



Treatment of sepsis-induced acute kidney injury in the ICU: the therapeutic targets do not seem to be established yet

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Provenance: This is an invited article commissioned by the Section Editor Linpei Jia, MD, PhD (Department of Nephrology, Xuanwu Hospital of Capital Medical University, Beijing, China).

Comment on: Pickkers P, Mehta RL, Murray PT, *et al.* Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury: A Randomized Clinical Trial. JAMA 2018;320:1998-2009.

Submitted Jun 21, 2019. Accepted for publication Jul 19, 2019.

doi: 10.21037/atm.2019.07.66

View this article at: <http://dx.doi.org/10.21037/atm.2019.07.66>

Acute kidney injury (AKI) is a frequent complication in patients hospitalized in the intensive care unit (ICU) for sepsis (1,2). It is associated with long-term sequelae such as chronic kidney disease (3) and high mortality (2,4), especially in case of severe AKI associated with septic shock.

It is now clear that in the absence of hyperkalemia or severe metabolic acidosis or pulmonary overload, its initiation can be safely delayed (5,6). Consequently, there is currently no therapeutic option other than to avoid nephrotoxic drugs in the early phase of AKI. However, new knowledge on the pathophysiology of AKI associated with sepsis could lead to new therapeutic strategies, and identify new targets (7).

AKI is a syndrome with a broad spectrum of etiologies, and several mechanisms, including ischemic/hypoxic, nephrotoxic, and inflammatory insults, contribute to its development. Depending on different clinical settings such as post-cardiac surgery, contrast media exposure, severe heart failure with low output, or sepsis, the pathophysiology and clinical features of AKI will be different. Among these etiologies, sepsis is the leading cause of AKI in ICUs. Reportedly, 45–70% of all AKI is associated with sepsis (8). Gomez *et al.* recently conceptualized a unified theory

of sepsis-induced AKI (9). During sepsis, inflammatory mediators derived from pathogens and activated immune cells (i.e., endotoxins, cytokines, etc. also known as Damage or Pathogen Associated Molecular Patterns) can exert their effect (through Toll-like receptors) on the renal tubular cells via the peritubular microcirculation or they can be filtered at the glomerulus. Tubular cells react with an adaptive response to this injurious and inflammatory danger signal. Inflammation and microvascular dysfunction amplify this signal (10), and in response, mitochondria within tubular cells develop metabolic downregulation. Tubular cell mitochondria reprioritize energy utilization for individual cell survival processes at the expense of “normal kidney function” (i.e., tubular absorption and secretion of solutes) (9).

In their recent paper, Pickkers *et al.* (11) investigate the optimal therapeutic dose, effect on kidney function, and adverse effects of human recombinant alkaline phosphatase in patients with sepsis-associated AKI. Alkaline phosphatase is an endogenous enzyme that exerts detoxifying effects through dephosphorylation of various compounds, including bacterial endotoxin and proinflammatory mediators such as extracellular adenosine.

In animal sepsis models, alkaline phosphatase attenuated

systemic inflammation and organ dysfunction and improved survival rates (12). In two small clinical studies in severe sepsis and septic shock patients, alkaline phosphatase was shown to significantly improve kidney function (13,14). Following on from these results, Pickkers *et al.* performed a randomized, controlled multicenter phase 2a/2b trial involving 301 patients, but failed to prove that human recombinant alkaline phosphatase can significantly improve short-term kidney function compared to placebo in patients with sepsis-associated AKI (11).

This study has two main limitations that should be taken into account in the interpretation of these findings. The first is the timing and definition of kidney injury (mean daily creatinine for days 1 through 7), which was used as the primary end point. The 7-day time-frame may have been too short, and both creatinine and creatinine clearance are recognized to be unreliable in critically ill patients who are not in steady state. The instability of renal function in this population significantly reduces the validity of measures based on creatinine assessment (15). The limitation of the 7-day time-frame of the primary endpoint is even more evident because the authors found a significant improvement in creatinine clearance at day 21 and 28 in the treatment arm, but that was only an exploratory secondary endpoint.

The second main limitation is the criteria for initiating RRT, which were those proposed by Bellomo *et al.* in 2012 (16). Besides well accepted emergency criteria for RRT, there are also criteria such as anuria for 6 hours, severe oliguria (urine output < 200 mL over 12 hours), urea concentrations >30 mmol/L or creatinine concentrations > 300 µmol/L). It has been shown that when these criteria are used to initiate RRT, 40% to 50% of patients probably receive RRT without actually needing it (5,6). It is evident that the interpretation of the area under the curve (AUC) of creatinine clearance in patients receiving RRT is not interpretable (especially if patient doesn't actually need RRT), and around 30% of patients underwent RRT in Pickkers' study. Moreover, data on delivered dialysis doses are not given. A third, albeit less important limit is that the lack of a reliable early biomarker of AKI causes significant delay in initiating therapy; this point has already been underlined for the initiation of RRT (17), but it could also apply to a drug treatment for AKI, such as recombinant alkaline phosphatase. For now, research has failed to identify valuable markers for AKI to identify early critically ill patients who are dying from, and not just dying with, AKI, underscoring that AKI is an independent risk factor

for mortality. Unfortunately, all the biomarkers currently under study have insufficient sensitivity to detect early severe AKI in the ICU, and diagnostic power may only increase if a combination of various biomarkers is used, including cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) in the serum and urine, IL-18 or kidney injury molecule-1 (KIM-1) (18,19).

It is important to note that reducing inflammation in sepsis has been a target since the early 1990s, with several studies testing extracorporeal therapies to reduce cytokine levels in the blood compartment. Reducing the unbound cytokine load was logically assumed to limit remote organ damage, hence reducing overall mortality. Experimental studies indeed showed that high-volume hemofiltration improved myocardial performance and systemic hemodynamics while removing inflammatory cytokines (20). However, no clinical counterpart for this interesting hypothesis was proven in human studies, high-volume hemofiltration having failed to decrease plasma cytokine concentration or improve organ dysfunction and survival in sepsis and septic shock (21). In the same register, with the target of reducing bacterial inflammatory molecules such as endotoxin in sepsis induced-AKI, a new generation of membranes (22) has been developed that focuses on endotoxin adsorption for blood purification. Despite promising preliminary results, large RCTs have been negative (23,24).

In conclusion, despite the negative results of this phase 2a/2b trial, numerous studies are ongoing in the field of septic-AKI and hopefully, within a few years, intensivists and nephrologists will have new a therapeutic option other than RRT. Until then, a deeper understanding of the role of kidney injury as an amplifier in sepsis and multiple organ failure might enable the identification of new drug targets for sepsis-induced AKI.

Acknowledgments

The authors thank Fiona Ecartot, PhD (EA3920, University Hospital Besancon, France) for translation and editorial assistance.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Quenot JP, Dargent A, Large A, Roudaut JB, Andreu P, Barbar S. Treatment of sepsis-induced acute kidney injury in the ICU: the therapeutic targets do not seem to be established yet. *Ann Transl Med* 2019;7(Suppl 6):S181. doi: 10.21037/atm.2019.07.66