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Short report

# Danish experience of meticillin-resistant *Staphylococcus aureus* eradication with emphasis on nose–throat colonization and supplementary systemic antibiotic treatment

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## SUMMARY

This study aimed to evaluate the Danish Board of Health's guidance for treating the carriage of meticillin-resistant *Staphylococcus aureus* (MRSA), focusing on nose–throat carriage and use of supplementary systemic antibiotics. The results of MRSA eradication treatment among 358 patients were analysed, focusing on those with nose ( $N=58$ ) or throat ( $N=183$ ) MRSA colonization. The Danish guidance for MRSA treatment was found to be more successful in patients with nose colonization (66%) compared with throat colonization (41%), despite the fact that the cumulative eradication rates were equal after three treatment cycles (71% vs 73%). This study found that supplementation of colonization treatment with systemic antibiotics does not have a positive effect.

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## Background

Meticillin-resistant *Staphylococcus aureus* (MRSA) is resistant to the antibiotics most commonly used as first-choice treatment of *S. aureus* infections [1]. The increasing incidence of MRSA poses a world-wide health challenge [2], and the spread of MRSA between healthcare settings and community settings is of great concern. Although great efforts have been made in Denmark, and other Scandinavian countries and the

Netherlands, to keep the occurrence of MRSA at a low level, increasing numbers of MRSA infections are still observed [3].

MRSA colonization at oropharyngeal (throat) and other sites poses a barrier for effective eradication despite progress in basic and clinical MRSA research [4]. Recently, a Danish study showed that MRSA could not be eradicated in more than one-third of 143 MRSA patients, and that eradication failure was dependent on throat carriage, treatment length and genetic characteristics [5]. As such, this larger observational study of 358 MRSA patients from another region in Denmark, focusing on MRSA nose–throat carriage and use of supplementary systemic antibiotics, was undertaken.

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## Materials and methods

Since 2009, MRSA patients in Region Zealand, Denmark have been served by an MRSA unit, organized under the Regional Clinical Microbiology Department. The unit takes daily care of MRSA patients in the region, and employs two full-time infection control nurses with direct access to medical microbiological knowledge and advice. The MRSA unit works on the control and prevention of MRSA, including MRSA carrier therapy, guidance and education of primary care staff on MRSA issues, development of treatment strategies and monitoring of success rates of MRSA treatments. Between 2014 and 2016, the MRSA unit visited all MRSA-positive patients in their own homes for guidance in relation to MRSA carrier treatment.

### Patients

This observational study was conducted in Region Zealand which has approximately 800,000 citizens (14.5% of Denmark's population). During this period, almost 9000 samples were investigated annually, leading to the diagnosis of 262, 327 and 457 patient cases with MRSA in 2014, 2015 and 2016, respectively (approximately 14% of incident MRSA patients in Denmark) [6]. Of the 1046 incident MRSA patients during this period, 688 were excluded from this study for the following reasons: (1) patients without nose or throat colonization; (2) patients with sepsis; (3) patients that could not be followed-up due to death, leaving the region, no personal or contact data, or residence in another region in Denmark; (4) patient age <2 years; or (5) patients with livestock-associated MRSA CC398. The two last groups were excluded as the Danish MRSA colonization treatment strategy varies considerably for patients aged <2 years and patients with livestock-associated MRSA CC398.

The remaining 358 patients were divided into two groups: Group T (MRSA found in the throat regardless of presence in other locations) and Group N (MRSA found in the nose but not in the throat, regardless of presence in other locations).

### MRSA eradication strategy

The MRSA eradication guidelines from the Danish National Board of Health [7] were followed; as such, all members of

the household were treated simultaneously to prevent cross-contamination. The standard treatment was usually 5 days, and 10 days for throat carriers. The treatment included: (1) mupirocin nasal ointment 2% (Bactroban Nasal) in both nostrils three times daily; (2) daily whole-body wash, including hair wash, with chlorhexidine soap 4%; and (3) cleaning and laundering (not described in detail). MRSA eradication treatment was offered to all patients who were considered able to adhere to the treatment protocol, who did not have MRSA infection or major skin problems. Patients admitted to hospital previously were also considered for MRSA eradication treatment.

Successful eradication was defined as negative samples (nose, throat and any other locations that previously tested positive) 1 month and 6 months after completion of MRSA eradication treatment. If samples were MRSA-positive at 1 or 6 months, the patient was offered a second standard MRSA eradication treatment. Systemic antibiotics were primarily used in patients considered to be at increased risk of secondary hospital transmission. This could include patients needing frequent hospital visits or admissions, or patients who worked in hospitals or other healthcare settings. Usage of supplementary systemic antibiotics was guided by resistance tests, and mainly consisted of clindamycin p.o. 600 mg x 3 for 7–10 days. In case of resistance to clindamycin or if the patient did not tolerate the treatment, the authors often refrained from treatment with systemic antibiotics.

### Identification and typing of MRSA isolates

MRSA was identified in samples from hospitalized patients using polymerase chain reaction (GeneXpert, Cepheid, Sunnyvale, CA, USA) and confirmed by culturing. Non-hospitalized patients were sampled by family doctors using an eSwab (COPAN Diagnostics, Murrieta, California) sample and tryptic soy broth for subsequent culturing. Culturing was performed on blood agar plate 5% (with polymyxin tablet) and on CHROMagar MRSA plate (biomérieux, Marcy l'Etoile, France). The CHROMagar MRSA plate has been shown to have sensitivity and specificity of 95.4% and 100%, respectively, after 24 h of incubation [8].

**Table 1**

Cumulative percentage of meticillin-resistant *Staphylococcus aureus* eradicated after the first, second and third eradication treatments

	All	Anatomical site				Systemic treatment				A vs B P-value	C vs D P-value
		Group T (throat) <sup>A</sup>		Group N (nose) <sup>B</sup>		No <sup>C</sup>		Yes <sup>D</sup>			
		N	%	N	%	N	%	N	%		
Baseline	358	228		130		-		-			
Drop-out	117	45	19.7	72	55.4	-		-			
First treatment	241	183		58		178		63			
Eradicated	113	75	41.0	38	65.5	89	50.0	24	38.1	0.001	0.10
Second treatment	92	85	46.4	7	12.1	63		29			
Eradicated	45	43	50.6	2	28.6	32	50.8	13	44.8		
Third treatment	31	28		3		20		11			
Eradicated	17	16	57.1	1	33.3	11	55.0	6	54.5		
Cumulatively eradicated	175	134	73.2	41	70.7	132	74.2	43	68.3	0.71	0.37

## Statistics

Differences in frequency distributions between the groups were determined using Chi-squared test. Statistical significance was defined as  $P < 0.05$ .

## Results

MRSA colonization occurred in 228 patients in Group T (throat) and in 130 patients in Group N (nose). Among these patients, 117 (33%) could not be reached for treatment, with Group N having the highest proportion (55%) of drop-outs (see Table I). Of the MRSA patients included in the study, the median age was 37 years (range 2–99 years) and 48% were female.

Of the 183 patients in Group T, MRSA eradication was achieved in 75 (41%) patients after the first treatment. Second and third courses of treatment were given to 85 and 28 patients, respectively, with a cumulative eradication rate of 73%. The success of throat MRSA eradication treatment per treatment course increased over time, from 41% at the first treatment to 57% at the third treatment ( $P = 0.06$ ).

Of the 58 patients in Group N, MRSA eradication was achieved in 38 (66%) patients after the first treatment. Second and third courses of treatment were given to seven and three patients, respectively, with a cumulative eradication rate of 71%. The nasal eradication rates per treatment course decreased after the first treatment from 66% to 33%, but the difference was not significant ( $P = 0.08$ ).

The eradication rates in Groups T and N differed significantly after the first treatment [60% higher in Group N ( $P = 0.001$ )], whereas the cumulative eradication rates did not differ (Figure 1).

Systemic antibiotic treatment was used in 63 (26%), 29 (32%) and 11 (36%) patients, respectively, during the three treatment

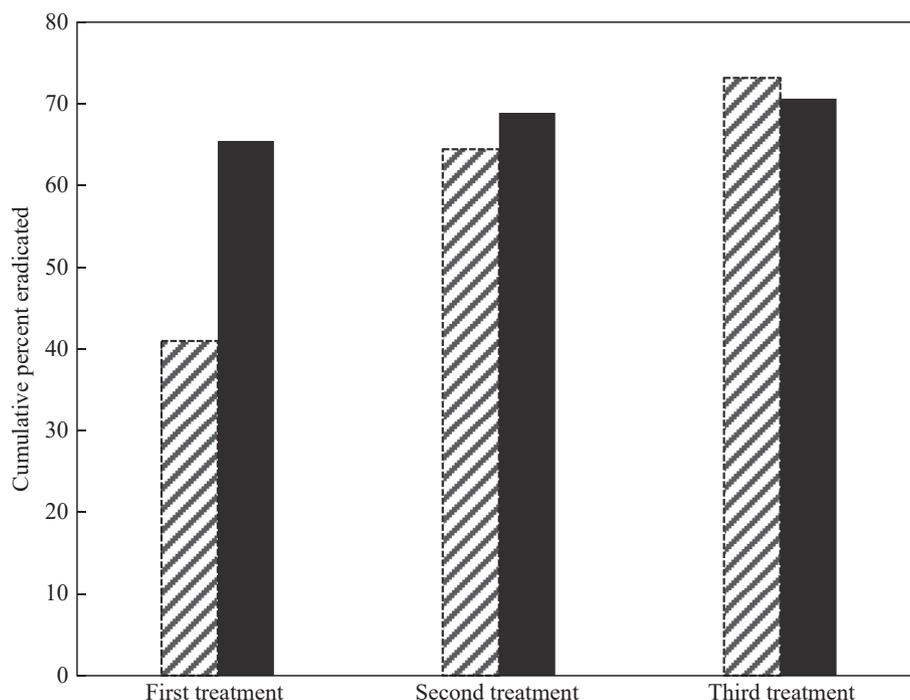
cycles, and yielded eradication rates ranging from 38% at first treatment to 68% cumulatively. In patients not treated systemically, the corresponding figures were higher (50% and 74%, respectively) but did not differ significantly (Table I). The cumulative MRSA eradication rates for systemic antibiotic treatment did not differ between Groups T and N (data not shown).

## Discussion

Addition of systemic antibiotics has been suggested to improve the eradication effects of treatment protocols based on topical mupirocin in throat MRSA carriers [9]. However, the present study did not find that the addition of systemic antibiotics improved MRSA eradication rates irrespective of throat or nose colonization. These findings should be interpreted with caution due to the retrospective and non-randomized study design. The authors cannot be sure that all patients complied fully with treatment, or that patients apparently not eradicated of MRSA were not, in fact, recolonized by other MRSA strains. However, these findings are in line with a recent Danish observational study using the same treatment protocol as the present study [5].

The sensitivity and specificity of the MRSA diagnostics used in this study are high [8]. However, an inferior sampling technique may reduce the sensitivity of MRSA diagnosis. This does not seem to be a problem in this study, as higher eradication rates (higher chance of negative sampling) were found in nasal samples compared with throat samples. In the case of an inferior sampling technique, a higher chance of negative sampling in the throat compared with the nasal cavity would be expected.

Higher initial eradication rates were observed for patients with nasal, as opposed to throat, colonization, which is also congruent with previous Danish observations [5]. This would be in keeping with direct application of mupirocin ointment



**Figure 1.** Outcome of the first, second and third attempts to eradicate meticillin-resistant *Staphylococcus aureus*. Solid bars, Group N (nasal colonization); hatched bars, Group T (throat colonization).

bilaterally to the nasal mucosa, giving high local antibiotic concentrations. In contrast, there is no effective means of delivering topical treatment to the throat mucosa. Further, efficient eradication from the oropharynx may be challenged by re-infection from the nasopharyngeal space [10]. However, the cumulative eradication rates after additional treatment cycles were equal in the two anatomical subsets of colonization, showing that persistent efforts will 'pay off', but that results might be achieved more quickly by using relevant topical treatments.

This study and others [5] found that following the Danish guidelines for MRSA eradication in nose and throat carriers is ineffective in approximately one-third of cases, indicating that there is still great room for improvement. The results of this real-life observational study support the notion that topical therapy directed against MRSA at relevant locations may be of greater importance than systemic antibiotic therapy in selected groups of patients.

#### Conflict of interest statement

None declared.

#### Funding sources

None.

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