

## Non Renal Indications of Renal Replacement Therapy (Hemodialysis).

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**Abstract:** While there is clear support for the use of continuous renal replacement therapy (CRRT) in critically ill acute renal failure patients, there are other illnesses without renal involvement where CRRT might be of value. These include sepsis and other inflammatory syndromes such as acute respiratory distress syndrome (ARDS) and cardiopulmonary bypass where removal of inflammatory mediators by hemofiltration is hypothesized to improve outcome. Adsorption appears to be the predominant mechanism of mediator elimination. However, the observed hemodynamic improvement can, at least partially, be attributed to a reduction of body temperature or to fluid removal, and the evidence for a clinically important removal of proinflammatory cytokines remains limited. Continuous and therefore smooth fluid removal may improve organ function in ARDS, after surgery with cardiopulmonary bypass, and in patients with refractory congestive heart failure. Continuous removal of endogenous toxins, eventually combined with intermittent hemodialysis, is probably beneficial in inborn errors of metabolism, severe lactic acidosis, or tumor lysis syndrome. Hemodialysis and Hemoperfusion are also effective in treatment of certain poisonings.

### SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND SEPSIS

Sepsis and other inflammatory syndromes represent the most popular non-renal indications for CRRT. The underlying hypothesis is that hemofiltration removes inflammatory mediators (cytokines, complement activation products, contact activation products, arachidonic acid metabolites, and so forth) from the circulation and thereby dampens the systemic inflammatory response while preserving the local effects that are thought to be beneficial. This is indeed an attractive hypothesis. However, at this moment, the evidence for a clinically important elimination of inflammatory mediators, as well as the evidence for a beneficial effect of hemofiltration on the outcome of septic patients, remains limited<sup>2</sup>.

### REMOVAL OF INFLAMMATORY MEDIATORS WITH HEMOFILTRATION

With the exception of endotoxin and the biologically active form of tumor necrosis factor (TNF), which is a trimer with molecular weight of 54,000 Da, the molecular weight of most inflammatory mediators is compatible with convective removal through high-flux membranes (cut-off  $\pm$ 30,000 Da). However, the reported sieving coefficients are frequently far beneath<sup>1</sup>. One possible explanation is that the membrane cut-off, which has mostly been determined in in vitro conditions, is reduced in clinical conditions because of the presence of a protein layer. Another explanation is binding of the circulating mediators either to each other, as in the TNF trimer, or to other substances such as aspecific binding proteins ( $\alpha$ 2-macroglobulin) or specific binding substances such as the soluble TNF receptor or the interleukin-1 (IL-1) receptor. Cell-bound mediators and adhesion molecules are also not accessible for removal through the membrane.

Another pathway of mediator elimination is adsorption to the membrane. This adsorption is at least semiselective and depends on both mediator and membrane characteristics (In general, the polyacrylonitrile membrane seems to have the highest adsorptive capacity. This adsorption, however, reaches saturation within a few hours. A quantitative important elimination therefore not only requires filters with a large surface area but also frequent changing of the membrane. Kellum et al recently compared hemodialysis and

hemofiltration in a cross-over design in septic patients and observed that only hemofiltration is associated with a decrease of the TNF plasma level. There were, however, no important amounts of TNF in the filtrate, suggesting adsorptive elimination and leading to the hypothesis that convective transport increases adsorption caused by exposure of the filtrate to the whole inner structure of the membrane (AN69) representing a tremendous increase of the available surface. However, despite their filtration and/or adsorption, most controlled clinical trials do not show an effect of hemofiltration on cytokine plasma levels<sup>4</sup>. This is not unexpected in view of their high endogenous clearance compared to which the extracorporeal clearance is probably irrelevant<sup>2</sup>. Braun et al, on the other hand, found a somewhat more pronounced decrease of TNF in the hemofiltered group<sup>5</sup>. Wakabayashi et al showed lower interleukin (IL)-6 and IL-8 levels during hemofiltration compared with a control period in the same patients, and Kellum et al showed lower TNF levels during hemofiltration compared with hemodialysis. De Vriese et al found a short-term decrease in the plasma level of proinflammatory cytokines during the first hour of hemofiltration and again after changing the filter. This decrease, however, is followed by an increase that exceeds the baseline level (uncontrolled observation)<sup>3</sup>.

Most trials on hemofiltration in sepsis have looked at the removal of proinflammatory mediators. The host response not only consists of an inflammatory response, but also of a so-called CARS (compensatory anti-inflammatory response) with release of anti-inflammatory mediators such as IL-4, IL-10, IL-11, IL-13, soluble TNF receptor, IL-1 receptor antagonist, and growth factors<sup>35</sup>. The preponderance of proinflammatory or anti-inflammatory mediators determines whether the result is hyperinflammation or immunosuppression. High levels of both proinflammatory and anti-inflammatory mediators have been associated with mortality, and we still do not know which patient at which time point needs more proinflammatory or more anti-inflammatory substances, nor are there routine parameters that allow us to determine whether the patient is on one or the other side of the balance. If hemofiltration removes both proinflammatory and anti-inflammatory mediators to the same extent, the net result may be zero. If, on the other hand, hemofiltration selectively removes proinflammatory or anti-inflammatory mediators, the resulting imbalance may as well be harmful as beneficial.

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Lonnemann et al demonstrated an increase of the ratio of the anti-inflammatory soluble TNF receptor to the proinflammatory TNF during hemofiltration with a polyamide membrane. De Vriese et al, on the other hand, found a stable balance between TNF and its soluble receptors and between IL-1 and its receptor antagonist during hemofiltration with an AN69 membrane<sup>3</sup>.

## **CLINICAL EFFECT OF HEMOFILTRATION IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND SEPSIS**

A statistically significant effect of zero-balanced hemofiltration on the short-term survival or the survival time of septic animals is found in three of six studies<sup>6-8</sup>. Grootendorst et al and Lee et al, both demonstrating a beneficial effect, used very high filtration rates of more than 100 ml/kg/hr. In these animal studies, the hemofiltration procedure was started before or shortly after the septic insult, which is mostly not achievable in clinical practice. Moreover, experimental sepsis was induced by infusion of endotoxins or bacteria, resulting in a hypodynamic shock that did not correspond with the hyperdynamic picture seen in clinical sepsis. In this regard, it is interesting to note that Freeman, using a true infection model of chronic intraperitoneal sepsis, did not establish an effect on survival and even a trend toward improved survival in the control group. In a subsequent study, Lee et al showed that the use of membranes with a very large pores, resulting in a cut-off of approximately 100,000 Da, leads to a further increase in survival.

Randomized controlled clinical trials comparing hemofiltration with no extracorporeal treatment in patients with inflammatory syndromes do not establish an effect on survival. However, the patient numbers in these studies are small, and the trends are in favor of the hemofiltered group<sup>5</sup>. Taking into account the lack of power of these studies, we have to conclude that a beneficial effect of hemofiltration on survival is not established, but neither is it excluded.

In animal studies, only two investigators, using very high filtration rates of more than 150 ml/kg/hr, established an effect of zero-balanced hemofiltration on the arterial blood pressure of septic animals or animals with gut ischemia [abstract; Rogiers et al, *Intensive Care Med* 22(Suppl 3):S396, 1996]. A positive effect on cardiac output or other parameters of myocardial contractility, pointing to the elimination of a myocardial depressant substance, is a more consistent finding. However, other investigators, including those who use true infection models, did not find an effect of hemofiltration on the hemodynamic parameters of septic animals.

A few controlled clinical trials compared zero-balanced hemofiltration with no extracorporeal treatment in patients with SIRS or sepsis. Cosentino et al did not find a statistically significant difference in the hemodynamic parameters of ARDS patients. Five randomized controlled studies in patients with sepsis or severe polytrauma found an attenuation of the hyperdynamic response [abstract; Armbruster et al, *Intensive Care Med* 20(Suppl 2):S2, 1994]. These studies therefore do not confirm the elimination of a myocardial depressant factor suggested by the animal studies. Wakabayashi et al observed a higher mean arterial pressure during hemofiltration than during the control period between two treatments. Using a cross-over design in septic patients, Bellomo et al compared high-volume hemofiltration (filtration rate 6 liters/hr) with low-volume hemofiltration (filtration rate 1 liters/hr). Preliminary results on six patients showed a decrease in vasopressor requirement during high-volume treatment<sup>10</sup>.

Whether the observed hemodynamic effects can be attributed to the removal of mediators remains to be proven. A recent study by Van

Kuijk showed that the extracorporeal blood temperature plays a critical role in the improved hemodynamic tolerance of hemofiltration versus dialysis. Matamis et al showed that mean arterial pressure is higher in patients developing hypothermia during hemofiltration. He also found an inverse relationship between the decrease of body temperature and the filtration rate, which could explain the hemodynamic effect of high-volume hemofiltration.

The effect of zero-balanced hemofiltration on oxygenation in experimental sepsis<sup>11,12</sup> was evaluated in six studies of which only one, using high volume hemofiltration, established a positive effect<sup>9</sup>. Cosentino et al found a better oxygenation in a control group of ARDS patients compared with a group treated with zero-balanced hemofiltration. Manasia et al (abstract; Manasia et al, *Blood Purif* 13:393, 1995), Wakabayashi et al, and Riera et al, on the other hand, found an improved oxygenation in the filtered group, but none of these studies gave information on the fluid balance in the control group.

Some authors looked beyond the cardiopulmonary effect and evaluated the influence of hemofiltration on the immune system. Lonnemann showed that endotoxin-induced TNF production by monocytes is decreased in septic patients and increases during hemofiltration, suggesting the elimination of an anti-inflammatory substance (abstract; Lonnemann, *Blood Purif* 15:6, 1997). Hoffmann et al, on the other hand, reported that in vitro exposure to the ultrafiltrate of septic patients stimulates LPS-induced TNF production by monocytes, suppresses lipopolysaccharide-induced IL-6 production by monocytes, and suppresses IL-2 and IL-6 release from lymphocytes<sup>15</sup>. DiScipio and Burchard demonstrated that CAVH attenuates the up-regulation of phagocytosis in septic animals. The significance of these findings remains to be proven.

## **ACUTE RESPIRATORY DISTRESS SYNDROME**

Beside the eventual elimination of inflammatory mediators, fluid removal with reduction of extravascular lung water (EVLW) is a second mechanism by which hemofiltration may be beneficial in ARDS. Fluid management in ARDS remains controversial. Theoretically, a reduction of the hydrostatic pressure in the pulmonary circulation will reduce the pressure gradient driving the formation of edema. Indeed, Humphrey et al showed that a reduction in pulmonary capillary wedge pressure (PCWP) is associated with an improved survival in ARDS patients. However, what they actually showed was a better survival in the patients who responded to diuretics, dialysis, or ultrafiltration with a lowering of PCWP compared with patients in whom the same treatment had no effect on the wedge pressure. In other words, they were probably comparing different patients. Laggner et al compared the effect of ultrafiltration on the EVLW of patients with cardiogenic pulmonary edema and ARDS, and showed a decrease of the shunt fraction in both groups. However, the reduction of EVLW was less pronounced in ARDS patients in whom hemofiltration also induced a decrease of cardiac output and O<sub>2</sub> delivery. Ultrafiltration in ARDS patients should therefore be performed only under close hemodynamic monitoring. Continuous renal replacement therapy-induced hypothermia can be used in patients with ARDS in order to reduce CO<sub>2</sub> production. The decreased ventilatory requirement reduces the risk of ventilator-induced lung injury. Reduced CO<sub>2</sub> production combined with the alkalinizing effect of bicarbonate in the replacement solution facilitates the institution of permissive hypercapnia.

## **CARDIOPULMONARY BYPASS**

Another possible indication for hemofiltration is surgery with cardiopulmonary bypass (CPB). CPB, especially in children, results

in tissue edema, pulmonary dysfunction, and poor cardiac performance caused by hemodilution and fluid overload and to activation of the inflammatory response. Isolated ultrafiltration, during and especially after CPB, in children has been shown to reduce weight gain, blood loss, and transfusion requirement, to improve left ventricular systolic and diastolic function, to decrease pulmonary vascular resistance and to improve oxygenation<sup>13,14</sup>. It remains unclear, however, if these beneficial effects are due to fluid removal alone or if the removal of inflammatory mediators also contributes to these effects.

To answer this question, Journois et al performed a randomized trial in which they compared simple ultrafiltration with high-volume, zero-balanced hemofiltration followed by ultrafiltration in children undergoing surgical correction of congenital heart disease under hypothermic CPB<sup>61</sup>. Immediately after hemofiltration, the hemofiltered group had lower levels of C3a and TNF. However, after 24 hours, the difference in TNF was more pronounced and also the levels of IL-1, IL-6, and IL-8 were lower at this time point. The author therefore concludes that hemofiltration removes cytokine-inducing substances. The dampened inflammatory response is manifested clinically as a lower body temperature, less blood loss, lower neutrophil count, and less oxidative damage to the lungs.

### CONGESTIVE HEART FAILURE

In congestive heart failure (CHF), the reduced systemic blood flow is perceived as a reduced effective circulating volume resulting in the activation of several neurohumoral systems such as the sympathetic system and the renin-angiotensin-aldosterone system, and in the release of vasopressin. This inappropriate activation results in arteriolar vasoconstriction (further increasing the afterload) and in water retention caused by enhanced renal sodium reabsorption leading to an increase in filling pressures and edema. The treatment of refractory CHF requires an interruption in the vicious neurohumoral hemodynamic cycle, and this can mostly be achieved with diuretics, vasodilators, and  $\beta$ -blocking agents.

Some patients remain refractory to this medical treatment, and in these patients, the removal of fluids and sodium can be achieved with simple ultrafiltration. Canaud treated 11 patients with chronic heart failure and New York Heart Association (NYHA) class IV with isolated ultrafiltration. In 35 surviving patients, ultrafiltration resulted in an increase of diuresis and sodium excretion, and a further decrease of body weight after interruption of the procedure. Despite fluid removal, arterial pressure remained stable and patients recovered to NYHA class II or III.

Other authors also report a decrease of neuroendocrine factors such as norepinephrine, aldosterone, vasopressin, and plasma renin activity, a striking increase of water and sodium excretion, a more sustained improvement in functional capacity than with supplementary doses of loop diuretics, a re-established response to traditional medical treatment, and an improvement of the quality of life<sup>15,16</sup>. Recently established guidelines for the treatment of chronic heart failure (Task Force of the Working Group on Heart Failure of the European Society of Cardiology) mention ultrafiltration as an aid to gain time while waiting for transplantation.

### INBORN ERRORS OF METABOLISM

Children with maple syrup urine disease, urea cycle disorders, and organic acidemia can produce high levels of branched-chain amino acids and hyperammonemia, inducing irreversible damage, especially in the central nervous system. Continuous venovenous hemofiltration (CVVH) and especially continuous venovenous hemodialysis

(CVVHD) are rapidly effective in clearing these low molecular weight toxic metabolites, allowing the patients to recover their neurological status<sup>17,18</sup>.

### LACTIC ACIDOSIS

A few case reports suggest that continuous hemofiltration, by extracorporeal elimination of lactate, may contribute to the correction of lactic acidosis<sup>19,20</sup>. Levraut et al recently demonstrated that in patients with a normal lactate level and stable hemodynamic and respiratory status, the contribution of continuous bicarbonate hemodiafiltration to the total body clearance of lactate only represents 0.5 to 3.2%<sup>79</sup>. They conclude that the reported reduction in lactate level during hemofiltration probably reflects an improvement in acid-base and metabolic status leading to enhanced lactate metabolism. However, in patients with an increased lactate level and reduced endogenous clearance caused by liver dysfunction, the contribution of extracorporeal elimination might indeed become clinically important, especially if extracorporeal clearance is substantial (high-volume hemofiltration or dialysis). In addition, bicarbonate hemo(dia)filtration minimizes hypervolemia and hypernatremia, both of which are side effects of bicarbonate administration<sup>80</sup>.

### CRUSH INJURY

because the molecular weight of myoglobin is 17,000 Da and thus compatible with convective removal, hemofiltration might represent a means to prevent renal failure in crush injury and other causes of rhabdomyolysis and myoglobin gaining access to the circulation. The presence of myoglobin in the filtrate has indeed been demonstrated<sup>21,22</sup>. However, the sieving coefficient reported by Nicolau et al was only 0.1584. In addition, other authors found a rapid fall in myoglobin levels, regardless of renal function or the method of blood purification, suggesting extrarenal catabolism of myoglobin. Adequate fluid resuscitation combined with urinary alkalization remain the mainstays in the treatment of crush injury.

### TUMOR LYSIS SYNDROME

Tumor lysis syndrome may lead to renal failure caused by tubular obstruction by uric acid crystals or to hyperphosphatemia with precipitation of calcium/phosphate complexes in renal interstitium and tubuli<sup>88</sup>. Both uric acid and phosphate are small molecules that require a highly diffusive clearance, and conventional dialysis is certainly more effective than the continuous techniques; however, CRRT can be used in unstable patients or in combination with intermittent dialysis<sup>23,24</sup>. The prevention of ARF in tumor lysis syndrome relies on the stimulation of diuresis combined with allopurinol. CRRT has been used to prevent ARF in high-risk patients, who were defined based on the level of LDH and the urine output.

### HEMODIALYSIS, HEMOPERFUSION IN POISONINGS

Many factors affect drug removal in hemodialysis ; Drug characteristics, Solute size, lipid solubility, protein binding, concentration gradient between plasma and dialysate, physical factors, blood flow rate (Qb) through the dialyzer, Dialysate flow rate, dialyzer surface area, characteristics of the dialyzer membrane  $E\%$ . An ideal dialyzable drug has low molecular weight, is water soluble, and has low protein binding and low Vd (eg, lithium). Drug removal is limited by membrane surface area  $\times$  permeability

### HEMOPERFUSION

Hemoperfusion is the method by which anticoagulated blood is passed

through a column containing sorbent particles. Activated charcoal particles and resin beads (with or without ligands) contained in hemoperfusion devices have been used. Platelet depletion is the main side effect of uncoated charcoal (carbon) hemoperfusion; substantial improvement is achieved by coating the particle surface with a thin biocompatible membrane. Carbon is efficient at removing lipid- and water-soluble drugs, certain resins are most effective for removal of lipid-soluble drugs. Antibody- or antigen-coated particle hemoperfusion devices have been constructed for the removal of specific toxins.

## SALICYLATES

Acute toxicity characterized by tinnitus/deafness, diaphoresis, vomiting, a mixed acid-base disorder, and eventual pulmonary edema and CNS dysfunction. Decontamination should include administration of activated charcoal and enhanced elimination should be attempted with urinary alkalinisation. Hemodialysis is indicated for evidence of severe acidosis, CNS dysfunction, pulmonary edema, or levels >80 to 100 mg/dL. Slow low-efficiency dialysis (SLED) and continuous venovenous hemodiafiltration (CVVHDF) also are efficacious for salicylate removal and correction of acid-base abnormalities.

## BARBITURATES

Overdose should be treated through initial supportive measures, decontamination with activated charcoal, and enhanced elimination with urinary alkalinisation. Hemodialysis (especially high flux) and hemoperfusion are both effective for extracorporeal drug clearance. In less severe poisoning or as addition to hemodialysis, urine alkalinization to pH 8 will enhance phenobarbital removal.

## THEOPHYLLINE

May present with acute and/or chronic toxicity, principally characterized by arrhythmias and CNS disturbances. Initial supportive measures should be followed by activated charcoal administration. Hemoperfusion is the preferred method of extracorporeal clearance and is recommended for rapidly increasing levels or those >60 mg/L. Hemodialysis, although less effective than hemoperfusion, may be more readily available and associated with fewer complications.

## LITHIUM

Although narrow therapeutic window, nonetheless frequently used for the treatment of bipolar affective disorder. Acute toxicity involves progressive neurologic impairment, whereas long-term sequelae include nephrogenic diabetes insipidus, cystic interstitial nephritis, and nephrotic glomerulopathies. For levels >2.5 mEq/L, extracorporeal removal using hemodialysis (or hemofiltration) is indicated. Levels may rebound after initial treatment and should be monitored carefully because repeated treatments may be necessary.

## METHANOL

Potentially fatal intoxicant that may be ingested, inhaled, or absorbed through the skin. Initial signs of intoxication include inebriation and stupor, during which time a serum osmolar gap may be present. Further toxicity follows a latent period of several hours. Prevention of biotransformation and extracorporeal elimination of methanol and metabolites are the goals of treatment. At methanol levels <20 mg/dL, fomepizole may be sufficient treatment, but requires prolonged (several days) infusion. Hemodialysis preferred for more severe intoxication.

## ETHYLENE GLYCOL

Toxic alcohol with a sweet taste. Often mixed with a fluorescein dye to aid in identification. Ingestion is followed by absorption within an hour, subsequent inebriation, and stupor, with an evident serum osmolar gap. As with methanol, toxicity and acidosis follow a latent period of biotransformation. Life-threatening CNS, cardiac, and kidney toxicity occur due to oxalate crystal deposition in blood vessels and tissues. Hypocalcemia and crystalluria also may be evident. Treatment consists of inhibition of metabolism and extracorporeal elimination of ethylene glycol and Hemodialysis is indicated for organ toxicity, acidosis, and levels >50 mg/dL. There is potential for rebound, and repeated treatments may be necessary to maintain levels <20 mg/dL.

## ISOPROPYL ALCOHOL (ISOPROPANOL)

An alcohol with toxic potential, readily available as a solvent or in "de-icing" and cleaning products. Often ingested by alcoholics in place of ethanol; for example, in-hospital hand sanitizer. Toxicity may result from ingestion, inhalation, or dermal exposure. CNS depression may result in intoxication/stupor or coma. Hypotension/shock can result from myocardial and brainstem depression. Gastritis with haemorrhage and rhabdomyolysis also described.

Treatment generally consists of appropriate supportive care, fluid resuscitation and/or pressors, airway protection, and mechanical ventilation. Although fomepizole effectively inhibits metabolism of isopropyl alcohol to acetone, toxic metabolites not of principal concern as with ethylene glycol and methanol.

Haemodialysis (standard intermittent or continuous) efficiently removes isopropyl alcohol and acetone. Recommended when evident hypotensive shock, respiratory failure, stupor, or coma and with isopropyl alcohol levels >400 mg/dL.

## PROPYLENE GLYCOL

An alcohol with low toxic potential used commercially as a coolant, in small quantities as a food or cosmetic additive, and as a medication solvent. Reported clinical effects include sepsis-like syndrome and acute kidney injury (possibly due to proximal acute tubular necrosis [ATN]).

Treatment consists of cessation of medication infusion (if applicable) and appropriate supportive care, although fomepizole effectively inhibits metabolism to lactate, role in therapy uncertain and clinical judgment is necessary.

Hemodialysis effectively removes propylene glycol and lactate.

## METFORMIN

A biguanide oral antihyperglycemic medication used in the treatment of type 2 diabetes mellitus and "off-label" for polycystic ovary syndrome and nonalcoholic fatty liver disease. Rare but well-recognized toxicity with high mortality reported with both therapeutic use and overdose: metformin-associated lactic acidosis (MALA). Clinical signs are insidious and include malaise, abdominal discomfort, nausea, and vomiting.

Initial treatment involves supportive care and sodium bicarbonate infusion. Hemodialysis efficiently removes metformin and lactate and corrects acidosis with volume-neutral bicarbonate delivery.

## VALPROIC ACID (VALPROATE)

A carboxylic acid used in bipolar disorder, seizures, and migraine with potential for overdose, symptoms varies in severity from cerebral edema to mild confusion. Also causes hypothermia, hypotension, nausea, vomiting, and diarrhea. Treatment generally consists of appropriate supportive care, hemodialysis (standard intermittent or continuous) or hemoperfusion efficiently removes the unbound fraction of drug.

## AMANITA MUSHROOMS

A wild mushroom species (*Amanita phalloides*) ingested by mistake for edible mushrooms. Results in GI discomfort and delayed hepatic damage. Often seen in outbreaks, for example, after family picnics, reported clinical effects include diarrhea and vomiting progressing to hepatic cell death, coma, and renal tubule necrosis. Hemodialysis and hemoperfusion controversial because amanitin is not readily measured and CI is unknown; anecdotal reports of recovery are positive and negative. Recent reports on the Molecular Adsorbents Recirculating System (MARS; uses resins and albumin to remove protein-bound toxins) have reported success in case series and case reports.

## METHOTREXATE

An inhibitor of dihydrofolate reductase; interrupts DNA synthesis of dividing cells. Manifestations of MTX toxicity are marrow suppression and its consequences and severe mucositis in the GI tract from mouth to intestinal mucosa; in addition, MTX may induce tumor lysis and has been shown to be teratogenic; may also induce hemorrhagic cystitis, which in the long term can cause bladder cancer.

Initial treatment involves supportive care and leucovorin rescue. It has been known for some time that MTX (molecular weight, 454 Da) is removable by hemodialysis (and its modifications CAVHD or CVVHD), multiple-exchange peritoneal dialysis, and hemoperfusion. High-flux hemodialysis efficiently removes MTX and may prevent toxicity, with CI values around 70-143 mL/min.

## PROCAINAMIDE

Class 1a antiarrhythmic drug introduced in 1951; was used for atrial fibrillation and Wolf-Parkinson-White syndrome; rarely used now. Hemodialysis (alone or combined with hemoperfusion) efficiently removes PA and NAPA; however, because the  $V_d$  is large, repeated treatment often is required to decrease their plasma concentrations.

## CONCLUSION

There are other illnesses without renal involvement where CRRT might be of value. These include sepsis and other inflammatory syndromes such as acute respiratory distress syndrome (ARDS) and cardiopulmonary bypass where removal of inflammatory mediators by hemofiltration is hypothesized to improve outcome. Adsorption appears to be the predominant mechanism of mediator elimination. However, the observed hemodynamic improvement can, at least partially, be attributed to a reduction of body temperature or to fluid removal, and the evidence for a clinically important removal of proinflammatory cytokines remains limited. Continuous and therefore smooth fluid removal may improve organ function in ARDS, after surgery with cardiopulmonary bypass, and in patients with refractory congestive heart failure. Continuous removal of endogenous toxins, eventually combined with intermittent hemodialysis, is probably beneficial in inborn errors of metabolism, severe lactic acidosis, or tumor lysis syndrome. Hemodialysis and Hemoperfusion are also effective in treatment of certain poisonings.

## BIBLIOGRAPHY

- Schetz, MRC: Classical and alternative indications for continuous renal replacement therapy. *Kidney Int* 1998 53(Suppl 66):S129-S132. | ISI |
- Schetz, M, Ferdinande, P, Van den Berghe, G, Verwaest, C, Lauwers, P: Removal of pro-inflammatory cytokines with renal replacement therapy: Sense or nonsense? *Intensive Care Med* 1995 21: 169-176. | Article | PubMed | ISI | ChemPort |
- De Vriese, AS, Colardyn, F, Philippé, R, Van Holder, R, De Sutter, JH, Lameire, NH: Cytokine removal during continuous hemofiltration in septic patients. *J Am Soc Nephrol* 1999 10: 846-853. | PubMed | ISI | ChemPort |
- Sander, A, Armbruster, W, Sander, B, Philipp, T, Schafer, C, Thurauf, N, Lange, R: The influence of continuous hemofiltration on cytokine elimination and the cardiovascular stability in early sepsis. *Contrib Nephrol* 1995 116: 99-103. | PubMed | ChemPort |
- Braun, N, Rosenfeld, S, Giolai, M, Banzhaf, W, Fretschler, R, Warth, H, Weinstock, C, Deppisch, R, Erley, CM, Muller, GA, Rister, T: Effect of continuous hemodiafiltration on IL-6, TNF-, C3a, and TCC in patients with SIRS/septic shock using two different membranes. *Contrib Nephrol* 1995 116: 89-98. | PubMed | ChemPort |
- Staubach, KH, Rau, HG, Kooistra, A, Shardey, HM, Hohlbach, G, Schildberg, FW: Can hemofiltration increase survival in acute endotoxemia: A porcine shock model. *Prog Clin Biol Res* 1989 308: 821-826. | PubMed | ChemPort |
- Stein, B, Pfenninger, E, Grunert, A, Schmitz, JE, Hudde, M: Influence of continuous haemofiltration on haemodynamics and central blood, in experimental endotoxic shock. *Intensive Care Med* 1990 16: 494-499. | Article | PubMed | ISI | ChemPort |
- 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: 914-924. | PubMed | ISI | ChemPort |
- Grootendorst, AF, van Bommel, EFH, van Leengoed, LAMG, Nabuurs, M, Bouman, CSC, Groeneveld, ABJ: High volume hemofiltration improves hemodynamics and survival of pigs exposed to gut ischemia and reperfusion. *Shock* 1994 2: 72-78. | PubMed | ISI | ChemPort |
- Bellomo, R, Baldwin, I, Cole, L, Ronco, C: Preliminary experience with high-volume hemofiltration in human septic shock. *Kidney Int* 1998 53(Suppl 66):S182-S185. | ISI |
- Stein, B, Pfenninger, E, Grunert, A, Schmitz, JE, Deller, A, Kocher, F: The consequences of continuous haemofiltration on lung mechanics and extravascular lung water in a porcine endotoxic shock model. *Intensive Care Med* 1991 17: 293-298. | Article | PubMed | ISI | ChemPort |
- Mink, SN, Jha, P, Wang, R, Yang, J, Bose, D, Jacobs, H, Light, RB: Effect of continuous arteriovenous hemofiltration combined with systemic vasopressor therapy on depressed left ventricular contractility and tissue oxygen delivery in canine *Escherichia Coli* sepsis. *Anesthesiology* 1995 83: 178-190. | PubMed | ISI | ChemPort |
- Elliott, MJ: Ultrafiltration and modified ultrafiltration in pediatric open heart surgery. *Ann Thorac Surg* 1993 56: 1518-1522. | PubMed | ISI | ChemPort |
- Journiois, D, Poulard, P, Greeley, W, Mauriat, P, Vouhé, P, Safran, D: Hemofiltration during cardiopulmonary bypass in pediatric cardiac surgery: Effects on hemostasis, cytokines and complement components. *Anesthesiology* 1994 81: 1181-1189. | PubMed | ISI | ChemPort |
- Rimondini, AA, Cipolla, CM, Bella, PD, Graci, S, Sisillo, E, Susini, G, Guazzi, MD: Hemofiltration as short-term treatment for refractory heart failure. *Am J Med* 1987 83: 43-48. | Article | PubMed | ISI | ChemPort |
- Cipola, MC, Graci, S, Rimondini, A, Susini, G, Guazzi, M, Della Bella, P, Guazzi, MD: Changes in circulating norepinephrine with hemofiltration in advanced congestive heart failure. *Am J Cardiol* 1990 66: 987-994. | PubMed |
- Sperl, W, Geiger, R, Maurer, H, Guggenbichler, IP: Continuous arteriovenous hemofiltration in hyperammonemia of newborn babies. *Lancet* 1990 336: 1192-1193. | Article | PubMed | ISI | ChemPort |
- Thompson, GN, Butt, WW, Shann, FA, Kirby, DM, Henning, RD, Howells, DW, Osborne, A: Continuous venovenous hemofiltration in the management of acute decompensation in inborn errors of metabolism. *J Pediatr* 1991 118: 879-884. | PubMed | ISI | ChemPort |
- Barton, IK, Streather, CP, Hilton, PJ, Bradley, RD: Successful treatment of severe lactic acidosis by haemofiltration using a bicarbonate-based replacement fluid. *Nephrol Dial Transplant* 1991 6: 668-670.
- Kirschbaum, B, Galischoff, M, Reines, HD: Lactic acidosis treated with continuous hemodiafiltration and regional citrate anticoagulation. *Crit Care Med* 1992 20: 349-353. | PubMed | ISI | ChemPort |
- Winterberg, B, Ramme, K, Tenschert, W, Winterberg, G, Rolf, N, Wendt, M, Teerling, K, Lison, AE, Zunkley, H: Hemofiltration in myoglobinuric acute renal failure. *Int J Artif Organs* 1990 13: 113-116. | PubMed | ISI | ChemPort |
- Berns, JS, Cohen, RM, Rudnick, MR: Removal of myoglobin by CAVH-D in traumatic rhabdomyolysis. *Am J Nephrol* 1991 11: 73-75. | PubMed | ISI | ChemPort |
- Pichette, V, Leblanc, M, Bonnardeaux, A, Outimet, D, Geada, D, Cardinal, J: High dialysis flow rate continuous arteriovenous hemodialysis: A new approach for the treatment of acute renal failure and tumour lysis syndrome. *Am J Kidney Dis* 1994 23: 591-596. | PubMed | ISI | ChemPort |
- Sakarcan, A, Quigley, R: Hyperphosphatemia in tumour lysis syndrome: The role of dialysis and continuous veno-venous hemofiltration. *Pediatr Nephrol* 1994 8: 351-353. | Article | PubMed | ISI | ChemPort |
- Anspach FB, Petschl DM: Membrane adsorbents for selective endotoxin removal from protein solutions. *Process Biochem*. 2000;35:1005-1012.
- Gelfand MC, Winchester JF, Kneppshield JH, et al. Charcoal hemoperfusion in severe drug overdose. *Trans Am Soc Artif Intern Organs*. 1977;23:599-605.
- Gibson TP, Lucas SV, Nelson HA, et al. Hemoperfusion removal of digoxin from dogs. *J Lab Clin Med*. 1978;92:673-682.
- Hadden J, Johnson K, Smith S, Price L, Giardana E. Acute barbiturate intoxication: concepts in management. *JAMA*. 1969;209:893-900.
- Hakim RM, Milford E, Himmelfarb J, et al. Extracorporeal removal of anti-HLA antibodies in transplant candidates. *Am J Kidney Dis*. 1990;16:423-431.
- Hampel G, Crome P, Widdop B, Goulding R. Experience with fixed-bed charcoal haemoperfusion in the treatment of severe drug intoxication. *Arch Toxicol*. 1980;45:133-141.
- Maher JF. Principles of dialysis and dialysis of drugs. *Am J Med*. 1977;62:475-481.
- Maher JF, Schreiner GE. The dialysis of poison and drugs. *Trans Am Soc Artif Intern Organ*. 1967;13:369-393.
- Palmer BF. Effectiveness of hemodialysis in the extracorporeal therapy of phenobarbital

## Next Issue Highlights

### Topic: Recent Advances & Future Trends In Healthcare

- The health care industry needs a change model (Editorial)
- Quality health care for the Numerous the challenge of numbers
- Recent advances and future trends in cardiology
- Current status of robotic surgery in India
- Healthcare from good to Exceptional Governance
- Concerns, Expectations and satisfaction of medical tourists attending territory care hospitals in New Delhi India
- Treatment outcome with weekly cisplatin concurrent with radiations therapy in locally advanced head and neck squamous cell carcinoma
- Professional Nursing: Trends and Adjustments
- Comparative analysis of various diagnostic techniques for tubercular lymphatis- A pilot study from a resource poor country

### Guest Editor: Dr. S. A. Tabish

- Cost Analysis of a Dialysis unit at a territory care multi specialty Technique hospital
- Advances in Management of Diabetes Mellitus
- Study of patient satisfaction at cardio Thoracic and Neurosciences centre at AIIMS, New Delhi
- Analysis of Drug Inventory of Drug and Pharmacy Dept of a tertiary care Hospital
- Future Medicine: Nanomedicine
- Futuristic Geriatric Hospital
- Detection of fetal Nucleic Acid in Maternal plasma A Novel Noninvasive prenatal Diagnostic Technique
- Hospital Role in Pandemic our experience
- Management of oral lichen planus: A clinical study
- Obesity, prevent rather than cure Histopathological and clinical perspectives

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Fulphus SW, characterization, isolation and purifications at chollnergicreceptors in motor Innervations of muscle: edited by Sloff S, Academic Press London 1976; page 1-26.

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