**RISK FACTORS AND OUTCOMES OF EXTENDED-SPECTRUM BETA-LACTAMASE-PRODUCING E. COLI PERITONITIS IN CAPD PATIENTS**

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**Objective:** To determine the risk factors and outcomes of peritonitis caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* in continuous ambulatory peritoneal dialysis (CAPD).

**Patients and Methods:** Episodes of *E. coli* CAPD peritonitis in our unit from October 1994 to August 2003 were reviewed. Demographic data, underlying medical conditions, recent use of gastric acid inhibitors (including H₂ antagonist and proton pump inhibitor), recent antibiotic therapy, antibiotic regimen for peritonitis episodes, sensitivity test results of the *E. coli* isolated, and clinical outcomes were examined.

**Results:** Over a 10-year study period, 88 episodes of *E. coli* peritonitis were recorded; 11 of the 88 cases were caused by ESBL-producing *E. coli*. Recent use of cephalosporins and gastric acid inhibitors were associated with the development of ESBL-producing *E. coli* peritonitis. Compared with non-ESBL-producing *E. coli* peritonitis, more cases in the ESBL-producing *E. coli* group developed treatment failure (45.5% vs 13.0%, p = 0.02) and died of sepsis (27.3% vs 3.9%, p = 0.02). Peritoneal failure rate was higher in the ESBL-producing *E. coli* group, although the difference was not statistically significant (18.2% vs 3.9%, p = 0.12).

**Conclusion:** Peritonitis caused by ESBL-producing *E. coli* is associated with worse clinical outcomes. The use of cephalosporins and gastric acid inhibitors may contribute to its development. Further studies are warranted to investigate and determine the predisposing factors for ESBL-producing *E. coli* peritonitis.

**KEY WORDS:** Extended-spectrum beta-lactamase; *E. coli*; peritonitis; cephalosporin; gastric acid inhibitor.

**Peritonitis** is a common and potentially serious infection in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). The complications of peritonitis are significant and include temporary or permanent catheter loss and hospitalization (1,2). In one study, peritonitis had an associated mortality rate of 15.8% in patients undergoing peritoneal dialysis (3). Unfortunately, despite improvement in peritoneal dialysis connectology leading to a marked decrease in the incidence of gram-positive peritonitis, the absolute incidence of gram-negative peritonitis has not been successfully reduced (4). It is also well recognized that gram-negative peritonitis is associated with more peritoneal catheter removal, increased dropout, and higher mortality than peritonitis caused by gram-positive micro-organisms (5,6).

The emergence of extended-spectrum beta-lactamase (ESBL)-producing gram-negative infection in the past decade has made the management of gram-negative infection more difficult. This group of organisms is highly efficient at inactivating third-generation cephalosporins such as cefotaxime, ceftazidime, and ceftriaxone. These ESBL-producing organisms are usually found in the hospital environment, particularly in intensive care units, pediatric wards, and oncology wards. A number of reports have also documented their emergence in long-term care facilities such as nursing homes and rehabilitation units. Ambulatory patients with chronic conditions may serve as reservoirs for ESBL-producing organisms (7–9).
In very recent years, we observed an increasing trend in CAPD peritonitis caused by ESBL-producing organisms. However, there is little information in the literature on the problem of ESBL-producing gram-negative peritonitis in CAPD patients. We decided to study the clinical course and predisposing risk factors for ESBL-producing *Escherichia coli* in our patients over the past decade.

**PATIENTS AND METHODS**

The study was conducted at the Tung Wah Hospital, Hong Kong, a 600-bed subacute medical and surgical hospital with a well-established renal dialysis center. There is no intensive care unit in this hospital but there is one in a neighboring acute hospital affiliated with the same university. All episodes of CAPD peritonitis due to *E. coli* in our unit from October 1994 to August 2003 were reviewed. Polymicrobial CAPD peritonitis and relapsing episodes of *E. coli* peritonitis were excluded from this study because they often had different etiology and outcome from single-organism peritonitis.

Peritonitis was diagnosed when abdominal pain and cloudy fluid occurred, with or without fever, and when peritoneal fluid white blood cell (WBC) count was >100/mm³, with >50% polymorphonucleocytes. Episodes with peritoneal eosinophilia but negative bacterial culture were excluded.

The peritoneal dialysis effluent (PDE) was sent for hematological and microbiological examination when patients complained of abdominal pain or had turbid peritoneal effluent. All isolates were identified by standard biochemical methods; the identity of the isolates was confirmed by the Vitek AutoMicrobic System (bioMerieux Vitek, Hazelwood, Missouri, USA).

Extended-spectrum beta-lactamase (ESBL)-producing organisms were detected by the double disk synergy test. The same test was used throughout the entire study period. Ceftriaxone (30 μg) and ceftazidime (30 μg) disks were placed adjacent to amoxicillin–clavulanic acid (20/10 μg) disks at inter-disk widths of 25 mm. Enhancement of the inhibition zones around ceftriaxone and/or ceftazidime disks by the beta-lactamase inhibitor-containing disk (amoxicillin–clavulanic acid) was interpreted as positive for ESBL. This approach was previously found to be highly sensitive for the detection of ESBL in *E. coli* (10).

Risk factors studied included demographic data, diabetes mellitus, recent use of gastric acid inhibitors (including H₂ antagonist and proton pump inhibitor), and recent antibiotic therapy. The latter two factors were chosen for their potential effects on intestinal flora.

Peritonitis episodes were treated with our center’s standard antibiotic protocol, which has been changed systemically over time. The first-line antibiotic regimen for CAPD peritonitis was first- or second-generation cephalosporin plus an aminoglycoside, either tobramycin or netilmicin. Cefazolin and ceftazidime combination has also been used since the year 2002 according to the International Society for Peritoneal Dialysis (ISPD) peritonitis guideline published in 2000 (4). Vancomycin was used as a second-line therapy for primary non-responding cases and in patients with severe peritonitis. Antibiotic regimens for individual patients were modified when culture results became available. Treatment usually lasted for either 2 weeks or at least 7 more days after normalization of effluent WBC count, whichever was longer.

Requirement of cessation of peritoneal dialysis, whether temporary or permanent, and death during peritonitis were defined as treatment failure. Relapse was defined as another episode of peritonitis caused by the same bacteria occurring within 28 days after the last dose of antibiotics.

Statistical analysis was performed using SPSS 11.0 (SPSS Inc., Chicago, Illinois, USA) for Windows operating system (Microsoft, Redmond, Washington, USA). Data are expressed as mean ± standard deviation. A p value of less than 0.05 was considered statistically significant. All probabilities were two-tailed. Chi-square test, Fisher’s test, and Student’s t-test were used to analyze differences between patients with ESBL-producing *E. coli* peritonitis (ESBL group) and those with non-ESBL-producing *E. coli* peritonitis (non-ESBL group). Where appropriate, multiple logistic regression analyses were used to establish the best determinants of associated factors.

**RESULTS**

Over the 10-year study period, 1066 episodes of peritonitis were recorded. The overall peritonitis rate was 1 episode every 22.6 patient-months. Among the 253 episodes of gram-negative bacterial peritonitis, *E. coli* was the most common causative organism (88 episodes, 35%), followed by *Pseudomonas* species (52 episodes, 21%) and *Klebsiella* species (35 episodes, 14%).

Of the 88 episodes of *E. coli* peritonitis, 11 cases were due to ESBL-producing *E. coli* (12.5%). There were another 2 cases of ESBL-producing *E. coli* peritonitis among polymicrobial peritonitis episodes (1 in year 1997 and another in 2000). The earliest episode was identified in November 1996. The ESBL rate of *E. coli* peritonitis since its first identification was 14.5%. None of those episodes was associated with intra-abdominal catastrophe.
Figure 1 shows the incidence of *E. coli* CAPD peritonitis during the study period. The ESBL rate in 1998 and 1999 was around 10% – 15%; in 2001 – 2003, the rate increased to around 20%. The demographic data and clinical characteristics of cases in the ESBL and non-ESBL groups are summarized in Table 1. None of the patients in either group had been admitted to an intensive care unit. There was no statistically significant difference in demographic data between the two groups. Seven patients in the ESBL group had a history of recent intake of antibiotics. Two of those patients had been given penicillin-group antibiotics for treatment of cellulitis and bronchitis. Three patients had been given the first-generation cephalosporin cefazolin for the treatment of exit-site infection and culture-negative peritonitis. Another 2 patients had been given the second-generation cephalosporin cefuroxime for the treatment of pneumonia and peritonitis caused by streptococcus. There was no statistically significant difference in the number of patients taking antibiotics in either group; however, more patients in the ESBL group had a history of recent use of cephalosporins (5 of 11 vs 11 of 77, *p* = 0.03) and gastric acid inhibitors (7 of 11 vs 24 of 77, *p* = 0.05). Multiple logistic regression analysis showed recent use of the cephalosporin group of antibiotics was the independent variable associated with the development of ESBL-producing *E. coli* peritonitis.

Table 2 shows the antibiotic sensitivity test results of the 11 isolates of ESBL-producing *E. coli*. Rates of resistance to ampicillin and amoxicillin plus clavulanate were 100% and 90% respectively. All the isolates were resistant to first- and second-generation cephalosporin;
rate of resistance to third-generation cephalosporin was 87.5%. Rate of resistance to gentamicin and amikacin was 36.4% and 37.5% respectively; 90.9% of the isolates were resistant to cotrimoxazole and 50% of the isolates were resistant to ciprofloxacin. None of the isolates was resistant to imipenem.

Of the 11 cases of ESBL-producing *E. coli* peritonitis, 6 cases responded to intraperitoneal antibiotics and 5 cases did not. Among the nonresponders, the Tenckhoff catheter was removed in 3 patients. Two patients died of sepsis before removal of the Tenckhoff catheter. One patient died before reinserter of a Tenckhoff catheter; the cause of death was acute myocardial infarction. Two patients underwent reinserter of a Tenckhoff catheter but both failed because of intraperitoneal adhesions. They were permanently transferred to hemodialysis. There was no statistically significant difference in the demographic characteristics and antibiotic treatment regimen between responders and nonresponders (Table 3).

Compared with the non-ESBL group, patients in the ESBL group had a higher treatment failure rate (45.5% vs 13.0%, *p* = 0.02) and mortality rate (27.3% vs 3.9%, *p* = 0.02), and a slightly higher failure rate of returning to peritoneal dialysis, although this difference was not statistically significant (18.2% vs 3.9%, *p* = 0.12).

**DISCUSSION**

Peritonitis is a common clinical problem that occurs in patients with end-stage renal disease (ESRD) treated by peritoneal dialysis. The peritonitis rate of 22.6 patient-months in our center was similar to many other centers (11,12).

In 1983, a novel group of enzymes subsequently named extended-spectrum β-lactamases (ESBL) was detected among *Serratia marcescens* and *Klebsiella pneumoniae* in Germany (13). This group of enzymes arose mainly from genes coding common plasmid-mediated enzymes that have undergone point mutations resulting in amino acid substitutions at the active site of the enzyme. The ESBLs are capable of hydrolyzing all β-lactams except the carbapenems (14–16). Among gram-negative bacteria, the production of β-lactamases is the most important mechanism of resistance to β-lactam agents (17).

For several reasons, ESBLs pose a serious clinical problem. The first of these arises directly from their wide substrate specificity, which in general includes almost all penicillins, cephalosporins, and monobactams. The second is the fact that ESBL producers frequently appear susceptible *in vitro* to some ESBL substrates, due, among other reasons, to high quantitative differences in the activity of certain ESBL variants against particular compounds.

In recent years, there was a significant increase in the ESBL rate reported from all parts of the world. In North America, the ESBL rate in *E. coli* was 3.3% – 4.7% (18–20); in South America, the reported rate was 6.7% – 25.4% (18,21–23). In the Far East–Western Pacific area, the ESBL rate in *E. coli* was 7.9% – 23.6% (10,18,24–26). We have observed an increasing trend in the rate of ESBL isolated from our CAPD patients with *E. coli* peritonitis. The ESBL rate of around 20% in the past 2 years is high compared to the above reports and is therefore worrying to us, although the absolute number of cases per year is still small.

Use of antibiotics alters body flora and provokes the development of resistant bacterial strains. The selection

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**TABLE 3**

Comparison of Demographic Characteristics and Antibiotic Treatment Regimen Between Responders and Nonresponders

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.3±12.1</td>
<td>64.7±14.3</td>
<td>0.511</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>0:6</td>
<td>3:2</td>
<td>0.061</td>
</tr>
<tr>
<td>Duration on dialysis (months)</td>
<td>35.5±17.2</td>
<td>62.0±46.9</td>
<td>0.287</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>1</td>
<td>2</td>
<td>0.545</td>
</tr>
<tr>
<td>Recent use of gastric acid inhibitors (n)</td>
<td>5</td>
<td>5</td>
<td>0.197</td>
</tr>
<tr>
<td>Recent use of cephalosporin (n)</td>
<td>4</td>
<td>1</td>
<td>0.175</td>
</tr>
<tr>
<td>Peritonitis treated with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-generation cephalosporins</td>
<td>5</td>
<td>5</td>
<td>0.545</td>
</tr>
<tr>
<td>Third-generation cephalosporins</td>
<td>1</td>
<td>3</td>
<td>0.197</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>6</td>
<td>4</td>
<td>0.455</td>
</tr>
<tr>
<td>Imipenem</td>
<td>3</td>
<td>1</td>
<td>0.348</td>
</tr>
</tbody>
</table>
pressure that drives ESBL evolution has usually been attributed to the intense use of cephalosporins, especially third-generation cephalosporins. Several previous studies have found an association between consumption of the extended-spectrum cephalosporins and the emergence of ESBL (27–29). We found that recent use of cephalosporin was associated with the development of ESBL-producing *E. coli* peritonitis in CAPD patients, although only first- and second-generation cephalosporins were used. Whether the increasing use of third-generation cephalosporins according to the ISPD peritonitis guideline 2000 would lead to further increase in ESBL-producing organism incidence would need investigation.

Treatment with gastric acid inhibitors may also increase the risk of developing enteric peritonitis. Gastric acid is a major defense factor against bacterial colonization of the small bowel and thus contributes to the prevention of bacterial overgrowth syndromes and intestinal infections. Patients with reduced gastric acid secretion due to nonpharmacological causes (as can be found after vagotomy and antral resection) develop gastric and duodenal bacterial overgrowth. Treatment with H₂ antagonists has been associated with an increased number of intragastric bacteria (30–33). The most frequent micro-organisms that colonize the upper gastrointestinal tract after gastric acid inhibitor treatment have been shown to be oral and fecal type bacteria (34). Thus, it is not unreasonable to speculate that treatment with gastric acid inhibitors may also favor intestinal bacterial overgrowth in patients on CAPD. Caravaca et al. found that treatment with gastric acid inhibitors was independently associated with the development of peritonitis caused by micro-organisms of enteral origin (35).

To our knowledge, there has been no report on the association between the use of gastric acid inhibitor and the development of infection caused by ESBL-producing organisms. Our observation of the association between consumption of gastric acid inhibitors and development of ESBL-producing *E. coli* peritonitis may be unique to patients on peritoneal dialysis. The causative micro-organisms in enteric peritonitis are thought to be the patient’s normal intestinal flora; therefore, a considerable proportion of intestinal flora would have to be changed to antibiotic-resistant strains in order to develop CAPD peritonitis caused by these strains. We therefore propose that gastric acid inhibitors and antibiotic use may be the facilitating factors for the selective overgrowth of antibiotic-resistant strains.

Outcomes of CAPD peritonitis caused by ESBL-producing organisms have not been reported previously. In our series, we observed a high treatment failure rate in the ESBL group (45%). Grave prognoses of spontaneous bacterial peritonitis caused by ESBL-producing organisms have been reported in patients with cirrhosis and ascites, and spontaneous bacterial peritonitis was found to be an independent predictive factor for mortality, with a 94% in-hospital mortality rate (36). This indicates that special attention to the emergence and treatment of ESBL-producing *E. coli* peritonitis is needed.

The emergence of antibiotic-resistant bacteria has been increasingly reported and has become a real threat in recent years. Zelenitsky et al. found that there has been a significant increase in antibiotic resistance, especially among *Staphylococcus epidermidis* (11). Dryden et al. observed a significant increase in resistance among normal flora and pathogenic isolates in patients undergoing CAPD (37). Even more dramatic was the emergence of methicillin-resistant *S. aureus* and *S. epidermidis*, which was less than 20% in 1991 and 1992, but more than 70% in 1997 and 1998. Internationally, the prevalence of vancomycin-resistant organisms has dramatically increased; this increase has been particularly evident in larger university hospitals, where up to 14% of enterococci may be resistant. This led to a change in treatment recommendations published by the ISPD in 1996 (38). To prevent unnecessary exposure to vancomycin and thus emergence of resistant organisms, it was recommended that a first-generation cephalosporin with an aminoglycoside be initiated as first-line treatment for CAPD peritonitis. This guideline was revised in year 2000 and a first-generation cephalosporin in combination with a third-generation cephalosporin, for example, ceftriaxone, was recommended as first-line treatment instead (4). The rationale behind this was avoidance of routine use of aminoglycoside in order to preserve residual renal function, which is an independent predictor of patient survival. Our finding in the present study causes us to worry that this regimen will lead to an increased incidence of CAPD peritonitis caused by ESBL-producing organisms, which were associated with worse clinical outcomes.

In a previous case-control study of 31 episodes of ESBL-producing *Klebsiella pneumoniae* and *E. coli* bacteremia, it was found that mortality was less likely if case patients received appropriate treatment within 3 days of the onset of bacteremia (29). This is in agreement with several other studies highlighting the importance of early appropriate antibiotic therapy in improving the survival of patients with *E. coli* bacteremia. Although some of our patients did respond to cephalosporins plus aminoglycosides, *in vitro* studies and observational studies strongly suggest that carbapenems should be regarded as drugs of choice, and may be considered first-line antibiotics in centers with a high incidence of
CAPD peritonitis caused by ESBL-producing organisms. We were unable to make any treatment recommendations from our study due to the small number of cases, and only a few of them were put on carbapenems.

In conclusion, we have observed a rising trend of ESBL-producing *E. coli* peritonitis in our center and found its development was associated with the use of cephalosporins or gastric acid inhibitors before peritonitis. Peritonitis due to ESBL-producing *E. coli* was associated with a higher treatment failure rate and mortality. Further studies are warranted to establish and confirm such associations, and measures should be developed to stop the emergence of ESBL-producing *E. coli* peritonitis.

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