Randomized, Double-Blind Trial of Antibiotic Exit Site Cream for Prevention of Exit Site Infection in Peritoneal Dialysis Patients

Judith Bernardini,* Filitsa Bender,† Tracey Florio,* James Sloand,‡ Linda PalmMontalbano,‡ Linda Fried,*§ and Beth Piraino*

*Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; †Department of Medicine, West Virginia University, Morgantown, West Virginia; ‡Department of Medicine, University of Rochester Medical Center, Rochester, NY; §Veterans Administration Hospital of Pittsburgh, Pittsburgh, Pennsylvania

Infection is the Achilles heel of peritoneal dialysis. Exit site mupirocin prevents Staphylococcus aureus peritoneal dialysis (PD) infections but does not reduce Pseudomonas aeruginosa or other Gram-negative infections, which are associated with considerable morbidity and sometimes death. Patients from three centers (53% incident to PD and 47% prevalent) were randomized in a double-blinded manner to daily mupirocin or gentamicin cream to the catheter exit site. Infections were tracked prospectively by organism and expressed as episodes per dialysis-year at risk. A total of 133 patients were randomized, 67 to gentamicin and 66 to mupirocin cream. Catheter infection rates were 0.23/yr with gentamicin cream versus 0.54/yr with mupirocin (P = 0.005). Time to first catheter infection was longer using gentamicin (P = 0.03). There were no P. aeruginosa catheter infections using gentamicin compared with 0.11/yr using mupirocin (P < 0.003). S. aureus exit site infections were infrequent in both groups (0.06 and 0.08/yr; P = 0.44). Peritonitis rates were 0.34/yr versus 0.52/yr (P = 0.03), with a striking decrease in Gram-negative peritonitis (0.02/yr versus 0.15/yr; P = 0.003) using gentamicin compared with mupirocin cream, respectively. Gentamicin use was a significant predictor of lower peritonitis rates (relative risk, 0.52; 95% confidence interval, 0.29 to 0.93; P < 0.03), controlling for center and incident versus prevalent patients. Gentamicin cream applied daily to the peritoneal catheter exit site reduced P. aeruginosa and other Gram-negative catheter infections and reduced peritonitis by 35%, particularly Gram-negative organisms. Gentamicin cream was as effective as mupirocin in preventing S. aureus infections. Daily gentamicin cream at the exit site should be the prophylaxis of choice for PD patients.


I nfection is the most common complication of peritoneal dialysis (PD) (1). Touch contamination, frequently leading to coagulase-negative Staphylococcus peritonitis, has decreased through improvements in PD connection technology (2,3). In contrast, the pathway to peritonitis caused by S. aureus and P. aeruginosa is often via infection of the peritoneal catheter exit site (4–8). Infections caused by S. aureus and P. aeruginosa are severe in PD patients, often requiring hospitalization and catheter removal to resolve (7–18). Therefore, prevention of S. aureus and P. aeruginosa exit site infections is important to decrease peritonitis from these organisms.

Mupirocin applied to the exit site effectively reduces S. aureus exit site infections and peritonitis (19–21). However, exit site mupirocin has not reduced Gram-negative infections, including P. aeruginosa (22,23). These are expected results as mupirocin is effective against Staphylococcus and Streptococcus, as well as Haemophilus, Neisseria, and Pasteurella but not Pseudomonas or Escherichia coli (24). Furthermore, mupirocin-resistant S. aureus has been reported in PD patients, suggesting that, eventually, this drug will not be efficacious (25,26). Exit site prophylaxis that would decrease both S. aureus and P. aeruginosa infectious complications therefore would be desirable.

Gentamicin is active against S. aureus and P. aeruginosa by inhibiting normal bacterial protein synthesis. We hypothesized that gentamicin cream applied to the exit site might reduce the risk for both S. aureus and P. aeruginosa exit site infections, the two most serious PD-associated infections. This is a double-blinded, multicenter trial to compare the effectiveness of daily application of gentamicin cream with mupirocin cream to prevent PD catheter infections.

Materials and Methods

Three centers participated: Dialysis Clinic, Inc., of Oakland Pittsburgh; University of Rochester Medical Center, Rochester, NY; and Fresenius Medical Care of Morgantown, WV. Data were managed centrally at the coordinating center at the University of Pittsburgh. Each site obtained study approval from their respective University Institutional Review Boards and from the Institutional Review Board of Dialysis Clinic, Inc., and Fresenius Medical Care. Written informed consent was obtained from each patient. All investigators adhered to the Declaration of Helsinki.
Enrollment was conducted by investigators at each center during routine clinic visits. Patients who were ≥18 yr of age, on PD, able to give informed consent, and already enrolled in a registry permitting data collection were eligible. Excluded were those with an allergy to either study cream (n = 2), those in another intervention study (n = 6), and those with catheter infections or peritonitis in the past 30 d (n = 6). Recruitment began July 2001 and continued until August 2003, with follow-up to December 1, 2003. Five patients gave consent but withdrew from PD before beginning study cream. Four eligible patients were never approached because of schedule conflicts.

Randomization lists were computer generated using a random-number generator. The sequence of allocation was known only by the investigators at the coordinating center. Investigators and patients were blinded to the cream used. Random assignment to mupirocin or gentamicin cream was central by telephone to the University of Pittsburgh and stratified by center and by S. aureus nasal carriage status, defined as a positive result of one nasal culture. The creams (gentamicin sulfate 0.1% and mupirocin 2%) were dispensed by the Investigational Drug Service at the University of Pittsburgh and hand delivered by University of Pittsburgh investigators to each dialysis program. The creams both are white, look exactly alike, and were dispensed in identical containers labeled Cream A or Cream B. The appropriate drugs were dispensed to each patient by the center’s investigators.

Drug refills were given at routine clinic visits, and compliance was determined from refill frequency. Each 15-g tube contained 150 doses if a daily application of 10 mg were used. Therefore, a 15-g tube provided approximately 5 mo of daily prophylaxis.

Routine exit site care by the patient consisted of daily washing with antibacterial soap, thorough drying, and application of a small amount of cream (approximately 10 mg, a ¼-inch dab) around the catheter exit site using a cotton swab. Catheters were anchored with tape and a small gauze dressing to prevent exit site trauma. The exit site was examined by the physician and the nurse at each clinic visit, both of whom were blinded to the cream assigned to the patient.

Catheter infection (exit site and/or tunnel) was defined as erythema, edema, tenderness, or drainage from the exit site. Only one was required to be present for the diagnosis. Cultures were obtained for drainage, but a positive growth was not required. Peritonitis was defined as cloudy effluent with ≥100/μl white cells with ≥50% of these polymorphonuclear cells. Effluent cultures were obtained using blood culture bottles. Treatment for infections was at the discretion of the nephrologists. Infection rates were calculated as the number of infections divided by the total time at risk and expressed as episodes per patient-year at risk. Catheters were removed for refractory exit site infections, refractory peritonitis, and recurrent peritonitis (defined as repetitive episodes with the same organism).

Patients were classified as incident when they entered the study within 3 mo of initiating PD. All others were considered prevalent. However, all patients used the standard protocol of daily exit site mupirocin before the study, except one on rifampin 300 mg twice daily for 5 d every 3 mo prestudy.

Sample size requirements were estimated before study initiation with the primary end point being P. aeruginosa exit site infection. The predicted incidence of P. aeruginosa exit site infections in the mupirocin group was based on data from the University of Pittsburgh Peritoneal Dialysis Registry from 1982 to 2001 (0.11 per dialysis-year) (23). Hypothesizing a 50% reduction with gentamicin cream, power calculations estimated that 140 patient-years of follow-up would be needed to demonstrate a difference. Interim analyses were reviewed every 3 mo by the safety coordinator. The study was stopped by the safety monitor at 118 patient-years when a difference in peritonitis rates in the groups was found.

The primary study outcome was P. aeruginosa and S. aureus catheter infection rates in the groups, with the hypothesis that gentamicin cream would be equally effective in preventing S. aureus exit site infections and more effective in preventing P. aeruginosa exit site infections. Secondary outcomes were Gram-negative and Gram-positive peritonitis.

Results

A total of 187 patients were assessed for eligibility for the study at the three centers (Figure 1). A total of 133 were randomly allocated to either mupirocin (n = 66) or gentamicin cream (n = 67). There was no difference in groups by age, gender, race, insulin dependence, S. aureus nasal carriage, or previous time on dialysis (Table 1). Median follow-up was 8 mo per patient (range, 0.13 to 28.2 mo).

Data are expressed as means with SD or medians with range, as appropriate for the distribution. Fisher exact test compared group proportions. Continuous variables were compared by the t test. Time to infection was analyzed using Kaplan-Meier survival analysis and log-rank test. Cox regression evaluated the effect of study drug allocation, age, race, gender, insulin dependence, dialysis center, and incident versus prevalent status. Rates were compared by Poisson analysis. The Poisson regression model tested the effect of independent variables on infection rates using univariate analysis. Variables with P < 0.15 on univariate analysis then were included in the multivariate analysis. Peritonitis has been shown to have a Poisson distribution in PD patients (27). Because peritonitis rates varied by center and incident versus prevalent patients, these variables were controlled for using Poisson regression.

Figure 1. Allocation of patients assessed for study eligibility.
There were fewer Gram-positive and Gram-negative catheter infections using gentamicin cream, resulting in a significantly lower catheter infection rate (0.23 versus 0.54 per patient-year; \( P = 0.003 \); Table 2). There were no \textit{P. aeruginosa} catheter infections with gentamicin. \textit{S. aureus} catheter infection rates were the same in both groups. Fungal catheter infections occurred in three patients who were using gentamicin cream at 2, 8, and 24 mo after starting the study. All were treated successfully with one course of oral fluconazole with resolution and no recurrence, despite remaining on gentamicin exit site cream for an additional 3, 6, and 19 mo, respectively. None developed fungal peritonitis.

Time to first catheter infection was longer using gentamicin cream compared with mupirocin (\( P = 0.03 \); Figure 2). Cox regression analysis of time to first catheter infection controlling for age, gender, race, insulin dependence, and center found only use of exit site gentamicin (\textit{versus} mupirocin) to have an independent reduced risk for infection (relative risk [RR], 0.43; 95% confidence interval [CI], 0.19 to 1.0; \( P = 0.05 \)). Both incident and prevalent patients had lower catheter infection rates with gentamicin compared with mupirocin cream (Figure 3). With multivariate analysis, only gentamicin exit site use was a significant predictor for lower catheter infection rate controlling for center and incident/prevalent status (RR, 0.41; 95% CI, 0.22 to 0.78; \( P < 0.007 \)). Gentamicin exit site use was a significant predictor of both lower Gram-negative catheter in-

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\caption{Patient characteristics}
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                    & Mupirocin Cream & Gentamicin Cream & \textit{P} Value \\
\hline
No. of patients    & 66               & 67               & 0.31          \\
Age (yr)           & 51 $\pm$ 15      & 54 $\pm$ 15      & 0.43          \\
Male (\( n \))     & 38 (58\%)        & 34 (51\%)        & 0.37          \\
White (\( n \))    & 58 (88\%)        & 62 (93\%)        & 0.37          \\
Insulin dependent (\( n \)) & 27 (41\%) & 27 (40\%) & 0.94          \\
\textit{Staphylococcus aureus} carriers (\( n \)) & 9 (14\%) & 9 (13\%) & 0.97          \\
Incident to peritoneal dialysis (\( n \)) & 39 (59\%) & 31 (46\%) & 0.14          \\
Study time, dialysis-years & 53.8          & 64.3          &            \\
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\caption{Infections\textsuperscript{a}}
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\hline
                     & Mupirocin Cream & Gentamicin Cream & \textit{P} Value \\
\hline
\textit{Exit site organism} &                     &                   &            \\
Gram-positive        &                     &                   &            \\
\textit{Staphylococcus aureus} & 17                 & 9                 & 0.005       \\
other Gram-positive   & 14                 & 4                 & 0.0001      \\
Gram-negative         & 9                  & 1                 & 0.001       \\
\textit{Pseudomonas aeruginosa} & 6                  & 0                 & 0.0025      \\
other Gram-negative   & 3                  & 1                 & 0.02        \\
yeast                & 0                  & —                 & 0.05        \\
sterile/no culture   & 3                  & 2                 & 0.42        \\
total                & 29                 & 15                & 0.003       \\
\textit{Peritonitis organism} &                   &                   &            \\
Gram-positive        &                     &                   &            \\
\textit{Staphylococcus aureus} & 14                 & 15                & 0.36        \\
other Gram-positive   & 15                 & 13                & 0.14        \\
Gram-negative         & 8                  & 1                 & 0.18        \\
\textit{Pseudomonas aeruginosa}\textsuperscript{b} & 2                  & 0                 & 0.03        \\
other Gram-negative   & 6                  & 1                 & 0.02        \\
yeast                & 2                  & 2                 & 0.68        \\
sterile              & 3                  & 4                 & 0.71        \\
total                & 28                 & 22                & 0.03        \\
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\textsuperscript{a}Rates are expressed as episodes per patient-year.
\textsuperscript{b}Both sensitive to gentamicin.
In a multicenter, double-blind, randomized trial, a simple regimen of daily exit site gentamicin cream resulted in a 57% reduction in peritoneal catheter exit site infections and a 35% reduction in peritonitis episodes, compared with exit site mupirocin. Gentamicin cream was highly effective in preventing not only *P. aeruginosa* but also other catheter infections and Gram-negative peritonitis. There are no previous studies of the use of gentamicin cream at the exit site as prophylaxis in PD patients. On the basis of the bactericidal properties of gentamicin, we hypothesized that it would be as effective as mupirocin in preventing *S. aureus* infections and, additionally, reduce the risk of *P. aeruginosa* infections. This proved to be so.

Mupirocin applied to the exit site has proved to be very effective in reducing *S. aureus* infections in PD patients (19–22). *S. aureus* exit site infections are associated with considerable morbidity, including peritonitis, catheter removal, and transfer to hemodialysis (9,10). Therefore, maneuvers to decrease *S. aureus* infections are an important part of improvement of outcomes in PD. Exit site mupirocin prophylaxis is currently using gentamicin. The only side effect reported in either arm was exit site irritation, which led to withdrawal of seven patients from each arm of the study.

There were no significant differences in end points. These included renal transplantation (14% versus 6%), death (11% versus 16%), transfer to hemodialysis (15% versus 28%), transfer to another unit on PD (3% versus 0%), and return of renal function (2% versus 0%), respectively, in the groups using mupirocin versus gentamicin cream. None of the deaths was related to PD infections. Reasons for transfer to hemodialysis in the mupirocin versus gentamicin group were peritonitis (five versus 10), medical complications (three versus five), and uremia (one versus three). Other reasons were catheter malfunction (one in mupirocin group) and noncompliance with dialysis (one in gentamicin group).

**Discussion**

Peritonitis rates were lower using gentamicin cream, 0.34/yr, compared with mupirocin, 0.52/yr (P = 0.03; Table 2). This was due to a reduced rate of Gram-negative peritonitis using gentamicin. There were no episodes of *P. aeruginosa* peritonitis using gentamicin cream. Only two patients who were using gentamicin cream developed PD-related Gram-negative infections (both *Escherichia coli*), and both organisms were sensitive to gentamicin. Three infections in the group on mupirocin were gentamicin resistant.

Exit site gentamicin use was a significant predictor of lower peritonitis rates (RR, 0.52; 95% CI, 0.29 to 0.93; P < 0.03), controlling for center and incident/prevalent patients. Gentamicin use was associated with lower Gram-negative peritonitis rates (P < 0.05), controlling for center and incident/prevalent patient status.

Catheter removal as a result of infection was similar in both groups (0.09/yr with mupirocin and 0.11/yr with gentamicin cream; P = 0.45). One catheter was removed for *P. aeruginosa* peritonitis and another for severe *E. coli* catheter infection resulting in peritonitis. Both patients were using mupirocin cream. Three catheters were removed in each group for Gram-positive organisms, two in each group for fungal peritonitis and two for Gram-negative bacilli with mupirocin and one for Gram-negative bacilli with gentamicin.

An intention-to-treat analysis, including patients who remained on PD after withdrawing from the study, revealed similar results to the treatment-received results. Catheter infection rates were significantly higher with mupirocin (0.56/yr versus gentamicin cream at 0.30/yr; P = 0.001). Peritonitis rates were 0.49/yr with mupirocin compared with 0.30/yr with gentamicin cream (P = 0.08). Catheter removal was not different in the two groups when analyzed as intention to treat.

Patients in both groups received refills an average of every 4 mo (range, 1 to 9 mo), close to the predicted interval of every 5 mo. Patients who did not ask for refills after 6 mo were asked to bring in their cream to verify that they still had it and asked whether they were using it daily. Nonadherence was present in two patients who were using mupirocin and four who were using gentamicin. The only side effect reported in either arm was exit site irritation, which led to withdrawal of seven patients from each arm of the study.

There were no significant differences in end points. These included renal transplantation (14% versus 6%), death (11% versus 16%), transfer to hemodialysis (15% versus 28%), transfer to another unit on PD (3% versus 0%), and return of renal function (2% versus 0%), respectively, in the groups using mupirocin versus gentamicin cream. None of the deaths was related to PD infections. Reasons for transfer to hemodialysis in the mupirocin versus gentamicin group were peritonitis (five versus 10), medical complications (three versus five), and uremia (one versus three). Other reasons were catheter malfunction (one in mupirocin group) and noncompliance with dialysis (one in gentamicin group).
recommended by the International Society for Peritoneal Dialysis Guidelines for *S. aureus* prophylaxis (28).

Any new protocol for exit site care thus should be compared with exit site mupirocin application. We found that gentamicin cream applied to the exit site was equivalent to mupirocin cream in preventing *S. aureus* exit site infections and peritonitis. There are now two reports of the emergence of mupirocin-resistant *S. aureus*, suggesting that eventually mupirocin will not be effective (25,26). We did not evaluate resistance to mupirocin (the methods to evaluate for mupirocin resistance are not available in the United States), but the continued effectiveness of mupirocin suggests that little resistance has developed in our programs. An explanation might be the intermittent use of mupirocin at the exit site in both sites reporting resistance, as opposed to daily use in our program. Possibly resistance to mupirocin will eventually become widespread, abrogating its usefulness for prophylaxis. In the meantime, prophylaxis results in a reduced incidence of PD-related infections and, thus, a decreased use of vancomycin and cephalosporins. Resistance to these two antibiotics is much more to be feared than resistance to mupirocin. Of note, methicillin-resistant *S. aureus* PD-related infections in our program have become rare as a result of the prophylaxis. It is important, however, to find an alternative prophylaxis for PD patients.

PD-related infections caused by *P. aeruginosa* have not changed with mupirocin cream at the exit site (23,29). *P. aeruginosa* infections in PD patients are associated with catheter loss, hospitalization, peritoneal membrane failure, and sometimes death (4,8–15,28,29). Previous studies, including those from our center, show that morbidity and technique survival are seriously affected by *P. aeruginosa* infections in PD patients (7,17,30,31). Catheter removal was not a primary outcome in the present study; therefore, there was inadequate statistical power to examine catheter loss from infection. However, our results indicate that it is possible to dramatically decrease *P. aeruginosa* infections in PD patients.

An important finding was lower Gram-negative peritonitis as well as Gram-negative exit site infections in the group that used gentamicin. This was somewhat surprising because the study was not designed to detect a difference in peritonitis rates. It suggests that some episodes of Gram-negative peritonitis may come from occult catheter infection. Szeto et al. (18) found that previous systemic antibiotic therapy was a risk factor for *Pseudomonas* peritonitis. Use of gentamicin cream thus may decrease the use of systemic antibiotics and therefore potentially decrease *Pseudomonas* peritonitis risk. Gentamicin cream at the exit site should not have an impact on Gram-negative organism peritonitis from the bowel or contamination. Gram-negative peritonitis episodes are severe, often require hospitalization, and sometimes lead to death (32–35). Therefore, reduction of this serious infection in PD patients is an important finding.

Systemic absorption from application of 0.1% gentamicin cream to the skin is negligible, 2% or less (36). Each 15-g tube of gentamicin cream costs $1.11, or less than a penny per day in our centers, which is much less expensive than mupirocin, which often costs $21.02 per 15-g tube.

There is an increased fungal exit site infections with gentamicin cream. However, these were readily treated with a course of antifungal medication, did not recur despite continuation of exit site gentamicin, and did not lead to peritonitis. Indeed, fungal peritonitis is not known to come from exit site infections but generally from colonization and touch contamination or, alternatively, bowel source.

To summarize, in a double-blind, randomized, multicenter trial, we found that gentamicin sulfate 0.1% cream applied daily to the exit site was highly effective in reducing *P. aeruginosa* exit site infections, associated with few side effects and as effective as mupirocin 2% cream in preventing *S. aureus* exit site infections. This effectiveness in prevention of *S. aureus* is important given the recent reports of resistance to *S. aureus* at two centers (24,25). Peritonitis, particularly episodes caused by Gram-negative organisms, also occurred less often using exit site gentamicin. Because *S. aureus* and *P. aeruginosa* are the leading causes of catheter-related peritonitis and catheter loss, decreasing these as well as other Gram-negative peritonitis will improve the care of PD patients. Gentamicin cream applied daily to the exit site, not mupirocin cream, should be the prophylaxis of choice for PD programs.

**Acknowledgments**

This study was supported by the National Kidney Foundation of Western Pennsylvania, National Kidney Foundation of Upstate New York, and the Paul Teschan Fund of Dialysis Clinic, Inc.

This manuscript was previously published in abstract form only (Perit Dial Int 24: S53, 2004).

We thank the home dialysis nurses in each of the three programs for consistently excellent care of the patients and Dr. Jean Holley for helpful comments.

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