Use of mupirocin–chlorhexidine treatment to prevent *Staphylococcus aureus* surgical-site infections

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Evaluation of: Bode LGM, Kluytmans JAJW, Wertheim HFL *et al.*: Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N. Engl. J. Med.* 362, 9–17 (2010). *Staphylococcus aureus* is the main pathogen responsible for surgical-site infections and nasal carriage is a major risk factor for subsequent infection with this bacteria. Mupirocin is considered to be the topical antibacterial agent of choice for eradication of nasal *S. aureus*. The paper by Bode *et al.* provides strong evidence that the combination of a rapid identification of a *S. aureus* nasal carrier, mupirocin nasal ointment and chlorhexidine gluconate soap, significantly reduces the rate of *S. aureus* surgical-site infection by nearly 60%. In conclusion, mupirocin nasal ointment use in *S. aureus* carriers before surgery has numerous advantages with few side effects.

Context, methods & results

Nosocomial infections represent an important public health problem in terms of morbidity, mortality and cost. Consequently, the prevention of these infections is a key priority for healthcare providers, particularly for patients undergoing surgery. Several evidence-based preoperative measures, such as antimicrobial prophylaxis and skin antisepsis have been recommended to reduce surgical-site infections. *Staphylococcus aureus* is the most common pathogen responsible for surgical-site infections, representing 25–40% of cases. Thus, eradication of *S. aureus* carriage would conceivably decrease the rate of surgical-site infections. Moreover, it has been demonstrated that nasal carriage of *S. aureus* is a major risk factor for subsequent infection caused by this microorganism (risk increased by three to six times) [1,2] and that over 80% of healthcare-associated *S. aureus* infections have an endogenous origin [3]. In summary, nasal *S. aureus* serves as a reservoir for the spread of the pathogen and predisposes the host to subsequent autoinfections.

Mupirocin is the topical antibacterial agent of choice for eradication of nasal *S. aureus*. In hospitals in which methicillin-resistant *S. aureus* (MRSA) is an epidemic, the intranasal administration of mupirocin to both patients and staff colonized with MRSA is appropriate [4]. Furthermore, mupirocin has been successfully used to prevent staphylococcal infections in hemodialysis patients [5]. However, several trials evaluating the efficiency of mupirocin to reduce *S.*

aureus infections in both surgical and nonsurgical patients provided contrasting findings. The first ones showed a decrease in infection rates in surgical patients, however, conclusions could not be drawn due to methodological bias and particularly due to the use of historic control groups [6]. Most of the other studies were inconclusive due to low infection rates or an insufficient number of patients included [6]. Finally, two randomized, controlled trials [7,8], did not demonstrate the efficiency of mupirocin in preventing healthcare-associated *S. aureus* infections, although a subgroup analysis suggested that this strategy could be effective in *S. aureus* carriers [7]. Several hypotheses have been proposed to explain this negative result. First, the delay between admission of patient and occurrence of *S. aureus* infection is short, and failure of decolonization may have been due to a late intervention. Moreover, the delay of microbiological culture, available 24 or 48 h after sampling, reduces the window of mupirocin treatment. Noncarriers, not differentiated from carriers, dilute the benefits of mupirocin ointment [6]. Second, nasal carriers are most of the time colonized at extranasal sites. For instance, skin colonization can represent an endogenous reservoir for subsequent *S. aureus* infection and is a reservoir for nose recolonization. Extranasal colonization could therefore limit the potential benefits of mupirocin nasal ointment.

In a recent issue of the *New England Journal of Medicine*, Bode and colleagues demonstrated, in a randomized, double-blind, placebo-controlled,

multicenter clinical trial that the rate of surgical-site *S. aureus* infection can be reduced by decolonization of nasal carriers [9]. This study points out limitations of previous studies in this field. *S. aureus* nasal detection was performed using real-time PCR. This allowed a rapid inclusion (several hours instead of 1 or 2 two days for bacterial cultures) of patients in the study, and consequently, a rapid administration of mupirocin. Moreover, the use of intranasal mupirocin twice per day for 5 days was associated with daily total-body wash with chlorhexidine gluconate. This treatment was continued for 5 days even when surgery was performed during the course treatment and patients who were still hospitalized after 3 and 6 weeks received a second and third decolonization treatment. The results of the trial provide strong evidence that this strategy significantly reduces the rate of *S. aureus* surgical-site infections by nearly 60%. Interestingly, a recent meta-analysis provides corresponding results with prophylactic intranasal mupirocin associated with a significant decrease in the rate of post-operative *S. aureus* infections (RR: 0.55; 95% CI: 0.34–0.89), and no effect in noncarriers patients [6]. Finally, Bode and colleagues also observed a significant decrease of the mean hospital stay by almost 2 days, suggesting the cost-effectiveness of *S. aureus* decolonization for surgical patients.

Discussion

This publication should be considered as a landmark paper in the prevention of *S. aureus* surgical-site infection. However, several minor points should be raised. First, the authors did not report the total rate of surgical-site infections. It is rather unlikely that *S. aureus* infections within the mupirocin-chlorhexidine group have been replaced by infections due to others microorganisms and the authors stated that the distribution of the species did not differ between the two groups. It would be of interest to compare the global rate of surgical-site infection in both groups of patients. Second, implementation of this prophylactic approach implies a specific organization in surgical departments. A short length of stay between hospital admission and the surgical procedure could hamper the decolonization. Furthermore, a rapid *S. aureus* screening technique must be available in the microbiology laboratory. During recent years, real-time PCR has become a popular technique, however its routine use for *S. aureus* screening generates additional costs and workload. Third, the subgroup analysis showed that

mupirocin–chlorhexidine treatment was efficient only for cardiothoracic surgery (RR: 0.14; 95% CI: 0.04–0.51). Additional studies, including more patients, are necessary to confirm the nonsignificant trend observed in orthopedics (RR: 0.25; 95% CI: 0.03–2.26). The positive impact of the strategy on other types of surgery (vascular, gastrointestinal and general surgeries) as well as internal medicine is not proven. Thus, preemptive *S. aureus* decolonization should be used in clean high-risk surgery, where the risk of *S. aureus* infection is high (open-heart surgery, orthopedic and neurosurgical implant procedures). Fourth, the study has demonstrated the efficacy of nasal mupirocin ointment combined with chlorhexidine gluconate soap, the relative contributions of these components are unclear. Consequently, the potential use of mupirocin should be associated with chlorhexidine wash. Fifth, the results suggest that the procedure can save money, based on the 2-day reduction of mean length of hospital stay and decrease of *S. aureus* surgical site infection, however, the real cost-effectiveness of the strategy should be measured including additional costs of rapid screening technique and healthcare workload.

Future perspective

Due to the fact that this study was performed in the Netherlands, where MRSA prevalence is low (one of the lowest rate worldwide), it could be necessary to conduct a similar trial in a country where the MRSA prevalence is higher, or at least, a multicenter multistate trial including countries with various levels of MRSA.

A potential argument against the use of mupirocin is the development of resistance, observed when the antibiotic is used for prolonged periods, especially as a skin ointment [10]. On the other hand, resistance has not been a significant issue for perioperative nasal ointment. Even when treatment failed, no resistant variants of *S. aureus* were found [6]. This was also observed in this study where more than 500 patients have been treated. Resistance does not seem to be a major issue when mupirocin is used intranasally for a short period. However, monitoring of mupirocin resistance among *S. aureus* should be mandatory in settings with a large use of this antimicrobial.

According to the 2006 French national prevalence study, *S. aureus* infection (of which 30% were MRSA) is responsible for 15% of the total nosocomial infections in intensive care units. It would be of interest to test whether the strategy tested by Lode and colleagues could be efficient in this setting. An American study evaluating

the effect of *S. aureus* decolonization (nasal mupirocin plus chlorhexidine bathing) has evidenced reduction of MRSA infection incidence [11]. Further studies are still required to determine whether this strategy would be of use for some types of inpatients, such as intensive care patients.

In conclusion, the overall morbidity and mortality associated with healthcare-associated infections are enormous, and their economic burden is substantial and increasing. The development of preemptive strategies to reduce hospital infection risk has become a priority. In this context, the paper of Lode and colleagues

strongly suggests that *S. aureus* decolonization is of great interest for better surgical patient outcome and improved cost–effectiveness.

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Executive summary

Objective of study

- To determine, for *Staphylococcus aureus* nasal carriers, whether decolonization with mupirocin nasal ointment together with a total body wash with chlorhexidine soap could prevent hospital-associated infections due to *S. aureus*.

Methods

- The trial was a large, randomized, double blind, placebo-controlled, multicenter trial.
- Rapid determination of the nasal carriage status by a real-time PCR.
- A total of 5 day treatment with mupirocin ointment and chlorhexidine soap versus placebo ointment and placebo soap.
- Monitoring of *S. aureus* infection during the follow-up period was carried out.

Conclusion

- The number of surgical-site *S. aureus* infections can be reduced by rapid screening and decolonization of *S. aureus* carriers.

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