Published in final edited form as:

Drug Discov Today Dis Mech. 2007 ; 4(2): 83–93.

Mechanisms of sepsis and insights from clinical trials

Nitin Seam and Anthony F. Suffredini

Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Maryland

Abstract

Multiple clinical trials of adjunctive therapy for sepsis and septic shock have been conducted to neutralize bacterial components or to modulate host inflammatory responses to infection but with limited success. Many therapies are only beneficial only in patients with a high severity of illness and have minimal or harmful effects in patients that are less severely ill. Improved measures of severity of illness and discovery of biomarkers to help identify these high-risk patients are needed.

Introduction

Severe acute life-threatening infections remain a major challenge in health care. The terms used to characterize the severity of illness that develops from serious infections reflect the magnitude of the host inflammatory response and associated organ dysfunction. Sepsis describes the presence of fever, tachycardia, tachypnea and altered leukocyte numbers with evidence of a presumed or known site of infection. This syndrome has a crude mortality of 15%. Patients with sepsis and evidence of organ dysfunction such as respiratory or renal failure are considered to have severe sepsis. Patients with severe sepsis who in addition have persistent hypotension are in septic shock. This latter category of patients has a crude mortality rate of 45%. The death rate from all three levels of sepsis severity is more than 200,000 cases per year.¹ A review of sepsis epidemiology from 1979 – 2000 noted that sepsis is increasing in incidence at an annualized rate of 8.7 % and was the tenth leading cause of death in the United States. During this period, mortality rates fell from 27.8% to 17.9% yet over 650,000 new cases occur per year with approximately 17 billion dollars in annual associated costs.²

Pathogenesis of Sepsis

The pathogenesis of sepsis is initiated by a nidus of infection that may occur anywhere in the body (Figure 1). Epithelial barriers in the airways, gastrointestinal and reproductive tract provide both a physical barrier and secrete antimicrobial substances (i.e. defensins). When this barrier is breached, microorganisms may enter tissues where they are recognized, ingested and killed by phagocytic cells. Inflammation at the site of infection is initiated by the response of macrophages to microbial pathogens. Depending on the virulence of the bacteria and the ability of the host to localize the infection, blood stream invasion by the pathogens or their cellular components may occur and will amplify the local response to the pathogen with activation of

Correspondence: Nitin Seam, M.D., Critical Care Medicine Department, Clinical Center, National Institutes of Health, Building 10, Room 2C145, 10 Center Drive, Bethesda, MD 20892-1662, Email: nseam@cc.nih.gov, Fax 301 480 3143.

We are no financial disclosures to report.

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phagocytic cells distant from the site of infection (i.e. liver Kupffer cells) and recruit inflammatory cells (i.e. neutrophils) to the site of infection.

Humoral and cell-associated pattern-recognition molecules are receptors that bind the common molecular structures found on microorganisms. These receptors are inherited in the genome, trigger immediate responses by innate immune cells and recognize broad classes of pathogens. The prototypic pathogen-associated molecular pattern is lipopolysaccharide, or endotoxin, and its respective pattern recognition molecule is Toll-like receptor 4 (Figure 2).³ The binding of endotoxin to TLR4 triggers an intracellular signaling cascade that activates nuclear factor kappa B (NF- κ B), a nuclear transcription factor. NF- κ B is a common pathway for intrinsic (i.e. tumor necrosis factor) and extrinsic (i.e. endotoxin) proinflammatory signals that regulates genes for cytokines, chemokines, adhesion molecules and receptors essential in inflammation. In addition, NF- κ B modulates the survival of neutrophils and the proliferation of B and T-lymphocytes at the site of infection. These actions contribute to both microbial killing and links to acquired immunity.⁴ The cascade of mediator release induced by the pathogens results in a crescendo of systemic inflammation. If the systemic inflammatory response is sufficiently intense, vasodilatation, hypotension and tissue ischemia will occur and culminate in shock.

Pathophysiology of septic shock

Two fundamental pathogenic processes contribute to the clinical manifestations of septic shock: cardiovascular dysfunction due to the combined effects of myocardial depression and vasodilatation and inflammatory tissue damage. The cardiovascular effects of sepsis include tachycardia, an elevated cardiac index with hypotension and a decreased systemic vascular resistance.⁵ Inflammatory effects on the myocardium cause the ventricular ejection fraction to fall and the end diastolic volumes to increase. After the onset of shock, ventricular performance is depressed for 2 to 4 days and during this period, left ventricular stroke work index is decreased. The ability of the ventricle to dilate (i.e. increased end diastolic volumes) helps sustain the stroke volume and cardiac index at normal or elevated levels. A small percentage of patients will develop profound myocardial failure resembling cardiogenic shock. The myocardial depressant effects of septic shock abate in survivors within 7 to 10 days.⁵

The second component of the hemodynamic abnormality in septic shock is peripheral vascular dysfunction due to systemic inflammation.⁶ In the early stages of septic shock, the skin may be flushed, warm and vasodilated while in late stages, decreased circulating volume with increased arteriolar constriction may result in cold hypoperfused extremities. During the initial stages of septic shock, reflex neurohumoral responses occur that attempt to sustain perfusion by maintaining cardiac output and blood pressure. These include baroreceptor reflexes, release of catecholamines, activation of renin-angiotensin, release of antidiuretic hormone, and generalized sympathetic stimulation.⁶ These compensatory responses may be manifested by tachycardia, vasoconstriction with cold extremities, mottled skin and a rapid weak pulse. The sensorium may be dulled and mentation impaired. Urine production is low or absent due to renal conservation of circulating volume and cardiovascular collapse may occur due to an absolute or relative decrease in circulating volume.

Progressive shock with tissue hypoperfusion and inflammation results in tissue damage in multiple organs due to diffuse endothelial cell injury with microemboli and thrombin deposition that further accentuate tissue ischemia.⁷ Tissue ischemia results in cellular anaerobic glycolysis and decreased ATP production that reduces the activity of plasma membrane energy-dependent sodium and calcium pumps. The compromised energy state of the cell disrupts mitochondrial function and impairs protein synthesis. This results in damage to membrane and cytoskeleton proteins and limits the effectiveness of anti-oxidant mechanisms. Cytosolic calcium accumulates activating proteolytic enzymes, which further

hastens cell damage. The outcome of sepsis is directly correlated to the degree of organ dysfunction.⁸

Therapy of septic shock

Three interventions are the mainstays of therapy in septic shock (Figure 1). If present, a nidus of infection such as an empyema or a perforated viscus must be drained to remove the source of the infection. Antibiotics must be administered as rapidly as possible. Often this is based on empiric judgment regarding the likely pathogens and their sensitivities, if available, for a specific clinical scenario. Recent retrospective data suggests that each hour delay in antimicrobial administration after the onset of hypotension resulted in 7.6% decrease in survival per hour of delay.⁹ Lastly, adequate methods must be provided to reverse the hypotension and hypoperfusion with prompt administration of intravenous fluids and when necessary, vasopressor agents. In addition to the standard therapies described above, several different approaches have been evaluated to modulate inflammation associated with serious infections.

Endotoxin as a therapeutic target

Purified preparations of endotoxin can elicit all of the manifestations of septic shock when administered to animals. Thus, endotoxin has been considered a potentially important therapeutic target. Eleven contemporary studies (Table 1) have evaluated the effects of either antiserum containing polyclonal (6 studies) or monoclonal antibodies (5 studies) directed against common epitopes of the endotoxin molecule.¹⁰ Three of the 11 studies used the anti-endotoxin therapy as prophylaxis and eight were therapeutic trials for gram-negative sepsis. A meta-analysis of these trials showed that, overall, no significant benefit on survival was found (Odds ratio: 0.11; 95% confidence interval, 0.93-1.32; $p = 0.24$)¹⁰. A trial of a human monoclonal antibody against Enterobacteriaceae common antigen, a surface antigen closely linked to endotoxin, similarly had no beneficial effect in septic patients¹¹ (Table 1).

One criticism of the anti-endotoxin antibody trials was the uncertain endotoxin neutralizing potential of the antibodies. Bactericidal/permeability-increasing protein (BPI), stored within neutrophil granules, can bind endotoxin and neutralize its effects. A human recombinant 21-kDa fragment of BPI (rhBPI) was evaluated in children with systemic meningococcal disease, an infectious syndrome associated with high levels of circulating endotoxin, but had no impact on mortality.¹² The drug, while highly active in neutralizing the inflammatory effects of endotoxin in preclinical studies, was not given until six hours after hospital admission. By this time point, the most gravely ill patients with this fulminant infection would have died leaving a group with a lower mortality to be enrolled in the study.¹³ This trial emphasized the critical issue of appropriate timing of targeted therapies in sepsis.

Immunoglobulin as an adjunctive therapy in sepsis

Intravenous immunoglobulin has been used as an adjunctive therapy for sepsis for many years. However, three meta-analyses reached differing conclusions regarding its efficacy in sepsis.¹⁴ The most recent meta-analysis, based on 20 trials, found that treatment with polyclonal intravenous immunoglobulin decreased the risk of death with sepsis (Table 1). However, a high level of trial heterogeneity across these studies confounds the analysis. Because most of the trials had methodological limitations and were performed prior to contemporary intensive care management strategies, additional large trials are recommended to confirm the findings of this meta-analysis.¹⁴

Mediator specific anti-inflammatory therapies

The decade of the 1990s was an active period of clinical sepsis trials of mediator specific anti-inflammatory agents. This coincided with the discovery of host-derived molecules such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) that play a fundamental role in the inflammatory response to infection. These mediators propagate the necessary host responses to infection yet are also integral components of the exuberant inflammatory response that may result in shock and organ injury. Twenty-nine sepsis trials have assessed the effects of anti-inflammatory agents in sepsis to neutralize or diminish the effects of specific mediators such as TNF, IL-1, platelet activating factor, prostaglandins, bradykinin and phospholipase A2^{15, 16} (Table 1). Many of the trials were underpowered and had equivocal effects on outcome, however, modest benefit was suggested in larger trials.¹⁰ When 27 trials were combined in a meta-analysis, a small but significant overall improvement in survival was found (Odds ratio of survival; 1.09; 95% confidence interval 1.01 – 1.18; $p = 0.03$) with an absolute risk reduction of 2% and a relative risk reduction of 7%.¹⁵ These data analyses suggest that the trials of mediator specific anti-inflammatory agents as performed in the past would require trials of more than 6,000 patients to demonstrate significant effects on mortality. Alternatively, identifying patients who have intense and potentially lethal inflammatory responses by novel biomarkers or elevated severity of illness scores may allow treatment of a targeted at-risk patient population.

Targeted anti-coagulant therapy

Activation of the endothelium is an essential component of the systemic inflammatory response to severe infections and is inextricably associated with the activation of coagulation and fibrinolysis. Some of the components of the coagulation system such as thrombin are proinflammatory and can lead to tissue injury. Microthrombi and fibrin deposition in injured organs is a common sequel of septic shock.⁷ Because of the relationship of coagulation, inflammation and tissue injury, 13 clinical trials have evaluated anti-coagulant therapies including anti-thrombin III, tissue factor pathway inhibitor, and activated protein C in sepsis (Table 1).^{17,18} All of these agents have an associated risk of bleeding with their use in phase III trials. Only activated protein C has been approved and is limited to patients with sepsis and a severity of illness (APACHE II) score of ≥ 25 . Post-marketing trials of activated protein C have not substantiated the purported beneficial effects seen in the original licensing trial and have resulted in further restrictions on its use in surgical patients with single organ failure.¹⁹ In almost 5000 patients who have been randomized to receive activated protein C in randomized trials, only 17% have been shown to have benefit from this intervention. Because the efficacy of activated protein C has not been reproduced in subsequent trials, a second post-marketing trial of activated protein C compared to placebo is being conducted (Table 2).

Reconciling preclinical success with clinical trial failures: the relationship of control mortality and effectiveness of anti-inflammatory agents in sepsis

A recent series of studies suggest a rationale behind the lack of concordance between preclinical effectiveness of anti-inflammatory therapies in sepsis and the marginal benefits observed when used in clinical trials. A meta-regression analysis of the preclinical studies of anti-inflammatory agents showed that the treatment effects were highly dependent on the risk of death.²⁰ Animals used in these investigations were studied at a higher mortality rate than in the human clinical trials. Similarly, an analysis of the clinical trials of anti-inflammatory agents in which stratification by severity of illness was available showed that in these subgroups, anti-inflammatory agents were effective in patients with the higher rate of death and harmful in those with low risk of death.²⁰ When tested prospectively in animal models using different doses and types of bacteria as well as sites of infection, the anti-inflammatory agents were

beneficial at high control mortality rates and had reduced effectiveness similar to the human trials at moderate control mortality rates (Figure 3). These data help to explain the apparent contradiction in preclinical success and clinical trial failures in sepsis. Further, this approach suggests that measures of severity of illness are essential to guide the clinical evaluation of mediator specific anti-inflammatory therapies.

Corticosteroids and Septic Shock

As early as the 1930s, case reports describe the beneficial effects of animal adrenal extracts in humans with infection. During a 25-year period prior to 1989, nine placebo-controlled randomized trials assessed the therapeutic effects of short courses (1 day) of high doses (total median administered dose 23,975 mg of hydrocortisone equivalents) of glucocorticoids in sepsis.²¹ After accounting for the effects of an outlier, the remaining eight trials of high dose steroids were associated with worse outcome.²¹ In the 1990s, investigators reevaluated the use of steroids because of a new understanding of relative adrenal insufficiency and its association with mortality. Five trials in the meta-analysis performed after 1997 used low doses of hydrocortisone (total median administered dose 1209 mg hydrocortisone) for longer duration (median 6 days) with tapering and found beneficial effects on survival and shock reversal (Figure 4).²¹ Since that analysis, two additional trials of low dose steroids in sepsis and septic shock have been published and show similar effects on shock reversal and survival.^{22,23}

Immunostimulatory therapies for sepsis

All patients with shock develop a state of immunosuppression that is manifested by decreased responsiveness to microbial antigens and is associated with an increased risk for secondary infections. This has been postulated to be an adaptive response to limit tissue damage.²⁴ Whole blood from patients with septic shock has a diminished capacity to produce proinflammatory cytokines in response to endotoxin.²⁵ Cell-mediated immunity is depressed and monocytes from patients with septic or traumatic shock have decreased responsiveness to secondary stimuli (i.e. endotoxin, anti-CD3/CD28) with impaired Th1 cytokine secretion, T cell proliferative responses, and decreased expression of HLA-DR molecules.^{24,26}

Only limited information is available regarding the use of immune enhancing therapies in sepsis. Colony-stimulating factors have been used as prophylaxis or therapy in patients with depressed immunity (i.e. cancer chemotherapy, stem cell transplantation or human immunodeficiency infection) to enhance host responses to infection. Granulocyte colony-stimulating factor (G-CSF) enhances neutrophil function by stimulating host defenses, improving microbial clearance and decreasing systemic inflammation and is clinically used in patients with neutropenia and high risks of bacteremia. When used as adjunctive therapy in non-neutropenic patients with sepsis due to community or hospital acquired pneumonia, it has not improved outcomes.^{27,28}

Granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances the production and half-life of neutrophils and monocyte/macrophages and increases the microbicidal activity of these cells. Only limited data are available in patients with adult sepsis.²⁹⁻³¹ Trials of GM-CSF and G-CSF in neonates have been equivocal regarding benefit and because of the immaturity of their immune system are not directly applicable to adults.³²

Interferon gamma (IFN-gamma) is a potent immunostimulant that enhances antimicrobial functions of blood monocytes and neutrophils as well as other host defense cells. Clinical trials of IFN-gamma as an immunoadjuvant to reduce infectious complications in traumatically injured or burn patients have not shown differences in infection rate compared to placebo³³⁻³⁵ and one trial³⁵ with improved outcome was confounded by imbalances in the study arms.

Conclusions

New approaches to resuscitation and modulation of inflammatory mediators in sepsis are the subject of ongoing and future clinical trials (Table 2). However, several challenges remain in the development of new therapies for sepsis and septic shock. Preclinical evaluation of inflammatory modifying agents must take into account the beneficial or harmful effects these treatments may have with differences in the sites of infection, differing pathogens as well as timing of the agents.^{13,36} Improved severity of illness measures and discovery of biomarkers to identify high-risk patients who may benefit from novel therapies in sepsis are needed.^{37,38}

Because of the high acute mortality rate in sepsis and septic shock, altering the host inflammatory response to infection with specific modulators has potential risks that are unique to this disorder. In the evaluation of novel therapies, it is crucial to minimize the potential for treatment-associated deaths. The Phase III trial of the nitric oxide synthase inhibitor L-N^G-methylarginine (L-NMA), a potent vasoconstrictor provides an example of problems that can develop with trials of new agents in septic shock.^{39,40} An interim analysis of the first 500 patients enrolled in the trial showed harm associated with L-NMA. By the time the interim analysis was completed, a total of 728 patients were enrolled and the mortality rate associated with L-NMA for all study end points was highly significant ($p < 0.005$).^{39,40} Preclinical testing of L-NMA had suggested the potential for toxicity in septic shock. Importantly, the Phase III trial used L-NMA at higher doses and for longer periods than previously tested in humans. To avoid these catastrophes, several issues regarding trial performance of new therapies in septic shock should be instituted. Phase III trials should be preceded by Phase I and II trials that are large enough with concurrent controls to estimate treatment effects since uncontrolled trials using novel agents preclude any ability to discern treatment-associated toxicities within the complex milieu of septic shock. Further, it is essential to give the new treatment in the same way and in the same type of patients as in the planned Phase III trial. Continuous monitoring of both control and treatment groups needs to be performed as close as possible to real time. Data safety and monitoring evaluation should never be limited to aggregate mortality rates or historical controls.³⁹

Acknowledgements

The Intramural Research Program of Clinical Center, National Institutes of Health supported this research.

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Figure 1. Pathogenesis and therapy of sepsis and septic shock

Outline of the sequence of events that occur during the pathogenesis of sepsis and septic shock including examples of standard therapy.

Figure 2. Toll-like Receptor 4 signaling, NF-κB activation and corticosteroid effects
Schematic representation of TLR4 signaling (adapted from references 3 and 4).

Lipopolysaccharide (LPS) binding to TLR4 stimulates both myeloid differentiation factor 88 (MyD88)-dependent and -independent pathways. The MyD88-dependent pathway involves activation of the IκB kinase (IKK) complex, which degrades the inhibitor of NF-κB IκB, allowing translocation of the NF-κB transcription factor to the nucleus. NF-κB binds to specific κB recognition sites and to coactivators, such as cAMP-response-element-binding-protein-binding-protein (CBP), that have intrinsic histone acetyltransferase (HAT) activity. The end result is acetylation of core histone H4, causing activation of gene transcription encoding multiple inflammatory proteins. The MyD88-independent pathway starts with engagement of

Toll / IL-1 receptor domain (TIR) domain containing adaptor-inducing interferon-beta (TRIF) and TRIF-related adaptor molecule (TRAM), which activates TANK-binding-kinase-1 (TBK1). TBK1 phosphorylates interferon response factor 3 (IRF3), resulting in its translocation to the nucleus and subsequent activation of interferon-beta and other genes. Corticosteroids decrease inflammation by two mechanisms: 1). activation of glucocorticoid receptors (GR), resulting in translocation to the nucleus and binding to coactivators that inhibit HAT, 2). binding to glucocorticoid-response elements (GREs) in the promoter region of steroid-sensitive genes, resulting in increased transcription of anti-inflammatory genes.

Figure 3. Relationship between the severity of illness and treatment effects of mediator-specific anti-inflammatory agents in preclinical and clinical trials of sepsis

The relationship between the control odds of dying (risk of death) on the X axis and the odds ratio of survival (Y axis) in 95 experiments (open circles) from 38 published animal studies cited in 22 clinical trials (open circles) of mediator specific anti-inflammatory agents in sepsis. The line is a weighted linear regression that shows that the treatment effect of these agents is significantly related to severity of illness as represented by the control odds of dying ($p < 0.0001$); these agents are beneficial in populations with a high severity of illness at a high risk of death and have minimal effect or are harmful in populations that are less severely ill with a low risk of death (Reproduced with permission)²⁰.

Figure 4. The effects of steroids on survival in sepsis: an analysis of clinical sepsis trials using high and low doses of corticosteroids

Relative survival benefits (closed boxes) are shown with 95% confidence intervals (horizontal lines). Meta-analysis of 13 trials (9 trials pre-1989 and 4 trials post-1997) demonstrated significant variability with no overall improvement in relative survival benefit (fixed-effects estimate, 1.01 [95% CI, 0.94 to 1.09]). The effect of steroids in the trials published before 1989 (high dose steroids) compared with those published after 1997 (low dose steroids) differed significantly ($P = 0.02$). One significant outlier trial was removed and the remaining, 8 pre-1989 trials had a consistent harmful effect of steroids on survival [fixed-effects estimate, 0.89 [CI, 0.82 to 0.97]]. In the 4 trials published after 1997, the effect of low dose steroids on the relative survival benefit was consistently beneficial (fixed-effects estimate, 1.23 [CI, 1.01 to 1.50]) (Reproduced with permission) ²¹.

Table 1
Past Clinical Trials of Novel Therapies for Sepsis and Septic Shock

Class of Agent	Ref No.	Mechanism of Action	No. of Clinical Trials	Odds Ratio of Survival (95% Confidence Interval)
Corticosteroids				
High-dose	21	Broad anti-inflammatory effects	9 ^a	0.89 (0.82-0.97)
Low-dose	21	Broad anti-inflammatory effects, restoration of vascular responsiveness to adrenergic stimuli	4	1.23 (1.01-1.50)
Anti-Inflammatory				
Anti-TNF monoclonal antibodies	15	Antibody-specific inactivation of circulating TNF	9	1.10 (0.97-1.25)
PAF antagonists		Receptor-specific inactivation or enzyme degradation of PAF	7	1.10 (0.93-1.30)
Soluble TNF receptors		Receptor-specific inactivation of circulating TNF	3	0.95 (0.78-1.16)
IL-1 receptor antagonist		Receptor-specific inactivation of IL-1	3	1.18 (0.97-1.44)
Prostaglandin antagonist		Cyclooxygenase inhibition of prostaglandin production	3	1.22 (0.78-1.58)
Bradykinin antagonist		Inhibition of kallikrein-kinin cascade	2	0.91 (0.65-1.27)
Phospholipase inhibitor	16	Inhibition of group IIA phospholipase A2	2 ^b	0.80 (0.61-1.05)
Anti-Endotoxin or Anti-Common Antigen				
J5 Antiserum	10	Human antiserum to endotoxin core	2	1.19 (0.25-5.62)
J5 Immune Plasma		Human plasma after immunization with E. Coli J5	2	1.38 (0.76-2.50)
J5 IV IG		Core-lipopopolysaccharide hyperimmune globulin that inactivates endotoxin by binding it	2	1.03 (0.60-1.78)
E5 Monoclonal Antibody		Murine monoclonal IgM antibody inactivates endotoxin by binding to lipid A domain	3	1.00 (0.83-1.22)
HA-1A Monoclonal Antibody		Monoclonal IgM antibody that inactivates endotoxin by binding to lipid A domain	2	1.40 (0.63-3.11)
Recombinant human bactericidal/permeability-increasing protein	12	Neutralizes soluble and membrane-bound endotoxin	1	1.37 (0.67-2.80)
MAB-T88 Monoclonal antibody	11	Human monoclonal antibody directed against enterobacterial common antigen	1	0.88 (0.66-1.17)
Anti-coagulant				
Antithrombin III	17-19	Inhibits thrombin and other serine proteases generated during coagulation	7	1.03 (0.88-1.20)
Tissue factor pathway inhibitor		Forms complex with tissue factor, inhibiting thrombin generation and fibrin formation	2	1.03 (0.81-1.29)
Recombinant human activated protein C (drotrecogin alfa)		Limits thrombin generation by inhibiting Factor V and VII and promotes fibrinolysis by inhibiting plasminogen activator inhibitor-1	4	1.12 (0.86-1.45)
Immunostimulatory				
Granulocyte colony-stimulating factor	27,28,32	Stimulates differentiation of stem cells into mature neutrophils, mobilizes mature neutrophils from marrow into circulation, improves bactericidal activity, stimulates phagocytosis	7 ^c	1.02 [0.65-1.61]
Granulocyte-macrophage colony-stimulating factor	29-32	Augments functional antimicrobial activity of neutrophils and up-regulates antimicrobial mechanisms in monocytes and macrophages	4 ^d	0.87 (0.05-16.53)
Interferon gamma	33-35	Enhances antimicrobial functions of monocytes and neutrophils	3	1.29 (0.87-1.92)
Immunoglobulin				
Polyclonal intravenous immunoglobulin	14	Improves bactericidal activity, stimulate phagocytosis, neutralize bacterial toxins	20 ^e	1.79 (1.29-2.48)
Nitric oxide synthase inhibition				
N ^G -methyl-L-arginine hydrochloride (L-NMA)	40	Inhibits of nitric oxide synthase, potent vasoconstrictor	2 ^f	0.82 (0.50-1.32)

^a One trial that was statistical outlier excluded

^b Higher mortality in treatment group (p=0.092) (16)

c_2 adult and 5 pediatric trials
 d_3 adult and 1 neonate trials

e_1 2– 44.9% for 20 trials, suggesting these trials should not be combined because of variability across the studies

f_1 Increased mortality with L-NMA in Phase III trial (p<0.001)

Abbreviations: TNF - tumor necrosis factor; PAF – platelet activating factor

Table 2
Current and future trials of adjunctive therapies for sepsis

Target / Intervention	Expected Outcome of Intervention	Sponsor	Clinicaltrials.gov Identifier	Phase
Resuscitation				
Protocol-Driven Hemodynamic Support for Patients With Septic Shock	To see if a protocol for fluid and vasopressors will improve outcomes in patients with septic shock	National Institute of General Medical Sciences (NIGMS)	NCT003335907	N/A
Optimal Endpoint of Early Sepsis Resuscitation	To compare blood lactate measurements with central venous oxygen saturation as an endpoint of shock resuscitation	National Institute of General Medical Sciences (NIGMS)	NCT00372502	N/A
Hydroxy-ethyl starch	To determine whether administration of hydroxyethylstarch and Ringer's lactate reduces intensive care unit and hospital length of stay in septic patients	Fresenius AG	NCT00273728	IV
Albumin	To determine whether the early administration of albumin as a volume expander and antioxidant would improve survival for septic shock patients.	Laboratoire Français de Fractionnement et de Biotechnologies	NCT00327704	IV
Methylene blue	To investigate whether the addition of methylene blue to the standard treatment of septic shock will reduce vasopressor requirements	Queen's University	NCT00486174	N/A
Methylene blue, inhaled nitric oxide	To test the hypothesis that the combination of methylene blue and inhaled nitric oxide improves clinical outcome in patients with septic shock and acute lung injury	Northern State Medical University, Helse Nord	NCT00159510	I
Terlipressin	To determine whether continuous infusion of ultra-low dose of terlipressin stabilizes hemodynamics in patients with septic shock	University of Roma La Sapienza	NCT00481572	II
Levosimendan	To compare the efficacy of levosimendan with that of dobutamine in patients with shock.	Wentworth Area Health Services / Abbott	NCT00093301	II
Dopamine and Norepinephrine in Shock Patients	To compare the efficacy of dopamine and norepinephrine, two commonly used vasopressor agents, in the treatment of shock	Sepsis Occurrence in Acutely III Patients	NCT00314704	IV
Dopamine, dobutamine, enoximone, nitroglycerine, noradrenaline	To assess the recovery of organ failure between pressure guided versus a microcirculation guided therapy	Onze Lieve Vrouwe Gasthuis	NCT00484133	IV
Near Infrared Spectroscopy	To study the utility of near infrared spectroscopy to optimize tissues perfusion and oxygenation in severe sepsis	University of Versailles, Hutchinson Technology Inc, AP-HP	NCT00167596	II/III
Coagulation cascade				
rhAPC Drotrecogin Alfa (Activated)	To evaluate the vasopressor requirement, hemodynamic response and measures of tissue perfusion in patients with septic shock receiving an infusion of drotrecogin alfa (activated) compared to patients not receiving drotrecogin alfa (activated)	Eli Lilly and Company	NCT00279214	IV
rhAPC Drotrecogin Alfa (Activated)	To determine whether continued administration of drotrecogin alfa (Activated) up to additional 72 hours - after the so far recommended 96 hour infusion period - results in a more rapid resolution of hypotension in patients with severe sepsis	Eli Lilly and Company	NCT00190788	III
Unfractionated heparin	To determine whether low dose continuous infusion of unfractionated heparin, in addition to the standard treatment, is efficacious as complementary therapy for sepsis patients	Universidad de Antioquia	NCT00100308	III
Recombinant human soluble thrombomodulin (ART-123)	To evaluate if ART-123 (recombinant human soluble thrombomodulin) decreases the mortality of disseminated intravascular coagulation that develops as a complication of sepsis	Artisan Pharma, Inc.	NCT00487656	II
Toll-like receptor inhibition				
TAK-242	To assess the effects of TAK-242 (ethyl (6R)-6-[N-(2-Chloro-4-fluorophenyl)sulfonyl]cyclohex-1-ene-1-carboxylate), a novel cyclohexene derivative that suppresses production of inflammatory mediators by inhibiting the signal transduction through Toll-like receptor 4, in sepsis	Takeda Pharmaceutical Company Limited	NCT00143611	III
Eritoran tetrasodium (E5564)	To assess the effects of eritoran tetrasodium (E5564), a synthetic Lipid A analog that blocks the binding of endotoxin to Toll-like receptor 4, in sepsis	Eisai Medical Research Inc	NCT00334828	III

Target / Intervention	Expected Outcome of Intervention	Sponsor	Clinicaltrials.gov Identifier	Phase
Systemic inflammation				
Rosuvastatin	To determine whether rosuvastatin is effective as a coadjuvant drug in the integral management of abdominal sepsis	Universidad Autonoma de San Luis Potosi	NCT00357123	II
Simvastatin	To determine whether treatment with simvastatin may mitigate the detrimental vascular effects of acute inflammation in patients with septic shock	Medical University of Vienna	NCT00450840	N/A
Atorvastatin	To determine whether atorvastatin can improve the inflammatory response in septic patients	Hospital de Clinicas de Porto Alegre	NCT00452608	II
Intensive insulin therapy, corticosteroids and mineralocorticoids	To compare the safety and efficacy of moderate doses of corticosteroids with and without fludrocortisone and intensive insulin therapy in patients with septic shock	University of Versailles	NCT00320099	III
Hydrocortisone and fludrocortisone	To compare hydrocortisone versus hydrocortisone plus fludrocortisone for the treatment of adrenal insufficiency in severe sepsis	CAMC Health System	NCT00368381	IV
Renal replacement therapy in sepsis				
Hemofiltration	To compare standard volume with higher volume hemofiltration in patients with septic shock complicated by acute renal failure	University Hospital, Bordeaux, Ministry of Health, France	NCT00241228	N/A
Plasma-Filtration and Adsorption	To assess whether the application of CPFA (coupled plasma-filtration adsorption) in addition to the current clinical practice reduces mortality and prevents organ failure in patients with septic shock	Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva	NCT00332371	N/A
Enteral nutrition				
Eicosapentaenoic acid (EPA), Gamma-Linolenic Acid (GLA) and Antioxidants	To evaluate the effects of an enteral formulation enriched with EPA, GLA and antioxidants in patients with early stages of sepsis and its capacity to prevent the development of sepsis into severe sepsis and septic shock	Abbott Ross Products	NCT00329680	IV

Active clinical trials involving potential sepsis therapies found at <http://clinicaltrials.gov/>. The trials are grouped by class of agent and the goal, sponsor and phase of each trial are listed (when available).