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Acute kidney injury: new studies

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Acute kidney injury (AKI) is common in critically ill patients and independently associated with important morbidity and mortality [1]. However, its pathophysiology and optimal management remain largely unknown. In this brief review, we present recent advances in the understanding, prevention and management of AKI.

Biomarkers

In the last decade, several molecules have been identified as potential early biomarkers of renal injury [2–4]. A growing body of evidence suggests that, at least in some subgroups of patients, these biomarkers may allow earlier and, perhaps, more sensitive identification of AKI than current creatinine-based diagnostic criteria. In particular, a recent multicentre prospective cohort study [5] aimed to determine the diagnostic performance of several urinary biomarkers [neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin (IL)-18, liver-type fatty acid binding protein and cystatin C] to predict AKI when obtained in the emergency department (1,635 unselected patients). After exclusion of patients with minimal creatinine rise and rapid (<72 h) renal recovery, all biomarkers were elevated in patients with AKI. Urinary NGAL was found to be the most specific (81 %) and sensitive (68 %) biomarker (cut-off 104 ng/ml) and to have good discriminatory ability for AKI. All tested biomarkers were found to have excellent negative predictive value (>95 %). Models including KIM-1 or urinary NGAL improved patient reclassification by more than 20 % as compared with creatinine-based models.

Similar analyses performed in 380 cardiac surgery patients with post-operative AKI showed that three biomarkers (urinary IL-18, urinary albumin-to-creatinine ratio and urinary and plasma NGAL) were useful in predicting AKI progression [6]. Each biomarker was able to improve risk stratification and to identify patients at risk for progression of AKI, with *plasma* NGAL performing the best. Altogether, these data confirm previous findings in similar populations [7, 8].

Further studies are still required to determine the clinical utility of renal biomarkers in heterogeneous critically ill patients. However, renal-specific biomarkers have already improved our understanding of the pathophysiology of AKI. This is illustrated by another study, which challenged the concept of "pre-renal" AKI [9]. In 529 patients with measurements obtained at 0, 12 and 24 h following intensive care unit admission, levels of urinary biomarkers (cystatin C, NGAL, γ-glutamyl transpeptidase, IL-18 and KIM-1) increased with AKI duration. In particular, pre-renal AKI—as defined by a rapid (<48 h) correction of uraemia and fractional sodium excretion <1 %—was also associated with such elevations, only to

a lesser extent. These findings suggest that pre-renal AKI is simply part of a continuum of injury and its reversibility can be more rationally and simply explained by the presence of less severe injury.

Prevention of AKI

In parallel, new strategies have been assessed for their ability to prevent cardiac surgery-associated AKI and contrast-induced AKI (CIAKI). A retrospective study [10] based on data from more than 700,000 patients found that off-pump coronary artery bypass graft (CABG) surgery was independently associated with decreased need for renal replacement therapy compared with standard on-pump CABG. This strategy seemed to particularly benefit patients with poor preoperative renal function. This better renal outcome was, partly, further supported by the findings of a large (4,752 patients) randomised controlled trial (RCT) [11] where off-pump CABG was shown to decrease the risk of AKI [relative risk (RR) 0.87; 95 % confidence interval (CI) 0.80–0.96]. However, this study with much higher evidence level did not show any decrease in the need for renal replacement therapy (RRT) or a survival advantage.

In 170 patients with chronic kidney disease who underwent coronary angiograms, a "furosemide with matched hydration" regimen was associated with a reduction in the risk of CIAKI compared with intravenous isotonic saline hydration [12]. Likewise, 100 patients with impaired renal function undergoing elective coronary angiography were randomly allocated to standard care or remote ischaemic preconditioning (obtained through four cycles of 5 min inflation and 5 min deflation of a blood pressure cuff) [13]. This intervention was associated with a lower incidence of CIAKI (40 versus 12 %, $p = 0.002$) and was well tolerated. These interesting preliminary observations now need to be confirmed or refuted by larger multicentre studies.

Fluids

Two large RCTs have now compared 6 % hydroxyl-ethyl starch (HES) with Ringer's lactate [14] or 0.9 % saline [15] for fluid resuscitation in intensive care unit (ICU). The first—the 6S study [14]—randomised 804 critically ill patients with severe sepsis and found that HES was associated with higher in-hospital mortality (RR 1.17; $p = 0.03$) and increased use of renal replacement therapy (RR 1.35; $p = 0.04$). The second—the CHEST trial [15]—randomised 7,000 critically ill patients and did not find a difference in mortality. However, it confirmed the increased need for renal replacement therapy in patients allocated to HES (RR 1.21; $p = 0.04$). In addition, HES was associated with increased serum creatinine levels and decreased urinary output in the first seven days after randomisation as well as a higher rate of adverse events (5.3 versus 2.8 %, $p = 0.001$). Taken together and in the context of previous observations, these results confirm that HES fluid resuscitation should now be avoided in critically ill patients.

Ultrafiltration

Finally, in direct contrast with previous promising preliminary findings, in 188 patients with acute decompensated heart failure, worsened renal function (cardiorenal syndrome type 1) and persistent congestion, ultrafiltration was found to be inferior to a strategy of stepped pharmacologic therapy [16]. Indeed, it was associated with an increase in creatinine concentration (+20.3 versus −3.5 μmol/l, $p = 0.003$), no difference in weight loss 96 h after enrolment, and a higher percentage of patients experiencing serious adverse events (72 versus 57 %, $p = 0.03$). These findings strongly challenge the previously widely accepted utility of ultrafiltration in patients with congestive heart failure.

In conclusion, a potential diagnostic role for biomarkers of AKI is now slowly emerging. Off-pump CABG appears to be a possible approach for prevention of post-cardiac surgery AKI, but its use must be seen within the wider context of its other effects on the quality of coronary revascularization. New therapies are being tested which might attenuate CIAKI, and preliminary results are encouraging. Finally, large trials have confirmed the long-suspected nephrotoxicity of HES and dampened enthusiasm for the use of ultrafiltration in congestive heart failure.

Conflicts of interest The authors declare no conflicts of interest in relation to this study.

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