ORIGINAL ARTICLE



Frequency and prognosis of peritoneal dialysis-associated peritonitis in children

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Abstract

Background Peritonitis is the leading cause of peritoneal dialysis (PD) discontinuation. However, few data concern risk factors of peritonitis development and catheter removal caused by treatment failure in pediatric patients.

Methods This single-center, retrospective study analyzed data from pediatric patients who underwent chronic PD between March 2002 and June 2022. The incidence rates of peritonitis by the person-year method were calculated, and they were stratified by patient age groups. Risk factors for peritonitis development and catheter removal were also analyzed by multivariate analysis using logistic regression model.

Results Ninety patients were enrolled, and 62 peritonitis episodes were observed in 41 (46%) patients. The incidence rate of peritonitis was 0.21 episodes per patient-year, which was the highest in children aged under 2 years old (0.26 episodes per patient-year). Moreover, 44 (71%) cases were successfully cured by antibiotics alone, although 17 (27%) cases required catheter removal, and 4 (6%) cases transitioned to chronic hemodialysis because of peritoneal dysfunction. One patient died. The risk factor for peritonitis development and catheter removal caused by treatment failure was PD insertion at under 2 years old (odds ratio = 2.5; P = 0.04) and *Pseudomonas aeruginosa* (odds ratio = 11.0; P = 0.04) in the multivariate analysis. *P. aeruginosa* was also a risk factor for difficulty in re-initiating PD (P = 0.004).

Conclusions The incidence rate of peritonitis was the highest in children under 2 years old. *P. aeruginosa* peritonitis is a risk factor for catheter removal and peritoneal dysfunction.

Keywords Peritoneal dialysis · Peritonitis · Pseudomonas aeruginosa · Catheter removal · Hemodialysis

Introduction

Peritoneal dialysis (PD) is the most common kidney replacement therapy in children with end-stage kidney disease. In pediatric patients, PD allows for home dialysis, gradual water and solute removal, and less food restriction, compared with hemodialysis (HD). However, PD-associated peritonitis is a serious complication. Sometimes, it might lead to catheter removal, peritoneal dysfunction, transition to HD, and death [1–3]. If PD re-initiation is difficult, they must switch to chronic HD. However, HD is a difficult

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² Department of Pediatrics, Graduate School of Medicine, Yokohama City University, Kanagawa, Japan modality, especially for infants. Thus, in pediatric patients, peritonitis must be prevented until kidney transplantation.

According to international guidelines, the incidence rate of peritonitis should be less than 0.40 episodes per patientyear [1]. Recently, with appropriate preventive measures, its incidence rate has decreased [4, 5]. Appropriate catheter placement, exit-site care, and PD training program for clean operation are important in preventing peritonitis. In previous reports, risk factors for peritonitis include young age, intraperitoneal insert other than PD catheter, and early PD initiation [6–11]. Antibiotic therapy is the first-line treatment, and catheters must be removed if antibiotics are ineffective. If the therapeutic effect is poor, PD could not be re-initiated because of peritoneal adhesions.

Fungi are a risk factor for PD discontinuation [1, 8, 12, 13]. The ISPD guidelines recommend catheter removal as an initial treatment for fungal peritonitis, and the catheter removal rate in fungal peritonitis is high [1]. However, few

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studies have focused on risk factors for PD discontinuation, other than fungal peritonitis. Moreover, risk factors for the incapability to re-initiate PD caused by peritoneal adhesion are not clearly known.

Therefore, this study aimed to investigate the incidence rate of peritonitis and determine the risk factors for peritonitis development in pediatric patients with PD in our institute. Moreover, we evaluated risk factors for treatment failure defined as catheter removal.

Materials and methods

Patients

This single-center, retrospective, observational study enrolled pediatric patients who received PD at our hospital between March 2002 and June 2022. The exclusion criteria were age over 20 years at the time of PD initiation and not on automatic PD machines such as infants in the neonatal intensive care unit. In most cases, the PD catheter was straight and double cuffed, and the downward exit was made downward on the left side.

Definitions

Peritonitis was diagnosed when at least two of the following factors were present: (1) clinical features consistent with peritonitis, that is, abdominal pain and/or cloudy dialysis effluent; (2) dialysis effluent white cell count > $100/\mu$ L with > 50% polymorphonuclear leukocytes; and (3) positive dialysis effluent culture (bacteria or fungi). Its definition is similar to those of the ISPD guidelines [1].

Treatment of peritonitis

If peritonitis was suspected based on elevated dialysis effluent white cell counts or cloudy dialysis effluent, empirical antibiotics covering both gram-positive and gram-negative bacteria were administered intraperitoneally or intravenously. As soon as the results of the dialysate culture were known, the antibiotics were changed based on sensitivity. In cases without clinical improvement within 5 days on appropriate antibiotics (persistent fever with elevated dialysis effluent white cell count and positive dialysate culture), the catheter was removed [1].

If patients required dialysis during the catheter removal period, they received transient HD. The catheter was reinserted after the peritonitis subsided (negative dialysate culture), usually at 4 weeks after removal. When injection and drainage of the dialysate were difficult because of peritoneal adhesion, patients transitioned to chronic HD, and the PD catheter was removed.

Study design

During the study period, the characteristics of all patients on PD from the medical charts were investigated (i.e., sex, primary disease, and age at PD initiation), and these were compared between the peritonitis group and the nonperitonitis group. For the peritonitis group, we investigated age at peritonitis onset, period from PD initiation to onset, cause of peritonitis, white blood test and C-reactive protein in the blood test at diagnosis, white cell counts in ascites at diagnosis, causative pathogens, treatment, and outcomes. Data collected during the observation period of all patients with PD were analyzed, and the incidence rates of peritonitis were calculated by the person-year method. The incidence rates were compared between the three age groups (<2, 2-6, and > 6 years). Children under 2 years old have immature immune systems, and a previous study reported that the incidence rate was the highest in children under 2 years old [8]. We adopted 6 years old, which is the age at the start of school.

Risk factors for peritonitis development were also analyzed. Extrarenal complications (respiratory, circulatory, neurological, and gastrointestinal diseases), intraperitoneal devices other than PD catheter (gastrostomy, colostomy, vesicocutaneous fistula, etc.), and age under 2 years old at PD introduction were adjusted as risk factors. The prognosis of all patients and risk factors for catheter removal were reviewed. Age at peritonitis onset, exit-site/tunnel infection, early PD initiation (PD initiation < 14 days after PD catheter insertion), white cell count in the dialysis effluent at diagnosis, and *Pseudomonas aeruginosa* were adjusted as risk factors. The incapability to re-initiate PD was also analyzed.

Statistical analyses

All statistical analyses were performed using JMP Pro 16 (SAS Institute Japan, Tokyo, Japan). Values were expressed as medians with interquartile range for continuous variables and as a percentage for categorical variables. The Mann–Whitney U test and Fisher exact test were used for the comparison of continuous and categorical variables, respectively. Multivariate analysis of risk factors for developing peritonitis and catheter removal was performed using logistic regression analysis. A two-sided P-value of <0.05 was considered to indicate statistical significance.

Ethics

This study was conducted according to the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labor, and Welfare, Japan, and was approved by the institutional ethics committee of the National Center for Child Health and Development (Approval no. 2022–169). Informed consent was waived for the retrospective study.

Results

Characteristics of patients and peritonitis

Of the 90 PD patients, 41 patients experienced 62 episodes of peritonitis. Table 1 shows the clinical characteristics of the patients. During the study period, the median age at PD initiation was 0.5 [0.1–5.9] years in the peritonitis group and 3.2 [0.4–9.7] years in the non-peritonitis group (P = 0.03).

Table 2 shows the clinical characteristics of 62 episodes of peritonitis. The incidence of peritonitis was 0.21 episodes per patient-year. The most common cause of peritonitis was exit-site/tunnel infection (15%), followed by surgical procedures (catheter insertion, replacement, or reposition; 9%) and exit-site leakage (6%). Two episodes were caused by surgical procedures and leaks, and one episode was caused by exit-site infection and surgical procedures.

Incidence rates of peritonitis stratified by patient age

The incidence rates stratified by patient age are shown in Table 3. It was the highest in children under 2 years of old (0.26 per patient-year).

Pathogen of peritonitis

Gram-positive bacteria were noted in 30 (48%) cases, of which *Staphylococcus aureus* was the most common (n=13, 21%), followed by *Enterococcus spp.* (n=6, 10%; E. faecalis, n=4; E. faecium, n=1; E. raffinosus, n=1 case). Gram-negative bacteria were found in 22 (36%) cases, of which*Klebsiella spp.*<math>(n=7, 11%: K. pneumoniae, n=4; K. oxytoca, n=3) and*P. aeruginosa*<math>(n=7, 11%) were the most common. Fungi were found in 2 (3%) cases, non-tuberculous mycobacteria in 1 (2%), and culture negative in 10 (16%). Multiple bacteria were detected in 3 cases (one with *E. faecium* and *Clostridium beijerinckii*, one with *S. lentus* and *E. faecalis*, and one with *S. aureus* and *Serratia marcescens*).

Clinical course and outcomes of peritonitis

Figure 1 shows the clinical courses of all peritonitis cases. All patients were treated with antibiotics immediately after diagnosis. Forty-four cases (71%) were cured with antibiotics alone. Seventeen episodes (27%) required catheter removal because of treatment failure (Table 4). After the

Table 1Patient characteristicsand comparison of theperitonitis and non-peritonitisgroup

Patient characteristics	Total $(n=90)$	Peritonitis group $(n=41)$	Non-peritonitis group $(n=49)$	P-value
Male sex	53 (59)	25 (61)	28 (57)	0.83
Primary disease				
CAKUT	29 (32)	13 (32)	16 (33)	
CNS/INS	24 (27)	12 (29)	12 (24)	
Nephronophthisis	7 (8)	2 (5)	5 (10)	
ARPKD	5 (6)	4 (10)	1 (2)	
Others	25 (28)	10 (24)	15 (31)	
Extrarenal complications	49 (54)	22 (54)	27 (55)	1.00
Intraperitoneal device	12 (13)	4 (10)	8 (16)	0.54
Limb disabilities	5 (6)	3 (7)	2 (4)	0.66
Age at initiation of PD (years)	2.2 [0.3-8.5]	0.5 [0.1–5.9]	3.2 [0.4–9.7]	0.03
<2	42 (47)	24 (59)	18 (37)	
2-6	18 (20)	7 (17)	11 (22)	
>6	30 (33)	10 (24)	20 (41)	
Observation period (years)	2.9 [0.9–4.7]	3.7 [2.1–5.6]	2.5 [0.7-4.0]	0.02

Values are expressed as numbers (%) or median [interquartile range]

ARPKD, autosomal recessive polycystic kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract; CNS/INS, congenital nephrotic syndrome/infantile nephrotic syndrome; PD, peritoneal dialysis

Table 2 Characteristics of

peritonitis

Number of patients who experienced peritonitis	41
Number of peritonitis	62
Total observation period of PD in all 90 patients (year)	293.1
Incidence rates of peritonitis (episodes/patient-year)	0.21
Number of patients in each number of peritonitis episodes	
1 time	30 (73)
2 times	5 (12)
3 times	4 (10)
4 times	1 (2)
6 times	1 (2)
Age at peritonitis (years)	3.9 [1.4–8.9]
<2	16 (26)
2–6	22 (35)
>6	24 (39)
From initiation of PD to onset of peritonitis (year)	1.0 [0.2–3.3]
Causes of peritonitis ^a	
Exit-site/tunnel infection	10 (16)
Surgical procedure	6 (10)
Leakage	4 (6)
Catheter breakage	3 (5)
Unclean procedures by patients	3 (5)
Previous peritonitis	2 (3)
Colon perforation	1 (2)
Cholangitis	1 (2)
Unknown	35 (54)
Pathogen of peritonitis ^b	
Gram-positive bacteria	30 (48)
Staphylococcus spp.	16 (26)
Enterococcus spp.	6 (10)
Streptococcus spp.	3 (5)
Other	5 (8)
Gram-negative bacteria	22 (36)
Klebsiella spp.	7 (11)
Pseudomonas spp.	7 (11)
Other	8 (13)
Fungi	2 (3)
Candida spp.	2 (3)
Non-tuberculous mycobacteria	1 (2)
Mycobacterium spp.	1 (2)
Culture-negative	10 (16)
White blood cell counts at diagnosis (/µL)	11,756 [8,925–17,885]
C-reactive protein at diagnosis (mg/dL)	3.8 [1.0–7.2]
White cell counts in the dialysis effluent at diagnosis (/mm ³)	2,424 [926–5,397]

Values are expressed as numbers (%) or median [interquartile range]

PD, peritoneal dialysis

^aThree cases had two causes

^bMultiple bacteria were detected in 3 cases

inflammation subsided, 16 patients (26%) received reinsertion of the catheter, except for one patient who continued HD because of scheduled kidney transplantation. Although PD could be re-initiated in 12 patients (19%), re-initiation was not possible in 4 patients (6%) because of poor drainage by abdominal adherence, small abdominal cavity or high

Age (years)	<2	2–6	>6
Number of peritonitis episodes	16	22	24
Observation period (years)	60.4	105.6	127.1
Incidence rates (episodes/patient-year)	0.26	0.21	0.19

peritoneal permeability, and transitioned to chronic HD. One patient (2%) died of sepsis. No patients suffered from encapsulating peritoneal sclerosis.

Risk factors for peritonitis

Multivariate analysis using logistic regression showed that PD initiation at age under 2 years old was a significant risk factor for peritonitis development (odds ratio [OR] = 2.5; 95% confidence interval [CI] = 1.1-5.9; P = 0.04) (Table 5).

Risk factors for catheter removal

Multivariate analysis using logistic regression showed that P. *aeruginosa* (OR = 11.0; 95% CI = 1.0–124.9; P = 0.04) was a significant risk factor for catheter removal (Table 6).

Outcomes of peritonitis caused by P. aeruginosa

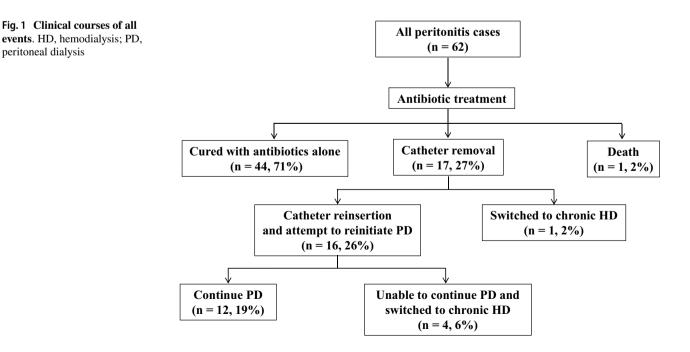
Table 7 shows the comparison of outcomes between peritonitis caused by P. aeruginosa and that other than P. aeruginosa. Of the seven episodes of P. aeruginosa peritonitis, 6 (86%) did not respond to antibiotics and required catheter removal. After the inflammation subsided, PD re-initiation

was tried in all these six patients, although dialysis was not possible in three because of peritoneal adhesions and transition to HD. The bivariate analysis showed that P. aeruginosa was a risk factor for the difficulty in re-initiating PD (P = 0.004).

Discussion

This single-center, retrospective, observational study investigated the incidence of PD-associated peritonitis, risk factors for peritonitis development, and risk factors for poor prognosis in patients undergoing PD. Of the 90 patients, 41 (46%) had 62 episodes of peritonitis, with an incidence of 0.21 episodes per patient-year. The younger the PD initiation age, the higher the incidence of peritonitis. Moreover, 27% of all episodes required catheter removal, 6% resulted in transition to chronic HD, and 2% of the patients died. One patient who died had congenital nephrotic syndrome combined with WEST syndrome and chronic lung disease. He developed peritonitis at the age of 8.7 years. The causative agent was unknown, and he died of sepsis on the 23rd day after the onset of peritonitis. Multivariate analysis identified age under 2 years old at PD initiation as a significant risk factor for peritonitis development. In addition. P. aeruginosa was a significant risk factor for PD catheter removal and difficulty in PD re-initiation after catheter removal.

The peritonitis guidelines by ISPD recommend that the incidence of peritonitis should be less than 0.40 episodes per patient-year [1]. In the present study, the incidence of peritonitis was lower in our cohort than in those reported



peritoneal dialysis

Patient	Sex	Age at onset (years)	Causes of peritonitis	Causative pathogens	Antibiotics	RRT after peritonitis
1	F	6.9	Catheter insertion	MRSE	VCM	Continue PD
2	Μ	12.7	Unclean procedures by the patient	P. aeruginosa	SBT/CPZ+GM+MEPM	Continue PD
3	Μ	15.1	Tunnel infection	PRSP	TEIC+CTRX	Continue PD
4	F	4.7	Catheter replacement	MRSA	VCM	Continue PD
5	Μ	18.0	Previous peritonitis	MRSA	VCM	Continue PD
6	Μ	0.6	Unknown	Candida albicans	FLCZ	Continue PD
7	М	0.0	Unknown	P. aeruginosa	MEPM	Continue PD
8	F	6.0	Unknown	Corynebacterium	VCM	Continue PD
9	F	8.6	Unknown	Klebsiella oxytoca	CAZ	Continue PD
10	F	1.4	Exit-site infection	Serratia marcescens	CAZ	Continue PD
11	F	3.0	Exit-site infection	P. aeruginosa	CAZ+TOB	Continue PD
12	Μ	0.1	Leakage	Candida albicans	FLCZ	Continue PD
13	F	21.8	Unknown	P. aeruginosa	CAZ	Switch to HD
14	М	2.2	Colon perforation	Enterococcus faecalis, Clostridium beijerinckii	MEPM + VCM	Switch to HD
15	М	2.2	Unknown	P. aeruginosa	CAZ	Switch to HD
16	М	0.0	Leakage	P. aeruginosa	CAZ+VCM	Switch to HD
17	Μ	4.2	Unclean procedures by the patient	Mycobacterium avium	CAM + EB + RFP	Switch to HD

Table 4 Cases requiring catheter removal (17 episodes)

CAZ, ceftazidime hydrate; CTRX, ceftriaxone sodium hydrate; EB, ethambutol hydrochloride; F, female; FLCZ, fluconazole; GM, gentamicin sulfate; HD, hemodialysis; M, male; MEPM, meropenem hydrate; MRSA, methicillin-resistant *Streptococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; *P. aeruginosa*, *Pseudomonas aeruginosa*; PD, peritoneal dialysis; PRSP, penicillin-resistant *Streptococcus pneumoniae*; RFP, rifampicin; RRT, renal replacement therapy; SBT/CPZ, sulbactam sodium/cefoperazone sodium; TEIC, teicoplanin; TOB, tobramycin; VCM, vancomycin hydrochloride

	Univariate			Multivariate		
	Odds ratio	95%CI	<i>P</i> -value	Odds ratio	95%CI	P-value
Extrarenal complications	0.9	0.4–2.2	1.00	1.0	0.4–2.4	0.99
Intraperitoneal device	0.6	0.2-2.0	0.54	0.5	0.1-2.0	0.32
< 2 years old at PD initiation	2.4	0.2-1.0	0.06	2.5	1.1–5.9	0.04

95% CI, confidence interval; PD, peritoneal dialysis

	Univariate			Multivariate		
	Odds ratio	95% CI	<i>P</i> -value	Odds ratio	95% CI	P-value
Age at peritonitis onset	1.0	0.1-8.7	0.76	1.2	0.1–16.9	0.89
Exit-site/tunnel infection	1.2	0.3-5.1	1.00	1.6	0.3-8.6	0.60
Early PD initiation	1.7	0.4-8.1	0.67	2.3	0.3-17.2	0.43
White cell counts in the dialysis effluent	3.7	0.3–54.5	0.05	2.8	0.2–49.7	0.50
P. aeruginosa	24.0	2.6-220.5	0.001	11.0	1.0-124.9	0.04

95% CI, confidence interval; PD, peritoneal dialysis; P. aeruginosa, Pseudomonas aeruginosa

in the SCOPE study and studies conducted in China, Brazil, and Saudi Arabia, with 0.30, 0.29, 0.43, and 0.6 episodes per patient-year, respectively [1, 5, 14, 15]. A previous study in Japan also reported a lower value (0.17 episodes per patient-year) [16]. In our center, standardized instruction in exit-site care and dialysis machine operation for caregivers may have contributed to the low incidence of peritonitis.

Table 6Risk factors of catheterremoval by univariate andmultivariate analyses (logisticregression)

Table 5 Risk factors ofperitonitis by univariate andmultivariate analyses (logistic

regression)

Table 7Comparison ofprognosis between peritonitis byP. aeruginosa and others

	P. aeruginosa (n=7)	Other than <i>P</i> . <i>aeruginosa</i> (n=55)	P-value
Number of patients with catheter removal	6 (86)	11 (20)	0.001
Number of patients in whom PD could not be re-initiated	3 (43)	1 (2)	0.004
Death	0 (0)	1 (2)	1.00

Values are expressed as numbers (%)

P. aeruginosa, Pseudomonas aeruginosa

The incidence of peritonitis is higher in younger patients [4, 7, 8]. In this study, a similar result was obtained. Possible reasons include immature immunity, fragile skin and tendency to leak easily, high failure risk in clean operation because of the inability to keep rested, use of a single-cuff catheter, and difficulty in securing the distance to the exit site. The prevention of peritonitis through exit care, training in hygiene techniques, response to unclean operations, etc., is important in young patients.

The risk factors for peritonitis development include young age, short stature, PD initiation under 2 years old, intraperitoneal devices such as gastrostomy and colostomy, and early PD initiation after PD catheter insertion [4-7, 9-12, 17, 18]. Induction of PD under 2 years old was also a risk factor in this study, but the younger the age of induction, the longer the duration of PD treatment and naturally the higher the risk of developing peritonitis. In our study cohort, patients with heart disease, lung disease, neurological disease, and gastrointestinal disease were included, although the rates of peritonitis and its prognosis were similar between these groups. There were no patients with primary immunodeficiency, such as asplenia. Whether the way of antibiotics, such as intravenously or intraperitoneal, affects the prognosis is difficult to evaluate. In patients under 2 years of age, 4 were administered intravenously, 7 intraperitoneally, 3 both (intravenous administration was changed to intraperitoneal administration due to persistently positive culture), and 3 unknown (medical records are outdated and cannot be evaluated). There was no poor prognosis for intraperitoneal administration, and poor prognosis for intravenous administration (catheter removal in 3 cases, and difficulty in restarting PD in 1 case). However, in two cases of intravenous administration, the catheter was immediately removed due to fungal infection, making evaluation difficult.

In this study, *P. aeruginosa* was a risk factor not only for catheter removal but also for difficulty in re-initiating PD. As kidney replacement therapy for children, HD is technically difficult, especially for infants, because arteriovenous shunt cannot be created for them. Infants require vascular catheter placement and long-term hospitalization for HD management. As the difficulty in re-initiating PD is the most critical problem for children, strategy for P. aeruginosa peritonitis is crucial for childhood PD management. No study has examined the proportion of poor prognosis cases of P. aeruginosa peritonitis in pediatric patients with PD. In adult cases with P. aeruginosa peritonitis, catheter removal rates of 26%-44%, difficulty resuming PD rates of 11%-35%, and mortality rates of 3%-12% were reported [19, 20], [21]. In this study, the rates of both catheter removal and difficulty resuming PD were higher than those in previous studies, which may be because our study analyzed pediatric patients, and they may have immature immunologic defense. The poor prognosis of P. aeruginosa peritonitis was speculated to be due to biofilm formation, which increases antimicrobial resistance and makes it physically difficult for antimicrobials to penetrate [1], [21]. We believe that the poor prognosis of P. aeruginosa peritonitis was not due to the patient factors, as all cases of P. aeruginosa peritonitis in our study were first-peritonitis, not recurrence, and there was no difference in the primary disease or age at the time of peritonitis. ISPD recommends the administration of effective antibiotics with different mechanisms, and if no improvements were observed after 5 days, the catheter must be removed. The protection of peritoneal function is more important than catheter maintenance, and rapid catheter removal should be considered in patients with poor response to antibiotic therapy. In P. aeruginosa peritonitis, early catheter removal has a higher PD resumption rate and a lower mortality rate than delayed catheter removal [20], [22]. Given the poor prognosis of *P. aeruginosa* peritonitis, treatment with two antibiotics should be started, and if there is little improvement in 5 days, the catheter should be removed immediately.

This study has a few limitations. First, it is a single-center study, and the number of patients is relatively small. Second, some neonatal cases were excluded because they could not be transitioned to automated PD. Third, the protocol of antibiotic selection and time to catheter removal in the case of treatment failure were not restricted. However, all these choices were determined by kidney specialists and infectious disease experts. Fourth, fungal peritonitis, a known risk factor for catheter removal, could not be evaluated because of the small number of cases.

Conclusion

In the present study, we found that the incidence rate of peritonitis was the highest in children aged under 2 years old. *P. aeruginosa* peritonitis is a risk factor for catheter removal and peritoneal dysfunction. The treatment strategy for *P. aeruginosa* peritonitis is crucial for the long-term preservation of peritoneal function in childhood PD.

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Author contributions All authors were physicians treating the patients in this report. Misaki Akiyama prepared the manuscript and performed data collection and analysis. Kentaro Nishi, Mai Sato, and Masao Ogura edited and reviewed the manuscript. Shuichi Ito revised the manuscript. Koichi Kamei oversaw the work as the corresponding author and revised the manuscript. All authors reviewed and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are not publicly available because permission for their publication was not obtained from the participants or approved by the ethics committee. However, they are available from the corresponding author on reasonable request.

Declarations

Conflict of interests Koichi Kamei has received research funding from the Public Foundation of Vaccination Research Center, and the Taiju Life Social Welfare Foundation; donations from Chugai Pharmaceutical Co. Ltd., Teijin Pharma Ltd., Kyowa Kirin Co. Ltd., Shionogi & Co. Ltd., Daiichi Sankyo Co. Ltd., Mitsubishi Tanabe Pharma Co. Ltd, and Otsuka Pharmaceutical Co. Ltd.; and lecture fees from Terumo Co. Ltd., Baxter Ltd., and Zenyaku Kogyo Co., Ltd., Shuichi Ito has received research funding from Zenyaku Kogyo Co., Ltd., and Teijin Pharma Ltd.; and honoraria from Astrazeneca PLC and Alexion Pharmaceuticals Inc.

Ethics approval This study was approved by the Ethics Committee of the National Center for Child Health and Development (Approval no. 2022–169).

Consent to participate Not applicable.

Consent for publication Not applicable.

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