

## DIALYSIS/TRANSPLANTATION ΑΙΜΟΚΑΘΑΡΣΗ/ΜΕΤΑΜΟΣΧΕΥΣΗ

### Historical misconceptions in peritoneal dialysis

In the long history of medicine, scientific assumptions based on pathophysiological mechanisms, case reports of a number of interesting cases, authority statements and tradition have often been the guides of clinical practice, but have never been scientifically substantiated. As a result, many perceptions in medicine, although wrong, were popular and resistant to change. Some of these appeared in the history of Peritoneal Dialysis (PD). Their understanding changed the course of the method and –perhaps more importantly– the future of its patients. The scepticism surrounding the introduction of continuous ambulatory PD as we know it today and the “flush before fill” system, the supposed worse outcomes in high transporters aiming towards high dialysis doses and the inappropriate twice daily use of icodextrin were some of the misconceptions that were eventually revised. In conclusion, several breakthroughs in the history of PD, at first disapproved, changed the application and future of the method.

In the history of medicine, evidence-based practice has only recently gained worldwide acceptance.<sup>1</sup> Before this era, pathophysiologic assumptions, case reports, authority statements and especially tradition had been the guides of clinical practice. Unfortunately, many standards of care were never tested but were promoted based on their longevity. As a result, several conceptions in medicine, though distorted, were popular and resistant to change. Some of these misconceptions appeared in the brief, but exciting history of Peritoneal Dialysis (PD), which together with haemodialysis (HD) represent the two renal replacement therapy modalities currently applied worldwide for the treatment of end-stage renal disease (ESRD). In PD, compared to HD, these misconceptions initially discouraged the global implementation of the method and led to the belief that it was not appropriate for ESRD patients. The understanding of these misconceptions changed the course of the method and the fate of patients.

In its infancy, PD was presented as a therapeutic alternative for ESRD therapy and was prescribed as intermittent PD (IPD) sessions with catheter removal and reinsertion.<sup>2</sup> In 1959, Mae Stewart, a 33-year-old black woman with

childbirth complications and glomerulonephritis, was referred to Dr Ruben in San Francisco. With the help of his associates, Ruben applied the method on the patient and after the first PD session, she improved significantly, and her creatinine decreased impressively from 20 to 13 mg/dL. The method was discontinued but, unfortunately, after 7 days without treatment, the patient’s condition deteriorated once again, as she suffered from chronic renal failure. She was set on a 48-h weekend in-hospital PD regimen, while on weekdays she stayed at home. The Murphy-Doolan PD catheter was left in place and it was replaced only once during the 7-month period that the patient was on PD. Mae Stewart was the first patient with ESRD maintained on long-term PD without periodic replacement of the PD catheter. Ruben and his associates submitted a paper on this case report to the *New England Journal of Medicine* but the manuscript was rejected.<sup>3,4</sup>

Several years later, in 1975, Moncrief and Popovich in Austin, Texas reviewed the case of a young patient who was started on HD but could not continue due to access thrombosis. The patient refused to move from Austin to Dallas to receive IPD, which was crucial for his survival.

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Ιστορικές παρανοήσεις  
στην περιτοναϊκή κάθαρση

*Περίληψη στο τέλος του άρθρου*

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This challenge led Moncrief and Popovich to establish a new form of PD, which would allow complete equilibration of plasma urea with PD fluid solution and eventually maximum urea removal during each dwell. They calculated the volume of the dialysis fluid solution needed to remove the urea generated daily on a 1 g/kg protein diet and thus prescribed five exchanges per day of 2 litres fill volume each for a dwell time of at least 3 hours. They used standard 2-litre glass bottles containing the PD solution, attached a tube and used a Tenckhoff catheter as access. The regimen was called “portable/wearable equilibrium PD technique” and achieved the appropriate laboratory results along with the desirable euvolemia and clinical condition. In 1976, the American Society for Artificial Internal Organs (ASAIO) rejected an abstract by Popovich and Moncrief describing this method, probably due to its “confusing title”.<sup>5</sup> Yet, later in 1977, they met Karl Nolph who became interested in the method and started working with the Austin group. They decided to name this new method Continuous Ambulatory PD (CAPD). They studied 9 patients on this method for 136 patient-weeks. The treatment included continuous presence of PD solution in the peritoneal cavity, manual exchanges 4–5 times daily and the PD catheter was capped between exchanges. This “portable” dialysis method allowed the patient to take part in everyday activities. The results, published in the *Annals of Internal Medicine*, established the use of CAPD.<sup>6</sup> Despite the method’s advantages, increased peritonitis rates discouraged the wide implementation of CAPD.

In the late 70s, at the Toronto Western Hospital in Canada, Oreopoulos was the first to widely apply CAPD via a “standard” connection and wearable bags.<sup>7</sup> Yet, peritonitis rates were still high, threatening the method’s survival. In 1980, Buoncrisiani et al proposed an innovative Y-set technique, which astonishingly reduced peritonitis rates from one episode every 12 months to one episode every 36–40 months.<sup>8</sup> They suggested that after the connections and before draining, fresh dialysate should be washed into the drainage bag flushing away with it any bacteria that could have possibly contaminated the tubing system during the connection. Then, drainage of the dialysate into the bag should take place and the new solution should fill the PD cavity. This technique became widely known as “flush before fill”. Despite promising results, scepticism in Canada and USA PD centres regarding the validity of the results delayed the acceptance of this development for at least five years. Once accepted and implemented, these changes reduced the high peritonitis rates and significantly increased the overall use of CAPD around the world.<sup>9</sup>

In the next years, the question raised concerned the delivery of the appropriate dose of dialysis. In 1996, a multicenter Canada-USA PD Study (CANUSA Group) randomised 680 PD patients in 14 centres in Canada and the USA.<sup>10</sup> The results supported a strong, positive association between the level of small, solute clearance with survival. Based on the CANUSA results, the National Kidney Foundation – Dialysis Outcome Quality Initiative (NKF-DOQI) published guidelines in 1997, recommending a weekly Kt/V target of 2.0 for CAPD and 2.1 for Continuous Cycling PD (CCPD).<sup>11</sup> The higher clearance targeted by these guidelines led to an increase in APD cyclers use, since the machines allowed higher daily dialysate volume delivery and thus could achieve higher targets. However, in a subsequent re-evaluation of the CANUSA study in 2001, Bargman et al showed that the favourable results in those patients were mainly due to their residual renal function.<sup>12</sup> This suggested that lower weekly Kt/V targets might be appropriate. This was confirmed by another large, prospective study, adequacy of PD in Mexico (ADEMEX), which randomised 965 PD patients to either standard or increased small solute clearance at a 1:1 ratio.<sup>13</sup> They showed that increased doses of peritoneal small molecule clearance delivered by PD were not associated with patient survival or better quality of life. These findings overruled the misconception of the high targets proposed by the NKF-DOQI guidelines.

The CANUSA study, in line with similar studies, suggested that CAPD patients with high membrane permeability had increased mortality, possibly due to fluid overload resulting from low ultrafiltration (UF) volumes. Reanalysis of the CANUSA study showed that renal and peritoneal clearance do not contribute in an analogous manner in solute clearance.<sup>12</sup> This rendered anuric patients, especially those with high peritoneal permeability, as a group difficult to effectively dialyse while on CAPD<sup>14</sup> and a clinical concern about poor outcomes in fast transporters emerged. The European APD Outcomes Study (EAPOS) recruited 177 anuric patients on APD, 58% of which using icodextrin for the long day-dwell. The EAPOS study showed that baseline membrane transport status was not related to ultrafiltration achieved at one year and had no effect on patient survival.<sup>15</sup> The results suggested that by implementing APD especially in combination with icodextrin for the long day-dwell, it is possible to achieve sufficient small solute clearance and UF and this may have a positive impact on the clinical outcome in high transporters.<sup>16</sup> Thus, the concern about poor outcomes for fast transporters on PD was proved again a misconception.

Another overruled misconception was that icodextrin

solutions should be used only once daily. The use of dextrose as the principal osmotic agent in PD solutions was suggested to be associated with peritoneal membrane toxicity and systemic adverse effects.<sup>17</sup> The interest in minimising exposure to glucose introduced an alternative solution based on icodextrin. This glucose polymer was shown to increase UF and at first was recommended for only one exchange per day in high or high-average transporters.<sup>18</sup> Gobin et al were the first to suggest twice-daily icodextrin exchanges in CCPD patients. They showed a significant decrease in patient exposure to glucose after 6 months of treatment. The authors did not observe an increase in UF because of the scheduled dwell of the two icodextrin exchanges (one exchange for 4–5 hours and the other one for 9–10 hours dwell time).<sup>17</sup> Another study by Sav et al demonstrated a significant decrease in body weight and left ventricular mass index in 40 patients CAPD using twice-daily icodextrin.<sup>19</sup> Moreover, in a study from Toronto General Hospital, where 5 CAPD and 4 CCPD patients with poor UF were recruited, the authors reported a significant decrease in body weight in 6 out of 9 patients with UF failure after 6 months of therapy. In addition, a decrease in the mean blood pressure of all patients was observed.<sup>20</sup> In another study, 28 patients with UF failure on CAPD were randomised to receive either one or two icodextrin exchanges per day. Both groups experienced a decrease in serum natriuretic peptide, left ventricular mass, heart rate, and cardiothoracic index. In addition, the authors reported an increase in the ejection fraction at 8 weeks in both groups. Yet, the percentage of change of all parameters was enhanced in the patient group on twice-daily icodextrin exchanges.<sup>21</sup> In a retrospective study, 8 PD (5 APD and 3 CAPD) patients with inadequate UF were switched from once daily to twice daily icodextrin exchanges. A significant increase was observed in net UF after 6 months. Moreover, osmolality and residual urinary output remained unchanged throughout the study.<sup>22</sup> These studies established the safety and potential benefits of twice-daily icodextrin use in PD patients, although prescribing more than one icodextrin exchanges is still off-label.

Finally, the use of disinfecting devices with sterilisation properties on the connecting surfaces initially appeared attractive. The implementation of ultraviolet (UV) light, as

well as heat sterilisation at the connection site, achieved with either electric resistance or microwaves was appealing. In a large randomised study by Nolph et al, the UV-flash® disinfecting device did not reduce peritonitis rates.<sup>23</sup> A retrospective, multicenter study from Japan showed that the UV-flash® system could be used in CAPD patients with impaired dexterity or vision in order to achieve lower peritonitis rates.<sup>24</sup> Another study tried to evaluate *in vitro* if, by themselves and without the help of disinfecting devices, PD system designs could prevent bacterial contamination into the peritoneum during accidental touch and airborne transmission.<sup>25</sup> This study selected a Y-set and a double-bag system and showed that the “flush before fill” and the fluid path flow designs were those that contributed significantly to the safety and protective action of these PD systems.<sup>25</sup> Many other disinfecting devices were tested, such as the Terumo Flame-Lock System using heating over a flame and ceramic connections,<sup>26</sup> the Fresenius Thermoclave device, which was used with the Safe Lock 5F® connector,<sup>27</sup> the Sterile Connection Device using a heated blade to cut through parallel placed tubing of transfer set and fresh dialysate bag<sup>28</sup> and microwave moist-heating devices.<sup>29</sup> However, despite some good *in vitro* results, these devices never proved patient-friendly, beneficial or practical. They added to the complexity of the method and increased its cost without offering significant germicidal effectiveness. Eventually, and especially after the implementation of disconnecting systems, the use of these devices was abandoned.<sup>30</sup>

In conclusion, despite the short history of PD, several innovations and milestones were at first doubted, rejected by respected contemporary medical journals or even widely adopted without eventually proving their efficacy. Some of these breakthroughs include the importance of a permanent PD catheter, the daily, chronic PD regimen with the 2-liter exchanges, the “flush before fill” system, the appropriate weekly Kt/V targets, the use of APD in high transporters and the twice-daily use of icodextrin. Several misconceptions were overruled and the innovations eventually established in current PD practice changed the application and future of the method. These emphasise that knowledge in medicine is ever-evolving and, as Heraclitus noted, “change is the only constant in life”.

## ΠΕΡΙΛΗΨΗ

## Ιστορικές παρανοήσεις στην περιτοναϊκή κάθαρση

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Στη μακρά ιστορία της Ιατρικής, επιστημονικές παραδοχές με βάση παθοφυσιολογικούς μηχανισμούς, δημοσιεύσεις που αφορούσαν σε ολιγάριθμα ενδιαφέροντα περιστατικά, τη γνώμη των ειδικών αλλά κυρίως η παράδοση αποτελούσαν συχνά οδηγό της κλινικής πρακτικής, χωρίς όμως να έχουν ποτέ τεκμηριωθεί επιστημονικά. Ως αποτέλεσμα αρκετές αντιλήψεις στην Ιατρική ήταν λανθασμένες, αλλά δημοφιλείς και ανθεκτικές στην αλλαγή. Ορισμένες από αυτές τις παρανοήσεις εμφανίστηκαν στην ιστορία της περιτοναϊκής κάθαρσης, μιας εκ των δύο μεθόδων υποκατάστασης της νεφρικής λειτουργίας. Η κατανόησή τους άλλαξε την πορεία της μεθόδου αλλά και –ίσως σημαντικότερο– το μέλλον των ασθενών της.

**Λέξεις ευρητηρίου:** CAPD, CCPD, IPD, Ιστορία περιτοναϊκής κάθαρσης, Παρανοήσεις στην Ιατρική

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