

REVIEW

Year in review 2009: *Critical Care* – nephrology

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Abstract

We summarize original research in the field of critical care nephrology accepted or published in 2009 in *Critical Care* or, when considered relevant or directly linked to this research, in other journals. Four main topics have been identified for a rapid overview: (a) post-surgical acute kidney injury (AKI); (b) timing of renal replacement therapy (RRT): different authors examined this critical issue of RRT in different settings (post-surgical patients, burned patients, and intensive care unit patients); (c) DoReMi (Dose Response Multicentre International) and other important surveys on dialysis dose and management; and (d) pediatric AKI and RRT: interest in this last topic is increasing, and studies on biomarkers, complications of pediatric dialysis, and application of RRT to extracorporeal membrane oxygenation are discussed.

Post-surgical acute kidney injury

Acute kidney injury (AKI) has been proven to increase patient mortality in all clinical settings: general out-of-hospital population, in-hospital admissions, adult and pediatric intensive care units (ICU), adult and pediatric cardiac surgery, and (last but not least) the relatively high portion formed by post-operative general surgery patients. In a study population of 1,166 patients without previous renal insufficiency, Abelha and colleagues [1] elegantly showed that 7.5% met AKI criteria. Interestingly, AKI was diagnosed when criteria of class I (or greater) of the Acute Kidney Injury Network (AKIN) classification were present. On multivariate analysis, American Society of Anesthesiologists (ASA) physical status, Revised Cardiac Risk Index (RCRI) score, high-risk surgery, and congestive heart failure were identified as the independent pre-operative risk factors for AKI during the post-operative period. The RCRI score includes the following variables:

high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, and insulin-requiring diabetes mellitus. According to these data, AKI patients were the most severely ill after ICU admission (higher Simplified Acute Physiology Score II and Acute Physiology and Chronic Health Evaluation II), had the longest ICU length of stay, and were independently at risk for hospital mortality. In our opinion, even if the accompanying editorial points out that one of the most important limitations of this report was the exclusion of patients with pre-operative renal dysfunction [2] (which has been identified as a major risk factor for peri-operative AKI in most studies), patients with pre-operative renal dysfunction are already those who receive the greater attention for prevention or treatment (or both) of further renal insult. So it must be remarked that an important message of this study is that post-operative AKI must be suspected in all patients with the clinical characteristics analyzed by Abelha and colleagues [1]. The next step will be to analyze such a cohort for the effect of intra-operative and post-operative therapeutic strategies on AKI risk: the prevention from use of nephrotoxins (nephrotoxic antibiotics, nonsteroidal anti-inflammatory drugs, and some forms of hydroxyethyl starch), the effort to avoid extreme intra-operative hypotension or anemia, and finally the contribution of specifically targeted therapies (for example, bicarbonate infusion, N-acetylcysteine, fenoldopam, polymyxin hemoperfusion, and prophylactic dialysis).

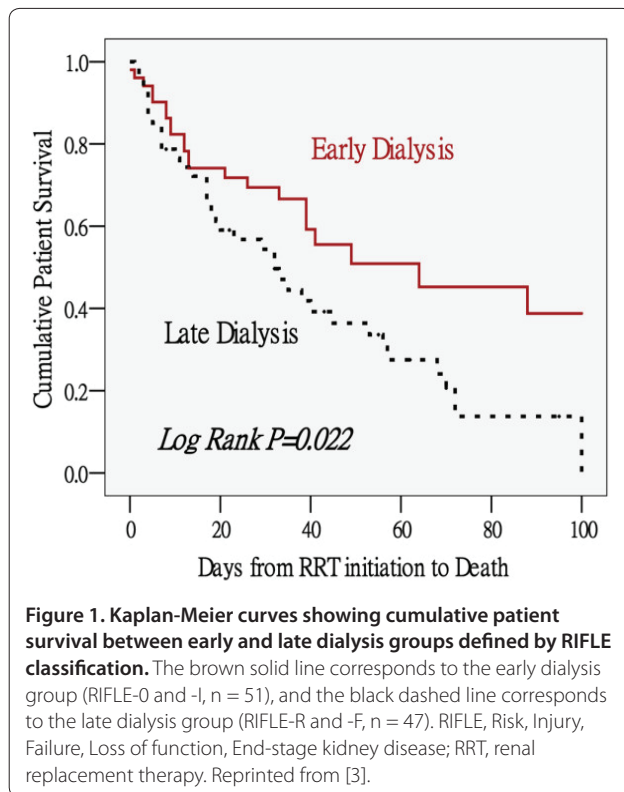
Timing of renal replacement therapy

The study by Abelha and colleagues [1] did not provide data on how many AKI patients underwent post-surgery renal replacement therapy (RRT). Shiao and colleagues [3] examined the impact of RRT timing in 98 patients affected by post-abdominal surgery AKI. The patients were divided according to RIFLE (Risk, Injury, Failure, Loss of function, End-stage kidney disease) classification into early dialysis (ED) (RIFLE-0 or Risk = 52%) and late dialysis (LD) (RIFLE-Injury or Failure = 48%). Fifty-seven patients (58.2%) died during hospitalization; LD had a death hazard ratio (HR) of 1.846; other factors independently associated with risk of dying were old age (HR 2.090), cardiac failure (HR 4.620), and pre-RRT SOFA (Sequential Organ Failure Assessment) score (HR 1.152).

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The findings of this study support earlier initiation of acute RRT (Figure 1). Interestingly, the authors used RIFLE classification as a prognostic tool in patients with post-major abdominal surgery AKI. However, defining ED and LD on the basis of RIFLE criteria may be only partially correct since AKI severity criteria do not necessarily indicate that the clinicians ‘delayed’ or ‘anticipated’ the dialytic therapy. (A RIFLE-F stage may occur and require RRT soon after ICU admission. Is this an LD?)

As a matter of fact, timing of RRT is crucial in AKI critically ill patients, and there is general agreement that a survival benefit is provided by early initiation of RRT. In clinical practice, however, to start early RRT remains quite a difficult choice. The differentiation between ‘early’ and ‘late’ RRT is based on arbitrary thresholds of traditional parameters such as serum urea, serum creatinine, urine output, time from ICU admission, or time from AKI diagnosis [4]. Furthermore, it may happen that RRT is indicated at an early ICU admission stage, whereas late initiation of renal support is prompted in an advanced phase of multiple organ dysfunction syndrome; the different clinical pictures of these two RRT prescriptions may not be classified simply as ‘early’ or ‘late.’ The detractors of a strategy of early initiation of RRT, finally, claim that patients who would recover renal function with conservative treatment alone may be subjected to

unnecessary risks. Recently, in an interesting retrospective analysis of 1,847 critically ill patients with AKI requiring RRT, Ostermann and Chang [5] evaluated the relationship between biochemical, physiological, and comorbid factors at time of RRT and ICU mortality. Multivariate analysis showed that, at time of initiation of RRT, independent risk factors for ICU mortality were mechanical ventilation (odds ratio [OR] 6.03), neurological failure (OR 2.48), liver failure (OR 2.44), gastrointestinal failure (OR 2.04), pre-existing chronic illnesses (OR 1.74), hematological failure (OR 1.74), respiratory failure (OR 1.62), oligoanuria (OR 1.6), age (OR 1.03), serum urea (OR 1.004), and cardiovascular failure (OR 1.3). A higher pH at initiation of RRT was independently associated with a better outcome. Failure to correct acidosis and development of more organ failure within 48 hours after initiation of RRT were also associated with an increased risk of dying in the ICU. Even if these results come from a retrospective analysis and are, by definition, inconclusive, the message they carry seems to be that RRT should be commenced for AKI critically ill patients before organ failure and metabolic derangements have reached the slippery threshold of irreversibility. An interesting and controversial part of the paper concerns serum creatinine and urea concentrations on the day of RRT start. At RRT start, survivors tended to have lower urea and higher creatinine levels. This finding further suggests that the decision when to start RRT for AKI should be guided more by associated dysfunction of other organ systems, urine output, and serum pH than by absolute serum creatinine or urea levels (or both). Clearly, creatinine is not an ideal biomarker for decisions on RRT timing. Creatinine can result normal in the case of RRT for fluid overload (that decreased creatinine levels because of hemodilution) or ‘extrarenal’ RRT indications (a subgroup of patients with normal creatinine but still poor outcome). However, patients who received RRT before they met the creatinine criteria for AKIN stage III had a significantly lower ICU mortality than patients who were started on RRT on the day when they met the AKIN stage III criteria (49.8% versus 64.6%). The early start of RRT was recently supported by a retrospective cohort study that showed how initiating dialysis with a blood urea nitrogen of more than 100 mg/dL predicted death at 14 days (OR 3.6, 95% confidence interval [CI] 1.7 to 7.6), 28 days (OR 2.6, 95% CI 1.2 to 5.7), and 365 days (OR 3.5, 95% CI 1.2 to 10) [6]. Though imperfect, biomarkers for RRT initiation are the simplest guide that clinicians commonly follow in clinical practice. In this light, the new biomarkers (see below) will hopefully improve the performance of creatinine and urea.

Last year, in the ‘Year in review 2008: Critical Care--nephrology’ [7], we commented on the work by Steinvall and colleagues [8], who analyzed AKI incidence in a

cohort study of patients with burns to more than 20% of total body surface area (TBSA). Of these patients, 24% developed AKI and 3% required dialysis. Interestingly, Steinvall and colleagues found that approximately one half of patients developed AKI during the first week and the other half developed AKI during the next week. Apparently, the authors' resuscitation protocol was successful in preventing AKI but only when renal injury occurred in the very early phase of ICU admission. In a 2009 study of a population of patients with TBSA burns of more than 40% and AKI, Chung and colleagues [9] aimed to determine the effect on mortality of early application of high-dose continuous venovenous hemofiltration (CVVH) versus conservative management (fluid resuscitation, minimization of nephrotoxic agents, utilization of intermittent hemodialysis in case of refractory acidosis, electrolyte abnormalities, symptomatic fluid overload not responsive to conservative interventions, and intoxication with a dialyzable agent). The control group was formed by a historical cohort. AKI was diagnosed on the basis of AKIN criteria. The CVVH group was initiated on therapy (T_0) at a median of 9 days after admission, whereas the control group was diagnosed with AKI (T_0) at a median of 19 days after admission ($P = 0.32$). 'Early AKI', defined as the presence of AKI within 14 days from time of admission, occurred in 62% of patients in the CVVH group and 46% of patients in the control group ($P = 0.24$). Patients in the CVVH group were initially prescribed a mean hemofiltration dose of 57 ± 19 mL/kg per hour. The mean duration of treatment was 5.6 ± 4.1 days. The 28-day mortality was significantly lower in CVVH patients than in controls (38% versus 71%, $P = 0.011$) as was the in-hospital mortality (62% versus 86%, $P = 0.04$). The authors also evaluated the effect of CVVH on multiple organ failure and showed that a significant decrease in vasopressor requirement and a significant increase in the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen were seen in the CVVH group in comparison with controls. This study strongly encourages the use of early CVVH even in a peculiar setting such as that of burned patients. A randomized trial should now definitely confirm these results and overcome all of the limitations of matched controlled studies: as the authors acknowledge, the two populations had some small differences (in age, severity of disease, and time to AKI diagnosis) that might have favored the CVVH group. Furthermore, AKIN II patients were included in controls (whereas it looks like all AKI patients were treated by CVVH in the treatment group), and no information on how many controls were treated by intermittent hemodialysis is provided. It looks like the historic cohort was undertreated, and no conclusions on RRT modality and dose by this study can be drawn.

DoReMi and the importance of surveying

The Acute Dialysis Quality Initiative workgroup [10] recommended that researchers study technical aspects of RRT and worldwide utilization of different techniques in order to clarify which renal replacement technique or schedule (or combination of the two) might increase outcomes of critically ill patients. Hence, several surveys on management and practice of RRT have been conducted in recent years [11-15]. These studies depict 'real world' clinical practice patterns and their possible correlation with patient outcomes. A typical example of this kind of observational study is the Beginning and Ending Supportive Study (BEST). This is a multicenter, multinational, prospective, epidemiological study with the aim of elucidating different aspects of AKI worldwide. The study, conducted at 54 centers in 23 countries, lasted only one year and yielded information on about 1,700 AKI patients, of whom about 70% required RRT. Several studies have been published after analysis of data provided by the survey, and six of them concerned technical aspects of RRT [16-21]. RRT results of the BEST study showed that continuous renal replacement therapy (CRRT) is often the preferred choice (80%) over intermittent renal replacement therapy (IRRT) (20%), probably because critically ill patients who receive CRRT are likely to be hypotensive and severely ill [16]. Nevertheless, it was shown among dialysis survivors that CRRT was an independent predictor of recovery from dialysis dependence at hospital discharge with respect to IRRT [17]. The median prescribed CRRT dose during the survey was 20 mL/kg per hour. No technical CRRT feature (dose, modality, type of filter, or anticoagulation technique) seemed to correlate with mortality at multivariate logistic regression analysis [18]. Cost of RRT, according to BEST authors, is higher for continuous therapies with respect to intermittent dialysis. The cost difference is due primarily to the utilization of dialysis and replacement fluids: a dose prescription modification from 35 to 20-25 mL/kg per hour and consequent decrease of fluid requirement might allow a significant saving of CRRT expense [19]. From the BEST database, it seemed that late RRT start, when considered as time from ICU admission, was associated with greater mortality [20]. Among CRRT patients, survival was around 50%; 60% of survivors were successfully weaned from renal replacement (no RRT need for at least 7 days after dialysis interruption); when compared with the 'repeat-RRT group' (those who failed weaning), these patients had lower mortality, lower creatinine concentration, and higher urine output at the time of CRRT discontinuation [21].

Another important observational study, the Dose Response Multicentre International (DoReMi) collaborative initiative, examined delivered RRT dose in patients

enrolled at 30 ICUs of eight European countries [22]. Patients were treated with either CRRT or IRRT during their ICU stay. Data were entered by operators into electronic case forms on a web server. Dose was categorized as more intensive (CRRT at least 35 mL/kg per hour, IRRT at least six sessions per week) or less intensive (CRRT less than 35 mL/kg per hour, IRRT fewer than six sessions per week). The authors analyzed 553 AKI patients treated with RRT: 338 received CRRT only, 87 received IRRT only, and 128 received both forms of dialysis. Of note, only 22% of CRRT patients received a more intensive dose. As in the BEST study, no evidence emerged from the DoReMi study for a survival benefit afforded by higher-dose RRT: crude ICU mortality rates among intensive CRRT patients were 60.8% versus 52.5% in less intensive patients. In IRRT, this was 23.6% versus 19.4%, respectively. On multivariable analysis, there was no significant association between RRT dose and ICU mortality. Among survivors, shorter ICU stay and duration of mechanical ventilation were observed in the more intensive RRT groups. Overall, the median prescribed CRRT dose was 34 mL/kg per hour, and the median delivered dose was about 27 mL/kg per hour. It might be that, in the clinical field, theoretic prescription schedules do not fit with practical problems encountered during continuous therapies; the most common causes for CRRT interruption were clotting of the circuit (74% of episodes), vascular access problem (11%), and clinical reasons (10%). For IRRT, the median delivered dose was relatively high: seven sessions per week. In regard to the cost issue, it should now be evaluated whether the actual reduction of length of stay and reduced medical resources utilization (that is, mechanical ventilation), together with the possibility that CRRT improves renal recovery among AKI survivors, justify the utilization of such a relatively expensive therapy.

The results of the BEST and DoReMi studies do not seem to encourage or support the prescription and delivery of 'intense' RRT (that is, 35 mL/kg per hour or more during continuous RRT) versus less intense RRT (that is, 20 to 25 mL/kg per hour during continuous RRT). Two recent multicenter clinical trials – the randomized evaluation of normal versus augmented level (RENAL) replacement therapy study [23] and the Veterans Administration/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network (ATN) study [24] – examined the impact of RRT dose on mortality in critically ill patients. Neither study showed a benefit in outcomes by increases in intensity of RRT dose. In the RENAL trial, when the *post hoc* analysis was focused on the subgroup of septic patients, there was a tendency to lower mortality with the higher intensity approach only (OR 0.84, 95% CI 0.62 to 1.12). However, the definition of 'normal dose' should be re-evaluated and compared with

standard clinical practice [25]. It must be considered that both trials were rigorous clinical trials and greatly minimized the discrepancy between prescribed and delivered doses. Hence, in clinical practice, when 20 mL/kg per hour is prescribed during continuous RRT (consistently with those in the RENAL and ATN studies), the possibility of a significant reduction in dialysis dose delivery should be considered. As clearly shown by DoReMi, when clinicians prescribe RRT, they must consider a 25% safety margin, targeting 25 to 30 mL/kg per hour in order to meet the actual delivered dose of 19 to 22 mL/kg per hour [25].

Pediatric acute kidney injury and renal replacement therapy

In recent years, application of AKI knowledge from the adult critically ill patients to the pediatric setting has revealed a new and interesting field of research. In particular, cardiac surgery-associated AKI is a convenient clinical setting for the study of early AKI biomarkers since there is a temporally predictable insult to the kidneys and since it is possible to measure urine and blood levels of these biomarkers before the actual injury and compare them with levels at pre-specified time points afterwards. The NGAL (Neutrophil Gelatinase-Associated Lipocaline) Meta-analysis Investigator Group recently published the results of the analysis of data from 19 studies and 8 countries; the data involved 2,538 patients, of whom 487 (19.2%) developed AKI [26]. The authors found that NGAL levels clearly appeared to be of diagnostic and prognostic value for AKI, RRT, and mortality, especially in cardiac surgery patients and in children. Levels of serum interleukin (IL)-1-beta, IL-5, IL-6, IL-8, IL-10, IL-17, interferon-gamma, tumor necrosis factor-alpha, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) as early biomarkers of AKI were also measured in a case control study of children undergoing cardiac surgery (18 cases and 21 controls) [27]. AKI was defined as a 50% increase in serum creatinine from baseline within 3 days. IL-6 levels at 2 and 12 hours after cardiopulmonary bypass and IL-8 levels at 2, 12, and 24 hours were associated with the development of AKI. In patients with AKI, IL-6 levels at 2 hours had excellent predictive value for prolonged mechanical ventilation (defined as mechanical ventilation for more than 24 hours post-operatively) by receiver operator curve (ROC) analysis, with an area under the ROC of 0.95. IL-8 levels at 2 hours had excellent predictive value for prolonged mechanical ventilation in all patients. Serum IL-18 levels between subjects with AKI and those without AKI were not different. A panel of several AKI biomarkers, similar to those in ischemic heart disease diagnosis, is expected in the future in order

to diagnose, prevent, and possibly treat AKI and its complications.

Possibly owing to the lack of specifically designed devices, pediatric AKI requiring RRT is currently managed with a high occurrence of side effects in many centers. Santiago and colleagues [28] prospectively analyzed complications during CRRT in 174 critically ill children over a 13-year period. Of the studied patients, a relatively low percentage (7.4%) presented problems of venous catheterization (hematoma at the puncture site, hemorrhage, altered venous drainage of the lower limbs, and incorrect position of the jugular venous catheter requiring change). Hypotension at CRRT start was detected in one third of patients. Clinically significant hemorrhage occurred in 10% of patients. In the first 72 hours of CRRT, the levels of sodium, chloride, and phosphate fell significantly; total calcium increased significantly; and the levels of potassium and magnesium remained unaltered; the changes in electrolyte levels during the course of treatment were not associated with mortality. This study, the first large analysis of the complication of pediatric CRRT, finds that complications in this cohort of patients are still high and may be greater than in adults. The historical observational nature of the study design does not allow any definitive conclusion to be drawn and some questions are left unanswered. For example, are adult RRT materials safe and effective when adapted to children and newborn patients?

However, experience with pediatric CRRT is increasing and improved technical features of 'pediatric-adapted' dialysis machines warrant safer treatments. In particular, a peculiar and complex category of pediatric patient is the infant with multiple organ dysfunction, requiring both RRT and extracorporeal membrane oxygenation (ECMO). AKI occurs to the vast majority of ECMO children, who suffer from severe cardiac dysfunction (cardio-renal syndrome) or required aggressive mechanical ventilation (lung-renal syndrome). The CRRT circuit is placed in parallel (blood flows in the same direction as the ECMO circuit) or in series (counter-current to the ECMO circuit). Santiago and colleagues [29] described how to connect the CRRT device to the ECMO circuit: the inlet (arterial) line of the CRRT circuit was connected after the ECMO blood pump by a three-way tap that was also used for the infusion of heparin, and the outlet (venous) line was connected to the circuit at another tap before the oxygenator. In contrast to what was suggested by the authors, the inlet of the CRRT machine may be connected after the ECMO pump and the filter outlet then returned to the ECMO circuit before the pump (into the reservoir, if present); the CRRT circuit, running countercurrent to extracorporeal assistance, allows the blood to be infused into the venous ECMO section (where the patient is drained) and then to

be aspirated from the arterial ECMO section (where blood returns to the patient) [30]. This second set-up might reduce blood flow resistance and turbulence after the centrifugal pump and improve reservoir drainage when a roller pump is present. The blood recirculation induced by these circuit set-ups is negligible, considering that the ratio of CRRT to ECMO blood flow is never greater than 0.1. Shaheen and colleagues [31] recently reported their experience with two different subgroups of children: one that required hemofiltration alone and one that required hemofiltration and ECMO. Not surprisingly, the authors identified a higher mortality rate in those patients requiring CVVH and ECMO compared with those patients requiring hemofiltration alone. The authors promoted the concept that certain therapies should be reserved for experienced teams. Performing CVVH in a heterogeneous population with large ranges of age and weight poses significant clinical and technical challenges. The low frequency of CVVH use, as well as the use of other extracorporeal therapies, also raises problems with maintaining nursing skills. Objective clinical and biochemical markers for commencing CVVH alone or in combination with ECMO remain to be defined. Several studies, however, already showed safety and feasibility of this connection in the pediatric setting [32], and even if concerns about such difficult interaction have been raised (that is, fluid balance accuracy [33]), the application of CRRT to all ECMO patients is claimed by some authors [34]. In 15 patients matched with 46 historical controls, it has been shown that adding continuous hemofiltration to the ECMO circuit in newborns improves outcome by significantly reducing time on extracorporeal assistance and on mechanical ventilation. Such a strategy might improve fluid balance management and capillary leak syndrome. Furthermore, according to these authors, fewer blood transfusions are needed and overall costs per ECMO run are lower.

Abbreviations

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ATN, Acute Renal Failure Trial Network; BEST, Beginning and Ending Supportive Study; CI, confidence interval; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; DoReMi, Dose Response Multicentre International; ECMO, extracorporeal membrane oxygenation; ED, early dialysis; HR, hazard ratio; ICU, intensive care unit; IL, interleukin; IRR, intermittent renal replacement therapy; LD, late dialysis; NGAL, Neutrophil Gelatinase-Associated Lipocalin; OR, odds ratio; RCRI, Revised Cardiac Risk Index; RENAL, randomized evaluation of normal versus augmented level; RIFLE, Risk, Injury, Failure, Loss of function, End-stage kidney disease; ROC, receiver operator curve; RRT, renal replacement therapy; TBSA, total body surface area.

Competing interests

The authors declare that they have no competing interests.

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