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ORIGINAL ARTICLE

Effects of Chronic Ethanol Consumption in Experimental Sepsis

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Abstract — Aims: To evaluate the effects of chronic ethanol consumption on the development and the pathophysiology of sepsis, using an experimental model of polymicrobial peritonitis by feces i.p. injection. **Methods:** Forty-day-old male Wistar rats were divided into groups for two experiments: A and B. Experiment A was performed for determination of mortality rates, while experiment B was designed for biochemical analysis and measurement of cytokines before and after sepsis. In both the experiments, treated animals were exposed to a 10% ethanol solution as the single drinking source for 4 weeks, while untreated animals were exposed to tap water over the same period. Food was provided *ad libitum*. After this period, the animals underwent i.p. fecal injection for induction of sepsis. **Results:** Experiment A showed that higher doses of ethanol resulted in early mortality from sepsis that was correlated with the alcohol consumption (high dose = 85.7%, low dose = 14.3%, $P = 0.027$). In experiment B, cytokine analysis demonstrated important changes resulting from sepsis, which were further affected by ethanol exposure. In addition, glucose and creatinine levels decreased and increased, respectively, after sepsis, but a significant change occurred only in the ethanol group ($P < 0.003$ glucose, $P < 0.01$ creatinine). The levels of pro-inflammatory cytokines, interleukin-6 and tumor necrosis factor-α, increased after sepsis, but were less evident after ethanol exposure. **Conclusion:** These differences may be the result of either early mortality or an increase in the severity of the septic process. Taking into account the high mortality rate and the extreme severity of sepsis after alcohol consumption, often encouraged by advertising, a caution should be given to patients with severe infections and a history of alcohol abuse.

INTRODUCTION

Alcohol consumption has a negative impact on various organ systems, affecting the central nervous system, gastrointestinal tract, the hematopoietic organs and immune system (Zhou *et al*., 2003; Schuckit, 2005). Besides, its consequences are multifactorial (Esper *et al*., 2006). Not only may alcohol abuse lead to health problems such as liver disease and hematological, pancreatic, gastrointestinal, cardiovascular and respiratory disorders as well as malnutrition, but it may also interfere with fetal development (Edward *et al*., 1999). Furthermore, heavy consumption may result in intoxication with respiratory failure, an increased risk of an infection, such as pneumonia (Fernandez-Soja *et al*., 1995).

Sepsis, considered to be the greatest challenge in intensive care medicine throughout the world, is currently the leading cause of morbidity and mortality in intensive care units (ICU). Although, there have been striking advances in early detection of pathogenic microorganisms, the development of new drugs designed to interfere in the inflammatory and coagulatory cascade, the management of mechanical ventilation and nutritional therapy, patient death rate is still high, affecting 30–70% of ICU patients in the USA (Angus and Wax, 2001). In Brazil, the mortality rates in ICU patients with severe sepsis and septic shock are quite similar, affecting 34.4 and 65.3%, respectively (Sales Junior *et al*., 2006).

Most patients with sepsis have at least one serious comorbidity. It is crucial to point out that the presence of comorbidities such as liver disease (Foreman *et al*., 2003), cancer (Willians *et al*., 2004) and therapeutic interventions, such as in-dwelling catheters (Groeger *et al*., 1993) and red cell transfusions (Raghavan and Marik, 2005) have been associated with an increased risk of developing sepsis.

Few studies that link alcoholism to the development of sepsis have been carried out. However, there is an increased predisposition to infection for alcoholic patients due to changes in innate immunity and the presence of malnutrition (Szabo, 1999). Alcohol itself is known to be a potent modulator of the immune system. In addition, both acute and chronic alcohol use can affect the immune system at the level of innate or acquired immune responses. Altered inflammatory neutrophil, leukocyte and macrophage functions after acute or chronic alcohol use contribute to impaired host defense against microbial infections, but studies of the mechanisms for this change are still controversial (Khoruts *et al*., 1991; McClain *et al*., 1993; D'Souza *et al*., 1996).

O'Brien *et al*. (2007) have recently reported that alcohol dependence affects the prognosis of sepsis. Thus, alcoholic patients who developed sepsis had a higher hospital mortality and fewer hospital-free days compared with non-septic patients with alcohol dependence. However, this study did not measure cytokine levels or the influence of covariates, such as malnutrition and smoking, common in alcoholic patients, which may influence the development of sepsis.

Given the controversy still present in the literature on the effects of alcohol on the inflammatory mechanisms for the control of sepsis, the aim of this study was to evaluate the effects of chronic ethanol consumption on the development of sepsis, including its pathophysiology, through an experimental model of sepsis induced by polymicrobial peritonitis.

MATERIALS AND METHODS

Alcohol exposure

The male Wistar rats used were 45-days-old, weighed between 150 and 165 g and were from the animal facility at the Center

for Behavioral Sciences and Development, Biomedical Institute, Universidade Federal Fluminense. The animals were kept in individual polyethylene cages (41 × 34 × 16 cm) and exposed to 12 h of a light/dark cycle (7–19 h). The procedures were approved by the Ethics Animal welfare Committee at the Center for Laboratory Animals at the Universidade Federal Fluminense, under registration number 0092/09.

In experiment A, the animals were assigned randomly to two groups: a control group (C, $n = 10$) and an ethanol group (E, $n = 10$), receiving water and ethanol solution *ad libitum*, respectively, as the only liquid source during the 4 weeks of the experiment. Both the groups were fed commercial NUVILAB CR1 (NUVITAL®) *ad libitum.* In order to induce alcohol consumption, an ethanol solution was administered as a single source liquid with a concentration of 5% v/v for adaptation in the first week and 10% v/v in the following weeks, as described by Macieira *et al*. (1997) and Aguiar *et al*. (2004). During the 4 weeks, their body weight was monitored weekly as well as the ethanol consumption was checked every 48 h. As this period came to an end, the animals underwent induction of sepsis.

In experiment B, the animals were assigned randomly to four groups categorized as follows:

- Control group (C) ($n = 10$) received water *ad libitum* and concentrated NUVILAB CR1 (NUVITAL®) *ad libitum* during the 4-week experiment and did not undergo induction of sepsis;
- Ethanol group (E) ($n = 10$) received ethanol solution 5% v/v in the first week and 10% v/v in the following weeks as the only liquid source and commercial feed NUVILAB CR1 (NUVITAL®) *ad libitum* during the 4-week experiment and did not undergo induction of sepsis;
- Sepsis group (S) ($n = 10$) received water *ad libitum* and concentrated NUVILAB CR1 (NUVITAL®) *ad libitum* during the 4 weeks of the experiment and underwent induction of sepsis;
- Ethanol + Sepsis group (E+S) ($n = 10$) received ethanol solution 5% v/v in the first week and 10% v/v in the following weeks as the only liquid source and commercial feed NUVILAB CR1 (NUVITAL®) *ad libitum* during the 4 weeks of the experiment and underwent induction of sepsis.

Experimental sepsis

Following the chronic consumption of ethanol, all the animals in experiment A and the animals of the sepsis group and ethanol + sepsis group in experiment B were injected i.p. with feces as described previously (Oliveira *et al*., 2010). In Brief, fresh feces were collected in 50 ml polypropylene conical tubes. They were added to saline (0.9% NaCl) for dilution of the stool (15 ml of saline for each 5 g of feces). The resulting solution was centrifuged at 800 revolutions per minute (rpm) for 5 min. The supernatant obtained was removed, and 1 ml of solution for every 100 g of the rat was injected intraperitoneally. As a result, 6 h after the induction of sepsis, the animals began showing signs of illness (ruffled fur, hypothermia, lacrimation, lethargy). At this time, the antibiotic meronem (Zeneca Farmacêutica do Brazil) 6 mg/kg, diluted in saline, was injected subcutaneously. AE and AC groups underwent the same procedure as described earlier, but received only vehicle injections. This technique is relevant from a clinical standpoint for mimicking various aspects of sepsis in humans through initiating the process from the focus of infection at the peritoneal cavity (Benjamim, 2001; Brealey *et al*., 2004).

Alcohol intake and mortality evaluation

Survival of animals subjected to sepsis was assessed over a period of 72 h. The data concerning levels of ethanol consumption were analyzed. Therefore, the median ethanol consumption (Md = 11.7 g/kg body weight) was calculated to classify the ethanol group into low ethanol consumption ($n = 14$) (values bellow the median) and high ethanol consumption ($n = 13$) (values above the median). The results were compared between them and with those from a control group which was never exposed to ethanol. Also, samples of liver, lungs, spleen and intestine were collected for hystological analysis.

Biochemical analysis—experiment B

After 4 weeks of experiment, blood was collected by cardiac puncture, under anesthesia, from groups C ($n = 10$) and E ($n = 10$) and 8 h after induction of sepsis in groups S ($n = 10$) and E+S ($n = 10$). Biochemical parameters analyzed were glucose, urea, creatinine, total protein, albumin and globulin, as described by the manufacturer's protocol (Diagnostic Kit LABTEST, MG, Brazil).

Analysis of cytokines—experiment B

The blood collected by cardiac puncture was centrifuged to obtain plasma, which was frozen at −70°C for further cytokine quantification by ELISA using specific monoclonal antibodies as described by the manufacturer's protocol (Kit DuoSet, R & D Systems, USA). Plasma levels of cytokines [interleukin (IL)-4, IL-6, IL-10, IL-12, IL-13 and tumor necrosis factor-α (TNF-α)] were quantified from groups C ($n = 10$) and E ($n = 10$) and 8 h after induction of sepsis in groups S ($n = 10$) and E+S ($n = 10$).

Statistical analysis

The results were analyzed using SPSS for Windows 12.0. Body weight data, cytokines and biochemistry were expressed as mean ± SD. Ethanol consumption data were presented as medians.

Survival time was presented with the aid of the program GraphPrism version 5.0.

The experimental groups were compared using both parametric and non-parametric tests. Analysis of variance two-factor (two way) was used to compare two independent factors: ethanol and sepsis (without sepsis and with sepsis). Biochemical and cytokine data were analyzed using the nonparametric statistical test Mann–Whitney-*U* (C × S and E × E+S). The significance level was set at *P*-values ≤ 5%. Comparisons of proportions were set using Fisher's exact test.

RESULTS

Bodyweight

Ethanol consumption did not alter body weight in the control group (mean + SD: controls:165.1 ± 20.2 g/kg; ethanol:151.1 ± 18.5 g/kg, $P > 0.05$).

Mortality

As ethanol was offered ad libitum, rats presented different individual intake. Therefore, it was possible to classify them according to their spontaneous ethanol consumption. The median (Md = 11.4) of ethanol consumption in g/kg body weight of the total sample was used to classify animals into high and low ethanol consumption groups, that is, above and below the median.

Results of mortality taken 24 h after sepsis induction suggested a significant effect of ethanol on mortality by sepsis. Animals with high ethanol consumption ($n = 14$) showed a significantly higher mortality rate (85.7%) compared with the low ethanol consumption ones (14.3%), $P = 0.027$, the Fisher exact test (Fig. 1). As these results were observed in the first 24 h, they suggest that higher ethanol consumption anticipated mortality in the septic group. Mortality of the animals in the low ethanol consumption group ($n = 13$) was not different from that observed in the control group ($n = 30$), ($P > 0.34$, Fisher).

There were no significant hystological changes among septic animals whether exposed to ethanol or not. All in all, both the groups presented intense congestion in vital organs.

Biochemical analysis

Sepsis increased urea levels and decreased globulin, albumin and total protein levels independently of ethanol exposure. Moreover, it induced hypoglycemia and increased creatinine blood levels. The last-named changes were more remarkable in ethanol-exposed rats. (Fig. 2)

Cytokines

Sepsis significantly increased levels of pro-inflammatory cytokines IL-6 and TNF-α (Fig. 3). The same tendency was observed for IL-4 and IL-13, but was not statistically significant. Ethanol significantly decreased the effect of sepsis in the levels of IL-6 and TNF-α.

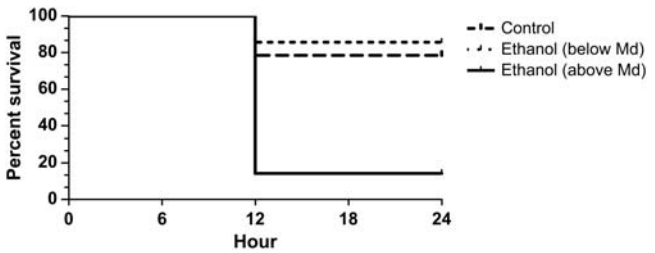

Fig. 1. Comparison of mortality among animals with low consumption of ethanol solution 10% v/v (below Md), those with high consumption of ethanol solution 10% v/v (above Md) and control rats. The ethanol group above the median showed a high mortality rate ($P < 0.027$) compared with the ethanol group below the median and the control group ($P < 0.34$). Md: median (11.4 g/kg body weight).

DISCUSSION

The effects of alcohol on human body are complex and depend on many factors, such as patterns of drinking (chronic or acute/binge), the amount of consumed ethanol (moderate or excessive), the body organ or system and the sex of the user. The epidemiological analysis of the effects of ethanol on health leads to the conclusion that the key factor is the amount of alcohol consumed (Goral *et al*., 2008).

The current study suggests that alcohol influences sepsis in a dose-dependent way, in which animals ranked above the median (high ethanol consumption) had earlier death compared with animals ranked below the median (low ethanol consumption) and animals that did not received ethanol (control group). These data suggest that ingestion of ethanol, depending on the dose, can affect the progression of experimental sepsis, with a significant death rate within the first 24 h. Multiple epidemiological reports demonstrate a U-shaped relationship between ethanol intake and general mortality (Djousse *et al*., 2002). The lowest death rate correlates with low to moderate amounts of ethanol (15–45 g or 1–3 drinks per day) (Gigleux *et al*., 2006), whereas both abstaining from ethanol or excessive drinking are associated with higher mortality (Power *et al*., 1998).

The clinical manifestations of sepsis result from the primary infection process, the underlying inflammatory process and organ dysfunction (Hotchkiss and Karl, 2003). Clinical manifestations secondary to inflammatory activation are non-specific and include fever or hypothermia, tachycardia, tachypnea and respiratory alkalosis, leukocytosis or leukopenia, inadequate intake of oxygen, hypoperfusion, peripheral glucose intolerance, elevated plasma urea and creatinine levels and a hyperdynamic circulatory state (Sibbald *et al*., 1995).

Our results showed that sepsis interfered in all biochemical parameters, as reported in literature, which confirms the usefulness and relevance of our model. Ethanol intake during sepsis significantly increased the levels of urea and creatinine and decreased the levels of plasma total protein, albumin, globulin and glucose. These biochemical changes, more evident in the ethanol group, may be independent risk factors for poor prognosis of sepsis among alcoholic patients. After ethanol doses of 0.05%, blood alcohol concentration changes can be detected in motor coordination and critical concentration.

Alcohol itself is considered a potent modulator of the immune system. Both acute and chronic use can affect the immune system at the level of innate or acquired immune responses. Altered inflammatory neutrophil, leukocyte and macrophage functions after acute or chronic alcohol use contribute to impaired host defense against microbial infections (Szabo, 1999). Macrophages are the first line of defense against infection, following the natural barriers of skin and mucous membranes. Activated macrophages produce pro-inflammatory cytokines (TNF-α and IL-6) that act on other cells or blood elements (neutrophils, endothelial cells, fibroblasts, platelets and monocytes). The local effect of these cytokines involves the recruitment of phagocytic cells, essential for the elimination of microorganisms. This is particularly important for TNF-α, a key mediator in septic shock (Hack *et al*., 1997). *In vitro* and *in vivo* studies showed that exposure to alcohol can impair the

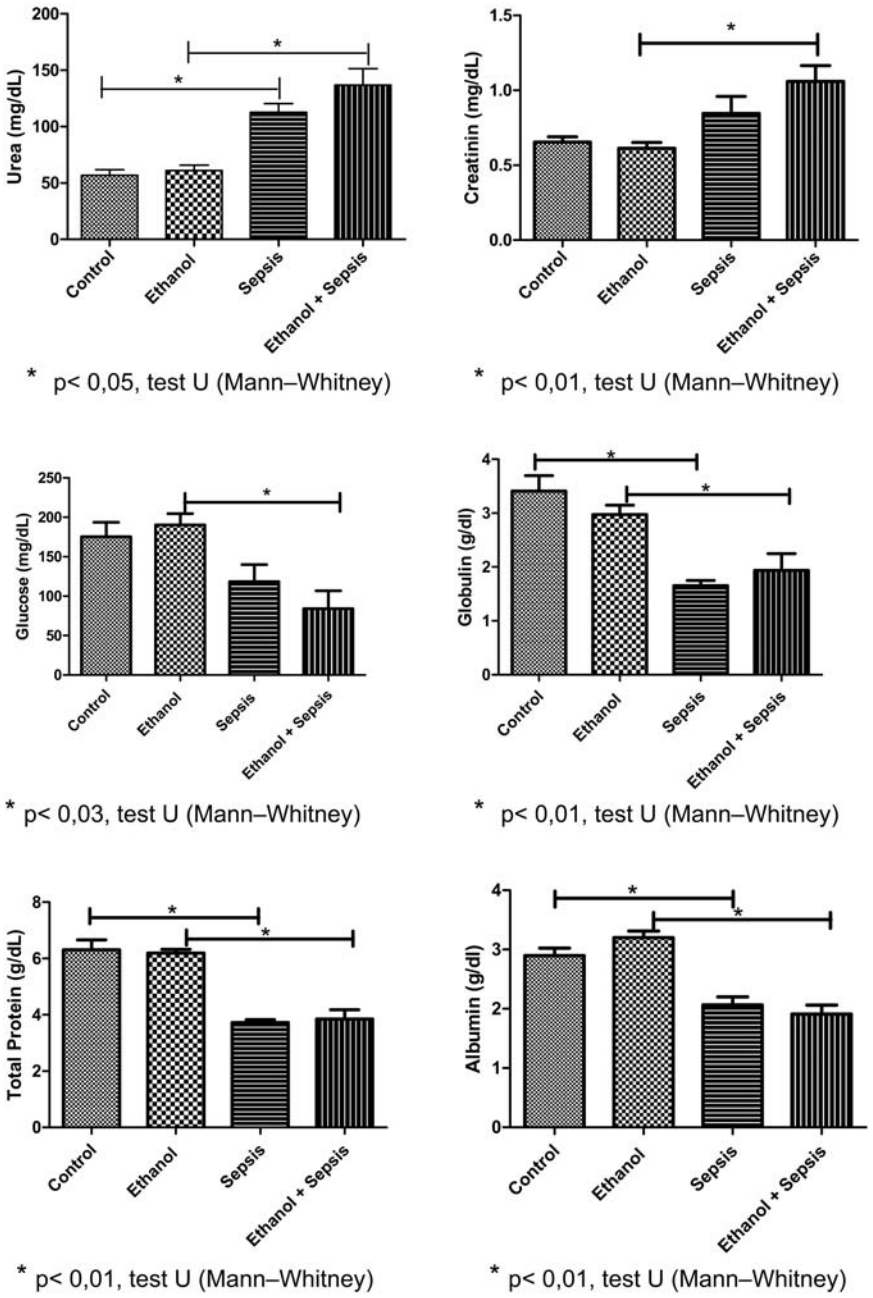

Fig. 2. Comparison of biochemical parameters between the control group and the ethanol group.

production of pro-inflammatory cytokines (TNF-α) and neutrophil recruitment in response to an immune challenge (Boe *et al.*, 2003).Our results are in agreement with clinical studies, which claim that alcohol abuse predisposes to infections, mainly because of suppression of production of important cytokines in the inflammatory response such as TNF-α, IL-6 and IL-10 (D'Souza *et al.*, 1996) impairing the recognition of microorganisms, the migration of macrophages and the fight against infection. Other studies showed that in the presence of sepsis, alcohol dependence increases mortality and decreases levels of TNF-α, IL-6, IL-8, IL-1β and IL-12 (Frank *et al.*, 2004; Von Dossow *et al.*, 2004).

The experimental model made it possible to control important variables associated with alcohol consumption such as dose and timing of ingestion and decrease of body weight, yet there is no agreement with the literature. Some studies suggested that there is an increase in circulating levels of the same cytokines (Khoruts *et al.*, 1991; McClain *et al.*, 1993) which would induce an exaggerated inflammatory response. Still, there is no straightforward and clear evidence that all cytokines are good biomarkers predictors of a worst outcome in sepsis. In fact, levels of several cytokines are of no predicable value in sepsis and some have only a limited predictor value depending on the model and time of observation (Bozza *et al.*, 2005, 2007).

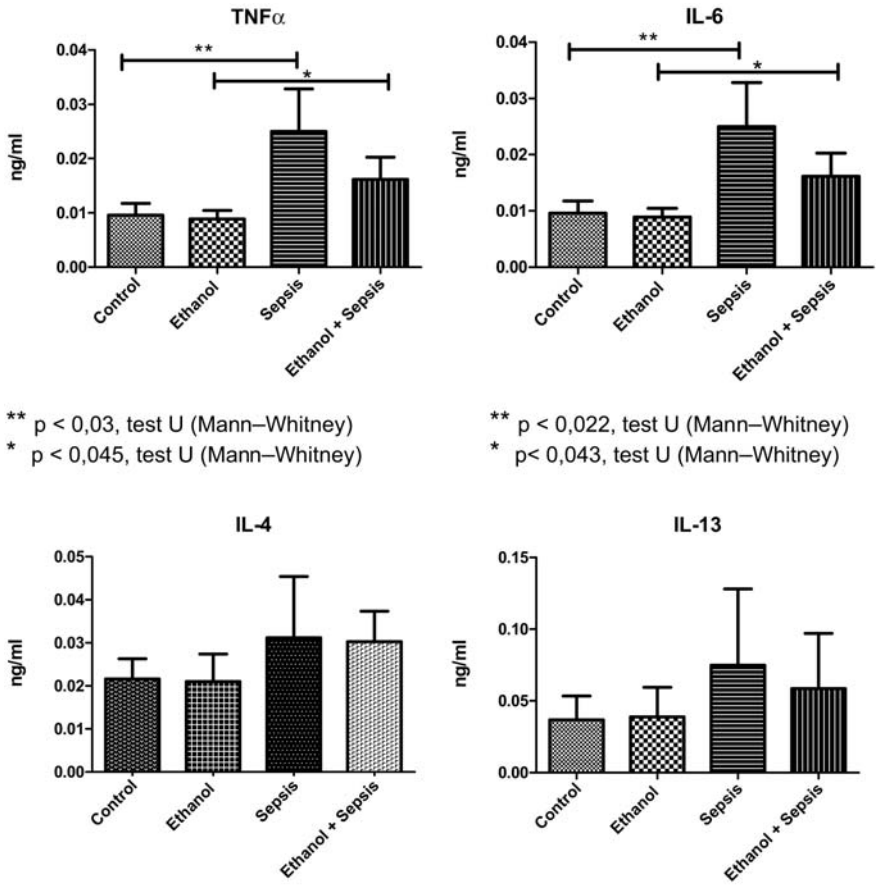

Fig. 3. Comparison of cytokine levels between the control and the ethanol groups.

This study evaluated the effects of alcohol consumption on the production of pro-(TNF-α, IL-6) and anti-inflammatory cytokines (IL-4, IL-10, IL-12 and Il-13) 8 h after induction of sepsis. There was no detection of serum levels of IL-10 and IL-12, possibly because these are considered anti-inflammatory mediators and are usually found in a later stage in the evolution of sepsis (Mandrekar *et al*., 2006), although in some models the detection of IL-10 is obtained at an early stage of infection (Pruett *et al*., 2010). Even though the IL-4 and IL-3 were detected, the results were not significant, probably for the same reason as mentioned earlier for cytokines IL-10 and IL-12.

Typical inflammatory cytokines such as TNF-α, IL-1 and IL-6 are primarily produced by inflammatory monocytes, macrophages, while other cell types, including neutrophils, lymphocytes and endothelial cells, may also be the source of the inflammatory response. Studies have shown that cytokine levels increase 3 h after an immune challenge (El Guindy *et al*., 2007). All models of sepsis in the literature have considerably contributed to a better understanding of the pathophysiological mechanisms involved in the development of sepsis. The intraperitoneal injection of feces is a model that resembles the cecal ligation and puncture model to produce polymicrobial sepsis, but without the use of anesthetics or surgical procedures. This model is rarely used as there are reports on rapid onset of sepsis, leading to death or recovery of the animal in a short time (Rittirsch *et al*., 2007), following the standard model of endotoxemia. This study showed that with the use of fluid replacement and antibiotics, it was possible to produce a model of fecal peritonitis and sepsis with characteristics similar to those of humans, including mitochondrial dysfunction and multiple organ dysfunction syndrome (Brealey *et al*., 2004). The model of sepsis by intraperitoneal injection of feces used in this study was very effective in inducing sepsis in the animals, as inferred by significant alterations in all biochemical parameters and the release of pro-inflammatory cytokines. Despite the fact that significant mortality was still present, the rapid administration of effective antibiotic therapy (6 h after sepsis induction) could have affected the magnitude of the inflammatory response in our model as indicated by the low amounts of cytokines detected in those animals. This apparent discrepancy may be related to the acute characteristic of mortality in this model, indicating that shock is the most probable cause, which would have been better treated with vigorous fluid reposition.

Notwithstanding the associated high mortality rate, the complexity of interactions on the immune system and the extreme severity of sepsis with heavy use, alcohol consumption continues to be encouraged through popular advertising. It is important to mention that better understanding of the controversial mechanism of the interaction between alcohol consumption and sepsis is still required, and for that, future studies through histopathological analysis of animal organs involved in sepsis and analysis of cytokines and genetic factors will be indispensable

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