Yes, AKI Truly Leads to CKD

Chi-yuan Hsu
Division of Nephrology, University of California–San Francisco, San Francisco, California

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In the past few years, there has been a great deal of interest regarding the long-term sequelae of AKI, including the impact of an episode of AKI on development of incident CKD or acceleration of pre-existing CKD. In *JASN*, Rifkin *et al.*[1] argue that the observed AKI–CKD associations should be considered noncausal as long as they are based on epidemiologic or observational studies. I disagree based on the following considerations.

1. There is much plausibility to the idea that AKI causes CKD. It seems *a priori* physiologically implausible that the healing process is 100% perfect, especially when the injury is severe.

2. Numerous animal models illustrate plausible mechanistic pathways by which AKI can lead to CKD. Residual renal structural damage, which has been identified after AKI in these models, includes tubular atrophy and dilation, interstitial fibrosis, and reduction in peritubular capillary density.[2–7] One recent review concluded that identification of the AKI–CKD nexus represents the single most important advance in understanding of the mechanisms of progression since hyperfiltration was shown to occur after renal ablation.[8]

3. Careful studies of young patients who were otherwise healthy before severe AKI have consistently found abnormal renal function after. For example, based on para-aminohippurate and inulin clearance studies, Lowe[9] concluded in a study of 14 patients (average age=32 years) that renal function tended to remain below the lower limit of normal, and the work by Finkenstaedt and Merrill[10] observed (in 16 patients averaging 31 years old) that subnormal renal function late in the follow-up period occurred in the majority of patients studied. When looked for, other subtle abnormalities, such as inability to maximally concentrate urine, are very common among survivors of severe AKI.[11]

The notion that even severe AKI is completely reversible probably originated as a misreading of this older literature, which reported that patients usually have good clinical recovery in so far as they returned to active lives, resumed their occupations, and were able to carry future pregnancies. This older literature never concluded that there was no residual damage.

Newer publications assessing degree of recovery based on serum creatinine measurements after AKI systematically paint an excessively optimistic picture. Patients who suffered a serious hospitalization (such as that involving a stay in the intensive care unit and renal replacement therapy)[12] lose muscle mass and thus, have decreased creatinine production. Use of alternate filtration markers such as cystatin C may more accurately reveal the true extent of residual kidney dysfunction. In the study cited in the work by Rifkin *et al.*,[1] there was no difference in serum creatinine, but estimated GFR using cystatin C showed that children who suffered hemolytic–uremic syndrome had a 10 ml/min per 1.73 m^2 lower estimated GFR 5 years after the injury ($P=0.02$).[13]

4. The epidemiology literature that AKI is an independent risk factor for CKD, including ESRD, is strong and consistent. A recent meta-analysis by Coca *et al.*[14] showed an unequivocal association between AKI and CKD in a number of large, well-conducted studies. This relationship between AKI and CKD or ESRD was graded, with a greater risk associated with increasing severity of AKI.[14] The 13 studies included were remarkably consistent considering the variety of patients examined and the diverse settings for AKI.

5. Confounding is a very legitimate concern but does not discredit the literature. I agree that confounding is an important source of bias in numerous published studies of CKD after AKI.[15] However, several studies have gone to very reasonable lengths to address this concern. For example, in addition to conducting multivariate regression analyses, the work by Lo *et al.*[16] also matched on pre-AKI levels of estimated GFR and comorbidities such as diabetes mellitus. However, a 28-fold increase in risk of stage 4 or higher CKD after dialysis-requiring AKI was still identified.[16] A strong argument against confounding is this very large effect size, which is an order of magnitude stronger than the effect size of numerous traditional risk factors for kidney failure, such as hypertension.[17] Similarly, the work by James *et al.*[18] found that, within each substratum cross-classified by estimated GFR and proteinuria, AKI remained an independent and very strong predictor of future doubling of serum creatinine or ESRD.

6. Ascertainment bias seems to be more of a hypothetical than actual threat to validity. I agree that relying on serum creatinine measurements obtained as part of routine care to determine presence of CKD post-AKI may be prone to ascertainment bias. However, serum creatinine is a routine and

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Correspondence: Dr. Chi-yuan Hsu, Division of Nephrology, University of California–San Francisco, 521 Parnassus Avenue, C443, Box 0532, San Francisco, CA 94143-0532. Email: hsuchi@medicine.ucsf.edu

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inexpensive laboratory test that is ordered liberally. Previous publications have compared numbers of posthospitalization serum creatinine measurements among AKI and non-AKI patients (they are similar)[19] and conducted sensitivity analyses specifically to address this concern (for example, by ignoring serum creatinine values observed between 6 or 12 months after index hospitalization[16] or limiting the analysis only to subjects who had similar creatinine measurement frequencies[19]), and the conclusions are robust. Thus, there is no empirical evidence that there is substantive ascertainment bias. Additionally, studies that solely examined ESRD as the outcome,[20,21] thus not susceptible to this bias, gave very consistent results.

7. The unique example of kidney donation in healthy altruistic volunteers is unpersuasive. Counterexamples of unique "AKI" scenarios abound: patients with recurrent flares of lupus nephritis develop progressive CKD, repeated episodes of acute cellular rejection lead to failure of the transplant kidney allograft, and acute interstitial nephritis has its own natural history.[21] The discussion regarding AKI and CKD should center on the long-term sequelae of what clinicians usually diagnose as acute tubular necrosis. Thus, more weight should be given to epidemiologic studies focusing on acute tubular necrosis[19] or severe, dialysis-requiring AKI,[16,22] which are unlikely to be caused by prerenal azotemia, an assumption confirmed by chart review.[16,22] It is pathophysiologically more plausible that a serious rather than equivocal injury causes long-term permanent damage.

8. Every experienced nephrologist has seen patients with CKD suffer severe acute tubular necrosis and not recover to come off dialysis. There is little doubt in these instances that the AKI caused the abrupt loss in GFR, which resulted in ESRD that clearly would not otherwise have developed for months or years in the future, if at all. A recent study quantifying this finding found that, among those patients with prehospitalization estimated GFR of 30–44 ml/min per 1.73 m^2, over 40% of the survivors of renal replacement therapy-requiring AKI did not recover to come off dialysis. For those patients with preadmission eGFR of 15–29 ml/min per 1.73 m^2, nonrecovery was seen in over 60% of the survivors.[21]

9. The bar to satisfy causality set in the work by Rifkin et al.[1] is unrealistically high and not consistent with how clinicians and policy makers accept causality in other settings. The question is not whether every AKI episode causes accelerated loss of kidney function to an equal extent in all patients. The questions are whether patients who had AKI are more likely to suffer accelerated loss of kidney function compared with those patients who did not with all else being equal and whether this finding is causal. We should use the usual criteria to judge causality as accepted in other areas of medicine. For example, no one argues that every single exposure to tobacco will lead to lung cancer, just that smokers are more likely to develop lung cancer than nonsmokers; causality is accepted based on a wealth of epidemiologic and mechanistic research.

To satisfy concerns raised in the work by Rifkin *et al.*[1], one would have to enroll patients into a prospective trial, randomize them to a variety of interventions known to cause AKI, and then document increased risk of subsequent CKD in all the AKI arms compared with placebo. This design clearly is not an ethically feasible study. Using their logic to its extreme, even a randomized trial of a successful intervention for AKI, which is associated with lower subsequent rates of CKD in the treatment arm, would still preclude definitive causal inferences, because it is possible that the intervention could have directly ameliorated future risk of CKD independently through mechanisms unrelated to its prevention of AKI (that is, there is confounding).

In conclusion, certainly more rigorous studies of the long-term sequalae of AKI are welcome and needed. At least one study is currently underway, the National Institutes of Health-sponsored prospective Assessment, Serial Evaluation, and Subsequent Sequelae of AKI study, that will quantify kidney function at predetermined time points after the AKI episode using creatinine, cystatin C and other novel biomarkers. Attention will be paid to less severe AKI cases.[23] However, the evidence is unequivocal for severe acute tubular necrosis. To the questions of whether patients who had AKI are more likely to suffer accelerated loss of kidney function compared with those patients who did not with all else being equal and whether this outcome is causal, the answers are clearly yes and yes.

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DISCLOSURES

None.

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See related article, "Does AKI Truly Lead to CKD?," on pages 979–984.

A Photo Shoot of Proteinuria: Zebrafish Models of Inducible Podocyte Damage

Roman-Ulrich Müller*†‡ and Thomas Benzing*†‡
*Department 2 of Internal Medicine and Center for Molecular Medicine Cologne,†Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, and ‡Systems Biology of Ageing, University of Cologne, Cologne, Germany

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Diseases of the renal glomerulus, the site of plasma filtration and the production of primary urine, account for a majority of chronic renal diseases.[1] The prevention of ESRD would require therapies that specifically interfere with the pathogenesis of the various underlying glomerular diseases, as well as appropriate models to develop and study targeted interventions.[2] However, although the last decade has witnessed a breakthrough in our understanding of the pathogenesis of proteinuria and the function of the glomerular filtration barrier, animal models for the study of onset and recovery from glomerular damage are still scarce.

A number of rodent models of inducible podocyte injury have been developed.[3] However, these rodent models cannot be used for high-throughput drug screening and have major limitations as a tool for drug discovery aiming at prevention of progressive glomerular damage. In a remarkable paper in this issue of *JASN*, Zhou and Hildebrandt[4] now present a zebrafish model that allows the induction of glomerular injury and the visualization of a surrogate of proteinuria in real time. The authors used an inducible model of podocyte damage utilizing podocyte-specific expression of prokaryotic nitroreductase. This enzyme converts metronidazol to a cytotoxin. Thus, feeding of metronidazol leads to dose-dependent podocyte loss and glomerular dysfunction.

Podocytes are the visceral epithelial cells of the kidney glomeruli.[5] Neighboring podocytes extend long, regularly spaced, interdigitated foot processes that enwrap the glomerular capillaries and form a 40-nm-wide filtration slit bridged by a membrane-like cell contact, the slit diaphragm. Together with fenestrated endothelial cells of the glomerular capillaries and the glomerular basement membrane, which separates these two communicating cell types, podocytes form the kidney filtration barrier and restrict the passage of macromolecules on the basis of their size, shape, and charge.[6,7] Upon podocyte injury, the intercellular junctions and cytoskeletal structure of the foot

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Correspondence: Dr. Thomas Benzing, Department 2 of Internal Medicine, University of Cologne, Kerpener Strasse 62, 50937 Cologne, Germany. Email: thomas.benzing@uk-koeln.de

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