Conventional versus biocompatible peritoneal dialysis fluids: more questions than answers?

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Abstract
The most important challenge in peritoneal dialysis (PD) is long-term preservation of peritoneal membrane structure and function. Introduction of dialysis fluids into the peritoneal cavity induces changes. These changes are related to duration of dialysis, occurrence of peritonitis and components of the dialysis solution. Bioincompatibility is considered to be the major cause of the development of morphological changes of the peritoneal membrane. pH neutral PD fluids that are low in glucose degradation products (GDP) seem to better preserve the peritoneal membrane and have less systemic effects than the conventional ones. However, the long-term effects are not clear. An overview of the effects of conventional PD fluids and glucose-based PD fluids with neutral pH in ex vivo and in vivo animal and clinical studies is presented.

Keywords: biocompatibility; peritoneal dialysis fluids; peritoneal dialysis

Introduction
Today, about half of the patients who have received predialysis care choose peritoneal dialysis (PD) as their first dialysis modality [1]. Besides personal preferences, in the first 2 years, PD preserves residual renal function (RRF) better and possibly has a better patient survival [2]. However, long-term technique survival of PD is poor because of technical problems and peritoneal membrane failure; the latter is considered to be a consequence of bioincompatible characteristics of PD fluids. Therefore, the most important challenge in PD is long-term preservation of peritoneal membrane structure and function. Several studies have shown that introduction of dialysis fluids into the peritoneal cavity induces changes, ultimately leading to "membrane failure". Features of membrane failure include dysfunction of local host defence mechanisms, signs of peritoneal sclerosis and neovascularization resulting in ultrafiltration failure (UFF). UFF remains one of the most important reasons for treatment dropout. The cumulative risk of UFF was reported to be 3% after 1 year and 40% after 6 years [3]. The incidence of UFF seems to increase with time on PD [4].

The above-mentioned observations in humans have been studied in more detail in animals: chronic daily instillation of conventional PD fluids leads to an angiogenic response in the omentum, mesentery, liver surface and parietal peritoneal wall [5–8]. In addition, detachment of the mesothelial cell layer, submesothelial extracellular matrix deposition and fibrotic alterations [9,10] were described after exposure to these dialysis solutions. These changes are related to duration of dialysis, occurrence of peritonitis and components of the dialysis solution. Although bioincompatibility, in general, is considered to be the major cause of the development of morphological changes of the peritoneal membrane ultimately resulting in UFF, the major culprit is not known. Conventional dialysis fluids are acidic (pH 5.5), contain supraphysiologic concentrations of lactate (35–40 mmol/L) and have a high osmolality (347–486 mosmol/kg H2O) as a result of high glucose concentrations (75–215 mmol/l) that, after heat sterilization, turn into glucose degradation products (GDP). Which of them is most harmful remains the question. New PD fluid formulations have become available: they have different osmotic agents and buffers such as glucose polymer-based and amino acid-based PD fluids. This report focuses on the effects of conventional PD fluids and glucose-based PD fluids with neutral pH.

In vitro and ex vivo studies: effects of PD fluids characteristics on mesothelial cells and defence
Cells that are continuously exposed to dialysis fluids are mesothelial cells and (in part) macrophages. A majority of data on the in vivo effect of PD fluids are derived from ex vivo measurements of effects of PD fluids characteristics on cell function.

In a number of studies with animal and human mesothelial cells, apoptosis was observed after incubation with PD fluids [11–13]. This indicates an imbalance between proliferation and apoptosis of mesothelial cells. The characteristic or combination of characteristics in PD fluids that was responsible for the imbalance in these studies remained unclear.
The low pH and high osmolality in PD fluids have an inhibitory effect on proliferation of mesothelial cells and their functions because of the production of cytokines and prostaglandins [14]. Adding fresh PD fluid to residual PD fluids with normal pH within the peritoneal cavity resulted in a pH value of 7 after ~10 min [15]. In an ex vivo experiment, the combination of low pH and high concentrations of sodium lactate in PD fluids did result in suppression of respiratory burst activation, a cell host defence mechanism, which is not because of either low pH or lactate concentration alone [16]. Inhibition of the respiratory burst activation was related to the extreme sensitivity of NADPH oxidase to low intracellular pH. This was reduced to >70% at pH 5.0. In this situation, the presence of lactate and glucose can lead to pseudo-hypoxia. These findings suggest that the clinical importance of low pH alone might be overestimated and that other factors are more important. The high osmolality in PD fluids is mainly because of glucose concentrations. Glucose inhibits proliferation of human mesothelial cells in a dose-dependent way [17]. Other hyperosmotic solutes, which were used in the same concentrations as glucose (mannitol and glycerol), did not decrease proliferation of the mesothelial cells as much as glucose did. This implies that the toxicity on proliferation of the mesothelial cells depends not only on the hyperosmolality but also on some metabolic effects. Basal cytotoxicity in vitro tests on PD fluids show that all major commercial brands of PD fluids are cytotoxic to cell proliferation, ranging from 53 to 75% inhibition of cell growth. This was found to be as a result of GDP and not because of interference with the PVC plastic of the bag as previously thought [18].

As the combination of low pH, lactate and the presence of GDP in PD fluids seems toxic to mesothelial cells, experiments were conducted with fluids that might be more biocompatible, such as isosmolar solutions with glucose polyomers. These solutions show better phagocytic capacity for common peritonitis-causing bacteria, and a significantly higher chemiluminescence response was found [19]. Other studies demonstrated that exposure to solutions that consisted of a combination of lactate and bicarbonate buffer was less cytotoxic to the migratory capacity of normal human polymorphonuclear granulocytes. Bicarbonate and lactate alone reduce cellular function [20,21]. Bicarbonate/lactate-buffered PD fluids also improve ex vivo peritoneal macrophase TNFα secretion, which might improve host defence status [22].

Recent ex vivo findings suggest that human mesothelial cells not merely suffer, but are partly culprits for peritoneal injury. In long-term PD, new fibroblast-like cells arise from local conversion of mesothelial cells, which invade the submesothelial tissue and contribute to peritoneal fibrosis and angiogenesis. This can ultimately lead to peritoneal membrane failure [23].

Thus, the combination of low pH, lactate and the presence of GDP in PD fluids seems cytotoxic to and weakens defence mechanisms of mesothelial cells in ex vivo and in vitro studies.

Animal studies: effect of PD fluids on mesothelium and peritoneal membrane

To avoid limitations of in vitro studies, animal models of PD have been developed. Rat, rabbit and occasionally mouse models have been used to examine physiological effects of PD fluids on mesothelium and the peritoneal membrane.

Mesothelium

Daily intraperitoneal injections of 3.86% glucose PD fluid in rats caused hyperplasia of mesothelial cells after 6 weeks [24]. Di Paolo [25] and Gotloib [26] had similar results in rabbits and mice, respectively, and concluded that the alterations observed after long-term exposure of the mesothelium to PD fluid are mainly caused by the high concentration of glucose, whereas the eventual role of low pH seemed marginal. The basement membrane of omental capillaries also shows marked lamination after 20-week daily exposure to hypertonic glucose (3.86%) PD fluid. This was in contrast to the same period of exposure to Ringer’s lactate solution [27]. These data suggest a relation between glucose and damaging effects to the peritoneal mesothelial layer in long-term PD. However, concerning this issue, animal studies differ in their results. In chronic peritoneal exposure studies in mice, mesothelial viability and integrity of the peritoneal membrane was examined by trypan blue staining and by assessing mesothelial denudation. The mesothelial viability was better upon 30-day exposure to bicarbonate-buffered PD fluids [28] or 12-week exposure to lactate/bicarbonate-buffered PD fluids [29]. Other researchers [25,30,31], however, did not find any differences in mesothelial morphology between both types of fluid in rats and rabbits.

Peritoneum

A rat experimental model in 10 nonuraemic rats, which were dialyzed twice daily for 4 weeks with high glucose concentration fluids, showed healing of the peritoneum after cathether implantation. Still, hyaluronic acid levels in the dialysate increased and a tendency to thickening of the peritoneum was observed when compared to nondialyzed animals [32]. In a long-term exposure model in rats by Zarieie et al. [33], instillation of the current lactate-based PD fluid had deleterious effects on the peritoneal tissue. Exposition of the mesothelium to low pH lactate buffer solutions increased the number of mast cells, milky spots and milky spot areas, which are considered to be consequences of immune activation. A clear thickening of the endothelial cell layer, suggestive of endothelial activation, and an increase in the number of blood vessels were also found. Addition of glucose to this buffer (filter-sterilized PD fluid) especially strengthened the induction of fibrosis and the number of omental vessels. In addition to low pH and glucose, the presence of GDP (heat-sterilized PD-fluids) showed a further increase in the number and size of milky spots, parietal blood vessels, loss of mesothelial cell integrity, the number of Fc-receptor positive cells, a thickening of the
mesenteric submesothelial extracellular matrix and an increase in the number of rolling leucocytes. Interestingly, acidification of bicarbonate/lactate PD fluid did not contribute to peritoneal worsening [34], which confirms the findings earlier mentioned in ex vivo studies. During chronic exposition to bicarbonate/lactate solutions with fewer GDP and neutral pH, the increase in milky spots and the formation of new blood vessels were reduced [5]. By means of a total histological score by light microscopy, reduced peritoneal fibrosis upon bicarbonate-buffered PD fluid dialysis has also been suggested [35], together with a diminished non-specific inflammatory response and increased production of inflammatory cytokines upon endotoxin challenge [36].

In another PD model for rats, a standard lactate-buffered PD solution was compared with a bicarbonate/lactate-buffered solution during a 12-week study period [37]. In rats treated with a standard low pH solution, an increase was demonstrated in vascular endothelial growth factor (VEGF), micro-vascular proliferation and submesothelial fibrosis. Furthermore, an accumulation of advanced glycation end products (AGEs) and an up-regulation of the receptor for AGEs were found. The peritonitis rate was not different between rabbits that had been treated for 4 weeks by lactate/bicarbonate-buffered PD fluid, but the severity of peritonitis was significantly higher in the lactate group. Likewise, the dialysate leukocyte count had only declined significantly in the lactate group [30].

Therefore, in animal models, mainly glucose and GDP are associated with submesothelial thickening, fibrosis, neangiogenesis, the presence of AGEs and the poorer inflammatory response. Low pH per se in PD fluids does not seem damaging. The difference in peritonitis incidence between the conventional and the more biocompatible PD fluids has not been established.

Animal studies: peritoneal transport

Experiments have been performed in rabbits and rats to study the direct effects of neutral pH bicarbonate-buffered PD solutions on peritoneal transport, appetite and microcirculation. These data point in the same direction, namely, an improved ultrafiltration [38,39], no vasodilation of peritoneal arterioles [40], improved appetite [41] and leukocyte recruitment [42] by bicarbonate-buffered PD fluids compared to lactate-buffered PD fluids.

Park et al. [29] demonstrated that in rats, peritoneal ultrafiltration had decreased after 12-week exposure to the conventional PD solution, but administration of a neutral bicarbonate/lactate-buffered PD fluid resulted in less loss of peritoneal ultrafiltration. However, contrasting results were reported by Suzuki et al. [35], who showed increased glucose absorption in rats along with decreased creatinine and protein clearance upon dialysis with bicarbonate-buffered PD fluid, which imply an increased peritoneal permeability compared to conventional lactate-buffered PD fluid. Wieczorowska et al. [31] suggested reduced transperitoneal protein transport after 4-week treatment in rats with a bicarbonate-buffered PD solution. In the study by Pawlaczyk et al. [36], no differences were seen in the transport characteristics between bicarbonate/lactate- and lactate-buffered PD fluids in rats.

Therefore, at present, it is not clear whether bicarbonate-buffered PD fluids improve peritoneal transport physiology in chronic peritoneal exposure animal models. However, this might be related to the animal model, as it is difficult to achieve statistically significant differences in peritoneal transport data in small laboratory animals such as the rat. However, the data summarized so far indicate that at least in in vitro studies and in preclinical rat PD models, the new generation of pH neutral, two-chamber PD fluids are more biocompatible than conventional acidic PD fluids.

Clinical studies

UFF is the main reason for discontinuation of PD therapy [43]. Several clinical studies have been conducted to investigate parameters reflecting technique survival and peritoneum preservation in patients using conventional PD fluids versus the new more physiological, biocompatible ones. Tranaeus et al. [44] designed a large randomized clinical trial comparing lactate-buffered PD fluids to bicarbonate/lactate solutions. They showed reduced pain on infusion. Rippe et al. [45] had similar though not significant results. Topley’s group demonstrated that bicarbonate/lactate solutions might improve peritoneal host defence [22]. The previously mentioned study groups [44,45] did not show differences in the occurrence of peritonitis between the two solutions.

With respect to ultrafiltration, a significant increase in ultrafiltration after 6 months was seen by Tranaeus’s group, but these results were in contrast to those of Rippe et al., who did not find any increase in ultrafiltration over a period of 2 years. The Eurobalance study even found less ultrafiltration in the group that used the new PD fluids [46].

Thus far, differences in peritoneal creatinine, urea clearance and Kt/V have never been seen. In the Eurobalance study, renal creatinine and urea clearances were higher when patients had undergone 3-month treatment with PD fluids that were pH neutral, lactate buffered and low in GDP [46].

Several publications underline the importance of RRF for the morbidity and survival of PD patients [47–49]. Williams et al. [46] also showed that urine volume was higher in patients treated with the new PD fluids. This was not shown in the NEPP (Nutrineal, Extraneal, Physioneal, Physioneal) study, which compared conventional fluids with a regimen low in glucose and GDP with icodextrin and amino acids [50].

In peritoneal biopsies and postmortnal studies in long-term PD patients, a predominant finding was revealed that was the development of peritoneal fibrosis that had a deleterious effect on membrane function [51,52]. Over the last 15 years, interest has increased in the identification of potential markers that can be measured in the dialysis effluent that can provide information concerning the state of the peritoneum in vivo. Rippe et al. [45] also investigated peritoneal mesothelial and interstitial integrity by analysing effluent dialysate. After 2 years, a decrease in hyaluronan acid (marker of inflammation) and an increase in CA 125 were
found in pH neutral PD fluid. CA 125 reflects peritoneal mesothelial cell mass in stable PD patients [53]. Jones et al. [54] had similar results after 6 months and found no changes in CA 125 and hyaluronic acid in the lactate group. No differences were found in markers of fibrosis (procollagen I peptide and TGF-ß1). In the NEPP study, CA 125 levels in the effluents were higher in the group using NEPP, suggesting a better preservation of the mesothelium [50]. However, levels of VEGF, hyaluronic acid and II-6 were also higher. Williams et al. [46] demonstrated higher levels of CA 125 in the effluent of patients using Balance®, a low GDP and neutral-pH PD fluid. Hyaluronic acid was lower but VEGF and TNFα were not different.

Currently there are not many data on the effects of biocompatible solutions on survival. In a retrospective observational study, Lee et al. [55] showed an advantage in survival rates in those who used Balance® compared to conventional fluids (74% versus 62% at 28 months). A limitation in this study was the difficulty to interpret survival based on observational data.

In conclusion, at present, the long-term effects of pH neutral PD fluids that are low in GDP are not clear. They seem to better preserve the peritoneal membrane and have less systemic effects than the conventional ones. None of the previously mentioned studies investigated local and systemic markers of inflammation, transport characteristics, RRF as well as technique survival in the same cohort of patients. It is also not always clear whether patients had used biocompatible fluids before being included in the study. Furthermore, most of these studies, except for one, had a follow-up of only 6–12 months. The effects on peritoneal transport, technique survival and patient survival remain unanswered. Today, there is still a lack of quality prospective studies that directly compare these solutions to conventional glucose/lactate-based PD fluids. To answer questions that remain, such studies are of utmost importance.

Conflict of interest statement. None declared.

References

1. Jager KJ, Korevaar JC, Dekker FW et al. The effect of contraindications and patient preference on dialysis modality selection in ESRD patients in The Netherlands. Am J Kidney Dis 2004; 43: 891–899

2. Jansen MA, Hart AAM, Korevaar JC et al. Predictors of the rate of residual renal function in incident dialysis patients. Kidney Int 2002; 62: 1046–1053

3. Heimburger O, Waniewski J, Weynyski A et al. Peritoneal transport in CAPD patients with permanent loss of ultrafiltration capacity. Kidney Int 1990; 38: 495–506

4. Smit W, de Waart DR, Struijk DG et al. Peritoneal transport characteristics with glycerol-based dialysate in peritoneal dialysis. Perit Dial Int 2000; 20: 557–565

5. Hekking LH, Zareie M, Driesprong BA et al. Better preservation of peritoneal morphologic features and defence in rats after long-term exposure to a bicarbonate/lactate-buffered solution. J Am Soc Nephrol 2001; 12: 2775–2786

6. Matesjens MA, Van Der Wal AC, Hendriks PM et al. Vascular and interstitial changes in the peritoneum of CAPD patients with peritoneal sclerosis. Perit Dial Int 1999; 19: 517–525

7. Krediet RT, Zweers MM, Van Der Wal AC et al. Neangiogenesis in the peritoneal membrane. Perit Dial Int 2000; 20(Suppl 2): S19–S25

8. Margetts PJ, Kolb M, Yu L et al. Inflammatory cytokines, angiogenesis, and fibrosis in the rat peritoneum. Am J Pathol 2002; 160: 2285–2294

9. Wieczorowska-Tobis K, Berlinska R, Breborowicz A et al. Morphologic aspects of chronic peritoneal dialysis in a rat model. Perit Dial Int 2001; 21(Suppl 3): S342–S344

10. Margetts PJ, Gyorffy S, Kolb M et al. Antiangiogenic and antiﬁbrinolytic gene therapy in a chronic infusion model of peritoneal dialysis in rats. J Am Soc Nephrol 2002; 13: 721–728

11. Yang AH, Chen YJ, Lin YP et al. Peritoneal dialysis solution induces apoptosis of mesothelial cells. Kidney Int 1997; 51: 1280–1288

12. Ha H, Yu MR, Choi HN et al. Effects of conventional and new peritoneal dialysis solutions on human peritoneal mesothelial cell viability and proliferation. Perit Dial Int 2000; 20(Suppl 5): S10–S18

13. Zheng Z, Ye R, Yu X et al. Peritoneal dialysis solutions disturb the balance of apoptosis and proliferation of peritoneal cells in chronic dialysis model. Adv Perit Dial 2001; 17: 53–57

14. Liberek T, Topley N, Jorres A et al. Peritoneal dialysis fluid inhibition of phagocyte function: effects of osmolality and glucose concentration. J Am Soc Nephrol 1993; 3: 1508–1515

15. Pedersen FB, Ryttov N, Deleuran P et al. Acetate versus lactate in peritoneal dialysis solutions. Nephron 1985; 39: 55–58

16. Liberek T, Topley N, Jorres A et al. Peritoneal dialysis fluid inhibition of polymorphonuclear leukocyte respiratory burst activation is related to the lowering of intracellular pH. Nephron 1993; 65: 260–265

17. Breborowicz A, Rodela H, Oreopoulos DG. Toxicity of osmotic solutes on human mesothelial cells in vitro. Kidney Int 1992; 41: 1280–1285

18. Wieslander AP, Nordin MK, Kjellstrand PT et al. Toxicity of peritoneal dialysis fluids on cultured fibroblasts. L-929. Kidney Int 1991; 40: 77–79

19. de Fijter CW, Verbrugh HA, Oe LP et al. Biocompatibility of a glucose-polymer-containing peritoneal dialysis fluid. Am J Kidney Dis 1993; 21: 411–418

20. Schambye HT, Pedersen FB, Wang P. Bicarbonate is not the ultimate answer to the biocompatibility problems of CAPD solutions: a cytotoxicity test of CAPD solutions and effluents. Adv Perit Dial 1992; 8: 42–46

21. Schambye HT, Pedersen FB, Christensen HK et al. The cytotoxicity of continuous ambulatory peritoneal dialysis solutions with different bicitonate/lactate ratios. Perit Dial Int 1993; 13(Suppl 2): S116–S118

22. MacKenzie RK, Holmes CJ, Moseley A et al. Bicarbonate/lactate and bicarbonate-buffered peritoneal dialysis fluids improve ex vivo peritoneal macrophage TNF-alpha secretion. J Am Soc Nephrol 1998; 9: 1499–1506

23. Lopez-Cabrera M, Aguilera A, Arocia LS et al. Ex vivo analysis of dialysis effluent-derived mesothelial cells as an approach to unveiling the mechanism of peritoneal membrane failure. Perit Dial Int 2006; 26: 26–34

24. Slater ND, Cope GH, Raftery AT. Mesothelial hyperplasia in response to peritoneal dialysis fluid: a morphometric study in the rat. Nephron 1991; 58: 466–471

25. Di Paolo N, Garosi G, Petriini G et al. Morphological and morphometric changes in mesothelial cells during peritoneal dialysis in the rabbit. Nephron 1996; 74: 594–599

26. Gotloib L, Wajsbrut V, Shostak A et al. The cytochemical profile of visceral mesothelium under the influence of lactated-hyperosmolar peritoneal dialysis solutions. Nephron 1995; 69: 466–471

27. Zweers MM, Splint LJ, Krediet RT et al. Ultrastructure of basement membranes of peritoneal capillaries in a chronic peritoneal infusion model in the rat. Nephrol Dial Transplant 2001; 16: 651–654

28. Gotloib L, Wajsbrut V, Shostak A et al. Population analysis of mesothelium in situ and in vivo exposed to bicarbonate-buffered peritoneal dialysis fluid. Nephron 1996; 73: 219–227

29. Park MS, Choi SR, Song YS et al. Effects of bicarbonate/lactate solution on peritoneal advanced glycosylation end-product accumulation. Perit Dial Int 2000; 20(Suppl 5): S33–S38
30. Schambye HT, Flesner P, Pedersen FB et al. Bicarbonate- versus lactate-based CAPD fluids: a biocompatibility study in rabbits. *Perit Dial Int* 1992; 12: 281–286
31. Wieczorowska-Tobis K, Korybalska K, Polubinska A et al. Long-term effects of glycylglycine peritoneal dialysis solution with neutral pH on peritoneum in rats. *Adv Perit Dial 1997; 13: 42–46*
32. Wieczorowska-Tobis K, Korybalska K, Polubinska A et al. In vivo model to study the biocompatibility of peritoneal dialysis solutions. *Int J Artif Organs* 1997; 20: 673–677
33. Zareie M, Hekking LH, Welten AG et al. Contribution of lactate buffer, glucose and glucose degradation products to peritoneal injury in vivo. *Nephrol Dial Transplant* 2003; 18: 2629–2637
34. Zareie M, Keuning ED, ter Wee PM et al. Improved biocompatibility of bicarbonate/lactate-buffered PDF is not related to pH. *Nephrol Dial Transplant* 2006; 21:208–216
35. Suzuki K, Khanna R, Nolph KD et al. Effects of bicarbonate dialysis solution on peritoneal transport in rats. *Adv Perit Dial 1996; 12: 24–26*
36. Pawlaczik K, Kuzlan-Pawlaczyk M, Wieczorowska-Tobis K et al. Bicarbonate/lactate dialysis solution improves in vivo function of peritoneal host defense in rats. *Perit Dial Int 1999; 19(Suppl 2): S370–S377*
37. Mortier S, Faict D, Schalkwijk CG et al. Long-term exposure to new peritoneal dialysis solutions: effects on the peritoneal membrane. *Kidney Int* 2004; 66: 1257–1265
38. Yatzidis H. Enhanced ultrafiltration in rabbits with bicarbonate glycylglycine peritoneal dialysis solution. *Perit Dial Int 1993; 13: 302–306*
39. Musi B, Carlsson O, Rippe A et al. Effects of acidity, glucose degradation products, and dialysis fluid buffer choice on peritoneal solute and fluid transport in rats. *Perit Dial Int 1998; 18: 303–310*
40. Mortier S, De Vriese AS, Van de Voorde J et al. Hemodynamic effects of peritoneal dialysis solutions on the rat peritoneal membrane: role of acidity, buffer choice, glucose concentration, and glucose degradation products. *J Am Soc Nephrol 2002; 13: 480–489*
41. Zheng ZH, Sederholm F, Anderstam B et al. Acute effects of peritoneal dialysis solutions on appetite in non-uremic rats. *Kidney Int 2001; 60: 2392–2398*
42. Mortier S, De Vriese AS, McLoughlin RM et al. Effects of conventional and new peritoneal dialysis fluids on leukocyte recruitment in the rat peritoneal membrane. *J Am Soc Nephrol 2003; 14: 1296–1306*
43. Kawaguchi Y, Hasegawa T, Nakayama M et al. Issues affecting the longevity of the continuous peritoneal dialysis therapy. *Kidney Int 1997; 62(Suppl): S105–S107*
44. Tranaeus A. The Bicarbonate/Lactate Study Group. A long-term study of a bicarbonate/lactate-based peritoneal dialysis solution—clinical benefits. *Perit Dial Int 2000; 20: 516–523*
45. Rippe B, Simonsen O, Heimburger O et al. Long-term clinical effects of a peritoneal dialysis fluid with less glucose degradation products. *Kidney Int 2001; 59: 348–357*
46. Williams JD, Topley N, Craig KJ et al. The Euro-balance trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. *Kidney Int 2004; 66: 408–418*
47. Rocco M, Souci JM, Pastan S et al. Peritoneal dialysis adequacy and risk of death. *Kidney Int 2000; 58: 446–457*
48. Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol 2001; 12: 2158–2162*
49. Termorshuizen F, Korevaar JC, Dekker FW et al. The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Am J Kidney Dis 2003; 41: 1293–1302*
50. Le Poole CY, Welten AG, Weijmer MC et al. Initiating CAPD with a regimen low in glucose and glucose degradation products, with icodextrin and amino acids (NEPP) is safe and efficacious. *Perit Dial Int 2005; 25(Suppl 3): S64–S68*
51. Rubin J, Herrera GA, Collins D. An autopsy study of the peritoneal cavity from patients on continuous ambulatory peritoneal dialysis. *Am J Kidney Dis 1991; 18: 97–102*
52. Pollock CA, Ibels LS, Eckstein RP et al. Peritoneal morphology on maintenance dialysis. *Am J Nephrol 1989; 9: 198–204*
53. Visser CE, Brouwer-Steenbergen JJ, Betjes MGH et al. Cancer antigen 125: a bulk marker for the mesothelial mass in stable peritoneal dialysis patients. *Nephrol Dial Transplant 1995; 10: 64–69*
54. Jones S, Holmes CJ, Krediet RT et al. Bicarbonate/lactate-based peritoneal dialysis solution increases cancer antigen 125 and decreases hyaluronic acid levels. *Kidney Int 2001; 59: 1529–1538*
55. Lee HY, Park HC, Seo BJ et al. Superior patient survival for continuous ambulatory peritoneal dialysis patients treated with a peritoneal dialysis fluid with neutral pH and low glucose degradation product concentration (Balance). *Perit Dial Int 2005; 25: 248–255*

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