Continuous Hemofiltration in 2009: What Is New for Clinicians Regarding Pathophysiology, Preferred Technique and Recommended Dose?

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Key Words

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Abstract

In the last years, publications have questioned the classical dose of 35 ml/kg, but are those studies strong enough in terms of scientific power in order to change our practice? We will try to settle some recommendations for clinicians. Manipulation of dose, porosity, and combinations have yielded promising findings. However, conclusive evidence based on randomized trials remains scarce, limiting the practical implementation in daily practice. From the few designed studies, it is safe to say that optimization of delivered dose has a proven positive effect. An ultrafiltration rate of around 35 ml/kg/h, with adjustment for predilution, can be recommended for the septic patient. Recent studies do not have enough power to change this recommendation in view of its shortcomings. Finally the recommendation is to keep going with a continuous technique, a pure continuous veno-venous hemofiltration mode, and at a dose of 35 ml/kg/h while waiting for other studies to be published.

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Introduction

In the last years several publications have questioned the so-called classical dose of 35 ml/kg, but are those studies strong enough in terms of design and scientific power in order to change our practice? We will try to review all the data and set some recommendations for clinicians. In the past, continuous hemofiltration was often provided as 1,000 ml/h. Nevertheless, practice began to change as results from new studies were published in the early 2000s demonstrating a beneficial effect on outcome of increasing the ultrafiltration rate to 35 ml/kg/h in patients with acute kidney injury (AKI). Two methods of high-volume hemofiltration (HVHF), with different underlying concepts and results, have become prevalent: continuous high-volume hemofiltration (CHVH) providing 50–70 ml/kg/h 24 h/day, and intermittent high-volume hemofiltration (IHVH) with brief, very high-volume treatment at 100–120 ml/kg/h for 4–8 h (previously called ‘pulse’ HVHF). Two recently published studies highlight the crucial role of an adequate dosage of continuous veno-venous hemofiltration (CVVH), demonstrating that, in critically ill patients with renal failure, a dose of 35 ml/kg/h was associated with a dramatic improvement in survival of nearly 20% [1, 2]. The incorporation of the results from these studies into daily clinical practice can now be deemed to be urgent, although the

results of other ongoing confirmatory (or not) studies are awaited. In a world increasingly guided by evidence-based medicine, two level-I studies lead to a grade-A recommendation, and this intervention should, therefore, be applied by every intensivist instigating continuous hemofiltration, while awaiting the results of the ongoing studies. For a number of reasons that we will explain, the results of the so-called VA/NIH study cannot be applied outside the US [3]. Nevertheless, the implementation process is prone to a number of potential difficulties. These encompass items such as blood flow requirements, vascular access problems, pre- and postdilution policy, type of membranes used, as well as restitution fluid, and the possible need for associated dialysis. Implementation of these findings will necessitate a collaborative network between medical staff members and the entire nursing staff.

New Pathophysiological Insight: Hemofiltration Can Be Seen as a 'Cure' against the 'Chaos Theory' and 'Complex Nonlinear Systems' in Sepsis

Hemofiltration was first used in AKI, which is an independent factor for increased severity of illness and poor outcome in critically ill patients. Early studies have shown that the mortality rate of patients requiring renal replacement therapy (RRT) for AKI in the ICU was nearly twice as high compared to those without AKI (62.8 vs. 38.5%) [4, 5]. This suggests, therefore, that AKI is independently responsible for increased mortality, even if RRT is used. In fact, while standard RRT significantly reduced mortality in patients with AKI in comparison with mortality rates before RRT was used, mortality rates were still not as low as in patients without AKI. The new concept of 'purification plasma challenge' was then developed to try to decrease mortality. The systemic inflammatory response syndrome (SIRS), sepsis and septic shock, and acute pancreatitis are known to be the leading causes of AKI in ICU patients, creating an immunologic disturbance with a cytokine storm. Sepsis and inflammatory pathologies disrupt homeostasis with a cellular and humoral response, generating secretion of cytokines such as interleukins and tumor necrosis factor (TNF)- α . Over the years, many attempts have been made to block some parts of the inflammatory cascade or to destroy specific components; some positive results were obtained in animal models, but were not translated into clinical benefit [6]. It has been suggested that a large and nonspecific reduction in cytokines in the blood compartment could in

theory reduce mortality more than simply concentrating on removing or blocking one specific element [7]. However, this approach is complicated by the fact that neither the pharmacodynamics nor the pharmacokinetics of cytokines and other immune components are well known, not even their precise functions. Some of the leading theories in this field are provided by current experts in hemofiltration. First, the 'peak concentration hypothesis' of Ronco et al. [8, 9] postulate that removing the peak cytokine concentration from the blood circulation during the early phase of sepsis could stop the inflammatory cascade and the accumulation of free cytokines, which are the leading cause of organ damage and homeostasis disruption.

The second concept is called the 'threshold immunomodulation hypothesis', also called the 'Honoré' concept [10, 11]. In this concept, the removal of cytokines not only affects the cytokine concentration in the blood stream, but also in the tissues. Indeed, when cytokine concentrations are reduced in the blood, blood and tissue concentrations may equilibrate to remove the immune components trapped in the organs. This could explain why no crucial reduction in cytokine concentration is observed in the blood stream during hemofiltration, because cytokines from the organs permanently replace those lost in the blood. The third theory, proposed by Di Carlo and Alexander [12], sheds new light on the mediator delivery hypothesis, in which the use of HVHF with a high volume of crystalloid fluids (3–5 liters/h) is able to increase the lymphatic flow by 20- to 40-fold [13]. Indeed, this increase is correlated with the infusion of a high dose of fluids. Since cytokines and other immune components are transported by the lymphatic stream, this could explain their removal even though large amounts of cytokines are not found in ultrafiltration fluid [14]. Thus, the use of high volumes of exchange fluid might be the principal motor of cytokine removal.

To achieve a wider view of these theories, we need to explore the new paradigm of chaos and 'complex nonlinear systems' in sepsis and SIRS [15]. The principal goal underlying these theories is not only removal of cytokines but also immunomodulation and control of the inflammatory response, which becomes deleterious when it surpasses its designed purpose. Indeed, the immune response of the host against septic aggression could be compared to a complex nonlinear system which is defined by the infinite number of possible actions in response to a lone stimulus. In a complex nonlinear system, e.g., the situation by which a flight of butterflies in China can change the weather in Boston 3 days later, a bacterial

attack or cytokine secretion will have repercussions in the whole body. This explains why homeostasis is not a state of stability per se but rather the ability to stay stable while the status is permanently changing. Yet this incredible adaptability is halted when the system is drowned by an excess of information and when the 'endocrine effect' of cytokines and other immune messages are lost in the storm [16, 17]. The resources of the body system become depleted, and the complex nonlinear system becomes a linear system, with only one course of action. This heralds the onset of multiple organ dysfunction syndrome. It may be that hemofiltration could play a role at this point by decreasing the cytokine storm and by allowing the efficacy of the immune messages to be recovered. Thus, the system's own resources increase, allowing a return of the complex nonlinear system and homeostasis.

Which Technique Is Best: Increasing Volume or Increasing Porosity?

In the setting of the peak concentration hypothesis, techniques that remove cytokines or mediators from the blood compartment more rapidly and substantially are favored. Intrinsically, both convective and diffusive techniques are able to clear the blood compartment of mediators. However, in both the threshold immunomodulation hypothesis and the mediator delivery hypothesis, effects are brought to bear outside the blood compartment in the interstitium and at the tissue level, while in the mediator delivery hypothesis, a high-fluid replacement rate is obligatory. Prominence is then given to HVHF (and possibly very HVHF) techniques as well as to a number of hybrid techniques using high-fluid replacement, though as yet these conclusions remain speculative [18, 19]. It is reasonable to assume that some forms of extracorporeal removal, such as high-flow hemofiltration, could dramatically increase lymphatic transport of mediators and cytokines from the tissues and interstitial space to the blood compartment for potential removal. Other forms of extracorporeal removal, such as high-permeability hemofiltration (HPHF) or coupled plasma filtration and adsorption (CPFA), with the capacity to remove larger amounts of mediators and cytokines from the blood compartment are, in their present form, unable to increase lymphatic flow and, as a consequence, are unable to mobilize crucial cytokines and mediators at the interstitial and tissue level (where they do harm) [20]. This fact can go some way to explaining why, despite high hopes, some recent studies with these techniques have been shown to

be ineffective in improving hemodynamics and survival in animal models for acute sepsis [11]. Despite the complexity of the rationale for mediator removal, it seems sensible that increasing filter porosity would have an overall beneficial effect [21]. More sophisticated techniques, such as HPHF, super high-flux hemofiltration, and hemo-adsorption, are favored in this context as many mediators have a high molecular weight. Although these techniques likely remove more substantial amounts of these larger mediators from the blood compartment, the repercussions of this at the tissue level remain unclear. Furthermore, many important nutrients, hormones, drugs, in particular antibiotics, and unknown metabolites may also be lost. For this reason investigators have chosen to use hybrid techniques, utilizing some of the advantages of the different techniques, whilst avoiding some of the more obvious drawbacks. Indeed, because a large portion of treated blood is returned to the patient, both CPFA and cascade hemofiltration [19, 22] are able to retrieve large amounts and large molecules without risking the loss of important nutrients. In theory, further development of hybrid techniques, such as cascade hemofiltration and CPFA, will one day offer the possibility of optimal and precise targeting of molecules, with negligible loss of beneficial molecules. We should also be aware of a completely neglected domain in the filter porosity 'spectrum'. At present, most activity is concentrated at either end of the molecular spectrum. At the lower end, HVHF and derived techniques seek to modify concentrations of molecules below 45 kDa, whereas at the higher end, in plasma filtration, molecules of around 900 kDa are targeted. The domain in between begs attention both from clinicians and investigators and remains largely neglected at present. Studies utilizing high cutoff hemofiltration (filter cutoff at 60 kDa), demonstrating better filter clearance of some mediators, are a first small step in the right direction [21, 23]. As a consequence of this new knowledge, clinicians should be aware of these new insights regarding the rationale for extracorporeal removal in severe septic shock, thereby enabling them to make well-informed choices regarding adjunctive treatment for severe septic shock at the bedside.

Which Mode of (C)RRT and Which Dose Are Superior?

In clinical practice, it is safe to say that dose most definitely plays an important role, despite the fact that no mode of RRT is superior [24]. Both in the paper published

Table 1. Summary of the most important studies on CRRT in sepsis or SIRS AKI during the last decade

Reference year of publication	Number of patients	Clinical setting	Design	Dose ml/kg/h	Improved survival	p
Bouman et al. [30], 2002	106	SIRS, ARF, MOF	RCT	48	No	0.8
Jiang et al. [31], 2005	37	SAP, sepsis	RCT	54	Benefit of Ob vs. Ex Morta	<0.05
Laurent et al. [32], 2005	61	OHCA, MI, SIRS	RCT	200	Yes	0.018
Oudemans-van Straaten et al. [33], 1999	306	SIRS, shock, ARF	P, cohort, UNC	65	Benefit of Ob vs. Ex Morta	<0.05
Piccinni et al. [34], 2006	80	Septic shock, ARF, ALI	R, UNC	45	Benefit of Ob vs. Ex Morta	<0.05
Honoré et al. [35], 2000	20	Refractory septic shock	P, cohort, UNC	115	Benefit of Ob vs. Ex Morta	<0.05
Honoré et al. [36], 2006	38	Refractory septic shock	P, cohort, UNC	100	Benefit of Ob vs. Ex Morta	<0.05
Cornejo et al. [37], 2006	20	Refractory septic shock	P, cohort, UNC	100	Benefit of Ob vs. Ex Morta	0.03
Joannes-Boyau et al. [38], 2004	24	Abdominal refractory septic shock	P, cohort, UNC	60	Benefit of Ob vs. Ex Morta	<0.05
Ronco et al. [1], 2000	425	ICU-ARF	RCT, subgroup	45	Yes	<0.05

P = Prospective; R = retrospective; UNC = uncontrolled; RCT = randomized controlled study; ALI = acute lung injury; ARF = acute renal failure; Benefit of Ob vs. Ex Morta = benefit of observed versus expected mortality in a prospective cohort uncontrolled study; ICU = intensive care unit; MI = myocardial infarction; MOF = multiple organ failure; OHCA = out-of-hospital cardiac arrest; SAP = severe acute pancreatitis; SIRS = systemic inflammatory response syndrome.

by the ADQI group and in the more recent guideline [25, 26], an effluent rate of at least 35 ml/kg/h is recommended in continuous RRT (CRRT). In intermittent hemodialysis, a similar dose corresponds to a single pool Kt/V of 1.4/day, implying the need for daily intermittent hemodialysis if this mode is chosen [27]. Currently, the dose recommendations apply to all critically ill patients with acute renal failure whether it is secondary to sepsis or not. In classic hyperdynamic septic shock, especially accompanied by acute septic renal injury or acute septic renal failure based on the risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure (RIFLE) classification [28], the results of a number of dose outcome studies (the RENAL study in Australia and New Zealand, and the IVOIRE study in Europe) are awaited with interest [29]. One of the two dose outcome studies (the RENAL study) is not restricted to acute septic injury, including also patients with nonseptic renal failure. The IVOIRE study has the potential to provide us with important insights for the future, hopefully giving us further tools to determine optimal dosing in subgroups of septic patients with acute renal injury. More than 480 ICU patients with septic shock plus acute renal injury as defined by the RIFLE classification will be included. After computer randomization into 2 groups, 1 group will receive standard vol-

ume hemofiltration (35 ml/kg/h) and the other early HVHF (70 ml/kg/h). In the light of the findings of the study by Ronco et al. [1], whereby septic patients in the 45-ml/kg/h group tended to have better survival, this study was designated to demonstrate an increase in overall survival in the higher dose group (70 ml/kg/h). This study is now fast approaching its first interim analysis [29]. In order to give a better overview regarding the studies looking at CRRT and dose mostly in septic AKI, we summarized the positive and negative studies (table 1). Ranking of studies was done according to their level of evidence, choosing the ones which had the most scientific merit in terms of design and number of patients included [30–38].

Strategy Regarding Technique, Dose and Mode Revisited via the Prism of Recent Studies

Studies have shown benefits in terms of survival when 'early' and 'large' hemofiltration doses were applied in septic animals. Early use of hemofiltration has been thoroughly investigated in animal models [39, 40]. In most of the earlier studies, hemofiltration was used before or just after the injection of a bolus or even before the infusion of endotoxin. It was only in the late 1990s that investiga-

tors started to wait about 6–12 h before using HVHF after a sepsis challenge, thereby ‘allowing’ the animals to become extremely ill, hemodynamically unstable, and to develop early multiple organ dysfunction before starting hemofiltration [41]. In this way, animal models were able to ‘mimic’ some aspects of the clinical situation. Only animal models in which HVHF was applied early proved to be very beneficial (some spectacularly), mainly due to the fact that in addition to early application the investigators administered a much ‘stronger’ dose of HVHF. However, the differences between human and animal models do not allow these results to be extrapolated to humans. One of the greatest remaining problems with human studies (and especially the mechanistic studies) is the fact that the number of patients is very limited since the technique is so expensive. Moreover, clinical studies have fallen far short of the mean exchange obtained in animal models (only 40 vs. 100 ml/kg/h in animal studies) [42]. As a consequence, many effects seen in animal models can never be reproduced in human settings owing to the use of inadequate doses of HVHF. On the other hand, there is huge variability between clinical trials concerning the range of doses applied, ranging from 1- to 15-fold in recent studies [42]. The foundations of the high-volume technique were laid by Ronco et al. [1] who showed that, in their subgroup of sepsis patients, increasing the volume of treatment from 35 to 45 ml/kg/h could improve outcome. That study effectively demonstrated that hemofiltration could be considered as a viable medication in the ICU. The volume of treatment not only has to be adapted to body weight but also to the severity of illness of ICU patients. If nonseptic acute renal failure is being treated, then a lower dose may be optimal; however, a septic patient with AKI may need a higher dose close to 50 or 70 ml/kg/h and perhaps even higher or with different modalities for catecholamine-resistant septic shock, refractory hypodynamic septic shock, or even acute severe pancreatitis. At the end of the 1990s, Journois et al. [43] used HVHF (100 ml/kg/h) in 20 children during cardiac surgery and reported a reduction in postoperative blood loss, earlier extubation time, and reduced cytokine plasma levels. The first large study using pulse HVHF, at about 100 ml/kg/h for 4 consecutive h (then 35 ml/kg/h), was in 20 septic patients with refractory hypodynamic shock [35, 44]. In this study, pulse HVHF-treated patients had dramatically increased survival compared with classical treatment. The observed mortality (55%) was significantly lower than that predicted by two severity scores (79%). However, some patients were hemodynamic non-responders (9/20) with disastrous mortality rates. At the

same time, a monocentric study by Oudemans-van Straaten et al. [33], with a prospective cohort design of mainly cardiac surgery patients with oliguria (306 patients), showed an observed mortality that was statistically lower in the group treated by intermittent HVHF with a mean volume of 3.8 liters/h (nearly 50 ml/kg/h for a 70-kg patient) than the predicted mortality evaluated by three validated severity scores. Studies in the early 2000s concentrated on effects on hemodynamic response and cytokine removal; for example, Cole et al. [45] showed interesting hemodynamic improvement in septic patients treated by HVHF. Recently, Cornejo et al. [37] in South America did a study similar to that by Honoré et al. [35] and obtained comparable results. They created an algorithm based on the international recommendations for sepsis treatment and incorporated intermittent HVHF (100 ml/kg/h for a single 12-hour period) as a salvage therapy for patients in refractory septic shock [37]. However, as in the study by Honoré et al. [35], although the observed mortality (40%) was lower than expected (60%), there was also a responder and a non-responder group. In contrast, Joannes-Boyau et al. [38] studied the effect of HVHF at 50 ml/kg/h maintained for 96 h in patients with septic shock and multiple organ dysfunction syndrome, and found that, although results in terms of mortality were comparable to those in previous studies (45% observed vs. 70% predicted), all the patients were hemodynamic responders. A retrospective study by Piccinni et al. [34] recently reported the same results with HVHF maintained at 45 ml/kg/h in 40 septic patients, in comparison with a historical group who were treated by standard CVVH. Finally, a prospective study by Ratanarat et al. [46] confirmed the earlier results of Honoré et al. [35] and Cornejo et al. [37], with a similar protocol of pulse HVHF (85 ml/kg/h for 6–8 h) in 15 septic patients with multiple organ dysfunction syndrome. All these studies were only single-center, non-randomized and uncontrolled, but they all showed the same results and proved that HVHF can be delivered safely. The sole difference in results among the studies is in the occurrence of hemodynamic responders and non-responders in studies using intermittent hemofiltration which was not reported in studies using the continuous method. A single study comparing HVHF with standard CVVH was conducted by Bouman et al. [30]: 106 patients were randomized into 3 groups: early HVHF (within the first 12 h of AKI), early standard CVVH, and late standard CVVH. There were no differences in terms of 28-day mortality or recovery of renal function, but no statistical conclusions could be drawn owing to the lack of power, with only 35 patients in each

Table 2. CRRT dose adapted to body weight at constant blood flow of 300 ml/min

Body weight, kg	Total dose 35 ml/kg/h	Predilution 1/3 total dose	Postdilution 2/3 total dose	Qs = 300 Qs fixed
50	1,800	600	1,200	FF 13%
55	1,900	600	1,300	
60	2,100	700	1,400	
65	2,300	800	1,500	
70	2,400	800	1,600	
75	2,600	900	1,700	FF 17%
80	2,700	900	1,800	
85	3,000	1,000	2,000	
90	3,200	1,100	2,100	
95	3,300	1,100	2,200	
100	3,500	1,200	2,300	
105	3,700	1,200	2,500	
110	3,900	1,300	2,600	
115	4,000	1,300	2,700	
120	4,200	1,400	2,800	

group. Indeed, the very specific patient population, most coming from cardiac surgery, perhaps explains the low mortality rate, making the possibility of finding any statistical differences among the groups even more remote. Several studies, in particular in Asia, have also explored the effects of HVHF in severe acute pancreatitis. Wang et al. [47, 48] in animals and humans and Jiang et al. [31] in humans demonstrated the clinical benefit of HVHF in this context. They studied the effects of HVHF alone, or in comparison with standard CVVH, on mortality and organ function recovery and showed a clear benefit in using high volumes with early initiation. While all these studies were promising, it is now time for larger studies and randomized controlled trials. The results from one such study, the so-called VA/NIH study, were published in 2008 [3]. This was a very large and well-conducted randomized study comparing two different doses of CRRT (20 vs. 35 ml/kg/h) and two different intensities of intermittent RRT depending on the hemodynamic status of the patient; nevertheless, several criticisms have been made [49, 50], including the supposed 35 ml/kg dose of CCVH in the intensive-treatment group which was split into 18 ml/kg/h of dialysis (1,500 ml/h) and 17 ml/kg/h of convection rate, giving an actual dose of roughly 15 ml/kg/h (when taking into account the predilution modality instead of full postdilution). Additionally, the patients were enrolled in the study after being a mean of roughly 7 days in the ICU and roughly 10 days in the hospital which represents a considerably longer delay in

treatment than used in any other study. Also of note, more than 65% of the patients received either intermittent hemodialysis or sustained low efficiency dialysis treatment within 24 h prior to the randomization. Needless to say, the results of the ANZICS clinical trials group renal study [51] comparing augmented with normal RRT in severe acute renal failure are eagerly awaited. A recent animal study has also highlighted the direct action of hemofiltration on the cellular mitochondria of the septic myocardium [52]. Indeed, this study was able to demonstrate that hemofiltration could reverse the negative effects of sepsis on myocardial mitochondrial respiratory chain complex activity in porcine septic shock [53]. This study could be seen as the missing link between the hemodynamic effects of HVHF and what is happening beyond in order to improve mortality.

How to Implement and Optimize at the Bedside

New treatment volumes imply changes in hemofiltration practice so as to guarantee the efficacy and safety of the technique. Indeed, to reach 60 or 100 ml/kg/h of treatment volume, important principles need to be respected. First, a high blood flow is necessary to maintain a filtration fraction of <25%, a level above which 'protein cake' clogging in the membrane becomes a major concern. In order to attain an exchange flow of 35 ml/kg/h, even in very heavy patients (up to 120 kg), for nearly 8 years we have used a constant high blood flow of 300 ml/min which allows the clinician to run a hemofiltration device at 35 ml/kg/h with a filtration fraction of <25% (table 2). However, to attain such a blood flow, excellent vascular access is required with a large catheter (13.5 or 14 Fr) using an adequate location (right jugular is best followed by a femoral approach, while the subclavian route should not to be used) [53] and good structure (coaxial with 360° arterial intake). Second, the best restitution fluid is probably buffered bicarbonate and should be administered 1/3 in predilution and 2/3 in postdilution, i.e., the best compromise between loss of treatment efficacy and optimization of blood rheology [54]; in patients with citrate anticoagulation, the proportions of pre- and postdilution might be different [55]. The choice of membrane is also primordial and a highly biocompatible synthetic filter with a high exchange surface is recommended (1.7–2.1 m²). Temperature control is not important with low fluid exchange volumes but becomes essential when the volume increases dramatically. Two systems are possible for temperature control: heating the fluid before restitution or heating the

blood directly. Empirically, heating the replacement fluid seems preferable to heating the blood, owing to possible deleterious effects of high temperatures on the blood. However, to date no problems have been recorded and the two systems have demonstrated their safety and efficacy. The new machines specifically dedicated to high volumes have extremely sensitive and precise pressure control and volume balance functions. Furthermore, it is important to stay in the normal pressure range for optimal use of high-flow hemofiltration. Indeed, staying below 120 mm Hg of arterial pressure is indicative of a catheter problem and likely early machine failure. The same is true with a venous line, where high pressure indicates catheter or bubble trap clotting. The transmembrane pressure reflects the state of clogging in the filter while high pressure indicates that many fibers are clogged. To alleviate the pressure problem, especially with high volumes, it is recommended that treatment is stopped when the patient is being handled or moved. HVHF also requires adequate management and control of fluid exchange and small solutes. In fact, small molecules are largely removed during hemofiltration and strict monitoring of sodium, glucose, and acid-base balance is mandatory. Detection of infection during hemofiltration may be difficult as this technique can blunt hyperthermia, but recent studies have showed interesting new tools for the early detection of infection under these conditions [56]. Adaptation of antimicrobials during HVHF is also crucial in order to avoid underdosing [57]. Finally, online techniques may be crucial in the future [58]. Surprisingly, widespread application of fluid substitution in hemofiltration at 35 ml/kg/h remains lacking; despite the evidence, recent unpublished surveys have shown that less than 50% of units apply this scientifically sound regimen.

Recommendations for the Clinician Regarding Indications, Mode, Dose and Technique

In terms of recommendations for clinical practice, patients with septic AKI should receive a renal replacement dose of at least 35 ml/kg/h (level-II evidence and grade-C recommendation) [25] and probably a higher dose if they have septic shock. As discussed earlier, the VA/NIH study did not have enough power to change this recommendation in view of its shortcomings [49, 50]. Catecholamine-resistant septic shock, either hypo- or hyperdynamic, could be seen as an indication for HVHF (level-V evidence and grade-E recommendation) for clinicians experienced in HVHF therapies [25, 35, 38]. However, HVHF should

be integrated into practice algorithms for use as a salvage therapy in ICUs as no other treatment has proved its efficacy in these patients with a very high risk of mortality [37]. CRRT should be reserved for patients with AKI; although the benefit of early treatment has been shown, initiating RRT before renal injury is not yet recommended. In fact, the best time to start hemofiltration may be the renal injury state (creatinine $\times 2$ from baseline or oliguria <0.5 ml/kg over the preceding 12 h) according to the RIFLE (Risk, Injury, Failure, Loss, and End-stage Kidney) classification, which could represent the best compromise between early initiation and renal impairment [28, 59]. To evaluate CRRT, further larger prospective randomized studies are needed which must respect certain conditions. First, the safest technique must be used, but this requirement is the easiest to meet as new hemofiltration machines are much safer and more efficient. Second, we need to define the exact time to start hemofiltration in relation to the start of sepsis and AKI. The best policy is to use a common classification for AKI, such as RIFLE, and to start in the first 24 h following the onset of sepsis. Third, it is of primordial importance to define the volume of treatment according to body size in milliliters per kilogram per hour. Finally, we should develop a greater understanding of the mechanisms of sepsis and SIRS in order to identify the targets for CRRT. In future trials, it would be interesting to detect any potential interference or possible synergy between CRRT and activated protein C, for example. The best design for the use of hemofiltration still remains to be defined and the sequences and the duration of high-volume 'rushes' need to be established [44]. Although prolonged CRRT seems more able to stop the initial inflammatory storm and late immunoparalysis, the efficiency and practicability of high-volume pulse should be explored. While several large randomized trials are currently in progress investigating hemofiltration doses in AKI patients, only one is comparing HVHF with standard CVVH [the IVOIRE (hIgh VOlume in Intensive caRE) study, clinicaltrials.gov ID NCT00241228] [29]. This study will try to expand the findings of the initial study by Ronco et al. [1] to septic patients. Indeed, this large randomized study will include patients with septic shock plus AKI, as defined by the RIFLE classification. After computerized randomization, patients will receive CRRT at either 35 or 70 ml/kg/h. This study will try to demonstrate that 'higher' doses (i.e., 70 ml/kg/h) will further improve the survival rate from septic AKI in ICU patients at 28, 60, and 90 days. The first interim analysis will be performed when 150 patients have been included and this is expected to happen sometime in 2009.

Conclusions

The use of hemofiltration has steadily increased in the last decade, from a simple treatment for AKI to adjunctive therapy for sepsis or other acute episodes of SIRS, such as acute pancreatitis. The story is continuing to evolve and we can be sure that with the development of further technology and better understanding of the pathology, hemofiltration doses and the efficacy of the machines will be better defined. For the moment, 35 ml/kg/h should be the standard hemofiltration dose in ICUs for all patients with AKI, while in some situations, like sepsis, the dose should be increased as a salvage therapy in view of the high mortality rates in these patients. However, more trials are needed before HVHF (CRRT with a dose higher than 35 ml/kg/h) can be recommended as routine treatment in ICUs, in order to determine the best scheme of use and to obtain some form of consensus. In recent years, a number of techniques have been studied and developed in the field of RRT in the septic patient. Manipulation of ultrafiltrate dose, membrane porosity, mode of clearance, and combinations of techniques have yielded promising findings.

However, at present, conclusive evidence based on well-designed, randomized controlled trials remains scarce, limiting the practical implementation of many techniques in daily practice outside the context of a study. From the few well-designed and documented studies that we have so far, it is safe to say that optimization of the delivered dose in RRT has a proven positive effect. An ultrafiltration rate of between 35 and 45 ml/kg/h, with adjustment for predilution and down time, can be recommended for the septic patient until other data are available. The results of further dose outcome studies with higher ultrafiltration rates will likely be the stepping stone to further improvements in daily clinical practice. As already discussed earlier, in view of its shortcomings the VA/NIH study did not have enough power to change this recommendation [49, 50]. Hybrid techniques will also likely play a role in the expanding field of RRT in the septic patient in the near future [18, 60, 61]. So, finally the recommendation for the clinician is to keep going with a continuous technique, in a pure CVVH mode and at a dose of 35 ml/kg/h while awaiting other studies, like RENAL, IVOIRE, DO-REMI, to be published.

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