Peritoneal Dialysis–Related Infection Rates and Outcomes: Results From the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)

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Rationale & Objective: Peritoneal dialysis (PD)-related peritonitis carries high morbidity for PD patients. Understanding the characteristics and risk factors for peritonitis can guide regional development of prevention strategies. We describe peritonitis rates and the associations of selected facility practices with peritonitis risk among countries participating in the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS).

Study Design: Observational prospective cohort study.

Setting & Participants: 7,051 adult PD patients in 209 facilities across 7 countries (Australia, New Zealand, Canada, Japan, Thailand, United Kingdom, United States).

Exposures: Facility characteristics (census count, facility age, nurse to patient ratio) and selected facility practices (use of automated PD, use of icodextrin or biocompatible PD solutions, antibiotic prophylaxis strategies, duration of PD training).

Outcomes: Peritonitis rate (by country, overall and variation across facilities), microbiology patterns.

Analytical Approach: Poisson rate estimation, proportional rate models adjusted for selected patient case-mix variables.

Results: 2,272 peritonitis episodes were identified in 7,051 patients (crude rate, 0.28 episodes/patient-year). Facility peritonitis rates were variable within each country and exceeded 0.50/patient-year in 10% of facilities. Overall peritonitis rates, in episodes per patient-year, were 0.40 (95% CI, 0.36-0.46) in Thailand, 0.38 (95% CI, 0.32-0.46) in the United Kingdom, 0.35 (95% CI, 0.30-0.40) in Australia/New Zealand, 0.29 (95% CI, 0.26-0.32) in Canada, 0.27 (95% CI, 0.25-0.30) in Japan, and 0.26 (95% CI, 0.24-0.27) in the United States. The microbiology of peritonitis was similar across countries, except in Thailand, where Gram-negative infections and culture-negative peritonitis were more common. Facility size was positively associated with risk for peritonitis in Japan (rate ratio [RR] per 10 patients, 1.07; 95% CI, 1.04-1.09). Lower peritonitis risk was observed in facilities that had higher automated PD use (RR per 10 percentage points greater, 0.95; 95% CI, 0.91-1.00), facilities that used antibiotics at catheter insertion (RR, 0.83; 95% CI, 0.69-0.99), and facilities with PD training duration of 6 or more (vs <6) days (RR, 0.81; 95% CI, 0.68-0.96). Lower peritonitis risk was seen in facilities that used topical exit-site mupirocin or aminoglycoside ointment, but this association did not achieve conventional levels of statistical significance (RR, 0.79; 95% CI, 0.62-1.01).

Limitations: Sampling variation, selection bias (rate estimates), and residual confounding (associations).

Conclusions: Important international differences exist in the risk for peritonitis that may result from varied and potentially modifiable treatment practices. These findings may inform future guidelines in potentially setting lower maximally acceptable peritonitis rates.

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Am J Kidney Dis. 76(1): 42-53. Published online January 10, 2020.

doi: 10.1053/j.ajkd.2019.09.016

Peritoneal dialysis (PD)-related peritonitis is the leading cause of a permanent transition to hemodialysis (HD).[1-3] Its occurrence is associated with hospitalization and death, increased PD-related treatment costs, and long-term adverse sequelae to peritoneal membrane structure and function.[4-8] The multistakeholder Standardised Outcomes in Nephrology–Peritoneal Dialysis (SONG-PD) study identified PD-related infection as part of a core outcome set for trials in patients receiving PD.[9,10]

Better understanding regarding the incidence and prevalence of PD peritonitis episodes in a contemporary representative cohort of patients is needed to develop and evaluate peritonitis prevention strategies. To date, the majority of reports of peritonitis are largely single center, using heterogeneous methods of data collection and variable reporting of peritonitis incidence and related factors.[11,12] A minority of national registries report peritonitis incidence.[11]

The Peritoneal Dialysis and Outcomes Practice Patterns Study (PDOPPS) is the largest international observational cohort study to collect detailed information in a uniform manner on the incidence of PD-related peritonitis and on peritonitis prevention practices and provides a platform for the prospective surveillance of peritonitis.[13] We report information on the incidence, facility variation, and microbiology of peritonitis across participating countries.

We also evaluated the impact of patient characteristics and treatment practices on the risk for peritonitis.

Methods

Data Source

PDOPPS is an international prospective cohort study designed to identify optimal practices for persons treated with maintenance PD. Study rationale and methods have been published.[13] Patients 18 years or older receiving maintenance PD were enrolled randomly from stratified random national samples of PD facilities treating at least 20 PD patients at the time of selection. Patients using hybrid (PD plus HD) therapy at study entry (primarily in Japan) were ineligible. This analysis included data from 2014 to 2017 from all countries presently participating in PDOPPS: Australia and New Zealand, Canada, Japan, Thailand, the United Kingdom, and the United States.

Patient demographics and comorbid conditions were captured at study enrollment. Peritonitis episode summaries (including causative organisms, if known) and hospitalizations (including diagnoses and procedures) were collected during study follow-up. Data were collected using uniform and standardized data collection tools, procedures, and processes. Data from patients receiving care at US large dialysis organization (LDO)-affiliated sites were provided as electronic files from each LDO; data from US non-LDO patients and patients from other PDOPPS countries were obtained by manual abstraction of data from medical charts and entry into a secure web-based data collection tool. PDOPPS was approved by a central institutional review board in the United States, with institutional review board study approval and informed patient consent obtained to meet national and local ethics committee regulations at each study site.

Outcome Definition

The primary outcome in this analysis was peritonitis, as recorded in the patient medical record and reported to PDOPPS by clinic staff. For each resolved peritonitis episode during PDOPPS follow-up, an infection worksheet capturing date of first presentation and causative organism (or culture-negative case) was completed. Peritonitis episodes were additionally ascertained from facility-reported hospitalizations that indicated a peritonitis diagnosis as a cause for the hospitalization. Peritonitis episodes ascertained from hospitalization records alone were assumed to have a first presentation date on the date of admission and unknown causative organism. Peritonitis episodes were included if they occurred after study entry and were ordered according to first presentation date. Relapsing episodes were defined as those occurring 22 to 50 days after a prior episode and: (1) both episodes were caused by the same organism, (2) either episode was reported as culture negative, or (3) both episodes had missing information regarding the causative organism. Recurrent episodes were defined as occurring 22 to 50 days apart and caused by a different (known) organism and were treated as a distinct peritonitis episode. We chose a 50-day threshold to reasonably align with International Society for Peritoneal Dialysis (ISPD) guidelines for defining relapsing and recurrent peritonitis, within the availability and limitations of our data. Relapsing peritonitis episodes were excluded when estimating peritonitis rates, whereas recurrent peritonitis episodes were included.[14] Outcomes secondary to peritonitis included hospitalization and concomitant exit-site infections, ascertained from the infection worksheet or facility-reported hospitalization data.

Statistical Methods

Unadjusted peritonitis rates by country were estimated using the total count of reported peritonitis episodes divided by total patient follow-up time. Comparisons of overall peritonitis rates by country used the United States as the common reference group and differences were assessed using the Dunnett method. Crude facility peritonitis rates were estimated using the total count of peritonitis episodes reported in the facility divided by total patient follow-up time in the facility. Peritonitis time at risk for each patient started at PDOPPS entry and continued until the earliest of the following: end of the study period for which data collection was expected for the patient (ie, administrative censoring), patient departure from the study (censored at transfer to another facility, transplantation, withdrawal, etc), transfer to HD for more than 84 days (censored at the date of transfer), or death.

Proportional-rates models[15] stratified by country were used to estimate associations (rate ratios [RRs] with 95% confidence intervals [CIs]) of peritonitis events with the following facility characteristics and practices: number of PD patients, facility age, percentage of patients using automated PD (APD) modality, icodextrin-based or neutral pH, low glucose-degradation product (GDP) PD solution, nurse to patient ratio, use of antibiotic prophylaxis at catheter insertion, exit-site prophylaxis strategy, and facility-reported duration (days) of PD training. Crude models included only the factor listed and random intercept terms to control for possible within-facility clustering of outcomes. Patient case-mix–adjusted models included age, sex, black race (United States only; entered as an interaction between race and an indicator for the US sample), kidney replacement therapy vintage, serum albumin concentration, 24-hour urine volume, and indicators of cardiovascular disease (ie, any history of coronary artery disease, congestive heart failure, cerebrovascular disease, or peripheral vascular disease at PDOPPS study entry), diabetes, gastrointestinal bleeding, and HD before PD. PD training duration (in days) was additionally adjusted for training hours (per day) to distinguish these components of total training time. RRs are reported separately for each country (1 model, interacting country indicators with facility factors) and across all countries (1 model, stratified by country). Associations of peritonitis risk with PD training duration are further stratified by

incident (<6 months using PD) versus prevalent (≥6 months) patients.

Missing data were imputed using the chained-equations method as implemented with IVEware for SAS.[16] Ten imputations each were performed for facility- and patient-level variables and merged according to replicate number. Rate regression models were fitted separately for each imputed data set, with results then combined using the Rubin method[17] implemented in SAS MIANALYZE.

Data analyses were performed using SAS, version 9.4 (SAS Institute).

Results

The analysis included 209 facilities and 7,051 patients. Mean patient ages were 56 years in Thailand; 58 to 61 years in the United States, Canada, and United Kingdom; and 63 to 64 years in Australia/New Zealand and Japan (Table 1). Kidney replacement therapy vintage by country was highest in Japan (median, 1.3 [interquartile range, 0.3-3.6] years) and the United States (median, 1.3 [IQR, 0.6-3.2] years). In Thailand, serum albumin levels (mean, 3.2 ± 0.8 [SD] g/dL) were slightly lower and 24-hour urine volume (median, 0.40 [IQR, 0.08-0.80] L) was noticeably lower than in the other study countries (mean albumin range, 3.3-3.5 g/dL; median urine volume range, 0.76-1.20 L). Cardiovascular disease (25%-51% by country) and diabetes (27%-51% by country) were commonly reported comorbid conditions.

APD was the predominant PD modality in all countries except Thailand (0% in 15 of 22 facilities) and Japan (median facility proportion, 39% of patients; IQR, 18%-57%; Table 1). There was essentially no use of icodextrin-based solutions in Thailand (0% in 19 of 22 facilities) and low use in US non-LDO facilities (median facility proportion, 11% of patients; IQR, 0%-45%); at least half of the facilities in the other countries used icodextrin-based solutions for >40% of their patients. Similarly, there was essentially no use of low-GDP neutral-pH solutions in Thailand or US non-LDO facilities. All facilities in Japan reported using low-GDP neutral-pH solutions in ≥90% of patients. Across the other countries, use of low-GDP neutral-pH solutions in the median facility ranged from 5% to 11% of patients. Use of antibiotic prophylaxis at catheter insertion was very common across countries (>80%) except for the United States (64%). Exit-site maintenance prophylaxis was common (>65%) except in Japan (3%) and Thailand (27%). Specific strategies varied by country, but primarily involved applying topical aminoglycoside or mupirocin.

Across all countries, we observed 2,272 peritonitis episodes during 7,876 years of follow-up. Overall country-specific peritonitis rates ranged from 0.26 to 0.29 episode/patient-year in the United States, Japan, and Canada to 0.35 to 0.40 episode/patient-year in Australia/New Zealand, the United Kingdom, and Thailand (Table 2). However, broad and overlapping variability in facility peritonitis rates was observed among Australia/New Zealand (IQR, 0.27-0.50 episode/patient-year), Canada (IQR, 0.20-0.32 episode/patient-year), Japan (IQR, 0.18-0.38 episode/patient-year), Thailand (IQR, 0.29-0.49 episode/patient-year), the United Kingdom (IQR, 0.22-0.60 episode/patient-year), and the United States (IQR, 0.14-0.33 episode/patient-year; (Fig 1). Peritonitis rates higher than the ISPD guideline limit of 0.50/patient-year were estimated for 10% of facilities overall, in 18% of Thai facilities, 22% of Australia/New Zealand facilities, and 33% of UK facilities. Gram-positive peritonitis rates in the United Kingdom and Australia/New Zealand facilities were 0.14/patient-year. Thai facilities reported a Gram-negative peritonitis rate of 0.12/patient-year and reported a culture-negative rate of 0.11/patient-year. Relapsing peritonitis was observed for 148 episodes; the most commonly associated organisms were coagulase-negative *Staphylococcus* and *Staphylococcus aureus*. Organism type was not specified in 18% of relapse episodes (Table S1).

The percentage of peritonitis episodes with a hospitalization involving a peritonitis diagnosis within 14 days of onset is shown in Table 3. Median length of stay was less than 1 week in all countries except Japan (median, 18; IQR, 13-36 days) and Thailand (median, 11; IQR, 5-20 days). In Japan and the United Kingdom, 19% to 20% of peritonitis episodes had a concomitant exit-site infection reported; this was 6% to 10% in the other countries.

Associations (rate ratios and 95% confidence intervals) of facility factors with all-cause peritonitis are shown in Table 4. In analyses combining data from all countries, lower peritonitis RRs were observed in facilities with a greater proportion of patients using APD (RR per 10 percentage points greater, 0.95; 95% CI, 0.91-1.00), facilities using antibiotic prophylaxis at PD catheter insertion (RR vs none [Australia/New Zealand, Japan, Thailand, and United States only; contrast not estimable for Canada or the United Kingdom], 0.83; 95% CI, 0.69-0.99), and in facilities using a training duration of 6 or more days (RR vs <6 days [Australia/New Zealand, Canada, Japan, Thailand, and United States only; contrast not estimable for the United Kingdom], 0.81; 95% CI, 0.68-0.96). Lower peritonitis risk was seen in facilities that used topical exit-site mupirocin or aminoglycoside ointment, but this association did not achieve conventional levels of statistical significance (RR vs no prophylaxis [Canada, Thailand, United Kingdom, and United States only; contrast not estimable for Australia/New Zealand or Japan], 0.79; 95% CI, 0.62-1.01). Associations with other facility factors were weaker. Variability in the country-specific associations was noted for facility size and percentage of APD use ($P<0.001$ and $P = 0.01$, respectively, for interaction by country). Associations of potential confounding variables (patient-level) with peritonitis are provided in Table S2. Serum albumin level and residual urine volume were associated with lower peritonitis rate; black race (United States only), male sex, heart disease, gastrointestinal

Table 1. Patient and Facility Characteristics and Facility-Reported Practices, by Country

	Australia/NZ	Canada	Japan	Thailand	UK	US	Missing
Patient Characteristics							
No. of patients	510	917	818	829	342	3,635	
Patient age, y	63 (14)	61 (15)	64 (13)	56 (14)	61 (15)	58 (15)	0%
KRT vintage, y	1.0 [0.3-2.1]	0.8 [0.1-2.0]	1.3 [0.3-3.6]	1.0 [0.2-2.8]	0.8 [0.2-2.4]	1.3 [0.6-3.2]	3% (1%-11%)
Albumin, g/dL	3.3 (0.5)	3.4 (0.5)	3.3 (0.5)	3.2 (0.8)	3.4 (0.6)	3.5 (0.5)	4% (0%-12%)
24-h urine volume, L	0.90 [0.42-1.36]	1.00 [0.50-1.52]	0.76 [0.34-1.30]	0.40 [0.08-0.80]	1.20 [0.71-1.77]	0.80 [0.40-1.33]	42% (18%-80%)
Prior HD experience[a]	20%	25%	12%	28%	15%	40%[a]	32% (13%-44%)[a]
Black race[b]	NA	NA	NA	NA	NA	25%	0%
Male sex	67%	62%	67%	50%	65%	56%	0%
Comorbid conditions							
CVD	51%	49%	44%	25%	44%	40%	1% (1%-3%)
Diabetes	44%	48%	40%	49%	27%	51%	1% (1%-3%)
GI bleeding	2%	4%	2%	2%	2%	1%	2% (1%-4%)
Facility Characteristics							
No. of facilities	17	20	29	22	18	103	
Size, no. of patients	55 [52-82]	51 [40-90]	30 [23-36]	102 [48-208]	51 [33-65]	31 [24-42]	0%
Years in operation	26 [20-30]	26 [16-34]	26 [24-31]	8 [7-10]	31 [25-35]	13 [8-24]	19% (0%-47%)
Proportion of patients using APD	60% [52%-79%]	78% [64%-87%]	39% [19%-57%]	0% [0%-7%]	64% [54%-87%]	88% [74%-95%]	4% (0%-11%)
Proportion of patients using icodextrin-based solution	42% [33%-68%]	44% [33%-94%]	48% [35%-64%]	0% [0%-0%]	65% [50%-83%]	11% [0%-45%][a]	5% (0%-17%)[a]
Proportion of patients using low-GDP neutral-pH solution	11% [0%-29%]	5% [0%-11%]	100% [100%-100%][c]	0% [0%-4%]	8% [0%-35%]	[d]	5% (0%-17%)
PD patients per nurse	12 [10-18]	15 [11-17]	6 [3-8]	38 [19-49]	8 [6-9]	11 [8-14]	11% (0%-18%)
Antibiotic prophylaxis at catheter insertion	82%	100%	89%	86%	100%	64%	22% (0%-44%)
Exit-site prophylaxis strategy							22% (0%-42%)
Topical aminoglycoside	0%	10%	4%	5%	0%	72%	
Topical mupirocin	53%	50%	0%	23%	47%	13%	
Other[e]	41%	20%	0%	0%	24%	5%	
None	6%	20%	96%	73%	29%	10%	
Duration of PD training							8% (5%-12%)
2-3 d	31%	22%	43%	19%	38%	13%	
4-5 d	54%	56%	17%	52%	63%	21%	
6+ d	15%	22%	39%	29%	0%	67%	

Note: Values shown as mean (standard deviation), median [interquartile range], or percentage of patients or facilities. Missing percentages are reported as overall (range across countries). Australia/NZ includes 15 sites from Australia and 2 sites from New Zealand.

Abbreviations: APD, automated peritoneal dialysis; CVD, cardiovascular disease; GDP, glucose-degradation product; GI, gastrointestinal; HD, hemodialysis; KRT, kidney replacement therapy; NA, not applicable; NZ, New Zealand; PD, peritoneal dialysis; UK, United Kingdom; US, United States.

[a]Excluding 77 US large dialysis organization–affiliated facilities from which prior HD experience was not available.

[b]United States only.

[c]100% of Japanese facilities reported using low-GDP neutral-pH solutions in ≥90% of patients.

[d]Low GDP neutral-pH solutions are not commercially available in the United States.

[e]Includes intranasal mupirocin (Australia/NZ, Canada, United Kingdom, and United States), topical medihoney (Australia/NZ only), and topical polysporin (Canada only).

Table 2. Overall and Organism Class-Specific Peritonitis Rates, Episodes per Patient-Year, by Country

Country	Australia/NZ	Canada	Japan	Thailand	UK	US
No. of peritonitis episodes	187	393	345	258	120	969
Time at risk, person-y	534.8	1,376.8	1257.1	639.6	314.1	3,754.6
Peritonitis rate/person-y (95% CI)	0.35 (0.30-0.40)[a]	0.29 (0.26-0.32)[b]	0.27 (0.25-0.30)	0.40 (0.36-0.46)[a]	0.38 (0.32-0.46)[a]	0.26 (0.24-0.27)
Gram-positive	0.14 (39%)	0.13 (45%)	0.10 (37%)	0.10 (26%)	0.14 (38%)	0.10 (37%)
Gram-negative	0.07 (20%)	0.05 (16%)	0.04 (13%)	0.12 (29%)	0.07 (19%)	0.03 (13%)
Culture-negative	0.05 (14%)	0.04 (16%)	0.06 (21%)	0.11 (28%)	0.05 (14%)	0.04 (16%)
Polymicrobial	0.04 (10%)	0.03 (9%)	0.02 (8%)	0.02 (4%)	0.03 (8%)	0.01 (5%)
Yeast	0.01 (3%)	0.01 (2%)	<0.01 (1%)	0.01 (2%)	0.01 (3%)	<0.01 (1%)
Other	0.05 (14%)	0.03 (11%)	0.05 (19%)	0.05 (12%)	0.07 (19%)	0.07 (28%)
Coagulase-negative *Staphylococcus*	0.052 (15%)	0.045 (16%)	0.014 (5%)	0.023 (6%)	0.048 (13%)	0.054 (21%)
Staphylococcus aureus	0.034 (10%)	0.034 (12%)	0.025 (9%)	0.027 (7%)	0.054 (14%)	0.017 (7%)
Pseudomonas aeruginosa	0.009 (3%)	0.007 (3%)	0.009 (3%)	0.009 (2%)	0.022 (6%)	0.004 (2%)

Note: Unadjusted rates and 95% CIs based on total event counts and person-years at risk in each country. Values in parentheses represent percent of episodes within country, unless stated otherwise.
Abbreviations: CI, confidence interval; NZ, New Zealand; UK, United Kingdom; US, United States.
[a]$P < 0.05$ and
[b]$P < 0.10$ versus United States after Dunnett adjustment for multiple comparisons against a common reference group.

bleeding, and previous HD experience were associated with higher peritonitis rate.

Discussion

In a cohort of patients receiving PD across 7 countries spanning 209 facilities, the median facility peritonitis rate was 0.26 episode/patient-year, with broad and overlapping variation in peritonitis rates among facilities within each country. Peritonitis rates were 0.35 to 0.40/patient-year in Thailand, the United Kingdom, and Australia/New Zealand and 0.26 to 0.29/patient-year in Canada, Japan, and the United States. More than two-thirds of peritonitis episodes were associated with a hospitalization.

Prior multicenter published reports of peritonitis rates include the Peritonitis Organism Exit Site Tunnel Infections (POET) Clinical Monitoring System developed by Baxter Healthcare, which captured 4,028 peritonitis episodes among 9,655 patients across 35 US and 26 Canadian centers between 1998 and 2004 and reported overall peritonitis rates of 0.37 episode/year among US patients, and 0.43 episode/year among Canadian patients.[18] Those rates are higher than the more recent peritonitis rates seen in the present study. It is possible that differences in peritonitis rates in the POET database compared with the present study reflect improvements in peritonitis prevention strategies over time. In the initial POET analysis, relapsing and recurrent peritonitis episodes were included as independent events. However, a follow-up study among Canadian patients estimated a peritonitis rate of 0.37 episode/year, excluding relapsing/recurrent episodes, which is still higher than for Canadian patients in the present study.[19] Peritonitis rates in the Australian registry (0.35 episode/year during a similar period to the PDOPPS data collection) were similar to those seen in Australia in the present study. The Australian registry and the present study used similar peritonitis definitions, methodology, and reporting, which may explain the congruent results.[1] The Japanese Renal Dialysis Registry reported a peritonitis rate of 0.21 episode/patient-year for 2014, slightly lower than we observed in Japan; however, this may reflect difficulties with retrospective data capture (as done by the Japanese Renal Dialysis Registry) rather than prospective data collection (as in the present study).[20] The UK Renal Registry reported a 2-year peritonitis rate for England at 0.45 episode/patient year between 2016 and 2017, which was higher than that observed in the present study, but this may reflect differences in the definitions used for peritonitis ascertainment and the fact that facilities participating in PDOPPS may be somewhat different in terms of peritonitis risk.[21]

Although the ISPD states that overall peritonitis rates as high as 0.5 episode/patient-year may be acceptable, the present findings should inform future guidelines in potentially setting lower maximally acceptable peritonitis rates.[14] However, >10% of facilities in the present study

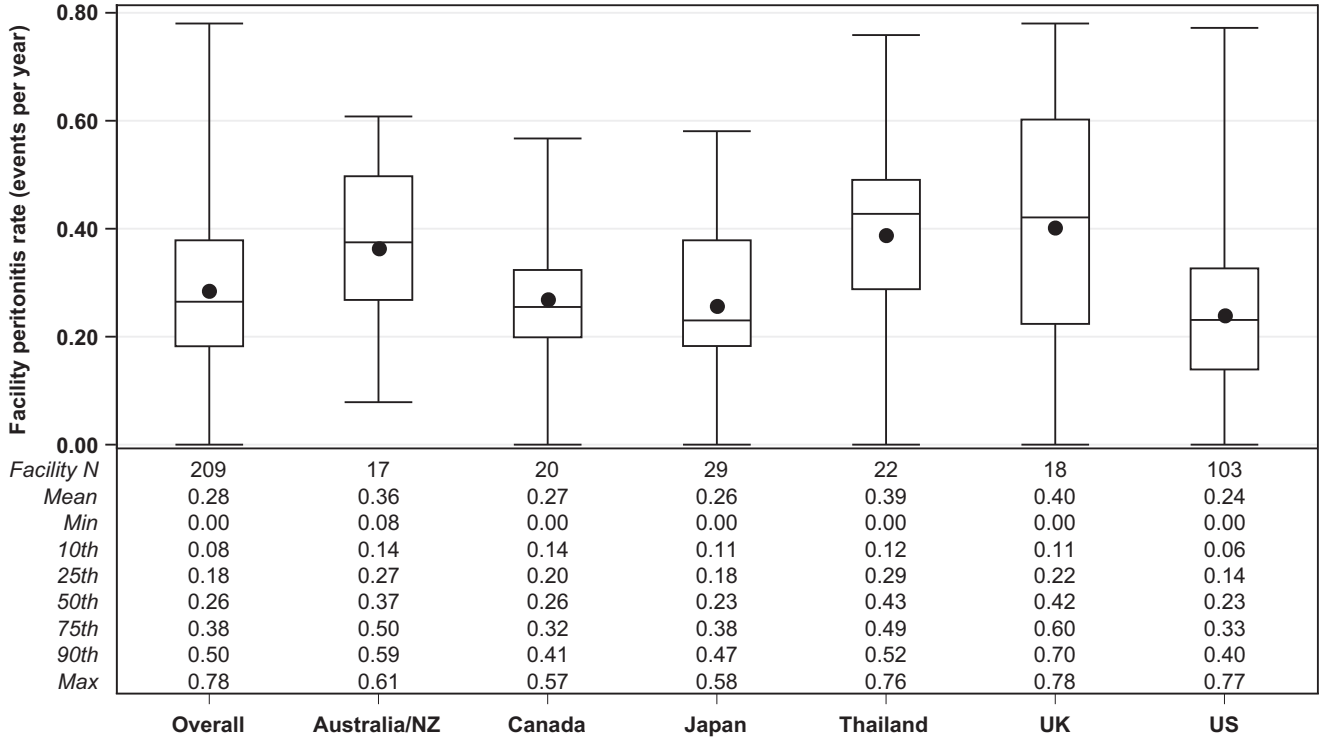

Figure 1. Distribution of facility peritonitis rates by country. Circle markers denote mean values. Boxes extend to 25th and 75th percentiles. Whiskers extend to minimum and maximum values. Abbreviations: NZ, New Zealand; UK, United Kingdom; US, United States.

had peritonitis rates that were higher than guideline recommendations. Thailand, a country in which a "PD first" policy has been enforced[22] with more limited resources, was able to achieve a median facility peritonitis rate of 0.43 episode/year, although 18% of Thai facilities in our study had peritonitis rates higher than the ISPD guideline limit. Lower peritonitis rates in Japan may reflect the tendency for better practice and better outcomes among dialysis patients in Japan than in other countries, as seen over several decades for HD patients.[23-25] Alternatively, lower peritonitis rates in Japan may reflect the impact of more stringent patient selection for PD given that PD use in Japan is lowest among all PDOPPS countries at 2.9% of all dialysis therapy.[26]

In Thailand, Gram-negative peritonitis rates exceeded Gram-positive rates. This likely reflects under-recognition of Gram-positive episodes, driven by a disproportionately high rate of culture-negative peritonitis in Thailand of 0.11 episode/year (28%), a rate almost double that in the United States, United Kingdom, and Canada. The ISPD recommends that if >15% of peritonitis episodes are culture-negative, sampling and culture methods should be

Table 3. Peritonitis-Related Events, Percent of Cases, by Country

	No. of Peritonitis Episodes	Proportion of Peritonitis Episodes With Hospitalization[a]	Median Hospitalization LOS, d[a]	Proportion of Episodes With Concomitant Exit-Site Infection
Australia/NZ	187	75.9%	5 [3-11]	9.6%
Canada	393	51.7%	6 [3-13]	9.2%
Japan	345	87.8%	18 [13-36]	19.1%
Thailand	258	78.7%	11 [5-20]	6.2%
UK	120	64.7%	5 [3-12]	20.8%
US[b]	386	54.7%	6 [3-11]	8.5%

Note: Hospitalization for peritonitis defined as inpatient admission or observation stay in which peritonitis was reported as a primary or auxiliary diagnosis within 14 days of a peritonitis episode.
Abbreviations: LOS, length of stay; NZ, New Zealand; UK, United Kingdom; US, United States.
[a]N=10 peritonitis events excluded from denominator due to missing hospitalization data in reporting facility. Values in brackets are interquartile ranges.
[b]Excludes 583 episodes in 77 US large dialysis organization facilities.

Table 4. Associations of Facility Factors With Patient-Level Peritonitis Rates, by Country

	Crude Association	Adjusted for Patient Factors	
	RR (95% CI)	RR (95% CI)	*P* for Country Interaction
Facility size, per 10 pts greater			
All countries	1.00 (0.99-1.01)	1.00 (0.99-1.01)	
Australia/NZ	1.03 (1.00-1.07)	1.03 (0.99-1.06)	<0.001
Canada	0.97 (0.94-1.00)	0.97 (0.94-1.00)	
Japan	1.07 (1.04-1.10)	1.07 (1.04-1.09)	
Thailand	1.00 (0.99-1.01)	1.00 (0.99-1.01)	
UK	1.01 (0.90-1.14)	1.00 (0.87-1.13)	
US	1.03 (1.00-1.06)	1.02 (1.00-1.05)	
Facility time in operation, per 5 y greater			
All countries	1.01 (0.98-1.05)	1.01 (0.97-1.04)	
Australia/NZ	1.00 (0.86-1.15)	0.99 (0.86-1.14)	0.2
Canada	1.02 (0.97-1.08)	1.02 (0.96-1.07)	
Japan	0.91 (0.78-1.05)	0.90 (0.77-1.05)	
Thailand	0.87 (0.76-1.00)	0.88 (0.77-1.02)	
UK	0.91 (0.73-1.13)	0.90 (0.72-1.14)	
US	1.05 (1.00-1.10)	1.04 (1.00-1.09)	
Facility proportion of pts using APD, per 10 pp greater			
All countries	0.95 (0.91-1.00)	0.95 (0.91-1.00)	
Australia/NZ	0.87 (0.80-0.94)	0.87 (0.80-0.96)	0.01
Canada	0.88 (0.81-0.95)	0.87 (0.80-0.93)	
Japan	1.02 (0.93-1.12)	1.02 (0.92-1.13)	
Thailand	0.87 (0.74-1.02)	0.87 (0.73-1.03)	
UK	0.95 (0.86-1.04)	0.95 (0.85-1.05)	
US	0.99 (0.94-1.05)	1.00 (0.95-1.06)	
Facility % of pts using icodextrin-based solution, per 10 pp greater[a]			
All countries	1.02 (0.99-1.06)	1.02 (0.98-1.05)	
Australia/NZ	1.09 (0.97-1.22)	1.10 (0.97-1.24)	0.3
Canada	1.00 (0.95-1.06)	1.00 (0.95-1.05)	
Japan	1.02 (0.92-1.13)	1.02 (0.92-1.14)	
UK	1.00 (0.92-1.08)	1.00 (0.92-1.09)	
US	1.04 (1.01-1.07)	1.01 (0.97-1.05)	
Facility % of pts using low-GDP neutral-pH solution, per 10 pp greater[a]			
All countries	1.02 (1.00-1.05)	1.03 (1.00-1.05)	
Australia/NZ	1.09 (1.05-1.13)	1.08 (1.03-1.13)	0.2
Canada	1.02 (1.00-1.04)	1.03 (1.01-1.05)	
UK	0.98 (0.89-1.06)	0.98 (0.89-1.08)	
PD pts per nurse, per 5 pts greater			
All countries	1.00 (0.99-1.01)	1.00 (0.99-1.01)	
Australia/NZ	1.03 (0.95-1.12)	1.03 (0.94-1.12)	0.4
Canada	0.95 (0.84-1.08)	0.94 (0.85-1.04)	
Japan	0.97 (0.80-1.19)	0.96 (0.78-1.19)	
Thailand	1.00 (0.99-1.02)	1.00 (0.99-1.02)	
UK	0.86 (0.69-1.08)	0.84 (0.69-1.03)	
US	0.98 (0.89-1.08)	0.96 (0.86-1.06)	
Facility % exit-site prophylaxis strategy (vs none)[b]			
Topical aminoglycoside or mupirocin			
All countries	0.81 (0.63-1.03)	0.79 (0.62-1.01)	
Canada	0.75 (0.44-1.26)	0.79 (0.46-1.35)	0.6
Thailand	0.75 (0.42-1.34)	0.78 (0.43-1.42)	
UK	1.17 (0.67-2.05)	1.17 (0.64-2.11)	
US	0.79 (0.56-1.13)	0.73 (0.52-1.03)	

(Continued)

Table 4 (Cont'd). Associations of Facility Factors With Patient-Level Peritonitis Rates, by Country

	Crude Association	Adjusted for Patient Factors	
	RR (95% CI)	RR (95% CI)	*P* for Country Interaction
Other prophylactic strategies			
All countries	0.96 (0.70-1.32)	0.93 (0.68-1.28)	
Canada	1.01 (0.57-1.80)	0.98 (0.55-1.75)	0.9
UK	1.05 (0.52-2.14)	1.02 (0.47-2.21)	
US	0.89 (0.58-1.36)	0.87 (0.57-1.32)	
Facility use of antibiotic prophylaxis at catheter insertion[c]			
All countries	0.84 (0.70-1.01)	0.83 (0.69-0.99)	
Australia/NZ	0.70 (0.45-1.09)	0.62 (0.40-0.94)	0.5
Japan	0.70 (0.47-1.05)	0.74 (0.46-1.19)	
Thailand	0.90 (0.49-1.64)	0.80 (0.47-1.35)	
US	0.89 (0.71-1.11)	0.89 (0.72-1.09)	
Facility duration of PD training ≥6 d (vs <6 d)			
All countries	0.83 (0.69-0.98)	0.81 (0.68-0.96)	
All countries, incident patients[d]	0.82 (0.62-1.09)	0.84 (0.62-1.12)	
All countries, prevalent patients[d]	0.82 (0.67-1.00)	0.81 (0.66-0.98)	
Australia/NZ	0.66 (0.30-1.43)	0.64 (0.26-1.57)	0.7
Canada	0.63 (0.38-1.06)	0.69 (0.44-1.09)	
Japan	1.01 (0.65-1.56)	1.01 (0.64-1.58)	
Thailand	0.86 (0.58-1.27)	0.88 (0.57-1.35)	
US	0.82 (0.67-1.01)	0.78 (0.64-0.95)	

Note: Estimates obtained using separate proportional-rates models for each facility factor, stratified by country and adjusted for patient-level age, sex, KRT vintage, prior hemodialysis experience, black race (United States only), serum albumin level, 24-hour urine volume, cardiovascular disease, diabetes, and gastrointestinal bleeding. Facility duration of PD training was additionally adjusted for training hours per day.

Abbreviations: APD, automated peritoneal dialysis; CI, confidence interval; GDP, glucose degradation product; KRT, kidney replacement therapy; NZ, New Zealand; PD, peritoneal dialysis; pp, percentage points; pt, patient; RR, rate ratio; UK, United Kingdom; US, United States.

[a]PD solution type not captured among US large dialysis organization–affiliated sites, low-GDP neutral-pH solutions not commercially available in the United States, <5% of facilities in Thailand used icodextrin-based or low-GDP neutral-pH solutions, and all Japanese facilities reported using low-GDP neutral-pH solutions in >90% of patients.

[b]Zero percent of facilities in Japan and Thailand reported predominant use of "other" exit-site prophylaxis, and <5% of facilities in Australia/NZ reported no exit-site prophylaxis (reference category). Other prophylactic strategies include intranasal mupirocin (Canada, United Kingdom, and United States) and topical polysporin (Canada only).

[c]Of facilities in Canada and the United Kingdom, 100% reported use of antibiotic prophylaxis at PD catheter insertion.

[d]Incident defined as less than 6 months with KRT initiation; prevalent defined as 6-plus months with KRT.

reviewed and improved.[14] It is likely that Thailand faces geographic and resource challenges that limit processing of PD effluent samples in a timely manner and in accordance with ISPD guidelines. A previous audit at a single Thai center revealed that culture-negative peritonitis was reported for 43% of episodes.[27] This may be due to suboptimal culture methods and/or the impact of antibiotic exposure before a PD peritonitis episode in Thailand, particularly where over-the-counter antibiotics are readily available. Better understanding of PD effluent culture sampling and adherence to international recommendations on diagnostic methods may reduce rates of culture-negative peritonitis.

Peritonitis-related hospitalization events were observed for 76% to 88% of episodes in Australia/New Zealand, Japan, and Thailand and 52% to 55% in the United States and Canada. Hospitalization for peritonitis substantially adds to peritonitis-related treatment costs and may be a marker of peritonitis severity in many cases. In keeping with findings in other countries and reports, peritonitis-related hospitalization occurred in 65% of peritonitis-treated patients in France.[28] Similarly, 61% of study patients with peritonitis were hospitalized in the BALANZ study in Australia, New Zealand, and Oceania.[29,30] The high hospitalization rate in Japan suggests a potentially lower threshold to admit patients coupled with a medical culture to preferentially address dialysis-related complications through hospitalization. In Japan, developing effective outpatient protocols for peritonitis treatment and ready and prompt access to home-administered intraperitoneal antibiotics may reduce the costs associated with peritonitis treatment and PD therapy. Most Thai patients live in rural and remote areas and have low levels of education and income, which limits their ability to pick up antibiotic-added PD solutions from the PD clinic every day. Most physicians believe it is appropriate to admit the patients until a primary response (resolution of chief concern and clearing of PD fluid cell count) is obtained and then refer to a networked primary hospital nearer to the patient's home for further care.

Center size (number of PD patients) was not associated with higher peritonitis risk except in Japan. Although larger

center size has been strongly associated with lower risk for technique failure,[31-34] its impact on the risk for peritonitis or peritonitis-related complications is less clear. In a recent study in Australia, larger center size was not found to be associated with improved peritonitis outcomes.[35] PD facility age and the patient-to-nurse ratio, two potential proxies for center experience, were not associated with peritonitis risk. Given that the PDOPPS sample is restricted to clinics treating at least 20 PD patients, we could not explore the risk for peritonitis among small clinics. Smaller clinics may have a higher peritonitis risk, although no difference in risk was seen across the wide range of clinic sizes recruited in the present study. The higher peritonitis rate with increasing clinic size in Japan may relate to less stringent eligibility criteria for PD as center size increases, enriching larger facilities with patients having characteristics that may increase peritonitis risk.

Higher facility APD use was associated with lower peritonitis risk across all countries, but particularly in Australia/New Zealand and Canada. There have been conflicting reports regarding the association between APD and peritonitis risk in the published literature.[36-44] The lower number of connections with APD compared with continuous ambulatory PD may minimize opportunities for touch contamination, thereby reducing the risk for peritonitis. However, differences in patient selection for APD versus continuous ambulatory PD and center characteristics for those treating more patients with APD may limit interpretation of our study and related publications.

We did not see a relationship between increasing facility icodextrin use and risk for peritonitis. This is reassuring because icodextrin may be associated with increased risk for sterile peritonitis, the incidence of which seems to have dramatically decreased over time.[45,46] Moreover, icodextrin use has not been shown to improve resolution during the course of peritonitis treatment.[35] Although a secondary analysis of a large randomized controlled trial suggested that low-GDP neutral-pH solutions may reduce the risk for peritonitis,[29] an ANZDATA analysis found higher risk for peritonitis with their use compared to use of conventional PD solutions in a follow-up observational study.[47] We did not observe a strong relationship between increasing low-GDP neutral-pH PD solution use by clinics and peritonitis risk, but our analysis was limited to countries in which these solutions were available and not used almost exclusively. Further randomized studies adequately powered for a primary peritonitis outcome are warranted to explore the relationship between low-GDP neutral-pH PD solution use and peritonitis risk.

Two ISPD-endorsed guideline recommendations to reduce the risk for peritonitis based on randomized controlled trial data are the use of prophylactic antibiotics at the time of PD catheter insertion[48] and the use of prophylactic topical exit-site mupirocin or aminoglycoside ointment or cream at the PD catheter exit-site.[14] Across all countries, facilities that used antibiotics at the time of PD catheter insertion had lower risk for peritonitis. Although the reduction in peritonitis risk may relate to adherence to this practice, these facilities may be more attuned in general to practices that lower peritonitis risk. In our study, lower peritonitis risk was seen in facilities that used topical exit-site mupirocin or aminoglycoside ointment, but this association did not achieve conventional levels of statistical significance. Although the overall rates of pseudomonal peritonitis were very low, they were even lower in the United States than in other countries. This may relate to the anti-pseudomonal properties of exit-site aminoglycoside ointment use, a practice overwhelmingly predominant in the United States based on its superiority over mupirocin in reducing peritonitis risk in a US trial.[49] Interestingly, in Japan, concerns about antibiotic resistance have limited the reimbursement for routine use of topical antibiotics at the exit site to <5% of facilities. In the United Kingdom, topical exit-site prophylaxis with either mupirocin or gentamicin was limited to less than half the facilities. We observed that >19% of peritonitis episodes were associated with an exit-site infection in Japan and 21% in the United Kingdom. Although the link between exit-site infection leading to subsequent peritonitis may be organism dependent,[50–52] more widespread use of exit-site prophylactic antibiotic cream or ointment may reduce the already relatively low rates of peritonitis in Japan. The rate of exit-site infections observed in Japan and the United Kingdom may also relate to the futility of certain exit-site prophylactic strategies in the context of possible differences in resistance patterns of organisms, a hypothesis that we could not test within the limitations of the available data.

Patient training is an important factor that may affect peritonitis risk. As a result, minimum standards for patient training have been developed.[53] The impact of a standardized PD curriculum for patients and trainers on peritonitis risk is currently being evaluated by a multicenter cluster-randomized controlled trial.[54] We found that facilities reporting an initial period of patient training that was 6 days or longer had lower risk for peritonitis as compared with facilities that had an initial period of 6 or fewer days. Previous surveys suggest that training duration varies substantially in the United States,[55] and similar to our study, a previous international survey found that 5 days appears to be the most common duration of patient training.[56] In a multicenter observational study in Brazil, a training session of less than an hour per session was associated with increased risk for peritonitis compared with 1 to 2 hours per session.[57] Taken together, regardless of whether there may be a critical and minimum duration of patient training needed to affect peritonitis risk requires further study. It is possible that enhanced reimbursement for PD training in the United States, which has been suggested to facilitate increased PD uptake, may also stand to reduce peritonitis risk if it enables longer training.[58] Alternatively, longer duration of training may be a proxy for the quality, content, and comprehensiveness of aspects of patient training and procedures that may reduce peritonitis risk at a facility.

To our knowledge, to date our study is the largest multicenter international cohort of PD patients using a standardized study design and methodology for data collection. We extend the study scope beyond national registries by examining facility practices and their impact on peritonitis.

However, our study has several limitations. As in most observational studies, patients and facilities agreeing to participate in the PDOPPS may be different and could have somewhat higher performance on average than other facilities, which may explain the lower rates of peritonitis that we observed when compared with some of the national reports. A PDOPPS internal validation of data collection in Thailand suggested accurate capture of nonmissing data. However, it is difficult to draw definitive conclusions about country differences given the limited number of facilities, missing data and heterogeneity within a given facility, and heterogeneity across facilities within a given country. Our sample consists of upper-middle-income and high-income countries and thus our results may not generalize to other countries with fewer resources. Although we adjusted for common patient demographic, comorbid condition, and treatment factors, unmeasured differences in patients or facility practices may explain the differences in peritonitis risks that we observed. For example, the reported nurse-to-patient ratios in certain facilities may have included providers other than nurses.

We have identified important regional differences in the risk for peritonitis and potentially modifiable practices that may reduce these risks. Improvement in culture-negative peritonitis rates should be a priority of all participating countries. Because PDOPPS collects data for patient-reported outcome measures, it will also be important to relate these measures to the risk for peritonitis to develop and better understand strategies for patient engagement that will reduce the risks for peritonitis. This study sets the stage for future PDOPPS studies of other practices related to peritonitis prevention; for example, highlighting differences in patient training strategies and novel technologies such as remote patient monitoring. In addition, PDOPPS has identified important gaps in translating best practices across facilities, including selected ISPD guideline recommendations that may affect the risk for peritonitis.

Supplementary Material

Supplementary File (PDF)

Table S1: Frequency of organisms associated with relapsing peritonitis.

Table S2: Rate ratios for patient-level peritonitis rates, by country (patient variables only).

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Support: Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details, see https://www.dopps.org/AboutUs/Support.aspx. No funding entity or sponsor had a role in study design; data collection, analysis, or reporting; or the decision to submit this work for publication. This project was partially supported by grant #1R01HS025756-01 from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services (HHS).

Financial Disclosure: Dr Perl has received consulting fees from Baxter Healthcare and DaVita and speaker honoraria from Baxter International, DaVita, Dialysis Clinic Inc, and Fresenius Medical Care. Mr Fuller, Mr Bieber, Dr Pisoni, Dr Robinson, and Dr Zhao are employees of Arbor Research Collaborative for Health. Dr Schreiber is an employee of DaVita. Dr Nessim has received consulting fees from Fresenius Medical Care and Otsuka and speaker fees from Baxter Healthcare. Dr Ito has received speaker fees from Baxter Healthcare, Terumo, and JMS. Dr Schaubel has received grant support from the US National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases). Dr Teitelbaum has received consulting fees from Zytoprotec GmbH. Dr Johnson has received speaker fees from Baxter Healthcare and Fresenius Medical Care and grant support from Baxter Healthcare. The remaining authors declare that they have no other relevant financial interests.

Acknowledgements: Jennifer McCready-Maynes, an employee of Arbor Research Collaborative for Health, provided editorial assistance for this article.

Disclaimer: The authors of this article are responsible for its content. Statements in the article do not necessarily represent the official views of or imply endorsement by AHRQ or HHS.

Peer Review: Received April 11, 2019. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form September 24, 2019.

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