**High Volume Hemofiltration in Sepsis**

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**Introduction**

Continuous renal replacement therapy (CRRT) in the intensive care unit (ICU) is a common treatment in acute renal failure. CRRT is mainly conceived as merely supportive and as a replacement of the lost kidney function. On the other hand, evidence accumulated over recent years demonstrates that many soluble mediators of the systemic inflammatory (and anti-inflammatory) response syndrome (SIRS) can be removed by CRRT. This has led to the suggestion that CRRT could play a major role in sepsis therapy as an immunomodulatory treatment and not only as a blood purification technique. In this perspective, whereas animal studies yielded encouraging results, early clinical trials showed only minor clinical benefits, mainly dealing with hemodynamic improvements. The question of treatment dose has appropriately been raised as it remains undefined and a matter of controversy. A large-scale clinical trial has clarified issues on treatment dose in acute renal failure but a sufficiently powered study on hemofiltration dose in sepsis is still lacking.

In this chapter, we will review the rationale for application of CRRT in the treatment of the septic syndrome with specific focus on the use of high ultrafiltration rates (i.e., high-volume hemofiltration, HVHF). We will integrate the discussion into the most recent hypothesis proposed to explain some of the clinical results obtained with high efficiency, non-selective removal of mediators of sepsis. Further, we will describe the necessary technical requirements for HVHF and the most recent machine development concurring with these.

**The Rationale of CRRT in Sepsis**

The sepsis syndrome has been described as a systemic malignant inflammation, where the circulation is invaded by enormous amounts of pro-inflammatory mediators produced by activated mononuclear cells. In fact, sepsis is associated with an overwhelming, systemic overflow of both pro- and anti-inflammatory mediators; this leads to altered immune cellular responsiveness, generalized endothelial damage and multiple organ failure (MOF) derived from a complete disruption of the ‘immunological homeostasis’ [1, 2].

The characteristics of the mediator network are of fundamental relevance in order to allow selection of the most rational and effective treatment approach. The network is redundant and synergistic; it acts like a cascade modulated by multiple positive and negative feedback loops. A vast array of humoral mediators have been identified as exerting pro-inflammatory effects; on the other hand, a seemingly
equally broad spectrum of molecules with opposite function has been demonstrated to emerge in the time course of the septic syndrome. Both pro- and anti-inflammatory mediators, while designed to mainly act in an autocrine and/or paracrine mode, spill over into the circulation during sepsis and display disastrous systemic effects. In some circumstances, depending on which additional stimuli are present, the same mediator can exert alternatively pro- or anti-inflammatory action. Apart from inciting substances (e.g., endotoxin, products of cell injury) and very early mediators of the septic process (e.g., complement factors, factor XIIa), chemokines and cytokines have a central role in the propagation of the inflammatory process including regulatory effects on immune cells. In fact, mortality in sepsis is correlated with persistently elevated levels of pro-inflammatory cytokines [3, 4] and in a parallel way, persisting immune cellular hypo-responsiveness associated with high levels of anti-inflammatory cytokines [5, 6]. This feature has been similarly observed early in the sequence of effects induced by endotoxin injection in animal models (Fig. 1) [7].

### The Peak Concentration Hypothesis

The concept of blocking one mediator has not led to measurable improvement in outcome in patients with sepsis [8]. Possibly more rigidly defined subgroups would profit from tumor necrosis factor (TNF)-antagonizing treatments [9]. On the other hand, it has been shown that antagonizing a cytokine could lead to deleterious consequences encompassing substantially higher mortality [10]. A low-level TNF response seems to be necessary for the host defense to infection [11, 12], and high levels seemingly need to be modulated by an anti-inflammatory feedback; in sepsis, however, failed regulation may cause an excess of the anti-inflammatory response which generates monocyte downregulation and exposes to further infections. Both these processes (inflammation and anti-inflammation) are designed to act in response to specific stimuli in a well-balanced fashion defined as immuno-homeostasis. The excess of one process over the other may produce a deleterious effect either leading to systemic inflammation or immune-cell hypo-responsiveness. In