Effective Treatment of PD Peritonitis

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Peritonitis has been the plague of patients on peritoneal dialysis (PD) since its inception. In an early article by the PD pioneer Karl Nolph and coworkers (1), peritonitis was defined as cloudy effluent with 100 white cells per millimeter, of which 50% were polymorphonuclear cells. Between 1977 and 1978, the peritonitis rate in patients on continuous ambulatory peritoneal dialysis (CAPD) using bottles was 5.5 episodes per year at risk. Treatment was intraperitoneal cefazolin at 125 mg/L dialysis fluid. An aminoglycoside (gentamicin or tobramycin) was added at a dose of 4–8 mg/L if Gram-negative infection was suspected. The catheter was removed in the presence of fungal peritonitis, peritonitis with a tunnel infection, and cloudy effluent after 3 days of appropriate antibiotic treatment. Within 2 years with increased experience and use of bags instead of bottles for the dialysis fluid, the peritonitis rate had decreased to one episode per year at risk. With the subsequent development of new technologies, including the Y set, the flush before fill technique, improved training, improved care of the exit site of the PD catheter, and better adherence to that International Society of Peritoneal Dialysis (ISPD) guidelines, peritonitis rates have fallen in many programs to 0.3 episodes per year at risk. In our program over the last 5 years, the peritonitis rate is 0.17 episodes per year at risk, with a rate of 0.04 episodes of coagulase-negative Staphylococcus per year at risk. Therefore, there has been considerable success in lowering peritonitis occurrence. However, much about treating peritonitis remains unknown and is on the basis of expert opinion rather than research.

The evidence on how best to treat peritonitis remains extremely sparse. A recent Cochrane review examined route of administration, dosing of antibiotics, schedule of administration, different antimicrobials, use of adjunctive therapy, and early catheter removal (2). The authors included randomized trials and quasirandomized, controlled trials in both adults and children that examined route of administration of antibiotics for peritonitis, dose of an antibiotic, the schedule of administration, comparisons of different antimicrobial agents, use of other interventions (such as fibrinolytic drugs), peritoneal lavage, and early catheter removal. Only 42 studies were found that met the criteria. No antibiotic regimen was found superior for relapse and need for catheter removal, although glycopeptides, such as vancomycin, were better at achieving complete cure compared with first generation cephalosporins. The evidence supports intraperitoneal administration of antibiotics over intravenous administration (on the basis of one study). Intermittent dosing is as effective as continuous dosing. There is almost no evidence of appropriate timing of the removal of the PD catheter for severe peritonitis. The authors conclude that studies of treatment of peritonitis in patients on PD are limited, are generally of low quality, and use different definitions. Some other aspects of treatment of peritonitis about which little is known include duration of treatment, whether it would be better to leave the abdomen dry during part of the treatment (enhancing peritoneal immune function), and use of adjuncts, such as intraperitoneal IgG (3). Very little is known about adjusting antibiotic dosing for residual kidney function.

The authors of the paper “Residual kidney function and peritoneal dialysis-associated peritonitis treatment outcomes” in this issue of the Clinical Journal of the American Society of Nephrology examine the relationship between kidney function and the outcome of peritonitis in the patient on PD (4). This was a retrospective, single-large PD center study examining the outcome of 339 peritonitis episodes over 8 years. Episodes were grouped by Gram-positive, Gram-negative, and culture-negative results as well as the level of kidney function of the patient (no residual kidney function, >0–5 ml/min, and >5 ml/min). Almost one half of the patients were hospitalized for treatment of the peritonitis, and the average antibiotic treatment duration was 22 days. The authors report on treatment failure defined as relapse (another peritonitis with the same organism within 4 weeks of completing antibiotics), recurrence (peritonitis with a different organism within 4 weeks of completing antibiotics), PD catheter removal, or death from any cause during treatment of the peritonitis. Repeat episodes (those with the same organism that occurred >4 weeks after the original episode) were not reported or included in the analysis. The analysis found that the type of PD modality—cycler versus CAPD—did not significantly interact with urinary creatinine clearance and outcome, and therefore, this was not included in the final model. The numbers of culture-negative episodes were small (13% of a total of 339) and included with the culture-positive peritonitis. Therefore, the final analysis had two groups by culture results and three groups of residual kidney function. There was 23% treatment failure in the Gram-positive/culture negative group.
compared with 34% in the Gram-negative peritonitis group. This higher proportion of failure with Gram negative is consistent with the literature. Approximately two thirds of the culture results were Gram-positive organisms, also typical of most published studies. Thus, the data presented in this single study center are similar to those of many other published studies and suggest that the results are widely applicable.

The important outcome of this paper was that, among the episodes that were culture negative or had Gram-positive organisms, those with no residual kidney function were less likely to have treatment failure than those with 5.0 mL/min creatinine clearance (adjusted odds ratio, 2.87; P=0.03, 95% CI, 1.12 to 7.35) and those with >5.0 mL/min creatinine clearance (adjusted odds ratio, 6.80; P<0.01, 95% CI, 2.37 to 19.6). These results are striking given the many proven benefits of residual kidney function, including an association with better survival and perhaps better immune function. The authors suggest that this worse outcome with increased residual kidney function is due to underdosing in those with residual kidney function given that the kidneys clear both cephalosporin and vancomycin.

The authors include episodes of peritonitis that were not the first episode for that patient. Indeed, almost one half (85 of 181 patients) had more than one episode of peritonitis, and these subsequent episodes were included in the analysis. Excluding these would have decreased the number of observations significantly, but inclusion raises the question of whether some of these subsequent episodes were due to the same organism as the first and might be due to repetitive episodes caused by biofilm of the catheter leading to multiple episodes. Indeed, 16 of the patients had four or more episodes. Cho and Johnson (5) have shown that the risk of repeat peritonitis, defined as peritonitis with the same organism >4 weeks after completion of antibiotics for a previous episode, is highest in the 3 months after an episode but that the risk continues to >24 months. Although not part of this study, this does raise the question of whether inadequate initial treatment of peritonitis contributes to multiple similar episodes in the same patient.

The authors did not find a relationship among residual kidney function and outcome of episodes due to Gram-negative peritonitis. They ascribe this to predominately use of tobramycin, generally at a dose of 0.9 mg/kg given via the intraperitoneal route daily. Of note, the ISPD recommendation is 0.6 mg/kg. Treatment failure was 34% in the Gram-negative peritonitis episodes, but this category of infection is notoriously difficult to treat without catheter removal, which was done in 20%. Only two (3%) of the patients in this group died, which is better than the findings in most of the literature on outcomes of Gram-negative peritonitis and raises the question of whether the higher dose of tobramycin should be the standard of care.

The ISPD has been publishing guidelines on the diagnosis, management, and prevention of peritonitis for many years, with updates approximately every 5 years. The most recent guideline on treatment of peritonitis was published in 2016 (6). The experts constructing these guidelines are markedly hampered by the paucity of data to support recommendations. Of note in the most recent guideline on treatment of peritonitis, a table is provided with recommendations for dosing of antibiotics for peritonitis. However, it is unclear if this dosing is adequate for those on cycler PD (6). Almost all of the references are from studies of patients on CAPD and are not from studies of those on cycler PD. It is unclear if dosing for patients on CAPD is translatable to patients on continuous cycler peritoneal dialysis, but this is widely done.

In previous versions of the ISPD guidelines for treatment of peritonitis, the recommendation was made to increase the dose by about 25% if residual kidney function was present (7,8). In addition, the previous suggestion was made to use continuous dosing as preferable to intermittent dosing, especially with cycler PD. With cycler PD, the levels of antibiotics in the effluent by the end of the night may be below the susceptibility level of the organism. The most recent guidelines on antibiotic dosing for the treatment of peritonitis indicate that increasing the dose for those with substantial residual kidney function may not be needed. The references for this change from the previous guidelines are two studies of vancomycin dosing, both of which showed that the usual approach of loading with 30 mg/kg per exchange led to inadequate levels at day 5 in a substantial number of patients (9,10). The authors of both papers recommended adjusting the dose upward if day 5 levels are low or dosing more often than every 5 days. The data are extremely limited on these important questions.

This paper is an observational, retrospective study with all of the limitations of this type of study. However, the results highlight the importance and urgency of further pharmaco-kinetic studies of appropriate antibiotic dosing in those with peritonitis to examine the effect of remaining kidney function. A search of the ClinicalTrials.gov website with the terms “peritonitis” and “peritoneal dialysis” yields only 31 studies, a number of which are completed. In contrast, a search of breast cancer treatment yields 6523 studies. There are few ongoing studies on this topic. The consortium peritoneal dialysis outcomes and practice patterns study might do further studies examining residual kidney function on the outcome of first episodes of Gram-positive peritonitis, including further episodes of the same organism >4 weeks after completion of antibiotics. Until we have more data, we should all consider residual renal function when dosing our patients with peritonitis.

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References


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