Editorial

Shooting for the bull's eye in septic shock

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The sine qua non of septic shock is hemodynamic failure, and it is expected that therapy for septic shock is directed at stabilizing the blood pressure, while avoiding complications such as volume overload. Some prior evidence existed to suggest that hyperoxia could induce vasoconstriction (1), while hypertonic saline could be used as a volume-sparing agent for fluid resuscitation. To simultaneously investigate the effectiveness of both hyperoxia and hypertonic saline in septic shock to reduce mortality, Asfar and colleagues conducted the HYPERS2S two-by-two factorial randomized controlled trial (2).

A factorial trial is an efficient and economical design (3). It combines the ability to test two interventions, while requiring a smaller sample size than for two separate trials (4). The simplest type of factorial trial involves two interventions which have purely additive effects, and which do not have any interaction with each other. The patient cohort can then be randomly allocated into four groups: group 1 receiving both interventions, group 2 receiving the first intervention and the second control condition, group 3 receiving the second intervention and the first control condition, and group 4 receiving both control conditions. Data from such a trial could then be analysed twice: once to compare the first intervention against its corresponding control, and again to compare the second intervention against its corresponding control.

Between November 2012 and June 2014, Asfar and colleagues recruited 442 patients who had septic shock and who were mechanically ventilated, from 22 centers in France (2). The first intervention studied was open-labelled mechanical ventilation either with 100% inspired oxygen (hyperoxia) or with inspired oxygen titrated to achieve an arterial haemoglobin oxygen saturation of 88–95% (normoxia) during the first 24 h. The second intervention was double-blinded fluid resuscitation with either hypertonic (3%) or isotonic (0.9%) saline during the first 72 h. Baseline characteristics were well-matched, except that the hypertonic saline group, compared to the isotonic saline group, had a higher proportion of patients with liver cirrhosis (7% *vs.* 2%, P=0.02) and a higher mean serum lactate level (4.0 *vs.* 2.9 mmol/L, P=0.043). Less than 2% of patients (mainly due to withdrawn consent) were excluded from the analysis.

The trial was prematurely terminated by the Data and Safety Monitoring Board when only about half the planned sample size of 800 was recruited, as interim analysis suggested futility in both intervention arms and excess mortality at 28 days when both hyperoxia and hypertonic saline were combined. Nonetheless, in the final analysis, no interaction between the intervention arms existed, and no differences in the primary outcome of 28-day mortality and in the secondary outcome of 90-day mortality were found for both interventions. Instead, more patients randomized to receive hyperoxia, compared to those randomized to attain normoxia, suffered from intensive care unit acquired weakness and atelectasis.

Unlike other trials on oxygen use, the HYPERS2S trial studied oxygen for its vasoconstrictor properties rather

than as a primary treatment for respiratory failure (1). Unfortunately, no differences in vasopressor free days or vasopressor dose requirements at 24 h were apparent. Rather, hyperoxia predictably induced greater absorption atelectasis (5), and could have increased oxidative muscle injury (6). It is therefore not surprising that hyperoxia had no impact on overall mortality.

The main justification for using hypertonic saline is to minimize the risk of fluid overload. This concern is founded on the observation that higher fluid balances have been consistently associated with increased mortality in sepsis, possibly via tissue edema and organ dysfunction (7). Separately, a clinical trial utilizing hypertonic saline among 44 Chinese children with septic shock demonstrated improved hemodynamics and reduced volume infused, without apparent side effects (8). It seems reasonable then to apply hypertonic saline fluid resuscitation to adults. However, despite confirming the reduced volume requirement when hypertonic saline is used instead of isotonic saline, no salutary effects on sequential organ failure assessment scores at multiple time points within the first week were observed. Again, it is therefore not surprising that hypertonic saline had no impact on overall mortality.

What can we learn from this trial? On the surface, we can conclude that hyperoxia and hypertonic saline should not be used to treat patients with septic shock. Avoiding hyperoxia would also be prudent, given a trend towards increased 28-day mortality (HR 1.27; 95% CI, 0.94–1.72, P=0.12) and 90-day mortality (HR 1.23; 95% CI, 0.93–1.63, P=0.16). From another perspective, perhaps we should rethink our focus on hemodynamics in septic shock. Is this an appropriate bull's eye to aim for? We now know that targeting supranormal cardiac output (9,10) or blood pressure (11) do not improve mortality for patients. On the other hand, targeting the beginning of the causal chain of septic shock may be more rewarding.

If unchecked, a patient with infection may develop a dysregulated host response, progressing through organ dysfunction (sepsis) and eventually circulatory decompensation (septic shock) (12). Treating infection early with antibiotics has been associated with improved survival (13). When foci of invasive infection can be identified, timely source control has also been associated with lowered mortality (14). Methods to eliminate the foci of infection can range from bedside removal of an infected central venous catheter, to radiologically-guided percutaneous drainage of a liver abscess, and to surgical debridement for necrotizing fasciitis. Early antibiotic administration and source control have been cornerstones of the Surviving Sepsis Campaign guidelines (15). And improving mortality from septic shock would require quality improvement efforts ensuring adherence of these guidelines, in both developed and developing countries (16,17).

Admittedly, the recognition of infection could be challenging, especially in three situations. Firstly, patients with bacteremia may not present with overt systemic inflammation, and may be afebrile (18). Secondly, patients with bacterial sepsis could have negative blood cultures. Thirdly, patients with sepsis may have viral or fungal infection, which do not respond to conventional antibiotics. To address these concerns, novel tests such as those employing molecular techniques are being developed to both detect and distinguish the etiologic agents (19,20). Such tests need be accurate and fast to avoid both missed diagnosis and overtreatment with antibiotics. These tests also need to be made affordable and widely available to create a global impact on sepsis management. Till then, for all patients who appear unwell, a high index of suspicion for infection must remain. Such vigilance is a critical pre-requisite for triggering the process of risk stratification, early antibiotics and source control. Prompt recognition of infection and early management of sepsis have consistently led to improved survival, and these may be better targets to shoot for in septic shock.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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