The future of extracorporeal support

Dinna Cruz, MD, MPH; Rinaldo Bellomo, MD, FRACP; John A. Kellum, MD, FCCM; Massimo de Cal, BS; Claudio Ronco, MD

Extracorporeal therapy has expanded significantly over the past few decades from solely artificial renal replacement therapy. In patients with multiple organ dysfunction syndrome, it becomes necessary to provide multiple organ support therapy. Technological advances have opened the door to a multifaceted intervention directed at supporting the function of multiple organs through the treatment of blood. Indications for "old" therapies such as hemofiltration and adsorption have been expanded, and using these therapies in combination further enhances blood detoxification capabilities. Furthermore, new devices are constantly in development. Nanotechnology allows us to refine membrane characteristics and design innovative monitoring/biofeedback devices. Miniaturization is leading down the path of wearable/implantable devices. With the incorporation of viable cells within medical devices, these instruments become capable not only of detoxification but synthetic functions as well, bringing us closer to the holy grail of complete replacement of organ function. This article provides a brief overview of current and future direction in extracorporeal support in the critical care setting. (Crit Care Med 2008; 36[Suppl.]:S243–S252)

KEY WORDS: acute renal failure; artificial membranes; bioartificial; continuous renal replacement therapy; extracorporeal membrane oxygenation; extracorporeal assist; hemodialysis; hemofiltration; liver support; multiorgan dysfunction syndrome; nanotechnology; plasma filtration; systemic inflammatory response syndrome

Acute kidney injury (AKI) is a common problem among critically ill patients with significant clinical and economic consequences, particularly when associated with sepsis and multiorgan dysfunction syndrome (1, 2). A significant proportion of patients have AKI severe enough to require renal replacement therapy (RRT). In the past we applied the standard of care established for chronic kidney disease and "adopted" this in the critical care setting, particularly with regards to adequacy or dose of dialysis. With the creation of the Acute Dialysis Quality Initiative, we have taken the first step toward the development of guidelines specifically suited for the acute setting (3). Recognizing the complexity of these types of patients, there has been a gradual paradigm shift in the attitude of intensivists and nephrologists toward RRT in the acute setting. Rather than solely replacing kidney function, we now aim to provide support for other organs during multiorgan dysfunction syndrome, from simple blood purification to restoration of homeostasis. This has been called multiple organ support therapy (4).

This evolution has occurred not only conceptually, but also technologically. In the field of acute RRT, technology has grown by leaps and bounds over the past decades, and changes have occurred in clinical practice. Initially, we were taking our dialysis machines from the chronic dialysis unit and bringing them into the intensive care unit (ICU), or building primitive blood purification circuits essentially from intravenous infusion pumps and hemofilters. Since then, there have a been of plethora of RRT monitors and medical devices specifically designed for the critical care setting, capable of delivering slow continuous or extended therapies with simplified user interfaces. We have moved from the use of nonbiocompatible membranes to more biocompatible ones, reducing to some extent the inflammatory cytokine response to extracorporeal treatments (5). Newer dialyzers, some developed through nanotechnology, have improved the efficiency of dialysis treatments (6). Although the issue of purity of dialysate has been addressed predominantly in the chronic hemodialysis (HD) literature, the importance of water quality in reducing inflammatory response is beginning to be recognized also in acute RRT (7). Furthermore, new technology is currently under development and testing. This article aims to briefly review future directions in the field of acute RRT. The terms RRT and extracorporeal blood purification (EBP) are used interchangeably in this article. However, we must acknowledge that RRT, in its current incarnation, is a misnomer. While we strive to provide this sort of therapy, all we can currently provide is partial support. The future of EBP will be to not only realize RRT, but go beyond this mark to therapy that can do more than any natural organ can.

Re-Evaluation of Clinical End Points

The introduction of continuous renal replacement therapy (CRRT) has solved many of the problems associated with the delivery of RRT in the ICU. Compared with "standard intermittent" HD, CRRT provides major biochemical and physiologic advantages, although, given the limitation of clinical trials, it remains unproven as to whether such advantages translate into a measurable survival advantage. Nevertheless, CRRT is now the dominant form of RRT in developed countries (8). Augmenting the dose of

From the Department of Nephrology, Ospedale San Bortolo, and International Renal Research Institute Vicenza, Vicenza, Italy (DC, MdC, CR); the Department of Intensive Care and Department of Medicine, Austin & Repatriation Medical Centre, Melbourne, Australia (RB); and the Clinical Research Investigation and Systems Modeling of Acute Illness Laboratory, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA (JK).

Dr. Ronco has received a Speaker Gouorarium from Gambro-Biosite-Edwards. The remaining authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: cronco@goldnet.it

DOI: 10.1097/CCM.0b013e318168e4f6

RRT beyond previous "standard" practice, whether in intermittent or continuous mode, has been demonstrated to have favorable effects on survival in four studies (9–12). These studies, as well as those still in progress, are discussed in further detail in a separate article in this issue. However, recent data suggest that perhaps we should look beyond survival, and take a broader view of what we consider "true" clinical benefits. Renal recovery is an equally important clinical end point that generally has been overlooked until recently. Chronic dialysis is an expensive therapy associated with significant impairment in health-related quality of life (13, 14). Moreover, chronic kidney disease of milder severity (stage 2 or 3) likewise is associated with adverse patient outcomes and high healthcare costs. This suggests that the presence of any sustained renal impairment after AKI is potentially significant (15). Therefore, treatment of all patients with intermittent HD on the presumption of equipoise based on mortality outcomes may be inappropriate from both clinical and economic standpoints, because it disregards potential downstream effects. Better rates of renal recovery may save significant resources and influence long-term well-being among survivors. Three observational studies and one randomized controlled study reported renal-related outcomes (16–19). In a single-center observational study, dialysis independence was significantly higher among patients initially treated with CRRT (87%) vs. intermittent HD (36%) (16). Similar results were seen in a Swedish multicenter study in which 91.7% of patients treated with CRRT were dialysis independent at 3 months, as compared with 83.5% of intermittent HD patients (17). A large international multicenter database confirmed these findings (18). Unadjusted dialysis dependence at hospital discharge was higher after CRRT (85.5%) than after intermittent HD (66.2%). Lastly, in a randomized, controlled trial frequently quoted as a "negative" trial, CRRT demonstrated some benefits regarding renal recovery (19). Chronic renal insufficiency at death or hospital discharge was diagnosed in 17% of patients whose therapy was intermittent HD vs. only 4% of those whose initial therapy was CRRT. Recovery of renal function was 92% for CRRT vs. 59% for intermittent HD among patients receiving an adequate trial of monotherapy. The gentle but effective correction of metabolic and fluid derangements and the maintenance of a steady correction of homeostasis by CRRT may influence the process of recovery of the kidney during and after the acute injury. When seen in this light, CRRT is a potentially valuable tool to aid renal recovery, and future technological advancements should be examined with this as one of the primary targets for further improvement.

Simplification and Cost Reduction

Despite the theoretical advantages of CRRT, the fact remains that it is a technically demanding therapy, requiring continuous supervision and the use of a single machine for a single patient per day. It often is associated with the need for continuous anticoagulation, which, in some patients, may be undesirable. The cost differences between standard intermittent HD and CRRT have remained a constant subject of discussion, and are largely driven by staffing models that are highly regional. Furthermore, cost analyses have not included long-term effects, and if the putative benefits of CRRT for renal recovery prove to be true, this will dramatically change estimates. Until definitive data becomes available, this remains an area of controversy (20). As we move to higher and higher doses of ultrafiltration (discussed below) and/or dialysis, and using large volumes of sterile bicarbonate-buffered replacement fluids or dialysate, this becomes an even thornier issue. This matter can be partially addressed with current technology. Hemodiafiltration is an RRT technique used in chronic renal failure, combining high biocompatibility and the use of ultrapure dialysate and replacement fluid. Online preparation of sterile and pyrogen-free solutions for infusion during hemodiafiltration is based on the use of water and concentrates that contribute a minimum of microorganisms and are mixed and distributed in a hygienically designed and maintained flow path (21). Ultrafilters with known retention capacity are placed in strategic positions and dimensioned to remove bacteria and endotoxins, which gives a satisfactory sterility assurance level. Microbiological safety of online hemodiafiltration has been shown in long-term clinical studies, with a notable absence of cytokine-inducing activity detected in the fluid or pyrogenic reactions in patients, despite the infusion of large volumes of fluid in every session (22). Online production of ultrapure replacement and dialysate fluid in "acute" RRT treatments would reduce the cost of fluid, storage space used for disposables, and nursing workload, and potentially allow significantly higher ultrafiltration rates with minimal increase in cost. To this point, we have been using standard dialysis machines with portable water treatment systems in our ICUs. Although some machines were capable of providing clean dialysate online, ultrapure replacement fluid was not available. We generally were limited to purely diffusive therapies. This deprived patients of the potential benefits of convective therapies with regard to removal of larger molecular weight solutes, such as humoral mediators of organ injury. At present, RRT machines capable of online production of ultrapure replacement fluid, as well as prolonged duration of therapy, have been introduced into the acute care setting (e.g., ARrT 4008S Plus and 5008, Fresenius Medical Care, Bad Homburg, Germany; Gambro AK200s, Gambro, Lund, Sweden). Initial clinical results have been encouraging (23, 24), and further studies are in progress. However, because this requires satisfactory preparation of tap water to rigorously high standards, this technology is new to the ICU and requires extremely careful attention by users. Only the strict application of recommendations for the maintenance of online hemodiafiltration equipment would guarantee the safety of this method. As we gain more experience with this technique in the ICU, this will greatly simplify our approach to high volume therapies, as well as convective therapies in general.

Sorbent cartridges also are being used on the "blood side" of the extracorporeal circuit to remove a variety of middle to high molecular weight solutes (discussed below). In the future, sorbents may play a further role in RRT, in both the blood and dialysate treatment. One of the limitations of high-volume therapies, such as high-volume hemofiltration (HVHF, discussed below) is the requirement of large amounts of fluid (dialysate or replacement) to allow for a significant increment of clearance. This contributes to increased cost, need for physical storage space for fluid, and higher staff workload. This fluid issue can be addressed in multiple ways: online production of fluid, as already discussed, or in the case of diffusive therapies regeneration of dialysate fluid. In theory, one could create a system that regenerates small amounts of dialysis solution placed in recirculation (25).

Sorbents placed in the circuit have the potential to reduce the cost of dialysate fluid by regenerating small batches of fluid. Another experimental possibility would be to fill the dialysate compartment with a sorbent material. The sorbent particles will have the double effect of retaining endotoxin and other impurities from the dialysate and the adsorption of middle molecules from the ultrafiltrate that could be regenerated and even reinfused by back-filtration (25).

Anticoagulation always has been a major issue for extracorporeal therapies. Several studies have shown improved circuit half-lives with regional citrate anticoagulation (26, 27). However, because the additional pumps necessary for the citrate and calcium infusion are not integrated into the RRT system, this adds a degree of complexity to the therapy, and increases room for human error. In an attempt to address these issues, some of the RRT devices have introduced an additional pump that can be used for citrate (e.g., Prismaflex, Gambro) or an integrated citrate-calcium module (e.g., Aquarius, Edwards Lifesciences AG, Irvine, CA; Prometheus, Fresenius Medical Care). Further integration of treatment and anticoagulation likely will occur in the future.

Improving the Clearance of "Septic Solutes"

In keeping with the paradigm shift toward multiple organ support, there has been increasing interest in utilizing EBP not only for renal support, but also for partial removal of humoral mediators of sepsis. The Acute Dialysis Quality Initiative group suggested that patients with AKI and sepsis/multiorgan dysfunction syndrome may benefit from different treatment prescriptions than those with AKI alone (28). In addition, patients with refractory septic shock could be considered for EBP, even in the absence of frank acute renal failure. EBP can be seen as a potent immunomodulatory treatment in sepsis. Because sepsis and systemic inflammatory response syndrome are characterized by a cytokine network that is synergistic, redundant, autocatalytic, and self-augmenting, the control of such a nonlinear system cannot be approached by simple blockade or elimination of some specific mediators. Therefore, nonselective removal of a broad range of pro- and anti-inflammatory mediators by EBP may be beneficial, as recently suggested on the basis of the "peak concentration" hypothesis (29).

Cytokine removal can be achieved in a variety of ways. In hemofiltration therapies, cytokines can be adsorbed by the filtering membrane during convective treatment and may be directly removed by the convective process itself. They can be removed by diffusion using membranes with pore cutoffs of 50 to 100 kD, the so-called "high cutoff" or "super high flux" membranes. They also can be removed selectively or nonselectively with the use of sorbents. Lastly, a combination of these therapies may further enhance cytokine removal. A common concern among all of these therapies is the loss of "good" substances (such as protein, amino acids, drugs) along with the "bad" (inflammatory mediators). This is a legitimate concern and remains an area for further investigation and development.

High-Volume Hemofiltration. The concept of a dose-response curve to RRT in the ICU was introduced with the publication of the work of Dr. Ronco and colleagues (9). In this study, patients were randomized to 3 doses of postdilution continuous venovenous hemofiltration: 20 mL/kg/hr, 35 mL/kg/hr, and 45 mL/kg/hr. Patients in the 20 mL/kg/hr group had a higher 15-day mortality compared with the other two groups. A *post hoc* analysis looking at only the septic patients suggested that the highest dose may be further beneficial for this subgroup. Thus, the concept of HVHF as a potentially effective adjunctive therapy in sepsis was born. The idea is that that the partial nonspecific removal of both pro- and inflammatory mediators, as well as promediators, cuts down the peak effective concentration of these mediators, restoring immune homeostasis. The Acute Dialysis Quality Initiative defines HVHF as >35 mL/kg/hr (28). Going further along the dose continuum, a proposition was made in 2001 at the International Symposium on Critical Care Nephrology to describe hemofiltration dosing as "renal ICU dose hemofiltration" (35–50 mL/kg/hr), HVHF or "sepsis ICU dose hemofiltration" (50–100 mL/kg/hr), and very high volume hemofiltration or "sepsis cardiodepression ICU dose hemofiltration" (100–215 mL/kg/hr) (30). The high dose that characterizes HVHF can be delivered either using a constantly high exchange rate (at least 45 mL/kg/hr) or by delivering a "pulse" (for 6 to 8 hrs) of very high–volume hemofiltration (85–100 mL/kg/hr) followed by standard doses (20 mL/kg/hr) (31). Animal studies using doses in the range of 100 mL/kg/hr early in sepsis have demonstrated improved hemodynamics and survival time after HVHF (32, 33). Human studies, largely uncontrolled, have generally used lower doses, in the range of 40 to 70 mL/kg/hr. In humans, HVHF has been associated with reductions in vasopressor requirement and mortality lower than that predicted by Acute Physiology and Chronic Health Evaluation and Simplified Acute Physiology scores (31–33). More recently, a randomized study on the use of very high volume hemofiltration (200 mL/kg/hr) after out-of-hospital cardiac arrest showed lower mortality and death by intractable shock in the very high volume hemofiltration group (34). In this and other studies, HVHF has been associated with clinical benefits without any dramatic fall in mediators in the blood compartment (34, 35). It has been hypothesized that these effects are seen because cytokine or mediator concentration at the tissue level, rather than in the blood compartment, is more affected by HVHF. A further theory states that the infusion of large volumes of replacement fluid during HVHF is able to increase lymphatic flow 20- to 40-fold, greatly augmenting intrinsic clearance of mediators and cytokines at the tissue level (35).

High Cutoff Membranes. Conventional hemofilters usually have a pore size of about 5 nm, allowing the elimination of molecules up to 30 kD. Another potentially useful strategy to increase mediator removal is to increase the porosity of membranes to at least 10 nm, to achieve the removal of larger molecules 50–100 kD in size. Such blood purification using high cutoff membranes in septic AKI has a widely accepted biological rationale. Its ability to remove cytokines has been demonstrated in *ex vivo* and *in vivo* studies (36–39). High cutoff membranes also appear to have beneficial effects on immune cell function (40). High cutoff membranes increased survival in experimental models of sepsis. Preliminary human studies—including short-term use of high cutoff membranes in intermittent HD—have confirmed their ability to remove marker cytokines such as interleukin-6, -8, and -10 (39). These immunologic effects have been found to be associated with a decrease in the need for vasopressor therapy (41). Albumin losses during treatment with high cutoff appear modest, especially when dialysis mode is used while cytokine clearances

are preserved (38). A phase II randomized controlled trial is now under way.

Sorbents. Sorbents in extracorporeal therapies work by direct adsorption, retention, or adsorption/retention of molecules. Early use of sorbent therapy, particularly with charcoal, was severely limited by nonbiocompatibility, which induces platelet activation, triggering the coagulation system and clot formation. In the last few decades, there have been remarkable developments in the chemistry and manufacturing of sorbents for biomedical use, rendering them more biocompatible (25). Recently, Dr. Kellum and colleagues (42) showed that hemoadsorption with a new adsorbent made of polystyrene divinyl benzene copolymer beads with a biocompatible polyvinylpyrrolidone coating (CytoSorb, RenalTech International, New York, NY) was associated with reduced inflammation and improved survival in a murine lethal model of septic shock. Adsorbents have been developed for an intended use depending on the target molecules that they are able to bind. Two techniques, one involving nonselective mediator removal, the other involving selective molecule removal (e.g., endotoxin), show promise as useful adjunctive therapies in sepsis.

Coupled Plasma Filtration Adsorption. The technique of coupled plasma filtration adsorption (CPFA) combines plasma filtration with plasma adsorption (43). A plasma filter separates plasma from blood. The plasma is then passed through a synthetic resin cartridge and returned to the blood. A second blood filter or dialyzer can be used to remove excess fluid and small molecular weight toxins when necessary. The CPFA therapy usually is performed for 10 hrs and is frequently followed by continuous venovenous hemofiltration for the rest of the day. *Ex vivo* studies have shown it to be technically feasible to adsorb mediators by this method. Use of CPFA in animal models of sepsis has shown that several markers of inflammation can be attenuated and that animal survival can be increased (44). In a phase IIa prospective randomized crossover trial comparing CPFA plus continuous venovenous hemodiafiltration vs. continuous venovenous hemodiafiltration alone, there was a significant decrease in vasopressor requirement and a significant increase in mean arterial pressure in the CPFA and continuous venovenous hemodiafiltration group (45). In addition, CPFA was associated with a resolution in the "immunoparalysis" of circulating leukocytes. This effect was seen in spite of the fact that no decrease in the circulating concentration of tumor necrosis factor and interleukin-10 was seen. This again raises the issue as to whether the real target is the lowering of measurable cytokine levels, or favourably altering their cell-tissue-blood kinetics (35). A prospective randomized crossover trial is in progress to compare biological and clinical effects of CPFA and HVHF in septic patients with severe acute kidney injury. Although a promising therapy, there is some complexity involved with CPFA, in which three separate filters are involved (a plasma filter, a sorbent cartridge, and a dialyzer). Some simplification has been achieved with a specifically designed disposable kit for a dedicated platform (Lynda, Bellco, Mirandola, Italy). An intriguing concept toward further simplifying this therapy would be the coextrusion of the membrane polymer and the sorbent material resulting in a multiple layer structure (25). If the porosity of the two external layers can be finely regulated, the membrane then becomes a site for multiple complex transport kinetics for different molecules.

Direct Hemoperfusion With Polymyxin B–immobilized Fiber Column. An alternative to nonselective removal of inflammatory mediators is the selective removal of specific mediators at a crucial point in the cascade of sepsis. Endotoxin, one of the principal components on the outer membrane of Gram-negative bacteria, is considered fundamental in the pathogenesis of sepsis. Polymyxin B is an antibiotic that has high affinity for endotoxin, although it is associated with neurotoxicity and nephrotoxicity, precluding its systemic use. However, polymyxin B has been bound and immobilized to polystyrene fibers in a medical device (Toraymyxin, Toray Industries, Tokyo, Japan) which aims to remove circulating endotoxin by adsorption, theoretically preventing the progression of the biological cascade of sepsis (46). This device is used for direct hemoperfusion. Several studies demonstrate efficient removal of endotoxin with polymyxin B direct hemoperfusion, as well as suppression of *Staphylococcus aureus* lipoteichoic acid–induced tumor necrosis factor-α production. A recent systematic review of 28 studies, including nine randomized controlled trials, showed that direct hemoperfusion with this device appears to have favorable effects on mean arterial pressure, vasopressor use, gas exchange, and mortality (47). Overall, mean arterial pressure increased by 19 mm Hg, while a decrease in vasopressor dose was seen after the therapy. The mean Pao_2/Fio_2 ratio increased by 32 units. Polymyxin B–immobilized fiber therapy was associated with significantly lower mortality risk with a relative risk of 0.53 (95% confidence interval [CI], 0.43–0.65) for death. However, the trials assessed were limited by methodologic quality. A multicenter randomized study of this therapy in abdominal sepsis is in progress, and its results will help clarify its role as an adjunctive intervention in severe sepsis.

Extracorporeal Support for Other Organs

In multiorgan dysfunction syndrome, the probability of death is directly correlated to the number of failing organs. A clinically sensible approach is to broaden the spectrum of physiologic end points targeted by extracorporeal therapy, and provide support for multiple organs rather than just the kidneys.

Cardiac Support. Fluid overload may occur in patients with myocardial dysfunction and different clinical problems. Myocardial dysfunction may be a consequence of heart dilation with reduced contractility, ventricular stiffness with diastolic dysfunction, or the consequence of myocardial injury or circulating myocardial depressant factors as seen in sepsis. In all cases, cardiac support can be achieved by the optimization of fluid balance, the reduction of organ edema, and the restoration of desirable levels of preload and afterload. Uncontrolled studies have suggested that myocardial elastance can improve after hemofiltration with restoration of adequate fluid balance (48, 49). Recently, a controlled randomized study in patients with decompensated heart failure demonstrated that continuous ultrafiltration produces a greater weight and fluid loss than intravenous diuretics, and reduces rehospitalization rates (50). This may be due to the fact that ultrafiltration removes more total body sodium than diuretics. Furthermore, ultrafiltration does not decrease sodium presentation to the macula densa, thus avoiding neurohormonally mediated sodium and water absorption (51). In addition, the ability to provide a "diuretic holiday" to these patients may improve their responsiveness to diuretics (52). Application of ultrafiltration tech-

nology previously was limited by the need for high flow rates, large extracorporeal volumes, and large-bore central venous catheters. At present, smaller and simpler ultrafiltration devices that can be used with a combination of peripheral, midline, and central venous catheters are now available (e.g., Aquadex System 100, CHF Solutions, Minneapolis, MN; Dedyca, Bellco). However these systems cannot provide effective blood purification, only fluid removal. Although cost-benefit analyses are needed, extracorporeal therapy may soon become a routine part of our armamentarium for cardiac support.

Liver Support. Acute kidney injury associated with liver failure has been shown to have particularly poor prognosis in several studies. Conventional hemofiltration and hemodialysis techniques are insufficient to clear albumin-bound toxins present with liver failure. Artificial extracorporeal liver support has been used with varying success over the last few decades, beginning with direct charcoal hemoperfusion (53). Ideally, complete liver support would entail a device capable of both detoxification and synthetic functions. At present, two commercially available systems are capable of performing detoxification functions, providing partial liver support (54). Both systems can remove albumin-bound and water-soluble toxins that are believed to have important roles in the pathogenesis of liver failure, but differ somewhat in terms of operational characteristics. The Molecular Adsorbents Recirculating System (Gambro) operates on the principle of albumin dialysis. The presence of albumin on the "dialysate side" of a high flux membrane maximizes the diffusive transport of albumin-bound solutes by maintaining a high concentration gradient from plasma to dialysate. The used dialysate is then regenerated in a secondary circuit by being passed through adsorbent cartridges to cleanse it of albumin-bound toxins and a low-flux dialyzer to clear water-solved toxins. In contrast, the Prometheus system (Fresenius Medical Care) operates on the principle of fractionated plasma separation and adsorption. A polysulfone membrane with a cut-off above 100 kD allows partial filtration of plasma components into a secondary circuit, where it is likewise cleansed by being passed through specific sorbents. Once the blood has been reconstituted, it is passed through a high flux dialyzer to remove water-solved toxins. Anticoagulation was a particularly important issue for this device, and a citrate-calcium model recently was added (53). Small head to head studies have shown some differences in the clearance of individual bile acids (55) and hemodynamic effects (56). A small randomized study using MARS for hepatorenal syndrome showed a significant decrease in bilirubin and creatinine levels in the MARS group, and suggested a survival benefit (57). A second small randomized, controlled trial in patients with acute-on-chronic liver failure showed improvement in hepatic encephalopathy with MARS therapy, but failed to demonstrate an improvement in renal function or blood pressure (58). The only available controlled study on hepatic encephalopathy with the Prometheus is published only in abstract form at this time, and likewise showed a reduction in the clinical grade of encephalopathy (59). Further studies on these therapies are in progress.

A new experimental direction in this area is the plasma filtration adsorption dialysis (Fig. 1) system, which utilizes a tricompartmental dialyzer (60). The patient's blood is purified through a combination of convection and adsorption performed on the patient's plasma and whole blood dialysis. The unique feature of this system is that the patient's own plasma, after purification, is used as dialysate in the third compartment. The tricompartmental dialyzer is composed of hollow fibers, forming three compartments along the extension of the dialyzer. The first compartment is formed by the inner space of hollow fibers in which the blood is pumped through the length of the whole fibers. The traditional dialysate compartment of the dialyzer is divided into two more compartments separated by a wall along the extension of the hollow fibers; the second compartment is the delineated space where the patient's plasma can be filtered from whole blood. The third compartment is the space in which the patient's regenerated plasma undergoes purification based on diffusion and adsorption. A detailed description of this promising technique has been published recently (60).

Lung Support. For patients with severe acute respiratory distress syndrome, conservative treatment with lung protective ventilation often is not sufficient to prevent life-threatening hypoxemia and/or hypercapnea, and additional strategies are necessary. Pump-driven extracorporeal gas exchange systems (extracorporeal lung assist or extracorporeal membrane oxygenation) have been advocated in these patients to provide sufficient gas exchange and lung rest. For newborns with severe respiratory failure, a prospective randomized study demon-

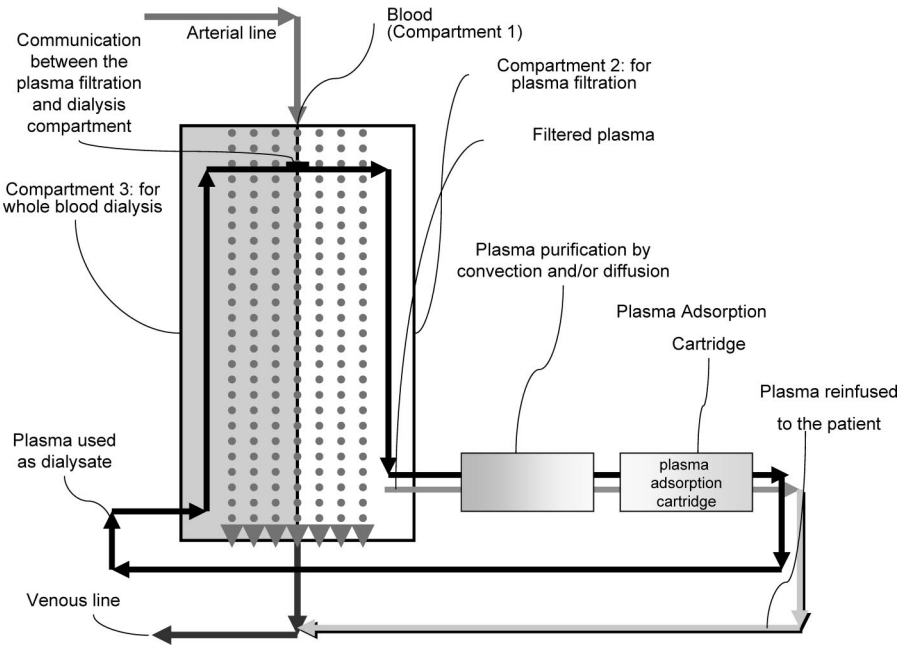

Figure 1. Plasma filtration adsorption dialysis: Compartment 1 is the inner space of hollow fibers in which the blood is pumped through. The traditional "dialysate compartment" of the dialyzer is divided into compartment 2, the space in which the patient's plasma can be filtered from whole blood, and compartment 3, the space in which the patient's regenerated plasma is used as dialysate.

strated that extracorporeal membrane oxygenation improved clinical outcomes and is cost-effective compared with conservative therapy (61). In adults with acute respiratory distress syndrome, however, the results have been disappointing, with one of the trials reporting significant technical problems in the extracorporeal membrane oxygenation group (62). Extracorporeal membrane oxygenation therapy is considered highly demanding in terms of personnel, technical requirements, and monitoring. More recently, a new generation of pumpless extracorporeal lung assist devices driven by the patient's own cardiac output have become available. The interventional lung-assist membrane ventilator device (ILA, NovaLung, Hechingen, Germany) utilizes newly designed oxygenators with reduced pressure drop, such that the difference between arterial and venous blood pressure is sufficient to achieve adequate extracorporeal blood flow (63, 64). This new device avoids all pump-related complications, reduces extracorporeal circuit volume, and simplifies clinical management. Potential disadvantages are the same as those encountered in continuous arteriovenous hemofiltration, including lack of control over blood flow and complications related to arterial cannulation. Another method to potentially reduce lung injury from invasive ventilation would be to remove carbon dioxide from the circulating blood by means of a special cartridge in series with a hemofilter (65). This may represent, in selected patients, a new chance for reducing the requirement for invasive mechanical ventilation, allowing instead for a noninvasive approach. Special membranes are under evaluation utilizing a dry/wet gas exchange process leading to significant values of CO_2 clearance in the extracorporeal circuit. Such systems may reduce the morbidity and mortality of acute lung injury and acute respiratory distress syndrome in the future. Well designed clinical trials are necessary to demonstrate a clinical benefit for this and all other experimental devices.

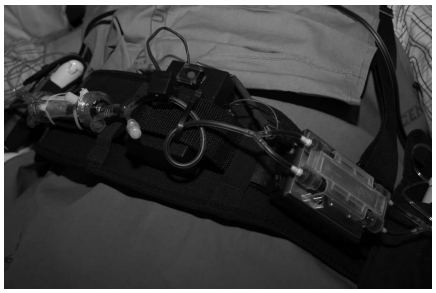

Figure 2. The Wearable Artificial Kidney consists of a hollow-fiber filter, a 9-V battery-operated pulsatile blood pump, a micropump for heparin infusion, and another micropump to control ultrafiltration rate.

Miniaturization: From Portable Devices to "Intracorporeal" Dialysis

The evolution of technology in recent years has made it possible to reduce device size and weight of pieces of equipment that in the past would have occupied an entire room. An example of this is the movement from mainframes to desktop PCs to laptops to personal digital assistants. Examples of miniaturization in the medical arena include pacemakers and automatic implanted cardiac defibrillators. In the field of nephrology, we have moved from large flat plate dialyzers and enormous vats of liquid dialysate to small compact hollow fiber dialyzers and the use of solute concentrates and bicarbonate proportioning systems. However, the size of dialysis machines has changed to a lesser extent, and leaves room for improvement.

Some progress has been made in this arena, with the creation of prototype wearable HD and peritoneal dialysis systems. Dr. Gura and colleagues (66) have made a wearable artificial kidney (Fig. 2) consisting of a small dialyzer, a sorbent-based dialysate regeneration system, and a main pump with two channels, one for blood and another one for dialysate, where both fluids are propelled in a pulsating fashion but on opposing cycles so that pressures "peak" in the first compartment while they "trough" in the second and vice versa. The device also features reservoirs with heparin to be infused into the blood circuit, as well as magnesium and calcium to be infused into the dialysate. These infusions are accomplished by auxiliary small pumps at prescribed rates. A volumetrically controlled auxiliary pump removes ultrafiltrate. Initial clinical experience with a small number of patients has been encouraging. Recently, the concept for a wearable artificial kidney device for peritoneal dialysis (Fig. 3) was introduced by Drs. Ronco and Fecondini (67). This consists of a double lumen peritoneal catheter, lines for dialysate inflow and outflow, a miniaturized rotary pump, a circuit for dialysate regeneration with four sorbent cartridges in parallel, filter for deaeration and microbiological safety, and a personal digital assistant as a remote control. The device remains to be tested clinically. Likewise, in the field of extracorporeal

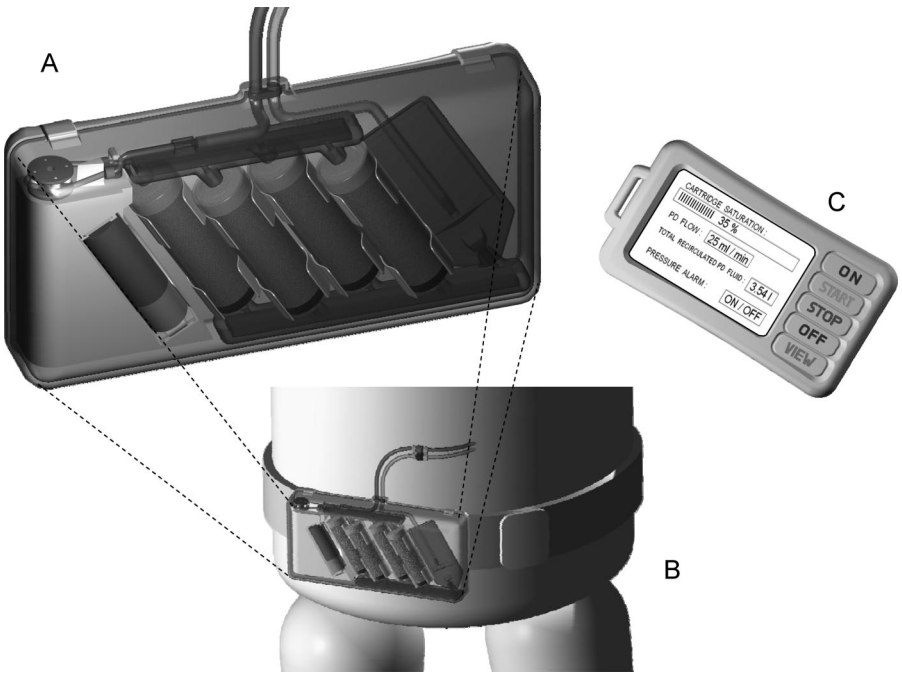

Figure 3. The Vicenza Wearable Artificial Kidney for Peritoneal Dialysis. *A*, waterproof adsorption unit. *B*, schematic representation of the device on a belt. *C*, handheld computer for remote wireless control of operations, which can be worn around the patient's neck.

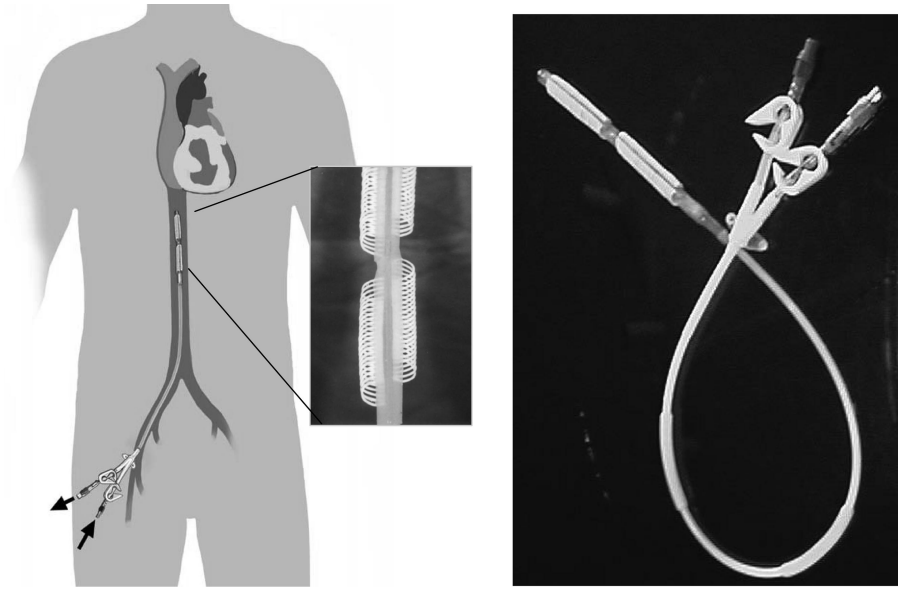

Figure 4. Intracorporeal plasma separation device. *A*, schematic representation of the device in the vena cava. *B*, magnification of the catheter tip. *C*, photo of the catheter.

lung assist, miniaturized versions of extracorporeal membrane oxygenation utilizing a small-sized rotary blood pump have been developed and are under further investigation (68, 69). Miniaturized systems such as these providing continuous therapy may be future options for EBP in the ICU. Because these devices are portable, truly continuous therapy can be provided, instead of interrupting therapy when patients go for diagnostic or therapeutic interventions.

Even further along the road of miniaturization are intracorporeal devices. Dr. Handley and colleagues (70, 71) have designed specially modified in-dwelling catheters with the capability for direct plasma extraction. This experimental "hemofiltration" catheter (Fig. 4) is under evaluation for slow-continuous intravenous ultrafiltration for fluid removal for congestive heart failure refractory to diuretics. In animal studies, this device performed ultrafiltration efficiently without need for systemic anticoagulation (71). This technique shows great promise in the treatment of fluid overload in heart failure, surgery, or trauma. Further modification of these intracorporeal filters may eventually lead to selective solute removal in addition to fluid removal. New concepts for an intravascular oxygenator, designed to be inserted directly into the vena cava, involve a combination of a cross-flow oxygenator and an intravascular microaxial blood pump to improve blood flow and gas exchange (69). These novel intracorporeal devices offer exciting possibilities for blood purification in the future.

Nanotechnology

Nanotechnology, defined as the science of material features between 10^{-9} and 10^{-7} of a meter in size, although common in the laboratory as proof of concept, has not yet made the leap into the clinical arena. There are theoretical advantages of micro- and nanometer scale engineering in the field of renal replacement, including the manufacture of high-hydraulic permeability membranes with implanted sensing and control structures. These can pave the way to autonomous hemofiltration systems (6). Nanotechnology can be implemented to produce membranes with superior performance. The pore structure is defined by deposition and patterning of a polysilicon film on the silicon wafer. Prototypes of silicon nanomer membranes with parallel slit-shaped pores and an electrostatic barrier to passage of specific molecules have been fabricated and tested in the laboratory, with favorable liquid and molecular flow patterns (72). Membrane modification using nanotechnology has led to the conceptual design for a human nephron filter (73). This device consists of two membranes operating in series within one cartridge device: One mimics the function of the glomerulus, while the other mimics the function of the renal tubules. This novel membrane system would eliminate the need for traditional dialysis. The membrane cartridge is part of a wearable system that includes a keypad and display, a high-capacity battery, and a waste bag. This device is intended to be a continuously functioning, wearable (or implantable) artificial kidney. As mentioned previously, a truly continuous blood purification therapy potentially will benefit critically patients with acute kidney injury.

A second area in which nanotechnology would be applicable is on-line real-time estimation of extracellular fluid volume. This would be a crucial component of any automated dialysis platform. Miniature components integrating sensors, actuators, and electronics are produced using many of the same microfabrication techniques as those used to manufacture integrated circuits on silicon substrates, and are called microelectromechanical systems (74). This manufacturing strategy enables the mass production of miniature, high performance, mechanical, fluidic, and optical components that can be integrated with electronics at low unit cost. This technology can be exploited to create miniature biofeedback sensors, be they blood volume monitors or bioimpedance. The telemetric application of microelectromechanical sensor technology to hemodialytic systems could involve both sensing and transmission of data.

Bioartificial Organs

All purely artificial forms of organ support described above provide clearance of various solutes, but cannot substitute for endocrine, synthetic, and other metabolic functions of these organs. Living cells placed on artificial scaffolding produce a "living membrane" and present a promising alternative that may result in improved biochemical and clinical outcomes.

Bioartificial Kidney. Renal tubular cells perform many vital functions. They are the main site of electrolyte resorption and secretion in the human nephron, and have endocrine functions, as well. Dr. Humes and colleagues (75–77) have successfully developed a renal assist device (RAD) by seeding human renal proximal tubular cells from cadaveric kidneys (deemed unsuitable for kidney transplantation) into a hollow-fiber high-flux polysulfone dialyzer. The renal tubular cells

line the inner surface of the hollow fibers. The bioartifical kidney is composed of this RAD in combination with a conventional continuous venovenous hemofiltration system. The hemofilter acts as the glomerulus. The ultrafiltrate from the hemofilter is pumped into the lumen of the RAD cartridge and bathes the proximal tubular cells, which perform their metabolic functions. Blood exiting the hemofilter is pumped into the exterior or "dialysate side" of the RAD. Fluid and solutes reabsorbed by the proximal tubular cells of the RAD into the dialysate side mix with the blood and are returned to the patient. The remaining fluid exiting from the RAD is discarded as urine. Animal studies with the RAD demonstrated increased ammonia secretion, glutathione metabolism, and 1,25-dihydroxy-Vitamin D3 production, and lower plasma circulating proinflammatory cytokine secretion with the use of the device (76). Clinically, there appeared to be better cardiovascular performance and longer survival times. Phase I trials with the bioartificial kidney in humans demonstrated increased diuresis from the native kidneys and decreased vasopressor requirement (77). A phase II trial in critically ill patients with AKI recently has been completed and further studies of this promising therapy are being planned.

Bioartificial Liver. The liver performs multiple metabolic functions ranging from protein synthesis to gluconeogenesis; metabolism of amino acids, lipids, and urea; and the detoxification of drugs and the byproducts of the intermediate metabolism. The liver also acts in the regulation of the immune system and the metabolism of many hormones. In a fashion similar to the renal assist device, bioartificial liver support systems use viable hepatocytes on a mechanical support in an extracorporeal device connected to the patient's circulation. These devices attempt to address to some extent the liver's complex tasks of regulation and synthesis. At present, there are the Extracorporeal Liver Assist Device (Vital Therapies, San Diego, CA), HepatAssist (Circe Biomedical, Lexington, MA), Modular Extracorporeal Liver Support system (Charite, Berlin, Germany), and the Amsterdam Medical Center bioartificial Liver (University of Amsterdam, Netherlands). The HepatAssist and the Amsterdam device use porcine hepatocytes, while the Extracorporeal Liver Assist Device and the Modular Extracorporeal Liver Support device use a human cell line (78). Although bioartificial liver systems have not been shown to improve the survival of patients, further development is under way. A particularly exciting notion is that of a double-compartment cell culture apparatus with renal proximal tubular cells on one side of a synthetic microporous membrane, while a cell line of hepatic origin was seeded on the opposite side (79). *In vitro* studies show that this novel membrane appeared to be capable of selective transport of certain solutes such as ammonium, glucose, and lactate, as well as lidocaine metabolism, suggesting some form of useful interaction between renal and hepatic cells. This type of dual compartment cell culture apparatus may represent a novel form of bioartificial liver capable of biotransport in addition to biosynthetic and metabolic activities.

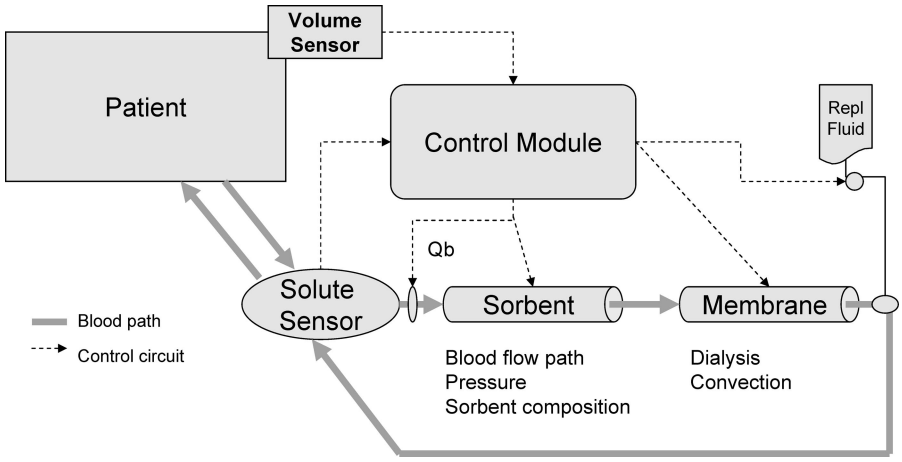

Figure 5. Integrated extracorporeal blood purification system. *Qb*, blood flow; *Repl*, replacement.

Information Technology

Many current machines collect a large amount of data, and allow the information to be downloaded and used in personal computers. In the future, wireless technology may permit the user to communicate directly with the machine in real time through personal digital assistants, such that the information can be used during clinical rounds or for research purposes. Information technology also would play an increasingly important role in international multicenter epidemiologic studies in the critical care setting, simplifying the collection of detailed data from geographically distant ICUs via a web-based interface (80).

Artificial neural networks are made up of interconnecting artificial neurons that may share some properties of biological neural networks. They may either be used to gain an understanding of biological neural networks, or for solving traditional artificial intelligence tasks without necessarily attempting to model a real biological system. With their ability to derive meanings from complicated or imprecise data, artificial neural networks can be used to extract patterns and direct trends in our data that are too complex to be noticed by either humans or other computer techniques (81). They can be valuable research tools in the arena of extracorporeal support.

Advances in information technology and monitoring may permit the eventual realization of a fully integrated extracorporeal blood purification system (Fig. 5). Advances in functional hemodynamic monitoring, online continuous solute sensing, and the myriad of technical advances described above may one day be integrated so that control of fluid and multiple solutes can be orchestrated within a single platform. Advances in computational biology and control theory also can be added to the list of future innovations that may ultimately lead to an "artificial organ" with much greater capacity to work with the native biological systems than previously thought possible (82, 83).

CONCLUSIONS

Extracorporeal therapy has expanded significantly over the past few decades, from solely artificial renal replacement therapy. Because our patients have multiple organ dysfunction, it seems logical to provide them multiple organ support. Technological advances have opened the door to a multifaceted intervention that

is directed at supporting the function of multiple organs through the treatment of blood. In the future, we may have a single machine platform with different options, flexibility in parameters and prescription and, most important, a user-friendly interface. This will allow us to be versatile and adjust our "technology score" to match our severity of illness score to restore metabolic and immunologic homeostasis. Exciting future developments are miniaturization and intracorporeal devices, and the use of viable organ cells incorporated into medical devices that will go beyond detoxification, and more closely mimic the function of intact organs.

REFERENCES

1. Uchino S, Kellum J, Bellomo R, et al: Acute renal failure in critically ill patients: A multinational, multicenter Study. *JAMA* 2005; 294:813–818
2. Brivet FG, Kleinknecht DJ, Loirat P, et al: Acute renal failure in intensive care units—causes, outcome, and prognostic factors of hospital mortality; a prospective, multicenter study. French Study Group on Acute Renal Failure. *Crit Care Med* 1996; 24:192–198
3. Ronco C, Bellomo R: Acute renal failure and multiple organ dysfunction in the ICU: From renal replacement therapy (RRT) to multiple organ support therapy (MOST). *Int J Artif Organs* 2002; 25:733–747
4. Bellomo R, Ronco C, Kellum J, et al: Acute renal failure—definition, outcome measures, animal models, fluid therapy, and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8:R204–R212
5. Subramanian S, Venkataraman R, Kellum JA: Influence of dialysis membranes on outcomes in acute renal failure: A meta-analysis. *Kidney Int* 2002; 62:1819–1823
6. Ronco C, Nissenson AR: Does nanotechnology apply to dialysis? *Blood Purif* 2001; 19: 347–352
7. Lonnemann G: Dialysate bacteriological quality and the permeability of dialyzer membranes to pyrogens. *Kidney Int* 1993; 41:S195–S200
8. Ricci Z, Picardo S, Ronco C: Results from international questionnaires. *Contrib Nephrol* 2007; 156:297–303
9. Ronco C, Bellomo R, Homel P, et al: Effects of different doses in continuous venovenous hemofiltration on outcomes of acute renal failure. *Lancet* 2000; 356:20–30
10. Schiffl H, Lang S, Fischer R: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002; 346:305–310
11. Saudan P, Niederberger M, De Seigneux S, et al: Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 2006; 70:1312–1317
12. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, et al: Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. *Crit Care Med* 2002; 30:2205–2211
13. Gokal R: Quality of life in patients undergoing renal replacement therapy. *Kidney Int* 1993; 43(Suppl 40):S23–S27
14. Manns BJ, Taub KJ, Donaldson C: Economic evaluation and end-stage renal disease: From basics to bedside. *Am J Kidney Dis* 2000; 36:12–28
15. Culleton BF, Larson MG, Wilson PW, et al: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999; 56:2214–2219
16. Jacka MJ, Ivancinova X, Gibney RTN: Continuous renal replacement therapy improves renal recovery from acute renal failure. *Can J Anaesth* 2005; 52:327–332
17. Bell M, Swedish Intensive Care Nephrology Group, Granath F, et al: Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. *Int Care Med* 2007; 33:773–780
18. Uchino S, Bellomo R, Kellum JA, et al: The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators Writing Committee: Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury. *Int J Artif Organs* 2007; 30:281–292
19. Mehta RL, McDonald B, Gabbai F, et al: A randomized clinical trial of continuous vs intermittent dialysis for acute renal failure. *Kidney Int* 2001; 60:1154–1163
20. Mehta RL, Chertow GM: In critically ill patients with acute renal failure, outcomes, not dollars, should drive modality choice. *Crit Care Med* 2003; 31:644–646
21. Ledebo I: On-line preparation of solutions for dialysis: Practical aspects versus safety and regulations. *J Am Soc Nephrol* 2002; 13: S78–S83
22. Canaud B, Bosc JY, Leray-Moragues H, et al: On-line haemodiafiltration. Safety and efficacy in long-term clinical practice. *Nephrol Dial Transplant* 2000; 5:S60–S67
23. Naka T, Baldwin I, Bellomo R, et al: Prolonged daily intermittent renal replacement therapy in ICU patients by ICU nurses and ICU physicians. *Int J Artif Organs* 2004; 27: 380–387
24. Marshall MR, Ma T, Galler D, et al: Sustained low-efficiency daily diafiltration (SLEDD-f) for critically ill patients requiring renal replacement therapy: Towards an adequate therapy. *Nephrol Dial Transplant* 2004; 19: 877–884
25. Ronco C: Sorbents: From bench to bedside. Can we combine membrane separation processes and adsorbent based solute removal? *Int J Artif Organs* 2006; 29:819–822
26. Marshall MR, Ma TM, Eggleton K, et al: Regional citrate anticoagulation during simulated treatments of sustained low efficiency diafiltration. *Nephrology* (*Carlton*) 2003; 8:302–310
27. Bagshaw SM, Laupland KB, Boiteau PJ, et al: Is regional citrate superior to systemic heparin anticoagulation for continuous renal replacement therapy? A prospective observational study in an adult regional critical care system. *J Crit Care* 2005; 20:155–161
28. Kellum JA, Bellomo R, Ronco C, et al: The 3rd International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). *Int J Artif Organs* 2005; 28:441–444
29. Ronco C, Bonello M, Bordoni V, et al: Extracorporeal therapies in non-renal disease: Treatment of sepsis and the peak concentration hypothesis. *Blood Purif* 2004; 22: 164–174
30. Honorè PM, Jamez J, Wauthier M, et al: Very high volume hemofiltration: A comprehensive review. Proceedings from the International Symposium on Critical Care Nephrology (ISCCN). Melbourne, Australia, Australasian Medical Pub Co, 2001
31. Ratanarat R, Brendolan A, Ricci Z, et al: Pulse high-volume hemofiltration in critically ill patients: A new approach for patients with septic shock. *Semin Dial* 2006; 19: 69–74
32. Honorè PM, Joannes-Boyau O, Gressens B: Blood and plasma treatments: High volume hemofiltration—a global view. *Contrib Nephrol* 2007; 156:371–386
33. Honorè PM, Joannes-Boyau O: High volume hemofiltration (HVHF) in sepsis: A comprehensive review of rationale, clinical applicability, potential indications, and recommendations for future research. *Int J Artif Organs* 2004; 27:1077–1082
34. Laurent I, Adrie C, Vinsonneau C, et al: High-volume hemofiltration after out-of-hospital cardiac arrest: A randomized study. *J Am Coll Cardiol* 2005; 46:432–437
35. Honorè PM, Joannes-Boyau O, Gressens B: Blood and plasma treatments: The rationale of high-volume hemofiltration. *Contrib Nephrol* 2007; 156:387–395
36. Mariano F, Fonsato V, Lanfranco G, et al: Tailoring high-cutoff membranes and feasible application in sepsis-associated acute renal failure: *In vitro* studies. *Nephrol Dial Transplant* 2005; 20:1116–1126
37. Lambermont B, Delanaye P, Dogne JM, et al: Large-pore membrane hemofiltration increases cytokine clearance and improves right ventricular–vascular coupling during endotoxic shock in pigs. *Artif Organs* 2006; 30:560–564
38. Morgera S, Slowinski T, Melzer C, et al: Renal replacement therapy with high-cutoff hemofilters: Impact of convection and diffusion on cytokine clearances and protein status. *Am J Kidney Dis* 2004; 43:444–453
39. Haase M, Bellomo R, Baldwin I, et al: Hemodialysis membrane with a high-molecular-weight cutoff and cytokine levels in sepsis

complicated by acute renal failure: A phase 1 randomized trial. *Am J Kidney Dis* 2007; 50:296–304
40. Morgera S, Haase M, Rocktaschel J, et al: High permeability haemofiltration improves peripheral blood mononuclear cell proliferation in septic patients with acute renal failure. *Nephrol Dial Transplant* 2003; 18: 2570–2576
41. Morgera S, Haase M, Kuss T, et al: Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure. *Crit Care Med* 2006; 34:2099–2104
42. Kellum J, Song M, Venkataran M: Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-κB DNA binding, and improves short-term survival in lethal endotoxemia. *Crit Care Med* 2004; 32:801–805
43. Bellomo R, Tetta C, Ronco C: Coupled plasma filtration adsorption. *Intensive Care Med* 2003; 29:1222–1228
44. Tetta C, Gianotti L, Cavaillon JM, et al: Coupled plasma filtration-adsorption in a rabbit model of endotoxic shock. *Crit Care Med* 2000; 28:1526–1533
45. Ronco C, Brendolan A, Lonnemann G, et al: A randomized cross-over study of coupled plasma filtration with adsorption in septic shock. *Crit Care Med* 2002; 30:1250–1255
46. Shoji H: Extracorporeal endotoxin removal for the treatment of sepsis: Endotoxin adsorption cartridge (Toraymyxin). *Ther Apher Dial* 2003; 7:108–114
47. Cruz DN, Perazella MA, Bellomo R, et al: Effectiveness of polymyxin B–immobilized fiber column in sepsis: A systematic review. *Crit Care* 2007; 11:R47
48. Ronco C, Ricci Z, Brendolan A, et al: Ultrafiltration in patients with hypervolemia and congestive heart failure. *Blood Purif* 2004; 22:150–163
49. Bart BA, Boyle A, Bank AJ, et al: Ultrafiltration versus usual care for hospitalized patients with heart failure: The Relief for Acutely Fluid-overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial. *J Am Coll Cardiol* 2005; 46:2043–2046
50. Costanzo MR, Guglin ME, Saltzberg MT, et al: Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007; 49:675–683
51. He X-R, Greenberg S, Briggs J, et al: Effects of furosemide and verapamil on the NaCl dependency of macula densa–mediated secretion. *Hypertension* 1995; 26:137–142
52. Guazzi MD, Agostoni P, Perego B, et al: Apparent paradox of neurohumoral axis inhibition after body fluid volume depletion in patients with chronic congestive heart failure and water retention. *Br Heart J* 1994; 72:534–539
53. Liu JP, Gluud LL, Als-Nielsen B, et al: Artificial and bioartificial support systems for liver failure. *Cochrane Database Syst Rev* 2004; 1:CD003628
54. Krisper P, Stauber RE: Technology insight: Artificial extracorporeal liver support—how does Prometheus compare with MARS? *Nat Clin Pract Nephrol* 2007; 3:267–276
55. Stadlbauer V, Krisper P, Beuers U, et al: Removal of bile acids by two different extracorporeal liver support systems in acute-on-chronic liver failure. *ASAIO J* 2007; 53: 187–193
56. Laleman W, Wilmer A, Evenepoel P, et al: Effect of the molecular adsorbent recirculating system and Prometheus devices on systemic haemodynamics and vasoactive agents in patients with acute-on-chronic alcoholic liver failure. *Crit Care* 2006; 10:R108
57. Mitzner SR, Stange J, Klammt S, et al: Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: Results of a prospective, randomized, controlled clinical trial. *Liver Transpl* 2000; 6:277–286
58. Sen S, Davies NA, Mookerjee RP, et al: Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: A randomized controlled study. *Liver Transpl* 2004; 10: 1109–1119
59. Kramer L, Bauer E, Scheuk P. Clinical experience with artificial liver support in chronic liver failure with encephalopathy. Abstr. *ASAIO J* 2000; 46:a211
60. Nalesso F, Brendolan A, Crepaldi C, et al: Albumin dialysis and plasma filtration adsorption dialysis system. *Contrib Nephrol* 2007; 156:411–418
61. Petrou S, Edwards L, UK Collaborative ECMO Trial: Cost effectiveness analysis of neonatal extracorporeal membrane oxygenation based on four year results from the UK Collaborative ECMO Trial. *Arch Dis Child Fetal Neonatal Ed* 2004; 89:F263–F268
62. Morris AH, Wallace CJ, Menlove RL, et al: Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; 149:295–305
63. Walles T: Clinical experience with the iLA Membrane Ventilator pumpless extracorporeal lung-assist device. *Expert Rev Med Devices* 2007; 4:297–305
64. Bein T, Weber F, Philipp A, et al: A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med* 2006; 34:1372–1377
65. Heulitt MJ, Marshall J: Kidney function during extracorporeal lung assist techniques (ECMO/ECCO2R). *In*: Critical Care Nephrology. Ronco C, Bellomo R (Eds). Dordrecht, The Netherlands, Kluwer Academic Publishers, 1998, pp 1073–1079
66. Gura V, Ronco C, Nalesso F, et al: The wearable artificial kidney is feasible: First human data with slow continuous ambulatory ultrafiltration. *Kidney Int* 2008; In Press
67. Ronco C, Fecondini L: The Vicenza wearable artificial kidney for peritoneal dialysis (ViWAK PD). *Blood Purif* 2007; 25:383–388
68. Dembinski R, Kopp R, Henzler D, et al: Extracorporeal gas exchange with the DeltaStream rotary blood pump in experimental lung injury. *Artif Organs* 2003; 27:530–536
69. Cattaneo G, Strauss A, Reul H: Compact intra- and extracorporeal oxygenator developments. *Perfusion* 2004; 19:251–255
70. Handley HH, Gorsuch R, Levin NW, et al: Slow continuous intracorporeal plasmapheresis for acute fluid overload. *Blood Purif* 2003; 21:72–78
71. Handley HH, Gorsuch R, Peters H, et al: Slow continuous intravenous plasmapheresis (SCIP): Clinical applications and hemostability of extracorporeal ultrafiltration. *Contrib Nephrol* 2005; 149:334–342
72. Fissell WH, Westover AJ, Humes HD, et al: Initial characterization of a nanoengineered ultrafiltration membrane. *J Am Soc Nephrol* 2003; 13:a602
73. Nissenson AR, Ronco C, Pergamit G, et al: The human nephron filter: Toward a continuously functioning, implantable artificial nephron system. *Blood Purif* 2005; 23: 269–274
74. Fissell WH, Humes HD, Fleischman AJ, et al: Dialysis and nanotechnology: Now, 10 years, or never? *Blood Purif* 2007; 25:12–17
75. Humes HD, Weitzel WF, Fissell WH: Renal cell therapy in the treatment of patients with acute and chronic renal failure. *Blood Purif* 2004; 22:60–72
76. Humes HD, Fissell WH, Weitzel WF, et al: Metabolic replacement of kidney function in uremic animals with a bioartificial kidney containing human cells. *Am J Kidney Dis* 2002; 39:1078–1087
77. Humes HD, Weitzel WF, Bartlett RH, et al: Renal cell therapy is associated with dynamic and individualized responses in patients with acute renal failure. *Blood Purif* 2003; 21: 64–71
78. Pless G, Sauer IM: Bioartificial liver: Current status. *Transplant Proc* 2005; 37:3893–3895
79. Takahashi M, Sakurai M, Enosawa S, et al: Double-compartment cell culture apparatus: Construction and biochemical evaluation for bioartificial liver support. *Cell Transplant* 2006; 15:945–952
80. Kindgen-Milles D, Journois D, Fumagalli R, et al: Study protocol: The DOse REsponse Multicentre International collaborative initiative (DO-RE-MI). *Crit Care* 2005; 9:R396–R406
81. Ronco C: Evolutionary artificial neural networks: Efficient analysis model or mathematical chimera? *Int J Artif Organs* 2005; 28:1–2
82. Sontag ED: Some new directions in control theory inspired by systems biology. *Syst Biol* 2004; 1:9–18
83. Paolini F, Bosetto A: Biofeedback systems architecture. *Adv Ren Replace Ther* 1999; 6:255–264