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DIAGNOSIS AND TREATMENT OF PATIENTS IN SEPTIC SHOCK

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Summary
Sepsis and septic shock are a clinical emergency. Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection, and organ dysfunction is defined as an acute change in Sequential Organ Failure Assessment (SOFA) score greater than 2 points secondary to an infectious cause. Septic shock is defined as sepsis with persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mm Hg or higher, and blood lactate level greater than 2 mmol/l (18 mg/dl) despite adequate volume resuscitation. The diagnosis of septic shock begins with medical history and physical examination focused on the signs and symptoms of infection, with the aim of recognizing complex physiologic manifestations of shock. Clinicians should understand the importance of prompt administration of antibiotics, vasopressors and intravenous fluids aimed at restoring adequate circulation. They should also be aware of the limitations of the protocol-based therapy.

Keywords: infection, sepsis, septic shock, diagnosis, treatment, intensive care unit

INTRODUCTION

Shock is a life-threatening circulatory failure that leads to inadequate tissue perfusion. The most typical signs of shock is hypotension (systolic blood pressure below 90 mm Hg or mean arterial pressure below 65 mm Hg), accompanied by clinical signs of organ hypoperfusion (1-3). Historically, the signs and symptoms of shock were attributed to the response of the nervous system to trauma associated with vasomotoric changes and hypovolemia. In the mid-twentieth century, Blalock and Weil divided shock into following groups: cardiogenic, obstructive, hypovolemic, and angiogenic (4, 5). While this simplified division is valuable from the point of view of the professional training, diagnosing shock is much more complex. Currently, septic shock is the most common form of the non-cardiogenic shock, and it also includes some patophysiological characteristics described by Blalock and Weil. In February 2016, a new definitions of sepsis and septic shock were created. According to the definition, septic shock is a form of sepsis in which severe circulatory problems lead to the disruption of normal cellular metabolism (6). Septic shock also has a higher risk of death compared to other forms of sepsis (6). Septic shock is characterized by the need of administering vasopressors in order to maintain mean arterial blood pressure above 65 mm Hg in spite of adequate fluid therapy, and blood lactate level above 2 mmol/l. The prevalence of sepsis and septic shock is steadily growing globally. Septic shock occurs in more than 230,000 patients in the United States each year, and is a cause of 40,000 deaths annually (7). Primary risk factors for septic shock are the fifth reason of premature mortality in people of working age. Up to this day, sepsis was diagnosed when an infection resulted in the occurrence of at least two criteria for systemic inflammatory response (SIRS) (tab. 1) (8-10). Due to the fact that diagnosing sepsis based on two SIRS signs does not have sufficient sensitivity and diagnostic significance, the need for a new definition and diagnostic criteria was determined. In 2016, a new working group was appointed. The working group suggested to replace the concept of severe sepsis with the term sepsis, and to base the severity of organ failure on the Sequential Organ Failure Assessment (SOFA) score (9, 11) and its simplified version – quick SOFA (qSOFA) score (tab. 2) (10, 11). The existing definition of severe sepsis is included in table 3. (8, 10).

ADVANCES IN DIAGNOSTIC PROCESS OF SEPTIC SHOCK

The diagnosis of septic shock is multifactorial and includes: an initial assessment of the etiology and clinical signs and symptoms, of the hemodynamic parameters, of the cellular changes, and of the grade of tissue dysfunction.

INITIAL ASSESSMENT

At the bedside, a clinician initiates the diagnostic process with the question: "is the patient in shock?". The guidelines for the diagnosis of the septic shock define the basic elements of diagnosis, i.e. suspected or documented infection with accompanying arterial hypotension

Tab. 1. Definitions and criteria of sepsis and septic shock (8-10)

Terms	Existing (1991, 2001)	Newly developed (2016)
Sepsis	Systemic inflammatory response syndrome (SIRS) due to infection	Life-threatening organ dysfunction caused by a dysregulated host response to infection. The response causes tissue and organ dysfunction (corresponds to the previous definition of severe sepsis)
Severe sepsis	Sepsis leading to organ failure or severe organ dysfunction (corresponds to the new definition of sepsis)	Term no longer used
Organ dysfunction criteria	Used for the diagnosis of severe sepsis, presented in table 3.	Used for the diagnosis of sepsis, an acute change in total Sequential Organ Failure Assessment (SOFA) score equal to or greater than 2 points in case of suspected or diagnosed infection (tab. 2.)
Septic shock	A type of severe sepsis with acute circulatory failure characterized by persistent hypotension despite adequate fluid therapy, requiring the use of vasopressors (systolic blood pressure < 90 mm Hg, mean arterial pressure < 65 mm Hg or a decrease in systolic blood pressure > 40 mm Hg	Sepsis in which circulatory, metabolic, and cellular disorders are so severe that they significantly increase mortality. Hypotension with elevated blood lactate level, persistent despite adequate fluid therapy and requiring the use of vasopressors in order to raise mean arterial pressure above 60 mm Hg (blood lactate concentration > 2 mmol/l = 18 mg/dl)
Scale recommended for the early identification of patients at higher risk of death	Imprecise: SIRS criteria, organ dysfunction and extended criteria for sepsis are all in use	qSOFA score, two or more of the following signs: 1. impaired conciousness 2. systolic arterial pressure ≤ 100 mm Hg 3. respiratory rate ≥ 22/min
Determination of the severity of the inflammatory response	SIRS, two or more of the following signs: 1. body temperature > 38 °C or < 36 °C 2. heart rate > 90/min 3. respiratory rate > 20/min or paCO2 < 32 mm Hg 4. white blood cells > 12,000/μl or < 4,000/μl or > 10% immature neutrophiles	Not specified. It has been concluded that inflammatory response was only one elements of the response to the infection and it is not the most important aspect of this response. It has been underlined that organ dysfunction significantly increases the risk of death

and organ hypoperfusion (e.g. oliguria, impaired consciousness, impaired peripheral circulation, and an increase in blood lactate concentration). However, some parameters of the definition of shock have not been clearly defined, e.g. adequate fluid resuscitation, no vasopressors, and threshold blood pressure. The recently published consensus of the European Society of Intensive Care Medicine (ESICM) suggest the possibility of a shock in the absence of arterial hypotension. Currently, there is no reference, bedside standard for diagnosing shock. The results of observational studies report a high mortality rate (from 29% to 46%) due to the imprecise diagnosis of shock (12). If the diagnosis of septic shock is made, the clinician must ask himself a question: "what is the reason for the patient's current state?". The identification of risk factors forces to take immediate action. Multiple biomarkers and molecular diagnostic tests are performed in parallel with blood culture in order to differentiate sterile inflammatory process from a similar pathophysiological process related to infection. Patients in septic shock present with impaired myocardial contractility in about 30% of cases. A quick evaluation of the underlying mechanism of shock is of paramount importance, as the delay in adequate treatment worsens patient's condition. Hemodynamic monitoring may help explain the patophysiological phenomena that are characteristic for septic shock. Clinical application of specialized monitoring equipment may depend on the hardware, built-in algorithms of the device, and static/dynamic target of the parameter. There is ongoing discussion concerning the usefulness of the devices in the diagnosis and treatment of septic shock.

Tab. 2. Sequential Organ Failure Assessment (SOFA) score (10, 11)

Organ or system	Score				
	0	1	2	3	4
Respiratory system					
PaO_2/FiO_2 [mm Hg (kPa)]	≥ 400 (53.3)	< 400 (53.3)	< 300 (40)	< 200 (26.7)	< 100 (13.3)
Coagulation					
platelets [× $10^3/\mu l$]	≥ 150	< 150	< 100	< 50	< 20
Liver					
bilirubin [μmol/l (mg/dl)]	< 20 (1.2)	20-32 (1.2-1.9)	33-101 (2.0-5.9)	102-204 (6.0-11.9)	> 204 (12)
Circulatory system					
Mean arterial pressure OR administration of vasopressors [μg/kg/min] required	MAP ≥ 70 mm Hg	MAP < 70 mm Hg	dobutamine (any dose) or dopamine < 5	norepinephrine ≤ 0.1 or epinephrine ≤ 0.1 or dopamine 5.1-15	norepinephrine > 0.1 or epinephrine > 0.1 or dopamine > 15
Central nervous system					
Glasgow coma scale	15	13-14	10-12	6-9	< 6
Kidneys					
Serum creatinine [μmol/l (mg/dl)]	< 110 (1.2)	110-170 (1.2-1-9)	171-299 (2.0-3.4)	300-440 (3.5-4.9)	> 440 (5.0)
Diuresis [ml/day]	–	–	–	< 500	< 200

Tab. 3. The classic diagnostic criteria of sepsis-related organ dysfunction (8, 10)

1) tissue hypoperfusion associated with sepsis or
2) organ(s) dysfunction caused by infection, i.e. ≥ 1 of the following:
a) hypotension caused by sepsis
b) blood lactate above the upper limit
c) diuresis < 0.5 ml/kg/h for > 2 h despite adequate fluid therapy
d) PaO_2/FiO_2 < 250 mm Hg, if lungs are not the source of the infection, and < 200 mm Hg, if the lungs are the source of the infection
e) serum creatinine > 176.8 μmol/l (2 mg/dl)
f) serum billirubin > 34.2 μmol/l (2 mg/dl)
g) platelets < 100 000/μl
h) International Normalized Ratio > 1.5)

INVASIVE HEMODYNAMIC MONITORING

For a long time, invasive monitoring devices, such as pulmonary artery catheter (PAC) or continuous central venous oxygen saturation (SCVO2) devices, have been the standard monitoring devices for patients in shock. PAC enables to measure cardiac output and oxygenation of mixed venous blood, as well as other parameters that facilitate to determine the etiology of shock and potentially improve treatment outcomes. However, various studies have shown that there is no difference in mortality between cases in which PAC was used when compared to the cases in which PAC was not routinely used, while treatment costs were significantly higher in

cases in which PAC was used. Therefore, current guidelines do not recommend the routine use of PAC during the treatment of shock, and it is suggested to use PAC only in selected clinical situations: in right ventricular dysfunction or acute respiratory distress syndrome. For the last 15 years, the use of PAC has been significantly limited in the United States.

MINIMALLY INVASIVE AND NON-INVASIVE HEMODYNAMIC MONITORING

The etiology of shock may be explained using minimally invasive or non-invasive monitoring techniques, such as contour analysis of arterial pulse wave or echocardiography. Calibrated devices analyzing the contour of arterial pulse wave provide real-time data, including cardiac output, stroke volume and pulse variation. Various studies of hemodynamically unstable ICU (intensive care unit) patients have not confirmed better outcomes in patients who were monitored with minimally invasive or non-invasive monitoring devices. However, current guidelines recommend the use of targeted ultrasound imaging as the best clinical practice in the preliminary assessment of hemodynamically unstable patients in septic shock.

MARKERS OF TISSUE DAMAGE

Systemic markers of local tissue injury may indicate the occurrence of organ stress due to shock. The markers include: an increase in blood lactate concentration, a base deficit, a decrease of tissue oxygenation measured with near infrared spectroscopy, and various changes in microcirculation. The tests measuring these parameters may improve the accuracy of the clinical diagnosis, as well as direct the optimization and stabilization of circulation in a shock patient. An increase in blood lactate concentration was not included in the definition of the septic shock from the 2001 of the European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine (SCCM) and was added by a panel of experts as a suggestion in 2014. In clinical practice, serial measurements of blood lactate level are in common use. A threshold blood lactate level required to diagnose a shock is unknown, neither is its role in monitoring patients in shock. The role of near infrared spectroscopy or tissue oxygenation in diagnosis and treatment of shock is also not clear.

UNIFICATION OF DEFINITIONS

There is no perfect definition of a shock, and guidelines, systems of quality improvements, and preliminary criteria for clinical trials all require a unified definition with acceptable sensitivity and specificity. Not all shock patients have classical signs and symptoms, and atypical cases are as important as the typical ones. For example, the outcomes of patients with normal blood pressure and elevated blood lactate level can be similar to those of patients with a full-blown shock, but the reasons for high lactate concentration may be different, including microvascular ischemia, increased glycolysis due to an inflammatory response, and impaired lactate clearance. The body's response to shock is also complex, consisting of proinflammatory and anti-inflammatory cellular and systemic components. Another issue is the need to unify the definition of shock at different levels of health care: from prehospital care, through hospital emergency departments, to the ICUs. It is also necessary to unify the criteria of blood lactate concentration and definition of shock in large clinical trials, as unclear criteria may lead to uncertainty in the choice of the optimal treatment.

ADVANCES IN TREATMENT

The gradual improvement of prognosis in septic shock is dependent on many factors, including early diagnosis and early treatment. An exemplary algorithm of the treatment of septic shock typically consists of emergency treatment, treatment optimization, stabilization and de-escalation. Life-saving procedures may vary depending on the etiology of shock. Adult patients in septic shock typically receive intravenous fluids, vasopressors and procedures offering efficient blood circulation. A broad-spectrum antibiotic should be administered in the first hour after the diagnosis and be effective against the suspected etiological factor. The administration of crystalloid fluids should be initiated as soon as possible in a dosage of 30 ml/kg body weight (13).

CRYSTALLOIDS

There is a large selection of crystalloids applicable in a situation of septic shock. Crystalloid solutions differ between each other in tonicity, content of organic and inorganic anions, few are similar in composition to the electrolyte composition of plasma. Both crystalloids with high chloride ion content and low in chloride solutions are in use. During short-term treatment, they do not affect renal function. However, the use of crystalloids with electrolyte content similar to plasma is advised.

COLLOIDS

Colloid solutions, such as albumins, dextrans, gelatins, and starch solutions are used in critical ICU patients in many countries. The choice of a colloid depends on its availability, price, and the need to reduce tissue edema. Many clinicians believe that colloids are a more effective way of increasing the intravascular volume in shock and that the efficacy depends on the molecular weight of particles in the solution, its concentration, and changes in vascular endothelium that occurs during inflammation. However, a randomized trial ALBIOS (Albumin Italian Outcomes Study) conducted on a group of 1,800 septic shock patients from 100 ICU departments did not reveal a difference in 28-day mortality between

groups treated with albumin solution and crystalloids alone (14). Other studies: Cristal (Colloids vs Crystalloids for the Resuscitation of the Critically Ill) (15); 6S (Scandinavian Starch for Severe Sepsis/Septic Shock) (16) and CHEST (Crystalloid vs Hydroxyethyl Starch) (17) compared the influence of therapy with colloids on the 28-day and 90-day mortality with the therapy with crystalloids alone. No difference in mortality was found, and the group treated with colloids had a higher risk of renal replacement therapy. Albumin solution and crystalloids are of use in septic shock, but the use of starch solutions may worsen the outcome (14).

VASOPRESSORS

In shock that persists despite adequate blood volume, it is recommended to use a vasopressor in order to maintain organ perfusion. Vasopressors, such as norepinephrine, epinephrine, dopamine, and phenylephrine, have a different half-life, alpha and beta specificity, and dosage. Based on a meta-analysis of 6 studies on the use of vasopressors, it is advised to use norepinephrine as a first-line drug (18). Vasodilation in septic shock can be reversed with the use of an endogenous hormone, vasopressin. The administration of vasopressin may lead to a reduction of epinephrine dose and is proven to be safe, however, it does not influence mortality. Guidelines recommend the administration of vasopressin in a continuous intravenous infusion (0.03-0.04 U/min) in patients with no contraindications who are receiving norepinephrine in a continuous intravenous infusion in a dosage equal or greater than 0.15 μg/kg/min (9, 11).

PROTOCOLS

Current recommendation and expert opinions encourage the clinicians to introduce a structured approach to the resuscitation of patients in septic shock. Early care should include a quick diagnosis, microbial culture collection, immediate antibiotic therapy, and the control of the source of the infection. However, multiple studies (PROCESS trial – Protocol-Based Care for Early Septic Shock; ARISE trial – Australasian Resuscitation in Sepsis Evaluation; PROMISE trial – Protocolized Management in Sepsis; Sepsis PAM trial – Sepsis and Mean Arterial Pressure; Scandinavian TRISS trial – Transfusion Requirements in Septic Shock) (19-23) do not confirm the decrease in mortality by introducing a treatment protocol when compared with to an existing treatment.

ADJUNCTIVE THERAPY

Attempts have been made to support the treatment of septic shock with therapeutic agents enhancing innate immune response and coagulation system. A few studies have shown improved outcomes after the administration of activated C protein. However, steroids are still being used in shock patients, despite the fact that a meta-analysis of 8 studies have not confirmed improved outcomes after administering 300 mg/d of hydrocortisone. The guidelines recommend low-dose steroid treatment only in septic shock patients receiving vasopressors, and only during the time of vasoconstrictive treatment (9, 11).

CONTROVERSIES IN FLUID THERAPY

An early initiation of intravenous fluid therapy is the basis of the septic shock treatment, but there are still many ambiguities in the subject. Should the intravenous fluid therapy be initiated in the prehospital care, or in the hospital emergency department? The efficacy of administration of a bolus is also questioned. There are no studies comparing the efficacy of balanced and unbalanced crystalloids in the early period of septic shock. The end point of the fluid resuscitation is yet to be determined, due to the possibility of the lack of correlation between regional and central circulation. Moreover, excessive fluid therapy is common in septic shock. More data is needed in order to understand the optimal duration of the therapy, as well as effective ways of removing excessive fluid.

CONCLUSIONS

Septic shock is an emergency state that requires a rapid diagnostic process that helps to discover signs and symptoms and the etiology of the shock. Clinicians should be aware of the importance of early diagnostic, antibiotic therapy and fluid therapy. Minimally invasive, non-invasive and invasive devices monitoring hemodynamic parameters are only recommended in selected subgroups of patients. Blood lactate concentration assessment is widely used in the assessment of the shock, but its usefulness in clinical algorithms and treatment is yet to be evaluated. The first step in treatment of the septic shock should be the search for the source of infection. A broad-spectrum antibiotic should be administered in the first hour after the diagnosis and be effective against the suspected etiological factor. The administration of crystalloid fluids should be initiated as soon as possible in a dosage of 30 ml/kg body weight. Treatment protocols of fluid therapy have not been proven to be superior to fluid therapy administered without any protocol. Albumin solution and crystalloids are of use in septic shock, but the use of starch solutions may worsen the outcome. A vasopressor of choice is norepinephrine.

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