Editorial

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Sepsis and acute kidney injury: Is there a role for activated protein C in 2011?

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Sepsis is a complex clinical syndrome that results from an infection-triggered systemic inflammatory response. (1) Due to the large amount of invasive procedures performed nowadays, increased life expectancy in the population of Western societies and frequent use of immunosuppressive therapy, the incidence of sepsis syndrome has significantly increased in the past few decades. (1,2) In the United States alone, every year, between 500,000 and 750,000 patients will develop sepsis, with an associated documented mortality rate of 20 to 40%. (2-4) This syndrome is commonly encountered in intensive care units (ICU). In a European study, 10-15% of all patients admitted to the ICU developed sepsis and septic shock. (5) Severe sepsis remains the leading cause of death in the non-coronary ICU and the 10th leading cause of death overall. (6, 7)

The currently accepted conception regarding this disease process is that inflammation, coagulation, and apoptosis are tightly related in the pathophysiology of sepsis. (3,8) This causes a characteristic loss of homeostasis between coagulation and fibrinolysis, leading to the clinical manifestations. (9) Sepsis induces alterations in the microcirculation. These are ubiquitous and are linked to both cardiovascular and renal failure (the so-called "type 5 cardiorenal syndrome"). Systemic vasodilation caused by inflammation leads to reduced tissue oxygen delivery (DO2), with progressive mitochondrial dysfunction/ disruption and cytopathic hypoxia, which can cause organ failure. (5) As this process develops, the appearance of refractory hypotension may become evident. (10) This cardiovascular response to sepsis can be predictive of survival, as demonstrated by Parker and associates. (11) Additionally, there is evidence that suggests that septic shock is associated with profound and sustained depletion of circulating dendritic cells, accounting for the immunosuppression in the so-called late phase of sepsis. (12, 13)

Key words: Septic shock, acute kidney injury, activated protein C, organ failure.

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In the acute sepsis process, protein C is depleted and its activation diminished. (14) Endogenous activated protein C (APC) is an important proteolytic inhibitor of cofactors Va and VIIIa, factors involved in the rate-limiting steps of the coagulation cascade. APC enhances fibrinolysis by neutralizing PAI-1, by accelerating t-PA dependent clot lysis and decreasing TAFI. (9)

The association of sepsis with acute kidney injury (AKI) is well known. The risk, injury, failure, loss and end-stage renal disease (RIFLE) classification has been proposed as a uniform standard for diagnosing and classifying AKI. (7) The RIFLE classification defines and stages AKI using serum creatinine (SCr), urine output (UO) and need for renal replacement therapy (RRT), making them simple to apply in a variety of clinical and research settings. (7,15) Sepsis and septic shock are known contributing factors for development of AKI among critically ill patients. (15-17)

The foundation for sepsis and septic shock therapeutic approach remains the timely administration of empirical antibiotics, intravenous fluids and the use of vasopressors to reverse the hypotensive state and maintain tissue perfusion, and when feasible, early identification and elimination of the source of the infection. (18) In the PROWESS trial (2001), evidence indicated that the infusion of activated drotrecogin-alfa reduced the mortality in patients at high risk of death when administered early. (19,20) This was the first trial to demonstrate a clinically and statistically significant effect on mortality by sepsis at 28 days after treatment and was also the first FDA-approved agent for severe sepsis. (9) Drotrecogin alfa used during acute sepsis overtakes the action of the endogenous protein C, which is normally depleted in this state. (14) Drotrecogin alfa is proposed to work as an antithrombotic, anti-inflammatory, profibrinolytic agent. Its antithrombotic effect is caused by its inactivation of factors Va and VIIIa, thereby indirectly decreasing thrombin production. (14) Additionally, it inhibits monocyte and neutrophil migration. (21) Drotrecogin alfa improves global hemodynamics and attenuates changes in microcirculation in septic shock. (3) Despite all of these beneficial effects, significant controversy regarding the utility of this agent in sepsis persists.

In this issue of Critical Care and Shock, Spapen and Janssen van Doorn investigated the possibility that sepsis-induced AKI influenced the outcome and evolution of sepsis-induced cardiorespiratory failure complicated by AKI. (22) The previously reported beneficial effects of APC on cardiovascular and respiratory dysfunction in septic shock were confirmed on this clinical trial. Therapy using APC was proven to be equally effective in spite of concomitant AKI. Therefore AKI should never be a limitation to consider APC in the context of sepsis. This study, although small and open-labeled, should trigger additional larger scale clinical trials.

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