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EDITORIAL

Statins in patients with sepsis and ARDS: is it over? No

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Sepsis and ARDS are diverse syndromes where the host response to an insult results in varied clinical manifestations and associated organ dysfunction. While the overwhelming impression of over 30 years of sepsis research is that nothing new seems to work, clinical outcomes have improved over time [1, 2] with the inference that we must be doing something right. Particularly for sepsis, but the principles apply no less to ARDS, the mainstay of therapy involves resuscitation, managing infection (with antibiotics and through source control), supportive care and finally adjunctive therapy [3]. It is the last of these that has led to the most disappointment [4].

It is as an adjunctive therapy that statins may play role in ARDS and sepsis. Statins have revolutionised clinical outcomes for patients with or at risk of cardiovascular disease. On the basis of basic science and preclinical studies, HMG CoA reductase inhibitors have a broad array of interactions with the inflammatory cascade that may be beneficial in various aspects of critical illness [5, 6].

A recent meta-analysis [7] of observational studies which pooled the data from over 330,000 patients concluded that statin use in sepsis is associated with improved outcomes. This conclusion clearly comes with many caveats, mainly that association does not confirm causation and the multiple occasions introducing bias. These data have prompted multiple randomised trials testing the hypothesis that statins could improve the outcome for patients with sepsis and acute lung injury. Many thought it unlikely that a "pill a day", let alone one that is currently used for an unrelated indication (lowering cholesterol), could influence outcomes from established organ failure. It looks as if they may have been right. At least four multicentre randomised controlled trials (RCTs) have now studied various aspects of this core hypothesis. Each has failed to confirm that statin use in established organ failure is a magic bullet that improves patient survival from sepsis or ARDS [8].

Prior to closing this chapter it would be reasonable to address some fundamental issues. Do we truly know what condition we are treating? Did we use the right drug, at the right time, in the correct dose, and what might be the effect of not doing so on the confidence we have in the results? Should we have focussed on treatment or on prevention? These are crucial questions that also touch many other studies in critically ill patients.

The diseases we have sought to cure are perhaps not real [9]. Both syndromes result in a diverse and heterogeneous group of patients with an illness that may have originated from a variety of causes, presented with an array of clinical findings, have differing severity, and are heavily modified by the presence of comorbidities that contribute significantly to an individual's outcome. Yet we studied an intervention in conditions in which the biological pathways that are not completely understood, with an agent that might act at various points in the biological pathways even though we are unsure about the existence of causal relationship between these pathways and the outcomes we seek to influence [10].

How confident can we be about the robustness of these results? It is highly likely that penicillin, an intervention known to have an enormous impact on clinical outcomes in patients with sensitive gram positive organisms, would be found wanting if put through the rigours of a multicentre randomised trial of all comers with severe sepsis. We know that when treating an infection with antibiotics, the correct dose, given at the right time, to the right patients (on the basis of known or highly likely causing organisms) will kill the target bacteria and prevent the

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immune cascade that ends in organ failure and death. An incorrect drug or dose, given too late, to all patients with a clinical phenotype that may or may not be caused by an infection means that only some may benefit, and any signal of benefit is lost in the noise. The concept of fragility is a construct that may help clarify just how "fragile" the results of a clinical trial may be by describing how many extra (or fewer) outcome events are required to alter a statistically significant result [11]. In both the STATInS and HARP-2 trials [12, 13] an alteration of just three events would have yielded statistically significant results in favour of statin use based on mortality outcomes.

Should we focus on treatment or on prevention? Statin use prior to the development of multiple organ failure may in part explain the discordance between observational studies (including patients who were on statins before their critical illness) with randomised trials (including patients with established organ failure). Of note a study by Patel et al. [14] suggests a lower rate of progression of sepsis with atorvastatin compared to placebo. Fortunately further studies assessing if statin therapy may have a preventive role very early in an illness or even as prophylaxis are now starting.

The prevention argument has another important component. Should pre-existing statins be continued during an acute illness? At this time randomised studies are inconclusive. While one trial suggests that prior statin recipients have worse clinical outcomes when continued on placebo rather than on atorvastatin [13], i.e. the statin therapy is stopped, another demonstrated no influence on inflammatory parameters or progression of sepsis in patients hospitalised with infection [15]. At least 30 % of hospitalised patients are taking statin therapy from the community. It is therefore vital to establish if statins should be continued or stopped when a prior recipient develops an acute illness.

Despite the failure of RCTs to show benefit, the sheer weight of numbers from observational data suggests a smoking gun that perhaps can not be ignored. Before we discard statins to the graveyard of "failed adjuvants" we should reconsider regarding patient selection, trial methodology and basic science understanding to better apply them as a targeted therapy. Let us not "discard the baby with the bath water", as we may have done already over the years with interventions that may well work if they were given to the right patient, at the right time, in the correct dose.

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Conflicts of Interest
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