PATHOBIOLOGY IN FOCUS

Pathophysiologic mechanisms in septic shock

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The systemic inflammatory response that occurs in the septic patient as a result of an infectious insult affects multiple organs and systems, causing numerous physiological derangements. Alterations in phagocytic, lymphocytic and endothelial cell function and immune regulation are evident, leading to heterogeneity in a host's response to a septic challenge. In addition, the normal hemostatic balance shifts toward a procoagulant state through alterations in tissue factor, antithrombin, protein C and the inhibition of fibrinolysis, which can result in thrombus formation and paradoxical hemostatic failure. In an effort to diagnose sepsis and predict outcomes, biomarkers such as C-reactive protein, pro-calcitonin, pro- and anti-inflammatory cytokines have been investigated with varying results. Targeted therapies for sepsis, most notably Xigris (recombinant human activated protein C), have proven unsuccessful and treatment continues to remain reliant on source control, antibiotics and supportive interventions, specifically early goal-directed therapy. This brief review gives an overview of the immunopathologic and coagulopathic alterations that occur in sepsis, soluble inflammatory mediators as potential diagnostic and prognostic biomarkers, and the clinical management of the septic patient.

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Sepsis, the systemic inflammatory response due to a microbial infection, is an extensive clinical problem with significant mortality and economic burden. Depending on a host's responses to an infectious challenge, many pathogens may lead to sepsis. Gram-positive infections are identified in over half of sepsis cases, but Gram negatives, anaerobes and fungi are all potential sources.¹ The etiology of the infection is also varied; Angus *et al*² analyzed over 6 million hospitalizations in seven states, identifying 192 980 cases of severe sepsis and attributed a respiratory source of infection in 44% of cases, with the remainder due to other causes including genitourinary, abdominal, soft tissue or an unspecified bacteremia.

In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference outlined definitions of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock (Table 1) in an effort to standardize the classification of host responses to infection.³

Despite continued advances in medicine and technology, the incidence of sepsis is increasing. From 2000 to 2008, hospitalizations for sepsis more than doubled from 326 000

to 727 000 according to the Center for Disease Control report examining hospital admission data from the National Hospital Discharge Survey.⁴ With an in-hospital mortality rate ranging from 15 to 30%, sepsis represents the 11th leading cause of death in the United States and is responsible for 7% of all childhood deaths.^{5–7} In addition to the many years of life which are lost, sepsis represents a significant economic burden with total hospital costs in 2007 for patients with severe sepsis estimated to be \$24.3 billion nationally, a 57% increase from 2003.⁸

The incidence of sepsis is greatest at the extremes of age, occurring in 5.3/1000 patients under 12 months of age and 26.2/1000 patients aged 65 years or older.² Age-related alterations in the host immune system affect an individual's response to an infectious challenge. Preterm and septic neonates have been demonstrated to have a decreased neutrophil storage pool, deficiencies in neutrophil function and an altered cytokine response as a result of an increased percentage of pro-inflammatory cells coupled with an immature compensatory anti-inflammatory response.⁷ Older individuals have been found to exhibit dysregulation in Toll-like receptor (TLR) trafficking, deficits in dendritic

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Table 1 Diagnostic criteria for sepsis

Systemic inflammatory response syndrome (two or more of the following):

- Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
- Heart rate >90 beats per minute
- Respiratory rate >20 breaths per minute or $\text{PaCO}_2 <32$ mm Hg
- White blood cell count $>12000/\text{cu mm}$ or $<4000/\text{cu mm}$ or $>10\%$ bands

Sepsis

- SIRS with an infectious source

Severe sepsis

- Sepsis with associated hypoperfusion, hypotension or organ dysfunction

Septic shock

- Systolic blood pressure <90 mm Hg or reduction of ≥ 40 mm Hg from baseline despite adequate fluid resuscitation along with perfusion abnormalities

Abbreviation: SIRS, systemic inflammatory response syndrome.

cell function secondary to decreased numbers and/or decreased receptor signaling, an increased proportion of naive B cells, signaling deficits in the T-cell receptor CD3 complex, increased numbers of inhibitory receptors and changes in cytokine signaling.⁹

The challenge of treating sepsis lies in the multiple organs and systems affected, with alterations in cellular function, immune regulation, disordered coagulation and metabolism manifesting in the septic patient. This brief review highlights some of the derangements observed in sepsis, beginning with alterations that occur on the cellular level.

CELLULAR DYSFUNCTION

Under normal conditions, bacterial entry into a sterile field activates resident macrophages to contain the initial infection. Oftentimes, the initial infectious insult is too great for resident macrophages alone to eradicate all bacteria. However, regardless of whether or not the primary infection is contained, macrophages, of the M1 phenotype, initiate the immune system response by releasing inflammatory mediators such as tumor necrosis factor (TNF), interleukin- 1β (IL- 1β), IL-6 and CXCL-8. This signals endothelial cells to upregulate adhesion molecules and begin the recruitment of other inflammatory cells to help control the infection. Neutrophils also have a role in cell recruitment signaling. Recent work by Cho *et al*¹⁰ using *in vivo* bioluminescence and fluorescence imaging demonstrated that neutrophils recruited early to the site of a cutaneous *Staphylococcus aureus* infection are the predominant source of IL- 1β , leading to amplification of the neutrophil response with abscess formation and bacterial clearance. These recruited inflammatory cells, including the phagocytic cells (polymorphonuclear cells, monocytes and macrophages) of the

innate immune response and lymphocytes of the adaptive immune response frequently become dysfunctional in sepsis.

Phagocytic Cell Dysfunction

Phagocytosis consists of recognition and engulfment of a pathogen and subsequent microbe killing by various mechanisms such as generation of reactive oxygen, use of anti-bacterial proteases and peptides, and alterations in pH. Neutrophil recruitment, phagocytosis and pathogen killing varies in particular hosts as a function of heterogeneity in the way each individual responds to sepsis. This was demonstrated in the murine cecal ligation and puncture (CLP) model where mice predicted to live or die, based on plasma IL-6 levels, demonstrated equal levels of peritoneal neutrophils and bacteria 6 h following CLP. However, by 24 h, the mice predicted to live had significantly fewer neutrophils and bacteria within the peritoneum. Meanwhile, mice predicted to die demonstrated an overwhelming inflammatory state with an increase in cytokines, cell recruitment and bacterial load. Craciun *et al*¹¹ thus concluded that this heterogeneity between the two host sub-populations was due to better phagocytosis and enhanced cell efficiency, which resulted in improved survival.

Although neutrophils are necessary to combat microbial infections, a prolonged and vigorous response may be detrimental to the patient by causing organ injury leading to the development of organ failure. MIP-2, a CXC chemokine released by macrophages in sepsis, binds to the CXCR1 and CXCR2 on neutrophils, and has been associated with neutrophil-induced organ injury and mortality in the CLP model.¹² Ness *et al*¹³ demonstrated that neutralizing the effects of CXCR2 stimulation in murine peritonitis resulted in an attenuated neutrophil response with less organ injury and improved survival. On the other hand, without an appropriate neutrophil response and the absence or attenuation of CXCR2 expression, patients become immunocompromised and are more susceptible to developing microbial infections. Evidence of this has been seen in neutropenic patients as a result of chemotherapy, malnutrition or hereditary disorders. Moreover, Adams *et al*¹⁴ demonstrated that patients who suffered major trauma went on to experience one of two fates: the group that developed an underwhelming CXCR2 response became 'immunocompromised' and went on to develop pneumonia and sepsis, while the group that experienced a hyperactive CXCR2 response went on to develop organ injury such as acute respiratory distress syndrome.

Although neutrophils may be hyperactive in the septic state, they may also have an extended lifespan lasting >24 h at the infection site. The prolonged lifespan is attributed to delayed apoptosis, resulting in an increased number of neutrophils, which may also contribute and further harm to the host. Taneja *et al*¹⁵ sampled whole blood from septic patients in an intensive care unit and determined that there

was significantly 'suppressed' neutrophil apoptosis as a result of NF- κ B activation and attenuated caspase-3 and caspase-9 activity compared with cells from healthy subjects.

Neutrophils also release neutrophil extracellular traps, a recently discovered network of extracellular filamentous DNA containing histones and neutrophil granular proteins such as elastases, proteases and cathepsin G. Although the function is not entirely clear, it appears these proteins are released in the presence of pathogen-associated molecular patterns (PAMPs) such as LPS to augment cell killing.¹⁶ They also demonstrate the ability to interact with the coagulation cascade and have the potential to induce a pro-thrombotic state.¹⁷

Monocytes and macrophages are also critical cell populations from the innate immune response as they are responsible for a variety of functions including mediating inflammation, phagocytosis, wound healing and remodeling. Certain signals are responsible for determining the activation and differentiation of monocytes/macrophages.^{18,19} For example, the M1 macrophage phenotype is activated by TLR or IFN- γ signaling to produce pro-inflammatory cytokines and promote the killing of bacterial pathogens by increasing bactericidal activity. On the other hand, the M2 phenotype is activated in the presence of IL-4 and IL-13 in the setting of parasitic infections and tissue remodeling.¹⁹

Macrophage function is also altered in sepsis. This dysfunction has been demonstrated in animal models²⁰ and human patients²¹ suffering from severe sepsis, but only recently have mechanisms been discovered detailing their functional decline. An example of this is the programmed death-1 receptor (PD-1R), which is responsible for intensifying the inflammatory response in sepsis, however, it also suppresses macrophage function. Huang *et al*²² demonstrated that mice have improved bacterial clearance with decreased mortality when macrophages do not express PD-1, highlighting the importance of immunosuppressive signaling in sepsis that macrophage function is altered without it. Similarly, the adenosine A2A and A2B receptors found on macrophages also regulate the immune response in macrophages but not neutrophils. Antagonizing the macrophage A2B receptor in the CLP model augments phagocytic activity with improved bacterial killing, reduces systemic inflammation with an attenuation of the pro-inflammatory cytokine response and improves survival.²³

Lymphocytic Cell Dysfunction

An increasingly important aspect in sepsis is the interaction between the innate and adaptive immune response systems. Macrophages or antigen-presenting cells communicate with T cells by means of the afferent signal, the HLA-2-antigen-T-cell receptor interaction. This interaction results in a CD4 T-cell activation with a variety of efferent responses. The responses affecting the innate immune response include: (1) IFN- γ release to activate phagocytes to kill intracellular bacteria, (2) upregulation of CD40L that binds to CD40 receptor on antigen-presenting cells resulting in a

sustained expression of costimulatory molecules with further promotion of the crosstalk between the innate and adaptive immune response systems²⁴ and (3) natural killer cell activation. The efferent responses affecting the adaptive immune response include IL-1 secretion resulting in CD4 and CD8 cell recruitment, as well as IL-4 release responsible for recruiting immunoglobulin-producing B cells.

The lymphocyte cell population declines in the septic state. A significant discovery was made detailing that this decline is due to lymphocyte apoptosis. Hotchkiss^{25,26} work has elucidated the importance of the reduction of the lymphocyte population, specifically CD4 T cells and B cells. His work has demonstrated in both animal models of sepsis, as well as the human septic population, that lymphocytes in all lymphoid organs including the spleen, thymus and bone marrow undergo apoptosis early in the acute phase of sepsis. As sepsis resolves, the progression of lymphocyte decline abates with subsequently less apoptosis.

Lymphocyte apoptosis is a potential reason that septic patients may develop an impaired immune response and thus become more vulnerable to developing nosocomial infections.²⁷ Although there are relatively few changes in circulating lymphocyte inhibitory receptors at the beginning of a septic insult, lymphocytes undergo significant upregulation of the inhibitory receptors including CTLA-4, TIM-3 and LAG-3, as well as downregulation of the IL-7 receptor. Ultimately, Boomer *et al*²⁸ concluded that these changes in receptor expression lead to 'immune cell exhaustion' in the acute phase of sepsis, potentially resulting in immunosuppression and increased risk of hospital acquired infections.

Interestingly, adoptive transfer of apoptotic splenocytes worsens survival compared with transfer of necrotic splenic cells following CLP in the murine polymicrobial sepsis model. The rationale for this finding is that apoptotic cells induce anergy that impairs the host response. Meanwhile, transfer of necrotic cells stimulates inflammatory cells. Prevention of apoptosis in lymphocytes by inhibiting caspases, the major enzymes involved in both the mitochondrial-mediated and death receptor pathways to reach apoptosis,²⁹ has been shown to improve survival in animal models of sepsis.^{30–32} This raises the possibility that caspase blockade may be a potential therapeutic target in managing the immunosuppressed state during sepsis.

IL-7, a cytokine critical for T-cell development, represents another potential immunotherapeutic agent.³³ A recent review by Hotchkiss *et al*³⁴ highlights the many functions of IL-7, including stimulating the proliferation of naive and memory T cells, improving the capability of T cells to become activated, increasing T-cell receptor diversity and expression of cell-adhesion molecules, decreasing lymphocyte apoptosis, restoring the delayed type hypersensitivity response and improving survival in murine polymicrobial sepsis.³⁵ IL-7 has also proven effective in human trials. In a trial of HIV-1

infected patients with persistently low CD4 T cells despite a viral load <50 copies/ml, administration of recombinant human IL-7 resulted in a two- to threefold increase in circulating CD4 and CD8 T cells.³⁶ Currently, clinical trials using IL-7 in patients with HIV-1, progressive multifocal leukoencephalopathy and cancer are in progress and this immunomodulatory therapy may represent an intervention to target sepsis-induced lymphopenia.³⁴

Endothelial Cell Dysfunction

Endothelial cells have an integral role in the vascular response of acute inflammation. This response is characterized by smooth muscle cell changes that result in vasodilation as well as endothelial cell contraction, which allows for leakage of proteins into the extravascular spaces and tissues, and an increased expression of adhesion molecules such as selectins that promote migration of leukocytes from the microcirculation into infected sites. These endothelial cell changes also lead to endothelial cell disruption, which disturbs their anticoagulant properties.³⁷

There is evidence of endothelial cells undergoing apoptosis when exposed to radiation, chemotherapeutic events or Fas activation via the extrinsic or death receptor-initiated pathway.³⁸ Studies involving inflammatory *in vitro* models such as *Haemophilus somnus* and LPS have been shown to be associated with endothelial cell apoptosis.^{39,40} However, demonstrating similar results in *in vivo* models of sepsis have been more challenging. For example, there was no evidence to suggest that endothelial cells undergo apoptosis in the rat thoracic aorta following CLP.³⁸ More work is required to further delineate this process.

SOLUBLE INFLAMMATORY MEDIATORS

The systemic inflammatory response can be initiated by a sterile or infectious challenge. Pattern recognition receptors of the innate immune system respond to microbial PAMPs, as well as endogenous damage-associated molecular patterns (DAMPs), which are released by cellular injury as a result of trauma, ischemia, malignancy, inflammatory diseases or other instances of cellular stress.^{41,42} The signaling pathways shared between PAMPs and DAMPs, including the TLR family and specifically TLR4, can result in a similar innate immune response in the presence or absence of an infectious process.^{43,44}

In the case of an infectious challenge, there are several theories regarding the nature of the immune response to a pathogen. Previous investigators hypothesized that early deaths due to sepsis were the result of an overwhelming inflammatory response and not due to the infection. Conversely, late deaths were due to a compensatory anti-inflammatory response (CARS) in which the immune system shut down such that overwhelming infection was the cause of death. Three separate pieces of information supported this idea. Patients with fulminant meningococcal septicemia had

high plasma levels of the pro-inflammatory cytokine TNF. Rapid production of TNF occurred after injection of endotoxin in experimental animals or human volunteers, and studies in experimental animal showed that blocking TNF improved survival in endotoxin experiments.^{45–48} It was believed that the early pro-inflammatory phase of the immune response was distinct from the later anti-inflammatory phase and that they occurred sequentially. However, research performed more recently has shown that in the initial response to a septic challenge both inflammatory and anti-inflammatory mediators are present from the onset of the immune response.⁴⁹ Additional research utilized steroids to suppress the immune response and confirmed the idea that the SIRS and CARS responses are not independent of each other.⁵⁰

Biomarkers assumed a prominent role in the study of sepsis research in an effort to identify which protein, cytokine, factor or combination of biomarkers will predict the outcome of a hospitalized patient with sepsis. The major difficulty is that most of these markers lack specificity and may be elevated in non-infectious inflammatory situations. Moreover, although cytokine expression and kinetics are clear in research utilizing animal models of sepsis, it has been more difficult to obtain a similar profile in septic human patients.

C-reactive protein (CRP) is an example of a marker that has been used for many years as an indicator of inflammation, but this protein is nonspecific. Elevated CRP levels at the time of ICU admission correlated with an increased risk of organ failure and death. In addition, failure of CRP to return to normal limits is associated with worse outcomes.⁵¹ However, the use of CRP has been contested and more specific biomarkers have been sought. Cytokines have been examined in order to ascertain their value as prognostic factors. Initial studies focused on a myriad of pro-inflammatory markers such as TNF- α and IL-6, whereas other groups have investigated anti-inflammatory cytokines.^{52,53} In addition, new markers are being explored such as pro-calcitonin (PCT). One study suggests that PCT be used as a way to rule out sepsis given its higher negative predictive value in patients in whom bacterial cultures were drawn, whereas another found that antibiotic days could be shortened by trending PCT levels.^{54,55}

As no single 'magic' biomarker has been identified, researchers have sought to devise panels of biomarkers to better diagnose sepsis and predict outcome. Shapiro *et al*⁵⁶ found that neutrophil gelatinase-associated lipocalin, protein C, and IL-1 receptor antagonist were among the best predictors. Other studies have shown that while some cytokines are good at predicting early deaths, they may not accurately predict the development of organ dysfunction.⁵⁷ Challenges to identifying diagnostic and prognostic makers include the timeliness in which a patient presents with sepsis, the varied degree of the septic insult and the heterogeneity of the host inflammatory response.

DISORDERED COAGULATION IN SEPSIS

The inflammatory state found in septic animals and patients leads to numerous alterations in the coagulation system, shifting the normal hemostatic balance toward a procoagulant state. Virchow's triad of endothelial injury, hypercoagulability and abnormal blood flow can all occur in the septic patient, creating a predisposition to thrombus formation. The coagulation abnormalities observed in the septic patient range from slightly prolonged bleeding times and mildly decreased platelet counts to fulminant disseminated intravascular coagulation (DIC). The development of DIC in the septic patient has been shown to be an independent predictor of mortality and multiple studies have shown the severity of DIC to be directly related to increased mortality.^{58–60}

The relationship between inflammation and disordered coagulation occurs via several interrelated mechanisms, mainly the release of pro-inflammatory cytokines (IL-1, IL-6, IL-12 and TNF- α) that induce expression of tissue factor (TF), decreased levels of antithrombin, inhibition of the normal anti-coagulant protein C system and impaired fibrinolysis.⁶¹ These changes lead to systemic formation of intravascular microthrombi and resultant tissue hypoxia, infarction and multisystem organ failure. This cascade of events consumes coagulation factors and platelets and triggers the activation of fibrinolytic pathways, which can result in paradoxical hemostatic failure.

Tissue Factor

Cell membrane-bound TF, a protein found at the blood–tissue barriers of the vascular adventitia, organ capsules, mucosa and skin epithelium, becomes exposed to blood with the disruption of vascular integrity, allowing it to interact with factor VIIa. This interaction activates the extrinsic coagulation pathway leading to generation of thrombin and subsequent fibrin formation.⁶² Early immunohistochemical analysis of TF led to the belief that it comprised an extravascular hemostatic barrier, however, TF expression is induced in CD 14+ monocytes and endothelial cells in the presence of inflammatory mediators.^{63–65} When activated, these monocytes express TF and shed TF-rich microparticles, leading to platelet aggregation and formation of the fibrin plug.^{64,66} In addition to the activation of the TF-mediated extrinsic coagulation pathway, bacterial surfaces of both Gram-negative and Gram-positive bacteria are capable of binding contact factors and activating the intrinsic coagulation pathway via factor XII,⁶⁷ which has been observed in children with meningococemia and septic shock.⁶⁸

TF-induced coagulation can be inhibited by TF pathway inhibitor (TFPI) expressed mainly by vascular endothelial cells, as well as a lipoprotein bound in plasma. TFPI both binds and directly inhibits FXa and decreases TF activity by complexing with TF-VIIa-FXa. Unsuccessful attempts have been made at blocking TF activity to target inflammation-induced coagulopathy. The most recent trial investigated the efficacy of tifacogin (recombinant TFPI) in two phase III,

double-blind, placebo-controlled trials: the OPTIMIST trial of 1754 patients where no effect was seen on all-cause mortality in patients with severe sepsis and a low risk of death⁶⁹ and the CAPTIVATE trial of 2138 patients with severe community acquired pneumonia in which recombinant TFPI also demonstrated no survival benefit, despite evidence of biologic activity in both studies by decreased levels of F1.2 (prothrombin fragment) and TAT (thrombin-antithrombin complex).⁷⁰

Antithrombin

The main inhibitor of both thrombin and factor Xa, antithrombin, is markedly decreased in inflammatory states such as sepsis. Several factors contribute to this decrease: reduced hepatic synthesis of this negative acute phase protein, consumption of antithrombin by the formation of thrombin–antithrombin complexes and degradation by elastase released from activated neutrophils.⁷¹

Protein C System

Protein C deserves special mention as it was the only FDA-approved drug for the treatment of severe sepsis, although the manufacturer has subsequently withdrawn the drug from the market. Protein C serves as a check to the clotting cascade, as activated protein C (APC) functions as an anticoagulant and profibrinolytic. Upon binding with endothelial cell protein C receptor and associating with thrombin bound to thrombomodulin, protein C becomes activated, dissociates, binds its cofactor protein S and causes proteolytic cleavage of factors Va and VIIIa.⁷² APC also promotes fibrinolysis through blocking plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI).⁷³ In the septic patient, pro-inflammatory cytokines downregulate thrombomodulin at the endothelial surface and there is both consumption and impaired synthesis of protein C, which results in a decline in APC and a shift toward a procoagulant state.⁷⁴

The 2001 PROWESS trial evaluating Xigris (drotrecogin alpha (activated), recombinant human APC) in the treatment of high-risk patients with severe sepsis showed an improvement in 28 day all-cause mortality.⁷⁵ The follow-up double-blind, placebo-controlled, multicenter, ADDRESS trial evaluating the efficacy and safety of Xigris in adult patients with severe sepsis and a low risk of death (defined as APACHE II scores of less than 25 or single-organ failure) failed to show a survival benefit, and the incidence of serious bleeding complications was similar to that seen in the PROWESS trial.⁷⁶ However, it was the subsequent PROWESS-SHOCK study, in which no improved survival was observed in patients with septic shock, which led to the voluntary withdrawal of Xigris from the market in 2011.⁷⁷

In addition, APC has various anti-inflammatory effects including decreased activation of the NF- κ B pathway, decreased leukocyte adhesion and activation, counter-acting thrombin-induced compromised endothelial barrier

function, decreased endothelial cell apoptosis and neutralization of cytotoxic extracellular histones.⁷⁸

Another therapeutic target in this system is thrombomodulin, an inhibitor of thrombin and a cofactor in APC generation, which also has both APC-dependent and APC-independent anti-inflammatory effects.⁷² Recombodulin (ART-123; Asahi Kasei, Japan) a recombinant human soluble thrombomodulin- α was found to be superior to low-dose unfractionated heparin in resolving DIC symptoms in one multicenter, randomized, double-blind phase III clinical trial in patients with DIC associated with hematologic malignancy or infection.⁷⁹

Inhibition of Fibrinolysis

The generation of plasmin from plasminogen via conversion by tissue-type plasminogen activator and urokinase-like plasminogen activator leads to fibrin degradation. In septic patients, the generation of fibrin stimulates an early increase in the expression of plasminogen activators.⁷³ However, despite increased levels of plasminogen activator antigen, fibrinolytic activity is rapidly inhibited by both TNF- α and endotoxin-stimulated production of the acute phase protein, PAI-1.⁸⁰ In addition, the thrombin-TM complex activates TAFI, which also functions to inhibit fibrinolysis.⁸¹

The disordered coagulation, alterations in cell function and immune regulation that occur on the cellular level can lead to clinically observable derangements for which early goal-directed therapy (EGDT), glycemic control and administration of steroids have been utilized in the treatment of the septic patient.

CLINICAL MANAGEMENT OF SEPSIS

Early Goal-Directed Therapy

Although antibiotics and source control have proven beneficial for treating sepsis, virtually all attempts using targeted therapies for sepsis have failed and treatment remains mainly supportive in nature. The list of recent and current treatments for sepsis was recently reviewed.⁸² Rivers *et al*⁸³ examined the use of EGDT, a protocol calling for the early identification of septic patients and initiation of a treatment algorithm with end points for resuscitation, which improved mortality in patients with severe sepsis and septic shock. Since its publication in 2001, EGDT has been influential in the development of a treatment paradigm for sepsis and its end points have been externally validated in subsequent studies.^{84–86}

EGDT is a central feature in the Surviving Sepsis Campaign (SSC), which provides current clinical practice guidelines for the management of severe sepsis and septic shock (Table 2).⁸⁷

The implementation of SSC guideline-based sepsis bundles have been evaluated in the performance improvement program phase of the SSC, which has provided evidence that increased compliance with sepsis performance measures defined in the bundle results in a reduction of hospital mortality.⁸⁸

Table 2 2012 Surviving sepsis campaign recommendations

Obtain appropriate cultures and source control
Implementation of broad-spectrum antibiotics within the first hour of recognition
Goals during first 6 h of fluid resuscitation:
Central venous pressure of 8–12 mm Hg
Mean arterial pressure $\geq$ 65 mm Hg
Urine output $\geq$ 0.5 ml/kg/h
Norepinephrine as initial vasopressor of choice
Intravenous insulin to control hyperglycemia with a target blood glucose $\leq$ 180 mg/dl
DVT prophylaxis
Ventilation strategies to reduce sepsis-induced ALI/ARDS

Abbreviations: ALI/ARDS, acute lung injury/acute respiratory distress syndrome; DVT, deep vein thrombosis.

However, it remains unclear as to whether this decrease in sepsis mortality can be attributed to some or all of the elements included in the SSC recommendations, improved identification of patients at risk for sepsis or unrelated factors.

Glycemic Control

Hyperglycemia and insulin resistance are metabolic derangements observed in sepsis, a result of multiple factors including the overwhelming activation of both pro-inflammatory and anti-inflammatory responses. In the critically ill patient, hyperglycemia is both a marker of illness severity, but also a predictor of increased morbidity and mortality.⁸⁹ Targeting hyperglycemia is a sensible approach, as elevated blood glucose has been shown to impair host defenses to infection, including the decreased function of polymorphonuclear neutrophils, as evidenced by reduced chemotaxis, phagocytosis of bacteria and formation of reactive oxygen species.⁹⁰

With the advent of Van den Berghe's research in 2001, intensive insulin therapy (blood glucose range of 80–110 mg/dl) became a popular therapeutic target in the intensive care setting. However, a meta-analysis of 22 randomized controlled trials comparing intensive vs conventional insulin therapy found that intensive glucose control did not reduce mortality,⁹¹ and the largest of the trials, NICE-SUGAR, demonstrated an increased mortality in the intensive insulin group.⁹² Furthermore, intensive insulin therapy significantly increases risk of hypoglycemic events, which are independently linked to increased ICU or hospital mortality.^{93,94}

In addition to the deleterious effects of both hyperglycemia and hypoglycemia, variability in blood glucose levels may also be associated with increased mortality in septic patients.^{95,96} Evidence of the effects of glucose variability have been shown in previous *in vitro* studies, which

demonstrate that endothelial damage and apoptosis is more enhanced by fluctuations of blood glucose than constant exposure to high glucose levels.⁹⁷ The current recommendations by the American Association of Clinical Endocrinologists and the American Diabetes Association are to target a blood glucose range of 140–180 mg/dl in critically ill patients.⁹⁸ An upper blood glucose level of ≤ 180 mg/dl is also outlined in the most recent SSC 2012 guidelines.⁸⁷

Steroids

Adrenal insufficiency of critical illness may occur in the septic patient, manifesting as hemodynamic instability and ventilator dependency. A total serum cortisol level < 10 mcg/dl in the setting of hemodynamic instability, or an increase in cortisol of < 9 mcg/dl after administration of cosyntropin provides evidence of adrenal insufficiency.⁹⁹ The use of corticosteroids as an adjunct therapy in septic shock has been controversial. Early small, randomized control trials demonstrated the benefit of low-dose steroids in the treatment of sepsis.^{100,101} In contrast, the randomized, double-blind, placebo-controlled CORTICUS trial showed no significant difference in 28-day mortality among patients treated with low-dose corticosteroids vs placebo.¹⁰² A meta-analysis of 12 studies by Annane *et al*¹⁰³ examining the effect of corticosteroids on 28-day all-cause mortality in patients with severe sepsis and septic shock demonstrated no clear benefit, however, in the subgroup of patients receiving prolonged low-dose steroids, a reduction in mortality was observed. A similar meta-analysis by Sligl *et al*¹⁰⁴ of eight studies found no statistically significant reduction in 28-day mortality. Conflicting results as to the benefit of steroids in sepsis led to the SSC's level 2C recommendation to consider exogenous steroids in patients with septic shock that are unresponsive to both fluids and vasopressors.¹⁰⁵

More recently, an analysis of the SSC's database of 17 847 patients requiring vasopressor therapy despite fluid resuscitation, showed that the administration of low-dose steroids was associated with an increase in adjusted hospital mortality.¹⁰⁶

Conclusions

Although the gold standard of management of sepsis is based on source control, antibiotics and EGDT with end-organ support in a timely manner, it is imperative that active research continues toward elucidating the mechanisms that comprise the syndrome of sepsis. This review highlights some of the immunopathologic and coagulopathic alterations that occur in the septic patient. It is clear that cell function, inflammatory mediators and the associated crosstalk with the coagulation system is altered in sepsis and that significant heterogeneity exists in the host response to a septic challenge. Further elucidating the mechanisms at the cellular level could bring us closer to improving morbidity and mortality at the clinical level, especially in the setting of increasing incidence.

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