Statins: the next anti-endotoxin

Sepsis is a systemic response to infection characterised by the triggering of many inflammatory pathways. Much of the organ dysfunction seen in sepsis is thought to result from the effects of inflammatory cytokines, the generation of reactive oxygen species, the production of nitric oxide, and the depletion of antithrombin III. Sepsis continues to be a major cause of morbidity and carries a 20%–50% mortality rate. Fluid resuscitation, vasopressor therapy, antibiotics and source control remain the mainstays of treatment. Activated protein C and glucocorticoids have been shown to improve outcome in randomised trials. However, there have been few other recent advances in the treatment of sepsis. It is intriguing that a widely used class of drugs — the statins — may provide serendipitous benefits to patients with sepsis.

The statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] reductase inhibitors) were introduced into clinical practice in the 1980s. Recent Australian prescribing data (2001) rank statin drugs first and second among prescription medicines for number of prescriptions used and cost. In fact, at least 15% of patients requiring admission to hospital each year take established statin therapy, and the number is growing each year. A similar trend is seen worldwide.

Statins have been shown to have benefits in many groups, including patients with coronary artery disease, those with stroke, high-risk elderly patients, patients having major surgery, and even those with normal lipid levels. Some beneficial effects of statins seem to be independent of their lipid-lowering ability, including effects on endothelial function, apoptosis and plaque stabilisation, and are mainly due to anti-inflammatory, anti-oxidant and immunomodulatory roles.

Could statin therapy affect outcomes in sepsis?

Two observational studies of patients with bacteraemia have shown that pre-existing statin therapy was associated with a significant reduction in mortality. In a retrospective study of 388 patients with bacteraemia, Liappis and colleagues reported that overall mortality was reduced from 28% to 6% (P = 0.002). Similarly, Kruger et al found that all-cause hospital mortality was reduced from 23.1% to 10.6% in 438 patients with documented bacteraemia. This difference was more pronounced in patients who continued to receive statin therapy after the onset of bacteraemia (18.3% versus 1.8%). These findings raise the possibility that ceasing pre-existing statin therapy in sepsis, as recommended by current prescribing guidelines, may be associated with increased mortality. A recent prospective observational cohort study also concluded that prior statin therapy is associated with a decreased rate of severe sepsis and may reduce intensive care unit admissions. The largest study to date assessed more than 90 000 patients discharged from hospital with cardiovascular disease. Statin therapy was associated with a reduction in the subsequent risk of developing sepsis in all patient subgroups.

The findings of all these studies have the inherent limitations of observational studies. In particular, they cannot fully account for the effect of greater illness severity leading to cessation of statin therapy, thus biasing study outcomes. Not all studies support a potential benefit associated with statin therapy. Fernandez et al recently...
reported an increase in mortality for ICU patients who continued statin therapy.17

Are there animal data supporting benefits in sepsis?
The potential beneficial effects of statins in sepsis have been tested in several animal models. In a murine model of caecal ligation and perforation, Merx et al demonstrated that mice pre-treated with statins had a fourfold increase in mean survival compared with control mice.18 The same investigators subsequently found that statin therapy commenced after induction of sepsis also significantly improved survival time, from 23 (SEM, 1.2) hours for placebo-treated mice to 37 (SEM, 3.6) hours for simvastatin-treated, 40 (SD, 4.2) hours for atorvastatin-treated, and 39 (SD, 3.9) hours for pravastatin-treated mice.19 The improvement was based on the preservation of cardiac function and haemodynamic status, improved responsiveness to dobutamine, and reduction in the inflammatory response. Interestingly, the benefits extended to several, but not all, of the statins tested.

Is there a biological rationale?
In addition to their main effect on low-density lipoprotein (LDL) cholesterol, statins exhibit a wide range of other biological effects. These effects are often termed pleiotropic (Greek for “many turnings”), and include actions on cell proliferation and endothelial function, immunomodulatory effects, antioxidant effects and effects on coagulation. As all statins lower LDL cholesterol levels, and LDL plays an important role in many of these functions, it is difficult to show that the effects of statins are not related to LDL-lowering.

Several authors have recently reviewed the biology of statins in sepsis.20,21 Emerging research on these pleiotropic effects provides a potential scientific basis for an outcome benefit with statin therapy in sepsis.

What are the potential mechanisms?
Increase or alterations in high-density lipoprotein cholesterol
Significant changes in lipid metabolism occur in sepsis. Total cholesterol and high-density lipoprotein (HDL) cholesterol levels are decreased in sepsis, and the magnitude of the changes seems to reflect the severity of inflammation.22,23 Both the amount and composition of HDL change in sepsis.24 potentially affecting the inflammatory cascade and outcome.22 Bacterial endotoxin (lipopolysaccharide) elicits dramatic responses in the host, including elevated plasma lipid levels due to the increased synthesis and secretion of triglyceride-rich lipoproteins by the liver, and the inhibition of lipoprotein lipase. This cytokine-induced hyperlipo-

proteinemia, clinically termed the “lipaemia of sepsis”, was customarily thought to represent the mobilisation of lipid stores to fuel the host response to infection. However, as lipoproteins can also bind and neutralise lipopolysaccharide, it is postulated that triglyceride-rich lipoproteins (very low-density lipoprotein [VLDL] and chylomicrons) are also components of an innate, non-adaptive host immune response to infection.25 In general, statin therapy increases HDL levels, in addition to its LDL-lowering effects.26,27 The effect of statin therapy on the lipid profile in sepsis remains unclear, but it may be that alterations in the lipoprotein balance have profound effects on inflammation.

Direct antioxidant mechanisms
Oxygen free radicals are involved in the pathogenesis and manifestations of sepsis, as they react with various biological substrates, especially polyunsaturated fatty acids, to induce membrane dysfunction, tissue damage and organ injury.28 Some pleiotropic effects of statins could be attributed to their ability to suppress the synthesis of isoprenoid intermediates, thereby possibly decreasing oxidative stress.29 Statins reduce the production of reactive oxygen species by vascular NAD(P)H oxidase, and inhibit the respiratory burst of phagocytes.30

Immunomodulatory effects of statins
It appears that statins are able to influence inflammatory processes at several levels. They have been shown to reduce the adhesiveness of monocytes to the vascular endothelium,31,32 and to directly inhibit the main β2-integrin leukocyte function antigen-1.33 Statins deplete isoprenoids, which, via membrane G proteins, play a pivotal role in the signal transduction pathways that regulate cellular migration and proliferation.34 Several studies have shown that statin therapy either lowers circulating concentrations of C-reactive protein or reduces the risk associated with systemic inflammation, in some cases independently of the reduction in cholesterol level.35

Statins have been shown to inhibit elements of the inflammatory cascade induced by Escherichia coli endotoxin36 and Staphylococcus aureus α-toxin.37 They have also been shown to reduce complement activation in vitro and in animal models.38

Improvement in vascular function: the role of nitric oxide
Endothelial cells play an important role in the control of vascular tone, permeability, blood flow, coagulation, thrombolysis, inflammation, tissue repair and growth.39 It is thought that endothelial activation, dysfunction and apoptosis play a crucial role in the pathogenesis of sepsis and subsequent multiple organ dysfunction. Considerable research has focused on the mechanisms by which statins
enhance endothelial anticoagulant and fibrinolytic properties. These studies show that statins increase expression and enhance activity of endothelial nitric oxide synthase,\textsuperscript{40} up-regulate prostacyclin\textsuperscript{41} and tissue-type plasminogen activator,\textsuperscript{42} and down-regulate tissue factor, endothelin-1 and plasminogen-activator inhibitor-1.\textsuperscript{43} Statins have been shown to affect serum levels of anti-thrombin III in patients with heart failure.\textsuperscript{44}

**What is not known?**

There is a paucity of data on the use of statins in critically ill patients. While a detailed discussion of the pharmacology of statins is beyond the scope of this article, several gaps in current knowledge are worth highlighting.

**How do statins work in sepsis?**

It is not known which, if any, of the biological mechanisms discussed above are important in determining outcome in patients with sepsis. It therefore follows that no dose–effect relationship has been described.

**When should they be administered?**

It is possible that part of the protective effect of statin therapy in sepsis is due to its pre-existing effects, perhaps through its stabilising vascular endothelium and so limiting subsequent organ dysfunction. It is not known whether continuing statin therapy confers additional benefit, whether cessation of pre-existing therapy is detrimental, or whether commencing de-novo statin therapy is an effective adjunct in managing patients with sepsis.

**What dose should be given?**

The plasma concentration of statins needed for a beneficial effect in sepsis is unknown. However, the pharmacokinetics of these agents are well described in the general population, with most agents having a high first-pass metabolism in the liver, and absorption being affected by food in the stomach. This suggests that changes in splanchnic perfusion associated with sepsis, or the timing of drug administration with enteral feeding might affect plasma levels. Most statin drugs are metabolised by hepatic cytochromes, and interactions with these enzyme systems are ubiquitous in clinical practice, particularly given the range of medications used in critically ill patients. Newer agents are metabolised to a lesser extent, with only 10% of rosvuastatin and pitavastatin being metabolised. This has the potential benefit of limiting the impact of drug interactions that alter serum levels. The impact of organ dysfunction, co-administration of drugs known to affect cytochrome function, and gastric dysmotility on the absorption, pharmacokinetics and pharmacodynamics of statin therapy in patients with sepsis is unknown.

**Are statins safe for critically ill patients?**

Current prescribing guidelines recommend that statin therapy be discontinued in patients with acute illness, such as severe infection, major surgery, trauma, or severe electrolyte, metabolic or endocrine disorders, for fear of increased risk of toxicity.\textsuperscript{45} There are limited data on the safety of statins in patients with sepsis, although rhabdomyolysis and liver dysfunction are well described in high-risk patients.\textsuperscript{45-47}

While recent publications support the benefits of continued statin therapy in acute coronary syndromes,\textsuperscript{48,49} it is not known what should be done with statin therapy when patients are admitted to hospital with sepsis. HMG-CoA reductase inhibition results in inhibition of ubiquinone or coenzyme Q10. It has been reported that this can, rarely, predispose to the development of lactic acidosis caused by paralysis of mitochondrial metabolism.\textsuperscript{50} The true relevance of this interaction may become apparent as these agents are increasingly investigated in critically ill patients.

**Which drug — are all statins equivalent?**

All statins except pravastatin and rosuvastatin are lipophilic. Whether this has any impact on differences in pleiotropic effects remains to be established. While statins as a drug class share many properties, they are not always therapeutically interchangeable.\textsuperscript{51} Individual statins have different effects on lipid profiles and possibly also inflammation and pleiotropic effects. They also clearly differ in their propensity to cause rhabdomyolysis, as illustrated by the withdrawal of cerivastatin from the market in 2001, because of a cluster of fatal cases of rhabdomyolysis.\textsuperscript{52}

**How should they be administered?**

The safety, efficacy and place of parenteral administration are unclear, and no intravenous preparations of these agents are marketed.

**Conclusions**

Emerging evidence suggests that statins have a potentially beneficial role in patients with sepsis, but much remains unknown. Statins are significantly cheaper than other therapies that have been shown to improve outcome in sepsis. Therefore, demonstration of a mortality benefit with statins would have enormous cost–benefit implications for society. Further investigation of the biology of statins in sepsis is warranted.

**Author details**

Peter S Kruger, Intensive Care Specialist
Intensive Care Unit, Princess Alexandra Hospital, Brisbane, QLD.
Correspondence: peter_kruger@health.qld.gov.au
References


