Association of Biocompatible Peritoneal Dialysis Solutions with Peritonitis Risk, Treatment, and Outcomes

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Summary
Background and objectives The effect of biocompatible peritoneal dialysis (PD) solutions on PD-related peritonitis is unclear. This study sought to evaluate the relationship between use of biocompatible solutions and the probability of occurrence or clinical outcomes of peritonitis.

Design, setting, participants, & measurements The study included all incident Australian patients receiving PD between January 1, 2007, and December 31, 2010, using Australia and New Zealand Dialysis and Transplant Registry data. All multicompartment PD solutions of neutral pH were categorized as biocompatible solutions. The independent predictors of peritonitis and the use of biocompatible solutions were determined by multivariable, multilevel mixed-effects Poisson and logistic regression analysis, respectively. Sensitivity analyses, including propensity score matching, were performed.

Results Use of biocompatible solutions gradually declined (from 7.5% in 2007 to 4.2% in 2010), with preferential use among smaller units and among younger patients without diabetes mellitus. Treatment with biocompatible solution was associated with significantly greater overall rate of peritonitis (0.67 versus 0.47 episode per patient-year; incidence rate ratio, 1.49; 95% confidence interval [CI], 1.19 to 1.89) and with shorter time to first peritonitis (hazard ratio [HR], 1.48; 95% CI, 1.17 to 1.87), a finding replicated in propensity score–matched cohorts (HR, 1.36; 95% CI, 1.09 to 1.71).

Conclusions In an observational registry study, use of biocompatible PD solutions was associated with higher overall peritonitis rates and shorter time to first peritonitis. Further randomized studies adequately powered for a primary peritonitis outcome are warranted.


Introduction
Peritonitis is a major cause of morbidity and mortality in patients undergoing peritoneal dialysis (PD) (1). Preclinical studies suggest that the use of conventional PD solutions may contribute to peritonitis through impaired peritoneal mesothelial cell viability and function, leading to compromised peritoneal immune defenses with it use (2–8). These adverse sequelae may be obviated by the administration of commercially available biocompatible PD solutions, characterized by neutral pH and low glucose degradation product (GDP) content. In vitro and ex vivo studies have observed significant improvements in peritoneal membrane cellular function and integrity after exposure to biocompatible solutions compared with conventional solutions (5,9–11), and observational cohort studies have reported superior inflammatory marker levels (12), peritonitis and exit site infection rates (13), and patient survival (14–16). However, these clinical studies were limited by single-center design, small patient numbers (12,13), potential indication bias, center effects, and exclusion of patients treated with automatic peritoneal dialysis (15,16). In contrast, data from randomized controlled trials (RCTs) are conflicting. Of the 13 RCTs that reported peritonitis (17–30), only 2 showed significant benefit with the use of biocompatible PD solutions (19,22); the remainder reported a neutral effect. However, most trials examined peritonitis as a secondary outcome only; they can therefore not be regarded as providing definitive evidence.

We performed a comprehensive multicenter study of biocompatible PD solution use and its association with peritonitis frequency and clinical outcomes in all Australian patients undergoing PD, as recorded in the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA).

Materials and Methods
Study Population
The study included all incident Australian adult patients from ANZDATA who started PD between

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January 1, 2007, and December 31, 2010. These patients were incident to renal replacement therapy and had not transferred from failed hemodialysis or renal transplantation. Collection and analysis of ANZDATA registry data were approved by the Princess Alexandra Hospital Human Research Ethics Committee. Permission to analyze the data was also granted by an ANZDATA executive. The analyses were performed on de-identified data extracted from ANZDATA.

Although ANZDATA collects information on buffer status of the neutral-pH and low-GDP PD solutions, these two types were grouped as biocompatible solutions in this study. Use of biocompatible solutions was recorded during the annual ANZDATA survey as used at December 31; if use recorded as "yes," we assumed that the solution was used for the entire survey year. Icodextrin was not considered a biocompatible solution.

Peritonitis rates were calculated according to the standardized recommendations made by the International Society for Peritoneal Dialysis (31). Relapsed peritonitis was counted as a single episode. Duration of PD therapy was defined as the time between first PD exchange and the first time PD was ceased.

The outcomes examined were peritonitis rate, peritonitis-free survival, microbiology, cure, relapse, peritonitis-associated hospitalization, catheter removal, permanent transfer to hemodialysis, and death. Given the complexities associated with analysis of multiple events within individuals wherein the assumption of independence of observations is not appropriate, only the first episodes of peritonitis for each individual were included in analyses of outcomes, except for peritonitis rates.

Statistical Analyses

Results were expressed as frequencies and percentages or mean ± SD, as appropriate. The changes in biocompatible solution use were analyzed per year of dialysis survey, and variation between each unit was assessed. Differences between groups were analyzed by chi-squared test for categorical data, t test for continuous normally distributed data, and Kruskal-Wallis test for continuous non-normally distributed data. The independent predictors of peritonitis and the use of biocompatible solutions were determined by multivariable, multilevel mixed-effects Poisson and logistic regression analyses, respectively. To account for the structure of the data, a multilevel hierarchical model was created with a random effect for treating unit and each dialysis survey era and with a fixed effect for treating unit size. Only time to the end of the first PD exposure time was considered as PD therapy time.

Time to first peritonitis was analyzed by multivariable Cox proportional hazards model. Use of biocompatible PD solution, age, sex, racial origin, body mass index, late referral (commencement of dialysis within 3 months of referral to a nephrologist), cause of ESRD, smoking status, PD modality, baseline comorbid conditions, and size of treating unit were explored as covariates. The criteria of unit categories were derived in keeping with the recent ANZDATA publication (32). During model building, covariates with P>0.2 from log-rank tests or collinear with biocompatible solutions were removed from the model. Transplantation was separately examined as a competing outcome using competing-risks regression (33). Biocompatible solution use was analyzed as a time-varying covariate for each dialysis survey year in all analyses, except that of time to first peritonitis, where fluid status at PD commencement and history of biocompatible PD solution use at any stage were adopted. Several sensitivity analyses were performed, including propensity score analysis (Supplemental Table 1). Methods for sensitivity analyses are described in the Supplemental Material. Data were analyzed using the software packages Stata/SE12.0 (College Station, TX). P<0.05 was considered to represent statistically significant differences.

Results

Population Characteristics

A total of 2245 incident patients commenced PD in Australia during the study period and were followed for 2970.9 patient-years (median follow-up, 1.1 years per patient). Of these 2245 patients, 157 (7.0%) were treated with biocompatible solutions at some time in the follow-up period (biocompatible-ever), while 117 patients in the biocompatible-ever group started PD using biocompatible solutions (biocompatible-first). On univariable analysis, patients who were ever treated with biocompatible solutions were younger and less likely to have diabetes mellitus. These features were replicated when patients were classified according to fluids received at PD commencement (Table 1).

The proportion of biocompatible solution use linearly decreased during the study period, from 7.5% in 2007 to 4.2% in 2010. Pattern of use varied widely according to treating unit (Figure 1), such that patients cared for in small to medium-sized units (7–42 patients) were almost twice as likely to start their therapies using biocompatible solutions (40.2%) as those in large units (>140 patients [23.1%]; Table 1). Lactate-buffered solutions (e.g., Balance) were the most commonly used type of biocompatible solution overall (73%) and for each year during the study period (Supplemental Table 2). With use of multivariable, multilevel mixed-effects logistic regression analysis, patients without diabetes mellitus were significantly more likely to receive biocompatible solutions (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.28 to 2.78). Conversely, increasing age by each year (OR, 0.98; 95% CI, 0.97 to 0.99) and patients receiving automatic PD (OR, 0.55; 95% CI, 0.35 to 0.86) were less likely to receive biocompatible solutions.

Peritonitis Rates

Peritonitis rates, expressed as episodes per patient-year, were 0.49 (95% CI, 0.46 to 0.51) overall, 0.47 (95% CI, 0.45 to 0.50) in the biocompatible-never group, and 0.67 (95% CI, 0.57 to 0.79) in the biocompatible-ever group. Because of a possibility that patients who had experienced peritonitis may have transferred therapy to biocompatible solutions before the first survey, a subgroup analysis restricted to peritonitis-free patients at the time of the first survey (n=1866) was performed. Peritonitis rates were consistently higher in the biocompatible-ever group, at 0.46 (95% CI, 0.37 to 0.56) episode per patient-year compared with 0.27 (95% CI, 0.25 to 0.29) episode per patient-year in the biocompatible-never group.
Multivariable, multilevel mixed-effects Poisson regression analysis showed that peritonitis occurrence was significantly and independently associated with use of biocompatible solutions (incident rate ratio [IRR], 1.49; 95% CI, 1.19 to 1.89; Table 2). Sensitivity analysis using incident as well as prevalent patients observed persistently higher peritonitis risk (IRR, 1.30; 95% CI, 1.12 to 1.50). Incorporation of "high" use of biocompatible solutions (defined as ≥20% in any calendar year period) in a random-effects model (IRR, 1.55; 95% CI, 1.24 to 1.93) or repeating the analysis restricted to those who were free of peritonitis at the first dialysis survey (IRR, 1.83; 95% CI, 1.36 to 2.48) did not alter the outcome.

**Peritonitis-Free Survival**

According to a multivariable Cox proportional hazards model analysis, a history of biocompatible solution use was associated with a significantly shorter time to first peritonitis (adjusted hazard ratio, 1.32; 95% CI, 1.06 to
Analyses based on propensity score yielded very similar results (Table 3 and Supplemental Table 3).

Microbiology of First Peritonitis Episodes

According to Poisson regression analysis, biocompatible-ever patients were significantly more likely to experience peritonitis caused by enterococci (unadjusted IRR, 4.47 [95% CI, 1.61 to 12.41]; adjusted IRR, 4.33 [95% CI, 1.56 to 12.07]), nonspecific gram-positive organisms (unadjusted IRR, 4.17 [95% CI, 1.66 to 10.51]; adjusted IRR, 4.24 [95% CI, 1.67 to 10.74]), and Pseudomonas species (unadjusted IRR, 4.87 [95% CI, 2.03 to 11.65]; adjusted IRR, 4.71 [95% CI, 1.97 to 11.37]) compared with biocompatible-never patients.

Outcome of First Peritonitis Episodes

The clinical outcomes after peritonitis were similar between the biocompatible-ever and biocompatible-never groups (Supplemental Table 4).
The present investigation is the largest observational study to date examining trends in biocompatible solution use and their effect on the frequency, treatment, and clinical outcomes of peritonitis in incident PD patients. A very low overall uptake of biocompatible solutions, with a gradual decrease in their use during the study period, was observed. There was a large variation among treating units, with preferential use among smaller units. Furthermore, patients who were younger and not diabetic were significantly more likely to be treated with biocompatible solutions. Use of these solutions was associated with a significantly higher peritonitis rate and a shorter time to first peritonitis. These findings were similarly replicated in numerous sensitivity analyses, including propensity score-matched analysis. Furthermore, patients treated with biocompatible solutions experienced more frequent peritonitis caused by enterococci, nonspecific gram-positive organisms, and Pseudomonas species compared with patients treated with only conventional solutions. Nevertheless, clinical outcomes after peritonitis were similar regardless of the type of PD solution used.

The results of this study differ from those of previous observational studies. For instance, Furkert and colleagues (13) reported significant improvements in peritonitis and exit-site infections with the use of neutral-pH, low-GDP PD solution. However, this study was potentially limited by small patient numbers (n=120), single-center design, vintage, and co-intervention biases (due to the switching of patients from conventional to biocompatible fluids in consecutive dialysis eras). A larger study of 1162 continuous ambulatory PD patients from 83 centers compared the effect of using Balance with Stay-Safe PD solutions and found that the former fluid was associated with similar peritonitis rates but superior patient survival (15). However, the proportion of patients using biocompatible solutions varied widely among participating treating units, thereby raising the possibility of center-effect bias. The findings from this study were similarly replicated in their subsequent extended observational data (16); however, the study design and findings have been criticized because of the failure to state the contribution of center effect and likely residual survival benefit conferred by significantly younger patients in the treatment group (34). Han et al.

Table 3. Cox proportional hazard models for time to first peritonitis

<table>
<thead>
<tr>
<th>Model</th>
<th>Time to First Peritonitis</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.33 (1.05 to 1.67)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Adjusteda</td>
<td>1.48 (1.17 to 1.87)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Unadjusted + PS</td>
<td>1.38 (1.09 to 1.74)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Unadjusted + PS in quintiles</td>
<td>1.37 (1.09 to 1.74)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Unadjusted in PS-matched cohorts (n=2242)</td>
<td>1.36 (1.09 to 1.71)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Unadjusted in 1:1 PS-matched cohorts (n=312)</td>
<td>1.38 (0.97 to 1.95)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Competing risk regressiona</td>
<td>1.32b (1.06 to 1.65)</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; PS, propensity score.
aAdjusted for body mass index, race, cause of renal failure, and size of the treating unit.
bSubhazard ratio.

Discussion

The present investigation is the largest observational study to date examining trends in biocompatible solution use and their effect on the frequency, treatment, and clinical outcomes of peritonitis in incident PD patients. A very low overall uptake of biocompatible solutions, with a gradual decrease in their use during the study period, was observed. There was a large variation among treating units, with preferential use among smaller units. Furthermore, patients who were younger and not diabetic were significantly more likely to be treated with biocompatible solutions. Use of these solutions was associated with a significantly higher peritonitis rate and a shorter time to first peritonitis. These findings were similarly replicated in numerous sensitivity analyses, including propensity score-matched analysis. Furthermore, patients treated with biocompatible solutions experienced more frequent peritonitis caused by enterococci, nonspecific gram-positive organisms, and Pseudomonas species compared with patients treated with only conventional solutions. Nevertheless, clinical outcomes after peritonitis were similar regardless of the type of PD solution used.

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also reported superior patient survival (14) in an observational study of 2163 incident PD patients that compared the effects of neutral-pH PD solutions (Physiogeneal) and 7.5% icodextrin with conventional solutions. In contrast to prior trials, that study accounted for socioeconomic status and comorbid conditions. However, interpretation of the findings was hindered by greater use of 7.5% icodextrin among the biocompatible PD solution group (41.3% versus 34.9%), which may have positively influenced the survival advantage. Furthermore, the study did not assess the effect of biocompatible solutions on peritonitis.

Data from RCTs are also unclear. Of the 13 RCTs that reported peritonitis (17–30), only 2 have shown significant benefit with the use of biocompatible solutions (22,36). To date, none of the studies reported an increase in peritonitis rates with the use of biocompatible solutions. However, none of these trials were adequately powered to address the issue. In fact, most trials reported peritonitis as a surrogate outcome and were at risk of attrition bias, with dropout rates exceeding 20% (17,21,24–26,30).

An increased risk of peritonitis with the use of biocompatible solution may represent a real phenomenon. However, it lacks biologic plausibility, and the present study had several limitations that may have contributed to the dissimilar outcomes compared with published literature. First, recorded use of biocompatible solutions was assumed to apply for the entire year of the dialysis survey period, although it is possible that patients may have been receiving biocompatible solution for only part of the survey period. Conversely, patients recorded as receiving conventional solution may have been treated with biocompatible solution for a portion of the survey period. Therefore, it was possible that patients who were categorized as biocompatible-first had started treatment using conventional solutions, followed by a clinical event (e.g., peritonitis), and subsequently transferred to biocompatible solutions. However, repeat analysis restricted to those free of peritonitis at the time of the first dialysis survey showed consistently greater peritonitis rates and shorter time to first peritonitis in the treatment group.

Second, ANZDATA does not collect information on the specific product of biocompatible solutions used beyond their buffer status, which limits ability to separately analyze the peritonitis risks associated with specific products. Third, biocompatible fluid use was restricted to a small minority of PD patients in Australia whose baseline characteristics differed significantly from those of the remaining PD patients. Even though many patient characteristics were adjusted for in the multivariable analyses and additional analyses incorporating propensity score were performed, the possibility of indication bias with residual confounding could not be excluded. Although analyses incorporating propensity score and propensity score–matched cohorts showed persistently shorter time to first peritonitis in the biocompatible group, these analyses were compromised by a narrow range of distribution in the obtained propensity scores and were probably underpowered (especially 1:1 match), thereby decreasing the probability of adequately accounting for all confounders (Supplemental Figures 1 and 2). It is also important to acknowledge that the proportion of patients included in the present study were participants of the balANZ (Balance in Australian and New Zealand peritoneal dialysis patients) trial (19), which showed decreased peritonitis rates with the use of Balance PD solutions (0.30 versus 0.49 episodes/patient-year). The trial participants would have made up almost 20% of the biocompatible-ever group (and 1.5% of the biocompatible-never group), and, given their much lower than average peritonitis rates, the rates in the rest of the patients who have had peritonitis in the biocompatible group would have been large. Further analyses to ascertain the causes and to test these hypotheses were constrained by the use of a de-identified dataset. However, because balANZ trial recruitment was completed by 2008, the patients who started PD in 2009 onwards would not have been trial participants. The mean peritonitis rates of the biocompatible-ever group who started PD in 2009 and 2010 were 0.53 (95% CI, 0.32 to 0.84) and 1.44 (95% CI, 0.66 to 2.74) episodes per patient-year, respectively (Supplemental Table 5).

Although it is possible that trial participants may not be a “true” representative of the PD population and may receive more intense follow-up with frequent scheduled trial visits, this alone is unlikely to be the major contributor given relatively similar peritonitis rates in the control group in the balANZ trial and the present study. A major weakness of the present study lies in the limitations of registry analysis that restrict the ability to provide a sufficient answer for observed discrepant outcomes from the balANZ trial.

Fourth, a center effect bias may have been operative, given that biocompatible fluid prescription differed markedly among Australian PD units. Adjusting for differences in the size of the treating unit did not significantly alter the outcomes of analyses. This finding is not unexpected because a recent study reported a wide variation in peritonitis rates among Australian treating units independent of their size (39). Although “high” use of biocompatible solutions in the present study was unable to explain the increased peritonitis risk with the use of these solutions, varying infection control practices among units with differential uptake of biocompatible solutions may still have played a role. The current study avoided further stratification by individual treating units because this would increase the risk of type 2 statistical error by introducing a large number of strata. In addition, propensity score did not include treating center, and therefore a residual center effect may be possible.

Finally, ANZDATA is a voluntary registry without external audit of data accuracy, including the diagnosis of peritonitis. Consequently, the possibility of coding/classification bias cannot be excluded. Data collected are restricted in their depth of information, with unexplained residual confounding as demonstrated in the present study.

The present investigation also identified a significant difference in the pattern of microorganisms responsible for peritonitis episodes. However, this finding should be interpreted with caution in light of the disproportionate number of peritonitis episodes between the two groups (biocompatible-ever, n=80; biocompatible-never, n=757), with small event numbers in each micro-organism category and analysis of organisms responsible for first peritonitis only. In contrast, an extended-recruitment RCT involving 267 participants with >7000 patient-months of follow-up found no significant overall difference in micro-organisms.
responsible for peritonitis (18). Similarly, the balANZ trial reported similar micro-organism profiles between the treatment and control groups, except for a significantly reduced risk of nonpseudomonal gram-negative peritonitis with the use of neutral-pH, low-GDP PD solution (36).

The findings of this study are strengthened by a very large sample size from 58 treating PD units over 4 consecutive years in purely incident patients. Inclusion of all PD units in Australia with varying practices and treatment approaches increase the external validity of our findings. In conclusion, the proportion of patients using biocompatible PD solutions has been declining in Australia. Patients with more favorable characteristics appeared to have been chosen to receive this "novel" therapy; however, its use was associated with significantly increased peritonitis rates and a shorter time to first peritonitis episode, albeit with similar outcomes after peritonitis. Although an increased risk of peritonitis with biocompatible fluids may represent a real phenomenon, the strong possibility of indication bias with residual confounding should also be considered given the highly selective nature of biocompatible fluid use in this study, the absence of a biologically plausible explanation for the findings, and the conflicting findings of previous studies. Because it is clearly important to know the effect of biocompatible solutions on PD peritonitis risk and outcomes, a well-designed, multicenter, multinational RCT adequately powered to examine peritonitis as a primary outcome is required.

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