Dialysis: learning dialysis through computation, experimentation, and implementation

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At the time the *International Society of Nephrology* was founded 60 years ago, a major advancement in the treatment of kidney disease occurred simultaneously—development of a blood-access device using Teflon-coated plastic tubes called the Scribner shunt.[1] This development subsequently led to the creation of arteriovenous fistulas and grafts that facilitated the use of intermittent hemodialysis for patients with end-stage kidney disease. Consequently, maintenance hemodialysis, along with the advancements in peritoneal dialysis, has transformed the field of nephrology and prolonged the life expectancy in patients with advanced kidney disease with limited or no kidney function, in an unprecedented manner.[2] As maintenance hemodialysis and peritoneal dialysis became a unique, but also routine, part of the nephrology discipline, multiple timely publications in *Kidney International* paved the way for in-depth understanding of the physiology, benefits, and adverse consequences of renal replacement therapies. The following articles were selected to illustrate the impact of the journal on dialysis therapies.

Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int. 1985;28:526–534. Measuring the clearance of solutes that accumulate in patients with advanced kidney disease is the backbone for assessing the adequacy of dialytic therapies, as both prescribed and delivered. In a seminal study using data collected during the National Cooperative Dialysis Study, Gotch and Sargent[3] developed the concept of Kt/V_{urea}. This dimensionless construct relates the clearance of urea to its volume of distribution in the patient, where K is the urea clearance of the dialyzer, t is the duration of dialysis, and V_{urea} is the patient's volume of urea distribution. They suggested that the relationship between the outcome of interest in the National Cooperative Dialysis Study (hospitalization) and Kt/V_{urea} was not a continuous function of the level of dialysis (and protein nutrition), but rather a stepwise function (Figure 1). Their conclusions were that a fully adequate dialysis prescription is provided with a protein catabolic rate equal to 1.0 g/kg/d and Kt/V_{urea} of 1.0, further suggesting that maintaining a Kt/V_{urea} range of 1.0 to 1.5 did not associate with treatment failure, that is, inadequate dialysis leading to increased hospitalizations. This concept of measuring dialysis adequacy has been readily adopted by the nephrology community, including the regulatory agencies. To date, urea kinetic modeling based on Kt/V_{urea} predicts morbidity and mortality better than kinetic modeling of any other known solute in maintenance dialysis patients.[4] Although there has been an adjustment period of appropriate implementation and use of Kt/V_{urea}, specifically defining the minimal adequate dose of dialysis and the optimal dose of dialysis above which no additional benefit of increased solute clearance is observed, there is now consensus within the nephrology community for the most appropriate Kt/V_{urea} target, for both hemodialysis and peritoneal dialysis. More recently, the separate and independent impact of dialysis time has been highlighted in several

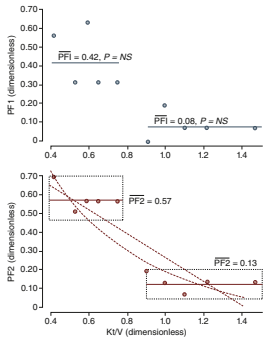

Figure 1 |

Editor's Note

This article is part of the *KI* 60th anniversary series. This month's topic is important contributions to the understanding of hemodialysis and peritoneal dialysis.

publications, along with the timeliness of measurement of dialysis adequacy as the primary outcome metric.[5,6] The implications of most appropriate treatment time, frequency of dialysis, and additional convective transport methods for more-relevant patient-related outcomes, such as quality of life and physical performance, are yet to be defined.[7]

Figure 1 shows the relationships between probability of failure 1 (PF1) and probability of failure 2 (PF2) to the level of dialysis, Kt/V. NS, nonsignificant. Adapted with permission from Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int.* 1985;28:526–534.[3] Copyright © 1985 International Society of Nephrology.

Rippe B, Stelin G, Haraldsson B. Computer simulations of peritoneal fluid transport in CAPD. Kidney Int. 1991;40:315–325. Despite its numerous advantages, maintaining successful long-term peritoneal dialysis has been an ongoing issue. Ultrafiltration failure is one of the leading causes of morbidity and mortality in patients on peritoneal dialysis and eventual transition to hemodialysis.[8] It is therefore crucial to understand the mechanisms of water and solute transport across the peritoneal membrane, in order to both prescribe optimal peritoneal dialysis and determine the drivers of ultrafiltration failure.[9] In a pivotal study published in *Kidney International*, Rippe *et al.* proposed a "three-pore" model, based on computer simulations, to describe the exchange of fluid and solutes across the peritoneal membrane.[10] Their model was based on the concept that approximately 90% of the peritoneal ultrafiltration coefficient was accounted for by small pores, and 5%–8% by large pores. Small solutes (glucose, urea), and larger molecules such as albumin, permeate through the small and large pores, respectively. In addition, they proposed that 2% of the peritoneal ultrafiltration coefficient is accounted for by "transcellular" (ultrasmall) pores, located in the capillary endothelium, which are only permeable to water. Their simulation model predicted that during peritoneal dialysis, the type of osmotic agent used markedly affects the mechanisms of osmosis, and the transcellular/ultrasmall pores are upregulated by infusion of hypertonic glucose into the peritoneum (Figure 2). These predictions led the way for better understanding of molecular mechanisms of peritoneal transport physiology. Further research demonstrated that the water channel AQP1 (aquaporin-1) was in fact the ultrasmall pore predicted by the three-pore model of Rippe and colleagues,[10] which thus far is the only molecular counterpart identified.[11] The molecular nature of the small pores and large pores remains to be studied.

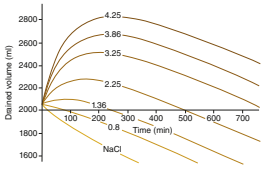

Figure 2|

Figure 2 shows computer-simulated drained volume versus time (V[t]) curves for varying glucose concentrations in the dialysate. Glucose concentrations in the dialysis solution infused are varied from zero (NaCl curve) to 4.25%. Adapted with permission from Rippe B, Stelin G, Haraldsson B. Computer simulations of peritoneal fluid transport in CAPD. *Kidney Int.* 1991;40:315–325.[10] Copyright © 1991 International Society of Nephrology.

Borah MF, Schoenfeld PY, Gotch FA, et al. Nitrogen balance during intermittent dialysis therapy of uremia. Kidney Int. 1978;14: 491–500. It is well known that a wide range of nutritional and metabolic abnormalities are commonly observed in patients with advanced kidney disease.[12,13] Accumulation of uremic toxins was thought to be the primary mechanism for these derangements, and early studies in patients initiated on maintenance hemodialysis (MHD) showed improvements in their appetite and weight.[14] However, these initial improvements in nutritional status are not sustained over longer periods of time, suggesting that hemodialysis therapy may not only fail to preserve nutrition stores but also could be contributing to the worsening of the overall nutrition state in patients on MHD.[15] In a series of elegant experimental studies performed in a clinical research center, Borah *et al.* examined the protein catabolic effects of hemodialysis treatments in 5 MHD patients during 2 different levels (high and low) of dietary protein intake over a period of 7 days for each intervention (Figure 3).[16] During ingestion of high (1.4 g/kg of body weight) protein intake, nitrogen balance was positive on nondialysis days but negative on dialysis days; during ingestion of low (0.54 g/kg of body weight) protein intake,

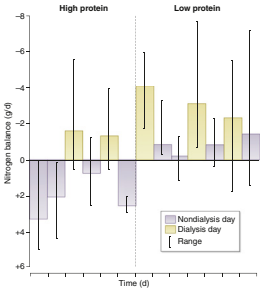

Figure 3|

nitrogen balance was approximately zero on nondialysis days but was remarkably negative on dialysis days. They concluded that the negative nitrogen balance during hemodialysis could result from amino acid loss in dialysate. This seminal study led the way to multiple subsequent studies showing the catabolic nature of hemodialysis—above and beyond just nutrient losses during dialysis—instigating systemic inflammatory response, increasing energy expenditure, and causing mitochondrial dysfunction.[17–19] It also formed the foundation for recommendations for nutritional supplementation during hemodialysis, which is now implemented worldwide.[12,20]

Figure 3 shows daily tissue nitrogen balance in 5 patients receiving intermittent dialysis therapy during ingestion of high (1.4 g/kg) and low (0.5 g/kg) protein intakes. Adapted with permission from Borah MF, Schoenfeld PY, Gotch FA, et al. Nitrogen balance during intermittent dialysis therapy of uremia. *Kidney Int.* 1978;14:491–500.[16] Copyright © 1978 International Society of Nephrology.

Hakim RM, Fearon DT, Lazarus JM. Biocompatibility of dialysis membranes: effects of chronic complement activation. Kidney Int. 1984;26: 194–200. As maintenance hemodialysis became a mainstay therapy for patients with end-stage kidney disease in the early 1980s, it also became clear that the treatment was associated with significant adverse effects. Complement activation, due to the interaction between blood and the dialysis membrane commonly used at the time (i.e., cuprophane membrane), was one of the early recognized undesirable aspects of hemodialysis.[21] The consequences of complement activation, such as leukoaggregation, histamine release from mast cells, and an increase in capillary pulmonary permeability, were aptly termed "bioincompatibility."[22] Hakim and colleagues studied 10 patients on MHD using 3 different types of hollow fiber membranes, namely cuprophane, cellulose acetate, and polymethylmethacrylate, to understand the effects of these biochemically different synthetic dialyzers.[23] Clinical and biochemical measures were obtained during each hemodialysis procedure at the first and last hemodialysis sessions over a month, for all 3 dialyzers. The same sequence was repeated for all patients using dialyzers that were treated with 2% formaldehyde for reuse. Their results showed that when using new membranes, cuprophane caused the most intense complement activation, whereas polymethylmethacrylate surfaces caused the least activation of the complement system (Figure 4). The extent of complement activation paralleled the ability of these membranes to induce neutropenia during hemodialysis. They also showed that recurrent dialysis with new cuprophane and cellulose acetate membranes led to a decrease in pre-dialysis neutrophil count, as well as a more intense activation of complement.[23] The implications of these results were that hemodialysis with intensely bioincompatible membranes not only induced acute intradialytic complications, but also predisposed MHD patients to weakened immune response and increased infection risk, and in subsequent studies, it was associated with higher mortality in patients on MHD[24] and a reduced recovery in patients with dialysis requiring acute kidney injury.[25] These data, along with other seminal publications, led the industry to develop dialyzers equipped with membranes that are better tolerated, which are now exclusively used, although these so-called "biocompatible" membranes do still induce adverse biological responses such as a low level of complement activation, an increase in systemic inflammatory response, and endothelial cell activation.

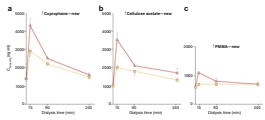

Figure 4|

Figure 4 shows C3a-desArg level for cuprophane, cellulose acetate, and polymethylmethacrylate membrane dialyzers as a function of dialysis time. Solid lines indicate efferent samples; dotted lines indicate afferent samples. Adapted with permission from Hakim RM, Fearon DT, Lazarus JM. Biocompatibility of dialysis membranes: effects of chronic complement activation. *Kidney Int.* 1984;26:194–200.[23] Copyright © 1984 International Society of Nephrology.

Ortiz C, Meneses R, Jaffe D, et al. Outcome of patients with human immunodeficiency virus on maintenance hemodialysis. Kidney Int. 1988;34:248–253. After the introduction of maintenance dialysis in the 1960s as a long-term therapy, the treatment was offered to only those individuals with minimal comorbidities, owing to

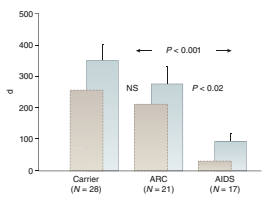

Figure 5|

scarcity of resources. The advances in technology over the next 2 decades allowed the opportunity to be on maintenance dialysis for patients who also had other chronic diseases and were deemed unsuitable for long-term renal replacement therapy. The epidemic of HIV led to a sizable number of HIV-infected patients developing renal complications, as well as some patients on maintenance dialysis acquiring the disease. Early case series reported dismal outcomes in patients with acquired immunodeficiency syndrome (AIDS) requiring MHD.[26] On the other hand, there was a noticeable increase in the number of patients with asymptomatic HIV carrier status and patients with AIDS-related complex. In a pioneering study, Ortiz *et al.* reported their experience and the outcome of 51 patients at different clinical stages of HIV infection who were on MHD.[27] Their results showed that 17 patients who developed AIDS died after a mean of 93 ± 32 days on MHD, whereas 12 asymptomatic HIV carriers were alive after a mean follow-up of 488 ± 75 days (Figure 5). Five patients with AIDS-related complex were alive after 564 ± 191 days. Notably, the improved survival in asymptomatic HIV carriers was evident for patients who had superimposed HIV infection while on MHD, and those for whom the etiology of renal disease was associated with primary HIV infection. This study was the impetus to offer patients with HIV who had advanced kidney disease the option for maintenance dialysis with notable improvement in life expectancy.[28] It also reemphasized the importance of considering patient-specific factors for initiation and management of maintenance dialysis.[29]

Figure 5 shows duration on maintenance hemodialysis of each clinical stage of HIV infection. Blue bars indicate means ± SE; brown bars indicate medians. AIDS, acquired immunodeficiency syndrome; ARC, AIDS-related complex; NS, nonsignificant. Adapted with permission from Ortiz C, Meneses R, Jaffe D, et al. Outcome of patients with human immunodeficiency virus on maintenance hemodialysis. *Kidney Int.* 1988;34:248–253.[27] Copyright © 1988 International Society of Nephrology.

DISCLOSURE

TAI reports personal fees for consultant service from Fresenius Kabi, Abbott Nutrition, and the International Society of Nephrology.

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