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Biomarkers for AKI improve clinical practice: yes

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Abbreviations

AKI Acute kidney injury
GFR Glomerular filtration rate
NGAL Neutrophil gelatinase associated lipocalin

KIM-1 Kidney injury molecule 1
RRT Renal replacement therapy

Up to 40 % of critically ill patients will develop an acute kidney injury (AKI) [1]. This renal complication is associated with high morbidity, high short-term and long-term mortality and a tremendous economic impact [1, 2]. Prevention and treatment of AKI mainly rely on hemodynamic optimization and avoidance of nephrotoxic agents [3]. Specific preventive or curative strategies or medications tested in this field over the last decades have been either inefficient or insufficiently validated to be routinely recommended [3]. One of the numerous reasons that may explain this failure is the unavoidable late recognition of renal injury leading to delayed interventions.

According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, diagnosis of AKI relies on functional criteria, namely oliguria and serum creatinine elevation [3]. These criteria are poorly sensitive, poorly specific and usually associated with late recognition of renal injury. Oliguria is neither sensitive nor specific, being poorly specific since it might occur as consequences of a renal injury but may also reflect an adaptative physiological response to both intracellular dehydration and hypovolemia [4]. In this line, only a small proportion of ICU oliguric patients indeed present a sustained drop in glomerular filtration rate reflected by a rise in serum creatinine [4]. Similarly, Mandelbaum and colleagues demonstrated that only profound (<0.3 mg/kg/h) or prolonged (>12 h) episodes of oliguria were associated with the need for renal replacement therapy or an increased hospital mortality [5]. Serum creatinine also has several limitations. First, creatinine excretion is not exclusively filtered by the glomeruli but also secreted by the renal tubule [6]. Hence, under normal conditions, this tubular secretion ranges from 5 to 10 % of the total

creatinine excretion, and might rise to 50 % when the glomerular filtration rate (GFR) is decreased [6]. In addition, while serum creatinine might introduce a delay in recognizing a drop of GFR, some genuine episodes of renal injury might not be associated with any drop in GFR as a consequence of the renal reserve. Lastly, even a decrease in GFR of up to 50 % might not be associated with a rise in serum creatinine during the first 24 h, especially in critically ill patients with positive fluid balance [7]. Therefore, even the perceived small increase in serum creatinine necessary to reach KDIGO stage 1 criteria for AKI reflects a profound and prolonged decreased in GFR. The negative results of trials aiming to improve the renal outcome in patients with already overt AKI is therefore unsurprising, with most of the patients receiving experimental therapy hours to days following the initial renal insult [8, 9]. The need of biomarkers, including functional biomarkers that may rapidly detect changes in GFR and biomarkers of injury that may allow detection of subclinical renal insult, is in this regard obvious.

Biomarkers have already changed our perception of AKI, and progress in critical care nephrology over the last decade is partly ascribable to the input of renal biomarkers with the emerging concept of high-risk patients [10] or of subclinical renal insult [11]. Detection of such patients might allow risk stratification that could ultimately help in validating preventive strategies or future promising therapies. Beyond early diagnosis and risk stratification, biomarkers have improved our understanding of pathophysiological mechanisms associated with AKI. They have helped in challenging the now outdated dichotomy between the so-called “pre-renal AKI” and

“acute tubular necrosis” [12]. Patients formally identified as “pre-renal AKI” with transient AKI and/or low urinary sodium excretion also have evidence of ongoing tubular injury making boundaries obsolete [12]. More theoretically, the large amount of literature exploring the relationship between renal function and injury in various critical conditions has provided us with insights into the disease’s pathophysiological process. This change in our global view of the pathophysiological mechanism of AKI will certainly help us in designing alternative therapeutic strategies in the very near future and in focusing on patients most likely to benefit from these strategies with an individualized and biomarker-driven approach.

We definitely lack and need a diagnostic tool that may allow an assessment of renal prognosis or the need for renal replacement therapy. Optimal timing of renal replacement therapy remains under debate but unanswered. The risk of unwarranted aggressive intervention is usually put into perspective with regard to the potential benefit of early renal replacement therapy in a heterogeneous population [13]. Although randomized trials are ongoing, these trials will not answer the underlying question of which patients will require renal replacement therapy. The performance of several biomarkers or renal imaging techniques have already been assessed in predicting the risk of worsening renal dysfunction or the risk of renal replacement therapy with interesting results, and might be promising in this regard [10, 14, 15].

We fully agree that the validation of biomarkers is insufficient to recommend their clinical use. Uncertainties in the accuracy and reproducibility of some biomarkers remains [16, 17], disappointing results have been published [16, 18] and validation with regard to hard clinical

Table 1 An example of future classification of AKI patients: this classification may take into account early detection of renal insult along with an assessment of renal prognosis, and every item would be coded for a single patient (e.g., F2 I2 Re1)

Classification	System	Biomarker
F	Renal function	
	Screat or measured GFR and urine output	
1	↑ Creatinine >26.4 $\mu\text{mol/L}$ or creatinine $\times 1.5$ – 1.99	
	UO <0.5 $\text{ml kg}^{-1} \text{h}^{-1}$ for 6–12 h	
2	Creatinine $\times 2$ – 2.99	
	UO <0.5 $\text{ml kg}^{-1} \text{h}^{-1}$ for 12 h+	
3	↑ Creatinine >354 $\mu\text{mol/L}$ or creatinine $\times 3$ + or need for RRT	
	UO <0.3 $\text{ml.kg}^{-1} \text{h}^{-1}$ for 24 h+ or anuria >12 h	
I	Renal injury/damage	Biomarker of injury
1		<Threshold “sensitive”
2		>Threshold “sensitive”
3		>Threshold “specific”
Re	Renal function recovery	Biomarker of function kinetic, biomarker of injury kinetic, renal imaging (e.g. CEUS)
1		High probability of full recovery within 72 h
2		Low probability of full recovery within 72 h
3		No rapid recovery expected within 1 week
4		End stage renal disease

endpoints is lacking. However, biomarkers are perhaps not to blame for this lack of evidence or these discordant results. Perhaps we have missed opportunities to answer the good questions, which are obviously not for the search for the optimal area under the ROC curve. We have missed the opportunity to carefully assess the population of interest. If biomarkers are to be used, they will certainly not be relevant in every one of our ICU patients but in a specific setting to answer a specific and clinical question. Surprisingly, the population of interest, i.e., the proportion of individual ICU patients who may ultimately require a biomarker is still unknown. Changes of endpoint prevalence according to the population of interest are theoretically likely to influence test diagnostic performance [19] as well as their clinical relevancy at the bedside. Beyond the population of interest, we still have

to move forward with adequately tested markers and start using them against usual practices in such a way as to assess their input with regard to a clinically relevant endpoint and therapeutic or diagnosis strategies. Only with such information will we be able to validate the above-mentioned theoretical interest and clinical input.

Biomarkers have already changed our pathophysiological perception of AKI, have increased our awareness toward renal insult, and may ultimately change renal injury classification (Table 1) and treatment. They still have to prove their point as a useful tool at the bedside but this promising and exciting next step is our challenge, not theirs.

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