Repeat Peritonitis in Peritoneal Dialysis: Retrospective Review of 181 Consecutive Cases

Cheuk-Chun Szeto, Bonnie Ching-Ha Kwan, Kai-Ming Chow, Man-Ching Law, Wing-Fai Pang, Chi-Bon Leung, and Philip Kam-Tao Li

Summary

Background and objectives The clinical behavior of repeat-peritonitis episodes, defined as peritonitis with the same organism occurring more than 4 weeks after completion of therapy for a prior episode, is poorly understood.

Design, setting, participants, & measurements We compared outcomes of 181 episodes of repeat peritonitis from 1995 to 2009 (Repeat Group) with 91 episodes of relapsing peritonitis (Relapsing Group) and 125 episodes of peritonitis preceded 4 weeks or longer by another episode with a different organism (Control Group).

Results In Repeat Group, 24% were due to Staphylococcus aureus, as compared with 5.5% in Relapsing Group and 15% in Control Group. The majority of the organisms causing relapsing peritonitis were Gram negative (62%), whereas the majority of that in Repeat Group were Gram positive (56%). Repeat Group had a lower complete-cure rate (70.7% versus 54.9%) than Relapsing Group, but rates of primary response, catheter removal, and mortality were similar. Repeat Group had a higher primary response rate (89.0% versus 73.6%) and a lower rate of catheter removal (6.1% versus 15.2%) than Control Group, whereas the complete-cure rate and mortality were similar. Repeat Group had a higher risk of developing relapsing (14.3% versus 2.2%) and repeat peritonitis (26.1% versus 5.4%) than Control Group, whereas the risk of recurrent peritonitis was similar.

Conclusions Repeat peritonitis is a distinct clinical entity. Although repeat-peritonitis episodes generally have a satisfactory response to antibiotic, they have a substantial risk of developing further relapsing or repeat peritonitis.


Introduction

Peritonitis is a serious complication of peritoneal dialysis (PD) and probably the most common cause of technique failure in PD (1–5). In the United States, 18% of the infection-related mortality in PD patients is the result of peritonitis (6). Although less than 4% of the peritonitis episodes resulted in death (7), peritonitis is a direct contributing factor to the death of 16% of PD patients (8,9).

In the recommendations for the management of peritoneal dialysis-related infections published by the International Society for Peritoneal Dialysis in 2005 and 2010 (10,11), two related terms, “relapsing” and “repeat” peritonitis, are defined. In essence, peritonitis that is treated with appropriate antibiotic therapy, appears to resolve, and yet returns with the same organism or as sterile peritonitis within 4 weeks is defined as a relapsing episode, whereas repeat peritonitis is defined as an episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism (10,11). Although considering repeat-peritonitis episode as a distinct clinical entity is logically sound, there has been no published evidence to support this approach. In this study, we reviewed the clinical outcome of repeat peritonitis in a large cohort of PD patients.

Materials and Methods

Patient Selection

All of the PD patients of our center gave written consent for reviewing their clinical data when they entered the dialysis program. All of the episodes of PD peritonitis in our unit from 1995 to 2009 were reviewed. The data were collected by reviewing the Hong Kong Renal Registry database as well as the hospital records of individual patient by the investigators. The diagnosis of peritonitis was based on at least two of the following (12,13): (1) abdominal pain or cloudy peritoneal dialysis effluent (PDE); (2) leukocytosis in PDE (white blood cells, >100/μl); and (3) positive Gram stain or culture from PDE. Episodes with peritoneal eosinophilia but negative bacterial culture were excluded. Exit-site infection was diag-
nosed when there was purulent drainage, with or without erythema, from the exit site (14). In this study, repeat peritonitis was defined as an episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism (or 5 weeks after the last dose of antibiotic if the patient was treated with a long-acting agent such as vancomycin) (10).

The peritonitis rate was reported as the number of episodes per patient-year as well as one episode per number of patient-months of follow-up. We counted all repeat episodes but excluded relapsing episodes when computing the peritonitis rate (11). In the 15 years of the study period, 2525 episodes of peritonitis were recorded; 238 episodes (9.4%) were repeat peritonitis in 181 patients. To avoid complex analyses that account for multiple events, we studied the first repeat episode of each patient (the Repeat Group). The result was compared with 91 episodes of relapsing peritonitis during the same period (the Relapsing Group), and 125 episodes of peritonitis who had been preceded by another episode caused by a different organism 4 weeks to 24 months ago (the Control Group). To avoid confusion and possible erroneous classification, we excluded culture-negative and polymicrobial episodes while selecting the control episodes. The demographic characteristics, underlying medical conditions, previous peritonitis, antibiotic regimen for the peritonitis episode, catheter removal, and clinical outcome were examined. Most of the patients in the Relapsing Group had been described in our previous report on relapsing peritonitis (15).

Microbiological Investigations
Bacterial culture of PDE was performed by BacTAlert® bottles (Organon Teknika Corporation, Durham, NC). Species identification was performed by the API 20E identification system (BioMerieux, Marcy l’Etoile, France). Antibiotic sensitivity was determined by the disc-diffusion method according to the National Committee for Clinical Laboratory Standards (16).

Clinical Management
As described previously (17–20), peritonitis episodes were treated with the standard antibiotic protocol of our center at that time, which was changed systemically over time (Table 1). Initial antibiotics for peritonitis were generally intraperitoneal administration of a third- or fourth-generation cephalosporin, plus or minus intermittent vancomycin every 5 days, or cefazolin as continuous administration plus an aminoglycoside or ceftazidime (5). The dosages of vancomycin and cefazolin followed the contemporary guideline (10). During the review period, two clinical trials on monotherapy of peritonitis by cefepime and imipenem/cilastatin had been conducted in our center (19,20); 58 episodes in this review were therefore treated initially with monotherapy. Antibiotic regimens for individual patients were modified when culture results were available.

Primary response was defined as resolution of abdominal pain, clearing of dialysate, and PDE neutrophil count less than 100/ml on day 10 with antibiotics alone. Complete cure was defined as complete resolution of peritonitis by antibiotics alone without relapse or recurrence within 4 weeks of completion of therapy. In general, patients received effective antibiotic for 14 days, whereas the effective antibiotic would be continued for a total of 21 days for episodes caused by Staphylococcus aureus or Pseudomonas species (18,21). When the PDE did not clear up after 5 days of effective antibiotics, the Tenckhoff catheter was removed irrespective of the in vitro sensitivity of the bacterial strain, and effective antibiotic was continued for another 2 weeks. Effluent cell count and bacterial culture were routinely sent at day 10 to confirm primary response; if the patient was asymptomatic, effluent was inspected manually at week 4 to confirm complete response.

Tenckhoff catheters were removed and patients were put on temporary hemodialysis when peritonitis failed to resolve with antibiotics. Tenckhoff catheter reinsertion was attempted in all patients. In our locality, as described in our previous study (4), patients were only switched to long-term hemodialysis when attempts of Tenckhoff catheter reinsertion failed because of peritoneal adhesion or when there was ultrafiltration failure caused by peritoneal sclerosis. All of the patients were followed for at least 6 months after their treatment was completed. Patient mortality was defined as death from any cause during antibiotic treatment (generally 2 to 3 weeks, depending on specific organism) or death during temporary hemodialysis (generally four weeks after catheter removal).

Statistical Analyses
Statistical analyses were performed by SPSS for Windows software version 15.0 (SPSS Inc., Chicago, IL). All of

| Table 1. Standard protocols for the treatment of peritoneal dialysis-related peritonitis at various times in the unit |
|------------------------------------------|--------------------------------------------------|
| Time                                      | Standard Protocola                               |
| January 1994 to December 1995            | Vancomycin + Ceftazidime                         |
| January 1996 to June 1996                | Cefepime + Vancomycin                           |
| July 1996 to July 1998                   | Vancomycin + Ceftazidime or Cefepimeb           |
| August 1998 to October 1998              | Sulperazone                                      |
| November 1998 to March 1999              | Vancomycin + Cefepime                           |
| April 1999 to February 2001              | Cefazolin + Netilmicin                          |
| March 2001 to February 2002              | Imipenem/cilastatin OR Cefazolin + Ceftazidimeb |
| March 2002 to the present                | Cefazolin + Ceftazidime                         |

aAll of the antibiotics were administered intraperitoneally unless the patient had features of systemic sepsis. Imipenem/cilastatin and all cephalosporins were administered continuously; vancomycin and aminoglycosides were administered intermittently.
bRandomized controlled trial comparing the two protocols.
the data were expressed as the means ± SD unless otherwise specified. Baseline data were compared by chi-squared test, Fisher’s exact test, t test, or one-way ANOVA as appropriate. Clinical outcome was compared between groups and choices of empirical antibiotic treatment by chi-squared test.

To avoid multiple statistical comparison and type I error for the subgroup analysis for the effect of concomitant exit-site infection and the choice of empirical antibiotic treatment, we tested the interaction between patient group and exit-site infection or the choices of empirical antibiotic on clinical outcome by logistic regression. In theory, if the interaction was statistically significant, we would present the subgroup analysis; otherwise we would consider only the global comparisons. In the former case, post hoc analysis was performed by chi-squared test, and the P values were adjusted by the Bonferroni method. A P value of less than 0.05 was considered significant. All of the probabilities were two-tailed.

Results

From 1995 to 2009, 2525 episodes of PD-related peritonitis (in 56,560 patient-months of treatment) were recorded in our unit. The overall peritonitis rate was 0.54 episodes per year or one episode per 22.4 patient-months of follow-up. We analyzed 181 episodes of repeat peritonitis. Among all of the repeat episodes, 74 (40.9%) developed within 12 weeks after antibiotic was completed for the previous peritonitis episode. The rate of repeat peritonitis was 0.038 episodes per year.

The baseline clinical characteristics at the time of peritonitis of the patients are summarized in Table 2. There is no significant difference in the baseline clinical characteristics between groups, except female patients were more common in the Repeat Group than in the Relapsing and Control Groups (P = 0.046 and P = 0.07, respectively) and the Repeat Group had been on dialysis longer than the Control Group (P = 0.0001).

Causative Organism

The microbiological cause of the second episode of peritonitis is summarized in Table 3. There was a significant difference in the distribution of the causative organisms between groups (overall chi-squared test, P = 0.0001). Specifically, as compared with the Control Group, a higher percentage of peritonitis episodes in the Repeat Group were caused by S. aureus, Pseudomonas species, or Escherichia coli, and there were lower percentages of episodes caused by other gram-negative organisms and Streptococcal species. As compared with the

<table>
<thead>
<tr>
<th>Table 2. Baseline characteristics of the patients at the time of peritonitis</th>
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</thead>
<tbody>
<tr>
<td>Repeat Group</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Sex (men:women)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
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<tr>
<td>Duration from last peritonitis episode (months)</td>
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<tr>
<td></td>
</tr>
<tr>
<td>No. of previous peritonitis episode</td>
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<td></td>
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<tr>
<td>Diagnosis, no. of cases (%)</td>
</tr>
<tr>
<td>glomerulonephritis</td>
</tr>
<tr>
<td>diabetes</td>
</tr>
<tr>
<td>hypertension</td>
</tr>
<tr>
<td>polycystic</td>
</tr>
<tr>
<td>obstruction</td>
</tr>
<tr>
<td>others/unknown</td>
</tr>
<tr>
<td>Major comorbidity, no. of cases (%)</td>
</tr>
<tr>
<td>diabetes</td>
</tr>
<tr>
<td>coronary heart disease</td>
</tr>
<tr>
<td>cerebrovascular disease</td>
</tr>
<tr>
<td>peripheral vascular disease</td>
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<tr>
<td>Charlson’s index score</td>
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</table>

The P values are adjusted for multiple comparisons.
Relapsing Group, a higher percentage of peritonitis episodes in the Repeat Group were caused by *S. aureus*; there were a lower percentage of episodes caused by other gram-negative organisms, whereas the incidences of *Pseudomonas* and *E. coli* peritonitis were similar. Fungal and mycobacterial peritonitis happened almost exclusively in the Control Group.

Concomitant exit-site infection was present in 27.1, 31.9, and 24.8% of the Repeat, Relapsing, and Control Groups, respectively ( \( P = 0.5 \) ). Exit-site infection with the same organism as the peritonitis episode was marginally more common in the Repeat Group (9.9%) than the Relapsing and Control Groups (3.3 and 6.4%, respectively) ( \( P = 0.1 \)), but the result did not reach statistical significance.

### Clinical Response

The major clinical outcomes are summarized in Figure 1. As compared with the Relapsing Group, the Repeat Group had a significantly lower complete-cure rate (70.7% versus 54.9%, \( P = 0.02 \)), but the primary response rate (89.0% versus 83.5%, \( P = 0.4 \)), rate of catheter removal (6.1% versus 7.7%, \( P = 0.6 \)), and mortality (5.5% versus 9.9%, \( P = 0.4 \)) were similar. As compared with the Control Group, the Repeat Group had a higher primary response rate (89.0% versus 73.6%, \( P = 0.0005 \)), lower rate of catheter removal (6.1% versus 15.2%, \( P = 0.016 \)), and marginally lower mortality (5.5% versus 12.0%, \( P = 0.084 \)), whereas the complete-cure rate was similar (70.7% versus 67.2%, \( P = 0.5 \)).

If primary response was achieved, the Repeat Group had a higher risk of developing repeat peritonitis than the Relapsing Group (26.1% versus 3.9%, \( P < 0.0001 \)), but they have similar rates of relapsing peritonitis (14.3% versus 23.7%, \( P = 0.15 \)) and recurrent peritonitis (6.2% versus 10.5%, \( P = 0.5 \)). As compared with the Control Group, if primary response was achieved, the Repeat Group had a higher risk of developing relapsing (14.3% versus 2.2%, \( P = 0.004 \)) and repeat peritonitis (26.1% versus 5.4%, \( P < 0.0001 \)), whereas the risk of recurrent peritonitis was similar (6.2% versus 6.5%, \( P = 0.9 \)). Among the patients who had their catheters removed, five patients in the Relapsing Group, four patients in the Control Group, but no patients in the Repeat Group could resume PD later ( \( P = 0.002 \)).

### Exit-Site Infection

There was no significant interaction between concomitant exit-site infection and patient group on the primary response rate, complete-cure rate, rate of catheter removal, or mortality (details not shown). Among patients who achieved primary response, however, the presence of concomitant exit-site infection of the same organism was significantly associated with the risk of developing relapsing peritonitis (but not repeat or recurrent episodes), irrespective of the patient group (odds ratio, 6.827; 95% confidence interval [CI], 2.336 to 19.954; \( P = 0.0005 \)), whereas the presence of concomitant exit-site infection of any organism was significantly associated with the risk of developing recurrent peritonitis (but not relapsing or repeat episodes), irrespective of the patient group (odds ratio, 4.787; 95% CI, 1.776 to 12.897; \( P = 0.002 \)).

### Initial Antibiotic Therapy

There was no significant interaction between the choice of initial antibiotic therapy and patient group on the primary response rate, complete-cure rate, rate of catheter removal, and mortality (details not shown). Among patients who achieved primary response, however, the empirical use of vancomycin as the coverage for Gram-positive organisms was associated with an increased risk of developing relapsing peritonitis (odds ratio, 2.171; 95% CI, 1.062 to 4.440; \( P = 0.034 \)), irrespective of the patient group. The choice of empirical coverage for Gram-negative organisms (*cephalosporin versus aminoglycoside*) did not affect the risk of relapsing, recurrent, or repeat peritonitis among patients who achieved primary response (details not shown).

### Time Lapse from the Previous Episode

The duration of time lapse from the previous peritonitis episode was not associated with the primary response rate, complete-cure rate, rate of catheter removal, or mortality (details not shown). Among patients who achieved primary response, however, the risk of developing repeat-peritonitis episodes (but not relapsing or recurrent episodes) was significantly higher when the previous episode was within 12
weeks (odds ratio, 2.660; 95% CI, 1.108 to 6.390, P = 0.029), irrespective of the patient group.

Discussion

In this retrospective study, we show that repeat peritonitis develops in around 10% of all peritonitis episodes. Our findings suggest that repeat peritonitis is a distinct clinical entity and provides support to the current terminology in the International Society for Peritoneal Dialysis recommendation (10,11). Although repeat-peritonitis episodes generally have a satisfactory primary response to antibiotic therapy, they have a substantial risk of developing a relapse.

In this study, we observed that the highest risk of developing repeat peritonitis was in the second month after completion of antibiotic treatment, which is similar to other published reports (22,23). In this study, around 10% of all peritonitis episodes were followed by repeat peritonitis. On a superficial look, the risk seems to be lower than other recent reports, which found that repeat peritonitis occurred in around 30% individuals with *S. aureus* and coagulase negative staphylococcal species (CNSS) peritonitis (22,23). However, our review encompasses peritonitis episodes of all microbiological causes, many of which have a risk of repeat peritonitis much lower than *S. aureus* and CNSS. Our previous studies actually showed that the risk of repeat *S. aureus* and CNSS peritonitis was around 25% (18,24), a figure similar to recent reports from Australia (22,23).

Contrary to the general expectation, we found that repeat-peritonitis episodes had a higher primary response rate and a lower rate of catheter removal than the Control Group. There are a number of factors possibly contributing to this paradoxical phenomenon. First, with the current definition of repeat peritonitis, polymicrobial, fungal, and mycobacterial episodes, all with less favorable therapeutic response, would unlikely appear in the Repeat Group (as reflected in Table 3). Moreover, with the information on antibiotic sensitivity from the previous episode, prompt adjustment to appropriate antibiotic regimen was probably more likely in the Repeat Group. Our result is consistent with a previous study showing that relapsing peritonitis episodes had a better primary response rate than recurrent episodes by different organisms (15).

However, it is important to note that the low rate of catheter removal in our Repeat Group may merely reflect our local practice and may not be entirely desirable. A careful look at our results showed that for the Repeat Group who had a primary response, 46.6% had relapse, recurrent, or repeat peritonitis subsequently, whereas for the Relapsing and Control Groups, it was 38.2 and 14.1%, respectively (see Figure 1). The result implies that perhaps with the first repeat episode (i.e. second episode in the same patient with the same organism), as well as all relapsing episodes, catheter removal or replacement should be considered. However, a randomized control trial is needed to prove this hypothesis.

Although it is often assumed that a repeat-peritonitis episode is merely a delayed form of relapsing episodes, we found that the two groups had different patterns of causative organisms and therapeutic response, implying that they are two distinct entities and that the pathogenic mechanisms are probably different. From a practical point of view, our results indicate that repeat-peritonitis episodes deserve special attention because although the initial response to antibiotic therapy may be satisfactory, there is a substantial risk of developing relapsing or further repeat episodes. Aggressive antibiotic treatment should be considered, and the presence of concomitant exit-site problems should be duly treated.

There are a number of limitations of our study. First, although the sample size seems large, the results are retrospective and uncontrolled. For example, as to the effect of empirical antibiotic therapy on the risk of relapsing peritonitis, we could not exclude the possibility of selection bias (although over 90% of the episodes were managed according to a predefined protocol). Second, we have performed a considerable number of statistical comparisons, which aim for generating a hypothesis. Although the P-
values are adjusted for multiple comparisons, type I statistical error remains possible.

Furthermore, many important microbiological details are not available in this retrospective study. For example, we have no data on the prevalence of bacterial carrier in our patient population. More importantly, data on antibiotic sensitivity are incomplete and therefore not reviewed, and we are not sure about the incidence of new resistance to specific antibiotics during the repeat episodes.

In fact, we do not know whether the repeat episodes were caused by the same strain of bacteria hidden in biofilm (which requires phage typing of the bacterial isolates for confirmation) or were the result of repeated infection caused by some persistent host factors. There are several possible causes of repeat peritonitis. A previous study on the pattern of infection in PD patients with multiple episodes of peritonitis suggested that bacterial biofilm on the walls of peritoneal catheters accounts for a substantial proportion of repeat-peritonitis episodes (25). In fact, a previous randomized trial showed that PD catheter replacement was significantly and importantly more effective than urokinase in preventing recurrence of peritonitis episodes (26). The benefits of other therapeutic strategies (for example, exit site care and root-cause analysis) (27,28) for the prevention of repeat peritonitis also require further studies.

Conclusions

Repeat peritonitis is a distinct clinical entity. Although repeat-peritonitis episodes generally have a satisfactory primary response to antibiotic therapy, they have a substantial risk of developing further relapsing or repeat peritonitis.

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Disclosures

None.

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