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Chapter 4.5

Decreased one-year mortality after rapid screening and decolonisation of *S. aureus* carriers undergoing clean surgical procedures: Observational follow-up study of a randomized, placebo-controlled trial

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Submitted

Abstract

Objective

To identify patients who benefit most from *S. aureus* screening and decolonisation treatment upon admission.

Summary Background Data

In *S. aureus* carriers, the risk of surgical-site infections with *S. aureus* is increased. Previously, we demonstrated in a randomized, placebo-controlled trial (RCT) that these infections can largely be prevented by detection of carriage and decolonisation treatment upon admission. In the present study, we use one- and three-year mortality rates in both treatment arms of the RCT to identify patient groups that should be targeted when implementing the screen-and-treat strategy.

Methods

The municipal personal records database was checked for mortality dates of all surgical patients three years after enrolment in the RCT. One- and three-year mortality rates were calculated for all patients, for subgroups according to type of surgery, and for patients with clean procedures.

Results

Of the 808 patients enrolled, 793 patients were included in the analysis. After three years, 44/431 (10.2%) and 43/362 (11.9%) had died in the mupirocin/chlorhexidine and placebo groups, respectively. No significant differences in mortality rates were observed between the treatment groups or the subgroups according to type of surgery. In the subgroup of 666 patients with clean procedures (382 cardiothoracic, 167 orthopaedic, 61 vascular, and 56 other procedures), mupirocin/chlorhexidine significantly reduced one-year mortality: 11/365 (3.0%) died in the mupirocin/chlorhexidine group versus 21/301 (7.0%) in the placebo group (RR 0.38, 95% CI 0.18–0.81, p=0.012).

Conclusion

Detection and decolonisation of *S. aureus* carriage not only prevents healthcare associated *S. aureus* infections, but also significantly reduces one-year mortality in surgical patients undergoing clean procedures. This subgroup should be the primary target when implementing the screen-and-treat strategy in clinical practice.

Background

Staphylococcus aureus (S. aureus) colonises the nares and skin of a substantial proportion of the human population. Carriage rates range from about 20 to 50%, depending on the population and the definitions used.[1,2] Colonisation with *S. aureus* is usually harmless in healthy individuals. However, carriage is known to be a risk factor for the development of healthcare associated *S. aureus* infections.[3,4] Prospective studies demonstrate that approximately 80% of *S. aureus* strains isolated from healthcare associated infections are identical to the nasal strains found in these patients upon admission.[5-7]

Hospital-acquired infections are associated with increased morbidity, mortality, length of stay and hospital costs.[8-10] Recently, we demonstrated in a multicentre, randomized, placebo-controlled trial (RCT) that approximately 60% of healthcare associated infections with *S. aureus* can be prevented by rapid screening of patients for *S. aureus* carriage upon admission, and subsequent decolonisation treatment with mupirocin nasal ointment and washing with chlorhexidine gluconate medicated soap: 17/504 (3.4%) patients in the mupirocin/chlorhexidine group, and 32/413 (7.7%) patients in the placebo group developed *S. aureus* infections.[6] The effect of the intervention was most prominent in surgical patients and largely due to the prevention of endogenous deep surgical site infections (SSI): 4/441 (0.9%) surgical patients in the mupirocin/chlorhexidine group, and 16/367 (4.4%) in the placebo group developed a deep *S. aureus* SSI infection.

The implementation of the screen-and-treat strategy poses a logistic challenge to clinical practice. The results of *S. aureus* screening have to be available within a few hours after admission to be able to start treatment with mupirocin and chlorhexidine in time. This requires participation of the patient, nurses, doctors, and laboratory personnel, including timely communication between the laboratory and the patient's attending physician and nurses. Results of reliable rapid diagnostic screens should be reported rapidly. The use of mupirocin without screening for carriage is discouraged, since it would not provide any benefit for the (*S. aureus* non-carrying) majority of patients, and increases the risk of emergence of mupirocin resistance.[11,12] Therefore, it is very important to identify those patient groups that benefit most from a screen-and-treat strategy.

We hypothesised that preventing deep surgical site infections would have a beneficial effect on mortality beyond the initial follow up period of the RCT. Thus, in the present study, we compared one- and three-year mortality rates of surgical patients treated with mupirocin nasal ointment and chlorhexidine gluconate soap, with the rates of those that had received placebo medication. Since the majority of deep SSI developed after cardiac, orthopaedic, and vascular surgery, we also assessed mortality rates in different subgroups of patients.

Methods

In a randomised, double blind, placebo-controlled, clinical multicentre trial, approved by the medical ethics committees of the participating hospitals, surgical and non-surgical patients (n=6771) were screened for nasal *S. aureus* carriage by real-time PCR. Of those, 1251 tested positive for *S. aureus* nasal carriage. Carriers of *S. aureus* who met the inclusion criteria and gave informed consent (n=917) were randomised to receive either mupirocin nasal ointment 2% and chlorhexidine gluconate soap 40 mg per milliliter, or placebo ointment and placebo soap, as previously described.[6] The duration of the study treatment was five days. Patients who were still hospitalised after three weeks and those still hospitalised after six weeks received a second and third course of the same trial medication, respectively. Follow-up for the development of healthcare associated *S. aureus* infections was until six weeks after discharge from the hospital. For each surgical patient enrolled in the RCT (n=808), three years after the date of enrolment the municipal personal records database was checked for the presence of a mortality date by using the patient's birth name, date of birth and zip code, which was done by a data manager who was blinded for the intervention. The municipal personal records database contains the personal details of all inhabitants of the Netherlands. Among other purposes it is used by the government to collect taxes.

We used univariate Kaplan Meier and the Mantel-Cox log-rank test to assess whether the use of mupirocin and chlorhexidine was associated with one- and three-year mortality rates. Analyses were performed for all surgical patients, as well as for the following subgroups: five subgroups according to the type of surgery (cardiothoracic surgery; orthopaedic surgery; vascular surgery; abdominal surgery; and other type of surgery), and two subgroups based on the CDC wound classification system[13]: patients with clean procedures and patients with clean-contaminated, contaminated or dirty procedures. If the Mantel-Cox log-rank P-value was less or equal to 0.1, the following determinants were analysed by Kaplan Meier and Mantel-Cox log-rank tests to be identified as a possible confounder for mortality rates: gender; diabetes mellitus; CAPD; renal insufficiency; end stage liver disease; solid or hematological malignancy; immune-compromised state; use of immunosuppressive medication; modified McCabe score[14]; and, if applicable, the surgical department where patients were admitted. Subsequently, a Cox-regression survival analysis was performed including age, and those determinants with a Mantel-Cox log-rank P-value less or equal to 0.1, to identify factors associated with mortality at one and three years after the date of inclusion.

Results

Of the 808 surgical patients enrolled in the multicentre RCT, 15 patients (1.9%) were lost to follow up because birth dates and zip codes did not match. Of the remaining 793 patients, 22/431 (5.1%) patients in the mupirocin/chlorhexidine treated group, and 29/362 (8.0%) in the placebo treated group had died within the first year after enrolment. After three years, 44/431 (10.2%) and 43/362 (11.9%) had died in the mupirocin/chlorhexidine and placebo groups, respectively. Table 1 shows the results of the univariate and, if applicable, multivariate analyses for all surgical patients together, as well as for the different subgroups. Figure 1 shows the cumulative hazard of mortality in both treatment groups. The median time to mortality did not significantly differ between the two treatment groups (mupirocin/chlorhexidine vs. placebo: median 99 vs. 135 days (P=0.49) after 1 year, and 365 vs. 273 days (p=0.11) after 3 years).

Of the 87 patients who died, 14 (16.1%) had a documented healthcare associated *S. aureus* infection according to CDC definitions within the follow-up period of the randomised controlled trial.[15] Eight of these infections were deep surgical site infections (SSI): two in the mupirocin/chlorhexidine group (2 out of 44 patients who died, 4.5%) and six in the placebo group (6/43 = 14.0%); p=0.13. Other healthcare associated infections were superficial SSIs (1 in the mupirocin/chlorhexidine group, 1 in the placebo group), lower respiratory tract infections (1 in the mupirocin/chlorhexidine group, 2 in the placebo group), and bacteraemia (1 in the mupirocin/chlorhexidine group).

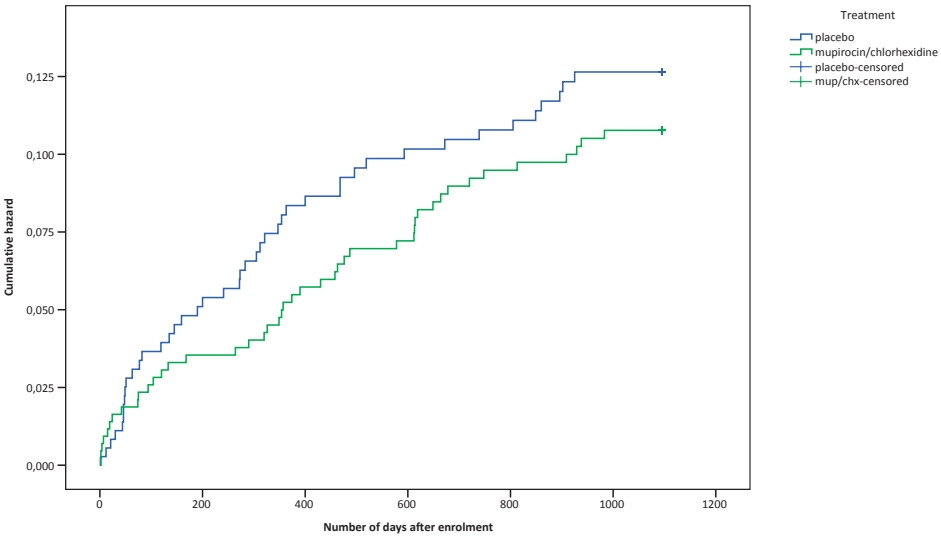

Figure 1. Kaplan–Meier curves showing cumulative hazard of mortality in the two treatment groups.

Table 1. Effect of treatment on one-year and three-year mortality in surgical patients, and in different subgroups.

	mupirocin / chlorhexidine			placebo					
	N =	***deaths year 1 no (%)***	***deaths year 3 no (%)***	***N=***	***deaths year 1 no (%)***	***deaths year 3 no (%)***	***P-value year 1***	***adjusted RR yr 1 [95% CI]***	***P-value year 3***
all surgical patients	431	22 (5.1)	44 (10.2)	362	29 (8.0)	43 (11.9)	0.099	0.65 [0.37-1.14]	0.435
cardiac surgery	231	6 (2.8)	14 (6.6)	171	13 (7.6)	18 (10.5)	0.032	0.38 [0.13-1.06]	0.153
orthopaedic surgery	85	1 (1.2)	6 (7.1)	85	2 (2.4)	5 (5.9)	0.561	NA	0.745
vascular surgery	52	5 (9.6)	7 (13.5)	39	6 (15.4)	9 (23.1)	0.394	NA	0.229
abdominal surgery	21	5 (23.8)	7 (33.3)	21	4 (19.0)	5 (23.8)	0.721	NA	0.514
other procedures	60	5 (8.3)	10 (16.7)	46	4 (8.7)	6 (13.0)	1.000	NA	0.592
clean procedures	365	11 (3.0)	27 (7.4)	301	21 (7.0)	30 (10.0)	0.017	0.38 [0.18-0.81]	0.221
non-clean procedures	48	8 (16.7)	11 (22.9)	51	6 (11.8)	9 (17.6)	0.483	NA	0.499

NA = not applicable.

In the RCT, a total of 47 surgical patients had developed a healthcare associated *S. aureus* infection within its follow-up period (16 in the mupirocin/chlorhexidine group, 31 in the placebo group). Twenty patients had a documented deep SSI (4 in the mupirocin/chlorhexidine group, 16 in the placebo group). Of these patients, six (30%) had died within a year (1 in the mupirocin/chlorhexidine group, 5 in the placebo group), and eight (40.0%) had died within three years after enrolment (2 in the mupirocin/chlorhexidine group, 6 in the placebo group). Of the 746 patients who had not developed any healthcare associated *S. aureus* infection within the follow-up period, 73 (9.8%) had died after three years (39/415 (9.4%) in the mupirocin/chlorhexidine group, and 34/331 (10.3%) in the placebo group).

One-year mortality rates

In the univariate and multivariate analyses of all surgical patients together, no significant difference in one-year survival was found between the two treatment groups (table 1). When in the univariate analysis the patients were stratified according to their type of surgery (orthopaedics, cardiothoracic surgery, vascular surgery, abdominal surgery, or other types of surgery), one-year mortality was significantly decreased in the mupirocin/chlorhexidine group compared to the placebo treated group in cardiothoracic patients (6/213 patients (2.8%) died in the mupirocin/chlorhexidine group versus 13/171 patients (7.6%) in the placebo group, p=0.032). In the multivariate analysis, the effect of mupirocin/chlorhexidine on the mortality rate was not significant (adjusted relative risk (RR) 0.38, 95% CI 0.13–1.06; p=0.064).

Of the 793 surgical patients, 666 patients underwent a clean surgical procedure (including 382 cardiothoracic, 167 orthopaedic, 61 vascular, and 56 other procedures). In this group both the univariate and multivariate analysis showed that mupirocin/chlorhexidine significantly reduced one-year mortality. According to the univariate analysis, 11/365 (3.0%) died in the mupirocin/chlorhexidine group versus 21/301 (7.0%) in the placebo group, p=0.017. In the multivariate analysis, the adjusted relative risk for mortality in the mupirocin/chlorhexidine group was 0.38 (95% CI 0.18–0.81, p=0.012). Other factors significantly associated with mortality in the multivariate analysis were the presence of a solid or hematological malignancy (adjusted RR 4.65, 95% CI 1.58-13.70, p=0.005), and age (adjusted RR per year 1.08, 95% CI 1.03-1.12, p=0.001). The median time to mortality did not significantly differ between the two treatment groups (mupirocin/chlorhexidine vs. placebo: 75 vs. 82 days (p=0.82)). Fifteen patients who had underwent a clean procedure had developed a deep SSI. In the placebo group, 5/12 (41.7%) of these patients had died within a year after enrolment. In the mupirocin/chlorhexidine group, 0/3 (0%) of these patients had died. In other words, 5/21 (23.8%) patients who had died in the placebo group, and 0/11 (0%) patients in the mupirocin/chlorhexidine group, had suffered

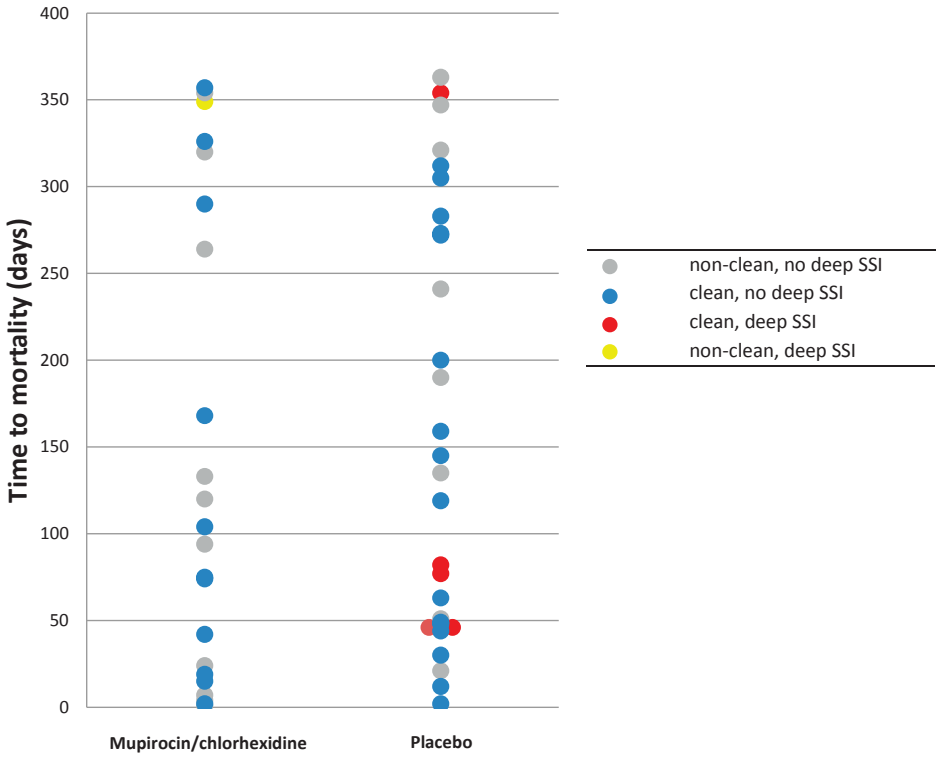

Figure 2. Scatterplot showing the time from enrolment to mortality for all patients who died within the first year of follow-up. Patients who underwent a clean procedure are depicted in blue (no deep SSI, n=11 in the mup/chx group and n=16 in the placebo group) or red (deep SSI, n=5 in the placebo group). Patients who underwent a non-clean procedure are depicted in grey (no deep SSI, n= 7 in the mup/chx group, and n=6 in the placebo group) or yellow (deep SSI, n=1 in the mup/chx group).

from a deep surgical site infection within the follow-up period of the randomised controlled trial.

The effect of mupirocin/chlorhexidine on one-year mortality in patients who did not undergo clean procedures (including clean-contaminated, contaminated, and dirty-infected wounds) was not significant (p=0.483, table 1).

Figure 2 shows the time to mortality for all patients in the two treatment groups who died within the first year.

Three-year mortality rates

No significant differences in mortality rates were found between the two treatment groups at three years after randomization (table 1). After excluding the first year, the mortality rates for the second and third years after randomization were not significantly different either (data not shown).

Discussion

With the present study, we show that one- and three-year mortality rates of *S. aureus* carriers undergoing surgery, and treated prophylactically with mupirocin and chlorhexidine, did not significantly differ from these rates in patients treated with placebo. However, in the large subgroup of patients who underwent clean surgery (cardiothoracic, orthopaedic, vascular and other procedures), one-year mortality was nearly three times lower in the mupirocin and chlorhexidine group than in the placebo group (adjusted relative risk 0.38, 95% CI 0.18–0.81).

Therefore, the reduction in the *S. aureus* infection rate that was previously reported clearly has a beneficial effect beyond 6 weeks after discharge from hospital.[6] Our findings can be useful to select those patients, which benefit most from the screen-and-treat strategy for *S. aureus* carriage. In the preceding RCT nonsurgical patients as well as patients undergoing cardiothoracic, orthopaedic, vascular, abdominal and miscellaneous other types of surgery were enrolled.[6] Within these categories, many different types of surgery were performed, ranging from prosthetic joint replacement to trauma surgery, and from coronary artery bypass surgery to low anterior resection of the rectum. However, for reasons of logistics and costs, it may not be needed, nor may it be feasible, to screen every surgical patient entering the hospital. Indiscriminately treating all patients is discouraged, since the use of mupirocin should be restricted to those that may benefit, and to avoid development of resistance.[16,17] Furthermore, without screening, the potential emergence of mupirocin resistant *S. aureus* clones cannot be detected at an early stage. Therefore, it is important to identify patient groups in which the screen-and-treat strategy for *S. aureus* carriage has the best preventive effect on morbidity and mortality. This study demonstrates that patients undergoing clean procedures should be targeted for this screen-and-treat strategy.

An important drawback of our study is that the causes of death were not available in the municipal records. Although a causal relationship with mortality cannot be demonstrated, the number of patients with a documented deep SSI who had died, markedly differed between the two treatment groups in favor of mupirocin and chlorhexidine. This provides further argument that the screen-and-treat strategy has a beneficial impact on mortality in clean surgery by preventing health-care associated *S. aureus* infections.

From the US Centres for Disease Control definition of a clean (class I) wound, it follows that these surgical procedures do not enter colonised tracts, but usually breach the skin only.[18] Clean wound infections are, therefore, most likely caused by skin flora, particularly *S. aureus*. Thus, it is not surprising that the effect of the screen-and-treat strategy for *S. aureus* carriage on mortality is most evident in patients who undergo clean procedures.

The size of the subgroups in separate surgical procedures was too small to have sufficient power to show any effect on mortality. Also, mortality was low in several surgical specialties, e.g. in the orthopaedic subgroup, where only 1/85 (1.2%) and 2/85 (2.4%) patients died in the mupirocin/chlorhexidine and placebo treated group, respectively. Even though it seems that patients who underwent an orthopaedic procedure do not die from *S. aureus* infections, these infections frequently have devastating consequences for the patient. We did not, however, analyse morbidity or quality of life. In another study we found a significant difference in costs between treated and non-treated patients that had undergone cardiothoracic and orthopaedic procedures.[19] The average cost to the hospital was € 2,841 lower for a cardiothoracic patient, and € 955 lower for an orthopaedic patient who had been treated with mupirocin/chlorhexidine, as compared to placebo-treated patients.

We did not only compare one-year, but also three-year mortality rates between mupirocin/chlorhexidine and placebo treated patients. After three years, no significant differences were found. The mortality rates during the second and third years after enrolment were, however, statistically not different. The screen and treat strategy, thus, only affects mortality within the first year after surgery; after three years this effect naturally wanes since patients will die from causes other than from deep surgical wound infections which occurred more than one year before.

Most studies on *S. aureus* screening in the last decade have focused on MRSA only.[20-22] Our results question this selected approach, since it neglects meticillin susceptible *S. aureus* (MSSA), which remains the leading cause of invasive infections in most countries.[23] For prevention of infections in surgical patients, screening for *S. aureus*, including both MRSA and MSSA, would be the preferred strategy. Meanwhile, the US Centres for Disease Control have now included this strategy in their top recommendations for safer health care. It has more impact on patient safety, and for the laboratory, it is technically simpler since only the presence of *S. aureus*-specific targets have to be covered. Our results support limiting the indication for the *S. aureus* screen-and-treat strategy to clean surgical procedures.

In conclusion, rapid detection and decolonisation of *S. aureus* carriers not only reduces the incidence of healthcare associated *S. aureus* infections, but also significantly reduces one-year mortality in surgical patients who undergo clean operations. We identified the patient group that benefits most from this screen and treat strategy in terms of one-year survival, and this group should thus be targeted when implementing a *S. aureus* screen-and-treat strategy in clinical practice. The results of this study provide an important stimulus to opinion leaders and decision makers to change current pre-operative protocols and allocate resources for this prophylactic strategy.

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