Flávia Ribeiro Machado[1], Luciana Coelho Sanches[1], Luciano César Pontes Azevedo[2], Milena Brunialti[3], Dayse Lourenço[4], Maria Aparecida Noguti[4], Reinaldo Salomão[3]

# Association between organ dysfunction and cytokine concentrations during the early phases of septic shock

*Associação entre a evolução da disfunção orgânica e as concentrações de citocinas na fase inicial do choque séptico*

1. Department of Anesthesiology, Pain and Intensive Care, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP), Brazil.
2. Intensive Care Unit, Department of Emergency Medicine, Hospital das Clínicas, Universidade de São Paulo - USP - São Paulo (SP), Brazil.
3. Discipline of Infectology, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP), Brazil.
4. Discipline of Hematology, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP), Brazil.

**Conflicts of interest:** None.

Submitted on November 2, 2011
Accepted on December 6, 2011

**Corresponding author:**
Flavia Ribeiro Machado
Rua Napoleão de Barros, 715 - 5º andar
Zip Code: 04024-900 - São Paulo (SP), Brazil.
Phone: +55 11 5576-4069 / Fax: +55 11 5576-4069
Email: fmachado.dcir@epm.br

## ABSTRACT

**Objective:** To investigate the correlation of organ dysfunction and its progression with inflammatory response during the early phases of septic shock by assessing baseline cytokine concentrations.

**Methods:** This study included patients over 18 years old with septic shock within the first 48 hours after the onset of organ dysfunction. Interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10) and C-reactive protein levels were assessed at inclusion and after 24 hours, and the differences between these values were calculated. The progression of organ dysfunction was assessed using the Sequential Organ Failure Assessment (SOFA) score upon admission and 24 hours later for a delta-SOFA determination and were categorized as either worsened or improved. The results were expressed as means + standard deviation or median (25–75% percentiles). Values with descriptive p values of 0.05 or less were considered significant.

**Results:** Overall, we included 41 patients with median SOFA scores of 8.0 (6.5–10.0) upon admission (T0) and 8.0 (6.0–10.0) 24 hours later (T1). Worsened, improved or unchanged SOFA scores were observed in 11 (Group 1), 17 (Group 2) and 13 (Group 3) patients, respectively. For Group 1, the baseline IL-6, IL-8 and IL-10 values were higher, and a significant increase of IL-8 levels was found after 24 hours. The change in the SOFA score after 24 hours was significantly, although weakly, correlated with baseline IL-6 and IL-8 concentrations.

**Conclusions:** Higher baseline IL-6, IL-8 and IL-10 levels are associated with unfavorable organ dysfunction outcomes. Increased IL-8 levels within the first 24 hours are correlated with a worsening dysfunction.

**Keywords:** Shock, septic; Multiple organ failure/etiology; Systemic inflammatory response syndrome; Cytokines

## INTRODUCTION

Sepsis is characterized by the activation of pro-inflammatory and anti-inflammatory cytokines.[1] After the inflammatory response starts, several mechanisms are activated by cytokines, e.g., inflammatory cell recruitment, endothelial cell activation, vasodilation, increased capillary permeability, microcirculation thrombosis, increased free radical production, the exacerbation of apoptosis and an impairment of mitochondrial function causing cytopathic hypoxia.[2,3] These factors may contribute to reduced oxygen availability or consumption, leading to, or aggravating, organ dysfunction. A concomitant anti-inflammatory response is, in turn, necessary for a return to homeostasis. Therefore, anti-inflammatory cytokines also have their role in the natural history of this disease.

Several previous studies have focused on the determination of plasma cytokine concentrations (both pro-inflammatory and anti-inflammatory) in sepsis.[4-8] In addition, other investigators aimed to correlate these concentrations with patient prognoses, particularly with mortality. During the initial phases of sepsis, IL-6, IL-8, IL-10 or TNF-α concentrations were shown to be increased in non-survivors when compared with survivors.[8,9] Bozza et al. reported that cytokine concentrations were accurate predictors of death within the first 48 hours (IL-6 and IL-8) or within 28 days (IL-8).[10]

In addition to this clear implication in mortality, other studies have focused on correlating baseline cytokine concentrations with sepsis phase[9] or the severity of organ dysfunction as assessed both by Multiple Organ Dysfunction Score (MODS)[11] and Sequential Organ Failure Assessment (SOFA) scores.[10,12] However, the dynamic course of baseline cytokine concentrations and their correlation with the course of organ dysfunction remain to be clarified.[9,10,13] Several studies have shown that the course of organ dysfunction following the first day of therapy is a key outcome determinant.[14-16] An analysis of the association between organ dysfunction and cytokine concentrations may contribute to a better understanding of this condition. Therefore, this study aimed to investigate the correlation of the progression of organ dysfunction and inflammatory response by assessing baseline cytokine concentrations during the early phases of septic shock.

## METHODS

We assessed patients with septic shock who were admitted to the intensive care unit of the Discipline of Anesthesiology, Pain and Intensive Care, Universidade Federal de São Paulo, São Paulo, Brazil from February, 2007 to August, 2009. This study was approved by the institution's ethics committee, and all patients or their legal representatives signed an informed consent form (ICF).

This sample was initially selected for inclusion in a study aimed at investigating the association between changes in coagulation and hyperglycemia in sepsis. Therefore, the inclusion and exclusion criteria were appropriate for that study. Patients over 18 years old who were diagnosed with septic shock within the first 48 hours after the onset of organ dysfunction and had signed an ICF were eligible for inclusion. Septic shock was defined according to the 1992 consensus criteria.[17] We excluded patients known to be diabetic or using full-dose heparin, oral anticoagulants, thrombolytic drugs or activated C protein, those who had received platelet or plasma transfusions within seven days or were receiving insulin at the time of inclusion, those who had a episode of sepsis in the previous 30 days, coagulopathy not related with sepsis or intermediate glycemic levels (between 150 mg/dL and 200 mg/dL) at inclusion.

For all patients, blood samples were collected from the arterial line at baseline for the measurement of inflammatory markers, interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10) and C-reactive protein (CRP). New samples were drawn 24 hours later and analyzed for the same markers. Blood samples were preserved on ice and transported to the immunology laboratory, where they were processed and stored at -80ºC for later analysis. All interleukins were determined by Enzyme-Linked Immunoabsorbent Assay (ELISA) (BD Bioscience®) using specific antibodies. Ultrasensitive C-reactive protein was determined by turbidimetry (Roche®).

Patient demographic data were collected along with data on the sepsis process and its severity using the Acute Physiology and Chronic Health Evaluation (APACHE)[18] and Sequential Organ Failure Assessment (SOFA)[19] scores. The progression of organ dysfunction was assessed using the SOFA score taken 24 hours later to determine the delta SOFA (SOFAD1 – SOFAD0). The delta SOFA variable was later categorized. Improving or worsening conditions were considered as changes of plus or minus one point, respectively, based on previous studies showing an association between this degree of change and clinical outcomes.[14-16]

The values of the differences in cytokine and CRP levels were transformed into delta percentages, calculated as ratios of the T1 to T0 values times 100, to express percentage changes (Delta% = (D1/D0) * 100). As the standard deviations from the mean were above 40% for all the variables, deltas were also calculated as T1 minus T0 (Deltasub = D1 – D0). Additionally, values for the individual cytokines were expressed as logarithmic scales, and their deltas were calculated by subtraction.

### Statistical analysis

Continuous variables values were expressed as means + standard deviation or medians (25–75% percentiles), depending on their distributions. The distribution normality was assessed using the Kolmogorov-Smirnov test, and the variance homogeneity was assessed using Bartlett's test. Cytokines and CRP values for the different delta-SOFA categories were compared using the Kruskall-Wallis test for both the absolute and log-transformed values, followed by Dunn test.

Possible associations between deltaSOFA and the baseline values of the various cytokine and CRP deltas were assessed using Spearman's correlation test; the results were expressed as r values. Possible associations with several severity-related variables were also assessed, i.e., the APACHE II score, lactate at admission and the number of organ dysfunctions.

The Epi Info version 3.5.1 and the SPSS v. 17.0 software packages were used for the statistical analysis. Values with descriptive p values of less than 0.05 were considered significant.

## RESULTS

Forty-one patients were included in the study; 65.9% were male, and the mean patient age was 61.5 + 18.0 years. The main causes for admission to the ICU were infection-related medical conditions (51.2%) followed by urgent surgery (29.3%) and elective surgery (19.5%). Most of the patients had comorbidities (63.4%). The most frequent source of infection were the lung (68.3%) and abdomen (22.0%) followed by urinary tract (7.3%) and bloodstream (2.4%). Nosocomial infections were more frequent (63.4%) than community-acquired infections (36.6%). The median APACHE II score was 14.0 (10.0–23.5). Most of the patients (85.3%) had three or more organ dysfunctions. The overall mortality rate was 61%. The patients' demographic characteristics are listed in table 1.

The median SOFA score upon admission was 8.0 (6.5–10.0); the T1 values were similar (8.0 (6.0–10.0). Eleven patients (26.8, Group 1) showed worsening organ dysfunction [deltaSOFA: 1.0 (1.0–2.0)], 17 patients (41.5%, Group 2) showed improving dysfunction (deltaSOFA: -1.0 (-2.0 to -1.0)], and 13 patients (31.7%, Group 3) had no changes in their dysfunction. The median deltaSOFA was 0.0 (-1.0 to 1.0).

When SOFA variations were categorized, significant inter-group differences were observed in the baseline IL-6, IL-8 and IL-10 levels. Patients with worsened SOFA had higher baseline concentrations of these cytokines (at inclusion) when compared with patients showing improvement and patients with unchanged dysfunction. Patients with worsened SOFA displayed a significant increase of IL-8 levels after 24 hours. No other significant inter-group differences were observed in changes in cytokine levels within the first 24 hours after admission, even when their log-transformed values were analyzed (Table 2).

When the initial SOFA score and its change after 24 hours were analyzed as a continuous variable (Table 3), a marginally significant correlation was observed between the SOFA changes and baseline IL-6 (Figure 1) and IL-8 (Figure 2) levels.

**Table 1 - Patient demographics and infectious process characteristics according to the SOFA score variation between admission and the first day of progression**

| Variable | Group 1 (N=11) | Group 2 (N=17) | Group 3 (N=13) | p value |
|---|---|---|---|---|
| Age | 58.0 (51.0–69.0) | 66.0 (53.5–76.5) | 57.0 (33.0–85.00) | 0.725 |
| Gender | | | | |
| Male | 6 (54.5) | 14 (82.4) | 7 (53.8) | 0.157 |
| Female | 5 (45.5) | 3 (17.6) | 6 (46.2) | |
| APACHE II | 12.0 (9.0–18.0) | 14.0 (11.8–26.0) | 14.0 (10.0–22.5) | 0.545 |
| SOFA | | | | |
| T0 | 7.0 (6.0–8.0) | 8.0 (6.5–11.0) | 8.0 (8.0–10.0) | 0.122 |
| T1 | 8.0 (7.0–10.0) | 6.0 (5.0–9.0) | 8.0 (8.0–10.0) | 0.131 |
| Lactate T0 (mg/dL) | 19.0 (12.0–30.0) | 15.8 (12.4–24.0) | 13.6 (8.6–23.8) | 0.415 |
| Delta SOFA | 1.0 (1.0–2.0) | -1.0 (-2.0 – -1.0) | 0.0 | 0.000 |
| Origin | | | | |
| Ward | 5 (45.5) | 3 (17.6) | 4 (30.8) | 0.627 |
| Emergency room | 3 (27.3) | 7 (41.2) | 5 (38.5) | |
| Surgery | 3 (27.3) | 7 (41.2) | 4 (30.8) | |
| Admission category | | | | |
| Medical infected | 4 (36.4) | 8 (47.1) | 9 (69.2) | 0.098 |
| Surgery – urgent | 3 (27.3) | 5 (29.4) | 4 (30.8) | |
| Surgery – elective | 4 (36.4) | 4 (23.5) | 0 (0.0) | |

Continue...

**Table 1 - Continuation**

| Variable | Group 1 (N=11) | Group 2 (N=17) | Group 3 (N=13) | p value |
|---|---|---|---|---|
| Comorbidities | | | | |
| Present | 6 (54.5) | 13 (76.5) | 7 (53.8) | 0.333 |
| Absent | 5 (45.5) | 4 (23.5) | 6 (46.2) | |
| Type of infection | | | | |
| Community-acquired | 4 (36.4) | 7 (41.2) | 4 (30.8) | 0.841 |
| Nosocomial | 7 (63.6) | 10 (58.8) | 9 (69.2) | |
| Focus | | | | |
| Pulmonary | 5 (45.5) | 12 (70.6) | 11 (84.6) | 0.260 |
| Intra-abdominal | 4 (36.4) | 3 (17.6) | 2 (15.4) | |
| Urinary | 1 (9.1) | 2 (11.8) | 0 (0.0) | |
| Bloodstream | 1 (9.1) | 0 (0.0) | 0 (0.0) | |
| Organ dysfunction | 4.0 (3.0-4.0) | 4.0 (3.0-4.0) | 3.0 (2.0-4.0) | 0.155 |
| >3 dysfunctions | 10 (90.9) | 16 (94.1) | 8 (61.5) | 0.054 |
| Mortality | 7 (63.6) | 10 (58.8) | 8 (61.5) | 0.967 |

APACHE, Acute Physiologic and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; T0, admission value ; T1, value after 24 hours. Group 1, worsened SOFA; Group 2, improved SOFA; Group 3, unchanged SOFA. The Delta SOFA scores are calculated as the T1 SOFA minus the T0 SOFA scores. The results are expressed as medians (25–75% percentiles), means ± standard deviation or numbers (%).

**Table 2 - Inflammatory parameters according to organ dysfunction progression profile**

| Variable | Group 1 (N=11) | Group 2 (N=17) | Group 3 (N=13) | p value |
|---|---|---|---|---|
| IL-6 | | | | |
| D0 | 4,120.0 (243.7–9321.0) | 340.0 (127.7–1,178.0) | 927.0 (42.7–2,047.5) | 0.049 |
| D0 log | 3.61 (2.38–3.96) | 2.53 (2.13–3.12) | 3.10 (1.87–3.33) | 0.075 |
| Delta% | 4.5 (3.0–39.2) | 43.3 (14.9–92.0) | 38.8 (6.6–106.1) | 0.203 |
| Deltalog% | 66.09 (57.8–88.6) | 84.8 (71.3–98.8) | 87.37 (60.6–101.4) | 0.372 |
| Deltasub | -3,935.0 (-9,068.1 – -144.2) | -63.7 (-455.95 – -4.35) | -268.9 (-1,270.0–3.6) | 0.097 |
| IL-8 | | | | |
| D0 | 362.1 (280.7–904.1) | 109.8 (66.6–333.3) | 102.9 (51.0–265.3) | 0.001**,†† |
| D0 log | 2.55 (2.44–2.95) | 2.04 (1.81–2.51) | 2.01 (1.63–2.41) | 0.001**,†† |
| Delta% | 46.5 (38.0–76.5) | 65.6 (49.8–195.9) | 90.5 (42.7–101.9) | 0.094 |
| Deltalog% | 86.2 (83.8–95.1) | 90.8 (84.2–98.0) | 97.7 (84.2–100.4) | 0.279 |
| Deltasub | -192.7 (-321.9 – -126.0) | -31.0 (-169.5–3.95) | -5.9 (-99.0–2.5) | 0.015* |
| IL-10 | | | | |
| D0 | 160.1 (61.7–295.0) | 63.4 (33.6–123.4) | 33.0 (18.0–74.35 | 0.010** |
| D0 log | 2.20 (1.79–2.47) | 1.80 (1.52–2.09) | 1.54 (1.29–1.91) | 0.019** |
| Delta% | 54.7 (26.8–78.9) | 60.0 (39.3–89.3) | 80.4(17.8–143.7) | 0.586 |
| Deltalog% | 88.9 (74.6–94.3) | 85.5 (79.5–96.9) | 94.1 (60.3–110.3) | 0.786 |
| Deltasub | -48.6 (-107.7 – -13.0) | -18.0 (-73.7 – -1.7) | -2.3 (-60.8–12.6) | 0.132 |
| CRP | | | | |
| D0 | 175.8 (129.4–247.1) | 136.5 (19.8–183.4) | 157.0 (55.3–211.4) | 0.171 |
| Delta% | 96.4 (71.7(140.6) | 99.7 (66.6–129.3) | 82.1 (63.6–91.0) | 0.103 |
| Deltasub | -4.6 (-40.1–72.4) | -0.05 (-9.51–27.0) | -18.4 (-61.5 – -4.6) | 0.077 |

IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; CRP, C-reactive protein. Group 1, worsened SOFA; Group 2, improved SOFA; Group 3, unchanged SOFA. Delta% refers to the variable T1 divided by the T0 value (×100). Deltalog% refers to the log value of variable T1 divided by the T0 log value (×100). Deltasub refers to the variable T1 value minus the T0 value. The results are expressed as medians (25–75% percentiles). Dunn post-test: *, p< 0.05 for Group 1 vs. Group 2; **, p< 0.01 for Group 1 vs. Group 2; †, p< 0.05 for Group 2 vs. Group 3; ††, p< 0.05 for Group 2 vs. Group 3.

**Table 3 - Correlation between inflammatory variables and organ dysfunction**

| Variable | SOFA D0 | | Delta SOFAsub | | Delta SOFA % | |
|---|---|---|---|---|---|---|
| | r | p value | r | p value | r | p value |
| IL-6 | | | | | | |
| D0 | 0.017 | 0.915 | 0.297 | 0.059 | 0.329 | 0.036 |
| D0 log | -0.102 | 0.536 | 0.302 | 0.062 | 0.328 | 0.041 |
| Delta% | 0.144 | 0.387 | -0.258 | 0.119 | -0.263 | 0.110 |
| Deltalog% | 0.062 | 0.712 | -0.193 | 0.245 | -0.202 | 0.223 |
| Deltasub | 0.037 | 0.817 | -0.292 | 0.064 | -0.322 | 0.040 |
| IL-8 | | | | | | |
| D0 | -0.078 | 0.627 | 0.373 | 0.016 | 0.394 | 0.011 |
| D0 log | -0.078 | 0.627 | 0.373 | 0.016 | 0.394 | 0.011 |
| Delta% | -0.065 | 0.685 | -0.227 | 0.153 | -0.258 | 0.103 |
| Deltalog% | -0.048 | 0.766 | -0.086 | 0.595 | -0.101 | 0.529 |
| Deltasub | -0.041 | 0.797 | -0.264 | 0.095 | -0.288 | 0.068 |
| IL-10 | | | | | | |
| D0 | 0.027 | 0.865 | 0.113 | 0.481 | 0.143 | 0.374 |
| D0 log | 0.065 | 0.689 | 0.126 | 0.438 | 0.158 | 0.332 |
| Delta% | -0.180 | 0.265 | -0.011 | 0.949 | -0.056 | 0.732 |
| Deltalog% | -0.120 | 0.461 | -0.007 | 0.967 | -0.043 | 0.791 |
| Deltasub | -0.170 | 0.287 | -0.052 | 0.747 | -0.081 | 0.614 |
| CRP | | | | | | |
| D0 | 0.177 | 0.269 | 0.218 | 0.172 | 0.234 | 0.141 |
| Delta% | 0.245 | 0.123 | -0.053 | 0.742 | -0.014 | 0.932 |
| Deltasub | 0.268 | 0.090 | -0.120 | 0.454 | -0.077 | 0.634 |

IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; CRP, C-reactive protein; SOFA, Sequential Organ Failure Assessment. Delta% refers to the variable T1 divided by the T0 value (×100). Deltalog% refers to the log value of the variable T1 divided by the T0 log value (×100). Deltasub refers to the variable T1 value minus the T0 value. The results are expressed as medians (25–75% percentiles).

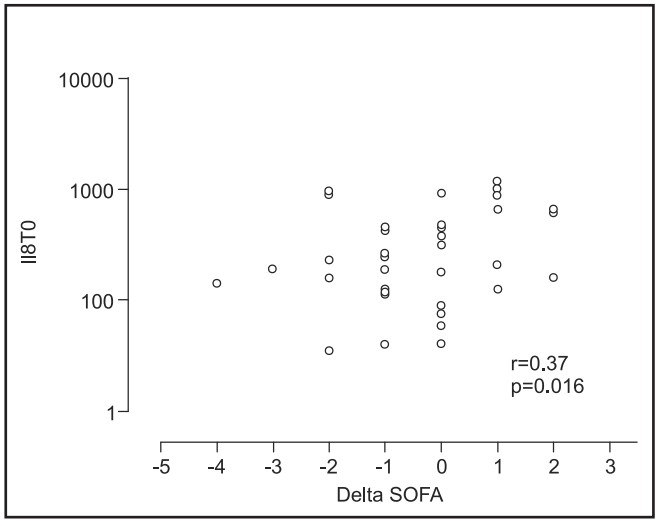


**Figure 1 - Baseline interleukin 6 (IL-6) values and their correlation with delta SOFA within the first 24 hours (Spearman's test).**

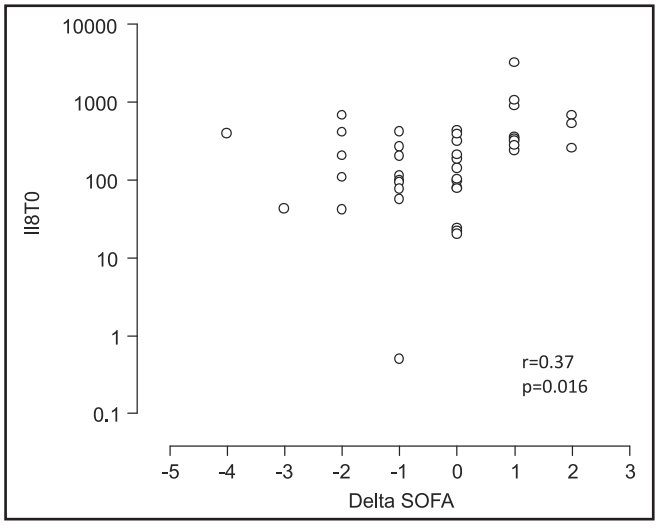


**Figure 2 - Baseline interleukin 8 (IL-8) values and their correlation with delta SOFA within the first 24 hours (Spearman's test).**

## DISCUSSION

In this study, we demonstrated that higher baseline IL-6, IL-8 and IL-10 levels are associated with unfavorable organ dysfunction outcomes, as assessed by SOFA scores. In addition, increased IL-8 concentrations within the first 24 hours after inclusion were associated with a worsening of this score within this time interval. Additionally, a significant although weak correlation was observed with worsened SOFA scores and an increase in baseline IL-6 values.

Our population consisted of severely ill patients, with an advanced median age, high admission SOFA scores and multiple organ dysfunctions. Most of the patients had more than three organ dysfunctions, and their mortality rate was high. In this population, none of the demographic variables or sepsis characteristics were shown to be associated with the intensity of organ dysfunction or progression as assessed with the SOFA score; however, baseline cytokine (IL-6, IL-8 and IL-10) concentrations were associated with both dysfunction progression and intensity, suggesting that these variables are relevant severity markers.

This association between baseline cytokine concentrations and the severity of organ dysfunction has been previously reported by Kellum, who showed that community-acquired pneumonia patients who did not develop sepsis had lower IL-6, IL-10 and TNF-α concentrations than patients with progressive inflammatory response and dysfunction.[9] Obberholzer et al. showed a marginally significant association between baseline IL-6, IL-10 and TNF-α concentrations and organ dysfunction intensity as assessed with the MODS score.[11] Bozza et al. reported that IL-8 concentrations were better correlated with the severity of organ dysfunction as assessed with the SOFA score on the first day of severe sepsis or shock diagnosis.[10] Livaditi found that IL-6, IL-8 and IL-10 concentrations within the first 24 hours after sepsis diagnosis were significantly different according to the organ dysfunction intensity as assessed with the SOFA score;[12] this finding was similar to those reported by others.[20]

However, in this study, we also found an association between baseline concentrations and a lower SOFA score within a short time period (24 hours). Studies assessing the time progression of dysfunction using the SOFA or another severity score system are scarce and showed inconsistent findings.[21,22] One of the limitations of this study regards inappropriate measurements due to the fact that these molecules have short half-lives and the presence of plasma inhibitors. Kellum et al. reported reduced IL-6, IL-10 and TNF-α levels on the second day, although the levels remained increased during the first week after diagnosis.[9] However, a possible correlation of this reduction within 24 hours and short-term organ dysfunction progression was not assessed in their study. Nguyen et al. stated that reduced IL-6, IL-8, IL-10 and TNF-α concentrations were directly associated with the capacity for clearing lactate, although a correlation between these cytokines and the progression of other dysfunctions was not assessed.[13] Bozza et al. identified baseline IL-6 and IL-8 concentrations as predictors of worsened dysfunction on the third day, i.e., the delta SOFA between this day and admission.[10] However, in our study, we observed this association occurs earlier, with a delta SOFA evident between the first and second days.

Interestingly, cytokines classically described as pro-inflammatory (IL-6) and anti-inflammatory (IL-10) were both associated with the progression of organ dysfunction within the first 24 hours. More recent studies have argued against the validity of this distinction of mediators as being only pro- or anti-inflammatory. For example, IL-6 has been associated with both processes, clearly showing the duality of some of these mediators in the septic process. Appropriate IL-6 concentrations have been described as being associated with beneficial effects such as protection against bacterial infection, the inactivation of pro-inflammatory mediators, increased cortisol production and insulin sensitivity. However, among the classical cytokines, IL-6 shows the best correlation between serum levels and unfavorable septic shock outcomes; this has triggered studies on this mediator as a severity marker.[23,24]

Interestingly, in our study, increased IL-8 levels were clearly associated with worsened dysfunction within 24 hours. Previous studies have shown this cytokine to have an important role in septic organ dysfunction, in particular, acute lung injury and respiratory distress syndrome.[25] In addition, Livaditi et al. reported that IL-8 baseline concentrations in sepsis were more appropriate to differentiate patients progressing with shock and to discriminate surviving from non-surviving patients.[12] Our results thus agree with the relevant literature, characterizing this marker as an important organ dysfunction mediator in sepsis.

This study has strengths and limitations. First, we studied a selected and homogeneous group of patients all presenting septic shock during the first hours of dysfunction. Cytokine concentrations are known to

change during disease progression. Therefore, blood samples drawn within the first 48 hours from the onset of organ dysfunction, rather than when the first hemodynamic changes are identified, render our data representative of early sepsis. This perhaps explains our statistically significant results despite the small sample size. One of the limitations of previous studies is related to patients at different sepsis progression times being assessed together.

In our study, the small sample size may be considered a limitation. In addition, although the SOFA score is widely used, several of its specific components have been criticized, e.g., the respiratory component does not take into consideration the positive end-expiratory pressure (PEEP) level for the assessment of the ratio of arterial oxygen pressure to inspired oxygen fraction ($PaO_2$/$FiO_2$). The renal component does not reflect the current Acute Kidney Injury (AKIN)[26,27] classification, and the cardiovascular component includes a threshold for the dose of noradrenalin that is considered too low by many authors. Additionally, the use of deltas has been criticized in the literature. Finally, our sample of patients was part of another cohort focused on the assessment of coagulation and hyperglycemia interactions. Therefore, the inclusion and exclusion criteria compromise the external validation of our findings.

## CONCLUSIONS

Higher baseline IL-6, IL-8 and IL-10 levels are associated with unfavorable organ dysfunction outcomes. Increased IL-8 levels within the first 24 hours are correlated with worsening dysfunction. Our findings may contribute to a better understanding of the physiology of septic shock.

Study conducted at Universidade Federal de São Paulo – UNIFESP – São Paulo (SP), Brazil.

## RESUMO

**Objetivo:** Analisar o comportamento das disfunções orgânicas e sua correlação com a resposta inflamatória, avaliada pelas concentrações basais de citocinas e pela evolução dessas concentrações, na fase precoce do choque séptico.

**Métodos:** Foram avaliados pacientes com idade acima de 18 anos e diagnóstico de choque séptico com menos de 48 horas de início das disfunções orgânicas. Foram mensuradas interleucina 6 (IL-6), interleucina 8 (IL-8), interleucina 10 (IL-10) e proteína C reativa na inclusão e após 24 horas, sendo calculado o delta desses valores. A evolução das disfunções orgânicas foi avaliada através do escore *Sequential Organ Failure Assessment* (SOFA) na admissão e após 24 horas para determinação do delta SOFA, posteriormente categorizado como piora ou melhora. Os resultados foram expressos como média ± desvio padrão ou mediana (percentil 25%-75%). Consideraram-se significativos resultados com valor descritivo de p menor que 0,05.

**Resultados:** Foram incluídos 41 pacientes com mediana do SOFA de 8,0(6,5 -10,0) e 8,0(6,0-10,0) na admissão (T0) e após 24 horas (T1). Piora, melhora ou ausência de alteração do SOFA foram encontradas respectivamente em 11 (Grupo 1), 17 (Grupo 2) e 13 pacientes (Grupo 3). No grupo 1 os valores basais de IL-6, IL-8 e IL-10 foram mais elevados. No Grupo 1 houve aumento significativo de IL-8 após 24 horas. A variação do SOFA após 24 horas mostrou correlação significativa, embora fraca, com as concentrações basais de IL-6 e IL-8.

**Conclusão:** As concentrações basais mais elevadas de IL-6, IL-8 e IL-10 associam-se a evolução desfavorável da disfunção orgânica. A elevação das concentrações de IL-8 nas primeiras 24 horas mostrou-se correlacionada a piora dessa disfunção.

**Descritores:** Choque séptico; Insuficiência de múltiplos órgãos/etiologia; Síndrome de resposta inflamatória sistêmica; Citocinas

## REFERÊNCIAS

1. Cohen J. The immunopathogenesis of sepsis. Nature. 2002;420(6917):885-91.
2. De Backer D, Donadello K, Taccone FS, Ospina-Tascon G, Salgado D, Vincent JL. Microcirculatory alterations: potential mechanisms and implications for therapy. Ann Intensive Care. 2011;1(1):27.
3. Abraham E, Singer M. Mechanisms of sepsis-induced organ dysfunction. Crit Care Med. 2007;35(10):2408-16.
4. Pinsky MR, Vincent JL, Deviere J, Alegre M, Kahn RJ, Dupont E. Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality. Chest. 1993;103(2):565-75.
5. Tanaka H, Ishikawa K, Nishino M, Shimazu T, Yoshioka T. Changes in granulocyte colony-stimulating factor concentration in patients with trauma and sepsis. J Trauma. 1996;40(5):718-25; discussion 725-6.
6. Marie C, Fitting C, Cheval C, Losser MR, Carlet J, Payen D, et al. Presence of high levels of leukocyte-associated interleukin-8 upon cell activation and in patients with sepsis syndrome. Infect Immun. 1997;65(3):865-71.
7. Ertel W, Kremer JP, Kenney J, Steckholzer U, Jarrar D, Trentz O, Schildberg FW. Downregulation of proinflammatory cytokine release in whole blood from septic patients. Blood. 1995;85(5):1341-7.

8. Hofer S, Brenner T, Bopp C, Steppan J, Lichtenstern C, Weitz J, et al. Cell death serum biomarkers are early predictors for survival in severe septic patients with hepatic dysfunction. Crit Care. 2009;13(3):R93.
9. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, Fine J, Krichevsky A, Delude RL, Angus DC; GenIMS Investigators. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Arch Intern Med. 2007;167(15):1655-63.
10. Bozza FA, Salluh JI, Japiassu AM, Soares M, Assis EF, Gomes RN, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. Crit Care. 2007;11(2):R49.
11. Oberholzer A, Souza SM, Tschoeke SK, Oberholzer C, Abouhamze A, Pribble JP, Moldawer LL. Plasma cytokine measurements augment prognostic scores as indicators of outcome in patients with severe sepsis. Shock. 2005;23(6):488-93.
12. Livaditi O, Kotanidou A, Psarra A, Dimopoulou I, Sotiropoulou C, Augustatou K, et al. Neutrophil CD64 expression and serum IL-8: sensitive early markers of severity and outcome in sepsis. Cytokine. 2006;36(5-6):283-90.
13. Nguyen HB, Loomba M, Yang JJ, Jacobsen G, Shah K, Otero RM, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. J Inflamm (Lond). 2010;7:6.
14. Levy MM, Macias WL, Vincent JL, Russell JA, Silva E, Trzaskoma B, Williams MD. Early changes in organ function predict eventual survival in severe sepsis. Crit Care Med. 2005;33(10):2194-201.
15. Minne L, Abu-Hanna A, de Jonge E. Evaluation of SOFA-based models for predicting mortality in the ICU: A systematic review. Crit Care. 2008;12(6):R161.
16. Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Crit Care Med. 2009;37(5):1649-54.
17. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644-55. Review.
18. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
19. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-10.
20. Cabioglu N, Bilgic S, Deniz G, Aktas E, Seyhun Y, Turna A, et al. Decreased cytokine expression in peripheral blood leukocytes of patients with severe sepsis. Arch Surg. 2002;137(9):1037-43; discussion 1043.
21. van Deuren M. Kinetics of tumour necrosis factor-alpha, soluble tumour necrosis factor receptors, interleukin 1-beta and its receptor antagonist during serious infections. Eur J Clin Microbiol Infect Dis. 1994;13 Suppl 1:S12-6.
22. van der Poll T, de Waal Malefyt R, Coyle SM, Lowry SF. Antiinflammatory cytokine responses during clinical sepsis and experimental endotoxemia: sequential measurements of plasma soluble interleukin (IL)-1 receptor type II, IL-10, and IL-13. J Infect Dis. 1997;175(1):118-22.
23. Fisman EZ, Tenenbaum A. The ubiquitous interleukin-6: a time for reappraisal. Cardiovasc Diabetol. 2010;9:62.
24. Dinarello CA. Proinflammatory and anti-inflammatory cytokines as mediators in the pathogenesis of septic shock. Chest. 1997;112(6 Suppl):321S-329S.
25. Mukaida N. Pathophysiological roles of interleukin-8/CXCL8 in pulmonary diseases. Am J Physiol Lung Cell Mol Physiol. 2003;284(4):L566-77.
26. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiological principles. Intensive Care Med. 2004;30(1):33-7. Review.
27. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.