

## Kidney diseases beyond nephrology—intensive care

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### Acute renal failure epidemiology

The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) investigators conducted a multinational, multicentre, prospective, epidemiological survey of acute renal failure (ARF) in intensive care unit (ICU) patients [1], with the intention of determining the association between outcome and different epidemiological parameters: period prevalence of ARF, aetiology, illness severity and clinical management of ARF. Examined patients were treated with renal replacement therapy (RRT) or fulfilled at least one of the pre-defined criteria for ARF. Pre-defined ARF criteria were oliguria, defined as urine output of <200 ml in 12 h and/or marked azotaemia, defined as a blood urea nitrogen level >30 mmol/l. The data were collected at 54 hospitals, in 23 countries. Of 29 269 critically ill patients admitted during the 16 months' study period, 1738 (5.7%) had ARF during their ICU stay, including 1260 (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 the patients had pre-admission renal dysfunction. 86.2% survivors 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.

Crude mortality assessment shows that the overall hospital outcome of ARF has remained high today, and has not changed in the last 30 years: nevertheless such analysis is profoundly misleading. Patients with ARF treated in hospitals 30 years ago were mostly treated outside the ICU, did not require or receive

mechanical ventilation or vasopressor drugs, were 20–30 years younger in age and their outcome was typically assessed retrospectively and in academic centres only. Despite such profound differences, indicating much greater illness severity for patients treated in 2005, the mortality of ARF has not increased, the duration of treatment has clearly decreased in terms of need for dialysis, time in ICU and time in hospital and the techniques of artificial renal support have also changed markedly [2]. It is a matter of fact, however, that 50–60% crude mortality associated with ARF will remain unchanged in the next decade or more as it most likely represents the level of performance acceptable to the healthcare system rather than a true reflection of its performance. In other words, as therapeutic capability improves and the system continues to accept a mortality of 50% as reasonable for these very sick patients, the healthcare system will progressively admit and treat sicker and sicker patients with ARF. In modern healthcare systems, hence, ARF and requirement for acute RRT has become an established reality.

### Acute renal failure and anaemia

The role of anaemia in ARF has been recently investigated by many authors in different settings with contrasting results. Du Cheyron and colleagues [3] showed that three factors were independently associated with 28-day death in a cohort of 209 critically ill patients requiring dialysis: haemoglobin <9 g/dl, age and Sequential Organ Failure Assessment (SOFA) score. Based on age and SOFA, a matched cohort analysis of 67 pairs of ARF patients with or without anaemia found similar results regarding the negative impact of anaemia on outcome. Finally, a multi-variable logistic regression analysis on matched cohort identified haemoglobin level below 9 g/dl, continuous RRT and vasoactive therapy as independent predictors of 28-day death. Habib and coworkers [4] demonstrated that cardiopulmonary bypass (CPB) haemodilution to haematocrit <24% is associated with a systematically increased likelihood of renal

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injury (including ARF) and consequently worse operative outcomes in a cardiac surgery adult population. This effect is exacerbated when CPB is prolonged with intraoperative packed red blood cell transfusions and in patients with borderline renal function. These findings were confirmed by Ranucci *et al.* [5], who prospectively collected data on oxygen delivery, haematocrit and pump flow during CPB as possible risk factors for acute renal failure and renal dysfunction. A total of 1048 consecutive patients undergoing coronary operations were studied. The authors found that the best predictor for acute renal failure and peak post-operative serum creatinine levels was the lowest oxygen delivery, with a critical value at 272 ml/min/m<sup>2</sup>. The lowest haematocrit was an independent risk factor with a lowest predictive value at a cutoff of 26%. When corrected for the need for transfusions, only the lowest oxygen delivery remained an independent risk factor. A high degree of haemodilution during cardiopulmonary bypass is a risk factor for post-operative renal dysfunction; however, its detrimental effects may be reduced by increasing the oxygen delivery with an adequately increased pump flow. The debate on transfusions and organ failure is still wide open: a small randomized controlled study from Von Heymann and co workers [6] allocated 54 low-risk patients to a haematocrit (Hct) of 20 vs 25% during normothermic CPB for elective coronary artery bypass graft (CABG) surgery. Calculated oxygen delivery, oxygen consumption and blood lactate were not significantly different between groups. Clinical outcomes were not different between groups: an Hct of 20% during normothermic CPB maintained calculated whole body oxygen delivery above a critical level after elective CABG surgery in low-risk patients. No differences were observed between the two groups regarding the incidence of neurological complications, cardiac, respiratory and renal failure and the combined endpoint of organ failure.

### Early markers of acute renal failure

Early therapeutic or preventive intervention after ARF occurrence is hampered by the lack of an early biomarker for acute renal injury. Recent studies showed that urinary neutrophil gelatinase-associated lipocalin (NGAL or lipocalin 2) is up-regulated early (within 1–3 h) after murine renal injury and in paediatric ARF after cardiac surgery. Initially discovered in neutrophils, the 25 kDa secretory protein NGAL was later shown to accumulate extensively in the kidneys after ischaemic renal injury. The 5,6NGAL may attenuate renal injury due to experimental ischaemic acute renal failure, by reducing apoptosis and enhancing proliferation of renal tubules, which are the most impaired structure. This effect is achieved because NGAL augments iron delivery to proximal tubular cells, and iron in turn up-regulates haeme oxygenase-1, an enzyme that protects tubular cells. Independently of iron transport, NGAL can

additionally promote renal tubule formation and might enhance tubule repair after ARF [7]. Wagener and coauthors [8] hypothesized that post-operative urinary NGAL concentrations are increased in adult patients developing acute renal dysfunction after cardiac surgery. Eighty-one cardiac surgical patients were prospectively studied. Urine samples were collected immediately before incision and at various time intervals after surgery for NGAL analysis. Acute renal dysfunction was defined as peak post-operative serum creatinine increase by 50% or greater, compared with pre-operative serum creatinine. Sixteen of 81 patients (20%) developed post-operative acute renal dysfunction, and the mean urinary NGAL concentrations in patients who developed acute renal dysfunction were significantly higher early after surgery, compared with patients who did not develop it. Mean urinary NGAL concentrations continued to increase and remained significantly higher at 3 and 18 h after cardiac surgery in patients with acute renal dysfunction. In contrast, urinary NGAL in patients without renal dysfunction decreased rapidly after cardiac surgery. Urinary NGAL may, therefore, be a useful early biomarker of acute renal dysfunction after cardiac surgery. Prospective multicentre studies in large unselected populations of different ages are needed to validate these results.

Lerolle and colleagues [9] interestingly evaluated the role of high renal arterial resistive index (RI) and assessed whether Doppler-measured RI on day 1 of septic shock could predict ARF. ARF was diagnosed according to the RIFLE multilevel classification. This definition is an acronym that identifies five steps of ARF severity: Risk of renal dysfunction (R), injury to the kidney (I), failure (F) or loss of kidney function (L) and end-stage kidney disease (E) [10]. RI measurement was possible for 35 of 37 patients. On day 5, 17 patients were at RIFLE-R level of ARF severity or without signs of renal dysfunction and 18 were classified RIFLE -I or -F. On day 1, RI was higher in these latter 18 patients ( $0.77 \pm 0.08$  vs  $0.68 \pm 0.08$ ,  $P < 0.001$ ). RI  $> 0.74$  on day 1 had a positive likelihood ratio of 3.3 (95% CI 1.1–135) for developing ARF on day 5. Interestingly, RI correlated inversely with mean arterial pressure but not with catecholamine type or dose or with lactate concentration. This study shows an alternative and non-invasive evaluation of kidney function, even if a learning curve is required to autonomously measure RI. Furthermore, the data confirm that catecholamine does not impact the value of renal vasculature.

### Renal replacement therapies

Vinsonneau and colleagues [11] conducted a large, prospective, randomized multicentre study in 21 ICUs over a 3.5-year period. The primary end-point was the 60-day mortality following the randomization of 360 patients with ARF to either continuous venovenous haemodiafiltration (CVVHDF) or

intermittent haemodialysis (IHD), in centres that were familiar with both techniques. Unfortunately, the eligibility criteria suffered from the need to change the criteria for entry into this study after 8 months, due to the inclusion rate being too low. No difference in 28, 60 (CVVHDF: 33%; IHD 32%) and 90-day mortality between the two groups was found and the authors conclude that all patients with ARF, as part of multiple-organ dysfunction syndrome, can be treated with IHD. The study was well conducted and, at the moment, it is the best example of randomized controlled study comparing effectively the two techniques. Nonetheless, the study started more than 7 years ago, during which time the practices in both CVVHDF and IHD have changed considerably. As stated by Vinsonneau and colleagues [11], this may have led to changes in investigator practices during the study period, particularly with respect to the delivered dose of renal support. This possibility, however, is hard to ascertain, given that the investigators started therapy with initial standardized settings and then adapted these settings to meet individual patient requirements to obtain the metabolic control objectives. Interestingly, the mortality decreased in the IHD arm of the study over the time of recruitment, which reflected a change in practice towards an increase in dialysis prescription. Given the lack of control regarding the dosage in both arms of the study, definitive conclusions are hard to make regarding treatment. As remarked in the accompanying editorial [12] the question of which treatment is better is influenced by the nature of the task. Continuous RRTs might be better in terms of total water and solute removal over 24 h and haemodynamic tolerance, but intermittent haemodialysis can remove much more water and solute per hour, is not associated with the need for continuous anticoagulation, and is not as confining for patients who do not require immobilization. Furthermore, the advantages of continuous therapy are largely supported when it is administered without prolonged interruptions, which is often not the case: again, unfortunately the study by Vinsonneau does not provide this information. Finally, if it is true that all patients with ARF as part of multiple-organ dysfunction syndrome can be treated with IHD, this means that they can also safely be treated by CVVHDF. The question of superiority of a modality for renal support might be artificial. In routine clinical practice, 80% of the centres use continuous therapy [1], and as designed by the Vinsonneau protocol, a change to an intermittent treatment is made when clinical status changes, even if this common sense approach has never been scientifically validated. Randomizing patients to receive one therapy or the other, regardless of the conditions, might yield results that are difficult to generalize for clinical practice. About 10 years ago, a similar passionate debate on ventilation weaning strategies (pressure support ventilation vs T-piece spontaneous ventilation vs continuous pressure airway pressure vs synchronized intermittent mandatory ventilation) was ongoing: the scientific community

finally agreed that it is difficult to select a method over the other and that the manner in which the mode of weaning is applied may have a greater effect on the likelihood of weaning than the mode itself [13].

High cut-off haemofilters are characterized by an increased effective pore size designed to facilitate the elimination of inflammatory mediators in sepsis. Morgera and colleagues, after an initial clinical experience on this kind of membranes [14], recently conducted a prospective study on 30 patients with sepsis-induced ARF [15]. Subjects were assigned to receive either high cut-off haemofilters or conventional haemofiltration in a 2:1 ratio. Median renal replacement dose was 31 ml/kg/h. For high cut-off haemofiltration, a high-flux haemofilter with an *in vivo* cut-off point of ~60 kDa was used. Conventional haemofiltration was performed with a standard high-flux haemofilter. The authors found that in an observation period of 48 h, the high cut-off group decreased adjusted norepinephrine dose over time. Clearance rates for IL-6 and IL-1ra were significantly higher in the high cut-off haemofiltration group with a corresponding decline in cytokines plasma levels. In this pilot study, the so-called high permeability haemofiltration (HPHF) was first compared with standard haemofiltration. Such therapy has interesting advantages over high volume haemofiltration (HVHF), another approach to extracorporeal blood purification of sepsis mediators [16]: technical complexity of HPHF appears limited with respect to the larger quantity of replacement solution, bigger catheters, higher blood flow rates and anticoagulant dosages needed for HVHF. HPHF could be performed in selected patients as a standard treatment with a special membrane, with a particular attention to protein and albumin loss that can occur over time. Further studies with a bigger patient sample are warranted on this promising technique.

*Conflict of interest statement.* None declared.

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