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Centre Effects in Peritoneal Dialysis

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Abstract

Peritoneal dialysis (PD)-related complications and outcomes have been shown to be influenced by both patient- and centre-level factors. There is a significant variability in outcomes across different centres, which is not explained by patient factors alone. This chapter aims to evaluate those modifiable centre-level factors that have been shown to impact PD outcomes, focussing specifically on peritonitis and technique failure, and the evidence that addressing these centre effects may lead to appreciable improvements in PD patient outcomes. Peritonitis rates have been shown to be related to a centre's degree of automated PD (APD) use, extent of icodextrin use, performance of home visits prior to PD commencement, the presence of a specialised PD nurse and duration of PD training. Better peritonitis outcomes have been shown to be associated with larger centre size, greater share of PD patients among dialysis cohorts and treatment of peritonitis with comprehensive empiric antimicrobial therapy. PD technique failure has been shown to be related to centre size and degree of PD experience. Although there is little evidence currently available to demonstrate that prospectively modifying centre factors improves PD outcomes, an Australian continuous quality improvement initiative has been associated with progressively improved peritonitis and technique failure outcomes.

Keywords: ambulatory care facilities/organisation and administration, centre effects, centre size, health facility size, kidney failure, outcomes, peritoneal dialysis, peritonitis, predictors, registries, technique failure

1. Introduction

Peritoneal dialysis (PD) is an important dialysis modality that offers key benefits compared with haemodialysis, including better preservation of residual renal function, superior quality of life and patient satisfaction and possibly an early survival advantage in the first few years

[1]. The major pitfalls associated with PD are peritonitis and relatively high technique failure rates [1]. Recent studies have demonstrated up to 10-fold variation in the frequencies of peritonitis and technique failure between different PD centres within the same country [2–5]. This between-centre variability is greater than between-country variability and appears to be predominantly driven by centre-related factors ('centre effects') rather than by patient-related factors ('casemix') [6–9]. This chapter aims to review the evidence for centre effects in PD patient outcomes (focusing on peritonitis and technique failure), the modifiable centre-related factors that may contribute to these centre effects and the evidence that addressing these centre effects may lead to appreciable improvements in PD patient outcomes.

2. Peritonitis rates

Rates of PD peritonitis vary considerably between centres and between countries. Reported rates vary from as low as 0.06 episodes per year in a Taiwanese programme to as high as 1.66 episodes per year in Israel [10]. In addition to variable peritonitis rates between countries, peritonitis rates vary significantly between centres within countries. For example, a 2011 analysis of the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) demonstrated 10-fold variation in peritonitis rates across 72 Australian centres (6639 patients (2003–2008)), which was not correlated with centre size [3]. In another registry analysis of all 10 PD units in Scotland between 1999 and 2002, Kavanagh et al. [5] reported significant differences in peritonitis rates across centres that did not correlate with centre size or mix of modality (automated peritoneal dialysis [APD] versus continuous ambulatory peritoneal dialysis [CAPD]). Similarly, Davenport et al. [4] analysed data from 12 PD units treating over 800 PD patients in the Thames area over 2002–2003 and demonstrated approximately sevenfold variation in peritonitis rates with no significant correlation with unit size or PD modality. More recently, Nadeau-Fredette et al. [6] reported on peritonitis outcomes from 8711 patients from 51 PD centres in Australia (2003–2013). They described wide variability in peritonitis rates across centres, ranging from 0.17 (95% confidence interval [CI], 0.04–0.50) episodes per patient-year to 1.74 (95% CI, 1.40–2.13) episodes per patient-year. This centre variation was reduced by 16% after adjusting for patient characteristics and by 34% after adjusting for centre characteristics. In this study, peritonitis rates were evaluated using a mixed-effects negative binomial regression model with a random intercept for dialysis centres. Patient-level effects (e.g. age, gender, primary kidney disease, race and comorbidities) and centre-level effects (e.g. centre size, PD proportion and proportion of APD) were analysed as fixed effects. The final model included age, gender, race, diabetes, body mass index, cardiovascular disease, PD as the first renal replacement therapy (RRT) modality, centre size, PD proportion, APD exposure, icodextrin exposure, PET use, hospitalisation and antifungal prophylaxis at time of peritonitis [6]. Finally, Bechade et al. [8] examined rates of the first episode of peritonitis among 5017 incident PD patients across 127 PD centres in France over 4 years (2008–2012). They reported significant variability between centres (variance of random effect 0.11) with only a 9% reduction in variance when adjusted for patient-level characteristics and a significantly higher 35% reduction of variance of random effect when adjusting for PD centre characteristics. In this study, the investigators used bivariate analysis with a Cox model to explore the association

between each patient-level and centre-level covariate. These studies therefore suggest that centre effects rather than patient characteristics (casemix) are the major driver for centre variation in peritonitis rates. A number of centre characteristics have been linked to these observed centre effects [7].

2.1. Centre size

Centre size has been variably associated with peritonitis risk in the literature. Several studies have found no association between centre size and peritonitis rate [3, 6, 8, 11–13]. However, a study by the Brazilian Peritoneal Dialysis Multicenter Study (BRAZPD) group [13] looking specifically at training methods and peritonitis risk noted a significant relationship between smaller centre size (<61 patients versus ≥ 61 patients) and shorter time to the first episode of peritonitis (subhazard ratio [SHR] 0.75; 95% CI, 0.62–0.90). In contrast, Nadeau-Fredette et al. [6] reported that smaller centre size, defined as less than 235 cumulative patient-years of PD exposure over the 10-year study period, was associated with *lower* peritonitis risk after adjustment for patient-level factors (incidence rate ratio [IRR] 0.78; 95% CI, 0.69–0.90, $p < 0.001$). They postulated that this seemingly paradoxical finding may have represented more favourable nurse:patient ratios or residual confounding related to PD patient selection. Overall, the association between centre size and centre peritonitis rates remains uncertain at this time.

2.2. PD experience

In addition to centre size, share of PD patients has been associated with lower peritonitis rate in a single study. Nadeau-Fredette et al. [6] reported that centres with a higher proportion of PD patients (>30%) were associated with lower peritonitis count (IRR 0.87; 95% CI, 0.77–0.99).

2.3. APD exposure

Centre APD exposure has been variably described as a risk factor for peritonitis [4–6]. Davenport et al. described no association between centre peritonitis rates and dialysis modality [4]. This was replicated in Kavanagh et al.'s study, which demonstrated variable results across centres with regard to peritonitis rates and dialysis modality but no clear association between APD and peritonitis rate. In contrast, in their Australian study, Nadeau-Fredette et al. [6] found that higher peritonitis rates were associated with centres with the lower use of APD compared with centres with average or higher than average APD exposure (<45% APD use compared to between 45 and 78% use or higher than 78% APD use). The lower use of APD at a centre level may have been associated with a higher peritonitis rate for several reasons. It has been hypothesised that APD offers fewer opportunities for contamination during connecting and disconnecting bags (with less overall connections taking place) or may represent unit management practices influenced by economic factors or flexibility with PD prescriptions.

2.4. PD management practices

PD centre practices, such as providing specialised PD nurses and home visits prior to PD commencement, have been shown to correlate with lower rates of peritonitis. In the French

study by Bechade et al. [8], 86 (68%) of 127 PD centres undertook home visits prior to PD commencement, and 24% offered specialised PD nurses. Centres undertaking home visits had a statistically significant 13% lower risk of peritonitis, while centres with specialised PD nurses had a 25% lower hazard of peritonitis. Furthermore, Chow et al. [14] observed an association between nurse experience among PD trainers and peritonitis rates, whereby the cohort of patients trained by the least experienced PD trainers (lowest tertile <3 years' time in practice) exhibited the lowest subsequent peritonitis rates. This somewhat surprising finding may have represented a failure to maintain contemporaneous learning for more experienced PD trainers. Alternatively, the finding may have been confounded by indication bias, whereby higher risk patients were more likely to be assigned to more experienced nurses for training. In keeping with the latter possibility, a single-centre, Chinese observational cohort study of 305 incident PD patients observed that increasing duration of nursing experience among PD trainers was associated with lower risks of Gram-positive peritonitis [15].

Training practices and their association with peritonitis rates have also been examined. Figueiredo et al. [13] undertook a prospective analysis of 2243 patients from 122 centres enrolled in the BRAZPD II cohort. The investigators reported significant differences both for cumulative amount of training received and timing of training with regard to catheter insertion and peritonitis rates. Establishing that the median amount of training across centres was 15 hours, they reported that centres providing >15 hours of training demonstrated significantly lower peritonitis rates compared to centres providing less than 15 hours of training (0.32 episodes per patient-year compared with 0.26 episodes per patient-year, respectively, $p = 0.01$). Peritonitis rates also significantly decreased with the amount of training provided per day, with centres providing <1 hour per day demonstrating a higher rate of peritonitis (0.35 episodes per patient-year) compared with centres providing >2 hours per day (0.27 episodes per patient-year, $p = 0.02$). Lastly, timing of training with regard to catheter insertion was also found to be associated with peritonitis rate. Patients trained within 10 days of catheter insertion had higher rates of peritonitis compared to those trained after 10 days or those trained before catheter insertion.

Another aspect of PD management is PD prescription practices, which have been examined by looking at icodextrin use. Nadeau-Fredette et al. [6] found that centres with a higher icodextrin exposure (>65% of patients) were associated with a higher peritonitis count (IRR 1.26; 95% CI, 1.10–1.44, $p = 0.001$). While icodextrin use has not been shown to represent a risk for peritonitis at the patient level [16], centre icodextrin exposure may be associated with higher peritonitis incidence by reflecting less flexible or personalised PD prescription practices (e.g. a 'one-size-fits-all' approach), or as Nadeau-Fredette et al. have hypothesised, it may reflect residual unmeasured differences in centre practices. For example, icodextrin use may have been used to extend the duration of PD treatment for a patient who might otherwise have been converted to haemodialysis [6].

2.5. Centre adherence to guidelines

Adherence to evidence-based best-practice guidelines has been postulated to correlate with better peritonitis-related outcomes but has been poorly studied outside of Australia.

Nadeau-Fredette et al. studied peritoneal equilibration test (PET) performance at PD commencement as a surrogate measure of centre compliance with best-practice guideline recommendations and postulated that higher PET use (and therefore better PET guideline compliance) would correlate with lower peritonitis rates. However, they found that the lower use of PET was associated with lower rates of peritonitis. While the reasons for this observation remain unclear, the authors speculated that centre adherence to guidelines might not be consistent across the board, such that some centres may have prioritised compliance with peritonitis prevention guidelines at the expense of complying with other guidelines (such as monitoring peritoneal solute transport rate). Other Australian investigators have reported higher peritonitis rates in centres that frequently deviated from the International Society for Peritoneal Dialysis (ISPD) guideline recommendations for peritonitis prevention, such as the use of antibiotic and antifungal prophylaxis [17]. The relationship between centre adherences to ISPD peritonitis prevention guidelines will be examined in detail by the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) [18].

2.6. Evidence that modifying centre practices leads to better peritonitis rates

Continuous quality improvement programmes have been shown to be associated with improved peritonitis outcomes at national levels [19, 20]. Strong evidence for this can be seen in the Australian and New Zealand approach, as reported by Nataatmadja et al. [19], which was characterised by the creation of a national peritonitis registry to monitor peritonitis incidence and identify risk factors for peritonitis (ANZDATA) and a commitment to ongoing cycles of data analysis and feedback to PD centres with a national PD peritonitis key performance indicator (KPI) project. This was supported by additional state-level initiatives and teaching programmes. Following these initiatives, peritonitis rates decreased by approximately one third, and between-centre variations in peritonitis rates decreased by 50%. These findings were supported by those of a PD CQI programme in Colombia [20] in which introducing six key programme elements (improved PD nurse:patient ratios, the use of an exit-site care protocol, standardisation of PD guidelines and protocols, nurse certification and continuing education, home visits and systematic follow-up and actioning clinic results) resulted in a reduction in peritonitis rates from 0.57 episodes per patient-year in 2006 to 0.20 episodes per patient-year in 2014. Similar improvements in PD peritonitis rates at the individual centre level have been reported by Yu et al. in China [21] and Qamar et al. in the United States [22].

3. Peritonitis outcomes

Centre-level characteristics have been shown to be associated with key peritonitis outcomes, such as peritonitis cure, PD catheter removal, transfer to haemodialysis, relapse or recurrence, hospitalisation and mortality. In their national registry analysis, Htay et al. [23] studied all incident PD patients in Australia who developed peritonitis between 2004 and 2014. They found that peritonitis cure rates for individual centres varied between 38 and 86%. The investigators explored the association between patient- and centre-related characteristics and peritonitis

outcomes by conducting multilevel mixed-effects logistic regression models, whereby patient- and centre-level characteristics were applied as fixed effects and patient and centres as random effects. This allowed for nesting of outcomes within patients and patients within each centre to allow analysis of clustered data. Covariates with *P*-values less than 0.2 on univariate analyses were included in the multivariate models. In addition, the era of PD commencement was also fitted as a fixed-effects covariate in the final model to adjust for era effect. Several patient-related covariates (e.g. gender, primary renal disease, late nephrology referral, initial modality of PD) and centre characteristic-related covariates (e.g. transplanting centre, exposure to APD, icodextrin, PET practice) were excluded during the model building process. The final model included era of PD commencement (2004–2009 versus 2010–2014), age, race, BMI, smoking status, diabetes mellitus, cardiovascular disease, chronic lung disease, causative microorganisms for peritonitis, PD as initial modality of RRT, socio-economic position (reported as Index of Relative Socio-economic Advantage and Disadvantage) and centre-level characteristics, including centre size, proportion of PD patients in a centre and the proportion of patients receiving complete empiric antibiotics covering Gram-positive and Gram-negative organism during peritonitis. The centre characteristics significantly associated with achievement of cure were higher share of PD patients (>29% PD patients, adjusted odds ratio [OR] 1.21; 95% CI, 1.04–1.40) and higher proportion of peritonitis episodes receiving complete antibiotic cover (as defined by receiving antimicrobial cover for both Gram-positive and Gram-negative organisms at presentation) (OR 1.22; 95% CI, 1.06–1.42). Similarly, centres with a larger share of PD patients were associated with lower odds of peritonitis-related catheter removal (>29% PD patients; OR 0.78; 95% CI, 0.62–0.97) and lower odds of HD transfer (>29% PD patients; OR 0.78; 95% CI, 0.62–0.97). Peritonitis relapse or recurrence was less common in centres with higher or lower PD patient share as compared to average PD patient share (>29% PD patients; OR 0.68; 95% CI, 0.48–0.98 and <18% PD patients; OR 0.68; 95% CI, 0.51–0.90). Finally, the authors reported significant improvements in peritonitis outcomes over time. Compared with the earlier study period, the contemporary period (2010–2014) was associated with significantly higher odds of achieving peritonitis cure (OR 1.17; 95% CI, 1.04–1.30) and lower odds of relapsed or recurrent peritonitis (OR 0.66; 95% CI, 0.55–0.80), likely reflecting the implementation of national quality improvement programmes and evidence-based best-practice guidelines.

4. Technique failure

Several studies have identified significant variability in technique failure rates between different PD centres [9, 24–27]. Technique failure was variably defined as transfer to haemodialysis (HD) for ≥ 30 days or death (including death within 30 days of transfer to HD) [9], death-censored transfer to HD for ≥ 60 days within the first 6 months of PD [25] or death-censored transfer to HD for ≥ 90 days [24]. One of the studies [26] did not define technique failure in their study. All studies were based on registry data, and patients who met systematic registry definitions of technique failure were included in the analyses.

Huisman [24] et al. examined data from RENINE, the Netherlands national dialysis registry, and observed that average annual technique failure rates varied between 10 and 59% across

the 43 centres reporting to the registry. Schaubel et al. [26] examined data from 86 renal centres contributing to the Canadian Organ Replacement Register and found significant differences in technique failure and mortality across different centres when stratified for size and casemix, suggesting that centre-level factors were strong predictors of outcomes in PD patients. The key role played by centre effects in technique failure was further reinforced by the findings of Guillouet et al. [25], who analysed outcomes for 5406 incident PD patients based on data from the French Language Peritoneal Dialysis Registry using a multilevel mixed-effects logistic regression model with centre as a random effect and all patient characteristics (level 1) and all centre characteristics (level 2) as fixed effects [25]. The patient-level characteristics examined in the study were gender, comorbidities (classified by Charlson comorbidity scores), diabetes mellitus, cause of renal failure, initial PD modality, assisted PD (family assistance, nurse assistance), initial modality of renal replacement therapy (RRT) and suboptimal PD initiation (defined by a time spent on HD before PD of less than 1 month). The centre-level characteristics examined in the study included the presence of a full-time nurse (nurses dedicated only to PD) versus a part-time nurse, number of nephrologists specialised in PD, number and types of home visits by PD nurses, centre size (defined as <10 versus ≥ 10 incident PD patients in centre per year) and types of centres (categorised by academic centre, community centre, non-profit centre and private centre). Looking specifically at early technique failure (defined as transfer to HD for >2 months within the first 6 months of PD, regardless of PD duration with censored renal transplantation and death during the first 6 months on PD), they reported a 52% difference in variation of outcomes between PD centres after adjustment for patient characteristics and centre experience.

This variability above and beyond patient-level characteristics was similarly observed by Htay et al. [9], who used Cox proportional regression with shared frailty models to account for clustering of patients within the centre and reported a sevenfold variation in technique failure rates across centres in their Australian registry-based study. This variation was reduced by 28% after accounting for patient-related characteristics and by a further 53% after accounting for centre-related characteristics. Technique failure in the study was defined as transfer to haemodialysis (HD) for ≥ 30 days or death (including death within 30 days of transferring to HD). The detailed statistical methods are available elsewhere [9]. All patient-level characteristics with p-values <0.2 in univariable Cox-shared frailty model were included as fixed effects in the first model. The patient-level characteristics in the first model and all centre-level characteristics with p-values <0.2 in the univariable Cox-shared frailty model were included in the final model. The era of PD commencement was also fitted as a fixed-effects covariate in the final model to adjust for era effect. The likelihood ratio test was used to compare the first and final models. The final model included era of PD commencement (2004–2009 versus 2010–2014), age, gender, race, BMI, smoking status, diabetes mellitus, cardiovascular disease, chronic lung disease, primary renal disease, late referral, initial modality of RRT, initial PD modality, socio-economic position (reported as Index of Relative Socio-economic Advantage and Disadvantage) and centre-level characteristics, including centre size, proportion of PD patients in a centre, APD exposure in a centre, proportion of patients on icodextrin in a centre, proportion of patients achieving baseline target phosphate level in a centre and proportion of patients on antifungal prophylaxis during peritonitis.

These studies therefore suggest that there is a large and unacceptable variation in PD technique failure rates between centres, which appears to be largely driven by centre characteristics. However, the precise centre characteristics underpinning these centre effects have received only limited study to date.

4.1. Centre size

Of all the centre characteristics that have been linked with PD technique failure, the relationship between smaller centre size and higher rates of technique failure has been the most robustly described [9, 12, 24–27]. Afolalu et al. [27] examined technique failure over the first 2 years of PD treatment in 5003 PD patients from 105 PD units in the United States. Defining smaller centre size as units with ≤ 25 patients and larger centre size as units with >25 patients, they reported significantly higher rates of technique failure in the smaller centre size group for both the first and second years of treatment (OR 1.36, $p < 0.005$ and OR 1.35, $p = 0.03$, respectively). These findings have been replicated in other large registry-based studies, including from the Netherlands [24], Canada [26] and Australia [9]. This ‘volume-outcome’ [11] relationship has also been confirmed in a systematic review by Pieper et al. [11], despite heterogeneity in definitions of centre size (ranging from greater than or less than 20 patients to greater than or less than 400 patients).

One of the problems with evaluating the relationship between technique failure and centre size based on the number of prevalent PD patients is that centres with higher technique failure rates will experience falls in the number of prevalent PD patients (i.e. the outcome reciprocally affects the predictor). This issue has been mitigated in some studies by examining the number of incident PD patients treated by a PD centre. For example, Guillouet [25] reported that centres treating more than 10 new patients per year had a lower risk of early PD failure (OR 0.71; 95% CI, 0.58–0.88). Similarly, in a study of Australian registry data between 2004 and 2014, Htay et al. reported higher rates of technique failure in centres with <16 new patients per year (HR 1.10; 95% CI, 1.00–1.21) [9]. Consequently, regardless of how centre size is defined, there appears to be a clear inverse association between PD centre size and technique failure rate.

4.2. PD experience

It has been hypothesised that total unit experience with PD provision and management would positively impact technique failure rates. Assessing this factor has been approached variably in the literature. Schaubel et al. [26] examined data from the Canadian Organ Replacement Register on 17,900 patients across 86 centres and defined ‘PD experience’ as the cumulative number of PD patients treated. After dividing centres into tranches of 100 with <99 patients treated with PD as the ‘least experienced’ and >500 as the ‘most experienced’, they observed a reduction in technique failure with increasing cumulative PD patient experience, which became statistically significant when the cumulative number of PD patients treated exceeded 200 (200–299 adjusted rate ratio [aRR] 0.89; 95% CI 0.80–0.99; 300–399 aRR 0.81, 95% CI 0.71–0.91; 400–499 aRR 0.82, 95% CI 0.72–0.94; ≥ 500 aRR 0.83, 95% CI 0.73–0.95; ≤ 99 reference).

The percentage of patients treated with PD within dialysis cohorts has also been studied to reflect a centre's 'degree of specialisation' towards PD. Schaubel et al. [26] reported a significant correlation between a lower percentage of patients initiating dialysis with PD at a centre and higher technique failure rates, which became statistically significant when the percentage of patients initiating dialysis on PD at a centre fell below 60%. Huisman et al. [24] also observed an inverse correlation between the fraction of dialysis patients on PD and annual technique failure rate ($r = -0.410$, $p = 0.006$). Finally, Htay et al. found that both technique failure and death-censored technique failure were significantly less likely when the proportion of dialysis patients treated with PD exceeded 29% [9].

4.3. Centre PD practices

Few studies have examined other centre characteristics that may affect PD technique survival. Htay et al. [9] hypothesised that PD centre practices, including prescription practices (such as APD exposure and icodextrin use) and management practices (such as proportion of patients who had had a PET within 6 months of PD commencement or target serum phosphate achievement), would correlate with technique failure outcomes. However, they found that none of these more specific centre-related factors was associated with death-censored technique failure.

4.4. Transplanting status/academic status

Schaubel [26] classified centres into academic or nonacademic centres based on affiliations with a medical school and did not find any association with technique failure rates. Similarly, Htay et al. [9] found no relationship between technique failure outcomes and whether or not the centre was a superspecialised service providing kidney transplantation.

4.5. Evidence that modifying centre factors leads to better technique failure outcomes

Although centre-based factors have demonstrable effects on technique failure outcomes for PD patients, there is currently little evidence prospectively examining the hypothesis that modifying centre factors improves technique failure outcomes in PD. An epidemiological study from France by Evans et al. [28] sought to hypothetically model interventions to improve technique failure outcomes for patients by constructing a probability-based model 'moving' PD patients from smaller centres to larger ones and by modelling outcomes based on a hypothetical 'PD first' initiative. Although entirely theoretical, the study found that lower technique failure rates could be expected by undertaking such initiatives. The quality improvement initiative in Australia described previously has also been associated with progressive improvements in national PD technique failure rates [19].

5. Conclusions

In conclusion, studies have demonstrated significant variability in both PD peritonitis rates and outcomes and in technique failure outcomes across different PD centres. This variation has

been shown to be driven in a significant part by PD centre-level characteristics, such as unit size, degree of PD specialisation and PD prescription, and management factors such as APD exposure, use of icodextrin and centre adherence to evidence-based best-practice guidelines. Focussing further study on characterising these centre-level factors thus represents an important opportunity to improve patient outcomes. Centre-level factors may be a more practical and efficient target for future intervention than focussing on patient-level factors.

6. Future directions

Studies on centre-level effects on PD outcomes have been limited by the challenge of collecting data at the multicentre level. Further work is needed to examine in more granular detail those centre practices that impact PD outcomes and to inform and prospectively evaluate quality improvement measures. It is hoped that further insights will be gained from the forthcoming Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) [18], which is an international research initiative to better understand and improve PD practice and outcomes for PD patients. It was launched in October 2013, and active data collection is in process involving over 4000 patients across 180 PD units from Canada, the United States, Japan, Australia, New Zealand, the United Kingdom and Thailand.

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