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ORIGINAL RESEARCH

Cefazolin Plus Ceftazidime versus Cefazolin Monotherapy in the Treatment of Culture-Negative Peritonitis: A Retrospective Cohort Study

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Background: Based on current ISPD guidelines, it is unclear as to whether ceftazidime should be discontinued in subsequent management of culture-negative peritonitis if it is used as empirical gram-negative coverage. Herein, we aim to compare the clinical outcomes of cefazolin plus ceftazidime versus cefazolin alone.

Methods: This was a retrospective cohort study. Adult peritoneal dialysis (PD) patients who were diagnosed with culture-negative peritonitis between 2014 and 2020 were included. Patients were categorized into two groups according to treatment regimen. Primary response rate, peritonitis relapse rate, and time to primary response were compared. Factors that predicted primary response were determined using Cox regression analysis.

Results: A total of 58 patients were included in the study. Of these, 42 received cefazolin plus ceftazidime and 16 received cefazolin monotherapy. Overall, the mean age was 65.7±10.4 years. Most of the patients (81.3%) were prescribed continuous ambulatory peritoneal dialysis. Initial effluent WBC was 4211±10357 in the combination group and 3833±6931 cell/mm^3 in the monotherapy group (p=0.89). There was no significant difference in primary response at day 5 between the two groups (95.2% in the combination group vs93.7% in the monotherapy group, p=0.82). However, cumulative probability of primary response by the Kaplan–Meier analysis in the combination group was higher than in the monotherapy group (p=0.02). Adjusted HR of serum potassium level to predict a primary response was 1.83 according to multivariate analysis (p=0.03). There was no difference between the two groups in terms of peritonitis relapse or catheter removal.

Conclusion: This is the first study to compare clinical outcomes between cefazolin plus ceftazidime versus cefazolin monotherapy in culture-negative peritonitis. Our results suggest that if peritonitis is resolving at day 3, discontinuation of ceftazidime could yield favorable treatment outcomes and might be appropriate for subsequent management. However, the risk of not having gram-negative coverage should be considered.

Keywords: culture negative peritonitis, peritoneal dialysis, antibiotic, treatment

Introduction

Peritonitis is a critical complication and can lead to death in peritoneal dialysis (PD) patients.[1,2] The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) reported that the rate of culture-negative peritonitis varied by country, from 14–28%.[3] Culture-negative peritonitis is significantly more likely to be cured and less likely to be complicated by catheter removal, conversion to permanent hemodialysis, or death compared to culture-positive peritonitis. However, patients with relapsing peritonitis were more likely to have their catheters removed.[4]

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In 2016, the International Society for Peritoneal Dialysis (ISPD) published revised guidelines for the prevention and treatment of peritonitis, according to which management of PD-related peritonitis should consist of (1) empirical antibiotic or initial therapy which is effective against gram-positive and gram-negative organisms, including *Pseudomonas* species, and (2) subsequent management, in which antibiotic selection should be adjusted depending on culture results.[5] Empirical antibiotic regimens vary by region based on the local prevalence. According to the PDOPPS, a combination of vancomycin and cephalosporin (second generation or higher) or aminoglycosides is commonly used in the US and UK, while first-generation cephalosporin and cephalosporin (second generation or higher) are frequently prescribed in Japan and Thailand.[6]

A crucial point of revision in the 2016 ISPD guidelines involves the subsequent management of culture-negative peritonitis. The 2010 guidelines recommended continuing gram-positive and gram-negative ATB in subsequent management as initial therapy for a total duration for 14 days.[7] However, the current guidelines state that if aminoglycosides are prescribed as empirical gram-negative coverage, they should be discontinued to minimize drug toxicity.[5] The guidelines do not specify, however, whether ceftazidime administration should be stopped when it is used as the initial treatment. In daily practice, therefore, ceftazidime might be continued or discontinued based on local prevalence of gram-negative peritonitis and the clinician's judgement. The aim of this study was thus to compare the clinical outcomes of cefazolin plus ceftazidime and cefazolin alone in the treatment of culture-negative peritonitis.

Materials and Methods

This retrospective cohort study was conducted at a tertiary university hospital in Thailand. Adult peritoneal dialysis patients who had been diagnosed with culture-negative peritonitis between January 2014 and December 2020 were included. Of those, we excluded patients who had received antibiotics other than cefazolin and ceftazidime in subsequent management (Figure 1). Eligible patients were divided into two groups according to subsequent antibiotic therapy: (1) those treated with cefazolin plus ceftazidime and (2) those treated with cefazolin alone.

Management of PD-related peritonitis in our hospital is based on current ISPD guidelines. Empirical antibiotic regimens cover both gram-positive and gram-negative organisms, vancomycin or a first-generation cephalosporin is used for the former and a third-generation cephalosporin or an aminoglycoside for the latter.[5] In our hospital, the most commonly used treatment is intraperitoneal cefazolin and ceftazidime unless the patient has clinical features of systemic sepsis or hemodynamic instability, in which case more potent broad-spectrum antibiotics or intravenous cefazolin and ceftazidime may be prescribed. After culture results and sensitivities are ascertained, the antibiotic regimen can be adjusted to narrow-spectrum agents, as appropriate. As stated above, the ISPD guidelines do not mention whether ceftazidime administration should be stopped when it is used as the initial treatment for culture negative PD-related peritonitis. Therefore, the antibiotic regimen used in subsequent treatment in each case depended on the clinician

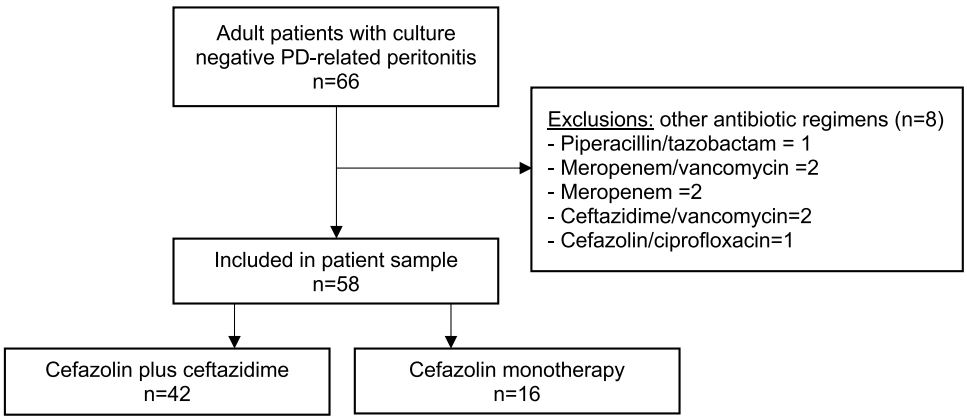

Figure 1 Flow diagram for selection of the study cohort.

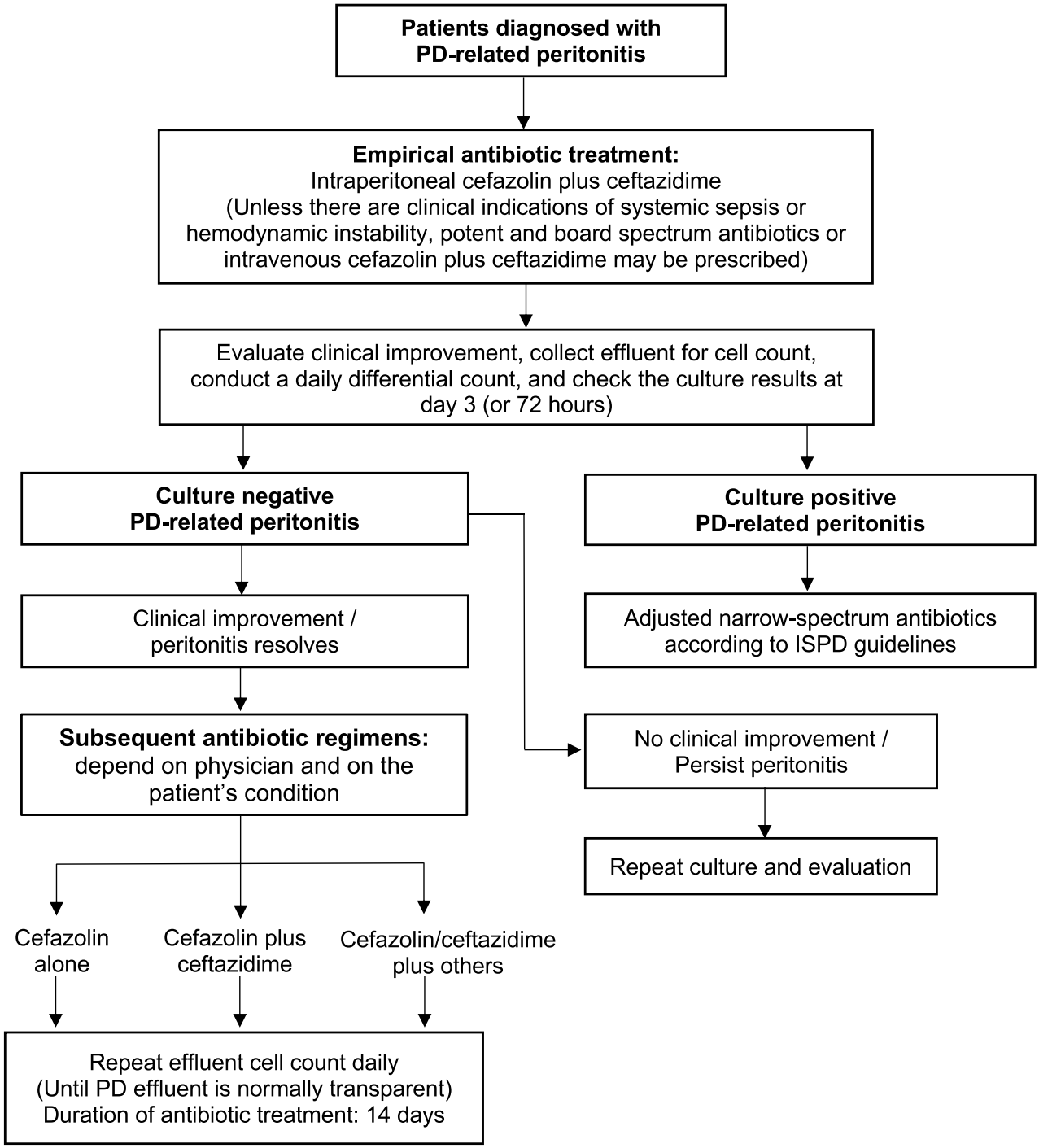

Figure 2 Flow diagram of the antibiotic prescription decision-making process in the management of PD-related peritonitis and routine of laboratory tests in our clinical practice.

(Figure 2). Peritoneal fluid cultures are performed using two rapid blood culture bottles (BACTEC, BACT/ALERT® FA plus) with 10 mL of drained fluid.[5]

Patient baseline demographic data, clinical features, laboratory results, empirical antibiotic regimens, and clinical outcomes were reviewed. Clinical data included age, sex, cause of end-stage kidney disease (ESKD), mode of peritoneal dialysis, dialysis vintage, Charlson comorbidity index (CCI), and clinical presentations. Laboratory results included

complete blood count, serum albumin, serum potassium, and peritoneal fluid analysis. Clinical outcomes were primary response, relapsing peritonitis, catheter removal, and death. The operating definitions in this study are as follows:

1. Culture-negative PD-related peritonitis was defined as the presence of abdominal pain and/or cloudy dialysate and a dialysate fluid cell count of >100 white blood cells (WBC) /μL (after a dwell time of at least 2 hours) with > 50% PMN and no microbiological growth at 72 hours.[5]
2. Primary response was defined as resolution of symptoms, clearing of dialysate, and effluent WBC less than 100 / μL on day 5.
3. Relapse peritonitis was defined as the occurrence of PD-related peritonitis within 4 weeks of completion of therapy for a prior episode.[5]
4. Refractory peritonitis was defined as failure of the effluent to clear after 5 days of appropriate antibiotics.[5]

See Figure 2 for a flowchart of antibiotic treatment and laboratory investigations in our clinical practice.

Statistical Analysis

Descriptive data were expressed as percentages. The χ^2 or Fisher's exact test was used to compare categorical data between the two groups, as appropriate. Continuous variables were expressed as mean ± standard deviation or median (interquartile range, IQR) and compared between groups using the *t*-test or Mann–Whitney *U*-test, as appropriate. The cumulative probability of primary response was determined using the Kaplan–Meier method. Factors with *p*-values of less than 0.20 by univariate Cox regression analysis were included in subsequent backward multivariate analysis. A *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using STATA version 14.1 (College Station, Texas, USA).

Results

Patient Characteristics

A total of 58 adult patients with culture-negative peritonitis were included in the study. The overall mean age was 65.7 ±10.4 years. The most common cause of end-stage kidney disease was diabetes (61%), followed by hypertension (16%). Forty-two (77%) patients received cefazolin plus ceftazidime, while 16 (27%) received cefazolin alone. Patient characteristics and clinical data based on antibiotic therapy are compared in Table 1. There was no significant difference in patient characteristics or clinical features between the two groups, with the exception of serum albumin and mode of peritoneal dialysis. Only one patient had been administered antibiotics within the previous 30 days.

Empirical Antibiotic Regimens

Initial antibiotic treatment data are shown in Table 2. Cefazolin/ceftazidime was the most common antibiotic regimen in both groups (used in more than 80% of the overall population). Other antibiotic regimens (vancomycin and ceftazidime, piperacillin/tazobactam, and meropenem) were administered as part of the initial empirical antibiotic regimen only in the combination group. There were no significant differences in antibiotic regimen between groups.

Treatment Outcomes of Culture-Negative Peritonitis

We found no significant difference between the two groups in terms of primary response, relapsing peritonitis, catheter removal, or death (Table 2). More than 90% patients in both groups had achieved primary response by day 5. Median time to primary response was 3.43 ± 1.80 days overall and was shorter in the combination group (3 vs 4 days). In addition, patients in the combination group had a higher of probability of achieving primary response than those in the monotherapy group (p=0.02). Kaplan–Meier curves are shown in Figure 3.

The crude hazard ratio (HR) and adjusted HR for primary response are shown in Table 3. Neither primary response rate nor relapsing peritonitis was associated with sex, duration of dialysis therapy, cause of ESKD, or initial dialysate effluent WBC. There were four factors with *p*-values less than 0.20 by univariate logistic regression analysis: age,

Table 1 Comparison of Patient Characteristics and Clinical Data Based on Antibiotic Therapy

Clinical Variables	Combination (n=42)	Monotherapy (n=16)	p-value
Age: (years) mean ± SD	66.6 ± 11.73	63.6 ± 9.3	0.32
Sex: male n (%)	23 (54.8)	7 (43.6)	0.56
BMI (kg/m^2): mean ± SD	22.87 ± 0.80	22.85 ± 0.81	0.98
PD duration (months)	40.5 ± 4.67	30.8 ± 8.12	0.27
PD mode: n (%)			<0.001*
-CAPD	39 (92.9)	8 (50.0)	
-APD	3 (7.1)	8 (50.0)	
Causes of ESKD			0.68
-Diabetic nephropathy	25 (59.5)	10 (62.5)	
-Hypertension	6 (14.3)	4 (25.0)	
-Obstructive uropathy	2 (4.76)	0	
-Unknown/other	9 (21.43)	2(12.5)	
CCI: mean ± SD	6.26 ± 1.83	6.25 ± 1.65	0.98
ATB usage 30 days prior peritonitis: n (%)	1(2.38)	0	0.52
Clinical presentation			
Fever: n (%)	12 (28.57)	4 (25.0)	0.78
Abdominal pain	33 (78.57)	12 (75.0)	0.77
Cloudy peritoneal fluid	9 (21.4)	5 (31.3)	0.43
Laboratory results			
WBC in PDF at initial diagnosis: mean ± SD	4211± 10357	3833± 6931	0.89
Hemoglobin (g/dL)	9.84± 1.77	10.01± 1.88	0.72
WBC (cell/mm^3): mean ± SD	8960± 6733	7386± 3037	0.37
Albumin (g/dL): mean ± SD	2.63 ± 0.53	3.02± 0.64	<0.02*
Potassium (mEq/L): mean ± SD	3.62 ± 0.56	3.60± 0.45	0.88

Note: *p-value less than 0.05.

Abbreviations: APD, automated peritoneal dialysis; ATB, antibiotic; CAPD, continuous ambulatory peritoneal dialysis; CCI, Charlson comorbidity index; ESKD, end stage kidney disease; WBC, white blood cell; PMN, polymorphonuclear neutrophil; PDF, Peritoneal dialysis fluid.

Table 2 Empirical Antibiotic Regimens and Clinical Outcomes of Culture-Negative Peritonitis by Antibiotic Treatment in Subsequent Management

Clinical Outcomes	Combination (n=42)	Monotherapy (n=16)	*p*-value
Empirical antibiotics			0.46
Cefazolin plus Ceftazidime: n (%)	36 (83.33)	16 (100)	
Vancomycin plus Ceftazidime: n (%)	1 (2.38)	0	
Piperacillin/tazobactam: n (%)	1 (2.38)	0	
Meropenem: n (%)	4(9.52)	0	
Clinical outcomes			
Primary response: n (%)	40(95.2)	15 (93.7)	0.82
Relapsing peritonitis: n (%)	2 (4.76)	0	0.37
Catheter removal: n (%)	2 (4.76)	1 (6.25)	0.82
Death: n (%)	1(2.38)	0	0.53

hemoglobin levels, serum K levels, and antibiotic therapy. These parameters were subjected to stepwise multivariate logistic regression analysis, after which only serum K was found to be independently associated with primary response, with an adjusted HR of 1.83 (95% CI: 1.06–3.20) and *p*-value of 0.03. Cox proportional-hazards assumption validation resulted in p=0.82. Tenckhoff catheter removal was performed in three patients – two in the combination group and one in the monotherapy group – after a median of 7 days.

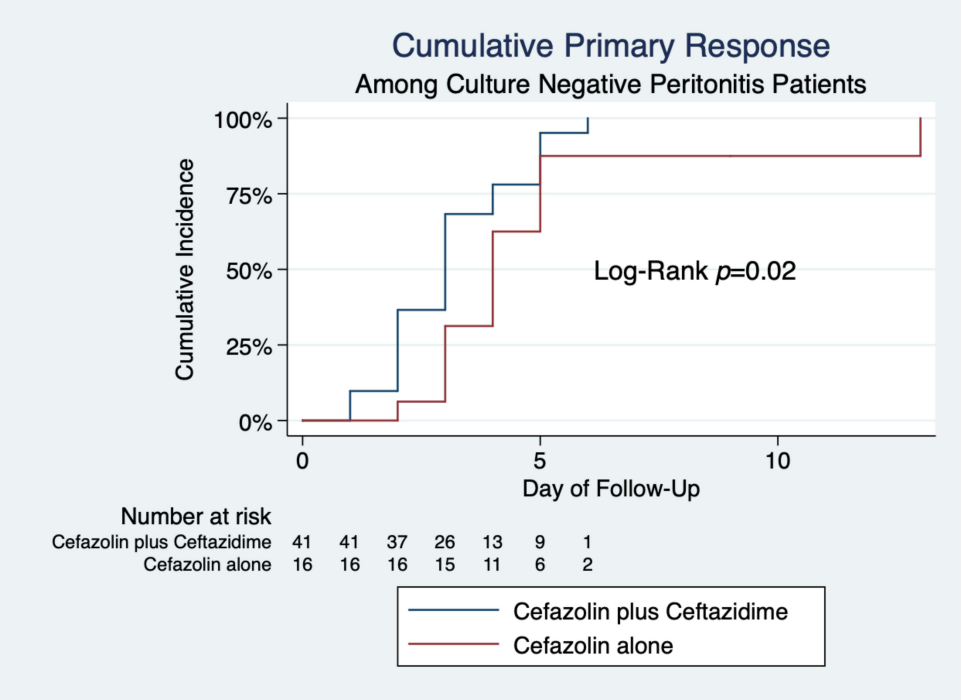

Figure 3 Kaplan–Meier curves of cumulative primary response in culture-negative peritonitis patients who received cefazolin plus ceftazidime (combination) and those who received cefazolin alone (monotherapy).

Discussion

Based on the current ISPD guidelines, it is unclear as to whether ceftazidime should be discontinued in the subsequent management of culture-negative peritonitis if it is used as empirical gram-negative coverage.[5] To the best of our knowledge, this is the first study that has attempted to compare clinical outcomes between ceftazidime/cefazolin versus cefazolin monotherapy in the treatment of culture-negative peritonitis. Our main findings showed that neither primary response nor relapsing peritonitis rate differed significantly between the two groups. However, the cumulative probability of primary response in the combination group was higher than in the monotherapy group (p=0.02). In addition, the median time to primary response was shorter in the combination group.

We found that more than 90% of patients in both groups achieved a primary response by day 5. Tenckhoff catheter removal was performed, and death occurred in 5.17% and 1.7% of patients, respectively. These results, as well as those

Table 3 The Results of Univariate and Multivariate Cox Regression Analysis Regarding Primary Response

Clinical Factors	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.04	0.99–1.04	0.18	1.04	0.98–1.04	0.24
CCI	1.07	0.93–1.25	0.34	1.03	0.82–1.28	0.78
Fever	1.25	0.29–2.28	0.45			
Cloudy fluid	0.77	0.40–1.47	0.43			
Initial effluent WBC	0.99	0.99–1.00	0.67			
WBC	0.99	0.99–1.0	0.34			
Hemoglobin	1.15	0.95–1.39	0.15	1.10	0.92–1.33	0.28
Serum potassium	1.96	1.13–3.40	0.02*	1.83	1.06–3.20	0.03*
Albumin ≥ 3.5 (g/dL)	1.47	0.66–3.26	0.34			
ATB monotherapy	0.58	0.31–1.07	0.08	0.57	0.31–1.06	0.07

Note: *p-value less than 0.05.
Abbreviations: ATB, antibiotic; CCI, Charlson comorbidity index; OR, odds ratio; WBC, white blood cell.

of previous studies, indicate favorable outcomes, a high cure rate (77–80%), and a low catheter removal rate (8–12%) in patients with culture-negative peritonitis.[4,8,9] Although median time to primary response was shorter and the probability of primary response was higher in the combination therapy group, the final clinical outcomes, primary response at day 5, and incidence of relapse peritonitis did not differ significantly between the two groups. The fact that the short-term outcomes are quite similar in the two groups suggests that the benefits combination of cefazolin and ceftazidime may not be clinically meaningful in terms of primary response at day 5 and in relapse peritonitis. It is well established that peritoneal infection is a predisposing factor for long-term complications, and peritoneal fibrosis and increased of effluent interleukin (IL)-6 are independent risk factors for peritonitis.[10,11] Although the median time to primary response in the combination group was shorter than in the monotherapy group (3 vs 4 days), the impact of the resolution of effluent WBC (less than 100 /μL) by day 5 on long-term outcomes, such as peritoneal function and peritoneal fibrosis, is unknown.

In our hospital, the culture negative rate was 23.7%. In culture positive PD-related peritonitis, the four most common microorganisms (unpublished data) were gram negative bacilli (22.8%), Pseudomonas aeruginosa (21%), Streptococcus spp. (14%), and Staphylococcus coagulase negative (12.3%). Most cases of culture-negative peritonitis are caused by gram-positive organisms. There are multiple factors which result in problems in microbiological detection such as patients having recently undergone antibiotic treatment, suboptimal specimen collection, and inadequate culture techniques.[4,12,13] A prior retrospective study showed dialysis effluent WBC count $\geq$ 1090 cell/mm^3 on day 3 to be an independent prognostic marker for treatment failure.[14] In this study, we found that two of three patients who experienced relapsing peritonitis had effluent WBC > 1000 cell/mm^3 on day 3. Our findings suggest that ceftazidime might be discontinued when no bacteria are established at 72 hours, the patient has no history of recent antibiotic treatment, and effluent WBC is less than 1000 cell/mm^3.

From a practical point of view, ISPD guidelines state that

> If the culture-negative peritonitis is resolving at day 3, [they] suggest discontinuing aminoglycoside therapy and continuing treatment with gram-positive coverage (eg, first generation cephalosporin or vancomycin) for 2 weeks.[5]

Thus, we consider that our data may support to discontinue ceftazidime if the peritonitis is resolving at day 3, when ceftazidime is used as the empirical treatment instead of aminoglycoside. However, it is important to emphasize that cefazolin monotherapy does not accomplish the ISPD guidelines, as a gram-negative causative organism would likely cause differences in the evolution. Therefore, the local prevalence of gram-negative peritonitis and the risk of having no gram-negative coverage should be considered.

Previous studies have found that hypokalemia is an independent risk factor for PD-related peritonitis,[15,16] which might be explained by hypokalemia promoting intestinal bacterial overgrowth.[17] As in this study, serum potassium has been shown to be a significant factor associated with primary response (adjusted HR 1.83; p=0.03). Hence, maintenance of normal serum potassium should be emphasized, particularly in patients who have had hypoalbuminemia, which is an important factor associated with peritonitis.[18]

There are some limitations to this study. First, the sample size was relatively small due to it having been conducted at a single center, thus potentially limiting its generalizability. Second, the retrospective nature of the study increases the likelihood of potential reporting bias, and the lack of randomization allows for possible selection bias (eg, the monotherapy group had statistically higher serum albumin levels, which may have predisposed them to doing better on one antibiotic or empirical antibiotic regimens). Third, the culture negative rate was relatively high according to ISPD guidelines (less than 15%), suggesting imperfect sampling and culture methods. Probable factors that may have contributed to these negative culture results were the clinical procedures in hour hospital, type of microorganism (especially those which are gram-positive, which may be positive after 72 hours of incubation), and over-the-counter drug usage. However, we were not able to examine these factors due to the retrospective nature of the study. Nevertheless, our findings provide useful data that may help guide antibiotic usage in the subsequent management of culture-negative peritonitis.

Conclusion

This was the first study to compare the clinical outcomes of subsequent treatment with cefazolin plus ceftazidime versus cefazolin monotherapy in culture-negative peritonitis. We found no significant differences in primary response, peritonitis relapse, or technical failure between the two groups. These findings support discontinuation of ceftazidime if the peritonitis is resolving at day 3, which could yield favorable treatment outcomes and might be appropriate for the subsequent management of culture-negative peritonitis patients. However, the risk of not having gram-negative coverage should be considered.

Data Sharing Statement

The datasets used and/or analyzed during the current study available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study involved human participants and was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Khon Kaen University Ethics Committee in Human Research Ethics Committee of Khon Kaen University (No. HE631440). Informed consent from the participants was not required because of the retrospective nature of the study and the research no more than minimal risk. Patient data were maintained confidentially.

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Disclosure

The authors declare no competing interests.

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