A Comment on the Diagnosis and Definition of Acute Kidney Injury

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A comment on “Singh: From the chair: becoming precise in diagnosing acute kidney injury. Nephrology Times 2018”; “Barasch et al: Acute kidney injury: a problem of definition. Lancet 2017;389:779–781”; and “Kellum and Lameire: The definition of acute kidney injury. Lancet 2018;391:202–203”.

Keywords

AKI · Acute Kidney Injury · Creatinine

Abstract

Context: International criteria for describing the presence and severity of acute kidney injury (AKI) based on changes in serum creatinine concentration and/or degree of oliguria are now widely accepted. **Subject of Review:** Three recent articles have debated the definition and diagnosis of AKI, offering conflicting opinions. On one side [Lancet 2017; 389: 779–781 and Nephrology Times 2018] an argument is made that a focus on creatinine-based staging has de-emphasised the traditional clinical approach of determining cause of AKI (pre-renal, renal or post-renal), and that any classification system based on serum creatinine is inherently flawed. The opposing argument, is that serum creatinine-based staging brings value via the consistent, robust and graded associations between AKI stage and outcomes, and that many cases of AKI have multiple co-existing intra- and extra-renal processes that do not fit neatly into the traditional aetiological groupings [Lancet 2018;391:202–203]. **Second Opinion:** Determining the cause of AKI is a key element of clinical man-

agement, so it is important that AKI is not regarded as a single disease, rather a syndrome with multiple potential causes. This article critiques current, clinical approaches to determining AKI aetiology alongside future areas in which significant developments in patient phenotyping based on pathophysiological principles may occur. In the absence of current alternatives to serum creatinine, current AKI criteria (e.g., those from Kidney Disease Improving Global Outcomes) bring significant advantages in clinical and research environments, including facilitation of efforts to address current variations in the delivery of AKI care. However, their application needs to be accompanied by 2 aspects: an appreciation of the limitations of serum creatinine as a diagnostic test; and an absolute requirement for clinical assessment and diagnostic workup to establish the cause of AKI.

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Three recent articles have debated the definition and diagnosis of acute kidney injury (AKI), conceivably originating from views on how the current Kidney Disease Improving Global Outcomes (KDIGO) classification is affecting clinical practice [1–3]. Some of the expressed

opinions are conflicting. Barasch et al. [2] suggest that a focus on creatinine-based staging has de-emphasised the traditional clinical approach of determining cause of AKI (pre-renal, renal or post-renal), which is inherent in determining patient management. Additionally, they argue that any classification system based on serum creatinine is inherently flawed. Supported by Singh [1], they make a case for “reintroducing” the traditional diagnostic approach; they then go on to describe how this may be advanced by using transcriptomic/proteomic approaches to better differentiate AKI phenotypes that ultimately will lead to targeted interventions. In the opposite corner, Kellum et al. [3] argue that serum creatinine-based staging brings value via the consistent, robust and graded associations between AKI stage and outcomes, and that many cases of AKI have multiple co-existing intra- and extra-renal processes that do not fit neatly into the traditional aetiological groupings.

So, how should we integrate these apparently opposing views from international leaders in the field? First, a point on which there is agreement is that all accept that determining the cause of AKI is a key element of clinical management. As Kellum et al. [3] point out, while the KDIGO staging classification of AKI refers only to serum creatinine and degree of oliguria, the accompanying clinical practice guideline specifically advocates clinical adjudication when diagnosing AKI. But how clearly has this message got through to clinicians, alongside widespread uptake of the KDIGO classification system [4]? Although there are no robust data to inform this, the varying degree to which diagnosing AKI aetiology is included in practice pattern surveys hints that this may be an issue, particularly as in some this is not mentioned at all [4–7]. On one level, this is about getting the messaging right: AKI is not a single disease, rather a syndrome with multiple potential causes; and that determining cause of AKI is central to patient management. Singh [1] discusses the importance of this in the training of nephrology fellows, but it must also be considered more broadly. AKI presents across all acute specialities with the majority of cases not receiving specialist input [8]. Dissemination must therefore also include colleagues more widely, for example, making this point more visible in local guidelines, during AKI education and in the published literature (e.g., review articles). There are good examples of the latter already [9].

On another level, the debate revolves around how best to determine the cause of AKI. Defining the presence of AKI based on change in serum creatinine alone is problematic in this regard, as it is a marker of renal excretory

function only. It cannot inform about the type of renal injury, or the subsequent cellular responses during the complex pathophysiological response that characterises AKI. Similar elevations in creatinine can represent vastly different clinical scenarios, including physiological responses to volume depletion. In the future, there is a clear need to move towards improved classification of AKI based on cellular and molecular mechanisms of disease. On this matter, Barasch et al. [2] and Kellum et al. [9] both agree, and there are a number of exciting avenues of research by which this may develop, including protein biomarkers, transcriptomic approaches [10] and the National Institutes of Health precision medicine initiative [11]. While these approaches may in future allow the definition of a new range of AKI phenotypes (or endo-phenotypes), they do not answer the question of what approach to take currently in our clinical practice. On the one hand, the traditional approach of pre-renal, renal and post-renal causes of AKI remains attractive and familiar to many, and can be used successfully in many cases to guide patient management. Singh’s response to the argument that many patients with AKI have more than one causative factor is that, “*As nephrologists we have long appreciated that some forms of AKI have overlapping prerenal and intrarenal causes. We can handle this moderate degree of complexity*” [1]. Although this is true, the “0by25” Global Snapshot study demonstrates the level of this complexity in the large number of causative factors, many of which often co-exist, reported in AKI patients across developed and low- and middle-income countries [12]. It is therefore not too surprising that it is not always possible to determine the cause of AKI on clinical grounds alone [13], and there can be a lack of agreement in clinical adjudication even when performed by experts [14]. As there are no immediate alternatives, and while we await a new dawn of precision medicine, it is also healthy to appraise the traditional approach to categorisation of the causes of AKI. The traditional paradigm of pre-renal AKI holds that haemodynamic change leading to reduced renal blood flow and renal ischaemia is the primary problem; if this rectified quickly then the AKI is reversed (pre-renal AKI), but more prolonged or severe episodes lead to acute tubular necrosis (a major cause of intrinsic renal AKI). This is the teaching that still remains in most major nephrology text books, that the causes of pre-renal AKI include volume depletion (e.g., haemorrhage, fluid losses from GI/renal/skin routes, surgery, nephrotic syndrome, cirrhosis), reduced cardiac output (e.g., cardiac failure), systemic vasodilation (e.g., sepsis) and renal vasoconstriction (e.g.,

hepato-renal syndrome) [15]. Within this, there is an implication that regardless of the original process, the downstream effects on the kidney are the same. However, observations over the last few years challenge this. For example, in sepsis-associated AKI, renal biopsy findings can show mild changes or even appear normal even in the presence of significant AKI, suggesting that acute tubular necrosis may be relatively uncommon in this setting [16]. A subsequent study, comparing post-mortem histological changes in patients with and without sepsis-associated AKI, also found varying degrees of tubular necrosis (often finding only patchy, focal change) and described how other pathological processes predominated, for example, capillary leukocytic infiltration and apoptosis [17]. Furthermore, in some animal models of sepsis, and in pilot studies in humans with sepsis-associated AKI, global renal blood flow has been shown to be preserved or even increased [18, 19]. In patients with heart failure, tubular necrosis is also uncommon, biomarker kinetics differ and a very different approach is required to patient management as compared to other causes of AKI [20, 21]. Surgical patients differ again, as do patients who are simply volume depleted. So, while we rely on clinical judgement to determine the causative factors for AKI, we should continue to strive to differentiate AKI subtypes, particularly those traditionally grouped as “pre-renal”, and maybe even guidelines or standardised criteria for disease adjudication should be developed as previously suggested [22]. Alongside this, we should be explicit in describing AKI severity and duration (as best we can using currently available tools) as 2 key clinical features that inform prognosis and recovery.

AKI has become a term that is widely understood in clinical discussions, in no small part due to the international adoption of AKI definitions (RIFLE, AKIN and most recently KDIGO criteria). There is no doubt that the introduction of the RIFLE, AKIN and then KDIGO criteria has been a major advance, replacing more than 35 previously used definitions in the medical literature [23]. A standardised definition is essential for robust epidemiological research, and as such has played an important part in highlighting the challenges posed by AKI to a wide audience. Applying such classifications to the syndrome of AKI in clinical practice does bring challenges, as Barasch et al. [2] describe, but is this adequate reason to abandon them? I would argue not. As with any diagnostic test, understanding the limitations of serum creatinine and interpreting results within the clinical picture is key (discussed elsewhere in respect to AKI definition) [24], and although it is an imperfect biomarker of AKI, serum creatinine re-

mains the only biochemical test that is in widespread clinical use for this purpose. There is a wealth of evidence to show clear associations between AKI based on serum creatinine staging (as per RIFLE, AKIN or KDIGO) and patient outcomes [25–28]. The magnitude of this association is strong (e.g., ORs for mortality in the range of 5–10) [29], is proportional to the severity of AKI, and remains remarkably consistent across every clinical condition and environment in which it has been studied. So, serum creatinine changes can inform more holistically about patients at higher risk of adverse outcome, but there is an additional consideration. In contrast to many other areas in medicine, creatinine changes (i.e., a single biochemical test) can be used to develop detection and alerting systems, as previously described [30, 31]. E-alerts for AKI may not be a panacea [32], but they are a tool that can underpin complex interventions targeting improvements in standards of AKI care delivery and that support early intervention [33]. This becomes important when looking at current ways to address the unmet clinical need – the extremely poor outcomes associated with AKI, its silent presentation and reports from across a range of health care systems of variable standards in the quality of AKI care [34–37].

So, in summary, the debate about detection, classification and clinical assessment of patients with AKI is an important one to have, not least to reinforce the message that AKI is not a single disease, rather a syndrome with multiple causes. I conclude that the serum-creatinine based KDIGO criteria bring significant advantages in clinical and research environments, including the ability for automated AKI detection and alerting. However, their application needs to be accompanied by 2 aspects: an appreciation of the limitations of serum creatinine as a diagnostic test; and an absolute requirement for clinical assessment and diagnostic workup to establish the cause of AKI. This allows the explicit description of AKI episodes in terms of primary cause, additional contributing factors, AKI severity (stage) and duration. In the future, there is huge potential for improving the status quo, in particular for improving our ability to differentiate different endo-phenotypes of AKI. However, for now, we must make the best of the tools that we have at our disposal in efforts to address the impact of AKI on patient outcomes.

Disclosure Statement

The author has no conflict of interest to declare.

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