Evolution of Daily Hemodialysis in Acute Renal Failure: From the Korean War to the Present

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Over half a century of hemodialysis therapy has brought significant progress in technology and in our approach to its use. This brief review has three objectives: (1) to describe what dialysis was like in the beginning, 50 years ago; (2) to review the origins and interval evolution of the paradigm of daily hemodialysis; and (3) to introduce some vistas for the future.

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Key words

Acute renal failure, uremic encephalopathy, malnutrition, history of dialysis

Introduction

The artificial kidney designs of the late 1940s and early 1950s shared such characteristics as continuous arteriovenous blood flow, newly accessed for each treatment using cannulated arteries and veins, exposure of blood to dialysate through cellophane membranes of large surface area, typically for 6 hours, "total body heparinization," and dialysis solutions whose electrolyte composition approximated that of normal plasma water. Significant hypertension was relatively infrequent and was controlled as well as possible with few pharmaceuticals. Most dialyzers were not ultrafilters, so fluid volume overload was avoided by restricting fluid intake. Anorexia, nausea, and vomiting limited oral intake, so carbohydrate calories were given intravenously in hypertonic solutions within the overall volume allowance.

Given the inherent technical complexities and the critical attitudes of uninvolved peers toward this unprecedented technology, it was reasonable to "use the machine" as infrequently as possible, only with patients who exhibited acute renal failure (ARF), dire indications of myocardial potassium intoxication, and/or significant uremic symptoms. Dialysis was also soon used for intoxication with dialyzable poisons.

If oliguric ARF persisted, this infrequent use of dialysis imposed an oscillating clinical course: progressive clinical and chemical deterioration partially reversed by one or more dialyses, until diuresis heralded renal recovery and potentially the patient's ultimate survival, or until infections, wound dehiscences, tissue wasting, or bleeding killed 30% – 70% of the patients, depending on the cause of the ARF.

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The highest ARF mortality rates followed traumatic injury and prompted the use of dialysis in a U.S. army renal center during the Korean War. The reports [1,2] suggested some benefit from early referral of casualties to disciplined renal care including dialysis using the Kolff-Brigham rotating drum dialyzer.

Origins and evolution of daily hemodialysis

After the experience in Korea we assumed that dialysis stateside should produce better results than dialyzing against the somewhat treated rice paddy water in Korea. Instead, our mortality rate was worse and contrasted with the optimism of the contemporary literature. So our question was this: Was our miserable experience unique?

With the support of the Surgeon General the world's published experts were gathered in a Study Group on Acute Renal Failure, in closed sessions over three days in October 1957, at the U.S. Army Surgical Research Unit, Fort Sam Houston, San Antonio, Texas. The combined data confirmed our findings: In 1044 cases of ARF, overall mortality was 49%, and in posttraumatic ARF it was 66%. Our miserable experience was *not* unique.

These data prompted a paradigm shift, a new way of thinking, a fundamental change from our training—from what was then standard practice. In the words of the Detroit assembly line worker: "The reason we only *get* what we always *got* is that we only *do* what we always *did*!" In other words, it is the definition of insanity to repeat the unproductive thing.

The paradigm shift we proposed was a significant departure from our training and from what was then standard practice. We named this new departure "prophylactic daily dialysis."

The rationale was simple: If a *big* dialyzer used infrequently could *reverse* the *developed* uremic illness and disordered plasma chemistry, then a *little* dialyzer used every day might *prevent* those abnormalities; and if the patient's *encephalopathic*, "uremic" symptoms of clouded mentation-on-to-coma, nausea, and vomiting implied some intoxication, not only of the encephalon but of the rest of the patient's cells, tissues and organs, then reversal of the encephalopathic symptoms by dialysis might also imply a more general, systemic relief from that ubiquitous toxicity and its sequelae.

Therefore, the paradigm of prophylactic daily hemodialysis predicted that if plasma chemical abnormalities could be controlled, then uremic symptoms would be minimal or absent, permitting normal ambulation and convalescence. Furthermore, nutrition would be preserved; wasting, sepsis,

and wound dehiscences would be avoided; and the bone marrow would resume its normal function.

There were several requirements: The Surgeon General authorized a team of enlisted clinical technicians, sergeants first class, who assembled the McNeill-Collins dialyzers and maintained the comprehensive flow charts so that all the data were visible at once. The plastic cannulas were prepared by dipping the middle of a length of polyvinyl chloride tubing into a deplasticizer, then pulling the ends until the middle achieved the right diameter, letting the tube harden, then cutting across the narrowed section. We developed a method for regional heparinization when bleeding threatened. Heparin was infused into the outflow to the dialyzer, and a balanced protamine solution into the return flow to the patient, so that clotting times remained infinite in the circuit and normal in the patient. The components were small and portable for military application.

The results were dramatic, to us—revolutionary

Instead of sick uremic patients and emergency dialyses, usually at night, we saw healthy individuals, alert, eating "regular food," and ambulatory to the extent that their injuries allowed, despite continuing oliguric ARF. We noted that the *disease* continued in their kidneys, but their *illness* was gone.

We reported the first 7 patients in *Transactions—American Society for Artificial Internal Organs* in 1959 [3] and the whole series of 15 patients in the *Annals of Internal Medicine* in 1960 [4].

Meanwhile, in the intervening 40 years, especially in the last 20, the "prophylactic daily dialysis paradigm" to prevent clinical illness and limit the chemical abnormalities has evolved mainly in three directions:

1. First, as continuous therapy for ARF, as perhaps first envisioned by Scribner in the 1960s [5,6], but now especially in intensive care units, using high ultrafiltration and fluid replacement rates, with or without dialysis. It also includes hyperalimentation because of the catabolic stresses and the association of mortality with the caloric deficits in patients with multisystem injury.
2. Second, routine "maintenance" dialysis treatment of end-stage renal disease (ESRD) patients is evolving with controversies over hemodialysis versus peritoneal dialysis, flux, time, ultrafiltration, dialysate composition, membranes, β-2 microglobulin, accesses, etc.
3. Third, in the more recent exploration of daily hemodialysis in ESRD. Heralded by DePalma in 1969 [7], by Bonomini in 1972 [8], by Kjellstrand's troublesome "unphysiology of dialysis" paper in 1975 [9], and as advocated by Twardowski [10], application of the paradigm of daily dialysis to ESRD patients has yielded supporting data from a growing number of workers.

As summarized in the 1997 Perugia Conference Report by Buoncristiani [11] and by Kjellstrand in 1998 [12], daily hemodialysis improves nutrition, anemia, chemical control, blood pressure control, symptom control, cognition, sexual, motor and sensory function, and reduces dialysis-induced symptoms and myocardial hypertrophy in ESRD patients.

A striking parallel is to be noted between these new findings in chronic renal failure and those surrounding the early experiences with daily dialysis in acute renal failure 40 years ago. Should it surprise us that renal failure is all one story? Indeed, the same questions that worried us then worry us now: How much dialysis is enough? What is "adequacy of dialysis"?

However, our modern insights and concerns about nutrition play out these questions on a different stage. Nutritional status is increasingly recognized as clinically and prognostically significant because of the apparent direct relationship between dialysis dose, appetite, and dietary intake, as if protein intake is regulated by appetite by the concurrent excretory rates of protein metabolites.

And that brings us to the final part of this review, some vistas for the future. First, let's consider some data related to dietary intake in ESRD. Ikizler *et al*. [13] measured spontaneous dietary protein intake in 90 patients repeatedly during the progression of their chronic renal disease. Four glomerular filtration rate (GFR) ranges were identified. Patients' dietary protein intake fell as their GFR declined. Deceptively small deficits in grams/kilogram/day are really huge when cumulated in grams/70 kg/month, for example, a delta of –1 kg of protein per month when the GFR drops from 50 to 10.

Also note that at GFRs below 25, calculated weekly Kt/V_{urea} equivalents below 3.8 imply levels of thrice-weekly underdialysis.

In the Modification of Diet in Renal Disease (MDRD) Study, average baseline dietary protein and calorie intakes (before dietary intervention) and body weights were related to average GFR. In both the phase II (pilot) [14] and the phase III (full-scale) [15] studies, all three above-mentioned mean values were lower when GFR was lower, that is, lower in study B than in study A.

Again, the differences in grams/kilogram/day seemed small but were impressive when expressed in grams/70 kg/month; thus the average patient's estimated deficits were 1/4 kg protein and 3000 calories/month in the pilot, and 1/2 kg protein and 4500 calories/month in the full-scale study. No wonder the body weights were lower when GFRs were lower.

From the MDRD phase III baseline data (again, before dietary intervention), a graph of estimated daily protein intake versus GFR reveals that a decline in average protein intake may *begin* somewhere between GFRs of 30 and 40 mL/min. This is critical information. Because if that is true, the question becomes, Should we, can we, dialyze to some equivalent of that GFR level? Put another way, how much hemodialysis would we need to prevent that suppression of protein and caloric intake and therefore reverse and prevent uremic wasting?

Assuming a 70 kg patient with 40 L of body water, zero residual renal function, and a urea clearance of 0.6 GFR, what dialysis time would be needed to approximate a GFR of 30 – 40 mL/min, on schedules of 3, 6, and 7 sessions/week at a Kt/V_{urea} = 1 (when K = 167 at t = 4 hr)? The answers are as follows: 3 – 4 hr/session at 6 sessions/week, or 2.5 –3.5 hr/session at 7 sessions/week, or 6 – 8 hr/session on the usual thrice-weekly schedule.

The sessions are shorter if our blood flow, dialysate flow, and membrane combinations provide a Kt/V of 1.2, and still shorter, down to 1 – 2 hours, if Kt/V levels of 1.4 or 1.6 can be achieved. At these levels even a thrice-weekly schedule might achieve the target GFR equivalent.

At least this arithmetic suggests that, in addition to all the other benefits of daily dialysis in ESRD patients, *if* these higher GFR equivalent levels of urea clearance can also reverse and then prevent patients' progressive, subtle and dangerous, cumulative nutritional deterioration, then only by daily dialysis, 6 – 7 sessions/week, presumably at home, or thrice weekly at very high Kt/Vs, can these levels of clearance be achieved within conveniently short treatment times.

The arithmetic also reveals that a much lower Kt/V_{urea} should achieve the same result if dialysis time is prolonged, as in overnight home hemodialysis.

All of these calculations notwithstanding, at least two other parameters of morbidity and mortality must be considered: first, the initiation of dialysis before "creeping uremia" compromises the patient's nutritional status, for example, when residual renal function approximates a weekly Kt/V_{urea} in the range of 3.0 – 3.6; second, blood pressure and lipid control and a healthy lifestyle must be active and continuous. Interesting!

But the foregoing considerations lead, in turn, to another vista. This review, so far, and our usual discourse in meetings suffer one great, and I believe, critically important deficiency: When we properly, and compulsively, attend to our "supply-side" prescriptions, to improving dialysis technology and instructing patients, we may effectively lose sight of the "demand side," ignoring the rest of our patients' worlds, and the net impact of our neat regimens on the remarkably dubious assumption that our instructions and exhortations will automatically accomplish the intended benefits. What is missing is adequate preparation of the consumer, the principal player in the drama of progressive chronic renal disease, from pre-end stage to ESRD.

What is missing among us is the living conviction that it's the patients who will do, or not do, what is needed to maintain nutrition and ameliorate progression, or do dialysis well, or not well, between visits to our clinics. What is missing is our understanding that, in our culture in these times, many patients may not be schooled or skilled in self-maintaining, rather than self-destructive, behaviors. This problem is not trivial.

But be of good cheer! As we learned in the MDRD Study, with a solid diagnosis and after remediable causes are excluded, the better scenario begins with the serum creatinine between 1 and 2 mg/dL. Each patient is thereafter recognized as the principal player and the entire health care team as the coaches, all reading from the same page, *believers* that each patient's life and well-being are precious, worth a focused and continuous effort to maintain.

As we learned in the MDRD Study, when the patient gets the message and becomes a believer, then all necessary things become possible. Then the coach–player team can prevent the player from developing undernutrition, establish blood pressure control, witness adherence to diet and medication schedules, and, in some patients, reduce rates of progression. And as a bonus we have found that such patients already have their act together if and when end-stage treatments are indicated.

Conclusion

We now recognize that uremia is a dangerous, wasting illness and that appetite suppression and wasting in patients approaching ESRD may begin much earlier, at much higher levels of GFR, than we have hitherto supposed, very likely contributing to our continuing, unacceptable rates of end-stage morbidity and mortality.

Should we, can we, achieve higher levels of dialysis? Should we, can we, begin dialysis before residual renal urea clearance falls below levels consistent with adequate dialysis? Can patients actually manage their diets, fluid intakes, blood pressure, and medications successfully? If so, will overall per-patient costs of ESRD care decline?

The answer to these questions is yes, provided that we use the two keys to any effective intervention: our expertise as coaches *and* our players' informed action for their own wellness.

The question is, Will our patients now be guided and encouraged toward a brighter, more hopeful future, or will we continue to *do* what we always *did* just to *get* what we always *got*?

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