New perspectives for prevention/treatment of acute renal failure

Norbert Lameire and Raymond Vanholder

Acute renal failure continues to be a difficult clinical problem in critically ill patients, despite advances in critical care and dialysis. This review focuses on some of the current issues in the nondialytic and dialytic management of these patients. Critical analysis of some still frequently used drugs in these patients such as diuretics and dopamine in so-called 'renal doses' has revealed little beneficial effect. Recent data are in conflict with previous suggestions that biocompatible membranes have a positive effect on the recovery of renal function and on patient mortality. The choice between intermittent haemodialysis and continuous renal replacement therapy should be made on an individual basis and not on the basis of 'dogmatic' opinion. Curr Opin Anaesthesiol 13:105–112.

Renal Division, Department of Medicine, University Hospital, Gent, Belgium

Correspondence to Norbert Lameire, Renal Division, Department of Medicine, University Hospital, 185, De Pintelaan, 9000 Gent, Belgium
Tel: +32 9 240 4524; fax: 32 9 2404599

Current Opinion in Anaesthesiology 2000, 13:105–112

Abbreviations

ARF	acute renal failure
ATN	acute tubular necrosis
CRRT	continuous renal replacement therapy
CVVH	continuous venovenous haemofiltration
CVVHDF	continuous venovenous haemodiafiltration
ICU	intensive care unit
IHD	intermittent haemodialysis
RCIN	radiocontrast-induced nephropathy
RRT	renal replacement therapy

0952-7907

Introduction

Acute renal failure (ARF) is defined as a rapid deterioration of renal function associated with the accumulation of nitrogenous wastes in the body that is not due to prerenal or postrenal factors. When ARF is not the result of primary vascular, glomerular, or interstitial disorders (approximately 15% of all cases), it has been referred to as acute tubular necrosis (ATN). ATN is caused by ischaemic (50%) or nephrotoxic (35%) injury to the kidney. In 50% of hospital-acquired ARF, however, the cause is multifactorial. The incidence of ATN is particularly high in patients admitted to an intensive care unit (ICU). Unfortunately, neither this incidence nor the morbidity and mortality associated with ATN have declined, despite ongoing improvement in the supportive care of these patients and the advent of intermittent and continuous renal replacement therapy (CRTT) [1–4]. The spectrum of ATN in the ICU, compared with that seen in other settings, is indeed different, with more patients developing ATN predominantly as part of a multiple organ dysfunction syndrome, whereas isolated ARF is the usual presentation in the non-ICU setting [5].

In an important paper that evaluated 105 patients admitted to five academic trauma centres during a 1-year period, Gill Cryer *et al.* [6] demonstrated that multiple organ dysfunction syndrome after trauma is established within 24 h of injury in the majority of patients who develop it. Two reviews that described the special circumstances of ARF in the ICU and cardiac care unit have recently been published [7••,8••].

The pathophysiological abnormalities in ARF include changes in the intrarenal haemodynamics, and ischaemic and toxic injury to tubular cells. The interplay of these abnormalities form the basis for the acute decrease in glomerular filtration rate, which is the result of intrarenal vasoconstriction with a fall in glomerular filtration pressure, tubular obstruction and transtubular backleak of the filtrate.

In recent years, research in experimental ATN has focused on the role of intrarenal vasoconstriction by decreased synthesis and release of nitric oxide; increased release of endothelin-1, the most potent vasoconstrictor found in humans [9,10]; and on two major mechanisms of cell injury and the possibilities of attenuating this damage •,12–19]. The first of these mechanisms pertains to the fate of the individual polarized tubular epithelial cell after injury. After injury, the cell becomes depolar-

ized and cell death can occur by either necrosis or apoptosis. If the cell survives, it can initiate a repair programme that will return it to its normal polarized state. This repair presumably follows developmental pathways, and growth and differentiation factors play a role. In the second mechanism tubule cells actively participate in immune and inflammatory events, whereby they interact with each other and release a variety of inflammatory mediators and cytotoxic substances into their local environment. Much attention has been devoted to damaging effects of free radicals such as oxygen free radicals and nitric oxide, and to the role of neutrophil infiltration into the renal interstitium and into the renal blood vessels. To what extent some, or all, of these pathophysiological mechanisms play a role in human ATN is of course difficult to confirm, but because human ATN is often multifactorial, all mechanisms may be involved.

This review summarizes the evidence of certain preventive or therapeutic strategies that can be applied in critically ill patients suffering from ATN. Because both the nondialytic (conservative) as well as the dialytic management of such patients are important, a critical evaluation of selected issues of both forms of treatment is provided.

Risk factors for acute renal failure

Risk factors for ARF after coronary intervention (mostly acute contrast nephropathy) have recently been analysed by McCullough *et al.* [20]. The preintervention creatinine clearance, the presence of diabetes mellitus, and the contrast dose were independent predictors of dialysis-requiring ARF. In a series of 447 consecutive adult patients who required cardiopulmonary bypass [21], the four most important independent risk factors were preoperative renal insufficiency, postoperative hypotension, cardiopulmonary bypass time greater than 140 min and old age. A similar analysis was performed by Conlon *et al.* [22]. Of 2672 patients who underwent coronary artery bypass grafting, 7.2% developed ARF with 0.7% of these needing dialysis. The mortality in coronary artery bypass grafting patients who required dialysis was 28%, compared with 1.8% among those who did not require dialysis. Variables independently associated with dialysis-requiring ARF included preoperative serum creatinine, duration of cardiopulmonary bypass, presence of a carotid artery bruit and presence of diabetes. In a series of patients with post-traumatic ARF [23•], the need for mechanical ventilation with a positive end-expiratory pressure greater than 6 cmH_2O, rhabdomyolysis with creatine phosphokinase greater than 10 000 IU/l, and haemoperitoneum were the three most strongly associated risk factors for the development of ARF.

Several medications – notably acyclovir, sulfonamides, methotrexate, indinavir and triamterene – are associated with the production of crystals that can precipitate in the lumen of the tubules, and thus may lead to ARF [24••]. Renal failure may be reversible if the drug is discontinued, and by volume repletion and alkalinization of the urine when appropriate.

Nondialytic management

Table 1 summarizes a list of therapeutic approaches that have most frequently been applied in several animal models of ATN. Some of the drugs listed have undergone clinical trials or are in several stages of clinical development, but are not yet applied on a wide scale [25,26•,27]. These drugs can be divided into those that act on haemodynamic factors and those that act against

Table 1. Current and future therapeutic approaches for the treatment of clinical and experimental acute tubular necrosis

Pathophysiological mechanism	Current or future interventions in humans	Current interventions in animals
Renal vasoconstriction	Low-dose dopamine	Low-dose dopamine
	Calcium channel blockers	Calcium channel blockers
	Atrial natriuretic peptides	Atrial natriuretic peptides
	Endothelin receptor antagonists	Endothelin receptor antagonists
	Leukotriene receptor antagonists	Leukotriene receptor antagonists
	PAF antagonists	PAF antagonists
		iNOS antisense oligonucleotides
Reperfusion injury	Anti-ICAM-1 mAB	Anti-ICAM-1 mAB
	Anti-CD18 mAB	Anti-CD18 mAB
	Biocompatible membranes	Free radical scavengers
		Protease inhibitors α-MSH
Tubular obstruction	Diuretics	Diuretics
		RGD peptides
		iNOS antisense oligonucleotides
Tubular regeneration	Insulin-like growth factor-I	Insulin-like growth factor-I
		Epidermal growth factor
		Hepatocyte growth factor

ICAM, intercellular adhesion molecule; iNOS, inducible nitric oxide synthase; mAB, monoclonal antibodies; MSH, melanocyte-stimulating hormone; PAF, platelet-activating factor; RGD peptides, peptides containing the arginine–glycine–aspartic acid motif.

tubular epithelial cell damage. The most promising drugs that will become available for prevention or treatment of clinical ARF in the coming years will probably be endothelin-receptor blockers and leukocyte adhesion blocking molecules.

A recent prospective, placebo-controlled, double-blind study examined the role of loop diuretics (furosemide and torasemide) in the treatment of oliguric ATN patients, who were all also treated with dopamine [28]. No significant difference in any major outcome parameter (renal recovery, requirement for dialysis, or death) after 21 days was observed. A recent review [29] on the role of mannitol in cardiac surgery thoroughly discussed its potential beneficial effects on the kidney, but emphasized its detrimental actions on the brain, lungs, heart, gastrointestinal tract and red blood cells. Circulatory overload, pulmonary oedema, depression of the central nervous system, and severe hyponatraemia may occur. These complications are more frequent when high doses of mannitol cannot be eliminated due to inadequate renal function.

The drugs used as renal vasodilators in clinical trials include low-dose dopamine, atrial natriuretic peptides and calcium channel blockers. The therapeutic use of ularitide and the usefulness of renal dose dopamine have been discussed [30•,31,32,33•]. Juste *et al.* [34] investigated the validity of a low-dose 'renal' dopamine regimen in critically ill adult patients by studying steady-state dopamine clearances. Plasma clearance is lower in these patients than in elective surgical patients, and there is a very large interindividual variation. It is therefore impossible to predict plasma levels from the infusion rate of dopamine and the concept of a selective renovascular low-dose dopamine infusion is invalid in critically ill patients.

Some of the drugs discussed above have recently been tested in the prevention of radiocontrast-induced nephropathy (RCIN). Earlier studies of single drug prevention strategies with atrial natriuretic factor, loop diuretics, dopamine, or mannitol [35] showed no clear benefit over hydration with 0.45% saline alone across a spectrum of patients at risk. A prospective, randomized, controlled, single-blind trial was conducted in which 98 participants were randomized to forced diuresis with intravenous crystalloid plus furosemide, mannitol, or low-dose dopamine or to intravenous crystalloid and matching placebos [36••]. That study suggested that forced diuresis with intravenous crystalloid, furosemide, and mannitol (if haemodynamics permit), beginning at the start of angiography, provides a modest benefit against RCIN, provided a high urine flow rate can be achieved. The efficacy of intravenous atrial natriuretic peptide (anaritide, ANP 4–28) in preventing RCIN was carefully investigated in a prospective, randomized, double-blind, placebo-controlled trial in patients with stable chronic renal failure, with or without diabetes mellitus [37]. There were no statistical differences in the incidence of RCIN. Although the patients with diabetes mellitus had a significantly greater incidence of RCIN, no beneficial effect of anaritide was detected in the diabetic or nondiabetic groups. In a prospective, double-blind, placebo-controlled study [38], the effect of the oral administration of theophylline, an adenosine receptor antagonist, was investigated with regard to changes in renal haemodynamics and tubular injury induced by radiocontrast media in 80 well-hydrated patients with pre-existing chronic renal insufficiency (creatinine >1.5 mg/dl). The results showed that the glomerular filtration rate is preserved by hydration alone in these patients, without further additional benefit from the administration of theophylline.

The effect of urodilatin on the peak value and course of serum creatinine in critically ill patients with ARF after major abdominal surgery and the necessity for renal replacement therapy (RRT) was recently investigated [39]. Although there was a tendency for a lower peak serum creatinine value in the urodilatin group, the difference did not reach statistical significance. Also the total number of haemodialyses due to oligouria/anuria or hyperkalaemia was the same in both groups.

An important double-blind, placebo-controlled multicentre study [40••] has explored the effect of subcutaneous administration of recombinant human insulin-like growth factor-I (100 μg/kg desirable body weight, twice per day for up to 14 days) on the enhancement of recovery of renal function in critically ill patients with ARF. Injections were started within 6 days of the onset of ARF. Insulin-like growth factor-I did not accelerate the recovery of renal function in ARF patients with substantial comorbidity.

Dialytic treatment

A number of controversial issues exist in this area. This discussion is limited to a brief review of two issues: the possible impact of the selection of biocompatible or bioincompatible dialysis membranes; and the choice between the CRRTs and the intermittent forms of haemodialysis (IHD).

Biocompatibility of the dialysis membranes

Membrane bioincompatibility issues cover more than complement and leucocyte activation. Other humoral pathways and cellular mechanisms can be activated during dialysis, leading to coagulation disturbances, allergy, leaching and spallation, making the biocompatibility issue more complex than was originally supposed.

Among the dialysis membranes, unsubstituted cellulosic cuprophane obviously imposes the most important complement and leucocyte activation; the remaining cellulosic membranes, even cellulose acetate, induce a less pronounced response. Although the synthetic membranes in general are considered to be more biocompatible, variable degrees of complement activation have been observed. Remarkably, the AN69 membrane appears to be a strong complement activator, but immediately adsorbs the activated complement [41]. Complement activation during the blood–dialyzer interaction with certain, especially unmodified, cellulosic membranes (but not with more compatible membranes) can lead to neutrophil infiltration into the kidney (and other tissues) and prolonged renal damage [42].

In older studies [42,43] the use of cuprophane membrane dialyzers had a negative impact on the survival rate of ARF patients, the occurrence of sepsis, the duration of oliguria and the rate of renal recovery compared with the use of biocompatible polymethylmethacrylate or AN69 membrane dialyzers. These benefits were limited to patients who were nonoliguric before the onset of haemodialysis. In an analysis by Mehta *et al.* [44] of the impact of the biocompatibility of the membranes, patient outcome was markedly better in patients on membranes with high biocompatibility. This relation disappeared, however, after correction for severity of disease (Acute Physiology and Chronic Health Evaluation III score over the entire observation period). Neveu *et al.* [45] analysed the prognostic factors in ICU patients with ARF with and without sepsis, and indicated the nature of the membrane as one of the contributing factors to increased mortality. They found that the outcome was more beneficial for noncuprophane dialyzers.

Two recent studies [46••,47••] analysed some of the factors that influence the incidence of early renal graft function after transplantation. It appeared that the use of bioincompatible haemodialysis membranes or peritoneal dialysis during pretransplant haemodialysis therapy and the application of ultrafiltration within 24 h before kidney transplantation enhance the risk of post-transplantation ARF and early graft dysfunction.

In one of the largest patient populations studied up to now [48], a prospective randomized multicentre evaluation of the outcome (survival and recovery of renal function) in 153 patients was performed. That study covered the 72 patients originally evaluated by Hakim *et al.* [43], with an additional 81 patients who were submitted to an identical protocol, and showed a positive effect of the biocompatibility of the membrane on survival and recovery of renal function. Divergent outcomes were virtually confined to patients who were nonoliguric at the start of dialysis. Overall trends were the same in all centres involved, and remained present after adjustment for severity of disease.

However, there are some studies, summarized by us [49], in which a beneficial effect of biocompatible membranes was not observed. The most recent prospective multicentre European study of the impact of biocompatibility of dialysis membranes on the outcome of patient survival, duration of stay in the ICU, and renal recovery [50••] did not show differences in the outcome parameters between the group of patients dialyzed with bioincompatible cuprophane or biocompatible polymethylmethacrylate membranes.

The effect of dialyzer membranes on protein and amino acid losses has not yet been widely investigated, but in a small crossover study [51] it was shown that amino acid losses with the use of high-flux polysulfone membranes exceeded those found with the use of low-flux cuprophane membranes.

In spite of the divergent results, however, we feel that there is more evidence that suggests a negative role for complement-activating, bioincompatible membranes on the outcome of ARF than vice versa.

Choice of dialysis modality

Several recent reviews [11••,52••,53•,54••] have extensively covered the choice of either IHD or CRRT in critically ill patients with ARF. Continuous therapies incorporate several at least theoretical advantages, such as improved haemodynamic stability, the possibility for unlimited alimentation, optimal fluid balance and gradual urea removal without fluctuations. Some of these advantages are not yet fully documented, however, and it has not yet been determined whether they have a significant impact on outcome and prognosis, which is the ultimate measure of treatment efficiency.

Many studies have suggested greater haemodynamic stability when CRRT instead of IHD is used [52••,55]. Although statistically significant, the clinical relevance of the observed differences was low (for review [17]). As far as we know, only one cross-over study has been performed to date [56] and did not find a difference in haemodynamic tolerance of CRRT compared with that of IHD. In that study, the frequencies of drops of mean arterial blood pressure of greater than 10 mmHg were 25 and 26% in CRRT and IHD, respectively; there was also no difference in need for vasopressor treatment.

It is also unknown whether continuous venovenous haemodiafiltration (CVVHDF) provides better control of azotaemia than IHD. In order to study the effect on azotaemic control of changing ARF treatment from IHD

to CVVHDF, 47 consecutive critically ill patients with multiorgan failure and ARF treated with IHD and 47 similar patients treated with CVVHDF were studied [57]. Analysis of daily morning urea and creatinine concentrations over the period of RRT in the ICU revealed that CVVHDF was associated with a significantly lower plasma urea and serum creatinine level at 24 h treatment, despite similar levels at the start of therapy. Throughout the duration of therapy, mean urea levels and mean serum creatinine levels showed significantly better control of uraemia with CRRT. It was concluded that changing the form of RRT from IHD to CRRT is associated with improved control of azotaemia. In this regard, an important study [58••] measured the delivery of dialysis dose in ARF patients, dialyzed with IHD. The conclusion was that blood-based urea kinetics used to estimate the dose of dialysis provide consistent results, but when compared with dialysate-side kinetics the blood-based method substantially overestimates the amount of solute removal.

Swartz *et al.* [59••] made an analysis of treatment modality (CVVH versus haemodialysis) in patients with severe ARF based only on the first modality chosen in an intent-to-treat manner in order to minimize the effect of patient assignment of other uncontrolled biases or of multiple switches in treatment. All 349 adult patients with ARF receiving RRT during 1995 and 1996 were analysed using multivariate Cox proportional hazards methods. Initial univariate analysis showed the risk of death when receiving initial CVVH to be more than twice that when receiving initial haemodialysis. Progressive exclusion of patients, in whom the RRT modality might not be open to choice and the risk for death was very high, left 227 patients in whom the risk for death was 1.09 (95% confidence interval 0.67–1.8) for initial CVVH, which is virtually equivalent to the risk with initial haemodialysis. These results show that the high crude mortality rate of patients undergoing CVVH was related to the severity of illness and not to the treatment choice itself. With the addition of more inclusive comorbidity data and a broader spectrum of interim outcomes, this type of analysis is a practical alternative to what would be a cumbersome and costly prospective, controlled trial comparing traditional haemodialysis with CVVH.

Major disadvantages of continuous therapies are the ongoing necessity for continuous anticoagulation, immobilization of the patient, and possible side effects from lactate-containing replacement fluid or dialysate. On the other hand, CRRT procedures have certainly made the management of critically ill patients easier. In particular, oligoanuric patients with diuretic-resistant volume overload, and haemodynamically unstable patients with ARF and concomitant sepsis or multiorgan failure appear to benefit most from continuous treatment. Noncritically ill patients with uncomplicated renal failure (e.g. due to the use of dye or antibiotics) can be treated with IHD or peritoneal dialysis. Furthermore, IHD is preferable in patients with haemorrhagic diathesis because it can be easily performed without anticoagulants.

An association between morbidity and mortality from sepsis or multiple organ failure and inflammatory cytokines has been suggested by several studies, but strategies aimed at abrogating the effects of proinflammatory cytokines, such as tumour necrosis factor-α, interleukin-1α and interleukin-6, in human forms of sepsis have shown equivocal benefit [60]. There has been interest in examining the effect of CRRT on these cytokines, and successful removal of cytokines with high-volume haemofiltration or frequent filter changes of polyacrylonitrile haemofilter has been described [61–63]. Our group [64••] was able to show, using an AN69 membrane, that CVVH led to a decrease in the concentration of tumour necrosis factor-α, interleukin-1β and interleukin-6. Most of the removal is due to adsorption to the AN69 membrane, and the concentration remains low only for a few hours after a filter change [64••]. A decrease in the concentrations of anti-inflammatory cytokines such as interleukin-10 and interleukin-1 receptor antagonist was also observed, however. There was no demonstrable relationship between cytokine removal and improved haemodynamic stability. A less sophisticated but similar study was performed by Kellum *et al.* [65]. Thirteen patients with systemic inflammatory response syndrome and ARF were randomized to receive either convective clearance using CVVH or diffusive clearance using CVVHDF for the first 24 h, followed by the other modality for 24 h. Only minimal amounts of mediators were recovered in the effluents with either therapy, except for interleukin-6. Although the clearances for interleukin-6 were different between therapies, these differences did not translate into significant changes in circulating interleukin-6 concentrations. Plasma endotoxin concentrations were not different between therapies.

The main advantages of either IHD or CRRT also represent their major weaknesses; the high efficiency of IHD allows short, intermittent therapy, which can potentially lead to haemodynamic intolerance, poor fluid control and a 'saw-tooth' pattern of metabolic control; and low-efficiency CRRT assures smooth metabolic control, and perhaps better haemodynamic stability, but neccesitates continuous treatment and thus continuous anticoagulation. For adequate metabolic control with CRRT, high ultrafiltrate volumes are needed, increasing the risk for errors in fluid balance calculations. The need for large quantities of industry-prepared dialysate, and for specially adapted artificial kidney sets make the application of

CRRT more expensive than IHD. Conversely, the need for on-line water treatment makes IHD more complicated, but reduces the cost of the treatment. Its intermittent nature also reduces the burden for the nursing and medical staff, and creates time for other diagnostic or therapeutic out-of-unit procedures, which are often needed in this type of patient.

It is thus not surprising that 'hybrid techniques' have emerged to provide alternative answers in the polarized discussion between IHD and CRRT. These 'slow, extended daily dialysis' techniques all combine the advantages of CRRT and IHD by using a dialysis monitor and water treatment module for on-line production of dialysate to perform slow, but extended and daily haemodialysis. Until now, no large-scale studies are available on slow, extended daily dialysis; however, the technique is increasingly being used, and the first preliminary reports are positive [66,67]. In our experience, the use of a single type of machine, the associated reduction of the workload and the intermittent nature make slow, but extended, daily dialysis very acceptable for the ICU nursing team.

Conclusion

Other than for correction of a disturbed circulation or volume depletion, or where possible a moderate overexpansion of the extracellular volume, there is little or no evidence that any of the pharmacological interventions discussed above are of proven and consistent efficacy in the prevention or treatment of ATN. The present options available to the clinician for the treatment of a patient with established ATN are limited to the following: institution of supportive dialytic interventions; providing nutritional support to these often very ill patients; avoiding or treating the life-threatening complications, such as hyperkalaemia and other severe electrolyte or acid–base disturbances, pulmonary oedema and infections; and passively awaiting the regeneration of the renal epithelium and its functional recovery.

The dialysis treatment modality of choice for ARF in the ICU patient remains a matter of controversy. In many centres, this controversy is enhanced by the conflict of interest between the ICU and the nephrology department. Furthermore, it is our impression that for intermittent as well as for continuous dialysis modalities, modifications of these techniques remain unused. This lack of flexibility in adapting the dialysis techniques to the individual needs of the patients limits their effect and efficiency. It is our opinion that all dialysis strategies should be mastered and utilized in the appropriate indications in the ICU patients. So far, no hard evidence is available that one technique above another is superior, if they are used for the correct indications and applied by a skilled ICU and dialysis team.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ. 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.

2 Chertow GM, Christiansen CL, Cleary PD, Munro C, Lazarus JM. Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. Arch Intern Med 1995; 155:1505–1511.

3 Chertow GM, Lazarus JM, Paganini EP, Allgren RL, Lafayette RA, Sayegh MH. Predictors of mortality and the provision of dialysis in patients with acute tubular necrosis. The Auriculin Anaritide Acute Renal Failure Study Group. J Am Soc Nephrol 1998; 9:692–698.

4 Liano F, Pascual J, The Madrid Acute Renal Failure Study Group. Epidemiology of acute renal failure; a prospective, multicenter, community-based study. Kidney Int 1996; 50:811–818.

5 Liano F, Junco E, Pascual J, Madero R, Verde E. The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. Kidney Int Suppl 1998; 66:S16–S24.

6 Gill Cryer H, Leong K, McArthur DL, Demetriades D, Bongard FS, Fleming AW, *et al.* Multiple organ failure: by the time you predict it, it's already there. J Trauma 1999; 46:597–606.

7 •• Briglia A, Paganini EP. Acute renal failure in the intensive care unit: therapy overview, patient risk stratification, complications of renal replacement, and special circumstances. Clin Chest Med 1999; 20:347–366.
See [8••].

8 •• Behrend T, Miller SB. Acute renal failure in the cardiac care unit: etiologies, outcomes, and prognostic factors. Kidney Int 1999; 56:238–243.
This paper and [7••] are excellent, concise and clear reviews covering most aspects of the management of ARF in ICU and acute cardiac patients.

9 Lieberthal W. Biology of acute renal failure: therapeutic implications. Kidney Int 1997; 52:1102–1115.

10 Hermann M, Schulz E, Ruschitzka F, Muller GA. Preventive strategies in endothelin-induced renal failure. Kidney Int Suppl 1998; 67:S202–S204

11 •• Star RA. Treatment of acute renal failure. Kidney Int 1998; 54:1817–1831.
A general overview is provided of both experimental and clinical therapeutic approaches in ARF.

12 Sutton TA, Molitoris BA. Mechanisms of cellular injury in ischemic acute renal failure. Semin Nephrol 1998; 18:490–497.

13 Wangsiripaisan A, Gengaro PE, Nemenoff RA, Ling H, Edelstein CI, Schrier RW. Effect of nitric oxide donors on renal tubular epithelial cell-matrix adhesion. Kidney Int 1999; 55:2281–2288.

14 Horton MA. Arg-Gly-Asp (RGD) peptides and peptidomimetics as therapeutics: relevance for renal diseases. Exp Nephrol 1999; 7:178–184.

15 Molitoris BA, Marrs J. The role of cell adhesion molecules in ischemic acute renal failure. Am J Med 1999; 106:583–592.

16 Chiao H, Foster S, Thomas R, Lipton JM, Star RA. Alpha-melanocyte-stimulating hormone reduces endotoxin-induced liver inflammation. J Clin Invest 1996; 97:2038–2044.

17 Edelstein CL, Ling H, Schrier RW. The nature of renal cell injury. Kidney Int 1997; 51:1341–1351.

18 Lieberthal W, Koh JS, Levine JS. Necrosis and apoptosis in acute renal failure. Semin Nephrol 1998; 18:505–518.

19 Lauriat S, Linas SL. The role of neutrophils in acute renal failure. Semin Nephrol 1998; 18:498–504.

20 McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997; 103:368–375.

21 Suen WS, Mok CK, Chiu SW, Cheung KL, Lee WT, Cheung D, *et al.* Risk factors for development of acute renal failure requiring dialysis in patients undergoing cardiac surgery. Angiology 1998; 49:789–800.

22 Conlon PJ, Stafford SM, White WD, Newman MF, King S, Winn MP, Landolfo K. Acute renal failure following cardiac surgery. Nephrol Dial Transplant 1999; 14:1158–1162.

23 Vivino G, Antonelli M, Moro ML, Cottini F, Conti G, Bufi M, *et al*. Risk factors for • acute renal failure in trauma patients. Intensive Care Med 1998; 24:808–814.
This study indicates that the need for artificial ventilation, the presence of severe rhabdomyolysis and haemoperitoneum are most strongly associated with the development of post-traumatic ATN.

24 Perazella MA. Crystal-induced acute renal failure. Am J Med 1999; 106:459– •• 465.
This is an excellent review of some less well known causes of ARF.

25 Vijayan A, Miller SB. Acute renal failure: prevention and nondialytic therapy. Semin Nephrol 1998; 18:523–532.

26 Lameire N, Vanholder R, Van Biesen W, De Vriese A, Dhondt A, Veys N, • Colardijn F. Evidence-based therapy of acute renal failure. Acta Clin Belgica 1999; 54:263–273.
A critical analysis is presented of the evidence for some of the nondialytic therapeutic strategies in ARF patients.

27 Rabb H, Bonventre JV. Leukocyte adhesion molecules in transplantation. Am J Med 1999, 107:157–165.

28 Shilliday IR, Quinn KJ, Allison MEM. Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study. Nephrol Dial Transplant 1997; 12:2592–2596.

29 Poullis M. Mannitol and cardiac surgery. Thorac Cardiovasc Surg 1999; 47:58–62.

30 Meyer M, Pfarr E, Schirmer G, Uberbacher HJ, Schope K, Bohm E, *et al*. • Therapeutic use of the natriuretic peptide ularitide in acute renal failure. Renal Fail 1999; 21:85–100.
This is an excellent summary of all studies performed with ularitide in ARF.

31 Perdue PW, Balser JR, Lipsett PA, Breslow MJ. 'Renal dose' dopamine in surgical patients: dogma or science? Ann Surg 1998; 227:470–473.

32 Denton MD, Chertow GM, Brady HR. 'Renal-dose' dopamine for the treatment of acute renal failure: scientific rationale, experimental studies and clinical trials. Kidney Int 1996; 50:4–14.

33 Burton CJ, Tomson CV. Can the use of low-dose dopamine for treatment of • acute renal failure be justified? Postgrad Med J 1999; 75:269–274.
A critical review is presented of the use of 'low' dose dopamine and the very weak evidence for its positive effects in ARF patients.

34 Juste RN, Moran L, Hooper J, Soni N. Dopamine clearance in critically ill patients. Intensive Care Med 1998; 24:1217–1220.

35 Solomon R, Werner C, Mann D, Elia J, Iva P. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994; 331:1416–1420.

36 Stevens NA, McCullough PA, Tobin KJ, Speck JP, Westveer DC, Guido AD, *et* •• *al*. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the PRINCE study. J Am Coll Cardiol 1999; 33:403–411.
This study suggests that forced diuresis with intravenous crystalloid, furosemide, and mannitol (if haemodynamics permit) and beginning at the start of angiography provides a modest benefit against RCIN, provided a high urine flow rate can be achieved.

37 Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 1998; 31:674–680.

38 Erley CM. Does hydration prevent radiocontrast-induced acute renal failure? Nephrol Dial Transplant 1999; 14:1064–1066.

39 Herbert MK, Ginzel S, Muhlschlegel S, Weis KH. Concomitant treatment with urodilatin (ularitide) does not improve renal function in patients with acute renal failure after major abdominal surgery: a randomized controlled trial. Wien Klin Wochenschr 1999; 111:141–147.

40 Hirschberg R, Kopple J, Lipsett P, Benjamin E, Minei J, Albertson T, *et al*. •• Multicenter clinical trial of recombinant human insulin-like growth factor I in patients with acute renal failure. Kidney Int 1999; 55:2423–2432.
This study describes the results of a multicentre trial with human insulin-like growth factor-I in critically ill ARF patients. The negative results as far as recovery rate of renal function and patient survival are possibly explained by the delay of onset of treatment in these patients (on average 6 days after admission).

41 Vanholder R, Lameire NH, Hoste E, Van Loo AA, Dhondt A, Ringoir S. Different types of dialyzer membranes: does the bio(in)compatibility matter in the treatment of ARF? Renal Fail 1996; 18:333–346.

42 Schulman G, Fogo A, Gung A, Badr K, Hakim RM. Complement activation retards resolution of ischaemic acute renal failure in the rat. Kidney Int 1991; 40:1069–1074.

43 Hakim RM, Wingard RL, Parker RA. Effect of the dialysis membrane in the treatment of patients with acute renal failure. N Engl J Med 1994; 331:1338–1342.

44 Mehta RL, McDonald B, Gabbai F, Pahl M, Farkas A, Pascual M, Fowler W, Collaborative Study Group. Continuous versus intermittent dialysis for acute renal failure in the ICU: results from a randomized multicenter trial [abstract]. J Am Soc Nephrol 1996; 7:1457.

45 Neveu H, Kleinknecht D, Brivet FG, Loirat P, Landais PJ. Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. The French Study Group on Acute Renal Failure. Nephrol Dial Transplant 1996; 11:293–299.

46 Van Loo AA, Vanholder R, Bernaert PR, Vermassen FE, Van Der Vennet M, •• Lameire NH. Pretransplantation hemodialysis strategy influences early graft function. J Am Soc Nephrol 1998; 9:473–481.
See [47••].

47 Vanholder R, Heering P, Van Loo AA, Van Biesen W, Lambert MC, Hesse U, *et* •• *al*. Reduced incidence of acute renal graft failure in patients treated with peritoneal dialysis compared with hemodialysis. Am J Kidney Dis 1999; 33:934–940.
This paper and [46••] describe a reduced incidence of acute renal graft dysfunction when either a biocompatible membrane or peritoneal dialysis is used as pretransplant dialysis strategy.

48 Himmelfarb J, Tolkoff-Rubin NE, Chandran P, Parker RA, Wingard RL, Hakim RM. A multicenter comparison of dialysis membranes in the treatment of acute renal failure requiring dialysis. J Am Soc Nephrol 1998; 9:257–266.

49 Vanholder R, Lameire N. Does biocompatibility of dialysis membranes affect recovery of renal function and survival? Lancet 1999; 354:1316–1318.

50 Jörres A, Gahl GM, Dobis C, Polenakovic MH, Cakalaroski K, Rutkowski B, *et* •• *al*. Haemodialysis membrane biocompatibility and mortality of patients with dialysis-dependent acute renal failure: a prospective, randomized, multicentre trial. Lancet 1999; 354:1337–1341.
This is a well-performed prospective multicentre study of the effect of dialysis membrane selection on outcome parameters in ARF patients. The study did not show any difference between the bioincompatible cuprophane membrane and the more biocompatible membrane polymethylmethacrylate.

51 Hynote ED, McCamish MA, Depner TA, Davis PA. Amino acid losses during hemodialysis: effects of high-solute flux and parenteral nutrition in acute renal failure. J Parenter Enter Nutr 1995; 19:15–21.

52 Manns M, Sigler MH, Teehan BP. Continuous renal replacement therapies: an •• update. Am J Kidney Dis 1998; 32:185–207.
This is an excellent and balanced review of the advantages and disadvantages of CRRTs in ARF.

53 Lameire NH, Van Biesen W, Vanholder R, Colardijn F. The place of intermittent • hemodialysis in the treatment of acute renal failure in the ICU patient. Kidney Int 1998; 53 (Suppl 66): S110–S119.
This is a review of the possibilities and indications for IHD in ARF patients.

54 Abramson S, Singh AK. Continuous renal replacement therapy compared with •• intermittent hemodialysis in intensive care: which is better? Curr Opin Nephrol Hypertens 1999; 8:537–541.
This is an excellent and concise review on the choice between the intermittent and continuous forms of RRT in ARF.

55 Ronco C, Brendolan A, Bellomo R. Continuous versus intermittent renal replacement therapy in the treatment of acute renal failure. Nephrol Dial Transplant 1998; 13 (Suppl 6):79–85.

56 Misset B, Timsit JF, Renaud B, Tamion F, Carlet J. Comparison of hemodynamic tolerance of sequential hemodialysis and continuous hemofiltration during acute renal failure in ICU patients: a randomized cross-over study. Intensive Care Med 1996; 22:742–746.

57 Bellomo R, Farmer M, Bhonagiri S, Porceddu S, Ariens M, M'Pisi D, Ronco C. Changing acute renal failure treatment from intermittent hemodialysis to continuous hemofiltration: impact on azotemic control. Int J Artif Org 1999; 22:145–150.

58 Evanson JA, Ikizler TA, Wingard R, Knights S, Shyr Y, Schulman G, *et al*. •• Measurement of the delivery of dialysis in acute renal failure. Kidney Int 1999; 55:1501–1508.
This important study showed that estimation of the dose of dialysis in ARF patients should be based on dialysate kinetics, because blood-based kinetics substantially overestimate the amount of urea removed.

59 Swartz RD, Messana JM, Orzol S, Port FK. Comparing continuous hemofiltra- •• tion with hemodialysis in patients with severe acute renal failure. Am J Kidney Dis 1999; 34:424–432.
These results show that the high crude mortality rate of patients undergoing CVVH was related to the severity of illness and not to the treatment choice itself. When patients with high risk for dying were excluded, no differences in outcome between IHD and CRRT were found.

60 Camussi G, Ronco C, Montrucchio G, Piccoli G. Role of soluble mediators in sepsis and renal failure. Kidney Int Suppl 1998; 66:S38–S42.

61 Van Bommel EF. Should continuous renal replacement therapy be used for 'non-renal' indications in critically ill patients with shock? Resuscitation 1997; 33:257–270.

62 Bellomo R, Baldwin I, Cole L, Ronco C. Preliminary experience with high-volume hemofiltration in human septic shock. Kidney Int 1998; 66(Suppl):S182–S185.

63 Stegmayr B. Apheresis of plasma compounds as a therapeutic principle in severe sepsis and multiorgan dysfunction syndrome. Clin Chem Lab Med 1999; 37:327–332.

64 •• De Vriese AS, Colardijn F, Philippé JJ, Vanholder R, De Sutter JH, Lameire NH. Cytokine removal during continuous hemofiltration in septic patients. J Am Soc Nephrol 1999; 10:846–853.

This study shows that during treatment with continuous haemofiltration in patients with septic shock, adsorption to the AN69 membrane was the main clearance mechanism, but inhibitors of inflammation as well as inflammatory cytokines were removed to the same extent.

65 Kellum JA, Johnson JP, Kramer D, Palevsky P, Brady JJ, Pinsky MR. Diffusive vs. convective therapy: effects on mediators of inflammation in patient with severe systemic inflammatory response syndrome. Crit Care Med 1998; 26:1995–2000.

66 Chatoth DK, Shaver MJ, Marshall MR, Golper TA. Daily 12-hour sustained low-efficiency hemodialysis (SLEDD) for the treatment of critically ill patients with acute renal failure: initial experience [abstract]. Blood Purif 1999; 17: A16.

67 Hu KT, Yeun JY, Craig M, Depner TA. Extended daily dialysis: an alternative to continuous venovenous hemofiltration in the intensive care unit [abstract]. Blood Purif 1999; 17:A15.