# Persistent Acute Kidney Injury*

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One of the more challenging aspects for the study and clinical evaluation of acute kidney injury (AKI) is the fact that initially, dysfunction is indistinguishable from a normal decrease in function in response to a number of abnormal clinical states (e.g., hypovolemia and hypotension). Indeed, even a normal stress response may result in transient oliguria. The problem for the clinician is to distinguish a physiological reduction in kidney function from a pathological state. Importantly, even when there is no pathology in the kidney per se, this does not necessarily make the condition benign. Analogous to pulseless electrical activity in a patient with a normal myocardium, the loss of function will nevertheless be fatal if not corrected. While a cardiac arrest will be fatal in just a few minutes, "renal arrest" (i.e., anuria) requires days—but the condition is fatal nonetheless. As far back as ancient times, it was appreciated that an "empty bladder" was a fatal disease although it was not until Galen who established the kidneys as the source of the problem (1).

Over the last decade, the definitions and staging criteria for AKI have been standardized (2–4) and operationalized for clinical management (4). They have formed the basis for quality improvement programs (5) and for biomarker development and registration (6, 7). Importantly, these definitions do not differentiate, in any systematic way, pathologic from "physiologic" decreases in renal function. The reasons for this are partly pragmatic, there are no gold standards for ensuring adequate resuscitation for example, and partly because even mild (8) or transient (9) AKI carries a hazard for long-term outcome.

Staging criteria have also been agnostic to the underlying cause of AKI, assigning a function-based stage without regard to the etiology. This too may be justified by the fact that in critically ill patients, the cause of AKI is usually multifactorial. Traditional approaches to acute alterations in kidney function were developed long before AKI was an established entity and certainly before any standardization in the criteria for diagnosis. These approaches emphasized a quasi-anatomic nomenclature, pre-, intra-, and postrenal as a way of organizing the differential diagnosis. The approach is "quasi-anatomic" because apart from postrenal (i.e., obstructive), the terms do not actually mean very much. For example, "prerenal" can mean low circulating blood volume and hypovolemic shock but can also mean reduced renal perfusion due to intra-abdominal hypertension. "Intrarenal" might refer to glomerular nephritis, but it might also be tubular ischemic injury after aortic cross-clamping in vascular surgery—a decidedly "prerenal" mechanism. The terms do not guide management either because there is no single therapy for intrarenal AKI or prerenal AKI might indicate the need for fluid resuscitation (hypovolemic shock) but equally might indicate the need for fluid removal (right ventricular failure). In an age where the term "AKI" has displaced terms such as "acute renal failure" or "acute tubular necrosis" and standard criteria have superseded vague clinical constructs, the concepts of "transient" and "persistent" AKI are probably more useful than pre- or intrarenal.

The importance of time as another dimension of AKI along with severity was first observed by Coca et al (10), who demonstrated that duration of AKI based on creatinine following surgery was independently associated with subsequent outcome. Earlier this year, we reported results of an analysis involving more than 32,000 patients admitted to one of eight ICUs at a single medical center during an 8-year period (July 2000–October 2008) (9). It was clear from our analysis that AKI persistence has a substantial influence on outcome. For example, 4 days at stage 3 (by serum creatinine) AKI results in an approximately 30% rate of death or dialysis at 1 year. It requires more than a week at stage 1 to incur the same hazard. Persistence of oliguria is more constrained because after 3 days almost all patients resolve, die, receive renal replacement therapy, or develop significant azotemia. Nevertheless, even over 3 days, one can observe an effect of duration on outcomes independent of stage (9).

On this backdrop, in this issue of *Critical Care Medicine*, Perinel et al (11) studied 283 patients with AKI admitted to one of four University hospital ICUs in France. They defined persistent AKI as absence of recovery within 3 days, and they defined recovery as resolution of oliguria (without diuretics) and return to baseline serum creatinine (or a 50% reduction). One hundred seventy-five patients (62%) had persistent AKI according to these definitions. They did not report on a requirement for recovery to be sustained, but otherwise their criteria were reasonably strict and consistent with published recommendations (12). Patients with persistent AKI were more severe and more likely to die prior to hospital discharge (39% vs 30% for transient AKI). Persistent AKI remained associated with hospital mortality after adjusting for severity of illness (odds ratio, 0.58; 95% CI, 0.36–0.95). It was no longer significant in a model that included severity of AKI, but this was likely a function of the relatively small sample size because

*See also p. e269.

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**TABLE 1. Kidney DAMAGE–An Approach to Patients With Persistent Acute Kidney Injury**

| Goal | Recommendations | Comment |
|---|---|---|
| Determine etiology | Evaluate for ongoing drivers of injury (e.g., sepsis and drugs)<br>Consider less common causes of AKI (e.g., vasculitis and interstitial nephritis)<br>Consider kidney biopsy<br>Nephrology consultation | Persistent AKI is more likely to be due to conditions that are less easily reversed (e.g., sepsis) or have not been recognized (e.g., drug induced and cardiorenal) |
| Avoid further injury | Avoid unnecessary nephrotoxic drug and IV radiocontrast exposure<br>Consider patient location that minimizes risk (e.g., ICU vs ward) | New nephrotoxic drug and radiocontrast exposures as well as fluid overload or hemodynamic instability may result in further kidney injury |
| Monitor | Serum creatinine (daily)<br>Urine output<br>Consider hemodynamic monitoring | Monitoring is helpful to assess not only recovery but also fluid balance and in select patients, cardiac function |
| Adverse drug events | Adjust medication selection and dosing | Not only are drugs important potential causes of persistent AKI but drugs may need to be changed or dosed differently in these patients |
| Goals of treatment | Assess treatment goals with respect to dialysis and other therapy | Patients with persistent AKI may ultimately require dialysis or other life support—a reassessment of goals and preferences may be warranted |
| Ensure follow-up | Assess renal function within 30 d<br>Assess cardiovascular risk<br>Monitor/treat hypertension | Patients with persistent AKI, especially those without recovery at discharge are at high risk for chronic kidney disease and for cardiovascular events |

AKI = acute kidney injury.

other studies have found an independent association between AKI duration and outcome (9, 10).

Interestingly, patients with persistent AKI more frequently exhibited concomitant creatinine elevation and oliguria compared with patients with transient AKI (30.3% vs 13.0%; $p < 0.0001$) and as per other studies, underscores the importance of urine output measurement in the evaluation of AKI (9, 13).

Based on these observations, the authors argue that persistent AKI could be a relevant endpoint for future studies. I would agree with this and argue one step further that we should target persistent AKI for clinical management. While AKI that rapidly resolves still has worse outcome compared to patients without AKI, the outcomes are far better compared to persistent AKI. There are a number of things that could be done, both from a diagnostic and management perspective, for these patients. **Table 1** provides a list of potential considerations—grouped under the acronym DAMAGE. Although these recommendations are derived mainly from clinical experience and common sense, they could serve as a trail to be followed, improved, strengthened, and eventually transitioned to a well-paved road.

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