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Statins in community acquired pneumonia: Evidence from experimental and clinical studies

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Summary
Statins are widely used to lower cholesterol and prevent complications of cardiovascular disease. The non-lipid lowering (pleiotropic) effects of statins may also have applications to the management of infections. These include effects on endothelial function, inflammation and coagulation pathways. Several observational studies have shown a significant reduction in 30-day mortality associated with prior statin therapy in hospitalised patients with sepsis and community acquired pneumonia.

This article explores the evidence for statins as novel therapy in community acquired pneumonia. Experimental and animal studies suggest statins attenuate acute lung injury by modulating neutrophil function, reducing pro-inflammatory cytokine release and reducing vascular leak. Statins reduce endothelial dysfunction and have anti-thrombotic effects that improve outcome from pneumonia and sepsis in animal models. Clinical studies have provided conflicting results, but many suggest that statins may have a role in preventing pneumonia, or improving prognosis in hospitalised patients with community-acquired pneumonia.

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Introduction

Community acquired pneumonia is the most common infectious disease requiring hospitalisation in western countries accounting for approximately 100,000 hospital admissions in England during 2004–2005. Hospital admissions for pneumonia are rising, particularly in elderly patients. The inpatient mortality for community acquired pneumonia is around 10%,2–5 This has not changed since the widespread introduction of antibiotics in the 1950's and there are still no established therapies beyond antibiotics for treatment of community acquired pneumonia.6

Mortality from community-acquired pneumonia is multifactorial, but is linked to excessive systemic and pulmonary inflammation, acute lung injury, vascular dysfunction and coagulopathy.2,7

Statins lower cholesterol through competitive inhibition of the enzyme HMG co-A reductase. Landmark studies such as the Scandinavian Simvastatin Survival Study (4S),8 Cholesterol and Recurrent Events (CARE),9 Long-term Intervention with Pravastatin in Ischaemic Heart Disease (LIPID)10 and the West of Scotland Coronary Prevention Study (WOSCOPS)11 have demonstrated that statin drugs are associated with reduced mortality from ischaemic heart disease and stroke, for which hypercholesterolaemia is a major risk factor.12,13 However, the observation that the protective effects of statins were significantly greater than that expected from the lowering of cholesterol alone led to speculation that statins may have other effects. Statins have now been shown to have multiple anti-inflammatory and anti-thrombotic effects, with potential applications beyond the cardiovascular system.14–18

There is growing evidence that these effects may be of therapeutic benefit in patients with community acquired pneumonia. The purpose of this review is to discuss the non-lipid lowering (pleiotropic) effects of statins, and their potential application to the management of community acquired pneumonia.

Search strategy

The authors conducted a systematic review of the PubMed database up to June 2009 using search terms “Pneumonia”, “sepsis”, “infection”, “inflammation” with terms “statin(s)”, “HMG-coA reductase inhibitors”. The search was supplemented by reviewing reference lists and the authors personal files.

The pleiotropic effects of statins

Alongside its effects on cholesterol biosynthesis, statins have now been shown to have effects on endothelial function in addition to anti-thrombotic, anti-inflammatory and immunomodulatory effects.19–25 HMG-CoA reductase controls the rate limiting step in cholesterol biosynthesis—the conversion of 3-hydroxy-3-methyl-glutaryl-CoA to mevalonic acid. Many of the non-lipid lowering effects of statins are attributed to the inhibition of mevalonic acid synthesis and the subsequent reduction in isoprenoid synthesis (Fig. 1). Multiple cellular processes are reliant on intracellular signalling molecules such as Rho, Ras, Rap and Rab (Fig. 1). These small GTP binding proteins require isoprenylation in order to function as intracellular messengers. By inhibiting the production of isoprenoid intermediates, statins inhibit these pathways leading to multiple effects on inflammatory cell signalling. These effects have been extensively reviewed.26,27 It is also thought that interaction with peroxisome proliferator-activated receptors (PPAR) are necessary for many of the pleiotropic effects of statins.28 Some of the known effects on immune cell function relevant to community acquired pneumonia are summarised in Fig. 2.

Endothelial dysfunction and overwhelming systemic inflammation have been proposed as major mechanisms for poor outcome in patients with sepsis and pneumonia. Through the effects described above, statins may have a role in improving vascular function and reducing inflammation in these diseases.

Potential mechanisms of the beneficial effects of statins

The effects of statins in experimental models are diverse, and which of these effects may be responsible for the benefit observed in clinical studies is not clear. Here we discuss some of the pleiotropic effects of statins focussing on how they may influence pneumonia outcome.
untreated mice. Similar findings were reported in rats, where systemic inflammation was provoked by superior mesenteric artery occlusion and reperfusion, with rats treated with simvastatin having significantly higher $P_{O_2}$, less neutrophilic lung inflammation and less vascular leak. Human studies have been lacking to date, but a recent key study has investigated the effects of simvastatin on lung injury caused by LPS administration to healthy volunteers. Shyamsundar et al. found a significant reduction in neutrophil influx into the lung, with reduced alveolar concentrations of TNF-alpha, CRP and matrix metalloproteinases. These effects appeared to be partly mediated through reduced macrophage NFkB nuclear translocation in statin treated subjects.

### Modulation of neutrophil function

Statins have powerful effects on neutrophils and there is now experimental evidence from a murine model of pneumonia that these effects attenuate pulmonary inflammation. In a study by Fessler et al., mice were treated with lovastatin and exposed to lipopolysaccharide (LPS) to simulate pneumonia. In the treated mice, there was a significant reduction in neutrophil influx into the lungs, decreased neutrophil chemotaxis and reduced levels of pro-inflammatory cytokines in bronchoalveolar lavage fluid. In a parallel model of *Klebsiella pneumoniae* pneumonia, statin treatment attenuated bacterial killing.

All of these processes were reversible with the administration of mevalonic acid (see Fig. 1) bypassing inhibition by statins and proving that the observed effects are the result of effects of statins on the mevalonic acid pathway.

A further study in mice by Erkkila et al. found an increase in pulmonary inflammation in a mouse model of pneumonia induced by *Chlamydia pneumoniae*. Simvastatin treatment was associated with reduced numbers of viable organisms. The results of this study appear to be in contrast to those of Fessler et al. One important consideration is that different statin drugs may have different effects. The same group repeated their experiments using pravastatin and found that, although they also saw increased pulmonary inflammation, pravastatin did not decrease pulmonary bacterial load.

Statins have been shown to increase neutrophil apoptosis. Neutrophil apoptosis is a critical mechanism in the resolution of inflammation and may aid recovery from pneumonia. Other important effects of statins on neutrophil function include decreased expression of LFA-1 and ICAM-1, decreased myeloperoxidase production, reduction in neutrophil reactive oxygen species, effects on neutrophil migration and on angiotensin-II type 1 receptor expression. In humans, simvastatin has been shown to reduce superoxide production from neutrophils in ICU patients with sepsis. Further studies are needed to delineate the different immunomodulatory effects of statins and their relevance to pneumonia.

### Anti-thrombotic effects

Coagulopathy is a central feature of pneumonia and other forms of acute lung injury. Intra-alveolar fibrin
deposition is a characteristic feature of many inflammatory lung diseases and may serve a physiological purpose in lung infection by sealing areas in which the alveolar-epithelial barrier is compromised. When widespread and persistent these processes are highly damaging and are characteristic of adult respiratory distress syndrome, a complication of pneumonia with a high mortality rate. Systemic coagulopathy is also evident in pneumonia and sepsis. Therefore therapies with anticoagulant properties may be a potential treatment for pneumonia. Statins have a number of important anti-thrombotic effects of relevance to cardiovascular disease. Statins inhibit the production of thromboxane A2 which promotes platelet aggregation in addition to vasoconstriction. As discussed below, statins have a marked effect on nitric oxide and this mechanism has been shown to be responsible for reducing platelet activation. Statins reduce the expression of plasminogen activator inhibitor-1 and thereby increase tissue plasminogen activator, aiding fibrinolysis.

An important role of statins appears to be in increasing the expression of thrombomodulin by endothelial cells. This glycoprotein serves an important physiological role in binding thrombin. When bound, thrombin loses its procoagulant properties and instead activates protein C. The effects of activated protein C as an anti-inflammatory and anti-coagulant agent in sepsis have been extensively described. During sepsis, thrombomodulin expression is downregulated by inflammatory cytokines. Statins have been shown to increase thrombomodulin expression via a mechanism dependant on nitric oxide. In the study by Shi et al., endothelial cells exposed to TNF-alpha had significantly reduced expression of thrombomodulin, expression that was restored by statins.

Whether modulation of the coagulation and fibrinolysis pathways by statins has therapeutic benefit in humans with pneumonia is not yet known. The major effects of statins on the coagulation pathways are shown in Fig. 3.

**Effects on vascular function**

Nitric oxide is a key mediator in sepsis, causing vasodilation through relaxation of vascular smooth muscle. Nitric oxide is thought to be beneficial to some degree as it has a role in mediation of inflammation. However, widespread vasodilatation leads to organ hypoperfusion and the clinical syndrome of septic shock. Statins have emerged as an important inhibitor of nitric oxide production with relevance to the management of sepsis.

Nitric oxide (NO) production from L-Arginine is mediated by nitric oxide synthase (NOS). This exists in two isoforms-
eNOS, the constitutive form that produces NO from endothelium under normal condition and iNOS, inducible nitric oxide.60 Endothelial dysfunction during sepsis leads to a loss of eNOS produced NO but an increase in iNOS activity.61 Increased iNOS relative to eNOS has been documented during sepsis in humans and animals and is associated with the progression of sepsis.62 iNOS appears critical, as iNOS deficient mice are resistant to LPS induced mortality.63

Treating vascular dysfunction induced by changes in nitric oxide expression is more complicated than it first appears. Therapeutic trials with the non-selective NOS inhibitor NG-methyl-L-arginine have been disappointing64 and mice studies in which eNOS was over-expressed during sepsis in humans and animals and is associated with the progression of sepsis.62 iNOS appears critical, as iNOS deficient mice are resistant to LPS induced mortality.63

Treating vascular dysfunction induced by changes in nitric oxide expression is more complicated than it first appears. Therapeutic trials with the non-selective NOS inhibitor NG-methyl-L-arginine have been disappointing64 and mice studies in which eNOS was over-expressed showed an improved survival in an LPS model of sepsis.65

Most, but not all studies, suggest that suppression of nitric oxide itself is unhelpful and a therapy to restore the balance between eNOS and iNOS is desirable.63

Statins have been shown to increase the half-life of eNOS in endothelial cells.66 A key role for statin effects on eNOS are suggested by the absence of a beneficial effect of statins on inflammation in eNOS deficient mice.67 Statins however, decrease, rather than increase the production of nitric oxide (measured as plasma nitrate concentration) because they decrease iNOS mediated nitric oxide production. This reduction in a rat model of sepsis was shown to correlate with an improved response to vasoconstrictor treatment.68 This suggests that statins have an important effect in reducing iNOS expression by endothelium during sepsis.

Human studies also suggest that statin pre-treatment can attenuate endothelial dysfunction and improve responses to vasoconstrictors. In one study, Pleiner and colleagues randomised healthy volunteers to receive 80 mg of simvastatin or placebo for 4 days prior to infusion of LPS into the forearm to cause transient acute inflammation. The results showed a decreased in endothelial dysfunction in the statin treated group and a superior response to noradrenaline- mirroring the findings of the animal studies.69

These effects suggest that statin may reduce the severity of septic shock and improve the response to vasopressors primarily through nitric oxide in patients with sepsis.

Disruption of the alveolar epithelial barrier and increased capillary endothelial permeability is an important component of acute lung injury.70 Important regulators of these phenomena include zinc homeostasis, PPAR signalling, effects of extracellular ATP and the role of TNF-alpha and heat shock protein 90.70 Statins have been shown to have powerful effects on the lung vasculature, attenuating LPS induced vascular leak with effects on the actin cytoskeleton of vascular endothelial cells helping to stabilise the alveolar epithelial barrier and reduce fluid leak in acute lung injury.71

Reduced cardiovascular risk

Statins reduce the risk of cardiovascular events, including myocardial infarction, through their effects of cholesterol, but also through effects on endothelial function, thrombosis and inflammation.8–25

Patients with pneumonia are known to be at increased cardiovascular risk72–75 (and as many as 25% of patients failing to respond to treatment were found to have acute myocardial infarction in one study75). Nearly 50% of all deaths in patients with pneumonia, and more than a quarter
of deaths within 30 days are related to co-morbidities such as vascular disease, rather than directly due to pneumonia. It is therefore plausible that the reduced 30-day mortality observed in cohort studies may simply reflect a lower incidence of cardiovascular events. A detailed discussion of the mechanisms of cardiac dysfunction in sepsis is beyond the scope of this review, and have been discussed in detail elsewhere. It is known, however that even in adequately resuscitated patients with sepsis, impaired left ventricular function and diastolic dysfunction are observed. In cellular and animal models, sepsis provokes depressed myocyte activity and reduces left ventricular ejection fraction.

Statins appear to have a cardioprotective effect in animal models of sepsis, with one study showing preserved cardiac function as assessed by echocardiography and isolated heart preparations in mice with experimental sepsis.

Fig. 4 summarises the proposed beneficial effects of statins in experimental and animal models.

Clinical studies of statin use in community acquired pneumonia

Prevention of pneumonia

Investigators hypothesised that through the effects discussed above, prior statin use may be associated with a reduced risk of developing pneumonia. The association between statin use and pneumonia has now been investigated in a number of large databases.

Table 1 summarises the 4 clinical studies to date that have investigated the role of statins in preventing pneumonia.

Van De Garde et al. performed a case control study in more than 20,000 diabetic patients identified using the General Practice Research Database (GPRD), a large database containing medical records of approximately 6.5% of the population of England and Wales. The study matched 4719 pneumonia cases with 15322 patients without pneumonia and found an odds ratio of 0.49 (0.35–0.69) suggesting a powerful protective effect of statins after adjusting for confounders.

Schlienger et al. further analysed the GPRD database by matching 1253 cases of pneumonia with 4838 matched control patients. The study found that use of statins was associated with a reduced risk of fatal pneumonia OR 0.47 (0.25–0.88) but found no significant effect on development of uncomplicated pneumonia.

Recently Myles et al. confirmed a similar effect. Using an alternative primary care research database (the health improvement network (THIN) database) they matched 3709 pneumonia cases with 22,174 matched controls and found an Odds ratio of 0.78 (0.65–0.94) for development of CAP. They have subsequently shown a reduced risk of short and long term mortality following pneumonia in patients treated with statins using the same database.

Each of these studies has significant limitations inherent to retrospective case control studies. The studies rely on the accuracy of pneumonia diagnosis made by primary care physicians. In addition, although the analyses were adjusted for some potential confounders such as vaccination status and use of other medications, other potential confounders were not available from these databases.

A recent study by Dublin et al. attempted to control for more of these potential confounders. They studied a large population of elderly patients (aged >65 years) from a large administrative database in the United States. Additional safeguards to ensure accuracy were used, such as reviewing chest radiograph reports to ensure correct diagnosis of pneumonia and the analysis was adjusted for a number of other factors not available in previous databases, such as functional status. The results of this study did not confirm the previous reports. In the Dublin study, statin use appeared to predispose to, rather than protect against pneumonia. In the minimally adjusted model, statin use had an odds ratio of 1.13 (0.95–1.34), while in the fully adjusted model statin use had an odds ratio of 1.26 (1.01–1.56). The authors speculate that the exclusion of nursing home residents, immunosuppressed patients and other high risk groups may have exposed a “healthy user bias” in previous studies.

Prior statin use and outcome in hospitalised patients with community acquired pneumonia

Statins have not only been implicated in preventing the development of pneumonia but also in improving the
prognosis of pneumonia and sepsis in hospitalised patients (Table 2).

A prospective study of 361 patients in 2004 found a decreased incidence of severe sepsis and a lower ICU admission rate in patients with sepsis pretreated with statins (predominantly simvastatin). More than 50% of patients in this study had pneumonia and this study provided the first prospective evidence that statins may improve outcome in pneumonia.87

Subsequently, confirmation of this effect in a community acquired pneumonia population was found in a retrospective study of predominantly elderly male patients in the United States. This demonstrated dramatically improved 30-day mortality in patients pre-treated with statins (OR 0.36 95% Confidence interval 0.14–0.92).88 The authors have subsequently published retrospective data showing a decrease in 30-day mortality from pneumonia and influenza in over 8000 elderly male patients,89 and similarly a reduction in 30-day mortality OR 0.48 (95% CI 0.36–0.64) in over 3000 patients with sepsis of any cause.90 These studies do however, suffer from limitations inherent to retrospective design.

There was therefore healthy scepticism about the effect of statins.91 Subsequently, a study derived from

| Table 1 | Studies of Statin use to prevent the development of community acquired pneumonia. Abbreviations: GPRD = General Practice Research Database; THIN = The Health Improvement Network; CAP = community-acquired pneumonia. |
| First Author (year) | Population | Disease | N | Design | Outcome | OR (95% CI) |
| Van De Garde (2005)82 | GPRD, UK | CAP | 4719 CAP cases 15322 controls | Development of CAP | 0.49 (0.35–0.69) |
| Schlienger (2007)83 | GPRD, UK | CAP | 1253 CAP cases 4838 controls | Development of fatal pneumonia | 0.47 (0.25–0.88) |
| Myles (2009)84 | THIN database, UK | CAP | 3709 CAP cases 22174 controls | Development of CAP | 0.78 (0.65–0.94) |
| Dublin (2009)85 | Group Health database, USA | CAP | 1125 CAP cases 2235 controls | Development of CAP | 1.26 (1.01–1.56). |

| Table 2 | Clinical Studies of the effect of prior statin use on outcome in hospitalised patients with sepsis and pneumonia. |
| First Author (year) | Population | Disease | N | Design | Outcome | OR (95% CI) |
| Liappis (2001)100 | USA | Bacteraemia | 388 | Retrospective cohort | Survival | 7.6 (1.01–58) |
| Fernandez (2005)97 | Spain | Sepsis (ICU) | 438 | Retrospective cohort | In-hospital mortality | 2.30 (1.08–4.89) |
| Kruger (2006)96 | Australia | Bacteraemia | 438 | Retrospective cohort | In-hospital mortality | 0.39 (0.17–0.91) |
| Schmidt (2006)101 | Germany | Sepsis (ICU) | 120 | Retrospective cohort | 28 day mortality | 0.53 (0.29–0.99) |
| Almog (2004)87 | Israel | Sepsis | 361 | Prospective observation | 28 day mortality | 0.43 (0.13–1.38) |
| Mortensen (2005)88 | USA | CAP | 787 | Retrospective cohort | 30-day mortality | 0.36 (0.14–0.92) |
| Hackam (2006)96 | Canada | Sepsis | 141,487 | Retrospective database | Fatal Sepsis | 0.75 (0.61–0.93) |
| Thomson (2006)102 | Denmark | Bacteraemia | 5177 | Retrospective database | 30-day mortality | 0.93 (0.66–1.30) |
| Majumdar (2006)91 | Canada | CAP | 3415 | Prospective observation | Composite in-hospital mortality or ITU admission | 1.10 (0.76–1.60) |
| Yang (2007)99 | Taiwan | Sepsis | 763 | Retrospective cohort | 30-day mortality | 0.95 (0.53–1.68) |
| Mortensen (2007)90 | USA | Sepsis | 3018 | Retrospective cohort | 30-day mortality | 0.48 (0.36–0.64) |
| Mortensen (2008)89 | USA | Pneumonia/Influenza | 8652 | Retrospective cohort | 30-day mortality | 0.54 (0.42–0.70) |
| Chalmers (2008)94 | UK | CAP | 1269 | Prospective observation | 30-day mortality | 0.46 (0.25–0.85) |
| Thomson (2008)95 | Denmark | CAP | 29,900 | Retrospective database | 30 day mortality | 0.69 (0.58–0.82) |
a prospectively collected database was published in the BMJ in 2006. This study suggested that confounding due to the "healthy user effect" may be responsible for the observed benefits of statins. In this study by Majumdar et al., prior statin use was assessed in a population of 3415 patients in 6 hospitals. In their "raw analysis" statin users were less likely to die or be admitted to the intensive care unit (although not statistically significant), but when these results were adjusted using a propensity score, a statistical technique to adjust for potential confounders, no significant association was found. The authors conclude that previous findings of benefit for statins were due to healthy user bias- the theory that patients taking statins are also more likely to do other beneficial health behaviours such as taking pneumococcal and influenza vaccination or stopping smoking that may be associated with better outcome.

The results of the study by Majumdar et al., however, are in variance with other studies. In the analysis by Majumdar et al., older age and the presence of congestive cardiac failure were found to be protective against poor outcome. The converse has been consistently found in other studies. This may have arisen as the study by Majumdar et al. used a combined outcome (mortality or admission to an intensive care unit) rather than mortality alone, or because of the use of a complex propensity score in an attempt to adjust for confounders. Statin use is strongly associated with age and underlying cardiac disease and therefore the interaction between these factors is difficult to interpret.

Following this, the present authors performed a prospective study that aimed to account for these factors. The study in the UK of 1269 patients found a significant reduction in 30-day mortality in patients pretreated with statins. We attempted to account for healthy user bias both by adjusting the multivariate analysis for important confounders, and also by assessing the impact of other cardiovascular drugs (ACE-Inhibitors/Angiotensin converting enzyme receptor antagonists/Aspirin/β-blockers). Our hypothesis was that the healthy user bias would lead to an apparent benefit for all cardiovascular drugs, not simply statins. No such association was found and only statins were associated with reduced 30-day mortality (OR 0.46, 95% confidence interval [CI], 0.25–0.85). Further, complications of pneumonia (complicated parapneumonic effusion and empyema) were reduced in statin users (AOR 0.44, 95% CI, 0.25–0.79) along with C-Reactive protein levels.

Cardiac events are common during acute pneumonia and risk is increased following episodes of pneumonia. It may be reasonably argued that statins exert their effect through reduced cardiovascular events. The reduced risk of complicated pneumonia in our study however, suggest that an immunomodulatory effect could also be responsible.

We must also accept however, that no observational study can fully adjust for all possible confounders.

A large study from Denmark published in 2008 provided further confirmation of a significant reduction in pneumonia mortality for patients prescribed statin treatment. This analysis is significant, both because of the large sample size and because of the detailed information collected about comorbidities and socioeconomic markers that allowed the authors to account for potential "healthy user bias". The authors found a significant reduction in 30-day mortality from CAP associated with statin use (OR 0.69 (0.58–0.82), even after adjusting for a propensity score, which Majumdar et al. had felt was a key feature of their study.

In sepsis, not limited to pneumonia, several further studies have suggested a protective role for statins. The study by Hackam et al. published in the Lancet in 2006 matched 34,584 statin treated patients with the same number of non-statin users in an elderly population following hospitalisation for acute cardiovascular events. The study was significant, because of the large sample size, but also because the statin user and non user populations were well matched for the majority of important potential confounders, such as comorbidities and residency status. Statin use was associated with a reduced risk of sepsis (Hazard ratio 0.81 95% CI 0.72–0.91) and a reduced risk of fatal sepsis HR 0.75 (0.61–0.93). Such an effect was not seen for non-statin lipid lowering therapy, which increases the likelihood of a true biological effect rather than healthy user bias. Studies by Fernandez et al., Kruger et al., Yang et al., and Mortensen et al., have produced conflicting results, but are limited by retrospective design and the limited data available in some of these studies to adjust for confounders.

Additional factors which should be considered include the possibility that not all statins may have the full range of beneficial effects, as illustrated by the experimental studies of Erkilla, Tirola and Fessler discussed above. The dose of statins required to produce a beneficial effect has not been studied and the duration of prior treatment required to produce a protective effect has not been established in these observational studies.

The major studies describing outcomes for statin treatment in hospitalised patients with pneumonia and sepsis are described in Table 2.

The majority of studies demonstrate a beneficial effect of statin therapy. The results of ongoing randomised controlled trials are awaited. One randomised controlled trial has recently been published. Novack and colleagues randomised 83 patients with suspected bacterial infections to simvastatin or placebo. Unfortunately the trial was terminated due to slow recruitment, but a secondary analysis demonstrates a reduction in proinflammatory cytokines (TNF-alpha and IL-6) in the statin treated group. Results of larger trials powered to detect mortality benefit are now awaited.

Observational studies show association rather than causation and only data from randomised control trials will establish conclusively if statins are effective in preventing or treating CAP.

Conclusion

Current evidence suggests that pretreatment with statins may have a beneficial effect in prevention of pneumonia and reducing severity of community acquired pneumonia. Randomised controlled trials are needed to establish if statins offer an innovative new adjunctive treatment to antibiotics for patients admitted to hospital with community acquired pneumonia.
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Author’s contribution

All authors contributing the literature review and to writing the paper.

Conflict of interest

All authors have no conflicts of interest in relation to the present manuscript.

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