INCIDENCE OF PERITONITIS AND ASSOCIATED FACTORS IN CHILDREN RECEIVING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS: A RETROSPECTVE SURVEY IN A HOSPITAL IN NORTHEASTERN THAILAND (2007-2016)

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Abstract. Chronic peritoneal dialysis (PD) is a preferable dialysis modality for children with end-stage renal disease (ESRD). However, peritonitis is a common and serious complication of PD. Incidence of peritonitis and associated factors in children receiving continuous ambulatory peritoneal dialysis (CAPD) at Srinagarind Hospital, Khon Kaen, a tertiary care hospital in northeast Thailand were evaluated in a retrospective cohort study by reviewing medical records of 39 ESRD patients (26 males and 13 females) aged under 18 years who underwent CAPD between 2007 and 2016. Twenty-two patients had 60 episodes of peritonitis, one episode (excluding relapsing peritonitis) every 19.57 patient-months (0.05 episode/patient-month). *Staphylococcus epidermidis* (25%) and *Enterobacter* spp (15%) were the most common Gram-positive and Gram-negative causative organism respectively. Dialysis duration >12 months is significantly associated with PD peritonitis (adjusted odds ratio = 22.03, *p*-value = 0.009). Fifty-nine percent of patients underwent PD catheter removal due to peritonitis and 14% had permanent change in dialysis modality to chronic hemodialysis. In conclusion, bacterial peritonitis in children receiving CAPD remains a critical problem and leads to peritoneal dialysis failure.

Keywords: child, end-stage renal disease, peritoneal dialysis, peritonitis

INTRODUCTION

Chronic peritoneal dialysis (PD) is a preferable dialysis modality for children with end-stage renal disease (ESRD) (NAPRTCS, 2011). Children undergoing PD have fewer diet and fluid restrictions, allowing for regular school attendance, preservation of residual renal function and better quality of life (Tokgoz, 2009). PD is becoming increasingly widespread, with expanding usage in developing countries (Chadha *et al*, 2010).

Peritonitis is a common and serious complication of PD, frequency of which in children exceeding that seen in adults (Chadha *et al*, 2010). The most common sequel to peritonitis is membrane failure requiring a change in dialysis modality. This study examined incidence of

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peritonitis and associated factors in children receiving continuous ambulatory peritoneal dialysis (CAPD) in Srinagarind Hospital, a tertiary care hospital in northeast Thailand during 2007 and 2016.

MATERIALS AND METHODS

Participants selection

Participants were children with end-stage renal disease (ESRD) aged under 18 years at the time of CAPD initiation, having received CAPD >3 months, and either the patient or caregiver having received training in CAPD from Srinagarind Hospital between 2007 and 2016. ESRD patients with missing data on their medical records were excluded. The follow-up ended either when the participants died during the study period, changed dialysis modality, transferred to the Department of Medicine, Faculty of Medicine, Khon Kaen University, or received kidney transplantation. Diagnosis of PD peritonitis is made when the patient exhibits at least two of the following three criteria: i) clinical presentations of peritonitis (abdominal pain and/or cloudy dialysis effluent), ii) a dialysis effluent with white blood cell counts >100 cells/mm^3 and >50% polymorphonuclear cells, and iii) positive dialysis effluent culture (Chadha *et al*, 2010).

PD-related peritonitis is categorized as relapsing, repeat and recurrent peritonitis. Relapsing peritonitis is defined as a peritonitis episode occurring within four weeks of completion of therapy for a previous episode caused by the same organism or one sterile episode. Relapsing peritonitis is not counted as another episode of peritonitis in the calculation of the peritonitis. Repeat peritonitis is indicated when a peritonitis episode occurs >4 weeks after completion of therapy for a previous episode caused by the same organism. Recurrent peritonitis refers to a peritonitis episode occurring within four weeks of completion of therapy for a previous episode caused by a different organism.

Sample size for estimation of incidence is calculated using the formula μ/e^2, when μ is the rate of the event and e is the required size of standard error (Kirkwood and Sterne, 2003). Peritonitis rate of a previous study of 1 episode/8.52 patient-months (Wisanuyotin *et al*, 2011) and 10 % of the standard error were used for the sample size calculation. The calculated follow-up time was 852 patient-months based on the sample size calculation.

The single-center retrospective study was approved by the Ethics Committee in Human Research, Khon Kaen University (no. HE601287). No prior written consent from parents or legal guardian was required as names of patients were stripped from medical records before examination.

Data analysis

Results are presented as percentages for categorical data. Normal distributed data are presented as mean ± SD and tested using an independent sample *t*-test, and non-normal distributed data as median with interquartile range (IQR) and tested using a Mann-Whitney U test. Associated factors of PD peritonitis were determined by univariate analysis and presented as crude odds ratio (OR) with 95% confidence interval (CI). Variables with *p*-values <0.25 based on univariate analysis were selected for multivariate analysis performed using a generalized estimating equation (GEE). OR was used to analyze associated factors in this retrospective cohort study because of

the low incidence of peritonitis and the possibility of re-infection in the same patient. The same set of demographic data was used for patients who had re-infection. A p-value <0.05 is accepted as statistically significant.

RESULTS

Median age of non-peritonitis and peritonitis groups is not significantly different, same as other demographic features (Table 1). Median serum creatinine

Table 1
Demographic profile and clinical features at time of peritoneal dialysis (PD) catheter insertion of patients admitted to Srinagarind Hospital, Khon Kaen, Thailand (2007-2016).

Characteristic	Non-peritonitis group (n = 17)	Peritonitis group (n = 22)	p-value[a]
Male, number (%)	10 (59)	16 (73)	0.497
Median age at PD initiation (IQR), years	11 (9-13)	11 (5-13)	0.671
Median weight (IQR), kg	24 (22-34)	30 (13-42)	0.661
Median height (IQR), cm	131 (124-137)	131 (92-150)	0.734
Median BMI (IQR), kg/m^2	14 (14-18)	17 (15-21)	0.070
Obesity[b], number (%)	1 (6)	4 (18)	0.363
CAKUT, number (%)	10 (59)	9 (41)	0.341
Prednisolone usage, number (%)	5 (29)	7 (32)	0.999
Type of Tenckhoff catheter, number (%)			
Single cuff	3 (18)	4 (18)	0.999
Double cuffs	14 (82)	18 (82)	
Straight	6 (35)	16 (73)	0.026
Coiled	11 (65)	6 (27)	
Antibiotics usage before Tenckhoff catheter insertion, number (%)	16 (94)	20 (91)	0.459
Cefazolin prophylaxis	14 (87)	19 (95)	0.574
Others	2 (13)	1 (5)	0.574
Timing of PD initiation after catheter placement, number (%)			
<2 weeks	11 (65)	17 (85)	0.251
≥2 weeks	6 (35)	3 (15)	
Mean hemoglobin (SD), g/dl	9 (2)	9 (1)	0.210
Median creatinine (IQR), mg/dl	8 (5-12)	5 (3-7)	0.019
Mean serum albumin (SD), g/dl	3.6 (0.9)	3.1 (0.6)	0.050
Residual urine, number (%)	14 (82)	19 (86)	0.999
Mean dialysis duration (SD), months	18 (12)	33 (21)	0.017

[a]Significance when p <0.05; [b]BMI ≥ 23 kg/m^2.
BMI: body mass index; CAKUT: congenital anomalies of kidney and urinary tract; IQR: interquartile range.

level is significantly lower in peritonitis group while the use of a straight PD catheter and mean dialysis duration are significantly higher when compared to non-peritonitis group (Table 1).

Out of a total of 39 CAPD patients, 22 (56%) had at least one episode of PD peritonitis. A total of 60 episodes of PD peritonitis were documented, including nine episodes of relapsing peritonitis over a total dialysis duration of 998 patient-months, with a peritonitis rate of one episode every 19.57 months (0.05 episode/patient-month). The two most common causes of ESRD were renal hypoplasia and rapidly progressive glomerulonephritis (Table 2).

Gram-positive pathogens were the most common type of organism (53%), with *Staphylococcus epidermidis* (67% methicillin-resistant) being predominant followed by *S. aureus* (25% methicillin-resistant), while among Gram-negative pathogens, *Enterobacter* spp was the most common followed by *Pseudomonas* spp (Table 3).

Four episodes of relapsing peritonitis caused by *Enterobacter* spp were documented in one patient, three episodes caused by methicillin-resistant *S. epidermidis* in two patients and two episodes by methicillin-sensitive *S. aureus* in one patient. One of the four patients was administered recombinant tissue plasminogen activator as adjuvant therapy via PD catheter for 2 hours for relapsing peritonitis caused by methicillin-resistant *S. epidermidis*. The patient remained infection-free for 12 months, but then the PD catheter developed a leak due to trauma. Catheter removal was performed in the remaining three patients, one of whom had to be permanently changed to hemodialysis. Concomitant infection with the same organism causing peritonitis was detected in two patients, one with a urinary tract infection caused by *Pseudomonas* spp, and another with an exit-site infection due

Table 2
Etiology of end-stage renal disease of patients admitted to Srinagarind Hospital. Khon Kaen, Thailand (2007-2016).

Etiology	Non-peritonitis group (n = 17) Number (%)	Peritonitis group (n = 22) Number (%)	Total (n = 39) Number (%)
Renal hypoplasia	8 (47)	4 (18)	12 (31)
Rapidly progressive glomerulonephritis	4 (23)	4 (18)	8 (20)
Lupus nephritis	1 (6)	3 (14)	4 (10)
Vesicoureteric reflux	1 (6)	3 (14)	4 (10)
Posterior urethral valve	0 (0)	2 (9)	2 (5)
Glomerulosclerosis	0 (0)	1 (4)	1 (3)
IgA nephropathy	0 (0)	1 (4)	1 (3)
Others	0 (0)	3 (14)	3 (8)
Unknown	3 (18)	1 (4)	4 (10)

Table 3
Causative organisms of peritoneal dialysis peritonitis in patients admitted to Srinagarind Hospital, Khon Kaen, Thailand (2007-2016).

Organism	Number of peritonitis episodes (%) (n = 60)
Gram-positive	
Staphylococcus epidermidis	
Methicillin-sensitive	5 (8)
Methicillin-resistant	10 (17)
S. aureus	
Methicillin-sensitive	9 (15)
Methicillin-resistant	3 (5)
Enterococci	
Enterococcus faecalis	1 (2)
Enterococcus spp	4 (7)
Gram-negative	
Enterobacter spp	9 (15)
Pseudomonas spp	6 (10)
Serratia marcescen	3 (5)
Salmonella group D	2 (3)
Fungus	2 (3)
Culture negative	6 (10)

to methicillin-sensitive *S. aureus*. Culture-negative peritonitis occurred in 10% of all peritonitis episodes. The two most frequent antibiotics initially administered were cefazolin and ceftazidime and the most common route of administration was intravenous (Table 4).

Overall re-infection rate was 63% with 15% being relapsing peritonitis, 5% recurrent peritonitis, 20% repeat peritonitis and 23% peritonitis occurring >4 weeks following the previous peritonitis episode and caused by different organisms or negative culture. Thirteen patients in the peritonitis group (59%) required PD catheter removal, and three (14%) had to change dialysis modality to hemodialysis. Fifteen patients (ten from non-peritonitis and five from peritonitis group) subsequently received kidney transplantation.

Univariate analysis of the 60 episodes of peritonitis indicate use of a straight PD catheter and dialysis duration longer >12 months are significantly associated with PD peritonitis (p-value <0.05) (Table 5). When factors with p-value <0.250 were subjected to multivariate analysis, the only independent factor associated with PD peritonitis was dialysis duration >12 months (Table 6).

DISCUSSION

Peritoneal dialysis is the most common dialysis modality used for children with ESRD, especially in developing countries (Szeto *et al*, 2003). Since 2008, there is a

Table 4
Initial antibiotic treatment of peritoneal dialysis peritonitis in patients admitted to Srinagarind Hospital,Khon Kaen, Thailand (2007-2016).

Route and antibiotic used	Number of peritonitis episodes (%) (n = 60)
Route of treatment	
Intravenous	34 (57)
Intraperitoneal	32 (43)
Antibiotic used	
Aminoglycoside	1 (2)
Cefazolin	35 (58)
Ceftazidime	50 (83)
Ceftriaxone	1 (2)
Ciprofloxacin	2 (3)
Cloxacillin	9 (15)
Meropenem	5 (8)
Vancomycin	12 (20)

Table 5
Univariate analysis of factors associated with peritoneal dialysis (PD) peritonitis episodes in 60 patients admitted to Srinagarind Hospital, Khon Kaen, Thailand (2007-2016).

Factor	Crude odds ratio	95% confidence interval	p-value[a]
Male	2.09	0.56-7.80	0.273
Age at PD initiation (per every additional year)	0.91	0.79-1.06	0.223
Obesity[b]	3.71	0.39-35.55	0.256
Prednisolone usage	1.05	0.27-4.09	0.941
CAKUT	0.50	0.14-1.76	0.279
Type of Tenckhoff catheter			
Straight	5.27	1.40 -19.86	0.014
Single	1.08	0.22-5.40	0.927
Timing of PD initiation <2 weeks after PD catheter placement	3.08	0.65-14.59	0.156
Dialysis duration ≥12 months	4.84	1.07-21.88	0.040
Hemoglobin <10 g/dl	0.85	0.48-1.51	0.578
Serum creatinine ≥10 mg/dl	0.48	0.10-2.44	0.379
Serum albumin <3g/dl	1.26	0.71-2.22	0.426
Vitamin D supplementation	1.22	0.57-2.61	0.609
Residual urine	1.36	0.49-3.77	0.556

[a]Significance at $p< 0.25$; [b]Body mass index ≥ 23 kg/m^2.
CAKUT: congenital anomalies of kidney and urinary tract.

Table 6
Multivariate analysis of factors associated with peritoneal dialysis (PD) peritonitis episodes in 60 patients admitted to Srinagarind Hospital, Khon Kaen, Thailand (2007-2016).

Factor[a]	Adjusted odds ratio (95% confidence interval)	*p*-value[b]
Age at PD initiation (per every additional year)	1.01 (0.81-1.26)	0.947
Type of Tenckhoff catheter: Straight	3.87 (0.74-20.14)	0.108
Timing of start PD <2 weeks after PD catheter placement	3.06 (0.53-17.64)	0.210
Dialysis duration ≥12 months	22.03 (2.14-226.61)	0.009

[a]Univariate *p*-value <0.25 (from Table 5); [b]Significance at $p<0.05$.

"PD first" policy for ESRD patients in Thailand (Chuengsaman and Kasemsup, 2017), but PD peritonitis is a critical complication that leads to peritoneal dysfunction and can necessitate a change in dialysis modality (Brown *et al*, 2011; NAPRTCS, 2011).

According to the 2016 International Society for Peritoneal Dialysis (ISPD) recommendations, the overall peritonitis rate should be ≤0.5 episode/patient-year or ≤0.04 episode/patient-month (Li *et al*, 2016). The North American Pediatric Renal Trials and Collaborative Studies found an overall peritonitis rate during 2007-2011 is one episode/27 patient-months (NAPRTCS, 2011). In Thailand between 1994-2007, PD peritonitis rate is one episode/3.50-8.52 patient-month (Nakwan *et al*, 2008; Wisanuyotin *et al*, 2011). At Srinagarind Hospital, PD peritonitis rate during 1994-2007 is 1 episode/8.52 patient-months (0.11 episode/patient-month) (Wisanuyotin *et al*, 2011), and the present study shows a reduction to 1 episode/19.57 patient-month (0.05 episode/patient-month), probably due to improvements in pediatric PD training program, exit-site care and proper PD effluent collected for culture. In the latter procedure 20 ml of effluent are collected in two blood-culture bottles for subsequent culture (Li *et al*, 2016). Culture negative rate decreased from 42.5% (Wisanuyotin *et al*, 2011) to 10%, comparable to the standard goal of <10.0-20.0% (Alfa *et al*, 1997; Azap *et al*, 2006; Li *et al*, 2016).

Identification of causative organisms is essential for prescribing appropriate antimicrobial agents, determining adequate duration of treatment and understanding probable route of infection, leading to better outcome and prevention of repeat peritonitis. In a previous study in Europe and North America, it was found that Gram-positive bacteria were the predominant causative organisms of PD peritonitis (Warady *et al*, 2007), but the primary pathogens causing dialysis-related peritonitis was shown to vary throughout the world (Schaefer *et al*, 2007).

In the present study, *S. aureus* and *S. epidermidis* were the most common Gram-positive pathogens, similar to

those in other reports (Schaefer *et al*, 2007; Warady *et al*, 2007). *S. aureus* peritonitis is associated with exit-site/tunnel infection and nasal carriage by patients and caregivers (Piraino, 2000; Vas and Oreopoulos, 2001; Warady *et al*, 2007); however, one patient in the present study experienced concurrent exit-site infection, but no nasal carriage was detected. *S. epidermidis* is transmitted through contact (Piraino, 2000; Vas and Oreopoulos, 2001) and patients and caregivers should be encouraged to undergo PD re-training programs to prevent repeat episodes of peritonitis, with special attention being paid to hand hygiene and exit-site care. *Enterobacter* was the most common Gram-negative organism detected, but no history of constipation nor gastrointestinal infection was documented in this group. It is worth noting nine episodes of relapsing peritonitis caused by *Enterobacter*, *S. aureus* and *S. epidermidis* occurred in four patients, with one patient permanently discontinued from PD treatment. These findings suggest physicians should not be reluctant to perform PD removal in cases of relapsing peritonitis to eradicate infecting pathogens and preserve peritoneal function.

Recombinant tissue plasminogen activator has been used concomitantly with antibiotics in cases of relapsing peritonitis caused by *Enterobacter cloacae* and *S. epidermidis* (Duch and Yee, 2001; Zorzanello *et al*, 2004). In the present study, this regimen was proved effective in treating a patient with relapsing *S. epidermidis* peritonitis.

Potential risk factors for PD peritonitis are patient age (NAPRTCS, 2011), presence of ostomy (Warady *et al*, 2007), catheter leakage (Warady *et al*, 2007), use of one-cuffed and straight catheter (NAPRTCS, 2011), failure to administer prophylactic antibiotics at time of catheter placement (Gadallah *et al*, 2000; Campbell *et al*, 2017; Prasad *et al*, 2007), hypoalbuminemia (Wang *et al*, 2003; Prasad *et al*, 2007), lack of vitamin D supplementation (Rudnicki *et al*, 2010; Kerschbaum *et al*, 2013), residual urine volume and exit-site/tunnel infection (Boehm *et al*, 2005; Cho and Johnson, 2014). In the present study, only dialysis duration >12 months is an independent factor significantly associated with PD peritonitis, suggesting healthcare providers should be encouraged to take steps to shorten the waiting time for kidney transplantation in pediatric ESRD patients. However, the study was limited due to its retrospective design and small sample size and further multicenter prospective studies in ESRD children should be conducted.

In conclusion, the study shows peritoneal dialysis peritonitis is an important complication in children receiving continuous ambulatory peritoneal dialysis and dialysis duration >12 months is significantly associated with this syndrome. Prevention and proper management of peritoneal dialysis peritonitis should be emphasized to reduce peritoneal dialysis peritonitis rate and optimize outcome of children with end-stage renal while awaiting kidney transplantation.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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