CENTER-CENTERED IN A PATIENT-CENTERED WORLD?

In the absence of randomized controlled trials, observational cohort studies in peritoneal dialysis (PD) continue to provide valuable insights into global patterns of PD care, identification of risk factors for adverse events (e.g., technique failure, death, peritonitis), and the description of temporal trends of these events over time. One of the major limitations with all observational studies is selection bias introduced by the non-random allocation of patients to a particular exposure group, and that residual confounding may remain on the basis of many unmeasured differences between study subjects that may influence both the exposure groups and the events of interest.

Patient characteristics at the start of PD therapy are important determinants of adverse events but are largely non-modifiable (1–7). Therefore, increasing emphasis has been placed on the observed center-level variability in the rates of adverse events for patients on PD (8). Working on the assumption that these differences exist even after adjusting for patient-level confounders provides a “natural experiment” to explore differences in these local, and potentially modifiable practices and their impact on the observed center-level variability in patient outcomes. In this regard, center-level analyses, particularly using modified instrumental variable approaches, are increasingly appearing in the dialysis literature as a means to minimize patient-level confounding and better understand the impact of center-level practice pattern variability on patient outcomes in observational studies (9,10).

In this issue of *Peritoneal Dialysis International*, we have 2 interesting national cohort studies across registry data in Australia and 1 from France exploring center effects on clinical outcomes, namely peritonitis and early technique failure.

In the Australian study by Nadeau-Fredette *et al.* (11), among the main findings was that the variation in peritonitis rates across Australian centers decreased by 16% with the inclusion of patient-level characteristics and a further 34% with the addition of center-level characteristics. Analyzing center-level predictors of peritonitis among 9,000 patients across 51 centers from the national registry (ANZDATA), the authors found an association between lower peritonitis rates and 1) smaller center size, 2) a center’s lower proportion of performance of peritoneal equilibration testing (PET) at initiation of PD, 3) a higher proportion of PD utilization, 4) a higher proportion of automated PD (APD) exposure, and 4) higher icodextrin exposure.

Somewhat reassuring was that centers with higher proportions of PD utilization had lower rates of peritonitis. This would argue against the notion that increases in PD utilization would have the deleterious effect of increasing adverse effects by inclusion of a greater pool of potentially marginal PD

candidates. However, many of the associations were somewhat surprising, including the association between greater icodextrin exposure and higher peritonitis rates. Since the authors defined center icodextrin use as the proportion of patients from each center treated at least once with these solutions during the study period, it is unclear (based on a patient-level analysis) how many patients were actually treated with icodextrin who actually developed peritonitis at the center and for how long. Moreover, other patient-level confounders including dialysis vintage, loss of residual kidney function, worsening peritoneal membrane function, or diabetes may have tracked along with the icodextrin use, thereby confounding the relationship between icodextrin use and peritonitis risk. Similar arguments can be made regarding the relationship between APD use and peritonitis risk.

Also surprising was an unexpected association between lower rates of performance of the PET at the initiation of PD with lower peritonitis rates. Does this finding reflect on the center or the patients being treated at the center? For example, centers with low PET performance rates may relate to the center not routinely deciding to perform them or the case mix of patients who may be reluctant to participate in a PET despite insistence by the center. The authors raised some possibilities to explain these findings, including that those centers that prioritized infection guidelines did so at the expense of adhering to adequacy recommendations. This argument would seem counterintuitive, as one would anticipate guideline adherence and adaptation of best practices at a center to correlate across many domains. Alternatively, it was suggested that centers with poor PET performance might also be subject to under-reporting of peritonitis rates, which is a significant concern across large registries. For example, in unpublished data from the BRAZPD II cohort, peritonitis reporting seems to be different according to center experience and also to have improved over time. This may be similarly the case in ANZDATA, where the association between PET performance and peritonitis risk seemed to disappear in analyses restricted to the more contemporary era (post-2008 cohort).

Yet another surprising finding was the observation of lower peritonitis rates among smaller centers. This is in contrast to some previous papers from several large American, Canadian, Dutch, Brazilian, and French cohorts that all point to larger center size being associated with improved clinical outcomes largely surrounding patient and technique survival (12–15). While each study has defined center size in a slightly different way, and while peritonitis was not the focus of previous analyses, larger center size has always been taken as a proxy for clinical expertise, greater resources, and experience, but

details regarding practice differences between larger and smaller centers as in the present study remain lacking. In the present study, the association between smaller center size and lower peritonitis rates in the ANZDATA was only significant in the more recent era (post-2008). It is interesting to note that according to the 2014 ANZDATA report, overall peritonitis rates have improved dramatically in Australia and New Zealand over the period of the present study (16). These 2 findings together may suggest that, in response to a recent call to action to improve PD outcomes in Australia and New Zealand (17), the smallest centers may have improved their peritonitis rates to a greater extent than did the larger centers.

The second study, by Guillouët *et al.* (18), retrospectively analyzed data from 127 centers of the French Language Peritoneal Dialysis Registry from 2008 to 2012. Using multi-level modeling, the authors found that 52% of the differences in early technique failure could be accounted for by a center effect. Centers that treated more than 10 incident patients per year had a 22% lower risk of early technique failure than centers that treated less than 10 patients per year. Patient-level predictors of early technique failure were a history of prior hemodialysis and kidney transplantation as compared to dialysis- and transplant-naïve incident PD patients.

It is worth noting that, in this study, the majority (76% of centers) was classified as small centers treating less than 10 incident PD patients per year. Early on particularly, greater failure is seen due to mechanical problems relating to catheter function, specifically during the first 3 months of therapy (2). As expected, PD catheter dysfunction was one of the main causes of dropout, accounting for 20% of early technique failure cases. It is therefore possible that differences in local expertise regarding PD catheter insertion practices may have been driving part of the differences in outcomes, as it is likely that, in centers that routinely insert fewer than 10 PD catheters per year, experience may be lacking. Hence, the association between greater center size and better technique survival is not unexpected if we consider center size as a surrogate marker for expertise in PD catheter insertion. Unfortunately, data for the method of PD catheter insertion and for the expertise and volumes of the operating team involved in PD access insertion at each center was not available in the registry. These factors may have been more relevant in predicting early technique failure than were nursing and nephrology physician staffing and characteristics, which had no bearing on the risk of early technique failure in the present study.

It is also worth noting that almost 34% of all technique failure cases were vaguely categorized as "other causes related to PD." In this regard, a more systematic classification of causes of technique failure is needed across and between studies, and a more detailed reporting by registries would have resulted in a better understanding of the causes of early PD technique failure in the present study.

Underpinning both studies above is the notion that, after accounting for differences in the case-mix of patients, national dialysis registries demonstrate considerable unexplained variability in the rates of PD technique failure across centers.

While both studies have elegantly examined the drivers of this variability, further efforts are needed to better understand and capture the scope and breadth of practice pattern variability across facilities in an effort to better understand the differences in outcomes. Therefore, taking a center-centered approach in PD research is inherently patient-centered as it will allow us to identify best practices in PD that may be more broadly applied to all in order to maximize patient and technique survival as well as quality of life.

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