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Acute kidney injury: a problem of definition

Individuals with acute kidney impairment can have defects 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 aetiology and anatomy. We learned to approach the patient with a pathophysiological focus: was the cause of defective excretion due to extrarenal volume deficiency, impaired blood perfusion, intrinsic kidney causes, or post-renal causes? If intrinsic damage was found, was the cause primarily related to sepsis, ischaemia, drugs or 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 suggested appropriate therapeutic interventions. Hence, excretory defects, which can result from various challenges to the kidney, must be understood in their pathophysiological context.

In contrast to our pathophysiological classifications, a new entity called acute kidney injury (AKI) was defined principally by changes in serum creatinine (sCr) concentrations and categorised into stages defined by the degree of increase in sCr, designated risk, injury, failure, loss, end-stage stages, or the related Kidney Disease: Improving Global Outcomes stages.[1] Changes in urine output are also part of AKI criteria, but they are not widely used. Unfortunately, the uniform application of sCr stages, in lieu of a primary aetiological or anatomical diagnosis, provides inadequate quantitative assessment of excretory dysfunction and confounds the important distinctions between fundamentally different aetiologies that raise sCr and require personalised therapy.

Acute changes in sCr cannot quantify the extent of the excretory defect until an indeterminate interval has elapsed. Hence, a patient might have florid tubular damage on presentation, despite the absence of a meaningful rise in sCr that will occur subsequently. In fact, a persistent but small increase in sCr has been shown to have a greater predictive effect on morbidity and mortality than a transient but larger increase,[2] indicating that sCr stage must be interpreted according to its duration. In light of these observations, sCr can only serve as a retrospective marker.

These data raise additional concerns about the quantitative accuracy of sCr because the stage classification can be greatly influenced by extracellular fluid volume and muscle mass, both of which reflect the health of the patient. As an illustration of this, it

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has been reported that an increase in sCr, associated with haemoconcentration, 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.[3] Additionally, sCr stage is confounded by renal reserve;[4] even unilateral obstruction or the donation of one kidney usually does not double sCr because the nephron deficit is partly compensated by functional nephrons. Hence, sCr staging cannot fully measure the responses of the kidney, a problem exemplified by the use of the term subclinical AKI.[5]

AKI stages not only poorly describe the extent of defective excretory function, but they are often inconsistent with kidney pathology and physiology—for example, by 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. Although sCr can be elevated in diverse experimental models and patient care scenarios, kidney genes and proteins can demonstrate specificity for the stimulus and its cellular targets. For example, many proteins are found in the urine after kidney ischaemia, yet few of these are upregulated by volume depletion—although in both cases sCr can be elevated to an equivalent extent. Instead, we and others have found that different genetic signatures are activated only by severe volume depletion and by kidney ischaemia. This finding was shown in thousands of patients presenting with a broad range of illnesses,[6] and in animal models, including large studies of rats by Yuen and colleagues.[7] In sum, new in-situ RNA and protein techniques[8] have identified a myriad of genes that provide aetiologically dependent and anatomically specific[9] transcriptomic and proteomic signatures from different segments of the nephron in humans, as well as in animal models.

The dissociation of kidney transcriptomics and urinary proteomics from sCr is well described, and has caused much consternation. This dissociation is likely due to differences in the intrinsic characteristics of sCr (delayed, insensitive, not specific to intrarenal damage) and the genetic response of the kidney (rapid, very sensitive, cell specific).[10] As an example, localised kidney damage will generate a rapid and highly detectable genomic response, whereas sCr might not increase in response to this localised insult. By contrast, parallel changes in the genomic response and in sCr concentrations can occur when kidney damage is diffuse and severe enough to overcome renal reserve. Additionally, sCr can be raised as a result of extra-kidney diseases such as heart failure, but this would likely 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 electrocardiogram, 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 individualise diagnostics and therapeutics, an effort that has been called precision medicine. We suggest that the re-introduction of aetiological and anatomical diagnoses as criteria in our diagnostic strategies for kidney disease is crucial because these characteristics will ultimately guide personalised therapeutic interventions. Subsequently, transcriptomics-proteomics and filtration markers will add to the diagnostic strategy by identifying different and often sequential phases of excretory failure. Although each analysis has its own intrinsic kinetics, sensitivity, and specificity, preliminary attempts to pair kidney transcriptomics and urinary proteomics with changes in sCr, evaluating epithelial cell damage and excretory function simultaneously, are capitalising on the informative differences between sCr and urinary proteins.[11] These efforts will hopefully rectify the problems of interpreting sCr. In conclusion, rather than a singular focus on sCr in isolation, the coupling of causation (medical and pathophysiological context) with sites of injury (anatomical responses) and their specific cellular responses (proteomics and transcriptomics), factoring in the extent of filtration and tubular dysfunction (sCr), are keys to advancing nephrology to a level of precision necessary to achieve diagnostic and therapeutic innovation.

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from Abbvie, Amgen, Astellas, Pfizer, UCB Pharma, and Takeda; has received a grant from Boehringer Ingelheim for research on acute kidney injury and chronic kidney disease; is a co-inventor on patents 6664385 and 7696321 related to kidney injury molecule-1 (KIM-1) assigned to Partners Healthcare with royalties paid by R and D, Astute, Biogen, Sekisui, and Ortho; and declares equity in Medibeacon (developing methods to measure glomerular filtration rate in real time), in Sentien (developing an extracorporeal device to potentially treat acute kidney injury), in Goldfinch Biopharma (developing precision therapies for kidney disease), and in Thrasos Therapeutics (developing BMP/Smad peptides to potentially treat acute kidney injury).

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Telling the human story of Asia's invisible malaria burden

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Malaria in Asia is a pervasive and diverse problem with about 2 billion people at risk.[1] Although *Plasmodium falciparum* and *Plasmodium vivax* account for most clinical attacks of malaria in Asia, all four human plasmodia occur, as do zoonoses involving plasmodia of southeast Asian macaques[2] and several dozen species of anopheline mosquito carry malaria in a wide variety of ecological habitats.[3] Despite the broad scope and complexity of malaria in Asia, it represents a fairly small fraction of research endeavour and public funding in global malaria control efforts.[4,5] This partly derives from quantitative WHO morbidity and mortality estimates that put less than 10% of the global burden in this region.[6] But do the large denominators of risk conceal more substantial burdens?

In 2010, a *Lancet* paper by Dhingra and colleagues[7] estimated deaths attributable to malaria in India at 205 000 during 2006 compared with WHO's estimate of 15 000 in the same year.[8] Many experts broadly criticised the verbal autopsy methods that underpinned the work of Dhingra and colleagues[7] and suggested their estimates were inflated.[9] Few experts dispute the epidemiological limitations of the WHO quantitative estimates of malaria morbidity and mortality, which amount to sums of confirmed cases and deaths reported by national malaria control programmes adjusted for surveillance systems of variable and often unquantifiable efficiency.[10] The value of those estimates lies in the useful analysis of trends over time. By contrast, since level of endemicity and human population can be confidently measured, relatively robust estimates of the populations living at risk of unstable or stable endemic malaria are available from the work of the Malaria Atlas Project and collaborators.[11] In Asia, people at risk of unstable *P falciparum* malaria in 2010 exceeded African estimates by a factor of 23 (1·03 billion *vs* 0·05 billion), whereas roughly equal numbers of people lived under stable malaria

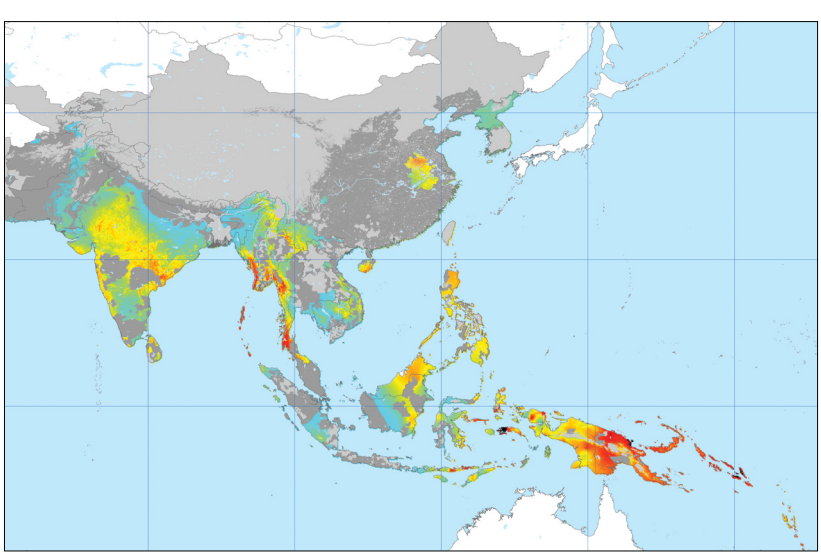

***Figure:* *Plasmodium vivax* endemicity in the Asia-Pacific region in 2010**
Detail taken from a map from the Malaria Atlas Project at Oxford University.