

Review Article

Organ Dysfunction Following Trauma, Shock and Sepsis: An Update

Yu-Ren Wang^{1,2}, Hsin-I Tsai^{1,3}, and Huang-Ping Yu^{1,3}

ABSTRACT

From the ¹Department of Anesthesiology, Chang Gung Memorial Hospital, Taiwan, China; ²Department of Physiology, College of Medicine, Chang Gung University, Taiwan, China; ³College of Medicine, Chang Gung University, Taiwan, China.

Correspondence to Dr. Huang-Ping Yu at yuhp2001@adm.cgmh.org.tw.

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Aim of review: Trauma, shock and sepsis are often associated with multiple organ failure. Despite the progress made in patient management over the last decade, sepsis and subsequent multiple organ failure continue to be the major cause of morbidity and mortality in injured patients.

Method: We reviewed the current information on the multiple organ dysfunction and use of therapeutic apheresis procedures as adjunctive therapy in such clinical situations as well as the exciting prospects for the near future.

Recent findings: Most of clinical trials have failed to demonstrate any outcome benefit. However, corticosteroids, anti-endotoxin antibodies, anti-tumor necrosis factor- α antibody, interleukin (IL)-1 β receptor antagonist and recombinant activated protein C are to date the possible drugs that may demonstrate mortality benefits in large randomized controlled trials. This could be attributed to their broad based attempts at modulating the inflammatory response to infection.

Summary: Basic research with related pathophysiologic approaches has driven clinical trials using molecules that might interfere with inflammatory processes. Against inflammatory response, the time to initiate therapy is thought to be crucial and the major determinant factor in surviving trauma, shock and sepsis. Despite substantial progress in trauma, shock and sepsis therapy, the important strategies between the discovery of new effective medical molecules and their implementation in the daily clinical practice of the intensive care unit remain a major hurdle. Fortunately, ongoing research continues to provide new information on the management of trauma, shock and sepsis. On this basis, new therapies could be tested to reduce mortality rates in trauma, shock and sepsis with respect to recently published studies.

Trauma and infectious diseases have been a leading cause of death throughout the human history, but only until recently have we begun to understand their effects on human body. As we continue to unravel the mysteries of trauma, shock and sepsis, more recent research and innovation have focused on the molecular mechanisms, hemodynamics and therapies for trauma, shock and sepsis (1). The mortality rate in the intensive care unit (ICU) for trauma, shock and sepsis is ranging from 25-70%, most often caused by shock and multiple organ failure (2). Therefore, the treatment for shock and sepsis consists of source control, early antimicrobial therapy, and supportive and adjunctive therapies. Adjunctive therapy, an expanding field that encompasses early administration of appropriate antibiotic therapy and source control, early goal-directed management of hypotension and perfusion abnormalities with fluid resuscitation and vasoactive agents support, and the use of lung protective ventilator support strategies, may further reduce mortality rate in the ICU (3).

The prominent role of inflammatory molecules and pathways suggests a possible therapeutic role in the management of trauma, shock and sepsis. However, numerous trials which targeted at inhibiting various essential inflammatory mediators and receptors involved in the trauma, shock and sepsis-mediated multiple organ dysfunction, have failed to show a reduction in mortality (4-8), thus raising the question whether mortality in trauma, shock and sepsis derives from an uncontrolled proinflammatory response. In this review, we emphasize on current information on the multi-organ dysfunction and the use of therapeutic procedures as adjunctive therapy in such clinical situations as well as the exciting future prospects.

Definitions of SIRS, Infection, Sepsis, Severe Sepsis, and Septic Shock

Systemic inflammatory response syndrome (SIRS) was first described as the nonspecific inflammatory process in adults in response to significant physiologic insults, such as infection, trauma, burns, sepsis and other disease processes in 1992 by the American College of Chest Physicians (ACCP) and the Society of Critical

Care Medicine (SCCM) (9, 10). SIRS has become a part of the common medical vernacular. The definitions of SIRS, infection, sepsis, severe sepsis, and septic shock in adult patients are described as follows.

SIRS

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count: 1) core temperature of more than 38.5°C or less than 36°C (must be measured by rectal, bladder, oral, or central catheter probe); 2) tachycardia, defined as a mean heart rate greater than two standard deviations above normal for age in the absence of external stimulus, chronic drugs, or painful stimulus; bradycardia, defined as a mean heart rate less than the tenth percentile for age in the absence of external stimulus, β -blocker drugs, or congenital heart disease; 3) mean respiratory rate more than two standard deviations higher than normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia; 4) leukocyte count increased or depressed for age or greater than 10% immature neutrophils (10).

Infection

A suspected or proven infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory test (10).

Sepsis

SIRS exists in the presence of or as a result of suspected or proven infection (10).

Severe Sepsis

Sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome (ARDS) or two or more organ dysfunctions (10).

Septic Shock

Sepsis with cardiovascular organ dysfunction is observed (10).

The causes of infection are usually bacterial,

viral, or fungal in origin. The diagnosis of infection may be supported by positive culture, tissue stain, clinical examination, radiologic imaging, or other laboratory test findings. Sepsis is characterized as SIRS in the presence of an infectious source as defined by the ACCP/SCCM Consensus Conference in 1992 (9, 10). Severe sepsis is defined as sepsis plus the presence of cardiovascular dysfunction, adult respiratory distress syndrome, or two or more organ dysfunctions. These definitions are useful for standardization of the diagnoses but may be less relevant in the clinical settings. Clinical suspicion for sepsis is more sensitive and should always supersede reliance on the presence of all components of the consensus criteria (11).

Organ Dysfunction in Trauma, Shock and Sepsis

Although the mechanisms that underlie organ failure in trauma, shock and sepsis have been only partially elucidated, impaired tissue oxygenation may play a key role. Inflammation can cause dysfunction of the vascular endothelium, accompanied by cell death and loss of barrier integrity (12). In addition, mitochondrial damage caused by oxidative stress impairs cellular oxygen use (13). Moreover, injured mitochondria release alarmins into the extracellular environment which can activate neutrophils and cause further tissue injury (14).

One of the many fascinating paradoxes of trauma, shock and sepsis is its variable effect on the body's organs. Organ dysfunction criteria in clinical is described as follows (15, 16).

The Criteria for Neurologic System

A Glasgow Coma Scale score greater or equal to 11; or acute change in mental status with a decrease of 3 or more points in Glasgow Coma Scale from abnormal baseline (16).

The Criteria for Cardiovascular System

Despite administration of isotonic intravenous fluid bolus 40 ml/kg or more in 1 hour: a decrease in blood pressure (BP) (hypotension) less than the fifth percentile for age or systolic BP less than two standard deviations below normal for age; or the need for vasoactive drug to maintain BP in the normal range (dopamine >5 mg/

kg/minute or dobutamine, epinephrine, or norepinephrine at any dose); or presence of 2 of the following 1) unexplained metabolic acidosis: base deficit greater than 5.0 mEq/l, 2) increased arterial lactate level greater than twice the upper limit of normal, 3) oliguria: urine output less than 0.5 ml/kg/hour, 4) prolonged capillary refill: longer than 5 seconds, 5) core to peripheral temperature gap greater than 3°C (16).

The Criteria for Respiratory System

Partial pressure of oxygen in arterial blood (PaO₂)/ fraction of inspired oxygen (FiO₂) less than 300 in absence of cyanotic heart disease or preexisting lung disease; or partial pressure of carbon dioxide in arterial blood (PaCO₂) greater than 65 torr or 20 mm Hg over baseline PaCO₂; or proven need for more than 50% FiO₂ to maintain saturation ≥ 92%; or the need for non-selective invasive or noninvasive mechanical ventilation (16).

The Criteria for Hepatic System

Total bilirubin level 4 mg/dl or greater; or alanine aminotransferase level 2 times upper limit of normal for age (16).

The Criteria for Renal System

Serum creatinine level 2 times or greater than the upper limit of normal for age or 2-fold increase in baseline creatinine (16).

The Criteria for Hematologic System

Platelet count less than 80,000/mm³ or a decline of 50% in platelet count from highest value recorded over the past 3 days for chronic hematology/oncology patients; or international normalized ratio greater than 2 (16).

The clinical manifestations of trauma, shock and sepsis are highly variable, depending on the initial site of infection and the causative organism. Acute organ dysfunction most commonly affects the respiratory and cardiovascular systems. Respiratory compromise is classically manifested as the ARDS, which is defined as hypoxemia with bilateral infiltrates of noncardiac origin (17). Cardiovascular compromise is manifested primarily as hypotension or an elevated serum lactate level (18).

In addition, brain and kidneys are also often affected. Central nervous system dysfunction is typically manifested as obtundation or delirium. Critical illness polyneuropathy and myopathy are also common, especially in patients with a prolonged ICU stay (19). Acute kidney injury is manifested as decreasing urine output and an increasing serum creatinine level. Paralytic ileus, elevated aminotransferase levels, altered glycemic control, thrombocytopenia and disseminated intravascular coagulation, adrenal dysfunction, and the euthyroid sick syndrome are all common in patients with trauma, shock and sepsis (20).

Precise mechanisms by which how trauma, shock and sepsis produce multiple organ dysfunction remain complex. For example, irrespective of changes in oxygen and substrate provision, the cells themselves may react to a septic insult by modifying their behavior, function, and activity (21). Some literatures indicate that cellular injuries implicated in trauma, shock and sepsis include peroxidation of lipid membranes, damage or modification to proteins and damage to DNA. However, despite all the above, previous evidence of cell death is seen in most affected multi-organ dysfunction during trauma, shock and sepsis (22). This may reflect the relatively slow progression of the disease, allowing cellular phenotypes to adapt more successfully to a reduced oxygen supply and damage external factors during trauma, shock and sepsis (Figure).

Anti-Inflammatory Directed Therapy for Trauma, Shock and Sepsis

Disruption of the self-recycling inflammatory cascade has become the focus of considerable research and clinical trials over the last 30 years. A large number of different inhibitors and biological antagonists have been developed to modulate one or more of the numerous steps in the sequence of SIRS and multiple organ dysfunction syndrome (MODS). Table 1 describes some traditional anti-inflammatory directed therapies for trauma, shock and sepsis.

Corticosteroid Therapy

Beginning in the 1960s, early efforts were made to use corticosteroids to "dampen" the generalized effects of shock due to infection. Richard

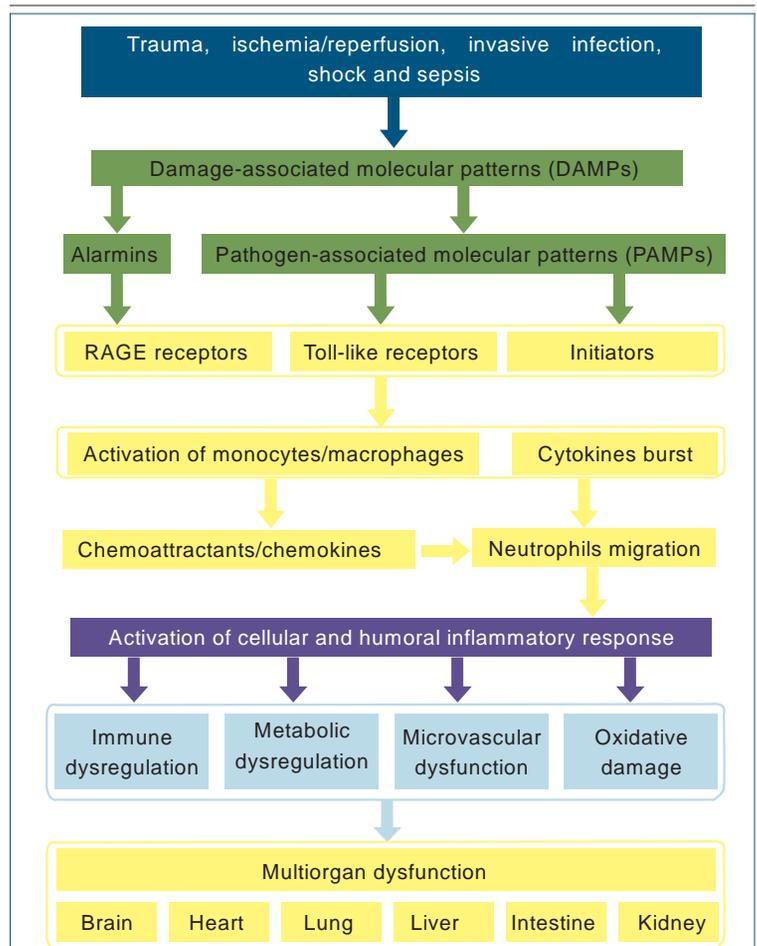


Figure. This Figure Illustrates the Numerous Components of the Innate Host Response that Leads to Trauma, Shock and Sepsis Mediated Multi-organ Dysfunction.

The release of danger-associated molecular patterns (DAMPs) from damaged cells or from bacteria results in binding to toll-like receptors, RAGE receptors, and activation of the initiators of inflammation. The initiators lead directly to the vasoactive changes in the tissue and phase I of the inflammatory response. With the systemic distribution of DAMPs, cytokines, and chemoattractants, the inflammatory cascade is activated systemically. Activation of leukocyte populations systemically results in margination and activation, which then leads to tissue damage from cellular products of the leukocyte and the consequences of damage to the microcirculation. Tissue ischemia and necrosis then result in the release of additional DAMPs, which recycle the whole process. A point can be reached where there has been resolution of the inciting activation events, but the results of tissue-level inflammation provide the stimulus to recycle the entire cascade.

Lillehei was a major early advocate for systemic corticosteroids use on the basis of experimental evidence in acute models of endotoxemia (23). Multiple experiments in multiple different animal models of endotoxemia reconfirmed these early observations about the benefits of steroids.

Table 1. Description of Traditional Anti-Inflammatory Directed Therapy for Trauma, Shock and Sepsis.

Strategy	Model	Benefit	References
Corticosteroid therapy			
	Shock dogs	Effective	(23)
	Shock patients	Effective	(27, 28)
	Septic patients	Invalid	(24, 26)
	ARDS patients	Invalid	(25)
Anti-endotoxin antibodies strategy			
	Bacteremic patients	Effective	(30, 31)
	Shock patients	Invalid	(32)
Anti-tumor necrosis factor-α antibody strategy			
	Septic rats	Effective	(33)
	Endotoxemia mice	Effective	(34)
	Bacteremia baboons	Effective	(35)
	Septic baboons	Effective	(39)
	Septic patients	Invalid	(36, 41)
	Shock patients	Invalid	(37, 40)
Interleukin-1β receptor antagonist treatment			
	Septic patients	Invalid	(43)
Recombinant activated protein C treatment			
	Septic patients	Effective	(3)
	Bacteremia baboons	Effective	(45)
	Shock patients	Effective	(46)
	Shock patients	Invalid	(47)
Other Approaches			
Bradykinin antagonists	SIRS patients	Invalid	(49)
Platelet activating factor antagonists	SIRS patients	Invalid	(50)
Platelet activating factor receptor antagonists	Septic patients	Invalid	(51)
Phospholipase A2 inhibitor	Septic patients	Invalid	(52)
Nitric oxide synthase inhibitor	Shock patients	Invalid	(53)
Granulocyte colony stimulating factor	Shock patients	Invalid	(54)
Antithrombin III	Septic patients	Invalid	(55)
TLR-4 receptor inhibitor	Shock patients	Invalid	(56)

ARDS, acute respiratory distress syndrome; SIRS, systemic inflammatory response syndrome.

On the other hand, several large prospective, randomized clinical trials demonstrated no benefit (24, 25). The obligatory meta-analysis of all available clinical trials of high dose corticosteroids demonstrated no therapeutic benefit (26). More recently, a revitalized push for using corticosteroids has emphasized that clinical adrenocortical insufficiency may exist in selected septic patients, and a low dose of corticosteroids was proposed as part of the treatment (27). There has been a controversy in the evaluation of published clinical trials with meta-analyses (28). The corticosteroid story demonstrated from the beginning that there was a disconnection in the translation of acute animal models to human

sepsis and SIRS.

Anti-Endotoxin Antibodies Strategy

The evolution of antibody technology ushered in new hopes for therapy of human shock and sepsis in the 1980s. Because of the perceived major role in initiating SIRS, endotoxin has been a principal target for experimental treatment designs (29). The clinical applicability of this concept appeared promising with the initial report by Ziegler et al. (30), who demonstrated a survival benefit for patients with gram negative bacteremia and treated with a polyvalent human antiserum derived from individuals previously vaccinated with a heat-killed mutant E. coli strain. A

human monoclonal antibody to human endotoxin was developed and a randomized, clinical trial was conducted with the experimental antibody versus placebo. Over 500 patients with shock and presumed gram-negative sepsis were enrolled in the trial (31). Although the results failed to demonstrate a survival benefit in the treatment group with the monoclonal antibody treatment, among the 192 patients with proven gram-negative bacteremia and shock at the time of entry, there was a statistically significant survival benefit (49% in controls vs 30% with antibody treatment) at the end of the study. Considering gram-negative bacteremia and shock as the primary endpoint, another clinical trial of septic shock was conducted and no difference in survival outcomes was identified in the antibody treatment group compared with the placebo patients (32). This treatment was not approved for use and has not been evaluated with additional trials.

Anti-Tumor Necrosis Factor- α Antibody Strategy

Tumor necrosis factor (TNF)- α has been considered as one of the most potent pro-inflammatory cytokines identified in shock, SIRS and sepsis. Administration of TNF- α to experimental animals created hemodynamic and metabolic derangement consistent with shock and sepsis (33), and experimental studies identified a survival benefit when anti-TNF- α antibodies were administered to animals in models of acute endotoxemia (34) and bacteremia (35). However, the discordance between hyperacute experimental models in the laboratory and human shock and sepsis again was observed as several clinical trials failed to demonstrate any benefit with anti-TNF- α monoclonal antibodies (36, 37). Another approach to the modulation of the systemic pro-inflammatory effects of TNF- α has been to bind the TNF- α with a soluble receptor that neutralizes its activity. Fusion proteins for TNF- α have been demonstrated to have in vitro affinity for the TNF- α membrane receptor (38), and protect primates from experimental gram negative bacteremia (39). Human clinical trials have failed to demonstrate any outcome benefit with this proposed treatment (40, 41).

Interleukin-1 β Receptor Antagonist Treatment

IL-1 β has been identified as another potent cyto-

kine, which is considered to be of significance in the excessive pro-inflammatory effects of trauma, sepsis and septic shock. Because IL-1 β is viewed as having beneficial effects in physiologic concentrations, there has been an interest in preventing excessive concentrations with soluble receptor modulation. IL-1 β receptor antagonist has shown to be promising as a potential clinical treatment; however, clinical trials thus far have not demonstrated an improved survival in shock and septic patients (42, 43).

Recombinant Activated Protein C Treatment

Activation of the coagulation cascade has been recognized as an important feature of human shock and sepsis associated with the consumption of coagulation proteins and fibrinogen. Pro-inflammatory cytokines activate coagulation and cause fibrinolysis. Inadequacy in the natural anticoagulation control mechanisms has been hypothesized as a potential issue that may represent an opportunity for treatment. Activated protein C is a naturally occurring modulator of human coagulation, and it has been identified in reduced concentrations in shock and septic patients (44). Like other proposed mediator therapies, activated protein C demonstrated a survival benefit in a primate model of gram negative bacteremia (45).

However, unlike the clinical trials of the other mediator-based therapies, the comparison of recombinant activated protein C with placebo resulted in a statistically significant difference in survival among shock and septic patients (46). Placebo-treated group and recombinant activated protein C group had a mortality rate of 31 percent and 25 percent ($P < 0.005$), respectively. The patients had acute physiology and chronic health evaluation II (APACHE II) scores that averaged 25, and treatment was initiated within 24 hours of randomization. Serious bleeding events occurred in 2 percent of placebo patients and 3.5 percent of treated patients ($P < 0.06$). A clinical trial of less severely septic patients with APACHE II scores less than 25 or a single organ failure subsequently showed no benefit in this population (47). Additional studies have shown highly variable results (48). Thus, the only inflammatory modulator to date with a positive clinical trial has remained mired

in controversy over its true efficacy, risk of subsequent complications such as bleeding and high cost. It should be considered for use in very ill patients (APACHE II > 25) with organ failure and commenced within the first 24 hours of treatment (3).

Other Approaches

Other potential treatment including bradykinin antagonists (49), platelet activating factor antagonists (50), platelet activating factor receptor antagonists (51), phospholipase A2 inhibition (52), nitric oxide synthase inhibition (53), granulocyte colony stimulating factor administration (54), and antithrombin III administration (55) for shock and sepsis have been explored. Disappointingly, they all showed promising laboratory results but no clear survival benefits in clinical trials. Most recently, a clinical trial with a TLR-4 receptor inhibition did not affect outcomes (56).

Outlook of New Therapies in Trauma, Shock and Sepsis

Recent Failures in Trauma, Shock and Sepsis

One of the great disappointments during the past 30 years has been the failure to convert advances in our understanding of the underlying biologic features of trauma, shock and sepsis into effective new therapies (57). Researchers have tested highly specific agents which can be divided into those designed to interrupt the initial cytokine cascade (e.g., anti-lipopolysaccharide or anti-proinflammatory cytokine strategies) and those designed to interfere with dysregulated coagulation (e.g., anti-thrombin or activated protein C) (58). The only new agent that gained regulatory approval was activated protein C (46). However, post approval concern about the safety and efficacy of activated protein C prompted a repeat study, which did not show a benefit and led the manufacturer, Eli Lilly, to withdraw the drug from the market (59). In addition, there are no current large-scale trials of anti-cytokine strategies in the treatment of shock and sepsis (60).

Among the agents with broader immunomodulatory effects, glucocorticoids have received the most attention. Intravenous immune globulin is

also associated with a potential benefit (61). Despite a large number of observational studies suggesting that the use of statins reduces the incidence or improves the outcome of severe infection, shock and sepsis (62), such findings have not been confirmed in randomized and controlled trials, so the use of statins is still not part of routine care for patients with shock and sepsis.

Problems with Therapeutic Development in Trauma, Shock and Sepsis

Faced with these disappointing results, many observers have questioned the current approach to the development of shock and sepsis drugs. Pre-clinical studies commonly test drugs in young, healthy mice or rats exposed to a shock and septic challenge (e.g., bacteria or bacterial toxins) with limited or no ancillary treatment. In contrast, patients with shock and sepsis are often elderly or have serious coexisting illnesses. There are large between-species genetic differences in the inflammatory host response (63).

New Strategies in Trauma, Shock and Sepsis

Activated protein C mutants were shown to provide some protection from shock and sepsis induced death in animals, without an increased risk of bleeding (64). Biomarkers such as whole-genome expression patterns in peripheral-blood leukocytes may aid in stratifying patients into more homogeneous subgroups or in developing more targeted therapeutic interventions (65). The insight that shock and severe sepsis can cause immunosuppression raises the possibility of using immune-stimulatory therapy (66), or interferon- γ (67). Thus, such therapies could be deployed on the basis of laboratory measures, such as monocyte HLA-DR expression (68).

Moreover, recent evidence suggests that the endothelial glycocalyx plays an important role in lethal outcomes following sepsis (69, 70). In a clinical study of 150 patients either with severe sepsis, septic shock or post-abdominal surgery without SIRS and healthy volunteers, the plasma concentrations of heparan sulfate and syndecan-1 strongly correlate with the severity of sepsis and the levels of inflammatory markers such as IL-6, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (69), as well as Sequential Organ Fail-

ure Assessment scores on day 1 (71). However, no specific therapeutic strategies exist to maintain glycocalix integrity for conserving endothelial function. In the future, detection of glycocalix compounds in the plasma can be utilized as diagnostic markers to evaluate sepsis-induced endothelial damage and estimate the severity of sepsis. A summary of new therapies in trauma, shock and sepsis is shown in table 2.

The considerable uncertainty at the beginning of a trial with regard to the appropriate selection of patients and drug-administration strategy and the possibility of treatment interactions may be better handled with the use of a Bayesian design (72).

Conclusions

Trauma, septic shock and severe sepsis represent one of the oldest and most pressing problems in clinical medicine. With advances in intensive care medicine and increased awareness and practice of evidence-based guidelines, clinicians have taken large strides in minimizing the risk of imminent death associated with trauma, septic shock and sepsis. However, as more patients survive from trauma, shock and sepsis, concern mounts over the lingering sequelae of what was previously a lethal event. Strategies are also needed to reach the many millions of patients with trauma, shock and sepsis who are far from modern intensive care. To further improve the outcomes of pa-

Table 2. Description of New Therapies in Trauma, Shock and Sepsis.

Strategy	Target	References
Anti-inflammatory response		
DrotAA	APC	(59)
Statins	Cytokine	(62)
APC mutant	APC	(64)
GM-CSF	Monocyte	(66)
Interferon- γ	Monocyte	(67)
HLA-DR	monocyte	(68)
Block bacterial products and inflammatory mediators		
Polymyxin B	Bacterial LPS	(60)
Afelimomab	TNF- α	(60)
CytoFab	TNF- α	(60)
Modulators of immune function		
Clarithromycin and omega-3 PUFAs	Antibiotic	(60)
Recombinant thrombomodulin	DIC	(60)
Immunostimulation		
ivlg	IgM	(60, 61)
Gene screening		
Gene arrays	leukocytes	(65)

DrotAA, drotrecogin alfa (activated); APC, activated protein C; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA-DR, human leukocyte antigens-MHC II receptor; LPS, lipopolysaccharides; TNF- α tumor necrosis factors; PUFAs, polyunsaturated fatty acids; DIC, disseminated intravascular coagulation; ivlg, polyclonal intravenous immunoglobulin; IgM, immunoglobulin M.

tients with trauma, shock and sepsis through the development of new therapeutic agents and new design of clinical trials is essential.

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