Commentary

# Hemofiltration in sepsis: where do we go from here?

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## Abstract

Hemofiltration as an adjunct to therapy for sepsis is now 10 years old. Despite early successes and significant theoretical advantages, the treatment remains experimental. Although feasibility has been established, efficacy has proved to be much more difficult. Clinical as well as technical difficulties remain important considerations to future studies. These issues are discussed and the brief history of hemofiltration in sepsis is reviewed.

**Keywords:** continuous venovenous hemodialysis, continuous venovenous hemofiltration, hemofiltration, multiple-organ failure, sepsis, systemic inflammatory response syndrome

A decade has past since Stein *et al* [1] first described an improvement in hemodynamics associated with hemofiltration in the pig after the administration of intravenous endotoxin. A short time later these findings were confirmed by Grootendorst *et al* [2], who also found that the ultrafiltrate removed from endotoxemic animals produced hemodynamic instability in healthy animals when it was infused intravenously [3]. Around this time, Lee *et al* [4] reported a survival benefit associated with hemofiltration in septic pigs, and Bellomo *et al* [5] showed that some of the interleukins and tumor necrosis factor could be removed from the circulation of humans with sepsis. With these advances, blood purification as a treatment for human septic shock was born. Despite its promising start, however, hemofiltration as a treatment for sepsis has been slow to mature.

There are numerous reasons for this stunted growth. First, several pharmacologic agents are more effective than hemofiltration in reducing serum cytokine activity, and yet none have been shown to produce a survival benefit. Indeed, several spectacular failures have occurred as a result of attempts to modulate the inflammatory response in sepsis, occasionally even resulting in increased mortality [6]. Another reason is that 10 years ago our concepts of sepsis were different. Sepsis was viewed as a condition in which the local inflammatory response had become generalized and uncontrolled. Immune effector cells, especially neutrophils, possess potent cytotoxic capacity, and when unchecked this response can cause significant tissue injury. More recently, however, we have come to appreciate that although this is true, sepsis is also a syndrome of immune suppression. Immune effector cells become dysfunctional and are no longer capable of normal immune surveillance. Such a condition results in increased susceptibility to recurrent infection, prolonged inflammation, and continued tissue injury. Therapy aimed at reducing the inflammatory response by removing some of the proinflammatory stimuli may not restore immunologic balance, and thus may not improve outcome. Finally, sepsis may not be a form of intravascular inflammation as originally thought, but rather may be a disseminated local inflammation in which the actual process occurs at the tissue level, and that which appears in the circulation is only the 'spill-over'.

CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis.

For these reasons, the ideal immune-modulating strategy would be one that restores immunologic stability, rather than blindly inhibiting or stimulating one or another component. Such a strategy would counter the immunologic instability of sepsis, perhaps by reducing the activity of a wide array of both proinflammatory and anti-inflammatory molecules. Such a strategy would 'autoregulate' itself, such that as one component of the response increased, so too would the effect on that component. Finally, the ideal strategy might well be limited in its effect to the circulating pool of mediators, rather than influencing the tissue levels where their activity may be beneficial. In theory, hemofiltration fulfills this ideal paradigm. Indeed, hemofiltration is perhaps the only available treatment strategy that can, in theory, achieve all of these goals.

Technical considerations must also be taken into account when assessing the current performance as well as the potential of blood purification therapies in sepsis. Not all hemofiltration modalities are the same. Continuous venovenous hemofiltration (CVVH) at 2 l/h of plasma water exchange is very different from continuous venovenous hemodialysis (CVVHD) with pure diffusive clearance when it comes to middle molecular clearance [7,8]. Adding 500 ml/h convective clearance will also yield a very different pattern of blood purification and very different effects. Clinicians need to understand that these 'technical' differences matter a great deal. Current membranes also differ very much from one another in their adsorptive capacity for mediators (ie not all membranes are created equal) [9]. Importantly, even with optimal membranes and convective clearance at 2 l/h we may be operating at inadequate levels of blood purification to meet the goal of restoring immune balance during severe sepsis. High-volume hemofiltration may be necessary to achieve degrees of blood purification that can make a predictable clinical difference [10]. Furthermore, cytokine clearance is still suboptimal with current membranes, and higher porosity devices need to be tested. If one uses plasmafilters to overcome the problem of limited porosity, one has to deal with the extraordinary logistics of continuous plasma exchange. Even when such problems are overcome for 48 h [11], the results are not impressive, possibly because clearances remain relatively low (20–30 ml/min). Presently, the cost of such plasma exchange therapy is also prohibitive. The use of plasmafiltration with sorbent technology may be another cost-effective and efficacious way of approaching this problem. Such coupled filtration–adsorption appears to restore *in vitro* monocyte responsiveness to endotoxin and to remove cytokines with high efficiency [12]. Thus, quite apart from conceptual issues of whether blood purification is a rational approach to sepsis treatment, there are major technical matters that need to be properly addressed if we truly wish to test the hypothesis that blood purification has a role as adjunctive management in sepsis.

In addition, testing this hypothesis will require the development of better tools to accurately assess the impact of 'broad-spectrum' immunomodulation on the inflammatory response. Sepsis and multiorgan failure are complex syndromes and the determinants of mortality in patients suffering from these syndromes are usually multifactorial. Very large randomized trials, perhaps enrolling thousands of patients, will be necessary to establish the efficacy of any therapy. Before these trials are established, however, it is necessary to understand whether hemofiltration has the capacity to affect the immune status of patients in beneficial ways. The first few steps in this process have already been achieved. Hemofiltration can remove a wide array of inflammatory mediators from the circulation [13,14]. To date, more than 30 studies have shown that cytokines and other small soluble molecules can be removed using this technique, although the size of the effects and the mechanisms (sieving versus adsorption) are still in question. Next, it has been established in both humans [8] and animals [15] that hemofiltration can alter the circulating concentrations of some mediators. The next logical step is to determine whether these alterations in the plasma produce beneficial effects on immune effector cells.

The study by Toft *et al* [16] in a recent issue of *Critical Care* is the first attempt to investigate the effects of hemofiltration on the activation status of leukocytes. The authors examined a panel of adhesion molecules, including CD11b, on the surface of granulocytes and lymphocytes, in order to assess their activation status, but were unable to find any effects of hemofiltration, save for the uncertain finding that the percentage of $CD3^+$ T cells increased over time. Unfortunately, their study design is reminiscent of many earlier studies, which also failed to show any important immunologic effects of hemofiltration. First, and most importantly, the study is uncontrolled. The immune status of patients with sepsis is not static. The activation status of leukocytes, like the circulating level of any given inflammatory mediator, varies with time. Without controlling for the effects of time, we cannot expect to discover what effect, if any, hemofiltration exerts on the immune status of the patient. Secondly, Toft *et al* used a less than ideal form of therapy. Although they did use AN69 membranes, they used CVVHD (actually continuous venovenous hemodiafiltration with very low-dose ultrafiltration). Because most of the mediators of inflammation are not removed to a significant degree, if at all, by diffusion, it is not surprising that this study was negative. Finally, even if the study had been controlled, the small sample size would make the study very difficult to interpret. Baseline heterogeneity was large for most of the key variables and therefore it would be difficult to compare individual patients. Thus, although Toft *et al* [16] set out in the right direction, their methods were inadequate to answer the important questions they were attempting to address.

It is hoped that future studies will not repeat the mistakes of the past. Hemofiltration may one day have a place in the management of sepsis and multiorgan failure. Then again it may not. The only way to tell will be to conduct carefully controlled studies designed to evaluate the effects of this therapy on immune effector cell function. If these studies prove that hemofiltration has the potential to be useful, as suggested by animal experiments, then large randomized studies comparing survival will be warranted. Even before this point is reached, however, clinicians who care for critically ill patients with sepsis and renal failure will need to decide whether hemofiltration or hemodialysis is the most appropriate therapy. This decision has traditionally been made on the basis of the hemodynamic stability of the patient. The results of the study by Toft *et al* [16], which albeit was small and uncontrolled, suggest that immunologic stability should also be considered. Although the study failed to show any change in immunologic status with CVVHD, other studies [17,18] have shown adverse immune consequences of intermittent hemodialysis. Studies that compare intermittent with continuous therapies are urgently needed, in hemodynamically stable patients, in order to understand what effects these therapies may have on immune function.

## References


1. Stein B, Pfenninger E, Grunert A, Deller A: **Influence of continuous haemofiltration on haemodynamics and central blood voulume in experimental endotoxic shock.** *Intens Care Med* 1990, **16**:494–499.
2. Grootendorst AF, van Bommel EF, van der Hoven B, van Leengoed LA, van Osta AL: **High volume hemofiltration improves right ventrictular function in endotoxin-induced shock in the pig.** *Intens Care Med* 1992, **18**:235–240.
3. Grootendorst AF, van Bommel EF, van Leengoed LA, *et al*: **Infusion of ultrafiltrate from endotoxemic pigs depresses myocardial performance in normal pigs.** *J Crit Care* 1993, **8**:161–169.
4. Lee PA, Matson JR, Pryor RW, Hinshaw LB: **Continuous arteriovenous hemofiltration therapy for *Staphylococcus aureus*-induced septicemia in immature swine.** *Crit Care Med* 1993, **21**:914.
5. Bellomo R, Tipping P, Boyce N: **Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients.** *Crit Care Med* 1993, **21**:522–526
6. Fisher CJ Jr, Agosti JM, Opal SM, *et al*: **Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein.** *N Engl J Med* 1996, **334**:1697–1702.
7. van Hamersvelt HW, Eggenhuizen E, Hejinis G, van Prooijen S, Huysman FTh: **Convective and diffusive clearance of large molecules during continuous veno-venous hemodiafiltration [abstract].** *J Am Soc Nephrol* 1999, **10**:198A.
8. Kellum JA, Johnson JP, Kramer D, *et al*: **Diffusive versus convective therapy: effects on mediators of inflammation in patients with severe systemic inflammatory response syndrome.** *Crit Care Med* 1998, **26**:1995–2000.
9. Lonneman G, Koch KM, Shaldon S, Dinarello CA: **Studies on the ability of hemodialysis membranes to induce, bind and clear human interleukin-1.** *L Lab Clin Med* 1988; 112:76–86.
10. Bellomo R, Bladwin I, Cole L, Ronco C: **Preliminary experience with high volume hemofiltration in human septic shock.** Kidney Int 1998, **53 (suppl 66)**:S182–S185.
11. Reeves J, Butt WW, Shann F, *et al*: **Continuous plasmafiltration in sepsis syndrome.** *Crit Care Med* 1999, **27**:2096–2104.
12. Tetta C, Bellomo R, Brendolan A, *et al*: **Use of adsorptive mechanisms in continuous renal replacement therapies in the critically ill.** *Kidney Int* 1999, **56 (suppl 72)**:S15–S19.
13. Kellum JA. **Immunomodulation in sepsis: the role of hemofiltration.** *Minerva Anesthesiol* 1999, **65**:410–418.
14. Bellomo R: **Continuous hemofiltration as blood purification in sepsis.** *New Horizons* 1995, **3**:732–737.
15. Bellomo R, Kellum JA, Gandhi C, Pinsky MR: **The effect of intensive plasma water exchange by hemofiltration on hemodynamics and soluble mediates in canine endotoxemia.** *Am J Respir Crit Care Med* 2000 (in press).
16. Toft P, Kehler D, Brandslund I, Tonnsen E: **The immunological effects of continued veno-venous haemodiafiltration in critically ill patients.** *Crit Care* 1999, **3**:159–165.
17. Alkhunaizi AM, Schrier RW: **Management of acute renal failure: new prospectives.** *Am J Kidney Dis* 1996, **28**:315–328.
18. Braun N: **Expression of adhesion molecules and activation markers on lymphocytes and monocytes during hemofiltration.** *Blood Purif* 1997, **15**:61–76.


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