

## Acute Dialysis Quality Initiative

3<sup>rd</sup> International Consensus Conference

Workgroup 1

Hemofiltration and Hemoperfusion in Sepsis and Septic Shock

*Rinaldo Bellomo\**

*James Matson*

*Claudio Ronco*

*James Winchester*

### Introduction

Extra-corporeal blood purification treatment (EBT) methods including hemofiltration and hemoperfusion have been used in the treatment of experimental and human sepsis and septic shock in a variety of settings and with variable reports of efficacy and safety. Their role in the management of sepsis and related conditions remains controversial.

### Is there a biological rationale for EBT in SIRS/Sepsis?

The systemic inflammatory response syndrome (SIRS) and sepsis are associated with increased blood concentrations of a vast array of immunologically and biologically active molecules (2, 3, 4). Experimental evidence and clinical observations support the concept that these molecules participate in the pathogenesis of organ injury and that their blood levels correlate with severity of illness and outcome (5, 6). Thus, it appears biologically reasonable to seek to test the hypothesis that modulation of this immunological and biological response by removal and/or modulation of a sufficient number of such molecules in a sufficient amount might improve patient outcome. In summary, there is a biological rationale for EBT in SIRS/Sepsis (Level III evidence). However, modulation of inflammation is not the only modulation possible through EBT. Indeed EBT in SIRS or Sepsis might work via a “pleiotropic“ effect (7). It can interfere with cardiovascular compounds in the blood as myocardial depressant factor, endogenous cannabinoids and endothelin and by doing so, it can modify septic shock hemodynamics without interfering with the immunological response to sepsis “per se”. It can affect also directly the coagulation system by affecting the blood concentration of PAI-1 factor (8) and thereby possibly reducing the severity of diffuse intravascular coagulopathy. EBT can also reduce the level of immunosuppression in the latter phase of sepsis (9).

Consensus Statement: The use of EBT in SIRS/Sepsis has a biological rationale and should be investigated with an appropriately designed and statistically powered randomized controlled trial (Grade D). The blinding of those studies will likely be impossible for reasons of safety and could thus complicate the interpretation of any such studies (10).

## Is there current consensus about the use of EBT in SIRS/Sepsis?

There is previously published consensus that the use of EBT in SIRS and sepsis in the absence of acute renal failure (ARF) should be restricted to randomized controlled studies (RCTs) (11). Since this consensus opinion was published, 3 RCTs of EBT for SIRS/Sepsis and not for renal replacement therapy have been conducted. The first was a small multicenter RCT of 30 patients of which 14 were randomized to plasmfiltration and 16 to conventional treatment alone (12). Plasmfiltration was performed by hollow fiber plasma filter continuously for 34 hours. This study showed no difference in mortality or organ failure. The concentration of several mediators was decreased. This study was not sufficiently powered to detect clinically important differences. The second study was a small single-center RCT of 24 septic patients without ARF of which 12 received CVVH at 2L/hr of UF and 12 received conventional treatment. This study showed no effects of CVVH on organ failure, survival or concentration of several immune mediators (13). This study was also not sufficiently powered to detect clinically meaningful differences in survival. Finally, the third trial was a somewhat larger single-center RCT of 106 patients with severe sepsis/septic shock, of which 52 were randomly assigned to conventional treatment and 54 to plasmapheresis. In this study, plasmapheresis was performed by intermittent continuous flow centrifugation. This study showed that patients treated with such therapy had a 33.3% mortality while the control group had a 53.8% mortality ( $p=0.049$  Fisher's exact test) (14). Together with the existing literature, these 3 studies suggest that CVVH at 2L/hr is not likely to be a useful form of EBT in SIRS/Sepsis in the absence of ARF (Level II). The studies of plasmapheresis in SIRS/Sepsis have so far been inconsistent in their findings making evaluation difficult (Level II-III). However, it remains possible that plasmapheresis might offer a clinical benefit and larger multicenter studies of this modality of EBT in SIRS/Sepsis should be considered (see workgroup 2). Nevertheless, in SIRS/Sepsis without ARF, a recent aggregation of animal and human studies showed a large difference between the dose used in human studies (40ml/kg/h) versus that used in animal studies (100 ml/kg/h) (7). Therefore, so far, the dose of blood purification may have been less than that needed to achieve a clinical effect. It is important to note also that in catecholamine-resistant septic shock (even without ARF), it might be extremely difficult to perform a suitably powered RCT. Therefore, this kind of intervention remains confined to Level V evidence and grade E recommendations (15).

Consensus Statement: In SIRS/Sepsis without ARF, there is consensus that conventional-dose CRRT ( $\leq 2$  L/hr of effluent) is unlikely to provide benefit over standard therapy and is a poor candidate for future studies (Grade C). There is consensus that other methods of EBT including high-volume hemofiltration (HVHF), plasma exchange or adsorption and hemoabsorption are perhaps more promising but relatively untested and require further study (Grade E). There is consensus that plasma therapies should also be

further explored to determine the importance of such technical aspects as plasmafiltration vs. centrifugation, continuous versus intermittent therapy, timing, intensity and type of replacement fluid. There is consensus that the existing preliminary data are sufficiently strong to recommend further investigation in the treatment of SIRS/Sepsis in appropriately designed and powered RCTs (Grade C) and that recent literature suggests that at least 35 ml/kg/h of ultrafiltration rate might be needed to optimize EBT (16) in patients with ARF in ICU (with or without sepsis) (Level II evidence and Grade C recommendation) and that possibly even greater ultrafiltration might be needed when dealing with ARF in ICU in the setting of sepsis (Grade E) (16).

### Should patients with Sepsis and ARF be treated differently from patients with other forms of ARF in studies and in practice?

Patients with SIRS/sepsis and concomitant ARF requiring renal replacement therapy (RRT) represent a particular subgroup of patients with SIRS/Sepsis. These patients typically receive one of a group of particular techniques of EBT (intermittent, extended or continuous hemodialysis, peritoneal dialysis, continuous hemofiltration or hemodiafiltration) for the purpose of providing renal support. These techniques are collectively referred to as renal replacement therapies (RRTs). In these patients with combined sepsis and ARF, the choice of EBT technique for renal support might be conditioned by the presence of sepsis. For example, a single centre RCT of 72 adult critically ill patients with ARF and sepsis treated with either CVVH at approximately 20 ml/kg/hr of ultrafiltration or peritoneal dialysis (PD) showed that CVVH was associated with a 15% mortality compared to a 47% mortality with peritoneal dialysis ( $p=0.005$ ) (17). A retrospective controlled study of patients with combined sepsis and ARF compared 40 consecutive patients treated with intermittent hemodialysis (IHD) to 87 consecutive patients treated with continuous hemodiafiltration. This study showed a decreased mortality with hemodiafiltration in those patients with > 4 failing organs from 53.1% to 26.9% (18). A prospective cohort study compared APACHE II and SAPS II predicted mortality to actual mortality in 306 ICU patients, of which 91 were patients with ARF and SIRS/Sepsis. These 91 patients received so-called high-volume HF with a mean UF rate of 63 ml/min as combined RRT/EBT and had a predicted mortality of 76% (APACHE II) and 71% (SAPS II) but an actual mortality of 47% (19). It is important to note that both APACHE II and SAPS scores are inaccurate predictors of mortality in critically ill patients with ARF (20). Collectively, these studies suggest that some forms of RRT might be superior to others in the treatment of ARF in association with sepsis (Level II). In particular CVVH appears to be superior to PD for patients with combined ARF and SIRS/Septic shock (Level II) and continuous hemofiltration might also be superior to intermittent dialysis in such patients (Level IV).

Consensus statement: There is consensus that patients with combined sepsis and ARF should be treated differently. There is consensus that, in adults, CVVH should be considered in preference to PD in patients with combined ARF and SIRS/Sepsis (Grade C) and that CVVH even at 20 ml/kg/h is likely superior to PD

in ARF when sepsis is also present (17). There is consensus that CVVH might be physiologically superior to IHD in sepsis with ARF in the presence of hemodynamic instability (18).

### **What is current practice with EBT in SIRS/Sepsis (with and without ARF)?**

There is limited information on current practice with EBT for SIRS/Sepsis in the presence or absence of ARF and outside of the confines of the 3 RCTs discussed above. Nonetheless, there appears to be some application of EBT to SIRS/Sepsis worldwide. Most of the information available on such uncontrolled use is based on case series and it involves a variety of techniques (21-25).

In some centers and in some patients with combined ARF and sepsis there appears to be a trend toward early and more intensive application of EBT (26). These observations are also based on case series involving a variety of techniques. Thus, EBT is currently used in an uncontrolled way in several centers worldwide (level V).

Consensus Statement: There is consensus that current practice worldwide is extremely variable with regional and center to center variability. No recommendations can be made beyond stating that there is a need for RCTs in this field (Grade E).

### **What kind of SIRS/Sepsis patients should be considered for EBT?**

EBT techniques have been extensively tested in animal models of sepsis and pancreatitis. Such studies show beneficial biological, physiological and clinical effects (27, 28). However, these results have not been adequately demonstrated in appropriate human trials. Accordingly, except for patients with ARF in whom RRT is indicated, EBT is only appropriate within the confines of RCTs. It is important to note, however, that new devices or techniques might be under development or that established techniques might require further technical definition to adapt their application to SIRS/Sepsis. Under such circumstances, their assessment should follow the appropriate pathway of initial ex-vivo and animal studies and subsequent human feasibility and safety studies prior to such RCTs (Grade E).

Pancreatitis may not be a suitable model for EBT. Indeed, most severe acute pancreatitis (SAP) have anti-inflammatory mediators in their bloodstream at the time of diagnosis (29). Yekebas and co-workers, however, have used an animal model of pancreatitis as a model of “pancreatogenic sepsis” and not as model of SIRS (9,28). They were able to show that, when used very early, EBT could dramatically reduce the risk of nosocomial infection and subsequent mortality. In this way, patients with SAP could perhaps benefit from EBT at some stage in the course of this illness.

Consensus statement: There is consensus that patients with severe ARF and SIRS/Sepsis require some form of EBT. Among such patients, some with refractory septic shock may benefit from high volume plasma water exchange. There is no consensus about the need for EBT in patients with severe pancreatitis in the absence of confirmed sepsis.

## What are suitable physiological, biological, biochemical and clinical end points for studies of EBT?

Physiological and biological end points are generally appropriate for early clinical studies (equivalent to phase I and IIa studies in drug evaluation programs). These endpoints help establish the safety of a given technique of EBT. They also help establish a degree of efficacy. Such early clinical studies are never powered to detect differences in clinical outcomes. If positive, they carry a high risk of type I error (false positive). If negative, they carry a high risk of type II error (false negative). Furthermore, such studies tend to be single center studies and their wider applicability remains limited. Nonetheless such studies are necessary to justify larger trials which may have major logistic and cost implications. Case series (Level IV evidence) of patients treated with EBT so far have shown possible effects on cardiac index, systemic vascular resistance, arterial blood pressure, PaO<sub>2</sub>/FiO<sub>2</sub> ratio and pH (24,30, 31). One such study (24) was an uncontrolled “prospective interventional study”. Some biological markers might be particularly useful in reflecting the effect of EBT on the overall functional state of immune cells (monocyte functional assays) (32). Furthermore, among mediators easily measured in blood, IL-6 (6) and procalcitonin (33) appear to show the tightest correlation with clinical outcome and might be particularly useful markers of change in inflammatory response over time (6,33) (Grade D recommendation based on Level IV-V evidence).

For early clinical studies equivalent to phase I and IIa studies in drug evaluation, the first end-point should be improved hemodynamics as many studies have shown this already (34,35,36). Assessment of survival in these small studies is of crucial importance especially for animal studies (27) as well as reduction in cytokine transcription (37). Larger clinical trials are required to test whether a given EBT clinical effects. Such trials are justified if earlier phase trials show significant beneficial physiological or biological effects. Larger clinical trials must be appropriately designed to avoid confounding variables, reflect current conventional practice with regard to associated treatment and achieve sufficient statistical power. These aspects of trial design are fundamental in minimizing the risk of type I and type II errors and maximizing reproducibility and wider applicability.

Consensus statement: Depending on the type of trial, there are numerous possible physiological and biological as well as clinical end points. Some examples are provided in Table 1. These are either in common use or there is consensus for their future use. The use of such end points and their selection must be seen within the context of the trial being conducted. In these larger clinical trials, one has to consider concomitant treatment with new therapies when they reach the “standard of care” (e.g. activated protein C and low-dose corticosteroids).

## What is the available technology for EBT in SIRS/Sepsis?

A large part of the available EBT technology bases its application on membrane separation methods which include hemodialysis, peritoneal dialysis, hemodiafiltration, hemofiltration, high-volume hemofiltration, super-high flux hemofiltration, plasma separation techniques and combination therapies. Current

combination therapies combine membrane plasma separation with plasma adsorption treatment of the separated plasma; treated plasma is then returned to the patients. Intermittent dialytic treatment or peritoneal dialysis have not been applied to the treatment of SIRS/Sepsis per se. On the other hand, continuous hemodialysis, hemofiltration and hemodiafiltration have been used in experimental and human studies (40,41,42). The human literature for the use of such techniques as EBT in SIRS/Sepsis is based on uncontrolled case series (21,22,23,24). Using the fundamental principles and technology of such techniques, various authors have manipulated the volume of ultrafiltrate in an attempt to increase mediator removal and thereby efficacy, giving rise to the various so-called high-volume techniques” (24, 26, 30). Studies of HVHF have shown possible beneficial physiological and clinical effects but remain confined to case series and, so far, provide limited feasibility and safety information (Level IV). Super-high flux membranes (nominal cut-off point of approximately 100 kD) have been developed and tested ex-vivo and in animal models of sepsis (43, 44). They have demonstrated increased sieving of mediators and improved survival in septic animals. No human studies, however, have yet been published. Plasma separation techniques have been more extensively studied in septic humans (12, 14). Their efficacy and effectiveness, however, remain a matter of controversy because no large trials have yet been conducted. Furthermore, from such studies, it appears that more information is needed on which combination of technique, dose, timing and replacement fluid for plasma therapy should be tested in future large clinical trials.

Another approach to EBT in SIRS/Sepsis is based on adsorption, which includes direct hemoperfusion through sorbents or adsorption of separated components of blood. Studies of these approaches have been conducted in animals and have shown promising results (37, 45). However, human studies remain confined to case series (32). The most frequently reported sorbent-based hemoperfusion technique of EBT applied to the treatment of sepsis has been polymyxin B hemoperfusion. The binding of endotoxin by polymyxin B with hemodynamic improvement under experimental conditions has been known for about thirty years (46) and numerous small clinical studies have been published describing its use and effects (47,48,49). The use of the polymyxin B sorbent device as a blood or plasma perfusion device for treatment of human sepsis is currently approved by the Japanese Ministry of Health and used by Japanese intensivists at clinician discretion. The polymyxin B device it is not commercially available outside Japan. Suitably powered RCT's conducted outside of Japan are needed to adequately assess this technology. In patients with combined ARF and sepsis, controlled pilot studies of EBT have been conducted to test the hypothesis that such intervention might have physiological and/or biological effects (13, 32). One such study (13) showed that high-volume HF (6L/hr for 8 hours) decreased complement anaphylatoxins levels in blood and vasopressor requirements in patients with septic shock. Another study of coupled plasmfiltration Adsorption applied for 10 hours to patients with septic shock, showed that vasopressor requirements were also decreased by such EBT and that blood pressure improved, monocyte function was restored and plasma toxicity was attenuated (32). While the level of evidence does not permit any conclusions about efficacy it strongly indicates the need for consistency, standardization and quantification of dose, timing and technical parameters for future applications and investigations of EBT. Importantly, ultrafiltration volume should

probably be at least indexed to body weight (Level IV). Animal studies (27, 32) and case series (24) suggest that higher than conventional doses, which are adjusted for body weight might be more appropriate in patients with severe sepsis. Furthermore it seems biologically and physiologically incorrect to offer the same dose of UF to both a 50 kg and 150 cm woman and a 100 kg and 190 cm man (Level V). Dose might have to be indexed to body weight and severity of disease (50-53).

Consensus statement: Many technologies exist for EBT. They include traditional membrane separation based technology, sorbent-based technologies or combinations of both. It remains unknown which EBT technologies offer the best hope for correct dosing, improved outcomes or offer greater patient safety.

## What are recommendations for future research?

Existing technology used in SIRS/sepsis consists mostly of devices developed for use as RRT or plasmapheresis for non-SIRS/sepsis conditions. As understanding of the pathophysiology of SIRS/sepsis is continuously improving, redesign of existing technology, or design of new technology for specific application SIRS/sepsis may be needed to achieve efficacy and safety.

Consensus statement: Future research should aim to achieve four major goals (Grade E):

1. Develop safer, technically simpler, more efficient and more efficacious techniques of EBT that might increase ease of clinical operation, ensure wider applicability and offer a greater chance of achieving clinical effectiveness.
2. Develop greater understanding of the biology of SIRS/Sepsis with the identification of molecular targets for EBT. This should allow better design of new EBT technology or modification of existing EBT technology for the specific purpose of controlling dysfunctional immune system activity in SIRS/sepsis.
3. Ensure that appropriately designed and suitably powered trials of EBT be conducted to test the clinical effectiveness of these therapies in patients with SIRS/sepsis.
4. Ensure that trials be conducted with indexing of exchange volumes to body size (e.g. dose adjustment), with attention to controlling or analyzing the effect of time delay from SIRS/sepsis onset to initiation of treatment, use of consistent duration of treatment, and use of consistent EBT technology. Reports should contain specific and detailed information on all important elements of the study or trial and of the EBT devices and methods used. In contrast to some studies involving new medications, clinicians should have sufficient expertise in the use of EBT technologies before embarking in a large study. The “learning curve” effect will be much longer compared with most medications. Every center participating in those studies should possess the proper technology to perform it and should also possess sufficient expertise before embarking.

**Table 1. Possible End-points for Initial Studies of EBT.**

<b>Physiological and biological end points</b>	<b>Report patient characteristics</b>
Improved hemodynamic profile	Survival ...to hospital discharge ...at 28, 60 or 90 days
Decreased need for vasopressor drugs	Dialysis-independent survival
Blood levels of mediators	Duration of ICU/hospital stay
Improved vital signs	Organ dysfunction-free days
Improved cardiopulmonary function	ICU-free days
Acid-base homeostasis	Total costs
Improved markers of renal function	Relationship between improved hemodynamic response, survival and immunological changes(38)
Improved immune cell responsiveness (e.g. endotoxin)	
Decreased cell toxicity of plasma	



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**Authors:**

In alphabetic order.

Rinaldo Bellomo, MD. Dept. of Intensive Care, Austin & Repatriation Hospital, Melbourne, Australia.  
Email: [rb@austin.unimelb.edu.au](mailto:rb@austin.unimelb.edu.au)

James Matson, MD. Immunocept, LLC. Dallas, Texas. Email: [jmatson@immunocept.com](mailto:jmatson@immunocept.com)

Claudio Ronco, MD. Department of Nephrology, St. Bortolo Hospital; Vicenza, Italy. Email: [cronco@goldnet.it](mailto:cronco@goldnet.it)

James Winchester, MD. Division of Nephrology & Hypertension, Beth Israel Medical Center  
New York, NY. Email: [jwinches@bethisraelny.org](mailto:jwinches@bethisraelny.org)

**Consultant:**

Patrick Honore, MD. Intensive Care Unit, St-Pierre Para University Hospital, Ottignies, Belgium. Email : [pa.honore@clinique-saint-pierre.be](mailto:pa.honore@clinique-saint-pierre.be)