

Recent advances in clinical acute renal failure

Norbert Lameire

Department of Internal Medicine. Renal Division.
University Hospital of Ghent. Belgium

DEFINITIONS

Acute renal failure (ARF) is the generic term for an “abrupt and sustained” decrease in renal function resulting in retention of nitrogenous (i.e. urea and creatinine) and non-nitrogenous waste products. Depending on the severity and duration of the renal dysfunction, this accumulation is accompanied by metabolic disturbances such as metabolic acidosis and hyperkalaemia, disturbances of body fluid balance, and effects on many other organ systems. The spectrum of definitions of ARF in the literature ranges from severe (e.g., ARF requiring dialysis) to relatively modest increases in serum creatinine (Scr) (e.g., of 0.3 to 0.5 mg/dl above baseline). Despite the absence of a universal definition, it is reasonable to define ARF as an

acute and sustained increase in Scr of 0.5 mg/dl (44.2 $\mu\text{mol/L}$), if the baseline is less than 2.5 mg/dl (221 $\mu\text{mol/L}$), or an increase in Scr by more than 20%, if the baseline is more than 2.5 mg/dl (221 $\mu\text{mol/L}$)¹.

Recently, the “Acute Dialysis Quality Initiative” (ADQI) group proposed the RIFLE system, classifying ARF into three severity categories (Risk, Injury and Failure) and two clinical outcome categories (Loss and End stage renal disease-RIFLE)²⁻⁴.

Table 1 details the criteria of the RIFLE classification (taken from²).

CAUSES OF ARF

These can be broadly divided into three categories:

- 1. Prerenal ARF** causes of a reversible increase in Scr and blood urea and results from decreased renal perfusion, which leads to a reduction in glomerular filtration rate (GFR).

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Table 1: RIFLE classification

	GFR criteria	Urine output (UO) criteria
Risk	Serum creatinine x 1.5	UO < 0.5 mL/kg/hr x 6hr.
Injury	Serum creatinine x 2	UO < 0.5 mL/kg/hr x 12 hr.
Failure	Serum creatinine x 3 or Creatinine \geq 4 mg/dL when there was an acute rise > 0.5 mg/dL	UO < 0.3 mL/kg/hr x 24 hr. or anuria x 12 hr.
Loss	Persistent acute renal failure = complete loss of kidney function > 4 weeks	
End stage kidney disease	End stage kidney disease > 3 months	

Prerenal ARF contributes to 30 to 60% of all cases of ARF and is frequently community-acquired⁵, especially in the aged population.

2. Postrenal ARF is due to obstruction of the urinary collection system by either intrinsic or extrinsic masses.

3. The remaining cases suffer from **renal ARF** whereby the structures of the nephron such as the glomeruli, tubules, vessels, or interstitium are affected.

The major **cause of intrinsic renal azotaemia is “acute tubular necrosis” (ATN)**. ATN is caused by ischaemic or nephrotoxic injury to the kidney and is a specific histopathologic and pathophysiologic entity, caused by a number of distinct renal insults.

Both prerenal azotaemia and ischaemic ATN occur on a continuum of the same pathophysiologic process and both conditions account for 75% of the cases of ARF^{6,7}.

Despite the terms have quite different definitions, ARF is often used synonymously with ATN

in the clinical setting and both terms will also be used in this paper.

DIAGNOSTIC APPROACH TO A PATIENT WITH ARF

This includes a careful history and record review, a thorough physical examination and the judicious interpretation of plasma and urinary laboratory data, including the examination of the urinary sediment, other urinary chemistries, urinary biomarkers, and appropriate ultrasound and radiological investigations^{8,9}.

Urine volume

Acute anuria or severe oliguria are quite specific indicators for ARF although severe ARF can exist despite normal urine output (i.e. nonoliguric). Changes in urine output can occur long before biochemical changes are apparent. Pre-renal

forms of ARF nearly always present with oliguria (< 400 ml/day) although non-oliguric forms have been reported¹⁰. Post-renal and renal forms of ARF can present with any pattern of urine flow ranging from anuria through polyuria.

Urinary parameters

As clearly explained in a very recent and lucid editorial¹¹, it is important for the clinician to assure that an early diagnosis of acute renal vasoconstriction can be made prior to the occurrence of tubular dysfunction, thus providing the potential to prevent progression to established ATN. The earlier approach relying on the patient response to a fluid challenge frequently led to massive fluid overload in the ARF patient with resultant pulmonary congestion, hypoxia, and premature need for mechanical ventilatory support and/or haemodialysis.

It is well established that as long as tubular function remains intact, renal vasoconstriction is associated with enhanced tubular sodium reabsorption. Specifically, the fraction of filtered sodium that is rapidly reabsorbed by normal tubules of the vasoconstricted kidney is greater than 99%. Thus, when nitrogenous wastes, such as creatinine and urea, accumulate in the blood due to a fall in glomerular filtration rate (GFR) secondary to renal vasoconstriction with intact tubular function, the fractional excretion (FE) of filtered sodium ($FE_{Na} = [(urine\ sodium \times plasma\ creatinine) / (plasma\ sodium \times urine\ creatinine)]$) is less than 1%. Pre-renal disorders also result in low urine concentrations of chloride, lithium, and uric acid and relatively high urine/plasma ratios of osmolality, urea and creatinine and low FE of uric acid (< 7%), and Fe lithium (<7%). An exception to this physiological response of the normal kidney to vasoconstriction is when the patient is receiving a diuretic, including mannitol and

dopamine, or has glucosuria, which decreases tubular sodium reabsorption and increases FE_{Na} . A recent study found that a low fractional excretion of urea (<0.35) may be more sensitive and specific than the fractional excretion of sodium in differentiating between pre-renal and renal causes of ARF, especially when diuretics have been administered¹². Also, renal vasoconstriction in a patient with advanced chronic renal failure may not be expected to be associated with an FE_{Na} of less than 1 because of chronic adaptation to an increased single-nephron GFR. Specifically, the adaptive decrease in tubular reabsorption to maintain sodium balance in chronic renal disease may make the interpretation of FE_{Na} difficult in this setting. It also should be pointed out that some causes of ARF, including radiocontrast media and myoglobinuria, may be associated with an FE_{Na} of less than 1¹³. This may be related to the early presence of severe renal vasoconstriction and intact distal tubule function, which can occur in the presence of proximal tubule injury.

While the fractional excretion of trace lithium appears to be a reliable index for differentiating pre-renal forms of ARF, the special analytical techniques required limit its use.

Biomarkers

Several biomarkers have been proposed for the early diagnosis of ARF and are currently under study^{14,15}. These include urinary IL-18¹⁶ and tubular enzymes, such as the intestinal form of alkaline phosphatase, N-acetyl- β -glucosaminidase, and alanine aminopeptidase¹⁷. Kidney Injury Molecule-1 (KIM-1), a type 1 transmembrane protein is extensively expressed in proximal tubule cells in biopsies from patients with confirmed ATN and the normalized urinary KIM-1 levels were significantly higher in ischaemic

mic ATN compared to levels in other forms of ARF or chronic renal disease¹⁸.

Identification of urinary proteins expressed during ARF may lead to the identification of novel targets for early diagnosis and therapy. Hampel et al.¹⁹ found that after radiocontrast administration, the protein expression differed between patients with normal renal function and patients with impaired renal function at baseline.

Serum creatinine (Scr)

In ARF renal function is frequently monitored by following the daily variations in Scr. However, important limitations are associated with the use of Scr as a marker of GFR in patients with ARF. The Scr level is not only dependent on its urinary clearance but also on its production rate and its volume of distribution. In addition, the Scr

will not be an accurate reflection of GFR in the non-steady state condition of ARF. Finally, a correct interpretation of Scr levels is hampered by the variation calibration of the different creatinine assays²⁰⁻²².

Serum cystatin C

Among newer GFR markers in ARF, serum cystatin C deserves evaluation since it has been shown more sensitive and accurate than plasma creatinine in several settings, but has not been very well validated as a GFR indicator in ARF^{23,24}. However, one recent study found serum Cystatin C to be an early and reliable marker of ARF in ICU patients and it detected ARF 1 to 2 days earlier than creatinine²⁵.

It appeared recently that cystatin C levels were also influenced by non-renal factors like

Table 2. The most important urinary parameters in the differential diagnosis between prerenal and renal ARF

Urinary Indices	Prerenal	Renal
Urinalysis	Hyaline casts	Abnormal
Specific gravity	> 1.020	1.010
Uosm (mOsm/kg H ₂ O)	> 500	> 300
UNa (mEq/l)	< 20	> 40
FE Na (%)	< 1	> 2
FE urea (%)	< 0.35	> 0.35
FE uric acid (%)	< 7	> 15
FE lithium (%)	< 7	> 20
Low molecular weight proteins	low	high
Brush border enzymes	low	high

cigarette smoking, body weight, male gender and inflammation²⁶. On the other hand, Cystatin C increased earlier after radiocontrast application compared with creatinine and in another small study in 14 patients in the ICU, the ability of cystatin C to detect a glomerular filtration rate under 80 ml/min per 1.73 m² was significantly better than that of creatinine^{27,28}.

Postrenal azotaemia (e.g. intra- or extrarenal obstruction of urine flow) is much less frequently encountered (1 to 10% of hospital-acquired ARF) and is almost always amenable to therapy. A sensitive approach to ruling out postrenal azotaemia is to identify post-void residual bladder urine as less than 50 ml and exclude pyelocalyceal dilatation using renal ultrasonography.

Ultrasonography exhibits a high degree of sensitivity (90 to 98 %) but a lower specificity (65 to 84 %) for detection of obstructive nephropathy²⁹. Patients with highly distensible collecting systems or with pyelocaliectasis may be misdiagnosed as having hydronephrosis. False-negative studies have been reported in patients with very early (less than 8 hours) obstruction^{30,31}. In many of these cases, the patients were of older age and the obstructing process, usually prostatic carcinoma or retroperitoneal fibrosis, encased the retroperitoneal ureters and renal pelvis, preventing their dilatation³². In the elderly, partial obstruction may be obscured by volume depletion. When there is strong suspicion of obstruction, the ultrasonographic examination should be repeated after volume repletion.

Acute vascular, glomerular, and interstitial processes may cause ARF, (approximately 15% of all cases of hospital-acquired ARF), and these causes should be carefully excluded before the diagnosis of ATN is accepted. The differential diagnostic approach of these diseases is beyond the scope of this paper.

The major renal cause of *intrinsic renal azotaemia* is “acute tubular necrosis” (ATN). ATN is caused by ischaemic or nephrotoxic injury to the kidney in 50% and 35% of all causes of hospital-acquired ARF, respectively. However, in 50% of the cases the cause is multifactorial.

Besides vascular derangements, tubular obstruction, and urinary backleak, newer concepts of the pathophysiology of ATN, including the role of interstitial inflammation, “sublethal” cell injury, apoptosis, and cell repair after injury are emerging.

Two components are important in the acute decrease of GFR; intrarenal vasoconstriction with a fall in glomerular filtration pressure, vascular congestion in the outer medulla, activation of the tubulo-glomerular feedback (TGF) (“*the vascular component*”), and tubular obstruction, transtubular backleak of the filtrate, and interstitial inflammation (“*the tubular component*”)^{7,33-35}.

Until recently, the evolution of clinical ATN was somewhat arbitrarily divided in an initiation, maintenance and recovery phase. Based on the recognition of the important role of outer medullary ischaemia and of endothelial-leukocyte interactions, a fourth “extension” phase has been described connecting the initiation and maintenance phases^{36,37}. It has been suggested that most of the preventive interventions in human ATN should be active in this “extensive” phase.

PREVENTION AND NON-DIALYTIC TREATMENT OF ARF

The general aspects of the management of patients with ARF are outlined in table 3.

Based on the progress made in the understanding of the pathophysiology, a plethora of therapeutic drug and non-drug interventions have

Table 3. Management priorities in patients with ARF

- Search for and correct prerenal and postrenal factors
- Review medications and stop nephrotoxins
- Optimize cardiac output and renal blood flow
- Restore and/or increase urine flow
- Monitor fluid intake and output, daily bodyweight
- Search for and treat acute complications (hyperkalaemia, hyponatraemia, acidosis, hyperphosphataemia, pulmonary oedema)
- Provide early nutritional support
- Search for and aggressively treat infections
- Initiate dialysis before uraemic complications emerge
- Dose drugs appropriate for their clearance

been developed and tested in animal and human forms of ATN³⁸⁻⁴³.

ATN can be prevented in a number of patients by careful attention to volume status and cardiac output, and the avoidance of nephrotoxic agents. These measures are more important in patients in whom renal blood flow (RBF) might already be compromised, such as the elderly or those with heart failure, liver disease, previous renal insufficiency, renal artery stenosis, and diabetes mellitus. Agents that impair autoregulation of RBF, such as NSAID or ACEIs or ARBs should be used with caution. Nephrotoxic agents should be minimized and plasma levels to guide dosing of aminoglycosides and cyclosporine should be measured. Allopurinol and the recently introduced Rasburicase, a recombinant urate oxidase preparation, decrease uric acid synthesis in patients with leukaemia and lymphoma who are prone to uric acid nephropathy⁴⁴. Forced alkaline diuresis prevents blockage of renal tu-

bules by uric acid or methotrexate in these malignancies, and by casts in rhabdomyolysis.

Volume expansion

The preventive and therapeutic value of volume expansion alone is not easy to estimate, because fluids are often included as part of the overall management of patients in clinical studies, together with the administration of diuretics and/or dopamine. The value of volume therapy and the nature of fluids (crystalloids versus colloids) to be used in critically ill patients with or without ARF have recently been reviewed and yielded conflicting results⁴⁵⁻⁴⁸. The recently published SAFE trial found that fluid resuscitation with saline gave similar results as albumin in critically ill patients⁴⁹. Hydration has been suggested to prevent postsurgery, contrast-platinum- and amphotericin B induced - ATN, and the intrarenal tubular precipitation of crystals after high doses of methotrexate, sulfonamides and acyclovir⁴³. Early fluid resuscitation with mannitol and bicarbonate has been known to prevent ATN in rhabdomyolysis^{50,51} and recently the preventive action of this fluid management has been demonstrated in victims of an earthquake in Turkey⁵².

Interestingly, a recent study found that hydration with isotonic saline is superior to the routinely recommended half-isotonic hydration in the prevention of contrast media-associated nephropathy⁵³. Overzealous fluid administration can of course lead to pulmonary oedema, particularly in the oligo-anuric patient.

Use of Diuretics and Dopamine in ATN

The evaluation of furosemide, mannitol, and low-dose dopamine in the prevention or reversal

of ATN gave inconsistent results (for reviews see^{54,55}. Mannitol was able to prevent ARF only in rhabdomyolysis and kidney transplant surgery. With adequate circulating volume loop diuretics promote diuresis in some forms of oliguric ARF^{55,56}, but their administration may be associated with increased mortality and delayed recovery of renal function^{57,58}. However, a recent prospective, multiple-center, multinational epidemiologic study including 1.743 consecutive patients concluded that diuretic use was not associated with a significantly increased risk of mortality⁵⁹. There is thus need for a randomized controlled trial of diuretics in critically ill patients with renal dysfunction.

Low-dose dopamine (1 to 3 µg/kg per minute, intravenously) is a renal vasodilator and has frequently been used alone or in combination with furosemide particularly in ICU patients. Prospective controlled trials and careful meta-analysis have concluded that dopamine does not reduce mortality nor promotes the recovery of renal function⁶⁰⁻⁶². The risks associated with dopamine in critically ill patients have recently been summarized (for review see⁴³).

N-Acetylcysteine (NAC)

Three recent meta-analyses⁶³⁻⁶⁵ concluded that compared with periprocedural hydration alone, oral acetylcysteine with hydration significantly reduces the risk of contrast nephropathy in patients with chronic renal insufficiency. One should emphasize that acetylcysteine without adequate hydration is not sufficient and that in some of these studies the individual contribution of acetylcysteine is difficult to delineate. However, in every meta-analysis also studies showing no benefit were found.

Furthermore, it has recently been suggested that acetylcysteine directly affects the tubular

handling of creatinine so that a decrease in Scr with this drug not necessarily points to a protective effect on the GFR⁶⁶.

Calcium channel blockers

Some investigators have demonstrated that the prophylactic administration of calcium channel blockers protects against post-transplant delayed graft failure⁴³. However, a critical meta-analysis⁶⁷ suggested that the issue of renal protection with calcium entry blockers in the prevention of post-transplant ATN is not settled. In other settings of ARF⁶⁸ and in post cardiac surgery⁶⁹, the preventive role of calcium channel blockers was more promising.

Natriuretic Peptides

Atrial natriuretic peptide (ANP), a hormone synthesized in the cardiac atria, increases GFR through vasodilatation of the afferent arterioles and vasoconstriction of the efferent arterioles, inhibits reabsorption of sodium, and redistributes renal medullary blood flow, resulting in an improved supply and reduced demand of oxygen in the tubules. Urodilatin is synthesized in the renal tubular cells by differential processing from the same precursor as ANP and has similar biologic effects.⁷⁰ Whereas non-controlled studies had shown transient improvement of renal function in ARF patients, in a randomized placebo-controlled trial including 504 critically ill patients with ARF (31% with sepsis), a 24-h infusion of the synthetic ANP anaritide did not improve the overall rate of dialysis-free survival⁷¹. A subgroup analysis indicated that anaritide improved dialysis-free survival rate in oliguric patients by reducing the need for dialysis but not by lowering mortality. In non-oliguric patients,

however, anaritide worsened dialysis-free survival. To further examine the potential benefit of anaritide in oliguric patients, a randomized placebo-controlled trial was conducted in 222 oliguric ARF patients (35% with sepsis)⁷². Anaritide (24-h) conferred a nonsignificant trend toward improved 14-d and 21-d dialysis-free survival, but 60-d mortality rates were similar to placebo. The study was criticized for administering anaritide too late, too shortly, and at an excessive dose, the latter leading to hypotension and jeopardizing renal perfusion. In two randomized placebo-controlled trials in critically ill patients with ARF, a long-term (96-h and 5-d, respectively) infusion of urodilatin did not improve renal function or reduce the need for renal replacement therapy^{73,74}.

However, a very recent prospective, double-blind, randomized, placebo-controlled study in two tertiary study cardiothoracic intensive care units demonstrated that infusion of h-ANP at a rate of 50 ng.kg.min enhances renal excretory function, decreases the probability of dialysis, and improves dialysis-free survival in early, ischemic acute renal dysfunction after complicated cardiac surgery.⁷⁵ As recently pointed out there are maybe further promises in the prevention of ARF with these peptides⁷⁶.

Other therapeutic measures

A number of other both older and novel therapeutic agents have been examined for potential use in experimental ATN. These include theophylline, epidermal and insulin-like growth factors, antibodies to adhesion molecules, oxygen free radical scavengers, amino acid infusions, and prostaglandins.

Recently, a remarkable protection against renal ischaemia-reperfusion injury was observed with a single administration of erythropoietin⁷⁷. A

direct tubular cell effect by prevention of caspase activation *in vivo* and reduction of apoptotic cell death was demonstrated. This indicates once more that erythropoietin is more than a promoter of erythropoiesis⁷⁸.

To date, two randomized, placebo-controlled trials with insulin-like growth factor I, one in critically ill patients and one in renal transplantation revealed negative results^{79,80}.

None of these experimental therapies have yet been proven to be safe and/ or to be effective for use in human ARF⁴³.

SUPPORTIVE TREATMENT OF ACUTE RENAL FAILURE

Current therapy is aimed mainly at prevention and treatment of the associated complications. Hyperkalaemia was a frequent cause of death in the past but has become less frequent with greater access to dialysis and with development of rapid, accurate laboratory procedures to identify and monitor the clinical course. Restriction of potassium in the diet and the infusions and avoidance of potassium-containing drugs are especially important. Patients who are oliguric, anuric, hypercatabolic or suffering from rhabdomyolysis may have a rapid increase in serum potassium. Emergency treatment of hyperkalaemia, primarily dictated by changes in the ECG, includes the use of intravenous calcium, driving potassium into cells with sodium bicarbonate and/or an infusion of glucose and insulin. These emergency measures do not remove potassium from the body, and additional therapy with a sodium-potassium exchange resin such as sodium polystyrene sulfonate (Kayexalate®) or by dialysis will be needed as a second step. Haemodialysis provides the most rapid mode of removing potassium.

Abnormalities in water and sodium metabo-

lism need careful management in ARF. Daily body weight, intake, and output should be measured. The oliguric patient's intake of fluid should be limited to 400 ml/day plus the previous day's urinary output unless physical signs of volume depletion or volume overload are present. Dietary sodium should be restricted to 2 g (87 mmol)/day. A patient with ATN, if not receiving hyperalimentation, is expected to lose 0.3 to 0.5 kg/day of weight. If this loss does not occur or if there is an actual weight gain, fluid therapy should be reevaluated. Hyponatremia may require stringent free-water restriction.

Acidosis occurs frequently in ARF⁸¹. Modest amounts of sodium bicarbonate may be administered if the serum bicarbonate level drops below 15 to 18 mmol/L, although the potential for volume overload should be recognized. Hyperphosphataemia should be treated with calcium carbonate or other phosphate binders. Hypermagnesaemia may be elicited after an exogenous load of magnesium, and magnesium-containing antacids should be avoided. Severe hyperphosphataemia or severe hypermagnesaemia can be treated with dialysis.

Nutritional support is an important aspect of the treatment of ARF. It should be designed to give adequate calories without excessive volume. The caloric requirement in ARF is relatively high, especially in patients who are hypercatabolic. Carbohydrate intake should be sufficient (more than 100 g per day) to avoid breakdown of endogenous protein for glucose. The protein requirements depend on the clinical status. With oral feedings one can start with a diet of 40 g/day of high-quality protein and increase it if deemed necessary. Meeting the nutritional needs of the patient may not be possible without dialysis, which allows larger quantities to be given. Enteral or parenteral alimentation may be necessary in the post-op-

erative patient or in those with anorexia or vomiting. The use of essential amino acids or their keto- analogs in the postoperative or trauma patient has been suggested but not proven to improve the outcome of ARF.

Recent attention has been given to the adverse effects of hyperglycaemia⁸² and an extensive, controlled trial has shown a reduction in mortality and morbidity of critically ill patients by strict glycaemic control⁸³. Multivariate analysis indicated that the lowered blood glucose level rather than the insulin dose was related to reduced mortality, critical illness neuropathy, bacteraemia and inflammation⁸⁴.

Doses of several drugs must be altered in ARF, especially those that are renally excreted or those whose pharmacokinetics are altered in azotaemia or dialysis.

FUTURE THERAPIES

Experimentally, recent stem cell research shows that haematopoietic stem cells (HSC) and other tissue-specific stem cells are capable of crossing tissue and even germ-line barriers and can give rise to a remarkable range of cell types⁸⁵. This plasticity of stem cells is thought to be useful in therapeutic strategies designed to enhance tissue regeneration after severe organ injury. Traditionally, stem cells were believed to be organ specific (for review^{86,87}). Experiments with whole-bone marrow transplantation demonstrated that bone marrow-derived stem cells (BMSCs) could populate the renal tubular epithelium^{88,89}. More recently, injection of mesenchymal stem cells of male bone marrow origin remarkably protected cisplatin-treated syngeneic female mice from renal functional impairment and severe tubular injury⁹⁰. However, haematopoietic stem cell mobilisation is associated with important granulocytosis

which may aggravate the intrarenal inflammation and impair renal recovery⁹¹.

RENAL REPLACEMENT THERAPY (RRT) OF ARF

There are no absolute rules as to when dialysis should begin, but it is better to begin too soon, and it should be started before complications occur⁹². Indications for immediate treatment in critically ill ARF patients include hyperkalaemia (causing significant ECG changes), severe pulmonary oedema, uraemic acidosis (causing cardiac compromise), and gross uraemia

Table 4 summarises the advantages and disadvantages of both intermittent haemodialysis and continuous renal replacement therapies

(CRRT) such as continuous venovenous haemofiltration (CVVH).

Up to now, no evidence-based guidelines on the optimal dialysis treatment of ARF are available⁹³⁻⁹⁵. For a long time, it has been claimed that CRRT was superior to intermittent haemodialysis. Many controlled studies⁹⁶⁻¹⁰⁰ and a recent meta-analysis¹⁰¹ could not find differences in outcome. In specific conditions however, one of both dialysis modalities is an absolute preference, like e.g. CRRT in patients with cerebral oedema or liver failure, or IHD in patients with increased bleeding risk.

A landmark study underscored the importance of dose of dialysis in CRRT. Patients receiving CVVH showed better outcomes with filtration rates of 35 or 45 ml/hr/kg than those treated at the lower rate of 20 ml/hr/kg¹⁰². Although a com-

Table 4. Advantages and disadvantages of intermittent and continuous dialysis strategies in ARF patients

	Intermittent haemodialysis	CRRT
Advantages	<ul style="list-style-type: none"> Less risk for systemic bleeding More ‘free time ‘ for diagnostic and therapeutic interventions More suitable for severe hyperkalaemia Less costs 	<ul style="list-style-type: none"> Improved haemodynamic stability Fewer cardiac arrhythmias Improved nutritional support Better pulmonary gas exchange Better fluid control Better biochemical control Shorter stay in ICU
Disadvantages	<ul style="list-style-type: none"> Availability of dialysis personnel More difficult haemodynamic control Inadequate dialysis dose Inadequate fluid control Inadequate nutritional support Not suitable for patients with intracranial hypertension No removal of cytokines Potential complement activation by non-biocompatible membranes 	<ul style="list-style-type: none"> Increased vascular access problems Increased risk of systemic bleeding Prolonged patient immobilisation More filter problems (ruptures, clotting) Increased cost

parable study in IHD is still lacking¹⁰³, it was shown that daily dialysis resulted in better control of uraemia, fewer hypotensive episodes during dialysis and more rapid resolution of ARF¹⁰⁴. "Classic" dialysis adequacy parameters like Kt/V urea should be used with caution because they need an estimate of total body water (TBW) which is conventionally based on anthropometric values which may be incorrect in critically ill ARF patients¹⁰⁵.

Meta-analyses further demonstrated that the use of biocompatible membranes could possibly influence patient survival positively, however, without effect on recovery of renal function¹⁰⁶⁻¹⁰⁹.

Slow extended daily dialysis (SLEDD) emerged as a hybrid RRT modality and has promising features because it combines the advantages of both CRRT and IHD^{94,110-113}.

"Hybrid therapies" such as SLEDD are those techniques where a conventional dialysis monitor with on-line fluid preparation is used for treatments that extend the usual duration of a "conventional intermittent dialysis" session of 3-4 hours/treatment. SLEDD treatments offer the best balance between advantages and disadvantages of both CRRT and IHD, as they allow a nearly unlimited capacity to tailor the treatment to the needs of the patient while using one single machine.

Although it appears that, based on personal contacts with nephrologists in charge of critically ill ARF patients, SLEDD-like approaches are being used in many centers around the world, the literature on this subject is rather limited. Lonneman et al used the Genius system, with a blood and dialysate flow rate of 70ml/min., during 18hours a day¹¹⁴. This resulted in a urea clearance of 65 l/day, and a mean ultrafiltration volume of 120ml/hour without any reported haemodynamic instability. Kumar et al used a Fresenius 2008H machine, with a mean blood flow of 200ml/min,

and a dialysate flow of 300ml/min during 6-8 hours, on a daily basis. They compared the clearance, haemodynamic stability and anticoagulation needs of patients on this treatment with those of patients treated by CVVH with a mean blood flow of 170ml/min, and an exchange volume of 2 liters/hour. There was no difference in haemodynamic stability, nor in the need for vasopressive agents. Patients treated with SLEDD required significantly less heparin compared to those on CVVH (4000 vs 21000Units/day).^{110,111}. They found a comparable haemodynamic stability in patients on SLEDD as compared to patients on CRRT.

The implementation of SLEDD allows the tailoring of the treatment to the needs of the patient and the ICU staff. With one single technique and machine, the treatment can be slow and gentle (if needed), and the intensity of the treatment can be increased (while reducing treatment time) if the patient's condition further improves during the course of his disease.

PROGNOSIS

When ARF is severe enough to require RRT, in-hospital mortality is high, exceeding 50%¹¹⁵⁻¹¹⁷; this mortality is extremely high in critically ill ARF with multiorgan failure¹¹⁸⁻¹²⁰. Mortality rates have changed little over the past decades despite significant advances in supportive care; however, this lack of improvement may be more apparent than real because patients are now older and have more preexisting chronic health conditions¹²¹. It was recently shown that certain combinations of gene polymorphism, are related to the risk of death among patients with ARF who require dialysis^{122,123}. The combination of a high TNF-alpha and a low IL-10 low producer genotype was associated with an increased risk of death compared to the TNF-alpha-low and

IL-10 intermediate/high producer genotype combination.

The long-term effects of ARF in patients are unclear and controversial because of the diverse (and often multiple) causes of ARF and the paucity of long-term follow-up studies. Nevertheless, the view that renal recovery is complete may be simplistic and progressive renal dysfunction following severe ARF has frequently been observed¹²⁴⁻¹²⁷. ARF is irreversible in 5% of patients, but in the elderly this may be as high as 16%¹²⁸. Recent reports of paediatric patients suggest that residual damage following ARF develops into progressive renal failure by adolescence or early adulthood¹²⁴⁻¹²⁷.

Correspondence:

Prof. Norbert Lameire
University Hospital
185, De Pintelaan
9000 Ghent
Belgium

e-mail: norbert.lameire@ugent.be

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