day 1 to day 7, but with no significant ($P=0.147$) difference between the treatment groups or interaction ($P=0.325$) between time and treatment type, which means – as the case in TLC – PSI decreased from day 1 to day 7 with antibiotics independent of atorvastatin inclusion in the treatment (Fig. 4).

The length of hospital stay was shorter in statin users (7 ±2 days) as compared statin naive patients (14±7 days). Such reduction in hospital stay duration induced by statin addition was statistically highly significant ($P<0.001$) (Fig. 5).

Finally, with regard to 30-day mortality outcome, there was no statistically significant difference ($P=0.489$) between the two groups (only one mortality case in statin naive patients). Precise mortality analysis with univariate and multivariate logistic regression could not be performed because of less number of mortalities.

Figure 2



Flow diagram of the study.

Discussion

In this prospective case–control study, we investigated whether or not adjuvant atorvastatin could improve the outcomes of CAP.

Most previous studies were retrospective or prospective observational studies, and most of the few interventional studies were examining the outcome in sepsis (not in pneumonia) and in patients already on statin therapy for other indications [6,7].

The agent most widely used in clinical trials was simvastatin [8–14]. With a dose range of 20–80 mg, which at its maximum dose of 80 mg is less potent [moderate intensity in terms of low density lipoproteins (LDL) reduction] than atorvastatin 40 mg (high potency), plus the high incidence of myopathy with this dose culminated to the food and drug administration (FDA) recommending against prescription of this dose [15]. Moreover atorvastatin is widely available, cheaper, and almost of equal potency to the most

Table 2 Baseline characteristics of recruited patients

Characteristics	Total (*N*=47)	Statin user (*N*=24)	Statin naive (*N*=23)	*P* value
Age	51±16	53±15	49±16	0.4
Male	30 (64)	13 (54)	17 (74)	0.2
Female	17 (36)	11 (46)	6 (26)	
Comorbidities				
Chronic pulmonary disease	6 (13)	5 (21)	1 (4)	0.2
Cerebrovascular	4 (9)	2 (8.3)	2 (8.7)	1
Immunocompromised[a]	4 (9)	3 (13)[a]	1 (4)[b]	0.3
Congestive heart failure	5 (11)	2 (8)	3 (13)	0.7
Chronic kidney disease	4 (9)	0	4 (17)	0.051
Chronic liver disease	4 (8.5)	2 (8.3)	2 (8.7)	1
TLC on day 1	11.9±5.1	12.3±5.5	11.5±4.8	0.6
CRP on day 1	212±152	211±159	211±147	1
PSI on day 1	110±38	108±41	111±36	0.8

Data are presented as mean±SD or number of cases (percentage of the total count of the respective group). CRP, C-reactive protein; PSI, pneumonia severity index; TLC, total leukocytic count. [a]Systemic lupus erythematosus on steroids, acute leukemia, and kidney transplant on immunosuppressives. [b]Crone's disease on infliximab.

Table 3 The effect of time, as well as treatment on total leukocytic count, C-reactive protein, and pneumonia severity index among the studied groups

	First day of treatment		Seventh day of treatment		Two-way ANOVA (*P* values)		
	Statin user (*N*=24)	Statin naive (*N*=23)	Statin user (*N*=24)	Statin naive (*N*=23)	Time effect	Treatment effect	Time×treatment interaction
TLC×10^3/ml	12.3±5.5	11.5±4.8	8.2±3.3*	8.8±4.4	<0.001	0.921	0.406
CRP (mg/l)	211±159	211±147	27±26†,*	72±69*	<0.001	0.145	0.049
PSI†	108 (±41)	111 (±36)	64±28*	81±36*	<0.001	0.147	0.325

ANOVA, analysis of variance; CRP, C-reactive protein; PSI, pneumonia severity index; TLC, total leukocytic count. *P<0.001 [compared to same treatment on first day (within-subjects effects), simple main effects following two-way ANOVA]. †P<0.01 [compared to antibiotic on the same day of treatment (between-subjects effects), simple main effects following two-way ANOVA].

potent, but more expensive member (rosuvastatin) [16,17].

We found profound reduction in CRP levels, significant shortening of hospital stay, non statistically significant difference in reduction of TLC count and pneumonia score, and finally no effect on mortality after 30 days of pneumonia diagnosis.

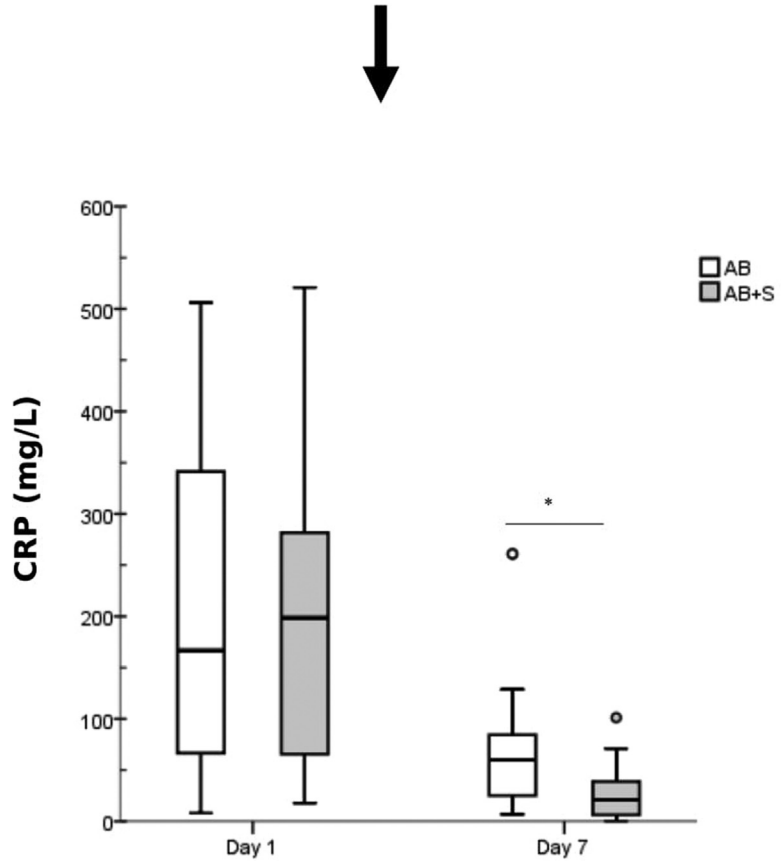
Our finding of nonsignificant difference in TLC reduction with atorvastatin over the time was consistent with the findings of the only available study, shedding light on TLC reduction in different types of infection including pneumonia (that represented the largest proportion of the study population, 51%) [18].

Incorporating atorvastatin with antibiotics in the treatment of patients with pneumonia resulted in undeniable statistically significant reduction of CRP levels after 7 days of treatment. This finding is reported for the first time in pneumonia and is consistent only with the finding reported by Craig *et al*. [11], who investigated simvastatin effects in acute lung injury, where sustained CRP reduction was observed on day 12 only in patients receiving statins.

Similarly, Steiner *et al*. [14] reported significantly lower plasma and BAL CRP level in healthy volunteers pretreated with statin for 4 days before intravenous administration of lipopolysaccharide antigens, coinciding with Shyamsundar *et al*. [12] who confirmed this finding, but this time after inhalation challenge with lipopolysaccharide antigens.

On the contrary, Viasus *et al*. [8] found no significant reduction of CRP after starting statin therapy in patients with CAP. That may be explained by the shorter duration and different type of statin therapy, 'simvastatin 20 mg for 4 days' and earlier estimation of CRP level, 'after 2 days versus 7 days', in the present study. The same was reported by Kruger *et al*. [6], but this time in patients with severe sepsis. This discordance may be attributed to using lower dose of atorvastatin, 20 mg.

Figure 3



C-reactive protein (CRP). Shown are CRP levels in patients receiving antibiotic (AB, white boxes) or antibiotic+atorvastatin (AB+S, gray boxes) on the first day (left) and on the seventh day (right) of treatment. Boxplots show median (middle line) and first and third quartiles (bottom and top of the box, respectively) with whiskers show minima and maxima within 1.5 interquartile range. AB, antibiotic; AB+S, antibiotic+atorvastatin. *$P<0.01$.

For PSI, atorvastatin showed no added benefits over antibiotics alone, and no up-to-date studies assessed pneumonia score reduction over time with statin therapy, except for only one study which compared the time to clinical stability in CAP patients after receiving antibiotics plus simvastatin (20 mg for 4 day) versus antibiotics alone, where the mean time to clinical stability was almost equal (3 days) [8].

Shorter hospital stay with atorvastatin also showed significant reduction as CRP reduction. This was in line with a large observational study conducted by Mortensen *et al*. [19], including 11 498 patients with pneumonia, confirming that prior use of statins resulted in significantly shorter hospital stay.

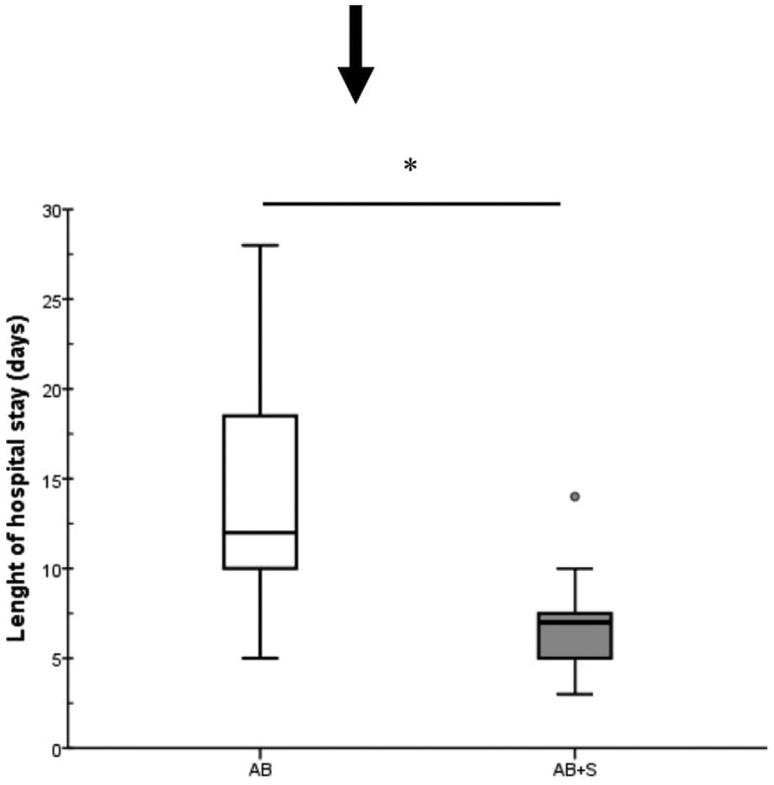
On the other hand, Havers *et al*. [20] found that prior and continued statin use did not affect the hospital stay in patients with CAP, but this could be probably because of selection of older age group (61% above 65 years vs. 27% in this study) and more comorbidities (46 vs. 18% for chronic pulmonary diseases, 24 vs. 10% for kidney disease, 17 vs. 12% for immunocompromised and cerebrovascular disease), when compared to our study. Introducing atorvastatin therapy in patients with sepsis was also not associated with shorter hospital stay [6,7].

As previously stated, adjuvant atorvastatin therapy improved the patient's inflammatory markers (in terms of CRP), and while such effect was well reflected by a reduced length of hospital stay, it did not translate into any improved survival within 30 days of diagnosis even after controlling for important mortality predictors in the study.

This finding is consistent with the results of the only interventional study investigating the effect of statin therapy on 28-day mortality in case of ventilator associated pneumonia (VAP) and found no improved survival [10].

Another large study – observational – concluded that statins are not associated with reduced mortality in CAP patients [21].

Figure 4



Pneumonia severity index (PSI). Shown are PSI scores in patients receiving antibiotic (AB, white boxes) or antibiotic+atorvastatin (AB+S, gray boxes) on the first day (left) and on the seventh day (right) of treatment. Boxplots show median (middle line) and first and third quartiles (bottom and top of the box, respectively) with whiskers show minima and maxima within 1.5 interquartile range. AB, antibiotic; AB+S, antibiotic +atorvastatin.

On the other hand, improved survival with reduced mortality was observed by Kruger *et al*. [6] when atorvastatin was initiated in patients with severe sepsis and prior statin use.

Moreover, reduced mortality with statin therapy was insisted upon in a large number of observational studies and meta-analyses. Bruyere *et al*. [9] concluded that continued statin use in suspected VAP patients with prior statin use resulted in better survival after correcting for potential confounders.

Cheng *et al*. [22] conducted a meta-analysis supporting the idea that statin users had less mortality caused by pneumonia.

Nielsen *et al*. [23] performed a large prospective observational study, indicating that current statin use is associated with lower 30-day mortality caused by pneumonia.

Mortensen *et al*. [19] proved in a retrospective observational study that prior, as well as in-patient statin use was associated with reduced pneumonia-related 30-day mortality.

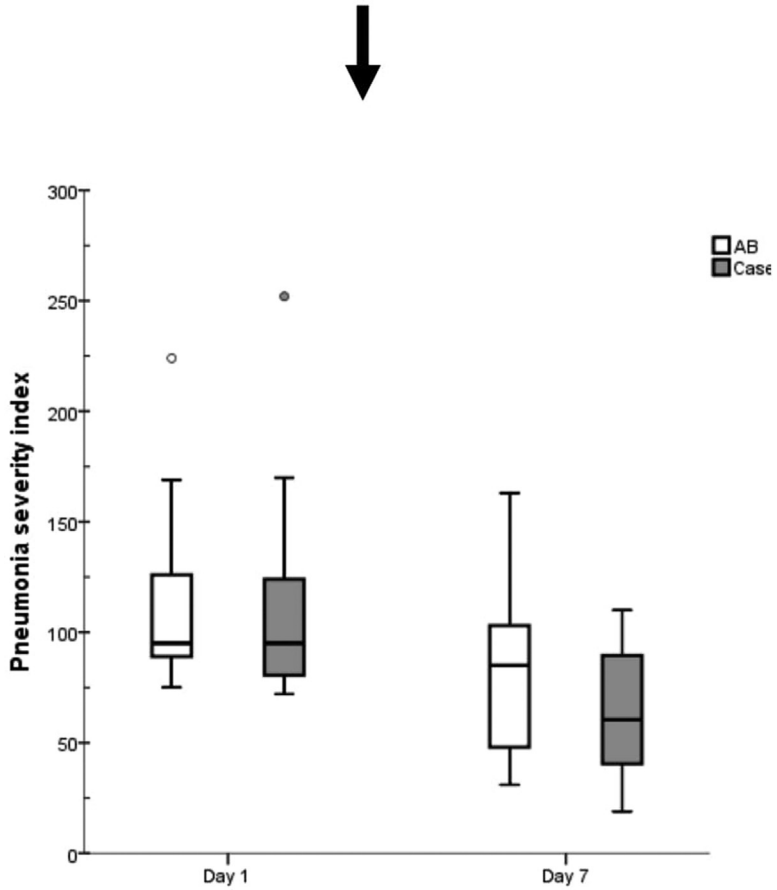
Significant findings in our study can be explained by the pleitropic effects of statins (effects unrelated to their antidyslipidemic properties) that have clear implications on many aspects of the inflammatory cascade [4].

The pleitropic effects of statins include anti-inflammatory, immunomodulatory, antioxidants, anticoagulant, and vascular effects, and each of them has a role in the inflammatory process [24].

The anti-inflammatory effect is related to inhibiting the formation mevalonate with its subsequent nonsterol derivatives that are responsible for post-translational modification of important secondary messenger proteins (small GTPases) – Ras proteins – that are associated with important downstream effectors such as nuclear factor-κB that stimulates production of cytokines, chemokines, adhesion molecules, and acute phase proteins [4].

Potential limitations of this study such as small number of patients and larger number of recruited patients combined with exclusion of potential confounders such as immunosuppression would make it easier for mortality impact to be more evident.

Figure 5



Length of hospital stay. The duration of hospitalization in patients receiving antibiotic (AB, white box) or antibiotic+atorvastatin (AB+S, gray box) is shown. Boxplots show median (middle line) and first and third quartiles (bottom and top of the box) with whiskers show minima and maxima within 1.5 interquartile range. *$P<0.001$ by Mann–Whitney *U*-test. AB, antibiotic; AB+S, antibiotic+atorvastatin.

In conclusion, incorporating atorvastatin therapy with antibiotics in the treatment of CAP resulted in significantly lower CRP levels that were well reflected by shorter hospital stay when compared with using antibiotics alone, but it did not affect mortality reduction.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts interest.

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