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REVIEW ARTICLE

Current concepts on hemodynamic support and therapy in septic shock

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Abstract Severe sepsis and septic shock represent a major healthcare challenge. Much of the improvement in mortality associated with septic shock is related to early recognition combined with timely fluid resuscitation and adequate antibiotics administration. The main goals of septic shock resuscitation include intravascular replenishment, maintenance of adequate perfusion pressure and oxygen delivery to tissues. To achieve those goals, fluid responsiveness evaluation and complementary interventions – i.e. vasopressors, inotropes and blood transfusion – may be necessary. This article is a literature review of the available evidence on the initial hemodynamic support of the septic shock patients presenting to the emergency room or to the intensive care unit and the main interventions available to reach those targets, focusing on fluid and vasopressor therapy, blood transfusion and inotrope administration.
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Conceitos atuais sobre suporte hemodinâmico e terapia em choque séptico

Resumo A sepse grave e o choque séptico são um grande desafio para a assistência médica. Grande parte da melhora na taxa de mortalidade associada ao choque séptico está relacionada ao reconhecimento precoce em combinação com a reposição volêmica oportuna e a administração adequada de antibióticos. Os principais objetivos da reanimação do choque séptico incluem reposição intravascular, manutenção adequada da pressão de perfusão e fornecimento de oxigênio para os tecidos. Para atingir esses objetivos, a avaliação da responsividade do volume e das intervenções complementares (vasopressores, inotrópicos e transfusão de sangue) pode ser necessária. Este artigo é uma revisão da literatura para identificar as evidências disponíveis do suporte hemodinâmico inicial aos pacientes com choque séptico admitidos em sala de emergência ou unidade de terapia intensiva e as principais intervenções disponíveis

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para atingir essas metas, com foco em terapia com reposição de líquidos e vasopressores, transfusão de sangue e administração de inotrópicos.

Introduction

Sepsis, a systemic inflammatory response associated to an infection, is a common disease with an estimated incidence of 300 cases per 100,000 people and with an incidence increase of 13% per year.[1,2] Approximately half of septic patients will develop the most severe spectrum of this disease, i.e. severe sepsis and septic shock.[3]

Septic shock carries an average in-hospital mortality rate around 20% and a 90 day mortality rate between 20% and 50%.[4–10] In Brazil, the 28 day mortality rate achieves around 50% with an incidence density of thirty cases per thousand patient-days.[11]

Septic shock is also associated with high burden of morbidity and costs. The average cost per patient is US$ 22,100, which accounts for an annual expenditure of approximately seventeen billion dollars in the United States alone.[1] Additionally, the quality of life and cognitive function of sepsis survivors may be permanently compromised.[12–14] Key interventions to improve outcomes in this population of critically ill patients include early recognition and early onset of adequate therapy, mainly broad-spectrum antibiotics and fluids.[15]

The initial attempts to optimize hemodynamics in critical care patients were deemed ineffective, increasing the risk of death.[16,17] During the past decade, the early goal-directed therapy principle encompassing early series of protocolized interventions, i.e. antibiotics, fluids, vasopressors, inotropes, red blood transfusion, etc., showed significant reduction of mortality rate.[18] This strategy has been recommended by specialty societies in their guidelines for severe sepsis and septic shock treatment and has been implemented in emergency departments and intensive care units in a global scale.[15]

According to these guidelines, septic patients presenting with signs of persistent hypotension (i.e. mean arterial blood pressure <65 mmHg despite initial adequate fluid resuscitation) or tissue hypoperfusion (i.e. arterial lactate concentration equal to or higher than 4.0 mmol/L) have a high risk of death and therefore must be promptly resuscitated.[15]

Nevertheless, there is increasing evidence coming from new randomized clinical trials challenging the efficacy of the early goal-directed therapy for septic patients.[8,9] Therefore, we propose a narrative review of the literature supporting the management of the early stages of septic shock, with special attention to hemodynamics evaluation and evidence-based interventions, taking into account the recently published data.

Objective

Our objective was to perform a narrative review of the available evidence on hemodynamic support for septic shock patients and provide an overview of the key available interventions for resuscitation, e.g. fluid therapy, vasopressors, inotropes and red blood transfusion.

Methods

We performed a systematic search in MEDLINE/Pubmed, Embase/OVID, LILACS/Bireme and Cochrane Library up to October 2014 using the Medical Subject Headings (MeSH) terms ''sepsis'', ''severe sepsis'' AND/OR ''septic shock'' combined with ''central venous pressure'', ''lactate'', ''lactate clearance'', ''mean arterial pressure'', ''blood pressure'', ''vasopressors'', ''norepinephrine'', ''epinephrine'', ''vasopressin'', ''central venous oxygen saturation'', ''blood transfusion'', ''transfusion'', ''dobutamine'', ''fluid responsiveness''.
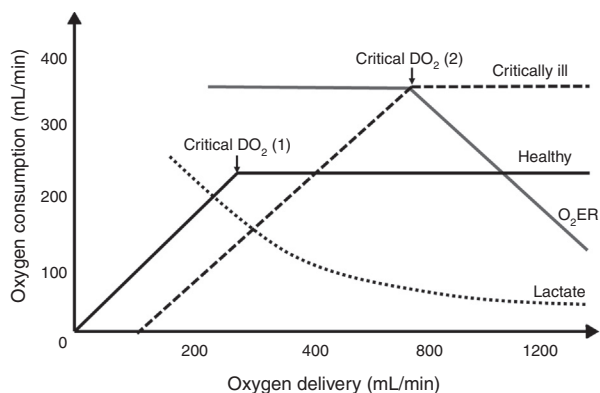
We have limited our search to articles written in English, human subjects and clinical trials. We also reviewed the current Surviving Sepsis Campaign Guidelines for the Treatment of Severe Sepsis and Septic Shock and their key related articles.[15] Additional studies were added at authors' discretion. One hundred and seventy-nine articles were retrieved from this search and further filtered for quality and originality before being included in this review.

Hemodynamic goals

The imbalance between oxygen consumption and oxygen delivery is the main determinant of the development and progression of organ dysfunction in septic shock patients. Therefore, the aim of the hemodynamic interventions commonly applied to these patients is to increase oxygen delivery to match oxygen demand (Fig. 1).

The currently recommended hemodynamic targets to be achieved during the initial six-hour of resuscitation include a central venous pressure (CVP) between 8 and 12 mmHg in spontaneously breathing patients or between 12 and 15 mmHg in mechanically ventilated patients or in those with reduced ventricular compliance, a mean arterial blood pressure (MAP) $\geq$65 mmHg, a central venous (ScvO2) or mixed venous (SvO2) oxygen saturations $\geq$70% and 65% respectively, a lactate clearance $\geq$10% and an urinary output $\geq$0.5 mL/kg/h (Fig. 2).[15]

Recently, two large randomized clinical trials confronted the efficacy of early goal-directed therapy in septic shock.[8,9]

Figure 1 Relationship between oxygen delivery, oxygen consumption, oxygen extraction rate and lactate in healthy (1) and critically ill (2) patients with shock. DO2, oxygen delivery; VO2, oxygen consumption; O2ER, oxygen extraction rate.

The first one, the ProCESS trial, assessed three different resuscitation strategies for septic shock patients.[8] This study showed no 60 day mortality difference when usual care (i.e. no pre-specified protocol), protocol-based early goal direct therapy (i.e. central venous line insertion with SvcO2 and CVP guidance) and protocol-based standard therapy (i.e. without central venous line placement nor ScvO2 and CVP guidance) were compared.[8] In the second study, the ARISE trial, septic shock patients were randomized for early goal-directed therapy or usual care (at clinical team discretion and without ScvO2 measurement during the first six hours of resuscitation).[9] There was no difference in the primary outcome, which was mortality on the 90th day after randomization. Additionally, the early goal-directed therapy group received significantly more fluids, vasopressors, inotropes and red blood cell transfusion.[9] A third ongoing trial (ProMISe), addressing the efficacy of the early goal directed in septic shock completed enrollment of patients (Controlled-trials.com: ISRCTN36307479).

Considering these results, it can be assumed that early recognition and treatment provision for septic shock patients should be the main concern and priority for clinicians at the bedside rather than strictly follow a goal-directed protocol. In the next sections, we will discuss the main hemodynamic interventions individually.

Central venous pressure and fluid responsiveness

Central venous pressure is the pressure recorded from the right atrium or at the superior vena cava by the insertion of a central venous catheter.[19] The CVP is determined by a complex interaction between cardiac function and venous return, and represents a static indicator of cardiac preload.[19] Central venous pressure is not an accurate predictor of fluid responsiveness in critically ill patients.[20] Nevertheless, it has been used widely with this purpose (Table 1).[20]

The evaluation of arterial pulse pressure variation due to heart–lung interactions represents a dynamic and accurate predictor of fluid responsiveness that can be used to discriminate between patients who will and will not increase cardiac output after a fluid challenge (Table 1).[21] However, an arterial line placement, absence of patient's respiratory efforts, usually obtained by deep sedation and neuromuscular blockers, volume controlled mechanical ventilation with tidal volume between 8 and 12 mL/kg, positive end expiratory pressure lower than 10 cm H_2O and a regular cardiac rhythm are required for pulse pressure variation assessment.[21] Other available methods to address fluid responsiveness in critically ill patients include bedside ultrasound analysis of the inferior vena cava[22] and the passive leg raising test (Table 1).[23]

The distensibility index of the inferior vena cava is calculated from the M mode of the thoracic echocardiogram at the subcostal window as follows: maximum inferior vena cava diameter minus minimum inferior vena cava diameter divided by maximum inferior vena cava diameter.[22] An inferior vena cava distensibility index above 18% is highly correlated with a 15% cardiac index increase after a fluid challenge.[22] Inferior vena cava analysis also requires deeply sedated, mechanically ventilated patients with mild or no respiratory effort and a regular cardiac rhythm to be accurately performed.[22]

The passive leg-raising test is a sequential maneuver in which the patient is initially in a semi-recumbent position and afterwards both legs are elevated 45 degrees in relation to the ground with the patient in the supine position for one minute.[23] This test simulates a fluid challenge in a way that blood from the inferior limbs is mobilized to the heart. An increase greater than 10% in measured blood flow is highly predictive of fluid responsiveness.[23] This maneuver can be performed in spontaneously breathing patients and in the presence of cardiac arrhythmia.[23]
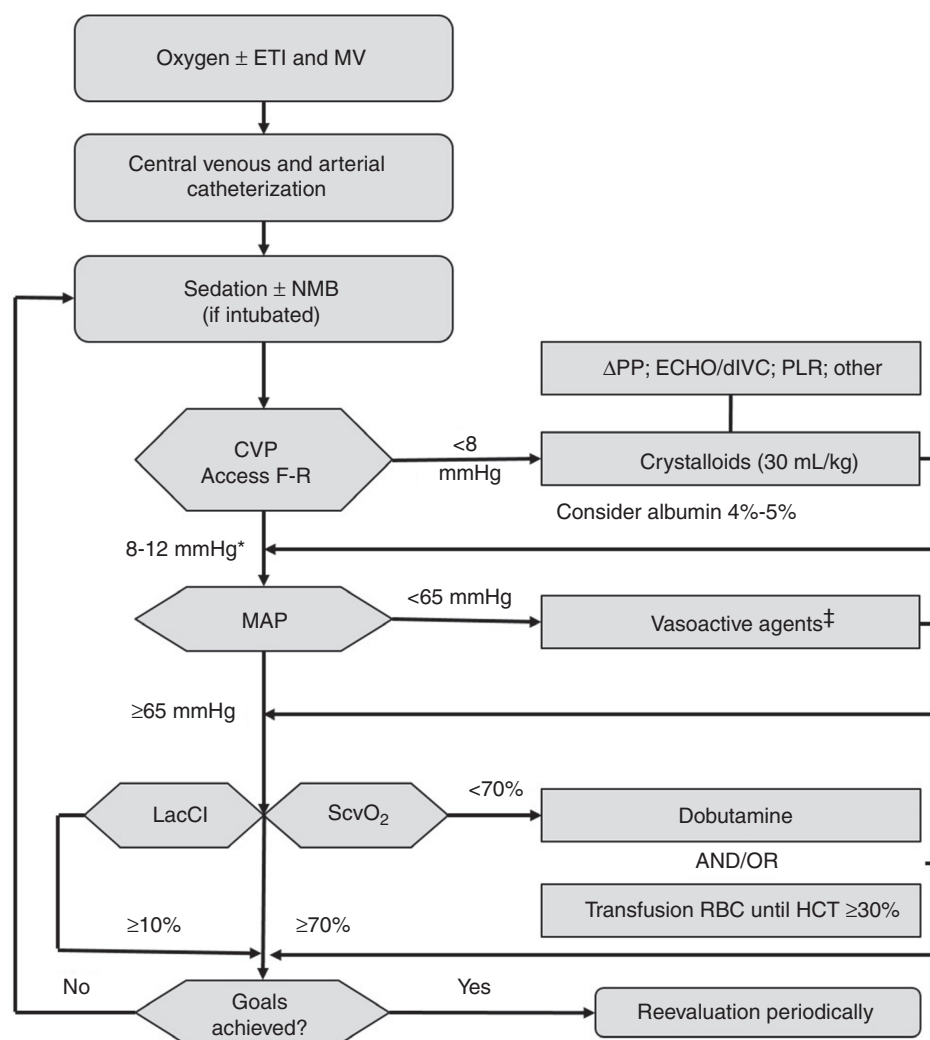
Arterial blood pressure

A mean arterial pressure ≥65 mmHg has been recommended during the initial resuscitation of septic shock (Fig. 2).[15] However, few studies are available to support this recommendation.[6,24–28] This lack of available data is

Table 1 Main methods available to address fluid responsiveness in critically ill patients.

Methods	Cutoff values	Mechanical ventilation?	Arrhythmia?	Limitations
CVP[4,5]	<8–12 mmHg	No/yes	Yes	Limited in critically ill patients
∆PP[6]	>13%	Yes	No	RV dysfunction
IVC distensibility[7]	>18%	Yes	No	US training
PLR[8]	CI >10%	No	Yes	N/A

CVP, central venous pressure; ∆PP, arterial pulse pressure variation; IVC, inferior vena cava; PLR, passive leg raising; CI, cardiac index; RV, right ventricle; N/A, not available; US, ultrasonography.
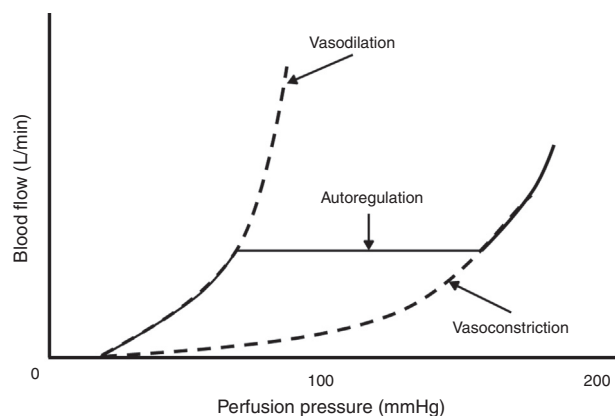
Figure 2 Suggested goal-directed therapy algorithm for septic shock resuscitation. It is important to note that only hemodynamic goals are depicted in this algorithm. The other components of sepsis bundles (e.g. antibiotic therapy, source control, etc.) are activated concomitantly. ETI, endotracheal intubation; MV, mechanical ventilation; NBM, neuromuscular blockers; CVP, central venous pressure; F-R, fluid responsiveness; MAP, mean arterial blood pressure; LacCl, blood lactate clearance; ScvO2, central venous oxygen saturation; ΔPP, pulse pressure variation; ECHO, hemodynamic echocardiography; dIVC, distensibility index of the inferior vena cava; PLR, passive leg raising; RBC, packed red blood cells; HCT, hematocrit; *, for patients under mechanical ventilation;+, norepinephrine is the first choice vasopressor (see text).

reflected in the wide range of MAP goals adopted in studies involving septic patients.[29] The rationale supporting the inclusion of arterial blood pressure in the septic shock resuscitation algorithm is based on the principle of blood flow autoregulation (Fig. 3). Accordingly, if cardiac output is maintained constant, blood flow to tissues does not change until the blood pressure falls below a critical value. When this critical value is approached, any additional reduction in arterial pressure will impair tissue blood flow. Since different organs have distinct critical thresholds, the optimal arterial blood pressure to be achieved remains undetermined.

Small prospective studies addressed the effects of different MAP levels in septic shock patients. Increasing MAP from 65 to 85 mmHg did not improve systemic oxygen consumption, skin microcirculatory blood flow, splanchnic perfusion

or renal function, and was associated with a higher left ventricular stroke work index and increased exposure to catecholamines.[24,25] Additionally, although increasing MAP from 60 to 90 mmHg[26] or from 65 to 85 mmHg[27,28] with norepinephrine improved systemic oxygen delivery and the cutaneous tissue partial pressure of oxygen, contradictory findings on sublingual microcirculation were reported.[26-28]

The impact of two MAP targets (65–70 mmHg and 80–85 mmHg) on 28 day mortality was recently evaluated in 776 septic shock patients.[6] Although the 28 day mortality did not differ between the groups, the incidence of atrial fibrillation was higher in patients randomized to the high blood pressure group in comparison to patients allocated to low MAP group.[6] Taking the available evidence together, we conclude that targeting higher MAP levels during the initial resuscitation of septic shock increases the exposure

Figure 3 Auto regulation of blood flow to the tissues driven by the perfusion pressure curve. In situations of severe hypotension (mean arterial pressure <50 mmHg), blood flow to the tissues is decreased, leading to hypoxia. On the other hand, during severe hypertension (mean arterial pressure >150 mmHg), there is an increase in blood flow to the tissues that can result in leakage of blood components into the interstitial space. In both situations, when the auto regulatory threshold is reached, auto regulation of the blood flow mechanism is lost. The mean arterial pressure represents the perfusion pressure.

to fluids, vasopressors and inotropes, which has been associated with increased incidence of side effects, morbidity and mortality.[30] Nevertheless, targeting lower MAP levels may increase the incidence of tissue hypoperfusion and contribute to the progression of organ dysfunction.[31,32]

Mixed venous and central venous oxygen saturation

In conditions under reduced oxygen delivery, the oxygen consumption can be satisfied if the tissue oxygen extraction increases proportionally. If the oxygen delivery reduction persists, anaerobic metabolism, lactic acidosis and organ dysfunction may develop (Fig. 1).[33] The mixed venous oxygen saturation is measured in the blood collected through a pulmonary artery catheter and its value provides information regarding to the systemic oxygen consumption.

The mixed venous oxygen saturation values are not equal to the central venous oxygen saturation, which represents the oxygen saturation measured in the blood collected from the superior vena cava at the entrance to the right atrium.[34] Although the differences between ScvO2 and SvO2 values can vary across different clinical conditions, the overall trends of both measurements are similar.[35]

Assuming arterial oxygen saturation of 100%, the oxygen extraction rate (O2ER) can be summarized by ''1 − SvO2'', in a simpler way than using oxygen consumption and delivery calculations to guide therapy at the bedside.[33] Nevertheless, it is important to empathize that the oxygen extraction rate needs to be analyzed as a function of the cardiac output and in association with other perfusion parameters.[33] A low mixed venous oxygen saturation can be adequate in compensated chronic heart failure patients or in patients recovering from shock (flow redistribution), and may be high and adequate in some chronic cirrhotic patients. Because of that,

the recommendations to reach ScO2 ≥65% or a ScvO2 ≥70% represent a simplification, only valid during the first 6 h of septic shock (Fig. 2).[15]

Lactate clearance

The lactate is an intermediate compound of the glucose metabolism, produced in the cytoplasm from pyruvate. In aerobic conditions, the pyruvate is produced via glycolysis and is metabolized by the mitochondrial aerobic oxidation pathway via the Krebs cycle, bypassing the production of lactate. In anaerobic conditions, the decreased mitochondrial oxidative phosphorylation results in a raised pool of pyruvate. This excess of pyruvate is converted into lactate. Lactate production occurs in multiple organs, such as muscle, skin, brain, intestine and red blood cells and its clearance takes ground in the liver, kidneys and heart. Thus, an impaired lactate clearance or excessive lactate production can result in high blood lactate levels. The normal arterial lactate level is below 2.0 mmol/L.[36]

In most shock states, particularly those presenting with low cardiac output, hyperlactatemia reflects end-organ cellular dysoxia due to tissue hypoperfusion. Indeed, even after normalizing the traditional hemodynamic parameters, such as CVP, MAP, cardiac output and SvO2, critically ill patients may still have ongoing tissue hypoxia (i.e. occult hypoperfusion).[37] Therefore, lactate has been used as a surrogate marker of tissue hypoperfusion and as a biomarker for morbidity and mortality in septic shock patients. Both intermediate (2.0–3.9 mmol/L) and high (≥4.0 mmol/L) serum lactate levels have been associated with increased risk of death.[37]

The lactate clearance is defined as the percentage of lactate cleared over a period, usually 2–6 h, from presentation in the emergency department or intensive care unit.[38] For each 10% increase in lactate clearance, there is an 11% decrease in the likelihood of death.[38] A lactate clearance lower than 10% from its baseline value is an independent predictor of increased in-hospital mortality.[38] In a multicenter, open-label, randomized controlled trial, Jansen et al. enrolled patients admitted to the intensive care unit with lactate ≥3.0 mEq/L.[39] In one group, the resuscitation was guided by the clearance of lactate (decrease of 20% or more per 2 h for the initial 8 h in intensive care unit). The control group had only the initial lactate measure and no lactate guided therapy. The patients in the lactate-guided treatment group had lower adjusted in-hospital mortality (hazard ratio 0.61, 95% CI 0.43–0.87; $p = 0.006$) and intensive care unit mortality (hazard ratio 0.66, 95% CI 0.45–0.98; $p = 0.037$).[39]

The lactate clearance was compared to central venous oxygen saturation as indicator of adequate tissue oxygen delivery during the initial resuscitation of severe sepsis and septic shock patients in a non-inferiority trial.[40] In this study, targeting a lactate clearance of at least 10% produces a similar short-term survival rate as a protocol using ScvO2.[40] These data support lactate clearance as an alternative to ScvO2 monitoring, with the advantage of not requiring a central line placement and its associated risks and costs (Fig. 2).

Therapy

Fluids

The correction of hypovolemia and tissue hypoperfusion through fluid administration aims to increase tissue oxygen delivery by increasing cardiac output. Currently, the fluid of choice for the initial resuscitation of septic shock patients is crystalloids, at an initial fluid challenge of 30 mL/kg.[15] Based on data from recently published trials, hydroxyethyl starch (HES) should not be used for fluid resuscitation.

Several studies and meta-analyses have shown the deleterious effects of HES compared to crystalloids for septic shock resuscitation.[41–45] Hydroxyethyl starch increases the risk of bleeding, acute renal failure and the need for renal replacement therapy.[44,45]

The VISEP trial assessed the safety and efficacy of intensive insulin therapy against conventional therapy and 10% HES 200/0.5 against Ringer's lactate in patients with severe sepsis or septic shock.[41] This study was stopped prematurely due to the high risk of hypoglycemia in the intensive insulin therapy group. The comparison between HES 200/0.5 and Ringer's lactate continued with all patients receiving conventional insulin therapy. The trial was stopped after the first interim analysis, because of increased rate of renal failure and a trend toward higher mortality at 90 days in the HES group.[41]

The 6S trial enrolled severe sepsis patients to fluid resuscitation with either 6% HES 130/0.42 or Ringer's acetate.[42] In this study, HES 130/0.42 significantly increased the risk of death (51% vs. 43%; $p = 0.03$) or dependence on dialysis at 90 days (22% vs. 16%; $p = 0.04$). The CHEST trial randomly assigned 7000 critically ill patients to receive 6% HES 130/0.4 in 0.9% saline or 0.9% saline alone for fluid resuscitation.[43] There was no significant difference in 90 day mortality between the two groups. Nevertheless, more patients who received HES 130/0.4 needed renal replacement therapy.[43] The CRISTAL trial compared colloids (gelatins, dextrans, HES or albumin 4% or 20%) vs. crystalloids (isotonic/hypertonic saline or Ringer lactate) in hypovolemic shock resuscitation (including sepsis, trauma and no-trauma no-sepsis). There was no difference between groups in 28 day mortality (relative risk 0.96, 95% CI 0.88–1.04; $p = 0.26$).[46]

Administration of albumin should be considered in patients requiring substantial amounts of crystalloids.[15] The largest trial to date that compared hypooncotic albumin (4% solution) with normal saline in a general critically ill population was the SAFE trial.[47] This study showed no difference 28 day mortality between the groups. A subgroup analysis including only severe sepsis patients demonstrated that albumin administration was independently associated with mortality reduction (odds ratio 0.71, 95% CI: 0.52–0.97; $p = 0.03$).[48] Nevertheless, this finding was not confirmed in the most recent trial in which 1818 severe sepsis and septic shock patients were randomized to receive either 20% albumin and crystalloid solution or crystalloid solution alone during ICU stay.[7]

Vasopressors

Systemic vasodilatation and arterial hypotension are landmarks of severe sepsis and septic shock. When adequate fluid resuscitation is not enough to restore the arterial blood pressure, vasopressor administration should be initiated (Fig. 2).[15] A meta-analysis including six randomized clinical with 1408 patients compared norepinephrine vs. dopamine as first-line vasopressors in septic shock.[49] Dopamine administration was associated with a higher risk of death (relative risk 1.12, 95% CI 1.01–1.20; $p = 0.035$) and a higher risk of cardiac arrhythmias (relative risk 2.34, 95% CI 1.46–3.77; $p = 0.001$). Based on these findings, norepinephrine has been recommended as the vasopressor of choice in septic shock patients (Fig. 2).[15] Alternative vasopressors include low doses of vasopressin, epinephrine (added or potentially substituted for norepinephrine) and dopamine in highly selected patients (low-risk for arrhythmia).[15]

Vasopressin, also known as antidiuretic hormone, is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and released into the systemic circulation from the posterior pituitary gland in response to decreased intravascular volume and increased plasma osmolality. The vasoconstrictive effect of vasopressin on vascular smooth muscle is mediated by V1 receptors. It is one of the most important stress-related hormones and a relative vasopressin deficiency may develop during septic shock progression.[50]

Low doses of vasopressin may be added to norepinephrine to maintain arterial blood pressure in refractory septic shock and to decrease exposure to norepinephrine.[15] The VASST trial compared the administration of low doses of vasopressin (0.01–0.03 U/min) vs. norepinephrine in septic shock patients.[51] The authors reported no significant differences between the two respective groups regarding 28 day mortality (35.4% vs. 39.3%; $p = 0.26$), 90 day mortality (43.9% vs. 49.6%; $p = 0.11$) or the rate of serious adverse events.[51] The main concern about vasopressin administration is related to decreased blood flow to the heart, intestine and limbs, especially when higher doses are used.[50]

Epinephrine is a potent α- and β-adrenergic catecholamine that increases MAP by increasing both cardiac output and systemic vascular resistance. Epinephrine administration may also transiently increase the lactate concentration, probably due to increased aerobic glycolysis through Na^+K^+ ATPase stimulation within the skeletal muscles rather than through tissue dysoxia.[52] Epinephrine alone was compared to norepinephrine associated with dobutamine administration in a prospective multicenter study, which included 330 septic shock patients.[52] The 28 and 90 day mortality rates, time to hemodynamic stabilization, number of vasopressor-free days and rate of serious adverse effects did not differ between the study groups. Nevertheless, a transient increase in the lactate concentration was observed between days 1 and 4 in the epinephrine group.[52]

Inotropes and blood transfusion

Dobutamine, a β1-agonist catecholamine, is recommended in the presence of myocardial dysfunction, suggested by elevated cardiac filling pressures and low cardiac output or in the presence of signs of hypoperfusion despite adequate intravascular volume replenishment and achievement of an MAP higher than 65 mmHg (Fig. 2).[15]

Finally, the Surviving Sepsis Campaign Guidelines recommend red blood cell transfusion aiming to reach an hematocrit of at least 30% (Fig. 2).[15] Nevertheless, there is no strong evidence that higher hemoglobin targets (>9.0 g/dL) are beneficial in the absence of coronary heart disease or stroke, and several concerns exist regarding higher oxygen affinity of stored hemoglobin.[53,54] The recently published TRISS trial was a randomized controlled study that compared two different hemoglobin transfusion thresholds ($\leq$7.0 g/dL and $\leq$9.0 g/dL) in almost a thousand septic shock patients.[10] The authors reported no significant 90 day mortality difference between the groups (relative risk 0.94, 95% CI 0.78–1.09, $p = 0.44$), although the lower threshold group received half of a red blood cell transfusion when compared to the higher threshold. Additionally, there was no difference in the incidence of cardiac and non-cardiac ischemic events.[10]

Conclusion

Prompt and aggressive treatment of septic shock patients improves morbidity and mortality. Early recognition in addition to fluid resuscitation and proper antibiotics administration to patients are the cornerstone of the treatment. Along with it, a comprehensive clinical bedside evaluation and an accurate assessment of fluid responsiveness seem to be the best available evidence-based medicine for septic shock resuscitation. In the light of the new findings presented in recently published trials, a review of the goal-directed therapy, as it was conceived, is necessary.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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