Epidemiology and Challenges to the Management of Advanced CKD

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Advanced CKD is a period of CKD that differs greatly from earlier stages of CKD in terms of treatment goals. Treatment during this period presents particular challenges as further loss of kidney function heralds the need for renal replacement therapy. Successful management during this period increases the likelihood of improved transitions to ESRD. However, there are substantial barriers to optimal advanced CKD care. In this review, we will discuss advanced CKD definitions and epidemiology and outcomes.

Key Words: CKD, Dialysis preparation, Epidemiology

INTRODUCTION

Although advances in health care have extended the average life span, they have also generated the unexpected consequence that chronic diseases are now a common condition. It is estimated that half of all US citizens have a chronic health condition.[1] Approximately 60% of all deaths, worldwide, are related to chronic conditions. This number is expected to increase an additional 15% by 2020.[2] Chronic diseases have a major economic impact, accounting for 83% of all US health care spending.[3] CKD is an important member of the family of chronic diseases.

Defining, diagnosing, and identifying kidney disease have always been challenging for all clinicians. A paradigm shift in the awareness of CKD and its subsequent management began in 2002 when the Kidney Disease Outcomes Quality Initiative CKD guidelines[4] were first published. The elaboration and definition of kidney disease in this model is based on kidney function irrespective of underlying diagnosis or disease type.[5] Implementation of these guidelines was the start of the progressive disease model, staging CKD from 1 to 5 as kidney function declines. Another breakthrough in management of CKD was the addition of estimated glomerular filtration rate (eGFR) reporting in most major commercial laboratories.[6] Still controversial at times, this addition has made it possible to detect kidney disease in those who are unaware that they have this condition. In addition, it has been clearly shown that there are ways to delay the progression of CKD.[7-9] For example, the sentinel report by Lewis and colleagues[10] showed that the rate of progression of diabetic nephropathy could be slowed with captopril. Since then, renin-angiotensin-aldosterone system (RAAS) blockade has become the hallmark of care for CKD patients with proteinuria. Furthermore, the use of erythropoietin-stimulating agents, vitamin D analogues, and bicarbonate have been added to our armamentarium. Indeed, delay of progression is now the cornerstone of CKD care.

Unfortunately, despite these improvements, advanced CKD has not been adequately addressed in terms of optimizing treatment plans, disease-specific outcomes, and long-term survival for this population. Advanced (or late-stage) CKD is defined as that stage of disease when eGFR is <30 mL/min/1.72m^2. In advanced CKD, one has to begin to consider that there is not as much that can be done to delay the progression of kidney disease "enough" to avoid the need for renal replacement therapy (RRT). The focus of care shifts greatly (Table 1). In addition to maintaining therapies to delay progression, care now also includes preparing the patient for RRT. Electrolyte, acid-base and mineral and bone disturbances become more pronounced and must be addressed. The burden of comorbidity and risk for hospitalization and death increase.[11] A major change in educational priorities and need for key decision-making takes prominence. It is this latter point, and the critical step of modality selection, that may play an important role in subsequent ESRD outcomes.

EPIDEMIOLOGY OF ADVANCED CKD

CKD is highly prevalent in the United States, affecting approximately 13% of the population based on the National Health and Nutrition Examination Survey 2005–2012 survey. Over time, the prevalence of more severe CKD has increased somewhat in the United States. The causes of the increase are not fully clear, but, it is likely that aging of the population and the increased prevalence of diabetes mellitus in the United States are important factors. For example, diabetes as a risk factor for advanced kidney disease has increased progressively from an odds ratio of 1.66 in 1988 to 1994 to 2.33 in 2007 to 2012.[11] It is interesting to note that hypertension has decreased as a risk factor over the same period with odds ratios, of

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3.75 to 3.17, respectively. Diabetes and hypertension frequently contribute to the development and progression of kidney disease, but, it is also important to recognize that kidney disease may make both the former entities more difficult to manage. In addition, cardiac disease is highly prevalent in advanced CKD, including coronary artery disease, congestive heart failure (CHF), and arrhythmias. Unfortunately, patients with advanced CKD or history of myocardial infarction, CHF, stroke, and coronary artery bypass surgery have a greater risk of dying than patients with earlier stages of CKD.[11] To what degree any one entity affects the other entity and to what degree these factors add to the overall disease burden are also difficult to assess. The MERENA[12] observational cohort in Spain provides an overview of the variations of clinical parameters between CKD 3 and 4 patients. Their result showed that compared with CKD 3 patients, those with CKD 4 had more cardiovascular disease, 42.2% (vs 35.6% for CKD 3) and more CHF 19.7% vs 15.1%, respectively but no differences in the prevalence of coronary artery disease, myocardial infarction, peripheral vascular disease, or cerebrovascular disease. CKD 4 patients also had more proteinuria, hyperkalemia, anemia, and secondary hyperparathyroidism than CKD 3 patients, as one would expect. However, no difference in the prevalence of hypertension between these 2 stages was found despite the fact that both the cohorts had equal percentages of patients on RAAS blockade. Diuretic use was more common in those patients with CKD 4 suggesting more overt volume expansion in this group compared with CKD 3 patients. In addition, other specific nontraditional risk factors have come to light, which include hemoglobin level, hypoalbuminemia, and elevated fibrinogen levels among other variables.[13]

CLINICAL SUMMARY

- Advanced CKD (eGFR < 30 mL/min) is a period of CKD that requires a focus on coordinated care and outstanding patient education.
- More than 500,000 patients in the United States have Stages 4/5 CKD.
- A successful transition to ESRD requires careful management during the period of advanced CKD.
- There are a number of barriers to achieving treatment goals in advanced CKD.

Another concern is that a patient's own awareness of CKD tends to be quite low. Fewer than 10% of individuals with stage 3 kidney disease by eGFR criteria are aware of possible kidney disease.[11] Among patients with Stage 4 CKD, the rate of awareness increases, but still to only approximately 50%.[11] For example, from 2003 to 2006 to 2007 to 2012, the rate of awareness of stage 4 kidney disease increased from 34.2% to 52.8%, respectively.[11] Not only is patient awareness low but referral to a nephrologist is generally low and quite variable among primary care physicians. This phenomenon is probably related to the fact that trajectories of CKD decline between patients and can be very different, and that for the elderly, there is a high likelihood that death from another cause will occur before needing RRT.[14]

VARIABILITY OF PROGRESSION

As mentioned previously, a major obstacle in the management of advanced CKD in regard to preparing for RRT is that the rate of decline in glomerular filtration rate (GFR) is highly variable between renal diagnoses, and progression is also variable among individuals with similar renal diagnoses. It also may vary by age. Suffice it to say, there is interpatient and intrapatient variability. Brussels, Demoulin and colleagues[14] evaluated factors affecting progression of disease in CKD 4 patients over a 30-month inclusion period. In this cohort, the risk of starting dialysis exceeded the risk of death before the initiation of RRT. Of interest, older patients with low-grade proteinuria were the subgroup most likely to die before requiring RRT. A reason for this observation could be that there is a risk of death in the elderly due to age alone and the likelihood of a slower rate of progression in this older group. However, the authors also emphasize that only 14% of their patients underwent futile pre-RRT advanced planning. These findings are similar to those of a study of over 200,000 elderly US veterans, which demonstrated that younger patients were at risk of reaching ESRD before death at a GFR < 45 mL/min/1.72m^2, whereas for older patients, the risk of ESRD exceeded death at a GFR of <15 mL/min/1.72m^2. For those patients aged older than 85 years, all reached death before the beginning of RRT.[15]

Others have also examined the trajectory of CKD progression in this population. Evans and colleagues,[16] in her cohort of Swedish patients, found that 10% of patients with CKD 4 or 5 die before receiving RRT, and 10% had slow enough progression that they did not reach the need for RRT during the 5-year follow-up period of the study. Likewise, O'Hare and colleagues observed substantial heterogeneity in the pattern of declining kidney function. Four patterns with different trajectories were identified and suggest that decisions regarding management and preparing for RRT should be based on eGFR, age, and trajectory of decline.[17] Finally, Sud and colleagues[18] performed a retrospective review of CKD 3 to 5 patients to estimate the risk of ESRD or death before ESRD for each stage. This study reports that death before ESRD was higher for stage 3 and lower for stage 5. For stage 4, they found the incidence of death before ESRD, and the initiation of RRT was approximately the same. In this regard, it seems clear that we need to address the modifiable risk factors earlier in stage 3 disease, and as one progresses into CKD Stage 4, these management tactics need to be appropriately adjusted to address the fact that stage 4 is a period of change "and" an ESRD end point is more likely to be reached. There will be more morbidity and mortality in this group than in earlier CKD stages. Hence, the need to prepare.

OUTCOMES IN ADVANCED CKD

As one might anticipate, the rate of death increases progressively through advancing stages of CKD. In stages 1