Chapter 2

Peritoneal Dialysis Solutions

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Additional information is available at the end of the chapter

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Abstract

Conventional peritoneal dialysis (PD) solutions are characterized by several undesirable characteristics, including acidic pH (5.2–5.5), high glucose concentrations (13.6–42.5 g/L), hyperosmolarity (360–511 mOsm/kg) and relatively high concentrations of glucose degradation products (GDPs). These characteristics have been shown to result in adverse clinical outcomes, including acute peritoneal membrane toxicity (manifested as inflow pain), chronic peritoneal toxicity (including membrane failure, ultrafiltration failure, peritonitis and encapsulating peritoneal sclerosis) and adverse systemic sequelae (including hyperglycaemia, dyslipidaemia, metabolic syndrome, cardiovascular disease and residual renal function decline). Consequently, there has been a great interest in manufacturing newer solutions with more 'biocompatible' features to mitigate these adverse effects. This has led to the development of neutral-pH, low or ultralow GDP solutions, glucose-sparing PD solutions (icodextrin and amino acid solutions), solutions using alternative osmotic agents (such as hyperbranched polyglycerol) and low-sodium PD solutions. The aim of this chapter is to provide an up-to-date comprehensive review of all types of PD solutions that are currently available, including their impact on patient-level outcomes.

Keywords: amino acids, biocompatible materials, controlled clinical trial, dialysis solutions, end-stage kidney disease, glucose, glucose degradation product, glycerol, icodextrin, kidney failure, peritoneal dialysis, polymers, sodium, treatment outcome

1. Introduction

Peritoneal dialysis (PD) is a form of renal replacement therapy used to treat patients with end-stage renal disease (ESRD). PD solution is introduced through a peritoneal catheter in the abdomen and replaced either by manual exchanges throughout the day (continuous ambula-

tory peritoneal dialysis—CAPD) or by a cycler overnight with or without daytime exchanges (automated peritoneal dialysis—APD). PD solutions can be broadly divided into conventional PD solutions and novel solutions with more biocompatible characteristics (e.g. neutral-pH, low glucose degradation products—GDPs solutions). The aim of this chapter is to provide an up-to-date comprehensive review of all types of PD solutions that are currently available, including their impact on patient-level outcomes.

2. Conventional PD solutions

During the very early days of PD, the composition of PD solutions varied widely from normal saline to 5% dextrose [1]. Maxwell and colleagues first developed PD solutions akin to currently used conventional PD solutions [2]. Glucose is still being used as the only osmotic agent in PD solutions available for clinical use. Conventional PD solutions contain an osmotic agent (i.e. glucose), lactate as a buffer and electrolytes (i.e. Na^+, Cl^-, Ca^{2+} and Mg^{2+}) (**Table 1**). GDPs, which have been shown to have adverse effects on both the peritoneal membrane and systemically, are produced during the heat sterilization process and/or prolonged storage. This will be discussed later in this chapter.

PD solution	Manufacturer	pH	Osmotic Agent	Na (mmol/L)	Ca (mmol/L)	Mg (mmol/L)	Lactate (mmol/L)
Dianeal	Baxter	5.5	Glucose 0.55%, 1.5%, 2.5%, 4.25%	132	1.0/1.25/1.75	0.75/0.25	35/40
Stay safe	Fresenius	5.5	Glucose 1.5%, 2.5%, 4.25%	134	1.25/1.75	0.25/0.75	35/35

PD, peritoneal dialysis.

Table 1. Commercially available conventional peritoneal dialysis solution formulations

2.1. Osmotic agent—glucose

Conventional PD solutions contain high levels of glucose (dextrose; 75.5–214 mmol/L) as a principal osmotic agent to achieve fluid removal (i.e. ultrafiltration across the peritoneal membrane). Preparations containing different dextrose concentrations (e.g. 0.5 or 0.55%, 1.36 or 1.5%, 2.27 or 2.5% and 3.86 or 4.25% for anhydrous or hydrous dextrose, respectively) are

routinely available with varying osmolalities (345–484 mOsm/L). Whilst glucose is a reasonable osmotic agent because it is cheap, easily metabolized, readily available, easily sterilized and associated with an excellent long-term safety profile, the quantity of glucose required for effective ultrafiltration can be problematic. Average systemic glucose absorption from repeated exposure to PD solutions ranges between 100 and 300 g/day [3] (equivalent to 25–75 teaspoons of sugar per day or 36–110 kg/year), depending on dialysate glucose concentration, exchange volume, dwell time and peritoneal transport status. This appreciable peritoneal glucose absorption has in turn been linked with adverse local peritoneal membrane effects and systemic metabolic effects [4]. Glucose in PD solutions triggers protein glycosylation and activates the polyol and protein kinase C pathways [5, 6]. This, along with GDP toxicity and hyperosmolality, potentially results in mesothelial cell death, peritoneal inflammation, neoangiogenesis, epithelial-to-mesenchymal transition (EMT), progressive fibrosis and ultimately peritoneal membrane failure in chronic PD patients [7–11]. Systemic glucose absorption has also been associated with worsening hyperglycaemia in diabetic patients, new-onset hyperglycaemia in incident non-diabetic PD patients, visceral obesity and dyslipidaemia, characterized by elevated levels of total cholesterol, triglyceride, very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) [12–14]. Consequently, the use of high peritoneal glucose concentrations has been associated with heightened risks of cardiovascular and all-cause mortality [15].

2.2. Buffer—lactate

Most of the commercially available conventional PD solutions contain lactate (30–40 mmol/L) as a buffer and are acidic (pH 5.2–5.5). Lactate diffuses into the bloodstream and is rapidly metabolized into bicarbonate. As conventional PD solutions use a single-chamber delivery system, it is not possible to store bicarbonate-buffered solutions, as calcium and bicarbonate will precipitate to form calcium carbonate. Lactate has been shown to inhibit key cellular functions involved in peritoneal defence mechanisms, including phagocytosis, bacterial killing and secretion of cytokines [16].

2.3. Electrolyte composition

The concentrations of Na^+, Cl^-, Ca^{2+} and Mg^{2+} are kept close to those of serum concentrations. Removal of these ions is therefore almost completely dependent on convection due to the low diffusion gradient. For a decilitre of fluid removed in a 4-h dwell, approximately 10 mmol of Na^+ and 0.1 mmol of Ca^{2+} are removed, given that serum Na^+ and Ca^{2+} are within the reference ranges [17]. Electrolyte concentrations of these solutions vary little by different manufacturers. They are devoid of potassium, and sodium levels mostly range from 132 to 134 mmol/L. Calcium concentrations range from 1.00 to 1.75 mmol/L, depending on the manufacturer (**Table 1**). Patients using calcium-based phosphate binders are recommended to use PD solutions with 1.25 mmol/L [18] calcium concentration to reduce the incidence of hypercalcaemia and adynamic bone disease, which have been previously associated with higher calcium concentrations in PD fluids [19]. The Mg^{2+} concentration is 0.25–0.75 mmol/L. For 1.5%

dextrose solution, 0.25 mmol/L is associated with zero Mg^{2+} transport but for higher glucose concentrations there will be net Mg^{2+} losses, which should be kept in mind.

2.4. Glucose degradation products

Several types of GDPs are generated during the heat sterilization process, which are recognized to be toxic at both intra-peritoneal and systemic levels [20, 21]. These include 3-deoxyglucose, 3,4-dideoxyglucosone-3-ene (3,4-DGE), 5-hydroxymethyl furaldehyde, formaldehyde and acetaldehyde. Of the identified GDPs, 3,4-DGE is considered to be the most harmful [22], including its ability to result in dose- and time-dependent renal tubular epithelial cell apoptosis, which raises concern for promoting nephrotoxicity from systemic absorption through PD [23]. Furthermore, various studies have demonstrated adverse effects of these GDPs on peritoneal mesothelial cells, fibroblasts, neutrophils and macrophages, including cytotoxicity, inhibition of proliferation, induction of apoptosis, down-regulation and disturbance of the homeostatic balance of cytokines, and inhibition of migration, bacterial killing, phagocytosis and respiratory burst in phagocytic cells [24–26]. They also promote peritoneal membrane damage and fibrosis, progressive vasculopathy, altered peritoneal transport characteristics, impaired host defence against infections and potentially adverse systemic effects such as increased circulating advanced glycation end products (AGEs) [23, 27, 28].

In summary, conventional PD solutions are characterized by several undesirable characteristics that have been shown to result in adverse clinical outcomes, including peritoneal membrane injury. Consequently, there has been a great interest in manufacturing newer solutions with more 'biocompatible' features in order to mitigate these adverse effects. Subsequent sections of this chapter aim to discuss the current evidence regarding the use of different types of these 'novel' PD solutions and their impact on outcomes.

3. Neutral-pH, low GDP PD solutions

Multi-chamber technology has led to the development of neutral-pH, low GDP solutions. Glucose is separated from other electrolytes in one or more chambers and sterilized at a very low pH (2.8–4.2) to minimize the production of GDPs. The remaining solution is kept at an alkaline pH (8.0–8.6) in the other compartment. When PD solution needs to be used, the contents of the two compartments are allowed to mix by breaking a lambda seal or a frangible pin, resulting in the infusion of neutral pH (6.8–7.3), and either a low GDP content (e.g. Physioneal, Baxter Healthcare) or an ultralow GDP content (i.e. less than 80 μmol/L (e.g. Balance or Bicavera, Fresenius Medical Care; Gambrosol Trio, Gambro)) PD solution into the peritoneal cavity. Experimental evidence has reported an improvement in cellular function (e.g. host immune system and peritoneal mesothelial cells), and better preservation of peritoneal membrane from exposure to these solutions [29]. There have been over 20 published randomized controlled trials (RCTs) evaluating the impact of neutral-pH, low GDP solutions on patient-level outcomes [30], and some of their key findings will be summarized in the following sections.

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3.1. Residual renal function

Treatments using neutral-pH, low GDP solutions have been shown to result in better preservation of residual renal function (11 trials, 643 patients; standardized mean difference (SMD) = 0.17 mL/min; 95% confidence interval (CI), 0.01–0.32; p = 0.04) [31]. Moreover, the benefit was evident across all follow-up durations, extending from less than 6 months (6 trials, 390 patients; SMD: 0.45 mL/min; 95% CI: 0.11–0.79), 6–12 months (9 trials, 568 patients; SMD: 0.24 mL/min; 95% CI: 0.08–0.41) and beyond 12 months in duration (5 trials, 279 patients; SMD: 0.25 mL/min; 95% CI: 0.01–0.48) [31]. Forest plot from cumulative meta-analysis favouring biocompatible PD solutions is shown in **Figure 1**.

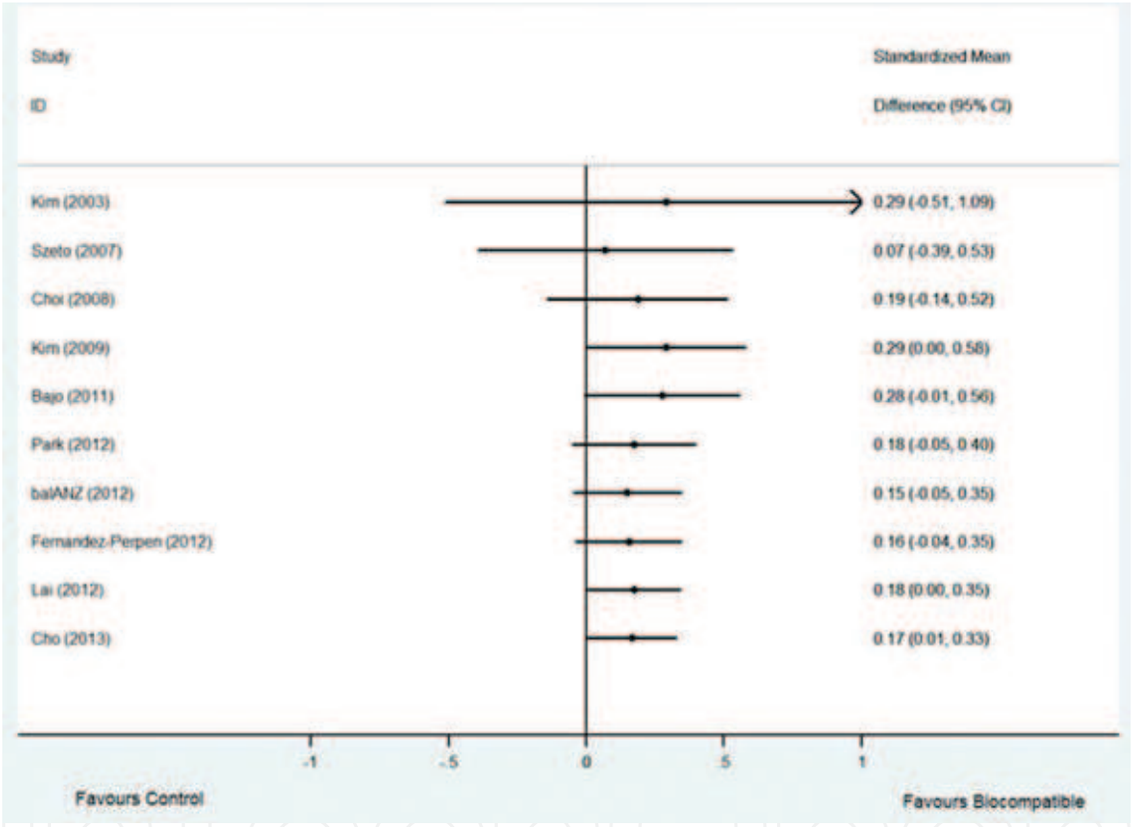

Figure 1. Cumulative meta-analysis demonstrating an impact of treatment using neutral-pH, low GDP PD solution on residual renal function (data from randomized controlled trials with follow-up duration greater than or equal to 12 months are included in the analysis) [32–41].

One potential mechanism underlying possible benefit of this solution on residual renal function is reduced systemic absorption of reactive carbonyls (GDPs) from the peritoneal cavity [28]. This could lead to reduced systemic exposure to advanced glycation end products (AGEs), which have been shown to exert direct pro-inflammatory, pro-apoptotic and pro-oxidative nephrotoxicity [23]. In response to the growing level of evidence, the International Society for Peritoneal Dialysis (ISPD) Cardiovascular and Metabolic current guidelines recommend treatments using neutral-pH, low GDP PD solution to better preserve residual renal function in PD patients [42].

3.2. Residual urine volume

Similarly, PD treatment using neutral-pH, low GDP solutions has been shown to better preserve residual diuresis (8 trials; 598 patients; mean difference: 127.93 mL/day; 95% CI: 57.54–198.31) [31]. This finding is further supported by previous outcomes from the balANZ trial where the intervention group experienced a significantly lower frequency of anuria (7% vs 20%) and a longer time to onset of anuria ($p = 0.009$) compared to the control group receiving conventional PD solution [38, 43].

3.3. Peritoneal ultrafiltration

Although there were concerns that an increase in residual diuresis from treatment using these solutions was a consequence of reduction in ultrafiltration, treatments using neutral-pH, low GDP solutions have not been shown to result in significantly different ultrafiltration when compared to conventional PD solutions (7 trials; 571 patients; mean difference: -110.29 mL/day; 95% CI: -311.67 to 91.09) [31]. Although there has been no RCT conducted to date which measured fluid status objectively (e.g. bioimpedance spectroscopy), clinical findings between patient groups (e.g. body weight, blood pressure) have been shown to be consistently comparable across the various studies [38, 41, 44, 45].

3.4. Inflow pain

Inflow pain, which is reported to occur in up to 73% of PD patients, has been attributed to the acidic pH of conventional solutions [29]. The use of neutral-pH solution appears to effectively alleviate this problem [30].

3.5. Peritonitis

The balANZ trial has reported a significant benefit in reducing peritonitis risk from treatments using neutral-pH, low GDP PD solutions, with lower peritonitis rates (0.30 vs 0.49 episodes per patient-year) and a significantly longer time to the onset of the first peritonitis episode ($p = 0.01$) [38, 46]. Furthermore, when peritonitis episodes occurred, patients in the intervention group experienced milder symptoms and required shorter hospital duration. Although improved peritoneal host defence mechanisms [46] resulting from exposure to these solutions have been considered as an underlying mechanism, these results have not been similarly replicated by other clinical trials. Nonetheless, none of these trials, including the balANZ trial, was designed to evaluate peritonitis as a primary outcome measure. Interestingly, a meta-analysis was able to demonstrate that some of the heterogeneity that exists amongst the published literature may be driven by the high prevalence of attrition bias (defined as drop-out rate >20%), as the balANZ trial was the only one of the six trials assessed to be at a low risk of attrition bias [47].

3.6. Adverse effects

Compared with conventional solutions, biocompatible solutions have not been associated with any harm [30, 47].

3.7. Cost

To date, there has only been one economic evaluation of neutral-pH, low GDP PD solutions compared with standard solutions. In a secondary analysis of the balANZ trial, neutral-pH, ultralow GDP PD solution was found to be a cost-effective alternative to standard solutions, primarily as a result of reduction in peritonitis-related hospital costs [48]. Since this time, the costs of biocompatible solutions have fallen significantly, thereby further enhancing their cost-effectiveness.

3.8. Other clinical outcomes: peritoneal solute transport and clearance, patient and technique survival

To date, treatments using biocompatible solutions have not been shown to exert a significant impact on outcomes relating to peritoneal solute transport rate, small solute clearance, or patient and technique survival.

3.9. Summary

PD using neutral-pH, low GDP PD solution improves clinically important patient-level outcomes, including better preservation of residual renal function, and residual diuresis with probable benefit towards reducing inflow pain. There has been no identified increase in the risk of harm from their use. Moreover, due to recent increase in the uptake of these biocompatible solutions, the cost of therapy has been substantially lowered, and is almost at par with conventional treatments. This has allowed for further increase in uptake in the clinical setting.

4. Glucose-sparing strategies

Due to the above-mentioned adverse effects of glucose on the peritoneal membrane as well as its impact at the systemic metabolic level, there has been a great interest in developing strategies for reducing glucose exposure in PD patients. From the PD solution perspective, these options include regular review of the PD prescription to ensure that the glucose strength of PD solution is appropriate and not excessive for an individual patient's needs. A patient's need for peritoneal ultrafiltration (and therefore higher peritoneal glucose concentration) may be further reduced through appropriate dietary salt and water restriction, administration of diuretics and use of strategies to preserve residual renal function (e.g. biocompatible fluids, angiotensin-converting inhibitors or angiotensin receptor blockers, avoidance of hypotension, etc.) [30, 49–53]. An additional option is to use PD solutions that contain non-glucose osmolar agents, such as icodextrin.

5. Icodextrin

Icodextrin is a starch-derived, iso-osmolar, high molecular weight (16,200 Daltons) glucose polymer PD solution. The structure of icodextrin is similar to glycogen, consisting of polysac-

charide polymers of D-glucopyranose linked by α-(1→4) and α-(1→6) glucosidic bonds. The pharmacokinetics of icodextrin in blood following intra-peritoneal administration conforms to a simple, single-compartment model that can be approximated by zero-order absorption and first-order elimination [54]. Icodextrin is slowly absorbed via the lymphatics and the resultant osmotic gradient dissipates slowly as compared to glucose, which is absorbed via the small pores of the peritoneal membrane. This provides much greater net ultrafiltration during the long dwell, especially in patients with high transporter status [55, 56]. Treatment using icodextrin has been shown to achieve ultrafiltration equivalent to fluid removal achieved with 4.25% glucose exchange during longer PD dwells (10–16 h) [57]. As such, the ISPD, Australian Icodextrin Consensus Working Group and the European Renal Best Practice (ERBP) Working Group recommend that icodextrin be used for the longer dwell in high transporters with net ultrafiltration of less than 400 mL during a 4-h exchange with a 4.25% dextrose solution [57–59]. The worldwide use of icodextrin has expanded beyond this traditional indication because of accumulating evidence of a favourable benefit:harm profile.

5.1. Effects on metabolism: glycaemia and lipid

The glucose-sparing effect of icodextrin has been shown to result in an improvement in metabolic profile based on several observational studies and RCTs [60–62]. The earliest study to demonstrate this was by Johnson et al., who demonstrated significant improvements in the glycaemic control of diabetic PD patients treated with icodextrin, whereby HbA1c levels fell from 8.9 ± 0.7 to 7.9 ± 0.7% [62]. In a subsequent study of 51 diabetic-prevalent patients, the replacement of one of glucose-based PD exchange with icodextrin led to significant reductions in total cholesterol, triglyceride and LDL levels [60]. The reductions were evident as early as 3 months, even though patients were not allowed to initiate or modify existing lipid-lowering treatments for the duration of the study. Similarly, Paniagua and colleagues observed a significant reduction in fasting glucose, insulin requirement, triglyceride and HbA1c levels in those who were randomly assigned to receive icodextrin ($n = 30$) in their multi-centre RCT [61].

5.2. Ultrafiltration and fluid status

Icodextrin utilization in a single, daily PD exchange has been shown to increase daily ultrafiltration (4 trials; 103 patients; mean difference: 448.54 mL/day; 95% CI: 289.28–607.80) and reduce episodes of uncontrolled fluid overload without compromising residual renal function (4 trials; 114 patients; standardized mean difference: 0.12, 95% CI: -0.26 to 0.49) [63]. This benefit has been shown to be present for all types of peritoneal membrane transporters, except for those with low transport characteristics [64]. Increases in fluid removal from prescriptions incorporating icodextrin have been shown to objectively improve volume status measured using bioelectrical impedance [65], reduce left ventricular mass index [66], improve ambulatory blood pressure control [67] and significantly reduce episodes of uncontrolled fluid overload (2 trials; 100 patients; relative risk: 0.30; 95% CI: 0.15–0.59) [66].

5.3. Patient and technique survival

Despite benefits relating to metabolic profile and fluid status, treatments using icodextrin have not been shown to improve technique (3 trials; 290 patients; relative risk: 0.58; 95% CI: 0.28–1.20) or patient survival [63] (6 trials, 816 patients; relative risk: 0.82; 95% CI: 0.32–2.13). However, the majority of studies included for analysis (more than 60%) had follow-up durations of less than 6 months [63], where one could argue to be too short a follow-up duration to adequately evaluate these outcomes. This, together with the small pooled sample size from studies to date, means that the effects of icodextrin on patient and technique survival remain uncertain.

5.4. Adverse effects

Treatments using icodextrin have been shown to increase the serum levels of its metabolites (i.e. maltose and maltotriose), which peak at 2 weeks after treatment commencement and return to normal levels after therapy cessation. Whilst the clinical significance of these metabolite elevations is uncertain, icodextrin is generally recommended to be used in no more than one exchange daily [57]. The accumulation of maltose may lead to overestimation of blood glucose levels due to interference with glucometers using the glucose dehydrogenase pyrroloquinoline quinone (GDH PQQ) method, such that patients may experience hypoglycaemia through inadvertent excessive insulin administration [68]. Guidelines therefore recommend that diabetic PD patients using icodextrin should perform blood sugar measurements using a glucose-specific method (e.g. glucose oxidase or hexokinase reference methods) [57]. Other potential risks from icodextrin use include skin rash, which can lead to therapy cessation (0–4.3% of patients) [69], and sterile peritonitis, which fortunately has not been problematic since the introduction of quality assurance programme monitoring of peptidoglycan levels [55].

5.5. Twice daily icodextrin

The use of twice daily icodextrin (8 h/exchange) has been proposed to take advantage of its glucose-sparing characteristics and high ultrafiltration efficiency. Not surprisingly, the studies have reported a reduction in glucose exposure, better ultrafiltration and blood pressure control with an improvement in cardiac parameters on echocardiogram [70–73]. However, all studies to date had small sample sizes and short follow-up durations (<6 months). Furthermore, the product information of icodextrin still recommends its use to be limited as a single exchange in each 24-h period as insufficient safety data are available on the effects of more frequent administration. Therefore, the routine use of twice daily icodextrin cannot be recommended until further data are available on safety and efficacy.

5.6. Summary

PD incorporating a single daily exchange of icodextrin results in significantly higher ultrafiltration, which leads to improvement in volume status and cardiac parameters, without adversely affecting residual renal function. Although there has been no convinc-

ing evidence to suggest an improvement in technique or patient survival from its use and icodextrin is more costly than conventional PD solutions, the utilization of icodextrin is likely to be a more cost-effective option in patients with ultrafiltration failure than transferring to haemodialysis.

6. Amino acid solutions

Peritoneal dialysis causes loss of protein and amino acids in the dialysate, which contributes to the development of protein and energy malnutrition in these patients. Amino acid solutions were developed with an aim to compensate for protein loss. These products are osmotically equivalent to 1.5% glucose PD solutions, although their use is limited to a single daily exchange due to a risk of worsening systemic acidosis and uraemia [74]. Amino acid PD solutions have been shown to improve surrogate markers of nutritional status (e.g. insulin-like growth factor-1, pre-albumin, transferrin) in malnourished PD patients over a 3-month period [75]. However, a subsequent 3-year RCT did not show any significant impact of amino acid PD solution on hospitalization or mortality in 60 malnourished PD patients. Therefore, the role of amino acid solutions remains uncertain in the absence of evidence relating to impact on patient-level clinical outcomes.

7. Combination glucose- and GDP-sparing solutions

More recently, there has been an interest in combining icodextrin, amino acid and neutral-pH, low GDP PD solutions as part of glucose-sparing PD therapy. The most recent and the largest RCT conducted was the IMPENDIA-EDEN study [76]. This was an open-label, parallel design trial combining two studies which in total randomized 127 patients to glucose only, and 124 to glucose-sparing treatment group (i.e. one exchange of amino acid PD solution, one exchange of icodextrin and two exchanges of glucose-based PD solutions) for 6 months. The primary outcome measure was a change in HbA1c from baseline. During the study, there was a significant decrease in the mean HbA1c in the glucose-sparing arm with a mean difference of 0.5% between the two groups (p = 0.006) [76]. However, patients in the glucose-sparing group experienced a significantly higher frequency of serious adverse events (105 vs 78) and more deaths (11 vs 5). A large proportion of these events were from fluid overload and hypertensive encephalopathy. This was an unexpected outcome as the glucose-sparing group received icodextrin, which is known to increase ultrafiltration. Later, the study investigators hypothesized that some participating centres attempted to overachieve HbA1c reduction at the expense of peritoneal ultrafiltration by inappropriately reducing the glucose strength of glucose-based PD solutions in the intervention group, which led to this devastating consequence.

In summary, glucose-sparing PD therapy has been shown to improve metabolic profile (i.e. glycaemic control and lipid profile). However, there are residual concerns about its safety, and therefore its use cannot be widely recommended at present **Figure 2**.

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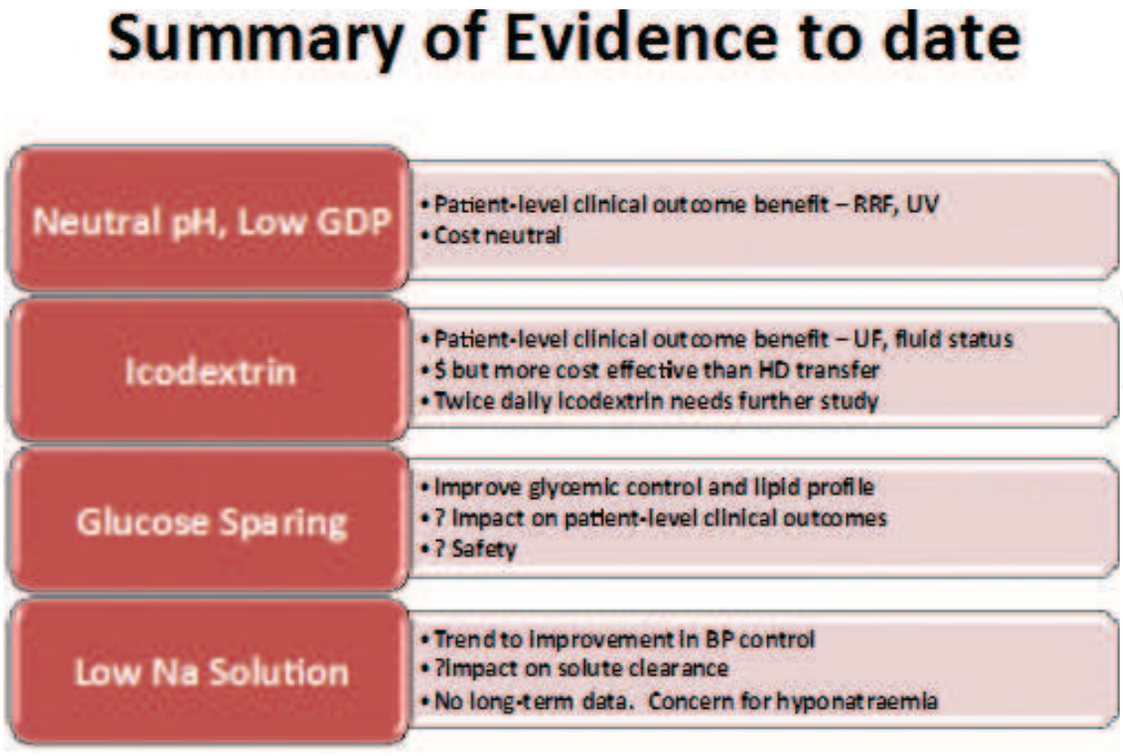

Figure 2. Current evidence regarding available PD solutions. RRF (residual renal function), UV (urine volume), UF (ultrafiltration), and HD (haemodialysis).

8. PD solutions: future

The ideal PD solution should have a physiologic electrolyte and buffer composition and have an osmotic agent that is non-toxic, non-immunogenic, and not be rapidly absorbed into the plasma compartment (or, if it is, it should ideally be rapidly metabolized). Furthermore, it should produce steady osmotic ultrafiltration over the course of a dwell. So far, glucose has been the universally used osmotic agent in peritoneal dialysis, based on its relative efficiency, low cost, safety and rapid metabolism in plasma. There has been a great interest in developing new osmotic agents that meet the above criteria. One such new agent is hyperbranched polyglycerol (HPG) [77], a branched compact polyether polymer (glycidol monomer). As an osmotic agent, HPG fulfills the criteria of being ideal in size and physical properties and appears to be non-toxic, non-immunogenic and highly biocompatible. It can be manufactured with different molecular weights to add in further flexibility if it is to be implemented in future clinical practice. About 60% is retained in the peritoneum but 25% is excreted in urine. However, its long-term safety, biocompatibility, metabolism and plasma accumulation during long-term use remains unknown and is currently in the preclinical evaluation phase. Other osmotic agents, which have been studied, include L-carnitine and alanyl-glutamine, but none of these solutions are currently available for clinical use.

Another type of PD solution currently undergoing further assessment is low-sodium PD solutions. The rationales for low-sodium PD solution are (i) to increase absolute sodium removal for a given glucose load and (ii) to reduce the 'gap' between sodium and water removal (a consequence of sodium sieving via the aquaporin pathway). As volume homeostasis is an important predictor of outcome in PD patients, an increase in sodium removal by manipulating the sodium concentration of PD solutions to increase net sodium loss is attractive. Several observational studies examining varying levels of sodium concentration (98–120 mmol/L), either as a single exchange or four exchanges daily, have shown an increase in sodium removal, reduction in blood pressure and a decrease in thirst response [78–80]. However, the most recent multi-centre, multinational RCT comparing low-sodium versus standard sodium (125 vs 134 mmol/L) PD solution in hypertensive CAPD patients over 6 month follow-up duration observed an inferior total Kt/V with low-sodium solution (mean difference -0.78), whilst peritoneal Kt/V was comparable between the two groups. These outcomes were attributed to a reduction in thirst and fluid intake in the treatment group, potentially reducing fluid overload and urine excretion (similar to salt-restricted diet intervention), which led to a significant reduction in renal Kt/V in the treatment group. There was a trend towards improved blood pressure control in the low-sodium group although more patients developed hyponatraemia than the control group [81]. In light of the paucity of evidence to date and the presence of some safety signals, low-sodium PD solutions cannot be routinely recommended for clinical practice at this stage.

9. Conclusions

None of the currently available PD solutions is perfect. The PD community needs to remain vigilant in its efforts to develop solutions that are more 'biocompatible', ideally using a non-glucose osmolar agent, which is non-toxic, easily metabolized, easily manufactured, cost-effective and metabolically efficient (i.e. predictable ultrafiltration profile with large ultrafiltration volume per unit mass absorption). Experimental models and international collaboration are required to advance this field of research. In the meantime, individualizing therapy to account for particular patient characteristics is necessary to improve clinical outcomes.

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