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# ARE ISPD GUIDELINES ON PERITONITIS DIAGNOSIS TOO NARROW? A 15-YEAR RETROSPECTIVE SINGLE-CENTER COHORT STUDY ON PD-ASSOCIATED PERITONITIS ACCOUNTING FOR UNTRAINED PATIENTS

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♦ ***Background:*** **Peritoneal dialysis (PD)-associated peritonitis remains by far the most important complication requiring patients to transfer to hemodialysis and has a major impact on patient morbidity and mortality. Current International Society for Peritoneal Dialysis (ISPD) guidelines on peritonitis recommend analysis of peritonitis episodes only in trained patients. In a large tertiary care center, we analyzed peritonitis episodes accounting for different groups of untrained patients and compared these with episodes in the trained patient population.**

♦ ***Methods:*** **We analyzed data collected prospectively over a 15-year time span regarding differences between peritonitis episodes in trained patients and episodes in untrained patients post-catheter insertion but prior to training completion as well as on in-center intermittent PD with respect to incidence rates, pathogenic organisms, outcome, and peritonitis predictors.**

♦ ***Results:*** **In 275 patients, a total of 160 peritonitis episodes in trained patients were counted. A total of 27 additional episodes in untrained patients were recorded. When accounting for these episodes, the peritonitis incidence significantly increased and the percentage of peritonitis-free patients decreased. Peritonitis episodes in untrained patients were most often culture-negative and the pathogen spectrum differed significantly compared with episodes counted as per ISPD recommendations, while outcome of peritonitis episodes did not differ. Predictors of peritonitis after multivariate logistic regression analysis included glomerulonephritis as primary kidney disease, being on home PD rather than being on in-center intermittent PD, and higher dialysis vintage.**

♦ ***Conclusions:*** **Depending on local practice patterns, we argue that centers should additionally monitor peritonitis episodes in untrained patients because computation of statistics as per ISPD recommendations could underestimate peritonitis incidence and may depict a distorted pathogen spectrum.**

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KEY WORDS: Post-catheter insertion episodes; in-center intermittent PD; PD training; practice patterns.

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Peritoneal dialysis (PD) remains underutilized in large parts of the world, partly because it is perceived as a complication-ridden dialysis modality with a significant proportion of technique failure. Although equivalent to hemodialysis (HD) with respect to adequacy, mortality, and other outcome parameters (1–3), serious PD-associated complications indeed culminate in ample damage precluding successful PD (4). Major reasons for PD dropout include transfer to HD, death, and transplantation. Peritoneal dialysis-associated peritonitis remains by far the most important complication requiring patients to transfer to HD (5,6) and has a major impact on patient morbidity and mortality (7,8).

It is known that peritonitis rates and outcomes vary substantially between and even within countries (9–11). Recently, increasing efforts have underpinned the importance of center-specific factors for the marked variation in peritonitis outcomes (12,13), and the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) initiative acknowledges that practice pattern variations crucially impact PD technique and patient outcome (14,15). The percentage of patients who have not been fully trained might contribute substantially to this variation. In our center, we have a large proportion of untrained patients performing PD. We start PD after a relatively short break-in period of only 3 – 4 days after catheter insertion using low-volume automated PD (APD) fills when patients are still in hospital. Patients are usually discharged 3 – 4 days after catheter insertion, and PD training is commenced in an outpatient setting from this point onwards by a nurse specifically appointed to a single patient. Following a standard operating procedure, every patient initially receives continuous ambulatory peritoneal dialysis (CAPD) training, regardless of his or her planned modality choice, followed by additional APD training as applicable according to peritoneal equilibration data at 6 – 12 weeks or to individual criteria (e.g. professional life, social situation). The individual patient's mileage to mastering all aspects of PD (personal hygiene, exit-site care, catheter handling, etc.) usually varies from 3 days to 3 weeks for CAPD and 5 days to 5 weeks for APD, after which we classify the patient as either "fully trained" or "failed training." Patients who fail PD training despite our most extensive efforts or those patients who—mostly due to their frailty, lack of autonomy, or acute situations (e.g. hernias, fractures of extremities)—are highly likely to fail training, are treated by in-center intermittent PD

(IPD). In our center, the proportion of IPD patients is relatively large and we have previously reported on our experience (16).

The current International Society for Peritoneal Dialysis (ISPD) peritonitis recommendations (17) state that "during the computation (of peritonitis rates), only peritonitis episodes that developed from the first day of PD training should be counted." We agree that harmonizing outcome measures is fundamental in order to understand potentially modifiable causes of PD technique failure. Still, we feel that a considerable proportion of our patients is not represented when looking at peritonitis incidence under the assumption that all patients included in the computation of peritonitis rates are fully trained. Along those lines, ISPD recommendations indeed recognize that "it may (...) be useful to monitor any peritonitis episode that develops after catheter insertion and before PD training is started." Therefore, we hypothesized that calculating peritonitis statistics as per recent ISPD recommendations, i.e. not including peritonitis episodes in untrained patients, may significantly underestimate peritonitis rates in our tertiary care center. We therefore explored over a 15-year time span differences between peritonitis episodes counted as per ISPD recommendations as well as per alternative methods (including episodes in untrained patients) with respect to incidence rates, pathogenic organisms, outcome, and predictors.

## PATIENTS AND METHODS

### STUDY POPULATION

This study included all incident and prevalent patients 18 years of age and older who underwent outpatient PD at the Hannover Medical School PD clinic from 1 January 2003 to 31 December 2017. It was approved as a retrospective cohort study of routinely collected data by the local medical ethics board (no. 3609-2017). All PD catheters were inserted surgically via mini-laparotomy. Throughout the study period, single-cuffed Oreopoulos-Zellermann "Reitinger Spezial" coil catheters were used. All patients on CAPD received biocompatible PD fluids during the whole study period. Patients on APD exclusively received biocompatible PD fluids from 2010 onwards and received mostly biocompatible PD fluids from 2003 to 2009 as 2.5-L and 5-L APD bag sizes were switched at different time points during this period.

### DIAGNOSIS AND TREATMENT OF PERITONITIS EPISODES

In accordance with the current ISPD recommendations on prevention and treatment of PD-related peritonitis (17), a diagnosis of peritonitis was made when at least 2 of the following were present: 1) clinical features consistent with peritonitis, i.e. abdominal pain and/or cloudy dialysis effluent; 2) dialysis effluent white cell count > 100/μL (after a dwell time of at least 2 hours), with > 50% polymorphonuclear; and 3) positive dialysis effluent culture. Relapsing peritonitis was defined as an episode occurring within 4 weeks after completion of therapy for a prior episode with the same organism or 1 sterile episode. Relapsing episodes were not counted as another episode during calculation of peritonitis rates, whereas recurrent and repeat episodes were. Of note, no routine prophylactic antibiotic exit-site treatment was performed. We performed nasal screening for methicillin-resistant *Staphylococcus aureus* in the incidence of clinical exit-site infection and nasal mupirocin was applied in case of a concomitant exit-site infection with *Staphylococcus* sp. During the whole study period, empiric antibiotic therapy consisted of vancomycin i.p. combined with gentamycin i.p. and was consecutively changed according to the resistogram of the causative pathogen. The treatment was continued for 3 weeks.

### ACCOUNTING FOR UNTRAINED PATIENTS

In addition to counting peritonitis episodes in patients from the first day of PD training as per current ISPD guideline definition (reference, method 0), we recorded additional peritonitis episodes as per 3 different methods: method 1 additionally included patients and peritonitis episodes from the first day of catheter insertion but prior to PD training; method 2 additionally included peritonitis episodes from patients receiving in-center IPD who were formally never fully trained; and method 3 combined methods 1 and 2.

### DATA COLLECTION

Basic patient data encompassed gender, age at PD start, age at PD drop-out, dialysis vintage, predominant dialysis modality (home CAPD, home APD, and in-center IPD, usually performed as APD for 7 hours thrice weekly, ranging from twice weekly to 5 times weekly), primary kidney disease (classified as either diabetic nephropathy; renal vascular disease, excluding vasculitis; glomerulonephritis; cystic kidney disease; interstitial nephritis; pyelonephritis, drug-induced; urolithiasis; cardiorenal syndrome [end-stage renal disease secondary to severe cardiac dysfunction]; congenital and hereditary, excluding cystic disease; other, including systemic diseases; or unknown), comorbidity data (expressed by the Davies comorbidity score) (18), encompassing ischemic heart disease, left ventricular dysfunction, peripheral vascular disease, malignancy, diabetes mellitus, collagen vascular disease, immunosuppressive medication use for longer than 3 weeks (glucocorticoids, rituximab, cyclophosphamide, and other immunosuppressive agents), and time to first peritonitis episode.

All peritoneal effluent cultures performed during the study period were reviewed for pathogenic organisms and categorized as follows: coagulase-negative *Staphylococcus* sp., *Staphylococcus aureus*, *Enterococcus* sp., *Streptococcus* sp., other gram-positive sp., *Pseudomonas* sp., *E. coli*, other gram-negative sp., polymicrobial, fungal, *Mycobacterium* sp., others, and culture-negative.

Patient and catheter outcome was categorized as peritonitis resolved, catheter change with continuing PD, catheter removal without any further requirement for renal replacement therapy, catheter removal with permanent transfer to HD, and death, which was defined as death with active peritonitis or

within 4 weeks of a peritonitis episode or any death during hospitalization for a peritonitis episode.

### STATISTICAL ANALYSIS

Data for categorical variables are presented as frequencies/percentages ± standard deviation and for continuous variables as mean ± standard deviation. D'Agostino & Pearson omnibus normality test was used to test for normality. Paired data were analyzed by either repeated measures 1-way ANOVA if parametric or by Friedman's test if non-parametric. Non-paired data were analyzed by either ordinary 1-way ANOVA if parametric or by Kruskal-Wallis test if non-parametric. We corrected for multiple comparisons using Holm-Sidak's *post hoc* correction if parametric or Dunn's *post hoc* correction if non-parametric. Fisher's exact test was used for analysis of categorical peritonitis outcome variables. A Kaplan-Meier curve was constructed to compare cumulative peritonitis-free survival. Group differences were analyzed by log-rank test and patients were censored for PD catheter removal, PD technique failure, death, loss to follow-up, and at 120 months' follow-up. Univariate and multivariate binary logistic regression analyses were performed to identify predictors of peritonitis. Factors with $p < 0.10$ in univariate analysis were included in multivariate analysis to ascertain the effects of these predictors on the likelihood of peritonitis. Wald's backward and forward elimination models yielded the same result. All tests were 2-tailed. $P < 0.05$ was considered to indicate statistically significant differences. IBM SPSS Statistics v22.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism v6.0 (GraphPad Software, La Jolla, CA, USA) were used for data analysis.

## RESULTS

### DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

During the study period, a total of 275 patients received PD during 7,928 cumulative patient months in our outpatient PD clinic. Characteristics of the patients are summarized in Table 1. A total of 105 patients (38.2%) received home CAPD, 106 (38.5%) received home APD, whereas 64 patients (23.3%) received in-center IPD.

TABLE 1
Patient Demographic and Clinical Characteristics

| Characteristic | |
|---|---|
| Total no. of patients | 275 |
| Cumulative patient months | 7,928 |
| Gender, F/M (%) | 116/159 (42.2/57.8) |
| Age at PD start, years±SD (range) | 56.3±16.8 (19.0–92.4) |
| Age at PD drop-out, years±SD (range) | 59.3±16.3 (21.7–93.2) |
| Dialysis vintage, months±SD (range) | 35.0±36.3 (0.3–210.9) |
| Predominant dialysis modality, *n* (%) | |
| Home CAPD | 105 (38.2) |
| Home APD | 106 (38.5) |
| In-center IPD | 64 (23.3) |
| Primary kidney disease, *n* (%) | |
| Diabetic nephropathy | 29 (10.6) |
| Renal vascular disease (excluding vasculitis) | 44 (16.1) |
| Glomerulonephritis | 76 (27.8) |
| Cystic kidney disease | 15 (5.5) |
| Interstitial nephritis; pyelonephritis, drug-induced; urolithiasis | 10 (3.7) |
| Cardiorenal syndrome | 18 (6.6) |
| Congenital and hereditary (excluding cystic) | 27 (9.9) |
| Other (including systemic diseases) | 32 (11.7) |
| Unknown | 20 (7.3) |
| Comorbidities | |
| Ischemic heart disease, *n* (%) | 97 (35.5) |
| LV dysfunction, *n* (%) | 103 (37.7) |
| Peripheral vascular disease, *n* (%) | 82 (30.0) |
| Malignancy, *n* (%) | 63 (23.1) |
| Diabetes mellitus, *n* (%) | 70 (25.6) |
| Collagen vascular disease, *n* (%) | 25 (9.2) |
| Significant other, *n* diseases±SD (range) | 0.83±0.81 (0–3) |
| Davies comorbidity score±SD (range) | 2.44±1.51 (0–6) |
| Immunosuppressive therapy, *n* (%) | |
| Glucocorticoids | 68 (25.8) |
| Rituximab | 6 (24.7) |
| Cyclophosphamide | 5 (2.2) |
| Other immunosuppressant | 36 (1.8) |
| Time to 1st peritonitis, months±SD (range) | 24.2±27.8 (0.1–122.9) |

PD = peritoneal dialysis; SD = standard deviation; APD = automated PD; CAPD = continuous ambulatory PD; IPD = intermittent PD; LV = left ventricular; post-cath = post-catheter insertion.

### TIME TO FIRST PERITONITIS, PERITONITIS INCIDENCE, RATE OF PERITONITIS-FREE PATIENTS, RATE OF CULTURE-NEGATIVE EPISODES

Median time to first peritonitis episode was 17 months and did not differ significantly between PD modalities ($p = 0.392$). Figure 1 depicts the corresponding Kaplan-Meier curve of cumulative peritonitis-free survival analysis for home CAPD, home APD, and in-center IPD patients.

Comparisons between methods 0 – 3 of peritonitis incidence, rate of peritonitis-free patients, and rate of culture-negative episodes, respectively, are summarized in Supplementary Table 1 and depicted in Figure 2. During the study period, 12 relapsing episodes occurred and were excluded from further analysis. In addition to 160 peritonitis episodes recorded as per ISPD guidelines (method 0), an extra 10, 17, and 27 episodes were recorded using methods 1, 2, and 3, respectively. Peritonitis incidence per patient-year at risk significantly increased from 0.24 ± 0.11 as per ISPD guidelines alone (method 0) to 0.26 ± 0.11 when including post-catheter insertion episodes (method 1, $p = 0.0395$), to 0.27 ± 0.11 when including episodes from IPD patients (method 2, $p = 0.0008$), and to 0.29 ± 0.11 when including both (method 3, $p < 0.0001$) (Figure 2A). Percentage of peritonitis-free patients decreased significantly from 85.7 ± 4.3 (method 0) to 84.6 ± 4.5 (method 1, $p = 0.0234$), 83.9 ± 4.9 (method 2,

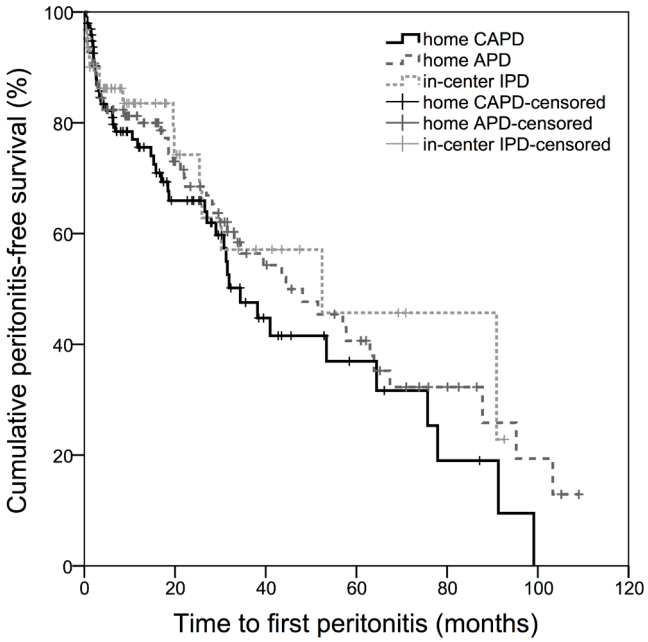


Figure 1 — Kaplan-Meier curve of cumulative peritonitis-free survival by peritoneal dialysis modality. Maximum follow-up was 120 months. APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; IPD = intermittent peritoneal dialysis.

$p = 0.0014$), and 82.8 ± 5.3 (method 3, $p < 0.0001$), respectively (Figure 2B). Regardless of the counting method, peritonitis incidence remained below the ISPD target of 0.5 episodes per patient-year for any given year during the study period (Figure 2A), whereas the rate of culture-negative episodes varied considerably and was above the 15% ISPD target most of the time (Figure 2C).

## PATHOGENIC ORGANISMS

Rates of various pathogenic organisms calculated as per different methods 0 – 3 are given in Supplementary Table 2. The spectrum of pathogenic organisms was fairly similar comparing methods 0 – 3, coagulase-negative *Staphylococcus* sp. accounting for most episodes (29.6% for method 0). When comparing episodes counted as per ISPD guidelines (method 0) directly with episodes in untrained patients (Figure 3), we found a significantly altered pathogen spectrum: additional episodes were significantly less likely to be due to coagulase-negative *Staphylococcus* sp., gram-positive organisms other than *Staphylococcus* sp., *Enterococcus* sp. or *Streptococcus* sp., gram-negative organisms other than *Pseudomonas* sp. or *E. coli*, and less likely to be polymicrobial. Most episodes in untrained patients were culture-negative, especially those post-catheter insertion (50%).

## OUTCOME OF PERITONITIS EPISODES

Patient and catheter outcome of all 187 peritonitis episodes (counted as per method 3) was analyzed and results are shown

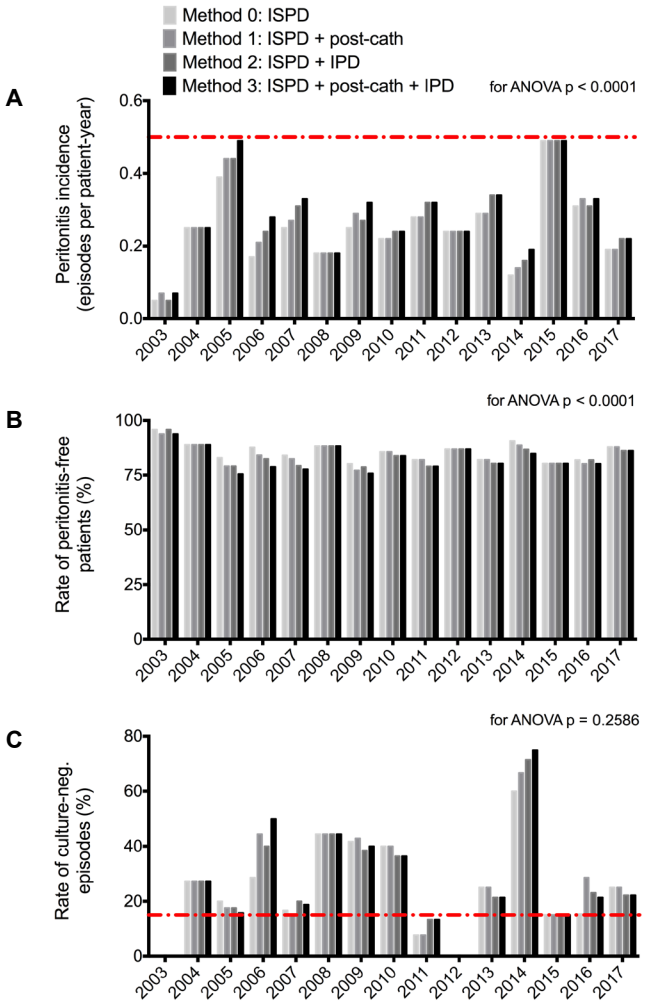


Figure 2 — Peritonitis incidence (A), rate of peritonitis-free patients (B), and rate of culture-negative episodes (C) during 15 consecutive years. Dotted lines in (A) and (C) represent thresholds as per ISPD 2016 recommendations. ISPD = International Society for Peritoneal Dialysis; IPD = intermittent peritoneal dialysis; post-cath = post-catheter insertion.

in Table 2. Outcome data on 1 peritonitis episode was not available because the patient was lost to follow-up. Of all peritonitis episodes, 155 (82.9%) resolved with antibiotic treatment. A total of 25 peritonitis episodes (13.4%) resulted in catheter removal, of which in 19 (10.2%) the patient was permanently transferred to HD, in 5 (2.7%) the patient continued PD with a new catheter, and in 1 case the patient did not require further renal replacement therapy (RRT) after catheter removal subsequent to peritonitis. There were no statistically significant differences between episodes counted as per ISPD (method 0) and additional episodes (Table 2).

With regard to differences between PD modality, IPD patients tended to have an increased rate of death after peritonitis (10.5%) compared with patients on home PD (2.4%, $p = 0.056$) and tended to have a lower rate of resolved episodes (68.4% vs 84.5%, $p = 0.077$), while rates of catheter removal and transfer to HD did not differ (data not shown).

PREDICTORS OF PERITONITIS

Univariate and multivariate analyses of patient predictors of peritonitis are shown in Table 3, where prevalence of characteristics are listed for patients without any episode of peritonitis ($n$ = 165) vs patients with at least 1 episode of peritonitis ($n$ = 108). Peritonitis episodes were counted as per method 3. Multivariate analysis was performed on variables with $p < 0.10$ (including gender, age at PD start, dialysis vintage, PD modality [home PD vs IPD], glomerulonephritis and cardiorenal syndrome as primary kidney diseases, and diabetes mellitus as comorbidity factor). The binary logistic regression model was statistically significant, $\chi^2 = 41.334$, $p < 0.001$. The model explained 25.8% (Nagelkerke $R^2$) of the peritonitis variance and correctly classified 69.6% of cases. Glomerulonephritis as primary kidney disease, being on home PD rather than being on IPD, and higher dialysis vintage were associated with an increased probability of experiencing peritonitis. All other variables were not statistically significant and were excluded from the model (Table 3).

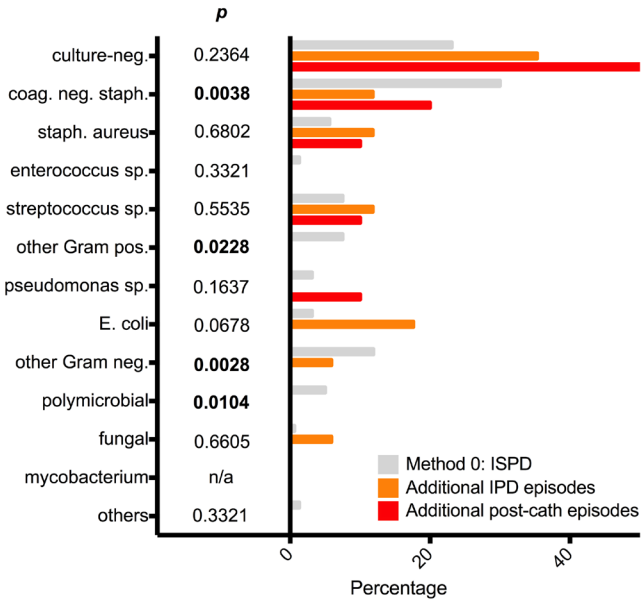


Figure 3 — Pathogenic organisms counted as per ISPD recommendations (method 0) compared with additional episodes in untrained patients. ISPD = International Society for Peritoneal Dialysis; IPD = intermittent peritoneal dialysis; n/a = not applicable (computation not possible due to identical values); post-cath = post-catheter insertion.

## DISCUSSION

In this study, we retrospectively analyzed peritonitis data prospectively collected over a 15-year period in our tertiary care center. We show that in our center, peritonitis incidence was significantly underestimated when computing statistics as per ISPD recommendations. We demonstrate that those episodes that would have been missed by statistics as per ISPD were present in 2 groups of patients: first, in patients who developed early peritonitis after catheter insertion but prior to PD training; and second, in patients on in-center IPD who—mostly due to their frailty and lack of autonomy—failed PD training. Furthermore, we demonstrate a significantly different pathogen spectrum in peritonitis episodes of untrained patients compared with conventionally counted episodes.

Interestingly, data on peritonitis in the first of these patient groups, i.e. early peritonitis after catheter insertion in untrained patients, are rather scarce. Indeed, there is substantial research on "early" peritonitis. However, definitions of early peritonitis vary substantially, ranging from 4 (19) or 8 weeks (20) up to several months (21–26) or even 1 year (27,28) post-catheter insertion, when a patient will most certainly have completed training. While aforementioned studies did not inform about training status of patients, Perl *et al.* touched on the issue of patient training and peritonitis risk and found that the overall risk of peritonitis was highest in the first 3 months of PD initiation (29). Herein, we demonstrate that including early episodes after catheter insertion but prior to training (method 1) into incidence statistics yielded a significant increase in peritonitis incidence compared with

TABLE 2
Outcome of Peritonitis Episodes

| Characteristic | All episodes ($n$=187) | Method 0 ($n$=160) $n$ (%) | Additional post-cath & IPD episodes ($n$=27) | $P$[a] |
|---|---|---|---|---|
| Resolved | 155 (82.9) | 135 (84.4) | 20 (74.1) | 0.266 |
| Catheter removal, transfer to HD | 19 (10.2) | 16 (10.0) | 3 (11.1) | 0.741 |
| Death | 6 (3.2) | 4 (2.5) | 2 (7.4) | 0.209 |
| Catheter change, PD continued | 5 (2.7) | 5 (3.1) | 0 (0.0) | 1.000 |
| Catheter removal, no RRT required | 1 (0.5) | 0 (0.0) | 1 (3.7) | 0.144 |
| Lost to follow-up | 1 (0.5) | 0 (0.0) | 1 (3.7) | 0.144 |

Post-cath = post-catheter insertion; IPD = intermittent peritoneal dialysis; HD = hemodialysis; PD = peritoneal dialysis; RRT = renal replacement therapy.
[a] Fisher's exact test for method 0 vs additional post-cath and IPD episodes.

TABLE 3
Patient Predictors of Peritonitis

| Characteristic | Peritonitis (–) *n*=165 | Peritonitis (+) *n*=108 | Univariate Odds ratio (95% CI) | *P* | Multivariate[c] Odds ratio (95% CI) | *P* |
|---|---|---|---|---|---|---|
| Gender (F/M), *n* (%) | 72/93 (43.6/56.4) | 43/65 (39.8/60.2) | 1.17[a] (0.72–1.92) | 0.532 | | |
| Age at PD start, years±SD | 58.7±16.8 | 52.5±16.3 | 0.98 (0.96–0.99) | 0.003 | 1.01 (0.98–1.03) | 0.532 |
| Dialysis vintage, months±SD | 21.9±27.7 | 47.4±40.9 | 1.02 (1.01–1.03) | <0.001 | 1.02 (1.01–1.03) | <0.001 |
| PD modality (home/IPD), *n* (%) | 117/48 (70.9/29.1) | 92/16 (85.2/14.8) | 0.42[b] (0.23–0.80) | 0.007 | 0.46[b] (0.21–0.99) | 0.048 |
| Primary kidney disease, *n* (%) | | | | | | |
| Diabetic nephropathy | 20 (12.3) | 9 (8.3) | 0.65 (0.28–1.49) | 0.308 | | |
| Renal vascular disease (excluding vasculitis) | 26 (16.0) | 18 (16.7) | 1.05 (0.55–2.03) | 0.876 | | |
| Glomerulonephritis | 34 (20.9) | 42 (38.9) | 2.41 (1.41–4.15) | 0.001 | 2.18 (1.10–4.32) | 0.026 |
| Cystic kidney disease | 9 (5.5) | 6 (5.6) | 1.01 (0.35–2.91) | 0.990 | | |
| Interstitial nephritis; pyelonephritis, drug-induced; urolithiasis | 5 (3.1) | 5 (4.6) | 1.53 (0.43–5.43) | 0.507 | | |
| Cardiorenal syndrome | 17 (10.4) | 1 (0.9) | 0.08 (0.01–0.61) | 0.015 | 0.14 (0.02–1.14) | 0.066 |
| Congenital and hereditary (excluding cystic) | 14 (8.6) | 13 (12.0) | 1.46 (0.66–3.23) | 0.356 | | |
| Other (including systemic diseases) | 23 (14.1) | 9 (8.3) | 0.55 (0.25–1.25) | 0.153 | | |
| Unknown | 15 (9.2) | 5 (4.6) | 0.48 (0.17–1.36) | 0.167 | | |
| Comorbidities | | | | | | |
| Ischemic heart disease, *n* (%) | 63 (38.2) | 34 (31.5) | 0.73 (0.44–1.22) | 0.229 | | |
| LV dysfunction, *n* (%) | 67 (40.6) | 36 (33.3) | 0.72 (0.43–1.19) | 0.198 | | |
| Peripheral vascular disease, *n* (%) | 48 (29.1) | 34 (31.5) | 1.10 (0.65–1.87) | 0.721 | | |
| Malignancy, *n* (%) | 35 (21.2) | 28 (25.9) | 1.28 (0.72–2.26) | 0.396 | | |
| Diabetes mellitus, *n* (%) | 50 (30.3) | 20 (18.5) | 0.51 (0.29–0.93) | 0.027 | 0.52 (0.23–1.15) | 0.151 |
| Collagen vascular disease, *n* (%) | 14 (8.5) | 11 (10.2) | 1.21 (0.53–2.77) | 0.657 | | |
| Significant other, *n* diseases±SD | 0.83±0.78 | 0.79±0.83 | 0.94 (0.69–1.28) | 0.685 | | |
| Immunosuppressive therapy, *n* (%) | 42 (25.5) | 29 (26.9) | 1.54 (0.31–7.79) | 0.600 | | |
| Glucocorticoids | 41 (24.8) | 27 (25.0) | 1.01 (0.58–1.77) | 0.977 | | |
| Rituximab | 3 (1.8) | 3 (2.8) | 1.54 (0.31–7.79) | 0.600 | | |
| Cyclophosphamide | 3 (1.8) | 2 (1.9) | 1.02 (0.17–6.20) | 0.984 | | |
| Other immunosuppressant | 18 (10.9) | 18 (16.7) | 1.63 (0.81–3.30) | 0.172 | | |
| Davies comorbidity score±SD | 2.49±1.47 | 2.30±1.57 | 0.92 (0.78–1.08) | 0.298 | | |

CI = confidence interval; PD = peritoneal dialysis; SD = standard deviation; IPD = intermittent PD; LV = left ventricular.
Prevalence of characteristics are listed for patients without any episode of peritonitis (*n*=165) vs patients with at least 1 episode of peritonitis (*n*=108). Two cases were excluded due to missing data. Peritonitis episodes were counted as per method 3.
[a] Odds ratio given for male gender (female gender served as reference).
[b] Odds ratios given for IPD (home PD served as reference).
[c] Variables entered into multivariate model: age at PD start, dialysis vintage, PD modality, glomerulonephritis, cardiorenal syndrome, diabetes mellitus.

method 0. Similarly, the importance of this specific patient subgroup was demonstrated for the first time by Ma *et al.*, who found that patients developing peritonitis post-catheter insertion and prior to PD training had significantly worse patient survival than control patients (30). This increased risk may be partly due to the sheer presence of a plastic foreign body. In a most recent study analyzing risk factors for peritonitis after kidney transplantation in patients with indwelling PD catheter, the authors found that not only PD catheter use, but also HD catheter use, within 6 weeks of kidney transplantation showed a marked increased risk of developing PD catheter-associated peritonitis (31), emphasizing that not only the need for PD catheter use, but also its mere presence as a plastic foreign body, is increasing peritonitis risk. Along those lines, ISPD

recommendations for prophylactic antibiotics to reduce post-catheter insertion peritonitis (17) underpin the increased risk once a connection between the abdominal cavity and the surrounding environment is made. In conclusion, we argue that peritonitis risk starts with catheter insertion. Peritonitis episodes prior to patient training are not of lesser importance to the specific center and, most importantly, to the specific patient and should therefore not be factored out.

In-center IPD patients constituted the second patient group with additional peritonitis episodes. In our center, we usually assess candidate suitability for a home-based therapy before considering in-center dialysis. Although we offer both home HD and home PD to all our patients, there still exist manifold factors such as patient preference, frailty, social status, serious comorbidities, training failure, etc. that might simply not allow a home-based approach in some patients. Therefore, we believe that in-center IPD offers the remarkable possibility of extending renal replacement therapy to some patients who otherwise would not be able to receive dialysis. We have been performing in-center IPD in our outpatient clinic since the 1990s and have previously described our experience with patient selection, peritonitis incidence, hospitalization rates, and survival of this PD subpopulation (16). Unfortunately, nationwide reimbursement for assisted APD is still lacking in Germany and negotiations with individual health insurance companies are time-consuming and oftentimes fail. Consequently, for patients that have failed HD and home PD, and in whom palliative care alone seems inappropriate, in-center IPD remains the only feasible treatment option. Traditionally, the proportion of IPD patients in our center has been comparatively high, as is underscored in this study, where 23.3% of patients during the 15-year study period were treated with an in-center IPD regimen. Unfortunately, there is noticeable scarcity of data on peritonitis in IPD patients (32). To the best of our knowledge, we herein present the largest experience with peritonitis incidence in an in-center IPD population.

Although, compared with home PD patients, IPD patients were significantly older (mean age at PD start was 69.8 years vs 52.0 years, $p < 0.0001$) and had substantially more comorbidities (Davies comorbidity score 3.17 vs 2.18, $p < 0.0001$), multivariate regression analysis showed that being on home PD, not on in-center IPD, was actually predictive for experiencing peritonitis. We hypothesize that this might be due both to a reduced number of connections of the PD catheter compared with home PD and to the fact that trained PD nurses were handling PD catheters instead of patients themselves. This would be in line with our previous observations that IPD patients can reach peritonitis incidence rates down to 1 peritonitis in 48.8 months (16), which equals about 0.25 episodes per patient-year at risk. Nevertheless, the finding of an increased peritonitis rate (method 2 vs method 0) together with a protective effect for peritonitis in multivariate analysis is counterintuitive. This might be explained, however, by the relatively larger effect a single peritonitis episode had on the incidence rate in IPD patients compared with home PD patients. The reason for this is that IPD patients—due to a poorer overall prognosis—had a significantly lower PD vintage compared with home PD patients, who were significantly younger and had significantly fewer comorbidities. Therefore, we cannot exclude that the higher PD vintage in home PD patients (representing time at risk) might have skewed multivariate analysis in favor of IPD patients.

Other patient predictors of peritonitis in univariate analysis included diabetes mellitus and glomerulonephritis as primary kidney disease. The predictive value of diabetes was lost in multivariate analysis, which might be due to the fact that a disproportionately high number of diabetics were actually IPD patients (data not shown). Also, data on diabetes mellitus as a risk factor for peritonitis are conflicting. Although it seems reasonable to consider diabetes as a risk factor for infections in general and several authors have found significantly increased risk (33), others have failed to do so (34,35). Of note, use of immunosuppressive medication was more than twice as common in patients with glomerulonephritis (42.1% of cases) as in patients with other primary kidney diseases (20.0% of cases, $p < 0.0001$). Still, in this cohort, immunosuppressive therapy was not predictive for peritonitis in univariate analysis. We therefore cannot exclude a confounding effect on multivariate analysis demonstrating glomerulonephritis to be an independent predictor for peritonitis.

Although patient numbers in our study were too small to demonstrate differences of peritonitis outcome between conventionally counted episodes (method 0) and episodes in untrained patients, we were able to show that peritonitis episodes in untrained patients demonstrated marked differences regarding pathogen spectrum. Overall, most peritonitis episodes were caused by coagulase-negative *Staphylococcus* sp., which is in keeping with reports from around the world (11,36–38). Episodes in untrained patients, though, demonstrated a markedly different distribution of pathogens. In particular, the high percentage of culture-negative episodes after catheter insertion but prior to PD training is not surprising considering that we used prophylactic vancomycin immediately before catheter insertion (39). We recognized an overall high variability in the rate of culture-negative episodes, which exceeded ISPD recommendations during most years. As a result, we have therefore changed our microbiology laboratory partner and now employ a method where we hang PD bags for 15 minutes prior to sampling with the idea that a certain degree of bacteria sedimentation might facilitate a higher yield of positive cultures.

Our study had several limitations. This was a single-center, retrospective cohort study. Our results may therefore not extrapolate to other centers, especially as many centers probably will not have such a substantial number of in-center IPD patients and given the lack of routine prophylactic antibiotic exit-site treatment in our center. However, data completeness and regularity are easier to control in a single-center study than with registry data. Moreover, data of all incident PD patients were prospectively collected. Compared with other studies, our sample size is relatively small. Still, we present

data on a 15-year period with consistent properties of treatment delivery.

In summary, peritonitis episodes after catheter insertion but prior to PD training as well as episodes in untrained patients such as in-center IPD patients should not be overlooked when computing peritonitis statistics, as incidence rates and pathogen spectrums may be distorted. Depending on local characteristics, additional episodes might represent a considerable proportion of overall peritonitis episodes of a specific PD center. Peritoneal dialysis practice patterns are enriched with, and sometimes based upon, experience and knowledge of exceptions from the rule. Not excluding peritonitis events in untrained patients from statistics might give PD centers new insights into their specific practice patterns.

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## DISCLOSURES

The authors have no financial conflicts of interest to declare.

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