Prognostic Value of Dialysis Effluent Leukocyte Count in Children on Peritoneal Dialysis With Peritonitis

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Introduction. Early prediction of the efficacy of treatment in peritonitis complicating peritoneal dialysis (PD) is the best way to reduce morbidity. We studied the prognostic value of the third-day dialysis effluent leukocyte count after antibiotic therapy for prediction of treatment outcomes.

Materials and Methods. Medical records of 31 children on PD, younger than 15 years old, admitted in Ali-Asghar Children's Hospital because of PD-related peritonitis, were reviewed retrospectively. Peritonitis was defined by fever, abdominal pain, and cloudy effluent with a leukocyte count greater than 100/mm^3 or a positive dialysis effluent culture for microorganisms. For each episode of peritonitis, the leukocyte count of the effluent was measured on the third day after initiation of empiric therapy and culture results were recorded. The receiver operating characteristic curve was used to perform predicting value assessments.

Results. Of 60 episodes of peritonitis, 68.3% were treated successfully. Of the remaining episodes, 15.8% resulted in mortality, 57.9% required catheter removal, and 26.3% led to both. The mean PD effluent leukocyte count on the third day after initiating empiric antibiotics was significantly higher in the group with treatment failure (2258 ± 796/mm^3) than in the group with successful treatment (1325 ± 669/mm^3; $P < .001$). The cutoff point of 1240/mm^3 was found with optimized sensitivity (100%), specificity (63.4%), positive predictive value (55.9%), and negative predictive value (100%) for prediction of treatment failure ($P < .001$).

Conclusions. This study showed that the third-day dialysis effluent leukocyte count predicted short outcomes of peritonitis.

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INTRODUCTION

Peritonitis is a serious complication and probably the most important cause of technique failure in patients who undergo peritoneal dialysis (PD). Complications of peritonitis are catheter removal, peritoneal loss, and death. It is a major cause of hospitalization in pediatric patients.[1] Therefore, early prediction of inadequacy of antibiotic therapy is the best way to decrease PD failure.[2] The International Society of Peritoneal Dialysis (ISPD) guideline recommended starting empiric therapy and evaluating the clinical condition, effluent cell count, and repeat culture 3 to 5 days after the initiation of therapy.[3]

A previous study on bacterial peritonitis demonstrated that peritoneal leukocyte and polymorphonuclear neutrophil counts on day 3, but not day 2, of antibiotic therapy had predictive value of peritonitis episodes that require removal of the Tenckhoff catheters.[4] We hypothesized that

early vanishing of PD effluent leukocyte count allows predicting the efficacy of antibacterial therapy. Dialysis effluent cell count test is readily available with a relatively low cost to be of practical clinical value and rapidly enough to influence clinical decision making. We aimed to study the prognostic value of dialysis effluent leukocyte count on day 3 of starting antibiotic therapy for prediction of treatment adequacy.

MATERIALS AND METHODS

In a retrospective study, medical records of 31 children, younger than 15 years old admitted to Ali-Asghar Children's Hospital between 1998 and 2009 because of peritonitis complicating PD, were collected and reviewed. The diagnosis of peritonitis complicating PD was based on at least 2 of the following criteria: abdominal pain or cloudy PD effluent (an effluent leukocyte count of at least 100/mm^3) or a positive PD culture. All of the patients had 2 separate PD effluent cultures. The first sample contained 50 mL of dialysis effluent drawn with sterile syringe and sent directly to laboratory for conventional culture. The second sample contained 10 mL of dialysis effluent poured in a blood culture bottle.

Empiric antibiotic therapy according to ISPD guidelines started until the result of cultures was reported. Routinely, it takes at least 5 to 7 days that the result of culture and antibiogram to be reported, and the antibiotic medication is changed accordingly in the case of resistance. The ISPD guidelines recommended that on day 3 to 5 of the symptoms, the effluent cell count to be re-evaluated, and samples be taken for culture.[3] For this reason, we considered the leukocyte count of dialysis effluent at day 3 of starting therapy, the time that we had not yet been aware of the result of culture and its antibiogram and could be a prognostic factor of therapy.

For each episode of peritonitis, we recorded the PD effluent leukocyte count on the 3rd day after initiating empiric therapy, culture result, patient age at the time of peritonitis, gender, duration of PD before the onset of the peritonitis episode, and the numbers of peritonitis along the PD, and the causative microorganisms. According to the policy of our center, all patients with PD-related peritonitis episodes would be admitted irrespective of the severity of the condition.

Treatment success was defined as complete resolution of peritonitis using antibiotics alone, without the need for Tenckhoff catheter removal. Conversely, treatment failure was referred to death of the peritonitis episodes or requiring Tenckhoff catheter removal.[5,6] Death related to peritonitis was defined as death of a patient with active peritonitis during hospitalization or within 2 weeks of a peritonitis episode.[6]

Statistical analyses were performed by the SPSS software (Statistical Package for the Social Sciences, version 16.5, SPSS Inc, Chicago, Ill, USA). The independent Student *t* test was used for comparing means, and 2-by-2 cross tables and the chi-square test were used to compare frequencies. Odds ratios and their 95% confidence intervals (CI) were reported for associations. To identify the cutoff level that maximized the sensitivity and specificity, the area under the receiver operating characteristic (ROC) curve was performed, and the sensitivity, specificity, and positive and negative predictive values at each threshold of leukocyte count were determined. *P* values less than .05 were considered significant.

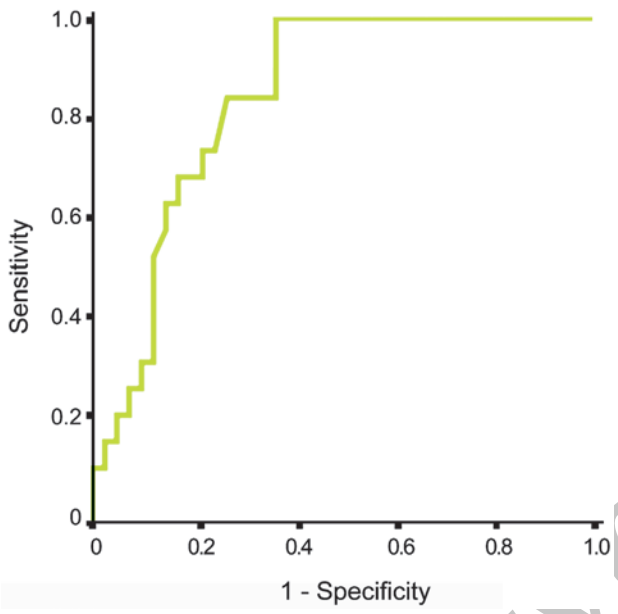
RESULTS

A total of 60 episodes of peritonitis in 31 PD patients aged 3 to 156 months old were reviewed. The median time of peritonitis episodes since the initiation of PD was 6.2 months (range, 0.5 to 17 months). The cumulative follow-up was 371.3 months. The incidence of peritonitis rate was 1:6.1 patient-months.

The majority of peritonitis episodes were due to Gram-positive organisms (41.7%), including *Staphylococcus aureus* in 21 episodes (35.0%), coagulase-negative *Staphylococci* in 2 (3.3%), and *Staphylococcus epidermidis* in 2 (3.3%). Of Gram-negative microorganisms, *Pseudomonas aeruginosa* was identified in 8 (13.3%), *Escherichia coli* in 9 (15.0%), and *Klebsiella* species in 1 (1.7%).

Treatment success was achieved in 41 episodes (68.3%). Of the remaining 31.7% episodes with treatment failure, 3 (15.8%) was accompanied by mortality, 11 (57.9%) required Tenckhoff catheter removal, and 5 (26.3%) resulted in both of them. The rate of catheter removal was 40.0% in fungi-induced, 28.6% in culture-negative, 24% in Gram-positive, and 22% in Gram-negative peritonitis episodes (P = .75). On the basis of examination of the ROC

curve, the dialysis effluent leukocyte count on day 3 that maximized sensitivity and specificity for the prediction of peritonitis complicating PD was approximately 1240/mm^3(area under the curve, 0.84; 95% CI, 0.74 to 0.93; $P < .001$). As shown in the Figure, for a PD effluent leukocyte count of 1240/mm^3 on day 3, the sensitivity was 100%, the specificity was 63.4%, the positive predictive value was 55.9%, and the negative predictive value was 100% ($P < .001$).



The receiver operating characteristic curve of leukocyte count in the dialysis effluent on the third day of treatment for prediction of treatment failure.

The Association of Peritoneal Dialysis (PD) Effluent Leukocyte Count on the Third Day of Empiric Therapy With Demographic Data and Outcome of Treatment of Peritonitis*

Parameter	Leukocyte Count		*P*
	> 1240/mm^3 (n = 34)	≤ 1240/mm^3 (n = 26)	
Gender			
Female	14 (41.2)	16 (61.5)	
Male	20 (58.8)	10 (38.5)	.19
Age, mo	48.4 ± 46.9	48.3 ± 43.8	.99
Duration of PD, mo	6.4 ± 4.9	5.9 ± 4.1	.69
Positive direct smear of PD effluent	33 (97.1)	5 (19.2)	< .001
Culture of PD			
Gram positive	14 (41.2)	11 (42.3)	
Gram negative	11 (32.4)	7 (26.9)	
Culture negative	2 (5.9)	5 (19.2)	
Fungi	7 (20.6)	3 (11.5)	.37
Catheter removal	16 (47.1)	0	< .001
Death	8 (23.5)	0	.008

*Values in parentheses are percents.

The Table shows the correlation between leukocyte count on the third day of empiric therapy with the demographics, etiologic microorganism, and the morbidity of PD-related peritonitis.

DISCUSSION

One of the most important findings of this study was the significant association between PD effluent leukocyte count on day 3 and the peritonitis outcome. The risk of catheter removal and mortality was higher with a persistent leukocyte count higher than 1240/mm^3 on day 3 after initiation of empiric therapy. This cutoff level had very high predictive value.

Peritonitis is a frequent complication of PD in children that can result in a variety of adverse outcomes, including PD failure, catheter malfunction, catheter removal, adhesion, and even death.[7] The high incidence of peritonitis in children and the need to preserve membrane function in these patients who face a lifetime of ESRD care mandates an effective approach to therapy and prevention.[8] Few studies have evaluated the ability of PD cell counts and other factors to predict treatment outcomes.[9] Shah and colleagues[4] evaluated 57 episodes of bacterial peritonitis in 25 continuous ambulatory PD patients and demonstrated that PD leukocyte and polymorphonuclear neutrophil counts on day 3, but not day 2, had predictive values for peritonitis episodes that require removal of Tenckhoff catheters. This study was a on selective sample with peritonitis episodes treated before the 1996 revision of the ISPD guidelines.[3] The finding, nevertheless, concurs with us that PD cell count on day 3 performed better in outcome prediction. Because treatment responses are weighed heavily by the microbiological factor and in vivo response to antibiotics, it might take approximately 3 days for the antibiotic to alter the course of infection. The superiority of PD cell count on day 3 is not surprising, because it simply incorporates the factor of the antibiotics effect.[4]

In a subsequent retrospective study of 399 peritonitis episodes, Krishnan and colleagues[10] reported that when the PD cell counts exceeded 100/mm^3 for 5 days, the odds of treatment failure were significantly higher. However, most causative organisms would have been identified by day 5 and the need to gauge the peritonitis

severity would become less essential. Chow and coworkers reported that using a PD leukocyte count cut point higher than 1090/mm^3 on day 3, the sensitivity was 75% and the specificity was 74% for the prediction of treatment failure (defined as catheter loss or peritonitis-related death).[11] In the present study, PD leukocyte count cut point of 1240/mm^3 on day 3 had a sensitivity of 100% and a specificity of 63.4% for the prediction of treatment failure. Overall, it is recommended by the current ISPD guidelines that patients who have unresolved cloudy effluent while on appropriate antibiotics after 5 days are to have their Tenckhoff catheters removed.[3,6] To be of clinical relevance, dialysis effluent leukocyte counts during the early course of illness (within 3 days of peritonitis as compared with day 5) would be more valuable to the clinicians who might desire to refine promptly the treatment strategy and antimicrobial therapy on the basis of the severity of peritonitis.[5]

Obviously, the type of microorganism has an effect on the course of disease progression and treatment outcome. The same as our previous report,[12] the bacteriologic profile of the peritonitis episodes was predominated by Gram-positive pathogens specially *S aureus*. Our result is somewhat different from that recently obtained by Mujais[13] in a survey of 4000 episodes of peritonitis in adult patients from the United States and Canada. In that study, coagulase-negative *Staphylococcus* was 3 times more common than *S aureus* as a cause of peritonitis. A main concern in our data was the finding of a high rate of culture-negative peritonitis. It happened because of either using antibiotics before peritonitis, nonadequate PD effluent, using antibiotic before sending specimens, and inadequate sample of dialysis effluent that was sent for culture. Most probably because of low power of this study, we could not find any correlation between the microorganism and therapy failure. However, fungal peritonitis is a rare but serious complication of continuous ambulatory PD. In our previous multicenter study, we showed higher risk of catheter removal and mortality in fungi peritonitis.[14]

To be of practical clinical value, the PD total leukocyte count is readily available with relatively low cost and rapid enough to influence clinical decision making, and most importantly, it can add independent information about the risk for adverse outcome. Our findings will be useful at several key stages in the management of dialysis-related peritonitis. First, in light of the prognostic information, cell count measurement probably should be repeated on day 3 of peritonitis on a routine basis. Second, on the basis of these predictive factors, the severity of peritonitis could be established early. In pediatric, it is the first study to predict peritonitis complicating PD with dialysis effluent leukocyte count. This easy and noninvasive test results in decreased mortality and morbidity and hospitalization of pediatric patients on PD.

Although the leukocyte count on the third day of therapy has a prognostic value but multiple factors including the specific antibiotic regimen, the causative agent, delay in starting treatment affect on the outcome. The ISPD guideline recommended starting therapy according to the guideline until the result of culture to be available, and it at least takes 3 to 5 days and this time gap has a major influence on the occurrence of PD complication secondary to peritonitis. Besides excellent predictive power of leukocyte count on day 3 with regard to outcome, the PD total leukocyte count is easy to obtain. This noninvasive test may offer opportunities for early prediction of the severity of peritonitis and more rational choice of treatment strategy.[5]

The morbidity and mortality was high in Iranian children on PD.[15] We observed 13% death of children on continuous ambulatory PD complicated with peritonitis and it was shown that the persistent leukocyte count higher than 1240 /mm^3 was accompanied with higher rate of mortality.

Our study has several limitations. First, the PD total leukocyte counts, as opposed to polymorphonuclear leukocyte counts, were measured. Another limitation of our study is that if bacterial culture of PD effluent was performed using automated kits, we could obtain accurate culture results and less culture-negative results. Such studies require large enough patient numbers to evaluate significant differences in outcomes, and such studies may need to be multicenter in design. Another limitation of this study was using retrospective data filled by various medical staff; therefore, by providing a national registry we are going to conduct a prospective cohort study.

CONCLUSIONS

This study showed that a third day dialysis

effluent leukocyte count after starting empiric therapy predicts the outcome of peritonitis. A leukocyte count higher than 1250/mm^3 was higher associated with mortality and morbidity.

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CONFLICT OF INTEREST

None declared.

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