Acta Med. Nagasaki 60: 145－151

Causative bacteria and risk factors for peritoneal dialysis-related peritonitis: A retrospective study

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Background: Although peritoneal dialysis (PD) is beneficial for patients with end-stage renal diseases (ESRD), there are some critical complications. PD-related peritonitis accounts for about 30% of all cases of catheter removal and transition to hemodialysis. We investigated the incidence, causative bacteria, and risk factors of PD-related peritonitis and peritonitis-related withdrawal in patients treated in the Nagasaki University Hospital.
Methods: Subjects were 43 PD patients in the Nagasaki University Hospital observed between January 1, 2008 and December 31, 2012. We established the incidence of PD-related peritonitis, investigated causative bacteria and culture-negative peritonitis rates, and examined potential risk factors, including laboratory data obtained at the commencement of PD.
Results: 20 episodes of peritonitis occurred in 12 patients during the observation period, and the incidence of PD-related peritonitis was one episode per 62 patient-months. The culture-negative peritonitis rate was 10%. In the isolated causative bacteria, 55% were Gram-positive cocci and 25% were Gram-negative rods. Two episodes were associated with methicillin-resistant *Staphylococcus aureus* (MRSA), and each episode was accompanied with an exit-site infection. PD catheter removal caused by PD-related peritonitis occurred in 4 patients. As a result of investigation for association between PD-related peritonitis and patient's factors including laboratory data, sex, age, and cause of ESRD, the patients who experienced PD-related peritonitis had significantly lower hemoglobin levels at the initiation of PD.
Conclusions: PD-related peritonitis remains an important complication of PD. We found that low hemoglobin level at the commencement of PD was a risk factor of PD-related peritonitis. In addition, MRSA peritonitis was a risk factor of peritonitis-related withdrawal. Thus, improvement in anemia might be important to prevent PD-related peritonitis. It is also important to prevent MRSA-associated peritonitis to avoid technical failure of PD.

ACTA MEDICA NAGASAKIENSIA 60: 145－151, 2016

Key words: peritoneal dialysis, peritonitis, methicillin-resistant *Staphylococcus aureus*, exit-site infection

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Received May 22, 2015; Accepted February 1, 2016

Introduction

Peritoneal dialysis (PD) is beneficial for patients with end-stage renal diseases (ESRD), along with hemodialysis (HD) and renal transplantation [1]. In addition to being superior to HD for maintenance of residual renal function (RRF), PD also provides better quality of life [2, 3]. Despite the fact that there are more than 300,000 chronic dialysis patients in Japan, only 10,000 or 3.1% of them use PD, this rate being substantially lower than the global average of about 11% [4, 5]. Although there are few discussions about why the PD population has not increased, one of the reasons is early withdrawal (within three years from commencement of PD). Importantly, PD-related peritonitis account for 32.5%–50% of cases of early withdrawal from PD [5, 6], and it may contribute to the lower PD rate in Japan.

In this study, we retrospectively investigated the incidence, causative bacteria, and risk factors of PD-related peritonitis in PD patients observed in our hospital to reduce the prevalence of PD-related peritonitis and prevent early PD withdrawal.

Materials and methods

Subjects were 43 ambulatory PD patients treated in the Nagasaki University Hospital from January 1, 2008 to December 31, 2012. We investigated the incidence, causative bacteria, and culture-negative rate of PD-related peritonitis. We also retrospectively analyzed risk factors of PD-related peritonitis such as age, sex, cause of ESRD, serum albumin level, serum β_2-microglobulin level, urine volume, serum hemoglobin level, body mass index (BMI), presence of diabetes mellitus (DM), and modality of PD (continuous ambulatory PD (CAPD) or automated PD (APD). These data were collected immediately (within 1 month) before commencement of PD. Peritonitis was diagnosed according to the guidelines of the International Society for Peritoneal Dialysis (ISPD) [7]. Causative bacteria were determined by culture of PD effluent.

All values are shown as means ± standard deviations (SD). We used the Mann-Whitney U test and the Fisher's exact test to analyze the presence of significant differences. Values of $p < 0.05$ were considered to indicate statistical significance. Statistical analyses were performed using the Stat View ver. 5.0 software (SAS institute Inc., NC, USA).

This study was approved by the ethics committees of the Nagasaki University Hospital (approval number: 14052653).

Results

Basic characteristics of the PD patients

The average age of the 43 patients at the initiation of PD was 55.7 years, and there were more men than women (69.8%). The main causes of ESRD included chronic glomerulonephritis in 46.5%, diabetic nephropathy in 27.9%, and nephrosclerosis in 18.6% of the cases. Patients who underwent CAPD and APD constituted 60.5% and 39.5%, respectively. The basic patients' characteristics, including mean BMI, laboratory data, and urine volume at initiation of PD, are shown in Table 1.

PD-related peritonitis

In the observation period, 20 episodes of PD-related peritonitis occurred in 12 PD patients, and the incidence of PD-related peritonitis was one episode per 62 patient-months. Thirteen patients were withdrawn from PD, including 4 (30.8%) because of PD-related peritonitis. The most frequent causative bacteria was *Streptococcus salivarius* (25.0% of the cases), followed by methicillin-resistant *Staphylococcus aureus* (MRSA, 10.0%). The culture-negative rate was 10.0% (Table 2). In the isolated causative bacteria, 55% were Gram-positive cocci and 25% were Gram-negative rods (Fig. 1a). The analysis of the flora revealed that the most frequent causative bacteria were oral bacteria (40.0% of cases), followed by skin bacteria (25.0%) and intestinal bacteria (25.0%) (Fig. 1b). Moreover, it is notable that 4 patients (33.3%) of all 12 patients experienced their first peritonitis within 12 months after the commencement of PD (Fig. 1c).

Two episodes of PD-related peritonitis caused by MRSA occurred in two different patients. One patient experienced an exit-site infection (ESI), whereas the other suffered from both exit-site and tunnel infections. MRSA was detected in all the infected tissues of these two patients. Attempts to treat these episodes of MRSA-associated peritonitis with anti-MRSA drugs were unsuccessful. The patients were eventually diagnosed with refractory peritonitis and transferred to HD from PD.

Risk factors of PD-related peritonitis

We retrospectively analyzed the risk factors of PD-related peritonitis such as age, serum albumin level, serum β_2-microglobulin level, urine volume, serum hemoglobin level, BMI, presence of DM, sex, cause of ESRD, and modality of PD. Urine volume and serum β_2-microglobulin level were

used as the indicators of RRF. We found that only hemoglobin level significantly correlated with the incidence of PD-related peritonitis (Fig. 2, 3). Multivariable logistic regression adjusted for relevant factors also showed that serum hemoglobin level significantly correlated with the incidence of PD-related peritonitis (Table 3).

Table 1 Basal characteristics of the 43 patients and reasons for the technical failure of PD from 2008 to 2012

Parameter	Value
Total number of patients	43
Age (years)	55.7 ± 16.1[a]
Male: Female	30/43 (69.8%): 13/43 (30.2%)
Cause of end-stage renal disease	
Chronic glomerulonephritis	20/43 (46.5%)
Diabetic nephropathy	12/43 (27.9%)
Nephrosclerosis	8/43 (18.6%)
Other	3/43 (7.0%)
PD modality	
CAPD	26/43 (60.5%)
APD	17/43 (39.5%)
Use of icodextrin	
Yes	10/43 (23.3%)
No	33/43 (76.7%)
Urine volume (ml/day)	1418.3 ± 389.1[a]
BMI (kg/m^2)	22.9 ± 4.0 [a]
Laboratory data	
Alb (g/dL)	3.6 ± 0.5 [a]
Hb (g/dL)	9.6 ± 1.4 [a]
β_2-MG (mg/dL)	14.6 ± 5.0[a]

Reason for technical failure	
Dialysis failure/UF failure	5/13 (38.6%)
Peritonitis	4/13 (30.8%)
Death	2/13 (15.3%)
Other	2/13 (15.3%)

Values are means ± standard deviations. CAPD: continuous ambulatory peritoneal dialysis; APD: automated peritoneal dialysis; Alb: albumin; Hb: hemoglobin; BMI: body mass index; β_2-MG: β_2-microgrobulin; UF: ultrafiltration

Table 2 Causative bacteria of PD-related peritonitis

Streptococcus salivarius	5	*alpha-haemolitic streptococcus*	1
MRSA	2	*Escherichia coli*	1
Propionibacterium acnes	1	*Clostridium perfringens*	1
Streptococcus mucilaginosus	1	*Edwardsiella tarda*	1
Enterococcus cloacae	1	*Klebsiella oxytoca*	1
Streptococcus oralis	1	*Acinetobacter baumannii*	1
MSSA	1	Unknown	2

MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*

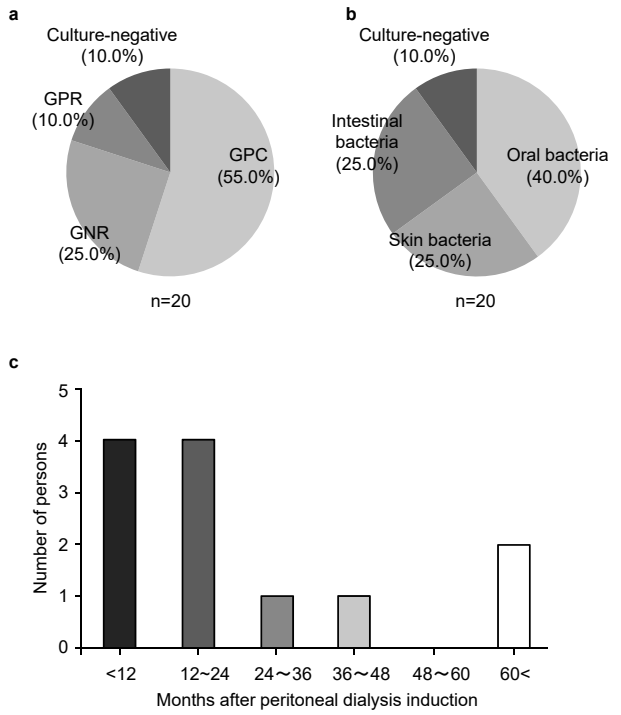

Fig. 1 Classification of causative bacteria of peritoneal dialysis (PD)-related peritonitis and periods until first PD-related peritonitis

a: Classification by Gram staining. GPC: Gram-positive cocci; GNR: Gram-negative rods; GPR: Gram-positive rods. b: Classification by the flora. c: The periods until first PD-related peritonitis in 12 patients from their commencement of PD

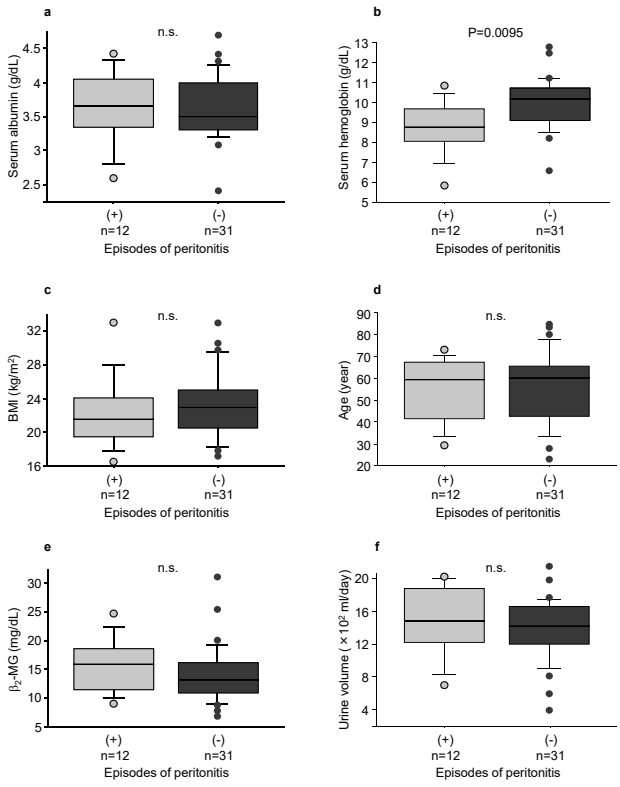

Fig. 2 Correlations between peritoneal dialysis (PD)-related peritonitis and clinical parameters at the initiation of PD

The values of clinical parameters including serum albumin level (a), hemoglobin level (b), body mass index (BMI) (c), age (d), β_2-microglobulin level (e), and urine volume (f) are compared according to the presence or absence of peritonitis.

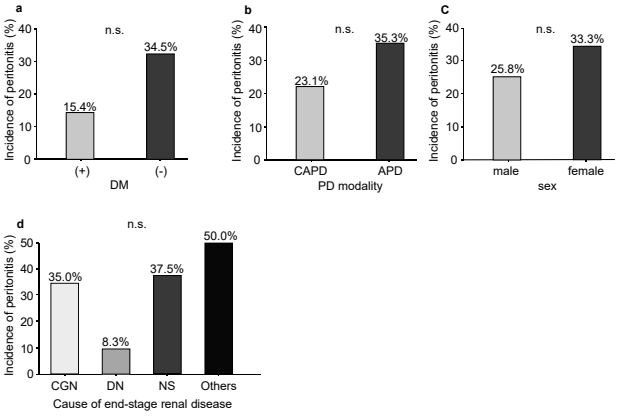

Fig. 3 Correlations between peritoneal dialysis (PD)-related peritonitis and the background of the patients

The incidences of peritonitis are compared according to the presence or absence of diabetes mellitus (a), PD modality (b), sex (c), and cause of end-stage renal disease (d).

CGN: chronic glomerulonephritis; DN: Diabetic nephropathy; NS: Nephrosclerosis

Table3 Multiple logistic regression analysis for history of peritonitis with relevant factors

	Odds ratio (95% CI)	P value
Hemoglobin	2.018 (1.048-3.887)	0.0357
Non-DM	0.204 (0.022-1.928)	0.1652

DM: diabetes mellitus, 95% CI: 95% confidence interval

Discussion

In this study, we investigated the background, causative bacteria, and risk factors of PD-related peritonitis in PD patients treated in our hospital.

In our hospital, the incidence of PD-related peritonitis was one episode per 62 patient-months, which is lower than that reported in other countries (one episode per 15–46 patient-months) and similar to that in Japanese reports (one episode per 42.8–73.5 patient-months) [9, 10, 20, 21, and

Table 4 A comparison of the incidences of peritonitis worldwide

Country or region	Number of patients	Incidence of peritonitis (per patients-months)
Australia [10]	147	19.4
New Zealand [10]	161	15
Korea [24]	1,395	46 (low GDP fluid)
	514	41 (normal fluid)
Hong Kong [25]	110	36.8–45
Brazil [26]	3,226	30
The United States of America [20]	3,111	32.7
Canada [20]	6,544	27.6
The United Kingdom [21]	1,943	14.7–18.1
Japan [9]	561	78.2
Japan [27]	2,086	42.8
This study	43	62

GDP: glucose degradation products

24-27] (Table 4). A recent report suggested that facilities that treat more than 20 PD patients at any given time are associated with better prognosis of PD therapy because of the experience of doctors and nurses and their attitude towards PD [8]. In our hospital, there are usually over 20 PD outpatients, and nurses who are experts in PD educate such patients about the exit site management in addition to consultation by doctors. This may be a reason for the low incidence of PD-related peritonitis. In this study, two-thirds of PD patients who developed peritonitis experienced their peritonitis in first 2 years from PD commencement. Similarly, previous literature reported that most of patients with PD-related peritonitis experienced their peritonitis in their first 2-3 years or shorter periods [11]. These findings might be caused by immature PD-techniques of patients for their first 2 years.

The ISPD guidelines recommend a target culture-negative rate of under 5%, and its value should not exceed 20% [7]. The published rates vary within a wide range (12%–37.3%) [9, 10, and 12]. The culture-negative rate of 10% achieved in our hospital was lower than those previously reported, likely because we strictly followed the ISPD guidelines when culturing the PD effluent (the combination of sediment culturing of 50 mL effluent and bedside inoculation of 5 – 10 mL effluent in two blood culture bottles).

Although previous reports have suggested low serum albumin level [13], anemia [14], obesity [15], advanced age [9, 16], RRF [17], and DM [16, 17] as risk factors for PD-related peritonitis, the underlying mechanisms connecting each of these factors to the disease are still unclear. Several hypotheses are outlined below. A low serum albumin level and anemia may be manifestations of malnutrition, which compromises immunity and increases the risk of the development of PD-related peritonitis [18]. Immune depression can also result from low RRF and the presence of DM [17, 19]. Furthermore, obesity can lead to an inability to obliterate dead space in the abdominal wall, resulting in an increased wound area and a high risk of colonization and infection of PD catheters after their insertion [15]. Therefore, PD patients with malnutrition, low RRF, or DM may require more thorough training for procedures of PD bag exchange and exit site care along with close observation of the exit site to detect early signs of infection. In the present study, only the hemoglobin level was significantly lower in the PD patients who developed PD-related peritonitis. The association between low hemoglobin level and peritonitis may be a consequence of the shorter administration period of the erythropoiesis-stimulating agent in the peritonitis-experienced patients than in the patients without peritonitis (data not shown), possibly leading to an inadequate treatment of anemia in the peritonitis-experienced patients. Therefore, early

theraputic intervention for anemia before the dialysis may be important for the prevention of PD-related peritonitis. The observational, retrospective nature of this study as well as its small sample size and relatively short observational period may explain why we did not identify associations between the other reported risk factors and PD-related peritonitis. A future study with a larger sample size, longer observational period, and more comprehensive data collection is therefore warranted.

We found that oral and skin bacteria accounted for >60% of all causative bacteria in the flora. This suggests that touch contamination with oral or skin bacteria was the primary cause of PD-related peritonitis in our hospital. Generally, the kinds of causative bacteria influence the patient's outcome. In the previous reports, the cure rates of peritonitis caused by non-*S. aureus* gram-positive micro-organisms and non-*Pseudomonas* gram-negative micro-organisms were 78.0-84.4% and 56.1-63.2%, respectively [20, 21]. On the other hand, MRSA, *Pseudomonas*, and Fungi, which have lower cure rate of peritonitis, were reported (7.7%, 21.4%, and 0%, respectively)[21]. In this study, the cure rates of peritonitis caused by non-*S. aureus* gram-positive micro-organisms and non-*Pseudomonas* gram-negative micro-organisms were 90% and 80%, respectively. Although these cure rates in our hospital were equal to or greater than those in the previous reports, the cure rate of MRSA peritonitis in our study was low (0%), similar to previous reports. Infection with *Staphylococcus aureus (S. aureus)* has been reported to cause severe peritonitis [22]. In particular, contamination with MRSA is more likely to lead to reccurence of peritonitis, catheter removal, transition to HD, and death compared to contamination with methicillin-sensitive *S. aureus* (MSSA) [23]. In this regard, despite the administration of multiple anti-MRSA antibiotics, the two patients infected with MRSA were diagnosed with refractory peritonitis, followed by the removal of the catheters and transfer to HD. Both patients were nasal MRSA carriers, and they were suffered from ESI with MRSA. In addition, the 4 cases which occured within 12 months after the commencement of PD included two MRSA-cases and one MSSA-case. These results show that early reeducation of exit site care and PD technique for patients after the commencement of PD is important to prevent *S. aureus* peritonitis.

In conclusion, the incidence of PD-related peritonitis in our hospital was similar to that in other Japanease facilities. PD-related peritonitis is still an important complication of PD therapy, with low hemoglobin level at the commencement of PD being a significant risk factor. In this regard, theraputic intervention for anemia before the dialysis is important. In addition, early detection and aggressive treatment of PD-related infections are crucial for preventing PD withdrawal in MRSA carriers because of the severity of MRSA-related peritonitis and its tendency to be refractory to the treatment. Furthermore, both the incidence and causative bacteria of PD-related peritonitis should be continuously surveyed, and these data should be utilized for educating the patients to prevent the development of PD-related peritonitis.

Conflict of interest

Potential financial conflicts of interest: The authors have declared that no conflict of interest exists.

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