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# Randomized, placebo-controlled, double-blind clinical trial to evaluate the efficacy of polyhexanide for topical decolonization of MRSA carriers

**C. Landelle[1], E. von Dach[1], T. Haustein[1], A. Agostinho[1], G. Renzi[2], A. Renzoni[3], D. Pittet[1], J. Schrenzel[2], P. François[4] and S. Harbarth[1]***

*[1]Infection Control Program, Geneva University Hospitals and Faculty of Medicine, Rue Gabrielle Perret-Gentil 4, 1211 Geneva 14, Switzerland; [2]Clinical Microbiology Laboratory, Geneva University Hospitals and Faculty of Medicine, Rue Gabrielle Perret-Gentil 4, 1211 Geneva 14, Switzerland; [3]Division of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, Rue Gabrielle Perret-Gentil 4, 1211 Geneva 14, Switzerland; [4]Genomic Research Laboratory, Geneva University Hospitals and Faculty of Medicine, Rue Gabrielle Perret-Gentil 4, 1211 Geneva 14, Switzerland*

*Corresponding author. Tel: +41-22-372-9828; Fax: +41-22-372-3987; E-mail: stephan.harbarth@hcuge.ch

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**Objectives:** The objective of this study was to evaluate the efficacy of polyhexanide (Prontoderm®) in eliminating MRSA carriage.

**Methods:** In a 1900 bed teaching hospital, MRSA-colonized patients were randomized into a double-blind, placebo-controlled superiority trial between January 2011 and July 2014. Patients were treated with either polyhexanide or placebo applied to the anterior nares (thrice daily) and skin (once daily) for 10 days. The primary outcome was MRSA decolonization at day 28 (D28) after the end of treatment assessed by ITT responder and PP analyses (microbiological follow-up ±7 days and topical treatment ≥5 days). Secondary outcomes included safety, emergence of resistance and MRSA genotype changes. Registered trial number ISRCTN02288276.

**Results:** Of 2590 patients screened, 146 (polyhexanide group, 71; placebo group, 75) were included. ITT analysis showed that 24/71 (33.8%) patients in the polyhexanide group versus 22/75 (29.3%) in the placebo group were MRSA-free at D28 (risk difference, 4.5%; 95% CI, −10.6% to 19.5%; $P=0.56$). PP analysis confirmed the results with 19/53 (35.8%) decolonized polyhexanide-treated patients versus 17/56 (30.4%) in the placebo arm (risk difference, 5.5%; 95% CI, −12.2% to 23%; $P=0.54$). Nine serious adverse events occurred in the polyhexanide group versus 12 in the placebo group; none was attributable to study medication. Emergence of polyhexanide resistance or cross-resistance between polyhexanide and chlorhexidine was not observed. No case of exogenous recolonization by a genotypically different MRSA strain was documented.

**Conclusions:** This study suggests that under real-life conditions, a single polyhexanide decolonization course is not effective in eradicating MRSA carriage.

## Introduction

Colonization with MRSA has been shown to be associated with an increased risk of acquiring an MRSA infection.[1] MRSA carriers also act as reservoirs and vectors for exogenous cross-transmission.[2] Thus, decolonization with antiseptics has the potential to serve two purposes: infection prevention and transmission control.[3,4] Recent studies have suggested that a decolonization strategy with chlorhexidine, and sometimes mupirocin, can be successful in decreasing MRSA rates.[5–7] However, the potential for emergence and spread of resistance because of widespread use of these agents remains a concern.[8,9] As such, alternative agents for MRSA eradication are urgently needed. A comparison of the antimicrobial efficacy *in vitro* of povidone-iodine, triclosan, chlorhexidine, octenidine and polyhexanide showed that if an immediate anti-MRSA effect is required, the agents of choice are povidone-iodine and octenidine followed by polyhexanide, chlorhexidine and triclosan.[10] Although cases series of successful MRSA eradication have been reported with polyhexanide,[11,12] the efficacy of this antiseptic agent for MRSA decolonization has not yet been evaluated in a controlled clinical trial. The aim of this study was to evaluate the efficacy of topical treatment with polyhexanide (Prontoderm®) in eliminating MRSA carriage compared with placebo.

## Methods

### *Trial design and study objectives*

This study was an investigator-initiated, double-blind, randomized, placebo-controlled superiority trial, was conducted in accordance with the Declaration of Helsinki and institutional standards and was approved by the Institutional Review Committee at the University Hospitals of

Geneva (HUG), Geneva, Switzerland. Written informed consent of all patients was required. This trial was registered at the ISRCTN registry (number ISRCTN02288276).

Potential participants were identified by daily review of culture results provided by the Central Microbiology Laboratory at HUG. Patient flow was monitored in agreement with the CONSORT statement.[13] Patients who fulfilled the inclusion criteria and agreed to participate were randomly assigned to one of the two treatment groups in a 1:1 ratio. Treatment was allocated randomly by using an internet-based randomization generator with a block size of 10. Based on the randomization sequence, containers with the study drugs were sequentially numbered and participants were given containers in numerical order. Participants were enrolled by physicians who were part of the study team. Patients, study staff, investigators and specimen and data analysts were masked to the assignment of trial medication. Clinical and bacteriological assessments were made at baseline and repeated during treatment and after completion of therapy.

The primary study objective was to assess the clinical efficacy of polyhexanide in eradicating overall MRSA carriage at day 28 (D28) after the end of treatment. Secondary study objectives included evaluation of the effect of polyhexanide on MRSA decolonization at day 2 (D2) and on MRSA nasal carriage or groin carriage, as well as assessment of MRSA genotype changes, safety, acceptability and emergence of polyhexanide resistance.

## Setting and study population

This study was conducted between January 2011 and July 2014 at HUG, a Swiss tertiary care centre with 1900 beds and ~48000 admissions annually. During the study period, the annual rate of newly identified MRSA colonization or infection decreased from 1.1 cases per 100 admissions in 2011 to 0.32 cases per 100 admissions for the first half of 2014.[14]

MRSA carriers older than 18 years were eligible, provided they were only colonized and not infected with MRSA at the time of study inclusion. Patients were considered colonized with MRSA when groin or nares yielded MRSA-positive cultures. Exclusion criteria included a history of any of the following: pregnancy or breastfeeding; critically ill patients; presence of tracheostomy; planned cardiac or orthopaedic implant surgery; active MRSA infection or concurrent treatment with anti-MRSA antibiotics; presence of external fixator or deep-seated wounds colonized by MRSA; known or suspected hypersensitivity or allergy to any of the study drugs or chlorhexidine; current or planned treatment with other agents that are topically applied to the skin or nares; unavailability of adequate help if the subject was unable to self-administer the investigational product; inability to follow the study protocol; participation in another clinical trial; and previous enrolment in the study.

## Study medication and procedures

After randomization, individual participants received either active treatment or placebo for 10 days. For patients receiving active treatment, a mix of polyhexanide, allantoin, a cationic component, surfactants and purified water (Prontoderm® Solution; B. Braun Medical AG, Sempach, Switzerland) was applied with single-use washcloths, once daily, to the hair and scalp and left in place for ≥3 min (followed by washing with a shampoo of choice) and to the entire skin after showering, bathing or washing (without rinsing off). All other items worn by patients such as spectacles, jewellery or prosthetics were wiped externally with the solution. A mix of polyhexanide, glycerol, cellulose polymer and purified water (Prontoderm® Gel Light; B. Braun Medical AG, Sempach, Switzerland) was applied intranasally three times daily by applying a sufficient amount of gel (0.5–1 mL) to the anterior nares. The entry sites of catheters, if present, were cleansed once daily by applying a sufficient amount of gel (0.5–1 mL) to the entry site using a sterile cotton-tip swab. Control patients applied two placebo solutions (one that was identical to Prontoderm® Solution for hair, scalp, skin and items worn by patients; and one that was identical to Prontoderm® Gel Light for nares and catheter entry sites); they were similar in appearance but did not contain polyhexanide. Recommendations to change clothes, towels and bed linen on a daily basis were given. When necessary, a nurse helped to administer the product to ensure optimal compliance. Concomitant infection control measures for all MRSA-positive patients consisted of contact precautions routinely performed at HUG.[15]

## Microbiological evaluation

Swabs were taken from both nares (one swab) and from the inguinal/perineal region (one swab) using sterile Dacron-tipped swabs premoistened with sterile saline solution, after signature of consent [day 0 (D0)] as well as at D2 and D28 after the end of therapy.

Identification of MRSA was performed using chromogenic agar plates (MRSAid®; bioMérieux, Marcy-l'Étoile, France) according to Cherkaoui *et al.*[16] A colistin-salt backup broth was inoculated with the same Copan swab immediately after inoculating the chromogenic agar. In the absence of suspect colonies at 24 h, the backup broth was streaked onto a second chromogenic plate and read 24 h later. The laboratory technician evaluated the MRSA load by determining the quantity of bacterial colonies on the plates from 0 to 3 '+': positive broth and '+' indicated low quantity, '++' medium quantity and '+++' high quantity. Suspect colonies were confirmed by picking one colony and assessing the presence of *femA_SA* (a *Staphylococcus aureus*-specific gene target) and the *mecA* gene using published PCR conditions.[17] An MRSA strain was defined by the presence of at least one colony that displayed the proper morphology and colour on chromogenic agar and the detection of both *femA_SA* and *mecA* signals by PCR, starting from that same colony. Molecular typing of MRSA isolates was performed using multiple-locus variable number of tandem repeats analysis assay and MLST.[18]

Antimicrobial susceptibility testing was primarily performed using Vitek 2 automatic susceptibility testing cards for Gram-positive bacteria (bioMérieux). Strains were saved frozen in skimmed milk for further determinations. Susceptibilities to chlorhexidine and polyhexanide were assessed for 27 pairs of strains (D0 and D28) showing polyhexanide decolonization failure by MIC determinations using a macrodilution method assay. Serial dilutions ranging from 0.25 to 16 mg/L chlorhexidine or from 0.25 to 2 mg/L polyhexanide were tested on fresh bacterial cultures according to CLSI recommendations.[19,20] The MIC was defined as the lowest concentration inhibiting bacterial growth.

## Sample size and statistical analysis

This study was designed to detect an absolute difference of ≥30% in the MRSA eradication rate (50% in the polyhexanide group versus 20% in the placebo group) with $\alpha = 0.05$ and $\beta = 0.1$ (power of 90%). The minimal number of evaluable patients required in each study group was 58.

The primary outcome was decolonization of MRSA carriage, expressed as the proportion of participants with a complete set of negative swabs (nose and groin/perineum) at D28 after the end of treatment. The secondary outcomes were: suppression of MRSA colonization at D2; decolonization of nasal carriage or groin carriage (pre-defined subgroup analyses); MRSA genotype changes; adverse events (AEs) and serious AEs (SAEs); acceptability of the product to patients; and development of resistance to polyhexanide among MRSA strains isolated at D28.

Two different patient populations were analysed. The ITT population included all MRSA-positive patients who were enrolled in the study. Missing outcomes were first treated by responder analysis (patients with missing primary outcomes were considered as failure), second, considered as missing at random and estimated using multiple imputation (based on a regression model[21] that estimated the missing value and generated five datasets; results were combined into one final result according to specific rules)[22] and finally, treated by complete case analysis (patients with missing primary outcomes were excluded, modified ITT). The PP analysis

included all patients with complete microbiological follow-up (D28±7 days) and topical treatment ≥5 days. Patients with a negative MRSA screen at baseline were excluded from all analyses.

Baseline characteristics were described by frequencies, medians and IQRs. Groups were compared by means of the Mann–Whitney *U*-test, Pearson $\chi^2$ test or Fisher's exact test as appropriate for continuous and categorical variables. All statistical tests were two-tailed and a *P* value ≤0.05 was considered statistically significant. Statistical analysis was performed with PASW, version 18 (SPSS, Chicago, IL, USA).

## Results

### *Participants*

The study groups and reasons for non-inclusion are shown in Figure 1. There were 2590 patients with at least one MRSA-positive clinical culture or swab during the study period. Of these, 217 (8%) were eligible and 150 (69%) agreed to participate in the study, provided written consent and were randomized. Four patients who were known for a history of MRSA carriage but had a negative MRSA screening swab at baseline were excluded.

The median age was 68 years (IQR, 57–78 years) and 60% were male. A majority of patients (64%) had acquired MRSA during their hospitalization and 11% had previously received MRSA decolonization treatment. Sites of MRSA carriage were nares and groin (53%), nares only (29%) and groin only (18%). Three main MRSA clusters were detected by molecular typing, with 69%, 14% and 12% of strains belonging to the prevalent MRSA-ST228, MRSA-ST5 and MRSA-ST8 clones, respectively. Fifty-two percent received the MRSA decolonization treatment during hospital stay and 48% at home. The two study groups had similar clinical and demographic characteristics at baseline, except that patients in the polyhexanide group were more likely to have a

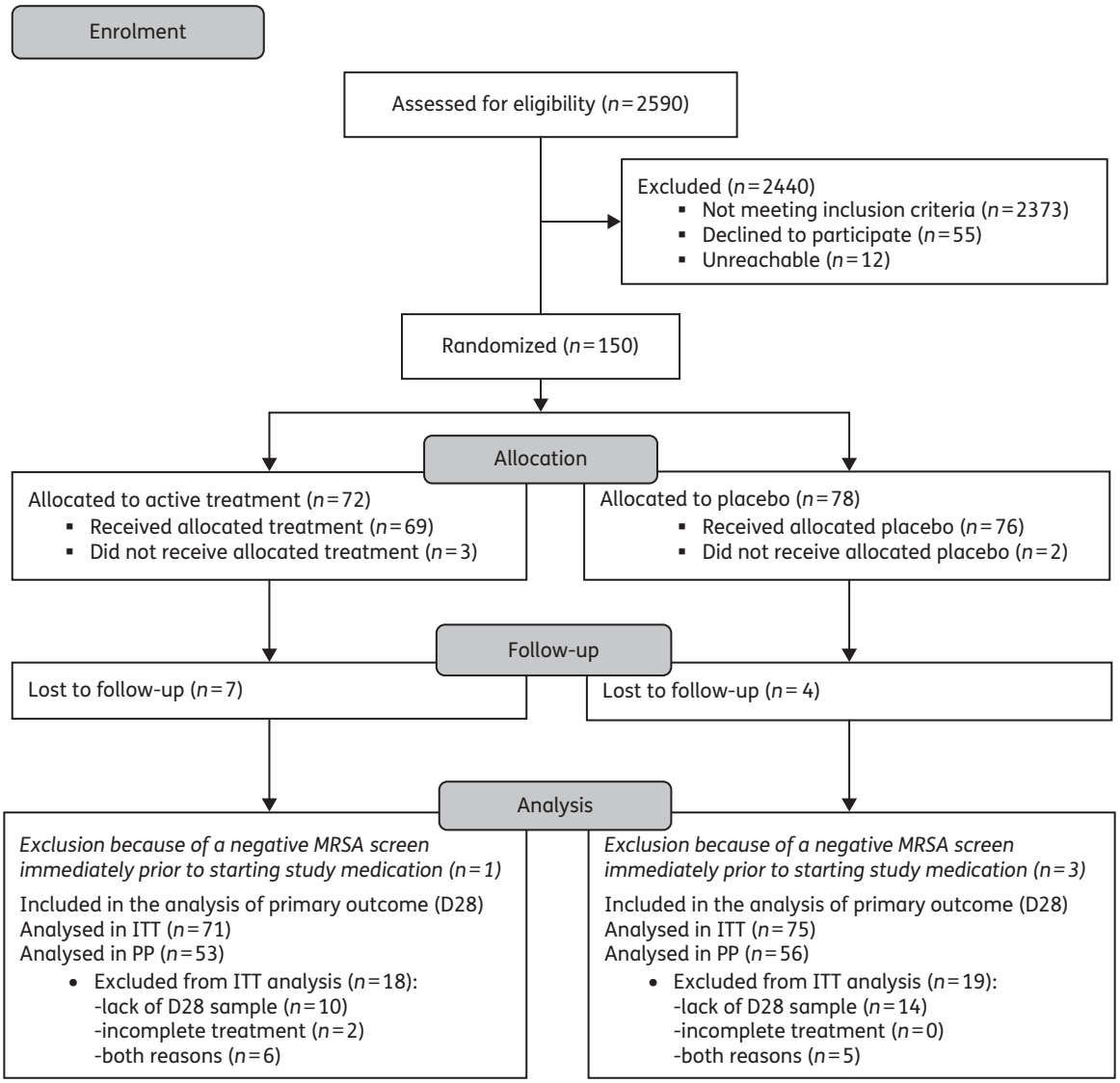


**Figure 1.** Flow diagram of patients. D28, the clinical efficacy of polyhexanide and placebo in eradicating overall MRSA carriage was evaluated at day 28 after the end of treatment.

**Table 1.** Baseline clinical, microbiological and demographic characteristics

| Variable | Intervention, *N*=71 | Placebo, *N*=75 |
|---|---|---|
| Male, *n* (%) | 41 (57.7) | 47 (62.7) |
| Age (years), median (IQR) | 67.2 (58–72.5) | 70.5 (55.4–78.3) |
| BMI (kg/m$^2$), median (IQR) | 25.9 (22.2–31.6) | 26.2 (23.5–30.5) |
| Reasons for hospital admission, *n* (%)[a] | *N*=70 | *N*=73 |
| infectious and parasitic diseases | 10 (14.3) | 13 (17.8) |
| neoplasms | 12 (17.2) | 6 (8.2) |
| endocrine, nutritional and metabolic diseases and immunity disorders | 5 (7.1) | 5 (6.9) |
| diseases of nervous system and sense organs | 4 (5.7) | 2 (2.7) |
| diseases of circulatory system | 8 (11.4) | 14 (19.2) |
| diseases of respiratory system | 6 (8.6) | 5 (6.9) |
| diseases of digestive system | 8 (11.4) | 12 (16.4) |
| diseases of genitourinary system | 1 (1.4) | 0 |
| diseases of skin and subcutaneous tissue | 2 (2.9) | 0 |
| diseases of musculoskeletal and connective tissue | 5 (7.1) | 1 (1.4) |
| injury and poisoning | 9 (12.9) | 15 (20.5) |
| MRSA status, *n* (%) | | |
| known MRSA carriage | 23 (32.4) | 30 (40) |
| newly identified MRSA carriage | 48 (67.6) | 45 (60) |
| Previous MRSA decolonization, *n* (%) | | |
| yes | 7 (9.9) | 9 (12) |
| no | 64 (90.1) | 66 (88) |
| MRSA-positive body site at admission, *n* (%) | | |
| nares and groin | 36 (50.7) | 41 (54.7) |
| only nares | 24 (33.8) | 18 (24) |
| only groin | 11 (15.5) | 16 (21.3) |
| Quantity of MRSA carriage at admission, *n* (%)[b] | | |
| low level of carriage | 45 (63.4) | 31 (41.3) |
| medium level of carriage | 16 (22.5) | 29 (38.7) |
| high level of carriage | 10 (14.1) | 15 (20) |
| MLVA ST, *n* (%) | *N*=57 | *N*=68 |
| ST228 | 38 (66.7) | 48 (70.6) |
| other STs | 19 (33.3) | 20 (29.4) |
| Comorbidity, *n* (%) | | |
| cardiovascular disease | 37 (52.1) | 40 (53.3) |
| COPD | 12 (16.9) | 13 (17.3) |
| chronic renal failure | 11 (15.5) | 16 (21.3) |
| diabetes mellitus | 13 (18.3) | 24 (32) |
| malignancy[c] | 18 (25.4) | 8 (10.7) |
| chronic liver disease | 5 (7) | 10 (13.3) |
| immunodeficiency | 11 (15.5) | 11 (14.7) |
| McCabe score, *n* (%)[d] | | |
| non-fatal | 60 (84.5) | 74 (98.7) |
| ultimately fatal | 1 (1.4) | 0 |
| rapidly fatal | 10 (14.1) | 1 (1.3) |
| Degree of dependence, *n* (%) | | |
| independent | 45 (63.4) | 41 (54.7) |
| needs some help with daily activities | 23 (32.4) | 27 (36) |
| fully dependent | 3 (4.2) | 7 (9.3) |
| Reduction of mobility, *n* (%) | 18 (25.4) | 19 (25.3) |

*Continued*

**Table 1.** *Continued*

| Variable | Intervention, $N=71$ | Placebo, $N=75$ |
|---|---|---|
| Presence of invasive devices, *n* (%)[e] | 13 (18.3) | 10 (13.3) |
| Presence of drains or stoma, *n* (%) | 7 (9.9) | 4 (5.3) |
| Presence of minor skin lesions, *n* (%) | 23 (32.4) | 22 (29.3) |
| Previous and current systemic antibiotic treatment not active against MRSA, *n* (%) | 12 (16.9) | 11 (14.7) |
| Length of hospital stay (days), median (IQR)[a] | $N=70$; 24.5 (11–59) | $N=73$; 26 (11–49) |
| Decolonization location, *n* (%)[f] | $N=68$ | $N=74$ |
| hospital | 38 (55.9) | 36 (48.6) |
| home | 30 (44.1) | 38 (51.4) |
| Duration of decolonization (days), median (IQR)[f] | $N=68$; 9 (9–9) | $N=74$; 9 (9–9) |

MLVA, multiple-locus variable number of tandem repeats analysis.
[a]Three patients seen at the outpatient clinic, without hospitalization.
[b]$P=0.03$.
[c]$P=0.02$.
[d]$P=0.002$.
[e]Invasive devices: central venous catheter, peripheral venous catheter, implantable venous access device and urinary catheter.
[f]Four patients did not receive allocated treatment or placebo.

**Table 2.** Analyses of efficacy

| Outcome measure | Intervention | Placebo | *P* | Risk difference (95% CI) |
|---|---|---|---|---|
| Patients without MRSA carriage on D28 | | | | |
| ITT analysis | | | | |
| results by responder analysis (available follow-up >D21; all 11 patients lost to follow-up considered as failure) | $N=71$; 24 (33.8%) | $N=75$; 22 (29.3%) | 0.56 | 4.5% (−10.6% to 19.5%) |
| results by multiple imputation method (5 stochastic imputations) | 39.4% | 31.7% | 0.27 | 8.8% (−6.7% to 24%) |
| modified ITT analysis | | | | |
| results by complete case analysis (available follow-up >D21; all 11 patients lost to follow-up excluded) | $N=64$; 24 (37.5%) | $N=71$; 22 (31%) | 0.42 | 6.5% (−9.5% to 22.4%) |
| PP analysis | | | | |
| results | $N=53$; 19 (35.8%) | $N=56$; 17 (30.4%) | 0.54 | 5.5% (−12.2% to 23%) |
| Patients without MRSA carriage on D2 | | | | |
| ITT analysis | | | | |
| results by responder analysis (all 24 patients without D2 swab considered as failure) | $N=71$; 11 (15.5%) | $N=75$; 11 (14.7%) | 0.89 | 0.8% (−11.1% to 13%) |
| results by multiple imputation method (5 stochastic imputations) | 19.7% | 20.8% | 0.81 | −1.6% (−14.8% to 11.8%) |
| modified ITT analysis | | | | |
| results by complete case analysis (all 24 patients without D2 swab excluded) | $N=59$; 11 (18.6%) | $N=63$; 11 (17.5%) | 0.86 | 1.2% (−12.7% to 15.3%) |
| PP analysis | | | | |
| results | $N=49$; 10 (20.4%) | $N=53$; 10 (18.9%) | 0.84 | 1.5% (−14.1% to 17.5%) |

low quantity of MRSA carriage (63% versus 41%), to have a malignant tumour (25% versus 11%) or to have a rapidly fatal McCabe score (14% versus 1%) compared with the placebo group (Table 1).

### *Primary and secondary outcomes*

Overall, 146 patients (71 patients in the polyhexanide group and 75 in the placebo group) were included in the ITT analysis. A total of 133 (91%) patients received study medication for ≥5 days; 111

**Table 3.** PP analyses of efficacy by pre-defined subgroups

| Outcome measure | Intervention | Placebo | *P* | Risk difference (95% CI) |
|---|---|---|---|---|
| Patients with nares and groin MRSA carriage at admission | | | | |
| results at D28 | *N*=29; 9 (31%) | *N*=32; 7 (21.9%) | 0.42 | 9.2% (−13.2% to 31.3%) |
| results at D2 | *N*=26; 5 (19.2%) | *N*=31; 3 (9.7%) | 0.45 | 9.5% (−9.3% to 30%) |
| Patients with nares-only MRSA carriage at admission | | | | |
| results at D28 | *N*=15; 6 (40%) | *N*=11; 2 (18.2%) | 0.40 | 21.8% (−15.6% to 52.2%) |
| results at D2 | *N*=15; 4 (26.7%) | *N*=11; 3 (27.3%) | 0.99 | −0.6% (−36.2% to 32.6%) |
| Patients with groin-only MRSA carriage at admission | | | | |
| results at D28 | *N*=9; 4 (44.4%) | *N*=13; 8 (61.5%) | 0.67 | −17.1% (−53.7% to 24.6%) |
| results at D2 | *N*=8; 1 (12.5%) | *N*=11; 4 (36.4%) | 0.34 | −23.9% (−57.2% to 19.2%) |

(76%) had an evaluation of MRSA carriage at D28 (±7 days) and 135 (92.5%) had an evaluation of MRSA carriage with follow-up >21 days (D21). Finally, 37 patients were excluded from the PP analysis, as detailed in Figure 1.

In the ITT responder analysis, 24/71 (33.8%) polyhexanide-treated patients versus 22/75 (29.3%) in the placebo group were MRSA-free at D28 (risk difference, 4.5%; 95% CI, −10.6% to 19.5%; *P*=0.56; Table 2). The difference was also not statistically significant by the multiple imputation method (*P*=0.27) and complete case analysis (*P*=0.42). The results were confirmed by the PP analysis, with 19/53 (35.8%) decolonized patients in the polyhexanide group versus 17/56 (30.4%) in the placebo group (risk difference, 5.5%; 95% CI, −12.2% to 23%; *P*=0.54).

MRSA decolonization rates at D2 were similar in the two groups by responder analysis [11/71 (15.5%) for polyhexanide versus 11/75 (14.7%) for placebo; risk difference, 0.8%; 95% CI, −11.1% to 13%; *P*=0.89; Table 2]. In the PP analysis, 10/49 (20.4%) patients in the polyhexanide group and 10/53 (18.9%) in the placebo group were MRSA-free at D2 (risk difference, 1.5%; 95% CI, −14.1% to 17.5%; *P*=0.84).

No significant difference in MRSA decolonization rate at D2 and D28 was recorded by pre-specified subgroup analysis according to the site of MRSA carriage (Table 3). In the subgroup of patients with nasal MRSA carriage only, PP analysis showed that 6/15 (40%) patients in the polyhexanide group versus 2/11 (18.2%) in the placebo group were MRSA-free at D28 (*P*=0.40).

None of the patients who had positive MRSA screening cultures after the end of the decolonization treatment was recolonized with genotypically different MRSA strains.

### *AEs, SAEs, acceptability and antimicrobial resistance*

A total of 25 AEs (9 unlikely, 3 possible and 13 probable relation to study medication) and 21 SAEs (2 deaths and 19 hospitalizations or prolongations of hospital stay, all unlikely to be related to the study drug) were recorded. The most common type of AE in both groups was itching. In the polyhexanide group, 12 patients presented an AE (two AEs resulted in study discontinuation) and 9 patients presented an SAE. In the placebo group, 10 patients presented an AE (two AEs resulted in study discontinuation) and 12 patients presented an SAE (one SAE, not related to the study product, resulted in study discontinuation).

Four patients developed MRSA infections during the study follow-up: one urinary tract infection (placebo group) and three surgical site infections (one in the polyhexanide group and two in the placebo group; *P*=0.62).

Acceptability of Prontoderm® versus placebo to patients was unpleasant for 9/69 (13%) versus 13/75 (17.3%) for the solution and unpleasant for 11/69 (15.9%) versus 6/75 (8%) for the gel in polyhexanide- versus placebo-treated patients, respectively.

Susceptibility levels after polyhexanide exposure did not show any trend towards emergence of resistance in 27 cases of decolonization failure. Susceptibility was ≤1 and ≤4 mg/L for polyhexanide and chlorhexidine, respectively. No cross-resistance between the two antiseptics was observed (data not shown).

## Discussion

The results of this placebo-controlled, double-blind, randomized trial suggest that under real-life conditions, a single polyhexanide decolonization course is not effective in eradicating MRSA carriage. Surprisingly, the rate of decolonization 2 days after the end of treatment was low (<20%) and similar between polyhexanide- and placebo-treated patients. This stands in contrast with other decolonization studies that showed a higher eradication rate immediately after treatment compared with the end of follow-up.[3] Polyhexanide seemed to be more effective in patients with nasal MRSA carriage only. Emergence of polyhexanide resistance or cross-resistance between polyhexanide and chlorhexidine was not observed.

A recent US study in critically ill patients showed a reduction of MRSA-positive clinical cultures by 37% after universal decolonization with chlorhexidine and mupirocin.[6] However, previous trials, with the same substances but in other settings, showed variable MRSA decolonization success rates (range, 25%–96%).[3,23–25] We hypothesized a difference in the rate of MRSA decolonization of 30% at 1 month after treatment between the polyhexanide and placebo groups. Our results refute this hypothesis, since we observed a lower-than-expected eradication rate in the polyhexanide arm and higher-than-expected success rate among placebo-treated patients.

What are possible explanations of these negative results? First, the possibility that successfully decontaminated subjects

were recolonized with a different clonal strain from external sources could be reasonably excluded by molecular typing. Second, antiseptic resistance could have emerged. In a previous case-controlled study conducted in Geneva, low-level mupirocin resistance in combination with the presence of *qacA/B* genes (genotypic chlorhexidine resistance) was significantly associated with persistent MRSA colonization after decolonization therapy.[26] Furthermore, a significant association was found between the presence of the *qacA/B* genes and the prevalent ST228 strain isolate. However, in the present study, we did not observe the emergence of resistance to polyhexanide or cross-resistance to chlorhexidine. Thus, antiseptic resistance cannot explain these results. Third, compliance with decolonization procedures could have been an issue. Half of the patients received the intervention at home and adherence to treatment could not be strictly monitored. Fourth, results could also have been impacted by applying only a single decolonization course. Studies that repeated decolonization had higher MRSA decolonization success rates.[27–29] Fifth, the risk of eradication failure increases with the presence of extranasal, MRSA-positive body sites.[3,30] Polyhexanide seemed to be more effective for nasal than multisite decolonization, since in the pre-planned PP subgroup analysis of patients with nasal MRSA carriage only, 40% of patients were decolonized in the polyhexanide group versus 18% in the comparator arm. Sixth, strain types and associated intestinal or throat carriage could also have an impact on the likelihood of failure of decolonization therapy.[27,28,31,32] Finally, the rate of decolonization in the placebo arm was 30%, which is higher than the rate previously reported, usually <20%.[3] We cannot exclude a relatively high rate of spontaneous decolonization. Furthermore, the physical cleansing activity of the placebo solution, especially for skin decolonization, may have played a more important role than expected. Most importantly, one of the ingredients of the topical placebo solution could have exerted a slight bacteriostatic effect. The cationic component, which was included in both the placebo and the active-treatment formulas, may inhibit MRSA growth, as shown in *post hoc in vitro* experiments.[33]

Our study has limitations. First, MRSA carriage among household contacts was not evaluated in our patients, although it has been shown to be a risk factor for eradication failure.[32] Screening of household contacts and simultaneous decolonization in case of MRSA positivity is only part of our eradication strategy for community-acquired MRSA.[34] Second, environmental cleaning practices were not evaluated, in particular at home. It has been recently demonstrated that patients with a higher burden of MRSA in their nares were more likely to contaminate their environment with MRSA.[35] Third, pre-specified subgroup analyses were realized without large enough sample size. Indeed, we included only 42 patients without extranasal MRSA carriage. Finally, the trial included only a small subset of MRSA-positive patients and was confined to a single institution in Switzerland with a specific hyperendemic MRSA strain,[36] possibly limiting the generalizability of the results.

In conclusion, our study revealed that a single polyhexanide decolonization course was not effective in eradicating MRSA carriage. Further studies are needed to evaluate the efficacy of polyhexanide for targeted decolonization of nasal *S. aureus* carriage. Finally, other alternative decolonization agents are urgently needed due to emergence of reduced susceptibility to mupirocin and topical antiseptics in clinical practice.[8,9]

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### *Author contributions*

Developed the original idea for the study, oversight of study integrity, had access to whole data and guarantor of data validity as Investigator: S. H.
Designed the study: T. H. and S. H.
Analysed the entire dataset: C. L.
Collected data/performed experiments for the study: E. v. D., A. A., G. R., A. R., P. F. and J. S.
Enrolled patients: E. v. D., T. H. and A. A.
Wrote the first draft of the paper: C. L. and S. H.
Contributed to the interpretation of study findings: all authors.
Contributed to the writing of the paper: all authors.
Agree with the manuscript's results and conclusions: all authors.

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