

SEEDS

Managing Cytokine Storm

Issue 18



INDIAN
SEPSIS FORUM

CYTOKINES LIE AT THE HEART OF ALL INFLAMMATORY RESPONSES



PRESENTING, AN INHIBITOR OF
INFLAMMATORY CYTOKINES¹

A Potent Serine Protease Inhibitor

In Patients with Sepsis & Acute Pancreatitis

U-Tryp
Ulinastatin
U-Turn Towards Life



1. Shao YM, Zhang LQ, Deng LH, Yao HG, Zhongguo Wei Zhong Bing Jiu Yi Xue. 2005 Apr;17(4):228-30.

U-Tryp - Abbreviated Prescribing Information

DESCRIPTION: Ulinastatin is a serine protease inhibitor that reduces the pro-inflammatory response as a result of sepsis, acute pancreatitis, trauma or surgery. Ulinastatin for injection is available in clear colourless liquid. **COMPOSITION:** Each vial contains Ulinastatin J.P., 1,00,000 I.U. Excipients: m-cresol B.P., Sucrose I.P., Disodium hydrogen phosphate dihydrate B.P. Tween 80 I.P., Phosphoric acid I.P. **DOSAGE FORM:** Liquid Injection. **CLINICAL INDICATIONS:** 1. Severe sepsis. 2. Septic, endotoxic or traumatic shock. Sepsis is defined as a systemic inflammatory response syndrome (SIRS) in the presence of, or as a result of, suspected or proven infection 1-3. Severe sepsis is defined as sepsis with one of the following features: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or dysfunction of two or more organs. Indian incidence is estimated to be about 750,000 cases per year. The most common causes for sepsis are trauma, burns, abdominal aortic aneurysm and septic shock. Sepsis shock is the most common cause of mortality in patients with sepsis. Despite its association with high mortality, sepsis is often preventable. It is important to identify sepsis early in patients and to treat it aggressively. Early resuscitation from sepsis to septic shock to Multiple Organ Dysfunction Syndrome (MODS). Common sepsis risk-modifying factors are diabetes mellitus, concurrent antineoplastic drugs and corticosteroids and immunocompromised status. The best two prognostic factors are APACHE II score and number of organ dysfunction. In a study of 10,000 patients, predicted mortality risk of 15%, scores of 15-19 indicate risk of 25% and scores of 20-24 indicate 40% mortality risk; scores of 25 and above indicate very high risk of mortality of > 55%. In a large Indian hospital based study of 5,476 ICU admissions, SIRS with organ dysfunction was present in 25%, sepsis in 52.77%, severe sepsis in 16.45% with median APACHE II score = 13 (IQR 13 to 14). The overall mortality in ICU patients was 12.08% but in patients with sepsis it was 59.26%. **DOSAGE AND ADMINISTRATION:** Administer 1 to 2 vials of 100,000 I.U. of Ulinastatin (Reconstituted in 100 ml of Dextrose 5% or 100 ml of 0.9% Normal Saline) by intravenous infusion over 1 hour each time, 1-3 times per day for 3 to 5 days. The dosage may be adjusted according to the age of patients and the severity of symptoms. **USE IN SPECIAL POPULATION:** The safety for pregnant woman is NOT determined yet. Whether or not Ulinastatin should be administered for pregnant woman or potentially pregnant woman is decided according to the patient's condition. 1. Ulinastatin is not used for nursing women in principle. If used, breast feeding should be stopped. 2. The safe dosage for children is NOT determined yet. **CONTRAINDICATIONS:** Hypersensitivity to the drug. **WARNINGS:** 1. Not to be used in patients who are hypersensitive. 2. Not to be used in lactating women. **PRECAUTIONS:** 3. Ulinastatin should be administered with caution if the patient has the history of allergy. 3. Ulinastatin can NOT replace the traditional therapeutic methods (transfusion, oxygen therapy and antibiotics) for shocks. **DRUG INTERACTION:** No drug interactions have been reported or tested. **ADVERSE EFFECTS:** 1. Common adverse reactions include rash, itchiness and pruritis at the site of injection. 2. Rare cases of allergic reaction. 3. Rare cases of elevation of Serum Creatinine. 4. Rare cases of increased, prolonged and clumped fibrinogen. **OVERDOSE:** No specific antidote is recommended. In case of accidental overdose, discontinue the drug and support under medical supervision. **STORAGE:** Store the drug in a dry place, protected from light and moisture. **EXPIRY:** 6 months. It has anti-thrombotic effect similar to steroid hormones. It inhibits coagulation and fibrinolysis and promotes platelet aggregation. Thus, Ulinastatin is an effective agent for immune modulation to prevent organ dysfunction and promote homeostasis. **CLINICAL STUDIES:** 1. A prospective, multicentre, double-blind, randomized, phase III clinical study was conducted to compare the efficacy and safety of intravenous Ulinastatin versus placebo along with standard supportive care in subjects of severe sepsis. Of the 122 randomized subjects, 114 completed the study (55 subjects in the Ulinastatin group and 59 subjects in the control group). The 28 day all-cause mortality was 4 subjects in the Ulinastatin group vs 12 in the placebo group ($p=0.0448$). This difference was statistically significant, 10 subjects in the Ulinastatin group and 20 subjects in the Placebo group had new organ dysfunction ($p=0.0569$). Though there was a trend towards less incidence of new organ failure in the Ulinastatin group, this was just short of statistical significance. Mean hospital stay in the Ulinastatin group was 13.59±6.83 days vs. 26.21±5.36 days in the Placebo group. This difference was statistically significant ($p=0.001$). Number of ventilator free days up to day 28 end-of-study were 19.44±10.61 days in the Ulinastatin group and 10.18±12.54 days in the Placebo group. This difference was found to be statistically significant ($p=0.019$). There were no infusional related toxicities in the study. Thus, treatment with Ulinastatin effectively reduced mortality in patients with severe sepsis when used as an adjunctive therapy in addition to standard therapy and ICU care. The reduction in mortality was accompanied by a shorter stay in the hospital and a shorter duration of ventilator and vasopressor usage with no side effects seen in the study population. 2. A prospective, multicenter, double-blind, randomized, phase III clinical study was conducted to compare the efficacy and safety of intravenous Ulinastatin versus placebo along with standard supportive care in subjects of severe pancreatitis. Of the 120 randomized subjects, 112 completed the study (56 subjects in the Ulinastatin group and 67 subjects in the control group). The 22-day all-cause mortality was significantly reduced from 18.8% in the placebo group to 34% in the Ulinastatin group. This was statistically significant. Hospital stay was shorter in the Ulinastatin group. The reduction of Serum CRP was comparable in the two treatment groups. There was only one incidence of infusion-related toxicity (transient rash). The number of adverse events, all of a non-serious nature, were less in the study group vs control group (in mild patients 24 vs 34 and in severe patients 23 vs 45). Thus, treatment with Ulinastatin effectively reduced mortality and morbidity in patients with severe pancreatitis when used as an adjunctive therapy in addition to standard therapy. The reduction in mortality was accompanied by a shorter stay in the hospital and less complications. **PHARMACOKINETICS:** After intravenous injection of 300,000 I.U./10ml into healthy man, its concentration in blood decreases linearly.³ The half-life of Ulinastatin is about 40 minutes.³ 6 hours after the administration, 24% of Ulinastatin is discharged in urine. **INCOMPATIBILITIES:** None Reported. **SHELF LIFE:** Two years from date of manufacturing. **PACKING INFORMATION:** Pack containing 1 vial of 1,00,000 I.U. of Ulinastatin. **STORAGE AND HANDLING INSTRUCTIONS:** Storage temperature 2°C to 8°C. Protect from light. Any unused portion should be discarded.



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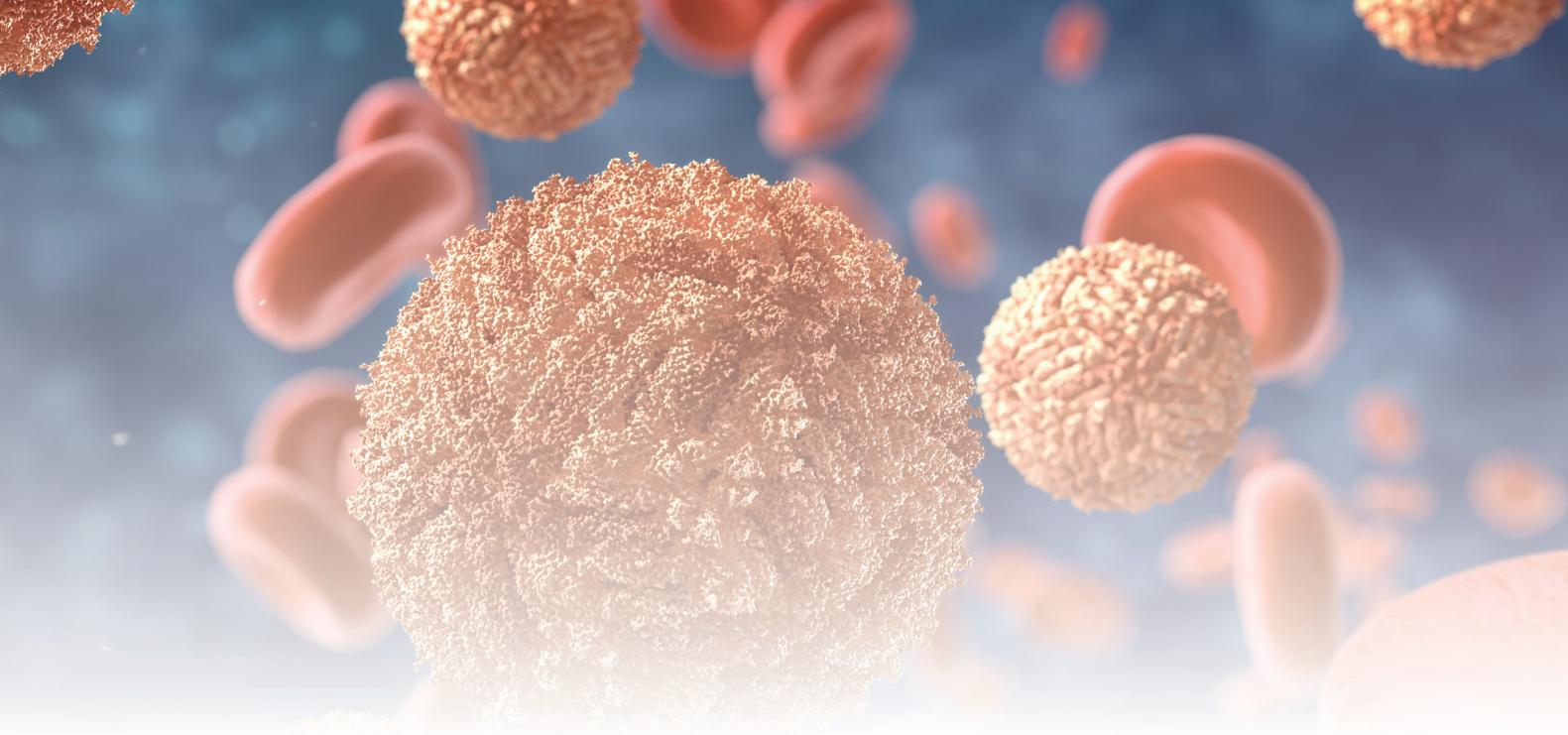
PREFACE

Sepsis is a life-threatening condition arising due to an immune response against invading pathogens. It has significant effects on inflammatory cells, immune response, and vascular endothelium which try to limit the spread or eliminate the infecting pathogen. Despite continuous preventive and therapeutic efforts aimed to curb the sepsis related mortality, it has remained one of the most common causes of death in critically ill patients. Projections in the past have estimated that each day thousands of people die from sepsis worldwide. A possible reason for this negative proposition is that multiple factors, related to the host, pathogen and the disease process, might converge in sepsis patients to increase the morbidity and mortality risk. These factors often render monitoring, evaluation, and therapy of patients extremely difficult for the clinician, thereby decreasing the survival rate. Although suitable early intervention has been reported to augment outcome, its identification and pressing management remain a challenge to healthcare professionals. The multiplicity and scope of sepsis demand attention by all.

The cytokines are significant pleiotropic regulators of the immune response, playing a pivotal role in the multifaceted pathophysiology underlying sepsis. Cytokines regulate both inflammatory and anti-inflammatory pathways, and are competent enough to coordinate efficient defense mechanisms against invading pathogens. The recent few years have seen a spate of information on the role of cytokines in human infectious diseases, leading to a profound understanding of the pathogenesis of infectious diseases and an approval for distinction of cytokine production profiles in response to various pathogens. Worth mentioning is the fact that ulinastatin, an acidic glycoprotein, is a leading therapeutic agent that effectively augments the outcomes in multiple cases involving injury and inflammation. The ensuing articles further address the current knowledge of the actions of pro- and anti-inflammatory cytokines, prolactin, adrenocorticotropic hormone and corticosteroids sepsis along with the possible ways to target them therapeutically to augment the clinical outcome of sepsis.

Thanks and regards

SEEDS Journal Team



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Proinflammatory versus anti-inflammatory response in sepsis: An update



An overview

Sepsis and sepsis-associated multi-organ failure impose considerable burden on the health-care system and considered as a major challenge for the clinicians.¹ Sepsis is regarded as a life-threatening organ dysfunction caused by a dysregulated host response to infection.² Sepsis comprises a whole-body or a systemic inflammatory response syndrome (SIRS), in the presence of a known or suspected infection that result in organ dysfunction causing low blood pressure, or insufficient blood flow to one or more organs due to lactic acidosis along with reduced urine production and altered mental status. Severe sepsis is described as sepsis which is associated with specific or multiple organ dysfunctions. It can also lead to septic shock, a condition of severe sepsis, in the presence of systemic hypotension associated with tissue hypoperfusion and anaerobic metabolism. Among sepsis patients, septic shock and multi-organ dysfunction are the most frequent causes of death.³ Sepsis accounts for considerable yearly mortality across the globe, and is a prime cause of death in intensive care units (ICUs); the mortality rates are 20% for sepsis, 40% for severe sepsis and more than 60% for septic shock. Sepsis accounts for one or more severe complications such as hypotension, cardiac failure, coma, renal failure, and intravascular coagulation, frequently leading to death. The highest rate of mortality observed in sepsis is seen among the infants, the elderly, and those who are immunocompromised. It is the second-leading cause of death in non-coronary ICUs, even in the industrialized countries. Of note, septic shock and multi-organ dysfunction are the most frequent causes of death in patients with sepsis.^{3,4}

The commencement of sepsis syndrome is often linked to a complex interplay of an array of mediators comprising lipid, proteins and possibly carbohydrate. A large body of growing

evidence is of view of the prime role of protein belonging to cytokines family playing the role of major decisive factors in determining the pathophysiology of the sepsis syndrome.⁵ Cytokines are important pleiotropic regulators of the immune response and implicated in dysregulating the immune response by promoting tissue-damaging inflammation. In sepsis, early septic deaths are originally presumed to be due to an unrestrained, overzealous spike in a host's sudden pro- and hyper- inflammatory immune response.^{6,7} Some researchers emphasize the significance of a compensatory anti-inflammatory response syndrome (CARS), that usually pursues the hyper-inflammatory phase, particularly in patients who develop severe sepsis.⁸ Thus, highlighting both pro- and anti-inflammatory cytokine mediated functions in coordinating effective defense mechanisms against invading pathogens (Table 1).⁵

Sepsis pathophysiology: The state of pro- and anti-inflammatory disequilibrium syndrome

The pathophysiologic mechanisms that underlie the heterogeneous sepsis syndrome commence when the initial host response to an infection becomes amplified and subsequently dysregulated. This results in an imbalance between proinflammatory and anti-inflammatory responses. The innate immune system, the "first line of cellular defense", responds immediately to invading pathogens causing release of cytokines, chemokines, and other inflammatory regulators.⁹

Cytokines regulate a variety of inflammatory responses, including the migration of immune cells to the locus of infection. The increased activation of the inflammatory response is evidenced from the increased levels of circulating proinflammatory cytokines in the blood, increased endothelial activation with increased expression of inducible nitric oxide synthase, and increased de novo CD11b expression on circulating immune effector cells, such as PMNs, monocytes and lymphocytes. However, a dysregulated cytokine release may lead to endothelial dysfunction, characterized by vasodilation and increased capillary permeability. The dysfunctional epithelial barriers enable pathogens and their products to further invade the host organism, disturb regulatory mechanisms, and ultimately, causing remote organ dysfunctions. This unregulated and hyper inflammatory flare further

disrupts other physiological mechanisms within the human host, such as coagulation, metabolism, and neuroendocrine activation. However, coexisting with this proinflammatory process is a profound anti-inflammatory state characterized by increased circulating levels of anti-inflammatory species that both directly block the binding of proinflammatory stimuli to their cell surface receptors (IL-1ra, soluble TNF receptors) and also induce an anti-inflammatory state (IL-10, TGF-beta). This humoral anti-inflammatory state further works at the cellular levels by decreased monocyte ability to process antigen, characterized by a reduced HLA-DR expression and impaired PMN upregulation in response to clearly proinflammatory stimuli. Thus, reflecting a combined pro- and anti-inflammatory state in severe sepsis (Figure 1).^{6,9}

Cytokines in Sepsis: Summary of the pro- and anti-inflammatory cytokines

Role of cytokines in sepsis

Cytokines are a group of small signalling proteins produced by a large variety of cells that are thought to be important for host defense, wound healing and other essential host functions. Although cytokines are important for these homeostatic functions, excessive production and release of cytokines initiate widespread tissue injury which can result in organ dysfunction by initiation and perpetuation of sepsis syndrome. In sepsis, the overwhelming systemic inflammation is the outcome of the excessive release of cytokines into the systemic circulation.⁵

Researchers have established the integral role of the cytokines in the pathobiology of sepsis syndrome. Four cytokines, tumor necrosis factor alpha (TNF alpha), interleukin 1 beta (IL-1), interleukin 6 (IL-6) and interleukin 8 (IL-8) have a strong association in sepsis syndrome. During sepsis, cytokines are released in a sequential manner resulting in a "cytokine cascade". The cytokine cascade is initiated when a stimulus such as Gram-negative bacterial endotoxin induces production and secretion of early or "proximal" cytokines, which include TNF-alpha and IL-1 beta mediating physiological disturbances which are characteristic of sepsis. These along with endotoxin, stimulate the production of later or "distal" cytokines, such as IL-6 and IL-8. Thus, proinflammatory cytokines (tumor necrosis factor [TNF]-a, interleukin [IL]-1a and

TABLE 1

Actions of various pro- and anti-inflammatory cytokines elaborating their direct association with sepsis pathophysiology

Cytokine	Main sources	Main functions	Interactions with other cytokines
Proinflammatory			
TNF- α	Immune cells of the innate and adaptive immune system (mainly macrophages and lymphocytes); fibroblasts	Differentiation and activation of immune cells; induction of fever and coagulation; cachexia; apoptosis	Promotes the release of downstream proinflammatory effector molecules
IL-1	-	Induction of fever and coagulation; hematopoiesis; promotes the extravasation of inflammatory cells	-
IL-6	-	Activation of B and T lymphocytes; modulation of hematopoiesis and acute phase response; induction of fever	Released in response to TNF- α and IL-1 but inhibits their release; promotes anti-inflammatory responses (sTNFRs, IL-1Ra, and TGF- β)
IL-8	Mononuclear phagocytes, polymorphonuclear leucocytes, endothelial cells, epithelial cells and a variety of mesothelial cell types in response to various stimuli, including endotoxin, IL-1 and TNF	Activate and chemoattract neutrophils to sites of inflammation. In addition, basophils and T-lymphocytes are attracted by nanomolar concentrations of IL-8, and has been implicated as an angiogenic factor	Released in response to various stimuli, including endotoxin, IL-1 and TNF
IL-12	Monocytes/macrophages; Neutrophils; dendritic cells	Promotes type 1 adaptive immune response and differentiation of TH1 T lymphocytes; induces antitumor immune response	Induces IFN- γ production
IFN- γ	NK cells; T _H 1 and CD8 ⁺ cytotoxic T-cells	Antiviral activity; potentially reverses immunoparalysis in sepsis	Released in response to TNF- α , IL-12, and IL-18
MIF	Pituitary cells; monocytes/ macrophages	Activation of macrophages and T-cells; overrides the anti-inflammatory effect of glucocorticoids	Released in response to infection, inflammation, and proinflammatory cytokines; promotes the release of proinflammatory effector molecules
Anti-inflammatory			
IL-10	Immune cells of the innate and adaptive immune system	Immunosuppressive properties, such as the impairment of antigen presentation and phagocytosis	Suppress the release of proinflammatory cytokines; stimulate production of sTNFRs and IL-1Ra
TGF- β	Macrophages; smooth muscle cells	Involved in tissue repair, fibrosis, and sepsis-induced immunosuppression	-
IL-4	T _H 2 T lymphocytes; mast cells; basophils; eosinophils	Promotes differentiation of T _H 2 T lymphocytes	Induces release of IL-4 and IL-13 from macrophages

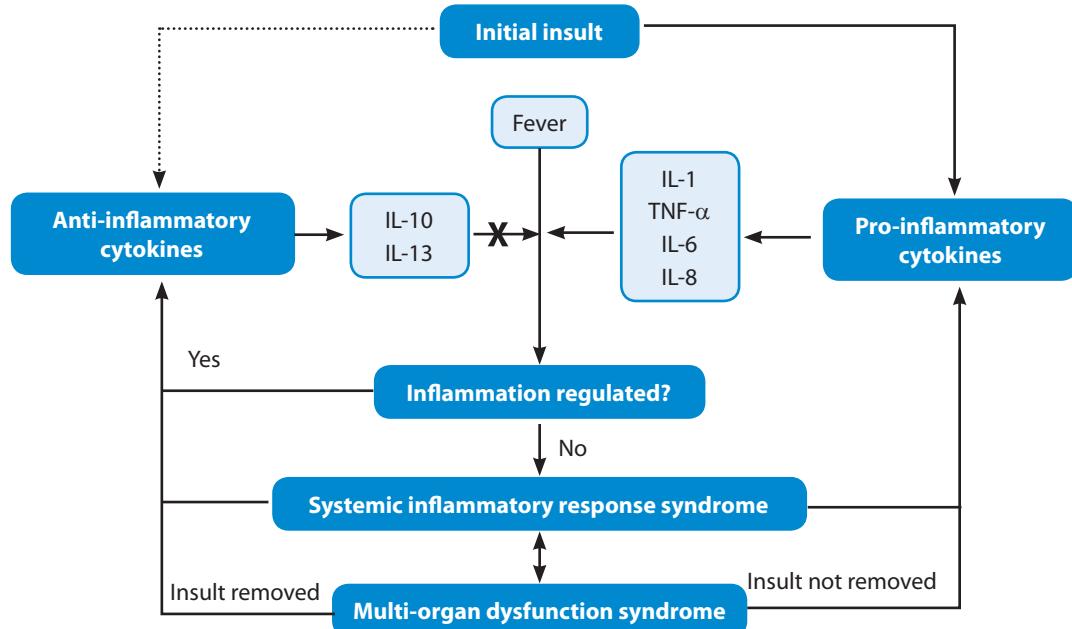
Adapted from: Schulte W, Bernhagen J, Bucala R. Cytokines in sepsis: potent immunoregulators and potential therapeutic targets--an updated view. *Mediators Inflamm.* 2013;2013:165974.

IL-1 β , IL-12, interferon [IFN]- γ , and possibly IL-6, IL-8) are prerequisite for initiating an effective inflammatory process against infection, whereas their excess production has been associated with multiple organ-system dysfunction and mortality.⁵

Cytokines also have synergistic, overlapping and

antagonist effects that control and down-regulate the inflammatory response leading to a depression of the immune system of patients. One counter-inflammatory cytokine, interleukin 10 (IL-10), is released into the circulation in human sepsis and has been shown to block the production of TNF alpha, IL-1 beta and IL-8 in

FIGURE 1 Pro- and anti-inflammatory processes in the pathophysiology of sepsis



Adapted from: Jaffer U, Wade RG, Gourlay T. Cytokines in the systemic inflammatory response syndrome: a review. *HSR Proc Intensive Care Cardiovasc Anesthet*. 2010;2(3):161-175.

vitro. IL-10 plays a crucial role in limiting the systemic inflammatory reaction by regulating pro-inflammatory cytokine gene expression. The clinical manifestations of sepsis syndrome are probably determined by a complex interaction between pro-inflammatory cytokines, counter-inflammatory cytokines and cytokine neutralizing molecules.^{5,10}

Cytokine filtration techniques: A need of the hour

The involvement of humoral mediators such as cytokines, pathogen-associated molecular process and alarmins has been outlined distinctively in the pathophysiology of severe sepsis, time and again. Increase in cytokines is believed to be pathognomonic and methods to reduce the load are supported to be beneficial. Therefore, removal of substances by blood purification is presumed to be useful for reduction of cytokines. Hemofiltration techniques used traditionally have contributed immensely in decreasing the cytokine burden and are now gaining interest in the present era.¹¹ In this context, a study¹² evaluated the

efficacy of different extracorporeal blood purification process for cytokine reduction. A systematic search for human clinical trials involving use of extracorporeal blood purification process for removal of cytokines was performed. A total of 41 articles were included. The cytokine removal according to clearance, sieving coefficient, ultrafiltrate concentration and percentage removal were assessed. The main techniques used for cytokine removal were standard-, high volume-, high cut-off –hemofiltration, adsorption techniques, plasma filtration techniques, ultrafiltration associated with cardiopulmonary bypass, extracorporeal liver support systems and hybrid technique such as combined plasma filtration adsorption. It was noted that standard and ultrafiltration related to cardiopulmonary bypass were less efficient at removing cytokines. However, high cut-off technique, and conceivably plasma filtration and extracorporeal liver support technique showed substantial cytokine removal. It may thus be perceived that despite the availability of blood filtration techniques since decades, its use for removal of cytokines and associated benefits have been founded in true essence only recently.

Conclusion

Sepsis is viewed as a major hurdle and a therapeutic challenge. It is often termed as a complex and dynamic disease process with excessive and suppressed inflammatory and immune responses. Researchers have elucidated many different pathophysiologic processes involved in sepsis and have revealed an important regulatory role of pro- and anti-inflammatory cytokines in sepsis progression. These findings can serve as medium to formulate and develop treatment strategies that can help in improvising sepsis management.

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2

Clinical significance of adrenocorticotrophic hormone and corticosteroids in sepsis and septic shock



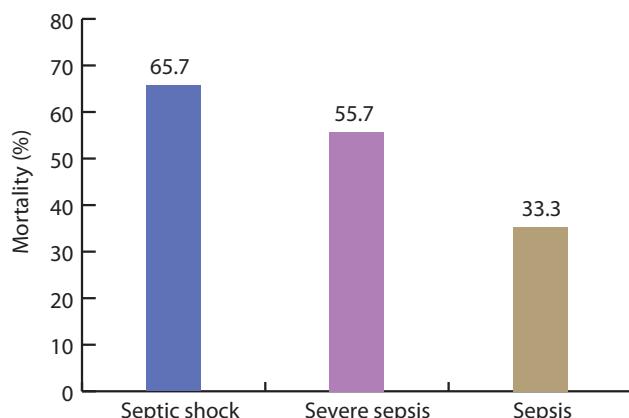
Septic shock in sepsis: A brief review

Sepsis is a systemic manifestation secondary to any infection in the body, with severe sepsis and septic shock being its more severe forms. It is one of the oldest and most evasive syndromes in the field of medicine. In severe form it is defined as the infection induced organ dysfunction or tissue hypoperfusion causing shock. Septic shock is the requirement for vasopressors after the failure of initial fluid resuscitation to correct sepsis induced hypotension (systolic pressure <90 mmHg or mean arterial pressure <70 mmHg).¹⁻⁴ According to the recent guidelines septic shock should be defined as a subset of sepsis in which predominantly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.⁵ The epidemiology of septic shock is difficult to establish, since the approach to its definition and diagnosis is discrepant. In other words, septic shock is not notifiable. In majority of patients with chronic disease sepsis may be the final stage and death occurs as a result of septic shock.⁶ At cellular level in septic shock, oxygen delivery to the cells is not sufficient to sustain cellular activity and support organ function. The primary role of microcirculation is to provide oxygen to the cells and determine organ functions. In septic shock, the alterations in macro- and micro-circulatory functions lead to the generation of organ dysfunctions. It is most frequently characterized by a deficiency of microcirculatory recruitment despite of macro-circulatory successful resuscitation. The lack of hemodynamic coherence between macro- and micro-circulation in septic patients results in treatment failure and increased mortality.⁷

Septic shock is a common cause for admission of patients to intensive care units. The morbidity and mortality always remain unacceptably high despite the advanced treatments.⁸ An observational, prospective ICU-based study⁹ was conducted to assess the predictors of mortality and morbidity of patients

FIGURE 1

Increased mortality among patients in ICU with septic shock than with sepsis and severe sepsis



Adapted from: De Kock I, Van Daele C, Poelaert J. Sepsis and septic shock: pathophysiological and cardiovascular background as basis for therapy. *Acta Clin Belg.* 2010 Sep-Oct;65(5):323-9.

admitted with sepsis, severe sepsis, and septic shock in a medical ICU. The study comprised a total number of 100 patients with equal distribution of males and females. Results reported that the overall mortality was 53%, with a distribution of 69.5% in females, and 38.8% in males. Mortality was reported to be 65.7%, 55.7%, and 33.3% in patients with septic shock, severe sepsis, and sepsis, respectively (Figure 1). Lower immune response, greater associated comorbidities, higher chances of health care-related complications and nutritional deficiencies may be probable explanations for this association.⁹

Since the lower immune response of the patients attempting to fight the infection causes the fatal outcome, instead of the infection itself; it is mandatory to recognize the incidence of severe forms of sepsis in the areas where more attention is given to infectious diseases and to their causes and complications.¹⁰

Clinical features and diagnostic considerations

Septic shock can be clinically identified in patients by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. The organ dysfunction in septic shock can be represented by an increase

TABLE 1 Diagnostic considerations for Septic shock

- Sepsis-induced hypotension
- Serum lactate: normal
- Urine output: <0.5 ml/kg/h for more than 2 h despite adequate fluid resuscitation
- Acute lung injury with $\text{PaO}_2/\text{FiO}_2$: <250 in the absence of pneumonia as infection source
- Acute lung injury with $\text{PaO}_2/\text{FiO}_2$: <200 in the presence of pneumonia as infection source
- Creatinine: >2.0 mg/dL (176.8 $\mu\text{mol}/\text{L}$)
- Bilirubin: >2 mg/dL (34.2 $\mu\text{mol}/\text{L}$)
- Platelet count: <100 000/ μL
- Coagulopathy: >1.5 INR

Adapted from: Schorr CA, Zanotti S, Dellinger RP. Severe sepsis and septic shock: Management and performance improvement. *Virulence.* 2014;5(1):190-199.

in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with in-hospital mortality greater than 10%. According to a new clinical criterion, namely the Delphi process for identification of septic shock, hypotension, need for vasopressor therapy, raised lactate, and adequate fluid resuscitation are the inclusions. Besides, urine output of <0.5 mL/kg/h for more than 2 hours despite adequate fluid resuscitation, acute lung injury with $\text{PaO}_2/\text{FiO}_2$ <250 in the absence of pneumonia as infection source and <200 in the presence of pneumonia, creatinine >2.0 mg/dL, bilirubin >2, platelet count <100 000 μL and coagulopathy of >1.5 international normalized ratio are the other diagnostic features that should be considered for the diagnosis of septic shock (Table 1).^{1,5}

Role of adrenocorticotrophic hormone in septic shock

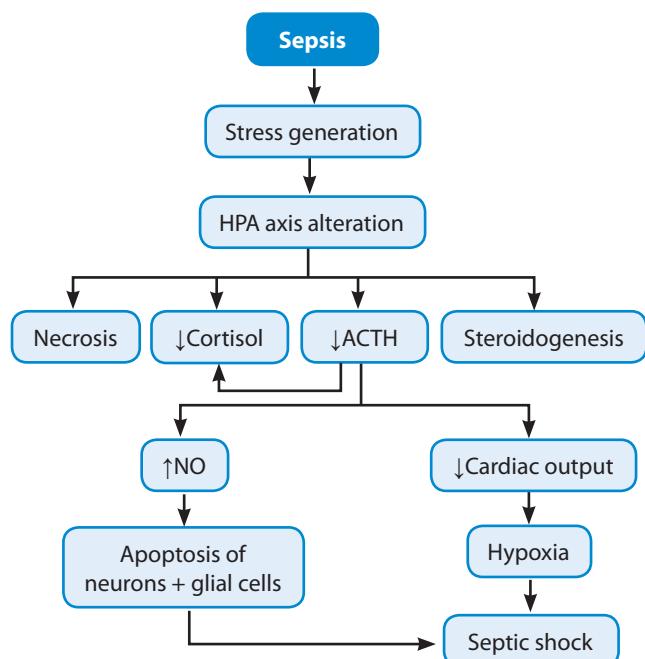
Adrenocorticotrophic hormone (ACTH) is a derivation of prohormone, pro-opiomelanocortin (POMC) which undergoes proteolytic cleavage to produce a number of different peptides which vary depending on the tissue. The POMC is then processed in the anterior pituitary to ACTH by the prohormone convertase, PC1 and stored in the secretory granules ready for stimulated secretion. ACTH is mainly secreted in response to stress by the corticotropin releasing hormone (CRH) from the pituitary cells which in turn causes release of glucocorticoids from the adrenal gland via hypothalamic-pituitary adrenal (HPA) axis.

The main purpose of the ACTH during stress, is to maintain homeostasis and cardiac output.¹¹ However, the pathophysiology of sepsis and septic shock involves the alteration in this axis. These alterations are defined in terms of necrosis or hemorrhage or inflammatory mediator-mediated decreased ACTH synthesis, steroidogenesis, cortisol delivery to tissues, clearance from plasma, and decreased sensitivity of tissues to cortisol. This disruption of the HPA axis may interpret in patients with sepsis into cardiovascular and other organ dysfunction, and ultimately an increase in the risk of death. The disruption in the HPA axis leads to the cessation of venous drainage in adrenal glands. The sepsis associated massive increase in the arterial blood flow causes the adrenal glands (particularly hypothalamus and pituitary) to enlarge and generate cytokines. The cytokines particularly IL-1 stimulates HPA axis and induces a biphasic response with initial proportional increase followed by progressive decline in anterior pituitary ACTH concentrations. A reduction in ACTH causes decline in cortisol levels, which in turn causes decrease in cardiac output and increased nitric oxide (NO) synthesis. An increased NO levels further cause apoptosis of neurons and glial cells (Figure 2).^{12,13}

The change in serum levels of ACTH and cortisol levels in patients with septic shock is associated with significant disease progress and mortality. Majority of studies indicate that reduction in ACTH and cortisol levels are associated with the development of septic shock.¹² However, some recent studies have also provided contradictory evidence supporting the association of increase in ACTH and cortisol levels with disease severity. In this context a study¹⁴ was conducted by Lin H and colleagues with an aim of determining the relationship between change in serum levels of ACTH and cortisol and disease severity. A total number of 25 children with decompensated septic shock and 24 with early septic shock were enrolled. The levels of serum cortisol and ACTH were determined on the day of admission and 3 to 8 days after admission. Results of the study reported that the patients with both decompensated and early septic shock groups had significantly higher serum cortisol and ACTH levels than the control group, while the decompensated septic shock group had significantly higher serum cortisol and ACTH levels than the early septic shock group. However, these results are still contradictory and further confirmation is still required.¹⁴

FIGURE 2

Role of Adrenocorticotropic hormone (ACTH) in septic shock



Adapted from: 1. Annane D. The Role of ACTH and Corticosteroids for Sepsis and Septic Shock: An Update. *Frontiers in Endocrinology*. 2016;7:70. 2. Polito A, Aboab J, Annane D. Adrenal insufficiency in sepsis. *Revista Brasileira de Terapia Intensiva*. 2006;18(1):86-94.

Role of corticosteroids in septic shock

The use of corticosteroids has been favored for more than 6 decades in the management of patients with severe infections. There exist a general agreement that corticosteroids improve sepsis-associated comorbidities including shock, organ dysfunction, and length of hospital stay. Corticosteroids are known to improve the cardiovascular function. They contribute to restore the effective blood volume by sodium and water retention with the help of mineralocorticoid receptors in the kidney and systemic vascular resistance. They also enhance the vascular contractile and blood pressure responses to α-1 agonists. The prolonged improvement in vascular responsiveness to corticosteroids is more likely a genomic transrepressive effect. Patients with septic shock and blunted response to 250 µg ACTH bolus (increase in total cortisol of <9 µg/dl) have more depressed systemic vascular resistance and a greater effect of hydrocortisone bolus on blood pressure response to norepinephrine than patients with intact HPA axis. Corticosteroids are also known to

improve microcirculation and tissue perfusion in septic shock. Moreover, they also attenuate inflammation in various organs in sepsis. For instance, various studies have reported a dramatic decrease in NF- κ B activity in peripheral immune cells or in the lungs. They have been shown to inhibit isoform of NO synthase (iNOS) activation in the renal cortex, preventing hypoxic injuries and restoring an adequate oxygen delivery to oxygen balance. They also ameliorate glomerular function, free water clearance, and sodium renal excretion and may rarify sepsis-associated brain inflammation particularly by preventing the breakdown of the BBB.¹²

Keeping this in view, a recent systemic review¹⁵ has reported the effects of corticosteroids on shock reversal. The review included randomized controlled trials of corticosteroids versus placebo or supportive treatment in patients with sepsis. Results reported that treatment with a long course of low-dose corticosteroids significantly reduced 28-day mortality in the intensive care unit (13 trials; RR 0.82, 95% CI 0.68 to 1.00; P value = 0.04, random-effects model) and at the hospital. Corticosteroids also increased the proportion of shock reversal by day seven (12 trials; RR 1.31, 95% CI 1.14 to 1.51; P value = 0.0001) and by day 28 (seven trials; n = 1013; RR 1.11, 95% CI 1.02 to 1.21; P value = 0.01). Furthermore, corticosteroids also reported a dramatic reduction in the number and degree of severity of failing organs, with a mean reduction in the SOFA score (a measure of organ dysfunction) of -1.53 (-2.04 to -1.03; P value < 0.00001). They also reduced ICU length of stay by -1.68 days (-3.27 to -0.09; P value = 0.04) and -2.19 days (95% CI -3.93 to -0.46; P value = 0.01), in ICU survivors.¹⁵

Given the efficacy of corticosteroids in septic shock patients with altered HPA axis and reduced ACTH levels, it is considered to be valuable in reversing septic shock and reducing complications.

Conclusion

Septic shock is defined as a subset of sepsis in which predominantly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. It is a common cause for admission of patients to intensive

care units. The morbidity and mortality always remain unacceptably high despite the advanced treatments. Adrenocorticotrophic hormone (ACTH) is a derivation of prohormone, pro-opiomelanocortin (POMC), the alteration in the level of which is associated with significant disease progress and mortality in patients with septic shock. Corticosteroids on the other hand improve cardiovascular function, microcirculation and tissue perfusion in septic shock patients with altered HPA axis and unresponsiveness to ACTH bolus.

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3

Procalcitonin-guided therapy in ICU patients with severe sepsis



Background

Sepsis is one of the most commonly encountered problems in intensive care units (ICUs). It is defined as acute dysfunction of one or more organs following an infection. Estimated hospital mortality rates of severe sepsis are as high as 43%. This high mortality rate warrants the need of an adequate antimicrobial therapy initiated at an early stage.^{1,2}

To guide antimicrobial therapy, there is a need of a laboratory marker to differentiate bacterial infection from viral infection or non-infectious inflammatory reaction; of note the most promising parameter among the wide array of inflammatory markers, that offers this possibility appears to be plasma levels of procalcitonin (PCT).^{1,3} The clinical utility of serum PCT levels as a biomarker continues to evolve.⁴

Rationale and clinical usefulness of PCT-guided therapy

While options for guiding appropriate therapy exist, however it has been speculated that conventional biomarkers such as C-reactive protein, leukocytes, erythrocyte sedimentation rate, and signs and symptoms, are not sensitive enough to formulate treatment plan in infectious diseases.^{2,4} Additionally, they also carry the disadvantages of diagnostic delays and lack of specificity for bacterial infections. Further, overuse of antibiotics and prolonged duration of antibiotic therapy in patients admitted in intensive care settings is associated with increased resistance for common bacteria, high costs of treatment and adverse drug reactions.⁵

However, a growing body of evidence supports the use of PCT as a pertinent candidate to diagnose the bacterial infections and subsequently guide antibiotic therapy and its duration. PCT has emerged as a promising marker for the

diagnosis of bacterial infections because higher levels of PCT are found in severe bacterial infections relative to viral infections and nonspecific inflammatory diseases. Hence, PCT may guide clinical decisions regarding the initiation or cessation of antibiotic therapy.⁴ Furthermore, controlled trials have demonstrated that a PCT-based algorithm allows safe reduction of duration of antibiotic therapy in patients admitted in ICU.^{2,4} Hyperprocalcitonemia occurs within 2 to 4 hours of infection and persists till the inflammatory process continues. PCT levels return to normal following recovery, therefore serves as an important diagnostic as well as prognostic tool.⁶

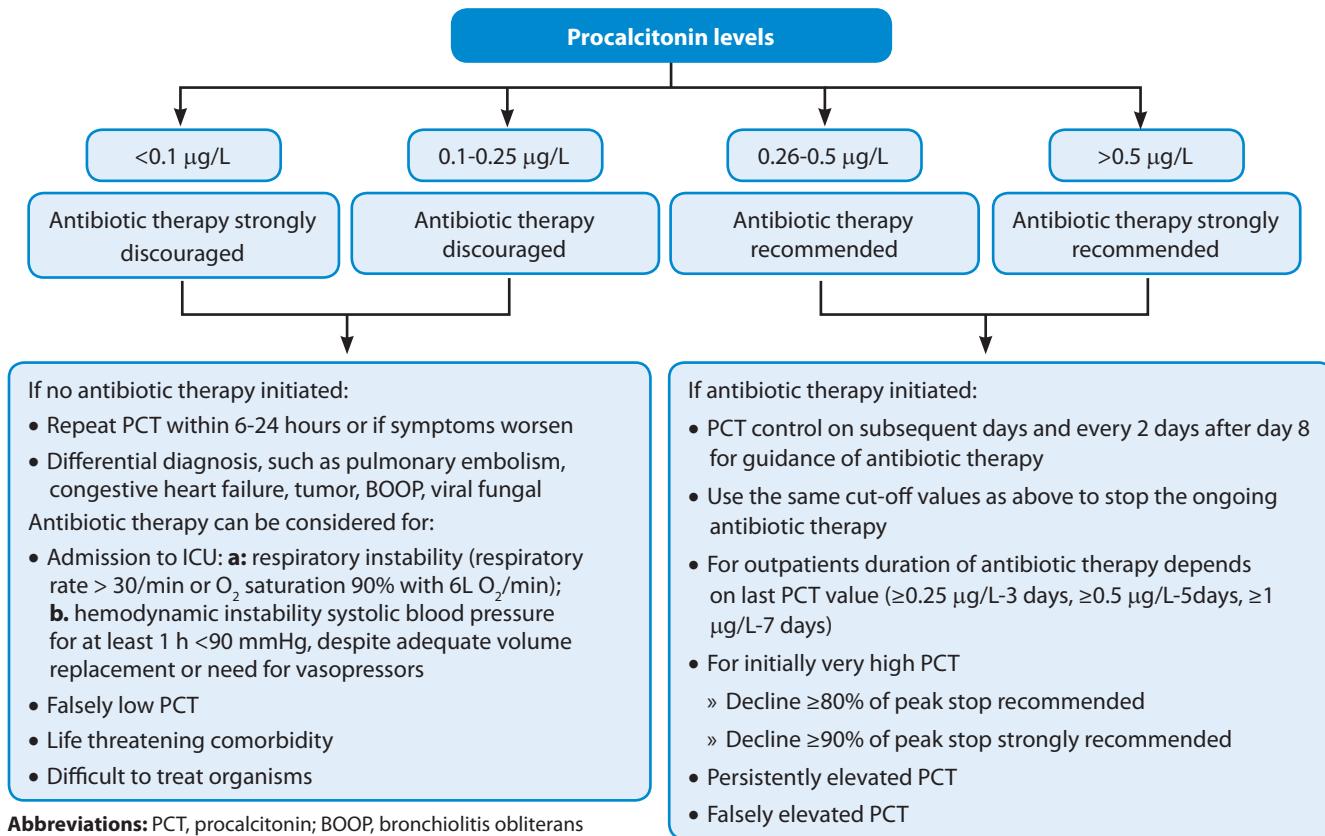
On the basis of clinical evidence, a cutoff value of 0.25 µg/L in non-ICU patients or of 0.5 µg/L in ICU patients seems to be reasonable to guide the initiation and discontinuation of antibiotic therapy. However, in significantly elevated baseline procalcitonin levels, a drop of >80% seems to be appropriate for discontinuing antibiotics (Figure 1).^{7,8}

Congregated data suggests that procalcitonin-guided antibiotic therapy may also reduce the hospital stay without any adverse outcomes.⁹ All the more, the levels of PCT are not affected by the use of nonsteroidal anti-inflammatory agents or glucocorticoids. Therefore, PCT holds the position of a valuable biomarker even when the patient is on nonsteroidal anti-inflammatory drugs and corticosteroids. However limitations still exist, because nonspecific PCT elevations can occur in massive stress, even in the absence of bacterial infection.⁴

Evidence substantiating the significance of PCT-guided antibiotic therapy

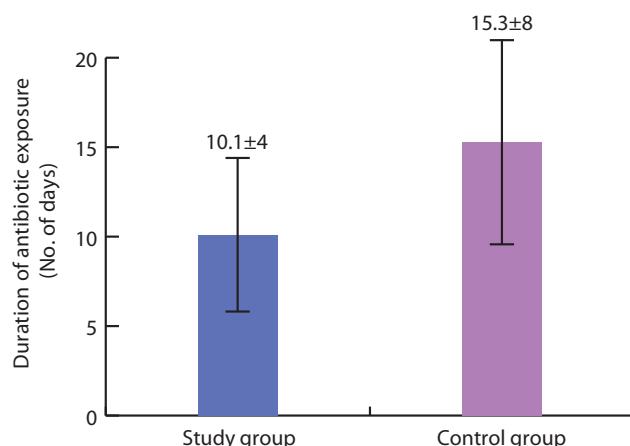
The promising prospects of PCT to help stratify patients at risk, and to guide decisions about optimal duration of antibiotic therapy, have been appraised in several robust clinical trials.¹⁰

FIGURE 1 Procalcitonin-guided antibiotic therapy



Abbreviations: PCT, procalcitonin; BOOP, bronchiolitis obliterans with organizing pneumonia; ICU, intensive care unit

Adapted from: Drozdov D, Dusemund F, Müller B, Albrich WC. Efficacy and Safety of Procalcitonin-Guided Antibiotic Therapy in Lower Respiratory Tract Infections. *Antibiotics*. 2013;2(1):1-10.

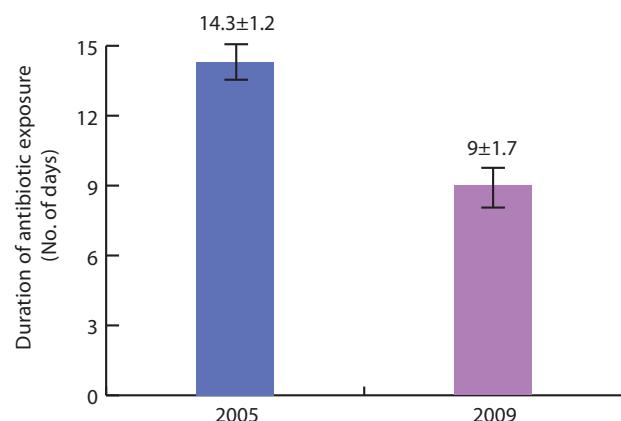
FIGURE 2
Reduction in antibiotic exposure using procalcitonin-guided therapy


Adapted from: Lavrentieva A, Kontou P, Soulountsi V, Kioumis J, Chrysou O, Bitzani M. Implementation of a procalcitonin-guided algorithm for antibiotic therapy in the burn intensive care unit. *Annals of Burns and Fire Disasters*. 2015;28(3):163-170.

A study was performed to assess the usefulness of procalcitonin-guided antibiotic therapy. The study enrolled a total of 46 patients admitted in ICU receiving antibiotic therapy. Patients selected were randomly assigned to either a study group (procalcitonin-guided antibiotic therapy) or a control group (standard antibiotic regimen). The results of the study divulged that PCT guidance is associated with reduced antibiotic exposure (10.1 ± 4 vs. 15.3 ± 8 days) in study group and control group respectively, without negative effects on mortality rate, percentage of patients with relapse, maximum SOFA score, length of ICU and hospital stay (Figure 2).¹¹

Taking this notion a step further, a study was done, in which patients with sepsis were randomly assigned either to the intervention group or the control group. In the intervention group, antibiotics were stopped when PCT levels decreased to $\geq 90\%$ from the initial value. In control group, the duration of antibiotic therapy was based on empirical rules. The study revealed that PCT guidance resulted in a 4-day reduction in the duration of antibiotic therapy and 2-day shorter ICU stay. Hence, it can be concluded that PCT based protocol permits reduction in duration of antibiotic treatment and exposure in patients with severe sepsis without any apparent harm.¹²

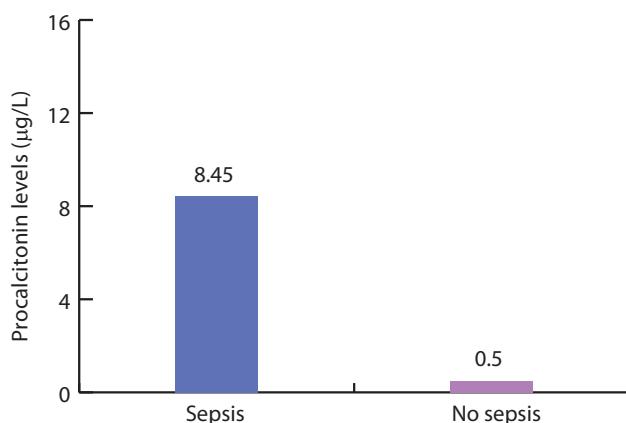
A retrospective ICU-database search was done

FIGURE 3
Reduction in duration of antibiotic therapy in patients with sepsis treated as per procalcitonin-guided algorithm


Adapted from: Hohn A, Schroeder S, Gehrt A, Bernhardt K, Bein B, Wegscheider K, et al. Procalcitonin-guided algorithm to reduce length of antibiotic therapy in patients with severe sepsis and septic shock. *BMC Infect Dis*. 2013;13:158.

between 2005 and 2009, in adult patients with sepsis treated as per PCT-guided algorithm. The study incorporated data from 141 patients. The results revealed that duration of antibiotic therapy was reduced by an average of 1 day per year from 14.3 ± 1.2 days in 2005 to 9.0 ± 1.7 days in 2009 (Figure 3). Similarly, ICU re-infection rate also reduced by 35.1% annually. Furthermore, annual decrease in ventilation hours and ICU- length of stay was 42 hours and 2.7 days, respectively, thus reducing the average yearly reduction of 28-day mortality by 22.4%.¹³

Diagnosis of sepsis is challenging, specifically in burn cases where signs of sepsis may be present without any underlying infection. A study was performed to explore the usefulness of daily consecutive PCT measurements as a valuable tool in monitoring the effectiveness of antibiotic therapy in ICU patients. It was observed that PCT thresholds of 1.5 ng/ml and 0.52 ng/ml were specific and sensitive to diagnose sepsis and respiratory tract infections, respectively. A yet another study showed significantly higher PCT levels in the septic group compared to those without sepsis (8.45 ± 7.8 vs. 0.5 ± 1.0 , respectively) (Figure 4); however the differences in CRP and WBC levels, neutrophil count, and ESR were insignificant. The area under the curve for the diagnosis of sepsis was 0.97 for PCT, associated with sensitivity and specificity of

FIGURE 4**Comparison of procalcitonin (PCT) levels in patients with and without sepsis**

Adapted from: Barati M, Alinejad F, Bahar MA, Tabrizi MS, Shamshiri AR, Bodouhi NO, et al. Comparison of WBC, ESR, CRP and PCT serum levels in septic and non-septic burn cases. *Burns*. 2008;34:770–4.

100% and 89.3%, respectively. Thus serum PCT level is an efficient laboratory parameter for the diagnosis of severe sepsis in ICUs.^{14,15}

Conclusion

Multiple trials corroborated the effectiveness of monitoring PCT to optimize antibiotic regimen, decrease rates of relapsing infections or other adverse outcomes and beneficial effects on microbial resistance, therefore integration of biomarker-guided antibiotic treatment may enhance the treatment results in ICU patients with sepsis. Composite interpretation of aforementioned tangible data suggests the usefulness of PCT-guided antibiotic therapy in patients with sepsis.

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World Sepsis Day: 13 September 2016

Thanks to the efforts of our supporters' ongoing commitment to organizing sepsis events on World Sepsis Day and a dedicated team, first crucial milestones in recognizing sepsis as a global burden have been achieved.

Different countries and regions contributed according to their local healthcare systems and economic means. We are proud to look back at such a successful World Sepsis Day 2016.

GLOBAL EVENTS

1st World Sepsis

Innovative online only congruence model

the world
15,000 people registered to participate, and all presentations
are available on YouTube and iTunes

Global Sepsis Alliance

Awarding healthcare authorities, sepsis initiatives with the 2016 **Global Sepsis Awards**
Centers for Disease Control and Prevention
Launch of "Sepsis Vital Signs Report", a global

UNITED STATES OF AMERICA

Cincinnati	University of Cincinnati	Pediatric Grand Rounds: World Sepsis Day
Cleveland, Ohio	MetroHealth Medical Center	Round table discussion review, 2016 and planning session to fight the sepsis battle in 2017
Colorado Springs, Co	Lisa Bartlett	3rd Annual Jeffrey Ray Davis Sepsis Challenge 5K
Columbus, Indiana	Columbus Regional Hospital	SEPSIS – Why We Do What We Do
Daly City, California	Seton Medical Center, Julie Mäykel, RN	Public informational display with poster, video and brochures Family Fun Day
Fleming Island, Florida	Sepsis Alliance	
Galveston, Texas	University of Texas Medical Branch	Keynote lecture
Harlingen	Harlingen Medical Center and the South Texas Emergency Care Foundation	Information table in the hospital lobby
Houston, Texas	MD Anderson Cancer Center	World Sepsis Awareness Day
Houston, Texas	MD Anderson Cancer Center	Sepsis Relay
Houston, Texas	Michael E. DeBakey VA Medical Center	Educational training
Indianapolis, Indiana	The Indiana Hospital Association	Rally Against Sepsis
Indianapolis, Indiana	Premier Inc.	Advisor Live: Sepsis Happens – The Stull Family Story: Sepsis survivor Sue Stull and her husband Jay
Juneau, Alaska	Bartlett Regional Hospital	Pester, educational training
Louisville, Kentucky	University of Louisville Hospital Critical Care Education	World Sepsis Day Education Fair
New York	THE RORY STOUNTON FOUNDATION	3rd international forum on sepsis
New York	Sepsis Alliance	5th Annual Sepsis Heroes Gala
Rochester, Michigan, Baypoint Beach Path	The MHA Keystone Center and Sepsis Alliance	Stamp Out Sepsis, 5k Walk
Salem, Oregon	Salem Health Sepsis Affinity Group	The Sepsis Matrix
San José, California	Santa Clara Valley Medical Center	Sepsis awareness exhibit in the hospital lobby
San José, California	Susan Bourgeois, Sepsis survivor	Zumba event -Shake Off Sepsis

MEXICO

Calz	Instituto Nacional de Rehabilitación	Symposium
La Paz, Baja California Sur	Hospital General ISSSTE La Paz, Departamento de Pediatría	Meeting, On Sepsis New Concepts and Terminology
Mexico City	Ciudad Juárez de México	Symposium
Mexico City	Hospital General de México Dr. Eduardo Liceaga	Symposium
Mexico City	ISSSTE Hospital Regional 1º de Octubre	Symposium
Mexico City	CENTRO CULTURAL RAFAEL SOLANA	Symposium
Mexico City	Gremio Atención integral de la Sepsis Abdominal - CASA - RGM	2º Carrera - "Corre por la CASA"
Mexico City	Hospital General Dr Dario Fernández Fierro	Symposium
Teziutlán	Hospital General Teziutlán	Conference

BRAZI

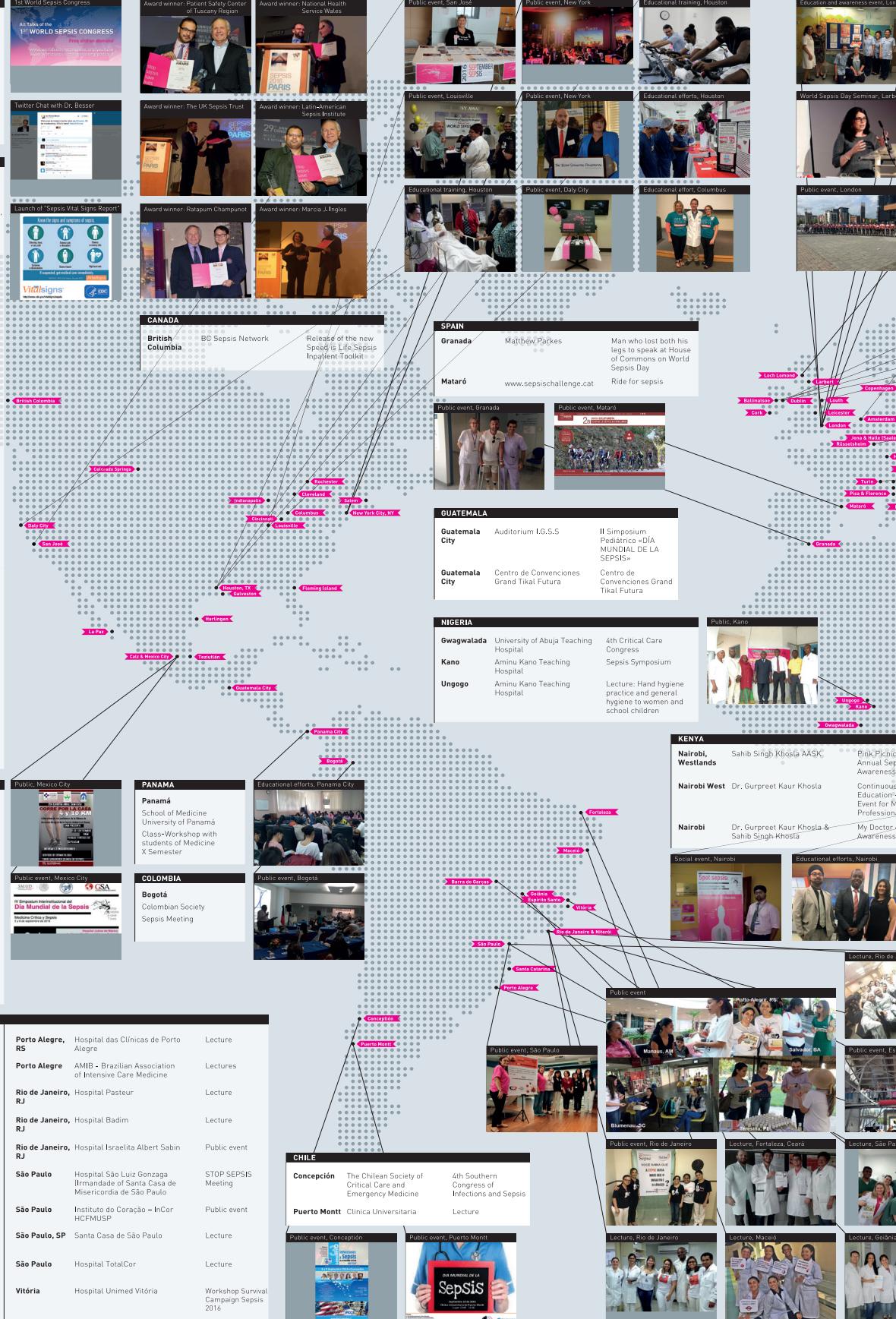
Barra do Garças, MT	Hospital Milton Pessoa Morbek	Public event
Espirito Santo	Vitória Apart Hospital Serra	Public event
Fortaleza, Ceará	Hospital Geral Dr César Cals	Lecture
Goiânia, GO	Hospital de Doenças Tropicais Dr Anuar Auad	Lecture
Icarai's beach, Niterói, Rio de Janeiro	SOTILESTE/SOTIERJ Intense Care Society of Rio de Janeiro - Leste Fluminense	Walking and talking about sepsis on Sunday Morning at the beach
Maceió	Santa Casa de Misericórdia de Maceió	Lecture
Niterói, Rio de Janeiro	Complexo Hospitalar de Niterói	Meeting with Specialists about Sepsis
Niterói, Rio de Janeiro	Complexo Hospitalar de Niterói	Lecture about Sepsis
Niterói beach, RJ	SOTILESTE/SOTIERJ/CHN	Public event

One day – an all year effort:

In 2017 we want to pursue our goal of raising global awareness as well as increasing knowledge about sepsis **to save lives.**

Join our fight against sepsis. **Sign the Declaration.** Because low sepsis awareness has a high price: **loss of life and reduced quality of life.**

www.world-sepsis-day.org/sign



6

World Sepsis Awareness is paid for with **ced quality of life.**



This figure is a world map illustrating the global impact of Sepsis Day 2016. It highlights numerous events and activities organized by medical professionals, patients, and advocacy groups in over 50 countries. The map is overlaid with a grid of dots representing the locations of these events. Each event is represented by a small image and a brief description of its nature and location.

Key Global Events:

- UNITED KINGDOM:** Activities included FEAT events in Luton, Farnborough, and London; a World Sepsis Day Seminar in London; and a promotional booth at the University Medical Centre in Ljubljana.
- HUNGARY:** A Hungarian Pediatric Sepsis Meeting was held in Budapest.
- SERBIA:** Special-Bynecological Hospital Dverenova staff conducted a lecture on sepsis in Belgrad.
- ISRAEL:** Information booths were set up in Haifa, Nahariya, and Tel Aviv.
- INDIA:** India Habitat Centre and LTEMRI organized an Indian Sepsis Meeting and Educational Training in Delhi. Lucknow UP hosted an Interdisciplinary meet, and an Educational training session was held in Lucknow UP.
- SRI LANKA:** The College of Anaesthesiologists & Intensivists of Sri Lanka and SSCCEM organized a Symposium for World Sepsis Day in Colombo.
- QATAR:** Hamad Medical Corp. held a Sepsis Awareness Symposium in Doha.
- AUSTRALIA:** Numerous events were held across Australia, including Armidale, Bankstown, Belmont District Hospital, Denman, Narrandera, Nimbin, Urangan, Tumbarumba, Waverley, and Perth.
- NEW ZEALAND:** Auckland hosted a seminar and discussion panel, and a launch event for Survive Sepsis Improvement Collaborative.
- INDONESIA:** Events included a World Sepsis Day Symposium in Bandung, West Java Prov, and an Annual Scientific Meeting in Makassar, South Sulawesi Prov.
- NEPAL:** Kathmandu organized a Motor-Bike/Scooter Rally.
- ITALY:** Events took place in Ancona, Florence, Milan, Modena, Pisa, Rom, and Turin.
- GERMANY:** Activities included a Public event in Halle (Saale), a Conference in Heidelberg, and a Short film workshop in Jena.
- DUBLIN:** Dublin City Marathon 2016 was held in Dublin.
- LOUTH:** Our Lady of Lourdes Hospital Supporting World Sepsis Day 2016 was held in Drogheda.
- OTHERS:** Events were also reported from Brazil, Chile, Colombia, Costa Rica, Ecuador, Egypt, France, Greece, Ireland, Japan, Mexico, Norway, Portugal, Spain, Turkey, and the United States.

Global Impact: The map shows a dense concentration of events in North America, Europe, and Asia, indicating a significant global effort to raise awareness about sepsis. The use of a grid overlay suggests a systematic approach to spreading information and resources across the globe.

Source: <https://pbs.twimg.com/media/C1wHw0IUUAAVp7b.jpg>

4

Endocrine and metabolic dysfunction during sepsis



Sepsis: An insight

Sepsis prevails as a critical life threatening condition with high mortality rate that can reach as high as 80% even in the modern era of advanced interventions, with over 1,50,000 deaths annually. Sepsis is a systemic, deleterious inflammatory host response which is triggered by an infective agent, which as a sequel can proceed to severe sepsis, septic shock and multi-organ failures. The host response to infection involves a complex interaction between the immune, autonomic, neuroendocrine and behavioral systems.¹⁻³ It is observed that individuals who are affected with severe sepsis exhibit a hypermetabolic and catabolic state. The hypermetabolic response that accompanies systemic inflammatory reaction places high demands upon the stored nutritional resources. The greatest increase in energy expenditure is seen when sepsis occurs in a previously healthy person.⁴ During sepsis there is uncontrollable activation of both pro- and anti-inflammatory responses that arise from the excessive production of mediators such as cytokines. Such inflammatory response can cause many kinds of endocrine and metabolic derangements.⁵

Sepsis induced dysfunction

Sepsis associated changes are important compensatory responses which are directed towards:

- Increasing the availability of fuel (glucose, fatty acids, and amino acids) in order to pace with the high metabolic demands
- Maintaining an adequate blood volume, blood pressure, and tissue perfusion.

Inadequately treated sepsis with prolonged hormonal stimulation may exhaust the patient's energy. State of energy

exhaustion can cause deleterious effects like muscle wasting, increased susceptibility to infection, and impaired wound healing.^{6,7}

Metabolic dysfunction related with sepsis

The metabolic changes associated with sepsis are conceptually complex. Many a time, the changes occurring in the endocrine and autonomic nervous system are responsible for mediating metabolic derangements.

Affected glucose metabolism

One of the most common metabolic derangement, hyperglycemia, is seen in the patients who present with sepsis, due to altered glycogen metabolism and profound insulin resistance. The molecular events that lead to sepsis-induced hyperglycemia are complex and can be ascribed to the effects of the inflammatory cytokines, production and secretion of glucagon, growth hormones, cortisol and catecholamines. The state of hyperinsulinemia can be attributable to the action of interleukin 1 (IL-1) and tumor-necrosis factors (TNF). Hyperglycemia impairs the functioning of innate-immune system which further affects the host ability to combat infections. Given these effects, hyperglycemia can independently predict the adverse outcomes in critically ill patients. At times it also unveils the unknown diabetic state and in known diabetics unmask hyperosmolar or ketoacidotic decompensations. Conversely, in some settings, hypoglycemia can be noted in meningococcal and pneumococcal sepsis, varicella or in patients with starvation, alcoholism, cirrhosis and hepatitis. Additional mechanisms that cause hypoglycemia are decrease in hepatic glycogen stores and impaired gluconeogenesis as well as shifting to anaerobic hepatic metabolism.^{5,8-10}

Dysregulation of the macro- and micro nutrients during sepsis

During sepsis, metabolism of macronutrients like carbohydrates, proteins and lipids are dysregulated. Sepsis results in increased protein breakdown; it also changes the concentration of amino acids in the circulation. Sepsis is also characterized by increased lipolysis, because lipids are considered the primary source of energy in patients with infection. Increased lipolysis can result in high serum triglycerides, which

increases the risk for heart disease, diabetes, and stroke. Mediators like catecholamine, IL-1, TNF and IL-6 possibly induce these effects, resulting in three-to fivefold increase in catabolism. The main goal of nutritional supplementation during sepsis in infected patients is to mitigate protein catabolism by providing adequate amount of amino acids for protein synthesis. Furthermore, both TNF and IL-1 promote lipoprotein lipase activity, which leads to the mobilization of triglycerides from adipose tissue stores. Hyperlipidemia may therefore be regarded as a prominent feature of sepsis.⁸⁻¹⁰ Sepsis can change the levels of various micronutrients, including minerals and vitamins. It is evinced that lower levels of micronutrients in patients who are critically ill are related with higher risk of death and multisystem organ failure. Two most important micronutrients, selenium that possess antioxidant and anti-inflammatory properties and zinc that play a key role in cellular homeostasis, immune function, and response to stress are deficient in patients having sepsis. Low selenium levels are associated with poor outcomes, supplementing patients with selenium has shown to decrease mortality in certain studies.⁹

Acid-base disturbances

Systemic acidosis can occur due to the increased production of lactate, during sepsis, tissue hypoxia and decreased catabolism because of liver failure. In patients who are on intensive care, lactic acidosis is frequently observed and is associated with a poor prognosis. According to a study that included 126 patients, with lactic acidosis, clearly related with septic episode in 58% of patients, despite therapeutic strategies, the death rate in patients was high with a survival rate of only 17% in 30 days.⁸

Electrolyte disturbances

Various kinds of electrolyte disturbances are reported during active infectious diseases, such as hyponatremia, due to inappropriate secretion of antidiuretic hormone. Hyponatremia can be observed in meningitis due to *Mycobacterium tuberculosis* and in other central nervous system infection such as pneumonia. Hyperkalemia, another type of disturbance, occurs secondary to the extracellular efflux induced by lactic acidosis. Hypophosphatemia can be regarded as a hallmark of sepsis, it happens due to the action of insulin, and may be aggravated by the glucose infusion. Insulin acts by promoting the intracellular entry of phosphate

TABLE 1 Metabolic changes during sepsis

Physiologic changes	Metabolic impact
↑ Gluconeogenesis , ↑ Glycolysis	Hyperglycemia
↑ Protein catabolism	Altered circulating amino acids
↑ Lipolysis	↑ Triglycerides
↓ Micronutrients	↑ Oxidative stress
↑ Neuroendocrine activation	↑ Catecholamines, ↑ counter-regulatory hormones
↑ Catecholamine	↑ Gluconeogenesis, ↑ glycolysis
↑ Cortisol	Hyperglycemia
↑ Cytokine release	Hyperglycemia, insulin resistance
Impaired oxygen utilization	↑ Reactive oxygen species

Adapted from: Bastarache JA, Seeley EJ. Metabolism, metabolomics, and nutritional support of patients with sepsis. Englert JA, Rogers AJ (Eds). *Clinics in chest medicine*. 2016;322-323.

from its extracellular location, and thus results in hypophosphatemia. Severe hypophosphatemia can lead to hemolysis and Guillain-Barre-like syndrome with respiratory muscle insufficiency. It is observed that chronic hypophosphatemia favors the loss of Mg, which in turn stimulates further renal phosphate and K loss.⁸ Summary of metabolic changes during sepsis are depicted in Table 1.

Endocrine abnormalities during sepsis

Altered endocrine physiology

Endocrinopathy during sepsis can manifest as hyperglycemia, insulin resistance or as insufficient production of both adrenal corticosteroids and vasopressin. The results from a recent trial have revealed that tight glycemic control with insulin can confer survival benefit to intensive care unit patients. Relative impairment of adrenocortical reserve has been suggested to be an important contributor in the pathogenesis of septic-shock. Replacement doses of glucocorticoids and mineralocorticoids have been related with improvement in the survival of patients. Production of vasopressin by posterior pituitary is also diminished in septic shock while, sensitivity to its vasopressor effects is enhanced.^{9,11,12} Sepsis induces activation of the hypothalamic-pituitary-adrenal axis (HPA) and increased cortisol release. High level

of cytokines in the circulation can directly impair adrenal corticosteroid production, medications that are prescribed for treatment can also impair adrenal functioning.⁹ In addition to the changes in the HPA axis, sepsis can alter the function of other endocrine organs, such as thyroid that can further lead to hormonal changes that will alter metabolism.²

Conclusion

Sepsis is a critical disease; uncontrollable activation of both pro- and anti-inflammatory responses that arise from the over production of mediators such as cytokines can cause endocrine and metabolic derangements. Inadequately treated sepsis depletes the patient fuel that is necessary for the maintenance of the increased metabolic demands. Manipulation of hormones during sepsis, particularly insulin, glucagon, and growth hormone, with an adequate caloric intake can promote a favorable responses in patients with sepsis.

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5

Inflammation and immunomodulation in acute pancreatitis



Acute pancreatitis: An overview

Pancreatitis is defined as the histological presence of inflammation within the parenchyma of the pancreas. Acute pancreatitis is a reversible process and represents a spectrum of disease ranging from a mild, self-limited course requiring only brief hospitalization to a rapidly progressive, fulminant illness resulting in the multiple organ dysfunction syndrome (MODS), with or without accompanying sepsis. It is often characterized by the presence of interstitial edema, infiltration by acute inflammatory cells, and varying degrees of necrosis, apoptosis, and hemorrhage.^{1,2} The incidence of acute pancreatitis is estimated at 30-113/100,000 where a majority develop mild acute pancreatitis, about 10-20% suffers the severe form with an estimated rate of overall mortality rate being 10-15%.³

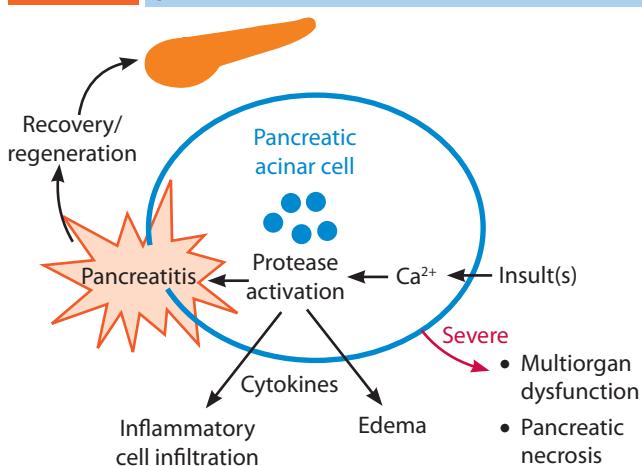
Acute pancreatitis is classified in two phases of the disease: early and late. Based on severity it is classified as mild, moderate or severe.⁴ The etiology of this disease is multifactorial with gallstones and alcoholism being the main protagonists.³ An array of other causes, such as hyperlipidemia, trauma of the pancreas, infectious diseases, drugs, postoperative pancreatitis, pancreatitis induced by ERCP or endoscopic sphincterotomy, congenital anomalies such as pancreas divisum, have also been incriminated in the induction of this inflammatory condition. Besides the aforementioned factors, dysfunction of sphincter of Oddi, biliary sludge, intraduct papillary mucinous tumor, hypercalcemia have also been shown to play a role in instigating acute inflammatory conditions in pancreas.^{5,6}

Pathophysiological mechanism of acute pancreatitis: The telltale of inflammation and immunomodulation response

The pathophysiology of acute pancreatitis remains elusive. However, it is posited that multifarious etiologies incriminated

FIGURE 1

Pathophysiological mechanism of acute pancreatitis



Adapted from: Bai HX, Lowe ME, Husain SZ. What Have We Learned About Acute Pancreatitis in Children? *Journal of pediatric gastroenterology and nutrition*. 2011;52(3):262-270.

in acute pancreatitis follow a common pathway. Aberrant non-physiological calcium signals within the pancreatic acinar cells are generated first, followed by the premature activation of intraacinar pancreatic proenzymes, or zymogens that are responsible for the release of certain inflammatory mediators (Figure 1). Inflammatory mediators are believed to be primarily responsible for the systemic manifestations of acute pancreatitis and its associated distant organ dysfunction.^{1,7}

The commencement of the tissue damage in acute pancreatitis has shown involvement of a number of inflammatory mediators. The pathway of damage comprises three phases of progression: local acinar injury, systemic response, and generalized sepsis. Cytokines are primarily involved in all aspects of the cascade leading to systemic inflammatory response syndrome and multiple organ dysfunction syndrome. This is attributed to an intricate balance between localized tissue damage with proinflammatory cytokine production and a systemic, anti-inflammatory response that restricts the inappropriate movement of proinflammatory agents into the circulation. Cytokines lead to an acute inflammatory response and varying degrees of extrapancreatic inflammation that is also followed by ischemic changes in pancreas. The proinflammatory response is countered by an anti-inflammatory response, and an imbalance between

these two systems leads to localized tissue destruction and distant organ damage.⁸ The critical players of this interaction include the proinflammatory cytokines IL-1beta, TNF-alpha, IL-6, IL-8, and platelet activating factor (PAF). The anti-inflammatory cytokines IL-10, as well as TNF-soluble receptors and IL-1 receptor antagonist, have also been shown to be intimately involved in the inflammatory response to acute pancreatitis.^{8,9} The systemic inflammatory response is kept at bay by local and systemic release of anti-inflammatory mediators and shown to reduce the severity of pancreatitis and pancreatitis associated organ failure.¹⁰

Conclusion

Acute pancreatitis is an inflammatory disease associated with high morbidity and mortality. Proinflammatory cytokines play a crucial role in the pathogenesis and progression of acute pancreatitis. An imbalance between pro- and anti-inflammatory responses leads to localized tissue destruction and distant organ damage. Thus, cytokines serve as potential therapeutic target and their blockade results in significant reduction in disease severity and associated mortality.

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6

Role of defensins in immunity and sepsis



All about defensins

Defensins are natural antibiotic peptides that contain 29-35 amino acid residues, contributing to the antimicrobial action of granulocytes, mucosal host defence in the small intestine and epithelial host defence in the skin and elsewhere.^{1,2} They are generated by the proteolytic processing of 93-95 amino acid precursor peptides, and constitute >5% of the total cellular protein in humans.² Defensins are important components of the natural defenses of most living organisms and are isolated from many bacteria, fungi, plants, invertebrates and vertebrates. These are known to be very heterogeneous in length, sequence and structure. However, majority of them are small, cationic and amphipathic. Defensins exhibit a broad spectrum of activity against a variety of Gram-positive and Gram-negative bacteria, mycobacteria, *Treponema pallidum*, fungi and some enveloped viruses.^{2,3} They exert a non-specific cytotoxic activity against variety of normal and malignant targets, including cell resistant to TNF-alpha and NK-cytolytic factor. They follow a common mechanism to kill mammalian target cells and microorganisms, which includes initial electrostatic interactions with negatively charged target cell surface molecules followed by insertion into the cell membranes which they permeabilize, forming voltage-regulated channels. Besides, the antimicrobial and cytotoxic properties, some defensins also behaves as opsonins, while others inhibit protein kinase C, bind specifically to the ACTH receptor and block steroidogenesis or act as selective chemoattractants for monocytes.²

There are two classes of defensins commonly found in humans, which include alpha-defensins and beta-defensins.³ The alpha-defensins are mainly expressed in human neutrophils [human neutrophil peptides (HNP) 1-4] or intestinal Paneth cells [human defensin (HD) 5-6]. On the other hand beta-

TABLE 1 Cell sources of human defensins

Peptide	Constitutive expression	Induced by proinflammatory cytokines and endotoxin
Alpha-defensins (HNP1–3)	Neutrophil granules	Monocytes, CD8 T lymphocytes, (CTL)9
Alpha-defensins (HD5–6)	Paneth cell granules	
Beta-defensins (HBD1)	Keratinocytes, Barrier epithelial cells	Keratinocytes, Monocytes and dendritic cells
Beta-defensins (HBD2–4)		Monocytes and dendritic cells, Keratinocytes, Barrier epithelial cells, Mast cell

Adapted from: 1. Oppenheim JJ, Biragyn A, Kwak LW, Yang D. Roles of antimicrobial peptides such as defensins in innate and adaptive immunity. *Ann Rheum Dis.* 2003;62(Suppl II):ii17–ii21. 2. Xie GH, Chen QX, Cheng BL, Fang XM. Defensins and Sepsis. *BioMed Res Int.* 2014;2014:180109.

defensins are mainly dispersed in the epithelial cells of the respiratory, digestive and genitourinary systems (Table 1). Both the classes have bactericidal action towards a wide range of bacteria, virus and fungi; however, beta-defensins even has bactericidal effect towards multiresistant *Staphylococcus aureus* and vancomycin-resistant Enterococcus. The mechanism behind the bactericidal effect of the defensins is the “pore formation” theory. The defensins being positively charged agents target negatively charged bacterial membrane components including lipopolysaccharides, teichoic acids, or phospholipids. They then form transmembrane pores, disrupt cell integrity, and result in bacterial lysis. In addition, another mechanism has also been reported recently which include killing of bacteria by the inhibition of bacterial cell wall synthesis through interaction with certain precursors such as lipid II.^{4,5}

Role of defensins in sepsis

Defensins have been identified since ages in the body fluids and on body surfaces after inflammatory stimulation. They are also reported to have modulating effects on both innate and adaptive immune response. It is well recognized that HNP1-3 (an alpha-defensin) participate in the host immune defense via multiple mechanisms, including enhancing

macrophage phagocytosis, facilitating neutrophil recruitment, modulating complement activation, and chemoattracting immature T cells and dendritic cells. Additionally, limited evidences are also available indicating the presence of defenses in patients with severe sepsis or septic shock. They have been found in patients with abscesses, peritonitis, or uninfected body fluid levels of the LPS-binding protein (LBP) and Bactericidal/permeability-increasing protein (BPI), which prevents endotoxin binding to CD14.^{4,6}

Various in vitro studies have shown that beta-defensins have potent chemotactic effect, resulting in the recruitment and maturation of naive dendritic cells and memory T cells in the inflammatory sites and the triggering of specific immune response in the host.⁷ Being an endogenous ligand of TLR-4, beta-defensins act together with TLR-4 of the immune cells and control the expression of inflammatory mediators via the NF-κB pathway. In addition, in vivo researches have also reported the abnormal expression of β-defensins with sepsis and various infectious diseases. In one such study the levels of beta-defensins were found to be elevated in both plasma and bronchoalveolar lavage fluid in patients with pulmonary infection.⁸

Likewise a prospective case-control study⁹ had also investigated the levels of beta-defensin (HBD-2) in patients with severe sepsis. The study included a total number of 34 patients, 16 among which were with severe sepsis, 9 critically ill but non-septic patients, and 9 healthy individuals with severe sepsis. Blood samples from all the patients were collected and the levels of hBD2 mRNA in peripheral white blood cells were determined and quantified by real-time polymerase chain reaction in native peripheral blood cells and following ex vivo endotoxin stimulation. Results reported that the HBD-2 plasma levels in septic patients were significantly higher compared to those in healthy controls and critically ill non-septic patients. The levels of Procalcitonin plasma and HBD-2 protein plasma demonstrated a positive correlation in patients with severe sepsis. Moreover, the endotoxin-inducible HBD-2 mRNA expression was significantly decreased in patients with severe sepsis compared to healthy controls and non-septic critically ill patients, which may contribute to the complex immunological dysfunction in patients with severe sepsis. The inconsistency between the diminished inducibility of HBD-2 in peripheral blood cells of patients with severe sepsis and the elevated levels of HBD-2 in

septic plasma are suggestive of circulating endothelial cells or reticuloendothelial cells (e.g., monocytes or macrophages) being a possible source of HBD-2 in vivo.⁹

Conclusion

Defensins are natural antibiotic peptides generated by the proteolytic processing of 93-95 amino acid precursor peptides, and constitute >5% of the total cellular protein in humans. They are important components of the natural defenses of most living organisms and are isolated from many bacteria, fungi, plants, invertebrates and vertebrates. There are two classes of defensins commonly found in humans, which include alpha-defensins and beta-defensins that are reported to have modulating effects on both innate and adaptive immune response. Additionally, evidences are also available indicating the presence of defensins in patients with severe sepsis or septic shock.

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7

An update on dengue pathogenesis



Global burden of dengue

Dengue is among the most widespread mosquito-borne viral infections of humans. It is currently estimated that there are about 390 million cases of dengue infections per year worldwide, 96 million of which manifest clinically.¹⁻³ The growing burden of dengue infection can be elucidated by the fact that while only 9 countries had experienced severe dengue epidemics before 1970, it is now endemic in more than 100 countries in different parts of the tropical developing world. Of late, the number of reported dengue cases has continued to increase, from more than 1.2 million in 2008 to over 3.2 million in 2015.^{3,4}

Not only is there a rise in number of dengue cases, but explosive outbreaks are also increasing. The year 2015 witnessed large dengue outbreaks worldwide, with Malaysia reporting more than 1,11,000 suspected cases of dengue, representing a 16% increase in case numbers to the previous year. In the same year in India, Delhi recorded its worst outbreak since 2006 with over 15,000 cases. Every year, almost 5,00,000 people with severe dengue are hospitalized, with a case fatality rate of around 20%. The epidemiological patterns of dengue, including hyper-endemicity of multiple dengue viruses in several countries incur a massive burden on both human health and the global and national economies, especially in the developing world.^{3,4}

Pathogenesis of dengue virus infection

Dengue virus (DENV) is a flavivirus, which is transmitted to humans by Aedes mosquitoes, mainly *Aedes aegypti*. The virus has four serotypes categorized according to their immunological properties –DENV-1, DENV-2, DENV-3 and DENV-4.⁵⁻⁷

Clinically, dengue infection has varied spectrum of illnesses including undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).⁸ Among these, DF is manifested as a debilitating disease in older children, adolescents, and adults. It is distinguished by the rapid onset of fever along with severe headache, retro-orbital pain, myalgia, arthralgia, gastrointestinal discomfort, and usually rash.⁵ DHF is identified by all the symptoms of DF, in combination with hemorrhagic manifestations, thrombocytopenia, and evidence of increased vascular permeability. The life-threatening DSS is distinguished by a rapid, weak pulse (≤ 20 mm Hg) or hypotension with cold, clammy skin in the early stage of shock. Absence of a prompt and appropriate treatment may lead to a stage of extreme shock, ultimately resulting in death within 12 to 36 hrs after onset of shock.^{5,8}

The pathogenesis of DENV infection involves various factors including viral virulence factors, antibody-dependent enhancement (ADE), host genetic factors, cytokines and chemical mediators, collectively leading to abnormal hemostasis and increased vascular permeability (Box 1). The virulence hypothesis points to variation in the viral genotypic nucleotide as being responsible for differences in disease severity.^{5,9-11}

BOX 1 Major factors that are contributory to the pathogenesis of dengue infection

- Virulent strains of dengue virus
- Anti-dengue virus antibodies
 - » Increase dengue virus infection by developing virus-antibody immune complex
 - » Activate complement
- T lymphocytes (serotype cross-reactive CD4+ and CD8+ T lymphocytes)
 - » Produce cytokines
 - » Cause the lysis of dengue virus-infected cells
- Complement
 - » Activation products induce plasma leakage
- Platelet
 - » Thrombocytopenia plays a major role in hemorrhagic manifestation
- Endothelial cells
 - » Play a key role in plasma leakage
 - » Produce cytokines

Adapted from: Kurane I. Dengue hemorrhagic fever with special emphasis on immunopathogenesis. *Comp Immunol Microbiol Infect Dis.* 2007; *v30(5-6)*:329-40.

Role of cytokines in the pathogenesis of dengue virus infection

Of late, studies have provided novel insights into the pathogenesis of DENV infection, which suggest that plasma leakage, characteristic of DHF, is caused by malfunction of vascular endothelial cells induced by cytokines and chemical mediators rather than by destruction of the small vessels.^{12,13} This is supported by the immune hypothesis, which suggests that individuals with secondary infections have an increased risk of developing DHF/DSS. The presence of cross-reactive, non-neutralizing antibodies from the primary infection lead to ADE, which augments viral replication by increasing the number of Fc receptor-bearing cells that are infected during secondary DENV infection. This in turn activates pre-existing cross-reactive T-lymphocytes and releases inflammatory cytokines and cellular mediators, thus resulting in the increased plasma leakage characteristic of DHF and DSS.^{10,11}

Cytokine secretion profiles can be differentiated into helper T (Th) 1 and Th2 cells, which are the major subsets of fully differentiated CD4+ Th cells. Apropos dengue infection, a marked shift is observed from the predominant Th1-type response in cases of DF to the Th2-type in severe cases of DHF.¹⁴ In some epidemic conditions, DHF cases among patients with primary infections have been reported, and even in primary cases, the progress from DF to DHF has been associated with increased levels of tumor necrosis factor (TNF)- α , interleukin (IL)-1, and IL-6.¹¹ Consistent with this, a study¹⁴ reported increased serum levels of IL-4, IL-6 and IL-10, particularly in cases of DHF grades III and IV, whereas the levels of IFN- γ and IL-2 were highest in cases of DF and low in DHF grade IV (Table 1). Initially, 66% of total cases of DF had Th1-type response, which shifted with an increase in severity of illness, to Th2-type in 71% of the cases of DHF grade IV.

Likewise, an immunopathological study of human tissues from patients with DHF suggested that the presence of dengue antigens in endothelial cells was due to deposition of virus-antibody complexes rather than the viral replication occurring in monocytes and macrophages. This further strengthened the likelihood that cytokines, rather than virus, are accountable for injury to endothelial cells during DHF. Thus, ample evidences suggest that cytokines along with other chemical mediators play important roles in the pathogenesis of DHF and DSS.^{4,11}

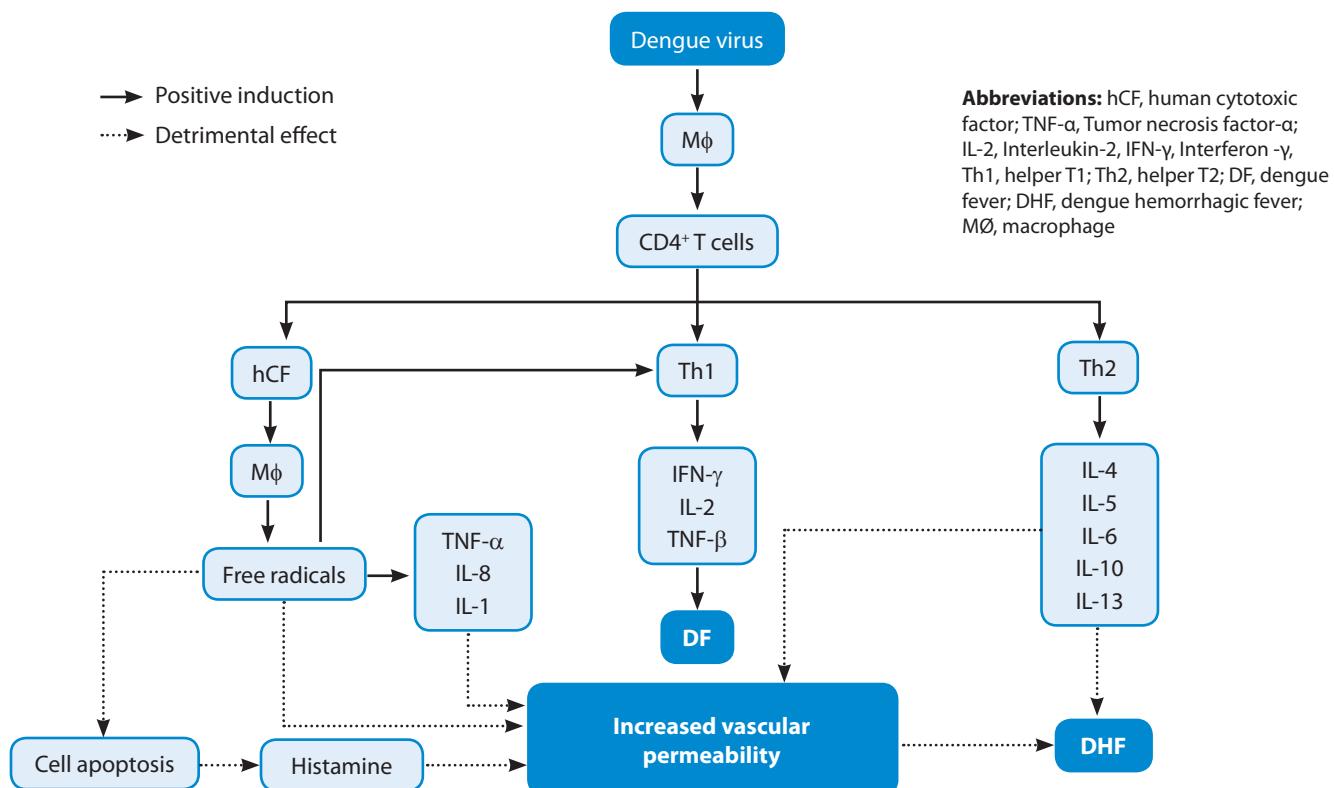
TABLE 1 Cytokines levels in patients with dengue

Cytokines	Dengue fever	Dengue hemorrhagic fever
Interleukin (IL)-2	✓/✓	✓
IL-4	x	✓/✓
IL-6	✓	✓/✓
IL-8	x	✓/✓
IL-10	x	✓/✓
IL-12	✓/✓	x
IL-13	x	✓/✓
IL-18	✓	✓/✓
Tumor necrosis factor (TNF)- α	✓/✓	✓/✓
Interferon (IFN)- γ	✓/✓	✓
hCF	✓	✓/✓

x, decrease; ✓, increase; ✓/✓, marked increase

Adapted from: Chaturvedi UC, Agarwal R, Elbishi EA, et al. Cytokine cascade in dengue hemorrhagic fever: implications for pathogenesis. *FEMS Immunol Med Microbiol*. 2000; 28(3):183-8.

Cytokines are well known to induce the release and production of other cytokines—this complex interactive network of induction leads to further increases in the levels of cytokines and other chemical mediators. Based on ample evidences, researchers have proposed a mechanism to elucidate the pathogenesis of DHF (Figure 1). DNV replicates in macrophages and quickly stimulates the CD4 $^{+}$ T cells to produce a unique cytokine, human cytotoxic factor (hCF). hCF further stimulates macrophages to produce free radicals—nitrite, reactive oxygen and peroxy nitrite. The free radicals, apart from killing the target cells by apoptosis also directly induce production of proinflammatory cytokines IL-1 α , TNF- α , IL-8, and hydrogen peroxide in macrophages. Further, the combined effect of histamine, free radicals, and proinflammatory cytokines lead to increased vascular permeability. Ultimately, a shift ensues from a Th1-dominant response to a Th2-biased response, resulting in an exacerbation of DHF and death of patients.^{4,14}

FIGURE 1 Dengue virus-induced cytokine cascade, resulting in dengue fever and dengue hemorrhagic fever

Adapted from: Chaturvedi UC, Agarwal R, Elbishi EA, et al. Cytokine cascade in dengue hemorrhagic fever: implications for pathogenesis. *FEMS Immunol Med Microbiol*. 2000; 28(3):183-8.

Conclusion

Dengue is one of the most important infectious diseases worldwide. The epidemiological patterns of dengue incur a massive burden on both human health and the global and national economies. Proinflammatory cytokines such as IL-12, IFN- γ , TNF- α , and IL-6 seem to be part of the processes that lead to increased vascular permeability, a characteristic feature of dengue hemorrhagic fever. Besides, other factors such as viral virulence factors, antibody-dependent enhancement, host genetic factors, and chemical mediators also play a role in and highlight the complex nature of severe dengue pathogenesis. Better understanding of dengue pathogenesis will pave the way for developing better strategies to the treatment and the prevention of dengue infection.

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Management of severe sepsis and septic shock



Introduction

Severe sepsis refers to sepsis complicated by organ dysfunction, and septic shock means acute circulatory failure in addition to severe sepsis.¹ Both severe sepsis and septic shock are generally regarded as the transition from systemic inflammatory response syndrome (SIRS).² During the past 30 years, the incidence of sepsis has increased significantly, which has led to the development of both severe sepsis and septic shock into one of the frequently encountered conditions throughout the world.³⁻⁵ Sepsis being a serious infection exerts substantial burden of mortality in the general population amounting almost equivalent to the burden posed by acute myocardial infarction in different parts of the world.^{2,6} According to results of a recent study, sepsis mortality rate due to severe sepsis and septic shock in 2012 was 14.2% and 22 %, respectively.⁴ In particular, in a resource-limited setting such as India, mortality rate due to severe sepsis is significant in the intensive therapy units (ITU). Moreover, compared to western literature, ITU mortality has been observed to be high.^{6,7} In order to restrict this escalating burden of mortality due to severe sepsis and septic shock, the process of their development needs to be addressed.

Severe sepsis and septic shock: An evolution of SIRS

The development of SIRS into severe sepsis and septic shock encompasses numerous pathogenic alterations such as circulatory abnormalities that cause global tissue hypoxia. Global tissue hypoxia is the principal development impending for the incidence of multiorgan failure and death. An underlying mechanism behind global tissue hypoxia in critical illnesses such as sepsis is hypotension.⁸ Hypotension in sepsis is the result of the peripheral vasodilation (which may be due to vasoactive mediators release from vascular endothelial

cells) and redistribution of intravascular fluids. These changes ultimately lead to tissue hypoperfusion and organ dysfunction. The tissue hypoxia can therefore be countered by maintaining adequate tissue perfusion with hemodynamic support.⁹ However, the global tissue hypoxia cannot be detected in early hemodynamic assessment on the basis of physical findings, vital signs, central venous pressure, and urinary output.² Management of sepsis is a complicated clinical challenge that requires early recognition and prompt management of infection, hemodynamic issues, and other organ dysfunctions.

Guidelines for the early management of sepsis and septic shock

The guideline was developed by the Surviving Sepsis Campaign (SSC), with funding and governance from the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). The guideline provides strong recommendations for a number of elements of standardized care, such as antimicrobial therapy, initial fluid volume, blood pressure goals, and vasopressor choice (Box 1).¹⁰

Conclusion

Severe sepsis and septic shock, which pose as significant risk factors for multiorgan failure, are associated with notably high mortality rates. The cascade of changes leading to this devastating impact on the patients include global tissue hypoxia as a major phenomenon. Global tissue hypoxia however cannot be detected in early hemodynamic assessment of various clinical parameters. There is therefore a need to set a protocol of management in case of severe sepsis or shock incidence in order to improve the outcomes and reduce the mortality rates.

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BOX 1

Guidelines for the management of sepsis and septic shock

Managing infection:

Antibiotics: Administration of broad-spectrum intravenous antimicrobials for all likely pathogens within 1 hour after sepsis recognition.

Source control: Obtain anatomic source control rapidly.

Antibiotic stewardship: daily assessment of patients for de-escalation of antimicrobials; narrow therapy based on cultures and/or clinical improvement.

Managing resuscitation:

Fluids: Patients with sepsis-induced hypoperfusion, are provided with 30 mL/kg of intravenous crystalloid within 3 hours with additional fluid based on frequent reassessment, preferentially using dynamic variables to assess fluid responsiveness.

Resuscitation targets: For patients with septic shock requiring vasopressors, targeting a mean arterial pressure of 65 mm Hg is strongly recommended.

Vasopressors:

Norepinephrine is regarded as a first-choice vasopressor

Mechanical ventilation in patients with sepsis-related acute respiratory distress syndrome:

A tidal volume of 6 mL/kg of predicted body weight is targeted and a plateau pressure of ≤ 30 cm H₂O is strongly recommended.

Adapted from: Howell MD, Davis AM. Management of Sepsis and Septic Shock. *JAMA*. Published online January 19, 2017.

Effect of ulinastatin administration on postoperative clinical outcomes



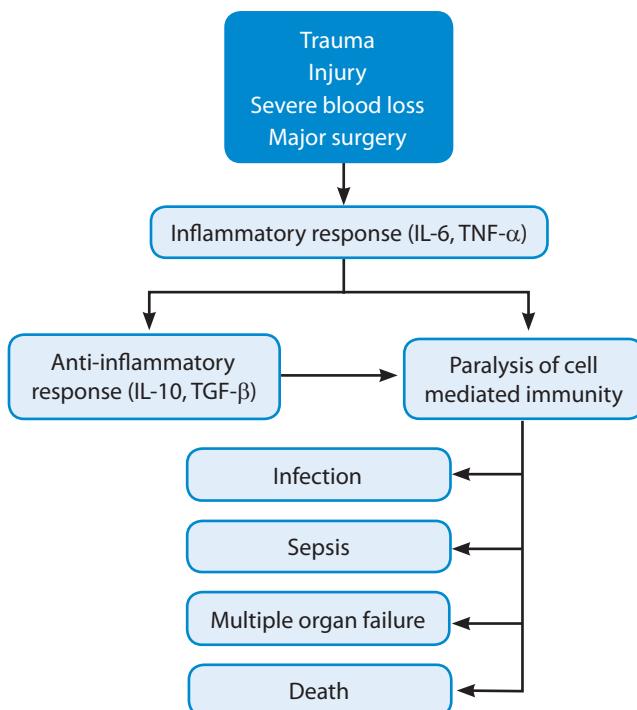
Introduction

Surgery remains one of the most effective treatment options in a number of cases; however, it is also burdened with sizeable frequency of postoperative complications. Multiple organ failure is one of the leading postoperative complications in surgical patients. Majority of cases of multiple organ failure are precipitated by infection. There exists a causal relationship between the surgical or traumatic injury and the predilection of these patients to develop septic complications and/or multiple organ failure.^{1,2} The stress responses to surgical manipulation and associated tissue trauma activate a systemic inflammatory response distinguished clinically by changes in various functions, such as those of nervous, endocrine, immune, and hematopoietic systems. The systemic inflammatory response is maintained by a series of factors, including cytokine production. The overproduction of proinflammatory cytokines and the inadequate release of anti-inflammatory cytokines during surgery may be deleterious to the organs.^{3,4}

In addition, surgical stress can beget immunosuppression in response to the complex interaction of various hormones, cytokines, and acute phase reactants. Ample evidences suggest an association between the loss of immunocompetence in patients following injury and major surgery, and an increased risk of sepsis, organ failure, and death (Figure 1).^{1,2} Therefore, it seems pertinent to find an effective option to offset the overproduction of proinflammatory cytokines, immunosuppression, and postoperative complications. Among a surfeit of therapies available, ulinastatin appears to be a valuable option in successfully combating various postoperative complications.^{1,5}

FIGURE 1

Cascade of events following major surgery, leading to immunodepression and increased susceptibility to sepsis



Abbreviations: IL-6, interleukin 6; TGF- β , transforming growth factor β ; TNF- α , tumor necrosis factor α .

Adapted from: Angele MK, Faist E. Clinical review: Immunodepression in the surgical patient and increased susceptibility to infection. *Crit Care*. 2002;6(4):298-305.

Amelioration of postoperative clinical outcomes: Focus on ulinastatin

Ulinastatin is a glycoprotein that acts as a urinary trypsin inhibitor. It is produced by hepatocytes and is found in human urine and blood. Under an inflammatory response, ulinastatin gets cleaved from inter-alpha-inhibitor proteins in the peripheral circulation or at the sites of inflammation.^{6,7} It inhibits various proinflammatory proteases including trypsin, chymotrypsin, thrombin, kallikrein, elastase and plasmin. Further, ulinastatin is also believed to decrease the severity of inflammation by suppressing the infiltration of neutrophils and release of elastase and inflammatory mediators from neutrophils. Ulinastatin also inhibits the production of tumor necrosis factor (TNF)- α , interleukin (IL)-1, and IL-6 probably through suppression of mitogen-activated protein kinases (MAPK) signalling pathway.^{5,7,8}

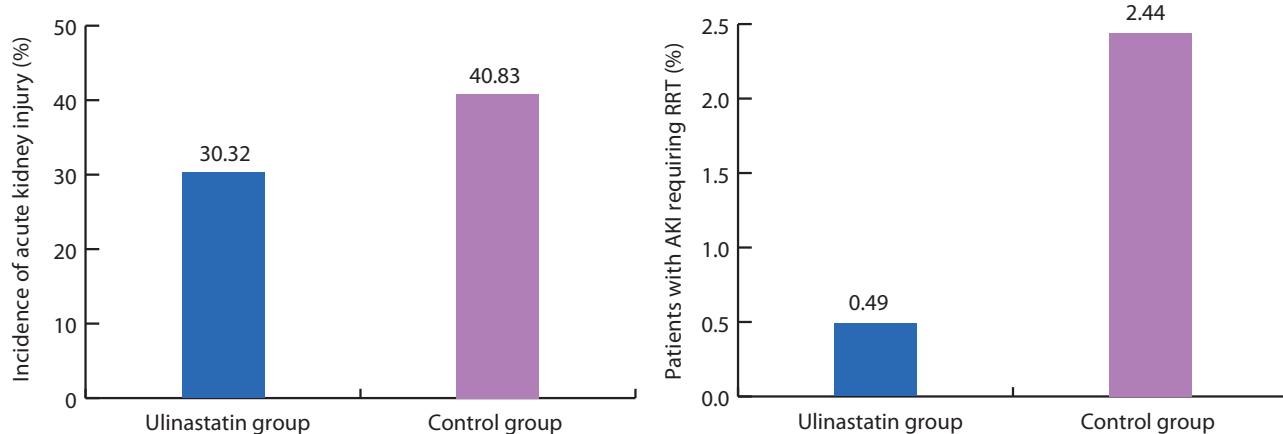
With its protease-inhibiting property, ulinastatin acts as an effective anti-inflammatory molecule that protects tissues and organs against neutrophil-mediated injury, and is regarded as a valuable therapeutic option in a variety of clinical setting involving multiple organs due to systemic inflammatory reaction. Of late, ulinastatin has been used to prevent postoperative complications in patients undergoing various surgical procedures.^{5,8} Several studies have attested the potential usefulness of ulinastatin in the management of postoperative complications and ameliorating clinical outcomes post-surgery.

Evidence based efficacy of ulinastatin in the amelioration of postoperative complications

The clinical experience with ulinastatin was reported in a study⁹ wherein patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) and were administered ulinastatin ($n=409$) were propensity score matched to 409 patients without ulinastatin administration (control group). The results revealed that acute kidney injury (AKI) (40.83 % vs. 30.32 %) and the need for renal replacement therapy (2.44 % vs. 0.49 %) occurred more frequently in the control group than in ulinastatin group (Figure 2). Further, ulinastatin was also found to play a protective role in the development of AKI post-cardiac surgery (odds ratio 0.71, 95 % confidence interval 0.56–0.90, $P=0.005$). The results thus suggested that the administration of ulinastatin seems favorable for patients undergoing cardiac surgery with CPB.

Likewise, in another study¹⁰ involving patients undergoing pancreaticoduodenectomy (PD), the incidence rate of severe postoperative pancreatic fistula (POPF) was considerably less in ulinastatin group (3 of 42; 7%) than that in placebo group (12 of 50; 24%). Ulinastatin also had remarkable protective effects on POPF for patients with small pancreatic duct diameter ($\leq 3\text{mm}$).

Ulinastatin is also shown to be effective in treating postoperative cognitive dysfunction (POCD). A meta-analysis¹¹ of randomized control trials involving 461 elderly patients that underwent surgical operations revealed a remarkable decrease in the incidence of POCD on postoperative day 3 and day 7, among patients on ulinastatin therapy compared with control treatment. Ulinastatin treatment also improved the Mini-Mental State Examination score on day 1, day 3, and day 7 after operation. In another study,¹² ulinastatin

FIGURE 2**Incidence of acute kidney injury (AKI) and AKI in need of renal replacement therapy (RRT) between ulinastatin group and the control group**

Adapted from: Wan X, Xie X, Gendoo Y, et al. Ulinastatin administration is associated with a lower incidence of acute kidney injury after cardiac surgery: a propensity score matched study. *Crit Care.* 2016;20:42.

administration was shown to ameliorate perioperative hyperglycemia by inhibiting the inflammatory reaction, as well as excessive release of inflammatory factors, and improve insulin resistance among patients undergoing partial hepatectomy.

Conclusion

The stress responses to surgical manipulation and associated tissue trauma activate a systemic inflammatory response, which is maintained by a series of factors, including cytokine production. The overproduction of pro-inflammatory cytokines and the inadequate release of anti-inflammatory cytokines during surgery may be deleterious to the organs. Surgical stress can beget immunosuppression in response to the complex interaction of various hormones, cytokines, and acute phase reactants, leading to sepsis, organ failure and death. Ulinastatin, owing to its protease-inhibiting property, acts as an effective anti-inflammatory molecule that protects tissues and organs against neutrophil-mediated injury, and holds an important position in a variety of clinical settings. Lately, a large slew of studies have substantiated the propitious role of ulinastatin in ameliorating postoperative clinical outcomes. It is now considered a valuable option in combating postoperative complications in patients undergoing various surgical procedures.

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CYTOKINES LIE AT THE HEART OF ALL INFLAMMATORY RESPONSES



PRESENTING, AN INHIBITOR OF
INFLAMMATORY CYTOKINES¹

A Potent Serine Protease Inhibitor
In Patients with Sepsis & Acute Pancreatitis

U-Tryp
Ulinastatin
U-Turn Towards Life



1. Shao YM, Zhang LQ, Deng LH, Yao HG, Zhongguo Wei Zhong Bing Ji Ju Yi Xue. 2005 Apr;17(4):228-30.

U-Tryp - Abbreviated Prescribing Information

DESCRIPTION: Ulinastatin is a serine protease inhibitor that reduces the pro-inflammatory response as a result of sepsis, acute pancreatitis, trauma or surgery. Ulinastatin for injection is available in clear colourless liquid. **COMPOSITION:** Each vial contains Ulinastatin J.P., 1,00,000 I.U. Excipients: m-cresol B.P., Sucrose I.P., Disodium hydrogen phosphate dihydrate B.P. Tween 80 I.P., Phosphoric acid I.P. **DOSAGE FORM:** Liquid Injection. **CLINICAL INDICATIONS:** 1. Severe sepsis. 2. Septic endotoxin or traumatic shock. Sepsis is defined as a systemic inflammatory response syndrome (SIRS) in the presence of, or as a result of, suspected or proven infection 1-3. Severe sepsis is defined as sepsis with one of the following features: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or dysfunction of two or more organs. Indian incidence is estimated to be about 140,000 cases per year. The most common causes for sepsis are trauma, burns, abdominal aortic aneurysm, and pneumonia. Sepsis shock is the most common cause of death in the ICU in India. Death due to septic shock to Multiple Organ Dysfunction Syndrome (MODS). Common organ protective factors are diabetes mellitus, use of anti-cancer drugs and corticosteroids given to immunocompromised status. The best two prognostic factors are APACHE II score and number of organ dysfunction. In a study of 10,142 patients mortality risk of 15%, scores of 15-19 indicate risk of 25% and scores of 20-24 indicate 40% mortality risk; scores of 25 and above indicate very high risk of mortality of > 55%. In a large Indian hospital based study of 5,476 ICU admissions, SIRS with organ dysfunction was present in 25%, sepsis in 52.77%, severe sepsis in 16.45% with median APACHE II score = 13 (IQR 13 to 14). The overall mortality in ICU patients was 12.08% but in patients with sepsis it was 59.26%. **DOSAGE AND ADMINISTRATION:** Administer 1 to 2 vials of 100,000 I.U. of Ulinastatin (Reconstituted in 100 ml of Dextrose 5% or 100 ml of 0.9% Normal Saline) by intravenous infusion over 1 hour each time, 1-3 times per day for 3 to 5 days. The dosage may be adjusted according to the age of patients and the severity of symptoms. **USE IN SPECIAL POPULATION:** The safety for pregnant woman is NOT determined yet. Whether or not Ulinastatin should be administered for pregnant woman or potentially pregnant woman is decided according to the patient's condition. 1. Ulinastatin is not used for nursing women in principle. If used, breast feeding should be stopped. 2. The safe dosage for children is NOT determined yet. **CONTRAINDICATIONS:** Hypersensitivity to the drug. **WARNINGS:** 1. Not to be used in patients who are hypersensitive. 2. Not to be used in lactating women. **PRECAUTIONS:** 3. Ulinastatin should be administered with caution if the patient has the history of allergy. 3. Ulinastatin can NOT replace the traditional therapeutic methods (transfusion, oxygen therapy and antibiotics) for shocks. **DRUG INTERACTION:** No drug interactions have been reported or tested. **ADVERSE EFFECTS:** 1. Local reactions: pain at the site of injection. 2. Rare cases of allergy. 3. Rare cases of elevation of Serum Creatinine. 4. Rare cases of increased, vomiting and diarrhea. **OVERDOSE:** No specific antidote is recommended in case of accidental overdose. **PHARMACOKINETICS:** Ulinastatin is a protease inhibitor restricted to the lungs during Ulinastatin is a potent inhibitor of trypsin and chymotrypsin, similar to steroid hormones. It inhibits coagulation and fibrinolysis and promotes microperfusion. Thus, Ulinastatin is an effective agent for immune modulation to prevent organ dysfunction and promote homeostasis. **CLINICAL STUDIES:** 1. A prospective, multicentric, double-blind, randomized phase III clinical study was conducted to compare the efficacy and safety of intravenous Ulinastatin versus placebo along with standard therapy in septic patients. The study included 122 subjects in the Ulinastatin group and 122 subjects in the Placebo group. The 28 day all-cause mortality was 4 subjects in the Ulinastatin group vs 12 in the placebo group ($p=0.0448$). This difference was statistically significant. 10 subjects in the Ulinastatin group and 20 subjects in the Placebo group had new organ dysfunction ($p=0.0569$). Though there was a trend towards less incidence of new organ failure in the Ulinastatin group, this was just short of statistical significance. Mean hospital stay in the Ulinastatin group was 13.59±6.83 days vs. 26.21±5.36 days in the Placebo group. This difference was statistically significant ($p=0.001$). Number of ventilator free days up to day 28 end-of-study were 19.44±10.61 days in the Ulinastatin group and 10.18±12.54 days in the Placebo group. This difference was found to be statistically significant ($p=0.019$). There were no infarction related toxicities in the study. Thus, treatment with Ulinastatin effectively reduced mortality in patients with severe sepsis when used as an adjunctive therapy in addition to standard therapy and ICU care. The reduction in mortality was accompanied by a shorter stay in the hospital and a shorter duration of ventilator and vasopressor usage with no side-effects seen in the study population. 2. A prospective, multicenter, double-blind, randomized, phase III clinical study was conducted to compare the efficacy and safety of intravenous Ulinastatin versus placebo along with standard therapy in patients with severe acute pancreatitis. The study included 122 subjects in the Ulinastatin group and 122 subjects in the Placebo group. The 22-day all-cause mortality was reduced significantly from 18.8% in the placebo group to 2.8% in the Ulinastatin group in the severe pancreatitis sub-group. Hospital stay was shorter in the Ulinastatin group. The reduction of Serum CRP was comparable in the two treatment groups. There was only one incidence of infusion-related toxicity (transient rash). The number of adverse events, all of non-serious nature, were less in the study group vs control group (in mild patients 24 vs 34 and in severe patients 23 vs 45). Thus, treatment with Ulinastatin effectively reduced mortality and morbidity in patients with severe pancreatitis when used as an adjunctive therapy in addition to standard therapy. The reduction in mortality was accompanied by a shorter stay in the hospital and less complications. **PHARMACOKINETICS:** After intravenous injection of 300,000 I.U./10ml into healthy man, its concentration in blood decreases linearly.³ The half-life of Ulinastatin is about 40 minutes.³ 6 hours after the administration, 24% of Ulinastatin is discharged in urine. **INCOMPATIBILITIES:** None Reported. **SHELF LIFE:** Two years from date of manufacturing. **PACKING INFORMATION:** Pack containing 1 vial of 1,00,000 I.U. of Ulinastatin. **STORAGE AND HANDLING INSTRUCTIONS:** Storage temperature 2°C to 8°C. Protect from light. Any unused portion should be discarded.



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