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EDITORIAL COMMENT

Longer antibiotic durations for treating peritoneal dialysis-associated peritonitis: helpful or harmful?

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ABSTRACT

Relapsing, recurrent or repeat peritonitis is a devastating complication for peritoneal dialysis (PD) patients and is usually associated with poor outcomes including prolonged hospitalization, catheter removal, hemodialysis transfer and even death. Despite its critical importance and frequent occurrence, there is limited available evidence to facilitate evidence-informed treatment of PD peritonitis. This editorial comments on the findings and limitations of a randomized controlled study published in this journal, which reported that extending antibiotic treatment duration for an additional week beyond that recommended by the International Society for PD did not reduce the risk of relapsing, recurrent or repeat peritonitis, and may have increased the risk of repeat peritonitis. These results are explored in the context of the existing literature and recommendations for practice and research are provided.

Keywords: anti-bacterial agents, peritoneal dialysis, peritonitis, randomized controlled trial, recurrence, relapse, treatment outcome

Peritonitis is a major, potentially life-threatening complication of peritoneal dialysis (PD). It is viewed as the top critical research priority in PD by patients, caregivers and clinicians [1–3], the major barrier to selection of PD as a kidney replacement therapy by patients with kidney failure [4, 5], the common reason for PD patients transferring to hemodialysis [6, 7], and the cause of death in 2–9% of cases [7, 8]. Although the majority of patients experiencing peritonitis can be successfully treated with antibiotics alone without needing to resort to PD catheter removal, up to 15% will experience relapsing peritonitis or recurrent peritonitis (Table 1) within 4 weeks of completion of antibiotic treatment [10]. Moreover, the risk of experiencing repeat peritonitis (Table 1) due to the same organism remains increased for up to 6 months after finishing antibiotic therapy for peritonitis [10–13]. While there is clearly an important and unmet need to maximize the effectiveness and durability of antibiotic treatment for PD peritonitis, randomized controlled studies (RCTs) in this field have been scarce [14].

One key area for future research endeavour is determining the optimal duration of antibiotic therapy for PD-associated peritonitis. Ideally, treatment duration should find the right balance between treating peritonitis for a sufficient length of time to minimize the risk of treatment relapse, recurrence or failure, but short enough to minimize the risks of promoting

Table 1. Terminology of relapsing, recurrent and repeat peritonitis [9]

Types of peritonitis	Definition as per ISPD
Relapsing peritonitis	Peritonitis episode occurs within 4 weeks of completion of antibiotics therapy for the previous episode with same organism or one culture-negative peritonitis
Recurrent peritonitis	Peritonitis episode occurs within 4 weeks of completion of antibiotics for the previous episode with different organisms
Repeat peritonitis	Peritonitis episode occurs again after 4 weeks of completion of antibiotics therapy for the previous episode with same organism

antimicrobial resistance and antibiotic-related adverse effects (including antibiotic-associated diarrhea and secondary fungal peritonitis) [15]. The International Society for PD (ISPD) Peritonitis Guidelines make weak Grade 2C recommendations that PD-associated peritonitis should be treated for 2 weeks for coagulase-negative staphylococcal, streptococcal and culture-negative peritonitis, and for 3 weeks for all other forms of organism-specific peritonitis [9]. The evidence underpinning these recommendations is low certainty and derived from observational cohort and registry studies or expert opinion, as there are no RCTs to inform treatment decisions. Previous registry studies have not found an association between antibiotic duration (<14 days versus ≥14 days) and outcomes for *Acinetobacter*, *Corynebacterium* and culture-negative peritonitis [16–18], while one registry study of culture-negative peritonitis paradoxically found that longer antibiotic duration (>21 days) was associated with poorer outcomes [18].

In this issue of *Clinical Kidney Journal*, Szeto *et al.* [19] report the findings of a parallel-arm, prospective, open-labeled RCT examining the effect of extending the ISPD guideline-recommended duration of antibiotics by an additional 1 week on the primary composite outcome of relapsed, recurrent or repeat peritonitis in 254 clinically stable PD patients treated for PD-associated peritonitis at a single center in Hong Kong between February 2016 and November 2018. The study excluded patients with fungal peritonitis, a surgical abdomen requiring laparotomy or clinical instability. A total of 254 patients (127 in each arm) were recruited and randomized at 5 days prior to the scheduled completion of antibiotics according to ISPD recommendations. The baseline characteristics were comparable between the two groups and the mean difference in total antibiotic duration was 6.4 days [95% confidence interval (CI) 4.6–9.1]. The primary outcome occurred in 36 (28.3%) patients in the extended group compared with 29 (22.8%) patients in the standard group and the difference was not statistically significant (P = 0.34). When the individual components of the primary outcome were examined, there were no significant differences in either relapsed peritonitis (8.7% versus 11.0%, P = 0.53) or recurrent peritonitis (4.7% versus 6.3%, P = 0.58), but repeat peritonitis within 6 months was significantly more common in patients receiving extended antibiotic therapy (15.0% versus 5.5%, P = 0.01). No differences were observed in the other secondary outcomes of peritonitis-associated hospitalization, PD catheter removal, long-term hemodialysis transfer, all-cause mortality or complete cure. Surprisingly, Szeto *et al.* reported no adverse effects during the study. However, it is noteworthy that fungal peritonitis, which is most strongly associated with recent antibiotic therapy, occurred in two patients in the extended antibiotic group and no patients in the standard group. The authors concluded that extending antibiotic therapy for 1 week beyond that recommended by ISPD Peritonitis Guidelines is not advisable.

When interpreting the results of this study, its important limitations should be noted. First, the total number of participants recruited into the study (254) was only 71% of the calculated sample size of 360 that was required to provide 80% power to detect a relatively large effect size of a 50% reduction in the primary composite outcome of relapsed, recurrent or repeat peritonitis. Thus, the study was appreciably underpowered and there was a reasonable chance of a type 2 statistical error. Second, since the study was conducted in an exclusively Asian population mostly treated with continuous ambulatory PD at a single Hong Kong center, the results may not be generalizable to other countries, ethnicities or people treated with automated PD. The results may also not be generalizable to antibiotic regimens other than the combination of cefazolin and ceftazidime that was used in the trial. Third, the study did not strictly follow an intention-to-treat analysis since the final analysis set did not include 10 patients in each group (or approximately 8% attrition overall) due to death, failed antibiotic therapy or mycobacterial or fungal peritonitis. Finally, adverse events and antimicrobial resistance were not pre-specified secondary outcome measures in the trial protocol (NCT02593201) and were not systematically reported, such that it is not possible to evaluate the potential harms of extending antibiotic therapy by an extra week.

Notwithstanding these limitations, it is tempting to speculate about the reasons why extended antibiotic therapy for PD-associated peritonitis was apparently ineffective at reducing the subsequent risk of relapsing peritonitis, which is, by definition, caused by (or assumed to be caused by) the original inciting organism. One possibility is that the types and antimicrobial sensitivities of the causative micro-organisms isolated in the study by Szeto *et al.* [19] rendered them less susceptible to durable cure by the cephalosporin combination employed, regardless of duration of treatment. The most common organisms identified were Gram-positive (52%), particularly coagulase-negative staphylococci, which differed somewhat from a previous Hong Kong study in which the most commonly observed organisms were Gram-negative organisms, particularly *Pseudomonas* species [12]. In contrast, a binational Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) study reported that the common causative organisms for relapsing peritonitis were Gram-positive, particularly coagulase-negative *Staphylococcus* (30%) and *Staphylococcus aureus* (18%) [11]. In the absence of knowledge of more detailed antimicrobial susceptibility data, it is possible that alternative antibiotic regimens, such as vancomycin-based strategies, may have led to different outcomes. In a previous single-center observational study in Hong Kong by Szeto *et al.* [12], vancomycin use was found to be superior to cefazolin in achieving a higher primary response rate, particularly for those who had experienced previous Gram-positive peritonitis. Furthermore, ceftazidime was associated with a higher primary response rate and lower risk of

catheter removal compared with aminoglycoside [12]. In contrast, a multicentre registry data study in Australia reported that relapsing and recurrent peritonitis episodes were more likely to be treated with vancomycin than cefazolin for empiric Gram-positive cover and antibiotics other than aminoglycoside or third- or fourth-generation cephalosporin for empiric Gram-negative cover [11]. The ISPD Peritonitis Guidelines [9] recommend that empiric antibiotic regimens be center-specific and cover both Gram-positive organisms (vancomycin or first generation cephalosporin) and Gram-negative organisms (gentamicin or third-generation cephalosporin). However, a Cochrane systematic review and meta-analysis of RCTs of antibiotic treatment for PD-associated peritonitis reported that intraperitoneal glycopeptides (vancomycin or teicoplanin) may be more effective at achieving a complete cure than other agents (3 studies, 370 episodes: risk ratio 1.66, 95% CI 1.01–2.72, low certainty evidence) [14].

Another potential reason for the observed ineffectiveness of extended antibiotic therapy in the study by Szeto et al. may have been related to bacterial colonization of the catheter with biofilm formation [20]. Bacteria can grow on polymer surfaces and produce a slimy, thick extracellular matrix below which they can embed and escape eradication or opsonization by leukocytes. Bacteria trapped in biofilm are less susceptible to antibiotics, such that substantially higher concentrations (100–1000 times) of antibiotics are required to eradicate them [21]. Therefore, increasing the duration of antibiotics alone may not be sufficient in and of itself to eradicate bacteria in biofilm. While there have been attempts to treat relapsing peritonitis with streptokinase or urokinase (which produce fibrinolysis by converting plasminogen to plasmin) with some studies showing promising results [22], a subsequent RCT [23] has demonstrated that catheter replacement was superior to intraperitoneal urokinase therapy for the prevention of relapsing or repeat peritonitis [23].

Inadequate systemic levels of antibiotics may also be associated with frequent relapsing or early repeat peritonitis, despite extended antibiotic durations, particularly if the drug levels fall below minimum inhibitory concentrations (MICs) [24, 25]. A previous observational study by Mulhern et al. [24] showed that an average vancomycin trough level of <9 mg/L at Day 7 and a cumulative mean vancomycin trough <12 mg/L at Week 4 were associated with a higher rate of relapsed or repeat peritonitis. Another study by Dahlan et al. [25] also reported that a higher serum vancomycin trough level (>18 mg/L) was associated with a lower risk of relapse or early repeat peritonitis. Similarly, serum concentrations of cephalosporins may fall below the MICs of peritonitis organisms, particularly with intermittent intraperitoneal dosing regimens [26]. Consequently, simply extending the duration of antibiotic therapy may not adequately address this issue and mitigate the risk of relapse.

Recurrent peritonitis is also a complication that may not be effectively prevented by extending antibiotic duration, since it is caused by an organism that is different from the inciting one and may not necessarily be sensitive to the original antibiotic regimen. Indeed, sometimes the original antibiotic course may actually engender recurrent peritonitis through promotion of antimicrobial resistance, altered gut microbiota and fungal overgrowth [27, 28]. In this regard, it is notable that the only two cases of fungal peritonitis reported in the study by Szeto et al. [19] occurred in the extended antibiotic group. A previous ANZDATA Registry study identified fungi as the most common cause (13%) of recurrent peritonitis [11], while a previous investigation by Szeto et al. [12] found that other Gram-negative organisms (35.2%) and mixed growth (17.6%) were most commonly isolated in recurrent peritonitis.

One of the most intriguing findings in the study by Szeto et al. was that extended antibiotics significantly increased the risk of repeat peritonitis by 3-fold. Caution should be exercised in interpreting this result given that it was (i) an individual component of the primary outcome (and therefore was hypothesis-generating only), (ii) the event numbers were small and (iii) the multiple comparisons performed in the study increased the risk of a type 1 statistical error (i.e. chance finding). The authors suggested that extended duration antibiotics may have deferred some relapsing peritonitis episodes to repeat episodes. However, this seems unlikely since the threshold distinguishing between relapsing and repeat peritonitis (4 weeks) is timed from completion of antibiotic therapy. Furthermore, the small reduction in relapsed peritonitis cases in the extended group did not account for the magnitude of increase in repeat peritonitis cases. As mentioned previously with relapsed peritonitis, it is conceivable that extended antibiotic therapy may paradoxically exacerbate the risk of repeat peritonitis through promotion of antimicrobial resistance, altered gut microbiota and fungal overgrowth [27, 28].

Interestingly, in a *post hoc* exploratory analysis of their study data, Szeto et al. [19] found that PD effluent bacterial DNA levels 5 days prior to antibiotic completion were lower in the extended group than in the standard group, despite comparable levels at randomization. However, it should be noted that the near-end-of-treatment samples were not collected at the same time point following randomization and were in fact separated by approximately 1 week. Thus, it is impossible to ascertain whether the observed differences were due to extended antibiotic therapy or the mere passage of time following initiation of antibiotic therapy. Szeto et al. further demonstrated that the fall in PD effluent bacterial DNA levels in the extended antibiotic group was only statistically significant in those who did not experience relapsing or recurrent peritonitis. This raises the possibility that PD effluent bacterial DNA levels may have a role in risk stratification and identification of patients with PD peritonitis who are at risk of relapsing or repeat peritonitis. Indeed, a previous observational study by the same group reported that PD effluent bacterial DNA levels measured at 5 days before completion of course of antibiotics for peritonitis had an 88.9% sensitivity and 60.5% specificity for prediction of relapsing or recurrent peritonitis [29]. Further confirmatory research in this area would therefore appear warranted.

Szeto et al. are to be commended for attempting to improve the quality of evidence in relation to antibiotic treatment of PD-associated peritonitis through the rigor of an RCT. Despite the highlighted limitations of their study, their findings do lend support to the current ISPD Peritonitis Guideline recommendations for antibiotic course durations, and have also hinted at possible harm from unduly prolonging antibiotic duration in terms of an increased risk of repeat peritonitis. Strengthening the evidence base in PD peritonitis treatment further will require the conduct of multi-center RCTs, ideally through PD trial networks.

CONFLICT OF INTEREST STATEMENT

REFERENCES

1. Manera KE, Tong A, Craig JC et al. An international Delphi survey helped develop consensus-based core outcome domains for trials in peritoneal dialysis. Kidney Int 2019; 96: 699–710
2. Manera KE, Johnson DW, Craig JC et al. Patient and caregiver priorities for outcomes in peritoneal dialysis multinational nominal group technique study. Clin J Am Soc Nephrol 2019; 14: 74–83
3. Manera KE, Johnson D, Craig J et al. Establishing a core outcome set for peritoneal dialysis: report of the SONG-PD (Standardized Outcomes in Nephrology–Peritoneal Dialysis) consensus workshop. Am J Kidney Dis 2020; 75: 404–412
4. Morton RL, Snelling P, Webster AC et al. Dialysis modality preference of patients with CKD and family caregivers: a discrete-choice study. Am J Kidney Dis 2012; 60: 102–111
5. Mehrotra R, Devuyst O, Davies SJ et al. The current state of peritoneal dialysis. J Am Soc Nephrol 2016; 27: 3238–3252
6. Cho Y, Johnson DW. Peritoneal dialysis-related peritonitis: towards improving evidence, practices, and outcomes. Am J Kidney Dis 2014; 64: 278–289
7. Ghali JR, Bannister KM, Brown FG et al. Microbiology and outcomes of peritonitis in Australian peritoneal dialysis patients. Perit Dial Int 2011; 31: 651–662
8. Mujais S. Microbiology and outcomes of peritonitis in North America. Kidney Int 2006; 70: S55–S62
9. Li PK-T, Szeto CC, Piraino B et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int 2016; 36: 481–508
10. Szeto CC, Kwan BCH, Chow KM et al. Repeat peritonitis in peritoneal dialysis: retrospective review of 181 consecutive cases. Clin J Am Soc Nephrol 2011; 6: 827–833
11. Burke M, Hawley CM, Badve SV et al. Relapsing and recurrent peritoneal dialysis-associated peritonitis: a multicenter registry study. Am J Kidney Dis 2011; 58: 429–436
12. Szeto CC, Kwan BCH, Chow KM et al. Recurrent and relapsing peritonitis: causative organisms and response to treatment. Am J Kidney Dis 2009; 54: 702–710
13. Thirugnanasambathan T, Hawley CM, Badve SV et al. Repeated peritoneal dialysis-associated peritonitis: a multicenter registry study. Am J Kidney Dis 2012; 59: 84–91
14. Ballinger AE, Palmer SC, Wiggins KJ et al. Treatment for peritoneal dialysis-associated peritonitis. Cochrane Database Syst Rev 2014; 4: CD005284
15. Doron S, Davidson LE. Antimicrobial stewardship. Mayo Clin Proc 2011; 86: 1113–1123
16. Htay H, Cho Y, Pascoe EM et al. Outcomes of acinetobacter peritonitis in peritoneal dialysis patients: a multicenter registry analysis. Perit Dial Int 2018; 38: 257–265
17. Htay H, Cho Y, Pascoe EM et al. Outcomes of Corynebacterium peritonitis: a multicenter registry analysis. Perit Dial Int 2017; 37: 619–626
18. Htay H, Cho Y, Pascoe EM et al. Multicentre registry data analysis comparing outcomes of culture-negative peritonitis and different subtypes of culture-positive peritonitis in peritoneal dialysis patients. Perit Dial Int 2020; 40: 47–56
19. Szeto CC, Ng JKC, Fung WWS et al. Extended antibiotic therapy for the prevention of relapsing and recurrent peritonitis in PD patients: a randomized control trial. Clin Kidney J 2020
20. Read RR, Eberwein P, Dasgupta MK et al. Peritonitis in peritoneal dialysis: bacterial colonization by biofilm spread along the catheter surface. Kidney Int 1989; 35: 614–621
21. Ceri H, Olson ME, Stremick C et al. The Calgary biofilm device: new technology for rapid determination of antibiotic susceptibilities of bacterial biofilms. J Clin Microbiol 1999; 37: 1771–1776
22. Innes A, Burden RP, Finch RG et al. Treatment of resistant peritonitis in continuous ambulatory peritoneal dialysis with intraperitoneal urokinase: a double-blind clinical trial. Nephrol Dial Transplant 1994; 9: 797–799
23. Williams AJ, Boletis I, Johnson BF et al. Tenckhoff catheter replacement or intraperitoneal urokinase: a randomised trial in the management of recurrent continuous ambulatory peritoneal dialysis (CAPD) peritonitis. Perit Dial Int 1989; 9: 65–67
24. Mulhern JG, Braden GL, O'Shea MH et al. Trough serum vancomycin levels predict the relapse of gram-positive peritonitis in peritoneal dialysis patients. Am J Kidney Dis 1995; 25: 611–615
25. Dahlan R, Lavoie S, Biyani M et al. A high serum vancomycin level is associated with lower relapse rates in coagulase-negative staphylococcal peritonitis. Perit Dial Int 2014; 34: 232–235
26. Booranalertpaisarn V, Eiam-Ong S, Wittayalertpanya S et al. Pharmacokinetics of ceftazidime in CAPD-related peritonitis. Perit Dial Int 2003; 23: 574–579
27. Simões-Silva L, Araujo R, Pestana M et al. The microbiome in chronic kidney disease patients undergoing hemodialysis and peritoneal dialysis. Pharmacol Res 2018; 130: 143–151
28. Miles R, Hawley CM, McDonald SP et al. Predictors and outcomes of fungal peritonitis in peritoneal dialysis patients. Kidney Int 2009; 76: 622–628
29. Szeto CC, Lai KB, Ching-Ha BK et al. Bacteria-derived DNA fragment in peritoneal dialysis effluent as a predictor of relapsing peritonitis. Clin J Am Soc Nephrol 2013; 8: 1935–1941