The Role of Peritoneal Dialysis in Different Phases of Kidney Transplantation

Ali I. Gardezi, Fahad Aziz, and Sandesh Parajuli

Abstract
The utilization of peritoneal dialysis (PD) has been increasing in the past decade owing to various government initiatives and recognition of benefits such as better preservation of residual renal function, quality of life, and lower cost. The Advancing American Kidney Health initiative aims to increase the utilization of home therapies such as PD and kidney transplantation to treat end stage kidney disease (ESKD). A natural consequence of this development is that more patients will receive PD, and many will eventually undergo kidney transplantation. Therefore, it is important to understand the effect of pretransplant PD on posttransplant outcomes such as delayed graft function (DGF), rejection, thrombosis, graft, and patient survival. Furthermore, some of these patients may develop DGF, which raises the question of the utility of PD during DGF and its risks. Although transplant is the best renal replacement therapy option, it is not everlasting, and many transplant recipients must go on dialysis after allograft failure. Can PD be a good option for these patients? This is another critical question. Furthermore, a significant proportion of nonrenal solid organ transplant recipients develop ESKD. Is PD feasible in this group? In this review, we try to address all of these questions in the light of available evidence.

Introduction
Ever since its conceptualization as a potential method of uremic toxins removal, peritoneal dialysis (PD) has endured a turbulent course (1–3). After the initial success in treating acute kidney failure in the 1940s (4), the use of PD gained traction in the treatment of ESKD in the 1960s (5–7). But the concerns about the high incidence of peritonitis, technique failure, and higher mortality compared with hemodialysis (HD) led to a steady decline in the prevalence of PD after peaking in the mid-1990s (8–10).

In the past decade, there has been a resurgence in the utilization of PD (11). With improvements in our understanding of peritoneal physiology, reduction in peritonitis rates, and overall improvements in the care of patients with ESKD, the mortality of patients on PD has improved dramatically (11). Additionally, multiple studies have shown benefits such as better preservation of residual renal function (12,13), better quality of life (14,15), and lower cost (16) compared with HD. An impetus to increase the use of PD was provided by the introduction of a new expanded prospective payment model by the Center of Medicare and Medicaid (CMS) in 2011, which incentivizes dialysis units to put more patients on home dialysis therapies (17). Furthermore, a key component of the Advancing American Kidney Health initiative, launched in 2019, is to have 80% of new patients with ESKD receiving either dialysis at home or kidney transplantation (18).

The Effect of Pretransplant PD on Transplant Outcomes
The effect of pretransplant dialysis modality on posttransplant outcomes has been the subject of multiple studies done across different eras, locations, and methodologies (19,20). A recurring theme in most research on this topic is the inherent differences between patients on pretransplant HD and PD (21–23). Most studies have attempted to reduce this selection bias by using models adjusting for some of these differences (Table 1).

Probability of Receiving a Kidney Transplant
Snyder et al. (24) used the Center of Medicare and Medicaid data to compare the posttransplant outcomes of patients who were initiated on either PD or HD from 1995 to 1998 and who underwent kidney transplantation before November 30, 2000. The relative likelihood of receiving a kidney transplant was 1.39 times higher in patients on PD than HD, even after adjusting for variables. Another study utilizing United Kingdom Renal Registry data showed a
<table>
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<th>Author</th>
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<th>Number Pretransplant Hemodialysis/Peritoneal Dialysis</th>
<th>Delayed Graft Function</th>
<th>Death Censored Graft Survival</th>
<th>Patient Survival</th>
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<tr>
<td>Goldfarb et al. (68)</td>
<td>Retrospective registry based</td>
<td>USA USRDS</td>
<td>January 1990–December 1999</td>
<td>66,223/20,204</td>
<td>Not reported</td>
<td>Better in pretransplant PD</td>
<td>Better in pretransplant PD</td>
</tr>
<tr>
<td>Molnar et al. (45)</td>
<td>Retrospective registry based</td>
<td>USA SRTR</td>
<td>Dialysis: July 2001–June 2006 Transplant by June 2007</td>
<td>12,416/2092</td>
<td>Lower in pretransplant PD in the unadjusted analysis</td>
<td>No difference in the adjusted analysis</td>
<td>Better in pretransplant PD</td>
</tr>
<tr>
<td>Schwenger et al. (69)</td>
<td>Retrospective registry based</td>
<td>Europe, North America, Australia, and New Zealand</td>
<td>1998–2007</td>
<td>45,651/11,664</td>
<td>Not reported</td>
<td>No difference</td>
<td>Better in pretransplant PD</td>
</tr>
<tr>
<td>Kramer et al. (70)</td>
<td>Retrospective registry based</td>
<td>Europe ERA–EDTA</td>
<td>1999–2008</td>
<td>18,953/10,135</td>
<td>Not reported</td>
<td>No difference in the adjusted analysis</td>
<td>No difference in adjusted analysis</td>
</tr>
</tbody>
</table>

HD, hemodialysis; PD, peritoneal dialysis; USRDS, United States Renal Data System; SRTR, Scientific Registry of Transplant Recipients; ERA-EDTA, European Renal Association–European Dialysis and Transplant Association.
significantly higher percentage of patients on PD on the transplant waitlist than age-matched in-center patients on HD (25). Other studies have shown similar results, with transplant rates 30%-60% higher in patients on PD (26,27). As mentioned earlier, selection bias may be an important factor in these results. The same qualities that make someone a better PD candidate might also positively affect the probability of receiving a kidney transplant. Additionally, it is possible that PD was selected more often in those patients who were more likely to receive a kidney transplant in the near future.

### Delayed Graft Function

Delayed graft function (DGF) is defined as the need for dialysis within 1 week of a kidney transplant (28). It has been associated with the increased risk of poor outcomes such as rejection, graft failure, and mortality (29–31). Most of the smaller single-center studies have shown a lower incidence of DGF with pretransplant PD (32–39), whereas some have shown no difference (40–43). Among the larger studies utilizing national databases, Snyder et al. (24) showed a lower incidence of DGF in the pretransplant PD group than in the pretransplant HD. Molnar et al. (44) linked data from the Scientific Registry of Transplant Recipients (SRTR) to patients who underwent PD or HD through a large dialysis organization between 2001 and 2006. Furthermore, they adjusted the outcomes on the basis of three additional models: the case-mixed adjusted model, the malnutrition inflammation complex syndrome adjusted model, and the transplant data adjusted model. They noted that pretransplant PD was associated with a 36% lower risk of DGF in the unadjusted model, but after applying the models mentioned above, this result no longer remained statistically significant. This further reiterates that reduced risk of DGF with pretransplant PD could be due to other favorable factors. The most important among these is the likelihood of higher residual renal function in patients on PD (12,13). Furthermore, it has been postulated that patients on pretransplant PD may have higher volume going into the transplant surgery than patients on HD, which may offer protection against DGF (45,46). Van Biesen et al. (47) looked at this theory in a small study including 40 patients on pretransplant PD and 79 on pretransplant HD. Even after adjusting for variables such as higher central venous pressure and weight gain before transplant, pretransplant PD was still associated with a shorter time required to attain >50% decrease in serum creatinine. Another proposed mechanism is lower inflammation and oxidative stress due to biocompatibility of peritoneal membrane compared with dialyzer membranes (19,20).

### Acute Rejection

Acute allograft rejection can have deleterious effects on long-term allograft survival (48). However, the incidence has diminished significantly in the past 30 years owing to the introduction of robust immunosuppression regimens (49,50). Van Holder et al. (35) noticed a higher incidence of rejection in patients on PD before transplant. They attributed this observation to a possibility of better immunity in patients on PD compared with those on HD (51). Other studies have not shown any difference in the incidence of rejection between these two groups (36,39,40,52). Tang et al. (20) studied this outcome in a meta-analysis of six studies with 3283 patients and did not find any difference between the two groups.

### Graft Thrombosis

Vascular thrombosis of the kidney allograft is a feared complication, resulting in immediate graft loss. Reported incidence is 0.1%-8% (53). Several studies have found pretransplant PD to be an independent risk factor for renal allograft thrombosis (24,54–56). Murphy et al. (54) were the first to report this risk. Ojo et al. (56) examined the United States Network for Organ Sharing data from 1990 to 1996. The incidence of graft thrombosis was 0.89%. Repeat transplantation and predialysis PD were the strongest predictors of graft thrombosis. Snyder et al. (24) looked at the causes of graft failure in patients on pretransplant HD and PD. Of all the causes, graft thrombosis was the only one found to be more common in patients on PD. Higher plasma fibrinogen, apolipoprotein A, and higher procoagulant activity in patients on PD have been proposed as the underlying

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### Table 2. Studies comparing outcomes of peritoneal dialysis versus hemodialysis during delayed graft function

<table>
<thead>
<tr>
<th>Author</th>
<th>Thomson et al. (74)</th>
<th>Yan et al. (75)</th>
<th>Gardezi et al. (76)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td>Peritonitis in PD-DGF</td>
<td>Retrospective observational</td>
<td>Retrospective observational</td>
<td>Retrospective observational</td>
</tr>
<tr>
<td>Wound leak or infection in PD-DGF</td>
<td>Not reported</td>
<td>36%. Significantly higher than HD-DGF</td>
<td>10%. No difference compared with HD-DGF</td>
</tr>
<tr>
<td>Duration of DGF</td>
<td>Shorter in PD</td>
<td>Longer in PD</td>
<td>No difference</td>
</tr>
<tr>
<td>Rejection</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Death censored graft survival</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Patient survival</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
</tr>
</tbody>
</table>

DGF, delayed graft function; HD, hemodialysis; PD, peritoneal dialysis; PD-DGF, PD during DGF; HD-DGF, HD during DGF.
mechanisms (57,58). It is also possible that some of the patients had to choose PD because of difficulty maintaining vascular access for HD due to underlying prothrombotic conditions and therefore had a higher inherent risk of thrombotic events. Concurrently, using heparin during perioperative HD may protect against thrombosis. The studies mentioned above were done on patients who received a transplant in the United Kingdom or United States in the late 1980s to mid-1990s. Thereafter, more studies done in other parts of the world showed no significant difference in the incidence of graft thrombosis between the two groups (59,60). Most recently, Lin et al. (61) also found no significant difference when utilizing the Taiwan national transplant registry. It is possible that more widespread use of anticoagulation during the perioperative period in this era may have conferred a protective effect on the risk of graft thrombosis with pretransplant PD.

Graft Survival
Death censored graft failure (DCGF) is one of the most important outcomes reported by the studies comparing the effect of pretransplant dialysis modality on posttransplant outcomes. Two large studies utilizing national databases done before the turn of the century yielded opposing results (24,62). Snyder et al. (24) showed a higher rate of DCGF in patients on pretransplant PD, mainly in the first 3 months. This was found to be due to a higher risk of graft thrombosis in this group. On the contrary, Goldfarb et al. (62) looked at 92,844 patients from USRDS data who received kidney transplants from January 1991 to December 1999 and found a 3% lower risk of DCGF in the pretransplant PD group. Considering these conflicting results, Molnar et al. (44) looked at this outcome in patients transplanted in the 21st century between July 2001 and June 2006 using SRTR data. This population was more representative of patients who received a transplant in the era of improved immunosuppression regimens. They made further adjustments on the basis of case mix, malnutrition inflammation complex syndrome, and transplant-related variables. Pretransplant PD was associated with a lower DCGF in the unadjusted analysis but not in the analysis adjusting for abovementioned variables. Similar results were shown in two other large, registry-based studies (63,64). Schwenger et al. (63) analyzed data from 60,008 patients from North America, Europe, Australia, and New Zealand. Meanwhile, Kramer et al. (64) utilized the European Renal Association–European Dialysis and Transplant Association Registry to analyze 29,088 patients. In both studies, pretransplant PD was associated with better graft survival in the unadjusted analysis but did not show any advantage when multivariable Cox regression analysis and instrumental variable method were applied. The results indicated that the advantage of PD shown in previous studies might have resulted from inherent differences between the two groups. The dialysis modality by itself may not influence graft survival. This notion is further strengthened by various single-center studies done in the past decade that have shown similar graft survival between the two groups (42,52,65).

Patient Survival
Although most large studies utilizing registry data have shown mortality benefit with pretransplant PD compared with HD (44,62,63,65), some have shown no difference (24,61,64). Interestingly, the mortality of nontransplanted patients on PD has improved in the past two decades and is now better than in those on HD (11,26). Being on pretransplant PD may confer benefits that continue after renal transplantation and contribute to better survival. Less fluctuation in volume status and blood pressure, no risk of myocardial stunning as opposed to HD, and better residual renal function may contribute to better cardiovascular (CV) outcomes in PD, although the results of studies are conflicting (66,67). The first large-scale study to show posttransplant mortality benefit with pretransplant PD was done by Goldfarb et al. (62), which showed 6% lower mortality in this group compared with pretransplant HD. However, the study done by Snyder et al. (24) using a similar population in the same era did not show any difference. As mentioned above, Molnar et al. (44) reexamined the difference in posttransplant outcomes according to pretransplant modality after the turn of the century. They utilized multiple models to adjust for the inherent differences between the two groups. After adjusting for the variables, patients on pretransplant PD had 43% lower mortality than patients on pretransplant HD. Most of this benefit was due to 66% lower CV mortality in patients on pretransplant PD. Similar results were noticed by Schwenger et al. (63), showing lower all-cause and CV mortality in patients on pretransplant PD. Around the same time, Kramer et al. (64) analyzed 10,135 PD and 18,953 patients on HD who underwent kidney transplantation in Europe. In addition to applying

Figure 1. Guidelines for undergoing peritoneal dialysis during delayed graft function in posttransplant patients.

- Initiate peritoneal dialysis in patient with delayed graft function only after consultation with the transplant surgeon.
- Confirm that none of the following contraindications are present:
  - Any peritoneal breach during the transplant surgery
  - Abdominal distention due to ileus
  - Any active intra-abdominal pathology like infection or bleeding
  - Life threatening hyperkalemia
  - Severe hypervolemia causing pulmonary edema and hypoxia
- Only do Continuous Cycler PD. Avoid Continuous Ambulatory PD
  - Prior to starting the treatment, do a test dwell with 500 ml of 1.5% dextrose peritoneal fluid.
  - Look for any pain or fluid leak
  - If no symptoms occur, start cycler PD with 1 liter fill volume, dwell time of 90 minutes and 6 exchanges.
  - Instruct the patient to stay supine during the treatment.
  - Gradually increase the fill volume to meet the dialysis needs but never exceed two thirds of patient's home prescription
  - Monitor for pain, cloudy fluid and fluid leak through the wound
  - Do not instill heparin in the PD fluid
The Role of PD Immediately after Kidney Transplant PD during DGF

Whether PD can be continued during DGF safely has been examined in several different retrospective studies (Table 2). Thomson et al. (68) showed a shorter duration of DGF and length of hospital stay but a higher incidence of infections and fluid leak in patients who received PD during DGF than in those who received HD. On the other hand, Yan et al. (69) found higher rates of peritonitis and longer DGF duration in patients who received PD during DGF. Our group established a low-volume, supine PD protocol for patients who were on PD before transplant and developed DGF (Figure 1). We found a lower risk of peritonitis than previous studies, no fluid leak or wound infection, and no difference in duration of DGF between those receiving PD compared with HD during DGF (70). In all three studies mentioned above, there was no difference in other outcomes such as acute rejection and graft or patient survival. Other studies have shown a higher risk of peritonitis, wound infection, and fluid leak with PD use during DGF (71–74). If PD is not employed in DGF, most of these patients would require a central venous catheter, which subsequently increases the risk of central line bloodstream infections and central venous stenosis (75,76). Considering these risks, if a patient on pretransplant PD develops DGF, PD could be done using low fill volumes in a strictly supine position, with close monitoring for side effects such as peritonitis, fluid leak, and wound infection.

Timing of PD Catheter Removal

There has been no consensus on the timing of PD catheter removal after a successful kidney transplant in pretransplant PD patients. European best practice guidelines recommend that earlier removal is advisable, but it can be left in the body for up to 3 months (77). Some have advocated removal at the time of transplant to prevent catheter-related complications (73). Others have suggested that it can be kept for up to 6 weeks (78). It is reasonable to remove the PD catheter at the time of transplantation in patients with very low pretransplant risk of developing DGF such as living donor kidney recipients. In others, it should be removed as soon as there is enough graft function to ensure no need for dialysis. Some centers have developed calculators to determine the risk of DGF, which could be used to decide on the timing of catheter removal (79).

PD after Kidney Transplant Failure

Despite improved graft survival, the number of transplant recipients initiating dialysis due to allograft failure is rising (80). A large majority of these patients receive HD, with PD utilization rates as low as 5%–16% (81,82). It is pertinent to note that history of abdominal surgery such as kidney transplantation is not a contraindication to PD (83). Multiple studies have compared the outcomes of patients initiating PD after failed kidney transplant with incident ESRD patients receiving PD. Although some small studies have shown poor outcomes in failed transplant patients (84,85), larger studies and a meta-analysis have demonstrated similar outcomes, including peritonitis rates, technique, and patient survival (81,86–88). One study compared the outcomes of patients who initiated PD after allograft failure with those who initiated HD (89). There was no difference in adjusted survival at short- and long-term follow-up. Stopping or continuing the immunosuppression is a critical decision in patients starting PD after renal transplant failure. On the one hand, immunosuppression may increase the risk of peritonitis, but on the other hand, it may help conserve residual kidney function, which may improve outcomes (90). Studies have shown a faster decline in residual kidney function in patients on PD after failed kidney transplant than those without a transplant (91,92), but none have compared these outcomes between patients receiving PD or HD after a failed transplant. Nonetheless, patients with a failing kidney allograft must be given opportunities to explore different dialysis modalities and to choose the one most suitable for their lifestyle. This is particularly important in younger patients with longer life expectancy who may require multiple RRT modalities throughout their life. Starting with PD would provide them more flexibility in their daily life and preserve their vasculature for future HD access should PD fail. This aligns with formulating an ESKD life plan for each patient according to the recently published KDOQI vascular access guidelines (93).

PD in ESKD Associated with Nonrenal Solid Organ Transplantation

Patients with nonrenal solid organ transplant (NRSOT), such as the liver, heart, and lung, have a high risk of developing ESKD due to factors such as long-term use of calcineurin inhibitors (CNI) (94). Studies have shown an ESKD incidence of 1%–2% per year in NRSOT (95). Concerns regarding the increased risk of peritonitis with immunosuppression use and resulting poor survival have limited the use of PD in this population (96,97). Several studies have compared the infection and survival outcomes of patients with NRSOT on PD with nontransplant patients on PD and have shown no difference between these groups (98–100). It is suspected that CNI may also increase the risk of encapsulating peritoneal fibrosis (94). Furthermore, exposure of peritoneum to high glucose in the presence of steroids and CNI may also increase the risk of...
posttransplant diabetes mellitus. However, these outcomes have not been studied in patients with NRSOT who have PD for ESKD. Even though the authors of the abovementioned studies have concluded that PD is a safe option for these patients, studies with larger number of patients are required to substantiate these findings.

Conclusion

Thanks to various initiatives, PD is now well placed to be more prevalent in the future. Owing to its better preservation of residual renal functions, pretransplant PD may offer benefits such as a lower incidence of DGF and better patient survival after kidney transplant. Although most of the benefits may be due to patient selection for PD and may no longer be significant once more patients are placed on this modality regardless of their health status, the available literature still does not show any major disadvantage of PD compared with HD when it comes to transplant. With more patients receiving PD and eventually undergoing a transplant, it is important to understand the relationship of PD with various stages of a kidney transplant. It is equally important to present PD as a therapeutic option to those whose kidney allograft is failing so that they have more understanding and knowledge of all the available options for RRT.

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F. Aziz and S. Parajuli reviewed and edited the manuscript; A.I. Gardezi was responsible for conceptualization, data curation, and formal analysis, and wrote the original draft of the manuscript; and S. Parajuli was responsible for supervision.

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