

The emperor has no clothes? Searching for dysregulation in sepsis

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Abstract

The core conception of sepsis – that it is a dysregulated state - is a powerful and durable idea – that has inspired decades of research into sepsis. But is it true that the body's response to sepsis is dysregulated? To answer that question, this review surveyed the history of trials of agents targeting the host response. Sepsis survival is not improved by blocking one or many immune pathways. Similarly, sepsis is resistant to treatment by normalizing one or many physiologic parameters simultaneously. The vast majority of interventions are either ineffective or harmful. With this track record of failure, it is time to consider the null hypothesis – regulation instead of dysregulation - and possibility that sepsis traits are often functional, and do more harm than good. This review discusses the implications of this perspective for the future of sepsis research.

Introduction

We have met the enemy and he is us? - Walt Kelly

For decades, sepsis research has been motivated by the idea of a dangerous overreaction of the immune system in sepsis. Lewis Thomas wrote about microbes in sepsis: “It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful . . . that we are more in danger from them than the invaders[1].”

In the Third International Consensus Definition of Sepsis and Septic Shock, Lewis Thomas's viewpoint is built into the definition of sepsis: “a life threatening organ dysfunction caused by a dysregulated host response to infection [2].” A dominant view of sepsis is that injury and death

results from a cascade of inflammatory products that damage the microvasculature and cause multi organ failure [3]. Thus, the hypothesis that sepsis is a dysregulated response implies that attenuating the immune response, or blocking some critical immune pathway will improve patient outcomes in sepsis.

Physicians use the infected, not the infecting agent, to define and detect sepsis. Instead of measuring the causative pathogen(s), we use proxy measures. Fever, low blood pressure, increased respiratory rate, and somnolence alert us that there is a problem. Nearly every physiologic change of sepsis - observable during physical exam or measured in routine tests or at the molecular level - has been viewed as a target for medical intervention. The assumption is that each sepsis-associated finding participates in the pathological process.

Recently, Alverdy and Krezaek wrote of the U.S. National Institute of Health, by far the largest funder of sepsis research: “with no exception, every funded grant based on the immunocentric theory of sepsis promises that...blockade of a pathway or molecule will improve the outcome of human sepsis research. In order for the immunocentric view to prevail, the cause of death from sepsis must be believed to be due to the response itself and not to the inciting pathogen.”[4]

Despite a well-funded effort to uncover the underlying mechanisms of septic shock, effective new therapies have proved stubbornly hard to find. Multiple randomized controlled trials have tested new agents with the aim of improving sepsis survival. Only one immune modifying drug, recombinant activated protein C, passed through phase 3 clinical trials, gaining FDA approval [5]. Despite this temporary success, later definitive trials of recombinant activated protein C showed it to be ineffective [6] and it was taken off the market in 2011.

These failures notwithstanding, many physicians, researchers, and grant agencies hold firm to the idea that the human body's response itself is a problem in sepsis. Many authors have pointed to the lack of progress in treating sepsis and have offered various solutions. These solutions range from more careful patient selection [7], focusing instead on immune exhaustion in sepsis [8], and more careful selection of targets for intervention [9]. While the search for new ways to protect the host from the immune response is ongoing, the track record of sepsis treatments should prompt a re-evaluation of the central premise of sepsis - that it is a dysregulated host response to

infection. A more fruitful solution might be to ask: where does dysregulation exist, if at all, in sepsis?

Dysregulation in sepsis, or function

The body of knowledge accumulated in the last half century can be thought of as a test of the dysregulation hypothesis –that the body’s response causes more harm than good in sepsis. Unlike the explanations for the lack of progress offered by others [10] the assumption that sepsis is dysregulated has gone mostly unchallenged [4]. This review will highlight the history of sepsis trials to see whether those cumulative results support a key prediction of the dysregulation hypothesis of sepsis: If sepsis involves dysregulation, then interventions targeting dysregulated pathways are predicted to improve outcomes.

An alternative hypothesis is that some sepsis phenomena are functional, regulated traits. Clinical trials in sepsis offer tests of the potential function of phenotypes in sepsis. In molecular biology, uncovering the function of a gene or protein is often accomplished by using knock-out mice, animals in which a genetic coding region is altered or deleted. By comparing those phenotypes to those of unaltered animals, a gene or protein’s function can be inferred. Immunomodulatory drugs are not the same as knock-outs, but they can have similar effects by blocking downstream effects of gene expression. Like knock-out models, many sepsis trials shed light on the question of function of the underlying traits. If those traits are functional, then blocking them should fail to improve outcomes, and might do more harm than good.

The failure of immunomodulators in sepsis

The treatment of septic shock is marked by pervasive and ongoing controversy involving nearly all elements of sepsis care, with the possible exception of antibiotics. At the core of sepsis treatment is the notion that sepsis is a dysregulated harmful response to an infectious challenge, with an out of control immune system [11,12]. However, if it is true that the immune response in sepsis is usually dysfunctional, then it should follow that interventions that block endogenous responses to sepsis should provide a survival benefit. In 2002, Eichacker identified over 20 randomized controlled trials of anti-inflammatory agents used in sepsis. Despite promising results using experimental animal models, these agents uniformly failed in phase 3 human

clinical trials. By 2014, the tally of failed trials was higher. John Marshall identified over 100 randomized clinical trials of immune modulating agents in sepsis. None has led to a durable new treatment [13], (Table 1).

Medical reversal is a problem that afflicts biomedical science generally [14], but it seems particularly an issue for clinical trials of sepsis therapies. A Nature review published in 2002 outlined four interventions targeting the host response in sepsis that each had been supported by human trials [11]. Results of each of these four treatment strategies, involving low dose corticosteroids, optimization of hemodynamic function [15] intensive glucose control [16] and activated protein C [5], have all failed to be replicated in subsequent trials as we will describe below.

The next sections will review the recent history of sepsis interventions and survey the record of trials testing key molecular and physiologic targets to see if evidence exists for dysregulation.

Lipopolysaccharide/TLR4 pathway

In 1985, Beutler et al. showed that mortality in mice could be reversed by blocking the host response to lipopolysaccharide (LPS) [17]. This apparent success spurred an explosion of research into immunomodulatory agents aimed at improving outcomes in human sepsis. Antibodies to LPS were among the first tested. Despite promising preclinical results, multiple trials of antibodies to LPS failed in humans [7]. Following those failures, additional efforts were undertaken to block the interaction between LPS and the toll-like receptor TLR4. In 2013, the results of a clinical trial of eritoran tetrasodium, a second generation anti LPS/TLR4 agent, was published. The ACCESS trial was a multicenter randomized controlled trial of eritoran involving 1961 sepsis patients in 3 ICUs. Patients with sepsis and evidence of organ dysfunction were randomized in a 2:1 ratio, with 1304 assigned to eritoran and 657 to placebo [18]. Unfortunately, the TLR4 blocker eritoran did not reduce all-cause mortality at 28 days or at 1 year. The drug joined a growing list of failed drugs for sepsis.

These results do not support the idea that the LPS/TLR4 pathway is dysregulated in sepsis. Instead, having a functional capacity to respond to LPS with TLR4 – the sensing and effector pathway triggered by invasive gram negative bacteria – is likely to be a functional trait in sepsis.

Recombinant activated protein C

Acquired deficiency in protein C was shown to be a predictor of mortality in patients with sepsis, reviewed in [19]. A recombinant form of activated protein C was shown in animal and human studies to have anti-inflammatory and anticoagulant properties. Since inflammation was thought to be out of control in sepsis, investigators reasoned that an inhibitor of inflammation and clotting would be a potential treatment in sepsis. The PROWESS trial, published in 2001, reported a survival benefit in patients with sepsis treated with recombinant activated protein C [5]. On the basis of those results, the FDA approved recombinant activated protein C (Xigris®, Eli Lilly), as the only immune modulating agent ever approved specifically for sepsis. The results and methodology of the PROWESS trial received criticism, mainly for a midstream change in protocol [20]. Reinforcing the skepticism of Xigris, subsequent randomized controlled trials failed to show benefit. The F1K-MC-EVBP trial of activated protein C in pediatric sepsis was terminated early for futility. A study involving patients with a low risk of death, the ADDRESS trial, also failed to show benefit [21]. Because of this increasing uncertainty, the European Medicines Agency requested another trial to confirm the results of PROWESS in patients with severe shock. The resulting PROWESS-Shock trial enrolled patients with severe sepsis and in contradiction to the original PROWESS results patients given recombinant activated protein C had no survival benefit [6]. A subsequent metaanalysis confirmed this absence of benefit and an increase in adverse effects, mostly bleeding [22]. 10 years late, on October 25, 2011, the FDA recommended that Xigris be withdrawn from the market.

Antithrombin III, an endogenous anticoagulant like activated protein C, has been tested to see its effect on sepsis survival. Like recombinant activated protein C, provision of high dose antithrombin III failed to improve sepsis survival and resulted in increased bleeding events [23]. These studies fail to support the hypothesis that the coagulation cascade is dysregulated, on average, in sepsis. Deficiency of activated protein C may be an artifact of mistaken assumptions of dysregulation. These studies provide a clue that decreased protein C activity, and increased activity of the coagulation system, may be functional in sepsis. One proposed hypothesis is that increased activity of the coagulation cascade during infection promotes pathogen trapping and clearance [24].

Statins

Statins inhibit the HMG-CoA enzyme that has the well-known effect of reducing LDL cholesterol. Because statins also have anti-inflammatory properties independent of their lipid lowering effects, statins have generated interest as a treatment for sepsis. Because of promising observational trials, the largest randomized controlled trial (SAILS trial) was recently undertaken to test the effect of rosuvastatin in patients with sepsis-induced lung injury. The SAILS trial failed to show a survival benefit of rosuvastatin and was stopped early for futility [25].

These results do not support the idea that HMG-CoA is dysregulated in sepsis. The available evidence supports instead the benefit of functional immune modulation by MHG-CoA in sepsis.

Corticosteroids

Recently the ADRENAL trial was designed to show whether glucocorticoids improve survival in sepsis. The ADRENAL study was a large well-designed trial that enrolled over 3600 patients with septic shock from 69 medical surgical ICUs in 5 countries (Australia, New Zealand, Denmark, Saudi Arabia, UK). It found no survival benefit to hydrocortisone in sepsis. Published after the ADRENAL trial, the APROCCHSS trial studied 1241 patients with septic shock and reported a survival benefit for those receiving hydrocortisone and fludrocortisone [26]. In that study, patients with septic shock treated with the combination had a slight mortality benefit.

Notably, the APROCCHSS study found no survival benefit at day 28. The fact the reported benefit appears, disappears, and appears again depending on the time point in APROCCHSS suggests that a survival benefit from giving steroids is minimal if it does exist. APROCCHSS has a fragility index of 3, meaning that the statistical significance in this study is not robust and may be a result of chance alone. Meanwhile the largest and best designed study, ADRENAL, showed no benefit. Taken together, these studies do not support the idea of pathological adrenal insufficiency in sepsis, nor do they support a view of sepsis as dysregulated inflammatory condition that is remedied by exogenous corticosteroids.

One of the most compelling arguments in favor of corticosteroids has been the well-documented “reversal of shock” – less requirement for vasopressors, fewer days on the ventilator in the ICU.

It is notable, however, that despite “reversing shock,” glucocorticoids have not, in meta-analysis, improved mortality in sepsis. And, as we shall see in the remaining sections, attempts to reverse shock by other means, e.g. by treating hypotension and hypoperfusion with IV fluids, have a poor track record of improving sepsis outcomes.

Normalization of sepsis physiology

Many recent advances in critical care medicine have highlighted the problem of over treatment, and have resulted in physicians often doing less to patients, not more [27]. For example, ventilating patients with "normal" lung volumes found in healthy patients, aggressive treatment of anemia with blood transfusion, and intensive glucose control have all recently been shown to be harmful in septic ICU patients [27]. Here we review some of the most recent trials involving normalization of physiology in sepsis to see whether they improved or worsened patient outcomes.

Fever

Several large observational trials have shown that among patients with sepsis or severe infection, the absence of fever is associated with a greater chance of death. A study of 2225 patients with sepsis in Sweden showed that increased body temperature was associated with improved survival, and that higher fevers were more protective [28]. In addition, large observational trials of ICU patients in Denmark, New Zealand, Australia and the UK., and in the US have shown similar improved survival in those with fever [29–31]. Lack of fever or low body temperature heralds a poor prognosis in sepsis.

Randomized controlled trials of interventions targeting fever have shown similar results as in observational trials. Using active methods to cool body temperature in the recently published CASS trial tended to increase mortality in sepsis [32]. The CASS trial authors wrote “After recruitment of 436 of the planned 560 participants, the trial was terminated for futility (220 [50%] randomly allocated to hypothermia and 216 [50%] to routine thermal management, e.g. with antipyretics) [32]. In the hypothermia group, 96 (44·2%) of 217 died within 30 days versus 77 (35·8%) of 215 in the routine thermal management group (difference 8·4% [95% CI -0·8 to

17·6]; relative risk 1·2 [1·0-1·6]; $p=0\cdot07$)).” The CASS trial was stopped early because of concern that cooling is harmful.

Two randomized controlled trials inform the question of whether antipyretic medications are helpful in sepsis. Bernard et al. in 1997 published the results of a randomized, double-blind, placebo-controlled trial of intravenous ibuprofen versus placebo in 455 patients who had sepsis.[33] Ibuprofen did not improve survival in that study. The effect of acetaminophen, the most commonly used antipyretic, on survival was the subject of a randomized controlled trial by Paul Young et al.; the HEAT trial showed no benefit to sepsis mortality from acetaminophen (paracetamol) [34].

Is fever a harmful state of dysregulation in sepsis? These trials do not support that hypothesis. The observational studies provide a strong signal instead that having a fever is protective. Increased mortality in the CASS trial casts doubt on the wisdom of fever reduction in the ED. Together these studies supports the concept that elevated temperature is a regulated, adaptive, reaction to infection and sepsis.

Elevated blood sugar

In 2001, the New England Journal of Medicine published a paper by van den Berghe and colleagues that showed improved survival in critically ill patients treated with intensive blood sugar control using insulin. This study led to an increase in “tight glycemic control” seeking to normalize hyperglycemia in the intensive care unit. In 2009, another paper refuted the results of the original trial. The NICE SUGAR study enrolled 6000 critically ill patients, randomizing 3000 of them to tight glycemic control. The investigators found that mortality was significantly higher (27.5% v. 24.9%) in the tight glycemic control treatment arm.

Because the NICE SUGAR study did not involve children, Agus et al. [35] performed a randomized controlled trial of aggressive insulin treatment of hyperglycemia in pediatric patients in intensive care. This was not a study of pediatric sepsis, specifically, but many enrolled patients had infection and sepsis. Agus et al. [35] enrolled 713 critically ill children and randomly assigned them to a lower target blood sugar group who received more insulin and to a higher target group who received less insulin. The main outcome measure, ICU-free days up to day 28,

was similar in both groups. Mortality was also similar. This study was stopped early, because the interim analysis determined a low likelihood of benefit from giving more insulin and a high risk of harm. In the enrolled group, children receiving more insulin had “higher rates of health care–associated infections” (12 of 349 patients [3.4%] vs. 4 of 349 [1.1%], $p=0.04$) in the group receiving less insulin.

NICE SUGAR and the Agus et al, study do not support the concept that acquired insulin resistance leading to high blood sugar is dysregulated in critically ill adults or children, although a study tailored to sepsis would be helpful. It may be time to consider this sepsis trait neutral or beneficial for critically-ill sepsis patients, not a pathological failure of metabolism.

Sepsis bundles and early goal directed therapy

Early Goal Directed Therapy (EGDT) for sepsis was an idea that gained relevance with the influential Rivers trial [15], a single center randomized controlled trial in which a variety of physiologic parameters were treated simultaneously, aiming to bring them closer to normal values in an effort to restore homeostasis. EGDT prescribed multiple simultaneous interventions in sepsis: blood transfusions for anemia, dobutamine for cardiac output, normalizing central venous pressure, and maximizing oxygen delivery (Figure 1). Unfortunately, many of those interventions were shown to be ineffective in later trials (e.g. dobutamine), when tested individually in later trials and were deleted from the bundle. Still, the concept of early goal directed therapy itself was not tested until three randomized controlled trials conducted during this decade. The ProCESS, ARISE and proMISe were three large scale randomized controlled trials of EGDT independently conducted on three continents [36–38]. In each study, EGDT failed to improve survival compared to usual care. The collective failure of these trials casts doubt on the notion of maladaptive dysregulation in sepsis. They also raise questions about the assumption of inadequate tissue oxygen and perfusion in septic shock, an idea that itself has been criticized [39].



EGDT was once enshrined in sepsis treatment bundles championed by The Surviving Sepsis campaign, which started as a marketing arm of Eli Lilly [20]. Not coincidentally, Eli Lilly was the maker of activated protein C, the medication that once was included in early Surviving Sepsis guidelines and was later withdrawn from the market. The Surviving Sepsis Campaign is no longer affiliated with the drug manufacturer. Since the original Rivers trial [15], sepsis bundles advocated by SSC have contained useless elements – measuring ScvO2, maintaining CVP of 8 mm HG, and also demonstrably harmful ones: Xigris, dobutamine, and high transfusion targets. The 2017 Surviving Sepsis treatment bundle has since de-emphasized EGDT, but it still prioritizes quick administration of antibiotics and fluids, controversially within one hour [40].

Acceptance of the dysregulation hypothesis explains the eagerness with which EGDT was adopted. If the body's response is the problem in sepsis, then reversing sepsis physiology by

normalizing a multiple parameters simultaneously is expected to make patients better, not worse. However, in the nearly two decades since the influential Rivers trial, EGDT has been shown to be ineffective, and the current SSC bundles rest on a thin evidence base, reviewed in [39].

We will examine the quality of that evidence, and the proposal that sepsis involves dysregulated hypoperfusion in the next section.

Fluid therapy

Fluid therapy is a mainstay of sepsis treatment, advocated by the Surviving Sepsis Campaign and aimed at normalizing blood pressure and increasing tissue perfusion. Despite much interest in optimal fluid therapy, only two randomized controlled trials of fluid boluses versus no boluses have been performed in patients with sepsis. The two randomized controlled trials were conducted in Africa, in countries where standard of care does not include intravenous crystalloid fluid therapy. Maitland and colleagues randomized children with sepsis in three African countries to receive intravenous fluid boluses or usual care [41]. In that study, the FEAST trial, pediatric patients with sepsis who were randomized to fluid boluses had higher mortality compared to pediatric patients with hypotensive shock who did not receive intravenous fluids [41].

A similar study in adults with septic shock was performed by Andrews et al. [42]. Adults with sepsis (n=209) presenting to an emergency department in Zambia who were randomized to receive intravenous fluids, vasopressors, and blood transfusion had significantly higher mortality in hospital compared with usual care (48.1% vs 33.0%, respectively [42]. In both these trials, one involving children and the other adults in African countries, more patients died when they received IV fluids. In other words, the care that is assumed to be life-saving in emergency departments and intensive care units in the developed world harmed study patients in these developing countries.

Giving no fluids is not thought to be an option in human trials of sepsis in developed countries. However, conservative or limited fluid strategies have been tested. Silversides et al. showed that a conservative fluid strategy was associated with better survival in sepsis [43]. At least for the

populations for which we have randomized controlled trials, these studies do not support the idea that we improve dysregulated tissue perfusion by infusing IV crystalloid in sepsis.

Marik and Bellomo have argued that the problem with IV fluids in sepsis includes damage to the endothelial glycocalyx and harmful tissue edema [39]. They advocated using vasopressors instead to treat the hemodynamic abnormalities of sepsis. Maitland, the principal investigator in the FEAST trial, suggested provocatively that those hemodynamic abnormalities (hypotension) have a defensive function, implying they should be left alone in some cases. Maitland was quoted in a recent Lancet article: “Our theory is that the shock response in severe febrile illness is a defense mechanism, and bringing [children] out of this too soon with a fluid bolus can be counterproductive” [44].

Organ failure

Mervyn Singer has pointed out the paradox of “clinical and biochemical organ failure in sepsis yet minimal cell death” and proposed that organ failure represents a state of hibernation in the face of overwhelming inflammation that helps promote survival [45]. Supporting the notion that organ failure does not occur because of tissue damage, the decrease in kidney function that accompanies sepsis was recently shown to occur without cellular changes or tissue damage to account for the marked reduction in glomerular filtration [46]. In an animal model of sepsis, blood flow to the kidney was preserved, there was no evidence of inflammation, no tubular cell necrosis or blood vessel damage. Recovery from acute kidney injury returned survivors to pre-sepsis levels of function, suggesting there is no long term damage. Maiden et al. concluded from these findings that septic acute kidney injury is a functional response, in other words an adaptation [46].

Studies examining the utility of renal replacement therapy, including high volume haemofiltration, have not shown a consistent benefit for sepsis patients although a multicenter randomized trial is ongoing. A Cochrane review published in 2017 concluded: no clear evidence showed any benefit of high volume haemofiltration in critically ill patients with severe sepsis or septic shock [47]. The failure of renal replacement to improve mortality in sepsis, and the

absence of cellular injury in renal failure, suggests that the decrease in glomerular filtration rate in sepsis may be a regulated trait, not a dysregulated one.

Discussion

The treatment of sepsis has been turbulent in recent decades, with some short-lived moves forward, often followed by medical reversal. Over time, many published reviews of the state of sepsis treatments have followed a repetitive pattern. Authors catalogue previous failures, bemoan the absence of progress, and point to upcoming trials of promising new therapies. Later reviews resemble their predecessors, except the list of failed treatments now contains the once-promising agent.

The preponderance of evidence indicates that sepsis survival is not improved by blocking one or many immune pathways. Similarly, sepsis is resistant to treatment by normalizing one or many physiologic parameters simultaneously. The vast majority of interventions are either ineffective or harmful. As a predictive heuristic, the dysregulation hypothesis of sepsis has a remarkable track record of failure, and an even more remarkable durability. Now, given the choice between the dysregulation and regulation, it is time to consider the null hypothesis – regulation instead of dysregulation - and take seriously the possibility that many sepsis phenotypes represent a regulated functional responses.

Natural selection is the force responsible for the evolution of function: the appropriate physiological activity of the body, organ, or cell. In addition, some disease-associated findings, such as fever, are hypothesized to occur because of natural selection acting on our vertebrate ancestors [43]. Adaptation by natural selection provides an explanation for normal human physiology, and constitutes a framework that can help recognize potential functional responses, or “defenses”, during disease [48]. It is outside the scope of this review to weigh the merits of all adaptive proposals for various sepsis traits. However, adaptive hypotheses in medicine, as in biology, must meet specific conditions, as described in 1966 by Williams [49]; these should include a biologically plausible mechanism, and should be prospectively tested against non-adaptive alternative hypotheses [50].

Some medical responses to overwhelming infection are no doubt needed. But which ones? Certainly we need to intervene to some degree. But when? Because of natural selection, many sepsis traits are more likely to be helpful than harmful, at least in historic contexts. Our ancestors faced infectious challenges since the first multicellular organism evolved. Organisms with effective host defenses against overwhelming infection were more likely to survive and reproduce, leaving extant organisms with a genetic toolbox of defenses.

Because pathogens evolve too, the toolbox is never perfect. This means that we will never see an organism perfectly adapted to resist lethal infection. Other reasons for non-optimal sepsis traits include aging, prior injury, environmental toxins, energetic or biological constraints, environmental changes for which we are not evolved (like the intensive care unit) and immune trade-offs that protect us from one pathogen while leaving an vulnerable to another. For these reasons, an individual’s response in sepsis may indeed be pathological in some instances. In other cases, the host may gamble and lose on an immune strategy that pays off on average. This concept has been termed immune brinksmanship, a high stakes contest in which hosts use defenses that preferentially harm invasive pathogens but that can also injure the host [51].

Is it true in sepsis as Lewis Thomas wrote, that “our arsenals for fighting off bacteria are so powerful . . . that we are more in danger from them than the invaders?” The record of sepsis human trials indicates that we may be better off with our immune arsenals than without them. Breakthroughs in sepsis are unlikely to come from targeting the host response. Future work on sepsis should direct more attention to the microorganisms that are ultimately responsible and to the tradeoffs of host-pathogen competition during sepsis and septic shock. The techniques of evolutionary biology applied in a systematic fashion to sepsis phenotypes and their genetic underpinnings can provide clarity about the sepsis response, including the nature of adaptive host defenses, and may lead to more effective treatments.

Table 1 Targets of treatment in sepsis

Dysregulated pathway	Sepsis treatment
Lipopolysaccharide (Endotoxin)	Monoclonal antibodies
	Anti-LPS: HA-1, E5
	Enterobacterial common antigen

	Toll-like receptor 4 antagonists
	Eritoran
	TAK-242
	Anti-CD14
	Taurolidine
	Alkaline phosphatase
	Polymyxin B
	Lipid emulsion
Tumor necrosis factor (TNF)	Monoclonal or polyclonal antibodies
	Soluble receptor constructs
Interleukin -1 (IL-1)	Recombinant IL-1 receptor antagonist
	Small molecule inhibitors
Platelet activating factor	PAF acetylhydrolase
	Ibuprofen
Eicosanoids	Phospholipase A2 inhibitor
	I-NNMA
Hypercoagulability	Methylene blue
	Activated Protein C
	Tissue factor pathway inhibitor
	Antithrombin III
	Anti-tissue factor antibody
	Thrombomodulin
Immune suppression	IV immunoglobulin
	G-CSF, GM-CSF
Adrenal insufficiency	Corticosteroids
	Statins
Organ failure	Extracorporeal hemoperfusion
Inadequate perfusion	IV fluid bolus
	Dobutamine
Insulin resistance, metabolism	Intensive insulin

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