

# Update In Nonpulmonary Critical Care

## Renal Replacement Therapy for Acute Renal Failure

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Acute renal failure (ARF) is defined as deterioration of renal function over days to weeks. The mortality rate of ARF is 50–80% in intensive care unit (ICU) populations, and has not declined significantly since the initial marked benefit of acute dialysis therapy (1–6). Although multiple system organ failure (MSOF) and other comorbidities contribute to its high mortality rate, ARF independently increases morbidity and mortality (7). ARF-specific severity of illness scoring systems have been validated to predict prognosis in ICU ARF, accounting for both severity of renal failure and associated MSOF (2, 3, 6, 8). A prospective multicenter ICU study of ARF found that subjects with septic ARF had a far higher mortality rate (74 versus 45%,  $p < 0.001$ ) than those without sepsis (6).

In concert with the search for ARF prevention and regeneration/repair strategies, it is imperative to focus efforts to reduce ICU ARF mortality. Septic ARF is the dominant problem in managing ICU patients requiring renal replacement therapy (RRT); because of hemodynamic instability, it is difficult to manage these patients with traditional intermittent hemodialysis (HD). Nevertheless, intermittent HD remains the dominant mode of RRT in the United States, used in more than two-thirds of cases in recent surveys (9, 10). In contrast, continuous renal replacement therapy (CRRT) is used with greater frequency elsewhere, and almost exclusively in Australian ICUs (8). There are many unanswered fundamental questions in this area, creating serious obstacles to the design and execution of clinical studies to improve outcome. Controversial issues include the impact of HD membrane biocompatibility on outcome, and the preferred initiation indications, modality (continuous versus intermittent), and dose for RRT prescriptions. There is also an emerging literature examining the use of RRT to remove septic inflammatory mediators, which is discussed briefly within the context of current RRT management.

### RENAL REPLACEMENT THERAPY TECHNIQUES: CLASSIFICATION AND SOLUTE TRANSPORT PROCESSES

Renal replacement therapies currently available include intermittent HD, peritoneal dialysis, and various forms of CRRT (1, 3, 11, 12). Peritoneal dialysis is now rarely used as RRT for critically ill patients. Increasingly, critically ill patients with renal failure are managed with CRRT, rather than intermittent HD, with expanding involvement of intensivists and ICU nurses in the provision of RRT. CRRT techniques are classified according to the driving force for blood flow (spontaneous/arteriovenous or pumped/venovenous techniques) and the predominant solute transport process employed.

Solute transport across semipermeable membranes occurs either by diffusion or convection. Diffusion ceases when an equilibrium of solute concentration across the membrane is achieved. Small solutes ( $< 500$ – $5,000$  Da) are efficiently cleared by diffusive transport, but larger solutes ( $> 5,000$  Da) are not. Hemodialysis removes solutes primarily by diffusion, during intermittent HD or continuous dialysis (continuous arteriovenous hemodialysis, CAVHD; continuous venovenous hemodialysis, CVVHD). Countercurrent flow of dialysate on the opposite side of the semipermeable membrane helps prevent attainment of equilibrium with the circulation, maintaining the concentration gradient for diffusion and efficient dialysis.

Solutes may instead be transported across a semipermeable membrane by convection. Ultrafiltration occurs when water is driven across a membrane by a pressure gradient. Solutes that are small enough to cross the membrane are freely transported with water (“solvent drag”) by convection, and are found in the ultrafiltrate at concentrations similar to those found in the original solution. Hemofiltration removes solutes by convection, which is not an efficient solute transport process, so that only large-volume ultrafiltration results in significant solute clearance. As a result, low-volume hemofiltration performed solely to maintain fluid balance does not result in significant clearance of uremic toxins; slow continuous ultrafiltration or SCUF, with ultrafiltration rates of 200 ml/h or less, is in this category. When hemofiltration is performed for uremia therapy, however, increased hourly ultrafiltration rates of 1–2 L/h are customary, and urea clearance by continuous arteriovenous (CAVH) or venovenous (CVVH) hemofiltration is substantial. During hemofiltration, administration of “replacement fluid” containing buffer (bicarbonate or lactate) and various electrolytes (sodium, potassium, calcium, magnesium, phosphorus) prevents iatrogenic acidosis and electrolyte depletion, and further lowers the plasma concentration of uremic solutes by hemodilution, augmenting the effect of simple transmembrane urea clearance. The most complex form of CRRT combines convective and diffusive solute transport during continuous hemodiafiltration (CAVHDF or CVVHDF) (12).

### INDICATIONS FOR RRT INITIATION

A number of the indications for RRT are uncontroversial, including uremic symptoms (anorexia, nausea, vomiting) or signs (uremic pericarditis, bleeding, encephalopathy); hyperkalemia refractory to medical management; volume overload unresponsive to fluid restriction and diuretics; metabolic acidosis that is severe or accompanied by volume overload, precluding adequate bicarbonate therapy; certain dialyzable intoxications (e.g., lithium, toxic alcohols, salicylate); some cases of hypocalcemia, hyperphosphatemia, or hypercalcemia; and anuric ARF unresponsive to acute interventions (reversal of prerenal factors, relief of obstruction).

The precise timing of RRT initiation is usually a matter of clinical judgment (1). Absent the preceding clinical indications, HD is commonly initiated when the blood urea nitrogen

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(BUN) concentration reaches 100 mg/dl, and repeated to maintain a predialysis BUN below 80 mg/dl (5). A U.S. ICU survey of ARF cases found that the mean BUN and creatinine values at initiation of RRT were 98 and 4.5 mg/dl, respectively (9). This pattern of practice is based primarily on early experience suggesting that uremic bleeding diathesis and hemorrhage were reduced when hemodialysis was initiated before the BUN exceeded 100 mg/dl (13–15), the results of small prospective ARF studies in 1975 and 1986 (1), and extrapolation from results of the National Cooperative Dialysis Study in chronic renal failure patients. This relatively prophylactic approach is balanced against potential adverse effects of RRT, including hypotension with worsening renal ischemic acute tubular necrosis (ATN), and the renal and systemic inflammatory effects of extracorporeal membrane exposure.

Similarly, the threshold to initiate RRT to remove volume varies among clinicians. The inability to severely restrict fluid intake in ICU patients results in adverse effects of volume overload more frequently than in less severely ill patients with ARF. It should be noted that the traditional definition of oliguria (< 400 ml/d) reflects the minimum urine output necessary to excrete the average daily uremic solute load, not accounting for hypercatabolism in septic patients, or the large obligate fluid intakes. CRRT is thought to permit fluid and solute removal with greater hemodynamic stability than intermittent HD for two reasons. The first is the fact that fluid removal is done slowly and continuously, rather than in 1- to 4-L increments over 2- to 4-h treatment sessions. Less intuitive is the fact that diffusive solute clearance by intermittent HD results in loss of intravascular solutes and acute plasma hypoosmolality relative to surrounding tissues, which in turn causes transfer of plasma water into tissues. In effect, intermittent HD results in an acute “double loss” of plasma volume, across both extracorporeal and internal membranes. Intermittent isolated ultrafiltration (also called IUF) sessions, which remove fluid without diffusive solute clearance, are commonly used for acute volume removal with greater hemodynamic stability than intermittent HD. The use of higher dialysate sodium concentrations, called “sodium modeling” (e.g., beginning HD with a 160-mEq/L sodium “bath,” decreasing to 140 mEq/L over 4 h), similarly improves hemodynamic tolerance of intermittent HD, by ameliorating the tendency toward plasma hypoosmolality (16). The use of cool dialysate (35.5° C) and increasing dialysate calcium concentration are among the other interventions proven to increase systemic vascular resistance and improve hemodynamic tolerance of HD; increased dialysate calcium also augments cardiac output (1, 3, 17). Numerous patients hemodynamically intolerant of isolated ultrafiltration, intermittent HD, their sequential combination, and the other modifications mentioned above, have been supported with CRRT. The capacity to alter fluid balance at will, even in hemodynamically unstable patients, is in large part responsible for the attractiveness of CRRT to intensivists.

Data have emerged suggesting that high-volume hemofiltration has beneficial hemodynamic effects in septic animals, and this therapy may have application in human sepsis (18). Most inflammatory cytokines weigh between 5,000 and 30,000 Da, and readily cross porous “high-flux” hemofiltration membranes. High-volume hemofiltration (6 L/h) applied early in the course of porcine sepsis has been shown to yield hemodynamic improvement (19). This benefit resulted from removal of mediators as opposed to their adsorption to the hemofiltration membrane. It is important to note that the ultrafiltration volumes required to replicate this technique are massive: 200 ml/kg per hour, or 14 L/h in a 70-kg human, compared with 15–30 ml/kg per hour, or 1–2 L/h, with standard CVVH for

RRT. Furthermore, hemodynamic parameters, not survival of septic animals, were the primary outcomes studied. Since the rates typically used for RRT (1–2 L/h) do not significantly augment inflammatory mediator clearance, and membrane adsorption of mediators is saturated within hours, it is unreasonable in principle to expect significant antiinflammatory benefit from current CRRT techniques. Other limitations and potential adverse effects of the therapy are important considerations. Technical limitations to extracorporeal removal of a substance include (in addition to inability to filter large solutes such as tumor necrosis factor [TNF] trimers and lipopolysaccharide [LPS]) inability to impact autocrine and paracrine effects of cytokines and other inflammatory mediators inaccessible to clearance prior to exerting their effects, difficulty in achieving relevant clearance of circulating cytokines and mediators because of high endogenous clearance and short half-life; and inability to remove protein-bound mediators. Assuming effective clearance of any cytokine were achievable, it is unclear which proinflammatory cytokines should be preferably removed, what effects the therapy might have on antiinflammatory cytokine levels, and the balance of these influences on sepsis. The last point is especially important: even a clear-cut hemodynamic benefit may translate into increased mortality, given the complexity of the pro- and antiinflammatory cascade in septic shock, although some animal data do suggest a survival benefit of this therapy. Absent human survival data, it is premature to prescribe hemofiltration purely for sepsis therapy, or to prescribe UF rates > 2 L/h in septic ARF in a specific attempt to augment cytokine clearance. Nevertheless, this is an active area of investigation, and high-volume hemofiltration remains an intriguing potential sepsis therapy.

#### **RRT MODALITIES: THE INTERMITTENT HD VERSUS CRRT DEBATE**

Hemodialysis-associated hypotension is estimated to occur in approximately 20–30% of treatments. Some of the causes are dialysis specific, such as excessive or rapid volume removal, changes in plasma osmolality, autonomic dysfunction, and anaphylactic membrane reactions (17). Interventions such as sodium modeling, intermittent isolated ultrafiltration, cool dialysate, and increased dialysate calcium concentration are among those shown to improve hemodynamic stability during intermittent HD (1, 3, 16, 17). CRRT is most frequently used in patients who are hemodynamically intolerant of intermittent HD, usually because of sepsis or severe cardiac dysfunction.

Control of azotemia with modern venovenous RRT is at least equivalent to alternate-day intermittent HD, and possibly superior to daily intermittent HD in large or hypercatabolic patients, as demonstrated by use of a urea kinetic model derived from 20 CRRT patients (20). It is interesting to note that daily treatments, while a commonly used comparison regimen for CRRT adequacy calculations, are not routinely prescribed for most ICU patients with ARF managed with intermittent HD (21). Although acute therapy of severe hyperkalemia, metabolic acidosis, or intoxications is more efficiently achieved with intermittent HD, lesser abnormalities are corrected relatively quickly and controlled effectively with CRRT (Table 1). Clinical data suggest that CRRT should be strongly considered for patients with severe hyperphosphatemia or elevated intracranial pressure (ICP), and might also be a useful component of therapy for lithium intoxication (22–24). Continuous removal prevents the postdialytic “rebound” elevation of plasma concentration typically seen with intermittent HD in patients with hyperphosphatemia (tumor lysis syndrome, rhabdomyolysis) or lithium intoxication (22, 23). In

TABLE 1  
INDICATIONS FOR SPECIFIC RENAL REPLACEMENT THERAPIES

Therapeutic Goal	Hemodynamic Condition	Preferred Renal Replacement Therapy
Fluid removal	Stable Unstable	Intermittent isolated ultrafiltration (IUF) Slow continuous ultrafiltration (SCUF) Peritoneal dialysis
Urea clearance	Stable Unstable	Intermittent hemodialysis CRRT: Convection—CAVH, CVVH Diffusion—CAVHD, CVVHD Both—CAVHDF, CVVHDF
Severe hyperkalemia	Stable/unstable	Intermittent hemodialysis
Severe metabolic acidosis	Stable Unstable	Intermittent hemodialysis CRRT
Severe hyperphosphatemia	Stable/unstable	CRRT

*Definition of abbreviations:* CAVH = continuous arteriovenous hemofiltration; CAVHDF = continuous arteriovenous hemodiafiltration; CRRT = continuous renal replacement therapy; CVVH = continuous venovenous hemofiltration; CVVHDF = continuous venovenous hemodiafiltration.

patients with cerebral edema complicating acute liver failure, intermittent machine hemofiltration but not continuous renal replacement therapies (CAVH, CAVHD) raised intracranial pressure and decreased cerebral perfusion pressure (24). Raised intracranial pressure in this setting is due to acute solute removal and resulting plasma hypoosmolality, causing a shift of water into the brain, with further reductions in cerebral perfusion pressure caused by dialysis-induced hypotension.

Despite apparent advantages over intermittent therapies in unstable patients, superiority of CRRT with respect to mortality or recovery of renal function has not been demonstrated. Data from two trials comparing intermittent HD versus CRRT in ARF have been published only in abstract form, and neither demonstrated an effect of modality on outcome (8, 25, 26). One study excluded patients with a mean arterial pressure below 70 mm Hg, and the study was flawed by unbalanced severity of illness despite randomization (25). Another study randomized patients with mean arterial pressures as low as 50 mm Hg, and found no difference in outcome between intermittent HD and CVVHD (26). Of interest, 15% of those randomized to intermittent HD in this study crossed over to CVVHD because of hemodynamic instability, whereas 20% of those initiating CVVHD were subsequently switched to intermittent therapy because of excessive filter clotting.

Most would agree that CRRT is preferred to provide RRT for a significant proportion of hemodynamically unstable ICU patients. In patients stable enough to tolerate either form of RRT, this benefit should be balanced against aspects of CRRT that might adversely affect outcome, such as continuous anticoagulation, prolonged membrane exposure (*see* discussion of biocompatibility below), hypothermia, and nonselective removal of drugs, nutrients, and inflammatory mediators. The high flux membranes used to achieve the high ultrafiltration rates for hemofiltration techniques are freely permeable to most non-protein-bound drugs. Drug dosing is usually based on minimal data in CRRT patients. Absent any CRRT-specific dosing guidelines, it is reasonable to use published regimens for moderate renal insufficiency (glomerular filtration rate [GFR] 10–50 ml/min) for dose adjustments during CRRT with standard 1- to 2-L/h flow rates, as opposed to assuming severe renal insufficiency (GFR < 10 ml/min) and considering possible intermittent dialytic drug removal with intermittent HD. Of course, for narrow therapeutic index drugs, therapeutic

drug monitoring is appropriate. Filter clotting is the Achilles's heel of CRRT, and causes hours of lost therapy, which is quantitatively important because these are inefficient solute removal processes, which must be as close to continuous as possible in order to achieve dose equivalence with intermittent HD (3, 11). Low-dose heparin infused directly into the hemofilter with minimal systemic anticoagulation achieves adequate filter longevity in many patients (at least 24 h, ideally 96 h or more); use of low molecular weight heparin has also been reported. CRRT without anticoagulation (using intermittent saline filter flushes in some centers) may be successful in some coagulopathic patients, such as those with end-stage liver disease, but in many septic patients with thrombocytopenia and elevated prothrombin time/partial thromboplastin time (PT/PTT) due to diffuse intravascular coagulation (DIC), increased filter clotting is the rule if no anticoagulation is used. In newly postoperative patients and others with contraindications to systemic anticoagulation, regional anticoagulation of the hemofilter alone is preferred. Some use regional heparin for this purpose (prefilter heparin, postfilter protamine). We prefer to use regional citrate anticoagulation in these patients, infusing citrate prefilter to chelate calcium and prevent filter clotting, and administering calcium through a central vein to prevent systemic ionized hypocalcemia. Regional citrate is also useful in patients with heparin-induced platelet aggregation; emerging alternatives include hirudin and prostacyclin. Taken together, this information suggests that apart from patients who are unable to hemodynamically tolerate intermittent HD, or in whom frequent hemofilter clotting precludes effective CRRT, the decision to use CRRT in ICU patients with ARF is mainly based on physician preference at this time. Differences in cost between intermittent and continuous RRT techniques vary widely between institutions and countries, because of variations in intermittent HD frequency, supply charges, and staffing practices (ICU nurse versus dialysis staff versus both); for example, it appears that the RRT costs are equivalent in some centers (London, UK) but CRRT is twice as expensive as intermittent HD in others (Cleveland, OH) (8). Apparently, in the United States at least, cost considerations are not among the arguments supporting the use of CRRT. A reasonable approach is to regard intermittent HD and CRRT as complementary techniques, to be used interchangeably in critically ill patients with ARF according to the circumstances.

## MEMBRANE BIOCOMPATIBILITY AND ARF RRT OUTCOMES

Biocompatibility refers to the degree to which blood exposure to a hemodialysis membrane activates complement and neutrophils; more complement activation signifies less biocompatibility, and may cause systemic and renal inflammatory injuries. Two major studies found that use of biocompatible membranes improved these outcomes in ARF, but each study suffered from methodologic flaws (27–30). Use of a biocompatible dialyzer that also has higher “flux” (permeability) than the bioincompatible dialyzer may have influenced outcome in one study (27). Potentially serious protocol problems such as lack of randomization (dialyzers were assigned in an alternating order), center-specific practice variations, unblinded interim analysis and publication by one center (28), and failure to perform an intention-to-treat analysis may have influenced outcome in the other major “positive” biocompatibility trial (28–30). Several subsequent studies have failed to confirm the benefits of biocompatibility in ARF, but have lacked the statistical power to definitively exclude any effect. For example, in the most recent trial, 180 subjects with ARF were randomized to HD with a bioincompatible (cuprophane,  $n = 90$ ) or biocompatible (polymethylmethacrylate [PMMA],  $n = 90$ ) membrane (31). The main outcome measure was survival for 14 d after the end of therapy (defined as treatment success). Forty-four patients (58%) assigned cuprophane membranes survived, as did 50 patients assigned PMMA (60%). There was still no difference in mortality between the two groups when the analysis was adjusted for age and APACHE II score, or (prospectively) stratified according to the presence or absence of oliguria. The study size of this trial was larger than in the two earlier positive investigations, but the power was still inadequate to detect a 25% mortality difference related to membrane biocompatibility, if such existed. Therefore, in light of a number of conflicting studies, the clinical relevance of this aspect of the acute dialysis prescription remains unproven, despite the fact that this strategy has already become standard in many centers. Of note, since the hemofilter membranes used for CRRT are among the most biocompatible, it is important that future studies comparing the effects of intermittent and continuous therapies use identical hemofilters in both groups, to eliminate any potential differential impact of this variable. On a practical level, although biocompatible membranes are more expensive, the data do not suggest any clinical adverse effect of their use in severe ARF, which is likely to continue unless proven ineffective or harmful by a major prospective trial.

## RRT DOSE AND ADEQUACY

The lack of a standardized measurement of RRT dose in ARF is a major deficiency in the field. Clearance of urea, a low molecular weight nitrogenous waste product, is the most commonly studied marker of adequate uremic detoxification by HD. The term  $Kt/V$  is a unitless measure of HD dose (based on urea removal):  $K$  is the urea clearance of the dialysis membrane used (ml/min),  $t$  is the duration of dialysis (min), and  $V$  is the volume of distribution of urea in the patient (ml). Thus,  $Kt/V$  is a measure of the volume of plasma cleared of urea during an HD session ( $Kt$ ) divided by the urea distribution volume ( $V$ , assumed to be total body water: 0.5–0.6 L/kg), and larger  $Kt/V$  values signify greater HD dose.  $Kt/V$  measurements of delivered dialysis dose are usually calculated using the ratio of postdialysis to predialysis BUN and a nomogram; for example, an HD session that decreased BUN from 100 to 30 mg/dl is consistent with a  $Kt/V$  of 1.3. To ensure adequate RRT, such measurements are performed monthly for most chronic dialy-

sis patients, by measuring pre- and postdialysis BUN and using the fractional reduction of urea concentration to calculate  $Kt/V$  from the nomogram.

The National Cooperative Dialysis Study found that larger  $Kt/V$  values in chronic HD patients were associated with lower morbidity and mortality. The recent Dialysis Outcomes Quality Initiative recommendations defined a  $Kt/V$  of 1.2 as the minimum acceptable dialysis dose in chronic HD patients. No such dosing guidelines have been established for the ARF population. Furthermore, numerous patient- and technique-related factors impede effective delivery of prescribed dialysis in critically ill patients. Extrapolation of HD data from the chronic HD population to the ARF setting is limited by numerous poorly quantifiable variables, including effects of critical illness on urea kinetic modeling. Furthermore,  $Kt/V$  measurements extrapolated from pre- and post-BUN measurements may be inaccurate in ARF, because “rebound” postdialysis increases in BUN from tissue stores hypoperfused during intermittent HD occurs. Some of these problems may be overcome by dialysate sampling, or even online urea measurements, but these remain research tools at this point. In this context, results of a prospective, observational study that examined the prescribed and delivered dialysis dose in 40 ARF patients dialyzed in two large tertiary level U.S. medical centers were deeply disturbing (21). This study found that 68% of ARF treatments failed to deliver the minimum dialysis dose recommended for maintenance HD of chronic renal failure patients, and that for 49% of treatments a minimally adequate dialysis dose was not even prescribed. Failure to adjust dialysis dose and/or achieve adequate dialysis delivery in larger patients was a major source of treatment failure.

Consistent with the somewhat nebulous guidelines for RRT initiation, the preferred duration and frequency of dialytic support in ARF are unclear on the basis of available data, and intermittent HD is commonly initiated at a BUN of 100 mg/dl, and repeated to maintain a predialysis BUN below 80 mg/dl (5). Paganini and colleagues demonstrated by retrospective analysis of a prospectively gathered database that delivered dialysis dose was predictive of mortality in critically ill ARF patients treated with RRT, if they had moderate-range severity of illness, as measured by the Cleveland Clinic Foundation ARF score; mortality of the most and least severely ill patients was independent of dialysis dose (2). Another intriguing study by Schiffel, published only in abstract form, found that daily intermittent HD resulted in a markedly lower mortality than alternate day therapy (21 versus 47%,  $p < 0.025$ ) in a group of 72 ICU patients with ARF (30, 32). Pending results of future prospective studies of the impact of dialysis dose on outcome in this population, a common-sense approach dictates provision of a dialysis prescription and delivered dose at least consistent with adequate therapy of chronic renal failure patients. Simple interventions should include use of anticoagulation whenever possible (to minimize loss of dialyzer surface area), replacement of catheters with suboptimal blood flow rates, and most importantly, prescription of an increased dialysis dose for larger patients.

The future holds many challenges in this area. HD dose and adequacy measurements and recommendations are urgently required. The intermittent HD versus CRRT debate is less important than identification of standardized goals for RRT. Intermittent HD and CRRT should be regarded as complementary techniques, which should both be available in institutions that care for critically ill patients, allowing RRT to be individualized to the needs of the complex patients who develop ARF in the ICU. ARF in the ICU is increasingly a component of sepsis and MSOF, and the development of rational

strategies for initiation, dosing, and effective delivery of RRT in this setting is among the greatest challenges facing intensivists and nephrologists today. It is hoped that a multidisciplinary approach will yield progress in this complex and challenging field.

## References

- Conger, J. 1998. Dialysis and related therapies. *Semin. Nephrol.* 18:533–540.
- Paganini, E. P., M. Tapolyai, M. Goormastic, W. Halstenberg, L. Kozlowski, M. Leblanc, J. C. Lee, L. Moreno, and K. Sakai. 1996. Establishing a dialysis therapy/patient outcome link in intensive care unit acute dialysis for patients with acute renal failure. *Am. J. Kidney Dis.* 28(Suppl. 3):S81–S89.
- Briglia, A., and E. P. Paganini. 1999. Acute renal failure in the intensive care unit. *Clin. Chest Med.* 20:347–366.
- Star, R. A. 1998. Treatment of acute renal failure. *Kidney Int.* 54:1817–1831.
- DuBose, T. D., D. G. Warnock, R. L. Mehta, J. V. Bonventre, M. R. Hammerman, B. A. Molitoris, M. S. Paller, N. J. Siegel, J. Scherbenke, and G. E. Striker. 1997. Acute renal failure in the 21st century: recommendations for management and outcomes assessment. *Am. J. Kidney Dis.* 29:793–799.
- Neveu, H., D. Kleinknecht, F. Brivet, Ph. Loirat, P. Landais, and the French Study Group on Acute Renal Failure. 1996. Prognostic factors in acute renal failure due to sepsis: results of a prospective multicentre study. *Nephrol. Dial. Transplant.* 11:293–299.
- Levy, E. M., C. M. Viscoli, and R. I. Horwitz. 1996. The effect of acute renal failure on mortality: a cohort analysis. *J.A.M.A.* 275:1489–1494.
- Silvester, W. 1998. Outcome studies of continuous renal replacement therapies in the intensive care unit. *Kidney Int.* 53(Suppl. 66):S138–S141.
- Lewis, J. L., G. M. Chertow, E. P. Paganini, J. Himmelfarb, T. A. Ikizler, T. Greene, and R. L. Mehta. 1997. A multicenter survey of patient characteristics, practice patterns, and outcomes in critically ill patients with ARF (abstract). *J. Am. Soc. Nephrol.* 8:A0673.
- Mehta, R. L., J. M. Letteri, for the National Kidney Foundation Council on Dialysis. 1999. Current status of renal replacement therapy for acute renal failure: a survey of U.S. nephrologists. *Am. J. Nephrol.* 19:377–382.
- Forni, L. G., and P. J. Hilton. 1997. Continuous hemofiltration in the treatment of acute renal failure. *N. Engl. J. Med.* 336:1303–1309.
- Bellomo, R., C. Ronco, and R. Mehta. 1996. Nomenclature for continuous renal replacement therapies. *Am. J. Kidney Dis.* 28(Suppl. 3):S2–S7.
- Kleinknecht, D. 1972. Uremic and non-uremic complications in acute renal failure: evaluation of early and frequent dialysis on prognosis. *Kidney Int.* 1:190–196.
- Horowitz, H. I., I. M. Stein, B. D. Cohen, and J. G. White. 1970. Further studies on the platelet-inhibitory effect of guanidinosuccinic acid and its role in uremia bleeding. *Am. J. Med.* 49:336–345.
- Kopple, J. D., S. I. Gordon, M. Wang, and M. E. Swenseid. 1977. Factors affecting serum and urinary guanidinosuccinic acid levels in normal and uremic subjects. *J. Lab. Clin. Med.* 90:303–311.
- Paganini, E. P., D. Sandy, L. Moreno, L. Kozlowski, and K. Sakai. 1996. The effect of sodium and ultrafiltration modelling on plasma volume changes and haemodynamic stability in intensive care patients receiving haemodialysis for acute renal failure: a prospective, stratified, randomized, cross-over study. *Nephrol. Dial. Transplant.* 11(Suppl. 8):32–37.
- Emili, S., N. A. Black, R. V. Paul, C. J. Rexing, and M. E. Ullian. 1999. A protocol-based treatment for intradialytic hypotension in hospitalized hemodialysis patients. *Am. J. Kidney Dis.* 33:1107–1114.
- Bellomo, R., I. Baldwin, L. Cole, and C. Ronco. 1998. Preliminary experience with high-volume hemofiltration in human septic shock. *Kidney Int.* 53(Suppl. 66):S182–S185.
- Grootendorst, A. F., E. F. H. Van Bommel, B. Van Der Hoven, L. A. Van Leengoed, and G. A. Van Osta. 1992. High-volume hemofiltration improves hemodynamics of endotoxin-induced shock in the pig. *J. Crit. Care* 7:67–75.
- Clark, W. R., B. A. Mueller, M. A. Kraus, and W. L. Macias. 1997. Extracorporeal therapy requirements for patients with acute renal failure. *J. Am. Soc. Nephrol.* 8:804–812.
- Evanson, J. A., J. Himmelfarb, R. Wingard, S. Knights, Y. Shyr, G. Schulman, T. A. Ikizler, and R. M. Hakim. 1998. Prescribed versus delivered dialysis in acute renal failure patients. *Am. J. Kidney Dis.* 32:731–738.
- Pichette, V., M. Leblanc, A. Bonnardeux, D. Ouimet, D. Geadah, and J. Cardinal. 1994. High dialysate flow rate continuous arteriovenous hemodialysis: a new approach for the treatment of acute renal failure and tumor lysis syndrome. *Am. J. Kidney Dis.* 23:591–596.
- Leblanc, M., M. Raymond, A. Bonnardeux, P. Isenring, V. Pichette, D. Geadah, D. Quimet, J. Ethier, and J. Cardinal. 1996. Lithium poisoning treated by high-performance continuous arteriovenous and venovenous hemodiafiltration. *Am. J. Kidney Dis.* 27:365–372.
- Davenport, A., E. J. Will, and A. M. Davidson. 1993. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. *Crit. Care Med.* 21:328–338.
- Mehta, R., B. McDonald, F. Gabbai, M. Pahl, A. Farkas, M. Pascual, W. Fowler, and ARF Collaborative Study Group. 1996. Continuous versus intermittent dialysis for acute renal failure (ARF) in the ICU: results from a randomized multicenter trial (abstract A1044). *J. Am. Soc. Nephrol.* 7:1457.
- Sandy, D., L. Moreno, J. C. Lee, and E. P. Paganini. 1998. A randomized, stratified, dose equivalent comparison of continuous veno-venous hemodialysis (CVVHD) versus intermittent hemodialysis (IHD) support in ICU acute renal failure (abstract A1146). *J. Am. Soc. Nephrol.* 9:225A.
- Schiff, H., S. M. Lang, A. König, T. Strasser, M. C. Haider, and E. Held. 1994. Biocompatible membranes in acute renal failure: prospective case-controlled study. *Lancet* 344:570–572.
- Hakim, R. M., R. L. Wingard, and R. A. Parker. 1994. Effect of dialysis membrane in the treatment of patients with acute renal failure. *N. Engl. J. Med.* 331:1338–1342.
- Himmelfarb, J., N. Tolckoff Rubin, P. Chandran, R. A. Parker, R. L. Wingard, and R. Hakim. 1998. A multicenter comparison of dialysis membranes in the treatment of acute renal failure requiring dialysis. *J. Am. Soc. Nephrol.* 9:257–266.
- Karsou, S. A., B. L. Jaber, and B. J. G. Pereira. 2000. Impact of intermittent hemodialysis variables on clinical outcomes in acute renal failure. *Am. J. Kidney Dis.* 35:980–991.
- Jorres, A., G. M. Gahl, C. Dobis, M. H. Polenakovic, K. Cakalaroski, B. Rutkowski, E. Kisielnicka, D. H. Krieter, K. W. Rumpf, C. Guenther, W. Gaus, J. Hoegel, for the International Multicentre Study Group. 1999. Hemodialysis-membrane biocompatibility and mortality of patients with dialysis-dependent acute renal failure: a prospective randomized multicentre trial. *Lancet* 354:1337–1341.
- Schiff, H., S. M. Lang, A. König, and E. Hald. 1997. Dose of intermittent hemodialysis (IHD) and outcome of acute renal failure (ARF): a prospective randomized study (abstract A1333). *J. Am. Soc. Nephrol.* 8:290A.