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Kristen Tillquist, Stephanie Floyd, and Ankur Shah

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Peritoneal Dialysis Adequacy: Too Much of a Good Thing?

Kristen Tillquist¹,², Stephanie Floyd¹,², Ankur D Shah²,³

¹ Kent Hospital/Brown University Internal Medicine Residency, Warwick, RI, ²Warren Alpert Medical School of Brown University, Providence, RI, ³Division of Kidney Disease and Hypertension, Department of Medicine, Rhode Island Hospital, Providence, Rhode Island

Corresponding author:
Ankur Shah, Division of Kidney Disease and Hypertension, Department of Medicine, Rhode Island Hospital, Warren Alpert Medical School of Brown University, 375 Wampanoag Trail, East Providence, RI 02915. (P) 401-649-4060 (F) 401-649-4061

Email: ashah8@lifespan.org
The concept of peritoneal dialysis (PD) was first discovered in 1877 when Georg Wegner placed fluids of varying tonicities in rabbits’ intraperitoneal cavity, discovering that the tonicity of the fluid administered effected the volume of fluid present in that space (1). In 1923, this was first applied in humans by Heinrich Necheles (2). Adequacy of dialysis as concept has for much of the history of dialysis been limited to kinetic modeling of a single small solute, urea. This was the evolution of other small solute targets including time-average urea, and urea reduction ratio in hemodialysis and creatinine clearance in PD (3). The evolution of adequacy targets in PD demonstrates the risk and reward of observational studies. Earlier observational studies prompted guidelines to change resulting in increased burden of dialysis on patients, but without subsequent observational we would not have seen a need for the randomized controlled trials that followed that continue to guide our care today.

The story begins with the CANUSA trial published in 1996. This, prospective observational cohort trial included 680 incident continuous ambulatory PD patients. The outcomes of interest included dialysis adequacy and nutritional status with various end points including mortality, morbidity, and technique failure (considered as the need to transition to either intermittent PD or hemodialysis). Adequacy was assessed by measuring Kt/V every week, total weekly creatinine clearance and serum beta-2 microglobulin. Of note, prescriptions were not standardized but rather at the discretion of the prescribing provider. They concluded that a higher clearance achieved by dialysis and residual kidney function combined was associated with both decreased mortality and technique failure as for every 0.1 unit Kt/V per week decrease, there was a 5% increase in the relative risk of death (4).

With this new information available, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines published in 1997 recommended that for CAPD patients the minimum weekly kt/v should be at least 2.0. Furthermore, in CCPD patients the minimum weekly kt/v was recommended to be set at 2.1, and in NIPD patients 2.2. These targets resulted in a population of patients who were clinically thriving but required an increase in delivered dialysis to be determined “adequate.” This increased dose of dialysis came at the cost of time, affecting quality of life (5). It is also recognized that increased dialysate exposure is not benign as an inherent risk of the procedure is glucose absorption. This understandably can cause metabolic issues such as increased secretion of insulin in response to elevated blood glucose levels and subsequent weight gain. Along with glucose, glucose degradation products are also absorbed and have been linked to vascular dysfunction not unlike that seen in diabetic patients as well as increased interleukin-6 levels which lead to an overall inflammatory state which has its own negative implications (6).

Between 1998 and 2000, four studies were published demonstrating the importance of residual kidney function on survival. Davies et. al. was the first, with data showing that residual renal function is lost at an accelerated rate in patients who did not survive during the 6 year period during which the study was completed when compared to those who did survive (7). A year later, Diaz-Buxo et. al. found similar outcomes when they concluded that there was a strong correlation between survival and residual renal function, but there were not similar findings when evaluating peritoneal clearance (10). Szeto et. al.’s data from 2000 supported this, also findings that residual renal function and not peritoneal Kt/V was an independent predictor of survival which made it clear that just increasing peritoneal clearance wasn’t equivalent to
preserving renal function when it came to mortality in this population (9). That same year, Rocco et al. contributed that the risk of death was decreased by 40% with each 10 L/week/1.73 m² increase in the urinary contribution of weekly creatinine clearance and by 12% for every 0.1 unit increase in the urinary contribution of weekly \( \text{Kt/V} \) (8). This data prompted Bargman et al to re-evaluate the relative contributions of peritoneal \( \text{kt/v} \) and residual \( \text{kt/v} \) on mortality in the CANUSA trial. It was discovered that for every 5 L/week per 1.73 m² increase in GFR, relative risk of death was decreased by 12%, but for every 250 mL increase in urine volume seen in these patients, the relative risk of death was decreased by 36% (11). These findings suggest that not only are residual kidney function and peritoneal clearance not equal, but that residual kidney function is more essential.

While the relative importance of residual kidney function compared to peritoneal clearance was becoming more accepted, it had not yet been testing in a prospective randomized controlled trial. The first study designed to address this concern was the Adequacy in Mexico (ADEMEX) trial. It was a randomized controlled trial involving 965 patients evaluating the impact of increased peritoneal clearance. Participants randomized to receive 60 L/week per 1.73 \( \text{m}^2 \) creatinine clearance vs 4 daily 2L exchanges which resulted in approximately 45 L/week per 1.73 \( \text{m}^2 \). The study showed no difference in overall survival between the two groups, even after considering other factors known to decrease life expectancy in PD patients including diabetes mellitus, anuria, serum albumin, etc (12). The study also re-demonstrated that residual kidney function was associated with patient survival.

Further supporting these findings, a subsequent study was completed by Lo et al. with a similar primary intention of investigating the role of peritoneal \( \text{Kt/V} \) on survival and clinical outcomes. This RCT evaluated 320 incident continuous ambulatory PD patient’s mortality and clinical outcome based on the level of \( \text{Kt/V} \) achieved. They were divided into 3 groups with increasing \( \text{Kt/V} \) goals from 1.5-1.7, to 1.7-2, and >2. There was no difference in survival amongst the three groups. In the group randomized to 1.5-1.7 there was an increase in patients being transferred to hemodialysis by their physicians due to inadequate dialysis or ultrafiltration and also increased requirement of erythropoietin (13).

These studies helped influence NKF-KDOQI to update their guidelines in 2006 to state that \( \text{Kt/V} \) should be at least 1.7 per week or above, which was less stringent than their prior recommendation of \( \text{Kt/V} \) of 2.0 or above (13). While these guidelines consider both peritoneal and residual clearance, they still consider the simple additive sum while the ADEMEX and Lo trials have demonstrated the greater importance of residual \( \text{kt/v} \) to peritoneal \( \text{kt/v} \). The importance of residual kidney function was also emphasized in the 2006 guidelines (14). The new guidelines resulted in many more patients being able to receive PD at a decreased burden, but still emphasized primarily small solute clearance.

While the 2006 guidelines stated “Regardless of delivered dose, if a patient is not thriving and has no other identifiable cause other than possible kidney failure, consideration should be given to increasing dialysis dose”, clinical practice developed a very \( \text{kt/v} \) centric approach to prescription writing in the US. In response, the KDIGO Controversies Conference on Dialysis Initiation Modality Choice and Prescription meeting in January 2018 focused on these guidelines and the need for change as it was recognized that achieving a set \( \text{Kt/V} \) goal is not enough to
decide if clearance is adequate or not, and this method was negatively impacting a large number of patients’ quality of life and health. They suggested that dialysis should now be assess as “goal directed” rather than “adequate”, and that this would mean the patient’s life goals were considered when the physician was preparing an individualized care plan. This would mean that not only lab values, volume status, nutritional status, and small solute clearance were deemed important when it came to evaluating a PD patient’s prescription, but also their overall goals and sense of satisfaction/well-being. As a result, the Guideline Committee of the International Society for Peritoneal Dialysis (ISPD) convened to produce a new guideline (15).

The updated January 2020 ISPD guidelines reflect the changes mentioned above including a shift in terminology used to describe the proper amount of dialysis attained from “adequate” to “goal directed”, including multiple aspects to meet optimal “goal directed” care including residual kidney function, nutritional status, as well as patient’s sense of well-being and satisfaction with their treatment. The impact of the burden of time spent fulfilling their dialysis prescription on their ability to carry out normal day-to-day tasks as well as psychosocial status are now included as important factors in assessing if dialysis prescriptions are adequate. Finally, it is now mentioned that there is no specific target for clearance to meet to ensure PD prescriptions are satisfactory (15).

Over the course of multiple decades, the question of “what goal should we attain to ensure PD prescriptions are optimal?” is still not fully answered, but there has been a clear evolution in the guidelines. We have seen observational evidence result in adequacy targets which brough undue burden to patients but which also spawned randomized controlled trials which have helped guide patient care for nearly 2 decades. Finally, we have seen a growth in the field of nephrology in which the term adequacy has developed from a synonym for clearance of a single small solute to a term for a holistic assessment of the patient. We have learned that in peritoneal dialysis, there is such a thing as too much of a good thing.

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