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Diagnosis, Management and Treatment of Septic Shock from Early Diagnosis to Infection Focus Control

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Abstract

Sepsis is a syndrome characterized by clinical signs and symptoms due to infection, with a high rate of mortality, especially if not recognized and treated promptly. In the last years, several definitions were explained about this syndrome. The aim of this review is to give a common and practical definition of septic shock, and to focus on diagnosis, early resuscitation and infection focus control.

Keywords: Sepsis; Septic shock; Antibiotic therapy; ARDS; Hypoperfusion; Emergency; Intensive cardiac unit

Introduction

Sepsis is a syndrome characterized by clinical signs and symptoms due to infection, with a high rate of mortality, especially if not recognized and treated promptly. In the last years, several definitions were explained about this syndrome. The aim of this review is to give a common and practical definition of septic shock, and to focus on diagnosis, early resuscitation and infection focus control.

Literature Review

The most important causes of sepsis are pneumonias, followed by intra-abdominal and urinary tract infections [1].

Diagnosis

Actually, the high use of endovascular prosthesis and devices represent an important risk factor of infection and its complications. Bacteria are the most common cause of sepsis, both Gram-positive and Gram-negative. *Staphylococcus aureus* and *Streptococcus pneumoniae* are the most common Gram-positive isolates, while *Escherichia coli*, *Klebsiella* spp., and

Pseudomonas aeruginosa are the most represented among Gram-negative isolates [2].

There is an increasing role of methicillin-resistant *Staphylococcus aureus* (MRSA), not only in hospitalized patients, but also in community acquired infections [3].

Until 2016, sepsis was defined as a "Systemic inflammatory response syndrome (SIRS) with a documented infection" while severe sepsis was defined as "A systemic inflammatory response syndrome with a documented infection, related to organ failure, hypotension or reduced tissue function".

SIRS is characterized by presence of two or more of following criteria [4]:

- Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
- Heart rate $>90/\text{min}$
- Respiratory rate $>20/\text{min}$ or $\text{PaCO}_2 <32 \text{ mmHg}$ (4.3 kPa)
- White blood cell count $>12.000/\text{mm}^3$ or $<4000/\text{mm}^3$ or $>10\%$ immature bands

These criteria to identify sepsis were unhelpful, because changes in white blood cell count, temperature, and heart rate reflect the physiologic response to infection and/or danger insult, and they don't necessarily indicate a dysregulated, life-threatening response, but they had a poor specificity [5].

For this reason, the Third International Consensus Definitions for sepsis and septic shock, published on February 2016, has established a new definition of sepsis underlining the role of organ dysfunction in sepsis rather than the systemic inflammatory response. In fact, sepsis is now defined as "A life-threatening organ dysfunction caused by dysregulated host response to infection"; for all this reason the term severe sepsis is now unnecessary.

Acute organ dysfunction most commonly affects respiratory and cardiovascular systems, but often also brain, kidneys and liver are involved. To help physicians to make diagnosis, the Consensus has introduced a new score to identify promptly

the sepsis-related organ damage: The Sequential Organ Failure Assessment Score (SOFA score) (Table 1).

Table 1 Sequential Organ Failure Assessment Score (SOFA score).

Organ	Score				
	0	1	2	3	4
Lung					
PaO ₂ /FIO ₂ , mmHg	≥ 400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation					
Platelets ×10 ³ /μL	≥ 150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Heart					
	MAP ≥ 70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine dose) ¹	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.11	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.11
Brain					
Glasgow Coma Scale score ²	15	13-14	10-12	6-9	<6
Kidney					
Creatinine, mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
Urine output, mL/d				<500	<200
Adapted from Consensus Definitions for Sepsis and Septic Shock, JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287					
FIO ₂ fraction of inspired oxygen; MAP, mean arterial pressure; PaO ₂ partial pressure of oxygen					
¹ Catecholamine doses are given as μg/kg/min for at least 1 hour					
² Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function					

The baseline SOFA score can be assumed to be zero in patients who don't know have pre-existing organ dysfunction. For patients with comorbidities determining organ dysfunction can be useful calculate a baseline SOFA score before the infection, also retrospectively, to evaluate an eventual change of this score during an infection. Patients with a SOFA score of 2 or more had a mortality risk of 10% in a general hospital population with presumed infection. A SOFA increase ≥ 2 points indicates the development of organ dysfunction induced by infection.

The calculation of SOFA score need laboratory tests, and it cannot be done promptly. For this reason, it has been introduced a simple bed-side score, called quick-SOFA (qSOFA), characterized by three clinical variables [6]:

- Respiratory rate ≥ 22/min
- Altered mental status
- Systolic blood pressure (SBP) ≤ 100 mmHg

The score is considered positive if there are 2 of 3 criteria.

Although qSOFA is less robust than SOFA score, it does not require laboratory tests and can be assessed quickly and repeatedly. Positive qSOFA criteria should also prompt

consideration of possible infection in patients not previously recognized as infected [7].

If not recognized and treated promptly, sepsis can determine cardiovascular dysfunction with consequent septic shock.

Septic shock is defined by the presence of these two criteria [7]:

- Persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mm Hg
- Serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

Septic shock is a distributive shock characterized by an extreme peripheral vasodilatation with normal or increased cardiac output and central venous oxygen saturation (ScvO₂).

Septic shock presents two phases [8]:

- An early warm phase, characterized by normal or increased cardiac output and central venous saturation, low peripheral vascular resistance, wide pulse pressure, bounding pulse, brisk capillary refill (< 3 sec)
- A late cold phase, characterized by low cardiac output and central venous saturation, high peripheral vascular

resistance, narrow pulse pressure, weak pulse, delayed capillary refill (> 5 sec)

According to these new definitions and scores introduced about sepsis and septic shock, the Task Force recommends a simple and systematic approach to a patient with suspected infection, to obtain an immediate diagnosis and treatment [7].

Treatment

The management of septic shock regards two aspects: the early management and the control of focus of infection. The early management involve the stabilization of airway and breathing and the assessment of perfusion.

First line breathing support is represented by oxygen supplement. Intubation and mechanical ventilation may be required in patient with increased work of breathing or for airway protection because encephalopathy and a depressed level of consciousness frequently complicate sepsis. Chest radiographs, lung echography and arterial blood gas analysis should be obtained following initial stabilization to monitoring patient and to diagnose acute respiratory distress syndrome (ARDS), which frequently complicates sepsis [9].

After breathing stabilization, the second step is to assess perfusion.

A compromised perfusion is characterized by [7,8]:

- Hypotension (SBP <90 mmHg, mean arterial pressure (MAP) <70 mmHg, decreased SBP >40 mmHg)
- Tachycardia
- Hypoperfusion (urine output <0.5 ml/kg/h, altered mental state which includes delirium, obtundation, disorientation, and confusion)
- Cutaneous alterations (flushed, and hot skin in early warm phase, and cyanotic, and cold skin in late cold phase)
- Hyperlactatemia (>2,0 mmol/l or >18 mg/dl) that express an abnormal cellular oxygen metabolism.

The first line therapy to restore circulation uses fluids to correct intravascular hypovolemia and vasopressors to correct peripheral vasodilatation. In fluids resuscitation it's important the type of fluids, the volume infused, and the timing of infusion. Randomized clinical trials have demonstrated that normal saline solutions (or other crystalloids as Ringer's lactate and Ringer's acetate) are better and safer than colloids which are associated with increased mortality and acute kidney failure, above all the solution hydroxyethyl starch (HES) [10,11].

A valid alternative to saline solution is represented by albumin. In SAFE trial there were no significant differences of outcomes between the group of ill critically patients treated with 0.9% sodium chloride (normal saline) and the group treated with albumin [12].

For these reasons, isotonic, balanced salt solution are a pragmatic initial resuscitation fluid for the majority of acutely ill patients, while albumin can be considered as alternative approach during the early resuscitation of patients with septic

shock. HES is not indicated in patients with sepsis or at risk for acute kidney injury [13].

Fluids should be rapidly infused as intravenous boluses (1000 mL of crystalloids or 300 to 500 mL of colloids over the course of 30 minutes) until the restoration of an appropriate tissue perfusion (maximum volume 3-5 l) [14-17]. Moreover, fluid can also administer by passive leg raise, that can predict fluid responsiveness, and can reduce excessive fluid administration and its consequences.

During fluid therapy it should be evaluated not only the tissue perfusion but also the eventual development of pulmonary oedema (because septic patients frequently develop ARDS). For this reason, a lung echographic monitoring is helpful to evidence the presence of lung congestion (represented by echographic B-profile) during fluid infusion. The presence of lung congestion is an indication to stop fluids and to administer furosemide to avoid the development of a pulmonary oedema [18,19].

When despite ad adequate fluid therapy, the hypotension and tissue hypoperfusion persist, vasopressors are indicated as next step of early resuscitation management. First line vasopressor is norepinephrine (0.01–³ mcg/kg/min in dextrose 5% water). Norepinephrine is a potent α -¹ adrenergic receptor agonist with modest beta agonist activity which renders it a powerful vasoconstrictor with less potent direct inotropic properties [14,20].

Dopamine can be used as an alternative vasopressor agent to norepinephrine only in highly selected patients (patients with low risk of tachyarrhythmias and absolute or relative bradycardia) [14].

Phenylephrine (0.01–0.1 mcg/kg/min in dextrose 5% water) is useful in patients with tachycardia or arrhythmias because of its pure α adrenergic activity and virtually no affinity for beta adrenergic receptors [21].

Vasopressin at the dosage of 0.03 units/minute in dextrose 5% water can be added to norepinephrine with intent of either raising MAP beyond 70 mmHg or decreasing vasopressors dosage. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension [22].

Higher doses of vasopressin are not recommended because increase the risk of collateral effects as low intestinal mucosal perfusion, high bilirubin and serum transaminases, and decreased platelet counts [23].

When septic shock evolves towards the cold phase, it is necessary to treat cardiac dysfunction (expressed by reduced cardiac output) using an inotrope drug. Dobutamine is the first-choice drug (2–20 mcg/kg/min either in 0,9% chloride solution or in dextrose 5% water) for treatment of sepsis-induced myocardial dysfunction [14].

Dobutamine is a potent inotrope with a low chronotropic activity. Its effect on vascular smooth muscle is related to dosage. Lower doses (<5 mcg/kg/min) determine mild vasodilatation with consequent decreased blood pressure,

whereas doses up to 15 mcg/kg/min increase cardiac contractility without affecting peripheral resistance [24].

Red blood transfusion is indicated only in patients with an haemoglobin level <7.0 g/dL. It's reasonable to obtain a haematocrit about 30% (haemoglobin level 10 g/dL).

The early resuscitation goals are:

- MAP \geq 65 mmHg
- Urine output \geq 0.5 mL/kg/h
- Central venous pressure (CVP) 8-12 mmHg (inferior vena cava >15 mm with an inspiratory collapse > 50%) if a central venous access is obtained
- ScvO₂ >70%

It is useful monitoring the lactate clearance. It has been demonstrated that a reduction of 10% of lactate levels in 6 hours correlates with a better prognosis in septic shock patients [25]. Therapeutic targets exposed should be achieved into 6 hours from the onset of hypotension.

The other aspect of management of septic shock is represented by identification and control of septic focus. Accurate anamnesis and physical examination are useful to address physicians to identify infective site and to choose an appropriate empirical antimicrobial therapy. Antibiotics should be administered promptly in sepsis, within the first hour ("golden hour") after the onset of hypotension [26,27].

It is necessary to obtain cultures of urine, expectorate, and blood. Cultures should be obtained before starting antimicrobial therapy, within maximum the first 45 minutes. At least two sets of blood cultures (both aerobic and anaerobic bottles) must have been obtained before antimicrobial therapy with at least one obtained percutaneously, and one through each vascular access device, unless the device is recently (<48 hours) inserted. Use of the 1,3 beta-D-glucan assays, mannan and anti-mannan antibody assays can be useful to detect an invasive candidiasis in differential diagnosis of cause of infection. The samples of cultures should not delay the empirical antimicrobial therapy administration over the first hour [14].

Discussion

The antibiotic empirical treatment should be a broad-spectrum therapy against both Gram-positive and Gram-negative bacteria, based on the use of at least two antibiotics with synergic action's mechanism (Table 2) There is growing recognition that MRSA is a cause of sepsis not only in hospitalized patients, but also in community dwelling individuals without recent hospitalization, and for this reason antibiotic choice should be always cover MRSA [28].

Vancomycin is the first line antibiotic therapy in septic patients thanks to its efficacy against MRSA. It should be infused at a dose of 15-20 mg/kg \times 2/die intravenous (IV) (1 g \times 2/die IV) with a velocity <15 mg/min. In very critical ill patients it is recommended to start with a loading dose of

25-30 mg/kg, followed by maintenance dose of 15-20 mg/kg \times 2/die IV (1 g \times 2/die IV).

Table 2 Most important antibiotics dosages using in patients without comorbidities.

Antibiotics	Dosage
Amoxicillin/Clavulanic acid	2.2 g \times 3/die
Ampicillin/Sulbactam	3 g \times 3/die
Ceftriaxone	2 g \times 3/die
Cefotaxime	1 g \times 3/die
Ceftazidime	1 g \times 3/die
Cefepime	2 g \times 2/die
Piperacillin/Tazobactam	4.5 g \times 3/die
Levofloxacin	500 mg \times 2/die
Ciprofloxacin	200 mg \times 2/die
Imipenem	1 g \times 3/die
Meropenem	1 g \times 3/die
Amikacina	1 g/die
Clindamicina	600 mg \times 3/die
Metronidazolo	500 mg \times 3/die
Teicoplanina	40 mg \times 2/die

Clearance of vancomycin is almost renal (about 80–90% of the drug is excreted unchanged in the urine within 24 hours in patients with normal renal function), and its clearance decreases with creatinine clearance (CrCl) in a linear mode. For this reason, vancomycin dose should be adjusted according to creatinine clearance (Table 3).

Table 3 Vancomycin dose scheme adjustment per kidney failure.

Maintaining dose Creatinine clearance (mL/min per 1.73 m ²)	Vancomycin dose
>90	15-20 mg/kg per 12 h
60-89	20-30 per 24 h
45-59	15-20 per 24 h
30-44	10-15 per 24 h
15-29	7-10 per 24 h
<15	10 per 48 h

Due to vancomycin intrinsic nephrotoxicity, renal function should be monitored during the treatment. It has been established that a minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dl or a \geq 50% increase from baseline, or a drop in calculated CrCl of 50% from baseline on two consecutive days) could be due to vancomycin, after several days of therapy. There are no data that support the

monitoring of vancomycin plasma level to predict its nephrotoxicity, even if a safety range of 15-20 mg/L has been established. For this reason, it is reasonable to obtain a monitoring of vancomycin plasma level only for long term treatment (more than 3 or 5 days) [29,30].

When vancomycin is contraindicated (intolerance to glycopeptide and pregnancy), daptomycin (4 mg/kg IV once/die) and linezolid (600 mg × 2/die per OS or IV) are good alternative. Daptomycin is not indicate for suspected pulmonary infection, because it is inactivated by the surfactant [31].

Whereas MRSA and Gram-positive infection are covered by vancomycin, a combined therapy is necessary to cover also Gram-negative. If *Pseudomonas* is an unlikely pathogen, it is recommended to combine vancomycin with one of the following antibiotics:

- Cephalosporin third generation (ceftriaxone or cefotaxime)
- Cephalosporin fourth generation (cefepime)
- Betalactam/betalactamase inhibitors (piperacillin/tazobactam, ticarcillin/clavulanate)
- Carbapenem (imipenem or meropenem)

If the infection is probably due to *Pseudomonas*, it is recommended to add to vancomycin two other antibiotics with different mechanism of action, chosen from the following:

- Anti-pseudomonal cephalosporin (ceftazidime, cefepime)
- Anti-pseudomonal carbapenem (imipenem, meropenem)
- Anti-pseudomonal beta-lactam/lactamase inhibitor (piperacillin-tazobactam, ticarcillin-clavulanate)
- Fluoroquinolone anti-pseudomonal activity (ciprofloxacin)
- Aminoglycoside (gentamicin, amikacin); monobactam (aztreonam)

It is reasonable suspect a fungal infection (*Candida* spp.), in the following conditions:

- Surgery
- Parenteral nutrition
- Prolonged antimicrobial treatment
- Severe sepsis
- Multisite colonization with *Candida* spp.

Empiric antifungal treatment, mostly with fluconazole, was not associated with a decreased risk of mortality or occurrence of invasive candidiasis. Thus, the routine administration of empirical antifungal therapy should be considered only in neutropenic critically ill patients [32].

Antiviral therapy must be initiated as early as possible in patients with severe sepsis or septic shock of viral origin.

Empiric antibiotic therapy should not during for more than 3-5 days. When the blood cultures results are available, it is recommended to start a more appropriate single therapy based on isolated bacteria susceptibilities. Duration of therapy is typically 7-10 days. Longer courses may be considered in patients who have a slow clinical response, undrainable foci of

infection, bacteraemia with *S. Aureus*, some fungal, and viral infections, or immunologic deficiencies, including neutropenia. Blood procalcitonin and reactive C protein (RCP) levels can be evaluated to guide physicians in the prosecution or discontinuation of therapy [14].

The use of corticosteroids in sepsis and septic shock has been discussed for a long time. The potential benefit of steroids therapy is related to its role as inflammatory response regulator and to its hormonal effects to restore cardiovascular homeostasis. Steroids improve hemodynamic status of septic patients because they determine hydric retention, direct vasoconstriction, and a better response to catecholamine [33].

Recent international guidelines on sepsis and septic shock recommend the use of hydrocortisone (200 mg per day) only in patients with a septic shock in whom the hypotension (systolic blood pressure <90 mmHg) persists for more than one hour despite adequate fluid resuscitation and vasopressor administration. The hydrocortisone use in this scenario is beneficial only if it is administered within the first eight hours [14].

Response to ACTH testing (Adreno Cortico Tropic Hormone) should not be used to select patients for corticosteroid therapy. Corticosteroids should be administered for 5-7 days. It is recommended a progressive dose reduction until to stop the steroid therapy. Fludrocortisone should not be added to hydrocortisone therapy because it can worsen splanchnic perfusion [34].

- The management of septic patient regards also other aspects:
- Nutritional support, both enteral and intravenous support
- Venous thromboembolism prophylaxis
- Intensive insulin therapy (glycaemia target 140-180 mg/dl)
- Antipyretics therapy

Recent data are investigating the role of fast-acting beta⁻¹ blocker (esmolol) in septic patients. The benefit of esmolol consist of an improvement of stroke volume (and tissue perfusion) through a reduction of heart rates and so an improvement of diastolic filling [35].

A randomized controlled trial conducted by Morelli et al. studied the role of esmolol in 77 patients with septic shock requiring norepinephrine to maintain a MAP >65 mmHg despite appropriate volume resuscitation and a heart rate of 95/min or higher. All patients included in the study had a preserved cardiac systolic function (cardiac index ≥ 2.2 L/min/m² in the presence of a pulmonary arterial occlusion pressure >18 mmHg). After 24 hours of hemodynamic optimization, the esmolol infusion commenced at 25 mg/h and progressively increased the rate at 20 minutes intervals, until to obtain a heart rate between 80-95 bpm. For patients in septic shock, the use of esmolol versus standard care was associated with reduction in heart rates, without increased adverse events. The observed improvement in mortality and other secondary outcomes (stroke volume index, arterial lactatemia, vasopressor and fluids requirement) warrants further investigations [36].

Conclusion

Sepsis and septic shock are still clinical syndrome with a worse prognosis. A rapid and clear approach is needful for a correct diagnosis. Quick SOFA, SOFA and the new definition of septic shock help to identify quickly patients with sepsis and septic shock and to start the appropriate treatment. Early resuscitation management consists of fluid administration and vasopressor therapy. Infective focus control requires an immediate broad spectrum empirical antibiotic therapy, preceded by the obtaining of cultures, even if they do not delay the starting of antibiotics.

All these measurements should be set in the first hour after the onset of hypotension, in the so called "golden hour" and optimized in the first six hours.

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