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ORIGINAL ARTICLE

# Extended antibiotic therapy for the prevention of relapsing and recurrent peritonitis in peritoneal dialysis patients: a randomized controlled trial

Cheuk-Chun Szeto[1,2,3], Jack Kit-Chung Ng [1,2], Winston Wing-Shing Fung[1,2], Gordon Chun-Kau Chan[1,2], Phyllis Mei-Shan Cheng[1,2,3], Ka-Bik Lai[1,2,3], Wing-Fai Pang[1,2], Kai-Ming Chow[1,2], Chi-Bon Leung[1,2] and Philip Kam-Tao Li[1,2]

[1]Department of Medicine, Carol & Richard Yu Peritoneal Dialysis Research Centre, Prince of Wales Hospital, Shatin, China, [2]Department of Therapeutics, Carol & Richard Yu Peritoneal Dialysis Research Centre, Prince of Wales Hospital, Shatin, China and [3]Faculty of Medicine, Li Ka Shing Institute of Health Sciences, Chinese University of Hong Kong, Shatin, China

Correspondence to: Cheuk-Chun Szeto; E-mail: ccszeto@cuhk.edu.hk

## ABSTRACT

**Background.** Relapsing and recurrent peritonitis episodes are major causes of technique failure in peritoneal dialysis (PD). We examined the efficacy of extended antibiotic therapy for the prevention of relapsing and recurrent peritonitis.

**Methods.** From February 2016 to November 2018 we recruited 254 PD patients who fulfilled the diagnostic criteria for PD peritonitis. They were randomized to a standard group, with the duration of intraperitoneal (IP) antibiotic treatment following the International Society for Peritoneal Dialysis (ISPD) guideline according to the causative microorganisms, and an extended group, with 1 extra week of IP antibiotics. The primary endpoint was relapsing, recurrent or repeat peritonitis episodes within 6 months.

**Results.** The primary endpoint developed in 36 and 29 patients of the extended and standard groups, respectively (28.3% versus 22.8%; P = 0.34). The rate of complete cure, without relapsing, recurrent or repeat peritonitis within 6 months, was 63.8 and 69.3% for the extended and standard groups, respectively (P = 0.35). Repeat peritonitis episodes were more common in the extended than the standard group (15.0% versus 5.5%; P = 0.013).

**Conclusions.** In patients with PD-related peritonitis, extending the antibiotic therapy for 1 extra week beyond the ISPD protocol should not be recommended. Extending the treatment does not reduce the risk of relapsing or recurrent peritonitis episodes but rather is associated with a higher risk of repeat peritonitis episodes.

**Keywords:** antibiotics, biomarker, infection, renal failure

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## INTRODUCTION

Peritoneal dialysis (PD) is the first-line treatment for end-stage kidney disease (ESKD) in Hong Kong [1]. Despite advances in antibiotic therapy, peritonitis remains a major complication of PD. Although <4% of the peritonitis episodes result in death directly, peritonitis is a major contributing factor to patient mortality in 16% of PD patients [2]. More importantly, peritonitis, particularly recurrent peritonitis episodes, is the major cause of peritoneal membrane failure in PD [1, 3–5]. Our previous study shows that ~15% of all PD-related peritonitis episodes are followed by relapsing or recurrent peritonitis, often resulting in prolonged hospitalization, expensive treatment, the need for catheter removal and conversion to hemodialysis [6].

The cause of the relapsing and recurrent peritonitis episodes is variable. Bacterial biofilm on the PD catheter and tunnel infection are common sources. Early relapse may also be due to antimicrobial resistance acquired during the antibiotic treatment, especially if the duration of therapy is inadequate [6, 7]. In the latest peritonitis treatment guideline of the International Society for Peritoneal Dialysis (ISPD), a course of intraperitoneal (IP) antibiotics of 2–3 weeks, depending on the causative organism, is recommended [8], but based on the clinical severity and response, a longer course of treatment is often undertaken in real-life practice. It remains unknown, however, whether extending the duration of antibiotic therapy prevents the development of relapsing and recurrent peritonitis episodes.

In the past, there was no accurate laboratory test to predict relapsing or recurrent peritonitis episodes after completion of antibiotic treatment. However, our recent study showed that bacterial DNA fragment levels in PD effluent are significantly higher 5 days prior to the completion of antibiotics among patients who subsequently develop relapsing or recurrent peritonitis than those who are cured [9]. However, it remains unknown whether extending the duration of antibiotic therapy in this group of patients will prevent the development of relapsing or recurrent peritonitis episodes. The primary objective of this study is to determine the efficacy of extended antibiotic therapy for the prevention of relapsing and recurrent peritonitis. We also test whether PD effluent bacterial DNA fragment levels could help to identify the high-risk group for extended antibiotic therapy.

## MATERIALS AND METHODS

The study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (reference number CREC-2015.327). All study procedures were in compliance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice. The study was registered at ClinicalTrials.gov (NCT02593201). The trial protocol and original plan of data analysis are summarized in Supplementary data 1.

### Case selection

This was a prospective randomized controlled study. The original plan was to recruit 360 patients who fulfilled the diagnostic criteria of PD peritonitis, which was based on at least two of the following [10]: abdominal pain or cloudy PD effluent, leukocytosis in PD effluent (white cell count >100/mL) and positive Gram stain or culture from PD effluent. Patients with fungal peritonitis or obvious surgical problems that required laparotomy were excluded.

### Study procedures

Once PD-related peritonitis was diagnosed clinically, empirical antibiotic treatment was started according to the ISPD guideline [10]. In general, we used IP cefazolin and ceftazidime unless the patient had penicillin allergy. IP antibiotics were administered continuously (i.e. into each bag of PD solution) by patients after training by dialysis nurses. According to the ISPD guideline, peritonitis episodes caused by coagulase-negative *Staphylococcus* species, *Streptococcus* species or culture-negative episodes should be treated with a 2-week course of appropriate antibiotics, while episodes caused by *Staphylococcus aureus*, *Enterococcus* species, *Pseudomonas* species, other Gram-negative bacilli or mixed bacterial growth require treatment for 3 weeks. Informed consent was obtained 5 days before antibiotic completion, according to the ISPD guideline, and patients were then randomized to receive 1 additional week of the effective antibiotic treatment on top of the ISPD guideline (the extended group) or completion of antibiotics according to the guideline with no additional treatment (the standard group). Individuals were randomized by computer-generated lists stored in sequentially numbered sealed envelopes, in block sizes of 8–12. The treatment arm allocation was open to the patient as well as the investigators. All patients received oral nystatin for the prevention of secondary fungal peritonitis.

### Quantification of PD effluent bacterial DNA level

A 20-mL specimen of PD effluent was collected on randomization (i.e. 5 days before antibiotic completion, according to the ISPD guideline) for the measurement of bacterial DNA fragment levels. For the extended group, a second PD effluent sample was collected 5 days before the completion of the extended treatment. DNA was extracted using the EZ1 DNA tissue kit and BioRobot EZ1 with the EZ1 bacteria card (Qiagen, Germantown, MD, USA), according to the manufacturer's instructions. Purified DNA was eluted in 50 μL of elution buffer before amplification. The bacterial DNA fragment level in PD effluent was measured by the QuantStudio 3D Digital Polymerase Chain Reaction (PCR) System (Life Technologies, Carlsbad, CA, USA). Briefly, the PCR mixture was prepared and loaded into the chip according to the manufacturer's protocol. PCR amplification was performed by the ProFlex μPCR system (Life Technologies). The result was captured by the QuantStudio 3D Digital PCR Instrument and analyzed by the QuantStudio AnalysisSuite Software (both from Life Technologies).

### Outcome measures

All patients were followed for 6 months after completion of antibiotic therapy. The primary endpoint of this study was relapsing, recurrent or repeat peritonitis episodes within 6 months. Relapsing peritonitis was defined as an episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism (or culture negative in the second episode) [10]. Recurrent peritonitis was defined as an episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism [10]. Repeat peritonitis was defined as an episode that occurs >4 weeks after completion of therapy of a prior episode with the same organism [10]. Secondary

outcomes included peritonitis that required hospitalization, catheter removal, conversion to long-term hemodialysis, death due to peritonitis and all-cause mortality.

### Sample size estimation

The sample size was estimated by the Power Analysis and Sample Size for Windows software (PASS 2000, NCSS, Kaysville, UT, USA). All calculations used a two-sided $\alpha$ of 0.05. Based on our previous studies [6, 9], ~15% of the patients would have relapsing or recurrent peritonitis. We assume prolonged antibiotic treatment reduces the incidence of relapsing or recurrent peritonitis by 50% (i.e. absolute risk from 15% to 7.5%), which is considered to be clinically relevant. A sample size of 300 would have 80% power to detect such a difference. Allowing for a 20% dropout rate, a total sample size of 360 was planned.

### Statistical analyses

Statistical analyses were performed using SPSS Statistics version 24.0 (IBM, Armonk, NY, USA). Descriptive data are presented as mean ± standard devaition (SD). Since the data on PD effluent bacterial DNA levels were skewed, they are described as median and interquartile range (IQR). Baseline demographic and clinical data were compared between the extended and standard groups by Student's *t*-test, Mann–Whitney U-test or chi-square test as appropriate. We performed exploratory analysis on PD effluent bacterial DNA levels before and after treatment and the data were compared by Wilcoxon signed-rank test. The incidence of relapsing, recurrent and repeat peritonitis episodes was compared by chi-square test. Data were further analyzed by the intention-to-treat approach with Kaplan–Meier plot and univariate Cox regression analysis, with patient death, fungal or tuberculous peritonitis or catheter removal treated as censoring events. For the accuracy of predicting relapsing or recurrent peritonitis episodes by PD effluent bacterial DNA level, receiver operating characteristics curves were constructed by standard methods. P-values $<0.05$ were considered significant. All probabilities were two-tailed.

## RESULTS

During the recruitment period from 1 February 2016 to 30 November 2018, we screened 440 patients in a single dialysis unit. The mean age was 65.0 ± 10.8 years; 261 (59.3%) were male. Of them, 138 did not meet inclusion criteria (78 had abdominal pain of another cause, 35 had blood-stained effluent and 25 had sepsis from another source). Another 42 patients were excluded because of unstable clinical condition (body temperature >39°C, systolic blood pressure <100 mmHg or severe concurrent medical conditions) and 6 patients fulfilled the inclusion criteria but declined to participate. Consent was obtained from 254 patients. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram that summarizes the trial profile is depicted in Figure 1. The baseline clinical characteristics of the 254 patients who were randomized as well as the 48 patients who had peritonitis but were excluded are summarized in Table 1. In essence, there was no significant difference in any baseline parameter between the extended and standard groups. The microbiologic causes of the peritonitis episodes are summarized in Table 2. There was no significant difference in the distribution of causative organisms between the groups (overall chi-square test, P = 0.5). A concomitant exit site infection was present in eight patients in each group. The baseline antibiotic regimen

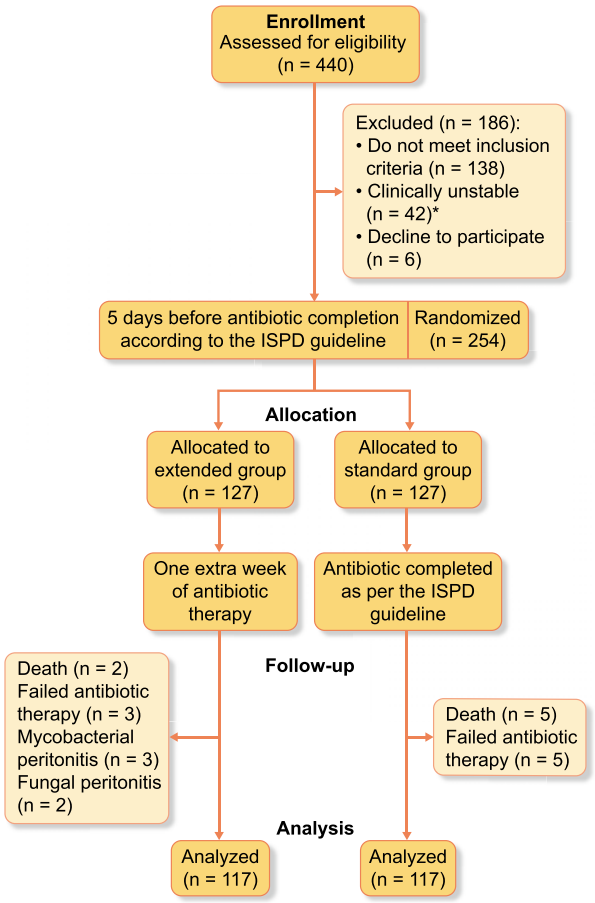


**FIGURE 1:** CONSORT flow diagram. PD effluent was collected for bacterial DNA levels at 5 days before the planned completion of antibiotics according to the ISPD recommendation and 5 days before the actual completion of antibiotics after 1 extra week of treatment for the extended group.

was cefazolin and ceftazidime in 121 and 125 cases of the extended and standard groups, respectively (P = 0.3).

For the standard group, the planned duration of antibiotic therapy according to the ISPD guideline was 14 days in 69 cases and 21 days in 58 cases. Their actual duration of antibiotic therapy was 14.5 ± 0.4 and 22.4 ± 1.5 days, respectively. For the extended group, the planned duration of antibiotic therapy was 21 days in 66 cases and 28 days in 58 cases and their actual duration of antibiotic therapy was 21.6 ± 0.4 and 28.0 ± 1.0 days, respectively. The mean difference in the duration of antibiotic therapy was 6.4 days [95% confidence interval (CI) 4.6–8.1 days] between the groups.

### Clinical outcome

The clinical outcome is summarized in Table 3. During the study period, two patients from the extended group died (both were due to myocardial infarction) and five from the standard group died (three cases died of nosocomial infections, one from fulminant peritonitis and one from myocardial infarction). A total of 117 patients from each group completed the 6-month follow-up period.

Relapsing or recurrent peritonitis episodes developed in 17 and 22 patients of the extended and standard groups, respectively (13.3% versus 17.3%; P = 0.38). However, repeat peritonitis episodes developed in 19 and 7 patients of the extended and standard groups, respectively (15.0% versus 5.5%; P = 0.013). By

**Table 1. Baseline characteristics of the patients**

| Characteristics | Extended group | Standard group | Excluded | P-value[a] |
|---|---|---|---|---|
| Patients, *n* | 127 | 127 | 48 | – |
| Sex (male:female), *n* | 71:56 | 80:47 | 29:19 | 0.25 |
| Age (years), mean ± SD | 63.2 ± 10.5 | 64.8 ± 11.0 | 62.4 ± 10.9 | 0.24 |
| Duration of dialysis (months), mean ± SD | 30.9 ± 29.7 | 35.3 ± 40.9 | 30.6 ± 30.2 | 0.33 |
| Diagnosis, *n* (%) | | | | 0.54 |
| Glomerulonephritis | 24 (19.0) | 17 (13.4) | 12 (25.0) | – |
| Diabetic nephropathy | 57 (44.9) | 72 (56.7) | 26 (54.2) | – |
| Hypertensive nephrosclerosis | 20 (15.7) | 17 (13.4) | 2 (4.2) | – |
| Polycystic kidney | 2 (1.6) | 3 (2.4) | 0 | – |
| Obstruction | 5 (3.9) | 2 (1.6) | 2 (4.2) | – |
| Others/unknown | 19 (15.0) | 16 (12.6) | 6 (12.5) | – |
| Major comorbidity, *n* (%) | | | | – |
| Diabetes | 71 (55.9) | 80 (63.0) | 30 (62.5) | 0.25 |
| Coronary heart disease | 21 (16.5) | 26 (20.5) | 14 (29.2) | 0.42 |
| Cerebrovascular disease | 23 (18.1) | 29 (22.8) | 16 (33.3) | 0.35 |
| Charlson's comorbidity score, mean ± SD | 6.2 ± 2.3 | 6.5 ± 2.4 | 6.7 ± 2.3 | 0.49 |
| Type of PD, *n* (%) | | | | |
| Machine-assisted | 11 (8.7) | 18 (14.2) | 8 (16.7) | 0.17 |
| Low GDP solution | 36 (25.2) | 32 (25.2) | 5 (10.4) | 0.57 |
| Glucose polymer solution | 58 (45.7) | 60 (47.2) | 20 (41.7) | 0.80 |
| Previous peritonitis episodes median (IQR) | 1.0 (0.0–2.0) | 1.0 (0.0–2.0) | 0.5 (0.0–2.0) | 0.50 |
| Baseline PD effluent bacterial DNA level (copies/μL), median (IQR) | 1.27 (0.77–1.72) | 1.44 (1.07–1.83) | – – | 0.50 – |

[a]Comparing extended and standard groups.
GDP, glucose degradation product.

**Table 2. Causative organisms of peritonitis episodes**

| | Extended group | | | | Standard group | | | | Excluded |
|---|---|---|---|---|---|---|---|---|---|
| Organism identified | All case | Relapsing | Recurrent[a] | Repeat[b] | All case | Relapsing | Recurrent[a] | Repeat[b] | All case |
| Gram-positive organisms, *n* (%) | 76 (59.8) | | | | 66 (52.0) | | | | 20 (41.7) |
| *Staphylococcus aureus* | 18 | 2 | 0 | 3 | 13 | 1 | 1 | 0 | 8 |
| CNSS | 9 | 2 | 0 | 0 | 13 | 2 | 1 | 0 | 5 |
| *Enterococcus* species | 5 | 1 | 1 | 3 | 2 | 0 | 0 | 1 | 0 |
| *Streptococcus* species | 38 | 1 | 2 | 6 | 30 | 2 | 2 | 3 | 4 |
| Others | 6 | 1 | 0 | 3 | 8 | 1 | 0 | 1 | 3 |
| Gram-negative organisms, *n* (%) | 18 (14.2) | | | | 22 (17.3) | | | | 11 (22.9) |
| *Pseudomonas* species | 3 | 1 | 0 | 0 | 4 | 1 | 0 | 0 | 3 |
| Enterobacteriaceae species | 15 | 1 | 2 | 1 | 18 | 2 | 1 | 0 | 8 |
| Mycobacterium[c] | 3 | | | | 0 | | | | 1 |
| Polymicrobial growth | 17 (13.4) | 0 | 0 | 1 | 21 (16.5) | 4 | 3 | 0 | 12 (25.0) |
| Culture negative, *n* (%) | 13 (10.2) | 2 | 1 | 2 | 18 (14.2) | 1 | 0 | 2 | 4 (8.3) |
| Total, *n* | 127 | 11 | 6 | 19 | 127 | 14 | 8 | 7 | 48 |

CNSS, coagulase-negative *Staphylococcus* species.
[a]Cause of the initial peritonitis episode.
[b]Repeat peritonitis within 6 months.
[c]Excluded from the final analysis.

the univariate Cox regression analysis that censored patients who died, were diagnosed with fungal or tuberculous peritonitis,or had catheter removal, there was no significant difference in the risk of developing the primary outcome between the extended and standard groups [unadjusted hazard ratio 1.069 (95% CI 0.649–1.761); P = 0.79] (Figure 2). The rate of complete cure without relapsing, recurrent or repeat peritonitis within 6 months was 63.8 and 69.3% for the extended and standard groups, respectively (P = 0.35). There were no specific adverse effects reported in either group.

## PD effluent bacterial DNA level

We further explored the effect of PD effluent bacterial DNA levels. At the time of randomization (i.e. 5 days before antibiotic completion according to the ISPD guideline), the PD effluent bacterial DNA level was similar between the extended and standard group [1.27 (95% CI 0.77–1.72) versus 1.44 (95% CI 1.07–1.83) copies/μL; P = 0.5]. Five days before the actual completion of antibiotics, the extended group had significantly lower PD effluent bacterial DNA levels than the standard group [0.87 (95% CI 0.74–1.05) versus 1.44 (95% CI 1.07–1.83) copies/μL; P < 0.0001].

**Table 3. Summary of clinical outcome**[a]

| Outcome | Extended group | Standard group | P-value |
|---|---|---|---|
| Primary outcome, *n* (%) | 36 (28.3) | 29 (22.8) | 0.34 |
| Relapsing episode | 11 (8.7) | 14 (11.0) | 0.53 |
| Recurrent episode | 6 (4.7) | 8 (6.3) | 0.58 |
| Repeat episode in 6 months | 19 (15.0) | 7 (5.5) | 0.013 |
| Secondary outcome, *n* (%) | | | |
| Peritonitis require hospitalization | 39 (30.7) | 36 (28.3) | 0.68 |
| Catheter removal | 5 (3.9) | 5 (3.9) | 0.99 |
| Conversion to long-term HD | 2 (1.6) | 2 (1.6) | 0.99 |
| Death due to peritonitis | 0 | 1 (0.8) | 0.32 |
| Death for all cause | 2 (1.6) | 5 (3.9) | 0.25 |
| Mycobacterium peritonitis[b] | 3 (2.4) | 0 | 0.08 |
| Secondary fungal peritonitis[b,c] | 2 (1.6) | 0 | 0.16 |
| Complete cure | 81 (63.8) | 88 (69.3) | 0.35 |
| Total | 127 | 127 | |

[a]Percentages depict those for the entire intention-to-treat group without exclusion.
[b]Secondary outcomes added *post hoc*.
[c]All patients had catheter removal and were put on temporary hemodialysis.

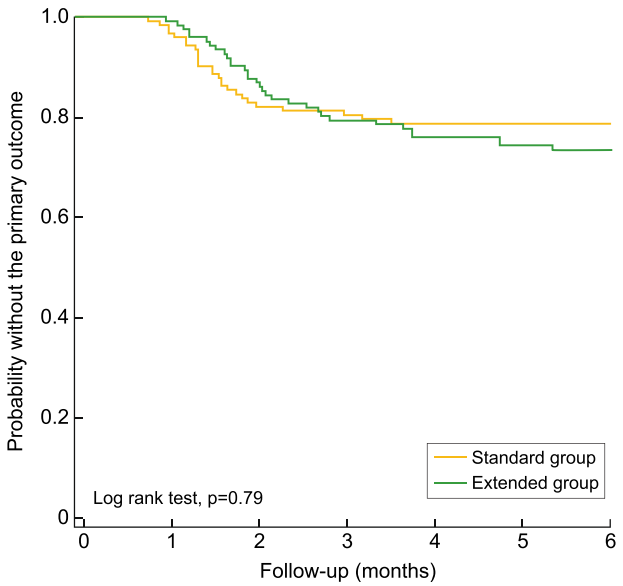


**FIGURE 2:** Kaplan–Meier plot for the probability of being free from the primary outcome. Patient death, diagnosed with fungal or tuberculous peritonitis and catheter removal were treated as censoring events.

When the extended group was analyzed alone, the PD effluent bacterial DNA level decreased significantly after 1 additional week of antibiotic therapy ($P = 0.0002$), but the reduction was significant only for patients who did not subsequently develop relapsing or recurrent peritonitis episodes [from 1.21 (95% CI 0.77–1.72) to 0.86 (95% CI 0.74–0.98) copies/μL; $P < 0.0001$] and not for those who subsequently developed relapsing or recurrent peritonitis episodes [from 1.33 (95% CI 0.96–1.74) to 1.40 (95% CI 0.84–2.66) copies/μL; $P = 0.9$].

## DISCUSSION

In this study we found that in patients with PD-related peritonitis, extending the antibiotic therapy for 1 extra week on top of the ISPD protocol did not significantly reduce the risk of relapsing or recurrent peritonitis episodes. In contrast, extending the treatment was associated with a higher risk of repeat peritonitis episodes and should not be recommended.

Our result essentially shows that extended antibiotic therapy will defer some relapsing peritonitis episodes to repeated episodes but offers no net benefit. There are several possible explanations for this observation. As shown by our previous study [9], patients who have relapsing or recurrent peritonitis episodes have higher PD effluent bacterial DNA levels before the completion of antibiotics. In this group of patients, our current result further shows that PD effluent bacterial DNA levels do not decrease significantly with extended antibiotic therapy. Taken together, these observations suggest that there exists a small number viable but probably dormant bacteria in certain sites so that they cannot be eradicated by prolonged antibiotic therapy. Biofilm on the PD catheter is a distinct possibility [11–13]; persistent colonization around the exit site or in the catheter tunnel is another [14, 15]. A previous study also showed that viable bacteria may be engulfed by and persist in peritoneal mesothelial cells [7].

A secondary objective of our study was to test whether PD effluent bacterial DNA levels can identify a subgroup of patients with a high risk of relapsing or recurrent peritonitis episodes for focused therapy. Our present result clearly shows that 1 extra week of antibiotic therapy did reduce the PD effluent bacterial DNA level significantly. However, patients who have relapsing or recurrent peritonitis episodes had persistently elevated PD effluent bacterial DNA levels despite extended antibiotic therapy and therefore a strategy that focused on the high-risk group would not improve the efficacy. It could be argued that 1 extra week of antibiotics may not be sufficient for the group that was destined to develop relapsing peritonitis, thus alternative measures (e.g. catheter exchange) may be necessary. In terms of risk prediction, this study showed that a bacterial DNA level >1 copy/μL should be used as the cutoff value. The result is similar but not exactly identical to our previous study [9], which found that a level of 34 PCR cycles by simple quantitative PCR (rather than digital PCR with exact copy number quantification) should be used as the cutoff. Our in-house analysis of archive samples from this previous study showed that the corresponding bacterial DNA level was ~1.5 copies/μL (C.C. Szeto, unpublished data).

It should be noted that the distribution of causative microorganisms in this study may be somewhat different from

our previous reports [4, 6, 16]. Although the incidence of culture-negative peritonitis was acceptable, the proportion of peritonitis episodes caused by Gram-negative bacilli, especially *Pseudomonas* species, was substantially lower than in our previous reports. A careful examination of the episodes that were screened but excluded showed that patients with Gram-negative peritonitis were more likely to be considered not clinically stable or were expected to require prolonged hospitalization, which were therefore not suitable for randomization.

The rate of treatment response in our study was similar to previous reports [4, 6, 16]. In a sense, the result of our study indirectly supports the duration of therapy recommended by the current ISPD guideline [8, 10], which is derived mostly from observational studies rather than randomized trials. In this study, most of the patients received cefazolin plus ceftazidime as their initial empirical regimen, and it remains uncertain if our result can be extrapolated to a regimen of vancomycin and aminoglycoside. However, extended aminoglycoside therapy (i.e. for >3 weeks) has been reported to be associated with vestibular toxicity [17, 18] and is generally not recommended.

Although a sample size of 360 was planned, we only randomized 254 patients during the study period. The slow recruitment was due to the unexpectedly high incidence of patients screened but who did not meet the inclusion criteria. It could be argued that our study, as it currently stands, may not have sufficient statistical power to detect the benefit of extended antibiotic therapy. However, based on the available results (especially the high incidence of repeat peritonitis episodes in the extended group), it seems unlikely that we would find any benefit even if the planned sample size was achieved. *Post hoc* sample size estimation showed that if the primary endpoint is revised to relapsing or recurrent peritonitis episodes, it would require 1392 patients to be randomized (i.e. 2410 patients to be screened) to achieve 80% power for the study, assuming the risk of the primary endpoint is 17.3% in the control group, an absolute risk reduction of 4% in the treatment group (i.e. relative risk reduction of 23%) and an $\alpha$-value of 0.05.

In addition to the lower-than-expected recruitment rate, there are a few other inadequacies of our study. Notably, the antibiotic regimen and duration of treatment was not uniform for all recruited patients but varied according to the causative microorganism, as dictated by the ISPD guideline [8, 10]. In a sense, it was a pragmatic approach so that the management of the standard group was exactly the same as our routine real-life practice. Moreover, both groups in this study had a similar number of patients who required 2- and 3-week treatment. It was possible that extended antibiotic therapy may be effective in preventing relapsing or recurrent peritonitis episodes in a certain subgroup of patients. Unfortunately, *post hoc* subgroup analysis of our results was limited by the small sample size. Second, this study was conducted in a single PD unit with most of our patients receiving continuous ambulatory peritoneal dialysis rather than machine-assisted PD. Our results may not be directly extrapolated to Western centers with a higher proportion of machine-assisted PD. It is also important to note that our study showed prolonging the antibiotic therapy does not offer any benefit. Further studies are needed to determine whether shortening the duration of treatment—especially in low-risk cases as predicted by the microbiological or clinical characteristics of the episode—would affect the therapeutic efficacy.

## SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

## FUNDING

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## CONFLICT OF INTEREST STATEMENT

None declared.

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