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# Adjunctive treatments for the management of septic shock – a narrative review of the current evidence

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**Summary**

Septic shock is a leading cause of death and morbidity worldwide. The cornerstones of management include prompt identification, early initiation of antibiotic therapy, adequate fluid resuscitation and organ support. Over the past two decades, there have been considerable improvements in our understanding of the pathophysiology of sepsis and the host response, including regulation of inflammation, endothelial disruption and impaired immunity. This has offered opportunities for innovative adjunctive treatments such as vitamin C, corticosteroids and beta-blockers. Some of these approaches have shown promising results in early phase trials in humans, whilst others, such as corticosteroids, have been tested in large, international, multicentre randomised controlled trials. Contemporary guidelines make a weak recommendation for the use of corticosteroids to reduce mortality in sepsis and septic shock. Vitamin C, despite showing initial promise in observational studies, has so far failed to demonstrate clinical effectiveness in randomised trials. Beta-blocker therapy may have beneficial cardiac and non-cardiac effects in septic shock but there is currently insufficient evidence to recommend their use in septic shock. The results of ongoing randomised trials are awaited. Crucial to reducing heterogeneity in the trials of new sepsis treatments will be the concept of enrichment, which refers to the selection of patients with clinical and biological characteristics that are likely to be responsive to the intervention being tested.

## Introduction

Sepsis, defined as 'life-threatening organ dysfunction caused by a dysregulated host response to infection' remains a significant global health challenge [1]. There were approximately 49 million cases of sepsis and 11 million sepsis-related deaths reported worldwide in 2017 [2]. There has been an improvement in the survival of patients with sepsis in recent years [3], but the mortality rate remains high [4, 5]. Long term morbidity in survivors of sepsis is increasingly recognised, such as increased likelihood of hospital readmission, development of new functional impairments, and increased prevalence of moderate to severe cognitive impairment and mental health problems [6].

The epidemiology of sepsis is complex [7] and it is likely that a high proportion of sepsis deaths are not preventable, as they afflict co-morbid, frail and elderly patients with limited physiological reserve and poor pre-sepsis health status [8, 9]. The current paradigm of sepsis treatment focuses on treating the underlying infection with prompt source control and appropriate antimicrobials, and supporting failing organ systems with fluids, vasopressors, respiratory support and/or renal replacement therapy. Many of the treatments targeting the dysregulated host response currently lack high quality evidence and are yet to be established in routine clinical practice. However, recent years have seen an increase in the number of studies evaluating adjunctive treatments for sepsis. Here, we review the underlying mechanisms and current evidence surrounding a selected subset of adjunctive treatments: vitamin C, corticosteroids and beta-blockers.

## Search strategy

We searched MEDLINE, PubMed, Cochrane Central Register of Controlled Trials, EMBASE and Google Scholar for available evidence on corticosteroids, vitamin C and beta-blockers. Titles and abstracts were screened and references of all identified systematic reviews, randomised controlled trials, observational studies, review articles and current treatment guidelines were checked for further relevant literature. The search was restricted to literature from 1 January 2000, but we did not exclude commonly referenced and highly regarded older publications. For topics of potential interest which are beyond the immediate scope of this review, we have referenced relevant narrative reviews, systematic reviews or clinical guidelines where applicable. Example literature search terms included: sepsis; septic shock; critically ill; intensive care; ascorbic; ascorbic acid; vitamin c; clinical trials; hydrocortisone; steroids; corticosteroids; fludrocortisone; beta-blockers; beta-blockade; catecholamines. The main studies discussed in this review, are those that, in the opinion of the authors, have either currently influenced guidelines and clinical practice or will do so

in future.

**The dysregulated host response**

The major organ systems affected by sepsis are summarised in **Fig. 1**. The main underlying cellular and molecular mechanisms that contribute to organ failure include immune dysfunction, excessive inflammation, metabolic failure and endotheliopathy [10]. These are complex, temporally dynamic and dependent on virulence factors of the invading pathogen and host factors (e.g. genetic susceptibility). Here, we summarise some key pathways (**Fig. 2**) that are targeted by the treatments discussed in this article and the reader is referred elsewhere for more detailed reviews on the immunopathology of sepsis [11-13].

*Immune dysfunction and excessive inflammation*

The presence of invading pathogens induces a host innate immune response mediated largely by leucocytes and parenchymal cells such as epithelial and endothelial cells. These cells detect pathogen-associated molecular patterns (PAMPs) through cell surface and pattern recognition receptors. The most widely studied PAMP is lipopolysaccharide, which is an outer membrane component of Gram negative bacteria. Other examples include peptidoglycans, flagellin and viral RNAs [14]. This response, along with localised release of cytokines and chemokines, activation of coagulation system and tissue repair, is often efficient in eliminating the pathogen in a balanced and protective manner [15]. However, during some infections, this host response becomes dysregulated and harmful. In this instance, target genes encoding potent pro-inflammatory cytokines such as TNF-$\alpha$, interleukin (IL)-1$\beta$, IL-12, and IL-18 are upregulated. These cytokines can trigger inflammatory programmed cell death causing the release of damage associated molecular patterns (DAMPs) – endogenous molecules released from damaged cells. DAMPs lead to further activation of the innate immune system.

These pro-inflammatory cytokines also: (i) initiate a cascade of other inflammatory cytokines (e.g. IL-6, IL-8) and chemokines; (ii) increase adhesion molecule and chemokine expression by endothelial cells; (iii) cause neutrophils to release extracellular traps (NETs), which form a base for platelet activation [16]; (iv) initiate the release of pro-oxidant and procoagulant proteins from microparticles [17]; (v) upregulate tissue factor expression by monocytes; and (vi) lead to complement activation [18].

The combination of platelet activation, upregulation of tissue factor and release of NETs results in

the formation of 'immunothromboses', where pathogens are trapped within thrombi resulting in a vicious cycle of activation of further leukocytes and disseminated intravascular coagulation [19]. Sepsis is also associated with lymphocyte exhaustion characterised by a depletion of CD4+ and CD8+ T cells, B cells and dendritic cells [20]. Studies have shown that CD4+ T cells obtained from patients who died from sepsis have increased expression of programmed death-1 (PD-1) [21] and its ligand - PD-L1. PD-L1 expression is independently associated with increased 28-day mortality in septic shock [22].

*Metabolic failure and endotheliopathy*

Metabolic failure is characterised by mitochondrial dysfunction, excessive generation of reactive oxygen species (ROS), DNA damage, insulin resistance and a state of catabolism [23-25]. Endothelial disruption is also common in sepsis and is caused by the disruption of normal cell-cell junctions as a result of inflammation-induced vessel injury. Implicated molecules include thrombin, vascular endothelial growth factor (VEGF) and matrix metalloproteinase 1 (MMP1) [26]. Increased permeability contributes to oedema formation and reduced microvascular perfusion. Integrity of the endothelium and microvasculature is maintained by the three key anticoagulant pathways – protein C, antithrombin and tissue factor pathway inhibitor [27]. Activated protein C is generated from protein C at the endothelial cell surface and facilitated by the binding of thrombin to thrombomodulin [13]. During sepsis, levels of activated protein C are lower because of impaired synthesis of protein C by the liver, increased consumption and reduced expression of thrombomodulin.

It is increasingly recognised that recovery from infection is a coordinated set of active processes and not simply resolution of the host response. Anti-inflammatory cytokine pathways such as IL-10 suppress the production of IL-6 and interferon, and have been shown to be activated even in the first hours of infection [10]. Autophagy eliminates DAMPs and PAMPs and reduces inflammasome activation [28]. However, the resolution of immune system changes is complex and frequently prolonged and many patients continue to have persisting inflammation, immune suppression, or both after sepsis [29].

**Vitamin C**

Vitamin C is an essential co-factor for many enzymes, and is a potent intracellular antioxidant, acting as an electron donor in many intracellular reactions [30]. Humans, along with other primates, have

lost the ability to synthesize endogenous vitamin C through a derived mutation in the *GULO* gene, and are therefore entirely dependent on dietary intake [31]. This is usually sufficient to meet physiological demands in humans and clinical manifestations of vitamin C deficiency are rare.

Observational studies have demonstrated acute depletion of vitamin C in critically ill patients, which is more pronounced in patients with septic shock [32, 33]. Some studies have demonstrated that greater degrees of deficiency correlate with poorer clinical outcomes. Animal studies of vitamin C in sepsis, using *GULO*$^{-/-}$ mice, which are unable to synthesize vitamin C, have demonstrated that vitamin C supplementation can improve endothelial function and decrease mortality [34]. A small number of randomised studies in humans have demonstrated that vitamin C supplementation in heterogenous critically ill patients has beneficial effects on leukocyte function and vasculature, whilst also reducing the duration of mechanical ventilation and vasopressor support [35, 36].

Interest in vitamin C as an adjunctive treatment for sepsis dates back several decades, but there is increasing evidence of biological plausibility from pre-clinical studies [37, 38]. Proposed mechanisms of action include: increased endogenous synthesis of norepinephrine by acting as a co-factor for dopamine ß-hydroxylase [39]; attenuation of oxidative stress with subsequent improvements in endothelial function, permeability and microvascular flow [40]; and improvements in immune function characterised by lymphocyte proliferation, increased neutrophil bactericidal action and improved chemotaxis [41]. Vitamin C has also been demonstrated to have bacteriostatic activity in murine models of septic shock [42]. Potential dose-dependent adverse effects of vitamin C include renal impairment secondary to a calcium oxalate nephropathy and inaccuracies in blood glucose measurements [40].

The widely publicised findings of a single-centre observational study by Marik et al in 2017 [43] spurred the inception of several large randomised controlled trials (RCTs) testing a metabolic resuscitation 'cocktail' incorporating vitamin C, corticosteroids and thiamine (vitamin $B_1$). Thiamine works as an important cofactor in cellular metabolism by facilitating conversion of pyruvate to acetyl-coenzyme A for entry into the Krebs cycle. Thiamine supplementation has been shown to improve lactate clearance and cardiovascular stability in animal and human studies [44, 45].

In their study, Marik et al reported the results of a retrospective before-and-after study following the adoption of a protocol to use intravenous (i.v.) vitamin C (6 g.day$^{-1}$), corticosteroids (50 mg i.v. hydrocortisone every six hours) and thiamine (200mg i.v. twice daily) in patients admitted to their

intensive care unit (ICU) with a primary diagnosis of severe sepsis or septic shock and a serum procalcitonin level > 2ng.ml$^{-1}$. There were 47 patients each in the treatment and control group and they demonstrated a difference in mortality between the groups: 8.5% mortality in the treatment group vs. 40.4% in the control group, with no adverse events. Another study of similar design reported similar findings in critically ill patients with severe pneumonia [46]. The study by Marik et al was a single centre retrospective observational study, and such studies are susceptible to bias and can produce exaggerated estimates of treatment effects [47].

Since then, several RCTs of vitamin C therapy in sepsis have been conducted to investigate the external validity of Marik's results. The results are summarised in **Table 1** [48-54]. These studies have established that the treatment is safe and well-tolerated, but there remains no clear evidence of a mortality benefit. Two of the more prominent studies investigating the role of vitamin C in sepsis are the multi-centre, Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury (CITRIS-ALI) [48] by Fowler et al [48], and Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock (VITAMINS) studies, by Fujii et al [49].

Fowler et al conducted a randomised, double-blind placebo-controlled trial allocating 167 patients with sepsis-induced acute respiratory distress syndrome to vitamin C (50mg.kg$^{-1}$ i.v. every six hours) or placebo [48]. There was no evidence of an effect of vitamin C on the primary efficacy biochemical (C-reactive protein and thrombomodulin) or clinical (change in sequential organ failure assessment (SOFA) score at 96 hours) outcomes. Reaction to this trial has focussed on positive secondary outcomes. Participants in the vitamin C group had lower 28-day mortality and more ventilator-free and hospital-free days when compared with the placebo group but the trial was not powered to detect any changes in these outcomes. Therefore, although this trial was methodologically robust with a low risk of bias, these results should be interpreted with caution. Fujii et al [49] conducted an open-label study which randomly allocated 216 adult patients with septic shock to receive either a combination of vitamin C (1.5g i.v. every six hours), hydrocortisone (50mg i.v. every six hours) and thiamine (200mg i.v. every twelve hours), or hydrocortisone (50mg i.v. six hourly) alone [55]. There was no evidence of an effect of vitamin C on their primary outcome of duration of time alive and free of vasopressors up to day 7. There were also no differences in 28-day and 90-mortality between groups. Whilst the open label approach used in this study introduces a risk of ascertainment bias, it is unlikely that such a bias would be towards the null. A potential criticism of both Fowler et al and Fujii et al is that the intervention was received relatively late in the course of sepsis, and that earlier treatment may have demonstrated benefit.

In summary, Vitamin C is a treatment with biological plausibility and is attractive in terms of simplicity and cost, yet the present clinical evidence of efficacy and effectiveness is unconvincing [55]. The results of the ongoing Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) trial, which aims to enrol 2000 participants, may alter this conclusion [56]. Vitamin C has also been added as an intervention arm in the ongoing Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial for patients with severe pneumonia caused by Coronavirus Disease-19 (COVID-19) [57]. It is important to note that Vitamin C has been investigated as monotherapy, at different doses, or as part of a combination with thiamine and corticosteroids. The combination effect and relative contribution of each intervention cannot be properly evaluated using conventional pair-wise meta-analysis and therefore alternative methods such as network meta-analysis are required [58].

**Corticosteroids**

There are two main rationales for the use of corticosteroids in septic shock: immunomodulation and maintenance of vasomotor tone [59]. Corticosteroids may downregulate pro-inflammatory cytokines, including Il-6 and TNF-$\alpha$, suppress activation of the innate immune system and have a permissive effect in the maintenance of vasomotor tone. Trials of high-dose steroids in the 1970s and 1980s demonstrated little efficacy and possible harm (largely secondary infection) as an adjunctive treatment in sepsis [60], but trials in the last two decades have revived interest in low-dose corticosteroids. Activation of the hypothalamic-pituitary-adrenal axis, together with inactivation of cortisol-degrading enzymes, result in the normal hypercortisolaemia associated with the stress response and critical illness [61]. It is hypothesized that in some patients this cortisol response may not be sufficient to meet the demands of critical illness, and that supplementation with exogenous corticosteroids may improve outcomes.

The first large randomised trial of corticosteroids in sepsis in the modern era was published by Annane et al in 2002 [62]. This double-blind, multi-centre placebo-controlled RCT randomly allocated participants with septic shock to receive either hydrocortisone 50mg six hourly and enteral fludrocortisone 50mcg daily or matched placebos. In order to identify those patients with relative adrenal insufficiency who may be more responsive to the intervention, patients were stratified by their response to a corticotrophin (Synacthen) stimulation test for analysis of the primary outcome. This study demonstrated an improvement in 28-day survival distribution (median time to death) and faster resolution of shock amongst non-responders to Synacthen stimulation who received the

intervention. No difference in 28-day mortality was observed. Although this trial was well designed with a low risk of bias, the use of survival distribution as an outcome has been criticised, as survival of a small number of patients for a small number of extra days may generate statistical significance without necessarily being clinically meaningful. The trial by Sprung et al (CORTICUS) [63] followed a similar methodology in stratifying participants by response to corticotrophin stimulation, however this trial did not demonstrate any heterogeneity between responders and non-responders, and there was no mortality benefit associated with steroids in this study. Recent data has raised questions about the reliability of stratification by Synacthen test in this context, with high levels of intra-patient and institutional variability [64]. Nevertheless, the results of these trials spurred further studies and in the last decade, further large randomised trials have contributed significantly to the evidence base for corticosteroid use in septic shock [63, 65-67]. The results of these trials are summarised in **Table 2**. The two largest and most recent trials have been the Adjunctive Corticosteroid Treatment In Critically Ill Patients With Septic Shock (ADRENAL) by Venkatesh et al [67], and Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) [65] by Annane et al, both published in 2018.

Annane et al [65] published the results of a double blind, placebo controlled, multicentre RCT (APROCCHSS), with a two-by-two factorial design, to investigate the role of recombinant activated protein C and corticosteroids (hydrocortisone plus fludrocortisone) in the treatment of patients with septic shock. The trial was suspended twice - between October 2011 and May 2012 following the withdrawal of activated protein C from the market, and between July 2014 and October 2014 at the request of the data and safety monitoring board to check the quality of the trial agents and distribution of serious adverse events. The authors found that corticosteroids resulted in a reduction in 90-day mortality when compared with placebo (264/614 (43.0%) vs. 308/627 (49.1%); RR (95%CI) 0.88 (0.78 to 0.99), p=0.03). The number of vasopressor-free days were also significantly higher in the corticosteroid group that in the placebo group (median (IQR) 23 days (5-26) vs. 19 days (1-26), p<0.001) as were the number of organ failure-free days (19 days (0-25) vs. 12 days (0-24), p=0.003).

Venkatesh et al. conducted a double blind, placebo controlled, multicentre RCT (ADRENAL), randomising 3800 patients with septic shock across 69 ICUs in 5 countries to receive either a continuous infusion of i.v. hydrocortisone or placebo. Unlike APROCCHSS, ADRENAL observed no reduction in 90-day mortality with hydrocortisone when compared with placebo (511/1832 (27.9%) vs. 526/1826 (28.8%), OR (95%CI) 0.95 (0.82-1.10), p=0.50). However, ADRENAL did replicate the finding of faster resolution of shock (median (IQR) 3 days (2-5) vs. 4 days (2-9); Hazard Ratio (HR)

(95%CI), 1.32 (1.23-14.1), p<0.001). In addition, participants allocated to receive hydrocortisone had a shorter duration of mechanical ventilation (median (IQR) 6 days (3-18) vs. 7 days (3-24); HR (95%CI) 1.13 (1.05-1.22, p<0.001), shorter time to discharge from ICU (median (IQR) 10 days (5-30) vs. 12 days (6-42); HR (95%CI) 1.14 (1.06 to 1.23), p<0.001) and lower odds of requiring a blood transfusion (683/1848 (37.0%) vs. 773/1855 (41.7%), Odds Ratio (OR) (95%CI) 0.82 (0.72 to 0.94), p=0.004) when compared with those allocated to placebo.

Available evidence from methodologically robust randomised trials indicates a consistent, replicable effect of steroids in quickening resolution of shock [68]. The conflicting findings regarding the mortality effect associated with receiving corticosteroids have attracted considerable attention [69]. The inclusion criteria of the trials by Venkatesh et al. and Annane et al. were different, with participants enrolled by in the Annane trial (APROCCHSS) having higher illness severity scores, requiring more vasopressors and having higher lactate concentrations. It is possible that sicker patients derive the strongest benefit from corticosteroids. However, a *post hoc* sensitivity analysis of the Venkatesh trial using the inclusion criteria for the trial by Annane et al showed no effect of corticosteroids on 90-day mortality [70]. The mortality benefit observed by Annane et al [65] has been attributed by some to the concomitant administration of fludrocortisone in addition to hydrocortisone. Fludrocortisone has glucocorticoid and mineralocorticoid properties that are 10- and 125-fold greater than that of hydrocortisone with beneficial effects on salt and water regulation, innate immunity and attenuating inflammation [71].

A possible alternative explanation for the disparate findings is a differential response to corticosteroids amongst patients with different sepsis phenotypes. A *post hoc* analysis of the Vasopressin vs. Norepinephrine as Initial Therapy in Septic Shock (VANISH) randomised trial stratified participants based on their transcriptomic phenotype and demonstrated that amongst patients with the immunocompetent sepsis response signature (SRS) 2 endotype, there was a higher mortality rate associated with receipt of corticosteroids when compared with those a relative immunosuppressed SRS1 endotype [72]. Deep phenotyping clearly reveals significant heterogeneity among participants enrolled into studies with broadly similar inclusion criteria. This may challenge the internal validity of studies, diluting any real treatment effect and rendering the study underpowered. This issue could be circumvented in future studies by adopting methodologies used in trials in other areas such as cohort enrichment.

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) platform trial by Horby and colleagues has demonstrated an impressive reduction in mortality with the use of dexamethasone in COVID-19 [73]. This study has two features which may be relevant to the design of future sepsis trials. Firstly, it included (by virtue of the disease) a relatively homogenous group of patients with severe viral pneumonia. Such homogeneity may be achieved in sepsis trials by identification of subgroups based on deep phenotyping. Secondly, patients were only eligible for certain arms of the trial if they met criteria which increased their likelihood of seeing a treatment effect with that treatment, thus maximising the power of those arms. This is referred to as "predictive enrichment" and is discussed in more detail at the end of this article.

In summary, corticosteroid administration may reduce the risk of death but mortality benefit is not a consistent finding across the recent studies. Corticosteroids do appear consistently associated with a number of clinically meaningful secondary outcomes however, such as faster resolution of shock and reduced duration of mechanical ventilation and ICU length of stay. Given this, shock refractory to fluid resuscitation and initial vasopressor use seems a reasonable indication for treatment with corticosteroids - as recommended, albeit a weak recommendation, in the 2016 Surviving Sepsis Guidelines. More contemporary guidance, incorporating data from the recent trials by Annane and Venkatesh, make a weak recommendation for the use of corticosteroids in all patients with sepsis, of any severity, to reduce mortality [74].

Potential harms associated with corticosteroids include secondary infection, hypernatremia, hyperglycaemia, gastrointestinal bleeding and neuromuscular weakness [68]. Annane et al (APROCCHSS) reported no significant difference in rates of GI bleeding or secondary infection between groups, although there was a significantly increased rate of hyperglycaemia (blood glucose levels > 8.3mmol/L) amongst those receiving steroids (89% vs 83%; OR 1.07 [1.03 – 1.12]). Venkatesh et al. reported a higher composite adverse event rate amongst those receiving steroids (1.1% vs 0.3%), but serious adverse events were rare. In that trial there were 3 incidences of myopathy amongst 1800 participants randomised to receive corticosteroids, and none amongst those randomised to placebo. Rates of new bacteraemia, fungaemia or bleeding were not significantly different between the groups.

**Beta-blockers**

Sympathetic activity is a key part of the physiological response to sepsis, ensuring that cardiac output and systemic vascular tone remain in a range where end-organ perfusion can be maintained.

Sympathetic overactivity in sepsis has however been linked with cardiac dysfunction which may manifest as sepsis-induced cardiomyopathy, diastolic dysfunction [75, 76] and new-onset atrial fibrillation [77], all of which have been associated with increased mortality. Underlying mechanisms include: mitochondrial dysfunction secondary to nitric oxide and reactive oxygen species; direct myocardial depression from inflammatory cytokines; disturbed coronary blood flow; impaired calcium trafficking [75]; and beta-adrenergic dysfunction. Sustained sympathetic stimulation leads to disturbances in beta-adrenergic signalling and downregulation of myocardial beta-adrenergic receptors [78, 79]. These processes are often accompanied by systemic organ dysfunction and upregulation of inflammatory and procoagulant pathways [80], which are further exacerbated by exogenous catecholamine administration.

Patients with sepsis who remain tachycardic despite adequate fluid resuscitation have a particularly poor prognosis [81]. This may be due to consequent impaired diastolic filling, reduced time for coronary perfusion and increased incidence of arrhythmia. Tachycardia could therefore be an important therapeutic target in the management of sepsis. Beta-blockers, in particular selective $\beta_1$ antagonists, already have an established role in the management of heart failure with reduced ejection fraction, where they reduce sympathetic neural activity and heart rate, improve diastolic function and prevent catecholamine elevation [82]. Animal models of sepsis-induced cardiac dysfunction treated with an esmolol infusion have demonstrated improvements in cardiac function, heart rate and blood pressure and a reduction in inflammatory cytokines [83, 84]. Human evidence indicates that beta blockade may improve diastolic function and reduce the incidence of arrhythmia amongst the critically ill, and continuation of long-term beta blockade during sepsis has been associated with a mortality benefit [85].

Morelli et al conducted the first randomised trial of beta-blocker therapy in patients with septic shock [86]. This was an open-label, phase-2 trial with a primary outcome of heart rate reduction below 95 bpm. The trial was not powered for morbidity or mortality outcomes. One hundred and fifty four patients with septic shock, requiring high-dose noradrenaline to maintain a mean arterial pressure > 65 mmHg despite adequate fluid resuscitation and persistent tachycardia (> 95 beats.min[1]), were randomly allocated to receive an esmolol infusion or 0.9% saline placebo infusion to achieve a target heart rate of 80 – 94 beats.min$^{-1}$. Esmolol infusion was commenced at 25 mg.hr$^{-1}$ and titrated in increments of 50 mg.hr$^{-1}$ at twenty minute intervals to achieve the target heart rate. Infusions were continued until ICU discharge or death with an upper dose limit of 2000 mg.hr$^{-1}$. All patients in the esmolol group achieved the primary outcome but esmolol also increased stroke

volume index and reduced fluid volume and noradrenaline requirements. The authors reported a significant reduction in 28-day mortality in patients receiving esmolol compared with placebo (38/77 (49.4%) vs. 62/77 (80.5%), p<0.001), without any adverse events or safety concerns related to esmolol administration. Although a survival benefit was demonstrated, this unblinded, single centre trial is potentially susceptible to bias and the trial was not powered for this outcome. The external validity of the trial is further limited by the extremely high mortality rate in the control group and the widespread use of levosimendan in the both study groups.

Further randomised trials with physiological endpoints have been conducted since, most notably by Kakihana et al [87]. These studies, supported by small prospective non-randomised studies, have indicated that beta blockade in sepsis successfully reduces heart rate whilst maintaining cardiac index and systolic function. However, high quality randomised data on patient-centred outcomes is lacking, and uncertainty persists regarding the optimal heart rate target.

A key challenge in the use of beta blockers amongst the critically ill is the identification of patients who will experience a haemodynamic decompensation as a result of their use. In order to minimise this risk it is widely accepted that these medications should be employed only in those patients who have been adequately fluid resuscitated. Identification of patients with a fixed stroke volume, who may be unable to maintain cardiac output in the context of beta-blocker-induced slowing, is challenging. The use of the systolic-dicrotic pressure difference to distinguish between these groups has been suggested, but there is no widely accepted method for identifying those at risk of decompensation [88].

In addition to direct cardiac effects, beta-blockers are known to have non-cardiac effects which may be beneficial in sepsis such as reduction in inflammatory cytokine production, improved glucose homeostasis, reduced catabolism and improved coagulation [75]. It is plausible that these pleiotropic effects contribute to any potential benefit of beta-blocker therapy in sepsis.

Overall, there is currently insufficient evidence to recommend routine use of beta-blocker therapy in septic shock. The results of four ongoing randomised trials (ESMOSEPSIS - Esmolol Effects on Heart and Inflammation in Septic Shock (NCT02068287); THANE - Hemodynamic Tolerance and Anti-inflammatory Effects of Esmolol During the Treatment of Septic Shock (NCT02120404); STRESS-L – Study into the Reversal of Septic Shock with Landiolol (ISRCTN12600919); and LANDI-SEP (EudraCT 2017-002138-22)) should provide a better understanding of the effect of beta-blockers on

haemodynamics, immune function and mortality.

**Implications for practice**

The core principles in the treatment of sepsis remain resuscitation, timely antimicrobial therapy and source control [3]. The available evidence supports a role for corticosteroids as an adjunctive treatment in septic shock, and contemporary guidelines make a weak recommendation for their use [74]. High quality evidence to support the routine use of vitamin C or beta-blockers in sepsis is currently lacking but the results of ongoing trials are awaited. Clinicians should seek, where possible, to enrol their patients in clinical trials exploring the role of adjunctive treatments.

**Implications for research**

A recurring theme in this review, which follows a broad theme in the critical care literature, is that positive findings from small, exploratory studies are disproven in large randomised controlled trials [89, 90]. These issues were highlighted in a recent editorial which argued that there is currently insufficient equipoise to continue enrolling more patients into more vitamin C trials, and that such trials are diverting funding away from much needed mechanistic and diagnostic sepsis research and studies to improve organisational infrastructures [91]. More detailed reviews on other adjunctive therapies such as immunomodulation and coagulation modifiers can be found elsewhere [92, 93].

In order for future sepsis clinical trials to be efficient and have sufficient internal validity to yield clear results, it is important that recruited patients have clinical and biological characteristics that are likely to be responsive to the intervention being tested and that the primary outcome, often death, is attributable to sepsis [94]. This latter concept acknowledges that although there may be many events (usually deaths) in a given trial of an intervention for sepsis, only those deaths due to sepsis will contribute statistical power to the trial. Therefore if the fraction of deaths attributable to sepsis is low, a very large sample size will be required to adequately power the trial. Shankar-Hari and colleagues recently demonstrated that the attributable fraction of deaths due to sepsis varies from 15% to 93%, and that existing trials may well be underpowered as a result [94]. This approach requires prospective validation to inform future sample size calculations.

A strategy to improve the trials in sepsis may be enrichment. This concept refers to selection of patients for entry to a trial or for specific arms of a trial on the basis of biological characteristics predicted to make them more responsive to the intervention in question. This strategy has the advantage of increasing the power of a trial with a given number of participants. Prognostic

enrichment identifies patients at high risk of experiencing an outcome event. These patients can be further subdivided with predictive enrichment, which identifies patients predicted to respond to specific treatments **(Fig. 3)**. Advances in precision medicine are likely to play a crucial role in defining patient cohorts likely to derive benefit from treatment interventions over the next decade. Prognostic and predictive enrichment can be achieved by combining "-omics" based approaches with recently identified clinical phenotypes, which are known to correlate with host-response patterns and clinical outcomes [95-97]. The current approach towards trial design with separate, sequential and often unrelated trials for each therapy is expensive and time consuming and limits the numbers of patients that can be recruited to studies. Adaptive platform trials may allow for testing of multiple treatments at multiple stages, with ineffective treatments being dropped earlier, as demonstrated recently by RECOVERY [73].

Whilst we await the results of ongoing and future trials of adjunctive treatments discussed in this review, other important research priorities for the management of septic shock include fluid resuscitation (restrictive vs. liberal), optimal antibiotic dosing, rapid microbiological testing and strategies for improving long-term outcomes for sepsis survivors [98].

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**Declarations of interest**

The authors declare that they have no conflicts of interest.

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**Table 1.** Summary characteristics of randomised controlled trials evaluating vitamin C in septic shock.

| Study and setting | Inclusion criteria and no. randomised | Intervention(s) | Comparator | Outcomes |
|---|---|---|---|---|
| Moskowitz et al 2020 [51]<br>Multicentre RCT<br>USA | Suspected or confirmed infection requiring vasopressor support<br><br>n = 205 | Vitamin C 1500 mg i.v. six hourly;<br>Hydrocortisone 50 mg i.v. six hourly; and<br>Thiamine 100mg i.v. six hourly<br>All for four days | Matched placebo | Primary: Change in SOFA score at 72 hours<br>Secondary: Incidence of renal failure, 30-day mortality, adverse events |
| Yeong Huang et al [50]<br>Multicentre RCT<br><br>South Korea | Septic shock in the ED Defined by sepsis 3 criteria<br><br>n = 111 | Vitamin C 50 $mg.kg^{-1}$ i.v. twice daily for 48 hours;<br>Thiamine 200mg i.v. twice daily for 48 hours | Matched placebo | Primary: Change in SOFA score at 72 hours<br>Secondary: 28-day mortality; resolution of shock; biochemical markers |
| Fujii et al 2020 [49]<br>Multicentre RCT<br><br>Australia, New Zealand and Brazil | Septic shock, based on Sepsis-3 consensus<br><br>n = 216 | Vitamin C 1.5g i.v. six hourly;<br>Thiamine 200mg i.v. twelve hourly; and<br>Hydrocortisone i.v. 50mg six hourly | Hydrocortisone 50mg i.v. six hourly | Primary: Vasopressor-free time alive at seven days<br><br>Secondary: 28-day mortality, 90-day mortality, ventilator-free days, ICU-free days, change in SOFA score |
| Fowler et al 2019 [48]<br>Multicentre RCT (n = 7)<br><br>USA | Sepsis, defined as confirmed or suspected infection with two out of four SIRS criteria, and ARDS as defined by the Berlin criteria<br><br>n = 170 | Vitamin C 50 $mg.kg^{-1}$ i.v. six hourly | Matched placebo | Primary: mSOFA score at 96 hours and levels of biomarkers (CRP and thrombomodulin) at 168 hours.<br><br>Secondary: Forty six secondary outcomes including mortality at day 28, ICU-free |

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|---|---|---|---|---|
| | | | | days at day 28 and hospital-free days at day 60 |
| Balakrishnan et al 2018 [52]<br>Single centre RCT<br><br>India | Septic shock following cardiac surgery (definition not provided) and procalcitonin level >7ng.ml$^{-1}$<br><br>n = 24 | Vitamin C 1.5g i.v. six hourly;<br>Thiamine 200 mg i.v. twelve hourly; and<br>Hydrocortisone 50 mg i.v. six hourly | Matched placebo | Primary: Vasopressor dose over 4 days<br><br>Secondary: In-hospital mortality |
| Zabet et al 2016 [54]<br>Single centre RCT<br><br>Iran | Septic shock requiring vasopressors to maintain mean arterial pressure >65 mmHg<br><br>n = 28 | Vitamin C 25 mg.kg-$^{1}$ i.v.six hourly | Matched placebo | Primary: Vasopressor dose and duration<br><br>Secondary: 28-day mortality; ICU length of stay |
| Fowler et al 2014 [53]<br>Single centre RCT<br><br>USA | Severe sepsis, as defined by the Surviving Sepsis Campaign<br><br>n = 24 | Low dose group: Vitamin C 50 mg.kg$^{-1}$ infusion over 24 hours<br><br>High dose group: Vitamin C 200 mg.kg$^{-1}$ i.v. over 24 hours | Matched placebo | Primary: Safety and tolerability<br><br>Secondary: Change in SOFA score; change in biomarkers (CRP and procalcitonin) |

ARDS, acute respiratory distress syndrome; CI, Confidence Interval; CRP, C-reactive protein; ED, emergency department; ICU, intensive care unit; RCT, randomised controlled trial; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment

**Table 2.** Summary of randomised controlled trials evaluating corticosteroids in septic shock.

| Study and setting | Inclusion criteria and no. randomised | Intervention(s) | Comparator | Outcomes |
|---|---|---|---|---|
| Annane et al 2002 [62]<br>Multicentre RCT<br>(n=19)<br>France | Septic shock defined as evidence of infection, fever or hypothermia, tachycardia, hypotension despite fluid resuscitation, renal or pulmonary dysfunction and a need for mechanical ventilation<br><br>n=300 | Hydrocortisone 50 mg i.v. six hourly and enteral fludrocortisone 50 mcg once daily for 7 days | Matched placebo | Primary: 28 day survival distribution among non-responders to corticotrophin stimulation test at baseline<br>Secondary: 28 day mortality, time to vasopressor withdrawal |
| Annane et al 2018 [65]<br>Multicentre RCT<br>(n = 34)<br>France | Septic shock, defined as confirmed or suspected infection, SOFA score of 3 or 4 for at least two organs and vasopressor therapy for at least six hours to maintain a MAP >65 mmHg.<br><br>n = 1241 | Hydrocortisone 50 mg i.v. six hourly and enteral fludrocortisone 50 mcg once every morning for 7 days | Matched placebo | Primary: All-cause 90-day mortality<br>Secondary: All-cause mortality at ICU discharge, hospital discharge, day 28 and day 180, time to vasopressor weaning, vasopressor-free days, time to ventilator weaning, ventilator-free days |
| Venkatesh et al 2018 [67]<br>Multicentre RCT<br>(n = 69)<br>Australia, UK, New Zealand, Saudi Arabia, Denmark | Sepsis, defined as strong clinical suspicion of infection, requiring mechanical ventilation, more than one 1 SIRS criterion and requiring vasopressors or inotropes for 4 hours or longer<br><br>n = 3800 | Hydrocortisone 200 $mg.day^{-1}$ a continuous infusion for 7 days or until ICU discharge | Matched placebo | Primary: All cause 90-day mortality<br>Secondary: All cause 28-day mortality, time to resolution of shock, frequency and duration of mechanical ventilation, recurrence of shock, ICU and hospital length of stay, frequency and duration of renal replacement therapy, requirement for red blood cell transfusion, incidence of new-onset bacteraemia or fungaemia |
| | Severe sepsis, as defined by the Surviving Sepsis Campaign | Hydrocortisone 50mg i.v. bolus, followed by | Matched placebo | Primary: Occurrence of septic shock within 14 days |

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|---|---|---|---|---|
| Keh et al 2016 [66]<br>Multicentre RCT (n = 34)<br><br>Germany | n = 380 | continuous infusion of 200 mg.day$^{-1}$ for 5 days, 100 mg.day$^{-1}$ for 6 and 7, 50 mg.day$^{-1}$ for day 8 and 9 and 25 mg.day$^{-1}$ on day 10 and 11 | | Secondary: Time to development of septic shock or death, ICU and hospital mortality, ICU and hospital length of say, SOFA score and duration of mechanical ventilation and renal replacement therapy, and secondary infection |
| Sprung et al 2008 [63]<br>Multicentre RCT (n = 52)<br><br>Austria, Belgium, France, Germany, Israel, Italy, Netherlands, Portugal, UK | Septic shock, as defined by the Surviving Sepsis Campaign<br>Patients underwent ACTH stimulation test at baseline<br><br>n = 499 | Hydrocortisone 50 mg i.v. six hourly for 12 days | Matched placebo | Primary: 28-day mortality in patients with relative adrenal insufficiency (i.e. lack of response to corticotrophin)<br>Secondary: reversal of organ system failure, 28-day mortality in patients without adrenal insufficiency, ICU and hospital mortality, ICU and hospital length of stay, one-year mortality |

ACTH, adrenocorticotrophic hormone; CI, Confidence Interval; ICU, intensive care unit; MAP, mean arterial pressure; SIRS, systemic inflammatory response syndrome; RCT, randomised controlled trial; SOFA, sequential organ failure assessment

**Figure legends**

**Fig 1.** The major organ systems implicated in sepsis.

**Fig 2**. The host reponse to sepsis. Activation of the innate immune system promotes the release of pro-inflammatory cytokines resulting in excessive inflammation, activation of the coagulation system, endotheliopathy, metabolic failure and T-cell exhaustion. DAMP, damage associated molecular patterns; IL, inter-leukin; LPS, lipopolysaccharide; NET, neutrophil extracellular trap; PAMP, pathogen associated molecular pattern; PD-L1, programmed death-ligand 1; ROS, Reactive oxygen species; TNF, tumour necrosis factor;

**Fig 3.** A simple approach to prognostic and predictive enrichment in sepsis.