Oral rifampin for prevention of *S. aureus* carriage-related infections in patients with renal failure—a meta-analysis of randomized controlled trials

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Abstract

**Background.** Rifampin has been studied as prophylaxis against *Staphylococcus aureus*-related infections in patients on dialysis.

**Methods.** We performed a meta-analysis of randomized controlled trials (RCTs) that compared the effectiveness and safety of oral rifampin with another regimen or no therapy in reducing *S. aureus*-related infections in dialysis patients.

**Results.** Four RCTs evaluated oral rifampin (administered for 5 days every 3 months, or for 5 days once) as prophylaxis in dialysis patients. Oral rifampin with or without bacitracin was associated with less access-site infections with *S. aureus* compared with no treatment (odds ratio = 0.16, 95% confidence intervals: 0.06–0.44, 3 RCTs). There was no difference between prophylaxis with oral rifampin and topical mupirocin applied at the catheter site, for all studied outcomes, in the RCT comparing these regimens. Withdrawal from the study due to drug-related toxicity occurred in 7/107 (6.6%) of the studied patients with renal failure. Development of resistance of *S. aureus* to rifampin ranged from 0 to 18.2% (reported in three out of four included RCTs).

**Conclusion.** Prophylactic use of oral rifampin reduces access-site infections with *S. aureus* in patients with renal failure undergoing dialysis. However, development of toxicity and antimicrobial resistance during the treatment with rifampin occur in considerable proportions of patients, limiting its use and supporting the guidelines that recommend the use of local antibiotics at the exit site, such as mupirocin, for these indications. The available data are rather limited and more studies should be performed to examine this important clinical question.

Keywords: bacitracin; catheter; mupirocin; peritonitis; rifampicin

Introduction

*Staphylococcus aureus* has been recognized as an important pathogen for the development of serious diseases in humans, such as skin and soft tissue infections, pneumonia and endocarditis [1,2], especially in high-risk populations including patients with renal failure on haemodialysis or continuous ambulatory peritoneal dialysis. *S. aureus* carriage has been associated with an increased risk (up to 3-fold) of nosocomial *S. aureus* bacteraemia [3,4]. In addition, *S. aureus* nasal carriage has also been associated with an increased incidence of *S. aureus* dialysis-related infections in patients with renal failure on haemodialysis or peritoneal dialysis [5]. Especially in peritoneal dialysis patients, the micro-organism can cause peritoneal catheter infections, leading to peritonitis and loss of the catheter.

Several antimicrobial agents have been used for the prevention of *S. aureus* carriage-related infections in patients with renal failure. Mupirocin is an antibiotic that has been used locally (in the nasal cavity and on the skin) for the eradication of *S. aureus* colonization with good results. Current guidelines support the use of mupirocin at the exit site of the dialysis catheter to reduce the exit site infections [6]. Also, systemic antimicrobial agents, such as ciprofloxacin, novobiocin, trimethoprim/sulfamethoxazole and rifampin have also been used for the eradication of *S. aureus* colonization in various populations. Among these antibiotics, rifampin has been the most studied drug for this indication [7].

However, various results have been reported regarding the effectiveness of rifampin *per os* in the decolonization of *S. aureus* from the nares in patients undergoing peritoneal dialysis or haemodialysis.
Oral rifampin in the prevention of \textit{S. aureus} carriage-related infections

In addition, there are several issues related to the safety of the use of rifampin \textit{per os}. This antibiotic increases the metabolism of several drugs, including $\beta$-blockers, corticosteroids, oral contraceptives, warfarin, ciclosporine, clarithromycin, azoles, protease inhibitors, theophylline and dimilant. It also changes the color of urine, saliva, tears and sweat to orange-pink [8]. Rifampin may cause chills, fever, myalgias, arthralgias, vomiting, diarrhoea, hepatotoxicity, autoimmune anaemia, thrombocytopenia, acute renal failure and the hepatorenal syndrome. Fatal reactions have also been reported [9,10].

Therefore, we performed a meta-analysis of randomized controlled trials (RCTs) that compared the effectiveness and safety of oral rifampin with another regimen or no treatment in reducing \textit{S. aureus}-related infections in dialysis patients.

\section*{Methods}

\subsection*{Data sources}

Relevant studies for our review were identified from PubMed (to December 2005) and the Cochrane Central Register of Controlled Trials, and references from relevant studies and review articles. Search terms included ‘rifampin’, ‘rifampicin’, ‘\textit{Staphylococcus aureus}’, ‘hemodialysis’, ‘peritoneal dialysis’, ‘colonization’, ‘carriage’ and combinations of these terms.

\subsection*{Study selection}

Two reviewers independently (K.N.F. and I.A.B.) did literature searches and examined the identified relevant studies for further evaluation of the data. A study was considered eligible if it was an RCT that compared clinical and/or microbiological outcomes in patients with renal failure who received rifampin \textit{per os} vs another regimen without rifampin or no treatment for the prevention of \textit{S. aureus} carriage-related infections.

\subsection*{Data extraction}

The following primary data were extracted from each study: clinical setting, number of patients studied, duration of follow-up, antimicrobial agents and doses used, incidence of catheter infection, incidence of peritonitis, incidence of catheter loss and percentage of \textit{S. aureus} eradication. The analysed secondary outcomes were the occurrence of adverse events and the emergence of bacterial resistance to rifampin. Two reviewers independently (K.N.F. and I.A.B.) extracted the data from the identified relevant studies. Any disagreement between the two reviewers was resolved by consensus in meetings with the other authors.

\subsection*{Outcomes}

The incidence or the proportion of patients with dialysis access-site infection, bacteraemia, peritonitis and catheter loss were considered as outcome measures in dialysis patients. We used data conforming to any outcome definitions reported in each study.

\section*{Data analysis and statistical methods}

Statistical analyses were performed using the ‘Meta-analyt’ software (Joseph Lau, Tufts University School of Medicine, Boston, MA). Pooled odds ratios (OR) and confidence intervals (CI) for all the outcomes were calculated using the Mantel–Haenszel fixed effects and the DerSimonian–Laird random effects models. A finding was considered statistically significant if there was a $P$-value $<$ 0.05 in the analysis of the outcomes. The results from the fixed effects models are presented when there was no heterogeneity between the analysed studies ($P$-value $>$ 0.1).

\section*{Results}

\subsection*{Selected trials}

Our literature search identified 34 potentially relevant clinical studies [5,11–43]. Figure 1 is a flow diagram showing the steps that we followed in order to identify the RCTs fulfilling the inclusion criteria of our review. Most of the studies were excluded because they did not evaluate the effectiveness of prophylactic use of oral rifampin. As shown in Figure 1, four RCTs were finally considered eligible for inclusion in our review [5,11,12,43]. All the RCTs included in the study reported the number of participants and the reasons for withdrawal from the study.

\subsection*{Access-site infections in patients with renal failure}

In Table 1, we present the trial characteristics and in Table 2, the main outcomes in patients with renal failure on peritoneal dialysis or haemodialysis in four relevant RCTs included in our review [5,11,12,43]. In two of the included studies [5,12], all the patients were \textit{S. aureus} carriers, whereas in the other two only a proportion of them were colonized by the bacterium. Oral rifampin with or without bacitracin was associated with less dialysis access-site infections with \textit{S. aureus} compared with no treatment (OR = 0.16, 95\% CI: 0.06–0.44, fixed effects model, three studies; Figure 2) [5,12,43]. The data for the rest of the outcomes of interest were few and subsequent pooling and meaningful analysis of them was not possible. However, as shown in Table 1, statistically fewer overall (regardless of the type of the infecting microbe) catheter infections were reported for the rifampin treatment group compared with no treatment group in the study by Zimmerman \textit{et al.} [43]. In addition, Bernardini \textit{et al.} [11], in the largest of the four studies, reported no difference between prophylaxis with rifampin \textit{per os} and mupirocin applied locally at the catheter exit site, for all the studied outcomes.
Drug-related toxicity in patients with renal failure

Details about withdrawals from the trials were provided in all studies, allowing for extraction of data regarding possible severe toxicity during treatment. Bernandini et al. [11] reported severe toxicity requiring drug discontinuation in five out of 41 patients (12%). Zimmerman et al. [43] reported toxicity in six out of 32 patients, four (13%) of whom required discontinuation of the treatment. In the remaining two RCTs, there were no withdrawals due to toxicity. Thus, overall 7/107 (6.6%) of the patients that were treated with rifampin discontinued therapy due to toxicity. Toxic drug interactions in patients receiving rifampin did not occur in the aforementioned studies.
Table 1. Characteristics of the included randomized controlled trials (RCTs) evaluating rifampin prophylaxis for the prevention of infections related to *S. aureus* in dialysis patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient population</th>
<th>Number of patients</th>
<th>Type of therapy and dosage</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rifampin group</td>
<td>Control group</td>
<td></td>
</tr>
<tr>
<td>Bernardini et al. [11]</td>
<td>Peritoneal dialysis patients</td>
<td>41</td>
<td>41</td>
<td>Rifampin <em>per os</em> 300 mg twice daily for 5 days every 3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifampin group</td>
<td>Control group</td>
<td>Mupirocin ointment 2% applied daily at the catheter exit site</td>
</tr>
<tr>
<td>Zimmerman et al. [43]</td>
<td>Peritoneal dialysis patients</td>
<td>32</td>
<td>32</td>
<td>Rifampin <em>per os</em> 300 mg twice daily for 5 days every 3 months</td>
</tr>
<tr>
<td>Blowey et al. [12]</td>
<td>Peritoneal dialysis paediatric patients</td>
<td>7</td>
<td>8</td>
<td>Rifampin <em>per os</em> (20 mg/kg/day) in 2 doses for 5 days plus bacitracin ointment 2 times a day for 7 days</td>
</tr>
<tr>
<td>Yu et al. [5]</td>
<td>Haemodialysis patients</td>
<td>18</td>
<td>26</td>
<td>Rifampin <em>per os</em> 600 mg twice a day for 5 days plus bacitracin ointment every 6 hours for 7 days</td>
</tr>
</tbody>
</table>

Table 2. Main outcomes of the included randomized controlled trials (RCTs) evaluating rifampin prophylaxis for the prevention of infections related to *S. aureus* in dialysis patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dialysis access-site infections with <em>S. aureus</em></th>
<th>Peritonitis with <em>S. aureus</em></th>
<th>Dialysis access-site infections, total</th>
<th>Peritonitis, total</th>
<th>Catheter loss due to infection with <em>S. aureus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence*, percentage (patients with outcome/all patients in treatment arm)</td>
<td>Incidence*, percentage (patients with outcome/all patients in treatment arm)</td>
<td>Incidence*, percentage (patients with outcome/all patients in treatment arm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernardini et al. [11]</td>
<td>0.15**</td>
<td>0.13</td>
<td>0.02</td>
<td>0.43</td>
<td>0.54</td>
</tr>
<tr>
<td>Zimmerman et al. [43]</td>
<td>0.22, 9% (3/32)†</td>
<td>0.65–41% (12/20)</td>
<td>0.11–9% (3/32)</td>
<td>0.16–9% (3/32)</td>
<td>0.26–13% (4/32)</td>
</tr>
<tr>
<td>Blowey et al. [12]</td>
<td>0% (0/7)</td>
<td>25% (2/8)</td>
<td>0% (0/7)</td>
<td>25% (2/8)</td>
<td>NR</td>
</tr>
<tr>
<td>Yu et al. [5]</td>
<td>0.44, 11% (2/18)††</td>
<td>1.84, 46% (12/26)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Episodes per patient-year. **Analysis of all outcomes was made on an intention-to-treat basis in this study, NR = not reported, ††P < 0.05 comparing rifampin with control group. ††The authors report 34 episodes of infections with *S. aureus* in 20 patients, of whom 14 were clinically evaluable. Fourteen episodes were access-site infections (9 of them led to bacteraemia), 5 were bacteraemias and 15 were wound infections or abscesses elsewhere (excluding access-site) on the body.
Emergence of resistance to rifampin

Three out of four RCTs evaluating the use of rifampin as prophylaxis in patients undergoing renal dialysis reported data regarding the development of bacterial resistance to antimicrobial therapy [5,12,43]. The reported emergence of rifampin-resistant S. aureus isolates was 18.2% (in four out of 22 patients treated with rifampin) [5], 12.5% (in four out of 32 patients) [19] and 0% (in seven paediatric patients) [12], respectively.

Discussion

The main finding of our analysis is that rifampin is an effective prophylaxis against S. aureus catheter infections in patients with renal failure undergoing dialysis, a group with high probability of colonization with this bacterium. No secure conclusion can be drawn for the rest of the studied outcomes (total catheter infections, total peritonitis, peritonitis with S. aureus and loss of catheter due to S. aureus) in this population due to the limited available data. However, the fact that fewer episodes of peritonitis due to S. aureus were reported in the rifampin treatment arm in all three studies examining this outcome provides some evidence that rifampin may also decrease the occurrence of peritonitis due to S. aureus. In addition, statistically significantly fewer overall catheter infections were reported for the rifampin treatment group compared with no treatment in the only study that reported this outcome [43].

A previous systematic review that evaluated the specific preventive measures against peritoneal catheter-related infections and peritoneal catheter loss due to S. aureus reported results in favour of systematic rifampin or local (nasal or exit-site) mupirocin use [44]. Specifically, it was reported that significant reduction in the occurrence of exit-site staphylococcal infections is achieved by the prophylactic use of either agent. However, there was weaker evidence regarding the reduction of staphylococcal peritonitis, similarly to the results of our meta-analysis. The conclusions of that systematic review regarding rifampin use were also based on the data from the studies included in our meta-analysis [11,43].

The two main concerns regarding the use of rifampin are the possible toxicity caused by the use of the antibiotic and the possibility of emergence of S. aureus antimicrobial resistance. The analysed studies reported a considerable proportion (6.6%) of withdrawals of patients due to toxicity, however no irreversible toxicity was noted. In addition, although rifampin has the potential of causing numerous drug–drug interactions, there was no report of such a problem in the studies included in our review. However, this fact may be partially explained by the short duration rifampin therapy is used in the studies, which may not suffice to cause clinically important interactions.

On the other hand, data for the emergence of resistance from all analysed studies show that
S. aureus develops resistance quite commonly, even to short duration regimens with rifampin. This is probably the biggest obstacle in using rifampin as prophylaxis in dialysis patients. Emergence of multi-drug-resistant strains of this bacterium is becoming very common worldwide [45,46] and as a result, any possible benefits from the use of rifampin in this setting should be weighed against the need to prevent the emergence of resistance to this antibiotic. Notably, even the use of local antibiotic therapies, such as mupirocin ointment, that have been shown to be effective in patients on dialysis or other populations, is sometimes associated with the emergence of resistance [47–49].

Our study is not without limitations. First, there are few RCTs, with a relatively small number of patients, which have examined the outcomes of our interest and were included in our meta-analysis. Second, not all patients included in the analysed studies were colonized with S. aureus. Specifically, two studies included only patients colonized with S. aureus [5,12] whereas there was no such inclusion criterion in the other two. Third, one of the studies in our meta-analysis examined paediatric peritoneal dialysis patients. Pooling these patients with adults may not be appropriate. However, we believe that since all the patients in the meta-analysis undergo dialysis due to renal failure there are many common characteristics among them and this suffices to pool them together, regardless of the variability in age. Fourth, only one study had some active regimen in the control group, whereas the rest compared rifampin with no treatment. Fifth, the available RCTs studied the effectiveness and safety of cyclic oral rifampin for a maximum of 24 months [11], with the majority of patients having <12 months follow-up. Thus, it is obvious that long-term prophylactic treatment may have substantially different effectiveness and safety compared with the results presented in the included studies.

Another limitation of our analysis is the fact that the included studies examining rifampin use in dialysis patients were performed 12–20 years ago, at a time when multidrug-resistant Staphylococci and especially methicillin-resistant Staphylococcus aureus (MRSA), strains were not as common worldwide as today. This fact makes extrapolation of our results to the current hospital settings difficult, since the overall increased resistance of Staphylococci to antibiotics may also decrease the effectiveness of rifampin. On the other hand, it should be noted that the abandoning of systemic rifampin as prophylaxis in dialysis patients or as a means of eradication of S. aureus colonization in various populations, led to the use of only local antimicrobial agents against S. aureus, with subsequent development of staphylococcal resistance to them [48,49]. Thus, there is a possibility that currently rifampin may retain its high activity and be more effective in decreasing staphylococcal carriage or infections related to it compared with local antibiotics, in certain high-risk patient populations.

In conclusion, our meta-analysis of RCTs showed that the prophylactic use of rifampin per os reduces catheter infections with S. aureus in patients with renal failure undergoing dialysis. However, our analysis also showed the development of toxicity and emergence of resistance during treatment with rifampin in a considerable proportion of patients, facts that represent the main concerns in using oral rifampin for these indications and support the current guidelines regarding the use of local antibiotics at the catheter exit-site in patients with dialysis catheters [6]. Nevertheless, available data are rather limited and more studies should be performed to examine this important clinical question.

Conflict of interest statement. None declared.

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