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## Chapter 4.3

# New approaches to prevention of staphylococcal infection in surgery

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## Purpose of review

The present review describes the literature about the prevention of *S. aureus* infections in surgery, published from August 2006 until January 2008 and puts it into perspective.

## Recent findings

To prevent *S. aureus* infections after surgical procedures three methods were described, i.e. isolation precautions after MRSA screening, vancomycin as antibiotic prophylaxis in patients at risk for MRSA and topical decolonisation of carriage. Identified MRSA carriers can be treated with the appropriate antibiotic prophylaxis to prevent infection with MRSA. Topical decolonisation with chlorhexidine gluconate resulted in a reduced overall nosocomial infection rate, but no effect was found on the *S. aureus* infection rate. Topical decolonisation with mupirocin reduced the overall *S. aureus* infection rate after surgery in *S. aureus* nasal carriers.

## Summary

Treatment of proven carriers of *S. aureus* with mupirocin is an effective method to prevent *S. aureus* nosocomial infections after surgery. Cost-analysis studies show that this screen-and-treat approach is cost-saving as long as the prevalence of mupirocin resistance in *S. aureus* is low. The effect of chlorhexidine gluconate on the *S. aureus* infection rate in carriers should be determined in future studies.

## Background

*Staphylococcus aureus* is the most important pathogen after surgical procedures. Although historically the focus has been on the control of cross infection, most infections are caused by strains that are carried by the patient on admission to the hospital. Nasal carriage of *S. aureus* is a well-known risk factor for subsequent infection in patients undergoing surgery.<sup>1</sup> New developments, like real-time PCR, enable detection of the nasal carriage status in <2 hours, which makes it possible to identify and treat carriers before they are operated.<sup>2</sup> This review focuses on literature published from August 2006 until January 2008, describing approaches to prevent both meticillin-sensitive and meticillin-resistant *Staphylococcus aureus* (MSSA and MRSA) infections in surgical patients.

## Risk factors for surgical site infections caused by *S. aureus* in surgery

Munoz *et al.* performed a one-year observational study to determine the risk factors for development of surgical site infections after major heart surgery (MHS).<sup>3\*</sup> 27% (96/357) of the patients undergoing MHS were found to be nasal carrier of *S. aureus* before surgery. The overall SSI rate was 6.4%, 15 (4.2%) patients developed a post-surgical mediastinitis and eight (2.2%) a superficial SSI. The most commonly isolated pathogen was *S. aureus*, causing 64% (16 of 23) of the infections, eight among nasal carriers and eight among non-carriers. Stratified stepwise multivariate analysis of risk factors for SSI showed that the independent risk factors for SSI were *S. aureus* nasal carriage (RR 3.1, 95% CI 1.4-7.3), reoperation (RR 3.1, 95% CI 1.8-19.2) and diabetes mellitus (RR 5.9, 95% CI 1.8-19.2). In this risk factor analysis, the SSI caused by any micro-organism was taken into account. The *S. aureus* SSI incidence of carriers was 8.3% (8/96), in contrast to 3.1% (8/261) of the non-carriers (RR 2.7, 95% CI 1.1-7.6). This study showed that nasal carriage is an important risk factor for the development of a SSI with *S. aureus*, which had been shown in other studies before.

## Routine MRSA screening and intra operative antimicrobial prophylaxis

Morange *et al.* determined the prevalence of nasal carriage of methicillin-resistant *S. aureus* in vascular surgery patients and performed a case-control study to define the risk factors of high-risk patients for MRSA nasal carriage at admission to the vascular surgery unit.<sup>4\*</sup> They included all patients hospitalized longer than 24 hr in a 19-bed vascular surgery unit over the 4-month study period between March and July 2004. A total of 468 swabs were taken from 308 patients. 35 (11.4%) were identified as MSSA carrier and 13 (4.2%) turned out to be positive for MRSA. The MRSA carriage rate at admission was 2.9% (n=9) and the rate of MRSA acquisition in the vascular surgery unit was 1.3% (n=4). To identify risk factors for MRSA carriage at admission to the vascular unit, the 9 patients with MRSA carriage at admission were matched to 36 controls, i.e. patients without MRSA or MSSA. Both the origin of the patient from another department and from another medical facility were identified as a risk factor for MRSA carriage at admission to the vascular unit. Four of the total of 13 MRSA carriers developed MRSA infection, i.e. infection of stump area after lower limb amputation in two patients and infection of femoropopliteal bypass in two other patients. MRSA infection was highly related to MRSA colonisation (OR=65, 95% CI 8.5-606,  $p < 0.001$ ). The MRSA infection rate was 30.8% (4/13) for patients with nasal colonisation versus 0.68% (2/295) for

patients without nasal colonisation. Both the MRSA carrier as other patients in the unit benefit from this early identification of MRSA carriers. Adequate isolation measures can be taken for MRSA carriers, to avoid spread of MRSA to other patients. The benefit for the MRSA carrier is the prescription of appropriate antibiotics, for example intra-operative antimicrobial prophylaxis. Morange *et al.* advise that the French recommendations on preoperative management issued for cardiac and orthopedic surgery should be extended to vascular surgery. Patients in this study did not undergo treatment to eradicate carriage of MRSA. It would be interesting to determine whether MRSA carriers treated with mupirocin ointment or antiseptic cleansing would have a reduced MRSA infection rate.

Muralidhar *et al.* determined the MRSA prevalence in emergency and elective patients admitted to a vascular surgery unit.<sup>5\*</sup> They showed a higher prevalence of MRSA carriage in emergency/transfer patients (30/153) than in elective patients (2/108). A simple decision analysis model suggested that gentamycin should be used as antibiotic prophylaxis when the prevalence of MRSA reaches 10% and vancomycin when the prevalence reaches 50%. However, there is a major concern that the use of vancomycin prophylaxis results in development of vancomycine-resistant *S. aureus*. Merrer *et al.* demonstrated that short-term use of vancomycin in patients undergoing femoral neck fracture surgery had similar impacts on the emergence of glycopeptide-resistant pathogens as cefazolin.<sup>6\*</sup> Patients without risk factors for MRSA were treated with cefazolin pre-operatively, while patients with risk factors (admission from a nursing home or long-term care facility, known previous MRSA carriage, or chronic wound) were treated with vancomycin. A SSI was detected in 6 (4%) of 152 patients in the cefazolin group and in 2 (2%) of 106 patients in the vancomycin group ( $p=0.47$ ). In the cefazolin group, 4 of the 6 SSI were caused by a *S. aureus* (1 MRSA) and in the vancomycin group 1 of the 2 SSI was caused by a *S. aureus* (MSSA). This was not statistically significant (RR 0.36, 95% CI 0.05-2.35), which indicates a protecting effect of vancomycin on the *S. aureus* SSI rate in patients at risk for MRSA. The authors suggested that a larger multicentre study should be initiated. The study design of Merrer *et al.* is from low quality. However, it is questionable if a double-blind randomized controlled trial on this subject would be ethical, because in that study design MRSA positive patients in the control group would be administered antibiotics that are known to be ineffective for MRSA.

The suggestions made by Muralidhar *et al.* and Merrer *et al.* to prescribe vancomycin to patients in a setting with a high MRSA prevalence (>50%) or to patients at risk for MRSA, respectively, will therefore probably never become evidence based.

## Topical *S. aureus* decolonisation

As *S. aureus* nasal carriage is the main risk factor for a SSI caused by *S. aureus*, one preventive approach is topical decolonisation. Several decolonisation measures are available. We will discuss chlorhexidine gluconate or intranasal mupirocin, eventually combined with chlorhexidine soap.

### Chlorhexidine gluconate treatment

Segers *et al.* studied the effect of perioperative decontamination of the nasopharynx and oropharynx with 0.12% chlorhexidine gluconate on the reduction of nosocomial infection after cardiac surgery.<sup>7\*\*</sup> This prospective, randomized, double-blind, placebo-controlled trial was conducted at the Onze Lieve Vrouwe Gasthuis, in Amsterdam, The Netherlands, between August 2003 and September 2005. In this 480-bed community hospital, 1200 cardiac surgical procedures were performed annually. Patients older than 18 years who were scheduled to undergo sternotomy for cardiothoracic surgery were included. Patients undergoing emergency procedures, preoperative infection, preoperative use of antimicrobials, hypersensitivity to chlorhexidine gluconate, and treatment with an alternative prophylactic regiment like selective decontamination of the digestive tract were excluded. 991 patients were randomized, 500 to the chlorhexidine group and 491 to the placebo group. Of these, 15 patients discontinued treatment, which resulted in analysis of 485 and 469 patients in the treatment and placebo group, respectively. 22 patients were excluded later from analysis because they received preoperative selective decontamination of the digestive tract after inclusion. Follow-up was complete in all patients and identical in both groups. Both groups received an oropharyngeal rinse and a nasal ointment containing either chlorhexidine gluconate or placebo. The oropharyngeal solution (10ml) was used as a mouth rinse and applied to buccal, pharyngeal, gingival, and tooth surfaces for 30 seconds 4 times daily. The nose ointment was applied 4 times a day in both nostrils. The protocol was continued until the nasogastric tube was removed, usually the day after surgery. Before intervention, there was no difference in the number of patients with *S. aureus* nasal carriage between treatment and placebo group (36.5% and 30.7%, respectively). At the time of the operative procedure, the number of *S. aureus* carriers in the treatment group was reduced from 36.5% to 15.5% ( $p < 0.001$ ), resulting in an Absolute Risk Reduction (ARR) of 37.5% (95% CI 27.7%–47.3%). In the placebo group no significant difference in *S. aureus* carriage rate was found between cultures taken at admission (30.7%) and those taken at surgery (24.5%). Primary outcome measure was the overall incidence of nosocomial infection, using the criteria developed by the Centres For Disease Control and Prevention. Secondary outcomes included the incidence of lower respiratory tract infection (LRTI) and SSI, *S. aureus* nasal carriage, nonprophylactic antimicrobial use,

duration of hospital stay, in-hospital mortality, and trial medication adverse effects. 96 patients (19.8%) in the chlorhexidine gluconate group developed 116 nosocomial infections compared with 123 patients (26.2%) with 164 nosocomial infections in the placebo group (ARR 6.4%, 95% CI 1.1–11.7%,  $p=0.002$ ). Patients in the treatment group developed significant less LRTI than patients in the placebo group ( $n=45$  versus  $n=74$ ,  $p=0.002$ ). Incidence of overall SSI was 9.9% in the chlorhexidine gluconate group and 10.9% in the placebo group, which did not differ significantly. However, less deep SSI were observed in the treatment group ( $n=9$  versus  $n=24$ ,  $p=0.002$ ). Patients treated with placebo suffered more often from a bacteraemia than patients treated with chlorhexidine gluconate ( $n=17$  versus  $n=9$ ,  $p=0.001$ ). An adverse effect from chlorhexidine gluconate was observed in 1 patient (0.2%) who experienced temporary minor discoloration of the teeth. Duration of hospital stay and in-hospital mortality did not differ between treatment and placebo group. This study looked at the overall nosocomial infection rate, but did not look specifically at the *S. aureus* infection rate. However, they mentioned the micro-organisms found in cultures from patients with LRTI and SSI. Using the Chi-square test, no statistical difference in *S. aureus* infection rate (both LRTI and SSI) was found between the treatment and placebo group.

## Mupirocin treatment

Recently, two systematic reviews about the effect of mupirocin on the *S. aureus* SSI rate were performed.<sup>8\*,9\*\*</sup> Trautmann *et al.* analyzed 4 randomized trials and seven sequential cohort studies investigating mupirocin nasal treatment for prophylaxis of SSI in elective surgery in comparison with placebo or no treatment.<sup>8\*</sup> Mupirocin application schemes varied widely, although there was no correlation between the duration of mupirocin treatment and reduction in SSIs. They concluded that mupirocin prophylaxis did not reduce the *S. aureus* SSI rate in patients undergoing orthopedic, gastrointestinal and cardiothoracic surgery. In contrast, mupirocin prophylaxis before surgery reduced the SSI rate due to MRSA and was therefore recommended in countries with high prevalences of MRSA. The weaknesses of this study are that non-English papers were excluded and that no analysis of the effect in carriers only was made.

In the review of Van Rijen *et al.*, the effect of intranasal mupirocin on the nosocomial *S. aureus* infection rate after surgery was studied in patients with *S. aureus* nasal carriage.<sup>9\*\*</sup> This in contrast to Trautmann *et al.*, who studied the effect in both patients with and without carriage.<sup>8\*</sup> Their search resulted in 3 randomized placebo-controlled trials and 1 randomized trial in which no placebo was used. 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;  $p=0.002$ ). Although mupirocin reduced the overall occurrence of nosocomial *S. aureus* infections, no significant reduction on surgical site infections caused by *S. aureus* was



seen (RR 0.64, 95% CI 0.38–1.06). The limit of this study is the fact that the outcome is mainly determined by the results of the study of Perl *et al.*, because they had the largest study group.<sup>10</sup> They conclude that pre-operative mupirocin can be considered when the *S. aureus* infection rate is high compared to literature, despite adequate infection control measures.

## Cost-effectiveness

Recently, two cost-effectiveness analyses about screening and decolonisation of *S. aureus* were performed.<sup>11\*\*,12\*</sup> Young *et al* compared three strategies, (1) screening and treatment of carriers, (2) treatment of all patients and (3) neither screen nor treat.<sup>11\*\*</sup> Model data inputs were obtained from literature search and government data sources. The rate of *S. aureus* carriage was estimated at 23.1%, efficacy of mupirocin treatment at 51%, mupirocin treatment costs at \$48.36, and hospital costs of bloodstream infection at \$25,128, of pneumonia at \$18,366 and SSI at \$16,256. Both screening strategies were cost-saving and prevented 86 *S. aureus* infections for every 10,000 patients undergoing surgery. The treat-all strategy prevented 1 infection for every 116 patients treated and 1 death per 10,000 patients treated, resulting in a cost saving of \$88 per patient undergoing surgery. The screen-and-treat strategy prevented 1 infection for every 27 patients treated and 1 death for every 2,500 patients treated. This yielded a saving of \$102 per surgical patient. Excluding home healthcare costs resulted in savings of \$ 117 per patient with the screen-and-treat strategy, compared with savings of \$109 per patient with the treat-all strategy.

Noskin *et al.* used a budget impact model to evaluate the economic impact of performing rapid testing and subsequent decolonisation of *S aureus* in patients undergoing elective surgery.<sup>12\*</sup> In 2003, the number of patients admitted for elective surgery in US hospitals was 7,181,484. Several model input variables were based on literature or hypothesised by the authors. The rapid diagnostic test for *S. aureus* was estimated to have 52% sensitivity and 85% specificity. Second, a baseline efficacy rate of 56.5% for decolonisation of *S. aureus* was selected. Third, treatment would be initiated prior to the scheduled hospital admission and would last for 5-10 days. The probability of *S. aureus* infections in *S. aureus* nasal carriers was estimated at 7.5% and in patients without nasal carriage at 1.5%. The costs for rapid testing was assumed to be \$25 and for decolonisation treatment \$72.5. Based on this model the cost savings in the year 2004 were estimated at \$231,538,400. The mean number of hospital-days was reduced by 364,919, and a mean of 935 in-hospital deaths due to *S. aureus* infection could be avoided.

## Conclusion

Several approaches to prevent *S. aureus* infections after surgery were described, which are mainly targeted at prevention of endogeneous infections. MRSA screening and subsequent isolation measures protect other patients and health care workers from being colonised and/or infected with MRSA and the index patient benefits by prescription of appropriate antibiotics. Vancomycin is recommended as antibiotic prophylaxis in patients at risk for MRSA, while topical decolonisation with mupirocin is recommended as prophylaxis for patients with *S. aureus* nasal carriage. This screen-and-treat approach was proven to be cost-saving. Chlorhexidine gluconate reduced the overall nosocomial infection rate, but no significant effect on the *S. aureus* infection rate was observed.

The future control of *S. aureus* (including MRSA) in surgical patients should focus on effective prevention of endogenous infection. Mupirocin nasal ointment and chlorhexidin are potential candidates. A placebo controlled randomized trial in carriers only is needed to determine the effectiveness of such a strategy.

## Acknowledgements

Potential conflicts of interest. All authors: no conflicts.

# References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

\* of special interest

\*\* of outstanding interest

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3. \* Munoz P, Hortal J, Giannella M, et al. Nasal carriage of *S. aureus* increases the risk of surgical site infection after major heart surgery. *J of Hosp Infect* 2008; 68:25-31.

The independent risk factors for SSI after major heart surgery were shown to be *S. aureus* nasal carriage, reoperation and diabetes mellitus.

4. \* Morange-Saussier V, Giraudeau B, van der Mee N, et al. Nasal carriage of methicillin-resistant *Staphylococcus aureus* in vascular surgery. *Ann Vasc Surg* 2006; 20(6):767-72.
5. \* Muralidhar B, Anwar SM, Handa AI, et al. Prevalence of MRSA in emergency and elective patients admitted to a vascular surgical unit: implications for antibiotic prophylaxis. *Eur J Vasc Endovasc Surg* 2006; 32(4):402-7.

A simple decision analysis model suggested that gentamycin should be used as antibiotic prophylaxis when the prevalence of MRSA reaches 10% and vancomycin when the prevalence reaches 50%.

6. \* Merrer J, Desbouchages L, Serazin V, et al. Comparison of routine prophylaxis with vancomycin or cefazolin for femoral neck fracture surgery: microbiological and clinical outcomes. *Infect Control Hosp Epidemiol* 2006; 27(12):1366-71.

Merrer et al demonstrated that no development of vancomycin resistance was observed after short-term application. They suggest to use vancomycin as antibiotic prophylaxis in patients at risk for MRSA to prevent MRSA infection.

7. \*\* Segers P, Speekenbrink RG, Ubbink DT, et al. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial. *JAMA* 2006; 296(20):2460-6.

This well-designed study showed that chlorhexidine gluconate resulted in a reduced overall nosocomial infection rate, but no effect was found on the *S. aureus* infection rate. Unfortunately, the results for *S. aureus* nasal carriers was not described separately.

8. \* Trautmann M, Stecher J, Hemmer W, et al. Intranasal mupirocin prophylaxis in elective surgery. A review of published studies. *Chemotherapy* 2008; 54(1):9-16.

This review showed that mupirocin prophylaxis did not reduce the *S. aureus* SSI rate in patients undergoing surgery. In contrast, mupirocin prophylaxis before surgery reduced the SSI rate due to MRSA. The weakness of this study is that non-English papers were excluded.

9. \*\* van Rijen MML, Bonten M, Wenzel RP, Kluytmans JAJW. Intranasal mupirocin for reduction of *Staphylococcus aureus* infections in surgical patients with nasal carriage: a systematic review. *J Antimicrob Chemother* 2008; 61(2):254-61.

This systematic review describes the importance of screening and treating *S. aureus* nasal carriers to prevent *S. aureus* infections after surgery. This is the first study describing the results in carriers only instead of all patients, i.e. carriers and non-carriers.

10. Perl TM, Cullen JJ, Wenzel RP, *et al.* Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. *N Engl J Med* 2002; 346:1871-7.
11. \*\* Young LS, Winston LG. Preoperative use of mupirocin for the prevention of healthcare-associated *Staphylococcus aureus* infections: a cost-effectiveness analysis. *Infect Control Hosp Epidemiol* 2006; 27(12):1304-12.

This model-based analysis showed that both screening of all patients and screening and subsequent treatment of carriers were cost-saving and prevented 86 *S. aureus* infections for every 10,000 patients undergoing surgery.

12. \*\* Noskin GA, Rubin RJ, Schentag JJ, *et al.* Budget impact analysis of rapid screening for *Staphylococcus aureus* colonisation among patients undergoing elective surgery in US hospitals. *Infect Control Hosp Epidemiol* 2008; 29(1):16-24.

This model-based analysis showed that the cost-savings of rapid testing and decolonisation of *S. aureus* before surgery in the year 2004 were estimated at \$231,538,400. The mean number of hospital-days was reduced by 364,919 and a mean of 935 in-hospital deaths due to *S. aureus* infections could be avoided.