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

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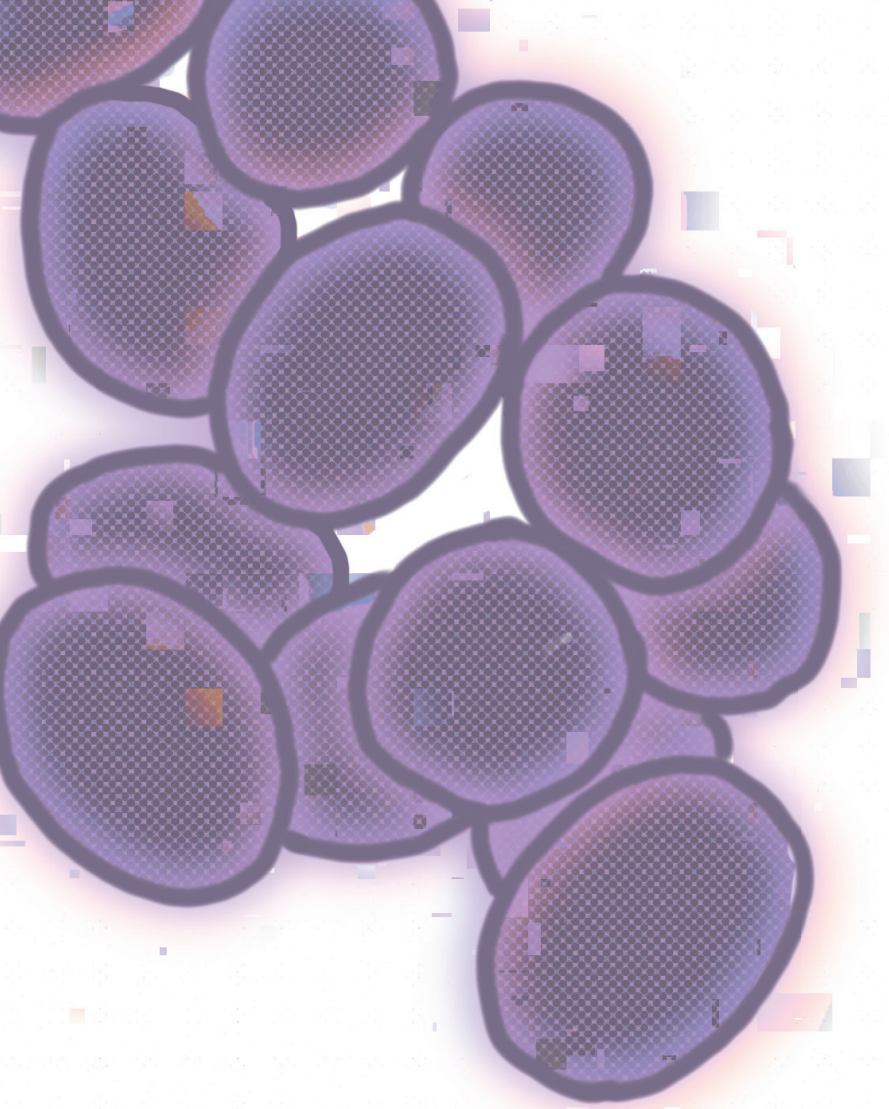

Chapter 3

Eradication of community-onset MRSA carriage: a narrative review

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Abstract

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization increases infection risk in both patients and healthy individuals. Decolonization therapy has been proven to reduce *S. aureus* infections, but data on the effectiveness of individual decolonization strategies in community-onset MRSA carriage are scarce.

Objectives

The aim of this narrative review was to summarize the evidence on strategies for the elimination of MRSA colonization in community-onset MRSA carriers.

Sources

PubMed database was searched for studies on MRSA eradication, from inception to July 2023. *Content:* Topical therapy is proven to be effective in nasal-only carriage and in temporary load reduction. Mupirocin nasal ointment in combination with chlorhexidine body wash is highly effective in nasal-only MRSA carriers in the community as well. In patients with extra-nasal colonization, addition of orally administered antibiotics likely increases success rates compared with topical therapy alone. Studies on systemic treatment of extra-nasal MRSA decolonization are subject to a high heterogeneity of antimicrobial agents, treatment duration, and control groups. The majority of evidence supports the use of a combination of topical therapy with rifampin and another antimicrobial agent. Decolonization treatment with probiotics is a promising novel non-antibiotic strategy. However, achieving long-term decolonization is more likely in countries with low MRSA prevalence, given the risk of recolonization in a context of high MRSA prevalence.

Implications

The decision to pursue community-onset MRSA eradication treatment in the individual patient should be based on the combination of the treatment objective (short-term bacterial load reduction in health care settings vs. long-term eradication in community settings), and the likelihood of successful decolonization. The latter is influenced by both individual risk factors for treatment failure, and the risk of recolonization. The addition of a combination of systemic antibiotics is rational for extra-nasal long-term decolonization. To determine the most effective systemic antimicrobial agents in MRSA decolonization, more research is needed.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the leading cause of mortality attributable to antimicrobial resistance [1]. The pathogen is notorious for its nosocomial transmission and hospital outbreaks. On top of that, community-onset MRSA (CO-MRSA) has emerged over the past decades and has become endemic in large parts of the world [2]. Although often carried asymptomatically in the anterior nares, skin lesions, and elsewhere, *S. aureus* is an important cause of severe infections such as bacteraemia. Isolates cultured from blood and the nares are identical in the large majority of patients with *S. aureus* bacteraemia, suggesting an endogenous infection route [3]. Colonization with MRSA increases infection risk even more than colonization with methicillin-susceptible *S. aureus* (MSSA), in both patients and healthy individuals [4-7]. In a North-American cohort of almost 30 000 patients who underwent MRSA screening at hospital admission, MRSA carriers had a 20-fold increased odds of developing MRSA bacteraemia compared with non-carriers [8]. In healthy athletes and soldiers, CO-MRSA colonization was associated with a notable increased risk for developing skin and soft tissue infections [4,9]. Decolonization therapy has been proven to reduce *S. aureus* infections in hospitalized patients, most pronounced in surgical patients [10-13]. Although evidence is limited, a 1-year survival benefit of *S. aureus* decolonization before clean surgical procedures is reported [14], as well as cost-effectiveness of active surveillance and decolonization at hospital admission [15].

However, data on the effectiveness of individual decolonization strategies in CO-MRSA carriage are scarce. This review discusses the evidence concerning strategies for elimination of MRSA colonization, with particular emphasis on CO-MRSA.

Methods

We searched PubMed from inception to 31 July 2023, using a combination of keywords to capture MRSA, colonization, and decolonization (search strategy in supplement). In addition, we hand-searched key references and international guidelines to identify citations not captured in the PubMed search. Screening was performed by one reviewer, and in case of uncertainty, a second reviewer was consulted. We screened 1335 titles and abstracts, and 129 articles were selected for a comprehensive full-text review. Studies published in languages other than English were excluded in the full-text review phase. Finally, 66 studies were included in this review. All studies were compiled in EndNote.

Results

Determining eligibility for eradication treatment

An important but complex question remains, which MRSA carriers should undergo eradication treatment. Worldwide differences in policies and attitudes towards MRSA carriage in the community exist between non-endemic and endemic areas. In countries with high MRSA prevalence, e.g. the United States, eradication treatment is not routinely recommended [16]. Some countries with low MRSA prevalence, e.g. the Netherlands and Denmark, successfully implemented a nationwide 'search and destroy' policy in the 1980s, targeting MRSA colonization [17,18]. This policy consists of screening and pre-emptive isolation of patients with an increased risk of MRSA carriage when hospitalized and subsequent decolonization treatment when persistent carriage is found. Two years after eradication treatment, 87% of CO-MRSA carriers in a non-endemic setting remained MRSA negative [19].

A major limitation in the generalizability of a 'search and destroy' approach to regions with high MRSA prevalence in the community is the high risk of recolonization. Currently, in countries with endemic MRSA, short-term *S. aureus* load reduction is often pursued to reduce infection risk in intensive care unit and surgical patients, either universally or targeted at MRSA carriers (or both MRSA and MSSA carriers) after screening [20]. This temporary suppression of MRSA is efficient in presurgical circumstances [21], but to prevent CO-MRSA transmission, complete eradication is desirable.

At an individual level, risk factors for failure of decolonization therapy can be a reason to refrain from pursuing this goal. Known risk factors for failure are indwelling catheters or medical devices, skin lesions, colonization of household contacts, chronic pulmonary disease, and an immunocompromised status [22,23].

As a result, two main factors should guide the decision for eradication therapy in an individual patient. First, the treatment goal, which can be either long-term eradication to prevent community transmission and infections, or short-term load reduction to prevent nosocomial infections and transmission. Second, the likelihood of long-term success of decolonization treatment, influenced by both the presence of individual risk factors for failure and the prevalence of MRSA in the environment, driving the risk of recolonization (Figure 1).

Lastly, when considering eradication treatment, potential adverse effects should be weighed in. This includes well-known effects such as (hepato-)toxicity and risk of *Clostridioides difficile* infection, but also newer insights such as potential disruption of the human microbiome [24].

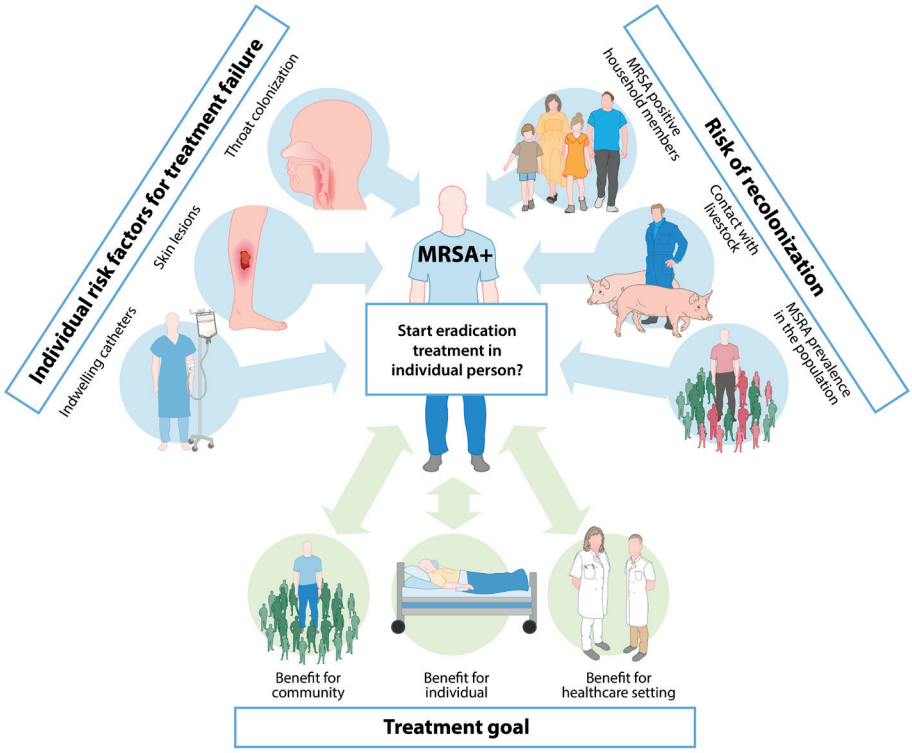

Figure 1. Factors of influence on the decision for eradiation treatment in an individual MRSA carrier. The decision to start eradication therapy in an MRSA carrier should be guided by the treatment goal and the likelihood of long-term success of decolonization treatment, influenced by both the presence of individual risk factors for failure and the prevalence of MRSA in the environment, driving the risk of recolonization. MRSA, methicillin-resistant *Staphylococcus aureus*.

Strategies for eradication therapy

MRSA eradication therapy usually exists of either topical - i.e. nasal ointment and skin wash-therapy alone or a combination of topical and systemic anti-staphylococcal agents. Topical therapy is proven to be effective in nasal-only carriage and in temporary (presurgical) load reduction [25,26]. In contrast, in patients with other body sites positive for MRSA, eradication with mupirocin and chlorhexidine skin wash is reported to be insufficient [27-29]. In a randomized controlled trial (RCT) of hospitalized patients colonized with MRSA on multiple body sites in a hospital

with endemic MRSA, mupirocin was only marginally effective [26]. In particular, throat carriage is associated with failure of topical eradication treatment [30]. In a small study on Swedish outpatients with MRSA throat carriage, topical therapy led to successful eradication in only 13%, as compared with 61% when topical therapy was combined with systematic antibiotics [31]. Positive household contacts were simultaneously treated. A similar outcome was reported in outpatient MRSA carriers in Canada initially; however, after 1 year, success rates with and without systemic antibiotics were found to be equal [32]. Canada is a high-endemic area, and because no screening of household contacts or genotyping was performed, it remains undetermined whether this outcome resulted from recolonization with a different strain, or long-term failure of eradication treatment.

Discriminating between nasal-only and extra-nasal MRSA colonization to guide optimal eradication therapy seems appropriate considering the abovementioned studies and from a pathophysiologic perspective. This distinction is also made in the Dutch MRSA eradication guideline, where mupirocin-sensitive, nasal-only MRSA carriage with intact skin is considered 'uncomplicated' and is recommended to be treated with topical agents only. MRSA carriers with extra-nasal colonization or other risk factors for (topical) treatment failure, e.g. active skin lesions and foreign body material, are considered 'complicated' and are treated with additional systemic antimicrobial agents [33]. This specific approach led to sustained decolonization in 85% of carriers after 1 year of follow-up [23].

MRSA carriage of household members was the most frequently encountered risk factor for CO-MRSA infections in Denmark between 1999 and 2006 [34], and was associated with failure of eradication treatment [22]. This emphasizes the need for screening and simultaneous eradication of all positive household members, especially in case of treatment failure.

In general, infection prevention and control measures are crucial in preventing further spread of MRSA [35], but are not included in this review.

Efficacy of topical decolonization therapy

The most commonly used topical treatment for *S. aureus* decolonization is mupirocin nasal ointment, which achieves its antimicrobial effect by inhibiting bacterial protein synthesis. It is often combined with daily antiseptic body wash. Mupirocin nasal ointment was proven to be effective in MSSA decolonization in the 1980s and 1990s [36-45]. In a systematic review that included studies analysing both MSSA and MRSA colonization, mupirocin resulted in negative MRSA cultures in 94% of patients after 1 week [25]. This percentage decreased to 65% after (mid- to long-term) follow-up.

All RCTs on topical MRSA eradication treatment are summarized in Table 1 [26,27,29,46-53].

Very high MRSA decolonization success rates have been reported with mupirocin treatment in a prospective study in hospitalized patients (98%), and an RCT involving long-term care facility residents (93%) [53,54]. Furthermore, in a retrospective analysis of MRSA-colonized patients who were readmitted during the study period, mupirocin was associated with being MRSA negative at readmission, compared with no treatment [55,56].

Focusing specifically on MRSA eradication in the community, little evidence is available on the effectiveness of mupirocin [57]. In an RCT involving 134 healthy MRSA-colonized American soldiers, mupirocin led to 88% nasal eradication compared with 65% with placebo after 8 weeks of follow-up [51]. Similarly, in 87 German hospital workers with nasal MRSA colonization, who were withdrawn from work until MRSA free, treatment with mupirocin nasal ointment and antiseptic mouth rinse and body wash resulted in successful eradication in 84% at 3 months of follow-up [58]. Prolonged mupirocin decolonization treatment (twice monthly for 5 days during 6 months) after discharge in patients that had been hospitalized in the United States with MRSA infections led to a higher decolonization rate compared with placebo (OR of colonization ¼ 0.44) [46].

Conflicting results on the effectiveness of mupirocin in CO-MRSA have been reported in regions with high MRSA prevalence, which may be indicative of an increased risk of recolonization rather than treatment failure. In an RCT comparing topical with systemic treatment in patients treated at a dedicated MRSA outpatient clinic, initial decolonization was achieved in 13 of 25 patients who received topical treatment, but this decreased to three after 12 months [32]. The vast majority of patients in this study were colonized at multiple body sites. Seven days of mupirocin nasal ointment combined with antiseptic body wash compared with placebo did not improve decolonization rate in 49 outpatients living with HIV in a RCT [50]. In addition, in a study involving 223 households with ambulatory MRSA skin and soft tissue infections, persistent MRSA colonization was similar in households with and without topical decolonization after 6 months of follow-up [49].

A concern with the use of mupirocin is the emergence of mupirocin resistance [59]. The prevalence of mupirocin resistance varies widely and is reported to be associated with its increased use [60]. Remarkably, a *post-hoc* analysis of the REDUCE-MRSA trial showed an overall low prevalence of mupirocin-resistant isolates and no increase after mupirocin decolonization treatment [61].

Table 1. Randomized trials on topical MRSA decolonization treatment

Author, year	Country	N	Population	Treatments	Duration[a]	Follow up[a]	Culture site(s)[b]	Decolonized	Other outcome
Miller, 2023 [51]	US	2121	Inpatients, post-discharge	1. Education 2. + mupirocin + chx	2x/month 5 days for 6 months	270	N,T,A, G,W	1. 57% 2. 73% (p <0.01)	
Pooveli-kunnel, 2018 [57]	Ireland	100	14% outpatients 86% inpatients	1. Medical-grade honey + Tricolsan 2. Mupirocin + Tricolsan	5	short-term	N, G, W	1. 43% 2. 57% (p 0.20)	Received 2 treatment courses: 1. 78% 2. 20%
Landelle, 2016 [59]	Switzer-land	146	Inpatients	1. Polyhexanide 2. Placebo	10	28	N, G	1. 34% 2. 29% (p 0.56)	
Cluzet, 2016 [53]	US	149	Households with SSTI	1. Education 2. + mupirocin + chx 3. + mupirocin + chx + reminders	7	180	N,A,G	1. +-80% 2. +-80% 3. +-80%	Time to clearance: 1. 19 days 2+3. 23 days
Weintrob, 2015 [52]	US	49	Outpatients with HIV	1. Mupirocin + chx 2. Placebo	7	180	N,A,G, T,P	1. 67% 2. 67%	
Fritz, 2011 [28]	US	300	Patients with SSTI + MSSA/MRSA colonization	1. Education 2. + mupirocin 3. + mupirocin + chx 4. + mupirocin + bleach baths	5	120	N,A,G	1. 48% 2. 56% (p 0.40) 3. 54% (p 0.51) 4. 71% (p 0.02)	Nasal decolonization: 1. 50% 2. 77% (p <0.01) 3. 76% (p <0.01) 4. 85% (p <0.01)
Ellis, 2007 [49]	US	134	Healthy soldiers	1. Mupirocin 2. Placebo	5	56	N	1. 88% 2. 65%	
Wendt, 2007 [26]	Germany	114	In- and outpatients, nursing home residents	1. Mupirocin + chx 2. Mupirocin + placebo	5	30	N,T,G, P	1. 8% (p 0.47) 2. 13%	Groin decolonization: 1. 93% (p <0.01) 2. 82%
Dryden, 2004 [58]	UK	224	Inpatients	1. Mupirocin + chx 2. Tea tree oil	5	14	N,T,G, S,W	1. 49% 2. 42% (p 0.03)	Nasal decolonization: 1. 86% 2. 58% (p <0.01)
Mody, 2003 [45]	US	127	Long term care facility residents with MRSA/ MSSA colonization	1. Mupirocin 2. Placebo	14	30	N,W	1. 88% (p <0.01) 2. 13%	
Harbarth, 1999 [25]	Switzer-land	98	Inpatients	1. Mupirocin + chx 2. Placebo + chx	5	26	N,G,U, W	1. 25% (p 0.40) 2. 18%	Nasal decolonization: 1. 44% 2. 23%

Legend: Chx, chlorhexidine; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SSTI, skin and soft tissue infection. [a] In days. [b] N = nasal, A = axilla, G = groin, T = throat, P = perineum/rectum, W = wounds/skin lesions, S = sputum, U = urine.

Given the risk of the emergence of mupirocin resistance, alternative topical therapies have been evaluated. Medical-grade honey was only marginally inferior to mupirocin in decolonizing nasal MRSA colonization in a small RCT [47]. Topical therapy with tea tree preparations was significantly less effective compared with mupirocin-based topical therapy for the clearance of intranasal MRSA colonization [52]. Polyhexanide was not effective in MRSA decolonization compared with placebo in an RCT [48], and inferior to mupirocin and chlorhexidine in a retrospective analysis [62].

Efficacy of decolonization therapy with addition of systemic antibiotics

Using systemic antibiotics in addition to the topical treatment for MRSA decolonization is common practice in case of extra-nasal colonization in some countries, reserved for cases of topical treatment failure in others, and seldom or never employed in a third category of countries. Most studies on systemic treatment for MRSA decolonization have been performed in health care settings, with a high heterogeneity of treatment agents and control groups. All RCTs on systemic MRSA eradication treatment are summarized in Table 2 [31,32,63-68].

The combination treatment consisting of antiseptic body wash, intranasal mupirocin, rifampin, and trimethoprim/sulfamethoxazole or doxycycline was highly effective in MRSA decolonization of hospitalized patients [63,69,70]. In a small RCT in long-term care facilities in the United States, rifampin monotherapy was superior to no treatment, as well as to minocycline monotherapy. Combination therapy with rifampin and minocycline was not superior to rifampin alone. The majority of patients had decubitus and indwelling catheters, and after 3 months only half of the treated patients remained MRSA negative [66]. Moreover, the risk of emerging resistance when using rifampin monotherapy makes this an inappropriate approach. Another randomized trial on oral fusidic acid monotherapy or no treatment showed no difference in MRSA decolonization rate in 16 intensive care unit patients. However, the study was terminated because of emergence of fusidic acid-resistant strains [64]. Two cohort studies on trimethoprim/ sulfamethoxazole plus rifampin in hospitalized patients resulted in 64e66% successful MRSA decolonization [71,72]. Oral vancomycin, combined with topical therapy, was effective in eradicating MRSA-colonized staff and residents of a nursing home during an outbreak, although 80% experienced side effects [73].

Compared with topical therapy with mupirocin only, the combination of oral trimethoprim/sulfamethoxazole plus topical fusidic acid (without mupirocin) performed marginally worse in MRSA eradication in hospitalized patients and personnel after 14 days [65]. Rifampin plus novobiocin resulted in a non-significant higher decolonization rate after 14 days compared with rifampin plus trimethoprim-sulfamethoxazole (respectively 67% vs. 53%) in an RCT on MRSA-colonized patients and personnel in the United States. Decolonization in both groups was significantly more often achieved in colonization sites other than wounds [67]. However, novobiocin has since been withdrawn from the market. Rifampin with ciprofloxacin was more effective compared with rifampin with trimethoprim/sulfamethoxazole in an RCT on MRSA-colonized patients (50% vs. 37% eradicated after 6 months of follow-up). Only 21 patients were enrolled when the study was terminated because of emergence of ciprofloxacin resistance in the hospital, unrelated to the study [68].

Few studies have been published specifically on systemic MRSA decolonization in the community, mainly from countries with low MRSA prevalence. The previously mentioned Swedish study randomly assigned 52 outpatients with MRSA throat carriage between chlorhexidine, nasal mupirocin, rifampin, and either clindamycin or trimethoprim/sulfamethoxazole (group 1) and chlorhexidine and nasal mupirocin only (group 2). At 6 months of follow-up, 61% of systemically treated vs. 13% of topical treated patients were successfully decolonized ($p < 0.01$) [31]. In a cohort of Dutch outpatients with extra-nasal MRSA colonization, decolonization treatment combination of chlorhexidine body wash, mupirocin ointment intranasally, and a combination of two systemic antibiotics (mostly rifampin with trimethoprim or doxycycline) was successful in 85% of patients and the vast majority was still negative after 1 year of follow-up [23]. Two Danish cohort studies did not show a benefit of adding clindamycin to decolonization treatment of MRSA throat carriage [74,75].

In the previously discussed Canadian study, a country with high MRSA prevalence, 98 outpatients with MRSA colonization at any site were randomized between a 7-day course of topical treatment alone or supplemented with oral rifampin and doxycycline [32]. The initial success rate was higher in the systemic treatment arm, but this difference had disappeared after 12 months of follow-up. As said, no genotyping was performed to elucidate whether this was because of long-term treatment failure or recolonization with a different strain.

Table 2. Randomized trials on systemic MRSA decolonization treatment

Author, year	Country	N	Population	Treatments	Duration[1]	Follow-up[1]	Culture site(s)*	Decolonized at end of follow-up
Eum, 2021 [31]	Canada	98	Outpatients and inpatients	1. Mupirocin + chx 2. Mupirocin + chx + rifampin + doxycycline	7	365	N,P,W	1. 32% 2. 50% (p 0.04)
Lindgren, 2018 [30]	Sweden	52	Outpatients with throat colonization	1. Mupirocin + chx + rifampin + clindamycin/ SXT 2. Mupirocin + chx	7	180	N,T,P,W	1. 61% 2. 13% (p <0.01)
Simor, 2007 [62]	Canada	146	Inpatients	1. Mupirocin + chx + rifampin + doxycycline 2. No treatment	7	90	N,P,W,D	1. 74% 2. 32% (p <0.01)
Chang, 2000 [65]	Taiwan	16	ICU patients	1. Fusidic acid 2. No treatment	7	28	N,T,W,S	1. 33% 2. 50% (p 0.95)
Parras, 1995 [69]	Spain	84	13% HCW and 87% inpatients	1. Mupirocin + chx 2. SXT + topical fusidic acid + chx	5	28	N	1. 96% 2. 95% (p >0.05)
Muder, 1994 [64]	US	35	Long term care facility residents	1. Rifampin 2. Minocycline 3. Rifampin + minocycline 4. No treatment	5	90	N,U,W	1. 67% 2. 38% 3. 50% 4. 14%
Walsh, 1993 [70]	US	94	HCWs and inpatients	1. Novobiocin + rifampin 2. SXT + rifampin	7	14	N,G,W, S	1. 67% 2. 53% (p 0.18)
Peterson, 1990 [71]	US	21	Inpatients	1. Ciprofloxacin + rifampin 2. SXT + rifampin	14	180	N,G,W	1. 27% 2. 40% (p >0.1)

Legend. [1] In days. [2] N = nasal, A = axilla, G = groin, T = throat, P = perineum/rectum, W = wounds/skin lesions, S = sputum, U = urine, D = medical device or catheter exit site. Chx = chlorhexidine. SXT = trimethoprim/sulfamethoxazole. ICU = intensive care unit. HCW = healthcare worker

Future perspectives

Concerns about emerging resistance and the impact on the microbiome resulting from current treatment strategies drive the search for alternative, non-antibiotic, decolonization therapies. A recently published phase-two trial showed promising results of oral probiotics for nasal and intestinal *S. aureus* decolonization, with a 95% reduction of *S. aureus* colonization without notable changes in the microbiota [76]. Ongoing research is focused on engineering a skin probiotic to selectively combat MRSA colonization [77]. In addition, novel non-antibiotic drugs are being evaluated for their potential in *S. aureus* eradication, including the porphyrin drug XF-73, the LL-37- derived peptide P10 and SAAP-148 [78-80], and bacteriophage therapy [77].

Despite multiple attempts, vaccines to prevent *S. aureus* infections have so far not been proven clinically effective [81]. However, the high burden of disease provides grounds to continue the search.

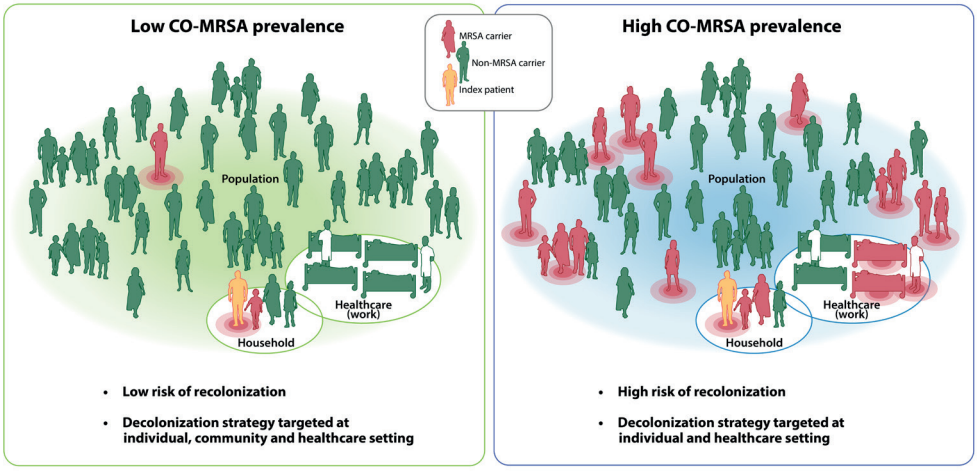

Figure 2. Implications of prevalence of MRSA carriage for the approach of the community and individual. In a low CO-MRSA prevalent setting, sustained decolonization of CO-MRSA is feasible and can prevent further spread in the community. This supports the 'search and destroy' policy, in which carriers are identified, household contacts screened, and decolonization is attempted. In this setting, this policy is effective in maintaining a low MRSA prevalence. In contrast, in high-endemic regions, there is high risk of recolonization. Consequently, routine eradication treatment of CO-MRSA aiming at achieving a non-carrier state for a prolonged period of time is less likely to be successful. In this setting, a standard 'search and destroy' policy is not likely to reduce the high MRSA prevalence, and an individualized approach is more rational. CO-MRSA, community-onset methicillin-resistant *Staphylococcus aureus*.

Discussion and conclusion

MRSA decolonization has been proven to reduce infections in both patients and healthy individuals. However, determining eligible treatment candidates and applying experiences and results from countries with low MRSA prevalence to countries with high MRSA prevalence continue to be challenging. In general, eradication studies in high prevalence areas are hampered by the indistinguishability of failing eradication treatment vs. recolonization. The likelihood of successful long-term decolonization is lower in a high endemicity setting compared with a low endemicity setting, because of the heightened risk of recolonization (Figure 2). Thus, both treatment goal (short-term bacterial load reduction in health care settings vs. long-term eradication in community settings), and likelihood of successful prolonged eradication should guide the eligibility for CO-MRSA decolonization treatment in the individual patient.

Although highly effective in decolonization of nasal MRSA carriage, the combination of mupirocin and antiseptic body wash appears to be insufficient in patients with extra-nasal MRSA colonization. The addition of systemic antibiotics is a rational approach in this patient category, but studies on systemic treatment of extra-nasal MRSA decolonization are subject to a high heterogeneity of treatment agents and comparator groups. Most evidence support a combination of topical therapy with rifampin and another antimicrobial agent for extra-nasal MRSA eradication. Future research would gain clinical applicability from reporting the carrier status of household contacts, long-term follow-up cultures, and reporting genotyping in case of failure. Eradication treatment with probiotics holds promise as a novel non-antibiotic strategy.

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Supplement 1. Seach strategy

(((“Methicillin-Resistant Staphylococcus aureus colon*”[tw] OR “Methicillin-Resistant s aureus colon*”[tw] OR “MRSA colon*”[tw] OR “Methicillin-Resistant Staphylococcus aureus carr*”[tw] OR “Methicillin-Resistant s aureus carr*”[tw] OR “MRSA carr*”[tw] OR ((“Methicillin-Resistant Staphylococcus aureus”[Mesh] OR “MRSA”[tw] OR “MRSA*”[tw] OR “methicillin resistant staphylococcus aureus”[tw] OR “methicillinresistant staphylococcus aureus”[tw] OR “methicillin resistant s aureus”[tw] OR “methicillinresistant s aureus”[tw] OR (“methicillin resistan*”[tw] AND “aureus”[tw]) OR “MSSA”[tw] OR “MSSA*”[tw] OR “methicillin sensitive staphylococcus aureus”[tw] OR “methicillin sensitive s aureus”[tw] OR (“methicillin sensitiv*”[tw] AND “aureus”[tw])) AND (“Carrier State”[Mesh] OR “colonization”[tw] OR “colonisation”[tw] OR “coloniz*”[tw] OR “colonis*”[tw] OR “carrier”[tw] OR “carriers”[tw] OR “carriage”[tw] OR “carriership*”[tw] OR “Nasal Cavity/microbiology”[Mesh]))) AND (“eradication*”[tw] OR “eradicat*”[tw] OR “treatment*”[tw] OR “decolonization*”[tw] OR “decolonisation*”[tw] OR “decoloniz*”[tw] OR “decolonis*”[tw] OR “elimination”[tw] OR “eliminat*”[tw]) NOT (“Animals”[mesh] NOT “Humans”[mesh]) AND (english[la] OR dutch[la]) AND (systematic[sb] OR “meta-analysis”[pt] OR “meta analysis”[tw] OR “clinical trial”[pt] OR “clinical trial”[tiab] OR “clinical trials as topic”[mesh] OR “clinical trials”[tiab] OR “control groups”[mesh] OR “control group”[tiab] OR “control groups”[tiab] OR “controlled clinical trial”[pt] OR “controlled clinical trials as topic”[mesh] OR “cross-over studies”[mesh] OR “cross over study”[tiab] OR “cross over studies”[tiab] OR “double-blind method”[mesh] OR “double blind”[tiab] OR “evaluation studies as topic”[mesh] OR “follow-up studies”[mesh] OR “follow up study”[tiab] OR “follow up studies”[tiab] OR “placebos”[mesh] OR placebo*[tiab] OR placebos*[tiab] OR “pragmatic clinical trial”[pt] OR “prospective studies”[mesh] OR “prospective study”[tiab] OR “prospective studies”[tiab] OR “RaCT”[tiab] OR “RaCTs”[tiab] OR “random allocation”[mesh] OR “randomised “[tiab] OR “randomized controlled trial”[pt] OR “randomized controlled trials as topic”[mesh] OR “randomized”[tiab] OR random*[tiab] OR “RCT”[tiab] OR “RCTs”[tiab] OR “Research Design”[MeSH:noexp] OR “Research design”[tiab] OR “Research designs”[tiab] OR “single blind”[tiab] OR “single-blind method”[mesh] OR ((single*[tiab] OR double*[tiab] OR triple*[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR volunteer*[tiab] OR “trial”[ti] OR “trials”[ti] OR “Multicenter Study”[Publication Type] OR “Cohort Studies”[Mesh] OR “Observational Study”[Publication Type])) OR ((“Methicillin-Resistant Staphylococcus aureus colon*”[ti] OR “Methicillin-Resistant s aureus colon*”[ti] OR “MRSA colon*”[ti] OR “Methicillin-Resistant Staphylococcus aureus carr*”[ti] OR “Methicillin-Resistant s aureus carr*”[ti] OR “MRSA carr*”[ti] OR ((“Methicillin-Resistant Staphylococcus aureus”[majr] OR “MRSA”[ti] OR “MRSA*”[ti] OR “methicillin resistant staphylococcus aureus”[ti] OR “methicillinresistant staphylococcus aureus”[ti] OR “methicillin resistant s aureus”[ti] OR “methicillinresistant s aureus”[ti] OR (“methicillin resistan*”[ti] AND “aureus”[ti]) OR “MSSA”[ti] OR “MSSA*”[ti] OR “methicillin sensitive staphylococcus aureus”[ti] OR “methicillin sensitive s aureus”[ti] OR (“methicillin sensitiv*”[ti] AND “aureus”[ti]))

AND (“Carrier State”[majr] OR “colonization”[ti] OR “colonisation”[ti] OR “coloniz*”[ti] OR “colonis*”[ti] OR “carrier”[ti] OR “carriers”[ti] OR “carriage”[ti] OR “carriership*”[ti] OR “Nasal Cavity/microbiology”[majr]))) AND (“eradication*”[ti] OR “eradicat*”[ti] OR “treatment*”[ti] OR “decolonization*”[ti] OR “decolonisation*”[ti] OR “decoloniz*”[ti] OR “decolonis*”[ti] OR “elimination”[ti] OR “eliminat*”[ti]) NOT (“Animals”[mesh] NOT “Humans”[mesh]) AND (english[la] OR dutch[la])) OR ((“Staphylococcus aureus colon*”[ti] OR “s aureus colon*”[ti] OR “Staphylococcus aureus carr*”[ti] OR “s aureus carr*”[ti] OR ((“Staphylococcus aureus”[majr] OR “staphylococcus aureus”[ti] OR “s aureus”[ti]) AND (“Carrier State”[Mesh] OR “colonization”[tw] OR “colonisation”[tw] OR “coloniz*”[tw] OR “colonis*”[tw] OR “carrier”[tw] OR “carriers”[tw] OR “carriage”[tw] OR “carriership*”[tw] OR “Nasal Cavity/microbiology”[Mesh]))) AND (“eradication*”[tw] OR “eradicat*”[tw] OR “treatment*”[tw] OR “decolonization*”[tw] OR “decolonisation*”[tw] OR “decoloniz*”[tw] OR “decolonis*”[tw] OR “elimination”[tw] OR “eliminat*”[tw]) NOT (“Animals”[mesh] NOT “Humans”[mesh]) AND (english[la] OR dutch[la]) AND (systematic[sb] OR “meta-analysis”[pt] OR “meta analysis”[tw] OR “clinical trial”[pt] OR “clinical trial”[tiab] OR “clinical trials as topic”[mesh] OR “clinical trials”[tiab] OR “control groups”[mesh] OR “control group”[tiab] OR “control groups”[tiab] OR “controlled clinical trial”[pt] OR “controlled clinical trials as topic”[mesh] OR “cross-over studies”[mesh] OR “cross over study”[tiab] OR “cross over studies”[tiab] OR “double-blind method”[mesh] OR “double blind”[tiab] OR “evaluation studies as topic”[mesh] OR “follow-up studies”[mesh] OR “follow up study”[tiab] OR “follow up studies”[tiab] OR “placebos”[mesh] OR placebo*[tiab] OR placebos*[tiab] OR “pragmatic clinical trial”[pt] OR “prospective studies”[mesh] OR “prospective study”[tiab] OR “prospective studies”[tiab] OR “RaCT”[tiab] OR “RaCTs”[tiab] OR “random allocation”[mesh] OR “randomised “[tiab] OR “randomized controlled trial”[pt] OR “randomized controlled trials as topic”[mesh] OR “randomized”[tiab] OR random*[tiab] OR “RCT”[tiab] OR “RCTs”[tiab] OR “Research Design”[MeSH:noexp] OR “Research design”[tiab] OR “Research designs”[tiab] OR “single blind”[tiab] OR “single-blind method”[mesh] OR ((single*[tiab] OR double*[tiab] OR triple*[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR volunteer*[tiab] OR “trial”[ti] OR “trials”[ti] OR “Multicenter Study”[Publication Type] OR “Cohort Studies”[Mesh] OR “Observational Study”[Publication Type])))