Organ Crosstalk in Critically Ill Patients: Hemofiltration and Immunomodulation in Sepsis

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Key Words

Sepsis · Septic shock · Immunoparalysis · Renal replacement techniques · Immune mediators · Lipopolysaccharides

Abstract

Despite substantial advances in our understanding of the pathogenesis of sepsis, the mortality of patients with severe sepsis/septic shock is unacceptably high. The potential role of extracorporeal therapies in the adjunctive treatment of sepsis is highly controversial. The present article reviews the current status of clinical research in this area. Conventional 'renal dose' continuous and discontinuous renal replacement technologies fail to achieve a biologically relevant reduction of target molecules. This may be accomplished by modified approaches, e.g. using high-dose protocols, high cut-off membranes, or (selective or unselective) adsorption techniques; however, their clinical value remains to be established by prospective studies using clinical end points.

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Introduction

A number of recent advances in the field of critical care medicine have influenced our understanding and approach towards patients with sepsis. Nevertheless, al-

though substantial advances in the understanding of the pathogenesis of sepsis have been made, the mortality from sepsis remains relatively unchanged. Sepsis still is a major medical challenge and accounts for a major burden on public health care systems. In the immunopathogenesis of sepsis, multiple endogenous and exogenous mediators such as lipopolysaccharides (LPS), tumor necrosis factor- α (TNF α), interleukins (ILs; e.g. IL-1 and IL-6), and interferon- γ are released in response to a microbial invasion which – at this point in time – cannot be controlled locally by the innate and adaptive immune system. In a long pyramid cascade, pro-inflammatory mediators and danger signals then yield the systemic release of anti-inflammatory mediators, activating numerous signal pathways including the complement and the coagulation cascade. This yields cellular damage, apoptosis, end-organ failure, and, importantly, failure of innate and adaptive host defense mechanisms. Consequently, death from secondary infection occurs in a large number of cases.

A number of intermittent and continuous extracorporeal treatment approaches have been designed to target circulating inflammatory molecules. Hemofiltration (HF) techniques have been employed in order to unselectively remove respective mediators and to beneficially influence the course of septic patients. Here, the impact on immune mediators and cellular immunity of these efforts will be reviewed in the context of recent clinical tri-

als. The data will be discussed before the background of other blood purification technologies such as selective plasmapheresis and adsorption.

Epidemiology of Severe Sepsis and Septic Shock

Severe sepsis and septic shock are the major reasons for death in noncardiologic intensive care units today [1–3]. Data from the United States demonstrate that about 215,000 patients die from sepsis each year (yearly incidence 50–95 cases per 100,000 inhabitants). The incidence rate of sepsis has been shown to increase by up to 9% each year [4] and the occurrence of sepsis peaks in the sixth decade of life. The major factors predisposing to sepsis are underlying malignant disease, all forms of exogenous and endogenous immunodeficiency, chronic organ failure, and a number of genetic factors (e.g. male gender). The estimated overall mortality rate from sepsis in the United States is about 30%. Recent efforts have now made additional data available. In Germany, the annual incidence rate of sepsis was found to be 85–116 per 100,000 inhabitants. For severe sepsis, the incidence rate was 76–110 cases per 100,000 inhabitants per year [5]. These data are in accordance with longitudinal data from a number of other countries worldwide. Moreover, septic shock, the most severe manifestation within the ‘sepsis syndromes’ affects 2–20% of inpatients. However, the incidence of septic shock has been demonstrated to rise [4, 6] and death rates of 33 up to 61% have been reported in the placebo arms of recent large-scale multicentre trials [7–10].

Acute renal failure (ARF) is an important element within the sepsis-induced multiple organ dysfunction syndrome (MODS). ARF occurs in about 19% of patients with moderate sepsis, 23% of patients with severe sepsis, and in 51% of patients with septic shock. The combination of ARF and sepsis is associated with a mortality of around 70% [11]. Most patients with ARF will require some form of extracorporeal renal replacement therapy during the course of the disease, thus amplifying the burden on public health care systems.

Definition and Diagnosis of Sepsis

A consensus on the definition of sepsis, severe sepsis and septic shock was reached earlier [12, 13, reviewed in 2]. Sepsis is now defined as infection with evidence of systemic inflammation, consisting of two or more of the following: increased or decreased temperature, increased or

decreased leukocyte count, tachycardia, and rapid breathing. Severe sepsis includes the presence of acute organ dysfunction (e.g. renal dysfunction). Septic shock is defined as sepsis with volume-refractory hemodynamic failure [2, 12, 13]. The diagnosis of the respective ‘sepsis syndromes’ is established according to the respective definitions.

Pathophysiology of Sepsis and Basic Science Mechanisms: A Starting Point for an Extracorporeal Intervention?

Uncontrolled infection due to microbial invasion (mostly bacterial, fungal, or viral) may be considered a hallmark of the pathogenetic scenario of sepsis. In the course of the disease, a pro-inflammatory phase of sepsis may be recognized. This phase may be characterized by an excessive release of pro-inflammatory mediators (e.g. LPS, TNF α , IL-6) in response to such an overwhelming microbial invasion [1–3]. Multiple pleiotropic danger signals then react in complex feedback-regulated dynamic pyramid cascades. Clinically, the overspilling of such mediators from local tissues to the systemic circulation is associated with hyperdynamic shock, increased shunting and the development of a MODS [1, 2]. Nevertheless, in the presence of modern intensive care medicine, overwhelming septic shock with fulminant hemodynamic failure and death within a few hours is observed in few cases only. In most cases of sepsis, persisting inflammation promptly yields anti-inflammatory mechanisms. This may be interpreted as a protective mechanism and may include, among others, an increased expression of IL-10 and transforming growth factor- β , thus inducing a compensatory anti-inflammatory response syndrome [3]. Importantly, as mentioned before, the vast majority of nonsurviving septic shock patients do not die from the initial burden, but rather from a ‘second’ or ‘third infectious hit’ in later course of the disease. This seems to be due to the fact that most nonsurvivors develop a state of functional immunodeficiency which may involve mechanisms including disturbed monocytic phagocytosis, altered cytokine profiles and inadequate antigen presentation capacities, as well as dysfunction and apoptosis of both T and B lymphocytes. This may finally induce a ‘shutdown’ of innate and adaptive immunity [1–3]. This state was termed ‘immunoparalysis’ and may best be approached via standardized quantitative measurement of a diminished monocytic HLA-DR expression [14]. Importantly, this functional monocytic failure is associated with reduced survival from sepsis [14–21]. Today, it seems well recognized that most septic patients die in this late ‘hypo-

responsive' phase from secondary 'infectious hits' in a state of anergy and chronic MODS [22].

Consequently, a large number of randomized trials aiming to neutralize LPS or to block single short-lived pleiotropic mediators using e.g. antibody-mediated approaches (e.g. LPS or TNF- α) were performed in the last 25 years. Nevertheless, these efforts have largely failed [1–3]. Such failure may be due to the therapies' unidirectional character and may be a consequence of an inability to prevent the severe immunologic dysregulation and failure of the cellular immune system which can often be observed in sepsis [22]. However, these sepsis trials taught a very important lesson as they suggested that the modulation of a single inflammatory molecule or a single immunologic pathway may not lead to significant clinical benefits in patients with sepsis. Afterwards, the scientific focus shifted towards nonspecific methods of modulating the inflammatory response. A number of extracorporeal approaches to restore an 'immunologic homeostasis' were then studied employing measures of convection, diffusion and adsorption. At the third Acute Dialysis Quality Initiative conference, a consensus statement was achieved in that there seems to exist a clear biological rationale for extracorporeal blood purification treatment (EBP) in sepsis [23] as most molecules of interest are water-soluble and have been demonstrated to fall into the 'middle-molecular weight category' (~5–60 kDa) [23–29]. However, previous reports indicate that conventional continuous renal replacement techniques (CRRTs) remove various inflammatory mediators from the circulation to a minor extent only. This was also observed in a recently published controlled trial [30, discussed in 31] and might indicate that conventional methods provide insufficient means in regard to a biologically relevant reduction of respective mediators.

Today, a biologically relevant reduction of LPS, cytokines (e.g. IL-6)/chemokines (high mobility group box-1; macrophage migration inhibitory factor), activated complement factors (C3a, C5a), coagulation factors, eicosanoids, and leukotrienes are of primary interest in regard to EBP.

Management Strategies: Adjunctive Extracorporeal Treatment in Sepsis

Conventional HF, Immune Mediators and Cellular Immunity in Sepsis

Recently, three major hypotheses were proposed on how CRRT might affect the disequilibrium which can routinely be observed in severe sepsis and septic shock.

First, Ronco et al. [reviewed in 32] proposed the 'peak concentration hypothesis' suggesting an attenuation of the inflammatory response by HF of excess cytokines/mediators spilling over to the circulation during hours of peak production. The attenuation of such peak inflammatory mediator concentrations by CRRT may then beneficially influence the clinical course of sepsis [32]. Nevertheless, Ronco's model does not explain how such attenuated peak concentrations would impact local and interstitial space mediator production. Importantly, a typical standard 'renal intensive care unit HF dose' (~30–45 ml/kg/h) is most likely not sufficient to effectively 'cut off' such peak concentrations. This is supported by the fact that although conventional HF in patients with sepsis leads to the presence of various inflammatory molecules/mediators in the ultrafiltrate, plasma levels of the respective mediators were mostly found unchanged during and following the procedure [24–29]. This was also found in a recently published randomized controlled trial. In this trial, several plasma cytokines were assessed in 18 out of 76 study patients, and the authors found that modifications in plasma cytokine levels may not be achieved using continuous veno-venous HF at a dose of 25 ml/kg/h [30, discussed in 31]. This is supported by data from another controlled trial [33] in which early use of CVVH did not reduce circulating concentrations of several cytokines and anaphylatoxins.

As mentioned above, this may indicate a lack of biological effectiveness of this specific conventional technique. In most investigations, however, cellular immunity was not used as a read-out, indicating that the influence of conventional HF on cellular immunity remains incompletely understood. Furthermore, the role of unspecific effects such as improved volume regulation, temperature control, acid-base status, electrolyte status, correction of uremia, adsorption to filters, and others, remains unclear. However, a successful intervention would most likely require more efficient removal techniques. Extracorporeal techniques with higher mediator clearance capacities such as HF techniques using a high-volume HF (HVHF) approach, techniques employing high-permeable/high cutoff (HCO) membranes, or even more potent approaches such as immunoadsorption or hemoperfusion techniques seem to be required in order to achieve a meaningful and – importantly – clinically/biologically relevant mediator reduction.

The second hypothesis ('threshold immunomodulation hypothesis') was proposed by Honoré and Joannes-Boyau [34]. The threshold immunomodulation hypothesis focuses on the complexity and the nonlinear

properties of inflammatory networks. It thus takes the redundancy of both pleiotropic pro- and anti-inflammatory mediators into account and provides a theoretical explanation why defined inflammatory cascades may still be functioning even if one or a few components are effectively blocked. However, nonselective filtration-based removal of various inflammatory molecules may interrupt a number of defined cascades, and effective depletion of a particular mediator would result in its redistribution from the tissue to the circulation, where it can then be assessed using an extracorporeal treatment technique. The proposed processes are then suggested to continue as far as to a 'threshold point'. The authors of the hypothesis speculate that at this point in time some cascades will shut down. This may attenuate end-organ injury [34]. Nevertheless, although an unselective reduction of various inflammatory mediators may then occur at both the tissue and interstitial space level, it may be regarded difficult to identify whether or not a 'threshold point' has been reached. However, the mechanism by which HF may facilitate mediator flow from the interstitium to the blood compartment remains unexplained by the threshold immunomodulation hypothesis.

Whilst both of the above-mentioned concepts mainly concentrate on the removal of circulating mediators, the 'mediator delivery hypothesis' proposed by J.V. DiCarlo and S.R. Alexander suggests that the kinetics of cytokine removal by HF mostly depend on interstitial mediator washout [35]. In the mediator delivery hypothesis model, the infusion of large volumes of replacement fluid is suggested to drive a dynamic interstitial circulation that delivers both pro- and anti-inflammatory mediators and middle molecular weight molecules from the interstitium via the lymphatic system to the bloodstream [35]. The respective molecules may then be subjected to removal using extracorporeal techniques. Extensive fluid infusion (3–5 l/h) was indeed demonstrated to increase lymphatic flow by about a factor of 20–40 [36]. The mediator delivery hypothesis thus suggests HF to exert a major effect on the lymphatic system rather than on just a 'simple' removal of respective molecules.

With the currently available data, however, it seems impossible to decide which of the above-mentioned models best characterizes the impact of HF-based techniques on patients with severe sepsis and septic shock. All of the three proposed models may contribute to some degree. Nevertheless, it seems reasonable to conclude that the ideal immunomodulatory strategy would both restore the immunologic equilibrium and effectively modulate cell-mediated immunity rather than just unselectively re-

moving or blindly stimulating one or another component of the complex redundant cytokine network.

It may be speculated that the ideal immunomodulatory strategy in sepsis would be an approach that would both allow the selective targeting of key mediators and to reach previously defined target levels of respective mediators. In addition, it seems important that cellular immunity is within the scope of future investigations. Nevertheless, various previously performed anti-cytokine trials in sepsis seem to point to the fact that a total inhibition/removal of e.g. TNF- α should not be the primary goal of an immunological intervention in sepsis, but rather an 'adjustment' of its respective blood levels. Thus, controllability of the target level of the respective mediator may be an important aspect in the future. However, the lessons learned from these sepsis trials suggest that 'adjustment' of a respective target mediator level rather than a simple 'removal' of a respective molecule may be necessary to achieve a 'goal-oriented immunomodulation'. Moreover, in addition to CRRT and its modifications, EBP approaches such as selective adsorption are currently developed and tested for the discontinuous and continuous treatment of septic patients.

High-Volume Hemofiltration

A number of clinical investigations compared convection and diffusion techniques in regard to their effectiveness on the removal of 'middle-molecular' weight molecules and large mediators. It was found that the respective molecules may be more effectively reduced using measures of convection [27, 29, 37]. In order to achieve a significant mediator reduction, however, a membrane of appropriately high permeability, large surface and a sieving coefficient close to 1 for molecules to approximately 60 kDa needs to be employed. Nevertheless, in addition to clearance induced by measures of convection and diffusion, adsorption of respective mediators to synthetic membranes may be considered at least partially responsible for the reduction of the respective molecules [27]. To augment convective clearance, HF rates were increased and HVHF was developed. Later, HVHF was defined as >35 ml/kg/h and filtration rates of up to 215 ml/kg/h were investigated. In a randomized trial including 425 intensive care unit patients with ARF (approximately 13% patients with sepsis), Ronco et al. [38] showed that increasing the CRRT filtration dose to 35 ml/kg/h improves survival (57 vs. 41%, $p = 0.0007$) when compared with a conventional dose of 20 ml/kg/h. Further improvement in survival rates at 15 days after termination of HF was not found in cases of further dose escalation (45ml/

kg/h). In the subgroup of septic patients, however, the highest survival rates were observed in the group treated with the highest filtration dose [38]. A number of non-randomized and mostly uncontrolled HVHF studies in septic patients using filtration doses of around 40–70 ml/kg/h and doses of about 100 ml/kg/h in animals found improvements in hemodynamics and vasopressor need under therapy. Some studies even reported lower mortality rates in the treatment groups [37].

In addition to the higher dose being delivered using constantly high exchange rates (>45 ml/kg/h), higher doses may also be applied via time-limited (usually 6–8 h) ‘pulses’ of HVHF [37]. Nevertheless, mediator removal from the blood compartment via HVHF is generally considered as unsatisfactory [37, 39–41]. The influence of HVHF on cellular immunity remains largely unknown.

HCO Membranes

To improve convective or diffusive clearances of middle molecular weight mediators, membrane pore sizes were increased and HCO membranes developed (cutoff of around 45–100 kDa in human blood, pore size of about 0.1 μm). Several types of HCO membranes of different chemical compositions (polyamid, polysulfone, polyarylethersulfone, cellulose triacetate) have then been tested in a number of ex-vivo and single-center clinical EBP trials [reviewed in 42]. A number of limitations make the interpretation or pooling of the data from respective ex-vivo and clinical trials difficult. First – as mentioned above – different types of HCO membranes were investigated. Moreover, most trials used different modalities of blood purification (hemofiltration, hemodialysis, hemodiafiltration) with different (blood, filtration, dialysate) flows, and different membrane sizes (ranging from 1.1 to 2.2 m^2). Moreover, most trials did not include an adequate control group.

Data on the clinical studies employing HCO membranes include four pilot trials (two uncontrolled trials, one blinded trial) investigating a total of 70 patients with septic ARF at two centers [reviewed in 42]. Nevertheless, the maximum reported IL-6 clearance was 40 ml/min (for HCO-CVVH), and was 42 ml/min for the IL-1 receptor antagonist (IL-1ra). In comparison with controls, a significant reduction in IL-6 and IL-1ra as well as vasopressor need was achieved under HCO treatment [43]. Two other feasibility trials on HCO-CVVH and HCO-CVVHDF did not report data on vasopressor need [44, 45]. Data on the effect of HCO therapy on cellular immunity are very limited. However, when HCO filtrate from

patients with sepsis was incubated ex vivo with mononuclear white cells from healthy volunteers, the proliferation rate of mononuclear cells was found to be reduced [46]. This was not observed in cases of septic patients’ standard filtrates or healthy volunteers’ HCO filtrates being incubated. The authors thus demonstrate that HCO membranes may remove a substance capable of blocking the proliferation of peripheral blood mononuclear cell under ex-vivo conditions.

As a side effect, a cumulative albumin (molecular weight 66 kDa) loss of up to 7.7 g per session was reported under intermittent HCO hemodialysis. Although this might theoretically imply a negative prognostical impact on patients with sepsis, stable plasma albumin levels may be achieved over HCO treatment [44]. However, only few data on the loss of other prognostically important molecules such as coagulation factors exist. Although HCO membranes seem to provide the basis for a more efficient unselective removal of middle molecular weight molecules, the optimal cut-off remains unknown. It remains furthermore unclear whether or not HCO treatment is capable of beneficially modulating cellular immunity. It remains to be elucidated whether this approach will translate into improved clinical outcomes of patients with sepsis.

Adsorption: An Alternative Strategy for Extracorporeal Immunomodulation in Sepsis

An alternative strategy for the reduction of soluble immune mediators and modulation of cellular immunity is provided by adsorption and hemoperfusion technologies. Such strategies employ membranes or surface-bound (mostly polyclonal) antibodies in the extracorporeal circulation in order to achieve a biologically relevant binding and thus removal of respective target mediators. The binding of these target molecules to the surfaces/antibodies is a result of hydrophobic interactions, electrostatic attraction, hydrogen bonding and van-der-Waals forces. Whole-blood-based (hemoperfusion) and plasma-based adsorption techniques can be distinguished. Hemoperfusion techniques usually employ the adsorber in the extracorporeal primary circulation. Plasma-based adsorption techniques (plasmapheresis) require plasma separation i.e. an additional secondary (plasma) circuit. Biocompatibility issues, which have limited this approach in the past, have generally been overcome. The development of such new biocompatible matrices and surfaces now presents new opportunities for the extracorporeal treatment of patients with sepsis and the number of indications for adsorption-based treatment is continuously

rising [47]. One major advantage of this technology is its ability to selectively intervene in defined cascades while being both highly biocompatible and biologically potent.

In sepsis, removal of LPS from the circulation via EBP methods has been considered for a long time. A rather wide variety of materials have been investigated and a number of LPS adsorbers have been developed. Polymyxin B, a neurotoxic and nephrotoxic cationic cyclic decapeptide antibiotic, binds LPS. Polymyxin B was immobilized to polystyrene fibers and septic patients were treated via direct hemoperfusion using this approach [reviewed in 48]. Numerous nonrandomized trials were performed, mostly in Japan. As far back as three decades ago, improved hemodynamic stability under LPS adsorption therapy was reported [49] and recent *in vivo* results may support such findings [48, 50]. A recent systematic review of 28 studies (9 randomized controlled trials) of mostly limited methodological quality indicates that adjunctive direct hemoperfusion using polymyxin B-based LPS adsorption might indeed beneficially influence hemodynamics and vasopressor need [48]. The authors of the respective systematic review calculate a relative risk of 0.53 (95% CI 0.43–0.65) [48]. However, no large-scale randomized trials exist and lower mortality has not been sufficiently demonstrated. In a multicenter randomized study on non-polymyxin B-based LPS adsorption, the primary endpoint (reduction of the APACHE-II score by >4 points after 4 days of therapy) was not found to be influenced under therapy [51]. Other authors confirm these findings in that single LPS adsorption did not improve morbidity or organ dysfunction [52–54].

Nevertheless, immunological interventions require evidence of immunological efficacy. Thus, an immunological characterization of the respective study cohorts seems necessary. Today, this may be regarded as a prerequisite in clinical investigations on the sepsis-induced immunologic disequilibrium. Not to use an immune-guided approach (which should include an assessment of cell-mediated immunity) in EBP trials aiming to reduce soluble immunological mediators may clearly be considered not up-to-date and may be doomed to failure. Unfortunately, the end points chosen in some of the above-mentioned EBP trials do not adequately portray the effectiveness of an immunological intervention. In a prospective controlled pilot trial, we investigated whether selective simultaneous LPS, IL-6 and complement factor C5a immunoadsorption improves monocytic and end-organ function [55] in sepsis. As assessed by the monocytic surface HLA-DR expression, immunoadsorp-

tion resulted in significant improvements in monocytic immunity. The procedure was found to reverse immunoparalysis and this was associated with improvements in hemodynamics and disease severity (as assessed using the APACHE II score) in the treatment group [55].

Despite encouraging initial results of whole-blood-based and plasma-based interventions, the clinical effectiveness of these strategies has not been sufficiently documented so far. Based on the currently available data, these therapies can therefore not be recommended outside of clinical trials.

Conclusion and Considerations for the Future

Severe sepsis and septic shock yield a profound immunologic disequilibrium. Strategies to resolve this immunologic disequilibrium have typically included adjunctive treatment using extracorporeal devices. Following consensus considerations [23], an obvious biological rationale for the use of respective extracorporeal techniques exists. Nevertheless, conventional continuous and discontinuous renal replacement technologies seem insufficient in regard to a biologically relevant reduction of target molecules. Modified renal replacement techniques, high cut-off membranes, and selective and unselective adsorption approaches are currently under research [24–29, 41, 42, 56–60]. Some of these approaches have not only been shown to effectively reduce target molecules, but have also been demonstrated to potentially modulate cell-mediated immunity. In the future, clinical trials on immunomodulation via extracorporeal techniques should comprise an assessment of the study populations' cellular immune status [22]. As of today, a strategy aiming to 'simply' remove a defined redundant pleiotropic mediator may be considered outdated.

Due to insufficient data, numerous questions regarding the approach, the modality, the dose, and the correct timing of EBP strategies in sepsis remain unanswered. In the absence of ARF, however, the use of these adjunctive therapies can currently only be recommended in the context of clinical trials.

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