Introduction and Options in Therapy

*Eli A. Friedman**

At the close of 2009, as this is revised, the severity and course of progressive chronic kidney disease (CKD) is defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative[1] in five stages, with diagnostic and management guidelines for each. Based upon estimated GFR (eGFR) values calculated from serum creatinine measurements, along with determination of urine albumin concentration, the stages are (see Table 1):

- Stage 1 CKD is present when there is evidence of kidney damage with a normal eGFR.
- Stage 2 CKD is present when there is kidney damage and decrease in the eGFR to 60–89 ml/min. Stage 1 or 2 CKD may be diagnosed through hypertension, hematuria or proteinuria, or a family history of kidney disease such as polycystic kidney disease. Supernormal levels of creatinine and/or urea in the blood are common.
- Stage 3 CKD is diagnosed by a reduced eGFR of 30–59 ml/min. Anemia and early metabolic bone disease may be detected.
- Stage 4 CKD is present when the eGFR falls to 15–29 ml/min. Most patients complain of fatigue, loss of appetite, difficulty in sleeping at night, reduced concentrating ability, and a loss of sexual drive.
- Stage 5 CKD is present when the eGFR falls below 15 ml/min.

*Distinguished Teaching Professor of Medicine, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York, 11203, USA. Email: Elifriedman@aol.com

PRESENT AND FUTURE THERAPIES FOR END-STAGE RENAL DISEASE

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Table 1. Stages of Chronic Kidney Disease

Stage	Description	eGFR[a] (mL/min/1.73 m^2)
1	Slight kidney damage with normal or increased filtration	More than 90
2	Mild decrease in kidney function	60–89
3	Moderate decrease in kidney function	30–59
4	Severe decrease in kidney function	15–29
5	Kidney failure requiring dialysis or transplantation	Less than 15

[a]Estimated glomerular filtration rate — a measurement of the kidney function calculated from serum creatinine concentration.

Interpreted by George E. Schreiner, the evolution of the medical–industrial complex that provides contemporary therapy for stage 5 CKD is the result of "so few stimulating so many!"[2] The story began when Willem J. Kolff (who died in February 2009 at the age of 97), stimulated modern therapy for acute kidney failure by both application of peritoneal dialysis and fabrication of a workable artificial kidney in 1943 under the German occupation of The Netherlands.[3]

In Boston, after his return from World War II service, John P. Merrill's Peter Bent Brigham Hospital Team redesigned Kolff's artificial kidney, affirming its utility in short-term substitution for failed kidneys.[4] Subsequently, the team's kidney transplantation in monozygotic twins initiated transplant medicine as a discipline.[5] Concurrently, Schreiner at Georgetown Hospital in Washington D.C., one of the 13 founders of the American Society of Nephrology and the "handful" of people who created the American Society for Artificial Internal Organs (ASAIO), pointed out that it was the increasing success in sustaining patients of acute renal failure for six or more months that stimulated the quest for long-term uremia therapy. After Belding H. Scribner, in 1960, reported his Seattle team's ongoing life prolongation in two uremic patients by "chronic hemodialysis" via an external Teflon radial arteriovenous shunt,[6] it became starkly evident that biotechnology could substitute for loss of a vital organ system.

When Scribner showed how dialysis could pre-empt death in stage 5 CKD, nephrology did not exist as either a discipline or a specialty, though groups of investigators and clinicians around the world maintained interest in kidney function, pathology, and clinical diseases. The International Society of Nephrology (ISN), at its first meeting in Evian, France, in 1960, attracted fewer than 100 attendees. Following Scribner's impact, however, at the American Society of Nephrology's (ASN) 1966 initial meeting, held jointly with the ISN, in Washington D.C., attendance reached 3000, signaling that nephrology was here to stay. Reaction to Scribner's report in the *ASAIO Transactions* combined surprise, disbelief, and excitement. The Public Health Service rapidly funded several "demonstration centers" to authenticate the validity of the Seattle "accomplishment" and formed an expert committee to explore funding mechanisms for advancing chronic hemodialysis as a treatment available throughout America.

For undecipherable reasons, the United States Congress, after reviewing the growing number of strongly positive reports from hemodialysis demonstration projects established by the Chronic Disease Division of the Public Health Service, in 1972, selected the term "end-stage renal disease" (ESRD) for what is currently called stage 5 CKD. Collaboration between the National Kidney Foundation, the ASN, and patient activist groups was able to convince the Ways and Means Committee of Congress to amend the Social Security Act (Public Law 92-603) to extend coverage for ESRD under Medicare. Indeed, individuals eligible for Medicare because of ESRD became entitled to all benefits available under the Medicare program, not just ESRD-related dialysis and kidney transplantation. Despite appreciation of the reality that no person wants to be considered an end-stage failure in anything, the designation has persisted until today. Further amendments in 1978 (Public Law 95-292) revised Medicare rules to encourage self-dialysis and kidney transplantation.

To gain ESRD benefits, a physician must certify that the individual requires chronic dialysis or a kidney transplant to maintain life. In addition to having chronic renal failure, the person must either be

entitled to a monthly insurance benefit under title 11 of the Social Security Act (or an annuity under the Railroad Retirement Act), be fully or currently insured under Social Security (railroad work may count), or be the spouse or dependent child of a person who meets one of the previous requirements.

Medicare ESRD entitlement begins when whichever of the following is earliest:

- The third month after the month in which dialysis is initiated.
- The month in which dialysis begins if the individual participates in self-dialysis training at an approved facility and is expected to self-dialyze thereafter.
- The month of a kidney transplant.
- The month of admission to an approved hospital for procedures preliminary to a transplant, if the transplant takes place within the following two months. If the transplant is delayed by more than two months, coverage starts in the second month prior to the month in which the transplant takes place.

Medicare ESRD coverage terminates when whichever of the following is earliest:

- The day of death.
- The last day of the 12th month after ending maintenance dialysis treatments.
- The last day of the 36th month after a kidney transplant. Re-transplantation within 36 months or return to dialysis does not interrupt the entitlement.

A person whose ESRD entitlement terminates continues with the entitlement if disabled or 65 years or older.

Nephrology began as a medical specialty once it became possible to forestall death from kidney failure by the use of devices and regimens that could be passed from teacher to student. It was also true that nephrology spurred a rebirth of medical ethics as there was recognition of the limitations on delivering ESRD treatments imposed by economics and other variables enumerated in Table 2.[7]

Table 2. Ethical Stresses Induced by Ability to Extend Life in ESRD

1. Is indeterminate life extension using a machine moral?
2. Must a physician propose machine-facilitated life extension to patients at the end of life?
3. What criteria should be used to begin ESRD therapy?
   a. An arbitrary eGFR below 10 ml/min?
   b. A nephrologist's clinical judgment that treatment is indicated?
   c. The patient's request irrespective of the eGFR?
   d. A family member or legal representative's request?
4. Does society (the government) have the right or obligation to regulate life extension?
5. Should a mentally incompetent person receive life extension by dialysis if he or she:
   a. Is demented?
   b. Is psychotic?
   c. Has a low IQ?
   d. Has respiratory intubation?
6. If demand for dialysis life extension exceeds supply, should allocation be decided by:
   a. Government?
   b. Physician?
   c. Committee (hospital or community)?
   d. Ethicist?
   e. Clergy?
7. When allocating scarce resources such as deceased-donor kidneys, should priority be determined by:
   a. Individual ability to pay?
   b. Social merit?
   c. Citizenship?
   d. Race?
   e. Gender?
   f. Age?
   g. Marital status?
   h. Employment status?
8. Should government remuneration to physicians permit:
   a. Corporate ownership (for profit) of dialysis units?
   b. Physician ownership of dialysis facilities?
   c. Self-referral of dialysis patients?

(*Continued*)

Table 2. *(Continued)*

9. Must dialysis-based life extension at government expense be proscribed for:
a. Criminals incarcerated for serious crimes (murder, rape)?
b. Recidivist substance abusers (narcotics, alcohol)?
c. Persistently nonadherent patients (smokers, morbidly obese)?
d. Transplant tourists who purchased marketed organs (kidneys)?
e. Incarcerated terrorists who have injured innocent civilians?
f. HIV + persons?

Consider the extent of decisions that might be prompted by the next uremic patient entering a modern emergency room with newly recognized advanced renal failure. After life-threatening hyperkalemia, pericardial tamponade, and bleeding are managed by urgent dialysis, if appropriate, assessment of the patient must address at least some of the following issues: (1) Which form of dialysis (peritoneal dialysis or hemodialysis) should be considered for the long term? (2) Is self-care or home dialysis the preferred option? (3) How can the patient be prepared for an informed decision as to whether or not to undergo kidney transplantation? (4) For this specific patient, is a live-donor or deceased-donor kidney preferable? The list goes on, underscoring the rationale for the topics of chapters included in this text.

No universal correct answers to the complex questions posed in Table 2 may be given without reflection on a specific patient's circumstances. It is the intent of this text to ease the burden of decision by discussing the major ESRD therapies in light of who might be best for which, when. Not addressed in Table 2, however, is the sad reality that the cost of uremia therapy is beyond the majority of the world's population.[8] Neither China nor India, as examples of nations with a population of greater than 1 billion, is able to treat even 5% of its ESRD patients. Similarly, for Sierre Leone, The Congo, Chad, North Korea or Uruguay, desperate concerns over feeding people defeat any effort to construct an ESRD program. Thus, consideration of one hope for the future — administration of probiotic bacteria deploying the gut as a substitute kidney — is included as a chapter, mainly to remove limitation in thinking about how kidney failure may be treated in the near future. Willem J. Kolff, who died in 2009 at 97, did not, as

he performed the first hemodialysis using sausage casing and heparin, 55 years earlier, imagine a world in which more than 1 million people would be alive because he discerned a means of stopping otherwise inevitable deaths due to the loss of kidney function.

References

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