

# The Nexus of Acute Kidney Injury, Chronic Kidney Disease, and World Kidney Day 2009

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**A**cute kidney injury (AKI) is a devastating disease that affects patients throughout the world and is associated with high morbidity and mortality. It has been traditionally thought that patients who do survive recover renal function; however, recent population-based evidence strongly suggests that this may not be the case in many instances. New data suggest that a strikingly large percentage of patients who have AKI require permanent renal replacement therapy or do not fully recover renal function, and that this population has an important and growing impact on the global epidemiology of chronic kidney disease (CKD) and end-stage renal disease (ESRD).

World Kidney Day is a campaign to increase global health awareness of the importance of CKD. This campaign, representing a joint initiative of the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations (IFKF) will be held on March 12, 2009 and will be celebrated in more than 100 countries and on six continents. The impetus for this campaign is to increase public awareness of the burgeoning impact of CKD and ESRD to global health. By some estimates based on the Kidney Disease Outcome Quality Initiative (K/DOQI)-defined stage 1 to 4, approximately 13% of the world population may have CKD (1,2). Current estimates suggest that 1.6 million individuals worldwide undergo maintenance dialysis; however, many developing countries remain without adequate access to renal replacement therapy (3). In the United States, 0.5 million patients were treated for ESRD (with dialysis or kidney transplantation) in 2005, a number which is projected to increase to 0.7 million by 2015 (4). Although nephrologists collectively expend considerable effort attempting to attenuate the progression of CKD with a variety of therapeutic strategies, only a small fraction of patients with CKD progress to ESRD because death from other causes, including cardiovascular disease, is far more likely, and the path toward progression is highly variable. Given recent evidence suggesting that episodes of AKI may not only result in high

rates of in-hospital mortality, but may also contribute to the burden of ESRD, either via nonrecovery (with ongoing need for dialysis) or via accelerated progression of CKD (5), AKI should be a fundamental part of World Kidney Day to increase awareness of its contribution to the world-wide problem of CKD and ESRD.

## The Global Problem of Acute Kidney Injury

A recent review of the world literature on AKI outlines potential similarities and differences among developed and developing countries (6). While community-acquired AKI occurs with variable frequency in developed countries, AKI is more consistently caused by community-acquired diseases in developing countries. For example, in Latin America, transmissible diseases such as malaria, cholera, leptospirosis, enterocolitis, and dengue, as well as exposure to animal venoms, are considered the foremost causes of AKI in small cities and in the countryside. In sub-Saharan Africa, HIV-associated AKI as well as malaria and diarrheal diseases are responsible for a large fraction of cases. In Asia, community-acquired AKI in otherwise healthy individuals is common, and the population is younger compared with its counterparts in Europe and North America. The etiologic spectrum across Asia includes infectious diseases, intravascular hemolysis caused by glucose-6-phosphate dehydrogenase deficiency, poisonings caused by industrial chemicals or copper sulfate, animal venoms, natural medicines, heat stroke, and complications of pregnancy. Several factors account for the high incidence and mortality of community-acquired AKI in developing countries. These include the lack of affordable community-wide preventive and treatment measures (*e.g.*, intravenous volume expansion in the case of infectious diseases), which causes patients to present late for treatment, often with multiorgan involvement and increased morbidity and mortality. Moreover, hemodialysis and related methods of renal support are not universally available in developing countries.

In the developing world, hospital-acquired AKI is generally restricted to densely populated cities, and results are similar to those observed in the United States and Europe. Interestingly, mortality rates associated with hospital-acquired AKI in developing countries appears somewhat lower than in developed

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countries (between 10% and 40%), perhaps owing to younger age, the spectrum of underlying disease, and/or differences in reporting (6). Because the costs of dialysis are prohibitive to most of the developing world, current efforts should be directed at public health programs aimed at enhancing nutrition and reducing infectious disease, and prompt and aggressive fluid resuscitation strategies to reduce morbidity associated with prerenal azotemia. Thus, although there are similarities and differences in AKI among developed and developing countries, the magnitude of the problem and its impact on global health care is increasingly evident.

### Chronic Kidney Disease Predisposes to AKI

Previous studies have shown that pre-existing kidney disease is one of the most important predictors of an acute decline in kidney function after exposure to radiocontrast agents, major surgery, and other medical conditions. A recent study examined the association between baseline kidney function and the risk of hospital-acquired AKI (7). Adults enrolled in an integrated health care system were followed during the period of 1996 to 2003; 1764 developed hospital-acquired AKI and were treated with dialysis. These patients were compared with more than 600,000 patients who were hospitalized but did not develop AKI requiring dialysis. All cases and controls had outpatient serum creatinine measurements before hospitalization. Of 1746 cases of dialysis that required AKI, 74% occurred among patients with an estimated GFR  $<60$  ml/min/1.73 m<sup>2</sup>. There was a graded inverse association between baseline eGFR and the risk of AKI, ranging from a two-fold increase among patients with eGFR 45 to 59 ml/min/1.73 m<sup>2</sup> to a 40-fold increase among patients with eGFR  $<15$  ml/min/1.73 m<sup>2</sup>. Thus these data and data derived from other studies strongly suggest that underlying CKD maybe the single most important risk factor for AKI.

### AKI Increases Risk of CKD and ESRD

The natural history of AKI in patients who survive AKI is illustrated in Figure 1, which attempts to merge existing pathophysiological concepts (8) with emerging data on the progression of renal injury after AKI. Renal function in patients who survive an episode of AKI may have several different outcomes: (1) full recovery, (2) incomplete recovery resulting in CKD, (3) exacerbation of preexisting CKD accelerating progression to ESRD, and (4) nonrecovery of kidney function leading to ESRD. Several factors taken together suggest that AKI is an important contributor to CKD and ESRD. First, using the Nationwide Inpatient Sample, a nationally representative sample of discharges from acute-care, nonfederal hospitals, Waikar *et al.* found that over 1988 to 2002, the incidence of AKI not requiring and requiring dialysis (per 100,000 population) rose from 61 to 288 and 4 to 27, respectively (9). Over the same period, in-hospital mortality in patients with AKI declined steadily (40.4% to 20.3%;  $P < 0.001$ ). This information suggests that more patients have AKI and fewer are dying, factors that could contribute to the increase in the ESRD population. Second, despite the increase in incidence of AKI, there is evidence, albeit controversial, suggesting that the prevalent CKD popu-

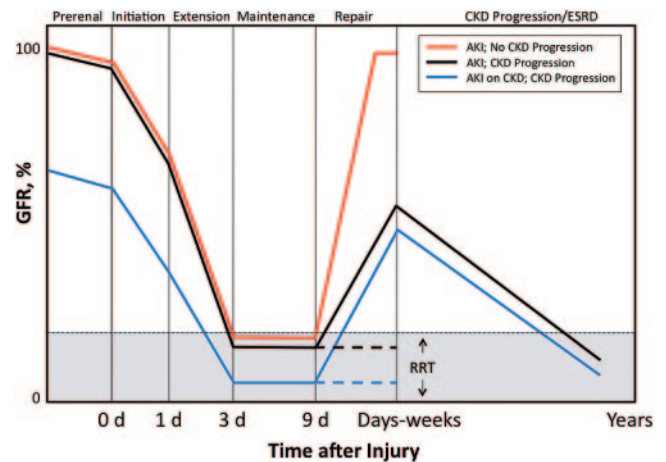


Figure 1. Natural history of acute kidney injury (AKI). The phases of AKI have previously been described by Sutton *et al.* (8). We now expand the concept to include progression to CKD/ESRD as an additional phase of AKI. Patients who survive AKI can have several different outcomes: (1) full recovery (red line), (2) development of AKI leading to CKD/ESRD (black line), (3) exacerbation of preexisting CKD leading to CKD/ESRD (blue line), and (4) nonrecovery of AKI leading to ESRD (dashed lines).

lation (stage 3 and 4) has not materially changed over time. Hsu *et al.* recently integrated data from prevalent CKD population and incident AKI population estimates from 1988 to 2002 (10). The calculated incidence of ESRD from AKI survivors (per 100,000 population) increased from 0.4 to 4.9 (a difference of 4.5) and the incidence of ESRD from the U.S. Renal Data System (USRDS) increased from 16 to 34 (a difference of 18). Thus, the potential fraction of the increase in ESRD incidence attributable to AKI was estimated to be 25%.

Ishani *et al.* used a 5% random sample of Medicare beneficiary claims from CMS and the ESRD database from the USRDS and studied a cohort of 233,803 patients who were hospitalized in 2000 with a discharge diagnosis of AKI (11). The likelihood of initiating ESRD treatment after AKI is shown in Figure 2 for CKD only, AKI only, and AKI and CKD compared with a group with no AKI or CKD. Patients with AKI only were 54% more likely to develop ESRD than patients with CKD only. Interestingly, when patients had AKI superimposed on CKD, the likelihood of developing ESRD was greater than the sum of the two.

Evidence for the important contribution of AKI to CKD/ESRD is not limited to adults. In a recent study,  $>50\%$  of pediatric patients showed evidence of progressive kidney injury (hypertension, microalbuminuria, and hyperfiltration) within 3 to 5 yr of an initial episode of AKI (12); longer-term mortality rates were also increased. Taken together, AKI affects both the adult and pediatric population and leads to CKD and ESRD.

In summary, population-based evidence strongly suggests an important and growing role of AKI in the global epidemiology of CKD and ESRD. Increased awareness at the World Kidney Day of the bidirectional relation between AKI and CKD

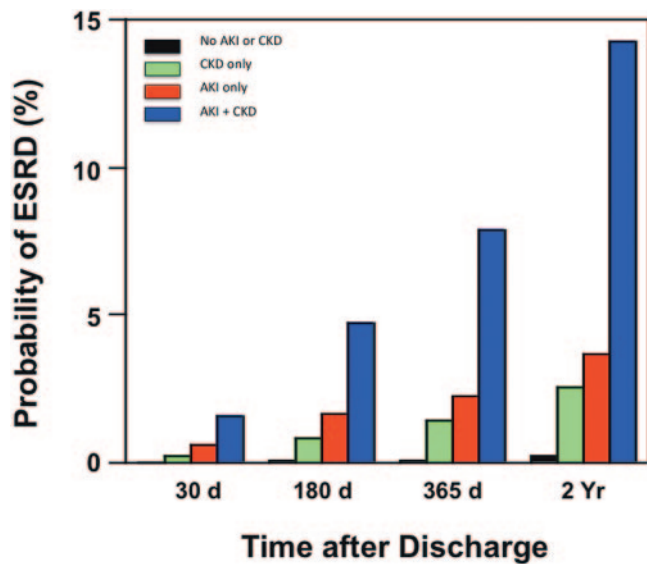


Figure 2. Likelihood of initiating ESRD treatment after acute kidney injury (AKI). The likelihood of initiating treatment for ESRD after surviving AKI was estimated from a 5% random sample of Medicare beneficiary claims from CMS and USRDS. A cohort of 233,803 patients hospitalized in 2000 with a discharge diagnosis of AKI was included in the study; ESRD information was obtained from the ESRD registration during the 2-yr follow-up (data from 11).

(AKI  $\leftarrow$   $\rightarrow$ CKD) and progression to ESRD should lead to improved worldwide care of patients with kidney disease.

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#### Disclosures

None.

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