Peritonitis in peritoneal dialysis patients in Japan: a 2013 retrospective questionnaire survey of Japanese Society for Peritoneal Dialysis member institutions

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Peritonitis in peritoneal dialysis patients in Japan: a 2013 retrospective questionnaire survey of Japanese Society for Peritoneal Dialysis member institutions

Chieko Higuchi[1*], Minoru Ito[2], Ikuto Masakane[2] and Hiroshi Sakura[1]

Abstract

Background: Peritonitis is the main cause of withdrawal from peritoneal dialysis (PD) therapy in Japan. The precise extent of PD-associated peritonitis in Japan has not been investigated since 2005; we aimed to clarify the recent incidence and prognosis of PD peritonitis.

Methods: The 248 institutional members of the Japanese Society for Peritoneal Dialysis were surveyed by questionnaire regarding peritonitis episodes during January 1 to December 31, 2013.

Results: Replies from 114 members were received regarding 3042 PD patients, including 516 peritonitis patients, covering a total observation period of 31,686 patient months. The incidence of peritonitis in this study was 0.195 episodes per year. Detailed data on 544 peritonitis episodes in 466 patients was obtained. The causes, in ranked order, were unknown reason, contamination at peritoneal fluid exchange, and extension of intra-abdominal cavity infection. Effluent culture methods included using a blood culture bottle (50.9 %), large-volume culture (culturing sediment after centrifuging effluent) (31.7 %), and direct culture of effluent using a culture dish (12.7 %). The rank order of microbes identified in peritoneal effluent cultures was culture-negative, *Streptococcus* sp. and *Staphylococcus aureus*. Empiric therapy with two kinds of antibiotics was administered to 406 cases (75.2 %), most commonly cefazolin + ceftazidime. Antibiotic administration methods included intraperitoneal (51.4 %), intravenous (46.4 %), and oral (2.2 %). After a peritonitis episode, 461 patients (84.7 %) continued PD therapy, 80 (14.7 %) withdrew from PD treatment, and 6 (1.1 %) died. Prognosis among patients grouped by antibiotic administration method was statistically significantly different; in the oral administration group, the rates of mortality and catheter replacement were higher. Logistic regression analysis showed that catheter exit-site infection and frequency of past peritonitis episodes were independent factors associated with PD treatment withdrawal.

Conclusions: Although the overall incidence of PD peritonitis in Japan was relatively low, several areas for future improvement were identified: unknown reason and culture-negative were the most frequently cited causes of peritonitis; 1.1 % of patients died, and 13.6 % discontinued PD therapy. Improvements in effluent culture techniques, antibiotic administration methods, etiology determination, and patient education could help. A more effective protocol must be established to further improve the treatment of PD peritonitis in Japan.

Keywords: PD peritonitis incidence, Effluent culture technique, Antibiotic administration methods, Catheter exit-site infection, Previous peritonitis episodes

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Background

Peritonitis is the major cause of discontinuation of peritoneal dialysis (PD) therapy, reportedly accounting for 34 % of such cases in Japan [1]. There is a recent report regarding PD peritonitis in Japan, but that study was not conducted nationwide [1]. The precise extent of PD-associated peritonitis in Japan has not been investigated since 2005 [2]. Annual nationwide statistical analysis of Japanese PD patients was begun in 2010 by the Japanese Society of Dialysis Therapy (JSDT), but only the peritonitis incidence rate was ascertained in those investigations [3, 4]. Therefore, we aimed to clarify the recent incidence and prognosis of PD peritonitis using a nationwide questionnaire survey.

Methods

We conducted a questionnaire survey of the 248 institutional members of the Japanese Society for Peritoneal Dialysis (JSPD) regarding PD-associated peritonitis episodes occurring for 1 year (January 1 to December 31, 2013). Replies from 114 institutions were received. The questionnaire sought information about each peritonitis patient as follows: clinical characteristics, frequency of past peritonitis episodes, PD fluid bag exchange system, cause of peritonitis, effluent microbiology and method of culture, type of antibiotics administered and administration methods, peritonitis treatment period, and prognosis (Additional file 1).

All study participants provided informed consent, and the study design was approved by the Institutional Committee on Human Research of Tokyo Women's Medical University and Yabuki Hospital.

Statistical analysis

We analyzed the influence of the antibiotic administration method on prognosis using Pearson's chi-square test. We also analyzed the association between various clinical findings and the interruption of PD (including mortality) using logistic regression analysis. Continuous variables are expressed as mean ± standard deviation. Differences having P values <0.05 were considered statistically significant.

Results

Incidence of peritonitis

From 114 institutions (26 university hospitals, 67 hospitals with more than 100 beds, 4 clinics with beds for admission, 17 clinics without beds for admission), information regarding 3042 PD patients, including 516 peritonitis patients, was obtained, covering a total observation period of 31,686 patient months. The incidence of peritonitis was calculated to be 0.195 episodes per year.

Peritonitis patient characteristics

We obtained the clinical characteristics of the 466 peritonitis patients who had a total of 544 peritonitis episodes; 59 patients had multiple peritonitis episodes (an episode that occurred within 2 weeks of completion of therapy for a prior episode was defined as 1 peritonitis episode). Characteristics of these 466 patients are shown in Table 1. The average frequency of past peritonitis episodes was 0.85 ± 1.20. There are two methods used in Japan for connecting a PD fluid bag to the catheter. One is by manual connection, and the other involves use of machinery for ultraviolet irradiation or heat sealing of the catheter to the PD fluid bag. The numbers of episodes using each were manual method, 206 and machinery device method, 303. There was no statistical difference between manual connection and machinery device connection methods for the frequency of past peritonitis episodes.

Characteristics of 544 peritonitis episodes are shown in Table 2. The average PD treatment duration at the time of a peritonitis episode was 36.1 ± 32.7 months; 407 patients had 1 episode of peritonitis, and 59 patients had several peritonitis episodes during the study period.

Table 1 Characteristics of 466 PD peritonitis patients

Clinical characteristics	
M/F/not described	296/167/3
Age (y/o)	65.2 ± 14.0 (range, 4–96)
Original disease	
Diabetes mellitus	159 (34.1 %)
Chronic glomerulonephritis	131 (28.1 %)
Nephrosclerosis	62 (13.3 %)
Polycystic kidney disease	18 (3.9 %)
Others	89 (19.1 %)
Unknown	7 (1.5 %)
Automated PD	140 cases
Combined therapy with HD	71 cases
Frequency of past peritonitis	0.85 ± 1.20
None	236 patients
1 time	139
2 times	44
3 times	22
4 times	13
5 times	2
6 times	5
7 times	1
Unknown	4
Connection method	
Manual/machinery device/unknown	206/303/35

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Table 2 Characteristics of 544 peritonitis episodes of 466 PD patients

Clinical characteristics	
PD treatment duration at the time of peritonitis (months)	36.1 ± 32.7
Frequency of peritonitis during the study (cases)	
1 time	407
2 times	43
3 times	13
4 times	3
Recurrent peritonitis	19
Relapsing peritonitis	11
Repeat peritonitis	14

Recurrent peritonitis an episode that occurs within 4 weeks of completion of therapy for a prior episode but with a different organism, *Relapsing peritonitis* an episode that occurs within 4 weeks of completion of therapy for a prior episode with the same organism or a sterile episode, *Repeat peritonitis* an episode that occurs more than 4 weeks after completion of therapy for a prior episode with the same organism

Causes of peritonitis

The causes cited for peritonitis episodes included the following: contamination during the peritoneal fluid bag exchange (touch contamination), 130 episodes (23.9 %); influence of intra-abdominal cavity infection, 58 episodes (10.7 %); exit-site infection, 55 episodes (10.1 %); and unknown, 207 episodes (38.1 %) (Fig. 1).

Bacterial cultures of peritoneal effluent

Figure 2 depicts the various methods of effluent culture reported in this survey, including the use of a blood culture bottle, 50.9 %; large-volume culture (culturing the effluent sediment after centrifugation, in a culture dish or blood culture bottle), 31.7 %; and direct culture of effluent in a culture dish, 12.7 %.
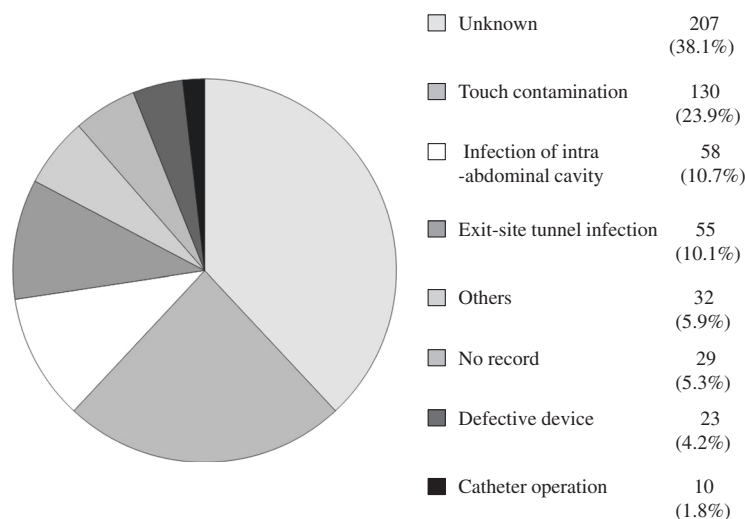
Microbiology of effluent cultures

Among effluent cultures, 131 episodes were culture-negative, 270 episodes yielded Gram-positives, 116 yielded Gram-negatives, and 42 yielded "other" microbes (Table 3). In addition, 32 episodes were poly-microbial. The rank order of infecting organisms was culture-negative bacteria, *Streptococcus* sp. and *Staphylococcus aureus.*
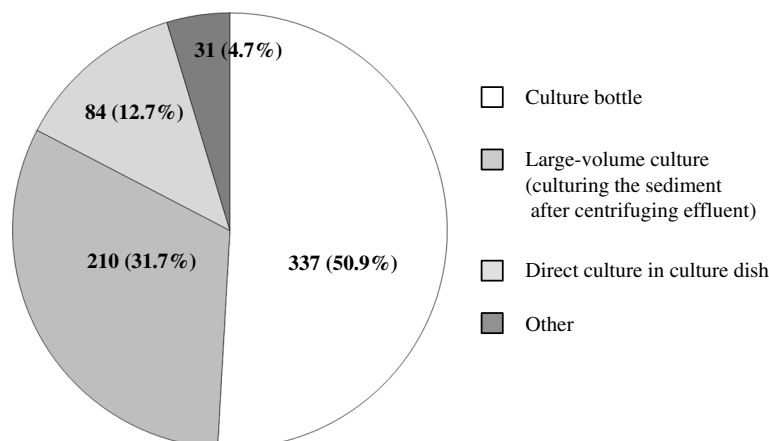
Antibiotic treatments

Initially, empiric antibiotic treatments were reported for 540 episodes (Fig. 3). Cefazolin (CEZ) was the most frequently selected agent, followed by ceftazidime (CAZ), vancomycin (VCM), cefotiam (CTM), and cefmetazole (CMZ). In total, 406 episodes (75.2 %) were treated with antibiotic combinations: the second antibiotic agents used in combination therapy included CAZ, tobramycin (TOB), VCM, CEZ, and amikacin (AMK). Only one case was treated empirically with three antibiotics. The most common combination therapy was CEZ + CAZ (112 cases).

Administration methods for first antibiotic agents included intraperitoneal (IP), 277 (51.4 %) cases and intravascular (IV), 250 (46.4 %) cases. Administration methods for second antibiotic agents were IP, 236 (59.4 %) cases and IV, 145 (36.5 %) cases. Mean treatment periods were 8.9 ± 5.6 days for first antibiotics and 8.0 ± 5.2 days for second antibiotics. The mean treatment period for cases receiving only empiric therapy was 10.8 ± 5.4 days.

After the first, empiric antibiotic administration, 278 cases were switched to targeted antibiotics; 79 of these were treated with two antibiotics and 5 were treated with three antibiotics. The mean total length of therapy with targeted antibiotics was 16.5 ± 9.3 days.

☐ Unknown	207	(38.1%)
☐ Touch contamination	130	(23.9%)
☐ Infection of intra-abdominal cavity	58	(10.7%)
☐ Exit-site tunnel infection	55	(10.1%)
☐ Others	32	(5.9%)
☐ No record	29	(5.3%)
☐ Defective device	23	(4.2%)
☐ Catheter operation	10	(1.8%)

Fig. 1 Causes of peritonitis

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Fig. 2 Effluent culture methods (including overlapping answers)

Legend:
- □ Culture bottle
- ▨ Large-volume culture (culturing the sediment after centrifuging effluent)
- ▨ Direct culture in culture dish
- ■ Other

Pie values: 31 (4.7%), 84 (12.7%), 210 (31.7%), 337 (50.9%)

Effect of treatment

Of the 544 peritonitis episodes, 461 (84.7 %) were able to continue PD treatments after the peritonitis resolved: 19 (3.5 %) underwent removal and reinsertion of the catheter. However, 80 (14.7 %) withdrew from PD treatment and

Table 3 Microbiology of peritoneal effluent cultures (including overlap)

Gram-positives	270
Staphylococcus aureus	52
Staphylococcus epidermidis	30
Methicillin-resistant *Staphylococcus aureus*	34
Other *Staphylococcus* sp.	23
Streptococcus sp.	75
Corynebacterium sp.	19
Enterococcus sp.	19
Other	18
Gram-negatives	116
Pseudomonas sp.	21
Serratia sp.	9
Alcaligenes sp.	0
Escherichia coli	25
Neisseria sp.	1
Stenotrophomonas maltophilia	3
Acinetobacter sp.	16
Klebsiella sp.	19
Citrobacter sp.	3
Other	19
Other	42
Candida sp.	6
Aspergillus	1
Other organism	35
Culture-negative	131

transferred to periodic hemodialysis treatment, and 6 (1.1 %) died. The prognosis of three patients was not obtained from the questionnaires.

The main microorganisms of cases withdrawn from treatment were as follows: methicillin-resistant *S. aureus* (MRSA), 12; *S. aureus*, 6; *Escherichia coli*, 6; other Gram-negative, 6; other bacteria, 6; *Streptococcus* sp., 5; *Pseudomonas* sp., 5; and culture-negative, 15. The total treatment period for peritonitis in these cases was 20.5 ± 13.7 (1~80) days.

Bacteria causative of the six deaths were as follows: MRSA, two; *Escherichia coli* (*E. coli*), one; *Pseudomonas* sp., one; other bacteria, one; and culture-negative, one. The course of one patient who died was complicated by hepatic carcinoma and relapsing peritonitis, and the infection routes in the other five patients were touch contamination, three; extension of intra-abdominal cavity infection, one; and unknown reason, one. Antibiotic administration methods were IP, one; IV, four; and oral, one. The mean treatment period for these six patients was 10.3 ± 5.5 days (range 1–17 days).

Antibiotic administration method and prognosis

We analyzed the influence of empiric antibiotic administration method on prognosis using Pearson's chi-square test (Fig. 4). In the oral administration group, the rates of mortality and catheter replacement were higher than those in the IV or IP groups. The rates of PD continuation, catheter replacement, withdrawal from PD, and mortality among groups of patients undergoing the three different antibiotic administration methods (oral, IV, and IP) were statistically different ($P < 0.0001$).

Clinical findings and PD treatment withdrawal

We examined the association of clinical findings and PD treatment withdrawal using logistic regression analysis. The dependent variable was withdrawal from PD

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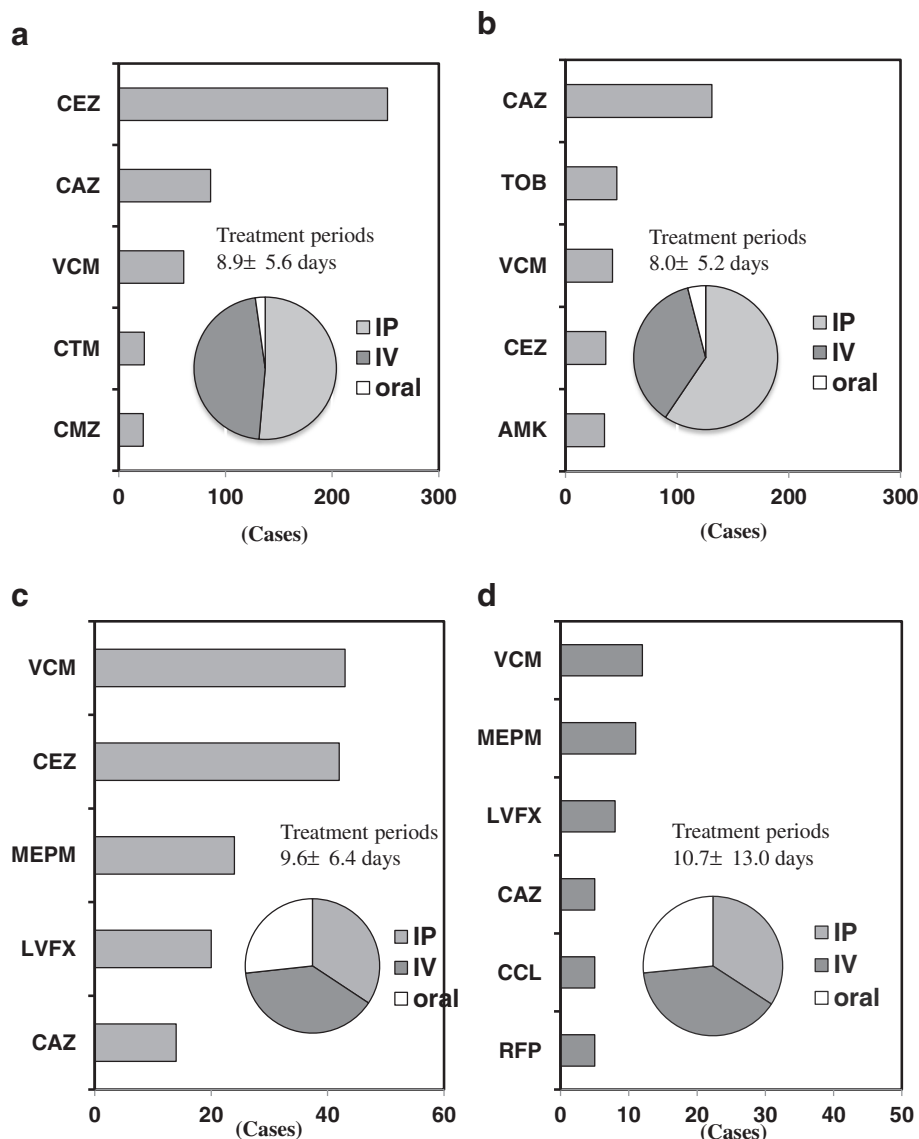
Fig. 3 Antibiotic therapy: administration methods and durations. **a** First empiric antibiotic (540 cases). **b** Second empiric antibiotic (406 cases). **c** Third antibiotic, targeted for known susceptibility (278 cases). **d** Fourth antibiotic, targeted for known susceptibility (79 cases). In total, 406 cases (75.2 %) were treated with combined empiric therapy; 278 cases were switched to targeted antibiotics after empiric antibiotic administration. Intraperitoneal administration: 277 (51.4 %) for first antibiotic and 236 (59.4 %) for second antibiotic. Total administration periods were 16.5 ± 9.3 days. *CEZ* cefazolin, *CAZ* ceftazidime, *VCM* vancomycin, *CTM* cefotiam, *CMZ* cefmetazole, *TOB* tobramycin, *AMK* amikacin, *MEMP* meropenem, *LVFX* levofloxacin, *CCL* cefaclor, *RFP* rifampicin, *IP* intraperitoneal cavity administration, *IV* intravenous administration

(including death); the independent variables were age, PD treatment period, original disease, exit-site infection, touch contamination, intra-abdominal cavity infection, infection from defective device and methodology, infection at catheter placement, and frequency of past peritonitis. We selected the statistically significant variables from these independent variables using the stepwise method; PD treatment period, exit-site infection, intra-abdominal cavity infection, and frequency of past peritonitis were then analyzed using logistic regression analysis. A significant association was observed between withdrawal from

PD treatment and exit-site infection (OR 2.56, $P = 0.007$) as well as between withdrawal from PD and frequency of past peritonitis (OR 3.041, $P < 0.0001$) (Table 4). Based on these results, exit-site infection and frequency of past peritonitis were considered important factors that affect the prognosis of PD peritonitis patients.

Discussion

In this study, we examined the characteristics of PD peritonitis patients in Japan in 2013 using a questionnaire survey. According to previous reports published by

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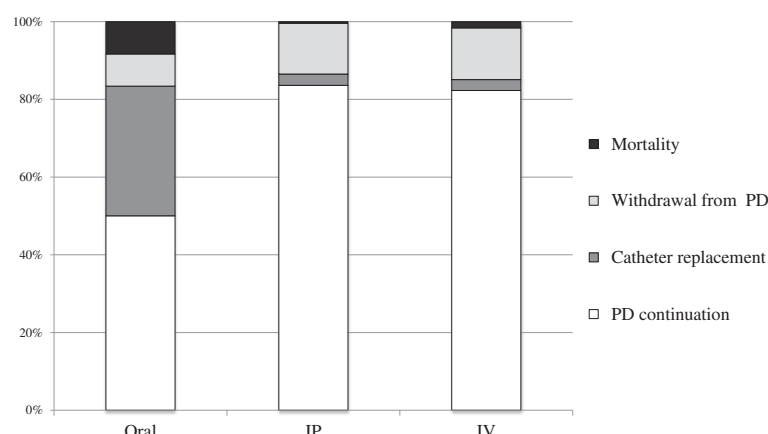
Fig. 4 Influence on prognosis of empiric antibiotic administration method. The rates of PD continuation, catheter replacement, interruption of PD, and mortality for the three different administration methods were statistically different (*P* < 0.0001). *PD* peritoneal dialysis, *IP* intraperitoneal cavity administration, *IV* intravenous administration

JSDT [3, 4], 9245 and 9510 patients were treated with PD therapy in 2013 and 2012, respectively, in Japan. In these statistical surveys, incidences of peritonitis in 2013 and 2012 were 0.22 and 0.21 episodes per year among 4197 and 4180 PD patients, respectively, compared to the current finding of 0.195 episodes per year among 3042 patients.

The reported incidences of peritonitis were 0.60, 0.95, and 0.29 episodes per year in Australia and New Zealand [5], the Netherlands [6], and Brazil [7], respectively. From these reports, the incidence of peritonitis in Japan can be considered a relatively good result. We think that one of the reasons for the low incidence of peritonitis is that in Japan, many patients use a machinery device to connect the dialysis fluid bag and the catheter. However, there was no statistical difference between manual and machinery device connection methods regarding the frequency of past peritonitis episodes. Since 2004, all glucose PD solutions have been changed to neutral-pH and low glucose degradation product (GDP) solutions in Japan. As there have been several reports that the peritonitis rate was

lower in patients using neutral-pH and low GDP solutions [8, 9], we considered whether this might be another reason for the low rate. However, a randomized study [10] demonstrated that the peritonitis rate was not statistically different between groups using the biocompatible PD solution or the conventional solution. This issue needs further analysis in future studies.

In this study, the main causes of peritonitis were "unknown cause," "touch contamination", and exit-site infections. Furthermore, about 50 % of patients experienced peritonitis one or more times before the study period. Physicians should evaluate in more detail the peritonitis etiology in each patient in an effort to prevent repeat and recurrent peritonitis.

In this study, and in previous national [2] and recent global [5, 6] studies, Gram-positive organisms were the most common pathogen. Coagulase-negative staphylococci and *S. aureus* were the most common organisms in many reports, but *Streptococcus* sp. were the most common in this study and in reports from Taiwan [11] and Spain [12].

In this study, 23.4 % of peritonitis cases were culture-negative. The International Society for Peritoneal Dialysis (ISPD) guideline recommendations [13] have stated that the culture-negative peritonitis rate should not be greater than 20 % of episodes and that the large-volume culture method (culturing the sediment after centrifuging the effluent) is recommended. However, only 31.7 % cases reported here included use of this method. We should encourage use of this culture method by educating the staff of PD hospitals.

Regarding empiric antibiotic treatment, CEZ was the most frequently selected therapy; 75.2 % cases were treated with combined antibiotics, and the most frequent second antibiotic was CAZ. ISPD guidelines/recommendations

Table 4 Association between interruption of PD and clinical findings

Catheter removed	Odds ratio	95 % CI interval	*P* value
PD treatment periods	1.005	0.997–1.012	0.1848
Exit-site tunnel infection	2.560	1.292–5.071	0.007
Infection of intra-abdominal cavity	1.585	0.769–3.269	0.212
Frequency of past peritonitis	3.041	1.787–5.1741	<0.0001

The association of several clinical findings and PD treatment withdrawal using logistic regression analysis. Four clinical findings were selected as statistically significant variables using the stepwise method, and exit-site tunnel infection and frequency of past peritonitis were significantly associated with withdrawal from PD treatment by logistic regression analysis

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[14] include use of combination antibiotics, such as vancomycin or cephalosporin along with third-generation cephalosporins, including CAZ, or aminoglycosides, to cover Gram-positive and Gram-negative organisms, respectively. This recommendation was introduced based on the efficacy results of a randomized controlled study of use of the combination CEZ and CAZ for empirical treatment [15]. Prolonged therapy with vancomycin may predispose to infections with vancomycin-resistant *S. aureus* (VRSA) or vancomycin-resistant enterococci (VRE). In this study, vancomycin was the third choice for empiric therapy. In Japan, there are no data regarding development of VRSA or VRE infection during use of vancomycin therapy in PD peritonitis patients. These issues need to be investigated in future studies. Treatment length with empiric therapy was 8.9 ± 5.6 days, and the next antibiotic regimen was administered for 16.5 ± 9.3 days in this study. ISPD guidelines/recommendations suggest that the minimum treatment period should be 2 weeks, and 3 weeks is recommended for more severe infections. In this study, 48.5 % were treated by only empiric therapy for 10.8 ± 5.4 days. We thought the treatment period in our country was shorter than the recommended period. However, the length of therapy in the ISPD guideline is based on opinions, and we need further research to firmly establish the optimal treatment period.

After a peritonitis episode, 84.7 % were able to continue PD treatment, 14.7 % withdrew from PD treatment, and 1.1 % (six patients) died. The obvious causative pathogens for these six were MRSA, *E. coli*, and *Pseudomonas* sp., and the treatment periods were 10.3 ± 5.5 days. Refractory peritonitis should be managed by catheter removal when treatment fails after 5 days of appropriate antibiotics [13]. MRSA and *Pseudomonas* sp. are known, common causes of refractory peritonitis, and we suggest that in these six cases, the catheter should have been removed at an earlier time.

The recommendations state that the preferred administration method of antibiotics is IP compared to IV or oral dosing, since IP dosing results in very high local levels of antibiotics. However, 46.2 and 2.2 % of cases in this study were dosed by IV and oral routes, respectively, for empiric therapy. Among the six patients who died, routes were IP, one; IV, four; and oral, one. We analyzed the influence of the empiric antibiotic administration method on prognosis and found that the rates of PD continuation, catheter replacement, withdrawal from PD, and mortality in the three groups were statistically different. We should emphasize the importance of IP antibiotic administration for PD peritonitis. We analyzed the influence of clinical findings on prognosis and found that exit-site infection and frequency of past peritonitis episodes were important factors. Ultrasonography can facilitate the diagnosis of exit-site infections

[16]. For prevention of peritonitis from these infections, management issues, such as use of ultrasonography, antibiotic administration timing and duration, and timing of catheter replacement, should be considered. Recurrent peritonitis has a lower primary response rate to antibiotics, a lower complete cure rate, and a higher mortality rate compared with first peritonitis episodes and relapse peritonitis [17]. It was reported that the total training time and the timing of training for performance of PD are associated with the peritonitis incidence rate [7]. We need to consider methods to lower the incidence of recurrent and repeat peritonitis, including better analysis of etiology and improved individual patient retraining.

Limitations

This study analyzed data from approximately one third of all Japanese PD patients. We could not obtain the demographics for all 3042 PD patients, and we could not make comparisons with data from non-peritonitis patients. Another weakness of this study was the retrospective nature of data collection. More large-scale and prospective studies that include non-peritonitis patients are needed to clarify the current status of Japanese PD peritonitis.

Conclusions

We summarized the state of peritonitis in the setting of PD in 2013 in Japan. The incidence of peritonitis was 0.195 episodes per year; 84.7 % continued PD therapy after peritonitis, and 1.1 % died. We identified some targets for improvement in Japan. There were high rates of peritonitis of unknown cause and culture-negativity and low rates of use of the large-volume culture method and IP administration of antibiotics. Exit-site infection and frequency of past peritonitis were independent risk factors for withdrawal from PD treatment. These results indicate that we need to improve etiology determination through the use of better effluent culture techniques and more rigorous pathogen identification, increased use of the optimal antibiotic administration method, and improved patient education.

Additional file

Additional file 1: Questionnaire regarding peritonitis. (XLSX 17 kb)

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