Septic shock: desperately seeking treatment

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Abstract

Septic shock results from the dysregulation of the innate immune response following infection. Despite major advances in fundamental and clinical research, patients diagnosed with septic shock still have a poor prognostic outcome, with a mortality rate of up to 50%. Indeed, the reasons leading to septic shock are still poorly understood. First postulated 30 years ago, the general view of septic shock as an acute and overwhelming inflammatory response still prevails today. Recently, the fact that numerous clinical trials have failed to demonstrate any positive medical outcomes has caused us to question our fundamental understanding of this condition. New and sophisticated technologies now allow us to accurately profile the various stages and contributory components of the inflammatory response defining septic shock, and many studies now report a more complex inflammatory response, particularly during the early phase of sepsis. In addition, novel experimental approaches, using more clinically relevant animal models, to standardize and stratify research outcomes are now being argued for. In the present review, we discuss the most recent findings in relation to our understanding of the underlying mechanisms involved in septic shock, and highlight the attempts made to improve animal experimental models. We also review recent studies reporting promising results with two vastly different therapeutic approaches influencing the renin–angiotensin system and applying mesenchymal stem cells for clinical intervention.

Key words: inflammation, mesenchymal stem cell, renin–angiotensin system, septic shock

INTRODUCTION

Septic shock is widely thought to be an infection that is followed by an uncontrolled immune response, and remains one of the leading causes of death in ICUs (Intensive Care Units), with mortality ranging from 20 to 50% of all cases. In absolute numbers, septic syndromes are responsible for over 200 000 deaths annually in the U.S.A. [1], with the incidence continually on the rise. The number of patients admitted to ICUs for severe sepsis increased by 71% from 2003 to 2007 in the U.S.A. [2]. Recent epidemiological studies confirm this global trend with increased numbers of patients with septic shock since 1997 and a mortality rate reaching 30% [3]. Sepsis claims as many victims as myocardial infarction, and is one of the ten leading causes of death in the developed world [4].

During infection, exogenous proteins, glycoproteins and lipoproteins are released defining PAMPs (pathogen-associated molecular patterns) that are recognized by immune cells via PRRs (pattern recognition receptors). This in turn leads to the activation of both the innate and acquired immune responses. The innate immune response activates adaptive immune processes through PRRs. Dendritic cells and macrophages recognize and phagocytize pathogens, promoting cytokine release and antigen presentation to the MHC, leading to the activation and differentiation of T-cells to Th1 and Th2 and, thus, regulating adaptive immune responses.

During severe sepsis and septic shock, this critical reaction is dysregulated for reasons that are not yet completely understood. The systemic release of inflammatory factors activates and propagates inflammation throughout the whole body. One of the first targets of these circulating inflammatory factors is the endothelium, the inner monolayer of blood vessels located at the border between blood and tissue. The endothelium controls oxygen and nutrient exchange between blood and organs. An ischaemic reperfusion insult can occur when the overwhelming inflammatory response causes endothelial damage and...
consequently an impairment in the microcirculation, thus inducing a mismatch between oxygen supply and demand. This phenomenon is well described in patients with sepsis using OPS (orthogonal polarization spectral) imaging [5,6].

Microcirculation impairment is now well accepted as being central in the progression of septic shock to severe clinical outcomes as it exacerbates the already existing inflammatory response, leading ultimately to multiple organ failure. Once this phenomenon is triggered, antibiotics alone are ineffective and patients in septic shock die from uncontrolled acute dysregulation of the inflammatory response leading to MOFS (multiple organ failure syndrome), rather than from septicemia itself.

Translating research findings into successful therapy remains the major challenge facing investigators in the search for improved clinical management for many disease states and particularly for sepsis. Over the last 30 years, 38 new experimental therapeutic agents have undergone advanced Phase II or Phase III clinical testing in patients with sepsis [7], but none have resulted in any significant positive findings. Most recently, a trial using Drotrecogin alpha [8] failed to confirm earlier positive trial findings first published in 2001 [9]. Indeed, only the early goal-directed therapy first described by Rivers and co-workers [10] remains part of the Sepsis Surviving Campaign guidelines [7], as other clinical trials using early goal-directed bundles have confirmed the result of the proof-of-concept trial [11,12]. This has enabled the improvement in the standard of care by early detection of patients with symptoms of severe sepsis, thereby allowing the administration of effective antibiotic therapy and the introduction of aggressive treatment to stabilize the haemodynamic state. However, despite this improvement, we are still lacking a treatment for patients already in septic shock and MOFS.

This critical treatment gap has led many to question their fundamental understanding of this condition. Some of the uncertainty arises from the fact that it had previously been accepted as dogma that the initial step leading to septic shock is an acute disproportionate pro-inflammatory response. However, current evidence suggests that, if pro-inflammatory profiles occur at all during septic shock, they would appear not to be the event triggering the fateful response. Furthermore, animal models had been a key step in the attempt to translate experimental findings into clinical trials. The appropriateness and clinical relevance of many of the animal models currently used is now in question. Finally, the use of a single agent to dampen the inflammatory response as a therapeutic intervention may not be beneficial and in fact may be detrimental. Therefore new therapeutic interventions with a broader and more moderate effect on the innate immune response should be considered.

In the present article, we review the most recent literature on the inflammatory profile occurring during the sepsis syndrome and the new experimental animal model approaches under consideration aimed at modelling clinical reality in septic shock. We will also address two of the latest therapeutic approaches which have thus far yielded promising results, i.e. modifying the RAS (renin–angiotensin system) and MSC (mesenchymal stem cell) therapy.

**UNCONTROLLED INFLAMMATORY AND ANTI-INFLAMMATORY RESPONSES DURING SEPTIC SHOCK: WHICH COMES FIRST?**

Bone and co-workers [13] published the clinical definition of the sepsis syndrome 20 years ago, which has since been used in every clinical trial to screen patients for septic shock. Septic shock is defined as a SIRS (systemic inflammatory response syndrome) complicated by refractory hypotension in the presence of an infection. The list of symptoms was updated in 2003 [14], where four sequential stages of this acute inflammatory syndrome were described: sepsis, severe sepsis, septic shock, and the most severe refractory septic shock (Table 1). The underlying pathophysiology of septic shock was considered to be an early and dramatic increase in the inflammatory response leading to death after an infection. Even though it was initially supported by limited experimental data [15,16], this definition has since been used in all experimental research.

This ‘reversed’ bed-to-bench side approach led to a vast amount of literature supporting the initial pathophysiological hypothesis where acute inflammatory models demonstrated that an increase in pro-inflammatory markers occurs and, moreover, that administration of key pro-inflammatory cytokines [for example, TNFα (tumour necrosis factor α), IL (interleukin)-1β and IFNγ (interferon γ)] alone were lethal in animal models [17,18]. These data were reinforced by early human studies showing an increase in pro-inflammatory cytokines in patients with septic shock and a correlation between the systemic levels of pro-inflammatory cytokines (TNFα and IL-6) and the clinical severity of patients with septic shock [19–22]. The conclusion drawn from these studies was that prolonged and overwhelming SIRS caused septic shock. The major limitation of these studies though is that the animal models were mainly endotoxaemic models and the cytokines measured were only restricted to the standard pro-inflammatory ones.

When it became apparent that monoclonal antibodies targeting endotoxin do not improve clinical outcome [23,24], Bone [16] hypothesized that SIRS may not be the only event occurring during septic shock and introduced the concept of CARS (contra anti-inflammatory response syndrome) and MARS (mixed anti-inflammatory response syndrome) [16].

However, it was not until Osuchowski et al. [25], using a mouse CLP (caecal ligation puncture) model, confirmed the association between SIRS and an anti-inflammatory response syndrome during septic shock [25] that these concepts gained ground. In these studies, the anti-inflammatory response in general occurred at the same time as the pro-inflammatory response. Critically, however, the authors also reported that the anti-inflammatory response (IL-10) was observed to peak earlier than the pro-inflammatory response (TNFα) specifically in the non-surviving animals, suggesting that an early immunosuppressive state may occur before SIRS. More recently, the same investigators [26] have also shown, using a murine model of septic shock, that SIRS and CARS may be mixed phenomena during acute and chronic sepsis, confirming the hypothesis of MARS as was first postulated by Bone [16].
They reported that, for patients who developed sepsis, there is an onset of sepsis. Measuring the concentration of IL-6 and IL-10, studied, allowing the authors to accurately document the time of when sepsis was triggered. On the other hand, in a study by Nobe et al. [32], they demonstrated that patients who died from sepsis had inflammatory profiles with the organ profile of brain-dead patients. They showed that patients who died, IL-10 levels were significantly increased compared with survivors, for whom there are no significant changes at day 1. They also showed a strong similarity between the cytokine profile in patients with those from a mouse model of CLP.

Recent Boomer et al. [32a] reported a characteristic immunosuppressive profile in patients who died from septic shock in ICU. Studying 20 such patients, they compared spleen and lung inflammatory profiles with the organ profile of brain-dead patients. They demonstrated that patients who died from sepsis had biochemical, flow cytometric and immunohistochemical findings consistent with immunosuppression. What they did not know was when sepsis was triggered. On the other hand, in a study by Novotny et al. [33], 80 patients with post-operative sepsis were studied, allowing the authors to accurately document the time of onset of sepsis. Measuring the concentration of IL-6 and IL-10, they reported that, for patients who developed sepsis, there is a significant increase in IL-10 and IL-6 levels at days 1 and 2. For patients who died, IL-10 levels were significantly increased compared with survivors, for whom there are no significant changes at day 1. They also showed a strong similarity between the cytokine profile in patients with those from a mouse model of CLP.

The potent anti-inflammatory effect of IL-10 has been demonstrated in various models of infection and inflammation [36]. It activates the JAK (Janus kinase)/STAT (signal transducer and activator of transcription) pathway and has a negative effect on various pro-inflammatory genes, inhibiting the secretion of IFN-α and TNFα, IL-1 and IL-6, as well as inhibiting NF-κB (nuclear factor κB) translocation. We recently demonstrated that IL-10 decreased leucocyte-endothelial interactions induced by TNFα by inhibiting ROS (reactive oxygen species) in endothelial cells [37]. Dampening inflammation by inhibiting the release of pro-inflammatory cytokines and thereby preventing leucocyte transmigration may be a positive effect during inflammation, but in the early phase of the infection this can decrease host-pathogen interaction, thereby reducing the initial innate immune response and allowing bacterial growth. It has also been demonstrated that prokaryotes and eukaryote pathogens are able to stimulate the secretion of IL-10 from cells creating a local anti-inflammatory environment favourable to bacterial growth [38].

This hypothesis is reinforced by the study published by Kalechman et al. [39]. By administrating AS-101 (an inhibitor of IL-10 synthesis) at the early phase of sepsis (7 and 12 h after induction of sepsis by CLP), a significant reduction in mortality was observed. A more recent study by Muenzer et al. [40] demonstrated in a two-hit model of infection (CLP followed by a pneumonia) that IL-10 levels were significantly increased.

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<th>Table 1</th>
<th>Clinical classification of the sepsis syndrome</th>
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<td><strong>Type of sepsis syndrome</strong></td>
<td><strong>Clinical classification</strong></td>
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<td>SIRS</td>
<td>Two or more of the following: (i) body temperature &gt;38.5°C or &lt;35.0°C; (ii) heart rate &gt;90 beats/min; (iii) respiratory rate &gt;20 breaths/min or arterial CO₂ tension &lt;32 mmHg, or need for mechanical ventilation; or (iv) white blood cell count &gt;12,000/mm³ or &lt;4000/mm³, or immature forms &gt;10%</td>
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<td>Severe sepsis</td>
<td>Sepsis and at least one sign of organ hypoperfusion or organ dysfunction: (i) areas of mottled skin; (ii) capillary refill time &gt;3 s; (iii) urinary output &lt;0.5 ml/kg of body weight for at least 1 h or renal replacement therapy; (iv) lactates &gt;2 mmol/l; (v) abrupt change in mental status or abnormal electroencephalogram; (vi) platelet counts &lt;100,000/ml or disseminated intravascular coagulation; (vii) acute lung injury/ARDS; or (viii) cardiac dysfunction (echocardiography)</td>
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<td>Septic shock</td>
<td>Severe sepsis and one of: (i) systemic mean blood pressure &lt;60 mmHg (&lt;80 mmHg if previous hypertension) after starch (20–30 ml/kg of body weight) or serum saline (40–60 ml/kg of body weight), or pulmonary capillary wedge pressure between 12 and 20 mmHg; or (ii) need for dopamine &gt;5 g/kg of body weight per min or noradrenaline or adrenaline &lt;0.25 g/kg of body weight per min to maintain mean blood pressure above 80 mmHg (80 mmHg if previous hypertension)</td>
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<tr>
<td>Refractory septic shock</td>
<td>Need for dopamine &gt;15 g/kg of body weight per min or noradrenaline or adrenaline &gt;0.25 g/kg per of body weight min to maintain mean blood pressure above 60 mmHg (80 mmHg if previous hypertension)</td>
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The first definition of septic shock only involved a SIRS (A). Later Bone [16] suggested a second hypothesis involving a more complex relationship between pro- and anti-inflammatory factors with the introduction of the concept of a CARS (B) and MARS (C). The most recent studies highlight the existence of an earliest increase of the anti-inflammatory response syndrome (D), leading to the concept of a PARS.

Recently, IL-6, which is a regulator of acute-phase inflammatory responses, has also been shown to have anti-inflammatory effects. ‘Non-damaging’ exercise has a positive effect during chronic inflammatory diseases (diabetes and hypertension) and this effect is mediated by myokines and, among these, IL-6 is the most studied. During exercise IL-6 is released into the systemic circulation in large amounts. It has been reported that IL-6 decreases TNFα secretion [41], stimulates catecholamine release and activates the PI3K (phosphoinositide 3-kinase) and AMPK pathways [42]. As high levels of IL-6 have been correlated with death in human and animal septic shock studies, more investigation is needed to determine whether IL-6 exerts more pro- rather than anti-inflammatory effects during septic shock.

One hypothesis is that a local and/or systemic PARS (primary anti-inflammatory response syndrome) may dampen the innate immune response (Figure 1). Thus the anti-inflammatory response initially thought to be beneficial may have a Janus face, i.e. it allows for inappropriate pathogen growth thus overwhelming host defences, leading to a desperate inflammatory reaction in an attempt to control the invasion of these pathogens. Taken together, these findings have a direct impact on therapeutic intervention that should be tested in the near future. Even though our understanding of the kinetics of the inflammatory response remains to be fully understood, we suggest that the current definition of the septic syndrome may be inaccurate and that it may not be relevant to target the inflammatory response at the early phase of septic syndrome as this may well impair the innate immune response. On the other hand, targeted treatment once the infection is controlled, but not the SIRS, is likely to be much more effective. The time of intervention thus needs to be carefully evaluated. The screening of patients who may best benefit can also be refined and large randomized clinical trials enrolling all types of patients corresponding to the usual definition of septic shock may not be the best approach for future clinical outcome studies.

ANIMAL EXPERIMENTAL MODELS: ARE WE USING THE RIGHT TOOLS?

The failure to translate experimental findings into clinical trials led researchers to challenge the validity of animal models used in septic shock research [4,43,44]. Seok et al. [45] reported that the gene activation profile of during sepsis significantly differed between humans and mice, therefore questioning the reliability of extrapolating experimental findings with clinical data.

Septic shock as observed in the ICU is a clinical phenomenon, which is very difficult to accurately model experimentally for several reasons. (i) The immune response to infection is never exactly the same between humans and rodents and clinical manifestations of acute sepsis differ. (ii) Septic shock is a fairly rapidly occurring acute condition evolving over a time scale of several hours or, at maximum, days. As discussed above, the timing of intervention under experimental conditions is critical and best practice would be to standardize the protocols. However, this is not always observed between studies even within the same laboratories. This is particularly important as a switch from an anti-inflammatory to a pro- or mixed inflammatory profile, as described above, can occur and any interpretation of the data needs to be considered in the context of when this occurs in the progression of the condition. (iii) The origin of the infection can lead to a different range in the severity of the illness, therefore requiring a different therapeutic management. For example, removal of an intra-abdominal abscess or drainage of infected urine will result in a rapid improvement in the patient when appropriately diagnosed, whereas a patient presenting with pneumonia and ARDS (acute respiratory distress syndrome) will not benefit from any specific therapeutic intervention aside from antibiotics. These
patients have much higher mortality rates. (iv) The patient’s age, underlying disease(s) and clinical state also have a significant impact on the evolution and outcome of the disease; factors that are seldom explored in experimental models.

Having acknowledged these limitations, the need for more relevant experimental models remains critical for a better understanding of the pathophysiology of septic shock and, more importantly, to test novel therapeutic interventions. The models currently in use include those that induce sepsis with bacterial bioproducts such as peptidoglycan or LPS (lipopolysaccharide). Others introduce live bacteria via CLP or induced pneumonia models. The advantages and limitations of all of these models have been reviewed extensively [44,46]. In principle, models involving LPS or peptidoglycan are considered to be models of endotoxaemic shock rather than models of septic shock, as they do not take into account the host–pathogen interaction occurring with live bacteria and only involve the TLR (Toll-like receptor) pathways.

The pneumonia models using live bacteria are attractive because they are highly clinically relevant as the most common cause of septic shock is acute pneumonia. They allow for a well-standardized approach, as the inoculum of bacteria can be well accurately determined. They produce detectable bacteraemia and distant organ damage following initial infection of the lung and delayed mortality. Therefore they must be considered as an important addition to the current models.

The CLP model, described 30 years ago, is generally regarded as the gold standard experimental model of septic shock and has been extensively used over the decades. It consists of a laparotomy followed by a ligation and a variable number of deliberate punctures of the caecum. It therefore combines tissue trauma (laparotomy), tissue necrosis (caecum ligation) and polymicrobial inoculum released into the peritoneum. However, data from this model can be contradictory [39,47], which may be due to the lack of the use of standardized protocols. The differences in the procedures used to induce the model (the size of the incision, the length of caecum ligate and the number and size of the puncture) can dramatically influence the onset and severity of the septic insult. The other major criticism is that, even if the initial procedure reflects a pathological situation (abdominal trauma with peritonitis), the experimental interventions tested are unlike what actually occurs clinically, i.e. surgery.

To overcome the pitfalls of animal modelling in septic shock research, several different approaches have been attempted. These range from more rigorous protocol standardization of the existing models to attempts at more accurately mimicking the clinical situation.

Mathiak et al. [48] reported an improved rat model of septic shock, replacing the CLP procedure by implanting an infected clot in the abdominal cavity. Their rodent model of intra-abdominal infection featured the key characteristic of clinical sepsis with an acute activation of the inflammatory response, but failed to reproduce the hyperdynamic state observed in resuscitated patients. Induction of sepsis using live bacteria inoculation represents a very standardized approach as it allows for the precise delivery of the number of colonies introduced. One of the major limitations of these models, however, is that they normally only involve the use of one strain of bacteria whereas, in the clinical situation, the patient often presents with polybacterial infection.

In an attempt to try and mimic clinical reality, some authors have suggested the use of ‘two-hit’ experimental models. The associated haemorrhage followed by sepsis, trauma followed by sepsis and sepsis followed by sepsis, have all been tried [49–51]. These models offer a complex approach to septic shock as they combine several inflammatory stimuli.

In brief, the issues faced in septic shock research are numerous and complex and require a more critical analysis of the current models. In order to study the time-related evolution of septic shock syndrome, well standardized, reproducible and comparable animal models are essential.

**FUTURE DIRECTIONS**

It is unlikely that a single and unique ‘magic bullet’ will ever be useful in treating the broad dysregulation of the inflammatory response that occurs during septic shock. Recent reports have shown that the inflammatory response during septic shock is a complex overlap of pro- and anti-inflammatory factors. Therefore interventions that have a broad and physiological impact on inflammation may be more relevant. Modulating the RAS and the use of MSCs are two such interventions that are currently being tested in septic shock models. Both are very different approaches but can lead to a broad effect on inflammation.

**The RAS**

The RAS has mediatory effects on inflammation in many differing cardiopathologies [52]. Although typically known as an endocrine system regulating body fluid homeostasis and blood pressure, the RAS has also been shown to possess pro-inflammatory and pro-oxidative effects [53,54]. The signalling pathway of the RAS begins with the release of the primary precursor peptide angiotensinogen, which is synthesized in hepatocytes. Angiotensinogen is initially cleaved into AngI (angiotensin I) by the renal-derived circulating enzyme renin. Subsequent conversion of AngI into AngII (angiotensin II) occurs by the activity of the endothelial-bound ACE (angiotensin-converting enzyme), which is abundant in the large surface area of the lungs. AngI and AngII can also be converted into Ang-(1–9) [angiotensin (1–9)] and Ang-(1–7) [angiotensin-(1–7)] respectively by ACE2.

The AngII signalling peptide mediates the effects of the RAS through two AngII type receptors: AT$_1$R (AngII type 1 receptor) and AT$_2$R (AngII type 2 receptor). AT$_1$R is the prominent AngII receptor in the adult body [55], whereas AT$_2$R is believed to mediate counter-regulatory roles against the typical effects of the RAS mediated by the AT$_1$R. This produces a dynamic equilibrium between the pro- and counter-regulatory effects of the system. The involvement of the RAS in the inflammatory events occurring during septic shock has been investigated, and increased circulating AngII levels have been reported. Indeed, the increased levels of AngII positively correlated with TNFα and IL-6 levels [56]. Modulation of the RAS signalling has also been shown...
to have positive effects in endotoxaemic shock models [57,58]. Hagiwara et al. [59] have shown that inhibition of the RAS by an ACE inhibitor decreased the in vivo release of cytokines and lung inflammation in a rat LPS model, whilst in in vitro models it inhibited the phosphorylation of IkB (inhibitor of NF-κB). They also demonstrated that blockade of AT$_2$R decreased the release of pro-inflammatory cytokines in a rat LPS endotoxaemic model [60]. This effect was followed by an inhibition of the LPS-mediated decrease in ACE2 activity, thus restoring the balance between ACE and ACE2. It has been hypothesized that LPS induces an imbalance between ACE and ACE2 activity, leading to a pro-inflammatory profile within the lung in LPS-treated rats [61].

As ACE is largely expressed in the lung, it has been considered as a potential therapeutic target in septic shock patients with ARDS. Imai et al. [62] have demonstrated that ACE2 and the AT$_1$R have a protective effect on survival and lung inflammation in a mouse CLP model, whereas ACE, AngII and AT$_1$R promote disease severity. Other studies have shown similar results using LPS-induced inflammation models [63].

**MSCs**

MSCs are pluripotent adult stem cells isolated from bone marrow. They have the capacity to differentiate into bone, muscle, cartilage and fibroblasts. Compared with ESCs (embryonic stem cells), MSCs possess less plasticity but are easier to isolate and propagate. They also have the additional benefit of being able to be isolated from bone marrow, placenta, adipose tissue and human cord blood. They are defined by the following criteria: (i) adherent to plastic under standard tissue culture conditions; (ii) express cell-surface markers, including CD105, CD90 and CD73, and should be negative for other surface markers, including CD45, CD34, CD14 and CD11b; and (iii) have the capacity to differentiate into mesenchymal lineages, including osteoblasts, chondroblasts and adipocytes, under appropriate in vitro conditions.

MSCs have the ability to modulate the immune system and have been shown to reduce mortality in a mouse CLP model after induction of sepsis [64]. In this study MSC-treated mice had decreased circulating inflammatory cytokines (TNFα and IL-6) and an increase in anti-inflammatory cytokines (IL-10). This effect seemed to be mediated via PGE$_2$ (prostaglandin E$_2$) reprogramming of host macrophages. Recently, the same positive effect was reported in a CLP model with an increase in phagocytic activity of monocytes in mice receiving intravenous injections of MSCs [65]. MSCs have also reported to inhibit in vitro bacterial growth by secretion of an antimicrobial factor (LL-37) [66]. These findings were confirmed by Mei et al. [67], who reported decreased mortality in a mouse CLP model using intravenous injections of MSCs. The treated group showed a decrease in circulating inflammatory markers and an increase in the phagocytic activity of the host immune cells. Other studies have demonstrated that MSCs have a positive effect on lung function in endotoxaemic models induced by LPS [68–70], suggesting that MSCs may be a promising therapy for patients with ARDS.

**CONCLUSIONS**

Septic shock remains a significant medical issue without an adequate treatment. It is now obvious that septic shock is a much more complex disease than just an ‘inflammatory storm’. Recent reports have shown a more complex association between pro- and anti-inflammatory reactions as the disease progresses. These reports are a paradigm shift, where the role of the ‘inflammatory storm’ is still acknowledged but, in the context of initial anti-inflammatory dysregulation leading to the concept of an inappropriate PARS. This, in turn, explains why anti-inflammatory therapies on their own, particularly at the onset of the disease, fail to improve outcome in patients with septic shock.

Animal studies of septic shock should take into account these recent findings to precisely target the appropriate treatment for each individual patient. Accordingly, interventions carried out on carefully defined cohorts are more likely to be successful than those done indiscriminately, whether in animal models or patients. Although this approach may be logistically challenging, as well as time and resource consuming, it is likely that in a condition of such complexity such an approach is necessary to translate the promising fundamental findings described in the present review into successful clinical trials and, ultimately, into improved treatment options.

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