Does AKI Truly Lead to CKD?

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ABSTRACT

Acute kidney injury (AKI) has been implicated as an independent risk factor for the development of CKD in recent observational studies. The presumption in the nephrology community is that this association represents a causal relationship. However, because of potential problems related to residual confounding (shared risk factors), ascertainment bias (sicker patients have more follow-up assessments), misclassification of exposure (problems with defining baseline kidney function and AKI representing a discrete event versus progression of renal disease), and misclassification of outcome (de novo CKD versus CKD progression), it is difficult to conclude with certainty that AKI is truly causal for CKD. In this review we highlight several of the Hill causality criteria to examine the existing evidence and point out the missing elements that preclude defining AKI as a cause of CKD in the general population. Only well-designed studies with rigorous assessment of kidney function in all participants (AKI and non-AKI) before and after the episode or hospitalization or randomized, controlled trials demonstrating that prevention or treatment of AKI reduces the incidence of subsequent CKD can clarify the causal nature of the AKI-CKD relationship.


The incidence of acute kidney injury (AKI) is on the rise. Approximately 600,000 cases of AKI are reported each year in the United States. Even though most cases of AKI are reversible within weeks of occurrence, with full recovery to baseline, data from recent observational studies suggest an association between AKI and subsequent CKD. In fact, the increasing incidence of AKI is suggested as an explanation for the increasing burden of CKD and ESRD. However, although AKI and CKD are frequently linked in epidemiologic studies, the evidence to date is entirely observational and precludes definitive causal inferences. Until causality can be clearly proven in nonobservational studies, such as randomized, controlled trials (RCTs), the observed AKI-CKD associations should be considered noncausal as long as they are based on epidemiologic or observational studies.

In this review, we highlight several of the standard criteria proposed by Sir Austin Bradford Hill° (Table 1) to examine the existing evidence and point out the missing elements that preclude defining AKI as a cause of CKD in the general population. Although it may at first seem academic to separate the evidence for association from the evidence for cause, this distinction is of critical importance in terms of assessing the value of discovery efforts for identifying preventive or treatment strategies for AKI. Furthermore, the discussion about the causality of the AKI-CKD association has major clinical, medicolegal, and public health implications. A recent and poignant example from nephrology is the seemingly causal association between anemia and poor outcomes in CKD; numerous rigorous RCTs demonstrate that anemia is probably a surrogate marker, but correction of anemia using erythropoiesis-stimulating agents does not improve outcomes and may even cause harm.°—°

BIOLOGIC PLAUSIBILITY, TIMING, AND STRENGTH OF ASSOCIATION BETWEEN AKI AND CKD

The first major tests of a putative causal relationship are that the causal event should have biologic plausibility as a cause of the outcome, should precede the outcome, and should be strongly associated with the outcome. For AKI and CKD,
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| 1. Temporality*       | The cause (exposure) must precede the effect (outcome)                               | Pro: AKI happens weeks, months, or years before CKD
Con: Acute-on-chronic does not follow this rule                                                  |
| 2. Strength of        | Stronger association may make causality more likely                                   | Pro: Some studies indicate a strong association between AKI and future CKD
Con: The reported strengths of the associations are not consistent                              |
| association            |                                                                                      | Pro: AKI severity or more frequent AKI episodes may be associated with a higher likelihood of CKD   |
| 3. Biologic gradient  | Greater exposure increases the incidence or magnitude of the effect                 | Con: Because patients with more severe forms of AKI are also sicker, the dose-response relationship may simply be detecting the residual confounding from severity of illness
Pro: Various forms of AKI in different clinical settings have been demonstrated to lead to CKD |
| (dose-response)       |                                                                                      | Con: Some forms of AKI (e.g., hemolytic-uremic syndrome) do not lead to future kidney disease for years to decades |
| 4. Consistency        | The association can be replicated in studies in different settings using different methods | Pro: Various forms of AKI in different clinical settings have been demonstrated to lead to CKD |
|                       |                                                                                      | Con: Some forms of AKI (e.g., hemolytic-uremic syndrome) do not lead to future kidney disease for years to decades |
| 5. Biologic plausibility | The association is consistent with known biologic or pathologic processes\b         | Pro: The tubular and glomerular injury may lead to permanent damage
Con: Even non–acute tubular necrosis human AKI (e.g., prerenal azotemia) is associated with future risk for CKD |
| 6. Experimentation    | The putative effect can be altered (prevented or mitigated) by an experimental regimen | Pro: In some animal models, permanent injury after AKI has been shown
Con: Some models show full recovery of AKI without renal dysfunction or fibrosis, particularly in younger animals |
| 7. Specificity        | A single cause produces the effect without other pathways                              | Pro: Prior AKI episodes can fully explain CKD incidence
Con: AKI is only one of the correlates of CKD; many cases of CKD happen in patients who have never had an AKI, and many of the factors that are present in patients with AKI are the same risk factors for CKD |
| 8. Biologic coherence | The association is consistent with the natural history of the disease or laboratory findings | Pro: A lower risk for CKD should occur as a result of preventing AKI
Con: Natural history of CKD has little, if anything, to do with AKI |
| 9. Analogy            | The effect of similar factors may be considered in other populations or under different settings | Pro: AKI precedes CKD irrespective, as seen in animal models; acute myocardial infarction can lead to remodeling and progressive chronic heart failure
Con: There is no analogy in other acute-leads-to-chronic setting, such pulmonary disease and liver disease |

*Note that temporality is the only necessary (but not sufficient) condition of causality.

\bStudies that disagree with established understanding of biologic processes may force a reevaluation of accepted beliefs.
Figure 1). There are many examples of such a noncausal association between an acute event and subsequent chronic disease states. A useful analogy to consider would be the epidemiologic link between preeclampsia and future CKD and ESRD. Pregnancy is a more discrete event and is easier to identify than the stressors that lead to AKI; in addition, preeclampsia in women with access to prenatal care does not generally go unrecognized, as episodes of AKI may. Nevertheless, even given these considerations, the observational data linking preeclampsia with future CKD/ESRD does not demonstrate causation; rather, pregnancy may be considered a kidney stress test that reveals a pathophysiologic milieu that was already present.

Another relevant example is gestational diabetes, an acute and temporary state of glucose intolerance during pregnancy with full recovery to normal glycemic state after the termination of pregnancy. Many women with gestational diabetes will eventually develop diabetes mellitus later in life, usually years or decades after the last gestational diabetes event. The undeniable fact that gestational diabetes precedes overt diabetes mellitus does not mean that the gestational diabetes is a cause of future diabetes mellitus; indeed, it is widely believed that pregnancy with gestational diabetes severe enough to require insulin therapy simply reveals a predisposition to diabetes and does not cause beta-cell damage or future chronic diabetes mellitus in these women.

CONSISTENCY AND BIOLOGIC GRADIENT

If AKI truly leads to permanent loss of kidney function or structure and causes CKD, similar models should be observed and reproducible in a variety of settings and under similar conditions. In sharp contradistinction to the forgoing hypothesis, the altruistic practice of living kidney donation, which involves the immediate loss of approximately 50% of the functioning kidney mass, has only rarely been associated with long-term consequences for the donor. Indeed, a recent study by Ibrahim and colleagues showed that even after several decades of follow-up, the kidney donors continued to live without higher risk for kidney disorders or other pathologic conditions. Whereas 50% kidney loss is irreversible in kidney donors, in most AKI cases there is near-complete to full recovery of kidney function or structure.

SPECIFICITY

Ideally, to make a causal claim one should be able to define the causal event and the outcome with high degrees of certainty and ensure that they and potential confounding variables are measured without bias in the observational setting. This proves to be perhaps the most difficult hurdle in observational studies of AKI and CKD. It should come as no surprise that AKI and CKD often occur in the same individuals, because each has similar antecedents. Factors that increase the risk for AKI are multiple and may include, but are not limited to, obesity; metabolic syndrome; diabetes mellitus; hypertension; cardiovascular disease; and possibly any pre-existing or ongoing abnormalities of the kidneys, such as microalbuminuria—factors that also increase the risk for CKD.

These pre-existing conditions also make the individual susceptible for AKI more likely to be exposed to procedures (catheterizations using contrast agents), medications (angiotensin-converting enzyme inhibitors), and acute illnesses...
(sepsis) that increase the risk for AKI in and of themselves. In a recent study, Hsu and colleagues\textsuperscript{24} compared 1746 hospitalized patients who had dialysis-requiring AKI with 600,820 hospitalized patients without AKI in the Kaiser Permanente of Northern California system. The unbiased likelihood of developing AKI, derived from the adjusted odds ratios, was significantly and progressively elevated from 1.95 to 40.07 for patients with CKD stages 3 to 5 compared with patients with better kidney function (i.e., with an estimated GFR > 60 ml/min per 1.73 m\textsuperscript{2} body surface area).

These investigators also observed, however, that predialysis baseline diabetes mellitus, hypertension, and proteinuria were additional independent risk factors for developing AKI. Hence, the study by Hsu and colleagues is important evidence that the likelihood of AKI is substantially higher under pre-existing conditions and that several common risk factors for CKD also increase the likelihood of AKI.\textsuperscript{24} This and other recent similar studies indicate that AKI per se should not be considered a cause of or contributor to CKD and that a higher likelihood of CKD in patients who have developed AKI may be due to the common ancestors of both AKI and CKD, including a host of diverse metabolic and vascular abnormalities. Nearly every observational study of AKI demonstrates a higher proportion of risk factors for CKD in the patients who developed AKI than in those who did not.\textsuperscript{2}

It may be argued that, in large studies, adjustment for these confounding variables can adequately allow for causal inference. In general, however, even the most robust multivariate adjustments are still crude and cannot fully capture the severity of the underlying illness. For example, observational studies that report that AKI is independently associated with CKD or ESRD adjust for diabetes mellitus at baseline but do not account for the severity of diabetes or the subsequent control of diabetes after the AKI episode. The difference in granularity of this critical risk factor for CKD can result in substantial misclassification in predictive models.\textsuperscript{35} Moreover, most observational studies allow all known AKI and non-AKI cases into the analysis, which can allow for biased parameter estimates. In fact, one observational study of severe dialysis-requiring AKI was unable to demonstrate an association with long-term survival despite a three-fold increase in the risk for ESRD after the episode.\textsuperscript{27} This finding may have resulted from use of propensity matching and the inability to include the percentage of the AKI patients in the analytic dataset because there was no adequate match within the control population. The ESRD and mortality risks of these patients were 100\% and 40\% higher, respectively, than those in the AKI cases used in the final analysis, demonstrating the tremendous amount of residual confounding that is present in observational studies. Regardless, studies demonstrating that a 0.1-mg/dl\textsuperscript{28} or 1\%–24\%\textsuperscript{29} change in serum creatinine from baseline to peak are independently associated with a 45\% increase in ESRD or two-fold increase in the risk for CKD may reflect the ability for confounders, and not AKI (true acute tubular necrosis), to influence this association. Small changes in serum creatinine imperfectly reflect AKI.\textsuperscript{30,31} These minor changes in serum creatinine are far more likely to be a barometer of overall health than a true marker of renal injury.

Furthermore, not only are the confounding variables in AKI studies difficult to adequately control, the AKI event and the outcome of CKD are also difficult to measure without bias. Most observational studies that demonstrate an association between AKI-CKD use retrospective methods and clinically available creatinine values to ascertain CKD status. However, this is a high-risk setup for ascertainment bias, in that patients who were sickest are more likely to have more health care visits and laboratory evaluation; thus, detecting an episode of CKD is more likely in the sicker patients. The choice of baseline kidney function in these studies is of critical importance;\textsuperscript{4} if outpatient progression of CKD is misdiagnosed as AKI, then the incorrect conclusion—that AKI preceded CKD—would be drawn. The use of serum creatinine to diagnose both AKI and CKD—essentially as both the exposure and the outcome—limits the ability to differentiate acute from chronic disease in a wide range of studies and settings and makes analyses of interactions between the two difficult. Although using ESRD as an outcome is more specific, relying on this outcome eliminates the possibility of investigating dose-response or understanding the magnitude of the effect of a given AKI event.

**EXPERIMENTATION**

Another method of demonstrating that AKI is causal would be to show that preventing AKI attenuates or eliminates the risk for downstream CKD or ESRD. At this point, however, no RCTs show a viable preventive strategy, so a causal association cannot be supported in this way. In fact, antipreventive withholding of beneficial agents may lead to CKD in those who experience AKI. The most important medications for prevention of renal progression are inhibitors of the renin-angiotensin-aldosterone system, but multiple studies show these medications tend to be withheld in patients with CKD.\textsuperscript{32} An episode of AKI is a likely trigger for holding an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker,\textsuperscript{33} and this failure to treat (or failure to tolerate treatment) on the basis of hypercreatinemia may itself be a cause of progression or long-term adverse outcomes.\textsuperscript{34}

**CONCLUSIONS**

In summary, more than half a million AKI events are reported each year in the United States, and most of them recover without causing long-term kidney compromise. Those without apparently normal kidney function after AKI may have had pre-existing kidney disease or other pre-existing conditions independent of the AKI-triggering factors. In many individuals, the risk factors that once predispose to an AKI event (such as metabolic syndrome, obesity, hypertension, diabetes, and cardiovascular diseases) usually continue to exist after AKI recovery and
may lead to future CKD without any causal association with the prior AKI. Although it is possible that some cases of AKI are also directly or even causally related to subsequent development of CKD, no definitive method can distinguish such a putatively causal and unidirectional association between AKI and CKD from other types of associations.

The likelihood of a causal relationship between an AKI and future CKD is further mitigated if the AKI recovers fast, with ensuing near-normal to normal kidney function. Prospective studies or clinical trials using more detailed assessment of kidney function with comprehensive ascertainment in patients with and those without AKI and better measures of comorbid disease severity would provide important evidence for this important question. Until then, we believe AKI is guilty only by association.

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DISCLOSURES

K.K.Z. has served as an expert witness in legal proceedings that pertain to the role of AKI as a cause of CKD.

REFERENCES


See related editorial, “Yes, AKI Truly Leads to CKD,” on pages 967–969.