Pediatr Nephrol (2011) 26:1137–1147
DOI 10.1007/s00467-011-1863-4

ORIGINAL ARTICLE

Solutions for peritoneal dialysis in children: recommendations by the European Pediatric Dialysis Working Group

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Received: 21 September 2010 / Revised: 11 February 2011 / Accepted: 14 February 2011 / Published online: 31 March 2011

Abstract The purpose of this article is to provide recommendations on the choice of peritoneal dialysis (PD) fluids in children by the European Pediatric Dialysis Working Group. The literature on experimental and clinical studies with PD solutions in children and adults was analyzed together with consensus discussions within the group. A grading was performed based on the international KDIGO nomenclature and methods. The lowest glucose concentration possible should be used. Icodextrin may be applied once daily during the long dwell, in particular in children with insufficient ultrafiltration. Infants on PD are at risk of ultrafiltration-associated sodium depletion, while anuric adolescents may have water and salt overload. Hence, the sodium chloride balance needs to be closely monitored. In growing children, the calcium balance should be positive and dialysate calcium adapted according to individual needs. Limited clinical experience with amino acid-based PD fluids in children suggests good tolerability. The anabolic effect, however, is small; adequate enteral nutrition is preferred. CPD fluids with reduced glucose degradation products (GDP) content reduce local and systemic toxicity and should be preferred whenever possible. Correction of metabolic acidosis is superior with pH neutral bicarbonate-based fluids compared with single-chamber, acidic, lactate-based solutions. Prospective comparisons of low GDP solutions with different buffer compositions are still few, and firm recommendations cannot yet be given, except when hepatic lactate metabolism is severely compromised.

Keywords Peritoneal dialysis fluids · Pediatrics · Biocompatible · Icodextrin · Amino acid · Consensus · Glucose degradation products

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Introduction

Peritoneal dialysis (PD) is the preferred renal replacement therapy in children until renal transplantation can be realized. The choice of PD solution has gained particular importance, in the light of the profound alterations of the PD membrane reported after exposure to some of the current PD solutions. Conventional, acidic PD solutions containing high concentrations of glucose, glucose degradation products (GDP). and lactate buffer confer marked local and systemic toxicity. Within a few years, the peritoneal membrane undergoes progressive mesothelial denudation, submesothelial fibrosis, hyaline vasculopathy, and neoangiogenesis [1]. Hypervascularization of the peritoneal membrane results in increased solute clearance, but also in rapid glucose uptake, and thus

ultrafiltration loss and eventually PD failure [2]. Peritonitis episodes, chronic inflammation, and a persistently elevated calcium phosphate product further accelerate membrane transformation and thickening, which may in severe cases result in life-threatening, encapsulating peritoneal sclerosis. GDP are rapidly absorbed from the peritoneal cavity and increase systemic advanced glycation end product (AGE) load [3, 4]. Long-term PD technique and patient survival are limited [5]. Three alternative technological measures have been realized to improve PD fluid biocompatibility: the separation of glucose at a very low pH from the buffer in double- and triple-chamber bag systems; the replacement of glucose by icodextrin; and the replacement of glucose by amino acids, with the original intention of improving nutritional parameters. All these solutions contain less GDP than conventional, glucose-based fluids (Tables 1, 2) [6, 7]. Knowledge of the specific features of each solution is essential to provide the most efficient and biocompatible PD regimen that allows for long-term PD in children with minimal morbidity.

The European Pediatric Dialysis Working Group (EPDWG) was established in 1999 and comprises pediatric nephrologists with a major interest in peritoneal dialysis from 13 European countries. The guidelines produced by the EPDWG have been endorsed by the European Society of Pediatric Nephrology. The first guidelines on the choice of peritoneal dialysis solutions in children were published in 2001 [8]. After 10 years, and in the face of the increased scientific evidence obtained in children and adults, revised recommendations have been developed, based on literature research (Medline, abstracts presented at international conferences), consensus meetings of the EPDWG, and extensive email discussions. A grading of the recommendations was performed based on the KDOQI nomenclature and methods [9]. Evidence level 1 indicates a recommendation that most experts would want to be the course of action in most patients. Evidence level 2 indicates a suggestion that the majority of experts would want to be realized, but some would not, and that different choices will be appropriate in different patients, in accordance with the patients' values and preferences. Level A indicates high-quality scientific evidence, B moderate, C low, and D very low quality of evidence, implying that the true effect will be close (A) or often far (D) from the estimate. Adult and pediatric evidence was taken into account. The authors acknowledge the difficulties associated with transfer of adult findings to young children and infants and emphasize the need for additional pediatric trials.

Choice of PD fluid components

Glucose

The standard osmotic agent is glucose at supraphysiological concentrations (1,360–4,250 mg/dl). This creates an osmotic gradient via the peritoneal membrane to achieve ultrafiltration. On the other hand, the hyperosmolar and hyperglycemic milieu is a major driving force for the peritoneal membrane transformation and the progressive increase in glucose reabsorption, which is the rate-limiting factor for ultrafiltration capacity [10]. The amount of toxic GDP in single-chamber as well as in multi-chamber PD fluids strongly depends on the

Table 1 Composition of conventional, single-chamber peritoneal dialysis (PD) solutions

	CAPD 2/3/4 17/18/19	Dianeal PD 1, PD2[b], PD4	Gambrosol 10/40
Sodium (mmol/l)	134	132	132
Chloride (mmol/l)	102.5	102/96/95	96/95
Calcium (mmol/l)	1.25/1.75	1.75/1.75/1.25	1.75/1.35
Magnesium (mmol/l)	0.5	0.75/0.75/0.25	0.25
Glucose (%)	1.5/2.3/4.25	1.36/2.27/3.86	1.5/2.5/4.0
Osmolarity (mosmol/l)	356–509	344–486	353–492
Lactate (mmol/l)	35	35/40/40	40
pH	5.5	5.5	5.5
Formaldehyde (μmol/l)[a]	5.4±0.4	6.8±0.2	6.4±0.5
3-DG (μmol/l)[a]	142±0.8	167±0.3	175±4
3,4-DGE (μmol/l)[a]	16.2±0.8	11.3±0.5	13.1±1.1
Bag size (l)	1.5/2/2.5	1.5/2/2.5/3/5 (APD)	0.5/1/1.5/2/2.5/3 (G40)/4.5/5

GDP concentrations taken from [10], for Gambrosol 10 / 40 from [6]

3-DG=3-deoxyglucosone; 3,4-DGE=3,4-dideoxyglucosone-3-ene; CAPD = continuous ambulatory peritoneal dialysis

[a] At medium glucose concentration

[b] Not available in all countries

Table 2 Composition of biocompatible PD solutions

	BicaVera	Balance	Gambrosol trio 10/40	Physioneal 35/40	Extraneal (7.5% icodextrin)	Nutrineal (1.1%AS)
Sodium (mmol/l)	132	134	132[b]	132	132	132
Chloride (mmol/l)	104.5	100.5	96[b]	101/95	96	105
Calcium (mmol/l)	1.75	1.25/1.75	1.75 /1.35[b]	1.75 /1.25	1.75	1.25
Magnesium (mmol/l)	0.5	0.5	0.25[b]	0.25	0.25	0.25
Glucose (%)	1.5/2.3/4.25	1.5/2.3/ 4.25	1.5/2.5/ 3.9	1.36/2.27/ 3.86	0	0
Osmolarity (mosmol/l)[a]	358–511	358–511	356–483	344–484	284	365
Lactate (mmol/l)	0	35	40[b]	10/15	40	40
Bicarbonate (mmol/l)	34	0	0	25/25	0	0
pH	7.4	7.0	5.5–6.5[a]	7.4	5.5	6.7
Formaldehyde (μmol/l)[b]	< 3.3	< 3.3	< 3.3	3.4±0	3.6±0.7	n.d.
3-DG[b] (μmol/l)	16.3±0.2	17.6±0.3	20.2±2.4	93.3±5.0	7.5±0.4	<0.1
3,4 DGE[b] (μmol/l)	< 2.4	< 2.4	< 2.4	14.3±2.5	<2.4	n.d.
Bag size (l)	2/2.5/3 (APD)	2/2.5/3 and 5 (APD)	2/2.5/5 (APD)	1.5/2/2.5/5 (APD)	2.0 and 2.5	2.0

GDP concentrations are taken from [6, 7], Nutrineal from [87]

3-DG=3-deoxyglucosone; 3,4-DGE=3,4-dideoxyglucosone-3-ene; n.d. = not done (other GDP measured were low in Nutrineal solutions)

[a] Low to high glucose concentration

[b] At medium glucose concentration

glucose concentration [6, 7]. The average peritoneal glucose and GDP exposure also increase with the number of exchanges per day. The detrimental effects may partially be compensated for by an empty abdomen during the daytime in nightly intermittent peritoneal dialysis (NIPD).

Considerable amounts of glucose are absorbed, according to the transporter status of the peritoneal membrane. A combination of short dwell times (optimal ultrafiltration) and long dwell times (optimal purification) may increase the ratio of ultrafiltration to glucose absorbed and thus reduce the total peritoneal glucose exposure [11].

The prevention of volume overload is essential to minimize cardiovascular sequelae [12, 13]. Infants with polyuria and salt wasting who require sodium chloride supplementation and high fluid intake should benefit from lower glucose concentrations than those currently available to prevent volume constriction.

Recommendation The lowest glucose concentration and number of cycles possible to achieve euvolemia should be administered (1B).

Buffer substances

Lactate has been the only buffer available for PD fluids until recently. It is added to PD solutions at concentrations far above the physiological range (Table 1), is rapidly absorbed via the peritoneal membrane, and is metabolized to bicarbonate in the liver. The net buffer gain is counterbalanced by the simultaneous loss of blood bicarbonate into the dialysate [14]. In vitro and animal studies have provided ample evidence that the high amounts of lactate, present in conventional PD solutions at a low pH, have detrimental effects on peritoneal mesothelial cells. Lactate alters specific cytokine release [15], reduces the availability of antioxidants, such as glutathione [16] and induces neoangiogenesis [17]. Adjustment to a physiological pH markedly improves, but does not normalize the ex vivo viability and function of mesothelial cells [18, 19]. Lactate inadequately buffers the metabolic acidosis in patients with acute kidney injury (AKI), especially with poor tissue perfusion states, such as shock, lactic acidosis, and multi-organ dysfunction. Particular attention is required in children with impaired hepatic metabolism, e.g., due to inborn errors of metabolism, cardiac surgery, and in newborns, in whom lactate needs to be monitored closely. Dialysis fluids containing bicarbonate, the physiological buffer of the blood, have been demonstrated to improve the outcome of patients who require acute dialysis [20, 21].

Superior control of metabolic acidosis has been demonstrated for the pure 34-mmol bicarbonate solution in children [22] and the 25/10-mmol bicarbonate/lactate

solution compared with single-chamber, 35-mmol lactate PD fluid in adults [23]. Overcorrection of metabolic acidosis, however, may occur with very frequent cycles and with higher dialysate buffer content [24]. Switching from a 40-mmol buffered PD solution to 34 or 35 mmol/l prevents the development of alkalosis in most patients [22].

Recommendation Bicarbonate-based PD fluids are recommended in children with AKI especially when liver function is severely compromised (1C). Bicarbonate-based PD solutions should generally be preferred to single-chamber lactate-based PD solutions in children (1B). Recommendations with regard to the buffer composition of reduced GDP fluids cannot be given at present.

pH

The pH of PD solutions varies between 5.5 and 7.4. In vitro, acidic incubation medium exerts higher toxicity on peritoneal mesothelial cells compared with medium with a physiological pH. Likewise, adjustment of the acidic pH of PD fluids to normal reduces cytotoxicity [17, 18]. Increased peritoneal capillary recruitment induced by perfusion of rat peritoneum with acidic, high GDP solutions, however, could not be reversed by adjustment of pH to neutral. In contrast, multi-chamber PD fluids with a reduced GDP content and a neutral pH induced little or no peritoneal hyperperfusion [25]. In humans, PD fluids with a neutral pH and a reduced GDP content reduce inflow pain, intraperitoneal pressure, and, at least within a 1-day cross over comparison, reduce capillary recruitment, compared with conventional single-chamber solutions [26, 27]. The relative contribution of pH still needs to be delineated.

Recommendation Acidic PD solutions should be avoided, a neutral to physiological pH (7–7.4) is suggested (2B).

Electrolytes

Sodium balance is closely related to the ultrafiltration rate. Depending on the dwell time and the relative contribution of free water transport via aquaporin-1 in the early phase of a dwell, more than 100 mmol of sodium per liter of ultrafiltrate may be lost. In infants, the relatively higher ultrafiltration rates may therefore result in reduced total body sodium chloride content, hypovolemia, and hypotension. Residual renal electrolyte losses can further disturb electrolyte and volume homeostasis. As a consequence, severe clinical complications have been observed in the past; in these infants, sodium chloride supplementation is mandatory [28]. In contrast, older children and adolescents are typically overloaded with salt and thus water, especially if anuric. Frequent short cycles result in a relatively higher contribution of free water transport, increased serum sodium chloride concentrations, and thirst, whereas long PD dwells result in fluid re-absorption. Thus, infants may substantially benefit from higher and older children from lower dialysate sodium chloride concentrations. All PD fluids currently available have a sodium concentration of 132–134 mmol/l. Dialysate solutions containing 115–126 mmol/l of sodium and increased glucose concentrations up to 2.5% to maintain osmolality have shown promising results in prospective studies in adults [29, 30]. These PD solutions, however, have not yet been admitted to the market.

Precise monitoring of the sodium chloride and hydration status by repeated determinations of body weight, blood pressure, nutritional supply, and serum electrolyte concentrations is essential. Determination of urine and effluent electrolyte concentrations give additional information on electrolyte losses and allow for an estimate of the required sodium chloride supplementation in children with insufficiently controlled blood pressure, electrolyte, and water homeostasis. Single-frequency bioimpedance analysis indicates intraindividual changes in hydration status [31, 32]. Margins of error, however, are large when total body water is predicted and the method is not yet broadly applied. Multiple-frequency bioimpedance analysis seems to be a promising method, but has not yet been sufficiently evaluated.

Recommendation Sodium chloride balance and volume status must be carefully monitored (1C). PD fluids with a high and low dialysate sodium chloride concentration appear beneficial in infants and older children respectively, but pediatric trials are needed.

Calcium

Optimal calcium control, i.e., serum levels within the normal range, is crucial for bone [33] and cardiovascular health [34]. Low dialysate calcium concentrations of 1.25 mmol/l allow for a neutral calcium balance, unless ultrafiltration occurs [35]. High dialysate calcium concentration, i.e., 1.75 mmol/l, usually results in a positive calcium balance. The net dialytic calcium balance can be estimated from the dialysate turnover, the difference between PD fluid and effluent calcium concentrations and the losses associated with ultrafiltration [36]. It adds to the total body calcium balance determined by urine losses and intestinal absorption from nutrients and phosphate binders and is modified by vitamin D treatment. Calcium balance should be positive to meet the mineral requirements of a growing skeleton, especially in infancy and during the

pubertal growth spurt. The use of solutions containing 1.0 mmol/l of calcium often aggravates secondary hyperparathyroidism and has become obsolete with the advent of calcium-free phosphate binders [37]. Of note, hypophosphatemia may develop in rapidly growing infants with low phosphate formula milk and good peritoneal phosphate clearance rates. Calcium and phosphate metabolism should be monitored closely according to the respective guidelines [38].

Recommendation The dialysate calcium concentration must be adapted to the individual needs of the growing child (not graded).

Magnesium

Since magnesium accumulates in advanced CKD, dialysate magnesium concentrations are low to low-normal relative to serum concentrations (Tables 1, 2). Hypomagnesemia has been reported in the majority of adult continuous ambulatory peritoneal dialysis (CAPD) patients treated with a single-chamber PD solution, containing 0.5 mmol/l of magnesium [39]. Serum albumin concomitantly declined, but clinical symptoms were not reported. Harmful effects of increased serum magnesium levels include altered nerve conduction velocity, pruritus, and altered bone and parathyroid gland function. On the other hand, hypermagnesemia may also slow the vascular calcification rate. An inverse relationship between serum Mg, hyperparathyroidism and vascular calcification has been demonstrated in adult dialysis patients [40, 41]. Thus, the clinical impact of magnesium homeostasis in children with CKD5d is not yet sufficiently delineated.

Recommendation We suggest maintaining high normal serum magnesium concentrations, i.e., 0.9–1.0 mmol/l (2D). Further studies are needed.

Choice of PD fluid type

Conventional PD solutions

Single-chamber PD solutions allow for efficient ultrafiltration, transperitoneal solute transport, and thus blood purification. However, they expose the patient to supraphysiological lactate concentrations at an unphysiologically low pH (Table 1). Sterilization of the glucose at a high temperature and at a relatively high pH (5.5) as well as prolonged storage promotes the generation of numerous toxic GDP. These impair peritoneal mesothelial cell function [15, 16, 42], induce pro-angiogenic factors such as VEGF [43], and affect local host defense mechanisms [44–46]. GDP are rapidly absorbed via the peritoneal membrane [3, 4] and contribute to inflammation, fibrosis, and vasculopathy. GDP are potent precursors for AGE formation. AGE accumulate in the PD membrane, but also in the entire body [47], and further accelerate the process of vascular and tissue aging.

Chronic exposure to single-chamber PD fluids impair local host defense, and lead to largely irreversible alterations of PD membrane morphology and function within a few years of usage [1, 2, 17]. Registry data suggest reduced patient survival with conventional PD solutions [48, 49]. Prospective, randomized, long-term studies are underway.

Recommendation Conventional, single-chamber PD solutions should be replaced by PD solutions with reduced GDP content (1B)

Multi-chamber PD fluids

By separating the glucose at a very low pH in double- and triple-chamber bags, formation of GDP is markedly reduced. Most, albeit not all, of the solutions are buffered at neutral or even physiological pH with lactate, bicarbonate or a mixture of both. Numerous experimental and clinical studies have demonstrated an improved biocompatibility profile of multi-chamber PD solutions. In vitro, multi-chamber PD fluids improve mesothelial cell viability and function, preserve innate peritoneal immune defense mechanisms, and reduce the synthesis and secretion of cytokines related to inflammation, fibrosis, and angiogenesis [46, 50–52]. Animal studies confirm improved in vivo peritoneal host defense [53, 54], reduced peritoneal TGF-ß and VEGF expression, reduced deposition of AGE, preservation of the mesothelial cell layer, and reduced fibrosis, vasculopathy, and neoangiogenesis [55]. The acute peritoneal hyperperfusion observed with conventional solutions is largely prevented when perfusion is performed with multi-chamber PD fluid [25]. Finally, multi-chamber fluids have been associated with preserved ultrafiltration capacity in an experimental long-term dialysis model [56]. In humans, effluent CA125 concentration, a surrogate parameter of peritoneal mesothelial cell mass, increases, whereas the inflammation markers IL-6 and hyaluronic acid decrease [4, 21, 57–59]. The effluent concentration of VEGF, a putative marker of peritoneal neoangiogenesis, decreased in some but not all studies [52, 58, 59]. Several prospective randomized trials demonstrate similar solute transport and ultrafiltration capacity in children and adults treated with multi-chamber compared with conventional PD solutions [14, 22–24, 60]. In the case of reduced ultrafil-

tration rate, this was compensated for by improved residual renal urine output [57, 61]. Long-term trials in PD patients with significant residual GFR (e.g., above 2 ml/min/1.73 m^2) demonstrate better preservation of renal function with multi-chamber PD fluids [62, 63], possibly due to reduced GDP resorption. GDP are toxic to podocytes and tubular cells [64]. Switch from conventional to reduced GDP solutions results in a peritoneal wash-out of AGE [65, 66] and a 15% decline in systemic AGE levels in children [3] and adults [4].

Clinical benefits of multi-chamber PD fluids include the reduction of abdominal discomfort due to reduced inflow pain and intraperitoneal pressure [26, 27]. Some clinical observations, furthermore, suggest a reduced overall peritonitis incidence in patients treated with low GDP solutions, new cyclers, and improved connection devices [67, 68]. These findings were not confirmed by others [48, 49], possibly because of the low over all peritonitis rates. Untoward effects have not been reported in any study. Two large-scale registries demonstrate significant improvement of patient morbidity and mortality in adults using multi-chamber as opposed to conventional fluids [48, 49]. Large-scale, randomized, comparative trials are currently underway.

Of note, the different available multi-chamber solutions still differ considerably with respect to their GDP content (Tables 2) [6, 7]. Some manufacturers reduced the total GDP content measured by 50%, others by more than 90%, compared with single-chamber PD fluid [6]. The clinical impact of these differences has not yet been delineated. All multi-chamber PD solutions are available for CAPD and APD/NIPD, the latter modality being most widely applied in children.

Recommendations Multi-chamber PD solutions with reduced GDP content should be the standard of care in children on PD (1B) in countries where these solutions are available. General recommendations with regard to the choice of specific multi-chamber PD solutions cannot be given at present.

Icodextrin solution

Exposure to glucose at high concentrations confers toxicity to the peritoneum even in the absence of GDP. Icodextrin is an alternative, less toxic osmotic agent. The GDP content of the icodextrin solution is low, lactate concentration is high, and the pH is low (Table 2). Although the transperitoneal absorption rate is much lower than that of glucose, 40–45% of the icodextrin molecules are absorbed in adults and in children within 12–14 h [69–71]. Icodextrin is metabolized to maltose and its derivatives, which accumulate in the human body and increase serum osmolality by 5 mosmol/l [72]. A clinical impact of chronic icodextrin metabolite accumulation has not yet been discerned. The caloric load associated with a single daytime dwell of 600 ml/m^2 of icodextrin is below 5% of the daily allowance of energy in children [70]. There are no data available on the potential long-term metabolic effects in a growing and developing child. After icodextrin discontinuation the plasma levels of the metabolites return to baseline within 3–7 days [69]. Icodextrin resorption has been studied in only a few children and appears to be faster in infants [73], suggesting a poorer ultrafiltration response compared with adults. The reduced GDP content improves peritoneal host defense mechanisms in an ex vivo model, but not to a similar extent to that of double-chamber PD fluids [54].

Icodextrin solution is characterized by iso-osmotic, colloid osmotic ultrafiltration via the small pores of the peritoneal membrane. Free water transport via the ultra-small pores, i.e., aquaporin-1, is absent. Thus, no dipping of the dialysate sodium concentration (sodium sieving) occurs during the initial phase of the dwell [70, 71]. The ultrafiltration pattern is delayed compared with glucose-containing PD fluids. With sustained net fluid withdrawal for more than 12 h, back-filtration is largely prevented [74]. Once-daily administration of icodextrin increases sodium removal and improves the daily ultrafiltration rate and hydration status [72, 75], independent of the prevailing peritoneal transporter status [76]. Blood pressure and left ventricular mass improve within 3–6 months in adults [77, 78]. The local and systemic glucose load is significantly reduced and the plasma lipid profile improved with icodextrin usage [79, 80]. In anuric, adult APD patients, icodextrin administration during the daytime dwell preserved peritoneal membrane function compared with patients receiving conventional, high-GDP solution only [81]. The relative contribution of icodextrin solution to the preservation of peritoneal membrane integrity in patients treated with multi-chamber PD fluids from the very beginning is still to be delineated. Many centers combine icodextrin with conventional single-chamber PD solution. Whether long-term results are comparable to those of the prescription of pH-neutral, reduced-GDP solutions only is as yet unknown. Of note, randomized controlled pediatric trials have not yet been performed. Twice daily administration of icodextrin has been proposed in seriously hypervolemic adult PD patients [82]. However, such treatment cannot be recommended in children, since the metabolic impact of the additional icodextrin and oligosaccharide load is unknown.

Disadvantages of icodextrin solution concern the high lactate concentration and the low pH (Table 2). Allergic skin reactions to icodextrin and exfoliative dermatitis have been reported in up to 10% of the patients. Discontinuation of icodextrin is usually curative. Transient contamination

with peptidoglycan, a bacterial membrane compound, resulted in aseptic peritonitis outbreaks previously [83, 84]. Glucose-specific assays are required to measure serum glucose levels in patients treated with icodextrin, and total alpha-amylase activity is significantly reduced [85].

Recommendation Icodextrin solution is a useful option, in particular in children with sodium and water overload, i.e., insufficient ultrafiltration (1C). It must be administered once daily during the long dwell. Twice daily administration cannot be advised owning to a lack of safety data.

Amino acid solutions

Amino acids are another alternative to glucose as an osmotic agent. Amino acid-based PD solutions contain very low amounts of GDP [86] and allow for a phosphate-free amino acid supply. The solution is only slightly hyperosmolar, contains 40 mmol/l of lactate at a slightly acidic pH of 6.7 (Table 2). Experimental studies, however, do not unequivocally support the notion of improved biocompatibility [55, 87]. Amino acids induce mesothelial nitric oxide production, a factor involved in neoangiogenesis [88]; increase effluent IL-6 concentrations, a potential surrogate marker of inflammation [89]; and suppress leukocyte recruitment in rats [54]. Long-term dialysis in rats, however, revealed only minor peritoneal changes and preserved ultrafiltration capacity, similar to double-chamber PD fluid [55]. In children and adults solute and water transport is similar compared with conventional, high-GDP fluids [90, 91].

With respect to the nutritional effect of amino acid solutions, early studies yielded disappointing results with no improvement in anthropometric indices, increased serum nitrogen levels, and metabolic acidosis [92]. Stable isotope studies in adult CAPD patients using simultaneous amino acid and glucose-containing PD fluid exposure at a ratio of 1 to 4 yielded increased protein anabolism [93] and a 4% higher protein synthesis rate compared with patients treated with a glucose-containing PD solution only [94]. Increases in serum nitrogen levels and metabolic acidosis were not observed, and protein breakdown was not affected. The anabolic effect was most pronounced in malnourished patients. This is in line with clinical observations in four malnourished patients followed over 3 years [91]. Outcome data from appropriately sized randomized controlled trials, however, are not yet available. The few pediatric reports available comprise 10 patients or less and suggest good clinical tolerance and similar transport kinetics compared with other solutions [71, 90, 95–97].

Adequate nutrition is essential, especially in infants. The limited anabolic effects of the relatively expensive solutions, concerns regarding their biocompatibility and the usual achievement of adequate nutrition with enteral feeding thus far have prevented wider administration of amino acid-based PD fluids in children, although the concept is intriguing. Whether long-term PD biocompatibility can be improved with the addition of amino acid solutions is unknown at present. Long-term randomized clinical trials evaluating PD efficacy and safety, nutritional status, and longitudinal growth are required.

Recommendation There is limited clinical evidence in adults and no evidence in children that amino acid-based PD solutions have a clinically relevant nutritional effect. They cannot be recommended for parenteral nutrition in malnourished children at present (not graded).

Combination therapies

Various combinations of biocompatible PD solutions are feasible. Icodextrin can be administered together with multi-chamber PD fluids. Combination of icodextrin with multi-chamber PD and amino acid-based fluid has been advocated to substantially reduce glucose and GDP exposure, e.g., by 40–50% in patients on CAPD. Observational clinical reports suggest that the triple combination is safe and effective [98] and may improve acidosis control [99]. Results from randomized controlled trials are not available. The anecdotally reported overcorrection of metabolic acidosis [100] may be related to intensive PD protocols with frequent cycles and could probably be mitigated by choosing PD solutions with lower buffer content.

Recommendation The use of PD solutions with an improved biocompatibility profile is advised (1B). General recommendations with regard to the combination of the different types of PD solutions available cannot be given; the PD regime must be adapted for each individual (not graded).

Perspectives

Sixty percent of the PD children in Europe were treated with reduced-GDP multi-chamber PD solutions in 2010, 15% with icodextrin solution (International Pediatric PD Network Registry; www.pedpd.org). Even lower numbers have been reported for Asia (25 and 15%) and North America (10 and 17%). In the face of the increasing scientific and clinical evidence of the local and systemic benefits of these solutions, the associated increase in costs

should be offset by reduced infectious complications [67, 68], improved long-term preservation of the PD membrane [55, 56, 81], improved cardiovascular health [75, 81, 82], and improved long-term patient survival. Ultimate scientific evidence proving this assumption, however, is still lacking. Future prospects should include the complete replacement of glucose by a non-toxic (and thus GDP-free), non-absorbable osmotic agent. Novel PD systems should furthermore allow for a more refined, continuous adaptation of electrolyte and buffer supply according to individual needs and thus allow for an optimized mineral and acid base balance with reduced CKD mineral bone disease and cardiovascular sequelae.

Acknowledgements European Pediatric Dialysis Working Group consists of: Gema Ariceta, Pediatric Nephrology, Hospital Cruces, Barakaldo, Vizcaya, Spain;Sevcan A. Bakkaloglu, Gazi University Hospital, Ankara, Turkey;Alberto Edefonti, Clinica Pediatrica De Marchi, Fondazione IRCCS Policlinico, Mangiagallie Regina Elena, Milan, Italy;Mesiha Ekim, Ankara University Hospital, Ankara, Turkey;Michel Fischbach, Hopital de Hautepierre, Strasbourg, France;Tuula Holtta, University of Helsinki, Finland;Günter Klaus, KfH Pediatric Kidney Center, Marburg, Germany;Claus Peter Schmitt, Center for Pediatric and Adolescent Medicine, Heidelberg, Germany; Cornelis Schroder, Gelre Hospital, Apeldoorn, The Netherlands; Constantinos J. Stefanidis, "A & P Kyriakou", Children's Hospital, Athens, Greece;Vladimirs Strazdins, Riga, Latvia;Johan Vande Walle, University Hospital, Ghent, Belgium;Karel Vondrak, University Hospital Motol Prague, Czech Republic;Alan R. Watson, Nottingham University Hospitals NHS Trust, Nottingham, UK (Convenor); Aleksandra Zurowska, Gdansk University Medical School, Poland.

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