Host Defenses and Infection
Peritonitis is one of the most serious complications of continuous ambulatory peritoneal dialysis (CAPD). Approximately 20% of peritonitis infections have been reported to be resistant to initial therapy, either failing to resolve with appropriate antibiotics or relapsing within 2 weeks of antibiotic discontinuation.

To investigate the current situation with regard to resistant peritonitis, we retrospectively examined the incidence and the organisms of resistant peritonitis in our unit over a period of 9 years. From January 1, 1994, to January 1, 2003, we introduced 325 patients onto CAPD. At January 1, 2003, we followed up 172 patients who were receiving CAPD in our unit.

During 1994–1996, 12 cases of peritonitis and 3 cases of resistant peritonitis (25%) occurred among our patients. Microbiologic examination revealed that the organisms involved in peritonitis were α-streptococcus (17%), coagulase-negative staphylococcus [CNS (17%)] and methicillin-sensitive Staphylococcus aureus [MSSA (17%)]. The organisms of resistant peritonitis were methicillin-resistant S. aureus [MRSA (67%)] and methicillin-resistant CNS (33%).

During 1997–1999, 39 cases of peritonitis and 13 cases of resistant peritonitis (33%) occurred among our patients. The most frequently cultured organisms in peritonitis were CNS (26%), Candida species (13%), and α-streptococcus (10%). The organisms of resistant peritonitis were methicillin-resistant CNS (46%) and Candida species (38%).

In the most recent 3-year period (2000–2002), our patients experienced 57 cases of peritonitis and 24 cases of resistant peritonitis (42%). The organisms of peritonitis were α-streptococcus (46%), CNS, MSSA, Escherichia coli, and Candida species (38%). However, the organisms of resistant peritonitis were methicillin-resistant CNS (13%), Candida species (21%), Pseudomonas aeruginosa (13%), Serratia (13%), Citrobacter (13%), and Corynebacterium (13%).

In the last several years, methicillin-resistant CNS has come to be main organism of resistant peritonitis. In addition, opportunistic infection has become a serious peritonitis problem. Given these data, we conclude that the incidence of resistant peritonitis is increasing and that the organisms of resistant peritonitis are changing.

Key words
Resistant peritonitis, micro-organisms, continuous ambulatory peritoneal dialysis, methicillin-resistant CNS

Introduction
The use of continuous ambulatory peritoneal dialysis (CAPD) to treat end-stage renal disease (ESRD) has become commonplace since 1976 (1). Peritonitis is one of the most important complications of CAPD. Early studies showed 1.7 episodes of peritonitis and 0.7 exit-site or tunnel infections per patient-year (2). Peritonitis remains the main complication of CAPD, but its incidence can be minimized with the provision of adequate facilities for performing CAPD (3). Approximately 20% of peritonitis infections are resistant to initial therapy (4), either failing to resolve with appropriate antibiotics (persistent peritonitis) or relapsing within 2 weeks of antibiotic discontinuation (relapsing peritonitis).

The probability of remaining peritonitis-free has been reported to be identical for elderly and younger CAPD patients (5). Thus, aging per se does not seem

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to be an important factor contributing to resistant peritonitis. An increasing number of patients on dialysis for ESRD are now over the age of 60—especially in Japan (6). The most important causes of ESRD in the elderly are diabetes mellitus and nephrosclerosis attributable to long-term arterial hypertension (7). Considering those factors, a possibility exists that the incidence and the organisms of peritonitis in Japan have changed in recent years.

To clarify the current situation with regard to peritonitis and resistant peritonitis, we retrospectively examined the incidence and the organisms of resistant peritonitis during the most recent 9 years in our hospital.

**Patients and methods**

From January 1, 1994, to January 1, 2003, we introduced 325 patients onto CAPD. In January 1, 2003, we followed up 172 patients who were receiving CAPD in our unit. The charts of the patients maintained on CAPD therapy in our unit (Saitama Medical School, Iruma-gun, Saitama, Japan) between January 1, 1994, and January 1, 2003, were retrospectively reviewed, and patients who developed peritonitis were identified. The patients had been examined and diagnosed for peritonitis by the physicians in our unit. We gathered data on microbial culture and sensitivity results and treatment outcomes for all peritonitis episodes. Cultures of peritoneal fluid were taken and studied using standard techniques (8).

**Criteria for diagnosis of peritonitis**

Peritonitis was diagnosed when a patient presented with cloudy dialysate, or abdominal pain, or fever, or a combination of those symptoms. A sample of the dialysate effluent was obtained for laboratory evaluation, including cell count with differential, Gram stain, and culture. A dialysate white blood cell count greater than 100 cells/mm³, of which at least 50% are polymorphonuclear neutrophils, supports a diagnosis of peritonitis and calls for immediate therapy (8).

We defined “resistant peritonitis” as either relapsing peritonitis or persistent peritonitis. We defined relapsing peritonitis as the reappearance of peritonitis within 2 weeks of discontinuation of antibiotic therapy for a previous episode of peritonitis, with the same organisms cultured on both occasions. Within 48 hours of initiating therapy, most patients with peritoneal dialysis (PD)–related peritonitis will show considerable clinical improvement. After 96 hours, if patients did not show definitive clinical improvement, we diagnosed persistent peritonitis and re-evaluated the patient’s clinical status.

**Results**

**Incidence and organisms of peritonitis, 1994–1996**

From January 1, 1994, to December 31, 1996, our patients experienced 12 cases of peritonitis and 3 cases of resistant peritonitis (25%). The incidence of peritonitis during that period was 0.022 episodes per patient–month.

Figure 1 shows our data regarding the changes in the organisms isolated from PD-related infections. Microbiologic examination revealed that the organisms of peritonitis were mainly α-streptococcus (17%), coagulase-negative streptococcus [CNS (17%)], and methicillin-sensitive Staphylococcus aureus [MSSA (17%)].

Figure 2 shows our data regarding the changes in the organisms isolated from PD effluent in cases of resistant peritonitis. The main organism of resistant peritonitis was methicillin-resistant S. aureus [MRSA (67%)].
Incidence and organisms of peritonitis, 1997–1999
During the next 3 years (January 1, 1997, to December 31, 1999), our patients experienced 39 cases of peritonitis and 13 cases of resistant peritonitis (33%). The incidence of peritonitis during the period was 0.027 episodes per patient–month.

The most frequently cultured organisms in peritonitis were CNS (26%), Candida species (13%), and α-streptococcus (10%). The main organisms of resistant peritonitis were methicillin-resistant CNS (46%) and Candida species (38%).

Incidence and organisms of peritonitis, 2000–2002
During the most recent 3 years (January 1, 2000, to December 31, 2002), our patients experienced 57 cases of peritonitis and 24 cases of resistant peritonitis (42%). The incidence of peritonitis during the period was 0.017 episodes per patient–month.

The most frequently cultured organisms in peritonitis were α-streptococcus (46%), CNS, MSSA, Escherichia coli, and Candida species (38%). However, the organisms of resistant peritonitis were methicillin-resistant CNS (13%), Candida species (21%), Pseudomonas aeruginosa (13%), Serratia (13%), Citrobacter (13%), and Corynebacterium (13%). In the last several years, opportunistic infection has become a serious problem in our peritonitis cases.

Discussion
End-stage renal failure may be treated by any of three regimens: renal transplantation, hemodialysis, and CAPD. The CAPD modality is convenient for patients, because they can maintain normal daily activity while dialysis proceeds (9).

From the beginning of CAPD, peritonitis is the main complication (2). Although the incidence of peritonitis in CAPD patients has declined with improvement in CAPD devices, peritonitis remains one of the most serious complications of the technique.

Peritonitis rates are usually reported in the literature as a collective statistic. In the present study, to clarify changes in the incidence and organisms of resistant peritonitis, we retrospectively examined the incidence and organisms of resistant peritonitis during the most recent 9 years in our unit. The incidence of peritonitis in the unit was about 0.02 episodes per patient–month during that time. Although we observed
no significant changes in the overall incidence of peritonitis during the 9 years, the rate of resistant peritonitis increased to 42% from 25% of peritonitis episodes.

In 1994–1996, the main organism of resistant peritonitis was MRSA. In 1997–1999, the main organisms were methicillin-resistant CNS and Candida species. However, during the most recent 3 years (2000–2002), the organisms of resistant peritonitis changed to methicillin-resistant CNS (13%), Candida species (21%), P. aeruginosa (13%), Serratia (13%), Citrobacter (13%), and Corynebacterium (13%). In addition to MRSA, methicillin-resistant CNS, and Pseudomonas, opportunistic infection attributable to multiple gram-negative bacteria became a serious cause of resistant peritonitis.

Resistant peritonitis represents either of two kinds of peritonitis: relapsing peritonitis or persistent peritonitis (8).

We defined relapsing peritonitis as the reappearance of peritonitis within 2 weeks after cessation of antibiotic therapy for a previous episode of peritonitis, with culture results showing the same organisms on both occasions. Relapsing peritonitis may be the result of several factors, including incomplete therapy, seeding of an external or internal cuff, or the presence of seeded fibrin plugs in the catheter (9,10). Incomplete therapy manifests itself in clinical recurrence within a short time after cessation of antibiotics (11). An intraperitoneal abscess may also cause recurrent symptoms within a day or two of cessation of therapy (12).

The two main routes of bacterial entry to the abdominal cavity in PD are contamination of the Tenckhoff catheter exit site and intraluminal touch contamination of the connecting tubing during dialysate bag changes. Both routes may result in bacterial biofilm colonization of the Tenckhoff catheter (13). Bacterial colonization in the form of biofilm creates reservoirs for acute infection, and those reservoirs may be protected from antibiotic penetration (14). Biofilm may also be implicated as a factor in the development of antibiotic resistance to certain antimicrobial agents, notably gentamicin (15).

In the present study, microbiologic examination revealed that the causes of resistant peritonitis in our unit were usually MRSA and methicillin-resistant CNS. That finding differs from previous reports in which the organisms were Pseudomonas (16), Enterococcus (17), and fungi (18), among others. However, methicillin-resistant staphylococcal (MRS) infections are of increasing concern in the hospital setting. Outpatient-acquired MRS infections are rarely reported. Patients hospitalized in tertiary-care university hospitals—that is, elderly, burn, immunodeficiency, and intensive-care patients—are at high risk for MRS infection (19). In addition, ESRD patients on PD are also at high risk. Staphylococcus is the leading cause of both catheter infections and peritonitis in such patients.

Klaus et al. (20) reported that the pathogens that most commonly cause relapsing peritonitis are gram-negative and gram-positive staphylococci and bacilli species. The staphylococci accounted for more than 50% of infections, and the bacilli species—which are usually rarely associated with peritonitis (21)—accounted for about 25% of relapsing peritonitis. Both germs caused a high incidence of recurrent peritonitis.

In the present study, the main organism of resistant peritonitis during 1994–1996 was MRSA. However, during the next 3 years and the final 3 years, the main organism of resistant peritonitis was methicillin-resistant CNS rather than MRSA.

In 1990, Holley et al. (4) reported that a low incidence of methicillin-resistant catheter infections, all due to MRSA, did not increase over the 5 years examined. In contrast, the percentage of peritonitis episodes attributable to methicillin-resistant CNS increased significantly to 28% (9/32) in 1987–1988 from 5% (3/57) in 1984–1986. That change occurred despite a stable percentage of CNS peritonitis episodes.

From the foregoing data, we conclude that a recent important organism of resistant peritonitis is methicillin-resistant CNS (in addition to MRSA). In such cases, vancomycin therapy is effective in treating the resistant peritonitis. However, the emergence of vancomycin resistance has recently been reported—specifically, vancomycin-resistant Enterococcus [VRE (22)]. Because vancomycin is not the first choice for treating peritonitis, we did not use it for our elderly patients with peritonitis. However, vancomycin should be used in cases of methicillin-resistant CNS and of MRSA peritonitis. When vancomycin must be used in elderly CAPD patients, the plasma concentration of the drug must be closely monitored to avoid side effects such as hearing loss.

During the last several years, the main organisms of resistant peritonitis have come to be gram-negative bacteria, including Serratia (23), Citrobacter (24),...
and Corynebacterium (25). Those organisms are usually antibiotic-sensitive. Still, many cases are resistant, and, unfortunately, catheters have to be removed because of lack of response to antibiotic therapy.

A review of the literature shows that gram-negative organisms have only rarely been reported as causing peritonitis in patients on CAPD. However some of the reports noted that peritonitis episodes associated with Serratia (26) and Corynebacterium (27) species were resistant peritonitis. The reasons why these gram-negative bacterial infections caused resistant peritonitis are unknown. One possibility is biofilm colonization (13–15). Another possibility is a problem with host defense.

In our unit, resistant peritonitis occurred more frequently in elderly diabetic patients on CAPD. The most prevalent causes of ESRD in elderly patients are diabetes mellitus and nephrosclerosis attributable to long-term arterial hypertension (7). Previously, Viglino et al. (28) demonstrated that elderly diabetic CAPD patients often suffer from serious infections. It is also generally agreed that diabetic patients—and especially elderly diabetic patients—can easily become malnourished (29). Nevertheless, some reports indicate that the incidence of peritonitis in diabetic patients is no higher than that of non diabetic patients on CAPD (30), and that response to therapy is good. The mechanism of host defense in patients on CAPD is complicated, and the mechanism of resistant peritonitis remains unclear. Further experiments are needed to clarify these points.

Conclusion
Our data lead us to conclude that the incidence of resistant peritonitis is increasing and that the organisms responsible have been changing over the last 9 years.

References
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Successful Treatment of *Candida* Infections in Peritoneal Dialysis Patients: Case Reports and Review of the Literature

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Infections with *Candida* species have been associated with significant morbidity and mortality in peritoneal dialysis (PD) patients. Such infections include peritonitis and exit-site infections attributable to *Candida* species, disseminated candidiasis in immunocompromised patients, and Candida esophagitis. In peritonitis and exit-site infections, both success and failure have been reported with commercially available medications. In disseminated candidiasis and Candida esophagitis, successful treatment and patient recovery depend on the overall nutritional and immune state of the patient.

One case each of peritonitis and exit-site infection with non-*Candida albicans* species were successfully treated with oral voriconazole. No literature currently exists on the use of this new product in dialysis patients. Presented here is a treatment strategy that resulted in maintenance of PD in the home setting and catheter survival following completion of treatment. A review of the English-language literature shows mixed outcomes associated with continuation of PD during treatment for *Candida* infection in PD patients.

In conclusion, a commercially available product can be used to successfully treat PD patients who have *Candida* infections and to maintain the PD catheter for PD.

**Key words**

Fungal peritonitis, voriconazole, exit-site infection, *Candida*

**Introduction**

Peritoneal dialysis (PD) is the method of renal replacement therapy for more than 24,000 patients in the United States with end-stage renal disease (1). Infectious complications of PD are the leading cause of morbidity and mortality, resulting in catheter loss, conversion to hemodialysis, and death in many patients. Effective antimicrobial agents exist for treating most cases of bacterial peritonitis and exit-site infection (ESI). However, most antifungal agents used to treat fungal peritonitis and ESIs are not effective for curative treatment without removal of the PD catheter. In the past 2 years, newer antifungal agents have been introduced that can be used to treat fungal infections; however, few data supporting their use in dialysis patients are available.

**Case reports**

**Case 1**

A 57-year-old woman with diabetic nephropathy developed an ESI despite using a consistent technique for exit-site care. Her initial treatment of the ESI included use of liquid antibacterial soap, copious irrigation with water, and topical triple antibiotic cream with three daily dressing changes. Despite that regimen, the ESI did not improve.

A culture obtained after 7 days of the aforementioned exit-site care showed *Candida* species. The patient had received 7 days of oral fluconazole when sensitivity testing indicated that the *Candida* species was resistant to fluconazole. At that time, therapy with voriconazole was initiated and was continued for 28 days. Voriconazole competes for the same metabolic substrate as simvastatin, and consequently the patient’s dose of simvastatin was reduced by half during therapy with voriconazole.

The exit-site improved markedly over the next 14 days, and clinically the infection appeared to have resolved. Following completion of the antifungal...
therapy, a repeat culture was negative. Liver enzymes were monitored and did not increase throughout the 28 days of therapy. The patient experienced no adverse outcomes during therapy.

Case 2
A 65-year-old woman with diabetic nephropathy, hypertension, coronary artery disease, severe osteoarthritis, secondary hyperparathyroidism, and anemia developed fungal peritonitis following an episode of bacterial peritonitis. Following 10 days of intraperitoneal cefazolin for *Staphylococcus epidermidis* peritonitis, a repeat culture yielded *Candida* species, subsequently identified as *C. parapsilosis*. Therapy with voriconazole was initiated, and liver enzymes were monitored until the subsequent completion of treatment. The patient’s dose of simvastatin was also reduced by half during therapy with voriconazole. Dialysate leukocytosis resolved during the treatment period, and the patient’s symptoms resolved as well.

Discussion
*Candida* species are the causative agent in most cases of fungal peritonitis in the adult and pediatric PD populations. In most reports, risk factors for fungal peritonitis include prior antibiotic use, prior peritonitis, and diabetes mellitus (2,3,4; Table I).

Treatment options for fungal peritonitis include several antifungal agents, most commonly amphotericin B, ketoconazole, flucytosine, and fluconazole. A new agent, voriconazole, is a triazole antifungal agent available in oral and intravenous formulations. The oral formulation can be administered to patients with renal impairment without dosage adjustment. However, the intravenous formulation contains sulfobutylether-β-cyclodextrin sodium as a vehicle. That compound accumulates in patients with renal impairment. Voriconazole is metabolized by multiple hepatic cytochrome P450 enzymes (CYP2C19, CYP2C9, and CYP3A4). Drugs co-administered with voriconazole may require adjustment because of competition with the enzyme substrate.

A review of the nephrology literature on fungal peritonitis with *Candida* species identified amphotericin B, flucytosine, and fluconazole as the agents most often used in the treatment of such infections (2–12; Table I). Treatment strategies included treatment with these antifungal agents alone or sequentially, and removal or salvage of the PD catheter (2–13). In the Table I series, which resulted in maintenance of PD with salvage of the PD catheter, fluconazole was the primary agent used in most treatment regimens for fungal peritonitis in most of the studies reviewed (2,4,6,7,9,11). Despite early recognition and treatment, morbidity associated with fungal peritonitis included catheter loss, conversion to hemodialysis, peritoneal adhesions, fungal septicemia, and death (2,4–6,9,10,12,13). Many patients were unable to resume PD and required conversion to hemodialysis (2,4–6,9–13).

Strategies to reduce the risk of fungal peritonitis include minimizing the use of broad-spectrum antibiotics for prolonged periods, maintaining glycemic control, and minimizing humidity in the environment. Recommendations for the management of fungal peritonitis include catheter removal, administration of antifungal agents, interruption of PD with temporary hemodialysis, and resumption of PD on an individual basis (14). Often, interruption of PD requires placement of a venous access, initiation of hemodialysis, and treatment with antifungal agents during the interval (9). In some patients, the conversion to hemodialysis may become permanent because of patient preference (5,9). However, in most cases of fungal peritonitis whose treatment requires interruption and hemodialysis, the rate of return to PD is high (5,15).

Conclusion
As newer pharmaceutical agents are developed, those new agents may have applications in PD patients. Oral voriconazole may be considered in the treatment of fungal peritonitis caused by *Candida* species without dosage adjustment. However, other medications that are concomitantly administered and that are metabolized via cytochrome P450 may require adjustment, monitoring, or discontinuation. Despite such adjustments, the present report demonstrates that patients with *Candida* peritonitis can be successfully treated on an ambulatory basis and can maintain PD. In an effort to determine the definitive agent for treating fungal peritonitis caused by *Candida* species, a randomized controlled trial should be considered.

References
**TABLE I  Candida peritonitis in the nephrology literature**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Journal</th>
<th>Organism</th>
<th>Antifungal therapy</th>
<th>Outcome</th>
<th>Cases (n)</th>
<th>Catheter salvage with treatment</th>
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<tr>
<td>Kleinpeter, 2004</td>
<td>Current article</td>
<td>Candida species</td>
<td>Voriconazole</td>
<td>Cure</td>
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<td>Bibashi et al., 2002 (2)</td>
<td>Perit Dial Int</td>
<td>Candida species, and others</td>
<td>FCZ, AmB</td>
<td>Variable</td>
<td>47</td>
<td>Variable</td>
</tr>
<tr>
<td>Kleinpeter and Butt, 2001 (3)</td>
<td>Adv Perit Dial</td>
<td>Non C. albicans</td>
<td>FCZ, AmB</td>
<td>Catheter loss, resumed PD</td>
<td>4</td>
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</tr>
<tr>
<td>Wang et al., 2000 (4)</td>
<td>Am J Kidney Dis</td>
<td>Candida (70%)</td>
<td>FCZ, FCZ + 5FU, AmB + catheter removal</td>
<td>37% PD, 44% death</td>
<td>70</td>
<td>26</td>
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<td>Warady et al., 2000 (5)</td>
<td>Kidney Int</td>
<td>33/42 Candida</td>
<td>FCZ, FCZ + 5FU</td>
<td>27 PD, 12 HD, 3 deaths</td>
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<td>Wong et al., 2000 (6)</td>
<td>Perit Dial Int</td>
<td>C. parapsilosis</td>
<td>AmB, FCZ, sequential removal</td>
<td>5 Complications, death, adhesions</td>
<td>7</td>
<td>2</td>
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<td>Kameoka et al., 1999 (7)</td>
<td>Perit Dial Int</td>
<td>Candida species</td>
<td>FCZ</td>
<td>Cure</td>
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<td>2</td>
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<td>Montane et al., 1998 (8)</td>
<td>Adv Perit Dial</td>
<td>Candida species</td>
<td>FCZ, AmB</td>
<td>18 HD or death, 37 catheter replacement</td>
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<td>Goldie et al., 1996 (9)</td>
<td>Am J Kidney Dis</td>
<td>Candida (74.5%)</td>
<td>FCZ, 5FU, AmB</td>
<td>4 HD, 2 deaths</td>
<td>6</td>
<td>0</td>
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<td>Amichi et al., 1994 (10)</td>
<td>Adv Perit Dial</td>
<td>5 Candida, other</td>
<td>AmB, 5FU, FCZ</td>
<td>21</td>
<td>13</td>
<td></td>
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<td>Chan et al., 1994 (11)</td>
<td>Nephrol Dial Transplant</td>
<td>Candida (85.7%)</td>
<td>FCZ +</td>
<td>catheter replacement (67%)</td>
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<td>Michel et al., 1994 (12)</td>
<td>Am J Nephrol</td>
<td>Candida (75%)</td>
<td>FCZ, 5FU</td>
<td>1 Death, 5 catheter removals</td>
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<td>Hoch et al., 1993 (13)</td>
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<td>Candida species</td>
<td>FCZ</td>
<td>Catheter removal</td>
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</tbody>
</table>

FCZ = fluconazole; AmB = amphotericin B; PD = peritoneal dialysis; 5FU = 5-fluorouracil; HD = hemodialysis.


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In the present study, we prospectively investigated the effects of once- or thrice-weekly prophylactic application of mupirocin to catheter exit sites on *Staphylococcus aureus* carriage, methicillin and mupirocin resistance, and catheter-related infections in continuous ambulatory peritoneal dialysis (CAPD) patients.

We enrolled 36 CAPD patients (men/women: 21/15; mean age: 55.1 ± 1.4 years) in the study. At the start of the study, patients had been on once-weekly mupirocin treatment for 3.1 ± 2.0 years. They were then randomly assigned to use mupirocin either once weekly (group I; n = 18; men/women: 10/8; age: 55.3 ± 1.8 years) or thrice weekly (group II; n = 18; men/women: 11/7; age: 55.0 ± 2.3 years). During the study period, swabs were taken monthly from nares, axillae, the inguinal area, and the catheter exit site. We evaluated a total of 806 samples in the first 6 months of the study. The two study groups were similar in terms of age and sex. In group I, 5 isolations of *S. aureus* in 3 patients came from initial *S. aureus* carriers. During the first 6 months of the study, only 2 new *S. aureus* carriers were detected in group I, for a total of 7 isolations. Mupirocin resistance (MuR) was present in only 1 isolate and methicillin resistance (MeR) was not observed. In group II, no *S. aureus* carriers were present at the initial evaluation, and we encountered only 1 new *S. aureus* carrier during the first 6 months of the study. During the same period, MuR and MeR were absent in group II. During the 6 months, we observed 1 exit-site infection and 1 peritonitis episode attributable to coagulase-negative staphylococcus (CNS) in group I. In group II, we observed 1 exit-site infection attributable to CNS.

During the first 6 months of the study, once- or thrice-weekly application of mupirocin to the catheter exit site has not led to any significant change in *S. aureus* carriage, MeR and MuR, or catheter-related infection in our CAPD patients.

**Key words**
Mupirocin, peritonitis, exit-site infection, mupirocin resistance

**Introduction**

In the more than 20 years since peritoneal dialysis (PD) was introduced as a treatment for end-stage renal failure, significant progress has been made in reducing the incidence of the most feared complication of the process: peritonitis (1). Most PD units now achieve a peritonitis rate of 1 episode per 24 patient–months or less. Exit-site management has contributed to that reduction (2).

Approximately one fifth of peritonitis episodes are temporally associated with exit-site or tunnel infection. Exit-site infections are predominantly attributable to *Staphylococcus aureus* or gram-negative organisms; *S. epidermidis* [coagulase-negative staphylococcus (CNS)] is the causative organism in fewer than 20% of patients (3). Infections by *S. aureus* appear to have a distinct pathogenesis, being associated with nasal or skin carriage of the organism (or both).
Eradication of the carrier state is therefore helpful in achieving effective control of exit-site and pericatheter colonization. The major risk factor for exit-site infection is staphylococcal nasal carriage. To eradicate nasal carriage, treatment protocols use drugs such as rifampin, mupirocin, and trimethoprim/sulfamethoxazole (4).

Mupirocin is a novel antibiotic that acts by blocking the activity of isoleucyl-transfer RNA synthetase. Mupirocin is available as an ointment and a cream. It appears to be safe, effective, and well tolerated (5). In some trials, mupirocin ointment applied to the exit site reduced the rate of both exit-site infection and peritonitis as compared with normal exit-site care in a control group (6). However, widespread long-term use of any antibiotic carries the risk of resistance emerging. Recently, the emergence of mupirocin-resistant \textit{S. aureus} (MuRSA) has been reported in chronic PD patients who use mupirocin prophylaxis to prevent exit-site infection (7).

Some current trials suggest that mupirocin must be applied to the catheter exit site 3 – 5 times weekly. However, few data compare the incidence rates of exit-site infection and peritonitis among patients applying mupirocin to the exit site once weekly and 3 – 5 times weekly (8).

In the present study, we prospectively investigated the effects of once- or thrice-weekly prophylactic application of mupirocin to the catheter exit site on carriage of \textit{Staphylococcus} species, on methicillin resistance (MeR) and mupirocin resistance (MuR) in staphylococci, and on the overall rate of catheter-related infection in chronic PD patients.

### Patients and methods

For this prospective study, we enrolled 36 end-stage renal disease patients who were undergoing continuous ambulatory peritoneal dialysis (CAPD) in an outpatient PD clinic. Prior to the study, these patients (15 women, 21 men; mean age: 55.1 ± 1.4 years) had been applying mupirocin prophylactically to the exit site once weekly for 3.1 ± 2.0 years.

The patients were randomly assigned to one of two groups. In group I (8 women, 10 men; mean age: 55.3 ± 1.8 years), patients continued to apply mupirocin (Bactroban: GlaxoSmithKline, Istanbul, Turkey) to the exit site once weekly. In group II (7 women, 11 men; mean age: 55.0 ± 2.3 years), patients applied mupirocin to the exit site 3 times weekly.

### Results

Both study groups were similar in terms of age and sex ($p > 0.05$). During the first 6 months of the study period, 806 swabs were taken from the patients. Tables I and II summarize the number of isolations and the causative organisms, the MuR and MeR, and the exit-site infections and peritonitis within the groups.

In group I, \textit{S. aureus} was isolated on 7 occasions, and MuR was present in only 1 of those instances. Of the 7 isolations, 5 came from 3 patients who were \textit{S. aureus} carriers before the study started. We therefore observed the emergence of 2 new \textit{S. aureus} carriers during the period. We observed no MeR in \textit{S. aureus} isolates.
Group II contained no *S. aureus* carriers before the start of the study. We observed only 1 *S. aureus* carrier in whom the bacteria were sensitive to both mupirocin and methicillin. Statistical comparisons for *S. aureus* were not performed because of the low number of isolates.

During the first 6 months of the study period, CNS was isolated in 225 of 229 cultures in group I. Among all 337 cultures, 190 (56.4%) showed MuR and 117 (34.7%) showed MeR.

In group II, 229 CNS isolations were found in 325 cultures. Among all 325 cultures, 197 (60.6%) showed MuR, and 98 (30.2%) showed MeR.

During the 6-month period, we observed 1 exit-site infection and 1 episode of peritonitis attributable to CNS in group I. In group II, we observed 1 exit-site infection attributable to CNS.

### Discussion

Peritoneal dialysis is an important and life-saving form of renal replacement therapy. But despite major advances in PD technology, catheter-related complications such as exit-site infection and peritonitis remain the major cause of morbidity and technique failure in chronic PD patients (2). Several reports have noted that gram-positive bacteria such as *S. aureus* and CNS are the major cause of exit-site infection and peritonitis (3). Prevention rather than treatment of exit-site infection has been the focus of the effort to reduce peritonitis, catheter loss, and transfer to hemodialysis.

Mupirocin is a topical bactericidal agent against *S. aureus* and CNS. In some trials, mupirocin ointment applied to the exit site reduced the rates of exit-site infection and peritonitis as compared with rates in control groups (6).
Bernardini et al. (11) published a randomized controlled trial that compared empiric cyclical oral rifampin with daily mupirocin ointment applied to the catheter exit site. Those authors observed no difference between the mupirocin and rifampin groups, but both treatments significantly reduced exit-site infection (by 55%) and peritonitis (by 33%).

Casey et al. (12) reported that daily application of mupirocin ointment at the catheter exit site reduced the rate of exit-site infection and peritonitis in PD patients. That study did not investigate MuR, but the authors observed a 49% reduction in the rate of exit-site infection and a 31% reduction in the rate of peritonitis.

Thodis et al. (8) reported that application of mupirocin ointment to the catheter exit site reduced *S. aureus* exit-site infections by 91% and peritonitis by 69% as compared with a control group that carried out normal exit-site care. The authors observed no differences in the incidence rates of exit-site infection and peritonitis among patients applying mupirocin ointment at the exit site daily and those applying the ointment 3 times weekly. In the follow-up period to that study, Vas et al. (13) reported no mupirocin-resistant isolates at the catheter exit-site.

Evidence is increasing that high-level MuR is developing during topical use of mupirocin as prophylaxis against CNS and *S. aureus*. Nevertheless, the appearance of resistance does not preclude a beneficial effect of regular prophylaxis.

Annigeri et al. (14) reported the emergence of high-level MuRSA in chronic PD patients after 4 years of continuous use of mupirocin in a small number of patients in their PD unit. High-level MuRSA were isolated from 3% of the total study population and from 15% of all *S. aureus* isolates. In that study, mupirocin users were classified as “intermittent users” if they applied mupirocin to the exit site 1–4 times per week, and as “continuous users” if they applied mupirocin 5–7 times per week. All MuRSA were isolated from patients who used mupirocin intermittently.

Conclusions
During the first 6 months of the present study, we observed that once- or thrice-weekly application of mupirocin to the catheter exit site led to no change in *S. aureus* carriage, in MeR and MuR *S. aureus* colonization rates, and in catheter-related infections in CAPD patients.

Normal skin flora consist of a relatively few species of organisms, with gram-positive bacteria such as CNS predominating. Several reports have noted that *S. epidermidis* and *S. aureus* are major causes of exit-site infection and peritonitis (15). Prolonged, widespread use of antibiotics is associated with the development of resistance. The data about the emergence of MeR and MuR CNS in chronic PD patients using mupirocin prophylaxis to prevent exit-site infection and peritonitis are currently insufficient. In our study, we observed similar MuR and MeR rates for CNS. In group I, the MuR and MeR rates for CNS were 56.4% and 34.7% respectively. In group II, the rates were 60.6% and 30.2%. During later follow-up in our study, we will also evaluate exit-site infections and peritonitis attributable to MeR and MuR CNS in both groups.

Long-term studies are needed to further investigate infectious complications attributable to MeR and MuR CNS in PD units. Follow-up in our study will have significant implications for the future use of mupirocin prophylaxis against *S. aureus* and CNS in chronic PD patients. It may also be helpful in establishing the most effective dose and schedule.

References

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