Peritonitis in children with automated peritoneal dialysis: a single-center study of a 10-year experience

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ABSTRACT
Peritoneal dialysis (PD) constitutes the preferred dialysis modality for children requiring renal replacement therapy with peritonitis being one of the most common complications of PD. This study was performed to evaluate the epidemiology, microbiology, and outcomes of PD-associated peritonitis in Greek children for a 10-year period. A total of 27 patients (16 males) with a mean age 121.8 ± 57.2 months were retrospectively analyzed. Patients were on PD therapy for a mean duration of 45.2 ± 26.1 months. We found 23 episodes of PD-associated peritonitis occurred in 9 out of 27 patients (0.23 episodes/patient-year), with four patients experienced two or more peritonitis episodes. Gram-positive bacteria were responsible for 15 (65.2%) peritonitis episodes, with Staphylococcus aureus being the predominant species isolated in 30.4% of cases. A total of seven episodes of exit-site infections (ESIs) were identified in five patients (0.069 episodes/patient-year) with the most common bacteria isolated being S. aureus (57.4%). Initial antibiotic treatment included intraperitoneal vancomycin plus ceftazidime in the majority of cases (82.6%). At the end of study, 12 (44.4%) patients remained on PD, 11 (41.8%) underwent renal transplantation, 2 (7.4%) shifted to hemodialysis and unfortunately, two patients (7.4%) died. Conclusively, our study revealed a noticeable low peritonitis and ESIs rate as compared to international data and represents the first evaluation of the characteristics and outcomes of peritonitis in the Greek pediatric PD population.

Introduction
Despite the fact that children suffering from chronic kidney disease (CKD) constitute a relatively small portion of total CKD population, end-stage renal disease (ESRD) remains one of the leading causes of increased morbidity and mortality among children. It affects serious aspects of early childhood and adolescent life such as growth, mineral, and bone metabolism in addition to development of the cardiovascular system and increased susceptibility to infections. In fact, it has been reported that age-specific mortality is about 30 times as high as among children without ESRD. Peritoneal dialysis (PD) has been established as the dialysis modality of choice among children for various reasons, including the simplicity of the procedure that allows performance at home so the child rapidly returns to regular school attendance and other activities. However, serious complications have been attributed to this therapeutic modality, with PD-associated peritonitis being the most important reason for morbidity, mortality, and technique failure. Following the establishment of the International Pediatric Peritonitis Registry (IPPR) several dialysis centers across the world have reported on the outcomes and complications of PD as well as the global bacteriology and antibiotic susceptibility associated with peritonitis in children. To the best of our knowledge, to date, there have not been published articles on the epidemiology, microbiology, and outcomes of PD-associated peritonitis in Greek children. To address this lack of evidence we retrospectively reviewed data from our patients for a 10-year period. This study presents the incidence, microbiology and clinical outcomes of PD-associated peritonitis in Greek pediatric PD patients at our center with the largest cohort of such patients in Greece.

Materials and methods
This study was performed at Hippokration General Hospital of Thessaloniki in Greece. The records of all patients hospitalized with PD-associated peritonitis...
between May 2005 and April 2015 were retrospectively reviewed and analyzed.

The diagnosis of peritonitis was based on established criteria. Peritonitis was defined by the presence of cloudy PD effluent with more than 100/mm$^3$ white blood cells (WBC) and a WBC differential of more than 50% polymorphonuclear leukocytes. The collected data included demographic characteristics such as age at time of peritonitis, age at commencement of PD, sex, and cause of ESRD, underlying medical conditions, type of PD (chronic ambulatory PD/ambulatory PD), data for each PD-associated peritonitis episode, including number of episodes, time interval between two episodes, time interval between initiation of PD and first peritonitis episode, microbiology of peritonitis episodes, antibiotics sensitivity, initial treatment modality, incidence of exit-site infections (ESIs), microbiology of ESIs; laboratory examinations for each episode, including WBC count and absolute neutrophil count (ANC), WBC in peritoneal dialysate; outcome of peritonitis episodes and cause of PD cessation. Peritonitis was treated intraperitoneally with empiric treatment consist mainly of a glycopeptide (vancomycin) plus third-generation cephalosporin (ceftazidime). Subsequent therapy depended in cultures and antimicrobial susceptibility tests obtained.

Results were evaluated using frequencies and percentages for categorical variables and means with standard deviation or median with ranges for continuous variables. The statistical program GraphPad Instat (Graphpad Inc., San Diego, CA) was used.

**Results**

A total of 27 patients, including 16 males (59%), were treated with PD during the study period (from May 2005 to April 2015). The mean age was $121.8 \pm 57.2$ months (range $14–232$ months). The total patient-months on APD were $1221$, with a mean duration of PD therapy of $14–232$ months. The total patient-months on PD ceased in six (22.2%) of the study patients. All patients were on automated PD (nocturnal intermittent PD).

During the 10 years of study, 23 episodes of PD-associated peritonitis occurred in 27 patients. The overall peritonitis rate was one episode per 53.09 patient-months or 0.23 episodes per patient-year. The mean time interval between initiation of PD and first peritonitis episode was $30 \pm 26.95$ months. Four patients (15%) experienced two or more peritonitis episodes while 18 (67%) experienced no episodes. The mean time interval between two episodes for patients with equal or more than 2 peritonitis episodes was $9.81 \pm 22.86$ months. The mean value of WBC count was $15,674 \pm 3843$ cells/$\mu$L with ANC being $10,659 \pm 2613$ cells/$\mu$L, while the WBC count in peritoneal dialysate was $1922 \pm 802$ cells/$\mu$L during peritonitis episodes.

**Table 1. Etiology of end-stage renal disease in study children.**

| Etiology of ESRD                     | No. of patients | %     |
|-------------------------------------|----------------|-------|
| Renal agenesis/hypoplasia/dysplasia | 6              | 22.2  |
| Obstructive nephropathy             | 5              | 18.6  |
| Chronic glomerulonephritis$^a$      | 5              | 18.6  |
| HUS                                 | 4              | 14.7  |
| Chronic interstitial nephritis       | 2              | 7.4   |
| Polycystic kidney disease           | 2              | 7.4   |
| Oxalosis type 1                     | 1              | 3.7   |
| Unknown                             | 2              | 7.4   |
| Total                               | 27             | 100   |

ESRD: end-stage renal disease; HUS: hemolytic uremic syndrome.

$^a$Including three patients with focal segmental glomerulosclerosis, one patient with membranous nephropathy and one patient with unclassified form.

**Table 2. Underlying disease in study children.**

| Underlying medical conditions        | No. of patients | %     |
|-------------------------------------|----------------|-------|
| Impaired cognitive development       | 7              | 25.9  |
| Impaired motor development           | 6              | 22.2  |
| Osseous abnormalities                | 5              | 18.5  |
| Cardiac abnormalities                | 3              | 11.1  |
| Pulmonary abnormalities              | 1              | 3.7   |
| Renal agenesis/hypoplasia/dysplasia  | 6              | 22.2  |
| Metabolic disorders                  | 2              | 7.4   |
| Central nervous system disorders     | 2              | 7.4   |
| Metabolic disorders                  | 2              | 7.4   |
| Other abnormalities$^a$              | 3              | 11.1  |

$^a$Other abnormalities included: a patient with Prader–Willi syndrome, a patient with neonatal hepatitis and a patient with possible Marfan syndrome.

Etiology of ESRD in all 27 patients is depicted in Table 1 and the underlying disease is presented in Table 2. The most frequent cause of ESRD was renal malformation (renal agenesis/hypoplasia/dysplasia), present in six (22.2%) of the study patients. All patients were on automated PD (nocturnal intermittent PD).

Gram-positive bacteria were responsible for 15 (65.2%) episodes of peritonitis and gram-negative for four (17.4%). There was one (4.3%) episode of polymicrobial peritonitis and three (13%) episodes with no causative bacteria found. *Staphylococcus aureus* was identified as the leading causative pathogen, isolated in seven (30.4%) cases. The overall distribution of causative bacteria among study patients in addition to the identification method presented in Table 3. Only in 29% of the *S. aureus* peritonitis episodes, nasal carriage of the causative organism was found. A total of seven episodes of ESIs were identified in five patients, resulting in an incidence rate of one episode per 174.43 patient-months or 0.069 episodes per patient-year. All ESIs episodes were identified in five out of nine of the patients who experienced a peritonitis episode. Two of them experienced two ESIs and the remaining three experienced one ESI episode. The most common bacteria responsible for ESI was *S. aureus*, isolated in four (57.4%) cases.

Among all peritonitis episodes, 19 (82.6%) were initially treated with vancomycin plus ceftazidime, two
and increased education of parents and patients. Nevertheless, the incidence rate remains relatively high on developing countries.12,18,19

The peritonitis rate in our 10-year study was one episode per 53.09 patient-months or 0.23 episodes per patient-year which is similar to that of prominent PD centers in the USA and China (0.26 and 0.22 episodes per patient-year respectively).20,21 Furthermore, we reported a lower incidence rate as compared to that of large epidemiological studies including extensive population groups, such the 2011 Annual Dialysis Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) (0.64 episodes per patient-year)22 and the University of California, Los Angeles (UCLA) pediatric dialysis program study (0.78 to 1.7 episodes per patient-year).7 In addition, our incidence rate was lower as compared to that of studies in centers across Europe (0.82–0.83 episodes per patient-year),23,24 Australia and New Zealand (0.71 episodes per patient-year).15 Our study reported a very low incidence rate of ESI of one episode per 174.43 patient-months or 0.069 episodes per patient-year. A brief review on the literature suggests that this is a disproportionally low rate compared not only to the above studies, in which it varies from 0.33 episodes per patient-year20 to 1 episode per 24.4 PD-months,21 but also to other studies regarding the characteristics of PD-associated peritonitis in the pediatric population.7,22 The possible explanation for the low rates in both peritonitis and ESIs found in our study, should be the close attention given to training and retraining, equipment, and strict protocols to prevent infections followed in all of our patients.

It has long been established that gram-positive bacteria account approximately for 50–60% of peritonitis episodes while gram-negative bacteria are responsible for 20–30% of them and cultures remain negative in a substantial percentage (<20%) of peritonitis.16 Not surprisingly, our study is in accordance with this evidence, with gram-positive bacteria accounting for 65.2% and gram-negative bacteria for 17.4% of the total cases while in 13% of the episodes no bacteria was found. Furthermore, recent studies suggest the existence of significant variation in the distribution of microorganisms among different global regions, with peritonitis due to gram-positive bacteria being predominant in Europe and specifically S. aureus infections prevailing in Western Europe.25 The results of our study confirmed the above finding, with S. aureus determined as the leading pathogen, isolated in 30.4% of cases. Remarkable is the fact that rare bacteria such as Kocuria spp., Ralstonia spp., Corynebacterium spp. or even rare species of common bacteria such as Staphylococcus capitis and Streptococcus equinus can cause peritonitis, as
was found in our study patients. This rare cases have been published in recent years, suggesting that these organisms, although are usually considered to be contaminants, they can cause severe disease and symptomatic peritonitis so the prompt diagnosis and effective treatment could be of great importance.

According to the current guidelines of the International Society of Peritoneal Dialysis (ISPD), empiric therapy of peritonitis episodes should consist of the combination of either a first-generation cephalosporin, such as cefazolin or a glycopeptide (vancomycin or teicoplanin) with a third-generation cephalosporin, such as ceftazidime or an aminoglycoside. The superiority of the combination of a glycopeptide and ceftazidime over cefazolin and ceftazidime has been demonstrated by a meta-analysis of studies performed in adults and its safety and efficacy profile in children. Also, the recommendation of ceftazidime over aminoglycosides for the coverage of gram-negative bacteria is based on the possible adverse effects of ototoxicity and nephrotoxicity after prolonged administration.

Taking into account the above findings and the limited availability of intravenous cefazolin in our center, the majority of the peritonitis episodes (82.6%) were initially treated with vancomycin and ceftazidime as based in our treatment protocol for empirical therapy.

Regarding the outcomes of the peritonitis episodes, we evaluated 85% of full functional recovery. This finding is in concordance with recent large multi-center studies with data extracted from the IPPR, in which rates of full functional recovery count as high as 89%. Moreover, concerning long-term outcomes of children on PD, our study demonstrated a rate of 7.4% shift to HD while studies from international, European, and Australasian registries assess comparable rates (8.1%, 21%, and 7%, respectively). Continuation of nocturnal intermittent PD was calculated in 44.4% of the study patients. Unfortunately, two patient died (7.4%), with a proportion, nevertheless, equally described in other studies, such as in Italy (9.5%), in Finland (9%), as well as internationally (1.2%).

The retrospective design and small sample size are the main limitations of our study. Results and conclusions extracted from retrospective studies, accompanied by their inherent risk of selection and classification biases, should be assessed with a considerable amount of doubt. However, our study illustrated a noticeable low peritonitis rate and represented the first evaluation of the characteristics and outcomes of peritonitis in the Greek pediatric PD population. In addition, this study was the first attempt to establish the problem of PD-associated infections, peritonitis and ESI, in Greece. Consequently, it is of great importance to implement prospective studies with large study groups in order to confirm the results of the present study.

Disclosure statement
The authors report no conflicts of interest.

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