

Management of Acute Kidney Injury: It's the Squeaky Wheel That Gets the Oil!

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Acute kidney injury (AKI) has attracted considerable attention with the recognition that even small changes in renal function may have profound effects on major outcomes, regardless of the setting. Despite advances in diagnosis and staging of AKI (1) with emerging biomarkers informing our knowledge of mechanisms and pathways, we do not as yet know how AKI contributes to the increased mortality and morbidity in hospitalized patients. We have blamed the lack of progress in this area on the heterogeneity of the population and disease mechanisms coupled with difficulties in ascertaining the attributable risk, particularly when AKI is a component of multiorgan failure. However, several pieces of evidence now suggest that we should consider additional process of care factors that may influence a patient's course and outcomes. Data from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) audit of 564 patients who died with a diagnosis of AKI in United Kingdom hospitals revealed significant gaps in performance for management of AKI, with over 50% of cases failing to meet criteria for good care, and only 30% of those who developed AKI in the hospital meeting these criteria (2). In 12% of cases, there was delayed recognition, 29% had inadequate assessment of risk factors, and both diagnostic and therapeutic interventions were subject to poor performance in a significant number of patients. The level of prior training of the physician influenced the quality of care, and senior physicians were deemed to provide better care. Only 31% of patients were referred to a nephrologist for advice or management support, whereas an additional 20% were considered as having needed nephrology support. 21% of the referrals to nephrology were considered by the advisors to be delayed. We have previously shown in a prospective observational study that delayed nephrology consultation (>48 hours from AKI diagnosis) in patients admitted to the intensive care unit (ICU) was associated with increased mortality and morbidity (3). Similarly, Perez-Valdivieso *et al.* (4) reported that an increase of >100% in serum creatinine level at the time of nephrology consultation was associated with higher mortality and impaired renal recovery on discharge. Most recently, Ponce *et al.* (5) have confirmed these findings in 148 ICU patients with AKI at a Brazilian teaching hospital. Nephrology consultation

was delayed (≥ 48 hours) in 62.3%, which was associated with increased ICU mortality (65.4% *versus* 88.2%, $P < 0.001$). These studies support the notion that early nephrology involvement in managing AKI may improve outcomes but raises several questions: what determines when a nephrologist is involved, what is the optimal time for nephrology involvement, and what is the nephrologist's role?

The study from Meier *et al.* (6) in this issue of *CJASN* provides additional information on some of these issues detailing the management of AKI in a large tertiary care academic hospital in Switzerland. The authors characterized the care of 4296 noncritically ill patients who experienced an episode of AKI over a 5-year period, determining whether a nephrologist was involved and whether the timing of nephrology involvement correlated with outcomes. They found that 22.3% of the patients were managed without nephrologist involvement, 58.3% were seen by a nephrologist >5 days after the onset of AKI (late referral), and the remaining patients were seen within 5 days (early referral). No or late referral to a nephrologist was associated with higher mortality, dialysis requirement, and worse renal outcome. Although patients with early referral were younger and had fewer co-morbidities, these factors did not mitigate the relationship of timing of referral with outcomes on multivariate analysis.

In hospitalized patients with AKI, nephrologists are generally involved only by invitation. Although 77.7% of the patients in the Meier study were seen by nephrologists, other studies have ranged from 29% to 58% for non-ICU and ICU patients, respectively (5,7). These differences probably reflect a variety of factors. Ali *et al.* (7) showed in a population-based analysis of 562 patients with AKI in Scotland that only 29% of patients were referred to nephrology. However, in those with creatinine values >3.4 mg/dl, over 49% were referred. Contrary to what one might expect, older patients with multiple co-morbidities, particularly those with congestive cardiac failure, nonhematologic malignancy, and dementia or cerebrovascular diseases, were referred less frequently. These are the very patient groups with higher risk of AKI. Meier *et al.* (6) similarly found that older patients with multiple co-morbidities also had a delay in consultation. It is difficult to ascertain whether these findings repre-

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sent gaps in knowledge, failure to recognize AKI because of lack of available data on serum creatinine and urine output or indicate that clinicians were comfortable managing the patients themselves or did not see any specific value in involving nephrologists.

An alternative intriguing possibility is that care providers are preoccupied with other vital organs such as the lung, heart, and brain as they “squeak” with their highly visible clinical manifestations and attract attention quickly. In contrast, the kidney is a silent participant, and the severity of kidney injury may be masked when urine output is maintained by diuretic use, and the serum creatinine level is diluted with fluid accumulation (8,9). Indeed, in both the Mehta (3) and Ponce (5) studies, delayed referral was associated with nonoliguria states and lower creatinine levels, reflecting dilution by fluid accumulation with an underestimation of severity of AKI. In a sense, these factors “distract” the clinician from the kidney and may give a false sense of security. Prior knowledge of a patient’s renal functional status appears to play a role in defining nephrology referral. In the Ali study (7), patients who had a known baseline value were much more likely to have an early referral. Similarly, data from the Project to Improve Care in Acute Renal Disease (PICARD) study showed that patients with a known history of chronic kidney disease (CKD) were much more likely to consult a nephrologist up to 2 days earlier than those with new-onset AKI (10). The “label” of kidney disease attracts attention and early recognition.

Recognition of an optimal time for nephrology involvement in AKI is somewhat complex. Timing of referral to a nephrologist has been an area of intense investigation for patients with CKD, and a recent meta-analysis has clearly demonstrated that early involvement of a nephrologist in the care of CKD patients improves outcomes (11,12). Unlike CKD, where the CKD stage is a relatively easy landmark for assessing timing of nephrology referral, in AKI studies, early referral has been defined as being within 48 hours of the onset of AKI. In the Meier study (6), a 5-day interval was chosen without any clear explanation for the choice, and it is unknown whether the authors would have had similar results if they had used a 48-hour time window. I believe that defining what is early (or appropriate) *versus* delayed should reflect not only the time point of initiation of AKI but an assessment of the underlying severity stage of AKI and its consequences on other organ function. It is now well recognized that AKI contributes to risk for sepsis and fluid accumulation (13,14). In the Meier study, incidence of wound infection was greater in late referral *versus* non-nephrology *versus* early. Thus, the effect of early nephrology intervention may simply be surrogate for earlier recognition of the consequences of AKI. Certainly the availability of emerging biomarkers in AKI will improve our ability to characterize the stage of AKI and whether it is progressing or not (15,16).

Finally, what is the role of the nephrologist in managing AKI? In the NCEPOD study, the quality of care was considered to be good in 69% of patients who were referred to nephrologists in a timely manner and for whom the advice given was appropriate (84%). More recently, a small randomized trial compared a single early nephrology inter-

vention within 18 hours of onset of AKI (serum creatinine change of >0.3 mg/dl) *versus* a control population who were consulted as usual showed that only 10.6% of the control patients were consulted (17). The intervention focused on a standardized protocol-driven approach-specific diagnostic, therapeutic, and preventative measures (identify risk factors, pharmacovigilance and dose adjustments of diuretics and angiotensin-converting enzyme/angiotensin receptor blocker agents, prophylaxis for contrast agents, *etc.*) and was associated with a significantly lower percentage of patients with an increase in creatinine to >2.5 times their baseline in comparison with controls. Although this study has several limitations, it adds to the knowledge that process of care interventions may have a significant role in managing AKI.

Given what we know now, what are the next steps? We need to develop a comprehensive program to raise awareness of AKI to educate all caregivers, including nephrologists, utilizing a multitude of platforms for disseminating information. Guidelines for management of AKI have been developed by the Kidney Disease: Improving Global Outcomes (KDIGO) group and will be published shortly. These guidelines could be utilized in conjunction with the recommendations from NCEPOD adapted for the U.S. healthcare system. It is evident that we must develop a team approach to manage AKI and conduct additional studies to demonstrate the value of process of care interventions in AKI. I strongly believe we must give the injured kidney a “voice” it should not need to “squeak” to be heard.

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Disclosures

None.

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