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## Sepsis: an update

### *Sepse: atualidades e perspectivas*

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#### ABSTRACT

This paper aims to provide an update on the main aspects of sepsis, a very relevant health care issue. A number of hypotheses have been proposed to explain its origin, involving interactions between microorganisms and the innate immune system, inflammation/immune mediation and the coagulation system. The clinical features of sepsis are variable and

depend on the primary site of infection. The identification of early signs and symptoms is crucial for starting therapeutic measures fundamentally based on volume resuscitation, antibiotic therapy, use of steroids, anti-coagulant therapy, biologic viability maintenance interventions and nutritional support.

**Keywords:** Sepsis/pathophysiology; Sepsis/diagnosis; Sepsis/therapy

#### INTRODUCTION

Sepsis is a condition where the systemic inflammatory response syndrome (SIRS) is triggered by either a suspected or confirmed infection.<sup>(1-3)</sup> From a clinical point of view, the presentation of sepsis is related to multiple possible interactions between the human being and the microorganisms,<sup>(4)</sup> manifesting with conditions such as infection, SIRS, sepsis, severe sepsis, septic shock and multiple organ system dysfunction (Table 1).<sup>(5-7)</sup> These concepts were proposed in a 1991 consensus conference sponsored by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM)<sup>(5)</sup> in Chicago, United States of America (USA). Ten years later, these concepts were reviewed in a new conference, as shown in chart 1.

From a public health point of view, sepsis is highly relevant. Angus et al. (2001) studied 192,980 cases of severe sepsis in a cohort of more than 6.5 million patients admitted to 847 hospitals in seven American states, estimating its incidence, economic burden and prognosis. The incidence of severe sepsis was 3 cases out of 1,000 inhabitants (751,000 cases/year for the US population), surpassing the incidence of the acquired immunodeficiency syndrome (AIDS) and the predominant types of cancer, resulting in 215,000 deaths per year (28.6% of the cases).<sup>(8)</sup> The figures from the European Union member states are not very different, with an estimated 150,000 deaths per year from sepsis.<sup>(9)</sup> In Brazil, the epidemiological aspects of sepsis have been investigated, deserving particular emphasis the BASES

**Chart 1 - Useful sepsis-related terms and definitions**

Term	Concept
Colonization	Refers to the presence of microorganisms in a given site, but with no harm to the host.
Infection	Presence of a given agent causing harm to the host (the presence of a host inflammatory response to the organism).
Bacteremia	Presence of viable bacteria in the blood, which may be transient; by extension, viremia, fungemia and parasitemia can be characterized.
Systemic inflammatory response syndrome (SIRS)	Characterized as a non-specific body response to a series of conditions causing inflammation including infection, burns, acute pancreatitis, trauma and others. At least 2 of the following conditions are required to meet the definition of SIRS: Temperature > 38.0 °C or < 36.0 °C Heart rate > 90 bpm Respiratory rate > 20 bpm or PaCO <sub>2</sub> < 32 mmHg White blood cell count > 12,000/mm <sup>3</sup> or < 4,000/mm <sup>3</sup> or > 10% bands
Sepsis	SIRS triggered by bacterial, viral, fungal or parasitic infection.
Hypotension	Systolic blood pressure < 90 mmHg or a 40 mmHg drop from the “baseline” pressure.
Severe sepsis	Sepsis associated with organ dysfunction, tissue hypoperfusion (chiefly characterized by oliguria, altered mental status and/or lactic acidosis), or arterial hypotension.
Septic shock	Hypotension (not ascribed to another cause) with tissue hypoperfusion caused by sepsis. It can be <i>early</i> when lasting less than one hour (in response to an infusion of crystalloid solution, 0.5 to 1 liter), or <i>late</i> , when lasting more than one hour and/or requiring vasoactive amines.
Multiple organ dysfunction syndrome (MODS)	Functional organ changes in a severely ill patient, so that homeostasis cannot be maintained without therapeutic intervention. It is <i>primary</i> if it is a consequence of the injury itself (e.g., respiratory failure due to severe community acquired pneumonia) or <i>secondary</i> if it is a consequence of the host response to the injury (e.g., acute respiratory distress syndrome in a patient with acute necrotizing pancreatitis).

**Sources:** American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med.* 1992;20(6):864-74. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; SCCM/ESICM/ACCP/ATS/SIS. SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31(4):1250-6.

Study (Brazilian Sepsis Epidemiological Study). This was a multicenter observational cohort study conducted in five public and private intensive care units (ICUs) where the incidence of sepsis was found to be 57.9 per 1,000 patient days (95% confidence interval (CI): 51.5-65.3).<sup>(10)</sup> The mortality rate for patients with SIRS (from either sepsis or any other cause), sepsis, severe sepsis and septic shock was 24.2%, 33.9%, 46.9% and 52.2%, respectively. Other studies such as SEPSE Brasil<sup>(11)</sup> and COSTS<sup>(12)</sup> showed similar mortality rates. Importantly, the PROGRESS<sup>(13)</sup> multicenter trial, involving seven Brazilian ICUs, showed that mortality rates in Brazilian ICUs were higher (56%) when compared to the rates in other developing countries (30%), although there were no differences in either the median ages or the prognosis and organ dysfunction scores for the populations studied.

The use of clear terminology has aided scientific investigation and early bedside detection of sepsis. Early diagnosis, combined with appropriate therapy, has been shown decisively to achieve improved outcomes in

sepsis. Based on these considerations, this paper aimed to revisit the main features of sepsis, especially its etiology, pathogenesis, clinical features, diagnosis and therapy, intending to outline a more evidence-based approach to caring for septic patients.

## METHODS

Research for this manuscript consisted of a literature review with a defined search strategy. The Scientific Electronic Library Online (SciELO) and the U.S. National Library of Medicine (PubMed) databases were searched for human studies published between January 1, 2000, and June 30, 2010. The following search terms were used: “sepsis and pathophysiology,” “sepsis and diagnosis” and “sepsis and treatment.”

Strategy 1 – sepsis + pathophysiology;

Strategy 2 – sepsis + diagnosis;

Strategy 3 – sepsis + treatment. In addition, relevant information was gleaned from a search of internal medicine, infectious disease and critical care textbooks.

The search provided the references distributed as shown in chart 2. Forty texts were selected, related to empirical investigations and literature reviews, mainly focused on the pathophysiologic and clinical-therapeutic aspects of sepsis. Information from the articles was organized into the following sections: (1) etiological aspects of sepsis; (2) pathophysiological aspects of sepsis; immunology, inflammation and coagulation; (3) diagnosis; (4) treatment and (5) closing remarks.

**Chart 2 - Literature search results: number of papers retrieved**

Search strategy	Database	
	PubMed*	SCIELO
Strategy 1 (sepsis + pathophysiology)	1,488	11
Strategy 2 (sepsis + diagnosis)	10,856	82
Strategy 3 (sepsis + therapy)	12,663	103

\*For the PubMed search, English language terms were used with the following parameters: human studies, adult patients (over 19 years old) and published between January 1, 2000, and June 30, 2010.

## ETIOLOGICAL ASPECTS OF SEPSIS

Sepsis can be a consequence of different infectious processes starting in different sites, identifiable based on a careful anamnesis and a detailed physical examination. However, eventually sepsis' signs and symptoms are the first presentation of the patient's disease. Identifying a plausible origin of the infection is helpful in determining the possible etiology, which in turn is crucial to estimate antimicrobials' sensitivity (e.g., differentiating between community-acquired and nosocomial infections).<sup>(1,14)</sup>

## PATHOPHYSIOLOGICAL ASPECTS OF SEPSIS: IMMUNOLOGY, INFLAMMATION AND COAGULATION

The development of sepsis depends on the interactions between the microorganism and the host.<sup>(1)</sup> However, many aspects related to the development of sepsis remain obscure, likely due to the lack of appropriate understanding of the interplay between immunity, inflammation and coagulation.<sup>(4)</sup>

### Microorganism/host interaction: the innate immune response

The interaction between microorganisms and a host starts by the recognition of the microorganism's

substances as non-self. Pathogen-associated molecular patterns (PAMP), non-variable molecules expressed by groups of pathogens that are typically crucial for the pathogen's virulence and/or survival, are identified by the standard recognition receptors (SRR) expressed by cells of the innate immune system.<sup>(15)</sup>

Endotoxins derived from the cell wall of Gram-negative bacteria and typically lipopolysaccharides (LPS), are among the most studied PAMP. These molecules are transferred to the CD14 and TLR4 receptors (the latter a Toll-like receptor family representative) on the surface of monocytes, macrophages, dendritic cells and neutrophils<sup>(16)</sup> by a binding plasma LPS known as LBP (LPS-binding protein). TLR4 is also apparently involved in the recognition of some viral proteins and lipoteichoic acid (*Staphylococcus aureus*), although this antigen is also recognized by another Toll-like receptor family molecule (TLR2).<sup>(17)</sup> Similarly, other Toll-like receptor family molecules are involved in the initial innate immune response, including TLR3 (presumed to be related to the identification of double-stranded RNA), TLR5 (able to identify flagellin) and TLR9 (responsible for identifying bacterial DNA non-methylated CpG sequences).<sup>(15)</sup> In Gram-positive infections, another Toll-like receptor protein, TLR2, is responsible for signaling these bacterial proteoglycans. It should be noted that polymorphisms in these receptors apparently have decisive implications on whether or not the infected host progresses to severe sepsis and septic shock.<sup>(18)</sup> Following this recognition phase, several cell activation and cytokine production events occur, resulting in the development of SIRS.

### Inflammation and immune mediation

Immediately following the host's recognition of PAMP and Toll-like receptors, different cell signaling pathways are triggered, including NOD (nucleotide-binding oligomerization domain) and MyD88 (myeloid differentiation protein 88) intracellular proteins.<sup>(19)</sup> The interaction of MyD88 with the enzyme IRAK (interleukin-1 receptor associated kinase, a serine-threonine-kinase) leads to the activation of the I $\kappa$ B and I $\kappa$ KB kinases, forming the dimer I $\kappa$ K. I $\kappa$ K "disconnects" the I $\kappa$ B protein (inhibitor of NF- $\kappa$ B) that is bound to the NF- $\kappa$ B nuclear transcription factor ( $\kappa$ B nuclear factor). The I $\kappa$ B protein is responsible for activating genes for the transcription of several cytokines that have a role in SIRS (whether or not they are associated with infection).<sup>(20)</sup>

This sequence, which ends with the release of NF-

$\kappa$ B, determines the production and secretion of several proinflammatory cytokines, such as interleukins (IL-1, IL-2, IL-6, IL-8 and IL-12); TNF- $\alpha$  (tumor necrosis factor alpha) and TNF- $\beta$  (tumor necrosis factor beta), which are considered crucial to the development of sepsis. It should be emphasized that some patients die early due to an intense systemic inflammatory reaction. However, the anti-inflammatory interleukins IL-4, IL-5, IL-10, IL-11 and IL-13 are produced as well, especially in conditions where the patient survives to develop a systemic inflammation-related disorder. The production of these anti-inflammatory interleukins allows the development of energy and slows the host's response to etiologic agents. This type of immunosuppression<sup>(3)</sup> has different descriptors in the context of sepsis, including immunoparalysis, the immunodeficiency window or compensatory anti-inflammatory response syndrome (CARS).<sup>(7)</sup> The regulation of this pro/anti-inflammatory balance is complex, with an emphasis on monocytes/macrophages and adaptive immune response activators. When phagocytizing necrotic or bacterial cells, macrophages induce lymphocytes to assume their Th1 phenotype, leading to the release of pro-inflammatory substances such as interferon alpha (INF- $\alpha$ ), interferon delta (INF- $\delta$ ) and IL-2. When apoptotic cells are phagocytized, the Th2 lymphocyte phenotype is activated, leading to the production of the anti-inflammatory interleukins IL-4 and IL-10.<sup>(21)</sup> In addition, neutrophil dysfunction, particularly related to derangements of neutrophil migration, as a consequence of a decrease in adhesion molecules and the CXCR2 chemokine receptor expression secondary to an intensive release of proinflammatory mediators, was shown to be one of the factors responsible for increased severity in sepsis.<sup>(22)</sup> Based on these considerations, the imbalance between the pro/anti-inflammatory mediators, which may include very severe "immunological dissonance" conditions called MARS (where SIRS and CARS are seen in a same patient)<sup>(7)</sup> is proposed to be the key to explain sepsis outcomes.

In this complex pathophysiologic grid, TNF- $\alpha$  has a relevant role, stimulating leukocytes and endothelial cells to release other cytokines (as well as more TNF- $\alpha$ ), express cell surface adhesion molecules and increase the turnover of arachidonic acid.<sup>(23)</sup> In addition, the reciprocal stimulation between TNF- $\alpha$  and IL-1 leads to the development of a pro-coagulant state due to the inhibition of thrombomodulin and promotes a series of septic hemodynamic changes, such as increased vascular permeability, reduced peripheral vascular resistance and negative inotropism.

Vascular disorders may also result directly from endotoxins. Activation of the alternative pathway of the complement cascade, resulting in the release of C3<sub>a</sub> and C5<sub>a</sub>, which induce vasodilatation, cause increased vascular permeability, increased platelet aggregation and neutrophil activation and aggregation. All of these changes lead to the microvascular alterations that occur with septic shock. Endotoxins also lead to release of kallikrein, kininogen and bradykinin (by activation of factor XII, or Hageman's factor). In particular, bradykinin is considered a potent vasodilator that causes hypotension. Factor XII activation may activate the intrinsic coagulation pathway resulting in disseminated intravascular coagulation (DIC).<sup>(24)</sup>

In addition, nitric oxide's role in vasodilatation should be highlighted. Its synthesis is increased in patients with sepsis with consequent vasodilatation, which can be antagonized using nitric oxide synthase inhibitors.<sup>(25)</sup>

### The coagulation system

Activation of the coagulation system via tissue factor expression, an event mediated by microorganisms, proteins and proinflammatory cytokines, and the inhibition of endogenous anticoagulants (antithrombin III, protein C, protein S and the tissue factor pathway inhibitor (TFPI) which modulate coagulation and accelerate fibrinolysis) have a decisive role in the development of severe sepsis and septic shock.<sup>(26)</sup> This scenario may include DIC, characterized by (1) activation of intravascular coagulation, (2) microvascular fibrin formation and deposition, (3) platelet consumption and (4) typical fibrinolytic changes. All of these changes are significant predictors of death. The consequent obstruction of the blood flow to organs and tissues contributes to poor tissue perfusion (although expected due to the critical hypotension) and organ system failure. Additionally, the consumption of fibrin and platelets (due to the activation of intravascular coagulation) may lead to severe bleeding with additional complications.

### Physiopathogenic outcomes

The progression to sepsis may lead to multiple organ system dysfunction. This mechanism likely results from disseminated endothelial injury, with fluid leakage and consequent interstitial edema and hypovolemia, in addition to the previously described coagulation disorders (e.g., micro-thrombi formation reducing tissue oxygenation and nutritional supplies). Moreover, in sepsis, anti-insulin hormones are increasingly released

(glucagon, corticosteroids, catecholamines and growth hormone). This results in hypermetabolism, including increased glycogenolysis and hepatic glycogenesis; increased lipolysis; and muscle, intestine and connective tissue protein catabolism. Together these mechanisms lead to tissue hypoxia, lactic acidosis (increased blood lactate is associated with an increased disease severity), and cell death.

## DIAGNOSIS

The diagnosis of sepsis is suggested by non-specific clinical and laboratory findings (Chart 3) and later confirmed by the isolation of the causative agent (from cultures of various biological materials). Imaging studies, such as radiography, ultrasound, echocardiogram, computed tomography and magnetic resonance imaging, may be very useful for both diagnosis and clinical follow-up.

A large number of biological materials have been investigated as candidates for sepsis biomarkers and/

or mediators. C-reactive protein (CRP), procalcitonin, IL-6 and IL-18 are considered useful for diagnosing sepsis and characterizing its severity, although they have limitations.<sup>(27-29)</sup> More recently, many researchers have studied a wide range of molecules to show their clinical usefulness as sepsis biomarkers, including high mobility group protein (HMGB-1) and triggering receptor expressed on myeloid cells (TREM-1). Some sepsis biomarkers, such as cytokines, are also considered significant sepsis mediators, and their modulation is therapeutically relevant.<sup>(30)</sup> Additionally, a combined set of molecular markers and/or more accurate severity and prognostic scores is believed to be predictive of outcomes in sepsis.<sup>(31)</sup>

Proteomic analysis methods can be used to investigate the protein profiles in patients with sepsis and septic shock and characterize the differences in protein electrophoresis mapping of surviving and non-surviving patients. Proteomic analyses can also be used to screen peptides to document the protein's distribution within a cell, organ or other tissue

**Chart 3 - Sepsis: medical and laboratory diagnostic criteria\***

Categories	Characteristics
Overall	Temperature: fever (temperature > 38.3°C) or hypothermia (temperature < 36.0°C) Heart rate > 90 bpm or > 2 SD above the normal age range Respiratory rate: tachypnea Altered mental status Clinically significant edema or positive FB (> 20 mL/kg/24 hours) Hyperglycemia (excluding preexisting diabetes mellitus): blood glucose > 120 mg/dL
Inflammatory	WBC: leukocytosis (WBC > 12,000 cells/mm <sup>3</sup> ) or leukopenia (WBC < 4,000 cells/mm <sup>3</sup> ) or normal WBC with > 10% immature forms (bands). Plasma C-reactive protein > 2 SD above the normal range Plasma procalcitonin > 2 SD above the normal range
Hemodynamics	Blood pressure: hypotension with SBP < 90 mmHg; MBP < 70 mmHg or a > 40 mmHg SBP reduction in adolescents; or SBP/MBP < 2 SD below normal for the patient's age Mixed venous oxygen saturation: > 70%** Cardiac index > 3.5 liters/min **
Tissue perfusion	Serum lactate: hyperlactatemia (> 2.5 mmol/L) Reduced capillary filling
Organ dysfunction	Arterial blood gas: hypoxemia (PaO <sub>2</sub> / FiO <sub>2</sub> < 300) Renal function: acute oliguria (diuresis < 0.5 mL/kg/hour) and serum creatinine > 0.5 mg/dL Blood coagulation: INR > 1.5 or PTT > 60 seconds or reduced platelet count (< 100,000/mm <sup>3</sup> ) GIT: ileus (no bowel sounds) Bilirubin: hyperbilirubinemia (TB > 4 mg/dl)

**Source:** Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; SCCM/ESICM/ACCP/ATS/SIS. SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31(4):1250-6.

FB – fluid balance; BPM – beats per minute; TB – total bilirubin; SD – standard deviation; FiO<sub>2</sub> – inspired oxygen fraction; INR - international normalized ratio; WBC – white blood cell count; PaO<sub>2</sub> – partial oxygen pressure in arterial blood; SBP – systolic blood pressure; MBP – mean blood pressure; GIT – gastrointestinal tract; PTT – partial thromboplastin time; WBC – white blood cell count. \*To meet the definition of sepsis, a patient must have one of these criteria in combination with either suspected or documented infection. \*\*Not valid for children.

sample; to identify and characterize the individual proteins of interest and to clarify their roles in the biologic function of cells. Using these lines of investigation, proteomic analyses have provided two relevant findings.<sup>(31-33)</sup> First, proteomic analysis can be used to identify early protein expression changes in septic shock patients. Second, in early septic shock, there are specific protein differences between Day 28 survivors and non-survivors. This can be verified in samples collected within the first 12 hours after a septic shock diagnosis. However, there are significant protein expression differences in early sepsis in patients surviving sepsis and septic shock compared to non-survivors. For instance, the BB segment of Factor B – a member of the alternative complement pathway which provides the first-line response to infection and participates in antibody-independent monocyte-mediated cytotoxicity, macrophage propagation, plasminogen activation and B lymphocyte proliferation – is strongly activated in patients who survive sepsis.

To follow patients with sepsis, one can use the Acute Physiologic Chronic Health Evaluation (APACHE II) score, created to evaluate in-hospital mortality and based on physiological evaluations to determine disease severity. However, the Sequential Organ Failure (SOFA) score, which includes respiratory, hematologic, hepatic, cardiovascular, neurologic and renal variables,<sup>(34)</sup> is the best strategy because it is more precise and specific. Recently, the addition of inflammatory biomarkers to these scores has been considered, aiming to improve sepsis patients' prognostic assessment.<sup>(35)</sup>

Another important assessment tool for septic patients is the PIRO concept, based on several elements which include predisposition (P), injury (I), host response (R) and organ failure (O).<sup>(36)</sup> The PIRO concept is useful for categorizing septic patients to develop studies both to better understand the pathophysiology and to improve therapeutics.<sup>(37)</sup>

## TREATMENT

The therapeutic approach to patients diagnosed with sepsis remains a medical challenge despite all of the recent advances. The therapy for sepsis, severe sepsis and septic shock and multiple-organ system failure (MOSF) includes: (1) volume resuscitation; (2) treatment of the infection; (3) the use of corticosteroids; (4) anticoagulant therapy; (5) blood glucose control; (6) respiratory support; and (7) additional therapeutic measures.

### Volume resuscitation

The management of sepsis of any severity necessarily requires initial volume resuscitation. Early goal-directed therapy (EGDT) was introduced in 2001 and recommended vigorous volume resuscitation every 30 minutes until reaching a central venous pressure (CVP) between 8 and 12 mmHg, a mean blood pressure (MBP) between 65 and 90 mmHg and at least 0.5 mL/kg/hour urinary output, therefore avoiding the injuries from inappropriate tissue perfusion. EGDT should be combined with measures aimed to keep the central venous oxygen saturation (SVO<sub>2</sub>) above 70% (e.g., the use of blood transfusions, vasoactive amines, ventilation support and other interventions).<sup>(38)</sup> In prior studies, the EGDT approach led to significantly reduced mortality for patients treated with this protocol compared to patients treated with traditional resuscitation protocols. Therefore, EGDT is considered the gold standard for resuscitation and treatment in patients with early severe sepsis and septic shock.<sup>(38)</sup>

In cases where volume replacement fails to restore the blood pressure and end-organ perfusion, vasopressors should be used. Until recently, norepinephrine was considered the drug of choice.<sup>(38)</sup> However, it was recently shown that there is no mortality difference between dopamine- and norepinephrine-treated shock patients, although noradrenalin's risk of adverse events is lower.<sup>(39)</sup>

### Treatment of infection

The Surviving Sepsis Campaign guidelines support the initiation of appropriate antibiotic therapy started within one hour after a sepsis diagnosis in an ICU or within three hours after diagnosis in the emergency room or in ward patients.<sup>(40)</sup> The initial antibiotic therapy regimen should be broad spectrum to provide therapy for all possible site-related organisms.<sup>(1,41)</sup> In addition, it is key for the selected antibiotics to have good penetration in the most likely infectious source, as there is solid evidence that inappropriate early antimicrobial therapy is associated with poorer prognosis, even when corrected later. Initial therapy should be always reviewed after 48-72 hours, after culture results are available, and tailored to reduce the spectrum, toxicity and costs.<sup>(40)</sup>

In association with appropriate antimicrobial use, every patient admitted with a sepsis diagnosis should be evaluated for the eventual need for surgical control of the primary infection site. This type of surgical site control may include abscess drainage, necrotic tissue

debridement and the removal of infected devices, among other measures.

### Corticosteroids

The use of corticosteroids (hydrocortisone 200-300 mg/day, given every eight hours for seven days) is recommended for septic shock patients who remain hypotensive after vigorous volume replacement requiring vasopressors to maintain satisfactory blood pressure.<sup>(42)</sup> However, the results of the CORTICUS trial<sup>(43)</sup> should be highlighted. This trial demonstrated that hydrocortisone failed to increase survival, failed to increase the number of septic patients whose shock could be reversed, although, in responsive patients, allowed faster shock reversion.<sup>(43)</sup>

### Anticoagulant therapy

C-protein bound to its endothelial cells and leukocyte receptor (C-protein cell receptor) is recognized to have an anti-inflammatory role. The "C-protein/receptor" complex is displaced to the nucleus where it triggers several effects:<sup>(44)</sup> (1) reduction of thrombin generation; (2) reduction of inflammatory cytokine production by means of an intracellular NF- $\kappa$ B action blockade; (3) prevention of LPS binding to its CD14 membrane receptor; (4) reduction of TF expression; (5) minimization of adhesion molecule expression; (6) reduction of pro-apoptotic gene transcription and (7) an increase in messenger RNA production from anti-apoptotic genes.

Early use of recombinant human activated protein C (drotrecogin alpha) reduced mortality in patients with an increased risk of death, although it increased the risk of bleeding events. Therefore, although drotrecogin alpha was recommended by the Surviving Sepsis Campaign,<sup>(40)</sup> a judicious evaluation of its efficacy is ongoing in the PROWESS-SHOCK trial; these study results are expected to be published soon.<sup>(45)</sup>

### Blood glucose control

Until recently, strict blood glucose control was targeted in sepsis treatment (blood glucose < 150 mg/dL, ideally between 80 and 110 mg/dL), with evidence of improved survival. However, the NICE-SUGAR trial, published in 2009, has shown that strict blood glucose control (81 to 108 mg/dL) increases mortality in ICU adult patients, proposing 180 mg/dL as a blood glucose target.<sup>(46)</sup> It should be highlighted that hypoglycemia, when diagnosed, should be promptly treated.

### Nutritional support

The provision of oral nutrition is not usually feasible in septic patients due to an array of factors that limit its use such as the patient's decreased level of consciousness level and gastrointestinal changes like ileus, among others. Therefore, alternative forms of nutritional support are necessary (if the patient is not hemodynamically unstable - a contraindication to nutrition therapy) to minimize the risk of malnutrition.<sup>(47)</sup>

Enteral nutrition (EN) is the preferred form of nutrition in septic patients. It has important advantages over parenteral nutrition including<sup>(47,48)</sup> (1) maintenance of the digestive tract integrity; (2) less frequent complications; (3) a decreased risk of bacterial translocation and (4) lower cost.

Parenteral nutrition (PN) is reserved for conditions where enteral nutrition is not sufficient to provide the estimated nutrition needs (combined EN/PN), or in cases where the use of the gastrointestinal tract is unfeasible (PN alone).

Intravenous glutamine supplementation has been recently recommended, with effects on activation of immune system cells Th1 effector response, and Th2 in enterocytes.<sup>(48)</sup>

### Ventilation support

Mechanical ventilation is indicated for many septic patients secondary to the acute respiratory failure associated with the underlying disease or due to the SIRS effects on the respiratory system, including the adult acute respiratory distress syndrome (ARDS). In such conditions, patients should be optimally sedated and mechanical ventilation should be used with appropriately adjusted respiratory parameters. For ARDS patients, protective ventilation is recommended, characterized by initially reduced tidal volumes (6 mL/kg body weight) in conjunction with < 30 cm H<sub>2</sub>O inspiratory peak pressure.<sup>(49)</sup> Some degree of positive end expiratory pressure (PEEP) should be maintained (above 8 cm H<sub>2</sub>O) to achieve alveolar recruitment and to prevent pulmonary collapse and provide appropriate oxygenation.

### Additional therapeutic measures

The different possible complications in septic patients, which include acute renal failure, metabolic acidosis, DIC, upper gastrointestinal bleeding (UGIB) and deep vein thrombosis (DVT), should be approached both prophylactically and therapeutically,<sup>(1,50)</sup> as shown in chart 4.

**Chart 4 - Sepsis: a therapeutic summary**

Condition	Proposed therapy
Fever, chills, myalgia	Analgesics, anti-pyretics
Hypotension	Target-guided volume replacement (CVP 8-12 mmHg, MBP 65 to 90 mmHg and urinary output $\geq$ 0.5 mL/kg/hour) and vasoactive amines
Hypoxemia	Oxygen supplementation, non-invasive ventilation or mechanical ventilation (as needed)
ARDS	Orotracheal intubation, mechanical ventilation (starting tidal volume = 6 mL/kg body weight and peak inspiratory pressure < 30 cmH <sub>2</sub> O) with PEEP (>8 cmH <sub>2</sub> O)
Metabolic acidosis	Appropriate hydration; bicarbonate evaluation (pH < 7.1)
Acute renal failure	Fluid and electrolyte management, initiate dialysis, correct drug dosages for the creatinine clearance
Thrombocytopenia	Platelet transfusion
DIC	Fresh frozen plasma and platelet transfusion; use of drotrecogin-alpha
Thrombosis	Heparin
UGIB	Nasogastric suction, H <sub>2</sub> or proton-pump inhibitors; blood transfusions if required
Hyperglycemia	Regular insulin (ideally blood glucose between 80-150 mg/dL)
Hypoglycemia	Continuous 10% glucose infusion
Heart dysfunction	Vasoactive amines (dobutamine and phenylephrine)
Hypercatabolism	Nutrition support, enteral nutrition preferred; avoid energy overload (risk of hyper-feeding)

ARDS – adult respiratory distress syndrome; DIC – disseminated intravascular coagulation; UGIB – upper gastrointestinal bleeding; CVP – central venous pressure; MBP – mean blood pressure

## CONCLUSIONS

Despite the remarkable production of scientific research on sepsis pathophysiology and therapy, the care of patients with this condition remains a medical challenge. Possible interventions in the area of the inflammatory response and coagulation, aimed to reduce the morbidity and mortality and improve the prognosis of sepsis, have been investigated extensively. Significant advances in the care of septic patients, such as early goal-directed therapy, have been achieved. However, a wide variety of possibilities remain to be explored.

The importance of providing *full care* to the patient cannot be overstated. Indeed, early diagnosis, based on judicious surveillance, and appropriate therapy remain the best ways to ensure better outcomes for septic patients.

## AUTHORS' ROLES

Siqueira-Batista R, Gomes AP, Calixto-Lima L, Vitorino RR, Perez MCA and Mendonça EG collaborated for writing the different parts of this manuscript.

Oliveira MGA and Geller M performed the critical review and final text corrections.

## RESUMO

O objetivo do presente artigo é oferecer uma atualização dos principais aspectos da sepse, complicação infecciosa extremamente importante do ponto de vista da clínica e da saúde pública. Algumas hipóteses têm sido propostas para explicar sua gênese, as quais encerram aspectos referentes a interação microrganismo/sistema imune inato, a inflamação/ mediação imunológica e o sistema de coagulação. As manifestações clínicas são variadas e dependem do local primário da infecção. A identificação precoce dos sinais e sintomas é de crucial importância para a instituição de medidas terapêuticas que se baseiam, fundamentalmente, em reposição volêmica, antibioticoterapia, emprego de corticosteróides, tratamento anticoagulante, medidas de manutenção da viabilidade biológica e suporte nutricional.

**Descritores:** Sepse/fisiopatologia; Sepse/diagnóstico; Sepse/terapia

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