

## Commentary

# Recently published papers: Sepsis – guidelines, treatment and novel approaches

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## Abstract

The choice of inotropic agent, particularly in catecholamine-resistant septic shock, remains an area of debate. Here we discuss a recent trial examining the use of vasopressin in a carefully controlled trial setting. Yet more data on the use of drotrecogin alfa (activated) in septic shock are described, as are novel but as yet experimental approaches to the treatment of sepsis. Finally, it is important not to forget to read the latest surviving sepsis guidelines.

“Man is a creature composed of countless millions of cells: a microbe is composed of only one, yet throughout the ages the two have been in ceaseless conflict”

*AB Christie*

Septic shock remains a common cause of death in intensive care units worldwide and presents the clinician with a variety of management problems. The Surviving Sepsis Campaign has gone far in collating the considerable wealth of information currently available about this devastating condition and provides excellent guidelines, which are essential reading for consultant and trainee alike [1]. However, new insights into the management of these patients continue to accumulate, and the last few months have been no exception. One of the basic tenets of treating septic shock is the provision of cardiovascular support through the use of catecholamines, although there is much interest in other agents as addressed in the study by Russell and colleagues in *The New England Journal of Medicine* [2]. They examined the use of the pituitary-derived peptide hormone vasopressin in patients with septic shock through a multi-centred, randomised trial involving 778 patients given low-dose vasopressin (0.01 to 0.03 U/min) in addition to noradrenaline (norepinephrine) compared with noradrenaline alone. No overall differences were found between the two groups in terms of either the

primary endpoint of 28-day mortality or the various secondary endpoints. Interestingly, the vasopressin-treated group had a 28-day mortality of 35% compared with 39% of the group treated with noradrenaline alone, which is clearly much less than one would expect. The authors do suggest that this may reflect an improvement in the overall care of patients with septic shock, but equally it could reflect the selection criteria used: 6,229 patients were assessed for eligibility but more than 5,000 patients were not enrolled, a significant proportion of whom had cardiac disease. The authors themselves do concede that the baseline mean arterial pressures observed (72 to 73 mmHg) were somewhat higher than expected and therefore the trial probably reflects the use of vasopressin as a catecholamine-sparing drug rather than being an evaluation of vasopressin as an agent in shock unresponsive to catecholamines. Subgroup analysis on those “thought to be more severe” (at least 15 µg noradrenaline per minute), on whom vasopressin might be deemed to have a greater effect, failed to show any decrease in mortality. What does this study add to our current clinical practice? It does show that, in this carefully selected patient cohort, vasopressin use is safe but does not confer any additional benefit over catecholamine use. As with many studies, we await the next randomised controlled trial!

The differences between everyday clinical practice and the restrictive environs of the randomised controlled trial are further highlighted in a retrospective observational study by Wheeler and colleagues on the use of drotrecogin alfa (activated; DrotAA) [3]. This is an interesting study that compares DrotAA use in five teaching institutions with that reported in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial [4] and demonstrates that in the group observed, which reflects current practice, patients who received DrotAA were younger, had more severe illness, increased comorbidities and received treatment later than those enrolled in the PROWESS study.

DrotAA = drotrecogin alfa (activated); PROWESS = Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis.

Indeed, nearly 50% of those treated would have been ineligible for the PROWESS trial principally through delayed onset of treatment, with 33.9% of patients receiving DrotAA later than 2 days after the onset of severe sepsis. What is clear is that those patients receiving early treatment (day 0) fared similarly in terms of mortality to those in the PROWESS study despite the disparity in the groups. Those treated later did not; for example, patients treated at day 0 had a 33% mortality, whereas those treated at day 2 or later had a 52% mortality. These results probably strengthen the case for DrotAA use when applied appropriately and yet again emphasises the need for the early recognition and treatment of sepsis.

The evolution of the treatment of our patients with septic shock requires continuing to search for improvements in outcome through alternative agents. The future may involve modulation of the immune response itself. Relatively recently, the anti-inflammatory role of the vagus nerve has been explored in an animal model of endotoxaemia and shock, the so-called 'cholinergic anti-inflammatory pathway', and is a mechanism for the neural inhibition of inflammation through regulation of the inflammatory response [5,6]. A recent study by Hofer and colleagues in *Critical Care Medicine* addresses this through assessing the role of pharmacological cholinesterase inhibition on survival in experimental sepsis [7]. A murine model of sepsis was employed, namely sepsis induced through caecal ligation and puncture. Animals were then treated with intraperitoneal injections of nicotine, physostigmine or lipopolysaccharide-free 0.9% normal saline. Animals treated with intraperitoneal injections of nicotine (400 µg/kg), physostigmine (80 µg/kg) and neostigmine (80 µg/kg) demonstrated improved survival, and treatment with physostigmine significantly reduced lethality as efficiently as direct stimulation of the cholinergic anti-inflammatory pathway with nicotine. Downregulation of the binding activity of nuclear factor-κB was observed, together with a significant decrease in the concentrations of the circulating pro-inflammatory cytokines tumour necrosis factor-α, interleukin-1β and interleukin-6 as well as a decrease in pulmonary neutrophil invasion. There was no observed difference in survival between the groups treated with neostigmine and physostigmine; interestingly, as in most things, septic delay of treatment beyond 6 hours negated any positive effects on survival. So far, studies on the cholinergic inflammatory pathway remain predominantly experimental in nature. The last 5 years has seen a small collection of studies that have demonstrated a potential role for cholinesterase inhibitors and nicotine in the management of sepsis and improved outcomes; we await further studies with interest.

Barnato and colleagues present a different slant on sepsis, performing a retrospective study on the racial variation of patients with sepsis admitted to hospitals within six US states [8]. This study demonstrates that the incidence of severe sepsis in blacks is significantly higher than in whites or

hispanics. The authors have made considerable efforts to negate the confounding effects of poverty and geography, although they admit that unmeasured differences in behaviour may be relevant to their results. However, they do raise the hypothesis that biological differences in susceptibility may also have a role. No doubt, with the rising tide of genetic studies, further information is not too far away.

Finally we return to the Surviving Sepsis Campaign guidelines, which 'recommend the protocolized resuscitation of a patient with sepsis-induced shock ... this protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission'. The studies highlighted here all reinforce the need for the prompt recognition and early treatment of sepsis. Adherence to these guidelines may have more of an impact on the outcome of our patients than any new, as yet unproven, treatments.

## Competing interests

The authors declare that they have no competing interests.

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