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Infectious and catheter-related complications in pediatric patients treated with peritoneal dialysis at a single institution

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Abstract. Continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD) are the predominant dialytic modalities for the majority of children while awaiting transplantation. Wide acceptability of peritoneal dialysis is hindered by infectious complications. A retrospective review of 367 pediatric patients treated with CAPD/CCPD for at least 3 months from September 1980 through December 1994 revealed that the peritonitis incidence ranged from 1.7 to 0.78 episodes per patient-year. No differences in peritonitis rates were observed between patients treated with CAPD or CCPD. Gram-positive organisms were responsible for the majority of peritonitis episodes. Age, sex, race, primary renal disease, presence of nephrotic syndrome, and serum albumin level were not associated risk factors. Longer time on treatment and diminished serum IgG level were associated with increased peritonitis incidence. Treatment was successfully completed at home in most cases. Almost half of the catheter losses were caused by *Staphylococcus, Pseudomonas*, and fungal peritonitis and tunnel/exit-site infections. Infectious complications are still the major causes of morbidity and treatment failure in patients treated with CAPD/CCPD. Thus, controlled studies are needed to assess methods for prevention or improvement of peritonitis rates in this patient population.

Key words: Infectious complications – Peritoneal dialysis

Introduction

End-stage renal disease (ESRD) for children 0–19 years of age is diagnosed in 11 per million population per year [1] and transplantation is the optimal form of renal replacement therapy (RRT) for these children and adolescents. At present, continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD) are the predominant dialytic modalities for the majority of children while awaiting transplantation in North America [2]. Although the concept of "novel portable/wearable equilibrium technique" (CAPD) was introduced by Popovich et al. [3] in 1976, the worldwide acceptance of peritoneal dialysis as the dominant modality for RRT for children has transpired only in the past decade. In North America, the percentage of children <15 years old on CAPD/CCPD rose from 11% in 1980 to 50% in 1989. Consequently, the proportion of patients on hemodialysis decreased from 75% in 1980 to 32% in 1989 [2]. Worldwide, there are 86,300 patients on peritoneal dialysis as of 1993, with a 16% annual growth rate from 1990 to 1993 [4].

Despite the wide acceptability of peritoneal dialysis as the dialytic modality of choice for children, it is hindered to a great extent by infectious complications. Peritonitis and catheter-related infections remain the most common cause of morbidity and treatment failure in patients undergoing CAPD/CCPD. Since the introduction of CAPD, there have been several technical improvements in the availability and packing of the dialysate solution, as well as catheter and tubing connections aimed at decreasing peritonitis risk [5–10]. Numerous modifications in the connection systems and disinfectants at the bag-tubing connection systems have resulted in a marked reduction of the peritonitis rates and have therefore made CAPD/CCPD a satisfactory alternative to hemodialysis [11, 12]. The most successful of these has been the Y-configuration used in CAPD, largely because of the "flush before fill" technique [11], where possible contaminants are flushed into the drain bag before the patient is filled. Although several reports have described the acceptability of CAPD/CCPD in children [2], there is limited reported experience on the long-term infectious complications in children treated with these modalities. We have therefore conducted a retrospective analysis of our 14 years' experience with peritonitis and catheter-related infectious in patients followed at the UCLA Pediatric Dialysis Program. Peritonitis rates, predisposing

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factors, etiological organisms, hospitalizations, and outcomes were analyzed.

Patients and methods

The medical records of all patients who were treated with CAPD/CCPD at UCLA Pediatric Dialysis Program for at least 3 months from September 1980 through December 1994 were reviewed. There were 367 patients (192 male, 175 female) aged 9.2±3.6 years. Age distribution is shown in Table 1. Approximately one-quarter of patients were less than 6 years old. The mean duration of therapy was 27 months with a range between 3 and 51 months. CAPD was the primary dialytic modality for 70 patients. CCPD was introduced in 1983, with the majority of patients converted to CCPD by 1985.

The CAPD procedure was performed as described by Oreopoulos et al. [13]. Each patient received four to five daily exchanges with a dialysate (Dianeal, Baxter Healthcare, McGaw Park, Ill., USA) volume of 0.5–2 l per exchange (range 20–60 ml/kg). The CCPD regimen usually consisted of five nocturnal exchanges delivered by an automated cycler (AMP 80/2, American Medical Products, Freehold, N.J., PAC-Xtra, Baxter Healthcare) over 10 h and one daytime dwell using less than half the exchange volume [13]. The number of daily exchanges and the concentration of the dialysate were adjusted according to the ultrafiltration requirement of the patient to control weight and blood pressure.

Straight, single- or double-cuffed Tenckhoff catheters (Quinton Instruments, Seattle, Wash., USA) were used in 86% of patients and column disk catheters (Lifecath, Physio-Control, Redmond, Wash., USA) were used in the remaining 14% of patients in the first 5 years of the study period, and since 1985, curled double-cuffed Tenckhoff catheters were exclusively used.

The following potential predisposing factors were evaluated: age, sex, primary renal disease, presence of nephrotic syndrome, length of peritoneal dialysis treatment, serum albumin, and serum immunoglobulins, mainly IgG levels. Peritonitis rates, etiological organisms, hospitalizations, and patient outcomes were also analyzed.

Exit-site infection was defined as purulent drainage and/or erythema of the skin at the catheter exit-site. Tunnel infection was defined as erythema and/or swelling over the subcutaneous catheter tunnel. Peritonitis was diagnosed when two or more of the following criteria were present: (1) abdominal pain and/or tenderness, (2) cloudy fluid, (3) dialysate cell count >100 white blood cells/ml and a differential count >50% polymorphonuclear cells, and (4) demonstration of organism in the peritoneal effluent by Gram stain and/or culture. Recurrent/persistent peritonitis was defined as isolation of the same organism within 4 weeks of discontinuation of previous antibiotic therapy.

Each patient/parent was instructed to begin treatment for peritonitis when the patient developed signs and symptoms of peritonitis (abdominal pain, cloudy effluent). A specimen from the first cloudy effluent was obtained for cell count and differential, Gram stain, and culture. Three rapid exchanges (flushes) using 1.5% dextrose at standard volume were then performed, draining each one immediately after it had infused. Since 1993, the fourth exchange contained vancomycin 500 mg/l as loading dose to dwell for 4 h, followed by 4-h exchanges of dialysate containing vancomycin 15 mg/l. Vancomycin levels were followed and the dose was adjusted accordingly. Gentamicin 5 mg/l or ceftazidime 500 mg/l loading dose then 125 mg/l maintenance dose were added to the dialysate solution if Gram-negative organisms were identified by Gram stain or culture. Heparin 500 U/l was added to the dialysate until the effluent was clear. Peritoneal fluid cell count, Gram stain, and culture were repeated if the patient failed to improve with 48–72 h of treatment. Intraperitoneal antibiotics were adjusted according to sensitivity patterns and were continued for at least 14 days. Peritoneal fluid cell count, Gram stain, and cultures were repeated within 1 week of completion of therapy.

Hospitalization, administration of intravenous antibiotics, and removal of catheters were determined individually based on the severity of symptoms and response to initial therapy. Fungal peritonitis was treated with intravenous amphotericin. The presence of fungal peritonitis and/or the persistence of cloudy effluent for more than 3–4 days after initiation of appropriate antibiotic treatment were used as strong considerations for catheter removal during the last 7–8 years.

Changes in the antibiotic regimen for treatment of peritonitis were based on the recommendations by the ad hoc advisory committee on peritonitis management [14]. Prior to 1993, cefazolin 250 mg/l and gentamicin 6–8 mg/l or tobramicin 8 mg/l were added to the dialysate solution for Gram-positive and Gram-negative coverage, respectively. Vancomycin has replaced first-generation cephalosporin because of increased prevalence of methicillin-resistant coagulase-negative staphylococci. Gentamicin, netilmicin, and tobramicin also appeared to have equal efficacy, but gentamicin was used preferentially because of cost, and serum gentamicin levels were followed and the dose adjusted accordingly.

In 1986, extended use of the cycler tubing was initiated. Dialysate tubing was used for the whole week and prongs soaked with povidone-iodine were reused to hang additional bags during the week. Preparation time, cost, parental satisfaction, and peritonitis rates using this system were compared with daily cycler tubing changes. Flush before fill in CCPD was introduced in 1994. In this regimen, flushing of dialysate from the manifold to the drainage bags and from the patient to weigh bags was done prior to patient filling.

Statistical analysis was performed using life-table analysis, Student's *t*-test and chi-squared where applicable [15]. Values were expressed as mean plus or minus standard deviation (SD). Serum IgG levels were expressed as Z-scores, calculated as the difference between the patient's serum IgG and the mean value in controls divided by the SD of the controls.

Table 1. Age distribution of patients included in the study

Age (years)	*n*	%
0–2	48	13.1
3–5	50	13.6
6–10	94	25.6
11–15	93	25.3
≥16	82	22.3

Results

Peritonitis incidence

Six hundred and thirty-five episodes of peritonitis occurred over the 14-year study period. Peritonitis incidence ranged from 1.7 to 0.78 episodes per patient-year, with a trend to a decreased rate during the last few years (Fig. 1). A similar peritonitis rate was observed between patients treated with CAPD or CCPD. The racial distribution was as follows: Hispanic 43%, white 39%, African American 9%, Asian 4%, and other 5%. There were no difference in peritonitis rates between different racial groups.

When data were analyzed by age, as a predisposing factor, peritonitis rates were 1.08, 1.0, and 0.96 episodes per patient-year for children less than 3 years, 3–5 years, and 6–10 years, respectively. Patients between 11 and 15 years and ≥16 years had 1.24 and 1.26 episodes per patient-year, respectively.

The extended use of the cycler tubing was employed from 1986, and it was not associated with an increased incidence of peritonitis. The main advantages of this

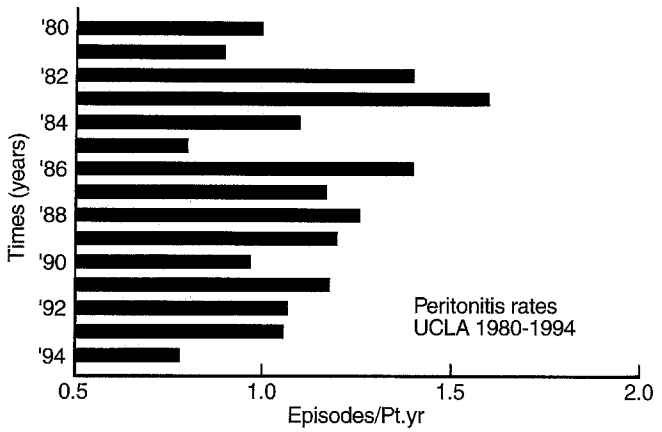

Fig. 1. Annual peritonitis rates since the initiation of the program at UCLA

modified technique can be summarized as follows: decreased parental burn-out, cost, in-patient nursing time, and preparation time to less than half. Using life-table analysis, 40% of patients had the first peritonitis episode at 12 months and 18% had the second episode at 24 months.

Etiological organisms

Gram-positive organisms were responsible for the majority (42.4%) of the peritonitis episodes, with an almost equal proportion caused by *Staphylococcus aureus* and *Staphylococcus epidermidis*. Peritonitis caused by Gram-negative organisms accounted for 27.4% of episodes. No organisms were cultured in 22.8% of episodes and 1.6% of the episodes were secondary to multiple organisms. Fungal peritonitis occurred in 2.8% of cases (Table 2).

Table 3 shows the relationship between the etiology of peritonitis and the dialysate fluid cell count. The total number of white cells in the dialysate solution did not predict the organisms involved.

Predisposing factors

Predisposing factors were analyzed during the period 1980–1990. The primary renal disease was acquired in 50%, congenital in 37%, and hereditary in 13% of the patients studied during this period. One hundred and twenty-nine patients (68%) had episodes of peritonitis and 62 patients (32%) had none. Age, sex, primary disease, and presence of nephrotic syndrome did not correlate with the incidence of peritonitis. However, time on treatment was significantly longer in patients who developed peritonitis ($P < 0.0001$) (Table 4).

Serum total protein and albumin were compared in patients with no episodes, 1–4 episodes, and >5 episodes of peritonitis and there were no differences between the three groups (Table 5). Mean IgG z-scores were correlated with peritonitis rates. Patients with mean IgG z-score <0 had 1.8 episodes per patient-year compared with 1.1 episodes per patient-year in patients with mean IgG z-score >0 ($P < 0.01$) (Table 6).

Table 2. Distribution of organisms in the etiology of peritonitis

Etiology	*n* (635)	%
Gram-positive	269	42.4
Gram-negative	174	27.4
Fungal	18	2.8
Multiple organism	10	1.6
No growth	145	22.8
No culture	19	3.0

Table 3. Relationship between the initial dialysate white cell counts (WBC) and the organisms involved

Etiology	Dialysate WBC (mean ± SD)
Gram-positive	5,059±2,446
Gram-negative	5,886±1,717
Multiple organism	5,301±852
Fungal	2,724±604

Table 4. Analysis of predisposing factors in patients with and without episodes of peritonitis

Peritonitis	Positive	Negative
Patients	129 (68%)	62 (32%)
Time on PD (months)	32±22	13±13*
Age (years)	11±6	13±13
Sex (F/M)	58/42	42/58
Race	ND	ND
Primary disease	ND	ND
Nephrotic syndrome	ND	ND

ND, No difference; PD, peritoneal dialysis
* $P < 0.0001$

Table 5. Relationship between the number of peritonitis episodes and the serum total protein and albumin levels

Episodes of peritonitis	Total protein (mean ± SD)	Albumin (mean ± SD)
0 ($n = 62$)	6.0±0.9	3.7±0.6
1–4 ($n = 88$)	6.1±0.7	3.6±0.5
>5 ($n = 51$)	6.1±0.6	3.6±0.4

Table 6. Relationship between the mean IgG Z-score and the number of episodes of peritonitis

Mean IgG Z-score ($n = 106$)	Peritonitis episodes per patient-year
<0 ($n = 71$)	1.8 episodes*
>0 ($n = 35$)	1.1 episodes*

* $P = 0.01$

Catheter survival

Renal transplantation accounted for 45% of the catheters removed. Infectious complications were responsible for 40.9% of catheter loss, 26.7% of which were because of peritonitis and 14.2% of which were caused by tunnel and/or exit-site infections. Mechanical problems such as catheter leak, obstruction, and migration accounted for 9.5% of catheters removed. Native kidney function returned in 4.2%

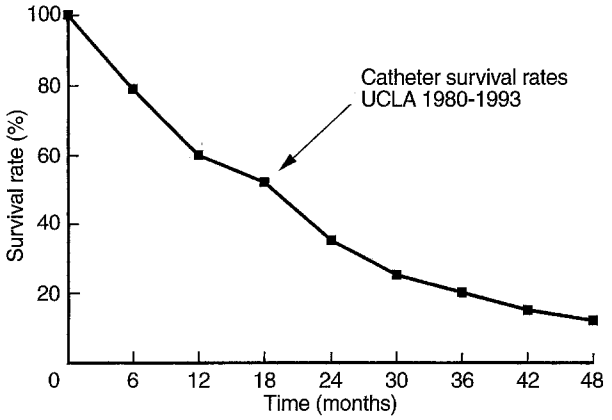

Fig. 2. Catheter survival rate, the *arrow* indicates the 50% survival rate

of cases. The median catheter survival time was 18 months (Fig. 2).

Hospitalization

From 1990 through 1994, 17.4% of total hospitalizations were due to peritonitis, with an average of 7.6 hospital days per episode. In 1992, the average hospital days were higher (10 days/episode) than the other years. In that year, 1 patient was hospitalized for 43 days for fungal peritonitis, bowel obstruction, and transfer to hemodialysis.

Patient outcome

One hundred and sixty-three (65.5%) patients underwent transplantation; 15 (6%) patients recovered renal function; 23 (9.2%) transferred to hemodialysis because of membrane failure, 22 of which were associated with peritonitis. *S. aureus, Pseudomonas*, and *Candida albicans* were the organisms involved. One patient developed membrane failure because of a ruptured appendix. There were 13 (5.2%) patient deaths during this study period, but the cause of death was not dialysis related. Thirty-five (14%) patients transferred to our adult peritoneal dialysis program or moved to another state/dialysis unit.

Discussion

Peritonitis and catheter-related infections remain the most common complications in patients treated with CAPD/CCPD. Review of our 14-year experience with pediatric patients revealed more favorable peritonitis rates compared with the 2.3–2.6 and 2.1 episodes per patient-year reported by the Southwest Pediatric Nephrology Study Group [7] and Neiberger et al. [16], respectively. Our peritonitis rates were comparable to the 0.72, 0.8–1.34, 0.98, and 1.58 episodes per patient-year published by the Italian Registry [17], Levy et al. [5], and Howard et al. [18], respectively. The higher peritonitis rates reported by the Southwest Pediatric Nephrology Group may represent a learning curve with the use of this new dialytic modality [7]. The improved peritonitis rates in recent years may be attributable to the widespread use of peritoneal dialysis as the primary dialytic modality in children.

It has also been postulated that peritonitis rates would be lower with the use of CCPD because of reduced number of daily catheter manipulations. Although this finding was noted by Levy et al. [5], we did not find any differences in peritonitis rates in patients on CAPD and CCPD [13], as observed by Neiberger et al. [16], Howard et al. [18], and von Lilien et al. [8].

Studies in adults have also shown decreased peritonitis rates in patients undergoing CAPD with the introduction of the "flush before fill" technique [11]. Over the last year, we have implemented the "flush before filling" protocol for patients undergoing CCPD and although the decrease in the peritonitis rate did not reach statistical significance ($P < 0.07$), there is a trend in that direction. The impact of this promising technique for patients treated with CCPD will await the results of a prospective randomized clinical trial in pediatric patients.

No differences in peritonitis rates were observed when the data were analyzed by age, as reported by Neiberger et al. [16] and Levy et al. [5]. However, compared with adult patients at UCLA and other centers, the incidence of peritonitis was higher in the pediatric population [18]. Since the dialysis techniques and protocols are similar between adults and children at UCLA, the higher incidence of peritonitis in children suggests that other factors, i.e., host defense mechanisms, psychosocial factors, and patient selection, should be considered in the pediatric population.

Age, sex, race, primary renal disease, presence of nephrotic syndrome, and serum albumin level were not associated risk factors for peritonitis. However, as reported by Levy et al. [19] and Watson et al. [6], the longer the duration of treatment with peritoneal dialysis the higher the risk for the development of a peritonitis episode.

Over the last few years, several studies have addressed the role of intraperitoneal immunological mechanisms in the pathogenesis of peritonitis [20, 21]. Furthermore, the concentration of IgG in the dialysate has been found to identify patients at high risk for peritonitis [22]. However, De Vecchi et al. [23] did not confirm such original findings. In our present review, diminished serum IgG levels were also associated with an increased incidence of peritonitis. This finding supports several studies that demonstrated an inverse relationship between opsonin activity and/or effluent IgG concentration and the frequency of peritonitis [20]. Effective phagocytosis of the peritoneal macrophage depends on opsonization of the organism by IgG and C3. However, the concentration of IgG and C3 are on average 1/30th and 1/70th of normal peritoneal fluid [24, 25]. Furthermore, Schroder et al. [26] found complete absence of serum IgG2 in 11 of 12 children on CAPD.

Thus, two uncontrolled studies have evaluated the potential benefits of intraperitoneal IgG therapy in patients with frequent peritonitis [21, 22]. Significant reduction in peritonitis rates in IgG-treated patients was observed in both studies. Nevertheless, it is difficult to identify high-risk patients based on effluent IgG alone. Controlled, randomized studies are needed to confirm the efficacy and safety of intraperitoneal IgG in the prevention of peritoni-

tis. Moreover, the cost of the IgG preparation will have to be taken into consideration in the evaluation of such studies. It may not be cost-effective to implement the use of intraperitoneal IgG in adult patients because the peritonitis rates are much lower. More physiological peritoneal dialysate solutions with improved biocompatibility may improve the host defense mechanisms in this group of patients [27].

Gram-positive organisms were responsible for the majority of peritonitis episodes, as seen in most studies. Compared with the ESRD Network 18, our data in 1993 revealed a higher incidence of infections with Gram-negative organisms. This may be due to reduced *S. epidermidis* infections from touch contamination. If this trend continues, addition of antibiotics with Gram-negative coverage may be warranted in the initial treatment regimen.

Treatment was successfully completed at home in most cases. Peritonitis accounted for 17.4% of total hospitalizations, with an average of 7.6 days per episode; this rate is more favorable than the 25.4% reported by the ESRD Network 18 and may be due to prompt initiation of home therapy. The number of hospital days per episode, however, was comparable at 9.7 days per episode.

Almost half of catheter losses were caused by *Staphylococcus, Pseudomonas*, fungal peritonitis, and tunnel/exit-site infections. Several studies have shown that *S. aureus* is the most common cause of catheters removed because of infectious reasons [28, 29]. Studies to prevent *S. aureus* infection have centered on eradication of the nasal carriage state and staphylococcal vaccination. Perez-Fontan et al. [30] observed that mupirocin was more effective than neomycin for the elimination of *S. aureus* nasal colonization in CAPD patients, but retreatment is necessary. Yu et al. [31] demonstrated that neither intravenous vancomycin nor topical bacitracin were effective, but intermittent rifampin in combination with intranasal bacitracin prevent *S. aureus* infection in the hemodialysis population. Zimmerman et al. [32] showed no difference in peritonitis rates but a delayed time to first episodes in rifampin-treated CAPD patients. On the other hand, several studies have focused on active immunization as prophylaxis for staphylococcal peritonitis. Initial reports related to the efficacy of vaccination with staphylococcus toxoid and whole killed organism were not confirmed by a randomized trial in Australia [33]. More recently, specific capsular polysaccharides, serotypes 5 and 8, have been shown to produce protective immunity against encapsulated strains of *S aureus* in animal models [34]. However, the vaccine for humans is still being developed.

Eradication not only of *S. aureus* but also *Pseudomonas* and *Candida* peritonitis is also important because of the potential complication of membrane failure from peritoneal scarring. Approximately 10% of patients were transferred to hemodialysis because of membrane failure. Thus, we believe that early catheter removal can prevent further damage of the peritoneal membrane in those cases that do not respond to the specific antibiotic therapy within the first 3 or 4 days.

Peritonitis rates remained the same when extended use of the cycler tubing was introduced in 1986. Because of the dramatic decrease in cost, preparation time, and parental burn-out, extended use of the cycler tubing is highly recommended.

In summary, peritonitis and catheter-related infections are still the major causes of morbidity in patients treated with CAPD/CCPD. Further studies are needed to identify patients at higher risk. From our present clinical experience, we recommend measurement of serum IgG levels at initiation of therapy and at periodic intervals according to the results. Controlled studies are warranted to investigate methods to prevent peritonitis, either by passive immunization with chronic intraperitoneal IgG administration or active immunization with staphylococcal vaccine.

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