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Randomized Control Trials

Randomized clinical trial: Long-term *Staphylococcus aureus* decolonization in patients on home parenteral nutrition

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SUMMARY

Background & aims: Staphylococcus aureus decolonization has proven successful in prevention of *S. aureus* infections and is a key strategy to maintain venous access and avoid hospitalization in patients receiving home parenteral nutrition (HPN). We aimed to determine the most effective and safe long-term *S. aureus* decolonization regimen.

Methods: A randomized, open-label, multicenter clinical trial was conducted. Adult intestinal failure patients with HPN support and carrying *S. aureus* were randomly assigned to a 'continuous suppression' (CS) strategy, a repeated chronic topical antibiotic treatment or a 'search and destroy' (SD) strategy, a short and systemic antibiotic treatment. Primary outcome was the proportion of patients in whom *S. aureus* was totally eradicated during a 1-year period. Secondary outcomes included risk factors for decolonization failure and *S. aureus* infections, antimicrobial resistance, adverse events, patient compliance and cost-effectivity.

Results: 63 participants were included (CS 31; SD 32). The mean 1-year *S. aureus* decolonization rate was 61% (95% CI 44, 75) for the CS group and 39% (95% CI 25, 56) for the SD group with an OR of 2.38 (95% CI 0.92, 6.11, $P = 0.07$). More adverse effects occurred in the SD group ($P = 0.01$). Predictors for eradication failure were a *S. aureus* positive caregiver and presence of a (gastro)enterostomy.

Conclusion: We did not demonstrate an increased efficacy of a short and systemic *S. aureus* decolonization strategy over a continuous topical suppression treatment. The latter may be the best option for HPN patients as it achieved a higher long-term decolonization rate and was well-tolerated (NCT03173053).

1. Introduction

The advent of home parenteral nutrition (HPN) was enabled by technical innovations related to both the nutritional formulations as well as the devices to deliver intravenous therapies in an outpatient setting. Because of this progress, currently more and more patients dependent on a long-term central venous access device (CVAD) can prolong their life with a substantial

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List of abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
AV-fistula	Arteriovenous fistula
CCI	Charlson Comorbidity Index
CRSBI	Catheter-related bloodstream infection
CS	Continuous Suppression
CVAD	Central venous access device
EUCAST	European Committee on Antimicrobial Susceptibility Testing
HPN	Home parenteral nutrition
IV	Intravenous
MCQ	Medical consumption questionnaire
MRSA	Methicillin-resistant *S. aureus*
MSSA	Methicillin-susceptible *S. aureus*
NMB	Net monetary benefit
OR	Odds ratio
PICC	Peripherally Inserted Central Catheter
PO	Per Os
QALY	Quality-adjusted life year
SA	*Staphylococcus aureus*
SBS	Short Bowel Syndrome
SD	Search and Destroy
SPSS	Statistical Package for the Social Sciences
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper level of normal
WTP	Willingness to pay

improvement in their quality of life [1]. Unfortunately, presence of a CVAD also increases the risk of acquiring severe complications, like catheter-related bloodstream infections (CRBSIs). Of these, especially CRBSIs caused by *Staphylococcus aureus* are feared because of the association with complicated (metastatic) infections that, often necessitate removal of the CVAD and require prolonged intravenous antibiotic treatment [2].

Various preventive strategies have been developed to decrease the risk of acquiring CVAD-related infections. For example, much effort is put into educating HPN patients and their caregivers on adequate hygienic measures when performing CVAD handling procedures. In addition, several prophylactic catheter lock therapies have been devised [3].

From certain patient populations requiring long-term vascular access (e.g., hemodialysis), it is known that pathogen-specific strategies, like *S. aureus* decolonization, are successful as infection prevention measures [4–6]. Therefore, such strategies have been implemented in the respective guidelines [7]. However, the strength of the evidence for these recommendations is considered low in the absence of well-designed clinical trials. Also, these guidelines describe *S. aureus* decolonization treatment options that, in general, are meant for patients with uncomplicated carriage, i.e., only nasal carriage and in the absence of prosthetic material. *S. aureus* carriage in patients with a vascular access device, however, should by definition be regarded as complicated. In addition, evidence is mounting that in general extra-nasal *S. aureus* colonization (per definition complicated carriage) is far more common than previously believed [8].

Our center implemented the use of monthly topical mupirocin ointment in HPN patients in 2012, afterwards the number of catheter-related infections by *S. aureus* and CVAD removals decreased [9]. However, these findings are limited by the retrospective design of this investigation and we only administered nasal mupirocin. Importantly, mupirocin resistance occurred in a few patients.

We hypothesized that only long-term *S. aureus* decolonization treatments can be effective in HPN patients with a long-term CVAD when these are aimed at the whole body (nasal and extra-nasal colonization), are given continuously or repeatedly, and with paying attention to the prevention of antimicrobial resistance. Our aim was to evaluate two rational whole-body long-term decolonization strategies for their safety and effectivity:

1. A *Search and Destroy* (SD) strategy: a quick and short, systemic antibiotic treatment with the benefit of a less intensive treatment for a long-term period, and considered as the most effective eradication that is currently available [10].
2. A *Continuous Suppression* (CS) strategy: a repeated topical treatment with the advantages of continuous carriage suppression and with possibly less development of antimicrobial resistance since no systemic antibiotics are used.

2. Material and methods

2.1. Study design

An international multicentre, open-label, superiority, randomized controlled trial was conducted at three Intestinal Failure expertise centres treating patients on HPN: 1) Radboudumc, Nijmegen, The Netherlands; 2) Amsterdam University Medical Centers, location Academic Medical Center, the Netherlands; and 3) University College London Hospital (UCLH), London, United Kingdom. The study period was from February 2018 through October 2021. The study received ethical approval from each participating hospital. Written informed consent was obtained from all study participants. The trial is registered at Clinicaltrials.gov (NCT03173053). A detailed description of the study design and method can be found in the published protocol [11]. The CONSORT guidelines were followed to report this study [12].

2.2. Participants

Inclusion criteria

To be eligible to participate in this study, the patient had to meet all of the following criteria:

- Fully able to understand the nature of the proposed intervention.
- Diagnosed with intestinal failure and had received parenteral nutrition and/or fluid and electrolyte supplementation at home for at least three months.
- Age $\geq$18 years.
- Estimated life expectancy $\geq$1 year.
- Colonized with *S. aureus* (nasal and/or extra nasal).

Exclusion criteria

Patients with any of the following criteria were excluded:

- Not expected to comply with the trial protocol (substance abuse, mental condition).
- Pregnant or breastfeeding women.
- Continuous exposure to methicillin-resistant *S. aureus* (MRSA) (e.g., pig farmer).

- No options for any of the study drugs (systemic and/or topical antibiotics) due to resistance, allergies and/or interacting co-medication.
- Active *S. aureus* infection.
- Currently on treatment with antibiotics active against *S. aureus.*
- Decolonization (including mupirocin) treatment in the previous 2 months.
- Presence of an irremovable nasal foreign body (piercing).
- Aspartate transaminase (AST) and alanine transaminase (ALT) levels >5 times ULN, or liver failure.

2.3. Interventions

A balanced sequence randomization with a permuted block of size 4 was created using statistical software (Castor EDC) [13]. Randomization was stratified per study site. Participants were randomly assigned by the local principal investigator to either the *Continuous Suppression* (CS) group or the *Search and Destroy* (SD) group.

2.3.1. Study treatments

Continuous suppression group

Participants randomized to the *Continuous Suppression* group were treated repeatedly according to the following treatment regimen for five consecutive days *every* month (12 months in total), independent of *S. aureus* carriage culture results:

- Thrice daily 2% nasal mupirocin—each nostril
- Once-daily chlorhexidine body wash
- Twice daily chlorhexidine oropharyngeal rinse (only in case of confirmed oropharyngeal carriage)

Search and destroy group

Participants randomized to the *Search and Destroy* group were treated according to the following treatment regimen *only* at start of trial and in case of carriage relapse:

- Combination of two systemic antibiotics for seven days (Table 1).
- Thrice daily 2% nasal mupirocin—each nostril
- Once-daily chlorhexidine body wash
- Twice daily chlorhexidine oropharyngeal rinse (only in case of confirmed oropharyngeal carriage)

2.3.2. Choice of systemic antibiotics

Participants were treated according to the respective marketing authorizations and (inter)national *S. aureus* carriage guidelines [10,14]. The choice and type of administration (intravenously or orally) of the antibiotic agents depended on known allergies, expected decreased absorption in case of underlying short bowel syndrome (SBS), and susceptibility patterns of the *S. aureus* isolate.

Table 1
Systemic antibiotic options for eradication of MRSA/MSSA carriage in complicated carriage according to the MRSA guidelines [10,14].

Antibiotics	
Teicoplanin (IV)	Ciprofloxacin (IV/PO)
Clindamycin (IV/PO)	Clarithromycin (PO)
Co-trimoxazole (IV/PO)	Fusidic acid (PO)
Doxycycline (IV/PO)	Rifampicin (IV/PO)

Combination therapy was used because of better effectiveness and a decreased chance of developing resistance.
Abbreviations: PO: per os; IV: intravenous.

All systemic decolonization antibiotic drug options target both methicillin susceptible (MSSA) and methicillin resistant (MRSA) *S. aureus*. Combination therapy was used because of the potentially improved effectiveness and a decreased chance of developing antimicrobial resistance [15,16]. If the treating physician or consulted Infectious Diseases specialist felt that a particular antibiotic drug was clearly indicated or contra-indicated in a participant, the choice of antibiotic wase changed at their discretion. If the eradication attempt failed (SD group only) or when a relapse occurred, the participant was offered a new attempt with a maximum of two new attempts.

2.3.3. Follow up

Follow-up assessments were performed at 3, 6, 9, and 12 months after enrollment. At every follow-up contact, *S. aureus* cultures (nose, throat, rectum, exit-site catheter, and other body regions on indication) were obtained by a (research) nurse or by the participants themselves. The occurrence of potential (serious) adverse events and compliance were checked using standardized questions by phone. Validated questionnaires regarding treatment satisfaction (TSQM v2) [17], Quality of Life (EQ-5D-5L) [18], and Medical Consumption (iMCQ) [19] were collected electronically.

2.3.4. Discontinuation of study treatment

Treatment was suspended in case of (severe) adverse effects, participant withdrawal, *S. aureus* carriage persisting after 3 systemic eradication attempts (SD group), or $\geq$2 *S. aureus* carriage relapses at follow-up.

2.3.5. Microbiology analysis

Microbiological analyses were performed following standard microbiological practices. For identification of *S. aureus* the Maldi-TOF (Briuker, Germany) was used [20]. Cultures were processed by laboratory staff during their daily work. They were blinded to the study purpose and treatment allocation.

Whole genome sequencing (WGS) was performed on all *S. aureus* positive cultures at baseline, follow-up and from the caregiver. DNA extraction was performed using Instagene Matrix (Bio-rad, Hercules, CA, USA). DNA sequencing was performed on a G400 sequencer (BGI Genomics, Denmark) using the DNA nanoball sequencing (DNBSEQ) technology [21]. For genome assembly and identification, the Bactopia pipeline version 1.6.5 was used [22]. *S. aureus* genomes were compared on core genome by identifying Single Nucleotide Polymorphisms (SNP) differences using kSNP3 [23]. Recent literature propose a SNP cutoff of >15 SNP after 6 months to exclude transmission [24]. Since our follow-up was 12 months we defined genetic relatedness in case SNP difference was $\leq$30.

2.4. Outcome measures

The primary outcome was the percentage difference in (mean) successful *S. aureus* eradication rates between both groups during follow-up (0—12 months), expressed as odds ratios (OR). Successful *S. aureus* eradication was defined as 100% of all swabs (nose, throat, rectum, exit-site catheter, and other body regions on indication) being negative for *S. aureus* per measured time point (3, 6, 9, and 12 months).

Secondary outcomes were success rate of systemic eradication at baseline (SD group only), and differences in incidence of infections, mortality, antimicrobial resistance, vascular access removals, relapse carriage rates, and (severe) adverse events. Other outcomes of interest were predictors for *S. aureus* infections and eradication failure, patient-reported outcome measures, and healthcare costs.

2.5. Statistics

2.5.1. Sample size calculation

Only limited literature is available regarding the long-term efficacy of *S. aureus* carriage eradication, and to delineate total body site (de)colonization [25–28]. Based on a 77% total eradication rate in the SD group versus 55% in the CS group, the sample size was calculated at 138 participants to have an 80% power to detect a 22% increase in eradication success rate for the SD group (p-value <0.05, two-sided).

2.5.2. Statistical analyses

The primary outcome was analyzed according to an intention-to-treat principle. Odds ratios were calculated using a mixed-effects logistic model that corrected for repeated outcome measures within the participant. Changes in *S. aureus* decolonization rates over time between the groups were analyzed by a logistic model with an interaction term *time* by group. Per-protocol analysis in which SD group participants who had failed baseline eradication were excluded from further analysis was also conducted. Risk factor analysis for *S. aureus* decolonization failure and *S. aureus* infection during study was performed with multivariate binary logistic regression analyses. Potential predictive variables for both endpoints were selected based on clinical knowledge and the literature [4,8,10]. Univariate predictive variables with a p-value of <0.1 were included in the multivariate model. Differences between the two groups regarding continuous variables were assessed using the Independent T-test or Mann–Whitney U-test in case data was not normally distributed. Categorical variables were analyzed with the Chi-square or Fisher exact test. An independent statistician performed a blinded outcome assessment. Actual numbers are provided in the respective tables in case of missing data. A description of the cost-effectiveness analysis can be found in the Supplementary files 2.1–2.3. All statistical analyses were performed using SPSS version 23.0 (Armonk, NY).

2.6. Interim analysis

An interim analysis was performed after two years because recruitment was behind schedule due to the COVID-19 pandemic and because of safety concerns for the SD treatment group, where adverse effects (mainly gastrointestinal disturbances) resulted in premature discontinuation of study treatment in several participants. In accordance with the SPIRIT statement [29], the interim analysis was performed when nearly 50% of the intended number of inclusions was reached, and these patients had completed at least the first three months of follow-up. The stopping boundary for futility was based on an adjusted alpha, as advised by O'Brien-Fleming [30].

3. Results

In total, 309 patients were assessed for eligibility between February 2018 and October 2021. *S. aureus* carriage was confirmed in 39% (n = 120) of these patients. Sixty-three patients were included in the study (Fig. 1): 31 (49%) were assigned to the CS group and 32 (51%) were assigned to the SD group. Baseline demographics and characteristics of the included patients are presented in Table 2. Distribution of the different *S. aureus* colonization sites is presented in Fig. 2. All cultured isolates concerned methicillin-susceptible *S. aureus* (MSSA).

After the interim safety review and analysis, the trial was discontinued because there were serious safety concerns about the participants in the SD group (e.g., a substantial percentage (22%) of adverse effects (paragraph 3.3.2) resulting in premature discontinuation of study treatment), and data did not show an advantage of the SD over the CS strategy. The results indicated that continuation of the trial would be unlikely to change the final outcomes.

3.1. SD group treatment

All SD-group participants received antibiotic combination treatment during the first treatment course (Table S1). In 21 participants (66%) *S. aureus* was successfully eradicated at baseline (Fig. S1). Seven participants remained *S. aureus* free during the whole study period. They were all successfully decolonized after the first decolonization attempt.

3.2. Primary outcome: percentage of successful S. aureus eradication

The *S. aureus* free rates per study group are presented in Table 3. The intention-to-treat analysis indicated that *S. aureus* was totally eradicated during the year with a mean percentage of 61% (95% CI 44, 75%) in the CS group compared to 39% (95 CI 25, 56%) in the SD group with an OR of 2.38 (95% CI 0.92, 6.11, $P = 0.07$). Over time, there was no difference in change of *S. aureus* free rates between the two groups ($P = 0.99$) (Fig. 3). Per-protocol analyses showed that the mean *S. aureus* free rate in the SD group increased to 55% if SD participants who failed eradication at baseline were excluded (Table S2).

3.3. Secondary outcomes

3.3.1. Incidence of S. aureus infections

Six *S. aureus* infections occurred in 6 participants (SD 3; CS 3). *S. aureus* eradication attempts had failed in all of them. Five *S. aureus* infections were CVAD-related (3 CRBSIs; 2 Exit-site infections) (Table S3). No *S. aureus* infections occurred in patients who remained decolonized during follow-up.

3.3.2. Side effects and (serious) adverse events

Significantly more adverse effects occurred in the SD group compared to the CS group (44 vs. 21, p = 0.01) (Table S4). Seven SD group participants (22%) discontinued systemic antibiotic treatment due to adverse effects (all gastrointestinal complaints), that were likely attributable to the study medication. None of the participants discontinued study treatment in the CS group because of adverse effects and they were all categorized as mild.

Incidence and type of (serious) adverse events are presented in Table S5. One severe adverse event was likely related to the study treatment in the SD group: the participant collapsed during the infusion of rifampicin, resulting in a femur fracture that required hospitalization and surgical intervention. No deaths occurred during the study.

3.3.3. Microbiological data

WGS analysis showed that 87% (40/46) of the relapses and/or persistent colonization concerned identical *S. aureus* strains (Table 4). 25% of the participants (16/63) had ≥2 *S. aureus* strains cultured during study (SD: 38% vs. CS: 13%, p = 0.03). Comparison of the participants' baseline *S. aureus* strain with their caregivers' strain (n = 23) showed that 52% had identical or closely related strains. This percentage increased to 78% if all the participants' *S. aureus* cultured strains during study were included.

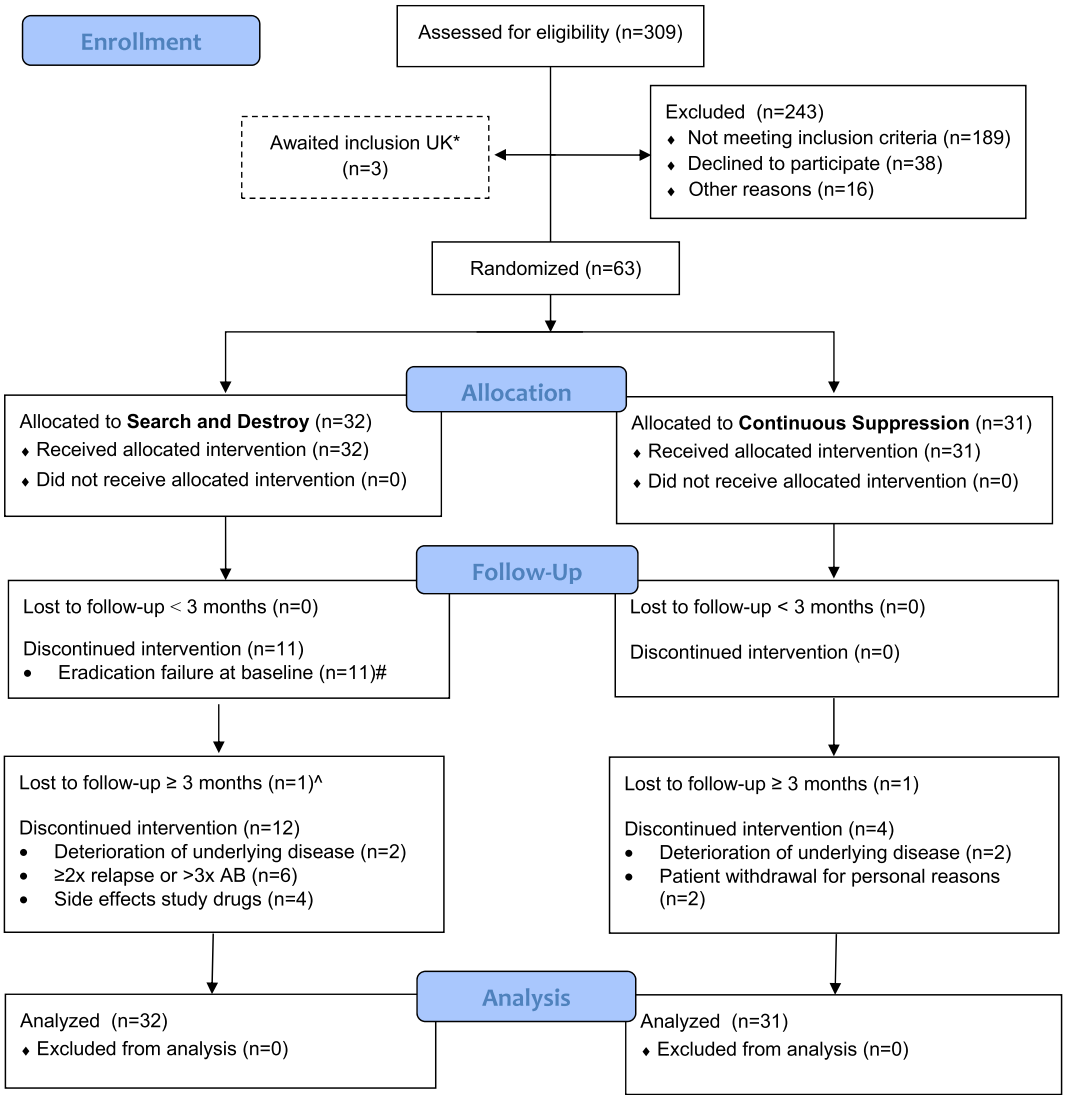

Fig. 1. Flow Diagram [10]. *Three eligible patients screened at the UK did not start trial due to the COVID-19 pandemic and premature discontinuation of the trial. #Three patients discontinued study antibiotics prematurely due to side effects. ^Patient failed eradication at baseline.

An overview with amount of non-study related antibiotic courses during the study are presented in Figs. S2 and S3. Changes in antibiotic susceptibility patterns during the study developed in 9 participants: 1 in the CS group and 8 in the SD group (Table S6). Three SD participants developed resistance to previously administered antibiotics occurred (three doxycycline, one mupirocin): WGS analysis showed that in two of these cases the susceptibility changes occurred in identical strains.

3.3.4. Treatment satisfaction (TSQM vII)

TSQM Global Satisfaction Scores (range 0–100) between both study groups were comparable at three months, with a mean (SD) score of 61.7 (17.2) in the CS group and 60.2 (26.9) in the SD group ($p = 0.93$) (Table S7). At three months, the side effect satisfaction domain score was significantly higher in the CS group compared to the SD group (92.5 vs. 83.6 $p = 0.02$).

At the end of the trial, participants were asked about their satisfaction with the study treatment: 33% of the SD participants compared to 13% of the CS participants ($p = 0.13$) responded that they found the trial too burdensome. The experienced side effects and certain study requirements (e.g. intense hygiene measures) proved challenging to combine with their daily CVAD handlings.

3.3.5. Patient compliance

Evaluation of the Medication Diaries and responses to the standardized questions about the fulfillment of study treatment showed that hygiene measures during the 7 days of systemic antibiotic treatments were carried out completely by all SD participants and repeatedly during 12 months by 70% of the CS participants ($p = 0.001$). Topical study medication was forgotten more often by the CS group than the SD group (33% vs. 3%, $p = 0.002$).

3.3.6. Cost-effectiveness analyses

The mean total costs per patient during the study were €34,854 for the SD group and €28,440 for the CS group with a mean difference of € 6414 (95% CI €-13,874, €26,359; $P = 0.53$) (Supplementary file 1. CEA). At baseline, the reported quality of life was better in the CS group (utility CS: 0.70 vs. SD: 0.53, $p = 0.03$). During follow-up utility values remained higher in the CS group (Fig. S4). The mean QALY difference was −0.064 (95% CI -0.138,

Table 2
Baseline demographics and participant characteristics.

	Continuous suppression (n = 31)	Search and Destroy (n = 32)
Age, mean (SD)	56 (14)	51 (16)
Gender, female (%)	25 (81)	21 (66)
Ethnicity, Caucasian (%)	29 (94)	30 (97)
CCI score (%)		
0	9 (29)	10 (31)
1	5 (16)	6 (19)
≥2	17 (55)	16 (50)
Type of intestinal failure (%)		
Type II	4 (13)	4 (13)
Type III	27 (87)	28 (88)
Indication for HPN (%)		
SBS	12 (39)	9 (28)
Motility disorder	16 (52)	19 (59)
Mechanic obstruction	1 (3)	1 (3)
Other	2 (7)	3 (9)
Type of vascular access (%)		
Venous port system	6 (19)	6 (19)
Tunneled CVC	17 (55)	19 (59)
Non-tunneled CVC/PICC	5 (16)	2 (6)
AV-fistula	3 (10)	5 (16)
Location of CVC (%)[a]		
subclavian vein	5 (16)	2 (6)
jugular vein	17 (55)	25 (78)
femoral vein	2 (7)	0
brachiochephalic vein	4 (13)	0
Number of CVAD removals (< 2yrs before study) (%)		
None	13 (42)	13 (41)
1–2	14 (45)	17 (53)
>2 removals	4 (13)	2 (6)
PEG (%)	7 (23)	7 (22)
Ileo- or colostoma (%)	8 (26)	10 (31)
Pet (%)	18 (58)	20 (63)
Household (%)		
One person	6 (19)	6 (19)
Two persons	17 (55)	16 (50)
> Two persons	8 (26)	10 (31)
HPN training received (%)	29 (94)	27 (84)
HPN administration (%)		
Patient self	18 (58)	15 (47)
Home care	3 (10)	6 (19)
Close contact	7 (23)	8 (25)
Combination	3 (10)	3 (9)
***S. aureus* carriage close contact**	13 (43)	12 (38)
CVAD-related infections < 2yrs (%)		
None	17 (55)	15 (47)
1–2	10 (32)	14 (44)
>2 infections	4 (13)	3 (9)
***S. aureus* infections < 2yrs (%)#**	4 (13)	9 (28)
Exit site infection	2 (7)	4 (13)
Tunnel infection	2 (7)	3 (9)
Bacteremia	0	3 (9)

Abbreviations: AV-fistula: arterio-venous fistula**;** CCI: Charlson Comorbidiy Index; CVAD: central venous access device; CVC: central venous catheter; HPN: home parenteral nutrition; PEG: Percutaneous endoscopic gastrostomy; PICC: peripherally inserted central catheter; SBS: Short Bowel Syndrome; SD: standard deviation.

[a] Excluding patients with an AV-fistula (shunt).

0.006; p = 0.09). Corrected for the baseline utility difference this changed to 0.011 (p = 0.57). The iNMB (corrected for the baseline utility values) became positive at a WTP of €100,000, but with negative and wide confidence intervals suggesting that the SD strategy was not cost-effective (Fig. S5).

3.3.7. Predictors for treatment failure and S. aureus infections

Multivariate binomial regression analysis showed that *S. aureus* carriage of the close contact and possession of a (gastro)enterostomy were associated with a higher risk for eradication failure (Resp. OR 9.09; 95% CI 1.54–53.7, $P = 0.02$ and OR 7.62; 95% CI 1.57–36.9, $P = 0.01$) (Table 5a).

Univariate risk analysis suggested that successful decolonization at three months was negatively associated with *S. aureus* infection (OR 0.10; 95% CI 0.01–0.90, $P = 0.04$). However, multivariate analysis showed no independent predictive risk factors for *S. aureus* infections (Table 5b).

4. Discussion

CRBSIs caused by *S. aureus* pose a significant threat to patients with long-term CVAD dependent on HPN. It has been demonstrated that *S. aureus* decolonization strategies effectively reduce *S. aureus* infections in carriers with a CVAD [4,9]. We aimed to investigate which type of decolonization strategy in the long term is the most effective and safe for HPN patients. We hypothesized that a short systemic eradication treatment (SD group) might be beneficial over a chronic repeated topical eradication treatment (CS group). Yet,

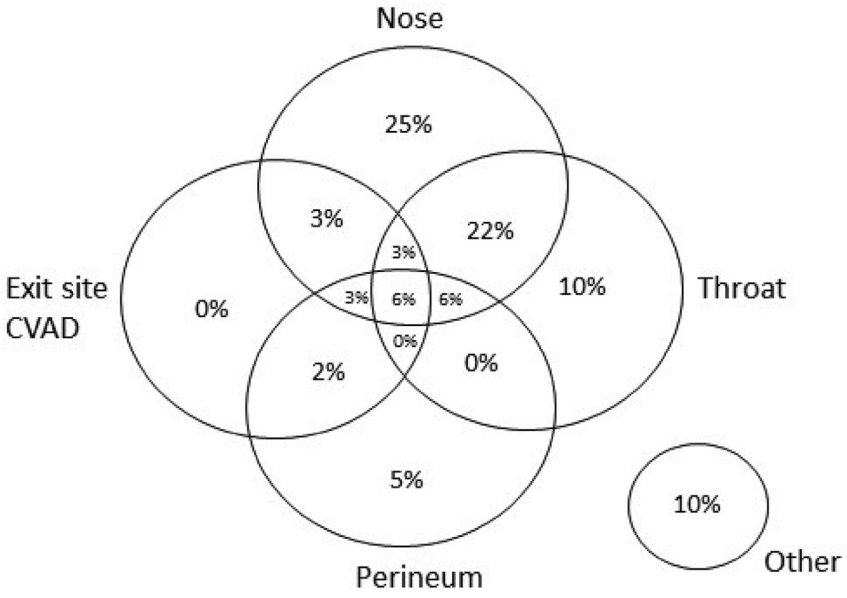

Fig. 2. Venn diagram showing *S. aureus* colonization of the nose, throat, and perineum, exit site of the central venous access device (CVAD), and other sites among study participants.

Table 3
Successful *S. aureus* eradication rates both study groups.

	Enrolled patients	*S. aureus* free	*S. aureus* isolated	Percentage *S. aureus* eradicated (95% CI)
Continuous Suppression	31			
1st culture (3 months)	30[a]	18	12	60% (41, 76)
2nd culture (6 months)	31	20	11	65% (46, 80)
3rd culture (9 months)	25	13	12	56% (36, 74)
4th culture (12 months)	24	14	10	58% (37, 77)
Mean (0–12 months)				**61% (44, 75)**
Search and Destroy	32			
1st culture (3 months)	32	13	19	41% (25, 59)
2nd culture (6 months)	31	15	16	48% (31, 66)
3rd culture (9 months)	27	10	17	37% (21, 57)
4th culture (12 months)	26	11	15	42% (25, 62)
Mean (0–12 months)				**39% (25, 56)**

Comparison of successful *S. aureus* eradication rates between CS vs. SD group during one year with a mixed-effects logistic model indicated an OR of 2.38 (95% CI 0.92, 6.11, P = 0.07, two-tailed). According to intention to treat analysis: all patients were re-cultured at every follow up moment independent of SA eradication success or not.
[a] One missing.

our results did not show any increased efficacy of SD over CS treatment and, in fact, hinted the opposite.

The hypothesis behind our trial, a short-term systemic *S. aureus* eradication treatment being the most effective, was generated by previous studies where a successful decolonization rate of up to 87% was seen [26,28]. Although the SD group in our trial achieved a *S. aureus* eradication rate of 66% at baseline, during the year, participants remained decolonized with a mean of only 39%. Important discrepancies with our trial are that previous studies were mainly observational, had a shorter follow-up time, mostly included MRSA carriers, and focused on uncomplicated *S. aureus* carriage. Moreover, most studies relied on the detection of nasal carriage only. This easily leads to the misclassification of patients with other sites of colonization that might stand to benefit from decolonization. A long follow-up duration seems important as recolonization is seen frequently in *S. aureus* carriers; between 30% and 60% of patients are recolonized within 7–18 months [31]. Recently, a randomized multicenter trial with a more comparable design, sample size, and follow-up duration was conducted in patients with cystic fibrosis and MRSA carriage [32]. At six months, the authors found a much higher decolonization rate of 63% in their systemic eradication group. This may be explained by an important limitation of their trial: only a per-protocol analysis was performed. By excluding all dropout patients (34%), an overestimation of the actual effectiveness of their study intervention is likely.

Several other factors may have contributed to the lower eradication rate of the SD-group as well, for example, the high dropout percentage (22%) due to side effects of provided systemic antibiotics. A third of the SD participants argued that they found the trial too burdensome to combine with their daily CVAD handlings and dropped out. Since we chose an ITT analysis, follow-up cultures were still performed in these patients (revealing persisting *S. aureus* carriage), although they received no new treatment. Next, we gave no further treatment attempts to the SD participants in case of a second relapse or three failed treatment attempts. In contrast, the CS group received treatment repeatedly during the year regardless of a positive or negative culture result. And indeed, the per-protocol analysis showed that the mean *S. aureus* decolonization rate in the SD group increased to 55% when baseline failures were excluded. Last, although WGS analysis showed that most relapse and persistent colonization strains seemed genetically related, 38% of the SD participants appeared to be colonized with

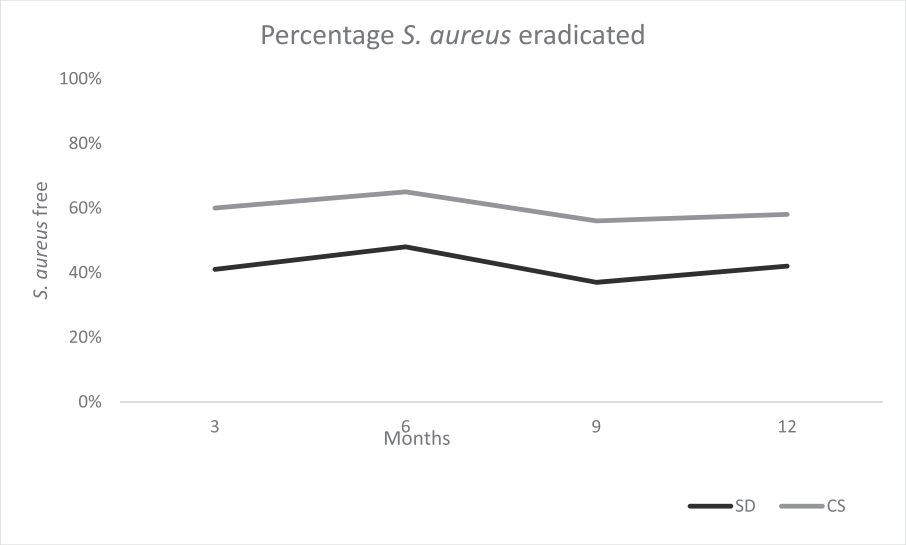

Fig. 3. Percentage of patients per study group in whom total *S. aureus* eradication was achieved, per follow-up time period (displayed in months). There was no difference over time in change of *S. aureus* free rates between the two groups (p = 0.99). **Abbreviations:** SD: search-and-destroy group; CS: continuous suppression group.

Table 4
Whole genome sequencing analysis results.

	Number of patients	Genetically related[b]
***S. aureus* carriage caregiver (n = 25)**[a]		
Baseline cultured strain	23	**12 (52%)**
Continuous Suppression	12	7 (58%)
Search and Destroy	11	5 (45%)
All *S. aureus* strains cultured during study included	23	**18 (78%)**
Continuous suppression	12	10 (83%)
Search and Destroy	11	8 (73%)
Relapse	46	**40 (87%)**
Continuous suppression	22	20 (91%)
Search and Destroy	24	20 (83%)
≥2 *S. aureus* strains cultured during study (n = 63)	16	N/a
Continuous suppression	4	N/a
Search and Destroy	12	N/a

[a] Two missings.
[b] Genetically related was defined as <30 SNP's difference between the compared *S. aureus* strains [25]. N/a: Not applicable.

Table 5a
Uni- and multivariate analysis of predictive factors for *S. aureus* decolonization failure.

	Univariate analysis[a]			Multivariate analysis		
	OR	95%-CI	p-value	OR	95%-CI	p-value
Patient characteristics						
Age, <60 years	1.51	0.44, 5.21	0.51			
Female sex	2.95	0.79, 11.0	0.11			
S. aureus positive caregiver	6.66	1.31, 33.8	**0.02**	9.09	1.54, 53.7	**0.02**
Pet	0.90	0.27, 3.01	0.86			
Skin disease	0.38	0.06, 2.69	0.34			
(Gastro)enterostomy	6.86	1.67, 28.2	<**0.01**	7.62	1.57, 36.9	**0.01**
Site of extranasal colonization						
CVAD	1.58	0.29, 8.78	0.60			
Throat	2.14	0.60, 7.70	0.24			
Perineal	1.08	0.31, 3.79	0.91			
(Gastro)enterostomy	N/a[b]					
Multiple sites colonized	4.26	1.14, 15.9	**0.03**	2.63	0.60, 11.6	**0.20**
Compliant	0.55	0.10, 2.93	0.49			
CS group (Ref: SD group)	1.19	0.36, 3.94	0.78			

Abbreviations: CI: confidence interval, Ref: reference category, CS: Continuous Suppression; CVAD: central venous access device; N/a: Not applicable; OR: Odds ratio; SA: *S. aureus*; SD: Search and Destroy.
[a] Univariate models were adjusted for treatment group. Predictive values (p < 0.1) were included in the multivariate model.
[b] Logistic regression analysis not possible since all participants with a *S. aureus* colonized (gastro)enterostomy had failed decolonization treatment.

Table 5b
Uni- and multivariate analysis of predictive factors for *S. aureus* infections.

	Univariate analysis[a]			Multivariate analysis		
	OR	95%-CI	p-value	OR	95%-CI	p-value
Patient characteristics						
Age, <60 yrs	0.55	0.09, 3.28	0.52			
Female sex	0.31	0.05, 1.78	0.19			
S. aureus infections <2yrs	5.18	0.85, 31.6	**0.08**	3.19	0.44, 23.4	0.25
(Gastro)enterostomy	1.81	0.31, 10.7	0.52			
***S. aureus* colonization CVAD**	6.33	0.95, 42.1	**0.06**	2.52	0.33, 19.3	0.37
***S. aureus* eradicated at 3 months**	0.10	0.01, 0.90	**0.04**	0.13	0.01, 1.32	0.08
CS group (ref: SD group)	0.97	0.18, 5.19	0.97			

Abbreviations: CI: confidence interval, Ref: reference category, CS: continuous suppression; CVAD: central venous access device; OR: Odd's ratio; SD: Search and Destroy; Yrs: years.
[a] Univariate models were adjusted for treatment group. Predictive values ($p < 0.1$) were included in the multivariate model.

≥2 *S. aureus* strains. This suggests that (re)colonization with different strains also played a role. Presumably, this concerned transmission from their caregiver since most of the SD participants (78%) had identical strains as their caregiver at some point during the study.

The percentage and severity of reported adverse effects in the SD group seem higher than reported before [33]. Since many HPN patients have severe underlying intestinal disease accompanied by gastrointestinal complaints, they may be more susceptible to gastrointestinal side effects. The distinction between actual side effects and disease-related symptoms might be more difficult.

Unexpectedly, the CS group had quite an impressive 1-year decolonization rate of 61%. This rate is higher for a topical decolonization strategy than reported before, mainly because it focused on complicated carriage for a long period [34,35]. The explanation may be the approach of total body eradication in this trial. However, when implementing a CS strategy as standard care, frequent notifications and provision of repeated patient instructions seem essential since they might need to remember the (topical) medication.

We found that possession of a (gastro)enterostomy and a *S. aureus* positive caregiver were independent risk factors for decolonization failure. Several guidelines state that certain patients are at higher risk for decolonization failure, like patients with skin conditions or in-dwelling devices [10,14,36]. However, none of the referred studies focused explicitly on possession of a (gastro)enterostomy. It might be beneficial to also apply mupirocin on a colonized (gastro)enterostomy since this was effective for infection prevention in patients with colonized peritoneal catheters [37]. Carriage among household contacts as a risk factor for eradication failure has been described before [38]. In our opinion, *S. aureus* eradication protocols for HPN patients should include decolonization of the caregiver since they may serve as a reservoir for recurrent or persistent *S. aureus* carriage.

Although both decolonization strategies focused explicitly on *S. aureus* decolonization, both topical drugs have the potential for much broader antibacterial action [9]; for instance chlorhexidine even has antifungal properties. For this reason, local chlorhexidine disinfectant is generally the preferred option for CVAD infection prevention [39].

Several cost-effective analysis studies on *S. aureus* screening and decolonization strategies have been conducted [40,41], many of which showed that decolonization seems cost-saving. The SD strategy, however, seems more expensive and less cost-effective when compared to the CS strategy. Also, mean yearly costs per CS patient (€28,440) were relatively modest compared to previous HPN cost analysis findings (between €13,000 and €71,000) [42]. This suggests that the study-related costs did not have much impact on the total costs for HPN patients, while healthcare-related costs for a *S. aureus* bacteremia are tremendous (€27,500) [43]. With a probability of developing *S. aureus* infections of 19% in carriers vs. 2% in noncarriers [44], we think it will be cost-beneficial to offer CS decolonization to all HPN patients, only once *S. aureus* colonization has been established.

A potential disadvantage of the CS strategy is the possible occurrence of mupirocin resistance by chronic use [5,9]. However, we did not find any mupirocin resistance in the CS group, perhaps because we used a whole-body approach. Nevertheless, periodic screening seems a reasonable strategy to target mupirocin resistance. One previous systematic review on effectiveness of chronic (nasal only) mupirocin as *S. aureus* decolonization approach reported increased rates of CRBSI's by other pathogens [6]. This is something we did not find in our previous and current study [9].

Strengths of our trial include its multicenter design, multiple antibiotic (PO/IV) options, treatment according to (inter)national guidelines, and a systematic investigation of all possible environmental factors of influence on *S. aureus* decolonization (e.g., carriage caregiver, extra nasal carriage, the occurrence of antimicrobial resistance) without affecting clinical care during the study. The chosen design best reflects the real-world situation for HPN patients and all patients with long-term CVADs and enhances our findings' generalizability. Other strengths of our trial are the extensive *S. aureus* screening (multiple sites and repetitive) and the long-term follow-up of participants, which enabled us to investigate both decolonization strategies more reliably.

Our trial has some limitations as well. First, we conducted a randomized controlled, yet nonblinded trial. Our study could not be performed double-blind due to the extent of the differences in the treatment strategies. It is unlikely, however, that the nonblinded design affected outcome measurements since the primary outcome -*S. aureus* colonization or not-was determined by cultures. Second, our final sample size was smaller than expected since patient inclusion went slow (also due to external factors such as the COVID-19 pandemic), and the study was terminated after an interim analysis. We only included patients with a CVAD receiving HPN to achieve a homogenous population. These patients often have critical and advanced underlying diseases, making them less eligible and reluctant to participate in a trial. Third, selection bias may be present since patients with a medical history of CVAD-related infections are more willing to participate in the trial. However, baseline characteristics showed that only half of the participants had experienced one or more CVAD-related infections in the previous two years, which is in line with an earlier trial performed in HPN patients [45]. Fourth, the interim analysis, which resulted in the trial's preliminary termination, was not part of the initial research protocol. Although, in general, an unplanned interim analysis should be avoided, the research team and the independent monitor had serious safety concerns for the SD group participants

due to the high rate of reported adverse effects. Eventually, the independent Ethical Committee decided that an interim analysis was unavoidable to prevent further participants from being exposed to undue risk. Despite these limitations, our trial helps to understand the efficacy and safety of the currently available *S. aureus* decolonization strategies for patients with long-term CVAD.

Based on our findings, a chronic repeated topical eradication treatment currently seems the best option to achieve *S. aureus* decolonization in HPN patients as it was well-tolerated, achieved a good long-term decolonization rate of 61%, had a sufficient treatment adherence of 70%, was less expensive, and no occurrence of mupirocin resistance was seen. Notably, no *S. aureus* infections occurred in the CS-group participants that remained decolonized during the study period. However, it seems wise to take patient-related factors (e.g., *S. aureus* carriage among caregivers, possession of a (gastro)enterostomy, and compliance) when implementing a *S. aureus* eradication protocol for HPN patients.

5. Conclusion

Our study provides physicians guidance for further policy development and implementation of (long-term) *S. aureus* decolonization protocols for HPN patients. It contributes to novel preventive strategies for both *S. aureus* transmission and infections. It will ultimately prevent antibiotic use and antimicrobial resistance in clinical practice. Although no superiority for a short and systemic eradication strategy was observed, continuous topical suppression decolonization seems a safe and effective alternative strategy for HPN patients, and without the risk of severe side-effects.

Author contributions

MG, YW, CBR, WK, HW and GJAW designed the study: conceptualization, methodology. MG, JBM, KCF and GW gathered data: resources and data curation. MG, GW, RA and WK analyzed the data and wrote the manuscript: formal analysis, investigation, visualization, writing – original draft; which was reviewed and approved by all authors: writing – review & editing. JC and IvW assisted in the WGS analysis. FR and MS supervised the project in the respective centers: supervision, project administration, funding acquisition. All authors jointly decided to publish. MG and GJAW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.03.010.

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