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Intranasal mupirocin for reduction of *Staphylococcus aureus* infections in surgical patients with nasal carriage: a systematic review

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***Objectives*: The majority of nosocomial *Staphylococcus aureus* infections originate from the patients' own flora, with nasal carriage of *S. aureus* before surgical procedures being a risk factor for subsequent infection. The objective of this review was to assess whether intranasal mupirocin treatment of nasal *S. aureus* carriers before surgery results in a reduction of the post-operative *S. aureus* infection rate.**

***Methods*: CENTRAL, EMBASE and MEDLINE were searched for the keywords *mupirocin*, *pseudomonic acid* or *bactroban*, combined with *nasal* or *intranasal*. Only randomized controlled studies investigating surgical patients were included. Titles and abstracts were screened independently by two reviewers. *S. aureus* infection data in nasal carriers with and without mupirocin treatment were pooled in the meta-analysis.**

***Results*: The literature search resulted in 211 hits, of which 4 articles met the inclusion criteria. Among the 686 mupirocin-treated surgical patients with *S. aureus* nasal carriage, there were 25 *S. aureus* infections (3.6%), compared with 46 (6.7%) in the controls (RR 0.55, 95% CI 0.34–0.89; $P = 0.02$).**

***Conclusions*: Prophylactic intranasal mupirocin significantly reduced the rate of post-operative *S. aureus* infections among surgical patients who were *S. aureus* carriers.**

Keywords: carrier, pre-operative, surgery

Introduction

Staphylococcus aureus is the leading nosocomial pathogen globally. Infection with *S. aureus* is associated with substantial morbidity and mortality—a trend that is increasing due to the widespread dissemination of methicillin-resistant *S. aureus*.[1] A large study in the USA estimated that 0.8% of all hospitalized patients suffered from infection with *S. aureus*, corresponding to a total of nearly 300 000 patients in US hospitals in 2003. Furthermore, after controlling for confounders, the annual impact in the US was estimated to be 2.7 million additional days in the hospital, $9.5 billion excess costs and at least 12 000 inpatient deaths.[2] Because of the serious consequences of these infections, effective prevention strategies are essential. Traditionally, prevention of *S. aureus* infections has been focused on minimizing cross-infection.[3] However, it has been shown repeatedly that a large proportion of nosocomial *S. aureus* infections originate from the patients' own flora.[4–6] Approximately 30% of the population carries *S. aureus* at a given moment in time, which has limited consequences in the extramural setting. However, nasal carriage of *S. aureus* is a well-known risk factor for subsequent infection in patients undergoing surgery, in patients on dialysis or with intravascular devices, and those with cirrhosis of the liver or in intensive care.[7–9]

Based on these findings, eradication of nasal carriage to reduce infection rates has been studied.[8] Mupirocin nasal ointment has often been used to eradicate carriage because of its effectiveness, safety and low costs. The only side effects

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reported were sneezing and an itching or running nose. The first interventions in surgery showed reductions in post-operative infection rates after orthopaedic and cardiothoracic surgery.[10,11] However, definitive conclusions could not be made due to methodological deficiencies. These studies used historic control groups and included both carriers and non-carriers. Subsequently, a number of randomized controlled trials (RCTs) were performed in patients undergoing orthopaedic, general, gynaecologic, neurologic or cadiothoracic surgery.[12,13] In general, the results of these studies showed a trend towards a beneficial effect of mupirocin. However, most studies failed to produce statistically significant results because of lower infection rates in the placebo groups than anticipated. Therefore, these studies did not have sufficient power to detect statistically significant differences. Moreover, due to the diagnostic delay of conventional microbiological culture techniques, carriers could not be identified before inclusion, with non-carriers diluting the potential benefits of mupirocin.[14] Recent technological advances in rapid diagnostics have provided the ability to detect nasal carriage of *S. aureus* within several hours instead of several days.[15,16] This will enable pre-emptive treatment of carriers only, which will enhance the efficacy of prophylaxis. To determine the impact of treating identified carriers of *S. aureus* preoperatively with mupirocin nasal ointment, a systematic review was performed. The objective of this systematic review was to determine whether the use of mupirocin nasal ointment preoperatively in patients with identified *S. aureus* nasal carriage reduces the post-operative *S. aureus* infection rates. Previously, several reviews in this area have been performed but these included both carriers and non-carriers.[17,18] This review is the first one that includes nasal *S. aureus* carriers only.

Materials and methods

Inclusion criteria

Prospective RCTs evaluating nasal mupirocin for the prevention of *S. aureus* infections in nasal *S. aureus* carriers after surgery were included.

Studies of patients from any gender and age were included. Nasal carriage must have been identified by microbiological culture techniques. In studies describing results of both carriers and non-carriers, the results of the carriers should have been available for a stratified analysis.

The studied intervention was the treatment with mupirocin ointment intranasally before surgery. Control groups were treated with a placebo or received no treatment.

The primary outcome measure, the post-operative *S. aureus* infection rate, had to be determined according to well-defined criteria [e.g. to Centers for Disease Control and Prevention (CDC) guidelines].[19] Infections caused by both methicillin-resistant and methicillin-susceptible *S. aureus* were included. When reported, the infection rate caused by microorganisms other than *S. aureus* and the development of mupirocin resistance were considered (secondary outcomes). When relevant data were not described in the article, the author was contacted.

Search strategy

The search strategy was based on the methods of the Cochrane Collaboration. Relevant trials were obtained by searching the electronic databases CENTRAL (The Cochrane Central Register of Controlled Trials, latest issue), EMBASE (January 1980–July 2007) and MEDLINE (January 1980–July 2007). The search terms were *mupirocin*, *pseudomonic acid* or *bactroban* in combination with *nasal* or *intranasal*.

Researchers and the manufacturer of mupirocin (GlaxoSmithKline, Zeist, The Netherlands) were contacted to identify unpublished trials. In addition, the authors searched their personal archives, including the abstracts from major scientific meetings [Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and The Society for Healthcare Epidemiology of America (SHEA)]. Additionally, the bibliographies of selected papers were searched in an attempt to identify additional studies. The search was not limited by language. Two independent reviewers (J. A. J. W. K. and M. M. L. v. R.) performed the search and screened the titles and abstracts for relevant studies. Discrepant findings and further analyses were also discussed with all authors. Appropriate studies were analysed based on the full text, using a standard data extraction form. When more than one publication of a trial existed, only the publication with the most complete data was included.

Data extraction

The standard data extraction form contained the following information:

(1) Authors.
(2) Year of study.
(3) Country where the study was performed.
(4) Study design (RCT).
(5) Patient population.
(6) Baseline characteristics of participants per treatment group (gender, age and presence of co-morbidity such as diabetes).
(7) Length, dose and timing of mupirocin treatment.
(8) Methods used for identifying microorganisms.
(9) Criteria used for identifying infections.
(10) Number of patients randomized per trial.
(11) Number of nasal *S. aureus* carriers per treatment group.
(12) Number of nosocomial *S. aureus* infections among mupirocin- and non-treated patients with nasal carriage.
(13) Mupirocin resistance.
(14) Number of nosocomial infections among mupirocin- and non-treated patients with nasal carriage.
(15) Adverse events.

When any of these items of the data extraction form was not described, the author of the included article was contacted.

Study quality

The quality of the included studies was assessed independently by J. A. J. W. K. and M. M. L. v. R. without blinding to authorship or journal, using the checklist as developed by the Cochrane Collaboration.[20] Randomization concealment was considered adequate if the method would not allow the investigator or the participant to know or influence the intervention group before the eligible participant was enrolled. An intention-to-treat analysis and blinding of investigators, participants, outcome assessor and data analysis were the preferred methods. Completeness of follow-up was recorded.

Statistical analysis

The results are shown in a forest plot using Review Manager 4.2.10, software from the Cochrane Collaboration. *S. aureus* infection rates were expressed as relative risk (RR) with 95% confidence intervals (CIs) for all outcomes of the individual studies. Data were pooled using the random effects model. Heterogeneity was analysed using a χ^2 test with $N-1$ degrees of freedom, with a two-sided P value of 0.05 used for statistical significance and the I^2 statistic.[21,22] Values of I^2 over 50% indicate a substantial level of heterogeneity. Subgroup analyses were planned when obvious differences were found between the included study groups, for example in type of surgery.

Results

Study selection

The initial search resulted in 211 references. After screening the titles and abstracts (by M. M. L. v. R. and J. A. J. W. K.), 18 full-text versions were read and analysed. There were only minor discordant results between the two reviewers that were readily resolved by discussion. Fourteen articles were excluded (Figure 1). Four papers met all pre-specified criteria.[12,13,23,24] Examining the references of the included studies, handsearching abstract books and contacting the researchers and the manufacturer of mupirocin (GlaxoSmithKline) resulted in one potential study.[37] However, this study included both surgical and non-surgical patients, and the data about surgical patients only could not be obtained.

Study characteristics

Characteristics and study quality of the four included studies are shown in Tables 1 and 2. Three of these studies were placebo-controlled, blinded and adequately randomized.[12,13,24] In these studies, an intention-to-treat analysis was performed. The study by Garcia *et al.*[23] was neither placebo-controlled nor blinded. Furthermore, randomization was not adequate. An intention-to-treat analysis was not described, but the authors confirmed that it had been done.

All of the included studies used standard culture techniques to identify microorganisms. The guidelines of the CDC were used to identify nosocomial *S. aureus* infections.[19] The frequency of mupirocin treatment was comparable in all studies; mupirocin was applied twice daily, but the treatment-days varied from 1 to 7 days before the operation.

Three of the included studies included both carriers and non-carriers. A total of 4669 surgical patients were included. After the initial screening, 1115 patients were identified as nasal *S. aureus* carriers. In the study by Konvalinka *et al.*,[24] only patients with *S. aureus* nasal carriage were included ($n = 257$). In total, 1372 nasal carriers were included and further analysed in this review. Both the mupirocin group and the control group consisted of 686 patients.

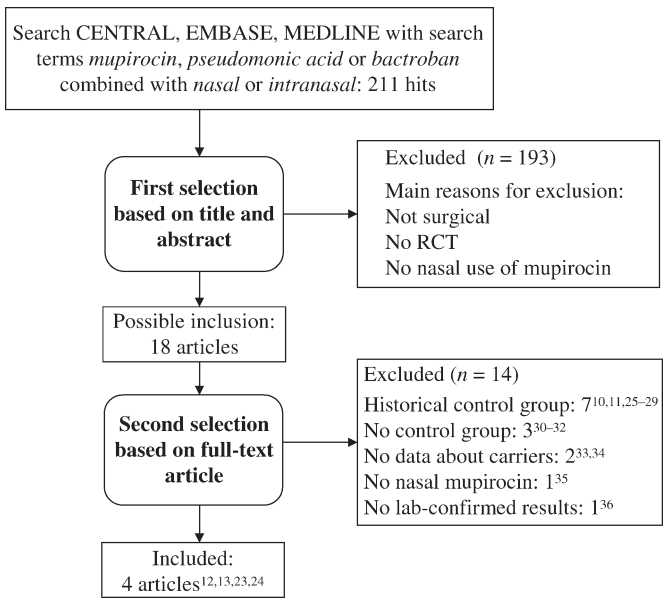

Figure 1. Selection procedure for studies meeting the inclusion criteria.

Eradication of carriage

Perl *et al.*[13] showed that nasal carriage of *S. aureus* was eliminated in 83% of patients who received mupirocin, as compared with 27% of patients who received placebo ($P < 0.05$). In the study by Kalmeijer *et al.*,[12] elimination occurred in 82% of patients who were initially carrying *S. aureus* in the mupirocin group and in 29% of patients in the placebo group ($P < 0.05$). In the study by Konvalinka *et al.*,[24] nasal carriage was eliminated in 81.5% of patients receiving mupirocin and 46.5% of patients receiving placebo ($P < 0.0001$).

Post-operative S. aureus infection rate

The study of Perl *et al.*,[13] the largest study, showed a significant effect of mupirocin on the *S. aureus* rate. In the studies of Garcia *et al.*,[23], Kalmeijer *et al.*,[12] and Konvalinka *et al.*,[24] no significant effect was found. Analysis of these four studies together in a forest plot showed a significant effect of mupirocin on the *S. aureus* infection rate after surgery in carriers (RR 0.55, 95% CI 0.34–0.89, Figure 2). Because no heterogeneity was shown ($I^2 = 0\%$), no subgroup analysis was performed. Perl *et al.*[13] recorded all nosocomial infections caused by *S. aureus*. In the mupirocin group ($n = 444$), 17 nosocomial *S. aureus* infections were found, including 16 surgical-site infections (SSIs) and 1 bloodstream infection. In the placebo group ($n = 447$), 34 nosocomial *S. aureus* infections were found; 26 SSI and 8 bloodstream infections, respiratory tract infections or catheter-related infections. Garcia *et al.*,[23] Kalmeijer *et al.*[12] and Konvalinka *et al.*[24] recorded surgical wound infections only. After contacting these authors, no more data about *S. aureus* infections other than wound infections became available. Analysis of the effect of mupirocin on *S. aureus* SSIs showed a trend in favour of mupirocin treatment, although this was not statistically significant (RR 0.64, 95% CI 0.38–1.06, Figure 3).

In surgical patients who were not carrying *S. aureus*, there was no effect of treatment, with a slightly higher infection rate noted in the treated group (RR 1.09, 95% CI 0.52–2.28).

Using molecular typing techniques, Perl *et al.*[13] reported that 85% of the *S. aureus* infections were endogeneous, and in the study by Kalmeijer *et al.*,[12] this percentage was 86%.

Table 1. Characteristics of studies comparing mupirocin prophylaxis before surgery with no prophylaxis in relation to the incidence of *S. aureus* infections

1. Study authors	Garcia *et al.*[23]	Kalmeijer *et al.*[12]	Konvalinka *et al.*[24]	Perl *et al.*[13]
2. Year of study	2001–02	Jan 1997–July 1999	March 1997–March 2003	April 1995–December 1998
3. Country where study was performed	Colombia	The Netherlands	Canada	USA
4. Study design	randomized, not placebo-controlled trial	randomized, double-blind, placebo-controlled trial	randomized, double-blind, placebo-controlled trial	randomized, double-blind, placebo-controlled trial
5. Patient population	cardiothoracic patients	orthopaedic surgery patients (elective first operation or revision + prosthetic implant material)	elective cardiac surgery	general, gynaecologic, neurologic or cardiothoracic surgery patients
6. Baseline characteristics of participants per treatment group	no significant differences between both groups	no significant differences between both groups	only COPD was significantly more prevalent in the mupirocin group compared with placebo group (10% versus 1.6%; $P = 0.006$)	patients that received placebo were more likely to have had renal disease; no other significant differences between both groups
7. Frequency of mupirocin treatment	twice daily for 5 days	twice daily from the day of admission (day before surgery) to the hospital until the day of surgery	twice daily for 7 days before surgery	twice daily for up to 5 days before surgery
8. Methods used for identifying microorganisms	standard culture techniques	standard culture techniques	standard culture techniques	standard culture techniques
9. Criteria used for identifying infections	CDC criteria	CDC criteria	similar to CDC	CDC criteria
10. Number of patients randomized per trial	included both carriers and non-carriers, mupirocin: 96, control: 95	included both carriers and non-carriers, mupirocin: 315, placebo: 299	included carriers only, mupirocin: 130, placebo: 127	included both carriers and non-carriers, mupirocin: 1933, placebo: 1931
11. Number of nasal *S. aureus* carriers per treatment group	mupirocin: 31, no treatment: 34	mupirocin: 95, placebo: 86	mupirocin: 130, placebo: 127	mupirocin: 430, placebo: 439
12. Number of nosocomial *S. aureus* infections	mupirocin: 1, no treatment: 3	mupirocin: 2 endogenous *S. aureus* SSI: 1, placebo: 5 endogenous *S. aureus* SSI: 5	mupirocin: 5, placebo: 4	mupirocin: nos inf 17 SSI 16, placebo: nos inf 34 SSI 26 (33 were endogeneous)
13. Mupirocin resistance	no data	all the strains were susceptible to mupirocin	short-term use did not select for mupirocin-resistant *S. aureus*	6/1021 *S. aureus* isolates were mupirocin-resistant; three of these were from patients treated with placebo
14. Number of any nosocomial infection among mupirocin- and non-treated patients with nasal carriage	no data	no data	mupirocin: 18/130, placebo: 11/127	mupirocin: nos inf 57/444 SSI 44/444, placebo: nos inf 72/447 SSI 52/447
15. Adverse events	no data	not stated; author contacted: none	none	itching and rhinorrhoea at application site, nasal burning, nasal bleeding, headache [mupirocin: 97/2012 (=carriers and non-carriers), placebo: 96/2018]

CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; nos inf, nosocomial infection; SSI, surgical site infection.

Table 2. Study quality of included studies

Study quality	Garcia *et al.*[23]	Kalmeijer *et al.*[12]	Konvalinka *et al.*[24]	Perl *et al.*[13]
1. Allocation concealment	C. inadequate consecutive numbers (odd numbers as controls and even numbers as treatment)	A. adequate	A. adequate	A. adequate, author contacted
2. Blinding	one group treated with mupirocin and the other without treatment, no blinding of investigators and participants	blinding of investigators, participants, outcome assessor and data analysis	blinding of investigators, participants, outcome assessor and data analysis	blinding of investigators, participants, outcome assessor and data analysis
3. Intention-to-treat analysis	not stated, but confirmed after personal contact	yes, stated and confirmed in results	yes, stated and confirmed in results	yes, stated and confirmed in results
4. Completeness to follow-up	nine withdrawals (mupirocin: 4, control: 5)	follow-up was complete	follow-up was complete	five withdrawals because of nasal burning, nasal bleeding, headache (mupirocin: 1, placebo: 4), death rate similar (mupirocin: 45, placebo: 55)

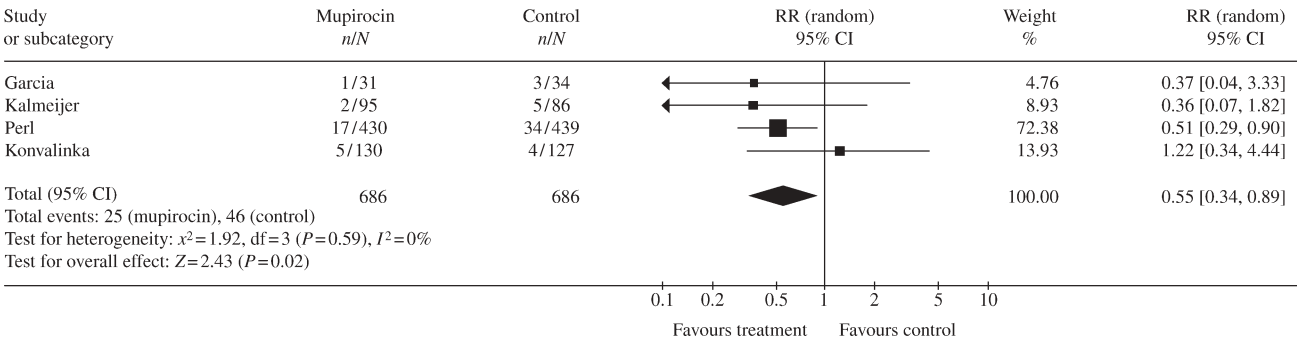

Figure 2. Nosocomial *S. aureus* infections among surgical patients with *S. aureus* nasal carriage.

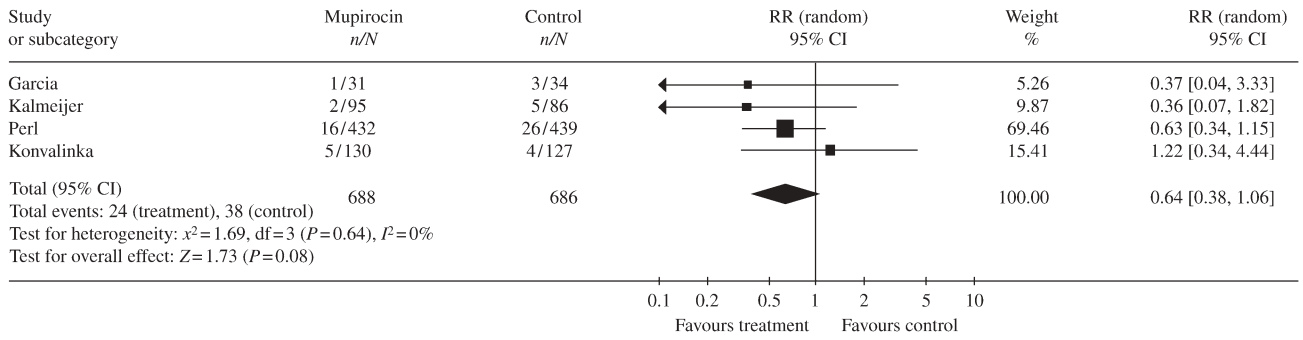

Figure 3. *S. aureus* SSIs among surgical patients with *S. aureus* nasal carriage.

Mupirocin resistance

Perl *et al.*[13] tested a total of 150 *S. aureus* isolates (90 from wounds and 60 from the nares) from 77 patients with SSIs and 871 isolates from the nares of patients for *in vitro* susceptibility to mupirocin.[13] Six of 1021 *S. aureus* isolates (0.6%), obtained from 6 patients, were resistant to mupirocin during the 4 year study period. Three of these isolates were obtained from patients who were not treated with mupirocin. In the studies by Kalmeijer *et al.*[12] and Konvalinka *et al.*,[24] all *S. aureus* strains from the nares and infected body sites were susceptible to mupirocin.[12]

Adverse events

None of the studies reported any significant side effects of mupirocin. Also, they did not explicitly state any difference in the severity of infections between the study groups. Perl *et al.*[13]

reported a similar death rate in the two groups (2.2% in the mupirocin group and 2.7% in the placebo group).

Nosocomial infection caused by any organism

Perl *et al.*[13] and Konvalinka *et al.*[24] reported the total number of nosocomial infections in patients with *S. aureus* nasal carriage (Table 1). There was no difference between the treatment and control group (RR 1.05, 95% CI 0.54–2.04). However, heterogeneity was too high to combine the data of these two studies ($I^2 = 67.4\%$).

Discussion

Reduction of post-operative S. aureus infections by mupirocin

A significant effect of nasal mupirocin treatment on the post-operative *S. aureus* infection rate in patients who were proven carriers before surgery was found. In total, there were 25 *S. aureus* infections among 686 mupirocin-treated patients and 46 among 686 patients without treatment (RR 0.55, 95% CI 0.34–0.89). When the SSIs are analysed as primary outcome, instead of all nosocomial infections, no statistically significant effect was found (RR 0.64, 95% CI 0.38–1.06). The results of our meta-analysis were mainly influenced by the results of the study of Perl *et al.*,[13] because they had the largest study group. One study had some deficiencies considering the randomization procedure. In fact it was doubtful whether the allocation of treatment was known before inclusion. Also it was a non-blinded study. Elimination of this study resulted in similar and significant results in carriers (RR 0.56, 95% CI 0.34–0.92). Three of the four studies included both carriers and non-carriers.[12,13,17] No effectiveness was observed among the non-carriers (RR 1.09, 95% CI 0.52–2.28).

Effect on the carriage status

Nasal carriage is eliminated in ~80% of patients treated with mupirocin and 30% in those treated with placebo. Elimination of *S. aureus* in patients receiving placebo can be partially explained by the fact that some of the carriers do not carry *S. aureus* persistently; these are called intermittent carriers.[38] That not all carriers are treated succesfully despite *in vitro* susceptibility can be caused by true treatment failure due to insufficient effect in the nares, which may be due to inactivation of mupirocin. Another possibility is recolonization of the nose from other untreated body parts or from the environment. The effect observed in the included studies is comparable to the effect in studies that specifically looked at the effect of a full 5 day course on nasal carriage.[39] So, the duration of treatment seems appropriate.

Overall effectiveness

This review shows that mupirocin reduces the post-operative *S. aureus* infection rate in carriers, but the overall effects in carriers are not clear. Therefore, it is unclear what effect mupirocin application in nasal *S. aureus* carriers has on the quality of life, length of hospital stay and mortality. Combining overall infection data from the studies of Konvalinka *et al.*[24] and Perl *et al.*[13] showed no difference between mupirocin-treated and placebo-treated patients (RR 1.05, 95% CI 0.54–2.04). Although unlikely, it is possible that infections with other microorganisms replace the infections caused by *S. aureus*. Perl *et al.*[13] showed a significant reduction in the *S. aureus* infection rate in the mupirocin group (RR 0.51, 95% CI 0.29–0.90), but the effect on the overall infection rate in this group was not significant (RR 0.80, 95% CI 0.58–1.10). The number of nosocomial infections caused by microorganisms other than *S. aureus* was similar in both groups (40 in the mupirocin group and 38 in the placebo group); in this study, the *S. aureus* infections that were prevented by using mupirocin were not replaced by infections caused by other microorganisms.

Surgical type

A recent systematic review by Kallen *et al.*[17] studied the effectiveness of mupirocin depending on the type of surgical procedure. Three randomized controlled and four before–after trials were included. No reduction in SSI rate was seen in randomized general surgery trials (RR 1.04, 95% CI 0.81–1.33). In non-general surgery, e.g. cardiothoracic and orthopaedic surgery, randomized trials showed a trend towards the reduction of the SSI incidence (RR 0.80, 95% CI 0.58–1.10). These results indicate that mupirocin is effective in clean high-risk surgical procedures, where the risk of *S. aureus* infection is high. The review by Kallen *et al.*[17] differed from ours because they included both carriers and non-carriers, and also they included non-randomized trials. More studies are needed to select the surgical procedures, in which mupirocin is most effective.

Development of resistance

A potential argument against the use of mupirocin is the development of resistance. This has been observed repeatedly when mupirocin was used for prolonged periods, especially when it was used as a skin ointment.[40] However, when patients are treated peri-operatively with nasal ointment, resistance has not been a significant problem. Furthermore, Fawley *et al.*[41] observed no trend towards increasing prevalence of mupirocin resistance during a 4-year study period with mupirocin use in surgical patients. In the hospital of one of the authors (J. A. J. W. K.), patients undergoing major cardiothoracic surgery have been routinely treated with mupirocin peri-operatively since 1993. More than 20 000 patients have been treated, and mupirocin resistance in *S. aureus* has not been found (J. A. J. W. K. unpublished results). Even when treatment failed, no resistant variants of *S. aureus* were found. Therefore, the conclusion is warranted that resistance is not a major issue when mupirocin is used intranasally for a short period as prophylactic agent peri-operatively.

Cost-effectiveness

Another important issue in considering mupirocin use before surgery is its cost-effectiveness. VandenBergh *et al.*[42] determined the cost-effectiveness of peri-operative mupirocin in cardiothoracic surgery. Their sensitivity analysis revealed that due to the immense costs of a SSI, an effective intervention with a relatively cheap agent like mupirocin is likely to be cost-effective, as a risk reduction of 1% would be cost-effective

already. The side effects of mupirocin are negligible. More recently, Young and Winston[43] estimated the cost-effectiveness of a screen and treat strategy. Based on a carriage rate of 31% and a risk reduction of 48%, which is comparable to what we estimated in our systematic review, a savings of approximately $1.5 million per 10 000 patients screened was predicted. In the US annually, ~30 million surgical procedures are performed. Extrapolation results in a potential cost savings of $4.5 billion when a screen-and-treat strategy is applied.

Limits

This review has several limits. The first one is the fact that the outcome is mainly determined by the results of the study of Perl *et al.*,[13] because they had the largest study group. A second limit of this meta-analysis is the lack of information regarding type and duration of antibiotic prophylaxis for surgical interventions that might have had a significant role in the development of *S. aureus*/nosocomial infections.

Recommendations

We do not recommend the use of mupirocin on all surgical patients, as there is no effect in patients that do not carry *S. aureus*. In proven nasal carriers, a significant and strong reduction on *S. aureus* infection was found. However, only one study defined the effect in proven carriers as a primary outcome measure. Therefore, conclusions should be made carefully. In view of the serious consequences of *S. aureus* infections and the safety, low costs and easy application of mupirocin combined with the limited risk for resistance associated with its short-term application, the application of mupirocin peri-operatively can be considered when the *S. aureus* infection rate is high compared to literature, despite adequate infection control measures.

Since it is now clear that the effectiveness of mupirocin is related to carriers only, future studies should only include these patients. An important obstacle for patient management in this regard has been the diagnostic delay of conventional microbiological culture methods. New developments, like real-time PCR, enable detection of the nasal carriage status in <2 h. This makes it possible to identify carriers shortly before they undergo surgery.[16] In combination with the short lead time for efficacy, this would enable a rapid screen and treat approach in this important group of high-risk patients. A large multicentred double-blind, RCT in nasal *S. aureus* carriers only is necessary for final recommendations on the routine use of mupirocin pre-operatively.

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