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Guidelines for the treatment of severe sepsis and septic shock – hemodynamic resuscitation

Diretrizes para tratamento da sepse grave/choque séptico – ressuscitação hemodinâmica

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ABSTRACTS

Sepsis has a high incidence, mortality and cost and is the main cause of death in intensive care units. Early recognition and treatment have been clearly associated with a better prognosis. Establishing new guidelines is a fundamental step for improving treatment. Patients with clear signs of hypoperfusion should undergo hemodynamic optimization. This guideline addresses the main strategies in the literature that are clinically available.

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INTRODUCTION

Patients with severe sepsis and septic shock experience vasodilation and large fluid loss to the interstitial space, with eventual additional myocardial depression. The consequent blood flow impairment may result in extensive ischemia and, if not timely reverted, can lead to multiple organ dysfunctions with an increased mortality risk (**B**).[(1)] During the initial treatment phase, early reversion of tissue hypoxia should be attempted by restoring the global blood flow (blood flow = cardiac output – CO) either by aggressive volume replacement and/or the use of vasopressors or inotropes. The most appropriate therapeutic choice should be guided by pre-determined targets, with an emphasis on blood flow and tissue oxygenation markers. The response to therapeutic measures can be evaluated using hemodynamic markers and adjusting these measures can improve the therapeutic outcome and prevent iatrogenic problems. These guidelines were based on the best evidence available in the literature for hemodynamic resuscitation in patients with severe sepsis and septic shock.

PURPOSE

The questions addressed in this guideline should provide guidance on the fundamental aspects of hemodynamic resuscitation in severe sepsis patients, suitable for the Brazilian population.

Method of evidence collection

The MEDLINE database, accessed via the PubMed [Pesquisa Bibliográfica em Publicações Médicas] service, was the primary database searched for this study. Using the MeSH (Medical Subject Heading) interface, the following keywords were used: (severe sepsis OR septic shock AND early

goal directed therapy), (severe sepsis OR septic shock AND early goal directed therapy OR central venous oxygen saturation OR venous oximetry), (severe sepsis OR septic shock OR critically ill AND right atrial pressure OR central venous pressure OR cvp AND pulmonary artery occlusion pressure OR POAP AND pulmonary artery catheter AND arterial pressure OR pulse pressure variation AND fluid responsiveness OR volume expansion OR fluid resuscitation OR cardiac preload), (severe sepsis OR septic shock OR critically ill AND fluid resuscitation OR crystalloids OR colloids OR albumin OR synthetic colloids), (severe sepsis OR septic shock AND resuscitation AND vasopressors OR dopamine OR norepinephrine OR epinephrine OR vasopressin), (severe sepsis OR septic shock AND resuscitation AND inotropics OR dobutamine OR dopamine OR epinephrine OR isoproterenol OR milrinone OR amrinone OR levosimendan), (severe sepsis OR septic shock OR critically ill AND hemodynamics AND bicarbonate OR bicarbonate therapy AND acidosis OR lactic acidosis), (severe sepsis OR septic shock OR critically ill AND volume expansion OR fluid resuscitation OR positive fluid balance OR negative fluid balance OR fluid balance OR fluid management OR fluid therapy). Secondary sources included the Cochrane, Ovid and Trip Databases. The searches were directed to meet the structured questions of the P.I.C.O. (Population, Intervention, Comparison and Outcome) methodology.

Grades of recommendation and strength of evidence

A: More consistent experimental or observational trials.

B: Less consistent experimental or observational trials.

C: Case reports (non-controlled trials).

D: Opinion without critical evaluation, based on consensus, physiological studies or animal models.

1. Is early goal-directed hemodynamic resuscitation indicated for all severe sepsis patients?

'Early Goal-Directed Therapy' is a hemodynamic resuscitation technique used to correct tissue oxygenation before multiple organ failure develops (**A**).[2,3] This strategy is indicated for severe sepsis patients with serum lactate above 4 mmol/L or hypotension (ABP < 90 mmHg or MBP < 65 mmHg) refractory to initial and early 20-30 mL/kg crystalloid fluid infusion or a corresponding colloid dose (**A**).[2] The following goals should be achieved within 6 hours: central venous pressure (CVP) between 8-12 mmHg, mean blood pressure (MBP) ≥ 65 mmHg, urinary output ≥ 0.5 mL/kg/hour, and central venous oxygen saturation ($SvcO_2$) ≥ 70%. In this context, several trials have demonstrated that this strategy is associated with a significant mortality rate reduction (**A**)[2](**B**)[4](**D**).[5] The original study demonstrated an absolute mortality risk reduction of 16% (NNT = 6) (**A**).[2]

Recommendation

• 'Early Goal-Directed Therapy' is recommended for severe sepsis patients with volume-refractory hypotension and/or increased serum lactate (≥ 4 mmol/L) (**A**).[2] There is no evidence available to support its use when hypotension and hyperlactatemia are not present (**A**)[2](**B**).[1,6]

2. Does monitoring central venous oxygen saturation ($svco_2$) provide any benefit?

$SvcO_2$ < 60% is a low CO marker in acute myocardial infarction (**C**)[7] and is associated with an increased mortality rate when diagnosed at the time of admission to the intensive care unit (ICU) (**B**).[8] $SvcO_2$ may be increased (> 70%) in septic patients due to poor blood flow distribution and low tissue oxygen utilization (**B**).[1] When sepsis begins, there is low tissue oxygen consumption due to hypovolemia-related and/or myocardial dysfunction (ischemic hypoxia)-resulting in low $SvcO_2$ (**B**).[1] In a set of 762 patients, the benefit from oxygen administration and consumption obtained from CO monitoring were similar to those from mixed venous blood oxygen saturation (SvO_2)-guided therapy (**A**).[9] In an observational study including 36 severely ill patients, 31 patients maintained $SvcO_2$ < 65% and lactate > 2 mmol/L after fluid expansion and MBP stabilization. Lactate and $SvcO_2$ were normalized only after additional fluid replacement (**B**).[8] When the two severe sepsis patient groups (either with or without $SvcO_2$-guided therapy) were compared, the traditional goals for the mechanical variables (MBP, CVP, and urinary output) were achieved in both groups. However, in the $SvcO_2$ guided therapy group, $SvcO_2$ was significantly higher and the mortality rate was significantly lower (**A**).[2]

Recommendation

• Restoration of hemodynamic stability based on traditional mechanical variables, including MBP, CVP and urinary output, is not sufficient to restore tissue oxygenation and or better the prognosis (**A**)[2](**B**).[8] $SvcO_2$-guided therapy and early normalization result in recovered blood flow (**A**)[9] and significant mortality reduction (**A**).[2] Therefore, this variable should be monitored.

3. Does monitoring $svco_2$ after resuscitation provide prognostic advantages? How long after the start of resuscitation should these goals be directed?

In a randomized clinical trial, 95% of severe sepsis and septic shock patients achieved an $SvcO_2$ > 70% within 6 hours when raising $SvcO_2$ was set as a therapeutic goal. In the control group, raising $SvcO_2$ was not a therapeutic goal, and only 60% of these patients achieved an $SvcO_2$ > 70% (P < 0.001). The following goals were also set in both groups: CVP ≥ 8 cmH_2O, MBP ≥ 65 mmHg and urinary output ≥ 0.5 mL/Kg/hour. Raising the $SvcO_2$ > 70% within 6 hours was associated with significant reductions in hospital mortality (P = 0.009), mechanical ventilation time (P = 0.001) and hospital length of stay (P = 0.001) (**A**).[2] Several other control trials have corroborated these benefits (**D**).[5] However, it is not clear if targeting $SvcO_2$ maintenance above 70% after the initial resuscitation phase (first 6 hours) provides any benefit. Patients might benefit of maintaining $SvcO_2$ above 70% for longer than 24 hours, although no evidence to support this is available.

Recommendation

• Raising $SvcO_2$ above 70% has an impact on mortality. Therefore, it should be achieved as early as possible, preferably within the first 6 hours of therapy (**A**).[2] It is possible to obtain benefits from maintaining the optimized parameters for the first 24 hours following resuscitation.

4. Are volume replacement appropriateness evaluation parameters (VCP, POAP, dynamic variables) useful in daily practice?

During the shock resuscitation phase, the most appropriate volume replacement evaluation is cardiovascular responsiveness (CR) to fluid infusion. CR evaluation is helpful for incremental volume expansion needs and indicating the use of inotropes for reversing tissue hypoxia.

Static cardiovascular responsiveness evaluation: central venous pressure (CVP) and pulmonary artery occlusion pressure (POAP)

Although ventricular filling pressures appear as preferential CR evaluation methods, recent evidence has emphasized the low sensitivity and specificity of CVP and POAP (**B**)[10-12](**C**).[13]

In a prospective trial involving 44 healthy subjects, both the CVP and POAP initial and post-volume infusion values were unable to predict volume CR (**B**).[10]

A retrospective analysis of 96 septic patients has shown that CVP < 8 mmHg and POAP < 12 mmHg were unable to predict volume responsiveness, with positive likelihood ratios of 1.34 and 1.57, respectively. Combined filling pressures were also unable to improve the accuracy of these variables (**B**).[12]

Patients with severe sepsis or septic shock were evaluated by setting a CVP between 8 and 12 mmHg (associated with MBP, urinary output and $SvcO_2$) as an early hemodynamic resuscitation goal. In the control group (no $SvcO_2$ measurement), the mean CVP after 6 hours was 11.8 ± 6.8 mmHg, while the treatment group (with $SvcO_2$) had a mean CVP of 13.8 ± 4.4 mmHg. CVP after the first 6 hours was above or below the goal in most of the patients. For the control group (with lower mortality), the CVP mean was closer to the initial goal relative to the mean of the treatment group. Therefore, using CVP values between 8-12 mmHg as the exclusive treatment goal during early hemodynamic resuscitation in patients with severe sepsis or septic shock may be harmful, especially if volume resuscitation is discontinued in responsive patients with CVP > 8 mmHg who have not reached the main therapeutic goal: $SvcO_2$ ≥ 70% (**A**)[2](**D**).[14]

In septic patients, CVP and POAP failed to discriminate volume-responsive from volume-non-responsive patients (area under the ROC curve: CVP = 0.51 ± 0.12; POAP = 0.40 ± 0.09) (**B**).[11] The findings of other similar trials have provided similar results (**B**).[15-18]

Recommendation

• Mean CVP and POAP and changes in these parameters after volume challenge are unable to discriminate responsive from non-responsive individuals (**B**)[10-12,15-18] (**D**).[14] CVP should be associated with other clinical parameters, such as MBP, urinary output and $SvcO_2$, as therapy subsides (**A**).[2] However, in sites were dynamic methods are unavailable, hemodynamic resuscitation may be based on CVP, as its optimization would assure minimal sufficient volume.

Dynamic cardiovascular responsiveness evaluation: respiratory blood pressure fluctuation (ΔPP) and respiratory CVP fluctuation (ΔCVP)

A blood pressure track analysis of 40 mechanically ventilated patients with sepsis showed the high sensitivity (94%) and specificity (96%) of respiratory pulse fluctuations (ΔPp) for the discrimination of responsive (ΔPp > 13%) and non-responsive (ΔPp < 13%) subjects, providing a 23.5 positive likelihood ratio (**B**).[11] This was

corroborated by subsequent prospective trials (**B**).[15,16] The method has been validated for controlled mechanical ventilation patients, with a tidal volume between 8 and 12 mL/Kg and a sinus rhythm (**B**).[11]

In an evaluation of 23 septic patients, the plethysmographic wave amplitude difference (ΔPplet) was shown to reflect the ΔPp behavior. As such, it was able to discriminate responsive from non-responsive patients with 94% sensitivity and 80% specificity and a 4.7 positive likelihood ratio (area under the ROC curve = 0.94) (**B**).[17] Two other trials corroborate these findings (**B**).[18,19]

Respiratory CVP fluctuation (ΔCVP) as a CR predictor was evaluated in 33 patients (**C**).[20] Both spontaneous (36%) and mechanical (64%) ventilation patients were included. In the latter group, ΔCVP was verified while the mechanical ventilator was quickly disconnected. A 1 mmHg CVP inspiratory decrease has been shown to have 84% sensitivity and 94% specificity and a positive likelihood ratio of 14 to identify fluid expansion-responsive patients. Patients not generating sufficient inspiratory effort to reduce POAP by 2 mmHg were excluded. Therefore, in clinical situations in which no POAP measurement is available, a possible false negative should be considered when ΔCVP < 1 mmHg is found (**C**)[20](**B**).[21] Additionally, in a study of 21 patients, ΔCVP was unable to predict CR. Nine patients were ventilated with support pressure, and four patients showed no 2 mmHg POAP inspiratory pressure drop (**C**).[22]

Recommendation

• ΔPp is a simple, sensitive and specific CR evaluation method in hemodynamically unstable patients under controlled mechanical ventilation (**B**).[11,15,16] ΔPplet is a non-invasive alternative to Δpp (**B**).[17,18] Inspiratory CVP fluctuation, although sensitive and specific for CR identification, has limited applicability in the need to concomitantly evaluate POAP fluctuation to prevent false negatives (**B**).[21]

5. Is there any clinical benefit from colloid (either natural or synthetic) versus crystalloid fluid replacement? Is there a benefit from albumin use in specific subpopulations?

In a systematic review including 30 randomized clinical trials with a total of 1,419 patients, human albumin was compared with crystalloid use in severely ill hypovolemic patients who had major burns or were hypoalbuminemic. Human albumin use was associated with a 6% increase in mortality risk (**A**).[23]

Another systematic review evaluated 37 randomized clinical trials, and 26 compared colloids to crystalloids (n = 1,622). Colloid volume resuscitation was associated with an absolute 4% mortality risk increase, with similar results for patient subgroups, including conditions requiring different volume resuscitation (**A**).[24]

In a more recent systematic review, 63 trials were identified, and 55 showed mortality-related data. Crystalloid solutions were compared with human albumin in 23 trials, 16 compared crystalloids to modified gelatin, 9 compared crystalloids to dextran and an additional 8 compared dextran in a hypertonic crystalloid to dextran in an isotonic crystalloid. No differences were identified over a 28 day follow-up period for mortality, mechanical ventilation time, ICU and hospital length of stay, renal replacement therapy duration or the number of organ dysfunctions (**A**).[25]

The SAFE study, a randomized clinical trial conducted in 16 Oceania hospitals, included 6,997 patients requiring fluid resuscitation due to volume depletion. The effects of fluid resuscitation on mortality compared 4% albumin to saline solution. No differences were identified over the 28 day follow-up period for mortality, mechanical ventilation time, ICU and hospital length of stay, renal replacement therapy duration or the number of organ dysfunctions (**A**).[26]

In the SAFE study subgroup analysis, significantly increased mortality (p = 0.009) was identified for severe head trauma (HT) patients receiving colloid at 28 days. This difference was confirmed in a *post-hoc* study on mortality at one year (**B**).[27] In septic patients, a trend to lower mortality rates was identified for colloid receivers (p = 0.09) (**A**).[26] No albumin infusion benefit was observed for patients with baseline albumin ≤ 25 g/L (**B**).[28] New studies are warranted to clarify the role of the colloids in these subgroups.

Recommendation

• The use of colloids as plasma expanders in severely ill patients provides no benefit to volume resuscitation. Septic patients also appear not to benefit from its use (**A**).[26] To date, no specific subpopulation has been identified to benefit from colloid infusion (**A**)[26](**B**).[27,28]

6. Is there an ideal vasopressor for the septic patient?

Vasopressor drug infusion should be started in septic patients whenever volume expansion fails to restore blood pressure and organ perfusion (**B**)[4](**D**).[29]

The effects of vasopressors were evaluated in several open trials. Both dopamine and norepinephrine have been observed to provide consistent MBP increases in

septic patients. However, norepinephrine is more potent than dopamine and probably more effective for septic shock reversal (**A**)[30,31](**B**).[32-35] In a prospective randomized trial that included 32 septic patients, dopamine was compared to norepinephrine. Septic shock was reverted in 31% of dopamine patients versus 93% of those receiving norepineprhine (**A**).[30]

The results of studies evaluating the effects of vasopressors on splanchnic perfusion are controversial (**B**)[32] (**A**).[36,37] When the effects of dopamine, norepinephrine and epinephrine on septic shock patients are compared, dopamine and norepinephrine have similar effects on splanchnic circulation (**B**).[38]

Vasoconstriction is noxious to renal function in hypovolemic patients (**D**).[29] A randomized clinical trial evaluated 328 severely ill patients with acute renal dysfunction to evaluate the renal protective effects of low-dose dopamine. No differences were found for creatinine levels, dialysis needs, urinary output or time to renal function recovery (**A**).[39] Other studies have demonstrated that norepinephrine trends toward the optimization of renal blood flow and vascular resistance in appropriately volume-expanded septic shock patients (**B**)[40,41](**C**).[42]

A recent observational study included 1,058 patients who experienced shock at any time during their hospitalization. A significant ICU ($p < 0.02$) and hospital ($p < 0.01$) mortality increase was identified for the patients who were given dopamine relative to those who were not. The mortality was not increased for those receiving norepinephrine (**B**).[43]

Epinephrine infusion may be an alternative for patients unresponsive to volume infusion or to other catecholamines. This drug provides an evident MBP increase in dopamine- or norepinephrine-unresponsive patients. However, adrenalin reduces splanchnic and renal perfusion and causes serum lactate levels to increase (**A**)[31](**B**).[32,38,44]

Vasopressin is a pituitary hormone usually released in response to hypovolemia and increased plasma osmolarity. Likely due to pituitary depletion, this release tends to be lower or even cease in septic shock patients. One-third of septic shock patients develop relative vasopressin insufficiency (**B**)[45](**C**)[46](**D**).[29] Small observational (**B**)[47,48] and randomized (**B**)[49,50] studies have shown that low-dose (0.01 to 0.04 units/min) vasopressin in catecholamine-refractory septic shock results in reductions in blood pressure increments and catecholamine infusion. However, vasopressin worsens splanchnic perfusion (**B**).[51,52] Recently, a double-blind randomized trial including 778 septic shock patients compared subjects using vasopressin in association with norepinephrine to other subjects with norepinephrine only. No overall mortality difference was identified. However, less severe sepsis patients (5 to 14 μg norepinephrine by the inclusion time) in the vasopressin group had a significant mortality reduction comparing to the more severe patients, in whom not benefit was found (>15 μg norepinephrine). These data suggest that early vasopressor infusion (and other therapies) is the decisive factor, rather than the specific vasopressor agent itself (**A**).[53]

Recommendations

- Both dopamine and norepinephrine (given by central access catheter whenever possible) are the first choice in drugs given to septic shock patients (**B**).[35] However, norepinephrine is more potent than dopamine, and it is more likely to be effective for septic shock reversal in some patients (**A**)[30,31](**B**);[34]
- Vasopressor infusion should be preceded and/or accompanied by appropriate volume expansion (**B**);[35]
- Epinephrine is not the first drug chosen to give to septic shock patients (**B**).[35] Epinephrine may be considered as an alternative drug for patients with septic shock or hypotension refractory to other vasopressor agents (**A**)[31](**B**);[44]
- Low-dose dopamine should not be used for renal protection (**A**);[39]
- Low-dose vasopressin (0.01 to 0.04 units/min) use in patients with appropriate volume expansion who are receiving catecholamines results in blood pressure recovery. Again, it is not the first-choice drug (**B**).[51,52] A combination of vasopressin and norepinephrine provides no mortality benefit (**A**).[53]

7. Is there an ideal inotropic agent for septic patients with signs of myocardial dysfunction?

Sepsis hemodynamics are characterized by a hyperdynamic condition, with low or normal blood pressure and low systemic vascular resistance. Although CO is frequently normal in appropriately volume-expanded septic patients, several authors have shown myocardial dysfunction (left ventricular ejection fraction drop, ventricular dilation, low contractile response to volume expansion) in a significant portion of these patients (**B**)[4,35](**D**).[29] In the event of persistent hypoflow signs after appropriate volume expansion and vasopressor administration, inotropes should be considered for early pre-established $ScvO_2$ therapeutic goal achievement (**A**)[2](**B**)[4](**D**).[29] A clinical trial randomized 263 patients

into two different groups. The treatment group used 'Early Goal-Driven Therapy' with $SvcO_2$ monitoring in addition to MBP, CVP and urinary output. The control group did not consider $SvcO_2$ as a therapeutic goal. Aiming to normalize $SvcO_2$ within the first 6 hours of therapy, the treatment group received more volume expansion (5 vs. 3.5 L; $p < 0.001$), a larger red blood cell transfusion (***P*** < 0.001) and more dobutamine inotrope therapy (13.7% vs. 0.8%; $p < 0.001$). Inotrope therapy began when the target $SvcO_2$ was not achieved following volume expansion and red blood cell optimization. The mortality rate was significantly lower in the treatment group (30.5% vs 46.5%; $p < 0.009$) (**A**).[2]

For conditions where MBP, CO and/or tissue oxygenation goals are not achieved with fluid expansion and vasopressors (dopamine or epinephrine), other studies have demonstrated that the addition of dobutamine is a good strategy for improving CO, tissue oxygenation and MBP (**A**).[54,55]

However, over-normalization of hemodynamic variables adds no prognostic advantages relative to CO or mixed venous oxygen saturation (SvO_2) normalization (**A**).[9] CO over-normalization and oxygen administration with high-dose dobutamine has been associated with a significant increase in mortality rate (**A**).[53]

Although infusion of epinephrine, a potent inotrope, positively influences cardiac output, it has been strongly associated with regional perfusion impairment (**A**)[31] (**B**).[44,56]

Phosphodiesterase inhibitors (amrinone and milrinone) are long half-life vasodilators that may cause prolonged hypotension, therefore requiring vasopressors. Small studies have shown the positive effects of these inhibitors on CO, but their prognostic effects could not be analysed due to sample issues (**A**)[57](**B**).[58,59]

Few studies have evaluated the use of isoproterenol in sepsis and septic shock. Although it promotes a significant CO increase, isoproterenol may cause hypotension and tachycardia, resulting in cardiac ischemia (**B**)[60](**C**).[61]

Levosimendan is a calcium sensitizer that favors actin-myosin coupling and improves heart contractility without increasing myocyte oxygen consumption. Additionally, levosimendan opens ATP-dependent K^+ channels, leading to vasodilation. No large studies have supported its use in septic patients. Two clinical trials (REVIVE II and SURVIVE) studied decompensated heart failure patients with < 35% ejection fraction. Although the first (n = 600) associated levosimendan with clinical improvement and a reduced hospital stay, the second (n = 1,327) failed to observe a benefit in mortality when compared to dobutamine (**A**).[62,63]

Recommendations:

- Dobutamine is the inotrope of choice in septic patients with signs of myocardial dysfunction (**A**).[54,55] Inotrope therapy with dobutamine is indicated when the goal of raising $SvcO_2 > 70\%$ is not achieved with appropriate volume expansion and, eventually, red blood cell transfusion (**B**).[4,35] In the event of hypotension, dobutamine use should be accompanied by a vasopressor (**B**);[35]
- Cardiac output should not be over-normalized (**A**).[53]

8. Should bicarbonate replacement be given to patients with severe metabolic acidosis of lactic origin?

Metabolic acidosis itself is not a disease, but it is a sign of severely unbalanced homeostasis. It may be categorized as either organic metabolic acidosis or mineral metabolic acidosis. Lactic organic metabolic acidosis (lactate > 4 mmol/L) is a severity marker in septic patients. Bicarbonate solutions are frequently used to treat this condition, targeting hemodynamic stabilization and the reduction of vasopressor infusion.

Two randomized, prospective, blinded clinical trials were conducted to evaluate treatment options for lactic metabolic acidosis. In both, sodium bicarbonate administration failed to change any hemodynamic parameter, catecholamine needs or overall tissue oxygenation rates. Even in extreme pH ranges (6.9 to 7.2; mean = 7.13), negative results persisted (**B**).[64,65]

Similarly, in diabetic ketoacidosis patients, sodium bicarbonate infusion adds no benefit to serum pH normalization, requiring additional potassium infusion (**B**).[66]

Several experimental reports are available on the protective effect of metabolic acidosis during tissue hypoxia. Several tissue cells under oxygen deprivation conditions, incubated at a pH between 6.5 and 7, survived for several hours. However, these same oxygen-deprived cells incubated at a pH of 7.4 died within less than one hour. During acidosis, cellular metabolism is globally reduced due to $[H^+]$ interference, modifying the spatial configuration of the cellular enzymes (**D**).[67-69]

Recommendation:

- Sodium bicarbonate infusion is not recommended for organic lactic acidosis or hemodynamic instability (**B**).[64,65]

9. Do excessive fluid infusion and a positive fluid balance have any prognostic implication?

Patients with severe sepsis and septic shock have large intravascular volume deficits due to huge fluid losses to the interstitial space and markedly reduced venous capacitance. Cardiac output and tissue perfusion restoration depend on fast and aggressive volume expansion (**A**)[2,3](**B**).[1,4] Blood flow and tissue re-oxygenation recovery are the emphasis of volume resuscitation. As such, the fluid gain versus loss ratio is not useful for establishing fluid requirements during early resuscitation (**A**).[3] Fluid infusion should be guided by pre-determined clinical goals, emphasizing tissue oxygenation and organ function markers (**B**)[1,4](**D**).[29]

'Early Goal-Driven Therapy' effectiveness was tested in patients with severe sepsis and septic shock. In the treatment group ($SvcO_2$-guided therapy), the administered fluid volume within the first 6 hours was shown to be significantly larger than in the control group (5.0 L versus 3.5 L; $p < 0.001$), resulting in higher $SvcO_2$. Between the 7^{th} and 72^{nd} hours, the control group required significantly more fluids ($p = 0.01$). This late fluid increment failed to increase $SvcO_2$ relative to the treatment group ($p < 0.001$), failed to reduce the organ dysfunction score MODS ($p < 0.001$) and had no impact on mortality, which was significantly higher ($p = 0.009$) (**A**).[2]

Over-physiological optimization of cardiac output and oxygen administration in a heterogeneous population of severely ill patients demonstrated no benefit when compared to extrapolating pre-defined goal physiological levels (**A**).[9,70] Therefore, there is no evidence that patients responsive to fluid challenge, with mild cardiac output increases or normalized oxygenation variables, benefit from additional volume loads (**B**).[71]

A prospective evaluation of 29 septic patients who developed renal dysfunction showed that a significantly larger fluid infusion (2,037 +/- 1,681 mL versus 1,116 +/- 1,220 mL; $p < 0.03$) did not result in improved renal function and was associated with significant worsening of tissue oxygenation ($p < 0.04$) (**B**).[72]

The SOAP study (an international multicenter observational study) included 393 patients who developed acute lung injury/acute respiratory distress syndrome (ALI/ARDS). Excess fluid was identified as an independent factor influencing mortality. The non-survivors had a significantly larger fluid balance relative to the survivors ($p < 0.001$) (**B**).[73]

A recent randomized trial compared the liberal versus restrictive fluid administration strategies in 1,000 ALI patients; 71% of patients had pneumonia or sepsis as the primary lung injury cause. The 72-hour cumulative fluid balances were 5,100 mL for the liberal strategy group and 400 mL for the restrictive strategy group. Although no mortality difference was identified, significantly reduced mechanical ventilation times ($p < 0.001$) and ICU lengths of stay ($p < 0.001$) were observed for the restrictive strategy group (**A**).[74]

In a retrospective analysis of 36 septic shock patients, all 11 patients with a 500 mL negative fluid balance in at least 1 of the first 3 days of treatment, survived. Conversely, 20 of the 25 patients without a negative fluid balance died ($p < 0.00001$). This suggests that achieving a negative fluid balance in 1 of the first 3 treatment days is a predictor of survival in septic shock patients (**B**).[75]

The SOAP study included 1,177 patients with diagnosed sepsis. The accumulated fluid balance within the first 72 hours from the sepsis diagnosis (OR: 1.1 for additional liter; 95%CI, 1.1 – 1.1; $p < 0.001$) and the daily fluid balance (OR: 1.8 per additional liter; 95%CI, 1.6-2.0; $p < 0.001$) were independent mortality predictors. However, these were more severely ill patients with more dysfunctional organs ($p < 0.001$) and higher mean SOFA scores ($p < 0.001$) (**B**).[76]

In an epidemiological, multicenter, prospective study, a heterogeneous sample of 265 patients was analysed. Eighty-five patients (32.1%) were diagnosed with abdominal compartment syndrome (ACS), and this group had significantly higher mortality (38.8% versus 22.2%; $p < 0.005$). The predictive factors for ACS were as follows: liver dysfunction (OR: 2.25; 95%CI 1.1-4.58; $p< 0.03$); abdominal surgery (OR: 1.96; 95%CI: 1.05-3.64; $p < 0.03$); volume resuscitation (OR: 1.88; 95%CI 1.04-3.42; $p < 0.04$); and ileus (OR: 2.07; 95%CI 1.15-3.72; $p < 0.02$) (**B**).[77]

To maintain appropriate tissue oxygenation, the initial 24-hour crystalloid infusion tends to be substantially higher (6 to 10 liters) than when colloid solutions are chosen (2 to 4 liters) (**A**)[2](**B**)[1](**D**).[29] The SAFE study, a randomized clinical trial conducted in 16 Oceania hospitals, included 6,997 patients requiring fluid resuscitation due to volume depletion and compared the effects of fluid resuscitation with 4% albumin or normal saline solution on mortality and morbidity. Although the 24-hour ($p < 0.001$), 48-hour ($p < 0.001$) and 72-hour ($p = 0.007$) fluid balances were significantly higher in the group treated with crystalloid solutions, no differences were identified in

the mortality rates, the mechanical ventilation times, the ICU and hospital lengths of stay, renal replacement therapy duration or the number of organ dysfunctions at the 28 day follow up (**A**).[26]

Recommendations

• Using aggressive volume expansion to normalize hemodynamic parameters, including MBP, urinary output and $SvcO_2$, and increase fluid balance within the first 6 hours of treatment reduces severe sepsis and septic shock mortality (**A**).[2] Late positive fluid balance (late fluid expansion) is associated with more organ dysfunction and higher mortality in patients with severe sepsis and septic shock (**A**).[2]

• Volume expansion targeting over-normalization of hemodynamic parameters should not be used because of its negative prognostic impact (**A**).[9]

• The cumulative fluid balance at 72 hours of therapy has no influence on the mortality and morbidity of a heterogeneous population (**A**).[26] Excessive fluid administration during the first 72 hours is associated with worsened pulmonary function, longer mechanical ventilation time, more organ dysfunction and increased mortality in patients with sepsis and/or ALI/ARDS (**B**)[73](**A**).[74]

• After renal failure development in septic patients, additional fluid infusion is not associated with renal functional recovery and may result in worsened respiratory function (**B**).[72]

• Excessive fluid administration may result in abdominal compartment syndrome in severely ill patients (**B**).[77]

RESUMO

A sepse tem alta incidência, alta letalidade e custos elevados, sendo a principal causa de mortalidade em unidades de terapia intensiva. Está claramente demonstrado que pacientes reconhecidos e tratados precocemente tem melhor prognóstico. A formulação de diretrizes de tratamento é fundamental para a adequação desse tratamento. Pacientes com claros sinais de hipoperfusão devem ser submetidos à otimização hemodinâmica. A presente diretriz aborda as evidências disponíveis na literatura em relação às principais estratégias para otimização hemodinâmica.

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