FOCUS EDITORIAL

Focus on acute kidney injury

Miet Schetz^{1*} and Antoine Schneider²

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Introduction

Acute kidney injury (AKI) is extremely common in critically ill patients. Prevention and supportive therapy with renal replacement therapy (RRT) are the only management options. This editorial comments on papers published in *Intensive Care Medicine* in 2015 and 2016 focusing on epidemiology, diagnosis, prevention, and extracorporeal treatment of AKI. Their main findings are summarized in Fig. 1.

Epidemiology

In their “My Paper 20 Years Later” article, Druml et al. discuss the metamorphosis of acute renal failure to AKI [1]. Acute renal failure was formerly considered the final stage of a single-organ reversible problem in previously healthy persons that can be supported by RRT. AKI, on the other hand, describes a continuum from risk situations to overt impairment of kidney functions with multiple insults and complex pathophysiology. Over the years, it has become clear that the incidence of AKI is high and increasing. It affects preferentially elderly patients and those with comorbidities and chronically compromised kidney function. In addition, AKI has evolved from a single-organ syndrome to a systemic disease and is associated with adverse short- and long-term patient and kidney outcomes. The extent of the AKI problem is illustrated in a prospective international cross-sectional study on the epidemiology of AKI in 1802 patients in 97 units all over the world (the AKI-EPI study). AKI, defined by the KDIGO criteria, developed in more than 50% of ICU patients: 18% had stage 1, 9% stage 2, and 30% stage 3, with RRT needed in 13%. The most prevalent etiology of AKI was sepsis followed by hypovolemia. AKI was independently associated with mortality (26.9% if AKI vs.

7.2% if no AKI). AKI patients had an increased length of stay and had worse kidney function at hospital discharge with CKD criteria in almost 50% [2]. Regarding kidney outcome after AKI it is important to realize that, because of muscle wasting, defining recovery based on creatinine levels and the derived eGFR might result in significant overestimation of the extent of kidney function recovery [3]. In patients treated with hypothermia after cardiac arrest, early AKI stage 3 occurred in 48% and was associated with mortality (OR 1.60, 95% CI 1.05–2.43) but, interestingly, not with neurologic outcome [4]. In a systematic literature review including 19 papers and 82,514 patients undergoing major surgery (not limited to ICU), O'Connor et al. found a pooled AKI incidence of 13.4% with a relative risk of postoperative death of 12.6 (95% CI 6.8–23.4). AKI patients also had a prolonged hospital stay and more non-renal complications [5].

Villeneuve et al. performed a systematic review of 18 studies using validated instruments to measure health-related quality-of-life (HRQOL) among survivors of (mostly RRT-requiring) AKI in the ICU. Follow-up varied between 2 months and 14 years. Compared with age- and sex-matched general populations, HRQOL of AKI survivors appeared significantly impaired and more so for the physical than for the mental component. However, four out of six studies found similar HRQOL in patients with and without AKI, HRQOL was perceived as acceptable, and the majority would undergo the same treatment again [6].

Diagnosis

Although the criteria to define AKI have now been clearly established [7] and are very useful in large epidemiological studies, their application in practice may require clinical judgment, as illustrated in a short piece by Kellum et al. The authors propose a checklist that can help to determine the likelihood of AKI accounting for the clinical context (risk factors and exposures), alternative diagnoses for AKI criteria, confirmatory tests, and biomarkers [8].

*Correspondence: marie.schetz@uzleuven.be

¹ Laboratory of Intensive Care Medicine, Division of Cellular and Molecular Medicine, Clinical Department, KU Leuven University, Herestraat 49, 3000 Louvain, Belgium

Full author information is available at the end of the article

The role of biomarkers for the early diagnosis of AKI and for prediction of dialysis need has been extensively debated over the past years. A series of biomarkers did not perform better than serum creatinine as predictors of progression of AKI in at-risk patients, defined by oliguria during at least 6 h [9]. The limitations of biomarkers in the prediction of AKI (mainly their heterogeneous nature, timing of measurement relative to the insult, absence of a gold standard, clinical application still unclear) are discussed in the accompanying editorial [10]. TIMP-2 and IGFBP-7, two markers of cell cycle arrest, which received FDA approval as point of care test, appear to outperform conventional biomarkers for the prediction of AKI stage 2 or more [11].

Prevention

With an effective treatment of AKI lacking, prevention becomes very important. Fluid resuscitation is one of the mainstays of AKI prevention. However, over recent years there is increasing evidence that not only hypovolemia but also fluid overload may be deleterious for the kidney. The CLASSIC randomized, parallel-group feasibility trial allocated 151 septic shock patients to a standard or restrictive fluid regimen after the initial resuscitation. Despite significantly lower resuscitation fluid volumes in the first 5 days and the entire ICU stay (the primary endpoint) the restrictive group showed significantly less worsening of AKI (36% versus 54%). This exploratory secondary outcome requires confirmation [12].

Statins, by their pleiotropic effects, could also exert beneficial effects on the kidney. However, Park et al. found no renoprotective effect of perioperative high dose statins in a placebo-controlled randomized controlled

trial (RCT) including 200 statin-naïve patients undergoing elective valvular heart surgery [13], confirming previous results [14, 15].

Renal replacement therapy

The optimal modality of RRT for ICU patients remains the subject of debate. Truche et al. performed a prospective observational analysis on a large multicenter database including 1360 ICU patients with at least one session of RRT, continuous or intermittent. They used a marginal structural Cox model that limits confounding by correcting for both baseline and daily characteristics that may influence the choice of modality. The adjusted analysis shows no effect of the RRT modality on the primary outcome (30-day mortality or dialysis dependence). Subgroup analysis showed improved outcome with CRRT in patients with substantial fluid overload but worse outcome in those without hemodynamic failure. The secondary endpoints of 6-month mortality and/or persistent renal dysfunction in the 295 patients that were dialysis-dependent at ICU discharge were also not affected by the RRT modality [16].

Two recent RCTs comparing early versus late initiation of RRT [17, 18] have generated conflicting results. Unfortunately, these studies differed in design, intervention definitions, and power. Therefore, the optimal timing for the initiation of RRT remains an unresolved issue. Schetz et al. discuss factors that may guide this decision and formulate absolute and relative indications and contraindications. In general, the start of RRT should be individualized considering not only the severity and trend of kidney function but also comorbidity, severity, and reversibility of the acute underlying disease and

potential harm associated with unnecessary RRT [19]. A meta-analysis of 11 RCTs in 992 patients showed the superiority of citrate compared with heparin anticoagulation regarding filter survival, bleeding complications, and heparin-induced thrombocytopenia during CRRT [20].

Conclusion

Recent literature confirms the high incidence and grim prognosis of AKI in the ICU. Limited progress in this field is probably related to the late diagnosis with current diagnostic criteria. Biomarkers may be helpful but further research is required to establish their clinical role. Fluid overload may result in worsening of AKI. The optimal modality and timing of RRT remain controversial. Citrate has become the preferred anticoagulant.

Author details

¹ Laboratory of Intensive Care Medicine, Division of Cellular and Molecular Medicine, Clinical Department, KU Leuven University, Herestraat 49, 3000 Louvain, Belgium. ² Adult Intensive Care Unit, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.

Compliance with ethical standards

Conflicts of interest

All authors declare that they have no conflict of interest.

Ethical approval

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