

Commentary

Recently published papers: Acute kidney injury – diagnosis and treatment

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Abstract

When faced with the management of the patient on intensive care with acute kidney injury, the clinician has various choices to consider. The conventional therapy, where appropriate, is renal replacement therapy. This technique used to be relatively straightforward but now a relative feast of alternatives is available, not least in choice of buffer and anticoagulant. Two recent studies add to the growing body of literature concerning alternative anticoagulant regimes, and one in particular should lead to a change in practice for many of us. We also review some new studies on biomarkers in the diagnosis of acute kidney injury as well as add yet another nail in the coffin for loop diuretics in the therapy of acute kidney injury.

'Where observation is concerned,
chance favours only the prepared mind'

(Louis Pasteur, 1822–1895)

A renal flavour this month, for which we make no apologies! As we all know, acute renal failure is no more: we now deal in acute kidney injury (AKI)! We are still plagued by the lack of a useful early indicator for kidney injury, however, and the search for this holy grail continues.

This prize may be getting closer, as a report by Haase-Fielitz and colleagues in *Critical Care Medicine* examines the role of serum biomarkers in predicting AKI in a cohort of patients following cardiac surgery [1]. They employed neutrophil gelatinase-associated lipocalin (a marker of tubular cell injury) and cystatin C (a marker of glomerular filtration rate) measured in serum together with conventional markers of renal function. The end points were development of AKI (defined as an increase in serum creatinine >50%), the need for renal replacement therapy and hospital mortality. This study demonstrated that the novel biomarkers predicted AKI approximately 48 hours before conventional measures, such

as creatinine. In particular, biomarker levels 24 hours post-operatively proved particularly useful. The study has some limitations, as the authors point out, but it is the largest adult study reported thus far.

Where does Haase-Fielitz and colleagues' study leave us? Clearly this field will continue to expand and no doubt many more papers will be produced on the role of novel biomarkers, but how will it change our practice? One hopes that early identification of patients that have undergone renal injury (in whatever guise) will lead to improved outcomes through augmented observations and avoidance of further renal insult. The acid test will be to demonstrate that early intervention improves outcome in these patients. Then the holy grail may well have been found.

Following on from this, a novel report from Heemskerk and colleagues examines the role of an infusion of alkaline phosphatase on renal function in patients with sepsis [2]. The rationale behind this study is that exogenous infusion of alkaline phosphatase appears to decrease inducible nitric oxide synthase activity, reduce nitric oxide metabolite production and perhaps maintain the integrity of the proximal tubule during severe sepsis. This is a small study and therefore no conclusions can be drawn regarding benefits in terms of mortality or morbidity; however, the study does demonstrate some novel findings. Induction of inducible nitric oxide synthase and renal nitric oxide metabolite production was reduced, as was the excretion of markers of proximal tubule damage. Whether such findings will eventually lead to a change in the management of such patients, only time will tell.

Unlike such new approaches, the use of loop diuretics in AKI has been applied in almost all scenarios despite a lack of any evidence that they result in any benefit in real terms – such as mortality or, indeed, renal recovery. It appears that the theo-

AKI = acute kidney injury.

retical benefits coupled with the reassurance of increased urine flow outweigh the lack of data demonstrating a benefit. Van der Voort and colleagues have further examined the use of furosemide in a randomised, double-blind, placebo-controlled study of intensive care unit patients after the use of haemofiltration [3]. The results are unsurprising. Those patients treated with loop diuretics had an increased urine output and sodium excretion. There was no benefit observed on renal recovery or on creatinine clearance. If anything, the placebo group fared better in terms of renal recovery – although the treated group did have a higher Sequential Organ Failure Assessment score and were older. For those diuretic zealots among you, this paper offers little solace.

After AKI has been diagnosed by whatever means, and all therapeutic options have been tried, we turn to our extracorporeal systems for help. The recent literature has demonstrated a great deal of interest as regards the choice of anticoagulant employed, and in particular the use of regional anticoagulation in order to address the loss of treatment time, additional costs and not least the nursing time associated with premature circuit loss.

A novel approach to this issue is described in intensive care medicine [4]. A cooling device was applied to a continuous venovenous hemofiltration circuit in order to cool the blood to 20°C, coupled with a warming device post filtration that ensured the returning blood was heated to 38°C. Twelve healthy pigs were selected as subjects and were exposed to 6 hours of either continuous venovenous hemofiltration with cooling or normothermia. Other factors, such as fluid balance, were identical. An array of parameters was measured but the main finding was that where cooling was not applied five out of six circuits clotted prematurely. None of the cooled circuits clotted prematurely. Clearly much more work has to be done – not least on the safety aspects of blood undergoing such regular cycles of rewarming, but also the period of study (6 hours) is much shorter than that applied clinically and also these were healthy animals not a patient in multiorgan failure.

Will such technology be coming to your intensive care unit in the near future? Probably not; however, if you are not a fan of regional anticoagulation, then the excellent study by Oudemans-van Straaten and colleagues should make you sit up and take notice [5].

This study on 200 patients receiving continuous venovenous hemofiltration randomised patients to systemic anticoagulation with nadroparin or regional citrate anticoagulation [5]: the largest such trial to date. Citrate inhibits coagulation through ionised Ca²⁺ chelation, with the calcium citrate complex being in part filtered or metabolised. The primary end points of this study were safety and efficacy powered on adverse events necessitating discontinuation of therapy as well as transfusion requirements, circuit survival and metabolic and clinical outcomes. Interestingly, there was a

significant increase in the number of adverse events seen in the nadroparin-treated group, little difference in transfusion requirements and no differences in circuit survival. So it appears that citrate is safer.

As Pasteur commented, however, chance favours only the prepared mind. The stunning result of Oudemans-van Straaten and colleagues' study is the significant and wholly unexpected survival benefit conferred by the use of regional citrate anticoagulation. Among the studied patients, the 3-month mortality was a staggering 17% lower in the regional citrate anticoagulation-treated group and *post hoc* analysis demonstrated that the observed survival benefit was most marked in patients with sepsis, severe multiorgan failure and after surgery [5]. Such a survival benefit cannot be ignored and, although some may point to this being a single-centre study and that fractionated heparins were used, the beauty of this study is that daily practice was not changed for the study purposes and that the survival benefit was seen throughout the study period. Single-centre studies do play an important role with regards to intensive care unit practice as we are not blessed with the huge, homogeneous numbers recruited to cardiology studies, for example. This work is already being applied to a multicentre study, which no doubt will be further replicated. This should lead to much more study into the basic mechanisms behind the observations, which may benefit all our patients. The question one must now ask oneself is not should I be thinking of using regional citrate anticoagulation, but when should I start? The emergence of commercially available systems can only accelerate this process.

Competing interests

The authors declare that they have no competing interests.

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