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IMPORTANCE OFHAEMODYNAMIC STABILITY AND ADJUVANT THERAPY IN THE TREATMENT OF PATIENTS WITH SEPSIS AND SEPTIC SHOCK

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Summary: Sepsis represents a life-threatening condition that requires prompt recognition, detailed initial assessment and energetic administration of therapy. Guidelines published in 2016 emphasized the importance of early fluids replacement and infection control together with assessment based on laboratory parameters and precise monitoring of hemodynamic status of septic patients within the first 3-6 hours after diagnosis. Revision that followed in 2018 stressed that all therapeutic actions should be initiated within the first hour after diagnosis. Urgent administration of isotonic saline and balanced crystalloids in a dose of 30ml/kg should provide adequate hemodynamic stability of septic patients. If the fluid replacement fails to achieve hemodynamic stability and mean arterial pressure >65 mmHg, addition of vasopressors is mandatory. The vasopressor of choice for septic patients is norepinephrine. It may be used alone or in combination with other vasopressors such as epinephrine, vasopressin, terlipresine or phenylephrine. Septic patients with inadequate cardiac output after fluid replacement, and cardiomyopathy induced by sepsis or those with combined shock may need treatment with inotropic medication such as epinephrine or dobutamine. Adjuvant therapy with steroids, immunoglobulins, anticoagulants, statins, vitamin C and B1, may be useful, but no benefit regarding the overall outcome was observed. In conclusion, early detection of sepsis and septic shock within the first hour and immediate adequate fluid administration with vasoactive medications to maintain hemodynamic stability, are crucial for achievement of better outcome of these patients.

Key words: sepsis, fluid replacement, vasoactive drugs, adjuvant therapy, corticosteroids, immunoglobulins

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INTRODUCTION

Sepsis is urgent medical condition caused by inadequate immune response to infection. Septic shock encompasses circulatory, cellular and metabolic disorders presented as hypotension resistant to fluid replacement with urgent need for vasopressor therapy [1]. Early recognition of these conditions, detailed initial estimation and prompt therapy are of primary importance for reduction of death rate in sepsis. Guidelines published in 2016, underlined the importance of early fluid supplementation and control of the source of infection. Furthermore, appropriate laboratory estimation and hemodynamic monitoring are crucial for improvement of treatment outcome. This literally implies lactate level measurement, hemoculture sampling before administration of antibiotics, preferred use of broad-spectrum antibiotics and rapid crystalloid supplementation in the dose of 30ml/kg. In hypotensive cases resistant to fluid replacement, vasopressors should be given within 3 - 6 hours since diagnosis was made [2]. The latest recommendations for treatment of sepsis from 2018 have confirmed all treatment modalities published in 2016 with the update concerning the timing of treatment initiation. The new recommendation stressed that treatment should be initiated and rapidly administrated within the first hour after diagnosis of sepsis [3]. The shift in timing needs reconsideration of fluid replacement intensity and dynamics, appropriate and timely vasopressor administration as well as the use of adjuvant

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therapy, which is going to be discussed in the following review.

FLUID REPLACEMNET, HEAMODYNAMIC STABILITY ESTIMATION, AND THE USE OF VASOACTIVE DRUGS IN SEPTIC PATIENTS

Sepsis is a life-threatening condition associated with generalized endothelial damage, increased capillary permeability, decreased circulatory blood volume and decreased preload into the right atrium. These hemodynamic effects result into decreased tissue perfusion and organ disfunction. One of the main goals in reanimation of septic patient is to renew circulatory blood volume and normalize oxygen delivery to tissues that is the prerequisite for improvement and elimination of organ damage. It is recommended to initiate fluid supplementation with crystalloid boluses within first hour in dose of 30 ml/kg. Dose should be completely administered within third hour after the sepsis or septic shock diagnosis [2].

Fluid supplementation in septic patients is usually performed in four phases:

- Rescue phase: initiated within few minutes, lasting for a few hours after diagnosis in cases with life-threatening decompensated shock (low blood pressure, signs of decreased tissue perfusion). The volume of given crystalloids should be 30 ml/kg.
- Optimization phase: is applicable for a patient with sepsis in a state of compensated shock, whose life is not immediately endangered. Administration of additional volume of fluids is more cautious and should be titrated until achievement of optimal cardiac output and tissue perfusion. Undesirable hypervolemia should be avoided in this phase.
- Stabilization phase usually occurs within 24-48 hours after diagnosis, with patient being in good general condition. Volume of administered fluid should be enough to compensate standard renal, gastro-intestinal or other unclear fluid losses. Patients are neither in the state of shock, nor in immediate danger to develop this condition.
- De-escalation phase is characterized by absence of shock in patient and by recovery of all organ functions. Fluids should be given in order to provide net-neutral or slightly negative fluid balance. In this way, iatrogenic unnecessary fluid overload is be avoided [4,5].

For initial fluid replacement, in rescue phase, recommendations are in favor for isotonic salt or balanced crystalloids solutions. In the last 10 years, Ringer or Ringer-lactate solutions are considered advanatagous. If non-balanced isotonic solutions are administered, hyperchloremic and metabolic acidosis is more likely to occur, with consecutive renal vasoconstriction and blood flow reduction through the renal cortex. If balanced solutions are used, renal insufficiency may develop less frequently with less need for dialysis and with decreased mortality in critically ill patients [6,7,8]. The clinical use of colloids was sometimes justified by the need to improve low oncotic pressure or to reduce capillary leakage or in some cases with the idea to reduce excessive fluid volume replacement. Unfortunately, the use of colloids showed no advantage over balanced crystalloids in sepsis and septic shock. Furthermore, no benefit was seen when albumins were administered during initial reanimation comparing to balanced crystalloids and the treatment cost was higher in this group of patients [9]. Other colloids such as hydroxyethil starch are also not recommended in sepsis, since their use was associated with renal insufficiency and increased mortality [10].

The goal of every fluid replacement strategy is to maintain median arterial pressure (MAP) above 65 mm Hg thus providing adequate tissue perfusion. While attempting to achieve desirable MAP, it is often possible to cause volume overload if large volumes of fluids are given. State of overload is manifested by pulmonary oedema, hypoxemic respiratory insufficiency, swelling of peripheral tissue, development of intrabdominal hypertension with prolonged duration of stay in intensive care (ICU) and higher death rate [4,11]. For this reason, continuous estimation of fluid volume status is mandatory through the measurement of both static (median arterial pressure, central-venous pressure, hourly urine output) and dynamic parameters. Static parameters have shown considerable inferiority comparing to dynamic measures for prediction of volume overload [12,13,14]. Also, dynamic parameters enabled more appropriate fluid replacement, affecting positively the cardiac output,

shortening duration of mechanical ventilation and ICU stay with the decrease in mortality [15,16,17]. Dynamic measures are performed after administration of bolus fluids or after passive leg elevation. The latter maneuver may return 200 - 300 ml of blood from lower extremities to systemic circulation. Consecutive changes in the cardiac output may be directly measured using thermodilution or echocardiography or by registering changes in pulse pressure. Changes of cardiac output during inspiratory and expiratory phase of mechanical ventilation could be estimated through the variations of the pulse pressure, stroke volume and diameters of v. cava inferior [16,17].

Apart from dynamic measurements, fluid replacement during rescue phase can beassessed through an analysis of lactate levels and central venous oxygen saturation (ScvO2). Increase in lactate levels during sepsis may result from tissue hypoxia, increased aerobic glycolysis induced by β-adrenergic stimulation, but the increase may also be the result of effects of certain drugs (epinephrine, β2 agonists) or hepatic insufficiency. Lactate follow up, may objectively estimate response to resuscitation attempts and predict its inferior outcome. This was particularly evidenced in septic patients with lactate levels above 4 mmol/l [18,19]. If serum lactate levels as markers of tissue hypoperfusion are above 2 mmol/l during initial assessment, measurements should be repeted every 2-4 hours until normalization [19]. Therapy driven by the levels of this biomarker, may significantly reduce mortality in septic patients [20,21]. Therapeutic effects of fluid supplementation may also be followed byScvO2and capillary refill assessment, although their follow up was not found to be advantageous,comparing to lactate level analysis [20,22].

Response to supplemented fluid in septic patients is considered adequate if systolic pressure rises above 90 mmHg, in case of hypotension reversion or when MAP reaches levels above 65 mmHg without vasopressor influence. Yet, certain number of patients (36.2%) remains refractory to fluid administration, as seen in a retrospective study done on 3686 patients [23]. These patients often need prolonged mechanical ventilation and longer stay at ICU with higher death rate. The most common causes of refractoriness to fluid supplementation are: delay in fluid administration after making diagnosis of sepsis (longer than 2 hours), the presence of heart failure as a comorbidity, hypothermia, coagulopathy, immunocompromised patients and serum lactate above 4 mmol/l at initial assessment of patients [23].

Rapid fluid renewal with satisfactory perfusion of vital organs aiming to correct MAP above the 65 mmHg, is essential for reanimation of critically ill patients and should not be delayed. If restoration of adequate tissue perfusion fails after initial fluid administration, vasopressor therapy, isolated orcombined with inotropic drugs should be initiated. Physiological effects of both vasopressor and inotropic drugs are the rise of blood pressure and cardiac output and improvement of oxygen delivery to tissues. Vasopressor dose should be carefully titrated until desirable MAP level, having in mind potential risks for development of arrythmiaor cardiac, mesenteric, cerebrovascular and peripheral ischemia caused by these drugs [24]. Failure of vasopressors to correct blood pressure above desirable threshold (MAP>65 mmHg), induces linear decline of tissue perfusion with significant reduction of hourly output of urine, with detrimental effect to mental status and lactate clearance [25]. Norepinephrine is the vasopressor of choice due to potent agonistic α-adrenergic effects and less potent β-adrenergic effects. Early administration of norepinephrine showed greater benefit in the treatment of septic shock due to better organ perfusion and reduced incidence of arrhythmias and mortality in these patients, compared to other vasopressors [26,27,28]. Immediate administration of norepinephrine (93 vs 192 minutes) after diagnosis of septic shock, was associated with better control of shock in the first 6 hours with reduced incidence of cardiogenic pulmonary oedema and newly arrhythmias compared to late administration of norepinephrine [29]. In order to implement this experience in everyday clinical practice, new studies with a higher degree of evidence are needed. Vasopressors other than norepinephrine such as: epinephrine, vasopressin, terlipresine or phenylephrine, may also be used [29,30]. Combined use of norepinephrine with any additional vasopressor may be applied if the isolated norepinephrine therapy was not able to achieve satisfactory MAP levels or if there is a risk for norepinephrine overdose (40 to 50 μg/min) in

septic patients. In spite of these recommendations, combined treatment showed no efficacy in a study of Zhou et al. [31]. Combination of norepinephrine and vasopressin in septic patients with preexisting cardiac insufficiency was associated with inferior survival of these patients due to occurrence of malignant arrhythmia compared to monotherapy with either norepinephrine or dopamine [31]. Considering these data, the choice of proper vasopressor for the treatment of septic shock, requires obtaining additional information about preexisting heart problems, before reaching the final decision. Apart from vasopressors, inotropic drugs are recommended especially in patients with inadequate cardiac output after fluid supplementation due to sepsis -induced cardiomyopathy or existence of a combined shock. Most commonlyused inotropic drugs are dobutamine and epinephrine [32,33]. Inotropic drugs may be given individually or in combination with vasopressors. It is worth saying that combined use of dobutamine with norepinephrine showed neither decrease in mortality nor influenced shock duration compared to sole administration of epinephrine [33]. Effects of inotropic drugs treatment must be checked through cardiac output, ScvO2 or through mesurments of other tissue perfusion parameters.

ADJUVANT THERAPY IN SEPTIC PATIENTS

Corticosteroids regulate inadequate inflammatory response that may be seen in sepsis and also may cause suprarenal gland insufficiency or may increase tissue resistance to glucocorticoids [34]. It is believed that in patients with septic shock, steroids may decrease the need for vasopressors and reduce the duration of a shock, the length of stay at ICU and duration of mechanical ventilatory support. So far, obtained results failed to prove any clinical benefit of corticosteroids on survival outcome for patients with sepsis or septic shock. For this reason, corticosteroids should not be given to septic patients, particularly if they achieve hemodynamic stability to fluid supplementation and vasopressors [35,36,37]. Corticosteroids are more frequently added as adjuvant therapy when there is a necessity for higher doses of vasopressors [34]. If the decision to use corticosteroids is made, recommended dose of hydrocortisone should be 200mg within 24 hours continusly or divided to 50mg every 6 hours through first three days [38]. With the administration of corticosteroids, the ICU and hospitalization stay was significantly reduced, while the 28-day and overall mortality of septic patients were reduced with moderate level of evidence. The risk of major complications occurrence, after corticosteroid use, was very low. Following its administration, one may also expect undesirable effects such as: muscle weakness, hypernatremia, and probably risk for hyperglycemia [39]. New studies are necessary in order to define proper timing and duration of corticosteroid treatment related to the beginning of septic shock, with close analysis of the patient's outcome.

With the administration of intravenous immunoglobulins in septic patients, the effects of antigen neutralization, blockade of Fc receptors on phagocytes and immunomodulation of the cytokine and cellular response can be achieved [40]. Although reduction of hospital mortality in septic patients after high doses (1.5-2 g/kg) of intravenous immunoglobulins, was observed in some studies, there are considerable limitations concerning these data, urging for stronger evidence before their use [41,42]. In order to get more adequate estimation of intravenous immunoglobulins efficacy in sepsis and septic shock, some authors suggest the need for analysis of additional parameters such as: the estimation of the amount of immunoglobulins present in administered drugs, timing of their administration related to sepsis onset (effects are better if immunoglobulins were given within 24 hours after sepsis onset), correlation between administeredimmunoglobulin dose and the degree of inflammation during infection [43]. Numerous contradictions and insufficient evidence about immunoglobulin efficacy in septic patients require further studies for the purpose of shedding light on immunoglobulin effects.

Even though numerous trials have shown efficacy of anticoagulant drugs in adjuvant treatment of septic patients, there is not much evidence about their benefit to mortality reduction in of septic patients. The greatest benefit in anticoagulant use was noticed in patients with sepsis-induced disseminated intravascular coagulopathy [44].

Statin drugs administration has been associated with significant reduction in mortality of septic patients in certain

observational studies compared to randomized studies. For this reason, further studies should answer the questions concerning efficacy, safety and finding the adequate dose of statins in septic patients [45]. Many other aspects of adjuvant therapy in septic patients need clarifications. This is the case of the usefulness of early administration of intravenous vitamin C and B1 considering the registered deficiency of these vitamins in these patients. Although the early administration of these vitamins had no impact on overall survival of septic patients, it is considered that along with standard therapy vitamin supplementation may be beneficial in septic patients [46,47].

CONCLUSION

Treatment of patients with sepsis and septic shock is extremely complex, considering that sepsis is multifactorial. Good understanding of pathophysiological processes, early diagnosis of sepsis and septic shock, urgent and adequate fluid supplementationis initiated within the first hour after the diagnosis with administration of vasoactive drugs aiming to achieve hemodynamic stability, may be crucial for better outcome of these patients. Adjuvant therapy like corticosteroids, immunoglobulins, anticoagulants or administration of vitamins C and B1, has some benefit in septic patients' treatment, but final decision about their use might be reached after collecting firm evidence from further clinical studies.

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