

Sepsis: A Review of Advances in Management

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ABSTRACT

Infections represent a common health problem in people of all ages. Usually, the response given to them is appropriate and so little treatment is needed. Sometimes, however, the response to the infection is inadequate and may lead to organ dysfunction; this is the condition known as sepsis. Sepsis can be caused by bacteria, fungi or viruses and at present there is no specific treatment; its management basically focuses on containing the infection through source control and antibiotics plus organ function support. This article reviews key elements of sepsis management, focusing on diagnosis, biomarkers and therapy. The main recent advance in therapy is the strategy of personalized medicine, based on a precise approach using biomarkers to identify specific individuals who are likely to benefit from more personalized attention.

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INTRODUCTION

Sepsis is one of the most common causes of death among hospitalized patients in the intensive care unit (ICU). It is particularly difficult to diagnose in this setting because of the multiple comorbidities and underlying diseases that these patients present [1, 2].

The definitions of sepsis and septic shock focusing on the host's inflammatory response have remained unchanged since the first consensus conference held in 1991. Advances in the understanding of the pathophysiology of sepsis, which is characterized today as a host reaction to infection involving not only the activation of pro- and anti-inflammatory responses but also modifications in non-immunological pathways (cardiovascular, autonomic, neurological, hormonal, metabolic and clotting), have led experts to revise the definitions. In 2016, the Sepsis-3 conference defined sepsis as a "life-threatening organ dysfunction caused by a deregulated host response to infection", and septic shock as a "subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality" [3]. This is a narrative review with the objective to update the advances in sepsis management. The first part focuses

on diagnosis, with a review of potential contribution of biomarkers, and the second part focuses on advances in therapy.

Compliance with Ethics Guidelines

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

DIAGNOSIS OF SEPSIS

Clinical Diagnosis

The Sepsis-3 definitions call for a new clinical tool to replace the criteria for systemic inflammatory response syndrome (SIRS) in identifying patients with sepsis. These criteria are non-specific, as they are not present in all patients with infection, and they do not necessarily reflect an abnormal host response. This is, for example, the case of fever: immunosuppressed patients do not always develop fever, so the infection is hard to detect. In contrast, critically ill patients have a certain degree of hyperthermia but may not present infection [4].

The current recommendation for identifying both sepsis and septic shock is the use of the SOFA score [Sequential (Sepsis-Related) Organ Failure Assessment]. SOFA is a simple system, which uses accessible parameters in daily clinical practice to identify dysfunction or failure of the key organs as a result of sepsis. It was developed at an expert meeting and the assessment of physiological changes in response to septic attack was scored by consensus. Despite this initial subjectivity, the SOFA calibration is correct and properly adjusted to the subsequent evolution of the patient. Regardless of the initial SOFA score, an increase during the first 48 h in the ICU predicts a mortality rate of at least 50% [5, 6].

In 2016, qSOFA (quick SOFA) was developed. This new score includes only clinical criteria that are easily and quickly measurable at the bedside:

- Altered level of consciousness, defined as a Glasgow Coma Scale score ≤ 13 .
- Systolic blood pressure ≤ 100 mmHg.
- Respiratory rate ≥ 22 rpm.

When at least two of these criteria are present, it has been suggested that qSOFA has a similar predictive validity to the original score for the detection of patients with sepsis and likely to have a poor outcome [3]. Further validation is required, and it has received initial criticism on the grounds that it may be difficult to use in low- and middle-income countries. Moreover, sensitivity may be only 50% in patients with pneumonia in the Emergency Department, and poor specificity in subsets like hematological patients is to be expected.

It should be noted that recognition of septic shock has usually been associated with the presence of hypotension. However, this criterion is insufficient, since in most patients the onset of hypotension is preceded by tissue hypoperfusion. Tissue hypoperfusion is detected by measuring the levels of lactate in blood. Hypotension often does not appear, or appears late, whereas tissue perfusion may be severely compromised on a global or regional level without necessarily being associated with hypotension. For these reasons, the recognition of septic shock must be based on identifying tissue hypoperfusion. As there is no single and specific criterion for its identification, several parameters need to be evaluated [7, 8].

Laboratory Diagnosis

Laboratory tests are required to help diagnose sepsis, distinguish it from other conditions, and evaluate and monitor organ function, blood oxygenation and the acid–base balance.

In the diagnosis of sepsis, the contribution of laboratory hematological, biochemical and microbiological test is essential. However, culture-based diagnosis is slow, and so, in recent years, major efforts have been made to find biomarkers that allow early diagnosis of this disease. In general, the markers that are studied are related to inflammatory mechanisms, in the hope that they could complement or replace

others already in use, such as C-reactive protein (CRP) and procalcitonin (PCT). These tools cannot be used alone, and should complement careful clinical assessment and other laboratory data. Many studies looking for the ideal biomarker are underway, although progress is slow [9, 10].

Other imaging tests are needed to evaluate the state of various organs, detect complications and identify the location of the infection. These tests are usually X-rays, CT scans or ultrasounds.

BIOMARKERS OF SEPSIS

What They Are and What They Are For

A biomarker is defined by the National Institutes of Health as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [11]. In various types of laboratory test, physicians use biomarkers for patient diagnosis and treatment. In clinical practice, biomarkers may also be used for diagnostic or prognostic purposes, or as an associate to treatment, to identify those who may benefit most from a specific therapy or to predict its efficacy or toxicity [12]. The use of biomarkers is on the rise and there is a high demand for new molecules able to identify sepsis and septic shock.

Sepsis can be divided into two sequential phases: first, an initial hyper-inflammatory phase characterized by SIRS, which may resolve; second, a subsequent immunosuppressive phase, usually characterized by organ dysfunction and commonly referred to as CARS (compensatory anti-inflammatory response syndrome). There are markers of both phases, although the markers of the hyper-inflammatory phase are more numerous.

Proinflammatory Biomarkers

C-Reactive Protein (CRP)

CRP is an acute-phase protein produced by the liver, although it can also be synthesized by

other cells like alveolar macrophages. Its plasma concentration remains stable in healthy patients, but its levels increase after trauma, inflammation, and other stimuli related to tissue damage. Bacterial infections are powerful stimuli that produce a rapid rise in CRP levels in a few hours. Interleukin-6 (IL-6) is thought to be the main mediator stimulating the production of CRP, but other cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF- α), also produce it. Changes in plasma levels of CRP may be useful in the diagnosis and prognosis of infection; a fall in plasma levels indicates infection resolution. Its short half-life of about 19 h makes CRP a useful tool in the monitoring of the inflammatory response, infection, and antibiotic therapy. In addition, CRP laboratory tests are less expensive than cytokine measurements [13].

In contrast to most acute-phase proteins which undergo large variations in plasma levels (depending on rates of synthesis, consumption and catabolism), CRP plasma levels remain almost constant. This means that they are determined solely by the rate of synthesis, and their values reflect the presence and scale of the disease. Certain studies have linked the number of organ failures in septic patients with the severity of the clinical condition and with the intensity of the inflammatory stimulus, finding a moderate relationship between CRP levels and the number of organ failures. The CRP plasma concentration appears to reflect the magnitude of the inflammatory stimulus and sepsis severity [14].

Isolated CRP values can be helpful in diagnosing sepsis. However, in clinical practice, serial measurements are more useful to monitor the patient's response. CRP is quite unspecific and it does not differentiate sepsis from other diseases, but it is commonly used to screen for early onset neonatal sepsis (within the first 24 h of life) because its sensitivity has been shown to be very high [15]. This sensitivity is also high after surgery, and so it is also used to monitor patients in the post-operative process [16].

Procalcitonin (PCT)

Procalcitonin (PCT) is widely considered to be the most useful marker of severe systemic

inflammation [17]. Procalcitonin is normally present in the blood at very low levels; however, its production can be stimulated by inflammatory cytokines and bacterial endotoxins, causing its release in greater quantities in response to infection, and, in particular, to systemic bacterial infections. Compared to all other currently available sepsis markers, PCT seems to also have potential for discriminating between infectious and non-infectious systemic inflammation in low-acuity patients [18]. It may also be able to differentiate between viral and bacterial infections and may indicate the presence of bacterial superinfection in patients with viral diseases [19].

Procalcitonin levels serve as a biomarker of inflammatory response, providing an indicator of risk of sepsis: the higher the level of PCT, the greater the likelihood of systemic infection and sepsis. Given its high sensitivity to most types of infections, procalcitonin is widely regarded as the most sensitive biomarker to help diagnose (or rule out) bacterial sepsis. Global guidelines also recommend its use as a tool to optimize antibiotic treatment.

Procalcitonin has a shorter half-life than CRP, and PCT levels rise sooner in cases of bacterial infection. These favorable kinetics may allow earlier diagnosis of sepsis and better monitoring of its progression.

Biomarkers of the Immunosuppressive Phase

The importance of CARS after the hyper-inflammatory phase of sepsis was recognized a long time ago, but it is only recently that several biomarkers of this phase have started to receive attention. Within this phase, assessment of human leukocyte antigen-D related (HLA-DR) expression in monocytes is producing good results.

The role of HLA class 2 molecules is to process and present antigenic peptide fragments to CD4 T lymphocytes at the onset of the immune response. The expression of HLA-DR on the cell surface is a significant indicator of the immune response due to its important role in antigen presentation. Several researchers have reported

an association between decreased expression of HLA-DR and functional inactivation of monocytes, and have established that the decreased expression of HLA-DR may be a sign of severe immunosuppression (considering sepsis not as a proinflammatory disorder but as an immune disorder including inflammation and immunosuppression) [20–22]. Monocytes with low expression of HLA-DR have reduced ability to secrete cytokines and present antigens; therefore, maintaining HLA-DR expression may be essential for an appropriate antibacterial response and for the prevention of infectious complications. The monocyte rate decreases in septic patients and, therefore, HLA-DR expression is also lower in septic patients. However, this also happens when the immune system is weakened [23].

Biomarkers of Organ Dysfunction

Lactate

Lactate is the marker of hypoperfusion par excellence. Increases in serum lactate levels imply progression to organ dysfunction and are associated with an increased mortality rate from 35% to 70%. Hyperlactatemia is considered a severe sepsis marker, as it reflects poor tissue perfusion. Numerous studies have established the use of lactate as a marker for diagnosis, prognosis, and treatment of tissue hypoxia in shock. In general, the determination of lactate is an indisputable criterion in the risk stratification of septic patients and provides guidance on the use of vasoactive drugs. The magnitude of the lactatemia reflects the severity of hypoperfusion and is directly related to mortality. A patient with severe sepsis with significant hypoperfusion (lactate > 4 mmol/l) is considered to be in shock even without the necessary hypotension criteria. Therefore, there is enough evidence to state that normotensive patients with severe sepsis and significant lactic acidosis should receive early antibiotics, hemodynamic monitoring and adequate resuscitation [24, 25].

Lactate biokinetics are also used as a prognostic marker in sepsis. The absence of blood lactate clearance is an independent predictor of

death. In septic processes, an elevated level of serum lactate may be due to altered clearance, overproduction or a combination of both, and so a high level of lactate may be a manifestation of organ dysfunction since this clearance depends on the liver and kidney function. Numerous studies have demonstrated the usefulness of lactate as a prognostic indicator of states of shock, and it has established itself in ICUs as a useful indicator of tissue hypoperfusion [26–28].

Venous to Arterial Carbon Dioxide Pressure Difference (ΔpCO_2)

Anaerobic metabolism is crucial in the pathophysiology of septic shock, and lactate and ΔpCO_2 are the tools used to monitor these patients. Carbon dioxide (CO_2) is produced in tissues during aerobic and anaerobic metabolism. During aerobic metabolism, the amount of CO_2 produced is determined by the basal metabolism and respiratory quotient. During anaerobic metabolism, CO_2 is produced from the bicarbonate that buffers acidic metabolites.

Because CO_2 is about 20 times more soluble than oxygen, it is likely to be available outside ischemic tissues to the venous stream, and so it is a very sensitive marker of hypoperfusion. Therefore, the measurement of ΔpCO_2 seems to be a good marker for correct microcirculation and a good prognostic indicator in septic shock, as it provides an index of tissue oxygenation [28]. The ΔpCO_2 , whether from mixed or central venous blood, has been considered as a predictor of the capacity of the cardiovascular system to eliminate the CO_2 produced in peripheral tissues [29]. Levels above 6 mmHg within the first 24 h in critically ill patients are associated with poor outcomes. However, the usefulness of this parameter remains to be explored [30].

MR-proADM

Adrenomedullin (ADM) is a 52-amino acid peptide that belongs to the same family as PCT. Quantification of ADM would be particularly useful for prognosis, but unfortunately it is impossible due to its rapid clearance from the blood (through the kidneys and lungs).

Furthermore, it circulates bound to proteins, making it inaccessible to immunometric analysis. [31]. The middle region of proadrenomedullin (MR-proADM), comprising amino acids 45–92, reflects the levels of active ADM (which is rapidly degraded), and can be identified in septic patients, as septic patients who die have higher concentrations of this molecule than those who survive. The prognostic value of MR-proADM tends to be superior to other biomarkers such as CRP and PCT, discriminating between sepsis and SIRS [32]. It has mainly been evaluated in community-acquired pneumonia (CAP) [33]. The level of MR-proADM at the time of admission to the ICU/ER is an early predictor of severity and poor outcome in severe sepsis and septic shock by CAP/respiratory tract infections, with an accuracy comparable to PSI and CURB-65 scores, and higher than other laboratory measurements such as PCT or CRP. During admission, it is also a predictor of evolution comparable to PCT and CRP and superior to other laboratory measurements. In combination with forecast scores, it would improve their ability to predict mortality in the short, medium and long term.

Other Biomarkers

Research has recently begun into other biomarkers like cell-free DNA (cf-DNA), but a great deal of work in this area remains to be done. cf-DNA basically comprises short fragments of DNA found in plasma and released from the cells due to necrosis or apoptosis. The interest in cf-DNA has recently increased and it is currently being investigated as a biomarker in critical patients. cf-DNA levels are higher in sepsis patients than in healthy controls and also in non-survivors. Cell death is a common event in sepsis but it is not sepsis-specific, so cf-DNA has been investigated as a prognostic biomarker.

In brief, the definition of sepsis is quite imprecise. It includes many signs and symptoms, which makes its determination difficult. A better understanding of the disease and the complex cellular processes that it involves is necessary in order to find the definitive marker or markers.

Studies of single biomarkers have shown that there is no ideal biomarker for sepsis. Due to the condition's complex pathophysiology, efforts should be focused on investigating combinations of multiple biomarkers to obtain more reliable and specific results [34, 35].

THERAPY

Septic shock is a serious state of tissue hypoperfusion triggered by a systemic inflammatory response of infectious origin with impaired microcirculation and cytopathic hypoxia, which involves intense hypovolemia, vasodilation and cardiac dysfunction [36, 37]. Despite therapeutic innovations, the mortality rate in septic shock remains high [38, 39]. The main causes of death in these patients are refractory multi-organ failure and hypotension. In septic shock, early initiation of treatment is crucial, since a delay may result in multiple organ dysfunction [40].

Given the high incidence, mortality rate and social impact of the condition, in 2002, the Surviving Sepsis Campaign (SSC) was set up to reduce sepsis-related mortality. The SSC proposed a series of care bundles organized in a protocol of early and simple goals [41, 42].

The first, named “the 3-h severe sepsis resuscitation bundle”, contains all the therapeutic steps to be performed within 3 h of the presentation of septic shock: measurement of lactate level, obtaining blood cultures before antibiotics, and administration of broad spectrum antibiotics and of crystalloid 30 ml/kg for hypotension or lactate ≥ 4 mmol/L. The second part, “the 6-h septic shock bundle”, contains all therapeutic steps to be performed within 6 h of the presentation with septic shock: application of vasopressors (for hypotension not responding to initial fluid replacement) in order to maintain a mean arterial pressure (MAP) ≥ 65 mmHg, measurement of central venous pressure (CVP) and venous oxyhemoglobin saturation (ScvO₂) when hypotension persists despite volume replacement or initial lactate ≥ 4 mmol/L, and re-measurement of lactate if the initial level was high [42].

As for “the 24-h management bundle”, some substantial changes have been introduced in response to the proposals put forward in subsequent studies, such as raising the level of glucose to establish insulin infusion to 180 mg/dl, and the withdrawal of the administration of recombinant-activated protein C (APCr). Only the controversy of adjuvant steroid therapy persists, remaining an indication for refractory shock in addition to adequate fluid resuscitation and vasopressor administration [42].

Initial Treatment of Septic Patient: “Time is Life”

Early administration of broad-spectrum antibiotics and early, intense fluid intake are the basis for effective treatment of septic shock. Vasopressors, although generally necessary, should initially be regarded as a second-line treatment with clear criteria for their use, administration of inotropic drugs and transfusion of packed red blood cells.

Oxygen and Mechanical Ventilation

The administration of oxygen via a mask or early endotracheal intubation is recommended in order to optimize and reduce oxygen consumption, by the increased work of breathing. It is also recommended for the protection of the airway in the case of impaired consciousness [42].

Early Antibiotic Treatment

Distinguishing the infection origin is a priority, because it favors early antibiotic treatment and/or surgical control of the focus. Kumar et al. reported that every hour of delay in antibiotic administration was associated with a reduced survival of 7.6% [43]. A large retrospective study of 17,990 patients with sepsis and septic shock found that delay in first antibiotic administration was associated with increase in the risk of mortality for each hour delay in antibiotic administration [44]. One recent retrospective cohort study found that each hour until initial antimicrobial administration was associated

with a 8.0% increase in progression to septic shock, and time to initial antimicrobial was also associated with in-hospital mortality [45]. Moreover, a recent systematic review and meta-analysis concluded that the association between timing of antibiotic administration and mortality in severe sepsis and septic shock found no significant mortality benefit of administering antibiotics within 3 h of emergency department triage or within 1 h of shock recognition in severe sepsis and septic shock [46].

Current standard of care is that antibiotics are recommended within the first 3 h if the patient comes from the emergency unit and 1 h if admitted to the ICU from another service. The antibiotic choice is essential in the patient's prognosis, since inappropriate antibiotic therapy has been associated with increased mortality [47, 48].

The initial antibiotic administered should be broad spectrum, and it must be reevaluated when microbiological culture results become available in order to adjust the treatment and target it specifically against the microorganism isolated. The rational use of antibiotics minimizes side effects, the emergence of bacterial resistance [49–51], toxicity, and the risk of superinfection, and it also reduces treatment costs (Table 1).

Initial Treatment of Hypoperfusion

Hypotension is the first clinical sign of impaired perfusion, but it may coexist with normal levels of arterial pressure (AP) [52–54]. The plasma level of lactate, though non-specific, is the best indicator of tissue perfusion and persistence of high levels is an important predictor of severity and mortality [55]. Other clinical signs such as capillary refill in skin and nails, persistent skin mottling, oliguria or disorders of consciousness may also indicate perfusion disorder [56]. The mottling score is reproducible and easy to evaluate at the bedside. The mottling score as well as its variation during resuscitation is a strong predictor of 14-day survival in patients with septic shock. [57].

Lactate values, CVP, urine output and SvcO₂ should be measured systematically in the early

hours of hospital treatment of patients in septic shock, regardless of their location. CVP is the most common measurement, despite its limitations [58]. In a practical sense, in addition to providing a reference for preload and effective blood volume, measurements of CVP provide a “safety threshold pressure” in fluid intake in resuscitation, as excessive fluid intake may be associated with subsequent oxygenation problems [59], though not comparable to the problem of establishing high doses of vasopressors without completing the proper administration of fluids.

The amount of fluids and the time to improve perfusion in septic shock are not well established; the time may exceed 24 h since the onset of symptoms, and is independent of hemodynamic and metabolic components [60].

An arterial catheter must be inserted invasively to monitor the AP, because it is generally underestimated when it is assessed with an oscilloscope system [61]. But it is important to check frequently for system failures that can lead to errors in the AP and in parameters derived from pressure waves [62]. We should also stress that the channeling of the central and arterial lines should in no way delay the intake of fluids, blood cultures, analysis and antibiotic therapy.

Several methods of continuous monitoring can be used which, together with echocardiography at bedside, help us to target treatment more precisely at late stages or when hypotension and respiratory failure is associated with normal lactate plasma levels [63, 64]. The pulmonary artery catheter should not be systematically used in septic shock patients because of the risk of increasing complications [65]. Figure 1 shows alternatives of hemodynamic monitoring according to the clinical situation of the patient in septic shock, based on personal experience of the authors.

The rapid restoration of perfusion is achieved with the initial energetic fluid intake. Targets in hemodynamic patients are: MAP > 65 mmHg, CVP between 8 and 12, SvcO₂ > 70%, lactate < 4 mmol/L and urine output > 0.5 mL/kg/h [42, 66, 67] (Fig. 2). The volume must be administered with crystalloid, although there is some debate about whether it should be saline

Table 1 Key points in the management of septic shock

- 1 Antibiotic treatment should be initiated early. Effective intravenous antimicrobials should be administered within the first hour of recognition of septic shock
- 2 If the causative agent is unknown, broad-spectrum antibiotic therapy with activity against all likely pathogens (bacterial, fungal or viral) is indicated
- 3 Only combination therapy should be used in patients with shock
- 4 Antibiotic choice is conditioned by the following factors:
 - a. Local epidemiology
 - b. Focus of infection
 - c. Comorbidity of the patient
 - d. Prior immune status
 - e. Prior antibiotic therapy
 - f. Patient's origin
 - g. Adherence to protocols
- 5 Close collaboration with the microbiologist is needed to obtain results of the cultures and antimicrobial susceptibility as early as possible. The antimicrobial regimen should be reassessed daily with a view to potential de-escalation. Once the cause is identified and its sensitivity to antimicrobial treatment is established, the spectrum can be narrowed
- 6 The duration of antibiotic treatment should be shortened; low biomarker levels (procalcitonin, MR-proADM) can be used to discontinue empiric antibiotics in patients
- 7 A reference infectious disease specialist in the intensive care unit is required

solution 0.9% or Ringer-lactate solution because high amounts of saline can produce chloride overload. The total volume is variable, depending on the situation of each patient, but studies proposing 3–5 L in the first 3–6 h have produced good results [58].

Transfusion of Blood Products

Oxygen supply to the tissues depends on the level of hemoglobin. Transfusion is recommended in patients with severe sepsis when hemoglobin levels descend below 7 g/dL [42]. Critically ill patients generally have a better prognosis when blood transfusion is managed conservatively [66]. It is recommended that levels be kept between 7 and 9 g/dL, although this threshold rises in certain conditions such as myocardial ischemia, acute hemorrhage, refractory hypoxemia and lactic acidosis [42].

Treatment of Septic Patients in the Late Phase: Organ Dysfunction Support

After the first hours of septic shock, a late stage starts with a predominant presence of multi-organ dysfunction. AP is generally maintained with progressively higher doses of noradrenaline; less frequently, patients may present refractory hypotension, evolving to poor outcome [37, 67]. The addition of other vasoactive drugs to noradrenaline may be required (adrenaline, dobutamine or vasopressin). Indeed, adrenaline could be administered as rescue therapy in patients with refractory shock associated with low cardiac output as an alternative or in addition to noradrenaline [68].

This phase is characterized by a combination of cardiac dysfunction and respiratory and renal failures. In this respect, better control of

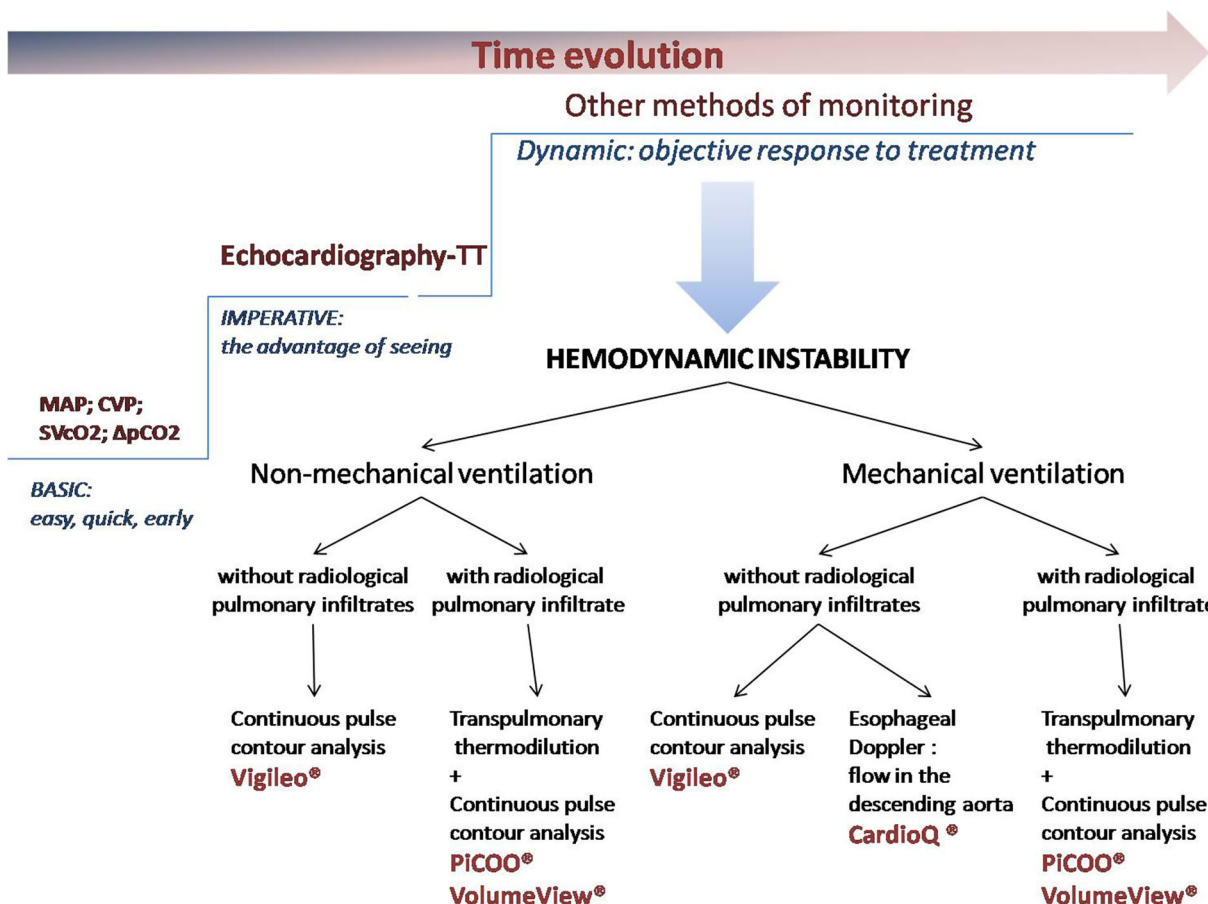


Fig. 1 Hemodynamic monitoring alternatives depending on the evolution and septic patient’s clinical status (in the authors’ practical experience). *MAP* mean arterial pressure, *CVP* central venous pressure, *SvcO₂* central venous

oxyhemoglobin saturation, *ApCO₂* venous to arterial pCO₂ difference, *TT* transthoracic, *PiCOO* pulse contour cardiac output

hemodynamic parameters and more complex objectives are necessary; and close dynamic monitoring is required [63, 64, 69] (Figs. 1, 2).

Treatment during this phase involves specific organic support, mechanical ventilation, continuous hemofiltration, supply of blood products, and nutritional support. This means that a personalized therapeutic approach is necessary.

Adjunctive Measures

Corticosteroids

There is no evidence to support treatment with corticosteroids from the beginning of resuscitation or in patients with hemodynamically stable sepsis [70–72]. An ACTH test is not recommended. In patients with persistent shock

after fluid challenge, who require high doses of vasoactive drugs and have not improved lactate levels in the first 6 h, the use of steroids may allow the withdrawal of vasoactive drugs. Although the evidence is limited, a combination of 200 mg of hydrocortisone followed by fludrocortisone seems to be the preferred option [42].

Control of Blood Glycemia

Hyperglycemia is toxic at the cellular level and may promote the development of organ failure in critically ill patients. There are many factors that cause the high incidence of hyperglycemia in these patients, especially in the most severe cases [73]. Hyperglycemia should be prevented by control of nutrition and triggers, and, if necessary, blood glucose can be contained using

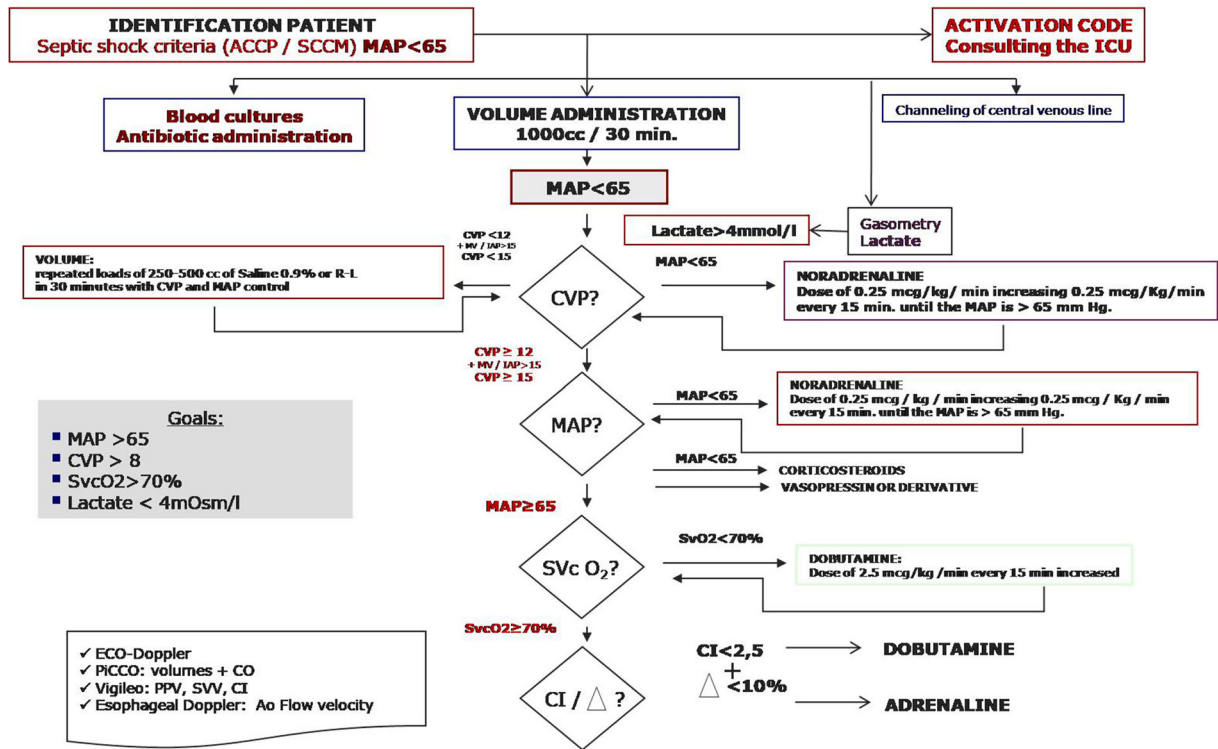


Fig. 2 Scheme of initial treatment of patients in septic shock. MAP mean arterial pressure, CVP central venous pressure, SvcO₂ central venous oxyhemoglobin saturation, VM mechanical ventilation, IAP intra-abdominal pressure, PiCCO pulse contour cardiac output, IC

Immunocompromised, CO cardiac output, CI cardiac index, PPV pulse pressure variation, SVV systolic volume variation, Ao aorta, Δ dynamics variables (systolic volume or pulse pressure variation)

insulin infusion therapy [74]; it should be moderately demanding (< 180 mg/dL) to avoid hypoglycemia while maintaining levels around 140 mg/dL [42, 75]. Hypoglycemia is very detrimental in critically ill patients, is accompanied by increased mortality, and may counteract the favorable effect of glycemic control [76]. Glycemic variability is harmful and is associated with mortality, especially in patients with higher mean levels of blood sugar and even in non-diabetic patients, in whom cell damage is increased by hypoglycemia [77]. Fluctuating blood sugar levels are worse than stable, moderate hyperglycemia.

Other Measures

Like other critical patients, septic patients must undergo supportive measures such as

mechanical ventilation, using ketamine rather than etomidate for intubation [78]. Mechanical ventilation with volumes of 6 ml per kg of ideal weight has been shown to decrease mortality in patients who develop acute respiratory distress syndrome (ARDS) [79]. It is recommended to maintain a plateau pressure below 30 cmH₂O, and to use moderate positive end-expiratory pressure and the prone position in the case of ARDS [80]; recruitment maneuvers should only be used in patients with refractory hypoxemia and normalized preload [81, 82]. Other measures that should be mentioned are enteral nutrition, deep venous thrombosis prophylaxis and renal replacement therapy [42]. Continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure.

Table 2 Adjuvant therapies investigated in septic shock

Treatment	Mechanism of action	Biological effect	References
E5564 (Eritoran)	Inhibition of TLR4 Due to its structural similarity with lipopolysaccharide (lipid A) of Gram-negative bacteria, it antagonizes TLR4	Anti-inflammatory/ immunomodulatory activities	[89]
TAK 242 (Resatorvid),	Inhibitor of TLR4 signaling; binds selectively to TLR4 and interferes with interactions between TLR4 and its adaptor molecules	Anti-inflammatory Blocking LPS-induced production of NO, TNF- α , IL-6 and IL-1 β	[90]
Polymyxin B fiber column	Hemoperfusion through adsorptive materials	Removes circulating endotoxin by adsorption, theoretically preventing the progression of the biological cascade of sepsis	[91]
CytoSorb	Hemoperfusion through sorbent-containing cartridges (hemadsorption)	Elimination of many key cytokines including IL-6, IL-1, IL-10 and TNF that cannot be filtered using current blood purification techniques	[92, 93]
Plasma or whole blood exchange	Whole blood exchange	Endotoxin removed	[94, 95]
Coupled plasma filtration adsorption (CPFA)	Permeable filter (plasma filter) followed by sorbent adsorption with a styrene resin	Endotoxin removed	[96]
Hemofiltration	Hemofiltration continuous with high volume	Removes proinflammatory molecules	[97, 98]
Afelimomab	Anti-TNF	Immunomodulatory activities by inhibiting the proinflammatory action of TNF	[86]
CytoFab	Anti-TNF	Immunomodulatory activities by inhibiting the proinflammatory action of TNF	[86]
Macrolides	Suppress NF- κ B and AP-1 signaling, inhibit the ERK1/2 pathway Anti-IL6, -IL8, and -TNF α	Anti-inflammatory/ immunomodulatory activities	[99–101]
N-acetylcysteine	Reduces NF- κ B and MAPKp38	Anti-inflammatory/anti-oxidant properties	[102]
Interferon gamma	Cytokine. Increases monocyte HLA-DR expression	Restores monocytic cell function	[103]

Table 2 continued

Treatment	Mechanism of action	Biological effect	References
Immunoglobulin	Increased IgA and IgM levels	Increases humoral immunity	[104]
Sargramostim	Cytokine that promotes maturation of the neutrophils, monocytes, macrophages, dendritic cells, T lymphocytes, and plasma cells	Granulocyte macrophage colony-stimulating factor	[105, 106]
Molgramostim	Cytokine that promotes maturation of the neutrophils, monocytes, macrophages, dendritic cells, T lymphocytes, and plasma cells	Granulocyte macrophage colony-stimulating factor	[105, 106]
Anti-MIF	Antibodies directed against macrophage migration inhibition factor (MIF)	Restores or augments the immunomodulatory actions of endogenous glucocorticoids	[107]
Superantigenantagonist	Inhibition of proinflammatory gene expression by limiting T cell activation	Blocks Th1 gene induction and lethal shock	[108]
Heparin	Antithrombotic and immunomodulating effects	Prevents DIC Anti-inflammatory	[109]
Recombinant thrombomodulin	Antithrombotic effects	Prevents DIC	[110]
Naloxone	Opioid receptor antagonist	Hemodynamic improvement	[111]
Pentoxifylline	Increases deformability and decreased erythrocyte aggregation	Improves the multiple organ dysfunction score and the arterial oxygen tension to a fraction of inspired oxygen (PaO ₂ /FiO ₂)	[112]
Statins	Inhibitors of the hydroxyl methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme. Suppression of endotoxin-induced up-regulation of TLR4 and TLR2	Anti-inflammatory/ immunomodulatory activities	[113, 114]
Beta-blockade	Pro-inflammatory mediators blockade and cell apoptosis in various tissues including the heart and immune tissues; attenuated systemic inflammation as well as inflammation in the lung, heart and liver	Attenuates the deleterious effects on the sympathetic adrenergic nerves Improves cardiac function	[115, 116]
Vasopressin	V1a receptor agonist	Improves cardiovascular function	[117]
Selepressin	Selective vasopressin V1a receptor agonist	Improves cardiovascular function	[118]

Table 2 continued

Treatment	Mechanism of action	Biological effect	References
GTS-21	Selective alpha7-nicotinic acetylcholine receptor agonist shown to block NF-kB and downstream cytokines	Stimulates the cholinergic anti-inflammatory pathway	[119]
IL-7	Pro-inflammatory cytokines	Prevents secondary immune suppression	[120]
IL-2	Pro-inflammatory cytokines	Prevents immunoparalysis	[121]
Thymosin-a1	Activity on innate and T helper-related immunity	Immunomodulatory activities	[122]
Inhibition of programmed cell death 1 (PD-1) and of its ligand (PD-L1)	Blockade of PD-L1 Prevents lymphocytes depletion, enhances pro-inflammatory mediators, down-regulates anti-inflammatory cytokines and improves bacterial clearance	Improved immune cell function	[123]
Inhibition of B- and T-lymphocyte attenuator (BTLA)	Blocks the BTLA inhibitor molecule in T cells. Increased activity and proliferation of T cells	Enhances resistance to endotoxin-induced shock	[124]
Inhibition of cytotoxic T-lymphocyte antigen 4 (CTLA- 4)	Blocks the CTLA- 4 inhibitor molecule in T cells. Increases activity and proliferation of T cells	Increases survival resistance to endotoxin-induced shock	[125]
Methylthiouracil	Inhibition of high mobility group box 1 (HMGB1)	Modulation of HMGB1-mediated inflammatory responses	[120]

Emerging Research Treatments: From the Visible to the Invisible

Mortality rates remain high despite the great efforts invested in implementing protocols. New emerging drugs focused on modifying the inflammatory response are currently being investigated for the treatment of septic shock [83, 84]. Immunomodulatory therapy for sepsis includes inflammatory cytokines, cellular receptors, nuclear transcription factors, coagulation activators and apoptosis regulators [85]. There are various therapies based on monoclonal antibodies that block inflammatory mediators and receptors, agents that block or eliminate bacterial products, modulators of immune function and immunostimulatory

molecules. They have shown promising results in animal tests and are currently at various stages of clinical evaluation [86]. This is an approach based on the more modern concept of “precision” or “personalized” medicine [87, 88]. An example of “personalized medicine in sepsis management” is the potential benefit of beta blockers infusion in the subset of patients with tachycardia. Table 2 summarizes the main molecules studied.

CONCLUSION

In summary, sepsis remains a major health problem because of its high mortality and morbidity. Identification and early treatment is

crucial in order to deliver prompt, correct treatment and increase the chances of survival. Currently, the diagnosis of sepsis focuses on the use of biomarkers. Progress in this field has been slow; most efforts have been centered on single markers, but, given the complexity of the sepsis response, the main focus should be on combinations of markers. The use of biomarkers in the future, using “omics” to individualize different subsets, will help improve the outcomes by improving diagnostic accuracy, reducing the time needed to identify the best treatment, and limiting unnecessary tests and treatments. Therapy remains based on source control, correct antibiotic prescription and supportive management. It is expected that the concept of precision medicine will establish itself as a way to identify subsets of patients able to benefit from individualized adjunctive therapy.

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