A Pragmatic Step Forward: AKI and Beyond

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AKI occurs commonly among hospitalized patients and has a high associated morbidity and mortality. Developing effective interventions for preventing and treating AKI has been a major challenge. Treatments targeting specific biologic pathways have, for the most part, been unsuccessful, and as a result, management of AKI largely centers on supportive care. Specific strategies for supportive care have been recommended in consensus guidelines, but they have not been tested in rigorous randomized clinical trials.[1]

In this issue of the *Journal of the American Society of Nephrology*, Selby *et al.*[2] report the results of a multicenter, pragmatic, stepped wedge cluster randomized trial of a multicomponent supportive care intervention for AKI. The trial was conducted in five hospitals in the United Kingdom over a 27-month period, during which there were 24,059 episodes of AKI. The intervention had three components: (*1*) an electronic health record alert for AKI events as defined by modified Kidney Disease Improving Global Outcomes criteria[3]; (*2*) a care bundle for assessing and managing AKI that included evaluating volume status, optimizing BP, performing urinalysis, modifying medications, treating sepsis, and consulting nephrology or critical care specialists; and (*3*) a program to educate health care personnel about AKI. The primary outcome was 30-day mortality, and secondary outcomes included AKI progression, length of hospitalization, AKI recognition, and implementation of the care bundle components. The intervention did not reduce 30-day mortality or progression of AKI, but it reduced length of hospitalization and duration of AKI (a post-hoc outcome), and it increased the recognition of AKI by clinicians as evidenced by greater use of AKI diagnosis codes. The implementation of the care bundle was higher during the intervention periods than during the control periods but not to the extent anticipated or desired.

This trial is important for several reasons. First, it provides evidence that a supportive care intervention can provide benefit for AKI. Second, its findings will inform the design of future trials evaluating interventions for AKI. Third, it provides a proof of principle for embedded pragmatic clinical trials (*i.e.*, clinical trials that are incorporated into the routine delivery of care in complex medical settings).

The trial intervention reduced the duration of AKI and the length of hospitalization, indicating that there was benefit from a multicomponent supportive care strategy, something that has not been previously shown in a multicenter, randomized, controlled trial. When interpreting the effect of the intervention and the trial results (*e.g.*, was the trial "positive" or "negative?"), how troubled should we be by the lack of benefit on the primary outcome of mortality? It is appealing to have a primary outcome for a trial that is both important to patients and objectively ascertained—mortality certainly meets these criteria. It is also appealing to have a primary outcome that occurs frequently in the population being studied, because a high outcome event rate reduces the required sample size. In the trial conducted by Selby *et al.*,[2] approximately 25% of participants died within 30 days; thus, the primary outcome of mortality met the high-event rate criterion. However, mortality may not be the best outcome when studying hospital-associated AKI, a complex condition with multiple etiologies that is often a manifestation rather than the cause of severe illness that leads to death. Expecting an intervention directed at AKI to substantially reduce mortality may be unrealistic, and as acknowledged by the authors of this study, focusing on mortality as the primary outcome for AKI trials may lead us to miss meaningful positive effects of interventions.

This trial has importance beyond the effect of the specific intervention on AKI. As one of a small number of large, multicenter, embedded pragmatic clinical trials in nephrology, it provides a proof of principle for this approach to generating practice-informing evidence.[4,5] Embedding randomized trials into routine clinical care delivery is a critical component of a learning health care system, in which creating new knowledge is an integral part of delivering care.[6] By leveraging the clinical infrastructure, embedded pragmatic trials markedly reduce the cost of research, and because interventions are tested under the real world conditions in which they will ultimately be applied, interventions found to be effective should be readily adopted and sustained after the trial has ended. The trial by Selby *et al.*[2] was highly pragmatic: the eligibility criteria were nonrestrictive; the settings were diverse; the investigators used clinically acquired rather than trial-generated data; the intervention was implemented by clinicians rather than researchers; and by design, the intervention was tailored to fit local needs. One of the greatest challenges for embedded pragmatic trials is achieving adherence to the intervention. Lower than desired uptake of the care bundle components likely reduced the effect of the intervention in the trial by Selby *et al.*[2]

This trial may be the first in nephrology to use stepped wedge cluster randomization. Cluster randomization is often used in

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pragmatic trials to simplify implementation of the intervention by clinical personnel and reduce the likelihood of contamination across treatment arms. In stepped wedge cluster randomization, the intervention is initiated in a staggered fashion from one site to the next in a random order. The stepped wedge design allows all participating sites to have access to the intervention by the time that the trial ends, something that might be appealing to sites considering trial participation, and it facilitates post-trial uptake of interventions. When the number of clusters is not large, the stepped wedge design can reduce the effect of cluster differences on outcomes, because all clusters contribute to both the intervention arm and the control arm. The approach can also introduce challenges. For example, because the timing for moving from the control period to the intervention period is established for each cluster before the start of the trial and typically cannot be modified, lower than anticipated enrollment during a control period cannot necessarily be addressed by extending the duration of enrollment, a strategy often employed in trials that use parallel group randomization. Stepped wedge cluster randomization seemed to work well for Selby *et al.*,[2] and it is likely that their experience will be helpful to other investigators weighing the advantages and disadvantages of this approach.

Pragmatic does not mean easy, and finding effective treatments for AKI has not been easy. Willingness within the nephrology community to try and to accept novel study designs provides important opportunities to identify beneficial treatments for even our most challenging problems.

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See related article, "An Organizational-Level Program of Intervention for AKI: A Pragmatic Stepped Wedge Cluster Randomized Trial," on pages 505–515.