Where Is the Epidemic in Kidney Disease?

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There has been much discussion lately regarding the epidemic of kidney disease, mostly focusing on chronic kidney disease (CKD) and end-stage renal disease (ESRD).1,2 Much less attention has been paid to acute renal failure (ARF)/acute kidney injury (AKI). But this imbalance may not be justified on the basis of careful review of the epidemiologic evidence.

ESRD

According to the latest U.S. Renal Data System (USRDS) Annual Report, the annual incidence of ESRD in the United States is 354 per million person-years in 2007 (adjusted for age, gender, and race), representing a slight drop from the prior year. This secular trend is quite different from that observed in the 1980s and 1990s when the incidence of ESRD increased at a rapid rate. In fact, the adjusted incidence of ESRD has more or less reached a plateau in the 7 prior years (Figure 1).3 The corresponding unadjusted incidence rates are 334.2, 338.2, 342.8, 347.1, 353.8, 364.7, and 361.0 per million person-years in 2001, 2002, 2003, 2004, 2005, 2006, and 2007, respectively,4 which represents an increase of about 1% per year.

It is notable that this slow growth in ESRD incidence is observed despite the fact that mean serum creatinine at the start of renal replacement therapy has dropped substantially in the past decade (Figure 2). This secular trend is almost certainly due to changes in practice pattern and more liberal initiation of dialysis, and hence would increase the number of ESRD patients even if there were no change in the underlying burden of kidney disease in the population.

The encouraging flattening of incidence in ESRD may reflect success in retarding the progression of CKD with more aggressive control of BP and use of drugs that block the renin-angiotensin system.3 Improved glycemic control among patients with diabetes mellitus may also be contributory. The effect of such treatment is illustrated by a Finnish study that tracked outcome among patients with type 1 diabetes over several decades. In that study, those diagnosed in 1980 through 1999 has less than half the risk of developing ESRD compared with those diagnosed in 1965 through 1969.6

The stabilization of incidence of ESRD reported by the USRDS is consistent with data from other national ESRD registries such as Canada7 and the United Kingdom.8 This favorable trend in disease incidence rates in the United States, however, may not be apparent when data are presented as incidence count (Figure 3) since the absolute number of new ESRD patients will continue to increase because of increasing growth of the population even if incidence rate were held constant.

Stabilization is also not obvious when prevalence rate of disease is reported (Figure 4) because disease prevalence (number of patients living with the condition) depends not only on incidence (number of new cases) but also on survival after disease onset,9 which is influenced by factors such as availability of transplantation.10 Although annual mortality rate is still high in the United States,11 survival has improved for both dialysis and transplant patients; this will increase the prevalence of ESRD.

The bottom line for ESRD: The population incidence of ESRD is increasing slowly by only 0 to 1% per annum in recent years. Secular trends in incidence rates should be distinguished from secular trends in absolute counts or prevalence rates.

CKD

The best national level data regarding CKD epidemiology come from the National Health and Nutrition Examination Surveys (NHANES) in the United States, which provide data on disease prevalence. There are few reliable estimates of the incidence of CKD and no reliable data regarding temporal changes in CKD incidence.
With use of data from the 1999 through 2004 NHANES, a widely quoted paper estimated that, among adults, the prevalence rate of CKD stages 1 to 4 was 131,000 per million persons (13.1%). This translated into an absolute number of 26.3 million individuals, or 2 orders of magnitude larger than the absolute number of incident ESRD patients in 2004. In addition, this paper reported that stages 1 to 4 CKD prevalence increased from 10.0% based on 1988 through 1994 NHANES III to 13.1% based on the 1999 through 2004 NHANES. However, accurately defining secular trends in CKD prevalence is difficult because of calibration problems with serum creatinine measurements. In the past 2 decades in NHANES, serum creatinine measurements were done in several different laboratories using different methodologies that introduce systematic biases (Figure 5). NHANES made substantial efforts to standardize serum creatinine measurements to traceable gold standards. To do this, it was necessary to multiply the original 1988 through 1994 serum creatinine values by 0.960 and subtract 0.184 mg/dl; it was necessary to multiply the original 1999 through 2000 serum creatinine values by 1.103 and add 0.147 mg/dl; values from 2001 through 2004 were left unchanged.

After these maneuvers, it was found that for young participants (20 to 39 years) without diagnosed hypertension or diabetes—presumably a healthy stratum of the population—serum creatinine levels were 0.04 mg/dl lower in 1988 through 1994 than in 1999 through 2004 (P < 0.001). This could very well represent residual calibration error. A conservative trend analysis that factors in such potential assay drift eliminated almost all of the apparent increase in prevalence of CKD from 1988 through 1994 to 1999 through 2004.

Further evidence that estimates of CKD prevalence in NHANES over time have been confounded by creatinine calibration problems comes from an analysis in which cystatin C was used instead of creatinine to quantify renal function (Figure 5). This cystatin C–based analysis shows that there is in fact no change in CKD prevalence from 1988 through 1994 to 1999 through 2004.

The bottom line for CKD: Creatinine calibration issues confound the best data regarding temporal trends in disease prevalence. Plausible range of change in CKD disease prevalence varies from 0% per year to at most 3% per year.

**ARF/AKI**

The systematic study of population epidemiology of ARF/AKI is relatively new. ARF/AKI clearly associates with in-
creased mortality,19 particularly in the elderly,20 and may depend on the day of the week and the size of the hospital providing care.21 Many prior studies were limited as they were based on hospitalized patients or patients in the intensive care unit (ICU).22–28 The denominator in these studies is often hospitalization or ICU admission, which is suboptimal because rates of hospitalization or ICU admission per population are not defined and vary across time and place. For example, one study found among patients from Tufts-New England Medical Center in Boston from 1978 through 1979 that the incidence of AKI was 4.9% per hospitalization.22 Applying the identical criteria to patients admitted to Rush Presbyterian-St Luke’s Medical Center in Chicago in 1996, the same investigative team found that the incidence of AKI was 7.2% per hospitalization.23 However, it is not possible to determine how much of this change is influenced by variation in threshold for hospital admission compared with underlying changes in the incidence of AKI.

Results from different population-based studies conducted over the past couple of decades hint that the population incidence of ARF/AKI has increased substantially.27–29 An analysis of a nationally representative database of hospitalizations in the United States show the incidence of dialysis-requiring ARF rose from 40 per million person-years in 1988 to 270 per million person-years in 2002.30 A question is whether this increase in incidence of dialysis-requiring ARF is simply a result of secular changes in practice pattern, particularly initiating dialysis earlier in the course of AKI.31,32 One study of a large integrated healthcare delivery system in northern California (Kaiser Permanente) provides good evidence against this. Between 1996 and 2003, the population incidence of dialysis requiring ARF/AKI within Kaiser Permanente increased from 195 to 295 per million person-years (Figure 6).33

There was a parallel increase in the incidence of non–dialysis-requiring AKI from 3227 to 5224 per million person-years (Figure 6).33 Thus, the increase in incidence of dialysis-requiring ARF does not appear to be simply due to more aggressive and earlier initiation of dialysis for patients with AKI.

The exact reasons for the increasing incidence of AKI are unclear. This may be due to increase in the incidence of sepsis,34,25 a dominant risk factor for AKI.26 In addition, there has also been more use of invasive procedures, which are nephrotoxic, such as cardiac catheterization.36–38

The bottom line for ARF/AKI: In the past 2 decades there has been a rapid increase in the incidence of dialysis-requiring ARF, >7% per year.

CONCLUSIONS

To summarize, for ESRD requiring renal replacement therapy and ARF/AKI requiring dialysis, the population incidences are actually similar—343 versus 295 per million person-years in 2003, the latest year where there is overlapping data. But incidence of ARF/AKI is rising at a much higher rate than the incidence of ESRD (>7% per year versus 0 to 1%). The high mortality of patients with incident ESRD is well-known (24% per year).4,11 But the mortality rate of patients who developed dialysis-requiring ARF/AKI is even higher, being approximately 28% in the hospital,39 and on the order of 10% per year after hospital discharge (Table 1).39,40 To date, most discourse regarding the global burden of kidney disease has not included the epidemic of ARF.41–43 I hope future discussions in this area will be more balanced and reflect the actual distribution of kidney disease and its public health burden in the population.
Table 1. Comparing kidney disease “epidemics”

<table>
<thead>
<tr>
<th>Disease Incidence (Unadjusted) in 2003</th>
<th>Trajectory</th>
<th>Annual Mortality Rate</th>
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</thead>
<tbody>
<tr>
<td>Renal replacement therapy–requiring ESRD</td>
<td>343 per million person-years</td>
<td>Annual increase of 0 to 1%</td>
</tr>
<tr>
<td>Dialysis-requiring ARF</td>
<td>295 per million person-years</td>
<td>Annual rate of increase &gt;7%</td>
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ACKNOWLEDGMENTS

Dr. Hsu has been supported by R01 DK67126, R01 DK70939, U01 DK82223, and U01 DK60902.

DISCLOSURES

None.

REFERENCES