Dialysis: Destination or Journey

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The continued poor survival and diminished quality of life for patients treated with dialysis, particularly elderly individuals, is an important health care issue. In this issue of *JASN*, Vandecasteele and Kurella Tamura propose a change from a process-driven approach to dialysis care to one that incorporates a realistic assessment, in collaboration with the patient, of the relationship between the treatment goals and future outcomes.[1] They argue against the current culture of applying clinical practice guidelines to all patients and challenge the benefits of using biochemical surrogate outcomes. Akin to the revolutionary changes in recent guidelines on cholesterol[2] and hypertension[3] management, they propose that the renal community should change the focus from directives given to physicians to decision-making that incorporates individual patient preferences. For patients with CKD who might require dialysis, the invasive and lifestyle-changing effect of the therapy makes this drive toward improved shared decision-making imperative.

The authors propose that health care providers responsible for the care of these patients should operationalize the proposed new model of care using three patient-centric paradigms.

The first and most familiar of these paradigms is labeled "dialysis as a bridge to transplantation or long-term maintenance." Patients considered to have a good prognosis and whose goal is transplantation or long-term maintenance dialysis, preferably self-care, would be included in this group. Treatment-specific goals include adherence to stringent treatment targets, similar to those currently used, with the anticipation that this will lead to better long-term health and a sustained ability to engage in professional and private life functioning.

A second identifiable group of patients includes those with a low probability of recovering independent social functioning and those at high risk of imminent death or recurrent hospitalizations. They recommend that these individuals and their families be provided with unbiased information that would allow an informed choice between dialysis therapy and a strategy labeled "active medical management without dialysis." In practice, this strategy is most applicable to patients with severe dementia and those with poor functional status and high comorbidity. Functional status is an important marker of poor outcomes. Fewer than one third of patients undergoing dialysis and admitted to long-term hospital care ever return home.[4] Among 3702 nursing home residents in the United States, all of whom had high baseline dependency levels, dialysis initiation was associated with further significant functional decline and a 1-year mortality rate of 58%.[5] Had these elderly individuals been offered a fully informed option for maximal conservative therapy, would their outcomes have differed? The data are limited to several single-center observational studies, each with unique flaws. The largest of these, from the United Kingdom,[6] compared the survival of 29 patients (median age, 81.6 years) who chose maximal conservative therapy with that seen in 173 patients (median age, 76.4 years) starting RRT. Although the median unadjusted survival duration was only 13.9 months for the maximal conservative therapy group compared with 41.9 months for the RRT group, the former required fewer days, per patient-year survived, in the hospital (16 days compared with 25) and were four times more likely to die at home or in a hospice compared with those starting RRT.

Despite these data, it remains unclear what is "best."[7] The cultural shift within medicine toward patient-centered care[8] leaves many questions unanswered. We know little of the patients' experiences, their satisfaction with their lives, or the socioeconomic costs of nondialysis care. Some answers may be provided by an ongoing prospective observational study of dialysis and predialysis patients aged 65 years or older.[9] This study will address not only survival but also health-related quality of life, economic burden, and comorbidity.

The circumstances under which the elderly initiate long-term dialysis must also be considered. Among 416,657 Medicare beneficiaries age 67 years or older, long-term dialysis was initiated in an inpatient setting in 64.5%; most patients (96.2%) survived to discharge. The patients were divided into five groups, one with outpatient initiation and four defined according to increasing intensity of inpatient care. The median duration of survival of those initiating dialysis as an outpatient was 2.1 years compared with 0.7 years in the group with the most intensive inpatient care.[10] For many of these patients, the discussion that incorporates their preferences will occur after dialysis has been initiated in the setting of AKI.

A third paradigm proposed is "dialysis as a final destination." Although it is the most likely to be controversial, it is consistent with patient-centered care and personalized medicine. It is also widely applicable to the most vulnerable of our dialysis patients. The authors' recommendation is that

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patients who have high levels of comorbidity or unclear prognosis be managed with the understanding that they are undergoing palliative dialysis. These are patients in whom the effects of the disease and the treatments preclude them from integrating back into their social and/or professional environments and who are not eligible for a curative strategy, such as transplantation. "Dialysis as a final destination" would likely be most applicable to a heterogeneous group of individuals, including older patients with poor prognosis who have chosen a trial of dialysis and younger patients with multiple comorbid conditions. It would also include patients previously managed with "dialysis as a bridge to transplantation or long-term maintenance," who have progressive disease limiting their chances of transplantation and who are unable to resume their previous level of social functioning.

Will this allow us to change our thinking? As we have "improved care standards," have we merely been slowly substituting a treatment for a disease? In the same way patients with diabetes are rarely renamed as "insulin patients" when they initiate life-long, life-sustaining insulin therapy, perhaps we need to alter how we practice so patients initiating dialysis no longer become "dialysis patients." Can we prevent the substitution of the treatment for the disease through modifications of our targets and goals of care? The suggestions for "dialysis as a final destination" made in the authors' Table 2 are modest and argue against using interventions for which there is little supporting evidence or planned clinical trials. They propose reduced attention to protocols used to manage dysphosphatemia, glycemia control, and vascular access. Instead, they advocate the use of protocols that increase psychological support, home care support, and physical rehabilitation. Whether this would improve quality of life by avoidance of treatment-related complications or lead to worse quality of life associated with a reactive rather than a proactive but conservative strategy is unknown.

An editorial in *JAMA*[11] addresses the potential effect of the new guidelines for management of cholesterol and hypertension with the focus on personalized medicine. Three recommendations in that editorial can equally be applied to the management of CKD and dialysis through uptake of these paradigms. The next steps are less clear. As a community we need to determine whether we believe in personalized medicine and, if so, start to evolve in a new direction.

The first recommendation is that informed choice requires strong evidence that can be personalized for patients needing to make a decision. The prospective observational study proposed by Walker and colleagues[9] should provide much-needed data, particularly for those who might consider "active medical management without dialysis." Many of the clinical trials that apply to the patients in the "dialysis as a final destination" group have involved single interventions that have failed to affect survival or composite cardiovascular outcomes. This group should be the subject of additional well designed and executed trials, which would include multiple interventions.

The second recommendation is to further evolve tools to help individualize care for patients while simultaneously avoiding inferior medical care. Current tools for shared decision making are being used in other areas of medicine and have been adapted for use in the renal population.[12,13]

But the third and perhaps most important recommendation is that we strengthen the patient's voice. The James Lind Alliance[14] in the United Kingdom is foremost in leading patient-centric research initiatives. They facilitate partnerships across multiple health areas, particularly between patient and clinician, and help prioritize future research directions. In Canada, priority-setting work has started within the renal research community.[15] The top priorities include improving communication between health care providers and the patient and how different modalities of dialysis affect the quality of life of patients and caregivers. However, it remains the ongoing responsibility of health care providers to proactively engage their patients in discussions that encourage and respect the individual patient's preferences in decisions regarding their health care.

A quotation often attributed to Ralph Waldo Emerson—"Life is a journey, not a destination"—could be applied to dialysis as it is a journey and requires constant re-evaluation over time as circumstances change.

Vandecasteele and Kurella Tamura[1] are to be commended in presenting their thoughts on this subject and for framing it as a proposal that invites thoughtful discussion.

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See related article, "A Patient-Centered Vision of Care for ESRD: Dialysis as a Bridging Treatment or as a Final Destination?," on pages 1647–1651.

Soluble Urokinase-Type Plasminogen Activator Receptor in FSGS: Stirred but Not Shaken

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The soluble urokinase-type plasminogen activator receptor (suPAR) has been proposed as a candidate circulating factor causing FSGS.[1] In this issue of *JASN*, Cathelin *et al.* further examine the short-term effects of two different types of suPAR on the kidney filtration barrier.[2] Although the authors show deposition of suPAR in the glomerular capillary wall of their experimental models, they do not find changes in albumin permeability. The activation of the suPAR target on podocytes, $\alpha v\beta 3$ integrin, is not examined, leaving the question of target engagement unanswered. Nevertheless, this study provides some additional insights into the complexity of suPAR-derived signals in kidney disease and offers a potential explanation as to why patients with elevated acute phase–associated suPAR may not readily develop nephrotic syndrome.

The debate regarding the existence of a serum factor that causes FSGS is certainly glorified, heated, and polarizing. Since Shalhoub first suggested the existence of such a factor in 1974,[3] the quest to find such molecules is ongoing and is in line with the ever-growing need for definitive treatments that eradicate pretransplant and post-transplant FSGS. Savin *et al.* are credited for demonstrating that serum and plasma from patients with FSGS induce kidney filter permeability changes.[4] Savin *et al.* also proposed that the FSGS factor is a protein with a molecular mass between 20 and 50 kD.[4] Studies in our laboratory showed that suPAR is a permeability factor in native and recurrent FSGS.[1] suPAR is a multidomain protein that is heavily glycosylated and precisely fits the suggested size range expected for the putative circulating factor. The proposed pathogenic role of suPAR is based on three observations: (*1*) variants of suPAR produced proteinuria in several mouse models, (*2*) total levels of glycosylated suPAR were elevated in the majority of patients with FSGS, and (*3*) suPAR can bind to and activate podocyte $\beta 3$ integrins allowing for activation of Rac-1 and podocyte motility (a surrogate for podocyte foot process effacement).

Several follow-up studies confirmed increased total suPAR serum levels in FSGS, which were validated in patients with normal or mildly reduced renal function compared with other glomerular diseases[5] but not necessarily in advanced renal failure in which suPAR accumulation may occur.[6] Furthermore, it should be noted that in certain recent studies, serum suPAR did not differentiate FSGS from other glomerulopathies in the setting of relatively preserved renal function.[7] However, healthy control patients in this study also had elevated suPAR levels at baseline, which is atypical and might be a confounder of the cohort. Nevertheless, these discrepancies around single-value suPAR testing in different cohorts with the current ELISA imposes an obstacle for bulk suPAR measurements in clinical practice.[6] Development of a more specific FSGS-suPAR ELISA and/or cell-based testing systems that can detect different forms of suPAR with strong podocyte integrin activation capacities is needed.[8]

suPAR is the cleaved product of the cell-bound urokinase-type plasminogen activator receptor (uPAR), a multifunctional receptor that binds both the protease urokinase and the adhesion protein vitronectin.[9] uPAR also functionally and physically interacts with integrins both directly and indirectly through signaling, with the latter in some circumstances due to uPAR vitronectin binding.[10] suPAR is normally heavily glycosylated and can be cleaved into various shorter molecules that determine variability in suPAR's cell signaling function and stability in body fluids, including serum. Cathelin *et al.*

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