

# Dialysis at a Crossroads: 50 Years Later

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## Summary

The ability to offer repetitive hemodialysis for treatment of chronic kidney failure has now reached its half-century anniversary. Although millions of patients have benefited from this life-extending procedure, current results in the United States have now stagnated with only small annual improvements in survival and continued high hospitalization rates. Recognition that this stagnation may be, at least in part, the result of inadequacies of current and prior paths utilized in dialysis treatment has led to the concept that dialysis therapy is at a crossroads and that new paths need to be articulated, explored, and applied. This article proposes some of these new paths and their rationale. Two elements of the new paths are emphasized: avoidance of indwelling catheters for vascular access and meticulous attention to control of extracellular volume and mitigation of left ventricular hypertrophy and fibrosis. It is postulated that progress in these two areas, along with continued attention to other elements embodied in the new and old paths, will unlock the stagnation in outcomes of dialysis therapy of end-stage kidney failure and allow it to realize its full potential of prolonging life and alleviating disability.

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## Introduction

The prospect for survival from chronic end-stage renal disease (ESRD) was dramatically and irrevocably altered in 1960 by the development of a semipermanent vascular access device allowing repetitive treatments by hemodialysis (HD) (1). Belding Scribner and his brave patient, Clyde Shields, transformed the landscape of medical care with this landmark event. Over the ensuing 50 years, millions of patients worldwide have benefited from this life-extending therapy for irreversible kidney failure. Early on it became apparent that a key to the success of dialytic treatment of ESRD was “uremic” solute removal and the achievement of euolemia with restoration of salt and fluid balance and normotension. Yet the renal community seemed to model care almost solely on the basis of on uremic solute removal. This may reflect the increased reliance on “quantitative” metrics of uremic solute removal and unease with the subjective clinical assessment of fluid status and euolemia. Over subsequent years, standards of practice (clinical practice guidelines [CPGs]) involving these quantitative metrics and others (especially those promulgated by the Dialysis Outcomes Quality Initiative) were introduced with the intent of improving outcomes from dialysis therapy (lowered mortality, reduced morbidity, better rehabilitation). Surrogate or process-related measures became the basis for clinical performance measures (CPMs) and subsequent dialysis facility certification requirements (2). Unfortunately, the evidence that these performance criteria (CPGs or CPMs) have directly led to improved outcomes is largely observational and potentially confounded by unmeasured variables (3). Nevertheless, the results of application of these CPGs “in the field” support the practice of using guidelines as a tool for

monitoring the performance of facilities and perhaps individual physicians as well. Current CPGs appear necessary but not sufficient to achieve optimal patient outcomes (3). It is also quite clear that over the last 2 decades, when such criterion-based guidelines reached their zenith, overall annual mortality in HD has declined by only a paltry 1% per decade in the United States (in absolute terms) (4,5). Average hospitalization rates have remained steady at approximately 15 days per year. Frequent, often avoidable, rehospitalization is not an endorsement for the effect of these performance guidelines on overall patient-centered outcomes (4,5). One could argue that even such a small decline in mortality is real progress because over this time period patients who started dialysis were sicker and older. However, as we propose here, the clinical paths described by these guidelines may not be the paths having the greatest potential effect on overall survival. Advocacy of the established guidelines may have diverted attention away from more important factors that influence outcomes. It is our shared opinion that a reorientation of the approach to treatment of ESRD needs to be considered. We do not suggest replacement of existing CPMs but rather support the notion that their augmentation by new suggestions made here may lead to significant improvements in patient-centered outcomes over the short and long term. Guideline-specific targets of management are necessary, but the current iterations are clearly insufficient to promote optimal patient outcomes. Our premise is that dialysis therapy is at a crossroads and that a new path needs to be actively and aggressively pursued. In this paper, we primarily address distinct areas of quality improvement in HD (the most prevalent modality of treatment for ESRD throughout most of the world),

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but it is likely that peritoneal dialysis (PD) will assume increasing importance in early management of ESRD in the future.

This paper represents the conjoint opinions of the authors. It is a way forward. It does not suppose to meet the strict guidelines of evidenced-based process. It is a product of our assessment of the preponderance of evidence leavened by our experiences in treating patients with ESRD.

### The Old and New Paths: A Crossroads

The contrasts between the old and new paths are summarized in Table 1.

#### The Old Path

The alarming increase in the frequency of “early” start of dialysis (on the basis of an arbitrary value of serum creatinine or estimated GFR [eGFR]) over the last decade has not achieved any notable benefits and may have been harmful (6,7). In particular, the high-risk period within the first 90 to 120 days after initiation of HD has not been well managed (8).

The emphasis on “Fistula First” has unfortunately been accompanied by augmented use of catheters, which in turn has resulted in an increase in the rate of infections (4). Whether the Fistula First program is responsible for this cycle of events is not known, but it is irrefutable that the use of catheters is very common in incident and prevalent HD patients and that this is associated with higher infection-related mortality, hospitalizations, and costs.

Using Kt/V or the urea reduction ratio as the primary criteria of dialysis adequacy has fostered a short-duration, thrice-weekly standard of care and has diverted attention from the importance of extracellular fluid volume (ECFV) control. The excessive focus on atherosclerotic coronary artery disease (ASCAD) has also led to a misguided emphasis on the control of lipids and antihypertensive medications and neglect of the left ventricle as a target of damage emanating from persistent ECFV expansion (9,10). Aggressive treatment of anemia and bone disease has

not yielded documented benefits on survival (11–13). Finally, restrictive diets have not dealt appropriately with the critical issues of fluid and sodium balance during inter- and intradialytic periods (14).

#### The New Path

A new set of paths is proposed to supplement these older and insufficiently effective precepts. This section will address each of these paths.

#### Initiating Dialysis and the First 120 Days

A renewed focus is needed for the period leading up to the initiation of dialysis and during the first several months of dialysis treatment. An astonishing annual mortality rate of 40% in certain populations of patients has been observed in the first 90 days after initiation of dialysis, particularly in patients starting dialysis with a catheter (15). On the basis of an arbitrary value of serum creatinine or eGFR, early start of dialysis has proven to be unwarranted (6,7). Solely basing decisions to start dialysis on eGFR values is wrong. Epidemiologic evidence now exists that early start of dialysis is harmful, particularly in the “infirm” very elderly (16). Many elderly patients with severe impairment of kidney function (stage 5 chronic kidney disease) may remain stable and do well on rigorous conservative therapy for months to years (17). Objective assessments as to the optimum timing of initiation of dialysis such as the extent of malnutrition, the ability to respond to diuretics, or the ability to maintain euvolemia are sorely needed. The focus should be on the management of comorbid conditions, duration of dialysis sessions, emphasis on nutrition and salt intake, rehabilitation, and the patient’s emotional health. Catheter avoidance and the use of PD for initiation of ESRD therapy will be discussed below.

We must advocate a timely start for dialysis on the basis of a thorough clinical review and assessment of the risks and benefits to the individual patient. Increases in left ventricular (LV) mass may predict (independent of BP control) a more rapid course to

**Table 1. A summary of the old and new paths**

The Old Path	The New Path
Early start	Timely start: meticulous management of first 90 to 120 days
Fistula First	Catheter Last
Kt/V for dosage adequacy (exclusively)	ECFV control (24 hours per day, 7 days per week)
Short sessions, thrice weekly	Longer or more frequent sessions
Emphasis on ASCVD	Mind the left ventricle
Aggressive anemia and bone disease management	Moderate use of ESA, iron, vitamin D, phosphate binders, calcimimetics
Treat active infections	Avoid infection
Dietary restrictions	Eat, eat, eat—but not salt

ASCVD, atherosclerotic cardiovascular disease; ESA, erythropoiesis-stimulating agents.

ESRD and the need for dialysis (18). An increase in LV mass at the time of initiating dialysis is a strong predictor of a future poor outcome (9). Thus, consideration should be given to the hypothesis that avoidance of an increase in LV mass is a logical target for predialysis chronic kidney disease interventional approaches (9).

### Catheters

Well in advance of the anticipated need for dialysis, every effort to secure a noncatheter-based vascular access must be pursued. Initiation of dialysis with indwelling catheters should be relegated to a “last choice” (whereas retaining fistulas should be a first choice) (4,8). Infection avoidance (through a “catheter last” *modus vivendi*) should become the new mantra. Avoidance of catheters as the initial and ongoing vascular access will reduce the high burden of catheter-driven infection and inflammation, thereby improving patient mortality, morbidity, and rehabilitation (4,8). Such infections have materially affected outcomes and have a lasting effect on morbidity well before and after the period of active infection because of associated proinflammatory effects, attendant “malnutrition,” and even acute electrolyte changes adjacent to the arteriovenous node nearby the catheter entry site (4,19,20). Catheter avoidance is the best and perhaps only answer to this conundrum. Using PD as a preferred mode of therapy for incident patients without a functioning arteriovenous fistula might mitigate some of the downsides of vascular catheter use for HD (21,22). Catheters remaining after 90 days of HD should be considered a serious outlier for the facility unless it is the only vascular access available, and even then thorough investigation must document the lack of other options. There must be accountability at all clinical levels for adherence to a catheter last prescription. A severalfold increase in morbidity and mortality is seen when catheters are used in comparison to fistulas or grafts. Perhaps the Centers for Medicare and Medicaid Services, as a part of the new Quality Incentive Program guidelines, should consider the overuse of catheters as a method of vascular access as a measure of substandard quality of care (19,20). High catheter prevalence is an iatrogenic problem that demonstrates a lack of education and involvement of the patient and family in decision-making.

Thus, during the first 60 to 120 days after dialysis initiation, a checklist-oriented and multidisciplinary approach to optimizing care should be rigorously and systematically applied that focuses on comorbidity and the duration of dialysis sessions as well as the patient’s emotional health. Incident patients need to be managed differently and more actively than the established prevalent patients.

### LV Disease, Salt, and Volume

In our opinion, careful attention to preventing or reversing the increase in LV mass (“mind the left ventricle”) should replace ASCAD in the hierarchy of

treatable cardiovascular morbidities (9). Ventricular hypertrophy is intimately linked to myocardial fibrosis, systolic and diastolic dysfunction, and markedly increased risk of arrhythmogenic sudden cardiac death or congestive heart failure (9). We hypothesize that short- and long-term outcomes will likely improve with rigorous monitoring and control of ECFV because its adverse effects on LV remodeling (eccentric LV hypertrophy), diastolic and systolic dysfunction, and arrhythmogenic myocardial fibrosis will be attenuated (9,23). Achieving euvolemia (on a continuous daily basis) in ESRD is a great challenge. However, a culture of frequent monitoring and control of ECFV excess needs to be cultivated and promoted to avoid unnecessary and repeated hospitalizations (23). Most facilities rely on crude techniques for frequently assessing normal ECFV using subjective “dry weight” decrees (24,25). Although it is true that tools for monitoring the magnitudes of ECFV excess have not been widely applied or tested in ESRD therapy, we strongly support a vigorous search for more dependable and objective measurements of ECFV. Bioimpedance measurements, ultrasound-measured inferior vena cava diameter, and dry weight probing by on-line assessment of hematocrit have all been advocated for this purpose, but each has its shortcomings, and no single test is yet accepted to be a gold standard (24–29). However, the recent literature supports applying such techniques. Equally important, maintaining normal ECFV in most patients, with or without these techniques, is extremely difficult (and often impossible) when dosing HD at  $\leq 3.5$  hours per session (30). Thus, we recommend that every patient should be periodically evaluated for LV disease and volume overload and the therapy should be modified to result in its amelioration. LV hypertrophy is common with current old path approaches to dialysis and it often does not regress despite “adequate” dialysis dosage (in terms of  $Kt/V$ ) (9).

Furthermore, fluid and salt balance during the interdialytic interval, which is less controllable by the physician, is equally as important as the intradialytic interval with regard to the long-term deleterious effects of chronic ECFV expansion on the cardiovascular system. As shown 5 decades ago (the Clyde Shields phenomenon), the importance of dietary salt restriction during the interdialytic interval can be crucial for long-term survival (30). A philosophy of “eat, eat, eat—but not salt” dietary advice should be widely adopted and become the standard for nutritional counseling. This salt restriction is not only dietary but must also occur during dialysis. Patients receive a sodium load when a higher sodium concentration dialysate compared with the patient’s plasma sodium concentration is used, when hypertonic saline is given for intradialytic symptoms, and when “sodium modeling” to aid in fluid removal creates paradoxical scenarios by increasing the total sodium load (14). These can initiate a vicious cycle of excessive ECFV expansion and symptomatic dialysis. Longer dialysis treatment time or more frequent dialysis ses-

sions can improve ECFV control and LV hypertrophy, in part by improved tolerance to intradialytic ultrafiltration (achieving dry weight with fewer symptoms) and by shortening the interdialytic interval (31). Many patients may be very “brittle” and poorly tolerate efforts to reduce excess ECFV by intradialytic ultrafiltration using conventional thrice-weekly short-duration dialysis. Excessive rates of intradialytic ultrafiltration may do more harm than good (cardiac stunning) (32).

BP control is most commonly an ECFV-related problem in ESRD. Using BP-lowering agents as a surrogate for good ECFV control in patients with hypertension is a practice that should be avoided (24). Almost all ESRD patients treated with multiple antihypertensive agents are likely ECFV overloaded. How can we consider these patients to be receiving adequate dialysis even when their Kt/V is within a desirable range?

Longer duration (or more frequent) dialysis with slower ultrafiltration and a shortened interdialytic interval may be the best approach to achieving euvolemia around the clock (31,33). We believe it will become the norm. Applying these concepts to dialysis at home makes common sense. The Frequent Hemodialysis Network trial is prospectively addressing this issue in a randomized controlled fashion (33). There is also some evidence that PD is a modality of ESRD care in which patients do better, at least in the first 2 to 3 years of renal replacement therapy (21,22,34). Also, there is some evidence that LV mass may improve more on PD compared with HD, perhaps as a consequence of “smoother” control of ECFV (35). As part of giving attention to therapies during the initial phases of therapy, PD should logically be given serious consideration as a viable alternative to traditional in-center HD. This consideration needs to be assigned a high priority during the first 120 days or before, especially if LV hypertrophy is present.

Indeed, better means are urgently needed to secure continuous euvolemia in dialysis patients. Any process that aggravates excess positive salt balance or increases plasma sodium concentration during dialysis should be scrupulously avoided. Limitation of salt intake during the interdialytic interval is a key to success, but it is often impeded by the patient’s lack of appropriate dietary education or noncompliance combined with excessive salt or fluid craving because of thirst. Better means are needed to secure continuous euvolemia in dialysis patients. Perhaps augmented gastrointestinal elimination of salt through orally administered exchange resins may help control inter- and intradialytic ECFV. Treatment of anemia has little effect on LV hypertrophy except when hemoglobin values are <10 g/dl (36).

The consequences of sustained excess volume on the left ventricle (even independent of systemic BP) (37) can be profound and very deleterious to patient outcomes in terms of mortality and recurrent hospitalization. It is our contention, on the basis of the available evidence, that mortality, hospitalizations,

and rehospitalizations would dramatically decrease if avoidance of catheters and attention to LV disease and volume status were pursued vigorously (9). Our patients die more often from infections and complications from LV hypertrophy and fibrosis than of ASCVD or any other cause (4). These two problems are avoidable, dangerous, and treatable. The broader use of PD as the entry modality to ESRD treatment could potentially have a salutary effect on the vascular catheter-infection nexus and might even provide a smoother control of ECFV compared with thrice-weekly HD (21,22).

## Issues and Controversies

The suggestion that HD therapy of ESRD is at a crossroads and that we need to change direction and emphasize new goals will inevitably provoke controversy. A large body of mainly observational clinical data can support the new paths elaborated here. It is hoped that the suggestions made here will stimulate interest (and financial support) in the design and execution of prospective studies to validate or reject the proposals. In the meantime, the preponderance of evidence suggests we cannot wait years for these studies to be completed. Our proposition is that the current approach of thrice weekly conventional short-duration dialysis using Kt/V as the exclusive measure of dialysis dosage adequacy that tolerates catheters as initial or permanent vascular access and subjective infrequent assessment of dry weight can no longer be justified. Two decades of stagnation in patient-centered outcomes is testimony to the validity of this position.

In our view, the rationale underlying these suggestions and opinions is very compelling. Nothing is to be lost given our modest record of improvement in patient outcomes to date. The old path need not be entirely discarded or ignored, but in our collective opinion the focus must be altered if we are to improve the outcomes of patients receiving care for ESRD.

Reduction in catheter use, infection avoidance, and better ECFV control with the left ventricle as a target for treatment should be sufficient to yield impressive results over the short term. It is our fervent hope (and conviction) that additional CPMs linked to just these new paths can quickly evolve into the mainstream of care as nephrologists adopt key elements of the suggestions articulated in this brief paper. We think that Belding Scribner (and Clyde Shields) would be enthusiastic about the prospects of this paradigm shift in our stewardship of their legacy. We owe it to the patients entrusted to our care.

## Disclosures

None.

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