

Research Article

Microbiology and Response to Treatment of Peritonitis: 237 Episodes in a University Medical Center Over A 14-Year Period

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Abstract

Purpose: Knowledge about local peritonitis rates, microbiologic profiles, and antibiotic resistance patterns is important in clinical practice. We analyzed the antibiotic resistance of commonly isolated pathogens and the clinical response to treatment for cases of peritonitis that occurred over a period of 14 years at a Korean university medical center.

Methods: For this study, we enrolled 312 patients who received Peritoneal Dialysis (PD) in Kangnam and Hallym Sacred Heart Hospital between January 2000 and December 2014, reviewed their microbiology and clinical outcomes, and analyzed associations between initial antibiotic treatment and clinical outcomes.

Results: There were 237 episodes of peritonitis diagnosed in 138 of 321 patients undergoing regular PD over a cumulative follow-up period of 1205.5 patient-years. The overall peritonitis rate was 0.20 episodes per patient-year. The main empirical antibiotic regimens prescribed for the treatment of peritonitis were intraperitoneal cefazolin plus ceftazidime (210 episodes) and intraperitoneal vancomycin plus ceftazidime (27 episodes). Thirty-nine percent of coagulase-negative *Staphylococcus* isolates and 53.8% of *Staphylococcus aureus* isolates were methicillin susceptible, while 79.1% of Gram-negative bacilli isolated were susceptible to ceftazidime. Antibiotic resistance did not affect the rates of resolution of peritonitis, catheter loss, shift to hemodialysis, or PD-related death. Gram-positive coverage with cefazolin was associated with a high-resolution rate (odds ratio = 12.001; 95% confidence interval = 1.058–136.14; p = 0.045) after adjusting for the existence of prior episodes and methicillin susceptibility.

Conclusion: Antibiotic resistance did not affect clinical outcomes of peritonitis. The empirical antibiotic regimen cefazolin plus ceftazidime may be appropriate regardless of antibiotic resistance

Keywords: Antibiotics; Antibiotic Resistance; Microbiology; Peritonitis; Peritoneal Dialysis

Introduction

Despite advances in Peritoneal Dialysis (PD), peritonitis remains a significant problem in PD and is a major reason for switching from PD to hemodialysis [1,2]. Although most cases of peritonitis associated with PD follow a benign course with appropriate antibiotic treatment, some episodes cause morbidity in patients [3,4]. The incidence of peritonitis depends on age, race, educational background, environment, and the type of dialysis system used, but the outcome depends only on the organism isolated [3]. Coagulase-negative *staphylococci* (CoNS) are the most

common etiological agents of PD-related peritonitis and generally are associated with benign outcomes with few complications [5,6]. However, a decrease in the incidence of Gram-positive peritonitis and an increase in the incidence of Gram-negative peritonitis have been reported, which were attributed to technical advances in connection systems and the routine use of mupirocin at the catheter exit site [7-9]. Changes in the prevalence of different etiologies of peritonitis and a gradual increase in the frequencies of methicillin-resistant CoNS and Gram-negative species resistant to commonly used antibiotics have been reported [10,11]. The incidence of peritonitis varies between centers and significant differences in rates are seen between countries. Several registries and centers have reported on the microbiology of organisms causing peritonitis and have evaluated treatment and subsequent outcomes [12,13]. Here

we analyze the incidence of peritonitis, its causative pathogens, the antibiotic resistance of commonly isolated pathogens, and clinical outcomes.

Methods

Our study included all patients who received PD in Kangnam and Hallym Sacred Heart Hospital between January 2000 and December 2014. All patients received a double-cuff Tenckhoff catheter inserted by standard surgical techniques, with prophylactic antimicrobial cefazolin administered in all cases. A continuous ambulatory PD disconnect system (Baxter Healthcare Corporation, Deerfield, IL, USA or Fresenius Medical Care, Bad Homburg vor der Höhe, Germany) was used with all patients. The type of dialysis prescribed at follow-up depended on individual requirements. Topical antibiotics were not used as prophylaxis at the exit site, and exit-site care was performed daily. Patients were followed until death, transfer to hemodialysis, renal transplantation, or the end of the study (i.e., December 31, 2014). Episodes of peritonitis that were associated with relapse were excluded.

The following data were collected: demographics, cause of end-stage renal disease, relevant biochemical data, comorbid conditions at the start of dialysis therapy (such as coronary artery disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, and hypertension), relevant PD-related parameters and the microbiological characteristics of the peritonitis episodes. Peritonitis was defined as the presence of two of the following three criteria: i) signs and symptoms of peritonitis, ii) cloudy dialysate with a white blood cell count $>100/\mu\text{L}$ consisting of $>50\%$ neutrophils, and iii) demonstration of organisms either by smear examination or by culturing the peritoneal dialysate. Recurrent peritonitis was defined as an episode that occurred within 4 weeks of the completion of treatment for a prior episode, but was caused by a different organism. Two protocols were used for treatment: intraperitoneal (IP) cefazolin plus ceftazidime and IP vancomycin plus ceftazidime. Therapy was evaluated and adjusted as soon as the culture results became available. In patients with peritonitis refractory to antibiotic treatment, the PD catheter was removed, and the patients were switched to hemodialysis. The centrifuged dialysate was examined microscopically and cultured in an automated BacTec blood culture system (BD Biosciences, San Jose, CA, USA) following standard protocols. Bacterial susceptibility was evaluated using the minimal inhibitory concentration as determined by the E-test (AB Biodisk, Solna, Sweden) and was defined based on the guidelines of the Clinical Laboratory Standard Institute. Strains yielding intermediate values were considered resistant. All peritonitis episodes for which signs and symptoms disappeared within 96 hours of the onset of antibiotic therapy were cultured again 28 days or more after the completion of treatment.

The following outcomes were considered: resolution, catheter loss, death related to peritonitis, and a shift to hemodialysis. Resolution was defined as the disappearance of signs and symptoms within 96 hours of the start of antibiotic therapy and a negative peritoneal fluid culture 28 day or more after the completion of treatment. Catheter loss was defined as the need to remove the catheter to achieve resolution of peritonitis. Death related to a peritonitis episode was defined as the death of a patient with active peritonitis or who was admitted with peritonitis or within 4 weeks of a peritonitis episode. The study was approved by the Ethics Committee of Kangnam Sacred Heart Hospital (2016-05-60). The need for informed consent was waived because of the retrospective nature of the work.

Statistical Analysis

Data are expressed as means \pm standard deviation. Binary variables were compared using the chi-squared test or Fisher's exact test, where appropriate. Multivariate analysis was performed via binary logistic regression using a backward stepwise procedure, which was applied to identify independent risk factors for clinical outcomes. $P < 0.05$ was considered statistically significant. All calculations were performed using SPSS software (v. 18.0; SPSS Inc., Armonk, NY, USA).

Results

There were 237 episodes of peritonitis diagnosed in 138 of 321 patients who underwent regular PD over a cumulative follow-up period of 1205.5 patient-years. The overall peritonitis rate was 0.20 episodes per patient-year. Fourteen of the 237 episodes were recurrent. (Table 1) lists the baseline characteristics of the patients.

	n (%)
Male gender	190 (59.2)
Age, years (mean \pm SD)	57.3 \pm 13.5
Diabetes	173 (53.9)
Body mass index, kg/m ² (mean \pm SD)	23.4 \pm 4.0
Comorbidities	
Coronary artery disease	131 (40.8)
Cerebrovascular disease	4 (1.2)
Peripheral vascular disease	6 (1.9)
Primary renal disease	
Diabetic nephropathy	158 (55.2)
Hypertension	102 (35.7)

Glomerulonephritis	17 (6.0)
Cystic disease	6 (2.1)
Others	3 (1.0)

Table 1: Characteristics of the 321 peritoneal dialysis patients.

Microbiological characteristics

Gram-positive and Gram-negative bacteria, fungi, and *Mycobacterium tuberculosis* organisms were isolated in 122 (51.5%), 67 (28.3%), 7 (3.0%), and 1 (0.4%) episodes, respectively, while 40 (16.9%) episodes were culture negative. (Table 2) lists the distribution of causative organisms. Among the Gram-positive organisms isolated, 2 of 9 (22.2%) were vancomycin-resistant *Enterococci*. Methicillin susceptibility was observed in 16 of 41 (39%) isolates of CoNS and in 21 of 39 (53.8%) isolates of *S. aureus*. The rate of resistance did not differ significantly between CoNS and *S. aureus* isolates ($p = 0.2$). Eight (24.2%) isolates of *Streptococcus* spp. were ampicillin resistant. The ceftazidime susceptibility rate was 79.1% overall for Gram-negative bacilli, and 88.5% for *E. coli*, 88.9% for *Klebsiella* spp., 33.3% for *Pseudomonas aeruginosa*, and 74.1% for *Acinetobacter* spp. The resistance rate was significantly higher for *P. aeruginosa* than for *E. coli* ($p = 0.01$). Two of 26 *E. coli* isolates were producers of extended-spectrum β -lactamases; however, no carbapenem-resistant strains were detected.

Organisms	Frequency	%
Gram-positive		
Coagulase-negative staphylococci	41	17.3
<i>Staphylococcus aureus</i>	39	16.5
Enterococcus	9	3.8
Streptococci	33	13.9
Gram-negative		
<i>Escherichia coli</i>	26	11
<i>Klebsiella</i> spp	9	3.8
<i>Pseudomonas aeruginosa</i>	6	2.5
<i>Acinetobacter</i> species	7	3.0
<i>Enterobacter cloacae</i>	2	0.8
Other non-fermentative gram-negative bacilli	17	7.2
Fungi	7	3.0
<i>Mycobacterium tuberculosis</i>	1	0.4

Negative Culture	40	16.9
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Table 2: Microbiological Characteristics of the Peritonitis Episodes (N=237).

Clinical outcomes

(Table 3) lists the clinical outcomes for Gram-positive and Gram-negative peritonitis. We found no significant differences between the groups. We compared resolution and peritonitis-related death according to etiology (Table 4).

	Gram-positive, n=122	Gram-negative, n=67	p-value
Resolution	112 (91.8)	59 (88.1)	0.4
Catheter loss	10 (8.2)	8 (11.9)	0.4
Death	3 (2.5)	3 (4.5)	0.4
Shift to hemodialysis	12 (9.8)	8 (11.9)	0.7

Note: Data expressed as number (percent) Episodes of Fungi, *Mycobacterium* and culture negative were excluded.

Table 3: Clinical outcomes for Gram-positive and Gram-negative peritonitis.

Organisms	Catheter loss n=32	Death n=8
Gram-positive		
<i>Coagulase-negative staphylococci</i>	2 (4.9)	0
<i>Staphylococcus aureus</i>	3 (7.7)	0
Enterococcus	5 (55.6)	3 (33.3)
Streptococci	0	0
Gram-negative		
<i>Escherichia coli</i>	4 (15.4)	1 (4.2)
<i>Klebsiella</i> spp	2 (22.2)	2 (25)
<i>Pseudomonas aeruginosa</i>	2 (33.3)	0
<i>Acinetobacter</i> species	0	0
<i>Enterobacter cloacae</i>	0	0
Other non-fermentative gram-negative bacilli	0	0
Fungi	7 (100)	0
<i>Mycobacterium tuberculosis</i>	1 (100)	1 (100)
Negative Culture	6 (15)	1 (3.1)

Note: Data expressed as number (percent)

Table 4: Catheter Loss and Peritonitis-Associated Death According to

Causative Organism.

Infections caused by fungi and *M. tuberculosis* were excluded because their outcomes differed from those associated with bacterial peritonitis. The resolution rates of CoNS and *S. aureus* episodes were similar ($p = 0.7$). Episodes caused by *Enterococcus* spp. ($p < 0.001$) and *Pseudomonas* spp. ($p = 0.04$) had significantly lower resolution rates than did those caused by CoNS. Although the death rate differed between etiological groups, the difference was not significant ($p = 0.6$). The main empirical antibiotic regimens prescribed for the treatment of peritonitis were IP cefazolin plus ceftazidime (210 episodes) and IP vancomycin plus ceftazidime (27 episodes). Of the 229 cases of peritonitis not caused by fungi or *M. tuberculosis*, 89.5% resolved, the catheter was removed in 10.5%, 11.4% were shifted to hemodialysis, and 3.1% died. (Table 5) lists the outcomes of the 237 episodes treated with the two standard two antibiotic protocols. Initial treatment that included Gram-positive coverage with cefazolin showed a higher resolution rate, lower catheter removal rate, and lower rate of shift to hemodialysis than coverage with vancomycin. Of the episodes treated using vancomycin for Gram-positive coverage, 17 of 27 were in patients who had experienced previous episodes of peritonitis; 6 of these previous episodes of peritonitis were culture negative, 9 were caused by Gram-positive organisms, and 2 by Gram-negative organisms. After adjusting for the existence of prior episodes, Gram-positive coverage with cefazolin was associated with a higher resolution rate (odds ratio [OR] = 3.0; 95% confidence interval [CI] = 1.21–7.51; $p = 0.04$) and lower catheter removal rate (OR = 3.0; 95% CI = 1.08–8.37; $p = 0.04$).

	Cefazolin plus Ceftazidime n=202	Vancomycin plus Ceftazidime n=27	p-value
Resolution	185 (91.6)	20 (74.1)	0.005
Catheter loss	17 (8.4)	7 (25.9)	0.005
Death	7 (3.5)	0	0.3
Shift to hemodialysis	19 (9.4)	7 (25.9)	0.01

Note: Data expressed as number (percent) Episodes of Fungi, *Mycobacterium* were excluded.

Table 5: Clinical outcomes and initial empirical antibiotics.

We compared the resolution according to the presence or absence of antibiotic resistance in Gram-positive cocci (CoNS and *S. aureus*) and Gram-negative bacilli (Figure 1). There were no significant differences between the groups in the rates of resolution, catheter removal, shift to hemodialysis, or death.

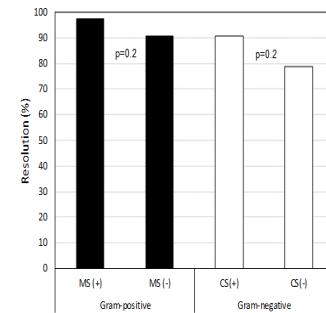


Figure 1: Association of resolution rate according to antibiotic susceptibility. MS (+), with methicillin susceptibility; MS (-), without methicillin susceptibility; CS(+), with ceftazidime susceptibility; CS(-), without ceftazidime susceptibility

Discussion

The overall rate of peritonitis was 0.2 episodes per patient-year, which is lower than the global average. In the United States, the peritonitis rate was 0.37 episodes per patient-year between 1998 and 2004 [14], and in the UK, it was 0.82 episodes per patient-year between 2002 and 2003 [15]. A Japanese study of 561 PD patients revealed a peritonitis rate of 0.28 episodes per patient-year from 2005 to 2007 [16]. The difference in peritonitis rates between Western and Asian countries may be attributable to differences in patient age, concurrent comorbidities, social support for older patients, and the smaller dialysis exchanges required in Asian patients because of their lower dialysis volumes [17]. Furthermore, the incidence of peritonitis has decreased in recent years, possibly because of better patient counseling and improvements in PD techniques. A study from a Korean center reported a sustained decrease in the rate of peritonitis over a 10-year period, from 0.57 to 0.29 episodes per patient-year [18]. In the present study, we found that the rates of Gram-positive and Gram-negative peritonitis were 51.5% and 28.3%, respectively. Recently, rates of PD-related peritonitis caused by Gram-positive cocci have decreased because of technological advances in connection systems and the routine use of mupirocin at the catheter exit site; as a result, the proportion of cases caused by Gram-negative bacilli has increased. We did not use topical antibiotics as prophylaxis at the exit site, and our results showed that Gram-positive cocci continue to be the main etiological agents of peritonitis. A recent study in Brazil also reported that Gram-positive cocci were the most common microorganisms causing peritonitis [19]. CoNS were the most common Gram-positive cocci detected in our study, which is consistent with the results of previous studies [19,20].

Streptococci are currently the third most frequent of all etiologies. The proportion of peritonitis episodes included in this study for which no organism could be cultured was acceptable according to international standards [21].

The emergence of antibiotic-resistant strains of bacteria is a growing problem and has become a major public health concern. Systematic data on the antibiotic susceptibility of pathogens from PD-related infections are limited. A previous study reported a significant increase in antibiotic resistance, observing that the rate of methicillin-resistant CoNS increased from 18.9% to 73.9% [22]. A recent study in India found that 54.3% of Gram-negative bacteria were resistant to third-generation cephalosporins, and that 23.5% of *Acinetobacter* species and 11.5% of *P. aeruginosa* were producers of metallo-β-lactamases and resistant to carbapenem [20]. However, in a larger series of peritonitis cases caused by Enterobacteriaceae reported in 2006, Szeto, et al. found that resistance to ciprofloxacin and ceftazidime had remained constant over time [23]. In the present study, we observed methicillin resistance in 61% of CoNS and 47% of *S. aureus* strains and a ceftazidime susceptibility rate of 79.1% in Gram-negative bacilli. These results represent a lower rate of antibiotic resistance compared with those reported in previous studies. Emerging vancomycin resistance in *Enterococci* is also a major concern. We found that 22% of *Enterococci* exhibited vancomycin resistance, and that 50% of cases caused by vancomycin-resistant *Enterococci* resulted in catheter loss and peritonitis-related death.

We found that, in contrast to previous reports [20], the rates of catheter loss, resolution, and death did not differ significantly between peritonitis episodes caused by Gram-negative and Gram-positive bacteria. This observation can be explained by the fact that in our study Gram-positive cocci were the main etiological agents of peritonitis, and the rate of antibiotic resistance was lower than those reported in other studies [10,20,23]. However, episodes of *Enterococcus* spp. and *Pseudomonas* spp. were characterized by lower resolution rates and higher rates of catheter loss than were episodes caused by CoNS. Death within 4 weeks of peritonitis was more frequent after episodes caused by *Pseudomonas* spp. (33.3%) than in those with other causes; however, the difference was not significant. Kim, et al. reported that the rate of catheter loss was highest for *Pseudomonas*-associated peritonitis, but that the mortality rate was highest for *Klebsiella*-associated peritonitis [10]. We examined the effects of antibiotic resistance on clinical outcomes, but found no significant differences in rates of resolution, catheter removal, or death between episodes caused by antibiotic-resistant or -susceptible organisms. Luiz, et al. reported that oxacillin resistance in Gram-positive cocci was a predictor of nonresolution, but that amikacin resistance in Gram-negative bacilli was not [19]. Although there are specific guidelines for

empirical therapy, guidance for therapy should ideally be provided by the local epidemiology and sensitivity pattern of the bacterial isolates, and there should be center-specific antibiotic policies for PD-associated peritonitis.

We observed that vancomycin was not superior to cefazolin as coverage for Gram-positive organisms. The lower catheter loss rate associated with vancomycin use may result from its prescription in high-risk patients with more severe peritoneal infections that may have a negative impact on preservation of the peritoneal membrane. This is consistent with the report by Fahim et al. that vancomycin prescriptions are associated with a higher risk of a permanent shift to hemodialysis [24]. Patients exposed to vancomycin typically had experienced previous episodes of bacterial peritonitis; after adjusting for this, we found that vancomycin was not superior to cefazolin. Thyago, et al. reported that vancomycin is an independent factor associated with technical failure in PD [25]; this supports the use by our center of cefazolin plus ceftazidime as an antibiotic combination. This study has a number of limitations. First, the results were retrospective and were not controlled. Second, although most peritonitis episodes were managed according to a predefined protocol, we were unable to exclude the possibility of an effect on clinical outcomes of selection bias in the empirical choice of antibiotics. Third, the small sample size limits the statistical significance of the relationship between antibiotic resistance and clinical outcomes. Fourth, because prophylactic antibiotic protocols (including the use of mupirocin ointment for nasal carriers of *S. aureus* and gentamicin cream for exit-site infection) were not used in our center, we were unable to draw conclusions about the efficacy of various prophylactic protocols. Fifth, the association between vancomycin and outcomes does not imply a cause-and-effect relationship, only an association.

The peritonitis rate was low in our study population. Gram-negative infections were not associated with a lower resolution or higher mortality rate. Rates of methicillin resistance in Gram-positive cocci and of third-generation cephalosporin resistance in Gram-negative bacilli were lower than those reported in previous studies and did not affect clinical outcomes. An association between vancomycin usage and poor outcomes was described; however, this relationship does not imply causality. Reports on the organisms responsible for peritonitis in PD patients and their antimicrobial sensitivity vary significantly from center to center, even within similar geographic regions and socioeconomic conditions. This provides motivation for continuous surveillance of emerging drug resistance in the development of antibiotic policies.

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgments

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