Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis. Was it effective?

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Peritonitis continues to plague patients on peritoneal dialysis (PD). A recent paper from the Australian and New Zealand registry showed that infectious mortality over time in PD patients exceeded that seen in haemodialysis (HD) patients [1]. Excluding the first 90 days of dialysis, PD patients had an infectious mortality of 2.8/100 patient-years, compared to 1.7/100 patient-years for HD patients. The relative increased risk of death from infections in PD vs HD developed after 6 months on dialysis and was attributed to peritonitis [1]. The rate of death related to peritonitis was 1.1/100 patient-years or 39% of the total infectious deaths in PD. For a period early in PD (1979–1994) when peritonitis was more frequent than today, peritonitis was a contributor to 16% of all deaths on PD [2]. In a study covering the period from 1986 to 2004, peritonitis-associated mortality was related to organism: 27.5% with fungal, 19.3% with enteric and 15% with Staphylococcus aureus peritonitis [3].

S. aureus continues to be a serious pathogen in PD patients, causing severe peritonitis and exit-site infections [3,4]. Therefore, targeting methods to reduce S. aureus peritonitis is of great interest. Herwaldt and colleagues have demonstrated that, in 95% of patients with nasal and peritoneal colonization, the subtype is the same, as is the ensuing peritonitis [5]. Swartz et al. demonstrated that 85% of those patients presenting with a S. aureus peritonitis episode were also culture-positive for the same organism at the exit site [6]. Since the patient is the source of the S. aureus causing peritonitis, interest has been focused on decolonization of the patient with S. aureus.

Mupirocin prophylaxis has long been proposed as a method for reducing infectious complications due to S. aureus in PD patients through decolonization. One of the first and most important studies on this was the multi-centre European trial using intra-nasal mupirocin for...
decolonization in those who were S. aureus nasal carriers [7]. This important randomized controlled trial (RCT) showed that mupirocin intra-nasally dramatically reduced S. aureus exit-site infections in these high-risk nasal carriers (0.12 vs 0.42/dialysis year in controls), as shown in Table 1. S. aureus peritonitis was reduced from 0.23 to 0.15/patient-year by the protocol, an insignificant decrease; the study does not appear to have been powered to detect a change in S. aureus peritonitis. These results may also be attributed to a preventive approach that was too late; as to qualify, patients had to have documented three positive nasal swabs for S. aureus with timing between swabs up to 10 weeks. This means that those at the greatest risk (the so-called continuous carriers) were targeted. By the time of study entry, it is quite possible that some already had colonization of the catheter.

We became interested in an alternative approach. Since the portal of entry of S. aureus into the peritoneum is most often the catheter exit site, targeting the exit site with prophylactic mupirocin appeared theoretically feasible as a method to reduce both S. aureus exit-site infection and peritonitis. Cyclical rifampin (a very effective, although temporary, method to eliminate nasal carriage), modelled after Zimmerman et al. [8], was compared in a RCT to daily exit-site application of mupirocin with the hypothesis that the two approaches would be equally efficacious [9]. This indeed was the case: both protocols resulted in strikingly low S. aureus exit-site infections and peritonitis risk. Exit-site mupirocin is preferable to oral cyclical rifampin as the later drug can result in allergic reaction, has drug interactions and results in fairly rapid development of resistance.

Two centres used mupirocin prophylaxis for over more than a decade and eventually found the development of some resistance [10,11]. In Spain, the initial approach was to culture the nares and treat with a course of intra-nasal mupirocin to eliminate carriage [10]. Nose cultures were done monthly. This was an effective approach to decrease S. aureus PD-related infections, both exit-site infections and peritonitis. Subsequently, exit-site cultures and exit-site mupirocin were added to the protocol. After many years, mupirocin resistance emerged, although S. aureus infections complications in the programme continued to be low. In the second programme, the patients were instructed to apply mupirocin to the exit site, and in some cases, this was done three times per week rather than daily [11]. After many years, some mupirocin resistance developed, particularly in those applying the mupirocin intermittently. While the development of resistance to mupirocin in the out-patient setting is of concern, clearly, this develops slowly over many years, perhaps because the patients have little contact with each other. While as yet unclear, it is possible that intermittent use (that is, less than daily application to the exit site) might foster the development of resistance.

The use of mupirocin in PD patients is highly effective in reducing both S. aureus exit site and peritonitis, as shown in the meta-analysis in this issue [12]. This meta-analysis combines approaches that use intra-nasal mupirocin with those that use exit-site mupirocin and excludes all studies comparing mupirocin to another agent. Intra-nasal mupirocin and exit-site mupirocin both appear to be effective. S. aureus peritonitis appears to most often develop from colonization of the exit site, subsequent infection of the exit site and tunnel and resultant peritonitis [6]. Therefore, use of exit-site mupirocin should be sufficient to prevent peritonitis by this route. S. aureus peritonitis can also arise from touch contamination, as patients colonized with S. aureus (with nasal reservoir being very common) have S. aureus on their hands, and if the connection is touched at the time of connection, peritonitis can ensue. Clearly, elimination of the nasal reservoir for S. aureus (which then results in elimination of hand carriage of S. aureus) would be an effective approach to diminishing S. aureus peritonitis from this approach. However, with the tremendous advances in technology (flush before fill, luer lock connections, elimination of the spike methodology), peritonitis due to contamination has diminished. Use of mupirocin at the exit site does not eliminate nasal or skin colonization, other than at the exit site, and yet is highly effective in markedly reducing S. aureus exit-site infections as well as peritonitis (Figure 1A). This is indirect evidence that today most S. aureus peritonitis relates to catheter colonization and infection, rather than touch contamination.

What is reasonable to expect from prophylactic use of mupirocin? With a protocol that has patients applying mupirocin to the exit site after bathing from the start of exit-site care (that is, shortly after catheter implantation), S. aureus PD-related infections will be much diminished. As a consequence, antibiotic use in the programme is very likely to decrease. This is particularly important with

### Table 1. Exit-site infection rates given as episodes per patient-year for those in the intervention arm (monthly course of intra-nasal mupirocin) vs placebo

<table>
<thead>
<tr>
<th>Infections/patient-year</th>
<th>Intra-nasal Mupirocin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exit-site infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>0.12 (42%)</td>
<td>0.42 (80%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Other</td>
<td>0.17 (58%)</td>
<td>0.11 (20%)</td>
<td></td>
</tr>
<tr>
<td>Total exit-site infection</td>
<td>0.29</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Peritonitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>0.15 (23%)</td>
<td>0.23 (37%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>0.51 (77%)</td>
<td>0.41 (63%)</td>
<td></td>
</tr>
<tr>
<td>Total peritonitis</td>
<td>0.66</td>
<td>0.62</td>
<td></td>
</tr>
</tbody>
</table>

This study was done in S. aureus nasal carriers and powered to detect difference in S. aureus exit-site infections (not peritonitis). Data from reference [7].
regard to the use of vancomycin. With fewer Staphylococcus infections, less vancomycin will be used and, hopefully, the risk of resistance to vancomycin will lessen.

What is unreasonable to expect from prophylactic use of mupirocin? Mupirocin is not likely to be effective in preventing S. aureus infection in a PD catheter that is already colonized with S. aureus with the organism imbedded in the slime layer of the catheter. This is why it is important to institute use of the antibiotic cream early in the course of PD. In addition, mupirocin is an antibiotic that is effective against gram-positive organisms. Therefore, it is not reasonable to think that it would diminish (or increase) infections due to gram-negative organisms. As rates of S. aureus fall, the proportion of infections in a programme due to gram-negative organisms rises, but not the rate [13]. It is important to differentiate between rates and proportions of infections from gram-positive and gram-negative organisms. In addition, mupirocin applied to the exit site will not prevent infections that are due to touch contamination (common skin organisms, such as coagulase-negative Staphylococcus). Prevention of peritonitis due to contamination most likely lies in attention to training, reinforcement of training and use of up-to-date connectology.

There are alternatives to prophylactic mupirocin. In a multi-centre blinded RCT, gentamicin was as effective as mupirocin in preventing S. aureus PD-related infections and more effective in preventing gram-negative infections [14]. As a consequence, total exit-site infection and peritonitis rates were lower with the use of gentamicin cream applied daily to the exit site. At the conclusion of the study in 2004, our centre converted to the use of exit-site gentamicin cream in all patients. Continued efficacy against both S. aureus and Pseudomonas aeruginosa is demonstrated in Figure 1A and B. This continues to be a good choice for many patients.

The present meta-analysis excluded those RCTs comparing one agent to another. The data on the efficacy of mupirocin at the exit site in reducing a serious pathogen is so convincing that one can question whether it is ethically correct to use a placebo arm in future studies. It is surprising to continue to read articles about peritonitis and exit-site care in which no protocol for S. aureus is used [4,15]. In an audit of 12 renal units within the greater London area, none used S. aureus exit-site prophylaxis [4]. S. aureus, Pseudomonas and other gram-negative organisms were the predominant cause of peritonitis with concomitant exit-site infection; all are preventable. In an Austrian nationwide survey, only 11 of 23 centres had a protocol for S. aureus carriers and none routinely used exit-site antibiotics [15]. Those centres with a protocol for S. aureus carriers had one-half the exit-site infection rate as those without such a protocol.

Currently, there are two ongoing RCTs comparing mupirocin to other agents: medihoney (which has antimicrobial properties) and polysporin triple, both applied to the exit site [16,17]. Medihoney, in particular, if proven as effective as mupirocin, may be an attractive alternative as resistance increases to mupirocin. Polysporin triple, a very-broad-spectrum antibiotic, is a less attractive choice. In the meantime, every programme should decide on a proven protocol to diminish S. aureus infections in their PD patients as shown in Table 2. What should no longer be acceptable is to allow our patients to continue at high risk for serious...
exit-site infections, and thus, peritonitis due to *S. aureus*, a largely preventable infection in PD patients.

**Conflict of interest statement.** None declared.

(See related article by G. Xu et al. Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis. *Nephrol Dial Transplant* 2010; 25: 587–592.)

### References


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