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# *Stenotrophomonas Maltophilia* Infection in Patients Receiving Continuous Ambulatory Peritoneal Dialysis

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**Background** : *Stenotrophomonas maltophilia* is a gram-negative bacillus that has become increasingly recognized as an important nosocomial pathogen, particularly in individuals with severe debilitation or immunosuppression. *S. maltophilia* is also characterized by its resistance to multiple antibiotics. *S. maltophilia* peritonitis in CAPD (continuous ambulatory peritoneal dialysis) patients is associated with a poor prognosis and loss of CAPD catheter. No report concerning this entity has been presented in Korea. Therefore, we describe and discuss five cases of the *S. maltophilia* infection associated with CAPD in three patients with peritonitis and two with exit-site infections.

**Methods** : We performed a retrospective search for episodes of *S. maltophilia* infections related to CAPD in our renal unit. The baseline levels of hemoglobin, albumin, cholesterol, BUN and creatinine were compared with age, sex and, if possible, the underlying disease-matched controls.

**Results** : All the patients with *S. maltophilia* peritonitis had diabetes mellitus as the underlying disease. The individual patients also had other significant combined morbidities, such as panhypopituitarism, COPD chronic obstructive pulmonary disease, cerebrovascular accident and myocardial infarction. The level of hemoglobin in these patients was significantly lower than in the controls, and the mean values of serum albumin, creatinine and BUN were also low.

**Conclusion** : Immune dysfunction due to uremia, anemia, malnutrition, other comorbidities (e.g. diabetes mellitus), and also, an indwelling peritoneal catheter may be predisposing factors for the *S. maltophilia* infection in CAPD patients. Once the *S. maltophilia* infection is diagnosed in CAPD patient, the patient should be treated based on the understanding of this particular organism.

**Key Words** : *Stenotrophomonas maltophilia*, Peritoneal dialysis

## INTRODUCTION

Peritonitis and exit-site infections are common and serious complications in continuous ambulatory peritoneal dialysis (CAPD) and they can cause significant morbidity.

*Stenotrophomonas maltophilia* is a nonfermentative, gram-negative bacillus that has become increasingly recognized as an important nosocomial pathogen, particularly in individuals with severe debilitation or immunosuppression[1]. Originally, included in the genus *Pseudomonas*[2], it was placed in the genus *Xanthomonas* in 1983[3]. Finally, a new genus, *Stenotrophomonas* was proposed, and *S. maltophilia* is the only recognized species[4]. This organism was found to be able to cause a wide spectrum of diseases[1, 5], and has been closely associated with the central venous catheter and prior antibiotic therapy[6, 7]. *S. maltophilia* is also characterized by its resistance to multiple antibiotics[7].

There are a few reports on *S. maltophilia* peritonitis in CAPD patients. These cases have been associated with serious results in morbidity and mortality, and the loss of CAPD catheter[8-10]. No report concerning this entity has been presented in Korea. Therefore, we describe and discuss five cases of *S. maltophilia* infection associated with CAPD over a three-year period in three patients with peritonitis and two patients with exit-site infections.

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## MATERIALS AND METHODS

We performed a retrospective search for episodes of *S. maltophilia* infections related to CAPD in our renal unit. Medical records of five patients with *S. maltophilia* infection were reviewed and the clinical data relevant to CAPD peritonitis and exit-site infections were analyzed. *S. maltophilia* peritonitis was diagnosed when abdominal pain, fever, cloudy peritoneal effluent with more than a 100 leukocyte/$mm^3$ count and growth of *S. maltophilia* from culture of the dialysate were present, and diagnosis of the exit-site infection was made based on the presence of pericatheter erythema, exudate and growth of *S. maltophilia* from culture of the exudate. The baseline levels of hemoglobin, albumin, cholesterol, BUN and creatinine were compared with the age, sex and, if possible, the underlying disease-matched controls in our CAPD unit (2 controls for 1 case). The antibiotic regimens applied in the treatment of the *S. maltophilia* infection and antibiotic sensitivity of *S. maltophilia* were also reviewed and examined. In our CAPD unit, intraperitoneal cefazolin and tobramycin have been used as a standard first-line therapy against peritonitis, while the culture results are pending. Subsequent antibiotic modifications are considered based on the sensitivity results of the cultured bacteria and the clinical response. Removal of the CAPD catheter is considered in persistent peritonitis or exit-site infections without improvement of the clinical and laboratory findings, although adequate antibiotic therapy was delivered in full.

The data (the levels of hemoglobin and biochemical data of cases and controls) were expressed as mean±SEM. Statistical analysis of the data was performed with Mann-Whitney U test. A $p$ value of less than 0.05 was accepted as statistically significant.

## RESULTS

Five patients with *S. maltophilia* infection were identified during the period from January 2000 to August 2003. The type of the infection, demographic features, the underlying illness, antibiotic therapy and the outcome of the episodes are presented in Table 1. The three patients with peritonitis were all females and two patients with exit-site infections were both males. The mean age was 51 years (age range, 34 to 62 years). All the patients with peritonitis had diabetes mellitus as the underlying disease. The individual patients also had other significant comorbidities, such as panhypopituitarism, chronic obstructive pulmonary disease, cerebrovascular accident and myocardial infarction. The levels of their hemoglobin, serum albumin, cholesterol, BUN and creatinine were compared with controls receiving CAPD in our unit (Table 2). The hemoglobin level of these patients was significantly lower than in the controls ($p<0.05$). The mean values for serum albumin, creatinine and BUN were lower than those in the other CAPD patients, but the differences were not statistically significant.

These five patients had been receiving CAPD for 12 to 56 months (mean duration, 28 months) before the *S. maltophilia* infection was detected. In the patients with peritonitis, the mean incidence of previous peritonitis was 1.1 episode per year. In the patients with the exit-site infection, the incidence of the exit-site infection was 0.55 episode per year. Two patients in our study had received antibiotic therapy within two months prior to the *S. maltophilia* infection. Patient 3 had received intraperitoneal cefazolin, tobramycin and, thereafter, vancomycin due to peritonitis for 2 months. Patient 5 had received oral cefaclor and intravenous vancomycin due to the exit-site infection. Both preceding peritonitis and the exit-site infection were caused by *Staphylococcus epidermidis*.

Four of the five episodes occurred after July 2002. None of the patients with peritonitis had a concomitant exit-site or tunnel infection.

Only one patient (patient 3) required removal of the Tenckhoff catheter because the effluent did not clear up, and she had a subsequent fungal peritonitis. This patient initially had peritonitis due to S. *epidermidis*. Although adequate antibiotic therapy had been continued, the peritonitis failed to improve, and S. *maltophilia* had been repeatedly isolated in the dialysate. Patient 1 suffered from recurrent peritonitis due to S. maltophilia for six months. Eventually, she was treated with intraperitoneal ceftazidime, amikacin and intravenous piperacillin and showed nearly complete resolution without removal of the catheter. However, she was lost to follow up. Patient 2 with panhypopituitarism and diabetes mellitus had peritonitis and she was initially treated with intraperitoneal cefazolin and tobramycin. Thereafter, *S. maltophilia* was isolated in the dialysate, and the microorganism was not sensitive to both antibiotics. However, the peritonitis resolved completely without a recurrence. Patient 4 had peritonitis and the exit-site infection concurrently. *S. maltophilia* was isolated in the exit-site, but nothing was cultured from the dialysate. Both infections improved with a short course of antibiotic treatment. In patient 5, the exit-site infection was effectively treated with oral antibiotics, but there was one reoccurrence.

The antibiotic sensitivity of *S. maltophilia* in the individual patients is listed in Table 3. *S. maltophilia* was sensitive to cefepime, piperacillin/tazobactam as well as to trimethoprim/sulfamethoxazole, ticarcillin/clavulanate, ceftazidime and ciprofloxacin. Mostly *S. maltophilia* were resistant to cefazolin and tobramycin (standard first-line therapy for CAPD peritonitis in our unit). But, as it was mentioned previously, patients 1, 2 and 4

**Table 1. Demographic and clinical characteristics of CAPD patients with *Stenotrophomonas maltophilia* infection**

| Patient No. | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Sex | F | F | F | M | M |
| Age | 61 | 34 | 48 | 62 | 50 |
| Renal disease | Diabetic nephropathy | Diabetic nephropathy | Diabetic nephropathy | Renal tuberculosis | Unknown origin |
| Comorbidity | Myocardial infarction | Panhypopituitarism | - | CVA | COPD,CHF |
| Period of dialysis (months) | 32 | 24 | 15 | 12 | 56 |
| Type of infection | Peritonitis | Peritonitis | Peritonitis | Exit-site infection | Exit-site infection |
| No. of previous infection* | 3 | 1 | 2 | - | 5 |
| Time of the last infection* (months ago) | 20 | 18 | 1 | 7 | 23 |
| Antibiotic therapy | CZOL (IP)<br>+TOB (IP)<br>→CAZ (IP)<br>+AMK (IP)<br>→CAZ (IP)<br>+AMK (IP)<br>+PIPC (IV) | CZOL (IP)<br>+TOB (IP) | VAN (IP)<br>+CAZ (IP)<br>+CPFX (IP)<br>→SXT (IP)<br>+CTRX (IP)<br>+CPFX (IP)<br>→Amphotericin(IV) | CZOL (IV, IP)<br>+TOB (IP) | 1st :<br>CPFX (PO)<br>+CCLO (PO)<br>2nd :<br>CPFX (PO)<br>+AMXCCV (PO) |
| Infection* duration (weeks) | 23 | 3 | 5 | 2 | 1st : 2<br>2nd : 2 |
| Outcome | Continued PD, F/U loss | Continued PD | Fungal peritonitis, transferred HD | Continued PD | Continued PD |

CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CZOL, cefazolin; TOB, tobramycin; CAZ, ceftazidime; AMK, amikacin; PIPC, piperacillin; VAN, vancomycin; CPFX, ciprofloxacin; SMX, trimethoprim/sulfamethoxazole; CTRX, ceftriaxon; CCLO, cefaclor; AMXCCV, amoxicillin/clavulanate; IP, intraperitoneal administration; IV, intravenous administration; PO, oral administration; PD, peritoneal dialysis; HD, hemodialysis; 1st, 1st infection; 2nd, 2nd infection; F/U, follow-up.
*Infection designates peritonitis in patients 1, 2 and 3, and exit-site infection in patients 4 and 5.

**Table 2. Hemoglobin and other biochemical data in cases and controls**

| | Cases (n=5) | Controls (n=10) | *p*-value |
|---|---|---|---|
| Hemoglobin (g/dL) | 7.2±1.4 | 9.2±1.2 | 0.028 |
| Albumin (g/dL) | 2.62±0.68 | 3.06±0.46 | 0.206 |
| Cholesterol (mg/dL) | 191±23 | 176±38 | 0.371 |
| BUN (mg/dL) | 39.2±14.0 | 52.7±13.4 | 0.099 |
| Creatinine (mg/dL) | 8.4±3.4 | 10.4±2.4 | 0.165 |

responded partially or completely to these antibiotics (or maybe to tobramycin).

## DISCUSSION

Well-known predisposing conditions for *S. maltophilia* infection include malignant disease, neutropenia, immunosuppressive therapy, prior treatment with broad-spectrum antibiotics and indwelling vascular devices[6, 7, 12-14]. Factors predisposing to the *S. maltophilia* infection in peritoneal dialysis patients have not been defined and they can only be speculated upon. Our retrospective study demonstrates that all the patients with *S. maltophilia* peritonitis had diabetes mellitus as the underlying disease. Also four of the five patients had serious concurrent diseases, and their values of hemoglobin, serum albumin, creatinine and BUN were lower than in other CAPD patients. Uremia, anemia, malnutrition, diabetes mellitus and other co-morbidities are related to non-specific suppression of the immune function. This finding coincides with the previous studies in which *S. maltophilia* is an important pathogen in individuals with severe debilitation or immunosuppression[1]. The *S. maltophilia* infection often is noted in connection with prosthetic materials. The majority of the patients with *S. maltophilia* bacteremia had a central venous catheter[7] and *S. maltophilia* endocarditis has been noted as a complication of

**Table 3. Antibiotic sensitivity of Stenotrophomonas maltophilia isolated from five patients**

| Patient No. | 1 | 2 | 3 | 4 | 5 | |
|---|---|---|---|---|---|---|
| | | | | | 1st | 2nd |
| Amikacin | R | R | R | R | R | R |
| Ampicillin | S | R | R | S | R | I |
| Ampicillin/sulbactam | S | R | R | S | R | R |
| Aztreonam | S | R | R | ND | R | R |
| Cefazolin | R | R | R | R | R | ND |
| Cefepime | S | S | S | ND | S | S |
| Cefoxitin | I | R | R | ND | R | ND |
| Ceftazidime | ND | ND | ND | S | ND | S |
| Ceftriaxon | S | R | R | I | R | R |
| Ciprofloxacin | I | I | S | S | S | S |
| Gentamicin | R | R | R | R | R | I |
| Imipenem | R | R | R | R | R | R |
| Piperacillin/tazobactam | S | S | S | ND | S | S |
| Ticarcillin/clavulanate | ND | ND | ND | S | ND | S |
| Tobramycin | R | R | R | R | R | S |
| Trimethoprim/sulfamethoxazole | S | S | S | S | S | S |

ND, not done; R, resistant; S, sensitive; 1st, 1st infection; 2nd, 2nd infection.

prosthetic valve surgery[12, 15]. Conjunctivitis and corneal ulcers in contact lens wearers have been described in S. maltophilia cases[16, 17]. Skin and soft tissue infections have frequently been noted at tracheostomies, suprapubic and vascular catheter sites[12, 18]. Indwelling peritoneal catheters in CAPD patients may be another predisposing factor to *S. maltophilia* infection.

The resistance of *S. maltophilia* to multiple antibiotics made the choice of drugs very difficult. Most *S. maltophilia* strains are resistant to aminoglycosides, extended-spectrum penicillins, and third-generation cephalosporins[19, 20]. Nearly all strains are resistant to imipenem[20-22]. Most studies have found trimethoprim-sulfamethoxazole to be active against most strains of the bacterium, and this drug has long been regarded as an agent of choice for the therapy of *S. maltophilia* infection[23-25]. The combination of ticarcillin and clavulanic acid was as effective as trimethoprim-sulfamethoxazole in the murine model of *S. maltophilia* pneumonia[26]. Muder et al. suggested that a combination of trimethoprim-sulfamethoxazole and either ticarcillin-clavulanate or an extended-spectrum cephalosporin may be superior in effect to trimethoprim-sulfamethoxazole alone[7]. In addition to antimicrobial therapy in the management of *S. maltophilia* infection, several investigators have stressed the importance of removal of the infected vascular devices or prosthetic material[6, 12, 27-29]. In our series of peritonitis, a Tenckhoff catheter was removed in one patient due to a subsequent fungal peritonitis. A prolonged attempt of antibiotic treatment in those patients with peritonitis would simply make them prone to further opportunistic, particularly fungal, peritonitis, without saving the catheter. This is one of the causes of mortality[8, 30]. Another patient had a long course of the disease due to frequent recurrence. However, the state of the last patient can be regarded as a mild, easily treatable condition. In this patient, the peritonitis completely resolved with antibiotics to which *S. maltophilia* was resistant. The isolation of *S. maltophilia* from the clinical material is often associated with colonization rather than infection[11]. With these facts in mind, the probability of colonization can be considered in this case.

*S. maltophilia* has been increasingly recognized as a nosocomial pathogen in patients with deficient host defense. *S. maltophilia* is a therapeutic challenge because it is resistant to multiple antibiotics. Immune dysfunction due to uremia, anemia, malnutrition, other comorbidities (e.g. diabetes mellitus), and indwelling peritoneal catheters may be the factors predisposing to *S. maltophilia* infection in CAPD patients. Once the *S. maltophilia* infection is diagnosed, the patient should be treated based on the understanding of this particular organism. Our experience with *S. maltophilia* infection in CAPD patients is similar to the previously described hospital experience. The prognosis of peritonitis is generally poor and a prolonged attempt of antibiotic treatment would make them prone to further opportunistic infection without saving the catheter. *S. maltophilia*-related exit-site infections are benign and are easily treatable without the removal of the catheter.

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