EDITORIAL

Continuous Ambulatory Peritoneal Dialysis—Quo Vadis?[1]

This issue of the *Journal* contains two seminal articles dealing with the relative risk of death on peritoneal dialysis (PD) compared with hemodialysis (HD)(1,2). They focus on the period between 1987 and 1989. In order to place these studies in perspective, it is helpful to understand how PD has evolved and especially how it was practiced during the late 1980s.

In 1979, the Northwest Kidney Center reported on a cohort of prevalent ESRD patients treated with intermittent PD between 1975 and 1978 (3). Patient survival at 3 yr was unacceptably low at 55%, and technique survival was less than 30%. The cause of each outcome was thought to be inadequate dialysis, and the authors concluded that technique survival could have been much better ". . . if dialysis time had been increased in proportion to the decline in residual renal function." In reviewing this study, many observers thought that the outlook for PD as a treatment modality for ESRD patients was dismal. However, during this same period, the technique of PD was undergoing a revolutionary change. In 1976 Popovich, Moncrief, and coworkers introduced the concept of continuous ambulatory peritoneal dialysis (CAPD) (4). On the basis of earlier studies of solute kinetics in PD, they proposed that the average ESRD patient could be maintained with five 2-L dwells and about 2 L of ultrafiltrate per day (see Ref. 6). Within 2 yr, clinical studies supporting the validity of CAPD appeared (5–8). The first patient treated with CAPD was transferred from HD because of vascular access failure and probably had no residual renal function. Perhaps that explains, in part, the original authors' recommendation of 12 L of equilibrated daily drainage. Although the concept of KT/V_{urea} had not been developed at that time, the amount of dialysis recommended by the authors would be equal to a KT/V_{urea} value of 0.29 daily, or 2.03 per week for an anephric, 70-kg patient. Today, this level of therapy is probably achieved only at the start of PD when patients have a significant amount of residual renal function.

In fact, as CAPD gained wide acceptance throughout the United States, Canada, and Europe, it became common practice to prescribe four 2-L exchanges daily or less. On the basis of the 1992 report of the USRDS, only 68% of PD patients had a prescription of four 2-L exchanges per day (55 to 60 L/wk). A lower dialysis volume was prescribed in 27% of patients, whereas only 4% of patients use larger weekly volumes (9). Only recently it has become clear that this diminished prescription is further compounded by poor patient compliance. Keen *et al.* (10) have shown, by following creatinine kinetics in PD patients, that only 78% of prescribed dialysis is delivered in CAPD. In 1985, it was suggested that the dose of dialysis should be measured by the use of urea kinetics and then adjusted as a function of the patient's urea volume of distribution and residual renal urea clearance (11). This approach, however, was not generally adopted. In recognition of the continuing widespread practice of prescribing just 8 L of instilled dialysate daily, similar suggestions (12,13) appeared again in 1989 and 1990. This was followed by a series of studies relating clinical outcome to the dose of dialysis, as measured by urea kinetics (13–18). These studies demonstrated a relation between dialysis dose and survival (14–16), hospitalization (17), and serum albumin (14) which, in turn, was also an independent predictor of survival. Although the target KT/V to achieve adequate clinical outcome in these studies varied from a weekly KT/V of 1.7 to 2.3, in general, these studies suffered from their small sample size and the cross-sectional nature of the analysis in several cases.

Nevertheless, these same studies anticipated the results of the first large-scale, prospective, multicenter study of CAPD, the Canadian-USA study (CANUSA) (19). This study enrolled a cohort of 698 patients and, at the time of the first report (19), monitored them for a period of 2 yr. The primary finding in this preliminary report is that the dose of dialysis, expressed as KT/V, is a significant predictor of outcome. Moreover, this is true even after confounding factors such as age, diabetic status, cardiovascular disease, and serum albumin level have been taken into account. Churchill *et al.* (19) showed a significantly higher mortality in patients treated at a KT/V_{urea} level of less than 2.3/wk compared with those treated at higher values. However, the relation between KT/V and survival was not a step function but rather a graded relation, indicating a gradually decreasing survival rate as weekly KT/V fell from 2.3 to 2.1, to 1.7, *etc.* Although this study has been published as an abstract, it has also been presented at the annual meetings of both the Canadian and the American Societies of Nephrology and no major shortcomings of the study design have yet to appear.

In a smaller study, Brandes *et al.* (15) have also demonstrated that good clinical outcomes are associated with a KT/V_{urea} level of 2.3/wk (and creatinine clearances of 71 L/wk). After reviewing these studies, Blake and Daugirdas (20) concluded that the optimal therapy achieved in the CANUSA study could only be

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prescribed for functionally anephric patients weighing less than 62 kg and then only with 12 L of infused dialysate. Nolph *et al.* had already come to a similar conclusion and suggested that underdialysis would also result in inadequate protein intake (21). They also insisted that quantification of delivered dialysis should be a practice standard in PD (22). Churchill has recently presented a concise but thorough review of the adequacy of PD (23).

The important conclusion to be drawn from these studies is that the dose of dialysis is a significant, independent predictor of clinical outcome in CAPD. Although the significance of dialysis dose in PD, and especially the contribution of residual renal function, has been recognized at least since 1971 (3), it is only recently that these factors have been adequately emphasized (19,24). Unfortunately, it remains doubtful that these principles have been incorporated into the routine practice of PD. For example, reporting on 634 incident CAPD patients treated between 1986 and 1987, the U.S. Renal Data System (USRDS) found that only 68.1% were prescribed between 7.8 and 8.6 L/day and for 25.2%, the prescription was 6.4 L/day or less (25). In a more recent survey of CAPD practice patterns, Gentile found that the vast majority of patients still use four 2-L dwells daily (26); the situation for cycler-based PD may be more dismal. In 1989, the mean daily solution volume was 11.2 L (27). Even if we assume a relatively high $D:P_{urea}$ ratio of 0.7, this modality would provide less clearance ($0.7 \times 11.2 = 7.84$ L/day) than standard CAPD.

The basis of these practice patterns and the sense of complacency that prevailed in the PD community during that period can be traced to a series of studies published between 1987 and 1991 (28–33). The focus of those reports was the risk of death on PD compared with that on HD. In aggregate, they tended to show no difference in mortality for the two modalities or, in one study (29), improved survival among patients treated with CAPD. It was reassuring to many to find that mortality on CAPD was equal to, or less than, that on HD. However, such comparisons suffered from two major drawbacks. The first is that these comparisons were limited to 1-yr survival rates and generally to the first year of dialysis. (An exception to this is the 5-yr study of Lameire *et al.* (17).) Several studies have since shown that PD patients maintain their residual renal function better during the first year than do patients initiating HD (34). Thus, such comparisons should span more than 1 yr to allow for the effect of the decline of renal function on survival to become apparent. Few such studies are available, but the 1995 USRDS report sheds light on this issue. For patients between the ages of 45 and 64 yr old, treated with CAPD/continuous cycling peritoneal dialysis (CCPD) on Day 90 of ESRD, only 39.8% remain on the therapy at 2 yr, whereas 30.6% had died and 15.5% had switched to center HD (and 9.2% had been transplanted). For the equivalent age bracket, 54.6% remained on HD at 2 yr, 28.4 died, and 3.5% switched to CAPD/CCPD. Such data point out the difficulty of conducting long-term studies on PD patients: because PD is a modality of approximately 20% of patients starting ESRD in the United States, only 8% of such patients remain on PD therapy at the end of 2 yr—too small a percentage to do statistically valid studies, even in large units. Hence, the importance of the two studies by Bloembergen *et al.*, which are based on a national sample accessible to the USRDS and presented in this issue (1,2). Studies deficient in the number of patients and/or limited in the duration of follow-up or less than optimal in study design (*i.e.*, not randomized or prospective) may not provide an accurate assessment of the relationship between dose of dialysis and survival in PD patients.

The other major drawback to such comparisons is the fact that the mortality rate on HD was also unacceptably high in the United States. This became apparent with the publication of the Dallas conference in 1990 (35) and the subsequent review of the adequacy of HD (36). Even after these publications, few in the PD community acknowledged that the death rate may also be unacceptably high among PD patients. It was not until Nelson *et al.* (37) examined the large data base contained in the Michigan Kidney Registry that a higher death rate was found in older, diabetic patients treated with PD. This finding was subsequently confirmed by Held *et al.* (38).

In this issue of the *Journal*, Bloembergen and her colleagues (1) used data gathered by the USRDS during the years 1987, 1988, and 1989 to address the question of the relative risk (RR) of death on PD *versus* HD. It is important to recognize that this data base reflects dialysis outcome from a large sample of U.S. facilities, not just those academic centers that are likely to conduct and publish studies, *i.e.*, this source is likely to reflect the outcome of dialysis modalities as commonly practiced in the United States. Bloembergen *et al.* reviewed 42,372 deaths occurring over 170,700 patient years. Thus, during the period studied by Bloembergen *et al.* (1,2), the dose of dialysis was fixed and clearly low and the PD community was secure that clinical outcome on this modality was comparable to that on HD. After adjusting for age, race, gender, diabetic status, and duration of dialysis, they found an RR of death on PD of 1.19 ($P < 0.001$) compared with that on HD. Although the risk was only significant after age 55 yr, the RR was significantly accentuated in patients with diabetes (1.38; $P < 0.001$) and in women *versus* men (1.30 *versus* 1.11; $P < 0.001$). In a companion article (2), also in this issue, the authors compare the cause of death between patients treated with HD and PD. Once again, each of the demographic factors listed above was adjusted for in this analysis. Five causes of death were significantly higher in PD- compared with HD-treated patients. These included infection (RR = 1.42; $P < 0.001$), myocardial infarction (RR = 1.31; $P < 0.001$), withdrawal from dialysis (RR = 1.21; $P < 0.001$), cerebrovascular disease (RR = 1.2; $P < 0.002$), other

cardiac causes (RR = 1.09; $P < 0.004$), and "other causes" (RR = 1.19; $P < 0.001$). Moreover, a number of important interactions were found, as indicated in their Table 2. For example, the PD/HD RR for death due to myocardial infarction was 1.51 for diabetic *versus* 1.20 for nondiabetic patients and there was a striking increase in PD/HD RR in women *versus* men for death due to infection (RR = 1.58 for women *versus* 1.28 for men; $P < 0.001$).

The authors acknowledge several shortcomings in their studies, the chief of which was that they were unable to include comorbidity in their analysis. Comorbidity is known to be a major predictor of survival in CAPD patients (39). They point out, however, that in the USRDS Case Mix Study, there was little or no difference in the type of comorbidity in patients assigned to HD or PD (38). They acknowledge, however, that there are no data on the relative *severity* of comorbidity in the two treatment groups. Another major shortcoming in these studies is that the dose of dialysis delivered in the two modalities is not known. A series of factors may have contributed to the delivery of a low dialysis dose in PD in the late 1980s. As indicated above, it was probably common practice not to quantify treatment, to prescribe only four 2-L exchanges daily, to allow noncompliance to go undetected, and to ignore the loss of residual renal function. The result of this approach to the PD prescription is that the dose of dialysis delivered during that period was probably far below the original recommendation of Moncrief and Popovich.

Although the authors avoid concluding that there is a causal relation between outcome and modality selection, the implications of these two articles are daunting. Patients assigned to PD, as practiced in the 1987 to 1989 period in the United States, had a significantly higher risk of death than did patients assigned to HD. Moreover, this risk is accentuated in patients with diabetes, those over 55 yr old, women, possibly patients at risk of coronary disease, those at increased risk of infection, and patients who are likely to be on PD for more than 1 yr. In effect, these articles suggest a list of risk factors that should be seriously considered when helping a patient to select a treatment modality for ESRD. We should also add to this list the proposition that if an optimal dose of dialysis ($KT/V_{urea} \geq 2.1$)(19) cannot be delivered and maintained, patients should be cautioned about selecting or continuing PD. An alternative approach would be to improve the dose of dialysis. Cycler-based PD seems to be an obvious alternative. However, as indicated above, with the typical $D:P_{urea}$ ratios in the range of 0.6 or 0.7 in automated PD, it would require a daily drain volume of 19 to 23 L to achieve the optimal KT/V_{urea} of 2.3/wk (0.328 daily) in a 70-kg anephric patient. Although current technology can achieve this goal, the nearly threefold increase in dialysate cost is clearly prohibitive and probably unacceptable to most patients' lifestyles in terms of immobility. If CAPD is to survive as a credible long-term therapy for ESRD patients, it must have the capacity to deliver optimal renal replacement therapy at a cost within reimbursement levels. In addition, innovative methods to monitor compliance, such as that used by Keen *et al.* (10), should become standard practice in this type of home therapy.

Although there is increasing evidence that the dose of dialysis is a major predictor of clinical outcome in PD, there are a limited number of studies that have not supported this conclusion. In a longitudinal analysis of 76 patients studied for a mean of 20 months, Blake and colleagues (40) found that urea kinetic parameters did not predict hospitalization, clinical outcome, or death. Comparing their high and low KT/V groups, those investigators found no differences in the number of deaths or days of hospitalization. Although they explored an exhaustive number of variables, Blake and colleagues did not include serum albumin in their initial analysis. In a subsequent analysis of their data, however, based primarily on a more accurate method of estimating urea volume of distribution, Blake *et al.* did find an excess mortality in patients with daily KT/V values less than 0.214 (41). More recently, it was particularly disappointing when the 1993 NIH Consensus Conference on Dialysis recommended a weekly KT/V_{urea} of just 1.7.

Finally, the contrast in outcomes between HD and PD is further accentuated by the recent report of Habach *et al.* (42). Those authors used the USRDS data base to examine the hospitalization rate of PD and HD patients during the late 1980s and found a 14% higher rate of hospitalization for PD patients (after adjusting for comorbid conditions). This difference was more pronounced in black patients, compared with white, 1.22 *versus* 1.11, and in older diabetic patients (RR = 1.12).

It is almost 25 yr since the PD community recognized the need to increase the peritoneal component of KT/V_{urea} as residual renal function declined; this issue has been recently emphasized by Diaz-Buxo (43,44). Dialysis doses similar to the optimal PD dose found in the CANUSA study were recommended as early as 10 yr ago, and clinical studies have now validated these recommendations. The only remaining questions are—will they be incorporated into routine practice? and how will clinical outcome with optimal CAPD therapy compare with that with HD therapy? Such a study is planned by the USRDS in their "dialysis morbidity and mortality study." Until then, it should be clear that the PD practice patterns of the late 1980s are no longer acceptable and that these patients deserve not only adequate but optimal dialysis, defined as "the dose at which no further improvement in morbidity and mortality can be expected" (36). If these studies by Bloembergen *et al.* stimulate the PD community to optimize therapy, perhaps we will see a comparable study in several years—one that compares CAPD as originally formulated by Moncrief and Popovich with concurrent HD therapy. In the mean-

time, one should be wary of halfway measures. As President Kennedy once said: "Good judgment comes from experience; experience comes from bad judgments."

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