

# Peritoneal Dialysis in Western Countries

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## Key Words

Peritoneal dialysis · Solutions · Peritoneal transport · Peritonitis · Costs

## Abstract

**Background:** Peritoneal dialysis (PD) for the treatment of end-stage renal failure was introduced in the 1960s. Nowadays it has evolved to an established therapy that is complementary to hemodialysis (HD), representing 11% of all patients treated worldwide with dialysis. Despite good clinical outcomes and similar results in patient survival between PD and HD, the penetration of PD is decreasing in the Western world. **Summary:** First the major events in the history of the development of PD are described. Then important insights into the physiology of peritoneal transport are discussed and linked to the changes in time observed in biopsies of the peritoneal membrane. Furthermore, the developments in peritoneal access, more biocompatible dialysate solutions, automated PD at home, the establishment of parameters for dialysis adequacy and strategies to prevent infectious complications are mentioned. Finally non-medical issues responsible for the declining penetration in the Western world are analyzed. **Key Messages:** Only after introduction of the concept of continuous ambulatory PD by Moncrief and Popovich has this treatment evolved in time to a renal replacement therapy. Of all structures present in the peritoneal membrane, the capillary endothelium offers the rate-limiting hindrance for solute and water transport for the diffusive and convective transport of solutes and osmosis. The functional

and anatomical changes in the peritoneal membrane in time can be monitored by the peritoneal equilibrium test. Peritonitis incidence decreased by introduction of the Y-set and prophylaxis using mupirocin on the exit site. The decrease in the proportion of patients treated with PD in the Western world can be explained by non-medical issues such as inadequate predialysis patient education, physician experience and training, ease of HD initiation, overcapacity of in-center HD, lack of adequate infrastructure for PD treatment, costs and reimbursement issues of the treatment. **Facts from East and West:** (1) PD is cheaper than HD and provides a better quality of life worldwide, but its prevalence is significantly lower than that of HD in all countries, with the exception of Hong Kong. Allowing reimbursement of PD but not HD has permitted to increase the use of PD over HD in many Asian countries like Hong Kong, Vietnam, Taiwan, Thailand, as well as in New Zealand and Australia over the last years. In the Western world, however, HD is still promoted, and the proportion of patients treated with PD decreases. Japan remains an exception in Asia where PD penetration is very low. Lack of adequate education of practitioners and information of patients might as well be reasons for the low penetration of PD in both the East and West. (2) Patient survival of PD varies between and within countries but is globally similar to HD. (3) Peritonitis remains the main cause of morbidity in PD patients. South Asian countries face specific issues such as high tuberculosis and mycobacterial infections, which are rare in

For peritoneal dialysis in Asia, see Kwong and Li, *Kidney Dis* 2015;1: 147–156.

developed Asian and Western countries. The infection rate is affected by climatic and socio-economic factors and is higher in hot, humid and rural areas. (4) Nevertheless, the promotion of a PD-first policy might be beneficial particularly for remote populations in emerging countries where the end-stage renal disease rate is increasing dramatically.

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## The Discovery of Peritoneal Dialysis

The theoretical foundation for dialysis is attributed to Thomas Graham (1805–1869), a professor in the field of chemistry in Scotland, and known for his famous ‘Graham’s law of effusion’ [1]. He described the principles of diffusion and osmosis and introduced the concept of a semi-permeable membrane. In 1877 in Germany, Georg Wegner experimented with intraperitoneal administration of hypo- and hypertonic solutions in rabbits and observed that the intraperitoneal volume either decreased or increased depending on the tonicity of the solution [2]. These experiments were confirmed by the famous English physiologist Ernest Starling and his collaborator Alfred Tubby, and they also concluded that the intraperitoneal transport of solutes was bidirectional, mainly to blood and not to the lymphatics [3]. In 1923 Georg Ganter published his investigations in animals and a few humans [4]. He performed exchanges of intraperitoneally administered saline solutions and observed near-equilibrium of non-protein nitrogen after dwell times of 3 h in combination with improvement of blood urea nitrogen levels. Also the uremic symptoms of the animals and humans improved transiently, but as the treatment could not be continued the patients died. A few decades later, in 1946, Howard Frank, Arnold Seligman and Jacob Fine, after first having experimented on dogs, were successful in treating a patient with acute renal failure with intermittent peritoneal dialysis (PD) for 7 days [5]. In 1961 Fred Boen, having previously worked in Amsterdam and known for his work on peritoneal transport kinetics [6], started one of the first long-term PD programs in Seattle. Permanent peritoneal access and peritonitis were the main obstacles for use on a larger scale. Despite his collaboration with Henry Tenckhoff, who designed a peritoneal catheter for permanent use [7] which is even today the most commonly used peritoneal access, in 1977 not even 800 patients were treated worldwide with intermittent PD.

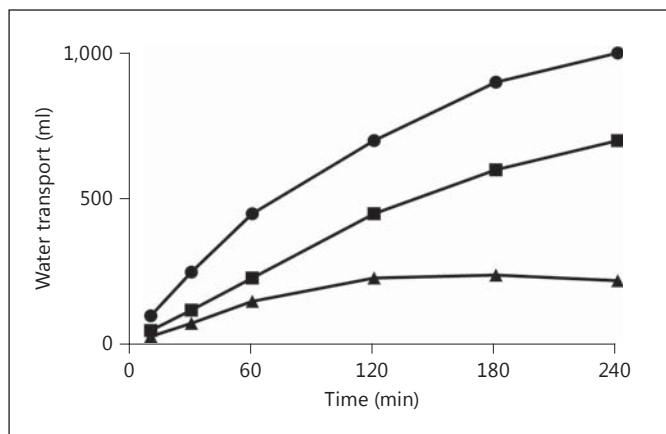
The great breakthrough in PD occurred when in 1975 Jack Moncrief and Robert Popovich introduced the concept of continuous PD, which eventually was named con-

tinuous ambulatory PD (CAPD). They calculated that when the abdominal cavity was continuously filled with dialysate, four to five exchanges of the intraperitoneal instilled solution per day would be enough for renal replacement in an average-sized person [8]. This concept was successfully tested in 9 patients treated for 136 weeks [9]. Shortly thereafter patient acceptance of the treatment was improved by introduction of plastic bags instead of glass bottles [10]. Also the peritonitis incidence due to touch contamination improved by the flush before fill concept using a Y-set around 1980 [11].

In the following 35 years the treatment has evolved and is now an established treatment for patients with end-stage renal failure, with approximately 272,000 patients treated worldwide in 2013 [12]. As PubMed search using ‘peritoneal dialysis’ [MeSH] and ‘peritoneal dialysis, continuous ambulatory’ [MeSH] resulted in almost 10,000 hits; only a highly selected summary of the advances in PD that originated in the Western world will be given in the following paragraphs.

## Peritoneal Anatomy and Physiology and the Effects of Peritoneal Dialysis in Time

Of all structures present in the peritoneal membrane, the capillary endothelium offers the rate-limiting hindrance for solute and water transport for the diffusive and convective transport of solutes and osmosis. The peritoneal transport of both solutes and water can accurately be described by a three-pore model [13]. Only the ultra-small pore has been anatomically identified as the water channel aquaporin-1 [14] and during a 4-h dwell time is responsible for around 40–50% of the total amount of ultrafiltration during glucose-induced osmotic free water transport (fig. 1) [15]. In clinical practice peritoneal transport is measured using a peritoneal equilibrium test introduced by Twardowski [16] or using one of its later modifications which can also be used to calculate free water transport [17]. In time, on average peritoneal transport of low molecular weight solutes increases, combined with a decrease in net ultrafiltration due to the more rapid dissipation of the osmotic gradient [18]. This can eventually lead to ultrafiltration failure, defined by the International Society for Peritoneal Dialysis as the ability to ultrafiltrate <400 ml during a 4-h dwell time with 3.86% glucose-containing solution. These changes in peritoneal transport are likely to be induced by glucose, glucose degradation end products or advanced glycosylation end products, given experimental data and the relation with



**Fig. 1.** Peritoneal fluid kinetics in an average patient during a 4-h dwell time using glucose 3.86%. The total water transport (circles), small-pore water transport (squares) and free water transport (triangles) are shown.

glucose exposure in time [19]. We found that in long-term PD the number of vessels in the peritoneal membrane is increased, simultaneously with increased fibrosis in the peritoneal interstitium [20]. Also vascular wall thickening of small arteries and vasodilation of capillaries was found. These findings of increased vessel density, vasculopathy and fibrosis in time as well as an increased thickness of the submesothelial compact zone were confirmed in a large biopsy registry [21]. The trigger of these changes could be cytokine release in the peritoneal cavity, resulting in epithelial-to-mesenchymal transition of the mesothelial cells lining the peritoneal membrane [22]. So the functional changes reflected by the increases in peritoneal low-molecular solute transport and loss of ultrafiltration can be explained by the increased vascular surface area as found in the biopsy studies. It was earlier suggested that the higher transport state had a negative impact on patient survival, but in a recent study on systemic and peritoneal inflammation only systemic inflammation negatively predicted patient survival [23].

### Peritoneal Access

Since the development of the Tenckhoff catheter a few new catheters were introduced. Adjustments were the Swan-neck configuration using an exit site directed downwards, other intraperitoneal configurations than the original straight catheter type, and a self-locating catheter. However, until now none of these catheters has proven to

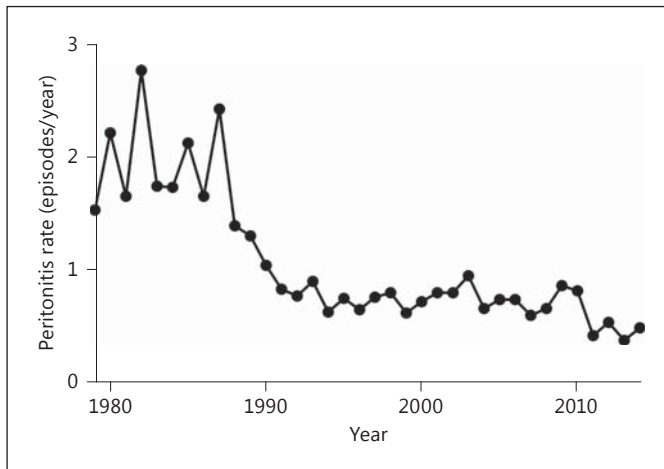
be more successful than the original design [24]. Catheters with a straight intraperitoneal segment like the Tenckhoff catheter showed in general slightly better results [24]. The skills of the surgeon who implants the catheter remained the most important factor for success. Moncrief and Popovich proposed a new catheter implantation technique where the distal part of the catheter was buried and exteriorized shortly before its clinical use [25]. The purpose of this technique was allowing the formation of a bacteriologic barrier by timely tissue healing and thereby minimizing the periluminal route of pathogen invasion. This has not been confirmed in randomized controlled studies, but the technique is helpful in assuring timely access management due to its logistic advantages.

### Infectious Complications

Peritonitis remains a major complication in PD and improvements were only modest since the introduction of the Y-set in the 1980s and double bags in the 1990s. In a prospective, randomized, open-label longitudinal study of 221 patients undergoing 254 PD catheter placements using a single dose of i.v. cefazolin 3 h or i.v. vancomycin 12 h prior to catheter placement resulted in a reduction of perioperative peritonitis from 12% of patients without preoperative prophylactic antibiotics to 7% of cefazolin-treated patients and 1% of vancomycin-treated patients [26]. Important in the reduction of infectious complications was the recognition of *Staphylococcus aureus* colonization for the development of exit site and tunnel infections as well as peritonitis [27]. Mupirocin was proven to be successful in reducing *S. aureus* exit site infections [28]. The effectiveness of mupirocin prophylaxis on preventing exit site infections and peritonitis due to *S. aureus* and other organisms in PD patients was confirmed in many other studies [29]. Recently it was found that exit site infections increased the risk of developing peritonitis >10-fold in the first 15 days, >6-fold in the first 30 days, and almost 5-fold up to 60 days [30]. In our clinic all these improvements have resulted in a peritonitis incidence of 0.5 episodes per year in 2014 (fig. 2).

### Solutions

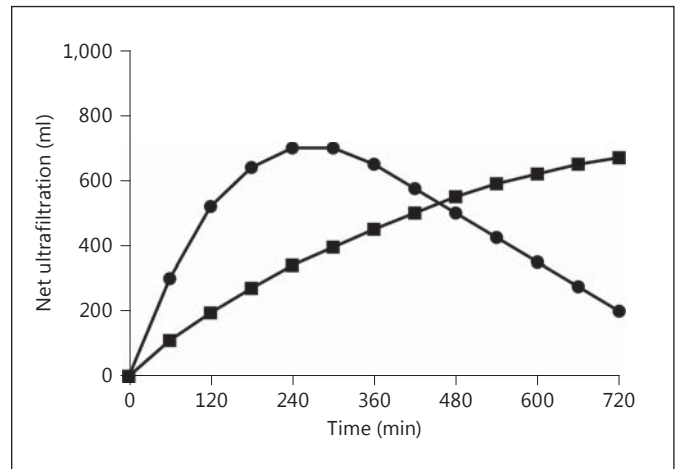
Throughout the years, glucose-containing dialysate remained the cornerstone in PD treatment. To improve the glucose-containing dialysate 'biocompatible' solutions with a more physiological pH, different buffers and



**Fig. 2.** Peritonitis incidence (episodes per patient) from 1979 to 2014 at the Academic Medical Center, Amsterdam, The Netherlands.

mostly reduced content of glucose degradation products (GDPs) were developed. GDPs are formed during heat sterilization of the fluid and their production is inversely related with the pH of the fluid. The reduction of GDPs became possible by the construction of multi-chamber bags, which made it possible to heat-sterilize the glucose in a separate compartment with a low pH. The clinical benefits of the newer solutions have been recently reviewed [31–33]. To summarize their findings, the authors concluded that although the newer PD solutions seem to improve at least some aspects of peritoneal membrane health and viability, no significant effects on peritonitis, technique survival or patient survival were identified with their use. However, the use of neutral-pH, low-GDP PD solution led to greater urine output and higher residual renal function after use exceeded 12 months.

In the 1990s, PD solutions containing icodextrin or amino acids as osmotic agent were developed. Icodextrin is an iso-osmolar mixture of glucose polymers, which makes it especially suited for long dwell times as it results in a prolonged ultrafiltration due to the slow absorption of the oncotic agent (fig. 3) [34]. This solution does not contain glucose and has a low content of GDPs. Icodextrin improves ultrafiltration compared to glucose-based solutions, resulting in a better control of the patient's fluid balance [35]. Amino acids were developed to improve nutrition in malnourished patients [36], but this has never been proven to result in improved patient survival. This solution can also be used once daily as an alternative to glucose-containing dialysate.



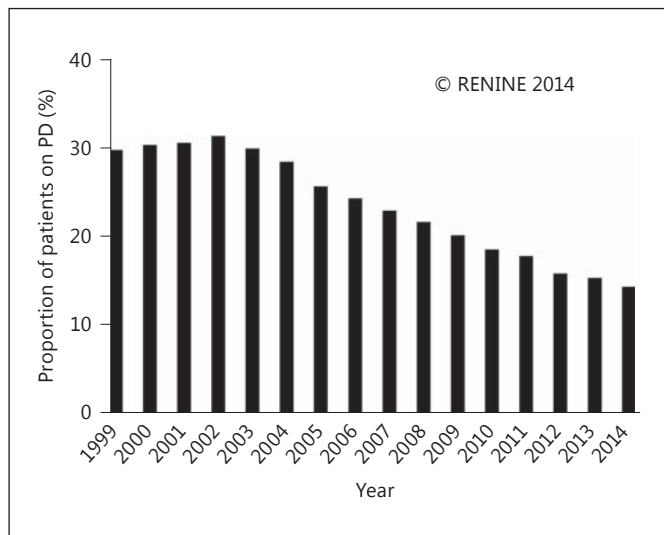
**Fig. 3.** Profiles of net ultrafiltration for a 3.86% glucose-containing solution (squares) and icodextrin (circles) using kinetic modeling in 10 patients (unpublished data).

### Dialysis Adequacy and Importance of Residual Renal Function

Dialysis adequacy in patients was historically based on a set of clinical and laboratory parameters. As the need for more objective parameters arose, the concepts of Kt/V and weekly creatinine clearance were tested in two large studies [37, 38]. The CANUSA study, although designed to investigate dialysis adequacy targets, was crucial in the recognition of the importance of residual renal function [38], while the prospective randomized ADEMEX study resulted in final adequacy targets (Kt/V >1.7 and weekly creatinine clearance >45 l/1.73 m<sup>2</sup> per week) that still are used nowadays in all guidelines. As earlier it was found that residual renal function is better preserved in PD than hemodialysis (HD) patients [38], this underlines the advantages of using PD as the renal replacement treatment of choice for patients starting with dialysis [39].

### Automated Peritoneal Dialysis

Cyclers for the treatment of patients at home with automated PD (APD) were developed. At first medical indications for this mode of treatment, such as increasing the dialysis dose and optimizing volume status in high transporters, prevailed; later social indications became more important. The size of the cyclers decreased and it created the possibility for PD treatment during the night. The proportion of patients treated with APD increased



**Fig. 4.** Proportion of patients on PD of the total number of dialysis patients in the Netherlands.

worldwide and in 2008 was 47.2% in developed countries and 14.6% in developing countries [40]. Crucial for the share of PD in dialysis treatments was the AEPOS study, which demonstrated that also anuric patients can be adequately treated with PD [41]. As analyzed in a recent review, no consistent differences were found between CAPD and APD in residual kidney function loss rate, peritonitis rate, maintenance of euvolemia, technique survival, mortality or health-related quality of life in individuals [42]. Special attention should be paid to the removal of sodium, as standard APD schedules are frequently associated with poor sodium removal rates [43]. For any degree of ultrafiltration, sodium removal is better in CAPD than in APD. Icodextrin, supplementary diurnal exchanges and longer nocturnal dwell times improved sodium removal in APD.

### Peritoneal Dialysis Penetration in the Western World

The number of PD patients globally is still growing. In 2013 approximately 272,000 patients were treated, which was 11% of all dialysis patients [12]. When nephrologists were asked in a survey, the optimal utilization rate for PD was believed to be around 30–35% [44]. However, in most Western countries this number was never reached, despite promotion of the concept of PD-first [39]. Moreover, just before the turn of the century, PD penetration

started to decrease in most Western countries [40]. In the Netherlands starting in the beginning of this century, the share of PD treatment gradually decreased by 50% from 31.3% to 14.3% (fig. 4). Globally, in 2008 about 41% of all 196,000 PD patients were treated in developed countries. Although the prevalence of PD grew in both developed and developing countries, from 1997 to 2008 in developed countries a significant decline in the proportion of dialysis patients treated with PD was found from 20.6 to 15.3%, whereas in developing countries the PD share remained stable (from 13.8 to 12.4%).

In the absence of evidence for better clinical outcomes with HD [45, 46], except for a lower but still modestly improving technique survival with PD [47], other factors must drive this shift to HD. Factors which may play a role in the preference for HD treatment are inadequate predialysis patient education, physician experience and training, ease of HD initiation, overcapacity of in-center HD, lack of adequate infrastructure for PD treatment, costs and reimbursement issues of the treatment.

### Effect of Patient Preference and Contraindications on Modality Selection

Patient selection starts with information and education for renal replacement therapy. Although in a large global survey in European countries patients reported to be satisfied overall with the information they received, this information seemed mostly to have been focused on one modality [48]. Around 50% perceived that they had no choice in the treatment selection. More than one third (39%) did not remember having received any information on alternative treatment options than their current one. A similar study in Australia also found that 49% of respondents indicated that they had had no choice in the type of dialysis [49]. Moreover, patients were twice as likely to receive information about HD than about CAPD or APD. The paucity of information was also the outcome of a systematic review on this topic [50]. Insufficient training experience of nephrologists in combination with low clinical experience in home treatments are likely to play a role in the low penetration of home treatments [51]. Several studies show that after adequate education and in the absence of contraindications, nearly half of the patients opt for PD [52, 53].

In a large Dutch multicenter study, 36% of the patients had a contraindication to either PD or HD therapy [52]. Eighty percent of all contraindications were directed to PD therapy. The most frequently reported contraindica-

tions were older age and social reasons, especially the expected incapability of patients to perform PD exchanges themselves. The likelihood of elderly people starting HD was confirmed in a study in seven European countries, even though they had a decreased mortality risk on PD [54]. Finally, the growing living donor program in many European countries has led to preemptive transplantation of younger patients who preferably would have started PD.

### Cost of Dialysis Treatment Modalities

In HD the major component of the costs are human resources, while in PD disposables represent the major expendables. In most of the Western world HD is more expensive than PD [55]. Given the higher PD technique failure rate, some have suggested that there is a significant cost associated with patients who switch from PD to HD. However, compared with patients who received only HD, those who received PD only and those who transitioned from HD to PD therapy had significantly lower total health care costs at 1 and 3 years [56]. Patients experiencing PD technique failure had costs similar to and not in excess of HD-only patients at 3 years. A cost analysis in Portugal found that in the first year the costs to establish and maintain an HD access were higher compared to PD [57].

Overall, reimbursement rates for hospital HD are higher than those for home dialysis treatments [58]. Also an important issue is the growth of the number of dialysis units in the Western world, the inverse relationship of the increasing share of private-for-profit HD and the decrease in patients starting with PD [59, 60]. For instance, from 1996 to 2004 in the United States the number of di-

alysis units increased by 53% [61]. In several countries the government changed the reimbursement system to promote home dialysis. Although this seems to be effective in some countries, in general increasing financial incentives to treat patients with PD showed no change in modality choice [58, 62–65]. Even if in-center HD is as costly as PD, the stimulus to use its capacity remains as the initial investment cost for every HD unit is high, resulting in a financial incentive to maximally utilize every dialysis station [58]. So the need to fill the dialysis stations might prevail above any advantage from the increased reimbursement for PD.

### Summary

In the last 40 years, PD has proven to be an effective treatment for end-stage renal failure patients. During this period the understanding of peritoneal membrane physiology and pathology has increased. Due to improvements in dialysis systems, availability of cyclers for APD, the development of new solutions and efforts to reduce complications such as peritonitis, the treatment has improved considerably. Nowadays patient survival in the first 5 years at least equals that of conventional HD, although PD technique survival is still lower. This has resulted in a globally still growing number of patients treatment treated with PD. However, in the Western world non-medical issues resulted in a decrease in the proportion of patients treated with PD.

### Disclosure Statement

The author does not have any financial conflicts of interest to declare.

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