Chapter 18

Continuous Renal Replacement Therapies in Patients with Severe Sepsis and Septic Shock

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Additional information is available at the end of the chapter

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1. Introduction

Acute renal failure (ARF) that requires replacement therapy is a common problem in critically ill patients. The treatment of ARF is one the aspects that has evolved over the management of critically ill patients in the last 25 years. Conventional Hemodialysis presents problems when used in these patients, often being unable to remove enough fluid, due to hemodynamic instability and hypotension that often results. In 1977, Kramer et al. describe the technique of continuous arteriovenous hemofiltration, which, by eliminating slow and continuous ultrafiltration allows good control of electrolyte balance in patients with ARF and oliguria, with good hemodynamic tolerance in critically ill patients. Later modifications of the technique, continuous venovenous hemodiafiltration and hemofiltration get the plasmatic clearance depends less on the ultrafiltration rate determined by blood pressure, and allow more effective clearance. This coupled with the fact that different forms of continuous hemofiltration allow control of uremic and intravascular volume without restriction of protein intake or liquids and requires no specialized personal in dialysis techniques, has become a technique widely used in intensive care units (1,2).

However, the use of continuous renal replacement techniques therapies (CRRT) in patients with severe sepsis or multiple organ dysfunction syndrome (MODS) to remove inflammatory mediators and, therefore, anticipate or mitigate multiorgan dysfunction is still controversial, since this involves the use of hemofiltration in patients that do not require (or not yet needed) replacement of their kidney function (3-6). The sequence of events leading to septic shock and MODS is initiated by endotoxins or other structural components of microorganisms that cause inappropriate inflammatory response through the cells responsible for immunity, and release of inflammatory mediators such as cytokines, active products of complement, arachidonic acid metabolites, nitric oxide, oxygen reactive substances, proteases, etc.. The consequences are tissue damage and hypotension by

myocardial depression and vasodilation (7). Current therapeutic strategies against sepsis are still based on the pharmacology of the immunoinflammatory cascade, however so far very few studies in stage III and IV with these "pro-sepsis" drugs who have achieved favorable results in improving the survival of patients. For this reason the hypothesis that CRRT may modulate this broad and inappropriate tissue inflammation by eliminating inflammatory mediators remains highly attractive (8,9).

2. Principal advantages of CRRT in severe sepsis patients

Theoretically, hemofiltration has several advantages over the pharmacological approach of the sepsis treatment:

- The simultaneous extraction of various mediators should be more effective than selective treatment against a single mediator.
- Hemofiltration only removes plasmatic mediators and thus limits the deleterious systemic effect preserving the local effect (which is considered essential for the elimination of microorganisms and damaged tissue).
- The effect of hemofiltration is more pronounced for those mediators who are in a higher plasma concentration (10).

But although hemofiltration may have some advantages over “prosepsis” drugs, is not a perfect solution, because this treatment also has limitations (2):

1. Hemofiltration can only extract substances present in plasma in unbound form to proteins, but the mediators may be absent because of transient release (TFN and IL-1 for example), being limited effect and release the tissue compartment, and so on. In addition, although they may be inflammatory mediators in the ultrafiltrate of CRRT, has not yet been able to demonstrate that their removal produces a significant decrease in serum levels or there is clinical improvement of the inflammatory response.
2. Most mediators have a molecular weight range (between 600 and 54,000 daltons) and thus can be eliminated by diffusion as this is a process dependent on molecular weight. However, this molecular weight if it is compatible with the extraction convective through high-flux membranes (threshold passage of substances close to 30,000 daltons).
3. Hemofiltration may even be detrimental for all substances indiscriminately remove circulating mediators including beneficial counterregulatory substances, other essential endogenous substances and drugs such as antimicrobials.
4. The use of biocompatible membranes may generate mediators of inflammation.
5. Hemofiltration is an invasive technique that requires the placement of catheters and continuous anticoagulation, and,
6. CRRT are expensive and represent a significant workload (2).

The choice of dialytic technique in severe sepsis patients is dependent upon a variety of factors including availability, the expertise of the clinician, hemodynamic stability, and the

degree to which solutes and/or fluid must be removed. In addition, comorbid conditions may affect the decision:

- Abdominal drains and/or new incisions generally preclude peritoneal dialysis.
- Severe peripheral vascular disease or coagulopathy are general contraindications to cannulation of a major artery. Patients at high risk for bleeding during CAVH can be treated with minimal dose heparin or regional citrate anticoagulation (if there is a diffusion component) to prevent clotting in the dialyzer (1).

Although hemodialysis is the standard modality in hemodynamically stable patients with acute renal failure, CRRT is used in selected cases. The determining factors of which modality is chosen include the catabolic state, hemodynamic stability, and whether the primary goal is solute removal (eg, uremia, hyperkalemia), fluid removal, or both (11,12).

CRRTs in patients with acute kidney injury are most often selected when hemodynamic instability precludes the use of standard three to four hour intermittent dialysis. While randomized controlled trials have failed to prove better outcomes with CRRTs when compared to intermittent dialysis, many clinicians prefer them because of their ease of use and the security perceived by slow therapy. Since there is no proven benefit of CRRT versus intermittent dialysis in this setting, the renal replacement modality selection is based on ease of operation and perceived benefit.

Solute removal occurs primarily by diffusion from the plasma into the dialysate during dialysis and, to a much lesser degree, by convection during ultrafiltration as solvent drag carries small and intermediate sized solutes with the water. Smaller solutes (such as urea and electrolytes) are removed in roughly the same concentration as the plasma with hemofiltration; as a result, the rate of solute clearance is equal to the ultrafiltration rate unless there is concurrent diffusive loss. There is also no change in the plasma concentrations of small solutes with hemofiltration alone, unless they are lowered by dilution by the administration of replacement fluid to prevent extracellular volume depletion.

The rate of solute diffusion is determined by a number of factors including:

- The surface area and unit **solute** permeability of the dialysis membrane.
- The blood and dialysate flow rates which, if increased, maintain a maximum concentration gradient between these two compartments.
- The duration of dialysis (only if a favorable concentration gradient persists for continued diffusion).

In comparison, the rate of solute removal by ultrafiltration is influenced by:

- The transmembrane pressure gradient that provides the driving force for ultrafiltration.
- The surface area and unit **water** permeability of the dialysis membrane.
- The duration of hemofiltration.
- The blood flow rate, which acts indirectly by moving nonfiltered plasma proteins away from the inner wall of the dialysis membrane; preventing local protein accumulation maintains water permeability.

These determinants apply to hemodialysis/hemofiltration, but not to peritoneal dialysis.

Hypotension, either at baseline or during the procedure, may be a limiting feature with conventional hemodialysis but should not occur with slow fluid and solute removal in peritoneal dialysis. However, the latter is often not an option in acutely ill patients.

Slow fluid and solute removal can also be achieved with CRRT. In addition to being better tolerated hemodynamically, CRRT is also as efficient in removing solutes over the course of 24 to 48 hours as conventional hemodialysis. Although the clearance rate of small solutes (such as urea) is slower per unit time with CRRT (17 mL/min with CAVHD versus more than 160 mL/min with hemodialysis), the rates are closer at 24 hours and more urea is removed over 48 hours with CRRT than with a single run of hemodialysis (13-18).

Hemodynamic stability: Daily or every other day conventional hemodialysis is the standard dialytic regimen for the hemodynamically stable patient with severe acute renal failure. However, hypotension, due in part to **rapid** fluid and solute removal, is one of the most common complications with this technique, making it less desirable in the patient who is hypotensive or hemodynamically unstable. In contrast, the rate of fluid and solute removal is **slow** and hypotension is less common with the CRRTs, such as continuous arteriovenous hemofiltration or hemodialysis (19-22). A review of the characteristics of the different types of CRRT is available elsewhere.

CRRT has the additional advantage of effectively removing excess fluid in hypotensive patients, while hemodialysis is frequently limited by a further reduction in blood pressure in this setting.

The relative hemodynamic instability associated with hemodialysis is related to several factors:

- The rapid rate of solute removal results in an abrupt fall in plasma osmolality that induces further extracellular volume depletion by promoting osmotic water movement into the cells. The reduction in plasma osmolality itself may contribute to the development of hypotension.
- Hemodialysis may impair the protective sympathetic response to volume depletion.

It must be emphasized, however, that the protection afforded by CRRT is **relative**, not absolute. Hypotension can still occur if too much fluid is removed or if fluid is removed too quickly.

Solute removal: In addition to being better tolerated hemodynamically, CRRT is also as efficient in removing solutes over the course of 24 to 48 hours as conventional hemodialysis. Although the clearance rate of small solutes (such as urea) is slower per unit time with CRRT (17 mL/min with CAVHD versus more than 160 mL/min with hemodialysis), the rates are closer at 24 hours and more urea is removed over 48 hours with CRRT than with a single run of hemodialysis (Table 1) (23).

Removal of immunomodulatory substances in sepsis: The less porous membranes used with conventional hemodialysis are less efficient in removing middle to large molecules with cardiodepressant, vasodilatory, or immunomodulatory properties in septic or highly

catabolic patients. Examples of such toxins are endotoxin, interleukin-1, complement anaphylatoxins, platelet activating factor, and tumor necrosis factor (21,24,25).

Technique	Operating conditions	Urea clearance mL/min	L/day	Inulin clearance mL/min	Inulin clearance L/day
CAVH	Postdilution, UFR 8 mL/min	8	11.5	6.4	9.2
CAVH	Postdilution, UFR 14 mL/min	14	20	11	16
CAVH	Predilution, UFR 14 mL/min	16	23.5	11	16
CAVHD	Qd 1 L/h, UFR 3 mL/min	19.7	28	2.4	3.5
CVVH	UFR 17 mL/min	17	24	13.6	19.6
CVVHD	Qd 1 L/h, UFR 12 ml/min Postdilution	29	42	9.6	13.8
CEPD	8 L/day, 1 L ultrafiltration	6.3	9	2	3
HD	4 hours	160	38	6	2

The clearance of small (urea) and intermediate (inulin) sized solutes with the different forms of continuous renal replacement therapy, continuous equilibrium peritoneal dialysis (CEPD), and standard hemodialysis (HD). Although urea clearance is much slower with CRRT than with hemodialysis per unit time, the quantity of urea cleared is almost the same over the course of one or two days because of the continuous therapy. When there is no dialysis (as with CAVH or CVVH), the urea clearance is **equal to the ultrafiltration rate** (UFR) unless there is predilution with replacement fluid. Intermediate sized solutes are cleared to a much greater degree with CRRT, since more permeable membranes are used. The values for inulin clearance assume a sieving coefficient of 0.8.
Qd: dialysate flow rate.

Table 1. Solute clearance continuous renal replacement therapy (23).

Experimental and some clinical evidence suggest that large volume hemofiltration more effectively removes some of these substances, possibly leading to better preservation of cardiovascular function (26-29). One report, for example, evaluated 16 patients with sepsis, multiple organ dysfunction, and acute renal failure (28). Hemofiltration did not induce significant mediator activation and did not lead to cytokine removal. There was, however, increased removal of complement anaphylatoxins. Furthermore, the ultrafiltrate from these patients significantly stimulated peripheral blood mononuclear cells in vitro and enhanced tumor necrosis factor release; on the other hand, it reduced lymphocyte production of IL-2 and IL-6. These effects were not seen with ultrafiltrate from normal volunteers.

The ability of hemofiltration to remove immunomodulatory substances may lead to an improvement in patient outcome among those with sepsis and acute kidney injury. Although not yet studied in large randomized prospective controlled studies, there is some evidence that hemofiltration may provide some benefit in those with sepsis and acute renal failure (30-36):

- In a pilot prospective study, 20 patients with septic shock and acute renal failure were randomly assigned to either high (65 mL/kg per hour) or low volume (35 mL/kg per

hour) hemofiltration (36). High volume hemofiltration was associated with decreased mean norepinephrine dose and increased urine output. Survival at 28 days was the same in both groups.

- One retrospective study evaluated the effects of isovolemic hemofiltration on physiological and clinical outcomes in 80 patients with septic shock and oliguric acute kidney injury (31). Prior to 1999, 40 patients had received conventional supportive therapy; subsequently, 40 patients received hemofiltration at 45 mL/kg per hour over the first six hours, which was followed by conventional CVVH. Incorporation of isovolemic hemofiltration into the treatment regimen significantly improved oxygenation and mean arterial pressure. Survival at 28 days was also significantly better (55 versus 28 percent).

Further study in larger better designed studies is required to understand the role of this modality in acute renal failure and sepsis. Furthermore, the early initiation of this intervention (isovolemic hemofiltration) may be very important. However, a randomized prospective study found that early intervention with low volume hemofiltration (25 mL/kg per hour) was deleterious in those with severe sepsis (37).

Effect on mortality: No modality of renal replacement therapy in the critically ill patient with acute renal failure, including intermittent hemodialysis, peritoneal dialysis, and the many forms of CRRT, has been clearly shown to have a survival benefit (1,38).

3. Terminology - Different models of CRRT

There are many variations of CRRT and the remainder of this topic will provide a general overview of the nomenclature that has been developed. The different modalities are categorized according to the access characteristics (blood or peritoneal, venovenous or arteriovenous) (Table 2) (39).

Blood access
Arteriovenous
Continuous arteriovenous hemofiltration
Continuous arteriovenous hemodialysis
Continuous arteriovenous hemodiafiltration
Venovenous
Continuous venovenous hemofiltration
Continuous venovenous hemodialysis
Continuous venovenous hemodiafiltration
Slow continuous ultrafiltration
Slow low efficiency dialysis or dialfiltration
Slow low efficiency daily dialysis
Extended daily dialysis
Peritoneal access
Continuous equilibrium peritoneal dialysis

Table 2. Continuous renal replacement therapies (39)

Arteriovenous or venovenous: Arteriovenous (AV) refers to the use of an arterial catheter that allows blood to flow into the extracorporeal circuit by virtue of the systemic blood pressure. A venous catheter is placed for return. Venovenous (VV) is an alternative modality in which both catheters or one dual lumen catheter are placed in veins. An extracorporeal blood pump is required to circulate blood through the extracorporeal circuit.

The advantage of arteriovenous access is that it is simple to set up and does not require an extracorporeal blood pump. It does, however, require arterial puncture with an attendant risk of arterial embolization. Blood flow may also be unreliable in patients who are hypotensive or have severe peripheral vascular disease.

Venovenous access, on the other hand, does not require arterial access, involves less systemic anticoagulation, uses only one dual lumen catheter, and has faster and more reliable blood flow than with arterial access. The only disadvantage is the requirement for an extracorporeal blood pump (39).

Hemodialysis: Hemodialysis (HD) refers to the transport process by which a solute **passively diffuses down its concentration gradient** from one fluid compartment (either blood or dialysate) into the other. During HD, urea, creatinine, and potassium move from blood to dialysate, while other solutes, such as calcium and bicarbonate, move from dialysate to blood. The dialysate flows countercurrent to blood flow through the dialyzer to maximize the concentration gradient between the compartments and therefore to maximize the rate of solute removal. The net effect is the production of desired changes in the plasma concentrations of these solutes: a reduction in the blood urea nitrogen and plasma creatinine concentration; and an elevation in the plasma calcium and bicarbonate concentrations (39).

Hemofiltration: Hemofiltration (HF) refers to the use of a hydrostatic pressure gradient to induce the filtration (or **convection**) of plasma water across the membrane of the hemofilter. The frictional forces between water and solutes (called **solvent drag**) results in the convective transport of small and middle molecular weight solutes (less than 5000 Daltons) in the same direction as water. Substitution fluid is usually required to prevent excessive fluid removal.

The process of HF itself removes smaller solutes (such as urea and electrolytes) in roughly the **same concentration as the plasma**. There is therefore no change in the plasma concentrations of these solutes by HF, in contrast to those achieved by HD. However, the administration of substitution fluid will lower by dilution the plasma concentrations of those solutes (such as urea and creatinine) not present in the substitution fluid (39).

Hemodiafiltration: Hemodiafiltration (HDF) refers to a combination of dialysis and filtration. Solute loss primarily occurs by diffusion dialysis but 25 percent or more may occur by hemofiltration (39).

Continuous replacement therapies (CRRT): the acronyms that have derived from the above concepts describe continuous therapies with the following general characteristics.

Continuous arteriovenous hemofiltration (CAHV): CAVH uses AV access to remove fluid and solutes by convection. Its per hour efficiency of solute removal is generally quite low,

since no diffusion occurs. Thus, 24 hour/day operation or the addition of enhancing techniques is required. Ultrafiltration in CAVH is allowed at a greater degree than required for the restoration of euvolemia to increase solute removal. As a result, replacement fluid is necessary to prevent volume depletion. However, the rate of solute clearance with CAVH is still relatively low even at a high UFR (table 1). One method to increase the removal of urea (and probably other small, lipid-soluble solutes) is to administer the replacement fluid before the filter; this **predilution** lowers the plasma urea concentration, thereby allowing urea to diffuse from within red cells into the plasma water. The increased total extracellular urea entering the filter enhances the urea clearance rate by approximately 15 percent, especially if 200 mmHg of suction is also used (40,41).

As with any hemofiltration procedure, the aim is to keep the filtration fraction at 10 to 20 percent. At 40 percent and above, sludging occurs in the filter, compromising further fluid removal (42).

Continuous venovenous hemofiltration (CVVH): CVVH is similar to CAVH except that an extracorporeal blood pump is required that allows the physician to control the flow rates within the system (43). The blood pump assures a fast and stable Qb that can be set, for example, at approximately 250 mL/min. If the hematocrit is 33 percent, then the plasma flow rate will be 167 mL/min. A filtration fraction of 10 percent in this setting results in a UFR of 16.7 mL/min, which is equal to 1 L/h or 24 L/day (four times greater than that with SCUF). Most of this fluid will need to be replaced; if given before the filter (predilution), the urea clearance will again be enhanced by approximately 15 percent. Water exchanges of 40 to 60 L/day are usually sufficient, but catabolic patients with an increased urea load may require more than 60 L/day (44).

The more predictable blood flow rate and the associated ability to achieve a high ultrafiltration rate make CVVH preferable to CAVH when solute removal is important, as in hypercatabolic patients with a high BUN (table 1).

Slow continuous ultrafiltration (SCUF): SCUF is strictly a dehydrating procedure with no intent to substantially remove solute. Access can be arteriovenous or venovenous. SCUF is similar to CAVH or CVVH except that the ultrafiltration rate is held at a lower rate; thus, SCUF is primarily used when the fluid removal goals are modest.

Slow continuous ultrafiltration (SCUF) is designed to remove up to **6 to 7 L** of fluid per day without requiring replacement fluid other than for hyperalimentation. Solute removal is **minimal** with this technique, being limited by the low ultrafiltration rate and lack of dialysis. As an example, the clearance of urea and other small solutes is equal to the ultrafiltration rate of approximately 4 to 5 mL/min. Thus, SCUF is not useful in patients who are uremic or hyperkalemic.

Either arteriovenous or venovenous access can be used for SCUF. Arteriovenous access, without an extracorporeal pump, is generally sufficient to achieve the desired rate of fluid loss. The low ultrafiltration rate (UFR) of about 5 mL/min does not require a high rate of blood flow (Qb) through the filter. The Qb can be estimated by flushing the extracorporeal

circuit with saline and then measuring the time for blood to refill the circuit. The volume of the lines and filter are noted in the manufacture's package literature.

Practical goals are a UFR of 5 mL/min and a Qb of 80 mL/min. If the hematocrit is between 35 and 40 percent, then this Qb represents a plasma flow of approximately 50 mL/min with a filtration fraction of 10 percent. If necessary, the UFR can be increased by raising Qb or by adding suction to the filtrate drainage system (45). The Qb can be raised by increasing the systemic blood pressure or by inserting an extracorporeal blood pump into the circuit. Short catheters with wide internal diameters that have been specifically designed for CAVH should be used for arterial access, since they maximize Qb (46).

In some cases, however, the UFR is too rapid. In this setting, ultrafiltration can be slowed by raising the level of the bag into which the ultrafiltrate drains. Most SCUF is now performed with venovenous access, and UFR is completely controlled by the operating parameters of the automated equipment.

Continuous arteriovenous hemodialysis *(CAVHD or CAVD respectively):* CAVHD or CAVD is similar to CAVH with two exceptions: dialysate is run at a low flow rate countercurrent to the direction of blood flow; and the ultrafiltration rate is not maximized to protect against the development of hypotension. Fluid removal is slower than with CAVH alone, but a greater reduction in solute concentration is achieved.

CAVHD differs from CAVH in that dialysis fluid flows through the filter in a compartment separated from the blood by the dialysis membrane. The efficiency of CAVHD is, as with CAVH, dependent upon Qb. However, the UFR is not as high as that achievable with CAVH alone. Thus, fluid removal with CAVHD is slower, but a greater rate of solute clearance can be achieved (table 1).

Clearance rates with CAVHD are dependent upon both blood and dialysate flow rates, which determine the concentration gradient between these two compartments. At Qb values above 80 mL/min, the dialysate fluid tends to become saturated with small solutes (ie, the concentration in the dialysate approaches that in the plasma, preventing further diffusive loss). In this setting, the main way to increase clearance is to raise the dialysate flow rate (Qd) from 1 up to 2 L/h (47,48). Once the Qd reaches 2 L/h, additional attempts to enhance clearance should be directed at increasing Qb, either by using a blood pump or turning up the pump rate if it is already in use.

A final way to raise solute clearance above that achieved by diffusion is to increase convective clearance. This can be achieved by enhancing ultrafiltration beyond the amount necessary to reestablish euvolemia, with replacement fluid then being given to prevent volume depletion. Thus, the highest solute clearances are achieved in CAVHD with a high Qb, high Qd, high UFR, and high rate of fluid replacement. For all the therapies discussed the highest clearances are in the extracorporeal pumped venovenous therapies.

Continuous venovenous hemodialysis (CVVHD or CVVD): CVVHD or CVVD utilizes venovenous access and a blood pump, but is otherwise similar to CAVHD. CVVHD combines the processes of diffusive and convective clearances; as with CVVH, it utilizes a

blood pump to maximize the delivery of blood to the extracorporeal device. The transmembrane pressure generated by the blood pump assures net ultrafiltration unless the dialysate outflow is regulated to ensure that ultrafiltration is retarded. Under routine operating conditions, the blood flow (Qb) varies from 150 to 300 mL/min and the dialysate flow (Qd) from 1 to 2 L/hour.

The equipment required to provide CVVHD can be simple or complex. As an example, components, such as a blood pump, may be combined with separate infusion pumps; by comparison, specialized equipment made by many vendors can be utilized alone to deliver fresh dialysate to the filter and to govern the rate of dialysate exiting the filter.

Some machines also can be utilized for CVVHD. This system uses a proportioning system to generate bicarbonate dialysate from concentrate. The Qd can be adjusted to as high as 6 L/h, thereby providing an enormous clearance potential with continuous therapy. This approach can be applied for as little as eight hours per day (or nocturnally) because the solute clearance is high and the ultrafiltration needs can frequently be realized in this short period (49,59). This hybrid dialytic intervention, named sustained or slow low efficiency dialysis (SLED), or extended daily dialysis (EDD), may soon become the "gold standard" for renal replacement therapy during acute renal failure.

Continuous arteriovenous hemodiafiltration (CAVHDF): CAVHDF is similar to CAVHD except that ultrafiltration is allowed at a rate beyond that necessary to reestablish euvolemia. From the viewpoint of solute removal, CAVHDF combines diffusion to aggressively removal small solutes with convection to remove large solutes. Because the volume of fluid ultrafiltered is so large, replacement fluid must be given to maintain euvolemia.

Continuous venovenous hemodiafiltration *or CVVHDF* is similar to CAVHDF, except that venovenous access is utilized and a blood pump is required.

Continuous equilibrium peritoneal dialysis (CEPD): CEPD is a long-dwell procedure similar to CAPD. A semipermanent peritoneal dialysis catheter is placed. Rapid exchanges are used initially to attain fluid and solute balance (as in acute PD). This is followed by longer dwell times to maintain this balance.

Continuous flow peritoneal dialysis: In this variant of peritoneal dialysis, there are two points of access into the peritoneal cavity, one for continuous inflow of fresh dialysate, the other for efflux of used dialysate. Clearances still primarily depend upon the flow rate of dialysate up to a point in PD, because peritoneal blood flow is limited. However, continuous flow PD clearances exceed those of CEPD (39).

4. Efficacy of CRRT in patients with severe sepsis or septic shock

Continuous renal replacement therapies (CRRTs) involve either dialysis (diffusion-based solute removal) or filtration (convection-based solute and water removal) treatments that operate in a continuous mode (22,51-53). Variations of CRRT might run 12 to 14 hours, especially during daytime periods of full staffing. This regimen has become more prevalent

in Europe and has been called "go slow dialysis." The major advantage of continuous therapy is the slower rate of solute or fluid removal per unit of time. Thus, CRRT is generally better tolerated than conventional therapy, since many of the complications of intermittent hemodialysis are related to the rapid rate of solute and fluid loss.

Severe sepsis and septic shock carry a high mortality and account for a large proportion of patients admitted to intensive care units (54-57). It is widely accepted that the release of large amounts of pro- and anti-inflammatory mediators that occurs in severe sepsis contributes to the development of multiple organ dysfunction syndrome (MODS) (8,58-60), including ARF. Theoretically, high-dose CRRT could remove mediators by convection and/or adsorption (44,61) and reduce mortality, even in the absence of ARF (62). However, most current clinical practice guidelines suggest that the traditional doses of CRRT used in ARF, with or without sepsis, are insufficient to remove these mediators and recommend using at least 35 ml/kg/hour of ultrafiltration (10,63).

In order to assess the efficacy of CRRT in patients with severe sepsis or septic shock, we performed a systematic search in Medline, Embase, Web of Knowledge, Cochrane Library and Clinicaltrials.gov and a hand search of the retrieved studies. We included both randomised controlled clinical trials and subgroups of randomised trials that assessed the effect of continuous renal replacement therapies (at traditional or high doses) and reported clinical outcomes in adult patients with severe sepsis or septic shock (effect on mortality, hemodinamic effect, pulmonary function, etc.). Recently, two large randomised clinical trials in patients with ARF (ATN study (64,65) and RENAL study (66,67) have seriously challenged these recommendations. Additionally, four recent meta-analyses about effectiveness of CRRT in critical patients with ARF have described no impact on the mortality or secondary outcomes of these techniques. The uncertainty regarding the effectiveness of CRRT in patients with sepsis without renal failure is even greater.

The results of systematic review about the efficacy in severe septic patients with ARF suggest that the addition of CRRT or its use at high doses does not improve the clinical outcomes of patients with severe sepsis or septic shock with or without ARF and irrespective of the technique used or the definition of ARF. Albeit conventional haemofiltration, haemofiltration using high cut-off filters, high volume haemofiltration and haemodiafiltration are clearly different, the results are consistent and homogeneous, evidencing a lack of effect. With regard to mortality, only one trial (68) reported a significant reduction in mortality. However this was a small study (based on 28 events) (69), which was stopped early by benefit (70-72), which reported an unusual reduction in mortality (risk ratio of 0.31). Therefore, there is a high probability that it was a false positive. After exclusion of this trial, the heterogeneity was greatly reduced and the pooled relative risk was 1.

A specific consideration should be done with respect to three studies comparing conservative treatment versus CVVH or high volume haemo-filtration (37,73), or in patients without ARF (8) respectively. Although it is doubtful whether these studies should be analysed together due to differences in design, a subgroup analysis did not reveal any subgroup effect.

Only one study (64) included different types of renal replacement therapies, specially continuous and intermittent, showed specifically that the schedule of application of renal replacement therapies was not a factor capable to modifying the effect on mortality.

With respect to other outcomes such as improvement in haemodynamic status or pulmonary oxygenation, much of the available evidence comes from animal and non-randomised studies (mainly pre-post studies without external control groups (35,74-76) not included in this review. However, the evidence based on randomised controlled trials is consistent with that of mortality. Only one study with significant methodological limitations reported a reduction in the use of vasopressors in the experimental group (36), and none of the trials reviewed reported an improvement in gas exchange, duration of mechanical ventilation, development of MODS or length of stay. Respect to other outcomes, two recent meta-analyses (77,78) found no effect of high-dose renal replacement therapy on dialysis dependence or length of stay in patients with ARF.

We did not detect any difference of effect of haemofiltration according to the three groups of doses used. However, only two small studies used doses higher than 65 ml/kg/hour. The dose for attaining a sepsis could very likely be different from the dose used for renal support in ARF. Currently there is an ongoing randomised clinical trial (79) addressing this issue. In any case, the results of our review do not support the routine use of doses higher than 35 ml/kg in patients with severe sepsis with or without ARF.

Similarly, this review is limited to studies comparing high-dose haemofiltration-haemodiafiltration or standard haemofiltration-haemodiafiltration versus traditional dosage or no haemofiltration. Thus, the study results cannot be generalised to other haemofiltration techniques with dialysis (e.g. highadsorption filters, filters of high porosity or plasmapheresis).

A further limitation of studies is that six of the 12 studies which met the inclusion criteria were actually not designed to study patients with severe sepsis and septic shock. These studies evaluated patients with ARF and some had very low numbers of septic patients. Furthermore, these groups of septic patients may not have been defined in the same way across studies. Therefore, the external validity of our study is limited by the scarcity of randomised controlled trials addressing specifically clinical outcomes of renal replacement therapies in septic patients. Indeed, almost all the studies that compared high versus low doses were performed in patients with ARF. The effect of high doses in septic patients without acute kidney injury therefore cannot be fully evaluated until well-designed and powered trials are performed.

Finally, the efficacy of haemofiltration in patients with non-infectious systemic inflammatory response syndrome is beyond the scope of this chapter. It is possible that patients with systemic inflammatory response syndrome (post-cardiac arrest syndrome (80), severe trauma (81,82), pancreatitis (83), severe burns (84) experience a massive release of mediators and therefore may benefit from early haemo-filtration. In contrast, patients with sepsis undergo haemofiltration at a later stage in the course of the disease. It can be hypothesised that the haemofiltration in patients with sepsis is performed outside the therapeutic window when organ damage has already occurred. Further research is needed to address this issue.

5. Conclusions

Regarding these theoretical limitations and potential deleterious effects, it is clear that we can not indicate sistematically hemofiltration in sepsis and SMDO according to hypothesis, however attractive they may be. We have to assess the use of these techniques derived from the knowledge of studies with scientific evidence. The systematic review of the Literature gives us the following conclusions:

1. Is not very strong the evidence that ultrafiltrate obtained from the septic patient's employing continuous hemofiltration remove any clinically important mediator. This is not so with respect to the NTF and the IL-1, two proinflammatory cytokines that are believed to play an important role in the pathogenesis of inflammatory syndrome (Evidence Class IIa or evidence for its usefulness or effectiveness) (85-87).
2. Most animal models using endotoxic or bacterial stimulus or suggest that hemofiltration plays a beneficial effect on survival. However, when we use a true model of infection in humans, nobody has been able to show beneficial effects. Clinical studies do not establish, nor excluded, a positive impact on mortality (Evidence Class IIb evidence or less evidence for utility and effectiveness) (88,89).
3. Experimental animal models of hypodynamic sepsis, again with the exception of true infection model, suggest that continuous hemofiltration allows the extraction of cardio depressor mediators, thereby producing a beneficial effect greater the higher filtration rate. Also controlled clinical studies show an attenuation of the hemodynamic response, suggesting a modulation of the inflammation (Evidence Class I or evidence or general agreement beneficial use, useful and effective) (90-94).
4. When analyzing the oxygen transport respiratory parameters they demonstrated a strong evidence of improved oxygenation and peripheral oxygen extraction with the use of continuous hemofiltration (Evidence Class I or evidence or general agreement beneficial use, useful and effective). The mechanism It is not clear. It may be reflect an improvement in blood flow through redistribution to peripheral level in hypoxic cells, or it may be that there are circulating factors that are eliminated by hemofiltration and they are responsible for the inadequate peripheral oxygen extraction (95).
5. Finally, the beneficial effects observed with hemofiltration it may be not necessarily attributed to the removal of inflammatory mediators. Some of these findings may be explained by reduced temperature, handling of the water balance (reducing the water extravascular lung or optimizing the Starling curve of patients) or metabolic changes (as may be the correction of acidosis), which increases the effect of catecholamines (5,6,15,96,97).

In summary, Continuous Renal Replacement Therapy (CRRT) may be required in patients with severe ARF. Although most patients are treated with hemodialysis, an alternative approach is the use of CRRT. A number of possible differences between intermittent hemodialysis and CRRT include hemodynamic stability, solute removal, removal of substances in those with sepsis, and effects on mortality. However, the best evidence available does not support the routine use of CRRT in patients with sepsis. Further research

is necessary regarding the efficacy of early high-dose CRRT in patients with severe systemic inflammatory response syndrome of non-infectious origin.

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