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Original Article

Clinical Significance and Outcomes of Initial No Growth Peritonitis from Peritoneal Dialysis Patients: Role of Mycobacterial or Fungal Peritonitis

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Purpose: Peritoneal dialysis associated peritonitis (PD peritonitis) is an important complication in maintaining. There have been only a few reports on the clinical outcome of initial no-growth peritonitis (INGP).
Methods: We reviewed 332 episodes of PD peritonitis between January 2002 and August 2009. INGP was defined as PD peritonitis with no growth of etiologic microorganism within 3 days of peritonitis. INGP was compared with initial positive growth peritonitis (IPGP) in view of clinical manifestations and outcomes.
Results: We divided PD peritonitis episodes into two groups: INGP (n=90) and IPGP (n=242). Peritonitis-related mortality was 5.6 % in INGP, while 0.8 % in IPGP (p=0.017). Further relapse was noted in INGP (10.0%) than in IPGP (vs. 4.1%; p=0.041). Salvage antibiotics were used more frequently in INGP (21.1%) than in IPGP (vs. 11.6%; p=0.027). Odds ratio of INGP to IPGP for peritonitis-related mortality was 7.14 (95% CI 1.36-37.51; p=0.017). Growth of mycobacteria or fungi increased the risk of peritonitis-related mortality with an odds ratio of 18.11 (95% CI 2.99-109.89; p=0.013). In multivariate analysis, growth of mycobacteria or fungi was the only independent risk factor for peritonitis-related mortality with an odds ratio of 10.63 (95% CI 1.27-88.75; p=0.029).
Conclusion: INGP revealed poorer outcome than IPGP. Higher growth rate of mycobacteria or fungi in INGP than in IPGP accounted for the poor outcome. Thus one should make vigorous efforts to detect surreptitious organism when there is no growth by 3 days, especially for the possibility of either mycobacteria or fungi.

Key Words: Peritoneal dialysis, Peritonitis, Mycobacterium, Fungi, Fatal outcome

INTRODUCTION

Peritoneal dialysis associated peritonitis (PD peritonitis) is one of the most important complication and is a leading cause of technique failure in PD patients [1-3]. Although gram-positive organisms are the most common cause of PD peritonitis[4], cultures of PD

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effluent may be negative for a variety of clinical or technical reasons with various rates[5-9]. By virtue of consecutive studies on PD peritonitis, several guidelines are available for effective prevention and treatment of PD peritonitis[10-12]. However, most studies and guidelines are based on identified organisms and few recommendations are available when the culture result is negative[10, 12]. This is due to the lack of concerns about culture-negative peritonitis (CNP) and their clinical outcomes. In fact, culture-negative peritonitis has been believed to have a benign[7-8, 13] or at least similar outcome[9], compared to culture-positive peritonitis (CPP).

However, previous studies on culture-negative peritonitis have limitations in clinical application, where the definition of culture-negative and/or -positive peritonitis relied on the final outgrowth of any micro-organism. Although in over 75% of peritonitis cases, microbiologic diagnosis can be made within 3 days[10], some fastidious microorganisms are not isolated within that period of time but isolated only by prolonged or repeated cultures. Therefore, microbiologic information for such micro-organisms is sometimes unavailable during early days of peritonitis, and for such cases, clinicians have to decide proper treatment strategy without microbiologic information.

ISPD guideline recommends for clinicians to repeat cell count with differential if there is no growth within 3 days after peritonitis development. It also suggests employing special culture techniques for the isolation of unusual organisms, if the repeated cell count has not resolved[10]. However, this recommendation is largely based on one outdated study[7] which adopted the concept of initial no growth peritonitis (INGP), but had no consideration of interim culture result. Thus, we performed this retrospective study for the clinical significance of initial no growth peritonitis (INGP), tentatively defined as the peritonitis with no growth of etiologic microorganism by 3 days. The purpose of the present study was to determine the clinical manifestation, treatment course and outcome of INGP as compared to initial positive growth peritonitis (IPGP) and to explore factors associated with their outcome.

MATERIALS AND METHODS

All episodes of PD peritonitis in our unit from January 2002 to August 2009 were reviewed. 82.8% of episodes were on continuous ambulatory PD (CAPD) and 17.2 % were on automated PD. 5.4% of episodes used icodextrin based dialysis solution at least one time of their dialysis sessions. In episodes on CAPD, 65.5% of episodes were prescribed to instill 2 L of dialysis solution every 6 hours. The diagnosis of PD peritonitis was based on at least 2 of the following criteria: 1) abdominal pain or cloudy effluent, 2) white blood cell (WBC) >100/μL with polymorphonuclear (PMN) leukocyte >50% in the effluent and 3) positive result on gram-stain/culture. Episodes with eosinophilc peritonitis and peritonitis due to mixed organisms as well as episodes without clinical follow-up were excluded (Fig. 1).

1. Culture methods and standard antibiotic protocol for PD peritonitis

Two types of culture methods were employed in the entire study period. From January 2002 to September 2007, we inoculated 20 mL effluent directly

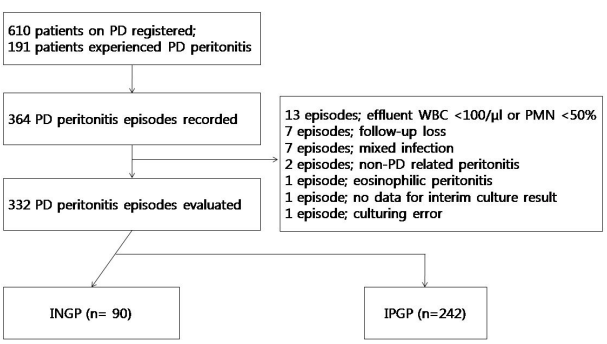

Fig. 1. Selection of PD peritonitis episodes for analysis. WBC, white blood cell; PMN, polymorphonuclear leukocytes; INGP, initial no growth peritonitis; IPGP, initial positive growth peritonitis.

into blood-culture bottles (direct inoculation method). Since October 2007, we centrifuged 50 mL effluent and inoculated the sediment (inoculation after centrifugation method), following the ISPD guideline[10].

Peritonitis was treated by the standard antibiotic protocol of our center, which had been adjusted to the contemporary consensus for covering both gram-positive and -negative organisms (Table 1). The antibiotics were administrated by intra-peritoneal route in 97.2% of peritonitis episodes, and by intravenous route in 2.8% of peritonitis episodes. If we had a positive interim culture result, then we adjusted the regimen according to the susceptibility test. In case of a negative interim culture result, we maintained the initial antibiotic regimen, unless the peritonitis course became worse. If any evidence of worsening peritonitis became apparent, vancomycin with or without carbapenem was instilled, and further efforts to identify causative microorganism, such as repeating culture, serologic test for fungi or virus, polymerase chain reaction (PCR) test for Mycobacterium tuberculosis were performed. Catheter removal was considered if PD peritonitis was further aggravated despite administration of appropriate antibiotics.

We reviewed demographic characteristics, underlying medical conditions, previous episode of peritonitis, antibiotic therapy within 30 days prior to the development of PD peritonitis and antibiotic regimen for each peritonitis episode.

2. Definition of clinical outcomes and each culture group

We defined the clinical outcomes of peritonitis as reported elsewhere[8-10]. In this analysis, peritonitis-related mortality was the primary outcome to be compared, which was defined as death without improvement of peritonitis. Relapse of peritonitis was defined as the recurrence of peritonitis by any organism in case of INGP and by same organism in case of IPGP, within 30 days after completing antibiotic therapy. Treatment failure was defined as removal of the peritoneal catheter, dropout to hemodialysis or death, while cure was defined as the complete resolution of peritonitis without relapse within 30 days following completion of therapy. Modality preservation was defined as no need of catheter removal in treating peritonitis or successful restart of PD in case the catheter was removed. We considered any hospital stay related to peritonitis as hospitalization due to peritonitis.

The definition of each culture group is as follows; INGP was defined as peritonitis with no isolation of causative microorganism within 3 days[10], while IPGP was defined as peritonitis with etiologic organisms identified by 3 days. We defined CNP as peritonitis with no etiologic microorganism identified throughout the peritonitis course, while CPP as peritonitis with the causative organisms identified at any time during the course.

3. Statistical analysis

Continuous variables were expressed as mean± standard deviations (SD). Nominal variables were expressed as percentages (%). Data which could not achieve completeness over 90% were discarded. Chi-square test and Fisher`s exact test were used for categorical variables. Student t-test and Mann-Whitney U test were used for continuous variables. SPSS

Table 1. Standard Antibiotic Protocols for the Initial Empirical Antibiotic Treatment of PD Peritonitis at Various Time Periods in Our Unit

Time	Standard antibiotic potocol
Jan/2002-Aug/2005	Cefazolin+(Ceftazidime or Tobramycin)+clindamycin
Sep/2005-Jun/2006	Cefazolin+(Ceftazidime or Tobramycin or Amikacin)
July/2006-Aug/2009	Cefazolin+Ceftazidime

ver. 17.0 statistical software program (SPSS, Chicago, Illinois, USA) was used for this analysis. Value of $p<0.05$ was considered to be statistically significant.

RESULTS

During the study period, a total of 610 patients were on PD in our unit. Among them, 191 patients experienced at least one episode of PD peritonitis and 7 patients died from it. A total of 364 episodes were recorded and treated as PD peritonitis, but 32 episodes were excluded: 13 episodes did not meet the diagnostic criteria, 7 episodes were mixed infection, 7 episodes lost their clinical follow-up before completion of the treatment, two episodes were non-PD associated peritonitis and each one episode with eosinophilic peritonitis, no data for interim culture result and culturing error, respectively, was noted (Fig. 1). However, there were no significant differences in the demographic and clinical profiles between included and excluded episodes (data not shown).

With the direct inoculation method from January 2002 to September 2007, the rates of CNP and INGP were 16.2% and 23.7%, respectively. However, as a new culture method of inoculation after centrifugation was employed since October 2007, higher rates of CNP (vs. 30.8%, p=0.003) and INGP (vs. 36.3%, p=0.021) were obtained. This might have resulted from technical instability of the new culture method. However, the rates of CNP and INGP decreased, as the culture technique became stabilized (22.6% and 25.8 %, respectively in the early 2009). Although culturing method affected the proportion of INGP, isolation of mycobacteria or fungi by direct inoculation method (3.7%, 9 of 241) was not different from that obtained by inoculation after centrifugation method (vs. 1.1%, 1 of 91; p=0.296).

Among the 332 peritonitis episodes included in the analysis, there were 90 episodes (27.1%) of INGP and 242 episodes (72.9%) of IPGP. As shown in the Table 2, INGP and IPGP showed similar profiles of baseline demographics and clinical data.

Organisms isolated from peritoneal dialysis fluid are shown in Table 3. In INGP, 67 episodes (74.4%) ultimately ended up with no growth. However, by prolonged and/or repeated cultures, gram-positive organisms were isolated from ten episodes (11.1%), gram-negative organisms from five (5.6%), fungi from three (3.3%), and mycobacteria from five (5.6%): gram-positive organisms were three *Corynebacterium* species, four *Enterococcus* species and each one of Methicillin-resistant coagulase-negative *Staphylococcus*, *Streptococcus* species and *Erysipelothrix* species; five gram-negative organisms were *Haemophilus* species, *Pseudomonas* species, *Acinetobacter* species, *Bacteroides* species and *Flavimonas* species; three fungi were two *Aspergillus* and one *Scedosporium* species ; five mycobacteria were two non-tuberculous mycobacteria and three *Mycobacterium tuberculosis*. In IPGP, 157 episodes (64.9%) exhibited gram-positive organisms, 83 episodes (34.3%) gram-negative organisms and two episodes (0.8%) fungi: the two fungi were *Candida albicans* and *Candida tropicalis*. Among the 23 microorganisms identified by prolonged or repeated culture, 11 organisms were isolated between 4 and 7 days, while 13 organisms were identified thereafter. In IPGP, most of organisms (n=237, 85.5%) were isolated between 24 and 72 hours.

There were 19 episodes of relapsed peritonitis during the study period. In INGP, nine episodes were relapsed and the relapsed microbes were two gram-positive organisms, three gram-negative organisms and five culture-negative organisms. In IPGP, ten episodes were relapsed and the relapsed microbes were seven gram-positive organisms and three gram-negative organisms (supplementary Table 1).

1. Clinical outcome

Overall clinical outcome is shown in Table 4. Peritonitis-related mortality was 5.6% in INGP, while 0.8% in IPGP (p=0.017). More relapse was noted in

INGP than in IPGP (10.0% vs. 4.1%; p=0.041). Salvage antibiotics were used more frequently in INGP than in IPGP (21.1% vs. 11.6%; p=0.027). Treatment failure was higher in INGP than in IPGP with only marginal significance (18.9 % vs. 11.6 %; p=0.083). INGP was not different from IPGP in term of cure rate (70.0% vs. 76.4%; p=0.230), modality preservation rate (85.4% vs. 90.9%; p=0.148) and hospitalization rate (38.9% vs. 32.6%; p=0.287).

Among 7 mortality cases, the causes were three uncontrolled sepsis, one intra-abdominal abscess and one bowel perforation in INGP, and one uncontrolled sepsis and one bowel perforation in IPGP. Unadjusted odds ratio of INGP to IPGP in peritonitis-related mortality was 7.14 (95% CI 1.36-37.51; p=0.017). Growth of mycobacteria or fungi did increase the risk of peritonitis related mortality with an odds ratio of 18.11 (95% CI 2.99-109.89; p=0.013, Table 5). Besides, there was no interaction between peritonitis-related mortality and various known and/or possible risk factors: age group, sex, history of recent antibiotics use, changing culture method, changing standard

Supplementary Table 1. Organisms Isolated from Relapsed Peritonitis after PD Peritonitis

	INGP* (n=9)	IPGP† (n=10)
Gram-positive- no.	2	7
Gram-negative- no.	3	3
Fungus- no.	0	0
Mycobacteria- no.	0	0
No growth- no.	4	0

*INGP is defined as peritonitis with no causative organisms isolated within 3 days.
†IPGP is defined as peritonitis with etiologic organisms isolated within 3 days.
Abbreviations: INGP, initial no growth peritonitis; IPGP, initial positive growth peritonitis.

Table 2. Baseline Demographic and Clinical Characteristics of PD Peritonitis

	INGP* (n=90)	IPGP† (n=242)	p-value
Age at PD Peritonitis (years)	50.9±14.0	51.5±14.0	0.744
Sex (female %)	41.1	33.9	0.222
Time on PD (years)	2.7±2.9	3.3±2.8	0.058
Type of PD (CAPD %)	83.3	82.6	0.882
No. of previous PD peritonitis (mean±SD)	0.9±1.1	1.2±1.6	0.086
Recent antibiotics use‡			0.250
No (%)	75.6	83.1	
Yes (%)	24.4	16.9	
Use due to peritonitis (%)	16.7	10.3	
Use due to infection other than peritonitis (%)	7.8	6.6	
Davies comorbidity score			0.417
0 (%)	45.6	42.1	
1-2 (%)	47.8	46.3	
3-7 (%)	6.7	11.6	
Diabetes (%)	35.6	45.0	0.120
Etiology of Renal failure			0.051
Unknown (%)	22.2	28.5	
Diabetic nephropathy (%)	25.6	36.0	
Chronic glomerulonephritis (%)	33.3	23.6	
Others (%)	18.9	12.0	
Culture method			0.021
Direct inoculation method (%)	63.3	76.0	
Inoculation after centrifugation method (%)	36.7	24.0	

*INGP is defined as peritonitis with no causative organisms isolated within 3 days.
†IPGP is defined as peritonitis with etiologic organisms isolated within 3 days.
‡Recent antibiotics use is defined as antibiotics used within 30 days prior to the onset of PD peritonitis.
Abbreviations: PD, peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; INGP, initial no growth peritonitis; IPGP, initial positive growth peritonitis.

antibiotic protocol, diabetes and Davies comorbidity score.

Fig. 2 depicts the proportion of mycobacteria or fungi in various conditions: 8.9% in INGP (8 of 90), 0.9% in IPGP (2 of 242) and 3.0% in the total peritonitis (10 of 332). The diagnosis of mycobacterial or fungal peritonitis was based on any outgrowth of mycobacteria or fungi on culture, positive serologic test, or positive PCR test in case of *Mycobacterium tuberculosis*. Mean duration from initial antibiotics instillation to confirmative diagnosis was 28.2±15.7 days in mycobacterial peritonitis, and 9.0±6.1 days in fungal peritonitis. Among the eight episodes of mycobacterial or fungal peritonitis in INGP, five (62.5%) were isolated by repeated culture, while three (37.5%) were isolated by prolonged culture. As soon as identification of the pathogen, anti-mycobacterial or anti-fungal agents were applied for 166.8±154.4 days in mycobacterial peritonitis and 43.3±32.5 days in fungal peritonitis. 2 of 5 mycobacterial peritonitis removed catheter on 8.0±1.4 days of the clinical course, whereas 4 of 5 fungal peritonitis did on 7.5±1.7 days of the clinical course. In multivariate analysis, growth of mycobacteria or fungi remained as a substantial risk factor for peritonitis-related mortality with an odds ratio of 10.63 (95% CI 1.27-88.75; p=0.029, Table 5), while INGP lost its significance (odds ratio, 5.77; 95% CI 0.99-33.66; p=0.051).

Table 3. Finally Identified Organism from Peritoneal Dialysis Fluid by Initial or Subsequent Culture

	INGP* (n=90)	IPGP† (n=242)
Gram-positive- no. (%)	10 (11.1)	157 (64.9)
Gram-negative- no. (%)	5 (5.6)	83 (34.3)
Fungus- no. (%)	3 (3.3)	2 (0.8)
Mycobacteria- no. (%)	5 (5.6)	0 (0)
Final no growth- no. (%)	67 (74.4)	0 (0)
Days of isolation		
Within 24 hours- no. (%)	0 (0)	35 (14.5)
24-72 hours- no. (%)	0 (0)	207 (85.5)
4-7 days- no. (%)	11 (12.2)	0 (0)
8 days - - no. (%)	12 (13.3)	0 (0)

*INGP is defined as peritonitis with no causative organisms isolated within 3 days.
†IPGP is defined as peritonitis with etiologic organisms isolated within 3 days.
Abbreviations: INGP, initial no growth peritonitis; IPGP, initial positive growth peritonitis.

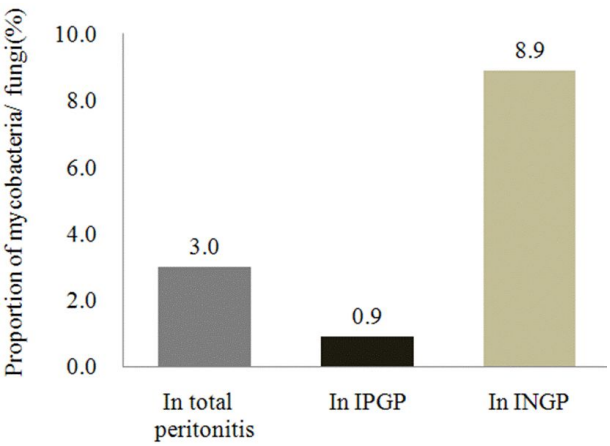

Fig. 2. Proportion of mycobacteria/fungi in PD peritonitis in various conditions. INGP, initial no growth peritonitis; IPGP, initial positive growth peritonitis.

Table 4. Hospital Course and Clinical Outcome of INGP and IPGP

	INGP* (n=90)	IPGP† (n=242)	p-value
Duration of antibiotics (days)	22.3±20.6	19.7±9.4	0.258
Peritonitis-related mortality (%)	5.6	0.8	0.017
Relapse (%)	10.0	4.1	0.041
Salvage antibiotics use (%)	21.1	11.6	0.027
Treatment failure (%)	18.9	11.6	0.083
Cure (%)	70.0	76.4	0.230
Modality preservation (%)	85.4	90.9	0.148
Hospitalization (%)	38.9	32.6	0.287

*INGP is defined as peritonitis with no causative organisms isolated within 3 days.
†IPGP is defined as peritonitis with etiologic organisms isolated within 3 days.
Abbreviations: INGP, initial no growth peritonitis; IPGP, initial positive growth peritonitis.

Table 5. Unadjusted and Adjusted Odds Ratio of Various Risk Factors for Peritonitis-Related Mortality

	Unadjusted		Adjusted*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
INGP (vs. IPGP)	7.14 (1.36-37.51)	0.017	5.77 (0.99-33.66)	0.051
McB/Fungi (vs. non-McB/Fungi)	18.11 (2.99-109.89)	0.013	10.63 (1.27-88.75)	0.029
Sex (female vs. male)	0.72 (0.14-3.76)	1.000	0.66 (0.11-3.93)	0.643
Age group (≥55 years vs.<55 years)†	2.63 (0.50-13.74)	0.277	3.12 (0.52-18.95)	0.216
Recent antibiotics use (vs. nouse)		0.718		0.980
Use due to peritonitis	1.35 (0.15-11.85)	0.569	0.79 (0.08-8.14)	
Use due to infection other than peritonitis	2.39 (0.27-21.38)	0.393	0.97 (0.07-13.48)	
Davies Comorbidity score (vs. 0)		0.735	-	-
1-2	1.85 (0.33-10.28)	0.686		
3-7	2.12 (0.19-24.10)	0.477		
Diabetes (yes vs. no)	0.53 (0.10-2.79)	0.703	-	-
Culture method‡ (method 1 vs. method 2)	2.31 (0.27-19.44)	0.678	-	-
Standard antibiotic protocol∬		0.771	-	-
Protocol B (vs. protocol A)	1.13 (0.12-10.45)	1.000		
Protocol C (vs. protocol A)	0.57 (0.10-3.14)	0.689		

*Adjusted variables are age group, sex, history of recent antibiotics use, INGP or IPGP, McB/Fungi or not.
†Age group is divided by median value of age in the total PD peritonitis episodes.
‡Method 1 designated direct inoculation method during Jan/2002-Sep/2007.
Method 2 meant inoculation after centrifugation method during Oct/2007-Aug/2009.
∬Protocol A denotes cefazolin & clidamycin and either ceftazidime or aminoglycoside (Jan/2002-Aug/2005).
Protocol B denotes cefazolin and either ceftazidime or aminoglycoside (Sep/2005-Jun/2006).
Protocol C denotes cefazolin and ceftazidime (Jul/2006-Aug/2009).
Abbreviations: INGP, initial no growth peritonitis; IPGP, initial positive growth peritonitis; McB, mycobacteria.

DISCUSSION

In this retrospective study, we analyzed 332 episodes of PD peritonitis in our unit from January 2002 to August 2009. We divided peritonitis episodes into INGP and IPGP, depending on whether any causative microorganism is identified within 3 days of peritonitis development. That is, the definition of INGP is based on the interim culture result, while CNP is based on the final outgrowth of causative organisms. In the clinical perspective, the concept of INGP could be more relevant, because clinicians are sometimes faced with therapeutic decisions for treating PD peritonitis without microbiologic information if timely identification of the etiologic microorganism is not made, regardless of final outgrowth of the causative microorganism. Following ISPD guideline[10], we defined the interim culture report as the microbiologic information obtained within 3 days after the onset of peritonitis. Although Bunke et al. classified peritonitis into culture-positive and culture-negative peritonitis, subsequently referred to as initial no growth peritonitis, he and his colleagues had no consideration of interim time courses. They defined INGP as peritonitis with negative initial culture results at the end, which was still based on the final outgrowth[7]. In the present study, INGP accounted for 27.1% of all PD peritonitis, while CNP was 20.2% of all PD peritonitis in the study period. The proportion of CNP in our study was similar to that of the previously reported series[5, 7-10]. The discrepancy between the proportion of INGP and CNP can be attributed to the presence of some organisms isolated beyond 3 days in INGP, of which proportion in the total PD peritonitis was up to 6.9%. As this was the first study which adopted the concept of "interim" in the course of PD peritonitis, the proportions of INGP and organisms isolated beyond 3 days among the total peritonitis are not comparable.

Various outcomes including peritonitis-related mor-

tality of CNP in our study were not different from those in CPP except for higher relapse rate in CNP compared with CPP (data not shown). Such finding was consistent with the previous reports[7-9, 13]. In contrast to CNP, however, the clinical outcome of INGP was not satisfactory. The risk for peritonitis-related mortality was 7 times higher in INGP than in IPGP. INGP relapsed more frequently than IPGP. Moreover, more salvage antibiotics were needed to treat INGP than to treat IPGP. We thought this poor outcome resulted from the presence of organisms isolated beyond 3 days, especially mycobacteria or fungi, since both mycobacteria and fungi were generally considered as risk factor for poor outcomes[14-17]. In this study, growth of mycobacteria or fungi increased the risk of peritonitis-related mortality up to 18 times higher than growth of other organisms. Moreover, from INGP, mycobacteria or fungi were 3 times more common than from the total peritonitis and nearly 10 times more common than from IPGP. But the risk factors of fungal peritonitis, such as recent antibiotics use, administration of systemic steroid or immunosuppressive agent, use of PD solution with high glucose concentration and the presence of leucopenia or malignancy were not different between INGP and IPGP. In multivariate analysis, growth of mycobacteria or fungi was the only risk factor for the peritonitis related mortality (p=0.029), while INGP lost statistical significance (p=0.051).

We noticed that the overall prevalence of mycobacterial or fungal peritonitis was low. As mycobacterial peritonitis itself rarely developed, and so there were a paucity of studies on this issue, it has been believed to constitute 1-2% of all cases of peritonitis[18]. This study revealed similar proportion (1.5%, 5 of 332). However, the prevalence of fungal peritonitis (1.5%, 5 of 332) in this study was somewhat low when compared with the previous studies, which reported the prevalence of fungal peritonitis in a range between 1% and 15%[15, 16, 19-22]. Furthermore relatively lower proportion of *Candida* species (40%, 2 of 5) was noted as causative organisms, which was different from the previous reports, where *Candida* species predominated[16]. We could not conclude that low prevalence of fungal peritonitis and lower proportion of *Candida* species in this study represented distinct characteristics of Korean patients or not, since this study was performed in a single PD unit of a tertiary care hospital. However, these uncertainties may not affect the above-mentioned poor outcome of INGP, as both yeast and filamentous mold grow slowly[15, 16] and tend to be classified as INGP with negative impact on the outcome of INGP.

We have changed our standard antibiotic protocol and culture method flexibly reflecting contemporary consensus, mostly based on the ISPD guideline[10, 23]. And the changing culture method and antibiotics protocol had no association with peritonitis-related mortality. In the present study, the direct inoculation method (January 2002-September 2007) revealed lower rate of CNP and INGP than inoculation after centrifugation method (October 2007-), but this did not mean the superiority of direct inoculation method. This finding might be confounded by technical instability, and we believed the rate of CNP and INGP in inoculation after centrifugation method would be further decreased as the new system got firmly established. Although changing culture method affected the prevalence of INGP, the prevalence of mycobacterial or fungal peritonitis was not influenced by that change. Despite remaining controversies[8, 9], history of recent antibiotics use is generally thought to be associated with the development of culture-negative peritonitis[9, 24] and poor outcome[9]. However, we could not find the association between recent antibiotics use and the development of INGP or peritonitis-related mortality. This controversial result of the effect of recent antibiotics use might be derived from the definition of the "recent". In this study, we defined "recent" as "within 30 days prior to the peritonitis development", following previous reports[8, 9, 13], and 30 days might be too long in assessing remaining effect of the previous

antibiotics, since most of the antibiotics used in PD patients[10, 25, 26] had half life of less than 2 days. For the accurate conclusion on the effect of recent antibiotics use, number of days between recent antibiotics use and peritonitis development needs to be analyzed as a continuous variable, albeit this was not always available in the retrospective setting[8, 9, 13]. Diabetes was not associated with the outcome of peritonitis in our study, as shown elsewhere[8, 9]. Furthermore, Davies comorbidity score which is related to the mortality in PD patients[27], had no relationship with outcome of PD peritonitis. As PD peritonitis is a local inflammation, growth pattern of the causative organism might be more important than the comorbidities.

As this was a retrospective single-center study, systematic collection of clinical information data was not always feasible. Furthermore, the number of organisms isolated beyond 3 days was not sufficient for statistical analysis. Prospective multi-center study needs to be followed.

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