What happens to the fluid balance during and after recovering from septic shock?

O que ocorre com o balanço hídrico durante e após a reversão do choque séptico?

ABSTRACT

Objective: We aimed to evaluate the cumulative fluid balance during the period of shock and determine what happens to fluid balance in the 7 days following recovery from shock.

Methods: A prospective and observational study in septic shock patients. Patients with a mean arterial pressure ≥ 65mmHg and lactate < 2.0mEq/L were included < 12 hours after weaning from vasopressor, and this day was considered day 1. The daily fluid balance was registered during and for seven days after recovery from shock. Patients were divided into two groups according to the full cohort’s median cumulative fluid balance during the period of shock: Group 1 ≤ 4.4L (n = 20) and Group 2 > 4.4L (n = 20).

Results: We enrolled 40 patients in the study; On study day 1, the cumulative fluid balance was 1.1 [0.6 - 3.4] L in Group 1 and 9.0 [6.7 - 13.8] L in Group 2. On study day 7, the cumulative fluid balance was 8.0 [4.5 - 12.4] L in Group 1 and 14.7 [12.7 - 20.6] L in Group 2 (p < 0.001 for both). Afterwards, recovery of shock fluid balance continued to increase in both groups. Group 2 had a more prolonged length of stay in the intensive care unit and hospital compared to Group 1.

Conclusion: In conclusion, positive fluid balances are frequently seen in patients with septic shock and may be related to worse outcomes. During the shock period, even though the fluid balance was previously positive, it becomes more positive. After recovery from shock, the fluid balance continues to increase. The group with a more positive fluid balance group spent more time in the intensive care unit and hospital.

Keywords: Sepsis; Shock, septic; Fluid therapy; Water-electrolyte balance

INTRODUCTION

Fluid replacement is the cornerstone of the treatment for septic shock, which is followed by vasopressors and inotropes. Venodilation, transudation of fluids from the vascular space into tissues, and reduced oral intake result in hypovolemia in the first hours of sepsis.¹

In septic patients, the microcirculation is markedly deranged with a lower flow velocity and more heterogeneous perfusion.²⁻⁵ Hypovolemia further exacerbates the altered perfusion of the microcirculation, resulting in inadequate oxygen availability for mitochondrial oxidative phosphorylation. Therefore, the main goal of early management is to treat hypovolemia and restore tissue perfusion.¹
In the early phase of sepsis, therapeutic goals have been proposed to guide fluid resuscitation, and they are widely accepted. The current guidelines recommend liberal fluid resuscitation in this phase. However, after initial monitoring, management and stabilization of the mean arterial pressure (MAP) with vasopressors, further fluids are often administered according to subjective data from the clinical examination, urine output, and measurements of the ventricular filling pressures.

Excess fluids may be harmful in critically ill patients and have been correlated with the mortality and various complications, such as heart failure, pulmonary edema, pneumonia, dilutional coagulopathy, decreased gastrointestinal motility, abdominal compartment syndrome, and more.

We hypothesized that patients in septic shock receive excess fluids even after they are weaned from vasopressors. Therefore, we evaluated the fluid balance during the period of shock and for 7 days after patients were weaned from vasoactive drugs.

**METHODS**

This was a prospective, observational, cohort study that was performed between May 2009 and October 2010 in a 10-bed intensive care unit at a university hospital. The study was approved by the Institutional Ethics Committee of Hospital de Base, Faculdade de Medicina de São José do Rio Preto, document nº 426/2008. Informed consent was obtained from the next of kin.

Septic shock was defined according to previously described criteria. Patients older than 18 years of age who had septic shock were evaluated if they had been weaned from all vasopressors for ≤ 12 hours, had a MAP ≥ 65mmHg and had a serum lactate < 2.0mEq/L (Figure 1). The exclusion criteria were pregnancy and lack of consent from the family or assistant physician or if the patient was considered unlikely to survive hospitalization.

The data recorded prospectively on admission included the following: age, sex, patient classification (medical or surgical), smoking history (active in the last year), alcohol consumption and comorbidities (based on the International Classification of Disease-10, anamnesis and electronic patient charts). Daily measurements of all fluid intake and output; use of vasopressors, dobutamine and furosemide; vital signs; MAP; central venous pressure (CVP) and urinary output were recorded for seven days after enrollment. Day 1 was considered the day that the patients had been weaned from all vasopressors for ≤ 12 hours, had a mean arterial pressure (MAP) ≥ 65mmHg and had a serum lactate concentration < 2.0mEq/L.

The cumulative fluid balance was calculated during the period of shock, after which the fluid balance was reinitiated from zero and registered during 7 days. Patients were divided into 2 groups according to the total cohort’s median cumulative fluid balance that was administered during the period of shock with vasopressors, which was calculated on study day 1. The fluid balance was calculated by the difference between the infused fluids (crystalloids, colloids, drug dilution fluids, blood products, and water by nasogastric drain) and eliminated liquids (diuresis, dialysis, and drains). It was attributed to the value of 400mL for endogenous water and 800mL for imperceptive losses, adding 100mL/h/for each degree above 37.8°C.

The Acute Physiology and Chronic Health Evaluation (APACHE II) was used to assess the severity of disease at admission in the intensive care unit (ICU), and the Sequential Organ Failure Assessment (SOFA) score was used to assess the severity of the disease at inclusion in the study. Comorbid diabetes mellitus was recorded for patients with current use of oral hypoglycemic agents or insulin. Acute respiratory failure and acute respiratory distress syndrome (ARDS) were defined according to the 1994 American-European Consensus Conference definitions. Nosocomial infection was defined as an infection acquired after 48 hours of hospitalization. Acute kidney injury was defined as an increase in creatinine ≥ 0.3mg/dL or an increase in the baseline value ≥ 150 - 200%
and/or a urine output < 0.5mL/kg/h for more than 6 hours. A major complication was considered as any life-threatening event or unexpected medical event that prolonged the length of hospital stay.

**Statistical analysis**

The categorical variables were treated as proportions and analyzed using the chi-square test. The continuous variables with a normal distribution were evaluated using the Kruskal-Wallis test and are presented as the medians and confidence intervals. p < 0.05 was considered statistically significant. ANOVA was used to test for repeated measures, which was followed by Bonferroni pair-wise comparisons.

**RESULTS**

We enrolled 40 patients in the study (Figure 1). The mean age of the patients was 61.6 ± 16 years, and their SOFA score was 7.4 ± 3.5 and APACHE II score was 23.4 ± 8.9. The median time to recovery from shock (duration on vasopressor drugs) before inclusion in the study was five days. Table 1 shows the clinical characteristics and epidemiological data of the two study groups. The most frequent site of infection was the respiratory tract (67%). The duration of shock prior to study inclusion was significantly higher in Group 2 than in Group 1 (8.5 ± 4.0 days versus 4.4 ± 3.3 days, respectively, p < 0.001).

The physiological variables and laboratory tests are shown in table 2. On study day 5, Group 2 had a significantly higher CVP (12 ± 5mmHg versus 9 ± 4mmHg, p = 0.04) and mean arterial pressure (86 ± 15mmHg versus 76 ± 14mmHg, p = 0.03) than Group 1. Compared to Group 1, Group 2 had significantly lower urea levels on day 7 (81 ± 40mg/dL versus 138 ± 78mg/dL, p = 0.006) and larger urine volumes on days 6 and 7. Group 2 had lower hemoglobin levels than Group 1 on day 1 and from day 4 to day 7 (p < 0.05 for all). The PO$_2$/FiO$_2$ ratio was lower in Group 2 than in Group 1 on days 1 and 6.

On day 1, the cumulative fluid balance was 1.1 [0.6 - 3.4] L in Group 1 and 9.0 [6.7 - 13.8] L in Group 2 (p < 0.001). On day 7, the cumulative fluid balance was 8.0 [4.5 - 12.4] L in Group 1 and 14.7 [12.7 - 20.6] L in Group 2 (p < 0.001), considering not only the fluid balance after shock but also the cumulative fluid balance during shock.

**Group 2** received more crystalloids (12.4 [6.0 - 15.7] L versus 8.6 [3.2 - 12.0] L, p = 0.051), colloids (2 [1.8 - 2.0] L versus 0.5 [0.5 - 0.9] L, p < 0.001) and packed red blood cells (2.3 [1.4 - 2.3] L versus 0.5 [0.4 - 0.6] L, p < 0.001) than Group 1 (Table 3). Diuretics and dobutamine were given more frequently in Group 2 (Table 3). Group 2 had longer lengths of stay in the ICU (21 versus11 days, p = 0.02) and in hospital stays (29 versus 16.5 days; p = 0.028) than the patients in Group 1 (Table 4).

We performed another analysis after zeroing the fluid balance and restarting the calculations on day 2 (first day without any vasopressors). The cumulative fluid balance ranged from -16.9 to 20.8L (median: 4.3L) (Figure 2). The cumulative fluid balances starting from day 2 were the following: day 2 (n = 40): 1.0L (0.05 - 1.6L), day 3 (n = 40): 1.7L (0.3 - 3.5L), day 4 (n = 38): 3.4L (0.05 - 4.8L),

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**Table 1 - Characteristics of the two groups**

|                         | Group 1 (N = 20) | Group 2 (N = 20) |
|-------------------------|------------------|------------------|
| Age (years)             | 64.2 ± 15        | 59.1 ± 17        |
| Gender, male            | 12 (60)          | 11 (55)          |
| Medical/surgical (%)    | (85/15)          | (95/5)           |
| APACHE II               | 24.8 ± 9.5       | 21.9 ± 8.4       |
| SOFA                    | 7.2 ± 3.9        | 7.6 ± 3.0        |
| Community/Nosocomial infection (%) | (80/20)       | (95/5)           |
| Time on shock (days)    | 4.4 ± 3.3        | 8.5 ± 4.0**      |
| Comorbidities           |                  |                  |
| Chronic obstructive pulmonary disease | 4 (20.0)       | 4 (20.0)         |
| Diabetes mellitus       | 3 (15.0)         | 2 (10.0)         |
| Acquired immunodeficiency syndrome | 3 (15.8)       | 2 (10.5)         |
| Systemic arterial hypertension | 3 (15.0)       | 0 (0)            |
| Heart failure           | 2 (10.0)         | 1 (5.0)          |
| Immunossupression       | 1 (5.0)          | 3 (15.0)         |
| Cancer                  | 1 (5.0)          | 0 (0)            |
| Others                  | 2 (10.0)         | 7 (35.0)         |
| Site of infection       |                  |                  |
| Pulmonary               | 9 (45)           | 18 (90)          |
| Urinary tract           | 4 (20)           | 0 (0)            |
| Blood stream            | 3 (15)           | 0 (0)            |
| Surgical wound          | 1 (5)            | 0 (0)            |
| Abdomen                 | 1 (5)            | 0 (0)            |
| Endocarditis            | 1 (5)            | 0 (0)            |
| Others                  | 2 (10)           | 4 (20)           |

Group 1: fluid balance at day 1 ≤ 4.4L; Group 2: fluid balance at day 1 > 4.4L. Some patients have more than one site of infection. APACHE II - Acute Physiology and Chronic Health Evaluation; SOFA - Sequential Organ Failure Assessment score. The results are expressed in numbers (%) or the mean ± standard deviation. ** p < 0.001 versus Group 1.
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**Table 2 - Physiological variables in the two groups**

| Day | Group 1 | Group 2 | p value |
|-----|---------|---------|---------|
| 1   | 12 ± 7  | 12 ± 7  |         |
| 2   | 14 ± 6  | 13 ± 5  |         |
| 3   | 11 ± 4  | 12 ± 4  |         |
| 4   | 12 ± 4  | 12 ± 5* | < 0.05  |
| 5   | 9 ± 4   | 11 ± 5  |         |
| 6   | 9 ± 4   | 11 ± 4  |         |
| 7   | 9 ± 4   | 9 ± 3   |         |

**Table 3 - Type of fluids, fluid balance and use of furosemide and dobutamine in Groups 1 and 2**

| Group 1 | Group 2 | p value |
|---------|---------|---------|
| N = 20  | N = 20  |         |
| Cumulative fluid balance on D1 (L) | 1.1 (0.6 - 3.4) | 9.0 (6.7 - 13.8) | < 0.001 |
| Cumulative fluid balance on D2 (L) | 0.1 (1.3 - 3.5) | 11.0 (7.4 - 14.7) | < 0.001 |
| Cumulative fluid balance on D3 (L) | 0.9 (1.2 - 3.5) | 11.2 (7.8 - 14.5) | < 0.001 |
| Cumulative fluid balance on D4 (L) | 3.0 (2.0 - 4.9) | 12.3 (0.3 - 16.0) | < 0.001 |
| Cumulative fluid balance on D5 (L) | 4.3 (2.0 - 6.1) | 14.0 (11.5 - 16.6) | < 0.001 |
| Cumulative fluid balance on D6 (L) | 7.2 (4.5 - 10.2) | 16.1 (11.4 - 18.7) | < 0.001 |
| Cumulative fluid balance on D7 (L) | 8.0 (4.5 - 12.4) | 14.7 (12.7 - 20.6) | < 0.001 |
| Crystalloids (L) (total doses) | 8.6 (3.2 - 12.0) | 12.4 (6.0 - 15.7) | 0.051 |
| Colloids (L) (total doses) | 0.5 (0.5 - 0.9) | 2 (1.8 - 2.0) | < 0.001 |
| Red blood cells (L) (total doses) | 0.5 (0.4 - 0.6) | 2.3 (1.4 - 2.3) | 0.001 |
| Furosemide (mg) (total doses) | 82 ± 102 | 242 ± 318 | 0.039 |
| Dobutamine (µg/kg/min) (maximum doses) | 3.5 ± 1.04 | 4.3 ± 1.15 | 0.027 |

**DISCUSSION**

Our main finding on fluid administration in patients with septic shock after a median of five days on vasopressors, considering the cumulative fluid balance during shock, was that they had a large accumulated fluid balance. In addition, after weaning from vasopressors, the fluid balance continued to accumulate by a median of 0.64L per day. The presence of a higher positive fluid balance during the shock period and at the end of seven days was associated with a more prolonged length of stay in the ICU and hospital.

Many studies have associated more positive fluid balances with worse outcomes. Boyd et al. conducted a retrospective review of the use of intravenous fluids during the first 4 days of care for patients included in...
Other authors reported correlations between higher fluid balance and death in patients with ARDS. Patients who had an increment of less than 1L of fluid by 36 hours had a better rate of survival, spent less time on the ventilator and had fewer days of hospitalization than other patients. Alsous et al. demonstrated, in a retrospective study of septic shock patients, that a negative fluid balance achieved in any of the first three days after admission is associated with better survival rates.

During the ICU stay, the degree of intravascular volume deficit in septic patients varies because of venodilation and continuous capillary leakage. In addition to initial hemodynamic resuscitation with fluids, targeting a CVP of 8 - 12cmH$_2$O, additional fluids are given on a daily basis for various reasons, including hypotension, fluid challenges, and dilutional and maintenance fluids, despite the presence of a positive fluid balance or even anasarca. The duration of shock is important to determining the degree of accumulated fluid balance; never the less, even after weaning from vasopressors, a positive daily fluid balance is common.

We found that five days was the median time to recover from septic shock. Recovery from septic shock depends on various factors, such as the number of organ systems affected, time to effective treatment, age and comorbidities. Studies in septic shock patients do not often publish the length of time in shock. Roman-Marchant et al. reported a duration of shock of nearly 42 hours in patients diagnosed with septic shock in the first 24 hours of ICU admission, and there was an estimated duration of shock of 93 hours for ICU patients who developed shock later in the ICU; the outcome was better in the former patients. Studies suggest that in patients without refractory hypotension, the cumulative vasopressor load is independently associated with mortality.

Initially, considering the analysis of the fluid balance during shock period, we observed higher CVP and MAP values in Group 2. This group also received more diuretics and dobutamine. The urea level decreased significantly from days 2 and 3 to day 7 in Group 2, but not in Group 1, which may be a sign of hemodilution. Although we cannot confirm this, it is possible that there may have been more patients with signs of pulmonary congestion or myocardial dysfunction in this group. Boyd et al. demonstrated that CVP is only correlated with fluid balance in the first 12 hours. After this period, it is not a reliable marker of volemia.

### Table 4 - Outcomes in Groups 1 and 2

|                      | Group 1 | Group 2 |
|----------------------|---------|---------|
| Number of complications | 45      | 47      |
| Major complications   |         |         |
| Septic shock/new episode of sepsis | 9 (45)  | 10 (50) |
| Nosocomial infection  | 11 (55) | 15 (75) |
| Arrhythmia            | 1 (5)   | 0 (0)   |
| Acute kidney injury   | 18 (90) | 12 (60) |
| Dialysis patients     | 6 (30)  | 6 (30)  |
| ARDS                  | 2 (10)  | 4 (20)  |
| Others                | 4 (20)  | 9 (45)  |
| Patients with major complications | 14 (70) | 17 (85) |
| Complications per patient | 3.2     | 2.7     |
| Length of ICU stay (days) | 11 [7.7 - 20.3] | 21 [13 - 30.5]* |
| Length of hospital stay (days) | 16.5 [11 - 22.5] | 29 [17 - 36.5]* |
| Ventilator-free (days) | 3 [0 - 8] | 2 [0 - 10] |
| Mortality rate        | 7 (35.0) | 9 (45.0) |

Group 1: fluid balance at day 1 ≤ 4.4L; Group 2: fluid balance at day 1 > 4.4L. ARDS - acute respiratory distress syndrome; ICU - intensive care unit. The values are expressed as absolute value, and percentage, or median (range) (25% - 75%). * p < 0.05.

[Figure 2 - Seven-day cumulative fluid balance after recovery from shock (in liters). The values are presented as the mean (standard error). ANOVA: p < 0.0001.]

The randomized controlled Vasopressin in Septic Shock Trial. They found that a more positive fluid balance both early in resuscitation and cumulatively over 4 days was associated with an increased risk of mortality. In this study, the accumulated fluid balances in the first 12 hours were + 4.2L and + 11L on the fourth day. These results are comparable to those observed in our study. A large European study reported that age and positive fluid balance are the strongest prognostic factors for death.
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Compared with patients in Group 1, patients in Group 2 had significantly lower urea levels and higher diuresis volumes on the 7th day. The creatinine levels were higher in Group 1, but this difference was not statistically significant. Fluids given in excess may increase diuresis, but there is no evidence suggesting that this increase improves the renal recovery or prognosis. In fact, a positive fluid balance may be observed because of renal failure. The Fluid and Catheter Treatment Trial (FACTT) showed that fluid restriction after recovery from shock was not associated with the increased development of acute renal failure. Van Biesen et al. demonstrated that the liberal use of fluids in the first 3 days of treatment for acute renal failure, leading to a positive fluid balance, fails to improve renal function, while worsening lung function.

In the adult ICU, weight is often neglected with respect to an accurate calculation of maintenance fluid requirements. Patients with very different weights are given similar fluid volumes. Despite growing evidence that a positive accumulated fluid balance correlates with worse outcomes, there is no standardization for fluid administration beyond the initial resuscitation phase, which is when myocardial performance and renal function may be most impaired. It would be advantageous for patients to be managed with supportive fluid therapy that restores the physiological status. Although this is intuitively obvious, it is very difficult to achieve in clinical practice. Our therapeutic approach tends to result in the administration of larger quantities of liquid to patients with a low body weight than to those with a greater weight.

In the early phase of sepsis, recommendations for therapeutic fluid management have been proposed to guide fluid resuscitation and are widely accepted. Frequently, fluids are liberally infused during this phase. However, after initial monitoring, management and stabilization of MAP with vasopressors, further fluids are often given based on the subjective data from clinical examination, urine output, and measurements of ventricular filling pressures. It is necessary to change the behavior to more individualized prescriptions of fluids. In the presence of a new episode of hypotension or signs of hypovolemia, use of dynamic predictors of fluid responsiveness may be safer and help guide fluid administration with a lower risk of fluid overload. When the risks associated with the extra fluid volume of a standard fluid challenge are high, such as in patients with oliguria, ventricular dysfunction or acute lung injury/ARDS, the use of echo-guided resuscitation, passive leg raising, mini-fluid challenges, and/or dynamic predictors of fluid responsiveness may be more effective and safe methods of guiding fluid resuscitation.

The most important limitation of the present study is the small sample size. In addition, it is possible that fluid balance recordings are inaccurate. Staff shortages or lack of training may lead to inadequate recordings. For these reasons, the use of fluid balance charts with cumulative input and output is being debated, and their use is questioned. Another limitation of the study is the consideration of the cumulative fluid balance without considering the time to recovery from shock, which will change the mean daily fluid balance. An additional limitation is the absence of regression logistic to determine the predictive variables for receiving higher fluid levels that correlate with a more prolonged length of stay in the ICU or in the hospital and complications. We only included those patients who survived until day 7, which might have biased our results.

On the other hand, a very important aspect of our study is establishing that the fluid balance in the period after recovery from septic shock continued to accumulate by a median of 0.64L per day. To the best of our knowledge, there are no reports on the fluid balance in this phase. In addition, this is very important clinical information for preventing adverse events related to excess fluids and guiding future studies. In addition, sepsis syndrome is very prevalent and better management could help many patients in our ICUs.

**CONCLUSION**

In conclusion, positive fluid balances are frequently seen in patients with septic shock and may be related to worse outcomes. During the shock period, although the fluid balance was previously positive, it becomes much more positive. After recovery from shock, the fluid balance continues to increase. The more positive fluid balance group spent more time in the intensive care unit and hospital. Interventional studies evaluating the effects of meticulous fluid administration in septic shock patients are warranted.
RESUMO

Objetivo: Avaliar o balanço hídrico acumulado durante o período do choque e determinar o que ocorre com ele nos 7 dias que se seguem à reversão do choque.

Métodos: Estudo prospectivo e observacional, realizado em pacientes com choque séptico. Foram incluídos pacientes com pressão arterial média ≥ 65mmHg e lactato < 2,0mEq/L desmammados há menos de 12 horas do uso de vasopressores, sendo esse dia considerado o Dia 1. O balanço hídrico diário foi registrado por 7 dias após recuperação do choque. Os pacientes foram divididos em dois grupos, segundo a mediana da coorte para o balanço hídrico acumulado durante o período do choque: Grupo 1 ≤ 4,4L (n = 20) e Grupo 2 > 4,4L (n = 20).

Resultados: Inscrivemos, neste estudo, um total de 40 pacientes. No Dia 1 do estudo, o balanço hídrico acumulado era de 1,1 [0,6 - 3,4] L no Grupo 1 e 9,0 [6,7 - 13,8] L no Grupo 2. No Dia 7 do estudo, o balanço hídrico acumulado era de 8,0 [4,5 - 12,4] L no Grupo 1 e 14,7 [12,7 - 20,6] L no Grupo 2 (p < 0,001 para ambos). A seguir, após a recuperação do choque, o balanço hídrico continuou a aumentar em ambos os grupos. Em comparação ao Grupo 1, o Grupo 2 teve um tempo mais longo de permanência na unidade de terapia intensiva e no hospital.

Conclusão: São frequentemente observados balanços hídricos positivos em pacientes com choque séptico, o que pode estar relacionado a desfechos piores. Durante o período do choque, mesmo que o balanço hídrico fosse previamente positivo, este se torna ainda mais positivo. Após a recuperação do choque, o balanço hídrico continua a aumentar. Esse grupo com um balanço hídrico mais positivo permaneceu por mais tempo na unidade de terapia intensiva e no hospital.

Descritores: Sepse; Choque séptico; Hidratação; Equilíbrio hidroeletrólítico

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