MICROBIOLOGY AND OUTCOMES OF PERITONITIS IN NORTHERN INDIA

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• Background: Peritoneal dialysis (PD) is an established treatment modality for end-stage renal disease (ESRD). Peritonitis remains a serious complication in PD patients and an important cause of drop-out from the program. Types of pathogens and their drug resistance patterns may determine the outcome of peritonitis. The present study was undertaken to determine the microbiology of peritonitis in PD patients, antibiotic resistance in commonly isolated bacterial pathogens and clinical outcomes.

• *Method:* We enrolled 211 patients with ESRD undergoing PD who developed peritonitis during 2002 to 2011. PD fluids were cultured and antibiotic susceptibility test of the bacterial isolates was performed.

• Result: A total of 303 peritonitis episodes with an overall incidence of 0.41 episodes per patient-year were recorded. Gram-positive, gram-negative, fungi, Mycobacterium tuberculosis and ≥ 2 organisms were isolated from 102 (33.7%), 89 (29.4%), 41 (13.5%), 11 (3.6%) and five (1.6%) episodes respectively; 55 (18.2%) episodes were culture negative. Coagulase-negative Staphylococcus spp. (CONS) was the most common isolate. Catheter loss and hospital admission in gram-negative peritonitis were significantly higher than in gram-positive peritonitis (36/89 (40.4%) vs 20/102 (19.6%), p < 0.001; and 56/89 (62.9%) vs 42/102 (41.2%), *p* = 0.004 respectively). Antibiotic susceptibility tests showed 54.3% of Enterobacteriaceae isolates were extended spectrum β -lactamase (ESBL) producers, 23.5% of Acinetobacter species and 11.5% of Pseudomonas aerugi*nosa* were metallo- β -lactamase (MBL) producers; 15.4% of enterococci and 28.6% of staphylococci were resistant to vancomycin and methicillin respectively. Mortality was significantly higher in patients having peritonitis due to vancomycin-resistant enterococci, ESBL- and MBLproducing bacteria.

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kashinprasad@gmail.com; knprasad@sgpgi.ac.in Received 11 September 2012; accepted 21 July 2013. • *Conclusion:* Emerging antimicrobial resistance calls for prompt diagnosis and aggressive empiric therapy based on the local sensitivity data.

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KEY WORDS: Antibiotic resistance; etiology of peritonitis; mortality in peritonitis; peritoneal dialysis; outcome of peritonitis.

Peritoneal dialysis (PD) has been an established treatment modality for end-stage renal disease (ESRD) for more than four decades. Approximately 10% to 15% of ESRD patients are on PD worldwide. Despite a dramatic reduction in peritonitis rate, it still remains a significant problem in PD and a major cause for switching from PD to hemodialysis. The most common organisms associated with PD peritonitis reported worldwide are coagulasenegative *Staphylococcus* spp. (CONS) and *Staphylococcus aureus* followed by streptococci, Enterobacteriaceae, non-fermenting gram-negative bacilli and gram-positive bacilli (1,2). However, in India, the spectrum of organisms associated with PD peritonitis showed a predominance of gram-negative organisms (3,4).

Peritonitis is an important cause of morbidity and mortality in PD patients. In the United States, 18% of the infection-related mortality in PD patients was due to peritonitis (5). Peritonitis was identified as a "contributing factor" in 16% of deaths of patients who were on PD (6). Other studies suggest that mortality can vary from 3.5% to 5% and it can be associated with specific organisms (1,7). In one retrospective Spanish study of 565 patients in 2005, mortality with fungal peritonitis was 28% followed by 19% due to enteric organisms and 15% due to *S. aureus* (8).

The International Society for Peritoneal Dialysis (ISPD) developed extensive guidelines for the treatment

of peritonitis in PD patients (9). Empiric antibiotic therapy should cover both gram-positive and gram-negative organisms and selection should be center specific based on local sensitivity data of the major causative organisms. Cross-sectional studies on the causative organisms of peritonitis have been reported frequently (10,7). However, long-term studies on changes in the causative organisms of peritonitis and their antibiotic sensitivity are scarce. The present study was designed to study the microbiology of peritonitis in PD patients, resistance patterns of commonly isolated bacterial pathogens and eventual outcome of peritonitis.

MATERIALS AND METHODS

A total of 211 PD patients who developed peritonitis from 2002 to 2011 were included in the study. During this study period, a total of 560 patients were enrolled in the PD program. For all patients, a double-cuffed straight Tenckhoff catheter was inserted by surgical technique and PD was started after a break-in period of 12 ± 4 days. All patients were started on a disconnect system using ultra-bag dianeal PD fluid (Baxter India, Manesar, India) with three 2-L exchanges daily. Dialysis prescription was changed according to individual requirements during follow-up. Diabetes, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, malignancy, cardiac arrhythmias, chronic lung disease, and chronic liver disease were considered as comorbidities. The diagnosis of peritonitis was made when the patients fulfilled at least two of the following three criteria: i) signs and symptoms of peritonitis, ii) cloudy dialysate with white blood cell count of > 100/µL with more than 50% neutrophils and iii) demonstration of organism either by smear examination or by culture of peritoneal dialysate. Centrifuged dialysate was examined microscopically and cultured in automated BACTEC blood culture system (BD Biosciences, San Jose, CA, USA) following standard protocol (11). The isolated bacterial pathogens were identified and subjected to antibiotic sensitivity test following Clinical Laboratory Standards Institute (CLSI) guidelines (12). The antibiotic discs were procured from Hi-Media, Mumbai, India. For detection of ESBL production in Enterobacteriaceae, cefotaxime and cefotaxime + clavulanic acid, and ceftazidime and ceftazidime + clavulanic acid discs were used and the results were interpreted according to CLSI guidelines, 2010. For metallo- β -lactamase production in non-fermenters, meropenem and meropenem + EDTA discs were used following standard guidelines (13). For outcome analysis, polymicrobial, fungal, tubercular and sterile peritonitis were excluded because of their

different outcomes from bacterial peritonitis. The outcomes were analyzed in terms of catheter loss, hospitalization, death within four weeks of peritonitis, and switch to permanent maintenance hemodialysis. Catheter loss was defined as catheter removal required for the resolution of peritonitis.

STATISTICAL ANALYSIS

Statistical analysis was performed using Fisher exact test with Yates correction and chi-square test for differences in proportions. Data were expressed as mean \pm standard deviation. Statistical significance was defined at a *p* value of \leq 0.05.

RESULTS

DEMOGRAPHY OF THE STUDY SUBJECTS

During the study, 742.33 patient-years were followed up and the mean duration of PD therapy was 3.52 years. A total of 211 patients (mean age 51.26 \pm 14.44 years; 150 male) developed 303 episodes of peritonitis (range: 1–6 episodes per patient) of which 12 episodes were relapsing peritonitis and 10 episodes were recurrent peritonitis. In all these patients, catheters were removed for the resolution of peritonitis. The overall peritonitis rate was 0.41 episodes/patient-year. Of these 211 patients, 114 had diabetes, 34 had cardiovascular comorbidities, two malignancies, and two chronic liver diseases with portal hypertension.

CAUSATIVE ORGANISMS OF PERITONITIS

Gram-positive, gram-negative, fungi, *Mycobacterium* tuberculosis and \geq 2 organisms were isolated from 102 (33.7%), 89 (29.4%), 41 (13.5%), 11 (3.6%) and five (1.6%) episodes respectively; 55 (18.2%) episodes were culture negative. The distribution of bacterial pathogens was as follows: CONS (71; 23.4%), *Escherichia* coli (32; 10.6%), *Pseudomonas aeruginosa* (26; 8.6%), *Acinetobacter* species (17; 5.6%), *S. aureus* (14; 4.6%) and *Enterococcus* species (13; 4.3%) (Table 1).

ANTIBIOTIC SENSITIVITY PATTERNS OF ORGANISMS

The antibiotic sensitivity patterns of the commonly isolated organisms are shown in Tables 2 and 3. It was observed that 54.3% of the Enterobacteriaceae isolates were resistant to third-generation cephalosporins and all of them were ESBL-producers. However, no carbapenemresistant strain was detected in the Enterobacteriaceae

Organisms	Number isolated (<i>n</i> =303)	Percent of gram- positive episodes	Percent of total episodes	
Gram-positive	102	_	33.7%	
Coagulase-negative <i>Staphylococcus</i> species (CONS)	71	69.6%	23.4%	
Staphylococcus aureus	14	13.7%	4.6%	
Enterococcus species	13	12.7%	4.3%	
Streptococcus species	3	2.9%	1.0%	
Rothia dentocariosa	1	1%	0.3%	
Gram-negative	89	-	29.4%	
Escherichia coli	32	35.9%	10.6%	
Pseudomonas aeruginosa	26	29.2%	8.6%	
Acinetobacter species	17	19.1%	5.6%	
Enterobacter aerogenes	7	7.9%	2.3%	
Klebsiella species	6	6.7%	2.0%	
Citrobacter species	1	1.1%	0.3%	
Fungus	41	-	13.5%	
Mycobacterium tuberculosis	11	-	3.6%	
Polymicrobial	5	-	1.6%	
E. coli + Klebsiella pneumoniae	1	-	0.3%	
K. pneumonia + E. aerogenes	1	_	0.3%	
P. aeruginosa + Citrobacter freundii	1	-	0.3%	
E. coli + CONS	1	-	0.3%	
Yeast like cells + <i>E. coli</i>	1	-	0.3%	
Sterile	55	-	18.2%	

TABLE 1 The Causative Organisms of Peritonitis in Patients Undergoing Peritoneal Dialysis

TABLE 2

Antibiotic Resistance in Gram-Negative Organisms Isolated from Dialysates of Patients with Peritonitis

Antibiotics	Enterobacteriaceae (<i>n</i> =46)	Acinetobacter species (n=17)	Pseudomonas aeruginosa (n=26)
Ceftraxione	25 (54.3%)	11 (64.7%)	NT
Ceftazidime	25 (54.3%)	14 (82.3%)	6 (23.1%)
Ampicillin-sulbactam	NT	5 (29.4%)	NT
Carbapenem (Imipenem/Meropenem)	0 (0.0%)	4 (23.5%)	3 (11.5%)
Amikacin	6 (13%)	8 (47%)	9 (34.6%)
Ciprofloxacin	35 (76.1%)	5 (29.4%)	6 (23.1%)
Piperacillin-tazobactum	15 (32.6%)	4 (23.5%)	9 (34.6%)
Tobramycin	NT	NT	10 (38.5%)

NT = not tested.

family. Resistance to third-generation cephalosporins was very high in non-fermenters (Table 2). Carbapenem resistance in *Acinetobacter* species and *P. aeruginosa* was 23.5% and 11.5% respectively and all of them were MBL-producers. Amikacin resistance in *Acinetobacter* species and *P. aeruginosa* was also very high, 47% and 34.5% respectively. Among the gram-positive organisms isolated from PD fluid, 15.4% were vancomycin-resistant enterococci (VRE) and 28.6% were methicillin-resistant

S. aureus. Of the 71 episodes of peritonitis caused by CONS, 15 (21.1%) were by methicillin-resistant strains.

OUTCOME ANALYSIS OF GRAM-POSITIVE AND GRAM-NEGATIVE PERITONITIS EPISODES

Catheter loss in gram-negative peritonitis was significantly higher than in gram-positive peritonitis (36/89 (40.4% vs 20/102 (19.6%); p < 0.001). The

hospitalization rate required for management of peritonitis was also significantly higher for gram-negative than for gram-positive peritonitis (56/89 (62.9%) vs 42/102 (41.2%); p = 0.004). The trend of death within four weeks of peritonitis was also higher for gram-negative episodes (10.8%), although the difference was not statistically significant (Table 4). Overall, death was higher in patients with peritonitis due to *E. coli*, and catheter loss had significant association with CONS infection. Catheter loss and death due to peritonitis caused by different organisms are shown in Table 5. Mortality was significantly higher in patients having peritonitis due to VRE, and ESBL and MBL producers (Figure 1).

DISCUSSION

Peritonitis in PD patients has been decreasing over the past years due to advances in PD technique (14–16),

	Coagulase-negative Staphylococcus species (CONS)	Staphylococcus aureus	Enterococcus specie	
Antibiotics	(<i>n</i> =71)	(<i>n</i> =14)	(<i>n</i> =13)	
Vancomycin	0 (0%)	0 (0%)	2 (15.4%)	
Oxacillin	15 (21.1%)	4 (28.6%)	NT	
Ciprofloxacin	18 (25.3%)	5 (35.7%)	12 (92.3%)	
Amikacin	6 (8.4%)	5 (35.7%)	NT	
Gentamicin	24 (33.8%)	8 (57.1%)	11 (84.6%)	
Amoxycillin	47 (66.2%)	8 (57.1%)	8 (61.5%)	

TABLE 3

NT = not tested.

TABLE 4

Comparison of Outcomes in Gram-Positive (n=102) and Gram-Negative (n=89) Peritonitis Episodes

Outcome	Gram-positive (<i>n</i> =102)	Gram-negative (<i>n</i> =89)	p value	
Catheter loss	20 (19.6%)	36 (40.4%)	<0.001	
Death	10 (9.8%)	19 (21.3%)	0.064	
Hospitalization	42 (41.2%)	56 (62.9%)	0.004	
Shift to hemodialysis	6 (5.8%)	9 (10.1%)	0.296	

TABLE 5 Catheter Loss and Peritonitis-Associated Death According to Causative Organism

Organism	No. of isolates	Catheter loss		Death	
	(<i>n</i> =191)	(<i>n</i> =55)	<i>p</i> value	(<i>n</i> =18)	<i>p</i> value
CONS	71 (37.2%)	10 (18.2%)	0.008	6 (21.4%)	0.103
Staphylococcus aureus	14 (7.3%)	2 (3.6%)	0.327	0 (0%)	NC
Enterococcus species	13 (6.8%)	7 (12.7%)	0.156	3 (10.7%)	0.458
Streptococcus species	3 (1.6%)	0 (0.0%)	NC	0 (0.0%)	NC
Rothia dentocariosa	1 (0.5%)	1 (1.8%)	0.346	1 (3.6%)	0.113
Escherichia coli	32 (16.7%)	14 (25.4%)	0.144	11 (39.3%)	0.005
Klebsiella pneumoniae	6 (3.1%)	2 (3.6%)	0.855	1 (3.6%)	0.903
Enterobacter aerogenes	7 (3.7%)	1 (1.8%)	0.496	1 (3.6%)	0.980
Citrobacter species	1 (0.5%)	1 (1.8%)	0.346	0 (0.0%)	0.141
Pseudomonas aeruginosa	26 (13.6%)	12 (21.8%)	0.137	2 (7.1%)	0.338
Acinetobacter species	17 (8.9%)	5 (9.1%)	0.965	3 (10.7%)	0.755

CONS = coagulase-negative *Staphylococcus* species; NC = not calculated.

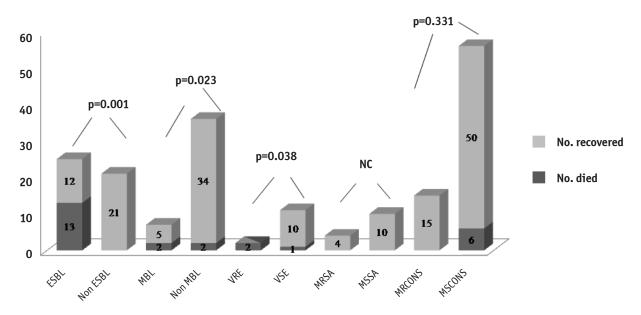


Figure 1 — Death related to ESBL, MBL, VRE, MRSA, MSSA, MRCONS and MSCONS. NC = not calculated; ESBL = extended spectrum β -lactamase; MBL = metallo- β -lactamase; VRE = vancomycin-resistant enterococci; VSE = vancomycin-sensitive enterococci; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; MRCONS = methicillin-resistant coagulase-negative *Staphylococcus* species; MSCONS = methicillin-sensitive coagulase-negative *Staphylococcus* species.

but it still remains a major cause of technique failure; in addition, it can also lead to death (9,14,16–18). The peritonitis rate at our center during the study period was 0.41 episodes per patient-year, which is comparable with other leading centers that reported approximately 0.5 episodes per patient-year (19,20). Currently, the incidence of peritonitis has further decreased to 0.33 episodes per patient-year; in some centers, the incidence is as low as 0.2 episodes per patient-year (21). Previously, in the year 2003, our center reported 0.63 episodes per patient-year (4). Hence the trend of peritonitis at our center is decreasing, possibly due to better patient counseling and improvement in PD technique. In the present study, the culture-positive rate was 81.8% and culture-negative rate was 18.2%. Earlier in 2003, our center reported 36.9% of culture-negative episodes and this decrease in culture-negative rate is due to improvement of microbiological culture technique. The present study showed that the rates of gram-positive and gramnegative peritonitis were almost equal (33.7% vs 29.4%) in contrast to our earlier study where a preponderance of gram-negative infections was reported (4). This shift might be related to better bacterial isolation technique since all the dialysates were cultured in BACTEC 9120 after at least 50 mL dialysate was centrifuged, thus increasing the isolation rate to 81.9%. There was a tremendous increase in the isolation rate of CONS (23.4% of total peritonitis episodes but 69.6% of all gram-positive episodes), possibly because of a better isolation technique. This is also concordant with reports from the developed world,

where CONS was identified as the most common pathogen (1,22–23). In our earlier study, the isolation rate of CONS was low (13% of total peritonitis episodes) with an overall culture-positive rate of 63% (4). The reason might be that around one-third of the samples in the earlier study were processed in private laboratories where dialysates were neither centrifuged nor cultured in appropriate media and the culture-positive rate in private laboratories was very low (around 20%). However, we found a lesser isolation rate for S. aureus (4.6%) compared to the typical pattern of 10–15% in the developed world (23). In other Indian studies, culture-positive rates varied between 30% and 72% (3,24-25) and gram-negative bacteria were responsible for 60–66% of the episodes, with E. coli being the most common pathogen (3,24). We also observed fungal peritonitis in 13.5% of the episodes. Fungal peritonitis usually constitutes 2-15% of the episodes and it is a serious complication of PD with mortality ranging between 25-53% (26). Immediate catheter removal is indicated in fungal peritonitis, which is strictly being followed at our center.

The emergence of antibiotic-resistant bacteria is being increasingly reported and it has become a major public health problem. Systematic data on antibiotic susceptibility of pathogens isolated exclusively from PD-related infections are limited. Zelenitsky *et al.*, in 2000, reported a significant increase in antibiotic resistance (20). In his study, the most dramatic increase in antibiotic resistance was seen among *S. epidermidis*. From 1991 and 1992 to 1997 and 1998, resistance to ciprofloxacin increased from 5.4% to 47.8% and resistance to methicillin increased from 18.9% to 73.9%. In our study, 54.3% of gram-negative bacteria were resistant to third-generation cephalosporin (ESBL producer) and 23.5% of Acinetobacter species and 11.5% of P. aeruginosa were MBL producers and resistant to carbapenem. Two different studies from India showed that resistance to third-generation cephalosporins in Enterobacteriaceae varied from 67.4% to 72.8% (24,27). A study from Bangladesh also found that gram-negative organisms were predominantly associated with peritonitis and around 50% of them were resistant to third-generation cephalosporins (28). Another study from Brazil reported that non-fermenter gram-negative bacteria showed a decline in ceftazidime susceptibility with only 25% resolution rate (29). Reporting on temporal changes in the susceptibility profile of gram-negative bacilli, Kim et al., in 2004, reported no changes in antimicrobial susceptibility to aminoglycosides, quinolones and imipenem for P. aeruginosa and E. coli (30). On the other hand, in the largest series study of Enterobacteriaceae peritonitis, Szeto et al., in 2006, observed an increase in resistance to gentamycin and netilmycin among E. coli and Klebsiella species, while resistance to ciprofloxacin and ceftazidime remained constant over time (31). In the present study, 15.6% of *E. coli* isolates were resistant to amikacin and 37.5% to gentamycin. Resistance to aminoglycosides in the current study was high in nonfermenters (47% in Acinetobacter species and 34.6% in P. aeruginosa). Aminoglycosides and ceftazidime are frequently recommended for gram-negative coverage in PD peritonitis. However, emerging resistance to thirdgeneration cephalosporins and aminoglycosides may restrict their use in developing countries. Vancomycinresistant enterococci accounted for 15.4% and 28.6% were methicillin-resistant staphylococci. Emerging vancomycin resistance in enterococci is also a major concern since this antibiotic is recommended for the empirical treatment of suspected gram-positive infections. Although there is a specific guideline for the empirical therapy, the local epidemiology and sensitivity pattern of the bacterial isolates should ideally quide the therapy and there should be a center-specific antibiotic policy for PD peritonitis.

In gram-negative peritonitis episodes, as compared with gram-positive episodes, the proportion of catheter loss (40.4% vs 19.6%, p = 0.001) and hospitalization (62.9% vs 41.2%, p = 0.004) were significantly higher. Death within four weeks of peritonitis was also more frequent in gram-negative episodes (21.3%) than in gram-positive episodes (9.8%) but the difference was not statistically significant. The above observations were similar to our earlier study (4). However, mortality was significantly higher in patients having peritonitis due to ESBL- and MBL-producing bacteria, and VRE. In an earlier study, the ESBL group had a mortality rate of 27.3% (32). Higher mortality in VRE, ESBL and MBL groups emphasizes the need for early detection of such resistant strains so that appropriate therapy can be initiated to have better therapeutic outcomes. Catheter loss was significantly higher in CONS infection. This might be due to biofilm formation by CONS that resulted in resolution failure. We also observed significantly higher mortality in E. coli-induced peritonitis. Kim et al., (2004) reported that catheter loss was highest among Pseudomonasassociated peritonitis but mortality was highest among Klebsiella-associated peritonitis (30). Poor outcomes in gram-negative peritonitis have also been observed in other studies (7,33).

It is evident from various studies and registry reports that the organisms responsible for peritonitis in PD patients and their antimicrobial sensitivity vary significantly from center to center even within similar geographic and socio-economic conditions. Therefore, there is a need for constant surveillance of emerging drug resistance to develop an antibiotic policy exclusively for PD-related infections based on local susceptibility of the isolated pathogens. Since the gram-negative infections with multidrug resistant pathogens are associated with higher mortality, their early detection in order to initiate appropriate therapy can lead to better clinical outcomes.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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