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Acute Kidney Injury: A Problem of Definition

Jonathan Barasch, **Richard Zager**, and **Joseph V. Bonventre**

Columbia University, New York, NY, Fred Hutchinson Cancer Center, University of Washington, Brigham and Women's Hospital, Harvard Medical School

Acute kidney failure connotes a defect in the excretion of water, salts, and metabolic products including creatinine. Classical Nephrology taught that defective kidney excretion should be described on the basis of etiology and anatomy. We learned to approach the patient with a pathophysiological focus: Was the cause of defective excretion due to extra renal volume deficiency or intrinsic kidney causes, or post-renal causes? If intrinsic damage was found, was the cause primarily related to sepsis, ischemia, drugs/toxins, interstitial or glomerular causes, or a combination of the above? These categories were useful because they provided prospective insights into the clinical course and they suggested appropriate therapeutic interventions. Hence, excretory defects, which can result from a variety of challenges to the kidney, must be understood in their medical context.

In contrast to our medical classifications, a new entity called “Acute Kidney Injury” or “AKI” was defined principally by changes in sCr levels or RIFLE, AKIN, KDIGO “stages”[1]. Changes in urine output are also part of “AKI” criteria but they are not widely utilized. Unfortunately, the uniform application of sCr “stages”, in lieu of a primary etiologic or anatomic diagnosis, provides (*i*) inadequate quantitative assessment of excretory dysfunction, and (*ii*) obfuscates the important distinctions among fundamentally different etiologies that raise sCr and motivate personalized therapy.

Acute changes in sCr cannot quantify the extent of the excretory defect until an indeterminate interval has elapsed. Hence, a patient may have florid tubular damage on presentation, despite still awaiting a meaningful rise in sCr. In fact, it was recently found that a persistent but small increase in sCr has a greater predictive effect on morbidity and mortality than a transient but larger increase, meaning that sCr “stage” must be interpreted according to its duration. In light of both of these observations, sCr can only serve as a retrospective marker[2].

These data raise additional concerns about the quantitative accuracy of sCr, because “stage” can be greatly influenced by extracellular fluid volume and by muscle mass, both of which generally reflect the health of the patient[3]. As an illustration of this, it has been reported that an increase in sCr, associated with hemoconcentration, actually predicts a better outcome during the treatment of heart failure. In this case, increased sCr identifies healthy volume sensitive responses to diuretics, rather than tubular damage[4]. Additionally, sCr “stage” is

Corresponding Author: Jonathan Barasch, Russ Berrie Medical Science Pavillion, Columbia University, 1150 St Nicholas Avenue, New York, N.Y. 10032, T: 917-671-6081, F: 212-305-3475, jmb4@columbia.edu.

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confounded by “renal reserve”[5]; even unilateral obstruction or the donation of one kidney usually does not double sCr[6] because the nephron deficit is partially compensated by functional nephrons. Hence, sCr “staging” cannot fully measure the responses of the kidney, a problem encapsulated by the term “subclinical AKI”[7].

“AKI stages” not only poorly describe the extent of defective excretory function, but they are often at variance with kidney pathology[8,9] and physiology[10], for example, failing to provide insight into damage to the secretory and reabsorptive functions of the tubule.

The advent of kidney transcriptomics and urinary proteomics has further highlighted the mismatch between AKI “staging” and the physiological and molecular responses of the kidney. While sCr may be elevated in diverse experimental models and patient care scenarios, kidney genes and proteins demonstrate specificity for the stimulus and its cellular targets. For example, many proteins are found in the urine after kidney ischemia, yet few of these are upregulated by volume depletion, although in both cases sCr may be elevated to an equivalent extent. Instead we and others have found that different genetic signatures are activated by severe volume depletion and by kidney ischemia. This was determined in thousands of patients presenting with a broad range of illnesses[11], as well as in animal models[12] including large studies in rodents by Star and colleagues[13]. In sum, new in-situ RNA and protein techniques[14] have identified a myriad of genes which provide etiologically-dependent, and anatomically specific[15] transcriptomic and proteomic signatures from different segments of the nephron in humans, as well as in model organisms.

The dissociation of kidney transcriptomics and urinary proteomics from sCr is well described, and has caused much consternation. This is likely due to differences in the intrinsic characteristics of sCr (delayed, insensitive, not specific to intra-renal damage) and the genetic response of the kidney (rapid, very sensitive, cell specific)[16]. As an example, localized kidney damage will generate a rapid highly detectable genomic response, whereas sCr might not increase in response to this regional insult. By contrast, parallel changes in the genomic response and in sCr levels occur when kidney damage is diffuse and severe enough to overcome renal reserve. In addition, sCr may be elevated as a result of extra-kidney diseases such as heart failure, but this may not engender the same genomic response in the kidney as would direct tubular damage. These findings are analogous to the comparison of the highly sensitive troponin assay, the EKG, and the echocardiogram, which dissociate from one another to varying degrees, depending on the severity of myocardial damage.

Many fields of Medicine are attempting to individualize diagnostics and therapeutics, an effort that has been called “Precision Medicine”. We suggest that the re-introduction of etiologic and anatomical diagnoses as criteria in our diagnostic strategies is critical because these characteristics will ultimately guide personalized therapeutic interventions. Subsequently, transcriptomics-proteomics, and filtration markers will add to the diagnostic strategy by identifying different and often sequential phases of the excretory failure. No doubt that each analysis has its own intrinsic kinetics, sensitivity, and specificity, but nonetheless, preliminary attempts to pair kidney transcriptomics and urinary proteomics with changes in sCr, evaluating epithelial cell damage and excretory function at the same time, are capitalizing on the informative differences between sCr and urinary proteins[17]

These efforts will hopefully rectify the problems of interpreting sCr. In sum, rather than a singular focus on sCr, the coupling of causation (medical context) with sites of injury (anatomic responses) and their specific cellular responses (proteomics and transcriptomics), factoring in the extent of filtration and tubular dysfunction (sCr) are the keys to advance Nephrology to a level of precision necessary to achieve diagnostic and therapeutic innovation.

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