Kidney360

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Title: Do novel biomarkers have utility in the diagnosis and prognosis of AKI?: CON

Manuscript Type: Debates in Nephrology

Manuscript Category:

Funders:
S.G.C is a member and was or is currently supported by funding related to the following NIH-sponsored Consortia: Assess, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI; U01DK082185), the CKD Biomarker Consortium (U01DK106962), and the Kidney Precision Medicine Project (U01DK133093). He also receives salary support from other grants funded by the NIH (R01DK126477, R01DK127139, and R01DK129467).

Disclosures:
S. Coca reports the following: Employer: Icahn School of Medicine at Mount Sinai; Mount Sinai owns part of Renalytix; Consultancy: Renalytix, Takeda, Nuwellis, Vifor, Bayer, Boehringer-Ingelheim, Reprieve Cardiovascular, Axon, 3ive; Ownership Interest: Renalytix, pulseData; Research Funding: Renalytix, ProKidney, Renal Research Institute, XORTX; Patents or Royalties: Renalytix; and Other Interests or Relationships: Associate Editor for Kidney360, Editorial Boards of JASN, CJASN, Kidney International.

Author Contributions:
Steven Coca: Conceptualization; Writing - original draft.

Study Group/Organization Name:

Study Group Members' Names:

Clinical Trial Registry Name and Registration Number:

Data Sharing Statement:

Kidney360 Publish Ahead of Print
DOI:10.34067/KID.0000000000000188

Do novel biomarkers have utility in the diagnosis and prognosis of AKI?: CON

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Acute kidney injury is most commonly recognized and defined by an acute increase in serum creatinine (SCr). However, SCr is an imperfect marker of AKI for a number of reasons. First, SCr can be not representative of true underlying GFR due to confounding factors including advanced age, increased or decreased muscle mass, excessive protein intake, and certain medications and that interfere with tubular secretion of creatinine. Second, the kinetics of SCr elevation often lag behind the time of acute stressor and the onset of tubular injury. Third, if the SCr is elevated due to kidney dysfunction, an elevation may reflect either decreased glomerular filtration with or without or acute tubular injury (ATI). Finally, it is believed that clinical AKI that involves ATI eventually leads to nephron dropout and fibrosis, and thus will likely result in higher risk of CKD/progressive CKD compared to AKI manifested by an equal amount of decrement in GFR due to hemodynamic perturbations without tubular injury.[1] Thus, the inadequate sensitivity, specificity, and prognostic ability of SCr in acute kidney injury has led to the search for biomarkers to accomplish the following:

a) Allow for earlier and more accurate diagnosis of AKI
b) Distinguish true tubular injury from decreased glomerular filtration
c) Prognosticate subsequent outcomes for patients with AKI

There have been hundreds to thousands of papers published in the last two decades on biomarkers in AKI.[2] Do we have biomarkers that accomplish the stated goals above? Moreover, as per question posed for this specific debate, do the biomarkers have *UTILITY*? Utility implies the biomarkers satisfy at least one of the three criteria above, and that *action* on the knowledge of the biomarker will *change and improve outcomes*.

There is no existing therapy for intrinsic AKI (ATI, AKA classic acute tubular necrosis). Indeed, we cannot apply a pan-AKI hypothesis of treatment, but rather have to examine most likely responses in the various clinical settings, including sepsis-associated AKI, AKI in acute decompensated heart failure (i.e., cardiorenal syndrome), AKI in advanced liver disease (i.e., hepatorenal syndrome), cardiac surgery-associated AKI, chemotherapy-associated AKI, and the generic multifactorial AKI that occurs in hospitalized patients in various wards. As shown in the Table below, there are some theoretical advantages, but also many potential disadvantages to defining or employing biomarkers indicative of ATI in these settings. Most certainly, there is a paucity of data on outcomes directly or indirectly related to actions taken towards biomarkers reflective of ATI.

Table. Various Clinical Settings for Which Implementation of Tubular Injury Biomarkers May Have Utility			
Clinical Setting	**Potential Advantages**	**Potential Disadvantages**	**Evidence (mostly indirect)**
Sepsis	Identify those most likely to require RRT earlier	-More fluids may be given for ATI, which is generally not volume responsive and will result in total body fluid overload -Earlier RRT based on ATI which may not be necessary (watchful waiting may allow for recovery and avoidance of RRT)	-Fluid overload always associated with worse outcomes in AKI in ICU[3] -No benefit of earlier RRT in severe AKI, including (in some trials) AKI defined by elevated NGAL[4]
ADHF	Distinguish those with hemodynamic SCr elevations vs. ATI with goal to avoid "over-diuresis"	-Less effective decongestion in ATI due to scaling back of diuretic regimens -Holding of GDMT therapies (especially SGLT2i, MRAs, and sacubutril/valsartan) upon observation of ATI	-Post-hoc analyses of ROSE-AHF[5] and CARRESS-AHF[6] demonstrated that those with ATI by urinary biomarkers in ADHF have evidence of better decongestion and associated with lower mortality[5] and better eGFR[6] at 60 days
Advanced liver disease	Better up-front management (volume for prerenal; pressors for HRS; neither for ATN)	-Vasoactive agents to increase BP should not necessarily be withheld from those with ATI/ATN	-Biomarker-directed therapy trials have not been conducted
Cardiac Surgery	Optimize hemodynamics and medications post-surgery in those with ATI	-in Prev-AKI trials,[7,8] there was more ACEi/ARB discontinuation, more fluids given, more inotropes in the intervention arms in response to elevated Nephrocheck®; all of these actions have dubious role in AKI	Randomization to multicomponent KDIGO bundle of potential kidney protective strategies for those with elevated Nephrocheck® reduced severity of AKI as defined by SCr metrics but has not been shown to improve clinical outcomes[7,8]
Chemotherapy	Alter dose of chemo, change chemo regimen	-May result in delay or less effectiveness in primary treatment of malignancy	- Biomarker-directed chemotherapy trials have not been conducted
General/ Or multifactorial	-Better identification of ATI on medical wards -Discontinuation of potential nephrotoxins	-Knee-jerk response will likely be more fluids for ATI which is generally not volume-responsive and will result in total body fluid overload	-Alert trials for SCr-based AKI have not led to improved outcomes[9] (and in some strata alert to AKI increased risk for mortality)[10]

Abbreviations: ATI- acute tubular injury, ICU- intensive care unit, RRT- renal replacement therapy, AKI- acute kidney injury, NGAL- neutrophil gelatinase-associated lipocalin, MRAs- mineralocorticoid antagonsits, SGLT2i- sodium glucose cotransporter 2 inhibitors, HRS- hepatorenal syndrome, ATN- acute tubular necrosis, ADHF- acute decompensated heart failure, ACEi- angiotensin converting enzyme inhibitor, ARB- angiotensin receptor blocker, KDIGO- Kidney Disease Improve Global Outcomes, SCr- serum creatinine, GDMT- goal directed medical therapies.

While this is not comprehensive list of all the theoretical benefits and disadvantages that might ensue with employment of biomarkers of ATI in these clinical settings, it serves the point to have the reader consider the non-intended consequences of having more ubiquitous testing and evidence for acute tubular injury. Most would agree that clinicians tend to favor more fluids/more hydration as "beneficial for the kidneys". However, numerous studies have demonstrated the

adverse consequences of fluid overload in AKI.[3] Furthermore, ATI/ATN is usually not a volume responsive form of AKI.[11] Moreover, the data that has been generated to date listed in the final column of the Table, even though far from definitive (and acknowledging that some data are "indirect evidence"), are not supportive for the hypothesis that more frequent ATI detection in these clinical settings will be beneficial to patients. Indeed, until it is shown in a randomized trial that action(s) in response to ATI detection with novel biomarkers leads to better outcomes,[12] it will remain a dubious strategy.

Before closing, there are two potential scenarios for biomarkers of ATI in clinical AKI that may have utility. The first clinical setting relates to distinguishing between ATN vs. acute interstitial nephritis (AIN). The urinary biomarkers TNF-alpha and IL-9 provide robust discrimination for AIN vs. other etiologies of AKI.[13-15] AIN has a specific therapy (holding of responsible agent and glucocorticoids), and thus better identification and treatment with these novel biomarkers has potential for utility in the cases where AIN cannot be ruled out easily (without kidney biopsy).

The second scenario relates to post-AKI care. There are millions of hospitalizations with concurrent AKI annually in the United States.[16] Only a minority of patients receive prompt and adequate post-AKI follow-up visits with nephrologists.[17] It would be impossible for nephrologists to meet the demand of consultations with all patients that survive AKI hospitalization. There may be a role for biomarkers to better define those at highest risk for post-AKI CKD/CKD progression.[18-20] While bundles of care and specific therapies to target AKI to CKD transition need to be tested prospectively,[17] the utility of prognostic biomarkers in this setting seems to have decent promise. The National Institutes of Health (NIH) has funded and initiated the Caring for OutPatiEnts after Acute Kidney Injury (COPE-AKI) Consortium that will develop and test interventions that aim to reduce morbidity compared with usual care in Stage 2 and 3 AKI survivors.

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Funding

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Acknowledgments

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *Kidney360*. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions

Steven Coca: Conceptualization; Writing - original draft.

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