Routine use of mupirocin at the peritoneal catheter exit site and mupirocin resistance: still low after 7 years

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Abstract

Objective. The purpose of this study (the third in a series of similar studies) is to evaluate the prevalence of Staphylococcus aureus (SA), methicillin-resistant SA (MRSA) and mupirocin-resistant SA (MuRSA) carriers in a peritoneal dialysis centre where patients have been instructed to use prophylactic mupirocin ointment at the catheter exit site over the last 7 years.

Methods. Swabs were taken from catheter exit site, nares, axillae and groin in 147 chronic peritoneal dialysis out-patients between November 2003 and January 2004. Axillae/groin and nasal samples were pooled and cultured in the same medium, whereas exit site swabs were cultured separately. All SA isolated were tested for methicillin and mupirocin resistance using oxacillin screening plates and E-test strips.

Results. Sixteen of 147 patients (10.9%) were found to be SA carriers: of these 13 (8.8%) had a positive nasal/axillae/groin culture; two (1.4%) had both nasal/axillae/groin- and exit site-positive culture; and one (0.7%) had only exit site-positive culture. In these 16 SA carriers, we found mupirocin-resistant strains (MuRSA) in four patients (25%) and MRSA in two patients (12.5%). Among the four MuRSA carriers, one had both nasal/axillae/groin- and exit site-positive culture and three had only nasal/axillae/groin-positive culture. Three high-level resistance and one low-level resistance MuRSA carriers were isolated. One MuRSA strain was also methicillin resistant. All MRSA strains were sensitive to vancomycin and rifampicin.

Conclusion. After 7 years’ routine use of prophylactic mupirocin ointment at the catheter exit site in non-selected chronic peritoneal dialysis patients, MuRSA was found in 25% of SA strains isolated or in 2.7% of the patients. Compared with our previous study, 3 years earlier, there is no significant increase in the MuRSA prevalence in peritoneal dialysis patients who routinely apply mupirocin ointment at the catheter exit site.

Keywords: catheter exit site; mupirocin; resistance; Staphylococcus aureus; peritoneal dialysis

Introduction

Staphylococcus aureus (SA) nasal and/or exit site carriage is accepted as a risk factor for both peritonitis and exit site infections [1,2]. Furthermore it has been shown that the site most frequently colonized with SA strains identical to that causing the peritonitis episode was the catheter exit site [3]. The efficacy of mupirocin ointment in treating SA carriage has been well documented [4,5]. Periodic re-treatment or maintenance therapy is necessary to prevent re-colonization because intermittent use of mupirocin is associated with a significant risk of relapse [6,7].

Three different studies in non-selected peritoneal dialysis patients have shown that maintenance of local application of mupirocin ointment at the catheter exit site at the end of the exit site care in non-selected peritoneal dialysis patients decreases the risk of exit site infection and peritonitis, when compared with historical groups [8–10]. Emergence of mupirocin-resistant strains has been described in peritoneal dialysis patients [11–13].

Previously we reported the emergence of mupirocin-resistant SA (MuRSA) after 4 years of mupirocin use in our unit where all the patients in our chronic peritoneal dialysis programme have been advised to apply mupirocin to the catheter exit site since 1996 [11,12].
The purpose of this study is to evaluate the point prevalence of SA, MuRSA and methicillin-resistant (MRSA) carriage in non-selected chronic peritoneal dialysis patients after 7 years of such practice in our unit.

Patients and methods

Since November 1996, all chronic peritoneal dialysis patients in the Toronto Western Hospital peritoneal dialysis programme have been instructed to apply mupirocin ointment 2% around the exit site at the end of each exit site care (daily or three times a week). Patients are not screened to determine if they are SA carriers.

Between November 2003 and January 2004, we performed a third point prevalence study. One hundred and seventy-four active patients on chronic peritoneal dialysis were asked to participate in a survey and 147 of them agreed to take part. Among these 147 patients, 63 patients were already on peritoneal dialysis during the previous survey. Three swabs were collected for each patient, one from the catheter exit site, one from the nasal area and one for both axillae and inguinal areas.

Nasal and axillae/groin swabs were pooled and cultured in the same media, whereas exit site swabs were cultured separately. All specimens were inoculated onto selective solid agar (mannitol agar plates) and incubated aerobically at 35°C. The plates were reviewed at 24 h and again at 48 h if no staphylococcal growth was observed. SA strains were identified using standards methods. All strains of SA isolated were tested for methicillin and mupirocin resistance. Methicillin resistance was tested using methicillin screening plates containing oxacillin 6 μg/ml and 4% NaCl. Mupirocin resistance was tested using E-test strips (AB, Biodisk, Solna, Sweden). Sensitivity was classified into three categories: no resistance [minimum inhibitory concentration (MIC) ≤2 μg/ml], low-level resistance (MIC 2–256 μg/ml) and high-level resistance (MIC >256 μg/ml). Clinical data were collected from patients at the time of swab collection. Proportions comparisons were performed with Fisher’s exact test. Means comparisons were performed with the Mann–Whitney test.

Results

The mean age of those 147 patients (75 male and 72 female) who agreed to be swabbed was 60±18 years (19–96). The median time on peritoneal dialysis was 27.87 months (1.21–202.15). The mean age of the patients who did not agree to take part in the survey was 53±19 years (22–87) and the median time on peritoneal dialysis was 39.98 months (9.72–109.04). There was no significant difference between the group of patients who agreed to be swabbed and the group of patients who did not agree to take part in the survey concerning the dialysis duration (P = NS, Mann–Whitney test).

Among 147 patients swabbed, 137 used mupirocin ointment (93.2%), 136 around the catheter exit site only (92.5%) and one in nares only. Among these 136 patients, 132 (97.1%) applied the ointment daily or three times a week, three (2.2%) intermittently and one applied mupirocin and polysporin ointment alternately. Three other patients applied polysporin cream and one gentamicin drops. Six patients did not use any ointment at the end of exit site care.

A total of 441 swabs were taken from 147 patients. Exit site swabs (147) were cultured separately, whereas nasal swabs (147) and axillae/inguinal swabs (147) were pooled and inoculated in the same media. Among these 147 patients, 16 (10.9%) were found to be SA carriers. Thirteen of these 16 patients had only pooled nasal/axillae/groin-positive culture (8.8% of total), two (1.4%) had both exit site- and pooled nasal/axillae/-groin-positive culture and one patient (0.7%) had a positive culture only from the catheter exit site (Table 1). These 16 SA carriers used mupirocin ointment on the catheter exit site regularly.

MuRSA strains were isolated from four patients (2.7% of the tested population, 2.9% of the mupirocin user group and 25% of the SA carriers group). Interestingly only one of them, who was a high-level MuRSA carrier, had both nasal/axillae/groin- and exit site-positive culture. The remaining three patients had pooled nasal/axillae/groin-positive cultures and exit site-negative cultures. Two MuRSA isolates had an MIC of >1024 μg/ml, one isolate had an MIC of >256 μg/ml and one had low level resistance; these results give a high-level MuRSA prevalence of 2% in the tested population. One of the MuRSA carriers had already been a high-level MuRSA carrier in the previous study (3 years earlier). One of the MuRSA carriers was diabetic. The mean age of the MuRSA carrier group was 70±24 years (38–91). These four patients have been on peritoneal dialysis for 42.6, 8.1, 12.8 and 27.1 months. Two of these carriers on peritoneal dialysis for 42.6 and 8.1 months had a peritonitis episode after 15 and 7 months of peritoneal dialysis, respectively. Staphylococcus coagulase negativity was identified in both cases. These two patients were treated successfully with cefazolin. All the MuRSA carriers applied mupirocin on their catheter exit site regularly. Two patients (1.4% of the tested population, 12.5% of the SA carriers group) were positive for nasal/axillae/groin-positive cultures.

<table>
<thead>
<tr>
<th>Table 1. Location of the SA strain isolated</th>
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<tr>
<td>Sensitivity of the strain isolated</td>
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<tr>
<td>4 year’s use (n = 26)</td>
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<tr>
<td>MSSA (n = 26)</td>
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<tr>
<td>MRSA (n = 0)</td>
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<tr>
<td>MuRSA (n = 4)</td>
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<tr>
<td>7 year’s use (n = 16)</td>
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<tr>
<td>MSSA (n = 14)</td>
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<td>MRSA (n = 2)</td>
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<tr>
<td>MuRSA (n = 4)</td>
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<tr>
<td>Nasal/axillae/groin</td>
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<td>Catheter exit site</td>
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<td>Nasal/axillae/groin and exit site</td>
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MSSA = methicillin-sensitive S. aureus; MRSA = methicillin-resistant S. aureus; MuRSA = mupirocin-resistant S. aureus.
MRSA carriers (nasal/axillae/groin pooled culture); one of these had both MRSA and MuRSA isolated; both of these patients belong to the mupirocin user group. All of the MRSA strains were sensitive to vancomycin and rifampicin and had macrolide resistance; also one was sensitive to trimethoprim sulfamethoxazole. There was no staphylococcal strain resistant to vancomycin.

There were no statistically significant differences ($P=NS$ by Fisher’s exact test) in the SA, MuRSA and MRSA carriage prevalence compared with the previous study (Table 2).

**Discussion**

We know little about the effect of maintenance mupirocin therapy on the MuRSA prevalence, especially in peritoneal dialysis patients. Therefore, regular monitoring of MuRSA prevalence is mandatory in peritoneal dialysis patients receiving such a treatment [14].

Our third survey shows that the prevalence of SA carriage remains low and stable after 7 years use of prophylactic mupirocin application [11,12]. In addition, the prevalence of SA carriage is lower than the prevalence reported by others authors [15,16]. However, SA carriage is intermittent in peritoneal dialysis patients. A point prevalence study may have underestimated SA carriage. Interestingly, only three patients (2%) had a positive culture from the catheter exit site, showing that maintenance mupirocin is particularly effective in eradicating SA exit site carriage. Although we may have underestimated SA carriage because specimens were not inoculated in broth, as in our previous study, we believe that this will not affect the prevalence of MuRSA (i.e. the percentage of SA resistant to mupirocin). Furthermore, the large number of swabs taken for each patient minimizes the risk of false-negative results. In our first and second survey, 26 out of 167 (15.6%) and 20 out of 149 (13.4%) SA carriers, respectively, had been identified using mannitol agar plate cultures only. In comparison with both direct and broth culture, 27 out of 167 (16%) and 26 out of 149 (17%) SA carriers, respectively, had been identified. Addition, detection of SA nasal carriage with direct culture remained acceptable in one study conducted to optimize the screening procedure for SA nasal carriage in hemodialysis patients [17].

After 1 year of mupirocin use, no MuRSA was isolated with the disk diffusion test in a first survey from our centre [11]. Thereafter, a second point prevalence conducted after 4 years of mupirocin use revealed the emergence of MuRSA carriers [14]. In one recent study by Cavdar and colleagues, MuRSA emergence was evaluated prospectively in 56 peritoneal dialysis patients randomly assigned to apply mupirocin ointment at their catheter exit site once weekly or three times per week [18]. Among a total of 864 swabs carried out over a 6 month period, only one MuRSA was isolated in both groups. The antibacterial activity of mupirocin is due to competitive inhibition with isoleucyl-tRNA synthetase that is encoded by the gene ileS. High-level mupirocin resistance is associated with a novel enzyme encoded by a plasmid-encoded gene (MupA), whereas low-level resistance is due to chromosomal mutations [19]. Some populations of MuRSA contain both plasmid-based and chromosomally based resistance. High-level resistance can be transferred, whereas low-level resistance is stable and non-transferable.

Nasal carriage may be a reservoir in which SA may become resistant in patients applying mupirocin to their catheter exit site. In our study, three of the four patients who were MuRSA carriers had only nasal/axillae/groin area-positive culture and only one had both exit site- and nasal/axillae/groin-positive culture. In our previous study, we isolated MuRSA only from the nasal/groin/axillae areas. When using mupirocin ointment, local mupirocin levels reach ~20 000 μg/ml so that low-level resistance is probably of little or no clinical relevance. High-level resistance is defined as an MIC >256 μg/ml and one may hypothesize that maintenance of local high mupirocin concentration can be effective in preventing MuRSA exit site carriage. In addition, mupirocin may treat MuRSA strains in vivo. Two studies have been performed to evaluate the efficacy of mupirocin in treating MuRSA strains. Walker et al. evaluated the ability of mupirocin applied twice daily in the nares for 5 days to eradicate MuRSA/MRSA carriage in 40 hospitalized patients [20]. Among 18 patients who were high-level resistance MuRSA carriers, five had negative culture 3 days post-treatment, but sustained culture negativity at 1–4 weeks was low (25%). In another study, mupirocin application four times daily for 2 weeks achieved MuRSA nasal carriage clearance in 44.4% of cases [21]. These two studies suggest that mupirocin dose and duration may play a role in MuRSA clearing.

No cross-resistance between other agents and mupirocin has been identified. In our study, three

<table>
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<th>Table 2. Comparison of SA carriage, MuRSA and MRSA point prevalence after 1 year, 4 years and 6 years of mupirocin prophylactic practice</th>
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<tr>
<td>Patients on peritoneal dialysis</td>
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<tr>
<td>Patients swabbed</td>
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<td>SA carriers/patients swabbed</td>
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<tr>
<td>MuRSA carriers/patients swabbed</td>
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<td>MuRSA carriers/mupirocin users</td>
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<td>MuRSA carriers/SA carriers</td>
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<td>MuRSA and MRSA strain</td>
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of the MuRSA strains isolated were susceptible to oxacillin and one MRSA/MuRSA strain that was identified remained sensitive to rifampicin, vancomycin and trimethoprim sulfamethoxazole, indicating that alternative therapeutic options are available if infections with this organism occur.

In conclusion, after 7 years use of maintenance mupirocin ointment in our centre in non-selected peritoneal dialysis, there is no significant increase in the prevalence of MuRSA. MuRSA prevalence remains low and SA exit site carriage seems to be rare. Discontinuation of the use of topical mupirocin prophylaxis is not indicated. However, SA resistance to mupirocin has to be monitored regularly in centres that have, policy of continuous mupirocin use in peritoneal dialysis patients.

Conflict of interest statement. None declared.

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