Adjunctive treatment in septic shock: What's next?

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Summary

Sepsis is a leading cause of death and long-term sequelae worldwide. For more than a decade, the scientific community is providing physicians, patients and policy makers with regularly updated guidelines. There is some evidence that implementation of the Surviving Sepsis Campaign guidelines is associated with improved patients outcomes. Though there were major advances in the understanding of sepsis, the management of sepsis mainly relies on anti-infective treatments and restoration of cardiovascular and respiratory function according to quantitative protocolized care. Except some hormonal interventions such as insulin to maintain blood glucose levels of less than 180 mg/dL and low doses of corticosteroids and vasopressin in highly selected patients, there is no adjunct therapy for the routine management of sepsis. Recent years have shown some interest in revolutionary concepts such as selective beta-1 receptor antagonists or interventions to boost the immune system. These provocative approaches yielded promising results in various experimental models of sepsis and in preliminary data in humans. The current narrative review summarized some of the numerous adjunct therapies that are currently being investigated in sepsis.

Septic shock: a global response
Marc Leone, France

Pathophysiology of septic shock: from bench to bedside
K.W. McConnell, C. Coopersmith, United States

Current haemodynamic management of septic shock
J.L. Vincent, D. Obergoo Cortes, A. Acheampong, Belgium

Adjunctive treatment in septic shock: What's next?
D. Annane, France

Antimicrobial therapy in patients with septic shock
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Sepsis is the most severe form of sepsis and places a major burden on healthcare systems around the world. It is estimated that roughly 100 per 100,000 inhabitants are hospitalized each year for an episode of sepsis [1], and septic shock may represent up to one out of ten ICU admissions [2]. The mortality in the short term from sepsis and septic shock is about 20% and up to 50%, respectively [1]. However, sepsis continues to kill people beyond hospital discharge with mortality rates reaching up to 80% at five years [3]. In addition, one out of two survivors presents with cognitive decline in the long term [3,4]. For about 15 years, the international scientific community gathered efforts toward improving patients' outcomes [5]. Subsequently, major achievements have been obtained with regards to anti-infective treatments and general
management, including quantitative protocolized care. Nevertheless, the Surviving Sepsis Campaign guidelines highlighted the lack of a significant adjunct therapy. Blood glucose levels should be moderately controlled and maintained of less than 180 mg/dL. Moderate doses of hydrocortisone should be given only to patients with refractory shock and up to the weaning of vasopressor therapy. The current narrative review aimed at identifying innovative adjunct therapies that are currently under investigation.

Modulation of the global response to stress

Acute illnesses such as sepsis are characterized by dysregulated host responses to stress, including inappropriate responses of the hypothalamic-pituitary adrenal and vasopressin axes and of the autonomic nervous system. Then, manipulating these systems has focused the attention of many researchers and physicians over time. Corresponding natural or synthetic hormones and neuropeptides have pleiotropic effects including modulation of the immune system, effects on the function of most organs mainly the brain, heart and vessels, the kidney and the liver and metabolic effects.

Corticosteroids

While many authors would consider that corticosteroids may be helpful in the management of septic shock, substantial uncertainty persists about the appropriate steroid to use, appropriate timing and dosing, and appropriate population to be targeted. A recent Cochrane systematic review and meta-analysis has summarized both the rationale and the current evidence for corticosteroids benefits, from 33 (n = 4268 patients) randomized trials [6]. Indeed, this treatment reduced 28-day mortality (27 trials, n = 3176, relative risk (RR) 0.87, 95% confidence interval (CI) 0.76 to 1.00; P = 0.05, random-effects model). Treatment with a long course > 3 days of low dose (< 400 mg per day) corticosteroids reduced mortality at 28-day (22 trials, RR: 0.87, 95% CI: 0.78 to 0.97; P = 0.01, fixed-effects model), at intensive care unit (ICU) (13 trials, RR: 0.82, 95% CI: 0.68 to 1.00; P = 0.04; random-effects model) and at hospital (17 trials, RR: 0.85, 95% CI: 0.73 to 0.98; P = 0.03, random-effects model). Corticosteroids also increased the proportion of shock reversal by day seven (12 trials, RR: 1.31, 95% CI: 1.14 to 1.51; P = 0.0001), reduced the sepsis-related organ failure assessment (SOFA) score by day seven (eight trials, mean difference (MD): −1.53, 95% CI: −2.04 to −1.03; P < 0.00001, random-effects model), and survivors’ ICU length of stay (10 trials, MD: −2.19; 95% CI: −3.93 to −0.46; P = 0.01, fixed-effect model), without inducing gastroenterodonal bleeding (19 trials, RR: 1.24; 95% CI: 0.92 to 1.67, P = 0.15, fixed-effect model), superinfection (19 trials, RR: 1.02; 95% CI: 0.87 to 1.20; P = 0.81, fixed-effect model), or neuromuscular weakness (three trials, RR: 0.62, 95% CI: 0.21 to 1.88; P = 0.40, fixed-effect model). Corticosteroids were associated with hyperglycaemia (13 trials, RR: 1.26; 95% CI: 1.16 to 1.37; P < 0.00001, fixed-effect model) and hypernatraemia (three trials, RR: 1.64; 95% CI: 1.28 to 2.09; P < 0.0001, fixed-effect model). This systematic review also suggested that the sickest patients (i.e. those with septic shock or ARDS), and those with lung infection were more likely to draw benefit from corticosteroids. Nevertheless, two large ongoing trials will provide further information for the management of septic shock about the benefit and risk of hydrocortisone alone [7] and of the combination of hydrocortisone and fludrocortisone and about any interaction between response to treatment and the adrenal status as determined by a standard ACTH test (NCT00625209).

Vasopressin and its analogs

Acute illness may be associated with a syndrome of inappropriate antidiuresis. In sepsis, vasopressin levels in plasma may follow a biphasic response with early high concentrations, from abrupt emptying of posterior pituitary stores, followed by a progressive decline over 72 hours to levels indicating relative vasopressin insufficiency, in about one-third of cases [8]. The delayed decrease in vasopressin levels in plasma is not related to altered hormone clearance from plasma, may be mediated by iNOS overexpression in the parvocellular nuclei [9], or by altered osmoregulation [10,11]. Vasopressin has been proposed as an adjunct therapy in a broad variety of conditions of cardiovascular compromise, including postoperative vasodilatory shock, septic shock, cardiac arrest, cardiogenic shock [12]. While treatment with vasopressin may help restoring cardiovascular homeostasis, its benefit on survival remains controversial [12]. A recent systematic review and Bayesian network meta-analysis suggested that in comparison to dopamine, combination of low dose vasopressin to norepinephrine was associated with an odds ratio for mortality in the short term of 0.69 (credibility interval: 0.48–0.98) [13]. A recently completed trial has compared vasopressin to norepinephrine as a first line vasopressor therapy in septic shock [14]. This trial found no evidence for any difference between these two drugs on renal function (trial’s primary outcome), shock duration, length of stay or mortality [15]. Thus, physicians may consider low dose vasopressin infusion as an adjunct hormonal treatment in norepinephrine-treated septic and not as a first line vasopressor therapy. Selepressin, a selective vasopressin V1a receptor agonist, was to show more effective than vasopressin in improving cardiovascular function and preventing vascular leaks in large animals with sepsis [16,17].

Beta-adrenergic receptor blockade

The effects of the adrenergic system on immune function is rather complex. Focusing on beta-adrenergic pathway, it is suggested that β1 stimulation induces the release of pro-inflammatory mediators and cells apoptosis in various tissues including the heart and immune tissues while β2 agonists may down-regulate innate immunity and prolong cell life [18,19]. Non-selective beta-blockade with propranolol has shown favorable
cardiovascular effects in dogs challenged with lethal dose of LPS [20]. By contrast, in small rodents, propranolol increased mortality following LPS [21]. It is likely that the blockade of β2 receptors promoted cells apoptosis and inflammation in the septic mice [21]. In keeping with these findings, in septic rodents, selective β1-blockade attenuated systemic inflammation as well as inflammation in the lung, heart, and liver, with subsequent improvement in organs function and in survival [22–24]. In large animals challenged with lethal dose of LPS, selective β1-blockade was associated with some improvement in the cardiovascular system and little immune effects [25]. In patients with septic shock, data are too scarce at this time to inform accurately physicians. One study found that the use of short-acting β1-blocker was well tolerated in patients with sepsis [26]. In a recent single center, open label, randomized trial, esmolol, a short-acting β1-blocker, was infused to control heart rate in catecholamine-treated septic shock with tachycardia [27]. Selective β1-blockade was associated with marked improvement in cardiac function, lactate clearance and survival (28-day mortality: 49.4% in the esmolol group vs 80.5% in the control group; adjusted hazard ratio: 0.39; 95% CI: 0.26 to 0.59; P < .001). Another randomized trial compared in patients with severe sepsis, the combination of milrinone an esmolol to milrinone alone [28]. Esmolol was also associated with survival benefit in this group of milrinone treated patients (P = 0.02). Further investigations are required to confirm or to rule out potential benefit from short-acting β1-blockade in patients with septic shock.

Targeting the cholinergic anti-inflammatory pathway

The central nervous system may downregulate both systemic and organs inflammation via activation of the vagus nerve [29]. The regulation of the production of monocytes/macrophages cytokines is mediated via the subunit α7 of the acetylcholine receptor on cells surface [30]. Then, in LPS challenged or septic mice, transcutaneous stimulation of the vagus nerve was associated with reduction in pro-inflammatory mediators such as HMGB1 and with improved survival [31]. Likewise, in cultured cells and in septic mice, G5S-21, a selective alpha7-nicotinic acetylcholine receptor agonist, was shown to block NF-κB and downstream cytokines and to improve survival [32]. However, so far, there are no data in human sepsis on the potential benefit of stimulating the cholinergic anti-inflammatory pathway.

Specific modulation of the immune system

Polyclonal and monoclonal immunoglobulins

The benefits and risks of intravenous polyclonal or monoclonal immunoglobulins (IVIG) have been investigated for years and remain controversial. A recent Cochrane systematic review has synthetized the evidence from the literature [33]. This review included 43 trials. Ten trials (1430 patients) on polyclonal immunoglobulins showed significant survival benefits (RR = 0.81; 95% CI: 0.70 to 0.93). Likewise, 7 trials (528 patients) showed that IgM-enriched IVIG significantly reduced mortality in the short term (RR: 0.66; 95% CI: 0.51 to 0.85). However, analysis based on trials with low risk of bias showed no more survival benefits (RR: 0.97; 95% CI: 0.81 to 1.15; five trials, n = 945). Eight studies (4671 patients) on monoclonal antibodies toward endotoxin failed to show survival benefit (RR: 0.99; 95% CI: 0.91 to 1.06) and 9 trials (7893 patients) of monoclonal antibodies targeting individual cytokines showed mild survival benefit (RR: 0.92; 95% CI: 0.86 to 0.97). So far, the evidence is insufficient to recommend the routine use of IVIG for the management of septic shock.

Immune stimulants

Growing evidence suggests that since sepsis, the initial pro-inflammatory phase induces a compensatory anti-inflammatory response preventing an overwhelming inflammatory reaction. Subsequent, secondary immune suppression may occur, the so-called immunoparalysis. Secondary immune suppression is characterized by increased production of anti-inflammatory interleukins [34] such as IL-4 and 10, leukocyte dysfunction including lymphopenia mainly due to apoptosis [35], expression of immature granulocytes (CD10dim/CD16dim) [36] as well as decreased expression of HLA-DR on circulating monocytes [37]. During this state of immunosuppression, patients may reactivate latent viruses such as CMV [38] may develop secondary infections [39], and may have increased risk of death [40]. Then, researchers have thought to boost the immune system. Interferon gamma (INFγ) was given with success in 9 patients with septic shock [41]. Nevertheless, there is no additional clinical data supporting its use and animal studies suggested increased risk of death [42]. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) have been investigated for several years. A recent systematic review suggested that these treatments were not associated with survival benefit in sepsis [43]. This review has pooled data from 12 trials accounting for 2380 patients. There was no evidence for any survival benefit when compared to placebo (RR = 0.93, 95% CI: 0.79 to 1.11) though G-CSF or GM-CSF were associated with prevention of secondary infections (RR = 1.34, 95% CI: 1.11 to 1.62). Infusion of pro-inflammatory cytokines has been investigated in experimental sepsis. Among these cytokines, the effects of IL-7 have been studied ex vivo on immune cells sampled in patients with sepsis [44]. In this study, ex vivo treatment with a recombinant of IL-7 significantly restored normal lymphocyte functionality and proliferations. Further investigations in patients with sepsis are awaited to confirm or rule out any potential benefit from infusion of IL-7. An interesting approach was based on boosting immune cells with IL-2 ex vivo before re-infusing them using an extracorporeal
circuit [45]. In this study, the authors suggested some survival benefit \( n = 173, \) short term mortality was 8% and 21% in the treated and control group, respectively. Thymosin-α1, a thymus derived peptides, has interesting immunomodulatory activities on both innate and T helper related immunity. Thymosin-α1 therapy improved survival of septic animals [46]. A recent systematic review and meta-analysis has summarized the current evidence [47]. This review included 12 trials accounting for 1480 patients. The pooled relative risk of dying was 0.68 (95% CI: 0.59–0.78) in favor of Thymosin-α1. Though there was no heterogeneity in the results, trials were on small size and showed moderate to high risk of bias. This treatment deserves to be investigated in a large phase III trial before recommending its use in routine. 

Inhibition of programmed cell death 1 (PD-1) and of its ligand (PD-L1) are new promising approaches to the management of sepsis. In experimental sepsis, blockade of PD-L1 prevented lymphocytes depletion, enhanced pro-inflammatory mediators, downregulated anti-inflammatory cytokines and improved bacterial clearance [48] and protected the liver from sepsis induced injury [49]. In patients with sepsis, some PD-1 single nucleotide polymorphism may be associated with higher organ dysfunction and risk of death [50]. In vitro treatment of cells from patients with sepsis, with anti-PD-1 or anti-PD-L1 improved immune cells function [51]. This therapeutic approach should enter the clinical phase of evaluation in the very near future. B- and T-lymphocyte attenuator (BTLA), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) may be less interesting targets for the management of sepsis [52].

There are numerous other potential adjunct therapies under investigations. Among them, one may consider blood purification techniques [53], or mediators involved in the resolution of inflammation [54]. More importantly, the next future will be characterized by personalized medicine for sepsis. Patients’ immune status will be closely monitored at the bedside, and immune homeostasis will be maintained by titrating immunomodulators on a daily basis.

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References


