Review

Year in review 2008: *Critical Care* - nephrology

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Abstract

We summarize original research in the field of critical care nephrology accepted or published during 2008 in *Critical Care* and, when considered relevant or directly linked to this research, in other journals. Three main topics have been identified for a rapid overview. (1) The classification of acute kidney injury, with particular attention to differences and similarities between the RIFLE and AKIN classifications. (2) Fluid balance in patients requiring renal replacement therapy (RRT) has been shown as an independent risk factor for mortality in critically ill patients: current evidence and uncertainties are described. (3) Management of anticoagulation during RRT has been explored by several researchers in 2008: diagnosis of heparin-induced thrombocytopenia, the use of tirofiban and optimal anticoagulation during drotrecogin A activated treatment have been evaluated.

Classification

Steinvall and colleagues conducted a cohort study on patients with a percentage burned total body surface area of 20% or more [1]. Acute kidney injury (AKI) was classified according to the Risk, Injury, Failure, Loss of kidney function, and End-stage (RIFLE) kidney disease international consensus classification [2]. They evaluated 127 patients, which corresponded to 0.11 per 100,000 people per year. Of these, 31 patients (24%) developed AKI (12% Risk, 8% Injury, and 5% Failure) and four patients (3%) required dialysis. The mean age was 40.6 years, the percentage burned total body surface area was 38.6%, and 25% were women. Renal dysfunction occurred within 7 days in 55% of the patients and after 7 days in the remainder. AKI recovered among all survivors. Age, percentage burned total body surface area, and extent of full-thickness burns were higher among the patients who developed AKI. Pulmonary dysfunction and systemic inflammatory response syndrome were present in all of the patients with AKI and developed before AKI onset. Sepsis was a possible aggravating factor in AKI in 48% of patients. Extensive deep burns (25% or more full-thickness burn) increased the risk for developing early AKI (risk ratio, 2.25). Mortality was 14% and, interestingly, increased with increasing RIFLE class (7% normal, 13% Risk, 40% Injury, and 83% Failure).

As the accompanying editorial correctly points out [3], even if the number of patients generally evaluated in post-burn AKI studies is generally low, the analysis from Steinvall and colleagues relates to another two studies on this subject [4,5]: all three studies confirmed that increasing RIFLE class was associated with a stepwise increase of mortality. The incidence of AKI in the studies of Coca and colleagues and of Steinvall and colleagues (26.6% and 24.4%, respectively), however, was significantly lower than that of Lopes and colleagues (35.7% incidence). This difference might be explained by the fact that Lopes and colleagues classified patients according to the original RIFLE classification, on both urine output and serum creatinine concentration [4], in contrast to the studies by Steinvall and colleagues and by Coca and colleagues, which only used serum creatinine [1,5]. In burn patients, serum creatinine levels make interpretation of kidney function particularly challenging: the early rise of creatinine concentration secondary to large muscle injury might cause an underestimation of kidney function. On the other side, the fundamental therapy of burned patients is large-volume resuscitation to compensate for the massive fluid losses and decreased effective circulating volume. This may lead to hemodilution, and to false low serum creatinine concentrations that do not reflect true kidney function. Finally, catabolism, leading to loss of muscle mass, may also contribute to low serum concentrations since less muscle mass will result in lower serum creatinine concentrations for the same glomerular filtration rate.

Another interesting point raised but still not fully addressed by these studies is AKI physiopathology and therapy.

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; CRRT = continuous renal replacement therapy; DrotAA = drotrecogin A activated; HIT = heparin-induced thrombocytopenia; ICU = intensive care unit; OR = odds ratio; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage; RRT = renal replacement therapy.

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 [1]. Apparently, the burn shock resuscitation schedule used was successful in preventing AKI in the very early phase of the disease. Burn shock is not the only cause of AKI, however, and inflammatory mechanisms may be responsible for late AKI and multiple organ failure. In their cohort, Steinvall and coauthors only treated four patients with renal replacement therapy (RRT), who were the most severely ill of the studied population: it might be interesting to explore the feasibility of RRT in all post-burn late AKI patients. An interesting study on this subject has been published online while we were writing [6], and will be probably commented on in the next issue of 'Year in review 2009: *Critical Care* - Nephrology'.

One of the major merits of AKI classifications, as shown in burn studies, is to allow epidemiology comparisons among different authors. As long as new data will be provided by studies on incidence, prognosis and therapy of AKI, a sort of multinational database is created where information found by different centers can be easily meta-analyzed and the knowledge on acute renal dysfunction increased [7].

An interesting contribution to this group of studies has been presented by Ostermann and coauthors [8]: the authors tried to apply the AKI classification proposed by the Acute Kidney Injury Network (AKIN) in September 2005 [9] to 22,303 adult patients admitted to 22 intensive care units (ICUs) in the UK and Germany between 1989 and 1999, who stayed in the ICU for 24 hours or longer and did not have end-stage dialysis-dependent renal failure. Of the patients, 7,898 (35.4%) fulfilled the criteria for AKI (19.1% had AKI I, 3.8% had AKI II and 12.5% had AKI III). RRT was delivered to 848 (4.6%) patients. Without RRT as a criterion, 21% of patients classified as AKI III would have been classified as AKI II or AKI I. Mortality in the ICU was 10.7% in patients with no AKI, 20.1% in AKI I patients, 25.9% in AKI II patients and 49.6% in AKI III patients. Multivariate analysis confirmed that AKI III, but not AKI I and AKI II, was independently associated with ICU mortality (odds ratio (OR) = 2.27). Other independent risk factors for ICU mortality were age (OR = 1.03), sequential organ failure assessment score on admission to the ICU (OR = 1.11), pre-existing end-stage chronic health (OR = 1.65), emergency surgery (OR = 2.33), mechanical ventilation (OR = 2.83), maximum number of failed organ systems (OR = 2.80) and nonsurgical admission (OR = 3.57). Cardiac surgery, AKI I and RRT were associated with a reduced risk of dying in the ICU. AKI II was not an independent risk factor for ICU mortality. According to these authors, RRT as a criterion for AKI III may inadvertently diminish the predictive power of the classification.

Ostermann and colleagues' study is limited by the fact that data were collected during a relatively long period (10 years) that dates from 20 years ago to about 10 years ago. It is possible that, even though the crude mortality of AKI patients has probably not changed significantly since 1989, capabilities have certainly improved and the healthcare system has progressively admitted and treated sicker patients with AKI. Even if the authors acknowledge the possible effect of such an old database on outcome, they might not have correctly estimated the change of illness severity and of eventual treatment strategies: hence, similar data collection from the year 2000 to the present day might have provided different results. The authors did present, however, some limits of the AKIN classification with respect to the RIFLE classification. In their analysis, Ostermann and coauthors found that 2,014 patients classified as having no AKI had serum creatinine levels >140 μmol/l; 316 patients even had serum creatinine values >270 μmol/l. Although it is possible these patients may have had a degree of pre-existing chronic kidney disease, it is also possible that they had AKI without the necessary changes in serum creatinine within the required time period. Using the RIFLE classification that suggested a 1-week timeframe instead of the 48-hour timeframe proposed for the AKIN scale, Ostermann and colleagues found a higher incidence of AKI (39.5% instead of 34.4%; AKI I, 19.3%; AKI II, 6.7%; AKI III, 13.5%). The ICU mortality would have altered only slightly with the change of timeframe (AKI I, 21.0%; AKI II, 24.9%; AKI III, 49.0%). Furthermore, the authors suggested that utilization of RRT as a criterion for AKI III might not be objective and may have had a confounding effect on the predictive power of the classification system as a whole. It must be said that this effect might be due to a particularly aggressive strategy of the authors, who probably treated AKI with RRT at very early stages of the disease: the protective effect of RRT on mortality found by Ostermann and colleagues on multivariate analysis interestingly confirms this assumption.

As already reported last year [10], a large retrospective analysis of the Australian and New Zealand Intensive Care Society database [11] compared RIFLE and AKIN classification in the first 24 hours after admission to the ICU. Even if these classifications were not conceived to be used only in the first 24 hours of admission, the authors found that estimates of prevalence and crude mortality were very similar between the two classification schemes, and concluded that – compared with the RIFLE criteria – the AKIN criteria did not substantially improve the sensitivity, robustness and predictive ability of the definition and classification of AKI.

Lopes and coauthors also evaluated the incidence of AKI and compared the ability of the maximum RIFLE and of the maximum AKIN within ICU hospitalization in predicting inhospital mortality of critically ill patients [12]. Critically ill patients admitted between January 2003 and December 2006 were retrospectively evaluated. Chronic kidney disease patients undergoing dialysis or renal transplant patients were excluded from the analysis. In total, 662 patients (mean age, 58.6 ± 19.2 years; 40% females) were evaluated. Different

from Ostermann and colleagues, the AKIN criteria allowed the identification of more AKI patients than the RIFLE criteria (50.4% vs. 43.8%, $P = 0.018$) and classified more patients with Stage 1 (Risk in RIFLE) (21.1% vs. 14.7%, $P = 0.003$), but no differences were observed for Stage 2 (Injury in RIFLE) (10.1% vs. 11%, $P = 0.655$) and for Stage 3 (Failure in RIFLE) (19.2% vs. 18.1%, $P = 0.672$). Mortality was significantly higher for AKI patients defined by any of the RIFLE criteria (41.3% vs. 11%, $P < 0.0001$; OR = 2.78, 95% confidence interval = 1.74 to 4.45, $P < 0.0001$) or of the AKIN criteria (39.8% vs. 8.5%, $P < 0.0001$; OR = 3.59, 95% confidence interval = 2.14 to 6.01, $P < 0.0001$) with respect to non-AKI patients. The area under the receiver operator characteristic curve for inhospital mortality was 0.733 for RIFLE criteria ($P < 0.0001$) and was 0.750 for AKIN criteria ($P < 0.0001$). There were no statistical differences in mortality by the AKI definition/classification criteria ($P = 0.72$).

Agreeing with previous authors, Lopes and authors concluded that although the AKIN criteria could improve the sensitivity of the AKI diagnosis, they did not seem to improve on the RIFLE criteria in predicting inhospital mortality of critically ill patients [12]. Interestingly, the authors showed that serum creatinine criteria seemed to be a better predictor of mortality than urine output. In fact, in >60% of patients with AKI, the creatinine criteria led to a worse RIFLE class or AKIN stage than urine output. Creatinine is also an easier marker to be recalled in retrospective studies, and an objective number to be reported in databases: this may also explain why the role of urine output for AKI diagnosis might be underestimated by epidemiologic studies. Owing to the routinely generous utilization of loop diuretics that modify the true urine output of dysfunctioning kidneys and the possibility of an early diagnosis offered by new serum biomarkers [13], however, it seems that AKI classifications should soon implement these molecules in their schemes.

It must be remarked that in recent years the use of the consensus definitions of AKI (RIFLE and AKIN) in the literature has increased substantially [7,10]. This increase has indicated a high acceptance by the medical community of a common way to identify and classify AKI. Some variation in how the criteria are interpreted and used in the literature still includes urine output criteria, use of the change in the estimated glomerular filtration rate rather than the change in creatinine, and choice of baseline creatinine. It is imperative to recognize that no single definition will be perfect. Furthermore, it must be admitted that, at present, RIFLE criteria have not been shown to be significantly superior to AKIN criteria and reported differences are very minor. A logical process would therefore now be to reconcile existing definitions, moving the medical community towards using a single consensus definition – as has been done for syndromes such as sepsis and acute lung injury. Integration of novel biomarkers into the final consensus definition will be an outstanding improvement. The next step will be for some research to test the use of such classifications on different interventions of AKI therapy in order to guide clinicians towards the best possible standard of AKI care.

Fluid balance

As has been clearly shown, AKI is an independent cause of mortality in critically ill patients. Creatinine is not the only marker correlating to this risk, patient fluid balance being another key parameter to consider and possibly treat.

Payen and coauthors [14], utilizing data from the Sepsis Occurrence in Acutely Ill Patients study, analyzed the influence of patient characteristics and fluid balance on the outcome of AKI in ICU patients. The Sepsis Occurrence in Acutely Ill Patients study is a multicenter observational cohort study: 198 ICUs from 24 European countries gave their contribution to its realization. For Payen and colleagues' analysis, patients were divided into two groups according to whether they had AKI. Of the 3,147 patients included in the Sepsis Occurrence in Acutely Ill Patients study, 1,120 (36%) had AKI at some point during their ICU stay. Sixty-day mortality rates were 36% in patients with AKI and 16% in patients without. Oliguric patients and patients treated with RRT had higher 60-day mortality rates than patients without oliguria or without the need for RRT. Independent risk factors for 60-day mortality in the patients with AKI were age, Simplified Acute Physiology Score II, heart failure, liver cirrhosis, medical admission, mean fluid balance, and need for mechanical ventilation. Among patients treated with RRT, the length of stay and mortality were lower when RRT was started early (<48 hours from ICU admission). According to these authors, a positive fluid balance and late RRT start were important factors associated with increased 60-day mortality.

Several studies previously showed a statistical difference in the percentage of fluid overload among children with severe renal dysfunction requiring RRT [15,16]. At the time of dialysis initiation, surviving children tended to have less fluid overload than nonsurvivors, especially in the setting of multiple organ dysfunction syndrome. Fluid balance is probably underestimated in critically ill adults where a huge fluid volume amount is infused in order to target hypovolemia and organ perfusion. Few clinical investigations, until now, have evaluated the impact that fluid balance has on clinical outcomes in critically ill adults with AKI. These data strongly support the view that there is a survival benefit from early initiation of continuous renal replacement therapies (CRRT) to prevent fluid accumulation and overload in critically ill patients, once initial fluid resuscitative management has been accomplished [17]. Moreover, this would suggest that prevention or management of fluid overload is evolving as a primary trigger/indicator for extracorporeal fluid removal, and this may be independent of dose delivery or solute clearance.

This concept is also supported by the recent Acute Renal Failure Trial Network trial [18] that was specifically based on

the hemodynamic stability of patients: in both study groups, hemodynamically stable patients underwent intermittent hemodialysis, and hemodynamically unstable patients underwent continuous venovenous hemodiafiltration or sustained low-efficiency dialysis. Interestingly, net ultrafiltration of patients undergoing intermittent techniques (<2 l/day) was apparently lower than that of patients undergoing continuous venovenous hemodiafiltration (130 ml/hour or 2.7 l/day, considering a median daily duration of therapy of 21 hours). In particular, a (nonsignificant) difference was present between net ultrafiltration of intense intermittent hemodialysis versus less intense intermittent hemodialysis (1.7 vs. 2.1 l/day), whereas intense continuous venovenous hemodiafiltration had very similar ultrafiltration rates compared with less intense continuous venovenous hemodiafiltration (130 vs. 130 ml/hour). Since hypotension events were significantly higher in the group treated with a higher RRT intensity, it might be speculated that these events were correlated with an excessively rapid fluid (and solute) shift of intermittent therapies, which did not allow adequate fluid balance control. For this reason, patients allocated to alternate-day, less-intensive hemodialysis not uncommonly had inadequate fluid volume control necessitating additional off-protocol ultrafiltration sessions.

The obtained evidence warrants the need for a prospective trial that targets fluid balance as the main outcome. We need to understand whether it is possible to apply RRT actively and in a timely manner, rather than only utilizing it as rescue therapy (fluid overload associated with pulmonary edema) [19]. We well know that this result might not be easily obtained: it is possible that more severely ill patients are those who receive the relatively higher amount of fluids, and this could explain, as an effect and not as a cause, the more positive fluid balance of nonsurviving patients. If it is evident that counterbalancing fluid accumulation, particularly in patients with oliguria or AKI, might be beneficial, then it is also clear that more severely ill patients might often miss any active attempt at achieving a negative balance.

Anticoagulation

In 2008 numerous articles published in *Critical Care* focused attention on the physiopathology of anticoagulation and optimization of filter patency, a critical point of acute RRT. In particular, heparin-induced thrombocytopenia (HIT) is a severe clinical picture, caused by a heparin-induced antibody that binds to the heparin–PF4 complex on the platelet surface. HIT is associated with a significant reduction of platelet number and a procoagulant state, and with eventual systemic thrombosis. The HIT incidence in critically ill patients is relatively low, around 0.5% [20], but it is destined to increase due to the great diffusion of extracorporeal techniques for organ support.

Lasocki and coworkers [21] retrospectively analyzed 28 patients who were tested for the presence of anti-PF4/heparin antibodies due to repeated hemofiltration-filter clotting. Seven patients were positive for anti-PF4/heparin antibodies and 21 patients were antibody-negative. Baseline characteristics, platelet counts, and activated partial thromboplastin time ratios were not different between the two groups. The continuous venovenous hemofiltration duration was significantly decreased in antibody-positive patients (5.0 vs. 12.0 hours; $P = 0.007$), as was the hemofiltration efficiency (urea reduction ratio 17% vs. 44%; $P = 0.04$) on heparin infusion. The anti-PF4/heparin antibody concentration was inversely correlated with the duration of continuous venovenous hemofiltration. The receiver operating characteristic curve showed that a 6-hour cutoff point was the best continuous venovenous hemofiltration session duration to predict a positive antibody test (sensitivity, 71%; specificity, 85%; and area under the curve, 0.83). The continuous venovenous hemofiltration duration (32 hours; $P < 0.05$) and the urea reduction ratio (55%; $P < 0.03$) were restored by danaparoid sodium infusion. The authors suggest that repeated hemofiltration-filter clotting in less than 6 hours may be reasonably associated with the presence of anti-PF4/heparin antibodies, regardless of the platelet count. In antibody-positive patients, replacement of heparin by danaparoid sodium allowed the restoration of the hemofiltration duration and efficiency.

A similar clinical approach for systemic heparin utilization and HIT diagnosis was proposed by Warkentin some years ago and was recently reproposed [22,23]. The so-called 4Ts score (thrombocytopenia, timing, thrombosis, other causes of thrombocytopenia) (see Table 1) was recently utilized in a series of 256 HIT referrals [24], and showed that none of the patients with a low 4Ts score proceeded to an ultimate diagnosis of HIT. While it is important to identify those patients with HIT, it is equally important to minimize the number in whom HIT cannot be adequately excluded. In cases where the diagnosis still remains in doubt, however, it is preferable and safer to manage the patients as possible HIT cases and alter the anticoagulation.

In the light of platelet protection, Link and coauthors evaluated the reversible effects of platelet glycoprotein IIb/IIIa receptor inhibitor tirofiban to preserve platelet number and activation in a small prospective open-blinded study [25]. The contact of blood with surfaces of the extracorporeal membrane circuits and different anticoagulants leads to platelet and leukocyte activation and to platelet–leukocyte coaggregation. All of these interactions result in glycoprotein IIb/IIIa receptor activation that becomes capable of binding soluble fibrinogen. Glycoprotein IIb/IIIa receptor antagonists primarily act on the platelet surface by inhibition of fibrinogen binding that is essential for platelet bridging and aggregate formation. The hypothesis that tirofiban preserves platelet number and function and shortens postoperative bleeding times was previously described in patients with type II HIT during cardiopulmonary bypass surgery [26]. Forty patients

Table 1

Warkentin's 4Ts scoring system

	Score		
4Ts	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall >50% or platelet nadir 20 x 10^9/l	Platelet count fall 30 to 50% or platelet nadir (10 to 19) x 10^9/l	Platelet count fall <30% or platelet nadir <10 x 10^9/l
Timing of platelet count fall	Clear onset between days 5 and 10 or platelet fall <1 day (prior heparin exposure within 30 days)	Consistent with days 5 to 10 fall but not clear (for example, missing platelet counts); onset after day 10; or fall <1 day (prior heparin exposure 30 to 100 days ago)	Platelet count fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; acute systemic reaction post intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions at heparin injection sites; suspected but unproven thrombosis	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

Scoring system modified from [23]: 0 to 3, low; 4 to 5, intermediate; 6 to 8, high.

with cardiogenic shock and AKI requiring CRRT were randomly assigned to two groups receiving unfractionated heparin ($n = 20$) or a combined anticoagulation with unfractionated heparin and tirofiban ($n = 20$). The primary endpoint was platelet loss during CRRT. Secondary endpoints were urea reduction, hemofilter life span, bleeding events, and necessity for platelet transfusions. In unfractionated heparin-treated patients, the percentage of platelet–monocyte aggregates significantly increased ($P < 0.001$) and consecutively the platelet cell count significantly decreased ($P < 0.001$). In contrast, combined treatment with unfractionated heparin and tirofiban significantly decreased platelet–monocyte aggregates and platelet numbers ($P < 0.001$). There were no significant differences between the groups regarding the efficacy of CRRT, the hemofilter lifespan, or bleeding events. Platelet transfusions were only necessary in three patients of the unfractionated heparin group.

As correctly pointed out in the accompanying editorial [27], the study by Link and colleagues showed that tirofiban prevents platelet activation and loss during CRRT. The data indicated a significantly reduced platelet loss with additional glycoprotein IIb/IIIa antagonist therapy compared with unfractionated heparin therapy alone. Owing to the small sample size, however, the potential impact of additional treatment variables (such as the concomitant and significantly variable administration of other anticoagulants, antiplatelet drugs or catecholamines and the presence of polysulphone CRRT membranes) could not be clarified. A substantially larger, adequately powered study is therefore warranted before these results can be generalized.

Camporota and coworkers [28] also addressed the importance of anticoagulation management during CRRT, particularly analyzing a cohort of patients who simultaneously received renal replacement and drotrecogin A activated (DrotAA). A single-center, retrospective observational study was conducted in an adult ICU. Thirty-five patients were identified. The proportion of filter changes due to filter clotting was similar during DrotAA infusion and with conventional anticoagulation post DrotAA infusion. There was no difference in the filter survival time and filter parameters during DrotAA treatment in the presence or absence of additional anticoagulation with heparin or epoprostenol. Red blood cell transfusion was not different among the different anticoagulant strategies, although a greater proportion of patients received platelet and fresh-frozen plasma during DrotAA infusion compared with the post-DrotAA period, with no difference between medical and surgical patients. Camporota and colleagues concluded that additional anticoagulation during DrotAA infusion does not appear to improve the filter survival time. The use of DrotAA in patients with severe sepsis requiring RRT is safe and is not associated with major bleeding events. Furthermore, in a multivariate logistic regression analysis, the authors identified the minimum value in platelet count as the only predictive factor of filter clotting during DrotAA infusion.

Camporota and colleagues' study is interesting and confirms previous observations that no additional anticoagulation is necessary during simultaneous DrotAA infusion and CRRT. The only information that should be interpreted with caution is the authors' finding that no difference in red blood cell requirements was found, either between DrotAA filters and post-DrotAA filters or between medical patients and surgical patients. It should be remembered that, among the 4,459 patients included in the International Integrated Database for the Evaluation of Severe Sepsis and Drotrecogin alfa

(activated) Therapy study, the bleeding incidence in surgical patients was about 10 times higher in the DrotAA group than in the placebo group (4.9% vs. 0.5%), and the incidence in medical patients was about 2.5 times higher than that in surgical patients (2.6% vs. 1%) [29,30].

Competing interests

The authors declare that they have no competing interests.

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