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EDITORIAL

Focus on critical care nephrology

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Dear Editor,

acute kidney injury (AKI) is a frequent complication, involving up to 60% of critically ill patients. It is associated with poor outcome, high risk of persistent renal dysfunction, and long-term morbidity and mortality. Consequently, this syndrome has led to extensive research aiming for a better risk stratification, an improved insight into its pathophysiology and search for optimal management strategies.

Obvious limits of usual markers of AKI, oliguria being unspecific and serum creatinine elevation being insensitive and delayed, have led to extensive research aiming to identify and validate alternative biomarkers and diagnostics of AKI or of AKI severity [1]. Identifying the more severe patients, those who will require renal replacement therapy (RRT) or are at risk of persistent AKI, was one of the theoretical aims of such studies [1, 2]. A large meta-analysis assessed the discriminative performance of functional and tubular damage biomarkers in identifying patients that will ultimately require RRT [1]. Interestingly, both biomarkers in plasma (e.g. NGAL Cystatine C) and urine (e.g.NGAL, Cystatine C, IL-18) were found to have at best fair discriminative ability close to that of serum creatinine (AUC 0.76; 95% CI 0.73–0.80), with the possible exception of urinary TIMP2 × IGFBP7 (AUC 0.857; 95% CI 0.789–0.925) [1]. This last finding was, however, limited by the small number of available studies [1]. Beyond biomarkers, Doppler-based resistive index (RI) was found promising in preliminary low level evidence studies. These results were, however, not confirmed in a multicenter cohort study where neither Doppler-based RI nor semi-quantitative renal perfusion, assessed by color Doppler, had adequate discriminative ability in predicting persistent AKI or need for RRT [2]. In fact, in this study both these markers were found to be inferior to mere clinical judgment of attending physicians for both these endpoints [2]. These studies strongly suggest disappointingly poor performance of new prognosis marker and the need for additional studies assessing not only discriminative ability, but also performance in risk stratification [3], or potential usefulness when used as part of a management strategy (NCT03244514, NCT01868724).

Increasing evidence points to an important role of venous congestion in the pathophysiology of AKI. A cohort study in 595 heart transplant recipients investigated the association between preoperative right heart hemodynamic parameters and postoperative AKI [4]. A lower pulmonary artery pulsatility index and a higher right atrial pressure were associated with both the occurrence and the severity of AKI. Interestingly, this association persisted after correction for several other risk factors including preoperative renal function and postoperative right ventricular failure. The association of pulmonary artery pulsatility index with AKI severity was stronger with increasing right atrial pressure suggesting that long-standing venous congestion increases vulnerability of the kidney to subsequent damage.

The deleterious impact of venous congestion on kidney function is also discussed in two editorials focusing on cardio-renal syndrome (CRS) [5, 6]. Worsening kidney function (WKF) during treatment of acute decompensated heart failure (CRS type 1) is a phenomenon characterised by an increase in creatinine which may reflect functional AKI due to transient hemodynamic changes or persistent AKI due to structural kidney damage. However, it may also point to the so-called pseudo-WKF that is associated with improved outcome and results from efficient decongestion with diuretics resulting in hemoconcentration and associated rise in creatinine. Biomarkers of kidney damage may play an important role in the differential diagnosis of these conditions [5]. Diuretic resistance, frequently observed in patients with CRS

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type 1, may not only be predicted but even caused by hypochloremia [6].

A lot of debate has been ongoing lately on the evidence for a causal association between contrast administration and AKI [7]. An analysis using the Bradford-Hill criteria points to significant uncertainty on a causal link mainly based on the consistent neutral results of recent case–control trials using propensity score matching, the presence of alternative explanations for AKI in most patients, the variability in incidences suggesting a weak association and the absence of benefit in well-designed RCTs on preventive measures that are supposed to alleviate the pathophysiological pathways leading to contrast-associated AKI [8]. Indeed, the PRESERVE study failed to show benefit of bicarbonate hydration compared with saline and of *N*-acetylcysteine compared with placebo in at-risk patients [9]. These data suggest that AKI risk following contrast can be judged considerably lower than previously assumed.

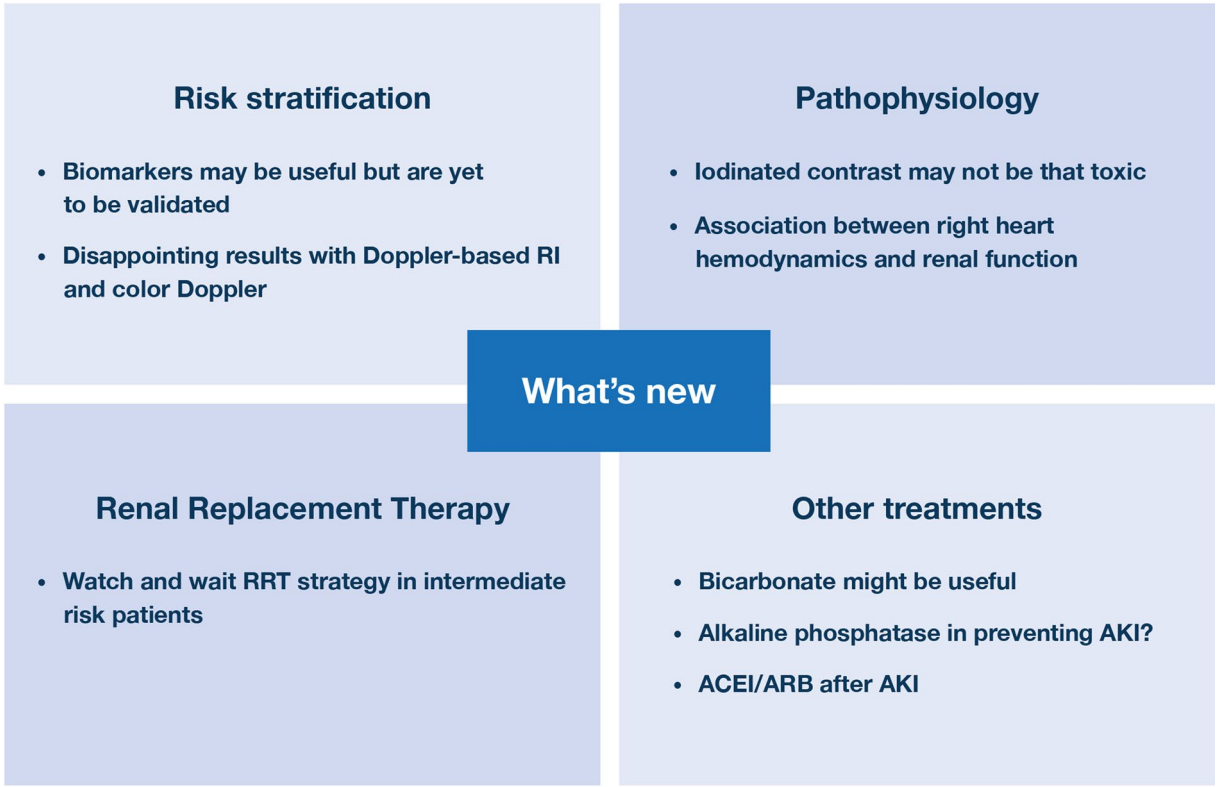
Sepsis is the most frequent cause of AKI in critically ill [9]. Therapeutic approaches to prevent and treat sepsis-associated AKI are highly relevant. Alkaline phosphatase (AP) plays an important role in the detoxification of LPS and in the degradation of ATP to adenosine, the latter having nephroprotective and anti-inflammatory effects. The STOP-AKI trial investigated the effect of recombinant AP in patients with septic shock and AKI not requiring RRT [10]. Though negative on primary endpoint, relevant secondary and exploratory endpoints, including creatinine clearance increases at day 14 and 28 as well as major adverse kidney events decreases at day 90, were significantly influenced by intervention.

Timing of initiation of RRT is a very specific issue in sepsis and has been investigated in the IDEAL ICU study [11]. Early start of RRT defined by AKI stage 3 did not affect survival when compared to RRT initiation when absolute indications occurred or after a maximum waiting time of 48 h [11]. In addition, 37% of the patients in the delayed arm did not require RRT, indicating the risk of unnecessary treatment in the early initiation group. The data confirm a secondary analysis of the AKIKI trial focussing on sepsis and ARDS showing similar results [12]. In addition, there may be a subgroup of patients suffering from CKD for which early RRT based on AKI stage may even be detrimental with respect to survival and need for RRT [13].

One of the interventions that may help to delay or avoid unnecessary RRT for AKI is the administration of bicarbonate in patients with metabolic acidosis (pH $\leq$ 7.2) and AKI stages 2 and 3. By increasing pH to levels > 7.3, requirement of RRT could be reduced by roughly 40% accompanied by a significant reduction of mortality in the group substituted with bicarbonate [14]. These results are supported by a large analysis using marginal structural Cox model and showing reduced mortality in patients with AKI stages 2 or 3 and acidosis receiving bicarbonate [15].

Long-term outcome is an important issue for AKI patients. Angiotensin-converting enzyme inhibitors or receptor blockers (ACEI/ARBs) have been demonstrated to be protective against progression to chronic kidney disease. An analysis of the FROG-ICU database could demonstrate a positive effect on one-year mortality of receiving ACEI/ARBs at ICU discharge in patients with acute kidney disease (AKD) [16]. Unfortunately, the lack of renal outcome data did not allow analysing effects of ACEI/ARB on recovery from AKD per se.

Despite progresses made during the last years, several of the advances discussed in this manuscript open the field for research rather than closing the debate. Several RCTs are needed or already ongoing to validate or explore potential benefit of recombinant AP in preventing AKI, of bicarbonate use in AKI patients or of ACEI/ARB use after ICU stay in patients who experienced AKI. These forthcoming studies will certainly help clarifying the path to follow in preventing or managing AKI in critically ill patients.



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Compliance with ethical standards

Conflicts of interest
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