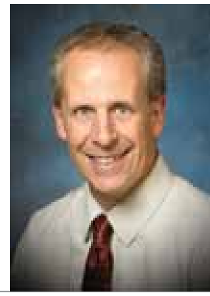
The Renaissance of Home Hemodialysis

Dialysis Done Frequently



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INTRODUCTION

In 1963 Belding Scribner developed the polyurethane arterio-venous shunt, allowing repeated high flow access to the circulation of patients with end-stage renal disease (ESRD). Soon after, the Seattle Area Kidney Center, a nonprofit, donor-funded foundation attached to Swedish Hospital, began offering chronic hemodialysis to highly selected patients. In a dramatic twist of fate, the 15 year-old daughter of a close friend of Dr. Scribner's collaborator Alan Babb developed end-stage renal disease. When the lay committee charged with selecting patients for the Kidney Center rejected this girl for participation, her father's pleadings prompted Babb to rapidly adapt the early dialysis equipment for home use. The girl's successful dialysis at home proved this approach practical, and less expensive as well; home hemodialysis (HH) was rapidly and widely accepted.

THE DECLINE OF HOME HEMODIALYSIS

The Medicare ESRD program was introduced in 1973, mandating coverage for most patients with ESRD. Dialysis centers became widespread and available; newly eligible patients were older, sicker, and less able to provide self-care. Home machines were so complex that patients and caregivers had high burnout rates. Chronic ambulatory peritoneal dialysis was developed and was a technically simpler home modality for suitable patients. The introduction of cyclosporine in 1983 allowed an increased number of younger and healthier patients to be transplanted. HH participation amongst patients and providers declined.

Medicare reimbursement policies consolidated the decline. Reimbursement for in-center hemodialysis in 1973 was initially quite generous, with much lower pay for comparable home dialysis. By 2001 only 0.6% of U.S. patients with ESRD received hemodialysis at home (USRD system data). Similar trends occurred in Lancaster County, with the HH population dwindling from nearly half of the 42 ESRD patients in 1977, to none by the 1990s.

THE CURRENT STATUS OF DIALYSIS

Thrice weekly dialysis became the standard in the 1960s based on clinical observations of the sense of well being of a small number of patients treated with this regimen.[1] Despite numerous medical advances to improve the lives of ESRD patients since, the dialysis regimen itself remains remarkably unchanged, and morbidity and mortality remain unacceptably high.

Attempts to define optimal dialysis 'adequacy' led to the National Cooperative Dialysis Study (NCDS) which randomized thrice weekly hemodialysis patients to longer versus shorter treatment times, and to higher versus lower time-averaged weekly urea levels.[2] A mechanistic interpretation of the NCDS data emphasized a unitless measure of urea clearance normalized for total body water, "KT/V" determinant of dialysis adequacy.[3] As a result of later concern that this strict focus on urea clearance led to chronic suboptimal dialysis dosing, and hence excess morbidity and mortality, the NIH-funded HEMO study was carried out in the 1990s.[4] 1,846 patients were prospectively and randomly assigned to thrice weekly dialysis with standard urea clearance (KT/V) or with increased urea clearance (increased KT/V). Unfortunately, the study categorically failed to realize the hope that, within the conventional thrice weekly dialysis model, better urea clearance would lead to improved outcomes.

THE RATIONALE FOR HOME HEMODIALYSIS

The failure of more intensive thrice weekly dialysis to improve outcomes in the HEMO study has stimulated the redefinition of dialysis adequacy to more than urea clearance alone. Multiple parameters, including salt and water removal, blood pressure control, phosphate control, nutrition, Vitamin D and parathyroid homeostasis, anemia management, and use of native fistulas have been examined. Recent experience with more frequent and/or longer dialysis has demonstrated better outcomes within most of these parameters.

Several concurrent observations have further influenced the trend to frequent hemodialysis. Chronic ambulatory peritoneal dialysis, developed in the 1970s, has allowed home dialysis for a small portion of ESRD patients, but its use has been limited by its slow urea removal. Multiple studies have suggested it may be associated with increased mortality, especially among large patients or those without significant residual kidney function. Transplantation remains the renal replacement modality of choice for most patients, but availability is limited by a marked shortage of organs, and by recurrent disease, allograft failure, age restrictions, and immunosuppressant intolerance. Thus, alternatives to in-center thrice weekly hemodialysis have been limited.

The above developments have led to a renaissance in home hemodialysis. Frequent and/or extended dialysis is offered only sporadically at in-center dialysis units, generally as thrice weekly nocturnal dialysis. Thus, long-term daily or extended hemodialysis is necessarily done in the *home*, and the two are largely synonymous. Cost and convenience are the primary issues.

Medicare, the primary insurer for more than 90% of all hemodialysis patients, only provides reimbursement for thrice weekly dialysis. Even with that approved schedule, dialysis centers only recoup about 95% of their costs from Medicare (including patient co-pays), so it is economically untenable to provide more frequent dialysis in-center. This is not true of home dialysis, however, since labor accounts for a large portion of all in-center dialysis costs, and these are dramatically lowered when the patient and caregiver provide labor gratis at home. Thus, with home dialysis, more of the thrice-weekly Medicare reimbursement may be applied to the increased supply costs of more frequent dialysis.

Further, each in-center dialysis treatment entails considerable patient travel time and cost. More time is spent waiting to be "put on" the dialysis machine, as actual dialysis times of earlier patients can be unpredictable. These time and cost demands multiply with frequent dialysis, but are largely abrogated by dialyzing at home.

Home dialysis may be delivered on multiple different schedules (Table 1). Frequency varies from conventional thrice weekly to seven day per week dialysis. Sessions can range from 'short' (generally 2 to 3.5 hours), to 'conventional' (generally 3 to 4.5 hours), to extended (generally 6 hours or more), with extended sessions typically being delivered as 'nocturnal' dialysis. Most home hemodialysis programs now use 'short' treatments 5-6 times per week (and often still refer to this as quotidian dialysis) or extended 'nocturnal' treatments 3-6 times per week.

TABLE 1. HOME HEMODIALYSIS SCHEDULES:

- Conventional thrice weekly dialysis, typically 3–4.5 hours per session
- Every other day conventional dialysis, typically 3–4.5 hours per session
- Nocturnal (extended) dialysis thrice weekly, typically 6–8 hours per session
- Quotidian short dialysis, typically 2–3.5 hours 6–7 days per week
- Quotidian (or frequent) nocturnal dialysis, typically 6–8 hours per session, 5–7 days per week

DIALYSIS MACHINES

Home hemodialysis machines can be the same as in-center machines, though the complexity of these machines remains high. NxStage® Medical, Inc. has developed a unique machine, called the NxStage System One™, specifically for the home market; it is currently the only available machine cleared by the FDA for home use. Its advantages include increased simplicity, smaller size, portability, and decreased use of energy and water, all of which have made it the most common device for home hemodialysis. It uses a unique procedure for toxin removal that is more akin to peritoneal dialysis. Conventional home hemodialysis uses around 600 ml of dialysate per minute, with access blood flows of 200–300 ml/min. The NxStage System One uses much higher blood flows (target 500 ml/min – only achievable with good fistulas and grafts) and much lower dialysate flows (about 150–200 ml/min). The dialysate becomes nearly fully 'saturated' with uremic toxins (particularly small molecules such as urea) which results in highly 'efficient' use of a small volume of dialysate. The NxStage system uses dialysate more efficiently at the expense of longer times on dialysis and decreased overall uremic toxin clearance. By using markedly less dialysate, however, NxStage is able to deliver dialysis using 'ultrapure' water at reduced cost, whether through prepackaged bags of sterile dialysate, or through their PureFlow™ SL dialysate preparation system (a prepackaged system of sequential filters, charcoal, and deionizers to remove water contaminants).

ADVANTAGES OF FREQUENT DIALYSIS

Extensive observational experience with frequent home dialysis has demonstrated robust benefits in survival,

Figure 1. NxStage System One hemodialyzer atop the PureFlow dialysate preparation system.

Image courtesy of NxStage Medical, Inc.

hospitalizations, quality of life, costs, and multiple intermediate outcomes. Testimonials and anecdotes abound, but most of the highest quality studies to date are observational. Two randomized trials are underway, and these are discussed further below.[5,6] One other has been completed and is also discussed below.[7]

In 1975 the "unphysiology" of thrice weekly chronic dialysis was proposed as a major cause of dialysis-related side effects and morbidity.[8] Unlike the continuous function of kidneys, standard intermittent dialysis causes wide cycling of volume, blood pressure, potassium, and uremic toxins. Naturally, the closer one comes to continuous dialysis the less 'unphysiology' persists.

Volume regulation: Maintenance of euvolemia, or physiologic salt and water balance, is an ongoing challenge in end-stage renal disease. Hemodialysis can only remove salt and water from the intravascular space. In the interdialytic interval, however, salt distributes throughout the extracellular fluid space and water distributes thoughout both the intra- and extracellular fluid spaces. The relatively slow salt and water exchange between fluid spaces is largely refractory to manipulation of the dialysis prescription. The consequence is frequent failure to attain euvolemia, with chronic volume overload between dialysis sessions, manifest as chronic hypertension and congestive heart failure. Paradoxically, removal of intravscular volume during dialysis leads to frequent intra- and post-dialytic hypotension, with resulting cerebral and coronary hypoperfusion, fatigue, and thirst.

Daily dialysis reduces the interdialytic time and hence interdialyltic salt and fluid gain, which decreases the requirement for intradialytic ultrafiltration (or salt and water removal). This phenomenon is associated with reduced mortality, cramps, thirst, and hypotension during dialysis.[9] Intradialytic hypotension occurs in 20% of all in-center dialysis treatments, but is uncommon in short daily dialysis or nocturnal dialysis.[10]

Post dialysis fatigue is a nearly universal complaint of chronic, in-center, thrice-weekly dialysis patients. This results from rapid ultrafiltration, and perhaps rapid solute shifts, during dialysis. Extensive observational experience indicates that post-dialysis fatigue can be greatly reduced or eliminated with either frequent or extended dialysis. Rather than finishing dialysis feeling fatigued, nauseated, dulled, and washed out, daily dialysis patients typically finish treatment ready to pursue the day's activities.[11]

Blood pressure control: Reduced blood pressure and antihypertensive medication requirement is a widely reported finding with frequent dialysis. Fagugli found that in 12 hypertensive patients who switched from conventional HD to SDHD, 24-hour average systolic BP dropped from148 mmHg to 128 mmHg, with a diastolic drop from 73 mmHg to 67 mmHg.[12] Others have reported similar benefits.[13] Better ultrafiltration, with patients coming closer to true euvolemia, contributes to improved control of blood pressure.

In the only randomized prospective trial to date comparing conventional dialysis with more frequent dialysis, 52 Western Canadian patients were assigned to conventional thrice weekly dialysis or frequent extended nocturnal dialysis. The primary outcome was a reduction in left ventricular mass. At 6 months, LV mass in the nocturnal group was reduced 15.3 g ($p = 0.04$) versus the control patients. Pre-specified secondary outcomes including kidney specific domains of quality of life, blood pressure, number of antihypertensive agents, and mineral metabolism, also showed significant improvements. Similar findings have been reported by others.[14]

Sleep disturbances: The majority of ESRD patients have significant sleep disturbances, including obstructive sleep apnea, central sleep apnea, and restless leg syndrome. Fourteen patients were studied with polysomnography while on conventional thrice-weekly dialysis and again after 6–15 months of nocturnal hemodialysis. There was substantial reduction in both obstructive and central apneic periods, with the greatest reduction in the seven patients with the greatest baseline disturbances, an outcome with the potential for improved quality of life and possibly reduced mortality.[15]

Potassium Regulation: Potassium accumulates between dialysis treatments and frequently reaches life threatening values in the extracellular space. The relative risk of sudden death increases 3 fold in the 12 hours preceding dialysis at the end of the "long stretch" (3 day) interval in patients who are dialyzed on a standard three times weekly schedule, in part due to potassium accumulation.[16] Frequent dialysis eliminates the 'long stretch' potassium rise, providing the opportunity for a reduction in sudden cardiac death.

Hyperphosphatemia is strongly associated with mortality in chronic dialysis patients. Conventional dialysis removes phosphorous poorly, typically less than 1000 mg per session. Even if a patient adheres to the recommended dietary phosphorous restriction (typically 1000 mg per day), significant excess phosphorous accumulates and requires the use of phosphate binders (typically big pills given in large doses up to 5 or more per meal). Phosphorous removal by dialysis tends to be quite time dependent, so patients with frequent and extended dialysis sessions typically have much greater phosphorous clearance. Overnight dialysis 5 days a week typically removes sufficient phosphorous to allow unrestricted diets without use of phosphorous binders. Patients are freed from the burden of these expensive pills, and their gastrointestinal side effects and calcium-loading. Other benefits include attenuation of the consequences of hyperphosphatemia, including vascular calcification, calciphylaxis, secondary hyperparathyroidism, renal osteodystrophy, and overall mortality. Though the improvement in phosphorous removal with shorter daily dialysis is less pronounced, it may be entirely offset by improved appetite and protein intake.

Anemia management: The use of erythropoietic agents (EPO) improves quality of life significantly, but is quite costly. 5–6 nights of extended dialysis per week causes a significant reduction in erythropoietin requirement, perhaps due to reduction in the uremic milieu. A similar drop in EPO requirement, and increase in hemoglobin, was found at 6 and 12 months in 63 patients converted from conventional HD to frequent nocturnal HD.[17] This reduction in erythropoietin requirement has not been uniformly noted in short daily dialysis, especially that with the NxStage machine, perhaps due to less robust uremic toxin clearance.

Serum albumin concentration, a reflection of both nutritional status and, inversely, systemic inflammation, is one of the strongest correlates of survival in chronic dialysis and is generally improved by frequent dialysis. In one study of 72 patients changed from thrice weekly to quotidian dialysis, serum albumin rose 0.29 gm%, with an increase in total nitrogen appearance rate (reflecting increased daily protein intake) and arm muscle area.[18]

Objective quality of life assessments have shown considerable improvement in studies of daily hemodialysis.[19] Reduction in cramping, headaches, hypotension, dizziness, dyspnea, and cold intolerance are seen, and dietary restrictions are reduced. In the London, Ontario study every one of the 23 patients enrolled in the quotidian limb chose to remain in that limb at the completion of the study because of improved quality of life.

Cognitive function at baseline and 6 months following conversion to frequent nocturnal HD in a group of 12 patients, showed statistically and clinically significant reductions in cognitive symptoms and improvement in psychomotor efficiency, attention, memory, and processing speed.[20]

Hospitalizations for cardiovascular or dialysis-related diagnoses fell from 0.5 to 0.17 per patient-year in 32 patients moved to frequent nocturnal HD, while there was no change in 42 matched controls who remained on conventional HD.[21]

Costs for supplies naturally increase with daily dialysis, but overall costs decrease. In one study they fell from Can. $72,700 for conventional dialysis to Can. $67,300 for short daily dialysis.[22] Hospitalizations, emergency room visits, laboratory tests, and drug costs all declined. A prospective study of 166 patients showed total outpatient dialysis and non-dialysis medical costs were reduced from $51,252 to $29,961 for home care hemodialysis patients.[23]

Survival is the ultimate indicator of any modality's success. Data from Australia show a strong correlation between frequency of hemodialysis and survival and between weekly time on dialysis and survival. Multiple other studies from the United States and Europe have confirmed greater survival, by as much as 2.3–10.9 years, compared with matched controls.[24]

POTENTIAL DISADVANTAGES OF HOME HEMODIALYSIS

Dialysis is a complex and highly technical procedure. Delivery of dialysis outside the highly controlled and regulated environment of the dialysis center has raised concerns about the safety and quality of care.

Safety of dialysis water remains an issue. Dialysate at in-center units is produced in a highly standardized and monitored fashion, as contaminants in dialysate pose real and severe risks to dialysis patients. Chloramines are commonly added to municipal water as disinfectants, and can result in fatal hemolysis. Nitrates, a common byproduct of fertilizers and farm waste, can cause hypotension, nausea, methemoglobinemia, and hemolysis. Various heavy metals cause a variety of well documented toxicities. Endotoxin and bacterial contaminants cause hypotension and contribute to the pro-inflammatory state found widely in the dialysis population.

Several methods have been developed for the home environment to produce high quality water, as demonstrated by bacterial and endotoxin studies and patient C-reactive protein levels. Home reverse osmosis machines can produce generous amounts of appropriate dialysate, but they consume large volumes of water and electricity and generate costs for the patient of well over $1000 annually. They also require specialized plumbing and electric requirements, and take significant in-home space. NxStage has developed their PureFlow technology, which produces 'ultrapure' water using tap water- with little waste, standard in-home plumbing, and small amounts of standard 110V electricity. The relatively small volume of water that results, mandates low dialysate flow rates, which extend dialysis time and limit clearance of uremic toxins.

Extended time on dialysis may theoretically yield more patient exposure to water borne contaminants, including endotoxin, especially if ultrapure water is not used. To date no empiric evidence of such toxicity has been demonstrated. Similar concerns have been raised, but not substantiated, about increased risk of proinflammatory and prothrombotic phenomena from increased exposure to artificial dialysis membranes.

Dialysis access has traditionally been the Achilles heel of chronic hemodialysis therapy, so there has been concern that more frequent needle cannulation of access sites may compromise their durability. Empiric observational data has demonstrated the opposite: daily dialysis has resulted in improved access durability and reduced complications.[25] The Christchurch New Zealand experience with 301 home hemodialysis patients reports fistula survival rates of 90% at 1 year and 66% at five years, far above U.S. averages. Wide adoption of the 'buttonhole' technique[26] for native fistula cannulation has reduced patient discomfort and the need for access intervention. With this technique, patients cannulate at the exact same sites and angle for every treatment. An anesthetic scar tract develops that can be readily cannulated with blunt needles. Despite concerns of increased risk of infection, at-home dialysis is associated with reduced rates of infection in central vein catheters too.

Accidental disconnection of dialysis needles or lines can rapidly result in fatal exsanguination. Monitoring of arterial and venous line pressure, along with patients' visual inspection, remain mainstays of safety measures. Nocturnal dialysis generates particular concern, and initial arrangements for home hemodialysis involved remote monitoring (via phone or internet). Since no safety benefit has been demonstrated, remote monitoring is less commonly used now. Multiple devices and techniques have been developed to secure blood lines and needles. Enuresis pads are sometimes used under accesses to detect excess moisture from a blood leak. A new device to detect blood leak, using a fiberoptic cable taped over the access and attached to a small monitoring device, is now available in some countries, though it is not yet approved in the United States.

BARRIERS TO HOME HEMODIALYSIS

Widespread modern acceptance of home hemodialysis has been limited by multiple factors.

Attitude barriers include patients' fear of needles and self-cannulation; fear of failure to perform self-care adequately; and fear of social isolation. Provider bias stems from a convictions that patients should not dialyze without direct supervision. Physician and patient inertia remains strong. Patient and caregiver burnout remains too common.

Physical barriers include the large space needed for dialysis itself, storage space for supplies and refuse, and arrangements for disposal of medical waste.

Financial barriers are formidable. CMS, the primary insurer of the vast majority of chronic dialysis patients, has shown remarkable indifference to the benefits of home hemodialysis. CMS denies reimbursement for more than three treatments a week, typically insufficient to cover the direct costs to providers. Huge water and electricity costs are entirely borne by the chronically ill patient. In the London Home Dialysis Study, initial home hemodialysis installation required an average of 75 hours labor time per site, and yearly servicing and maintenance was 58 hours per site. These costs are all unreimbursed in the United States. CMS shifts the financial burden of Vitamin D analogs to patients, as they won't cover the usual intravenous forms of Vitamin D in the home. Thus, CMS derives benefits from the reduction in hospitalizations, drug use, and possible decreased access costs, but assumes none of the increased direct costs.

THE FUTURE

The morbidity and mortality of end-stage renal disease remain unacceptable. The current standard of thrice weekly dialysis has been proven, in the randomized HEMO trial, to have reached its limits of efficacy. The preponderance of available evidence strongly supports frequent, and extended, hemodialysis as a preferred dialytic modality to reduce morbidity and mortality and improve the compromised quality of life associated with ESRD.

More patients could certainly be dialyzed successfully at home. In the United States, only 0.4% of all ESRD patients do so, while in Canada it is 2%, Australia 13%, and New Zealand 25%. Criteria for patient selection are not prohibitive, and appropriate selection criteria have been developed. A single simple selection criterion for home hemodialysis candidates has been proposed: "Can you drive?"

Barriers can be overcome. Crucial advances include improved pre-dialysis patient education of options for kidney replacement; an expanded curriculum for home dialysis in nephrology training programs; better understanding and embracement of this modality's advantages among renal nurses and physicians; better emotional support of patients at home; and simplified home equipment and water preparation. Insurers, with CMS in the lead, must recognize the medical, emotional, and cost benefits of home hemodialysis and support patients and providers to make it financially viable.

As previously noted, two NIH-sponsored randomized controlled trials are underway (The Frequent Hemodialysis Network Trials). The Freedom Home Daily Dialysis Trial is an industry sponsored trial comparing 500 daily home dialysis patients with a matched cohort from the USRD system database. The International Quotidian Dialysis Registry (cosponsored by the NIH/NIDDK and the International Society for Hemodialysis; www.quotidiandialysis.org) may provide more definitive and extensive support for frequent dialysis. Nonetheless, calls to delay coverage of frequent HH until prospective randomized trials confirm benefits seem excessive. No randomized trial has demonstrated survival benefit for *any* dialysis modality or schedule, not even for transplantation.

The renaissance of home hemodialysis offers much promise to the ESRD population. Patients, physicians, and other providers must push aggressively for broader availability and use of frequent home hemodialysis, and our government must accept its responsibility to those it insures. Hopefully, the current randomized NIH studies will provide solid, unequivocal confirmation of the ubiquitous benefits that have been observed with home dialysis, and be the final impetus to a widespread surge of frequent dialysis done at home.

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