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ORIGINAL ARTICLE

Eradicating MRSA carriage: the impact of throat carriage and Panton-Valentine leukocidin genes on success rates

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Abstract

In Denmark, eradication treatment is recommended for methicillin-resistant *Staphylococcus aureus* (MRSA) carriers. Here, we analyze factors associated with eradication outcome. MRSA carriers referred to the MRSA Knowledge Center at Hvidovre Hospital in 2013 were included. Carriers were sampled from nose, throat, and perineum. Eradication regimen was 5 days of mupirocin nasal ointment and chlorhexidine whole-body wash. Oral antibiotics were sometimes added. Factors associated with eradication after the first eradication attempt were analyzed by logistic regression and expressed as odds ratio (OR) with 95% confidence interval (95% CI). Of 164 individuals, 143 completed 1- and 6-month follow-up after 1st treatment. Eradication was achieved in 63 (38.4%) patients after one treatment and 101 (61.6%) individuals became MRSA free after up to 4 eradication treatments. Throat carriage was associated with a higher failure rate (OR 0.29 (0.10–0.80)), while the presence of Panton-Valentine leukocidin (PVL) genes (37%) was associated with higher success rate (OR 3.52 (1.44–8.57)). Other factors analyzed were not significantly associated with eradication outcome. None of the 26 patients lost to follow-up developed later MRSA infections. This study estimates the efficacy of treatment of MRSA carriage with an eradication rate of 38.4% after the first treatment and a total eradication rate of 61.6% after several treatments. Throat carriers had a lower eradication success rate. Adding oral antibiotics to the first treatment did not increase success. The finding of a significant higher success rate when having a PVL-positive clone should be further investigated.

Keywords Methicillin-resistant *Staphylococcus aureus* · Infection control · MRSA eradication · MRSA decolonization · Staphylococcal skin infections/prevention and control

Introduction

Staphylococcus aureus is a frequent colonizer of the anterior nares, throat, and skin of humans [1] and carriage can be associated with an increased risk of infection [2, 3]. When methicillin-resistant *Staphylococcus aureus* (MRSA) carriage is confirmed, the Danish Health Authority [4] recommends eradication treatment of MRSA carriers and their close contacts to reduce the transmission of MRSA and prevent infections [3]. Although still lower than the European average, the prevalence of MRSA is increasing in Denmark [5–7]. In 2016, 3550 new MRSA cases were identified in Denmark of which 35% had livestock-associated MRSA (LA-MRSA). LA-MRSA only accounts for around 5% of cases in the Capital Region of Denmark, where most cases are community-acquired MRSA (CA-MRSA). International data on the efficacy of eradication treatment differ in therapeutic strategies and lengths of follow-up periods making comparisons of eradication rates difficult [8, 9]. The Danish National MRSA guidelines [4] recommend a 5-day topical eradication treatment with mupirocin nasal ointment 2% and chlorhexidine 4% body- and hair-wash for carriers and close contacts with follow-up samples after 1 month and 6 months. Systemic antibiotics can be added to the treatment if it fails, but preferably following two topical treatments. Despite the common use of eradication treatment in Denmark, there is limited national data on the efficacy of the MRSA carrier treatment.

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The main aim of this study was to determine the overall eradication success rate in patients treated for MRSA carriage. It has been shown that throat carriage is a risk factor for failure [9–11], and that throat carriers have a better outcome if given rifampicin in combination with clindamycin or trimethoprim/sulfamethoxazole [12, 13]. The majority of our patients that had systemic antibiotics added to their topical treatment received clindamycin in mono-therapy (89%), and we evaluated if this improved the success rate in throat carriers. In addition, all isolates were routinely whole genome sequenced and *spa* types and the presence or absence of Panton-Valentine leukocidin (PVL) genes were included in the analysis to evaluate their possible influence on success rate.

Materials and methods

Design and inclusion criteria This study was a retrospective cohort study. Inclusion criteria were a first-time positive screening sample of MRSA in 2013 and an intent to eradicate the carrier state. If the first MRSA-positive sample in a patient was from a clinical sample, the infection was treated and then weeks later the patient was screened for carrier state from the nose, throat, and perineum. Inclusion and exclusion of patients are presented in Fig. 1. Patients with chronic wounds or active eczema were not offered eradication treatment.

Data on each patient was obtained by review of records at the MRSA Knowledge Center at Hvidovre Hospital, where eradication treatment was documented. The following data were collected: sex, age, number of persons in the household, MRSA infections prior to eradication treatment, anatomical location of any positive screening or control sample, phenotypic resistance of isolate, treatment given, and outcome.

Sampling Swabs were taken by family doctors and in hospitals as recommended in the Danish National MRSA guidelines [4]. Screening and control swabs were recommended from the nose, throat, and perineum. All screening samples were inoculated in an enrichment broth containing 2.5% NaCl, 3.5 mg/L cefoxitin, and 20 mg/L aztreonam for overnight incubation at 35 °C. From the broth, 10 μL was spread on a 5% blood agar and a MRSA chrome agar (Biomérieux). Susceptibility testing was performed by disk diffusion for the following antibiotics: cefoxitin, erythromycin, clindamycin, tetracycline, linezolid, gentamicin, fusidic acid, trimethoprim/sulfamethoxazole, rifampicin, moxifloxacin, and mupirocin. Isolates were confirmed to be MRSA by an in-house *mec*A PCR, only one colony was selected for PCR. Only the first MRSA isolate from each patient was sent to whole genome sequencing (WGS).

WGS data As a routine since late 2012, all first MRSA isolates from patients in our uptake area have been whole genome sequenced on a MiSeq (Illumina) as previously described [14]. An in-house script was used to extract *spa* types, sequence types (ST), and PVL genes if present.

Treatment regime The standard eradication regime was 5 days of mupirocin nasal ointment 2% applied inside the nostrils 3

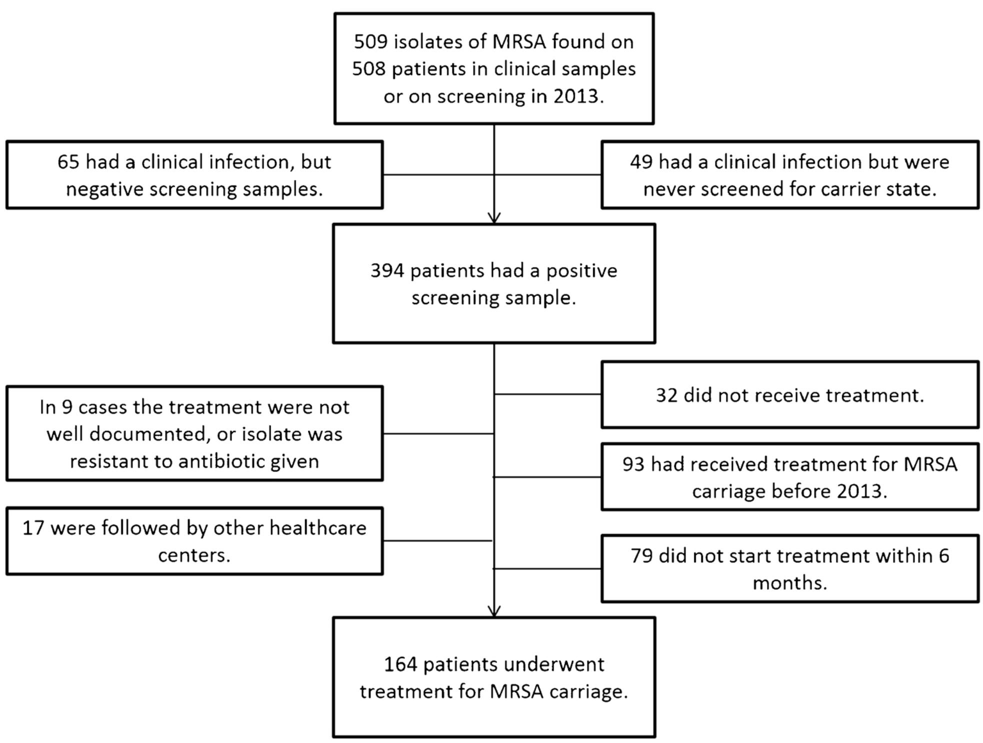

Fig. 1 Inclusion and exclusion of patients

times daily combined with daily use of chlorhexidine 4% as a whole-body and hair-wash. The first eradication regime was administered to every household member regardless of carrier state. Carriers and their close contacts were instructed to wash towels daily, bed linen every second day, and to do thorough house cleaning such as vacuum cleaning and wiping of door handles and other contact points with disinfectants. In this study, systemic antibiotics were often given at the discretion of the physician for the first or second treatment if the patient was a MRSA throat carrier.

Clindamycin was chosen as first-line systemic antibiotic unless the isolate was resistant, the patient had side effects or was allergic to clindamycin. Clindamycin was sometimes used when isolates were shown to be inducible resistant based on a D-zone between clindamycin and erythromycin.

Follow-up After eradication treatment, the patients were recommended MRSA screening after 1 month and if negative, again after 6 months. All household members were also screened 1 month after the first treatment, but were only screened again at 6 months if they had had at least one MRSA-positive sample. Healthcare workers were screened four times the 1st month (days 1, 7, 14, and 21 following treatment) and if negative, again after 6 months. The patient was declared free of MRSA if all follow-up samples were negative. If the patient did not have all recommended control samples taken, the patient was declared free of MRSA based only on one negative set of screening samples, if it was taken at a minimum of 6 months after the eradication therapy. If any of the samples taken within the first month were positive, it was considered as a failed treatment attempt, not a new colonization. In cases of failed treatment, the carriers were offered up to three more eradication attempts. Patients that did not complete the recommended follow-up program and had either no control swabs taken or only one negative control after eradication, but with the control samples taken earlier than 6 months following treatment, were regarded as lost to follow-up (LFU). The patients were followed until successful eradication, decision about no further treatment attempts, or LFU.

Data analysis Statistical analysis was carried out using SPSS software. All data were expressed as median and range or frequencies. Factors associated with eradication after the first eradication treatment were analyzed by logistic regression analysis and expressed as Odds ratio (OR) with 95% confidence interval (CI). Variables included were age, sex, household size, PVL, clinical infection, pharyngeal carriage, nasal carriage, perineal carriage, chlorhexidine wash, and systemic antibiotics. The multivariate analysis was run with LFU excluded. Eradication rate was estimated after every treatment round as number of patients who had a 6-month negative control out of total patients treated. A cumulative eradication rate was also calculated. Estimation of eradication rates is based on intention-to-treat analysis where individuals who did not return for follow-up were treated as failures, i.e., missing equaled failure.

Results

The 2013 database of MRSA isolates had 509 isolates taken from 508 patients. Two hundred and fifty were males and 258 were females. One hundred sixty-four patients fulfilled the inclusion criteria (Fig. 1) of which 59 were males and 105 females. Median age by the first positive screening was 31 with a range of 2–93. Only eight persons lived alone, while 156 lived in households, ranging in size from two to eight with a median of four. Fifty-nine of 164 had a documented clinical infection with MRSA prior to the treatment of carrier state, predominantly skin and soft tissue infections. There was a total of 53 different *spa* types and 24 STs, with the most frequent *spa* types being t002 (19), t019 (17), t304 (17), and t008 (15). PVL was identified in 65 MRSA isolates representing 19 different *spa* types. Twenty-one patients from the 1st treatment round had isolates that were inducible resistant to clindamycin. Seven of these were treated with clindamycin, and two became MRSA free on 1st intent.

Cumulative eradication rate Table 1 shows the outcome of the 1st, 2nd, 3rd, and 4th treatment. Of the 164 persons receiving eradication treatment, a total of 26 were lost to follow-up (15%), most of them after the first treatment. Eighteen of the LFU patients had a 1-month negative sample, and the eradication rates are also shown without LFU. The total eradication rate was 61.6% with individual eradication rate after the 1st, 2nd, 3rd, and 4th treatment at 38.4%, 42.9%, 32.0%, and 30.0% respectively.

Table 1 Outcome of the 1st, 2nd, 3rd, and 4th eradication treatment

	1st treatment	2nd treatment	3rd treatment	4th treatment	Total
Treated	164	63	25	10	164
Lost to follow-up	21	4	0	1	26
Treated with systematic antimicrobials	55 (33.5%)	43 (68.3 5)	17 (68.0%)	4 (40.0%)	
Number of these that received clindamycin	49 (89.1%)	38 (88.4%)	15 (88.2%)	4 (100%)	
Eradicated Eradication rate	63 (38.4%)	27 (42.9%)	8 (32.0%)	3 (30.0%)	101 (61.6%)

For the 80 patients that were not eradicated after the first treatment, comparing 1 and 6 months positive controls after the 1st treatment, 69 (86.3%) were found on the control swabs taken after 1 month.

Factors associated with eradication after the first attempt By univariate logistic regression analysis, the presence of PVL genes and throat carriage was associated with the outcome of eradication and both remained statistically significantly associated after adjustment for age, sex, household size, clinical infection, carriage site, length of chlorhexidine wash, and use of systemic antimicrobials (Table 2). None of the other factors were associated with the outcome of eradication treatment. The presence of PVL genes increased the odds of eradication by 252% (OR 3.52 (95% CI 1.44–8.57)) while throat carriage decreased the odds by 71% (OR 0.29 (95% CI 0.10–0.80)).

Looking at the 34 persons who never had a positive throat sample on any of the screenings, 33 (97%) became MRSA free (30 on 1st, 2 on 2nd, and 1 on 4th). On the other hand, only 68 of 109 (62%) that were positive in one or more swabs from the throat became MRSA free.

Table 2 Factors associated with eradication after the first eradication treatment attempt

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	*p* value
Age, per year increment	1.00 (0.98–1.02)	0.99 (0.97–1.02)	0.57
Sex			
Female (*n* = 90)	1.0	1.0	
Male (*n* = 53)	0.75 (0.38–1.49)	1.15 (0.50–2.62)	0.75
Household size			
< 4 (*n* = 68)	1.0	1.0	
≥ 4 (*n* = 75)	0.89 (0.46–1.72)	1.02 (0.44–2.41)	0.96
PVL			
0 (*n* = 90)	1.0	1.0	
1 (*n* = 53)	2.55 (1.27–5.12)	3.52 (1.44–8.57)	0.006
Clinical infection			
0 (*n* = 90)	1.0	1.0	
1 (*n* = 51)	0.83 (0.42–1.67)	0.54 (0.21–1.41)	0.21
Throat carriage			
0 (*n* = 47)	1.0	1.0	
1 (*n* = 86)	0.46 (0.22–0.95)	0.29 (0.10–0.80)	0.017
Nasal carriage			
0 (*n* = 61)	1.0	1.0	
1 (*n* = 81)	0.63 (0.32–1.24)	0.63 (90.27–1.46)	0.28
Perineal carriage			
0 (*n* = 82)	1.0	1.0	
1 (*n* = 43)	1.49 (0.71–3.14)	1.01 (0.36–2.83)	0.98
Chlorhexidine wash			
5 days (*n* = 91)	1.0	1.0	
10 days (*n* = 530	1.29 (0.65–2.56)	2.06 90.40–10.63)	0.39
Systemic antibiotics			
No (*n* = 97)	1.0	1.0	
Yes (*n* = 46)	1.10 (0.54–2.230	1.12 (0.20–6.22)	0.90

Systemic antibiotics in the throat carrier group alone A univariate logistic regression analysis was made on the throat carrier subgroup. We included days of chlorhexidine wash and PVL as it had shown to be a significant factor. No significant correlation was found between outcome and PVL (OR 2.12 (95% CI 0.84–5.35)), days of chlorhexidine wash (OR 3.69 (95% CI 0.30–44.93)), or systemic antibiotic (OR 0.53 (95% CI 0.04–6.31)) in the throat carrier group.

Discussion

The main aim of this article was to determine the eradication success rate in patients treated for MRSA carriage in the Capital Region of Denmark in 2013 and to determine whether adding systemic antibiotics to the eradication treatment has an effect on the outcome. The overall eradication rate was 61.6%, with an initial eradication rate of 38.4% after first round of treatment. Adding systemic antibiotics to the treatment, in this study mainly clindamycin, had no significant effect on the outcome. In addition, we found that having a positive swab from the throat was negatively correlated with the outcome of treatment, with an estimated OR of 0.29 (0.10–0.80), and that being carrier of a PVL-positive clone was correlated with better treatment outcome with an OR of 3.52 (1.44–8.57).

The success of MRSA eradication in different studies can be difficult to compare, as the populations are diverse, and the studies vary in treatment given and follow-up time. This has also been noted earlier in a review by Ammerlaan et al. [8]. In our study, we treated LFU as failed treatments, this is a conservative estimate. Excluding patients that were LFU, the overall eradication rate was 73.2%, the true eradication rate probably lie somewhere in between the two estimates, as some of the patients LFU most likely cleared the carrier state following treatment. It is worth noting that none of the patients LFU returned with a positive screening or clinical sample at a later point. We believe that by our indications for declaring a carrier free of MRSA after 6 months, we find almost all failed treatments. According to a study by Lekkerkerk et al., more than 95% of the treatment failures found after 1 year will be found already after 6 months [15].

A high rate of patients in our study received oral antibiotics on the 1st (33.5%) and 2nd (68.3%) treatment attempt. The multivariate analysis on the 1st treatment did not show better outcome when given oral antibiotics, not even when only including throat carriers. In our study, patients that received systemic antibiotics were mainly treated with clindamycin. Before 2013, we had often used a combination of fusidic acid and rifampicin, if the isolates were susceptible, but due to many side effects, it was decided to use clindamycin as the preferred treatment for eradication of MRSA. We do not have sufficient data on other antimicrobials as they were only used if an isolate was constitutive resistant to clindamycin. Other studies have found that adding systemic antibiotics improves the eradication rate. A recent randomized controlled study showed [10] that there was a better outcome for throat carriers receiving a combination of rifampicin and either clindamycin or trimethoprim/sulfamethoxazole. Another Swedish study [13] found that of 96 children with MRSA carriage only treated with topical treatment 36% achieved permanent eradication, but when adding systemic antibiotics to the topical treatment, 65% acquired permanent eradication. Rifampicin was used in combination with either clindamycin, fusidic acid, or trimethoprim/sulfamethoxazole for 14 days. Rifampicin has been shown to have a better intracellular effect than clindamycin against *S. aureus* which might explain the difference in outcome between our study and the two Swedish studies [16]. However, we believe that when considering systemic antibiotics for MRSA carriers, side effects in otherwise healthy individuals and the selective pressure gained by increasing use of antibiotics should also be considered. On the other hand, MRSA patients are often stigmatized both in the health care system and in the society and are very eager to become MRSA free [17].

A lot of different estimations have been made in order to asses if being carrier of MRSA in certain anatomical sites lead to a higher risk of failed treatment. Being a carrier in the throat has been described as a risk factor [10–12], so has perineal carriage, but less consistently [10]. Other studies have noted combined throat and nasal carriage as a risk factor [15]. Colonization in various locations has been associated with longer colonization [18]. Dutch guidelines define extra-nasal carriage as one criterion to complicated carriage [9]. We found that throat carriage was a risk factor for treatment failure with an estimated OR of 0.29 (0.10–0.80), nasal or perineal carriage was not associated with outcome in our dataset. Patients that never had MRSA in a throat sample ($N = 34$) had a total eradication rate of 97% with 88% being MRSA free after the first treatment.

As all isolates have been sent to WGS, we included some of these data and found a significant relation between outcome after the first treatment and the presence of PVL genes with an adjusted OR of 3.52 in favor of PVL-positive clones. PVL is often associated with skin and soft tissue infections [19, 20]. Why PVL also leads to easier decolonization is hard to tell. A Swedish study showed shorter colonization time in children with PVL-positive MRSA clones and also found increased eradication success in PVL-positive throat carriers [13].

The study has some limitations. There was no randomization of patients and using mostly clindamycin for carriage treatment did not give us the possibility to conclude whether some systemic antibiotics are better than others for the treatment of MRSA carriers. A randomized study including various centers in Denmark and different types of systemic antibiotics would add important information to the effect of systemic antibiotics. The data for this study were gathered looking through the patient records of MRSA Knowledge Center. The data might not be complete as the patients' family doctor could have prescribed further antibiotics without our knowledge and some co-morbidities and risk factors for failure such as eczema or chronic wounds might have been missed [10]. Transient colonization and spontaneous clearance of MRSA may have influenced our results. Recolonization after successful treatment from close contacts or the environment could also influence on our results.

Conclusion

The results of this study estimate the efficacy of treatment of MRSA carriage in the Capital Region of Denmark in 2013. The eradication rate was 38.4% after the first treatment and a total eradication rate of 61.6% was achieved. When excluding patients that were lost to follow-up, the total eradication rate was 73.2%. Surprisingly, we found that the OR of treatment success was 3.52 with a p value of 0.006 in carriers of a PVL-positive clone. As expected, we found that throat carriage is a risk factor for failure but adding clindamycin to the first eradication treatment did not improve the outcome neither in the throat carrier group nor in all patients. Based on our data, we cannot recommend adding clindamycin to the topical treatment for the initial treatment of MRSA carriers, and further studies are needed to evaluate whether clindamycin has a role in persistent MRSA throat carriage.

Compliance with ethical standards

This study was carried out in concordance with recommendations by The Danish National Committee on Health Research Ethics. All data were anonymized on data collection and no identifying information of any individual is included in this article.

Conflict of interest The authors declare that they have no conflicts of interest

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