

## Review

**Year in review 2005: *Critical Care* – nephrology**Zaccaria Ricci<sup>1</sup> and Claudio Ronco<sup>2</sup><sup>1</sup>Department of Pediatric Cardiosurgery, Bambino Gesù Hospital, Rome, Italy<sup>2</sup>Department of Nephrology, Dialysis and Transplantation, S. Bortolo Hospital, Vicenza, ItalyCorresponding author: Zaccaria Ricci, [z.ricci@libero.it](mailto:z.ricci@libero.it)

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*Critical Care* 2006, **10**:226 (doi:10.1186/cc4998)**Abstract**

We summarize original research in the field of critical care nephrology accepted or published in 2005 in *Critical Care* and, when considered relevant or directly linked to this research, in other journals. The articles have been grouped into four categories to facilitate a rapid overview. First, physiopathology, epidemiology and prognosis of acute renal failure (ARF): an extensive review and some observational studies have been performed with the aim of describing aspects of ARF physiopathology, precise epidemiology and long-term outcomes. Second, several authors have performed clinical trials utilizing a potential nephro-protective drug, fenoldopam, with different results. Third, the issue of continuous renal replacement therapies dose has been addressed in a small prospective study and a large observational trial. And fourth, alternative indications to extracorporeal treatment of ARF and systemic inflammatory response syndrome have been explored by three original clinical studies.

**Introduction**

During 2005, *Critical Care* accepted and published articles of original research focused on critical care nephrology and renal replacement therapy (RRT). These studies included papers on epidemiology, prognosis and medical therapy of acute renal failure (ARF), the issue of continuous RRT (CRRT) dose and alternative indications to extracorporeal therapies.

We present a review of these papers and other key articles on critical care nephrology published in 2005.

**Physiopathology, epidemiology and prognosis of ARF**

To assess changes in renal blood flow (RBF) in human and experimental sepsis, and to identify determinants of RBF, Langenberg and co workers [1] performed an electronic database search and tried to identify experimental and human studies of septic acute renal failure in which RBF was measured. Surprisingly, they found that no human studies measured RBF with suitably accurate direct methods. Where

it was measured in septic patients, however, RBF was increased compared with normal. The authors concluded that the impact of sepsis on RBF in humans is unknown. When examined in experimental models of sepsis, RBF was decreased in two-thirds of studies (62%) and unchanged or increased in one-third (38%). Multivariate analysis suggested that cardiac output might have a substantial effect on RBF during experimental sepsis, such that, in the presence of a decreased cardiac output, RBF is typically decreased, whereas in the presence of a preserved or increased cardiac output RBF is typically maintained or increased. This extensive analysis introduces a provocative hypothesis in the physiopathology of ARF: the traditional mechanism of ischemic ARF in critically ill septic patients is put to discussion and, if confirmed by specifically designed experimental and human studies, it could provide new important information about the prevention and therapy of septic ARF.

The impact on mortality of severe ARF (sARF), defined as the requirement for RRT with evidence of renal dysfunction (serum creatinine >150 mmol/l) during intensive care unit (ICU) admission, was examined by Bagshaw and co-authors [2]. A survey was conducted over a period of 36 months among an adult population of over 700,000 residents. sARF occurred in 240 patients (11.0 per 100,000 population/year). Rates were highest in males and older patients (≥65 years of age). Risk factors for development of sARF included previous heart disease, stroke, pulmonary disease, diabetes mellitus, cancer, connective tissue disease, chronic renal dysfunction, and alcoholism. The annual mortality rate was 7.3 per 100,000 residents with highest rates in males over 65 years. The 28-day, 90-day, and 1-year case-fatality rates were 51%, 60%, and 64%, respectively. An increased number of comorbidities, the presence of liver disease, a higher APACHE II score, septic shock, and the need for CRRT were independently associated with death at 1 year. Renal recovery

ARF = acute renal failure; CRRT = continuous renal replacement therapy; HVHF = high volume hemofiltration; ICU = intensive care unit; PHVHF = pulse high volume hemofiltration; PMX = polymixin; RBF = renal blood flow; RRT = renal replacement therapy; sARF = severe acute renal failure.

occurred in 78% (68/87) of survivors at 1 year, meaning that, although the majority of patients with sARF will die, most survivors will become independent from RRT within a year.

With a similar intention of determining the association between outcome and different epidemiological parameters (period prevalence of ARF, etiology, illness severity, and clinical management of ARF), the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators conducted a multinational, multicenter, prospective, epidemiological survey of ARF in ICU patients [3] who were either treated with RRT or fulfilled at least one of the predefined criteria for ARF. Predefined ARF criteria were oliguria, defined as urine output of less than 200 ml in 12 hours, and/or marked azotemia, defined as a blood urea nitrogen level higher than 30 mmol/l. The data were collected from September 2000 to December 2001 at 54 hospitals in 23 countries. Of 29,269 critically ill patients admitted during the 16 month study period, 1,738 (5.7%) had ARF during their ICU stay, including 1,260 (4.3%) who were treated with RRT. Overall hospital mortality was 60.3%. The most common contributing factor to ARF was septic shock (47.5%). Approximately 30% of patients had preadmission renal dysfunction. Of the survivors, 86.2% were independent from dialysis at hospital discharge. Independent risk factors for hospital mortality included use of vasopressors, mechanical ventilation, septic shock, cardiogenic shock, and hepatorenal syndrome.

From the findings of these studies we can reasonably conclude that the prevalence of ARF among the ICU population is between 5% and 6%, that more than 70% of these patients require RRT, that hospital survival among ARF patients is still disappointing (about 40%), and that renal recovery among survivors is very high. A systematic literature review [4] confirmed the suspicion that no evidence of a substantial improvement in outcome from ARF over the past 50 years has been observed. The mortality rates remain higher than 50%, despite new approaches to general management, such as advanced monitoring, and despite new available RRT machines and a trend to increased prescription of dialytic dose. Another point that should be commented on is the urgent need for a common definition of ARF, an essential instrument in comparing different epidemiological studies and for evaluating therapies during clinical trials [5].

### **Fenoldopam: a new medical approach to ARF?**

If the outcome of critically ill ARF patients is still poor, the issue of prevention and protection from this lethal condition becomes a priority. Four randomized controlled and one retrospective trial on fenoldopam utilization were published between January 2005 and January 2006: in all cases this relatively new drug was administered to prevent or treat ARF in critically ill patients or in post cardio-surgical patients, a specific population that is particularly prone to develop ARF.

At present, evidence-based medicine dictates that there is no place in clinical practice for dopamine infusion in the prevention or treatment of ARF [6]. Fenoldopam, unlike dopamine, stimulates only dopamine 1 (and not dopamine 2) receptors, thus theoretically inducing greater vasodilation in the renal medulla than in the cortex. Furthermore, fenoldopam has no  $\alpha$  or  $\beta$  adrenergic activity, properties that are believed to cause arrhythmias and other adverse effects during dopamine infusion.

Tumlin and co-workers [7] conducted a randomized placebo-controlled trial in 155 patients with early acute tubular necrosis with the hypothesis that administration of low-dose fenoldopam (0.1  $\mu$ g/kg/minute) would decrease the need for dialysis therapy and/or incidence of death at 21 days. Patients with a serum creatinine level increasing to 50% greater than a normal baseline level (creatinine >133 mmol/l) or a 25% increase greater than a baseline level greater than 1.5 mg/dL (133 mmol/l) during a single 24 hour period from ICU admission were considered to have a diagnosis of early acute tubular necrosis. The authors found a non-statistically significant 11% absolute reduction in the primary end point. Similarly, there was no difference in the incidence of dialysis therapy between patients randomly assigned to fenoldopam versus the placebo group. Finally, there was a non-statistically significant trend to 21-day mortality decrease in the fenoldopam group (fenoldopam, 13.8% versus placebo, 25.3%;  $P=0.068$ ).

Morelli and co-workers [8] conducted a randomized placebo-controlled trial in 300 septic patients with baseline serum creatinine concentrations <150 mmol/l. The peculiar design of this study considered as eligible patients all subjects with sepsis but without signs of acute renal dysfunction, in order to eventually obtain a prophylaxis from the occurrence of ARF. Patients received a continuous low-dose infusion of fenoldopam (0.09  $\mu$ g/kg/minute) or placebo. The authors observed that fenoldopam induced a significant reduction in mild ARF incidence (creatinine concentrations >150 mmol/l and <300 mmol/l), a non-significant trend to reduced severe ARF (creatinine concentrations >300 mmol/L) incidence and a non-significant difference in 28-day mortality with respect to placebo.

Brienza and co-workers [9] randomized 100 adult critically ill patients with early renal dysfunction (urine output  $\leq 0.5$  ml/kg over a 6 hour period and/or serum creatinine concentration  $\geq 1.5$  mg/dL and  $\leq 3.5$  mg/dL) for whom ICU stay was lower than 1 week. Patients were randomized to receive 2  $\mu$ g/kg/minute dopamine or 0.1  $\mu$ g/kg/minute fenoldopam. Drugs were administered as continuous infusion over a 4 day period. Fenoldopam produced a more significant reduction in creatinine values compared with dopamine after 2, 3, and 4 days of infusion. The maximum decrease in creatinine compared with baseline was significantly greater in patients who received fenoldopam. Total urinary output during drug

infusion was not significantly different between groups. Differences between the two groups in dialysis need and mortality were not examined by the authors.

These three works share a similar low-dose infusion of fenoldopam, which appears safe and free from hypotensive effects. All authors designed the studies in order to administer the drug at a very early stage after ICU admission. All studies showed a positive effect on creatinine levels. None of them was able to show significant effects on protection from dialysis and mortality. These puzzling results must be examined with care: the stage has been set for a large, phase III, multicenter, randomized, placebo-controlled trial to test renal-dose fenoldopam before its routine use in clinical practice.

Two important studies in high-risk post cardio-surgical patients were also conducted with the utilization of fenoldopam as a nephro-protective drug.

Bove and co-workers [10] performed a prospective single-center, randomized, double-blind trial with 80 patients undergoing cardiac surgery. Patients received either fenoldopam at 0.05 µg/kg/minute or dopamine at 2.5 µg/kg/minute after the induction of anesthesia for a 24 hour period. All these patients were at high risk of perioperative renal dysfunction as indicated by Continuous Improvement in Cardiac Surgery Program score >10. The primary end point was defined as 25% creatinine increase from baseline levels after cardiac surgery. No difference in outcome was observed between the two groups. Incidence of ARF was similar; peak postoperative serum creatinine level, intensive care unit and hospital stay, and mortality were also similar in the two groups. The randomization was interrupted at an interim analysis for lack of efficacy of the drug.

A small retrospective study [11] recently suggested a positive effect of fenoldopam on diuresis in 25 neonates who were failing to achieve an adequate negative fluid balance despite conventional diuretic therapy after high risk cardiac surgery and cardiopulmonary bypass. The particular setting of this paper and its initial results, however, deserve further data collection in order to draw any definitive conclusion.

### The dose of dialysis

It is still unclear whether a correlation between dialysis treatment dose and outcome exists and no consensus has been reached on how much treatment is adequate [12]. A Microsoft Excel based software called 'Adequacy Calculator for ARF' has been described and tested: it is a simple and manageable tool designed to prescribe RRT dose and to collect information about the quantity of delivered treatments [13]. Once the required parameters are entered, it calculates urea clearance and fractional clearance,  $spKt/V$  ( $sp$  = single pool,  $K$  = clearance,  $t$  = time,  $V$  = urea volume of distribution) for each CRRT modality. Data from 106 consecutive CRRT

treatments administered to 30 critically ill patients with ARF were collected.  $Kt/V$  has not yet been validated as a marker of adequacy in patients with ARF, but it seems that a rationale exists for its use in continuous therapies. We found that the Adequacy Calculator was able to predict the delivered urea clearance accurately: the value of clearance predicted by the calculator was strongly correlated with the value obtained from determination on blood and dialysate, regardless of which CRRT modality was selected. The correlation between prediction and effective delivery remained high over a time range of 24 hours and within a value of  $spKt/V$  of 1.4, which approaches the target of 35 ml/kg/h, when delivered for 24 hours [14]. This tool might help clinicians to correlate different dose prescriptions with different clinical outcomes.

The DOse REsponse Multicenter International (DO-RE-MI) collaborative initiative [15] is a multicenter observational study that aims to describe current practices of RRT in all ICU patients admitted to ICUs who are in need of RRT. It will also provide a center-based collection of data that will be useful for monitoring all aspects of extracorporeal support, such as incidence, frequency, duration, reasons to start and stop RRT, downtime, and, above all, eventual correlation between delivered dose and outcome. All data are entered in electronic case report forms that are available via the internet [16]. The study is still ongoing, and at interim analysis 199 patients (141 male and 58 female with a mean age of 56.7 and 61.5 years, respectively) from 42 centers in 5 countries (Spain, Italy, Germany, Portugal and France) have been recruited. Large variability in the delivered dose is anticipated and the study should hopefully show whether and to what extent RRT dose impacts on mortality and hemodynamics.

### Alternative indications to extracorporeal treatments

The sepsis syndrome is the most common cause of ARF and multiple organ dysfunction in critically ill subjects and continues to have high mortality. Normal immune homeostasis is interrupted by a complex storm of inflammatory mediators responsible for the deleterious effects. Extracorporeal blood purification therapy can confer benefits in sepsis by proven non-specific removal of these mediators (pro- or anti-inflammatory), and provide a rationale to treat this syndrome [17]. High volume hemofiltration (HVHF) has had the most dramatic effects, providing benefits in hemodynamics, enabling reduction of vasopressor doses and improving survival [18]. Pulse HVHF (PHVHF) is a different approach that may offer the most efficient results: it consists of a daily schedule of 6 to 8 hours at a pre-dilution replacement rate of 85 ml/kg/h followed by standard CVVH at a standard dose of 35 ml/kg/h [19]. In this study, 15 patients were treated, with no treatment prematurely discontinued [19]. Haemodynamics were improved by PHVHF, allowing a significant reduction in noradrenaline dose during and at the end of the PHVHF

session; this reduction was maintained at 6 and 12 hours after pulse treatment. There was also an improvement in systolic blood pressure. There were no changes in temperature, cardiac index, oxygenation, arterial pH or urine output during the period of observation. The mean daily spKt/V was 1.92. Predicted mortality rates were 72% (based on APACHE II score) and 68% (based on SAPS II score), and the observed 28-day mortality was 47%.

Another important randomized controlled trial of extracorporeal purification techniques evaluated the polymyxin B-immobilized (PMX) endotoxin removal hemoperfusion cartridge [20], which has been shown to remove endotoxin in preclinical and open-label clinical studies. In this study, 36 postsurgical patients admitted to 6 European ICUs with severe sepsis or septic shock secondary to intra-abdominal infection were randomized to PMX treatment of 2 hours or standard therapy. No statistically significant differences in the change of endotoxin and interleukin-6 levels from baseline to 24 hours after treatment between the two groups were shown. Patients treated with PMX demonstrated significant increases in cardiac index, left ventricular stroke work index, and oxygen delivery index compared with controls. The need for CRRT after study entry was reduced in the PMX group. There was no significant difference between the groups with regards to organ dysfunction, as assessed by the Sequential Organ Failure Assessment scores, from day 0 (baseline) to day 6.

A French group [21] randomized 61 critically ill patients into three hemofiltration treatment groups in order to evaluate the effect of isovolumic HVHF alone or combined with mild hypothermia on survival after out-of-hospital cardiac arrest with initial ventricular fibrillation or asystole. The three groups were control, HVHF (200 ml/kg/h over 8 hours) or HVHF with mild hypothermia (32°C for 24 hours) induced by cooling the hemofiltration substitution fluid. The primary end point was survival with a follow-up time of six months. The effect of hemofiltration on death by intractable shock was the secondary end point. After adjustment for baseline characteristics of cardiac arrest, hemofiltration (with or without hypothermia) was associated with improved survival. Compared to the control group, the relative risk of death by intractable shock was 0.29 in the hemofiltration-hypothermia group and 0.21 in the hemofiltration group.

These three studies show a beneficial effect of extracorporeal blood purification therapy on hemodynamics of patients with systemic inflammatory syndrome from different causes: despite intriguing results and promising improvement in patient outcome, the limited statistical power of these trials still limits the use of extracorporeal blood purification therapy to the strict boundaries of clinical research.

## Competing interests

The authors declare that they have no competing interests.

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