Biocompatible Solutions and Long-Term Changes in Peritoneal Solute Transport

Emma H. Elphick, Lucy Teece, James A. Chess, Jun-Young Do, Yong-Lim Kim, H. Bahl Lee, Sara N. Davison, Nicholas Topley, Simon J. Davies, and Mark Lambie

Abstract

Background and objectives The inflammation-driven increase in peritoneal solute transport rate that occurs during long-term peritoneal dialysis is associated with higher mortality, hospitalization, and encapsulating peritoneal sclerosis. Because biocompatible solutions were developed to mitigate these effects, we examined the association with their use and longitudinal peritoneal solute transport rate.

Design, setting, participants, & measurements We analyzed subjects from the multinational prospective Global Fluid Study with three or more peritoneal solute transport rate measurements >2 months from the start of peritoneal dialysis. Follow-up was for 7.5 years (median, 2.3 years; interquartile range, 1.8–3.6) in biocompatible solutions and 12.8 years (median, 3.2 years; interquartile range, 1.9–4.3) for standard solutions. Using a random intercept/slopes multilevel model, we examined the association of patients using biocompatible solutions and peritoneal solute transport rate over time, adjusting for center effects, dialysate dextrose concentration, baseline dialysate IL-6 concentration, icodextrin use, residual kidney function, and peritonitis.

Results Of 366 patients, the 71 receiving biocompatible solutions throughout their time on peritoneal dialysis had a mean adjusted dialysate-to-plasma creatinine ratio of 0.67 compared with 0.72 for standard solutions ($P$=0.02). With duration of treatment, there was a continuous increase in peritoneal solute transport rate in patients using standard solutions (range, 2 months to 4 years). In contrast, patients using biocompatible solutions had peritoneal solute transport rates that plateaued after 2 years of therapy. These changes in peritoneal solute transport rate were independent of baseline inflammation and time-varying predictors of faster peritoneal solute transport rate. In patients suffering episodes of peritonitis while using standard solutions, there was an associated increase in peritoneal solute transport rate of 0.020 (95% confidence interval, 0.01 to 0.03) per episode, whereas in patients using biocompatible solutions, there was no change in this parameter ($-0.014$; 95% confidence interval, $-0.03$ to $-0.01$).

Conclusions These data suggest that a different temporal pattern in changes in peritoneal solute transport rate occurs during the course of peritoneal dialysis according to solution type and that patients using biocompatible solutions may avoid the increase in solute transport associated with peritonitis.


Introduction

Over time, peritoneal dialysis (PD) can cause progressive injury to the peritoneal membrane. Local inflammation (with an increase in membrane vascularity) is the likely driver of this, evidenced by faster peritoneal solute transport rate (PSTR) (1,2). Faster PSTR is strongly associated with the likelihood of poor outcomes, including technique failure and mortality (3). Encapsulating peritoneal sclerosis is a rare but serious complication that is also associated with higher PSTR (4). Mechanisms leading to this increase are multifactorial but may include conventional (bio-incompatible) dialysis solutions, cumulative glucose (or glucose degradation product) exposure, and episodic peritonitis (5).

Animal model data suggest that biocompatible solutions are better able to preserve membrane integrity in vivo after exposure to PD solutions (6), and data on peritoneal morphology suggest fewer adverse changes with biocompatible solutions (7). An early crossover study in patients suggested that biocompatible solutions may increase PSTR (8), but more recent meta-analyses (9,10) have failed to show a consistent effect. As shown in the Balance in Australia and New Zealand Peritoneal Dialysis Patients (BalANZ) Study (11), differences may vary over time; however, the greatest clinical concern is over long-term changes in PSTR, which no randomized trials have directly addressed.

In this study, we undertook the first longitudinal analysis of the Global Fluid Study cohort to test the
hypothesis that biocompatible solutions reduces long-term rises in PSTR, leading to stable PSTR over longer periods on PD.

Materials and Methods

Study Design

The Global Fluid Study was an international, multicenter, prospective, observational cohort study, and it is detailed by Lambie et al. (12). The study included ten centers from the United Kingdom, Canada, and South Korea that enrolled patients from June 2002 to December 2008 and censored at center-specific dates during December 2010. Any patient on PD capable of informed consent was eligible.

Data were collected on a purpose-built access database. Ethical approval was obtained from the Multicenter Research Ethics Committee for Wales, the Kyungpook National University Hospital Ethics Committee, and the University of Alberta Ethics Committee. The study adhered to the Declaration of Helsinki. Written informed consent was obtained from all patients.

Comorbidity data used the validated Stoke Comorbidity Index (13). Data collected on PD regime included type of PD, use of icodextrin, brand of solution, and dose. PSTR was measured as the 4-hour dialysate-to-plasma creatinine ratio with 2.5% or 4.25% dextrose approximately every 6 months. Daily dialysate dextrose concentration was calculated as the average of the dextrose concentrations in all bags used in a 24-hour period (e.g., a regime of two bags of 2 L of 1.5% dextrose, one bag of 2 L of 2.5% dextrose, and one bag of 1.5 L of 7.5% icodextrin has a daily dialysate dextrose concentration $= (4 \times 1.5 + 2 \times 2.5 + 1.5 \times 0)/8 = 1.38\%$).

Dialysate and plasma samples were taken during routine clinical testing, stored locally at $-80^\circ$C, and transferred to a central laboratory (Cardiff, United Kingdom). Electrochemiluminescence immune assays for IL-6 levels used the commercially available proinflammatory i4-plex (Meso Scale Discovery, Gaithersburg, MD). Baseline dialysate and peritoneal IL-6 were used for this analysis, and they were log transformed due to their log-normal distribution.

Patients were included if they had had three or more PSTR measurements beyond the first 2 months on PD, with the first measurement <12 months from the start of PD, and remained on either biocompatible solutions or standard solutions during follow-up. Measurements over 7 years after the start of PD were removed due to low patient numbers and the fact that patients on biocompatible solutions did not measurements past 7 years. Two centers were not included: one lacked longitudinal follow-up data, and another did not use biocompatible solutions.

Statistical Analyses

A multilevel model with an unstructured covariance matrix was used to assess patterns of PSTR over time. Biocompatible solutions usage and the main effect of time were forced in, and a quadratic term for time was retained as highly significant. Center, icodextrin use, average dextrose exposure, dialysate and plasma IL-6 levels, urine volume, peritonitis count, age, sex, CAPD or APD, comorbidity score, and their interactions with time were tested for with backward selection. Dialysate and plasma IL-6 were transformed to $\log_{10}$ due to the log-normal distribution. A random intercept at patient level and random slopes for linear and quadratic time variables were significant, and between-person variance over time was determined from these. Homoskedasticity and level 2 normality assumptions were tested. Marginal plots were used for adjusted PSTR results. AIC and BIC were used to assess dialysate glucose measures in a sensitivity analysis.

Cox proportional hazards models adjusted for center, dextrose exposure, icodextrin, and dialysate IL-6 were tested for proportionality with log-log plots. Missing data, ranging from 0% to 5% for different variables, were considered missing at random, and complete patient analysis used stataIC version 12 (College Station, TX), with runmlwin for the multilevel model in MLwiN (v2.31).

Results

Patient Characteristics

In total, 366 patients with 2290 measurements were included in the final analysis (Figure 1). Of the 71 patients in the biocompatible solutions–only group, 58 (82%) used Baxter Physioneal, eight (11%) used Fresenius Staysafe balance, and five (7%) used Gambrosol-Trio. Of the 295 patients in the standard solutions–only group, 245 used Baxter Dianeal, 50 used Fresenius Staysafe, and one used Boryung Peresis. Patients using biocompatible solutions were less likely to be on APD and had a shorter duration on PD due to the small number of prevalent patients using biocompatible solutions (Table 1). Follow-up was for 7.5 years (median of 2.3 years; interquartile range [IQR], 1.8–3.6) for biocompatible solutions and 12.8 years (median of 3.2 years; IQR, 1.9–4.3) for standard solutions. There was no apparent difference in time to treatment failure between biocompatible solutions and standard solutions (Cox proportional hazards regression hazard ratio, 1.18; 95% confidence interval [95% CI], 0.67 to 2.06). Dropouts caused by death, transplantation, or treatment failure in the

Figure 1. Flow diagram showing inclusion of participants in analysis. m, Number of measurements; n, number of patients; PD, peritoneal dialysis.
biocompatible solutions and standard groups were 50% \((n=25)\) and 61% \((n=138)\), respectively, after 3.5 years; 124 patients recorded as using both biocompatible solutions and standard solutions at different time points were not included in the analysis. Baseline characteristics in this group compared with those of patients included in the final analysis were not clinically significantly different for age, sex, comorbidity score, and urine volume, but they were clinically significantly different with regard to time on PD and modality of PD (Table 1).

### Baseline Transport over Time

The adjusted PSTR 2 months after the start of PD was higher in standard solutions \((0.721)\) compared with biocompatible solutions \((0.622)\). With standard solutions, PSTR remains approximately level until an increase between 3.5 \((0.721)\) and 7 years \((0.741)\) of treatment (Figure 2) when adjusted for other known determinants of PSTR. With biocompatible solutions, PSTR was lower at baseline, with a steeper initial rise in PSTR. By 2 years of therapy, PSTR was similar for both solutions \((\text{adjusted PSTR standard solutions, } 0.724; 95\% \text{ CI, } 0.71 \text{ to } 0.74; \text{biocompatible solutions, } 0.722; 95\% \text{ CI, } 0.69 \text{ to } 0.75)\). There was, however, no further increase in PSTR in patients using biocompatible solutions between years 2 and 4 of treatment. Supplemental Figure 1 shows adjusted change over time overlaying individual changes over time.

Including measurements from the start of PD rather than 2 months after the start made no apparent difference (Supplemental Table 2). Both linear and quadratic time functions were included to allow for nonlinear changes, and these as well as random effects for them (allowing the trajectory to vary between individuals in a nonlinear way) remained significant within the model (Table 2). A sensitivity analysis retaining all variables without backward selection made little difference (Supplemental Table 5).

### Dialysate IL-6

Higher baseline dialysate IL-6 concentrations were associated with a faster PSTR for the duration of follow-up (Table 2). Plasma IL-6 levels had no significant association with PSTR (change in PSTR with one-log10 increase in plasma IL-6 concentration = 0.009; 95% CI, –0.05 to 0.07).

**Table 1. Baseline characteristics for patients using biocompatible or standard solutions**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Biocompatible Solutions, (n=71)</th>
<th>Standard Solutions, (n=295)</th>
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<tr>
<td>Measures per person</td>
<td>6.4 (0.45)</td>
<td>7.3 (0.21)</td>
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<td>Time to end of PD, yr</td>
<td>2.6 (2.0–3.9)</td>
<td>3.5 (2.2–4.8)</td>
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<td>Time to first measure, yr</td>
<td>0.52 (0.28–0.64)</td>
<td>0.53 (0.41–0.62)</td>
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<td><strong>Baseline measurements for fixed covariates</strong></td>
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<tr>
<td>Age, yr</td>
<td>55 (14)</td>
<td>54 (15)</td>
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<tr>
<td>Men, %</td>
<td>50</td>
<td>59</td>
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<tr>
<td>Comorbidity score, low/medium/high, %</td>
<td>48/46/6</td>
<td>40/52/8</td>
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<td>Dialysate IL-6 (log transformed), pg/ml</td>
<td>4.8 (1.8–12.9)</td>
<td>4.5 (1.5–10.8)</td>
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<td>Plasma IL-6 (log transformed), pg/ml</td>
<td>1.3 (0.64–2.4)</td>
<td>1.3 (0.7–2.5)</td>
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<td>APD usage compared with CAPD usage, %</td>
<td>6</td>
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<td>Country, Canada/United Kingdom/Korea</td>
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<td>16/163/116</td>
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<tr>
<td>Weight, kg</td>
<td>63 (55–76)</td>
<td>67 (58–77)</td>
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<tr>
<td><strong>Baseline measurements for time-varying covariates</strong></td>
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<td></td>
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<tr>
<td>Average dialysate dextrose concentration, g/L</td>
<td>15.0 (15.0–18.7)</td>
<td>15.0 (15.0–20.1)</td>
</tr>
<tr>
<td>Urine volume, L</td>
<td>0.96 (0.55–1.52)</td>
<td>0.86 (0.4–1.4)</td>
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<td>Icodextrin use, %</td>
<td>29</td>
<td>33</td>
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<tr>
<td>Peritonitis count, no. of episodes per 1 yr</td>
<td>0 (0–0.59)</td>
<td>0.23 (0–0.47)</td>
</tr>
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</table>

Baseline measurements are shown as mean with SD or median with interquartile range. Characteristics of patients who were excluded for using both biocompatible and standard solutions are included in Supplemental Table 1. PD, peritoneal dialysis; APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

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**Figure 2.** Change in solute transport for standard and biocompatible solutions and comparison with average change for both solutions. Solid gray and black lines represent the adjusted peritoneal solute transport rates (PSTRs) for standard and biocompatible solutions, respectively, and dotted lines indicate 95% confidence intervals. Standard solutions remain stable and then show a slight rise. Biocompatible solutions have a slower PSTR at baseline but a steeper increase in PSTR over time; this stabilizes at 2 years. PSTR values are adjusted for center, icodextrin use, daily dextrose concentration, baseline dialysate IL-6, peritonitis, and urine volume. There were 43 (60%) and 219 (60%) patients in the biocompatible and bioincompatible groups, respectively, at 2 years of follow-up and 11 (15%) and 96 (33%) patients in the biocompatible and bioincompatible groups, respectively, at 4 years of follow-up. Modeling of biocompatible solutions was stopped at 4 years due to the low patient numbers beyond that time. D/P, dialysate to plasma; PD, peritoneal dialysis.
Peritoneal Fluid Dextrose and Icodextrin

The median peritoneal daily dextrose concentration increased with time; from 1.5% (IQR, 1.38–1.88) dextrose at 1 year to 1.74% (IQR, 1.38–2.19) dextrose at 6 years. Icodextrin use also increased with PD duration (31% of patients in the first 6 months and 55% after 3.5 years), and it was associated with a faster solute transport in the fully adjusted multilevel model (Table 2).

In the fully adjusted model, icodextrin use had no association with the trajectory of PSTR over time, but the daily dextrose concentration did (Figure 3), with little difference in PSTR at the start and increasing difference with duration of PD. A 1.93% daily dextrose concentration (25th percentile; “high glucose”) had an adjusted PSTR of 0.720 (95% CI, 0.71 to 0.74) at 2 years and 0.811 (95% CI, 0.78 to 0.85) after 6 years on PD. A 1.33% daily dextrose concentration (25th percentile; “low glucose”) had an adjusted PSTR of 0.720 (95% CI, 0.71 to 0.74) at 2 years and 0.71 (95% CI, 0.68 to 0.75) at 6 years.

Sensitivity analysis included substituting daily mass of dextrose (grams per day) for daily dextrose concentration, and it resulted in a worse fit for the model (AICs, −335.9 and −333.5 and BICs, −3186.7 and −3174.4 for concentration and mass, respectively; more negative values represent an improved fit). Biocompatible solution usage had similar effects on PSTR in patients not using icodextrin (Supplemental Table 3). There was no interaction between icodextrin usage and biocompatible solutions usage.

Residual Kidney Function

A larger urine volume was associated with a higher PSTR (Table 2). Urine volume reduced with time on therapy, with the median volume at 1 year being 775 ml (IQR, 270–1223) and the median volume at 6 years being 375 ml (IQR, 0–1160). Neither kidney Kt/V nor mean urea/creatinine kidney clearance were associated with PSTR when substituted for urine volume (increase in PSTR; per unit of kidney Kt/V =0.001; 95% CI, −0.01 to 0.01; per unit of kidney clearance =0.0001; 95% CI, <−0.01 to <0.01). There was no significant interaction with biocompatibility. Biocompatible solutions use was not associated with urine

Figure 3. Changes in solute transport for standard solutions by dextrose concentration. Trajectories over time for low (1.33%; 25th percentile), medium (1.5%; 50th percentile), and high (1.93%; 75th percentile) daily dextrose concentrations. High dextrose concentration is associated with an increase in peritoneal solute transport rate (PSTR) over time compared with low or medium concentrations. This effect of dextrose concentration on the trajectory of PSTR has strong evidence (P<0.001) in the model. D/P, dialysate to plasma; PD, peritoneal dialysis.
volume in a separate multilevel model (biocompatible solutions coefficient, 120; 95% CI, −39 to 280).

Peritonitis
One or more episodes of peritonitis occurred in 198 of the patients studied: 29 patients with biocompatible solutions (41%) and 169 patients with standard solutions (57%). The most common organism in both groups was coagulase-negative *Staphylococcus* (biocompatible solutions, 24%; standard solutions, 28%), and culture-negative peritonitis/no organism reported was seen in 31% and 38% (biocompatible solutions and standard solutions, respectively) of patients. A postperitonitis rise in PSTR was seen in standard solutions, but no significant effect of peritonitis on PSTR was seen in biocompatible solutions (Table 2). In a Cox model, there was no difference in time to first peritonitis episode between biocompatible and standard solutions when adjusted for center, glucose exposure, icodextrin, and dialysate IL-6 (hazard ratio, 1.54, 95% CI, 0.94 to 2.52). There were no significant differences in outcome of first peritonitis episode between groups (Supplemental Table 4).

Effect of Time-Varying Covariates
Measures of peritonitis, urine volume, and daily dialysate dextrose concentration deteriorate over time, explaining a lot of the measured change in PSTR as illustrated by the small change in the adjusted models (Figures 2 and 3). If these time-varying covariates are not adjusted for, the change in PSTR is far greater (Figure 4).

Changes in Variance over Time
Examination of both the spaghetti plots and the covariance of the random effects suggested that the variance in PSTR decreased with time on PD (i.e., higher initial measurements are associated with a subsequent fall and vice versa). Avoiding problems with regression to the mean, the person-level variance was plotted against duration of PD (Figure 5), confirming a fall in variance with time. Most of this decrease is accounted for by the covariates included (i.e., dialysate dextrose concentration, dialysate IL-6, use of icodextrin, urine volume, and use of standard solutions/biocompatible solutions) (compare 4 with 1 in Figure 5).

Discussion
In the primary longitudinal analysis of this large, multinational cohort study, we tested the hypothesis that biocompatible solutions use would be associated with stable short- to medium-term membrane function. This hypothesis proved false, because PSTR, although starting slower in patients using biocompatible solutions, rises to similar levels seen in standard solutions after 2 years of treatment. After 2 years, there was a potentially beneficial effect of biocompatible solutions on PSTR, with abrogation of the increases in PSTR observed in patients using standard solutions. In addition, the increases in PSTR associated with peritonitis episodes were absent in patients using biocompatible solutions. The magnitude of these effects was less than the effect of using higher dialysate dextrose concentrations.

For standard solutions, when adjusted for peritonitis, daily glucose exposure, and urine volume, there was no evidence of an increase in PSTR over the first 2 years of treatment. This finding contrasts with previous studies finding either a reduction in PSTR between 1 and 4 months of treatment (14) or a significant increase in PSTR between 1 and 6 months in patients (1). Two explanations can potentially resolve these apparently contradictory observations. First, there may well be differences in the definition of PD start date and the exact timing of the first peritoneal equilibration test, a period with rapid changes in PSTR (15). Indeed, we found significant between-patient variability during the first year of PD that was visible on the spaghetti plots, with the PSTR falling during the early period in some patients and rising in others. Second, there is a significant effect of dialysate glucose and residual kidney function and a cumulative effect of peritonitis, all of which can change with time and have been adjusted for in our analysis. Therefore, the different conclusions in the previous studies could be due to differences in the definition of PD start date; unmeasured determinants of the early variability in solute transport; and variation in peritonitis, residual kidney function, and dialysate dextrose concentration.

The unadjusted model showed a clear overall increase in PSTR over time (Figure 4A), mostly accounted for by peritonitis, glucose exposure, and residual kidney function. This finding is in keeping with previous cohort studies describing membrane injury, which is explained by changes in peritonitis, glucose exposure, and residual kidney function (1,3,16,17).

As found previously (17,18), these results show that increasing daily glucose exposure is associated with long-term increases in PSTR. This could be a result of glucose-driven pathophysiologic changes in the membrane and/or a treatment response to increasing membrane permeability driven by other clinical factors (e.g., peritonitis).

The largest randomized study examining the effect of biocompatible solutions on membrane function is the BALANZ Study, and it showed that initial PSTR was faster with biocompatible solutions compared with standard solutions. Over 2 years, the PSTR remained stable in biocompatible solutions–treated patients, whereas it increased in patients treated with standard solutions (11). In contrast, in this observational cohort, we found a slower PSTR in biocompatible solutions at the beginning of therapy, but differences disappeared after 2 years of treatment. Between 2 and 4 years of treatment, average PSTR remained stable in the biocompatible solutions group but increased in the standard solutions group. One possible explanation for these observed differences could be differences in the manufacturer/composition of solutions used. Although the electrolytes in most solutions are similar, they are manufactured differently, contain different buffers, have different pH values, and are reported to have different levels of glucose degradation products. This study, although on the basis of larger numbers with longer spells on PD, contained three different brands of biocompatible solutions, with the majority on Physioneal using a bicarbonate/lactate buffer. The BALANZ Study exclusively used the lactate-buffered balance with a pH of 7.0. Unfortunately, we did not have sufficient numbers using the
Figure 4. | Change in peritoneal solute transport rate (PSTR) over time and effect of time-varying covariates. Unadjusted PSTRs (dialysate-to-plasma \([D/P]\) creatinine) and 95% confidence intervals over time by solution type. (A) With standard solutions an increase in PSTR is more apparent after a longer duration of PD. (B) With biocompatible solutions, PSTR starts slower, rises more quickly then the rise flattens out. (C) Effect of constant average versus time-varying actual values on sample patients selected using the random number generator. PD, peritoneal dialysis.
different manufacturers’ solutions for a meaningful comparison. Although the data may be viewed as inconsistent, taken together, these studies unequivocally show differences in PSTR changes in patients using standard and biocompatible solutions. Although the effect of these differences on clinical outcome remain to be robustly determined, stabilization of solute transport would generally be regarded as clinically beneficial (19,20).

We observed that patients using icodextrin had an overall faster PSTR, which may be the result of indication bias. As opposed to dialysate glucose, there was no deterioration over time in PSTR with icodextrin.

In keeping with previous research showing a robust association between intraperitoneal IL-6 production and faster PSTR (12,21,22), baseline dialysate IL-6 levels were associated with faster PSTR for the duration of follow-up, whereas plasma IL-6 had no effect. Although IL-6 has many immunomodulatory effects (23,24), recent observations linking IL-6 signaling to peritoneal VEGF production provide a mechanism by which IL-6, not itself vasoactive, might alter angiogenesis and vascular permeability in the peritoneal membrane (25).

Baseline urine volume has previously been associated with a faster solute transport (26), a finding replicated in this analysis, although with only weak to moderate evidence. Because there was no association in this study between PSTR and kidney Kt/V or clearance, the association with urine volume is more likely to be related to fluid balance than clearance per se.

Long-term rises in PSTR occur in patients with severe peritonitis or clusters of peritonitis episodes (1), and the increased power of this study extended this, showing a small but measurable long-term rise in PSTR after a single episode for patients on standard solutions. This is consistent with another report that suggested that the first episode of peritonitis results in PSTR changes (27).

Although we did find a significant change in solute transport over time with biocompatible solutions, the association between peritonitis and a faster PSTR disappeared in patients using biocompatible solutions. One potential explanation for this protective effect could be reduced severity of peritonitis with biocompatible solutions, such as was suggested in the BalANZ Study (16).

The strengths of this study are in the large size, which ensured adequate power, good generalizability with different centers in different countries, and the robust and validated statistical approach. The limitations of our analysis include the observational nature of the study, meaning that causality cannot be proven, although there were few clinically significant differences between the two patient groups with extensive adjustment for potential confounders. As with all PD studies, informative censoring is a potential issue with nonrandom dropout of patients. We used an “as-treated analysis,” excluding patients who switched between standard and biocompatible solutions, which limited the generalizability of the results, although there were few significant differences in baseline characteristics between those included and excluded. We did not have sufficient data within the first 2 months of PD to adequately model the rapid changes known to occur in this period. The biocompatible solutions group was a smaller cohort, and it had a lower number of peritonitis episodes compared with standard solutions cohort; however, the estimated effects had narrow 95% CIs. There were too few patients to test whether effects differed by manufacturer.

In conclusion, the use of biocompatible solutions (in this case, irrespective of manufacturer) was associated with alterations in solute transport rates at different phases of PD treatment. Initially slower and then equivalent at 2 years, biocompatible solutions have a stable PSTR between 2 and 4 years. These findings add weight to the notion that biocompatible solutions may have long-term clinical benefits, although appropriately powered studies will be required to definitively show that this is associated with improved outcomes.

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**Disclosures**

None.

**References**


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Correction

Because of author error, a correction has been issued for the above referenced article. The authors and editors have determined that the disclosures provided by Simon J. Davies, Mark Lambie, and Nicholas Topley at the time of initial publication were incomplete and not aligned with the disclosure policy for the journal. The original and corrected disclosures are indicated in the table below.

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