

# NEPHROLOGY

# Rounds®

AS PRESENTED IN THE ROUNDS OF  
THE NEPHROLOGY DIVISION OF  
BRIGHAM AND WOMEN'S HOSPITAL  
BOSTON, MASSACHUSETTS

## Making the Case for Peritoneal Dialysis

BY J. KEVIN TUCKER, MD

In 2004, there were approximately 310,000 prevalent patients receiving hemodialysis (HD) in the United States (US) compared with 25,765 patients who were receiving peritoneal dialysis (PD; Figure 1).<sup>1</sup> Thus, only about 8% of patients with end-stage renal disease (ESRD) in the US were receiving PD as renal replacement therapy (RRT), whereas in Canada, the United Kingdom, and continental Europe, the numbers were much greater.<sup>2</sup> PD offers patients with ESRD a home-based alternative to center-based hemodialysis and it is especially appealing to patients who are motivated to be involved in their own care, those who wish to continue working, and those with the competing demands of family life. This issue of *Nephrology Rounds* explores some of the reasons why PD deserves a "second look" and challenges some of the misconceptions that prevent its more widespread use as a form of RRT.

### Peritoneal dialysis as a treatment option: why choose PD?

While PD and HD both offer patients with ESRD a means of partially replacing the function of healthy kidneys, PD offers a clear advantage in terms of patient satisfaction, preservation of residual renal function, and preservation of vascular access sites.

#### Patient satisfaction

Studies of patient satisfaction with dialysis care indicate that PD patients are generally more satisfied with their care than their counterparts on HD. Among the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) cohort, patients receiving PD were 1.5 times more likely to rate their dialysis care as excellent than patients receiving HD.<sup>3</sup> PD patients in the CHOICE cohort were also more satisfied with the availability of their nephrologists than were HD patients, despite the fact that, typically, in-center HD patients are seen more frequently by their nephrologists. PD patients also report that dialysis therapy has less impact on their lives in a number of domains.<sup>4</sup>

#### Preservation of residual renal function

Residual renal function is an important predictor of survival in PD patients and may affect quality of life in HD patients.<sup>5</sup> In clinical practice, however, residual renal function is more routinely measured in PD patients than in HD patients because renal Kt/V is added to peritoneal Kt/V in measuring the adequacy of small solute clearance. Furthermore, PD patients have a slower rate of decline in residual renal function than do HD patients.<sup>6</sup> Since it is easier to meet small solute targets in the HD patient who has no residual renal function than in the PD patient who has no residual renal function, the case can be made for utilizing PD as the modality of first choice in young patients with ESRD. Such patients will likely need HD, PD, and renal transplantation as RRTs over their lifetime. PD may be offered as a bridge to transplantation, while the patient has good residual renal function, thus making it easier to meet small solute clearance targets and preserve renal function. If the kidney allograft fails, the patient could potentially return to PD and further delay the need for HD. Then, when a patient has to utilize HD, the upper extremities will have been preserved for vascular access. The preservation of residual renal function may also confer an important survival benefit in PD. Wang and colleagues reported that for every 1 mL/min/1.73 m<sup>2</sup> increase in residual glomerular filtration rate (GFR), there was a 50% reduction in all-cause mortality and cardiovascular death among their cohort of PD patients.<sup>7,8</sup>

#### Preservation of vascular access sites

Patients with long-standing ESRD are often referred for PD when they have exhausted their vascular access sites in the upper extremities. Many of these patients are anuric, relying completely upon dialysis for solute clearance and volume control. Given the survival benefit



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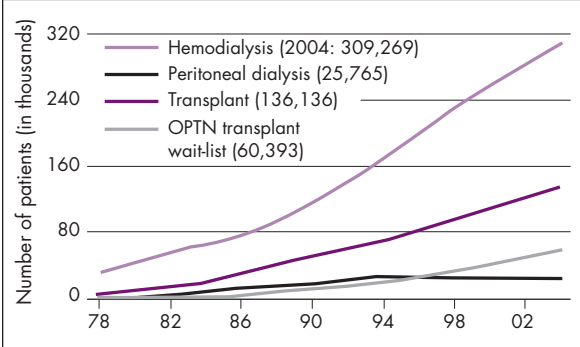
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**Figure 1: USRDS data from 2004 showing numbers of patients receiving various modes of renal replacement<sup>1</sup>**



USRDS = United States Renal Data System  
OPTN = Organ Procurement and Transplantation Network

associated with residual renal function and the prolongation of residual renal function with PD,<sup>8</sup> the preferred sequence of RRT is PD first, and HD second, often with transplantation intervening between the two dialysis modalities. Using PD first allows maximal utilization and preservation of residual renal function. If the patient can no longer sustain PD for any reason (eg, peritonitis, ultrafiltration failure, or burnout), he/she still has pristine upper extremity vascular access sites for fistula creation. This sequence of PD first is especially important for young patients who, in the course of their lifespan, will likely need all three modes of renal replacement.

### Mortality: PD versus HD

One of the factors that may influence nephrologists as they guide patients through their choices of RRTs, is the impact of the dialysis modality on mortality. Studies of mortality outcomes comparing HD and PD have yielded conflicting results. In a study of 4,921 dialysis patients from the Danish Terminal Uremia registry, Heaf and colleagues found a survival advantage for PD during the first 2 years of dialysis treatment.<sup>9</sup> A similar survival advantage for PD relative to HD in the first 2 years of dialysis treatment has been reported among Canadian patients.<sup>10</sup> Technical and nontechnical improvements in PD may also account for improved survival of Canadian PD patients over the 16-year period from 1981-1997.<sup>11</sup> However, among the CHOICE cohort, Jarr et al reported an increased mortality risk for PD relative to HD in the second year of dialysis, but not in the first year.<sup>12</sup> There are several potential explanations for these findings from the CHOICE cohort and they have been thoroughly reviewed by Bargman and Piraino.<sup>13,14</sup>

The primacy of patient choice in modality selection makes randomized trials of PD versus HD difficult to complete, forcing a reliance upon observational studies for conclusions about mortality differences between the 2 modalities. One such randomized study was undertaken in the Netherlands with a planned sample size of 100; however, after an inclusion period of >3 years, only 38 patients had been randomized and recruitment was discontinued.<sup>15</sup> In this small sample, the adjusted mortality hazard for HD versus PD was 3.6.

While the issue of survival differences between the two modalities remains unsettled, it is clear that when given education regarding the two modalities, patients often have clear preferences that may not change, even if there were proven differences in survival.<sup>3,13</sup>

### Infectious complications

Infectious complications, particularly peritonitis, remain the leading causes for modality failure in PD; however, advances in PD technology, such as “Y-set” catheter connections, the use of the “flush-before-fill” technique, and antibiotic prophylaxis have reduced the number of infectious complications.<sup>16</sup> Yet, there is a common perception among both patients and nephrologists that PD is associated with greater infectious risk than HD. Aslam et al examined infection rates among HD and PD patients in a single urban center and found that, overall, infection rates were the same in the two groups of patients, but differed by types of infections.<sup>17</sup> Bacteremia and fungemia occurred only in HD patients; peritonitis occurred only in PD patients.

Nasal carriage of *Staphylococcus aureus* is a major risk factor for tunnel infections, exit-site infections, and peritonitis.<sup>18</sup> The application of mupirocin cream at exit-sites has been shown to reduce rates of exit-site infections and peritonitis from Gram-positive organisms.<sup>19</sup> The reduction in *S. aureus* infections led to the emergence of *Pseudomonas aeruginosa* as a leading cause of exit-site infections. Gentamicin cream applied at the exit-site reduces the occurrence of both *S. aureus* and Gram-negative (including *Pseudomonas*) infections and should be applied as a best practice (Figure 2).<sup>20</sup>

### Adequacy

Stringent targets for small solute clearance may have discouraged nephrologists from offering PD to certain groups of patients (eg, large patients and those with no residual renal function). As with HD, Kt/V<sub>urea</sub> was thought to be an important predictor of survival. The Canada-USA Peritoneal Dialysis Study (CANUSA) of 680 patients in Canada and the US, examined the relationship between adequacy of dialysis to mortality, technique failure, and hospitalizations.<sup>21</sup> In CANUSA, a decrease of 0.1 unit

**Figure 2: Gentamicin was more effective than mupirocin in preventing exit site infections in both incident and prevalent PD patients<sup>20</sup>**

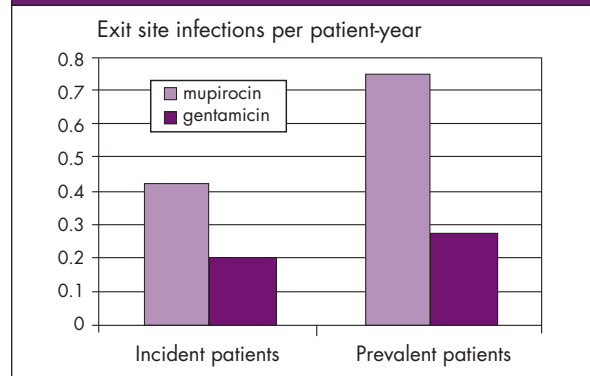


Table 1: Changing targets for PD adequacy		
	Kt/V	CrCl
DOQI 1997 CAPD	2.0	60 L/week
DOQI 2000 CAPD (Low or low average transporters)	2.0	50 L/week
DOQI 2000 CAPD (High or high average transporters)	2.0	60 L/week
K-DOQI 2006	1.7	No recommendation

CrCl = Creatinine clearance;  
DOQI = Daily Outcomes Quality Initiative

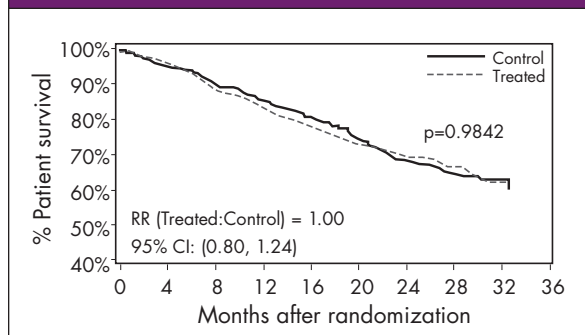
Kt/V per week was associated with a 5% increase in the relative risk of death. Similarly, a decrease of 5 L/1.73 m<sup>2</sup> in creatinine clearance (CrCl) was associated with a 7% increase in the relative risk of death. A weekly Kt/V of 2.1 and a weekly CrCl of 70 L/1.73 m<sup>2</sup> were associated with an expected 2-year survival of 78%. The survival data derived from CANUSA has influenced suggested targets for solute clearance (Table 1).

The CANUSA study assumed that renal and peritoneal clearances were equal and additive. When data from CANUSA were reanalyzed by Bargman and colleagues, they found that for each 5 L/week/1.73 m<sup>2</sup> incremental increase in GFR, there was a 12% reduction in the relative risk of death, but there was no association between peritoneal clearance and the relative risk of death.<sup>22</sup> These findings challenged the prevailing understanding that renal and peritoneal clearances were equal and further underscored the importance of residual renal function.

Additional evidence that peritoneal small solute clearance is not the whole story in PD came from ADEMEX (ADEquacy of PD in MEXico), the largest interventional study undertaken among PD patients. ADEMEX was a prospective, randomized, controlled trial designed to examine the effects of increased peritoneal small solute clearance on a cohort of 965 Mexican continuous ambulatory PD (CAPD) patients. The control group was randomized to a standard dialysis prescription of 4 exchanges per day of 2 liters, while the treatment group was prescribed enough dialysis to achieve a peritoneal creatinine clearance of 60 L/week/1.73 m<sup>2</sup>. The primary outcome in the study was mortality and there was no statistically significant difference in survival between the 2 groups (Figure 3). Not surprisingly, there were significantly more deaths in the control group than in the treatment group from congestive heart failure (13.4% vs. 5.7%, respectively) and from a combination of uremia, acidosis, and hyperkalemia (12.2% vs. 5.7%, respectively). There were more dropouts in the control group due to uremia, but there were more dropouts in the treatment group due to patient discomfort (probably related to the higher fill volumes required to achieve the small solute clearance targets).

Similar findings have been reported from Hong Kong; Lo et al prospectively randomized 320 incident CAPD

Figure 3: There was no difference in survival between the control group and the treatment group in the ADEMEX study<sup>26</sup>



patients who had a baseline renal Kt/V of <1.0 to 1 of 3 Kt/V targets: 1.5-1.7, 1.7-2.0, and >2.0.<sup>23</sup> There were no statistically significant differences in survival at 2 years among the three groups; however, more patients from the 1.5-1.7 Kt/V group were withdrawn from the study by their physicians.

Given the growing body of evidence that Kt/V<sub>urea</sub> is merely one part of the bigger clinical picture relating to patient outcomes, the 2006 Kidney Disease Outcomes Quality Initiative (K-DOQI) guidelines have suggested a minimum target for weekly Kt/V<sub>urea</sub> of 1.7 (Table 1). Greater weekly urea clearances are achieved with HD, yet data regarding mortality have not consistently shown a survival advantage for HD. On the contrary, several studies have shown a survival advantage in the first 2 years for PD.<sup>9,10</sup> This paradox may relate to one of several possible explanations.

- First, PD patients lose residual renal function more slowly than HD patients<sup>6</sup> and the preservation of residual renal function confers a survival advantage.
- Second, PD is a continuous form of dialysis allowing continuous ultrafiltration and, therefore, better and smoother volume control than that allowed by HD.
- Finally, the clearance of larger molecular weight solutes, the so-called “middle molecules,” is time-dependent and particularly enhanced by the long-dwell associated with PD.

As a result, urea clearance alone may not be the ideal method for measuring the adequacy of peritoneal dialysis.<sup>24</sup>

### Ultrafiltration failure

The inability to maintain volume homeostasis has been a common cause of PD failure as a modality.<sup>25</sup> Appropriate net ultrafiltration is not only critical for preventing clinically-significant volume overload, but it is also an important determinant of small solute clearance. In the ADEMEX study, while increasing peritoneal clearance did not improve survival, it is noteworthy that there were more deaths from congestive heart failure in the control group.<sup>26</sup>

Ultrafiltration failure has been defined as a net ultrafiltration of <400 mL after a 4-hour dwell using a high dextrose (4.25%) solution.<sup>27</sup> The prevalence of ultrafiltration failure leading to failure of the technique has been reported to be between 1.7% and 13.7%.<sup>28</sup> Inadequate

ultrafiltration may be due to any number of causes, other than peritoneal membrane dysfunction. Dietary indiscretion, particularly with respect to sodium and fluid intake, an inappropriate dialysis prescription (eg, the use of long-dwell times in a high transporter), loss of residual renal function without an appropriate change in dialysis prescription, and catheter malposition or malfunction may all lead to chronic volume expansion. Once these potential causes have been eliminated, peritoneal membrane dysfunction is the most likely etiology and should be confirmed by a 4-hour peritoneal equilibration test (PET) using a 4.25% dextrose solution.

### *Dietary sodium and fluid intake*

Particular attention should be paid to dietary sodium and fluid intake. Because PD is continuous and patients control their own ultrafiltration, the importance of dietary salt and fluid restriction may not be adequately emphasized, thus negating the potential advantage of PD over HD with respect to blood pressure control. Indeed, some patients choose PD because they are attracted by its less-stringent sodium and potassium restrictions and some investigators have suggested that the normally-prescribed diet is too restrictive.<sup>29</sup> As a result, inadequate dietary sodium and fluid restriction necessitates the use of more hypertonic dextrose solutions to achieve adequate ultrafiltration. The long-term consequence is that patients are at a higher risk of metabolic complications, including weight gain, hyperglycemia, and hyperlipidemia. Furthermore, long-term exposure to hypertonic dextrose solutions may alter the transport characteristics of the peritoneal membrane, causing a patient who is a low transporter to become a high transporter, which further necessitates the use of hypertonic dextrose solutions.<sup>30</sup>

### *Changes in membrane solute transport*

Peritoneal membrane transport characteristics are defined by measuring the dialysate to plasma ratio of creatinine after a 4-hour dwell. Individuals in whom the dialysate concentration of creatinine rapidly approaches that of plasma are said to be “high transporters.” High transporters are at the greatest risk of ultrafiltration failure. Due to the rapid dissipation of the osmotic gradient that drives ultrafiltration, they do well with short-dwell times, such as with an automated cycler. In order to prevent net fluid reabsorption during their long dwell, high transporters usually require hypertonic dextrose exchanges.

With increasing time on PD, ultrafiltration failure becomes more common because of long-term changes in the peritoneal membrane and the development of volume overload due to the loss of residual renal function. The exposure to hypertonic glucose solutions that enhance the formation of advanced glycosylation end products (AGEs) has been hypothesized to injure the peritoneal membrane, making it more porous.<sup>30</sup> The hypothesis is supported by the

finding of AGE deposition within the peritoneal membrane<sup>31,32</sup> and diabetic changes within the peritoneal blood vessels.<sup>33</sup>

To study the effect of glucose exposure on peritoneal transport characteristics, Davies et al examined glucose exposure and serial solute transport measures in a group of PD patients at a single center who had been on that modality for at least 5 years.<sup>30</sup> Patients who had increasing solute transport over the 5-year period were exposed to significantly more hypertonic glucose during the first 2 years of treatment that preceded the increase in solute transport. This study suggests that hypertonic glucose exposure may hasten the development of ultrafiltration failure, and further emphasizes the importance of minimizing the need for hypertonic glucose exchanges by preserving residual renal function and adhering to appropriate dietary salt and fluid restrictions.

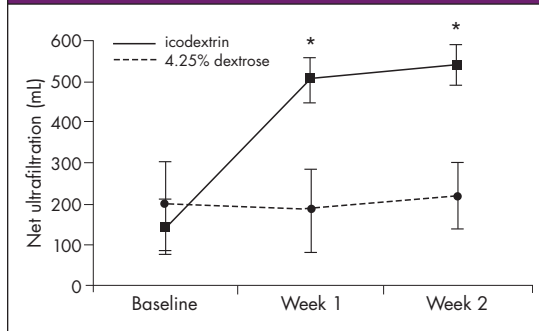
Peritonitis may induce a transient increase in solute transport such that the patient needs a change in dialysis prescription (shorter dwell times or increased tonicity of dialysate) in order to achieve adequate ultrafiltration.<sup>34,35</sup> These changes in transport characteristics are usually reversible; however, formal PET testing after recovery is generally recommended. Repeated episodes of peritonitis are likely to lead to long-term changes in peritoneal membrane transport that may put the patient at risk for ultrafiltration failure. Therefore, prevention of peritonitis by continuous patient education and the use of antibiotic prophylaxis may prolong the survival of this technique by preventing, not only catheter loss due to peritonitis, but also ultrafiltration failure.

### *Icodextrin in ultrafiltration failure*

Ultrafiltration failure is a common cause for technique failure and conversion to HD. The availability of an alternative solution, icodextrin, has been a major advance in the treatment of patients with ultrafiltration failure. Icodextrin is a glucose polymer that may be used as an osmotic alternative to dextrose in PD solutions. It has the benefit of sustained ultrafiltration in long dwells with greater efficiency of ultrafiltration per gram of carbohydrate absorbed; thus, it may also benefit patients who have metabolic complications such as weight gain and hyperlipidemia. In the Multicenter Investigation of icodextrin in Ambulatory PD (MIDAS) study, icodextrin was shown to produce 3.5 times greater ultrafiltration in 8-hour dwells and 5.5 times greater ultrafiltration in 12-hour dwells than 1.5% dextrose.<sup>36</sup> Icodextrin has generally been well-tolerated; the major adverse event associated with its use has been a rash.<sup>37</sup> Sterile peritonitis has been reported in some patients.<sup>38</sup>

A recent prospective, randomized trial compared the effects of icodextrin to 4.25% dextrose in the long dwell of a group of automated PD patients who were high transporters.<sup>39</sup> During the study period of 2 weeks, ultrafiltration increased significantly in the icodextrin group (Figure 4) compared with the

**Figure 4: Net ultrafiltration increased significantly in patients who were treated with icodextrin for their long dwell<sup>39</sup>**



control group and, in the icodextrin group, the incidence of net negative ultrafiltration was significantly lower. The marked increase in ultrafiltration with icodextrin suggests that patients who, previously, may have been forced to change dialysis modalities, may now have an extension in using the PD technique with icodextrin.

### Building a PD program

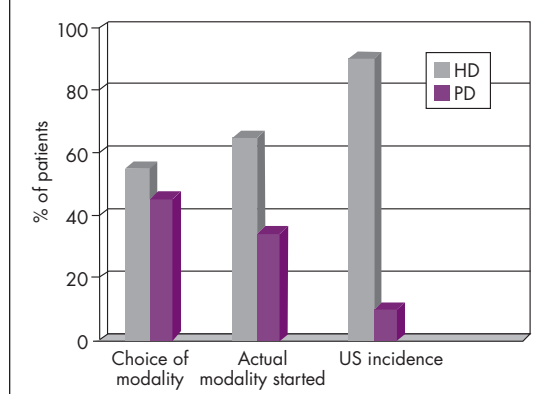
#### *The role of patient education*

The successful implementation of a PD program is dependent upon patients being educated regarding renal replacement modalities. When patients are educated about PD and given the option, more patients choose the modality. The National Pre-ESRD Education Initiative, which has involved 932 referring nephrologists and 28 educators from throughout the US, is the largest pre-ESRD program undertaken to date.<sup>40</sup> It enrolled 15,000 patients between 1997 and February 2001. Participants were educated regarding kidney function, kidney failure, and RRTs. Upon completion of the program, patients chose their dialysis modality; 55% of patients chose HD, while 45% chose PD (Figure 5).

#### *Hospital-based versus dialysis clinic-based programs*

Most PD programs are specifically affiliated with dialysis clinics and not with hospitals. Hospital-based programs have the advantage of on-site nurses who may be involved with everything from education of the predialysis patient to the day-to-day management of hospitalized patients. Dialysis clinic-based programs must ensure that their patients receive appropriate hospital care. It is, therefore, incumbent upon the program leadership to meet regularly with hospital nursing leadership to review the issues of PD care. A small PD program with a low complication rate will send patients to hospital infrequently, thus minimizing nursing exposure to PD. A nurse leader who is skilled in PD and who can be called upon to review the technique with other nurses when a patient is admitted to the hospital is one potential solution to the problem of nursing unfamiliarity with PD.

**Figure 5: The effect of dialysis education on modality selection. More patients choose PD when they receive predialysis education<sup>40</sup>**



Adapted from Golper, 2001.

#### *Training the next generation of nephrologists*

Nephrologists who are not comfortable with PD as a modality are less likely to offer it to their patients. In order to increase the number of patients who are offered PD, training programs must provide fellows with adequate exposure to PD. A survey of program directors by Mehrota et al found that trainees in the US spend < 5% of their time caring for PD patients and that the number of PD patients per trainee is significantly smaller than the number of PD patients per trainee in Canada.<sup>41</sup> Inadequate training in PD may lead to a vicious cycle in which nephrologists who are not comfortable with the modality do not offer it to their patients, further reducing the use of PD and further hindering training opportunities.<sup>2</sup> Moreover, the program should focus on the ambulatory PD experience; otherwise, the trainee is likely to develop a biased opinion about the modality, since he or she would be seeing primarily the patients who are acutely ill, for example, with peritonitis.

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## Upcoming Scientific Meetings

2-6 April 2008

### The National Kidney Foundation Spring Clinical Meetings

Gaylord, Texas

Contact: Tel. 212-889-2210

Email: [clinicalmeetings@kidney.org](mailto:clinicalmeetings@kidney.org)

Website: [www.kidney.org](http://www.kidney.org)

14-17 May 2008

### The American Society of Hypertension (ASH) 22<sup>nd</sup> Annual Scientific Meeting and Exposition

New Orleans Marriott

New Orleans, Louisiana

Contact: Tel. 212-696-9099

Website: [www.ash-us.org](http://www.ash-us.org)

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