VIEWPOINT

Progress in Prevention and Treatment of Acute Kidney Injury
Moving Beyond Kidney Attack

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In 2012, in an attempt to raise awareness about acute kidney injury (AKI), the term *kidney attack* was suggested,[1] given the widespread familiarity with terms such as heart attack (for myocardial infarction [MI]) and brain attack (for stroke). Lay terms, including the word *attack*, convey a sense of urgency and importance, which may have been lacking in conversations about AKI. The lack of understanding and focus on AKI may have contributed to lack of progress in improving outcomes. The gradual rather than sudden development of AKI, compared with the sudden onset of readily recognizable signs and symptoms that often characterize MI and stroke, may explain lack of uptake and adoption of the term *kidney attack*.

Nonetheless, the evidence is clear: AKI is common, with a yearly incidence of approximately 6800 per million population,[2] and it is now estimated to exceed the yearly incidence of MI (approximately 6000 per million population). AKI is also associated with a substantial increase in hospital mortality, with as much as a 7-fold increased mortality risk compared with patients without AKI.

However, care for patients with AKI has varied across centers. In 2012, clinical practice guidelines on AKI were developed by an international panel of experts (the Kidney Disease: Improving Global Outcomes [KDIGO]), which sought to standardize clinical care but noted insufficient evidence for many recommendations. Based on available evidence, a number of steps were proposed to improve care[1] (**Table**). Today, several of these actions have occurred, and the available evidence, although not all conclusive, supports each of them.

> Progress over the last 6 years has demonstrated that acute kidney injury can be successfully addressed; the need now is to expand and accelerate this work.

For example, single-center studies have tested care bundles based on the KDIGO AKI guideline. In a study of 276 patients undergoing cardiac surgery, Meersch et al[3] found a 16.6% absolute risk reduction (ARR) (95% CI, 5.5%-27.9%; *P* = .004) in AKI from 71.7% without use of the bundle to 55.1% with the bundle. In a study of 121 patients undergoing general surgery, Gocze et al[4] did not detect a significant difference in AKI rates between patients receiving the bundle (31.7%; 19 of 60 patients) and standard care (47.5%; 29 of 61 patients) (*P* = .08), but moderate to severe AKI was reduced to 6.7% (4 of 60 patients) receiving the intervention compared with 19.7% (12 of 60 patients) (*P* = .04; odds ratio [OR], 3.4 [95% CI, 1.04-11.3]).[4] Importantly, both studies[3,4] used a biomarker of kidney stress (the urine concentration of tissue inhibitor of metaloprotinases-2 multiplied by insulin-like growth factor binding protein 7, [TIMP-2] × [IGFBP7]) to enrich the population receiving the intervention, which focused the studies on patients at greatest risk. Clinical enrichment strategies were also key to the success of a novel intervention to induce self-protection of kidney cells. In a trial of 240 patients, Zarbock et al[5] reported that remote ischemic preconditioning showed a significant reduction in AKI (37.5%) compared with controls (52.5%; ARR, 15% [95% CI, 2.6%-27%]; *P* = .02), whereas larger trials in unselected patients showed no benefit with ischemic preconditioning.

Even when AKI cannot be predicted, early detection appears to confer benefit. In a before-and-after study design that included more than 500 000 patients, detection of in-hospital AKI increased and hospital mortality decreased following implementation of a computer decision support system.[6] The crude mortality rate declined from 10.2% before implementation to 9.4% afterward (OR, 0.91 [95% CI, 0.86-0.96]; *P* = .001) among patients with AKI but did not change among patients without AKI (from 1.5% before implementation to 1.4% afterward). Hospital stay and dialysis rates also decreased. The concept of an AKI rapid response team has also been proposed as a potential way to link specific actions with electronic alerts.

The importance of avoiding various nephrotoxic drugs and their combinations is receiving more attention. For example, 2 large pragmatic studies have compared 0.9% saline to crystalloids with more physiological chloride concentrations for intravenous fluid therapy.[7,8] Together, these studies included nearly 30 000 patients, and both studies found reduced rates of major adverse kidney events (death, dialysis, or persistent kidney dysfunction) when alternatives to saline, such as lactated Ringer solution or PlasmaLyte, were used (ARR≈1% in both studies). Importantly, these are all patient-centered outcomes, and because virtually all patients admitted to hospitals receive intravenous fluids, the effect on public health is substantial.

In addition, when patients develop severe AKI, they may receive dialysis. Although the time to initiate dialysis remains controversial, good evidence indicates that receipt of dialysis at an earlier stage of AKI is associated with better outcomes compared with receipt at a more advanced stage. Zarbock et al[9] reported that early

Table. Proposed Steps to Improve Outcome for Patients With Acute Kidney Injury[a]

Domain	Related Actions	Comments
Risk assessment	Identify patients at risk for acute kidney injury	Several risk factors are already established
	Develop preventive strategies	Preventive strategies have been tested—enrichment is key
Early detection	Identification of subclinical prodromes	More frequent monitoring of kidney function is possible
	Monitoring of kidney function injury/stress biomarkers	Computer decision support and biomarkers are available
Early management	Avoid nephrotoxins Avoid saline	
	Identify the cause	Causes can be identified
	Drug selection and dosing	Drug selection and dosing criteria and methods exist
		Bundles based on existing guidelines can be used
Organ support	Solute control	Level 1 evidence exists to guide dialysis intensity
	Fluid balance	Fluid overload can be addressed
	Proactive support	Timing for dialysis remains controversial, but more is known than before
Recovery	Avoid additional injury to the recovering kidney	Hypotensive episodes associated with dialysis can be prevented
	Follow up patients after recovery	Risk of continued loss of kidney function demands long-term preventive steps

[a] Updated from Kellum et al.[1]

initiation significantly reduced 90-day mortality (44 of 112 patients [39.3%]) compared with delayed initiation (65 of 119 patients [54.7%]; HR, 0.66 [95% CI, 0.45-0.97]; P = .03). However, Gaudry et al[10] found that when cases of AKI requiring urgent dialysis were excluded, randomizing patients to early dialysis initiation was not more effective than a wait-and-see approach. Mortality by day 60 occurred in 150 of 311 patients (48.5%) in the early-initiation group compared with 153 of 308 patients (49.7%) randomized to only receive kidney replacement therapy when an urgent indication arose (P = .79). Importantly only 51% of patients in this latter group received dialysis, and outcomes were best for patients who avoided dialysis entirely. Important differences between the trials include a mostly cardiac surgical cohort and continuous dialysis in the former study[9] compared mainly with patients from the medical intensive care unit and mostly intermittent dialysis in the latter study.[10] Thus, early initiation of dialysis, which risks unnecessary treatment, will not benefit all patients, whereas delayed dialysis is also potentially hazardous. This area then requires expert clinical decision making and will continue to be an active area for investigation.

The last 6 years have produced a substantial amount of research that will directly influence the likelihood of developing AKI, and it will influence the treatment for patients who develop AKI. Despite substantial progress, the number of clinical trials for prevention and treatment of AKI remains inadequate. To continue progress for treating AKI, research agencies, foundations, and industry will need to increase funding for clinical research. In particular, greater use of AKI biomarkers and automated computer alerting are needed to identify patients at risk for AKI so that interventions, including care bundles, can be implemented promptly. Clinical trials should focus on new and existing interventions for specific etiologies of AKI (eg, sepsis, cardiac surgery) rather than grouping multiple causes. Progress over the last 6 years has demonstrated that AKI can be successfully addressed; the need now is to expand and accelerate this work.

ARTICLE INFORMATION

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