The risk of death caused by the use of norepinephrine-resistant hypotension in the condition of septic shock in a patient

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Abstract **- Septic shock is associated with high mortality. Aged and multimorbid patients are not always eligible for intensive care units. Norepinephrine is an accepted treatment for hypotension in septic shock. It is unknown whether norepinephrine has a place in treatment outside an intensive care unit and when given peripherally To describe mortality, Acute Physiology And Chronic Health Evaluation (APACHE-II), time to mean arterial pressure >65 mmHg, and adverse events in patients with septic shock receiving norepinephrine peripherally in an intermediate care unit.From a retrospective chart review of 91 patients with septic shock treated with norepinephrine for hypotension, ward mortality, 30-, 60- and 90-day mortality, standardized mortality ratio (SMR) and adverse events (necrosis and arrhythmia) were analysed. Administration route via peripheral venous catheter or central venous catheter was registered. Despite timely intervention, there exists a small subgroup of patients with septic shock who develop progressive multi-organ failure. Seemingly refractory to conventional therapy, they exhibit a very high mortality. Such patients are often poorly represented in large clinical trials. Consequently, good evidence for effective treatment strategies is lacking. In this article, we describe a pragmatic, multi-faceted approach to managing patients with refractory septic shock based on our experience of toxin-mediated sepsis in a specialist referral centre. Many components of this strategy are inexpensive and widely accessible, and so may offer an opportunity to improve outcomes in these critically ill patients.**

INTRODUCTION

The measurement of systemic arterial pressure by mean arterial pressure (MAP) or systolic plus diastolic pressures (SAP, DAP) has been considered an appropriate way to achieve meaningful clinical information for more than a century. By measuring blood pressure, systemic hypertension has been identified and treated for years. It was noted that the development of hypotension associated with severe infection singled out patients with obviously worse prognosis. Thus, the distinction between “sepsis” and “septic shock” was established in 1992 [1]. In Sweden 210 per 100,000 people had sepsis, and 30 per 100,000 developed septic shock in 2012 [2]. In that same year, 1,000 patients died from sepsis according to the Cause of Death Register established by the Swedish National Board of Health and Welfare [3]. The ICU mortality in Sweden was 34% in 2012 according to the Intensive Care Unit Register Sweden [4].

In many trials and clinical materials, septic shock is defined as present when SAP is below 90 mmHg or MAP is below 65 mmHg, despite an intravenous (IV) fluid bolus [1, 5–7]. Patients with septic shock are typically treated in an intensive care unit (ICU). They receive an IV fluid bolus, often through a central venous catheter (CVC) that has been placed in addition to a peripheral venous catheter (PVC). Then, they are continuously monitored with pulse oximetry and repeated controls of blood pressure and heart rate, diuresis, breathing and consciousness. If hypotension

remains in spite of aggressive fluid administration, an infusion of a vasopressor like norepinephrine (NE) is usually started in a CVC with the aim to reach and maintain a MAP of at least 65 mmHg [5].

In 2001 Rivers et al. presented the concept of early goal directed therapy (EGDT) for severe sepsis and septic shock [6]. Lately, several studies have evaluated EGDT and found that EGDT is not superior compared to standard care [8–10]. Although standard care maybe more like EGDT now than prior to 2001, these studies suggest that extensive monitoring such as cardiac output via pulmonary artery catheter, SvO2 or central venous pressure in these patients may not be necessary.

ICU-resources often are stretched markedly thin in a modern busy city hospital. Many patients tend to be quite old (>80 years of age), displaying multiple organ deficiencies even before the onset of an acute illness with infection and hypotension. As a result of previously agreed-upon treatment limitations and general overcrowding, acutely ill patients may be stranded outside an ICU in emergency care or intermediate care facilities or elsewhere into the hospital system.

We were recently made aware of a local treatment algorithm established at the Intermediate Care Unit (IMCU), Division of Internal Medicine, Danderyd Hospital outside Stockholm, where patients with sepsis and hypotension were offered vasopressor support for up to 72 hours outside the ICU. Prior to treatment in the IMCU, a discussion regarding the patient's care was held with an intensivist, resulting in the decision to admit and treat the patient in the IMCU rather than in the ICU. The patients were placed in an intermediate care area with a nurse to patient ratio of at least 1:3. Then, they received IV fluids and an NE infusion and were monitored for possible arrhythmias with telemetry. This paper is a retrospective report describing the included patients, clinical outcomes, and observed complications.

The Surviving Sepsis Guidelines provide a suitable framework to guide therapy for the majority of patients with septic shock [1]. Appropriate and timely antimicrobial therapy, source control if indicated, fluid therapy, and targeted vasopressors remain the backbone of treatment. However, a small proportion of patients fail to respond to these measures and deteriorate precipitously into refractory shock and progressive multi-organ failure. This subgroup of patients is often poorly represented in large randomised controlled trials investigating the efficacy of interventions in septic shock. As a result, there is little conclusive evidence to guide management in this particular population.

Refractory septic shock is variably defined as the presence of hypotension, with end-organ dysfunction, requiring high-dose vasopressor support often greater than 0.5 μg/kg/min norepinephrine or equivalent [2]. Regardless of the precise definition, there is an associated mortality of up to 60%. Furthermore, patients with vasopressor requirements greater than 1 μg/kg/min norepinephrine or equivalent who continue to deteriorate clinically have a reported mortality as high as 80–90% [3, 4]. Microcirculatory failure and associated ischaemic consequences are frequently observed and alternative therapeutic strategies are desperately needed to improve outcomes in this small subgroup of critically ill patients.

In this viewpoint article we describe a pragmatic, multi-faceted approach to managing patients with refractory septic shock. The list of interventions described below is drawn from our clinical experience managing patients with confirmed, or suspected, toxin-producing bacteria in a specialist Severe Respiratory Failure centre in the UK. It is recognised that some of these interventions lack a robust evidence base. Our intention is not to rehearse the current evidence for each component of therapy, but merely to describe our institutional approach with brief reference to selected relevant literature.

Albumin

Early fluid requirements in these patients often significantly exceeds the standard recommended initial regimen of 30 ml/kg. Our practice is to use balanced crystalloids for initial volume replacement, guided by dynamic cardiac output monitoring and echocardiography, followed by 20% human albumin solution if ongoing fluid resuscitation is required. During the early phase of severe shock we target a serum albumin level of > 30 g/l. Albumin maintains plasma oncotic pressure and acts as an antioxidant and as a buffer for acid-base equilibrium. Although conclusive proof for resuscitation with albumin is lacking, a subgroup analysis of 1121 patients with septic shock in the ALBIOS trial demonstrated a reduced mortality [5]. Other studies have also suggested a beneficial effect. However, debate continues over the role of albumin in septic shock with

concerns mainly related to cost-effectiveness [6]. Our approach is informed by physiological rationale, a suggestion of benefit in clinical studies, and limited evidence for harm associated with albumin administration.

Hydrocortisone

The use of corticosteroids in septic shock has been frequently studied. It has been argued that steroid treatment reduces the duration of shock and length of intensive care unit (ICU) stay [7]. Large randomised controlled trials have failed to identify a clear survival benefit [8]. However, the beneficial effects may only be seen in those patients with the highest illness severity scores [9]. Our practice is to administer a hydrocortisone infusion (8 mg/h following a 50-mg bolus) to all patients with refractory septic shock on the basis that these patients are most likely to benefit and there is little evidence of harm. This is supported by results from the recently published APPROCHS study [10] where a survival benefit was seen in a population of septic shock patients with high mortality (43.0% vs 49.1% in controls). This compares to no difference in outcome in the ADRENAL study where the observed mortality was much lower (27.9% vs 28.8% in controls) [11].

Femoral arterial access

Radial arterial pressure waveforms often underestimate blood pressure in the context of severe hypovolaemia and peripheral vasoconstriction. This can lead to the administration of significantly higher doses of vasopressor to achieve the 'target mean arterial blood pressure (MAP)'. In early septic shock, the difference between radial and femoral invasive MAP measurements is reported to be around +5 mmHg; however, this discrepancy is increased in advanced shock [12]. We routinely use femoral arterial access for invasive blood pressure monitoring in this population. The subsequent increase in measured MAP frequently allows a significant reduction in vasopressor dosing in a considerable proportion of patients [13].

Lower the MAP target

Although retrospective analyses of haemodynamic variables are available [14], the traditional MAP target of 65 mmHg has not been subjected to scrutiny by many randomised controlled trials. In a recently published pooled analysis, lower blood pressure targets were not associated with adverse outcomes even in patients with pre-existing hypertension [15]. Individually selected goals are likely to be more appropriate than rigid prescriptive targets. Arguably, preservation of renal function is less vital as patients with refractory septic shock are often already receiving renal replacement therapy. Furthermore, splanchnic perfusion has been shown to be adequate with a MAP target above 50 mmHg if hypovolaemia is avoided in selected patient groups [16]. Young, previously well patients are particularly tolerant of lower systemic blood pressure. We therefore reduce the MAP target in patients with refractory septic shock to 50–55 mmHg. Our experience is that, in selected patients without intracranial pathology, this lower MAP target allows a worthwhile reduction in vasopressor requirements leading to improved tissue perfusion and an associated reduction of hyperlactataemia. Norepinephrine remains our vasopressor of choice and we avoid the use of vasopressin which, in our experience, appears to be associated with an increased risk of peripheral and mesenteric ischaemia in patients with refractory septic shock. Early enteral nutrition is also avoided in these patients with refractory septic shock on high-dose vasopressors; we prefer the use of parenteral nutrition until the shock state has resolved.

Minimise sedation

Sedative medications exacerbate hypotension through myocardial depression and systemic vasodilation. Microcirculatory flow may also be impaired. Current guidelines suggest minimising sedation in mechanically ventilated patients with sepsis [1]. However, our experience is that this approach is not always adhered to. Patients with refractory septic shock often have a reduced level of consciousness as a result of septic encephalopathy, and consequently sedation requirements may be even lower than the general ICU sepsis population. Furthermore, altered hepatic metabolism and reduced renal clearance may lead to accumulation of sedative agents in shocked patients [17]. Sedative strategies and agents are numerous. Perfusion may be improved using low-dose midazolam instead of propofol [18]. However, delirium, accumulation, and duration of action can limit the usefulness of long-term benzodiazepine infusion. We minimise sedation in patients with

refractory septic shock. Where sedation is required, our first-line strategy is to use a predominantly opiate-based regimen in conjunction with low-dose propofol titrated to a specified target sedation score.

Replacement of thiamine and vitamin C

Vitamin C (ascorbic acid) is an essential water-soluble substance that cannot be synthesised by the body. It has powerful antioxidant properties and functions as an important enzyme co-factor in the biosynthesis of endogenous catecholamines and vasopressin [19]. It also enhances host defence mechanisms by improving macrophage and T-cell immunity. Levels of vitamin C remain extremely low in critically ill patients despite regular supplementation. This is exacerbated in patients with septic shock where vitamin C deficiency is common despite achieving targeted intake via enteral or parenteral nutrition [20]. In a phase I study, high-dose intravenous vitamin C reduced organ failures and pro-inflammatory plasma biomarkers in severe sepsis with no reported adverse effects [21]. Others have reported a significant reduction in vasopressor requirements with intravenous replacement of vitamin C [22]. Further trials are ongoing, but intravenous replacement of vitamin C in septic shock is based on scientific rationale and appears to be a safe and useful intervention [23].

Vitamin B1 (thiamine) is a water-soluble vitamin with an essential role in carbohydrate metabolism and energy production. Absolute or relative thiamine deficiency is common in patients with septic shock [24]. Such a deficiency may present as an unexplained lactic acidosis but remains undetected since routine red cell transketolase measurements are rarely available and often very costly. Intravenous thiamine replacement has been shown to reduce lactate levels and mortality in patients with proven thiamine deficiency [25]. Furthermore, intravenous thiamine replacement may also be associated with a reduced need for renal replacement therapy and improved renal function in patients with septic shock [26].

Our practice is to give combined vitamin C (4.5 g/day) and thiamine (2.25 g/day) using three pairs of intravenous Pabrinex™ three times per day until shock has resolved. This dosing regimen has been used in our institution, hospital-wide, for several years to prevent Wernicke's encephalopathy in alcoholics. Combination therapy may be more effective with the suggestion of a synergistic effect between the two agents [27]. A recent retrospective cohort study demonstrated a dramatic reduction in organ failures, duration of vasopressor support, and mortality using combination treatment with intravenous hydrocortisone, vitamin C, and thiamine [28]. The presence of thiamine may mitigate concerns over renal oxalate crystal precipitation secondary to high-dose vitamin C and, whilst more robust evidence is awaited, there appears to be little harm with this approach.

Adjunctive antimicrobial therapy

In addition to broad spectrum antibiotics, we routinely administer clindamycin to patients with refractory septic shock until initial microbiological analyses have excluded toxin-producing pathogens or until stabilisation of organ dysfunction is achieved. Clindamycin inhibits bacterial protein synthesis and prevents generation of super-antigens. It is an inexpensive and accessible intervention with a proven efficacy in toxic shock syndrome [29]. Although recommended by several guidelines, clindamycin is often considered late into a patient's presentation despite maximal benefit being associated with early administration.

Intravenous immunoglobulin (IVIG)

Treatment with IVIG in patients with septic shock has been proposed for several decades. There is extensive biological plausibility as to the beneficial immunological effects of IVIG in patients with toxin-mediated septic shock [30]. However, the literature remains conflicting, with several meta-analyses failing to demonstrate improved outcomes. Although current guidelines recommend against the routine use of IVIG in septic shock, it is acknowledged that further trials are needed. Early administration is likely to offer the optimal prospect of benefit. We empirically initiate treatment with IVIG to progressively deteriorating patients with refractory septic shock secondary to suspected toxin-producing organisms such as group A streptococcus (1 g/kg on day 1, then 0.5 g/kg on days 2 and 3) or Panton-Valentine leukocidin (PVL) Staphylococcus aureus (2 g/kg on day 1, repeated on day 3 if no improvement).

Levosimendan

Septic cardiomyopathy resulting in a low cardiac output state is relatively common in patients with refractory septic shock. Central venous saturations

(ScvO2) may be difficult to interpret in this context due to significant impairment of oxygen utilisation. Screening echocardiography identifies those patients with moderate to severely impaired myocardial function and may exclude primary cardiogenic causes. Dobutamine has traditionally been used in this context, but exacerbation of existing tachycardia and increased myocardial oxygen consumption limit its usefulness. Alternatively, improved cardiac function can be achieved using levosimendan in conjunction with the maintenance of ionised calcium levels greater than 1.2 mmol/l. Although the LeoPARDS trial found no benefit with levosimendan in patients with sepsis [31], it is difficult to extrapolate these findings to a subgroup with refractory shock. Only 10% of the patients studied demonstrated evidence of a low cardiac output state and mortality was much lower than would be expected in this subgroup. Our practice is to administer levosimendan to patients with echocardiographic features of moderate to severely impaired left ventricular systolic function and impaired end-organ perfusion. Concerns over the potential need for increased vasopressor requirements can be mitigated by many of the points previously described in this article.

Epoprostenol and heparin

Intravenous prostacyclin has beneficial effects on microcirculatory flow. It has been shown to increase oxygen delivery in critically ill patients [32] and successfully reverse symmetrical peripheral limb ischaemia secondary to high-dose vasopressors in septic shock [33]. Its wider use is frequently limited by concerns over exacerbating hypotension; other vasodilators such as nitrates are used by other centres, but in our experience do not appear to be as effective. In patients with refractory septic shock with peripheral mottling we commence a low-dose epoprostenol infusion (0.5–5 ng/kg/min) to improve microcirculatory flow and prevent the occurrence of peripheral thrombotic events. Our experience is that peripheral ischaemic complications are reduced and haemodynamic compromise is rarely encountered if the prostacyclin infusion is titrated up very slowly. In the setting of disseminated intravascular coagulation and suspicion of end-organ microthrombosis, and in the absence of absolute contra-indications, we also initiate low-dose intravenous heparin infusion (fixed rate 250–500 IU/h).

Renal replacement therapy

Although the IVOIRE study did not identify a survival benefit with high-volume haemofiltration compared with standard dosing [34], in refractory septic shock our practice is to initiate early haemodiafiltration with doses of 40–60 ml/kg/h. This facilitates rapid temperature control and correction of metabolic acidosis which, in our experience, contributes to a reduction in vasopressor requirements and improved cardiac output. Whilst there are concerns about removal of antibiotics, water-soluble vitamins, and trace elements, a recent review concluded that high-volume haemofiltration is not associated with adverse effects [35]. Appropriate compensatory antibiotic dosing and vitamin/trace element supplementation must be taken into account. Correction of metabolic acidosis may be achieved with sodium bicarbonate [36] but this risks further fluid administration and sodium overload, both of which can be avoided with renal replacement therapy.

Extracorporeal support

Finally, in highly selected patients with refractory septic shock (often in the context of severe respiratory failure), extracorporeal technology providing respiratory and/or cardiac support achieves stability and buys time for the therapeutic interventions described above to have an impact. The benefits of extracorporeal support include improved global oxygen delivery, reduced intrathoracic pressures from reduced mechanical ventilatory requirements, improved carbon dioxide clearance and acid-base management, and improved myocardial performance. A recent publication has reported positive clinical outcomes using this approach [37].

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