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**Staphylococcus aureus colonization and infection:
optimizing MRSA decolonization and addressing challenges
in S. aureus bacteremia management**

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Citation

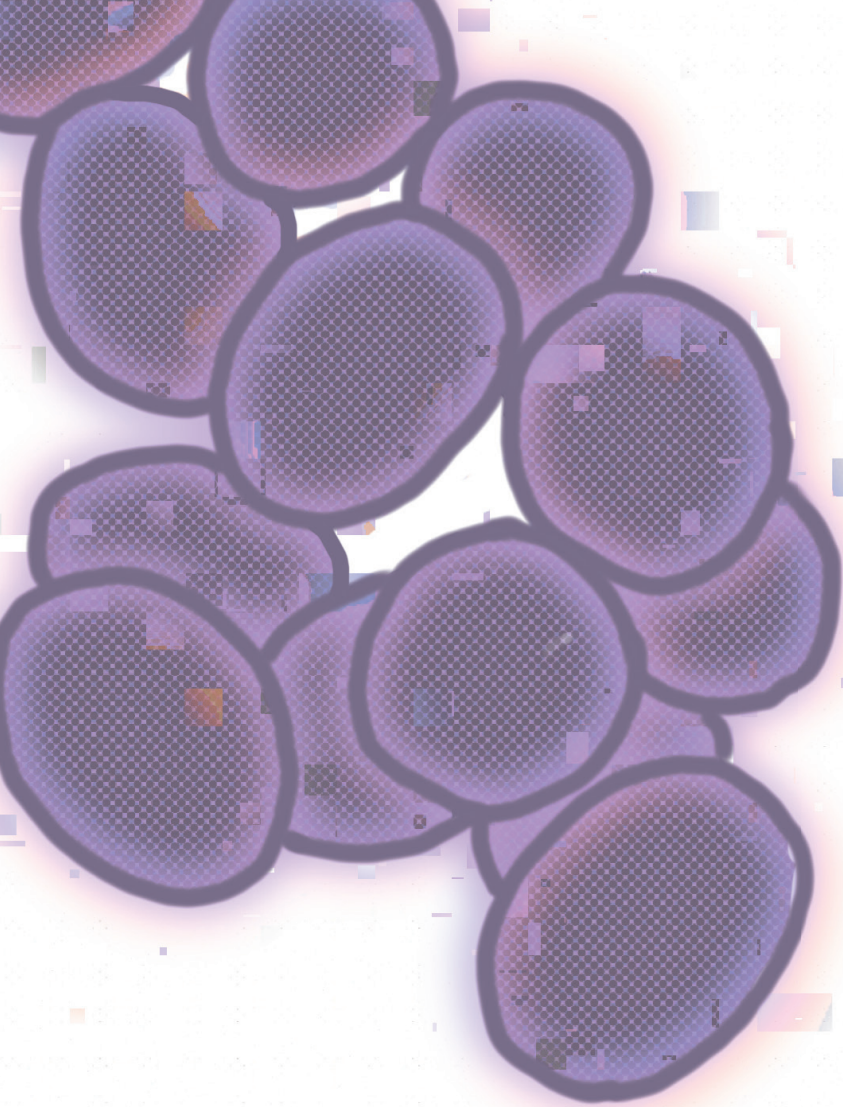
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Chapter 4

Complicated carriage with methicillin-resistant *Staphylococcus aureus*: evaluation of the effectiveness of decolonization regimens advised in the Dutch national guideline

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Abstract

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization leads to increased infection rates and mortality. Decolonization treatment has proven to prevent infection and reduce transmission. As the optimal antimicrobial strategy is yet to be established, different regimens are currently prescribed to patients. This study aimed to evaluate efficacy of the decolonization treatments recommended by the Dutch guideline.

Methods

A retrospective multicenter cohort study was conducted in five Dutch hospitals. All patients who visited the outpatient clinic because of complicated MRSA carriage between 2014 - 2018 were included. We obtained data on patient characteristics, clinical and microbiological variables relevant for MRSA decolonization, environmental factors, decolonization regimen and treatment outcome. The primary outcome was defined as three negative MRSA cultures after treatment completion. Outcomes were stratified for the first-line treatment strategies.

Results

A total of 131/224 patients were treated with systemic antibiotic agents. Treatment was successful in 111/131 (85%) patients. The success rate was highest in patients treated with doxycycline-rifampicin (32/37, 86%), but the difference with any of the other regimens did not reach statistical significance. There was no difference in success rate of a 7-day treatment compared to 10-14 days of treatment (OR 0.99, 95%CI 0.39-2.53, $p=1.00$). Side effects were reported in 27/131 (21%) of patients and consisted mainly of mild gastrointestinal complaints. In a multivariable analysis, an immunocompromised status was an independent risk factor for failure at the first treatment attempt (OR 4.65, 95%CI 1.25-17.25, $p=0.02$).

Conclusion

The antimicrobial combinations recommended to treat complicated MRSA carriage yielded high success rates. Prolonged treatment did not affect treatment outcome. A randomized trial is needed to resolve whether the most successful regimen in this study (doxycycline plus rifampicin) is superior to other combinations.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a challenging global health problem. Colonization with MRSA leads to increased infection risks, ranging from mild skin infections to severe clinical syndromes, i.e. pneumonia and bloodstream infection [1-3]. Compared to infections with their more susceptible counterpart, mortality is high in MRSA infections. [4] This may in part be attributed to decreased antibiotic effectiveness and increased toxicity of the antibiotic therapy.

Decolonization of MRSA in carriers has proven to be an effective preventive strategy in reducing infection- and hospitalization rates [5, 6]. In Europe, the prevalence of MRSA in *Staphylococcus aureus* blood isolates was 16.4% in 2018 with large inter-country variations [7]. In the Netherlands, the MRSA prevalence in blood culture isolates is 1.4%, along with the Scandinavian countries one of the lowest in the world [7, 8]. The low prevalence in the Netherlands is to a large part ascribed to the 'search and destroy policy', targeting MRSA carriers [9-11]. The aim of this policy is to minimize colonization and transmission in both health care workers (HCWs) and patients. Active screening e.g. after hospitalization abroad, isolation of MRSA carriers and pre-emptive isolation of risk groups are part of this policy [11]. The policy also urges for decolonization treatment in all MRSA carriers.

The Dutch guideline for the treatment of MRSA carriage differentiates between complicated and uncomplicated carriage [12]. Uncomplicated carriage, i.e. exclusively located in the nose and without active infection, is advised to be treated with topical therapy (mupirocin topically applied to the nares) and hygienic measures. In case of complicated MRSA carriage additional systemic antimicrobial therapy with a combination of two antibiotic agents is recommended. Due to the limited availability of data [13-17], it has yet remained undecided which combination of anti-staphylococcal agents is most effective. The individual treatment regimen, i.e. the choice of antibiotic agents and treatment duration in clinical practice is therefore variable [18]. The aim of this study was to describe the effectiveness of different MRSA decolonization treatments for complicated MRSA carriage.

Table 1: Oral antibiotic combination therapy for decolonization of MRSA colonization according to the Dutch national guideline

	Antibiotic agent 1	Antibiotic agent 2
Recommended	Doxycycline 200mg qd or Trimethoprim 200mg bid	Rifampicin 600mg bid
Alternative	Clindamycin 600mg tid or Clarithromycin 500mg bid or Ciprofloxacin 750mg bid or Fusidic acid 500mg tid	Fusidic acid 500mg tid

Legend: qd = once a day, bid = twice a day, tid = three times a day.

Methods

A multicenter retrospective cohort study was conducted in five Dutch hospitals (one university hospital and four large regional teaching hospitals).

Study population

All consecutive patients referred to the outpatient clinic with complicated MRSA colonization from January 2014 until December 2018 were eligible for inclusion. Exclusion criteria were the absence of MRSA colonization upon screening at the outpatient clinic, uncomplicated carriage and a patient's objection to the use of his medical file for research purposes.

Outpatient clinic

History taking and physical examination were performed during the first visit to the outpatient clinic. Physical examination included skin examination, as skin lesions such as eczema may impede effective decolonization. Furthermore, physical examination involved examination of the oral cavity. Culture swabs were routinely obtained from nose, throat and perineum. If skin lesions e.g. wounds were present, additional cultures were obtained from these sites. Household contacts were screened as well, and colonized household contacts were treated simultaneously and were included in the study. The standard treatment consisted of nasal mupirocin thrice daily, topical disinfectants daily (chlorhexidine soap and betadine shampoo) and hygienic measures. Hygienic measures included daily change of underwear, clothes and towels as well as change of bed linen on day 1, 2 and 5. The first choice recommended systemic antibiotic agent combinations were doxycycline-rifampicin and trimethoprim-rifampicin, according to the *in vitro* susceptibility (12). Alternative combinations were either rifampicin or fusidic acid in combination with clindamycin, clarithromycin or ciprofloxacin, or rifampicin and fusidic acid (Table 1). Standard duration of antibiotic treatment was a minimum of 7 days.

Microbiological methods

Culturing and susceptibility determination was performed according to the Dutch Society of Medical Microbiology guideline for laboratory detection of highly resistant microorganisms. Minimum inhibitory concentration (MIC) breakpoints and zone diameter breakpoints for resistance and intermediate sensitivity were based on EUCAST criteria (19).

Data collection

The electronic patient files were reviewed to record patient characteristics, clinical data relevant for MRSA decolonization (e.g., immune status and skin diseases), environmental factors (e.g., health care profession, household members) and microbiological data (culture results and antimicrobial susceptibility patterns). In each hospital, the prescribed antibiotic therapy and treatment duration for all treatment episodes were extracted from the hospital electronic prescribing system. Microbiological data were retrieved from the Department of Medical Microbiology of each hospital.

Definitions

Uncomplicated MRSA carriage was defined as the presence of MRSA exclusively located in the nose and no active infection with MRSA and in vitro sensitivity for mupirocin and the absence of active skin lesions and the absence of foreign material that connects an internal body site with the outside (e.g., urine catheter, external fixation material) and no previous failure of decolonization treatment. All other situations were considered complicated colonization [12]. An 'isolated patient' was defined as a solitude carrier without any known family or household members with MRSA colonization. In case of any known positive family or household member, these patients together were considered a cluster. A household member was defined as a person sharing the same house by day and night and sharing a bedroom and/or bathroom, and/or living room and/or kitchen [12]. Immunocompromised status was defined as either a hematologic malignancy, stem cell transplantation, organ transplantation, immunosuppressive medication (e.g., chemotherapy, steroids) or HIV infection. The primary outcome of the study was success rate of decolonization treatment, defined by three times negative MRSA cultures from swabs taken from nose, throat and perineum. The first culture needed to be taken at least 48 hours after treatment, with the follow-up cultures obtained with one-week intervals. The long-term success rate was defined as an additional set of negative MRSA swabs one year after decolonization treatment (data available for four hospitals).

Statistical analysis and outcome

Data were presented as rates (percentages or proportions) for categorical variables and as medians plus interquartile range (IQR) for continuous variables. The overall success rate of decolonization treatment was presented as a rate, with 95% confidence interval (95%CI), and was stratified for different treatment strategies.

In univariate analysis, Odds ratio's (with 95% confidence intervals) and Fisher's exact tests were applied to identify clinical risk factors of treatment failure. In the multivariable regression analyses variables from univariate analysis with a $p < 0.05$ were included, together with variables that were previously reported to be associated with treatment failure: MRSA throat carriage and perineal carriage [20, 21].

Ethical approval

Ethical approval was granted by the institutional ethical review committee of the Leiden University Medical Center and the participating hospitals.

Results

During the study period, 224 patients were referred to the outpatient departments because of MRSA colonization. Because of absence of colonization or uncomplicated carriage at the first evaluation, respectively 27 and 20 patients were excluded. Of the remaining 177 patients, only 131 received systemic antibiotics (Figure 1). Reasons for not starting decolonization with systemic antibiotics were spontaneous clearance of colonization (14/177; 8%), lost to follow up (6/177; 3%) and/or acceptance of colonization (23/177; 13%). Reasons for accepting colonization were either related to a high risk of failure, i.e. therapy resistant skin lesions in eczema, or to a high risk of recurrence, i.e. frequent livestock contact or regular visits to health care facilities abroad. Three patients (3/177; 2%) were successfully treated with topical therapy only.

The patient characteristics of all 177 patients with complicated colonization and of the 131 patients with complicated colonization that were treated with systemic antibiotic therapy are summarized in Table 2. Of the 131 patients with complicated colonization and treatment with systemic antibiotics, 19 (15%) lived alone, 103 (79%) lived with one or more household members and in 9 patients (7%) data on household members were missing. In 91/103 (88%) patients all household members were screened for carriage. In 5/103 (5%) only part of the household members were screened and in 7/103 (7%) none of the household members were screened. In total, 229 household members were screened, of which 91 (40%) tested positive for MRSA.

Decolonization treatment

In 131 patients systemic antibiotic treatment was prescribed (Figure 1), and in 125/131 (95%) the choice of antibiotic regimen was in line with the national guideline (Table 1). Six patients received antimicrobial combinations that were not in line with the guideline and 4 others were initially treated with hygienic measures and topical therapy only. The success rate of the first decolonization attempt was 97/131 (74%). Not all patients that failed on a first treatment were treated again. Of the 34 patients in whom the first decolonization attempt failed, 17/34 (50%) underwent a second treatment (Table 3). The success rate after this second treatment was 11/17 (65%). Of the remaining six patients, four were treated for a third time, which was successful in 3/4 (75%) of patients. The cumulative success rate was 111/131 (85%). Mean follow-up time was 13 months. In 78/111 (70%) of the initially successfully treated patients follow-up cultures at $T \geq 12$ months were available. In 4/78 (5%) of patients these cultures were positive for MRSA. Side effects were reported in 27/131 (21%) of patients and consisted of gastrointestinal complaints (21/131; 16%) and malaise (4/131; 3%). An allergic reaction occurred in 1 of the 131 patients.

Figure 1 (next page). Flowchart of treatment schedule. Uncomplicated MRSA carriage was defined as the presence of all of the following features: (i) MRSA exclusively located in the nose, (ii) no active infection with MRSA, (iii) in vitro sensitivity for mupirocin, (iv) the absence of active skin lesions, (v) the absence of foreign material that connects an internal body site with the outside (e.g., urine catheter, external fixation material), and (vi) no previous failure of decolonization treatment. All other cases were considered complicated. Successful decolonization was defined by three successive negative MRSA swabs from nose, throat, and perineum at least 48 h after treatment, with a minimum interval of 1 week. An asterisk (*) indicates that colonization was accepted under certain circumstances, e.g., active noncurable skin lesions, short life expectancy, wishes of the patient, or a high risk of recurrence due to frequent livestock contact or regular visits to health care facilities abroad. An arrowhead indicates patients added to another group.

Figure 1. Flow chart

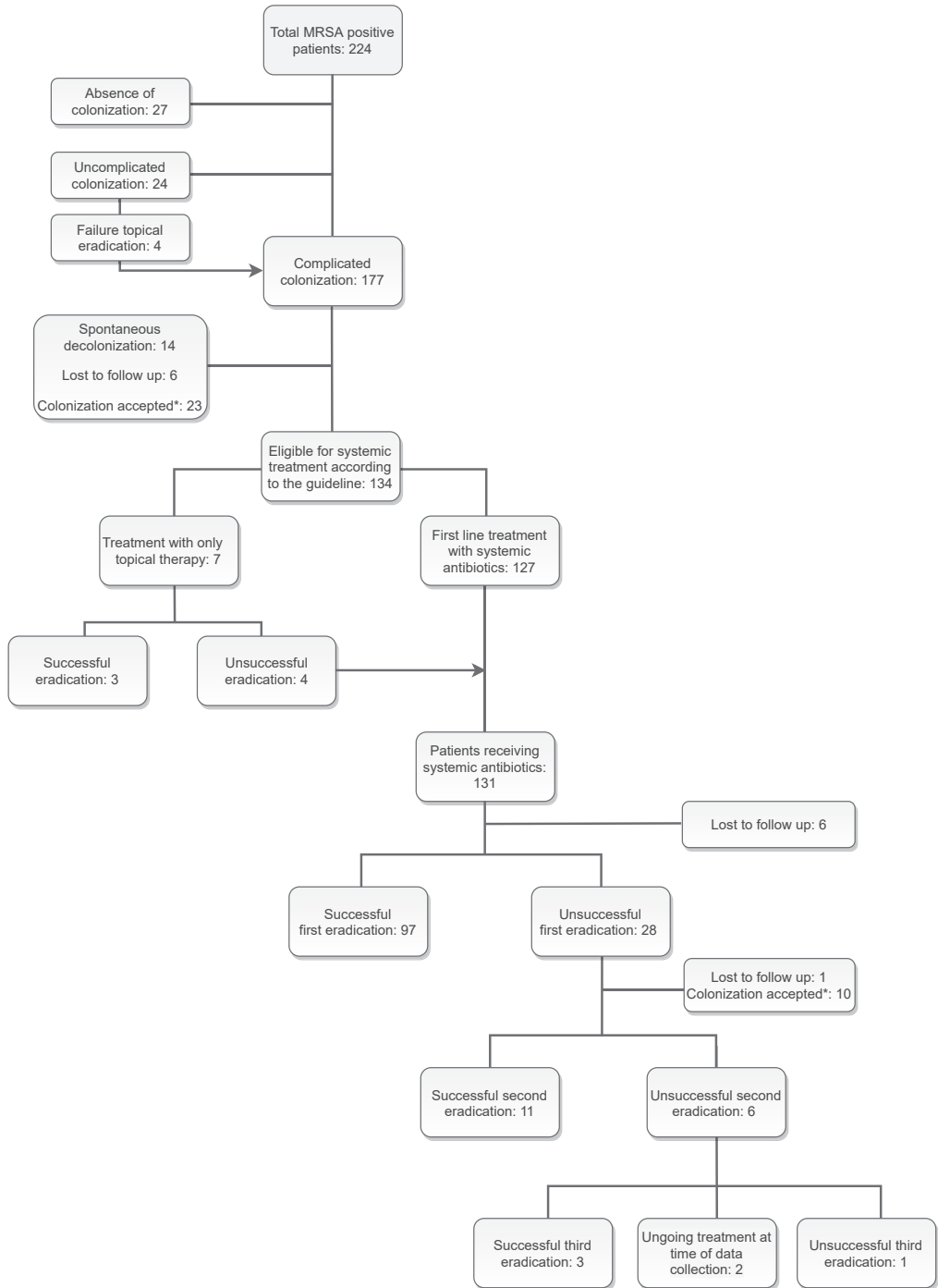


Table 2: Patient characteristics

	All patients with complicated MRSA colonization	Patients receiving treatment with systemic antibiotics
	N = 177 (100%)	N = 131 (100%)
Male sex	82 (46)	64 (49)
Age, median (IQR)	41 (12-70)	43 (13-73)
Positive household member)	76 (43)	61 (47)
<i>Risk factors for colonization</i>		
Immunocompromised status	17 (10)	12 (9)
Chronic antibiotic use	7 (4)	7 (5)
Health care worker	27 (15)	22 (17)
Professional livestock contact	4 (2)	3 (2)
<i>Reason for MRSA screening prior to referral</i>		
Positive household member	44 (25)	29 (22)
Contact with positive person in health care facility	32 (18)	26 (20)
Infection with MRSA	59 (33)	42 (32)
Screening after contact livestock	2 (1)	0
Screening after foreign hospital	25 (14)	22 (17)
Other	8 (5)	7 (5)
Unknown	7 (4)	4 (3)
<i>Site of colonization</i>		
Nose	118 (67)	88 (67)
Throat	114 (64)	87 (66)
Perineum	98 (55)	70 (53)
Other (e.g. skin lesions, infection sites)	58 (33)	40 (31)
<i>Reason for complicated colonization</i>		
Extranasal colonization	166 (94)	122 (93)
Foreign material internal-external	6 (3)	2 (2)
Mupirocin resistance	4 (2)	4 (3)
Skin lesions	33 (19)	24 (18)
Previous unsuccessful decolonization	20 (11)	14 (11)
<i>Infection during colonization</i>		
MRSA infection*	65 (37)	45 (34)

Table 2 continued

		All patients with complicated MRSA colonization	Patients receiving treatment with systemic antibiotics
		N = 177 (100%)	N = 131 (100%)
<i>Microbiology results</i>			
PVL	Present	36 (20)	27 (21)
	Absent	78 (44)	61 (47)
	n/a	63 (36)	43 (32)
Rifampicin	Susceptible	158 (89)	119 (91)
	Resistant	4 (2)	4 (3)
	n/a	15 (9)	8 (6)
Trimethoprim/sulfamethoxazole	Susceptible	136 (77)	103 (79)
	Resistant	27 (15)	20 (15)
	n/a	14 (8)	8 (6)
Clindamycin	Susceptible	111 (63)	79 (60)
	Resistant	43 (24)	36 (28)
	n/a	23 (13)	16 (12)
Doxycycline	Susceptible	72 (41)	60 (46)
	Resistant	38 (22)	28 (21)
	n/a	67 (37)	43 (33)

Legend: The first column includes all 177 patients with complicated colonization. The second column depicts the 131 (out of these 177) patients that received treatment with systemic antibiotics. Values are count (%) for categorical variables and median (IQR= interquartile range) for continuous variables. PVL = Panton Valentine Leucocidin. *MRSA infection = culture confirmed infection(s) with MRSA during colonization.

Table 3: Follow-up after decolonization treatment

		Follow-up cultures after treatment <i>Total treated patients = 131</i>		
		Week 1	Week 2	Week 3
First decolonization attempt	Available	130	111	103
	Positive	14	8	6
Second decolonization attempt	Available	17	15	13
	Positive	2	2	2
Third decolonization attempt	Available	4	4	3
	Positive	0	1	0

Legend: Follow-up cultures after decolonization treatment. Values are count. After one positive culture, no further follow-up cultures were performed.

Table 4: Decolonization success rates of antibiotic regimens

Antibiotic agents	Treated first attempt	Successful after first attempt	Treated second attempt	Successful after second attempt	Treated third attempt	Successful after third attempt
Doxycycline + rifampicin	37	32 (86%; 71-96)	1	1	0	-
Trimethoprim* + rifampicin	60	41 (68%; 55-80)	8	5	3	2
Clindamycin + rifampicin	19	15 (79%; 54-94)	2	1	1	1
Other	15	9 (60%; 32-84)	6	4	0	-
Total	131	97 (74%)	17	11 (65%)	4	3 (75%)

Legend: Values are count (%; 95% confidence interval). The most frequently used combinations of antibiotic agents are mentioned, the 8 other antibiotic regimens are bundled in 'other'. *Trimethoprim was with or without sulfamethoxazole. 'First attempt' is the first attempt with systemic antibiotic agents added to the treatment, i.e. first treatment episode in complicated colonization or second treatment episode after failure of first treatment with topical treatment in uncomplicated colonization.

Antibiotic regimens

For the treatment of complicated colonization in this cohort, 12 different combinations of antibiotic agents were prescribed with a duration ranging from 5 to 14 days. The most frequently prescribed combinations of antibiotic agents were doxycycline-rifampicin, trimethoprim (with or without sulfamethoxazole)-rifampicin and clindamycin-rifampicin. The success rates of the different antibiotic combinations at the consecutive decolonization attempts are summarized in Table 4. In the first treatment attempt, the combination of doxycycline-rifampicin showed the highest success rate (32/37, 86%) compared to trimethoprim(/sulfamethoxazole)-rifampicin (41/60, 68%), clindamycin-rifampicin (15/19, 79%) and 'other regimens' (9/15, 60%). The difference in success rate at first attempt of doxycycline-rifampicin versus all other regimens did not reach statistical significance (86 versus 69%, OR 2.20, 95%CI 0.77-6.31, $p=0.16$). There was no difference in outcome of addition of trimethoprim alone (success rate 19/24, 79%; 95%CI 58-93) or in combination with sulfamethoxazole (success rate 22/31, 71%; 95%CI 52-86).

Prolonged antibiotic treatment (10-14 days) was not associated with better treatment outcome (49/64; 77%) compared to a 7-day treatment (40/51; 78%) (OR 0.99, 95%CI 0.39-2.53, $p=1.00$). There was a trend towards a higher success rate in the patients in whom the guideline for treatment choice was followed (88/115; 77%) compared to the patients in whom the guideline was not followed (6/12; 50%, 95%CI 0.97-10.94, $p=0.08$).

Predictive variables

In the univariate risk analysis, being part of a known household cluster (OR 2.38, 95%CI 1.01-5.61, $p=0.05$) and an immunocompromised status (OR 6.27, 95%CI 1.81-21.68, $p<0.01$) were associated with failure at first decolonization attempt (Table 5).

Panton Valentin Leucocidin (PVL) was tested in 88 patients and was positive in 27/88 (31%). There was no correlation between PVL positivity and success of eradication in these patients (OR 0.57, 95%CI 0.15-1.82, $p=0.36$).

In the multivariable analysis an immunocompromised status remained an independent risk factor for failure at the first treatment attempt (OR 4.83, 95%CI 1.34-17.45, $p=0.02$) (Table 5).

Table 5: Univariate and multivariable analysis of predictive variables for failure of first decolonization attempt

Variable	Univariate analysis		Multivariable analysis		
	OR (95%CI)	p-value	B	OR (95%CI)	p-value
<i>Patient characteristics</i>					
Age >60y	0.68 (0.23-1.98)	0.61			
Male sex	1.54 (0.66-3.58)	0.39			
Part of a known household cluster	2.38 (1.01-5.61)	0.05	0.60	1.83 (0.74-4.51)	0.19
Healthcare worker	0.54 (0.15-1.99)	0.56			
<i>Comorbidities</i>					
Immunocompromised status	6.27 (1.81-21.68)	<0.01	1.58	4.83 (1.34-17.45)	0.02
Current skin disease	0.66 (0.21-2.11)	0.59			
Chronic antibiotic use	1.83 (0.32-10.53)	0.61			
MRSA infection*	1.29 (0.54-3.08)	0.65			
<i>Site of colonization other than nose~</i>					
Throat culture positive	0.84 (0.34-2.11)	0.81	0.07	1.07 (0.39-2.96)	0.89
Perineum culture positive	1.51 (0.62-3.71)	0.39	0.40	1.49 (0.57-3.90)	0.42
Other site culture positive	1.20 (0.49-2.97)	0.81			
<i>PVL genes</i>					
PVL positive	1.56 (0.49-4.93)	0.54			

Legend: Results of univariate and multivariable analyses. Values are OR=odds ratio (95%CI= 95% confidence interval), B= regression coefficients. PVL= Panton Valentine Leucocidin. *MRSA infection = culture confirmed infection(s) with MRSA during colonization. ~ = Sites of colonization reflects positive cultures at screening. Multiple sites could be positive within one patient.

Discussion

The main finding of our study is the success rate of decolonization of 74% after the first treatment attempt, which is relatively high when compared to previous literature. In the Dutch study by Ammerlaan et al. in 2011, this rate was 56% [18]. A possible explanation for this difference may be that the guideline adherence for treatment choice was much lower in the study by Ammerlaan (62%) compared to our study (90%). A second explanation may be that in our study - in the majority of cases - household members were screened and treated simultaneously, preventing failure because of recolonization by untreated colonized household contacts. In the time of the study by Ammerlaan et al, according to the Dutch guideline, household members were only screened if the first decolonization attempt had failed. Routine screening of household members before starting treatment was not included in the guideline until 2012.

The success rate of topical treatment in combination with systemic antibiotics - in our study - is decidedly high compared to topical treatment without systemic antibiotics in the literature, supporting the current guideline. Earlier studies have shown a success rate of approximately 40% after the first decolonization attempt in patients that were treated with topical treatment alone [21, 22].

There were no apparent differences in success rates between different antibiotic regimens. The combination of doxycycline-rifampicin had the highest success rate but this did not reach statistical significance. This combination is one of the first choice regimens in the Dutch guideline. There was no difference in effectivity between a treatment duration of 7 days as compared to 10-14 days. This supports the guideline recommendation of a minimum antibiotic treatment of 7 days [12].

Being part of a known household cluster and immunocompromised status were associated with failure at the first treatment attempt. In multivariable analysis only immunocompromised status remained an independent risk factor for failure at the first treatment attempt, although there were few patients (12) in this group. This differs from an earlier study by Ammerlaan et al, in which chronic pulmonary disease, ADL dependency, throat carriage, perineal carriage and the presence of a device were associated with treatment failure [20]. This difference may be explained by the difference in study population, as Ammerlaan et al did not exclude uncomplicated carriers from their analyses.

The fact that 27/224 (12%) of the referred patients were no longer colonized with MRSA at the time of visiting the outpatient clinic is a relevant observation. It illustrates the possibility of spontaneous clearance and the importance of repeated screening before starting treatment.

In the current search and destroy strategy, MRSA carriers are exposed to systemic antibiotic therapy, for the benefit of society, even if they are asymptomatic. The side-effects of treatment should be weighed against the benefits of a search and destroy policy. Reported side effects in this study were mild and the effectivity of decolonization high, supporting the current that MRSA decolonization strategy in a low prevalence country like the Netherlands.

There are several limitations of our study. Due to its observational design, confounding limits the determination of the most effective antibiotic strategy. However, so far there is only one small randomized trial published comparing the efficacy of ciprofloxacin-rifampicin and trimethoprim-sulfamethoxazole combinations in MRSA decolonization. This study showed no significant difference in success rates, but did not include a doxycycline based regimen and was underpowered [14]. The majority of previously published studies are limited to the comparison of different antibiotic combinations versus topical treatment alone or no treatment at all [15, 17]. A second limitation of our study is that group sizes are small due to the low prevalence of MRSA colonization and the variety of different antibiotic regimens that were prescribed, reflecting the current guideline. A third limitation is that a proportion of patients were lost to follow-up one year after treatment. However, only 5% of the initially successfully treated patients that were cultured after one year were recolonized with MRSA. In the study of Lekkerkerk et al. [23], the median number of days to detect a MRSA recurrence was 24 and 12% of recurrences was detected between 62 and 200 days. Therefore, the majority of recurrences is expected to have been detected in our study, but late recurrences may have been missed. However, these late recurrences could also be ascribed to re-colonization from an unidentified source rather than to failure of the initial decolonization treatment.

In conclusion, treatment for complicated MRSA colonization according to the guideline has a high success rate. These findings endorse the current strategy of 'search and destroy'. For future research, a randomized trial would be necessary to further distinguish whether doxycycline-rifampicin has a higher efficacy rate compared to alternative treatment combinations, as suggested in this study.

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