Robert A. Weinstein, Section Editor

Eradication of Methicillin-Resistant *Staphylococcus aureus* Carriage: A Systematic Review

Heidi S. M. Ammerlaan,[1] Jan A. J. W. Kluytmans,[3,4] Heiman F. L. Wertheim,[5,6] Jan L. Nouwen,[5] and Marc J. M. Bonten[1,2]

[1]Department of Medical Microbiology, University Medical Centre Utrecht, and [2]Julius Center for Health Sciences and Primary Care, Utrecht, [3]Department of Medical Microbiology and Infection Control, VU University Medical Center, Amsterdam, [4]Laboratory for Microbiology and Infection Control, Amphia Hospital Breda, Breda, and [5]Department of Medical Microbiology and Infectious Diseases, Erasmus Medical Centre, Rotterdam, The Netherlands; and [6]Oxford University Clinical Research Unit, National Institute of Infectious and Tropical Diseases, Bach Mai Hospital, Hanoi, Vietnam

A systematic review was performed to determine the effectiveness of different approaches for eradicating methicillin-resistant *Staphylococcus aureus* carriage. Twenty-three clinical trials were selected that evaluated oral antibiotics (7 trials), topically applied antibiotics (12 trials), or both (4 trials). Because of clinical heterogeneity, quantitative analysis of all studies was deemed to be inappropriate, and exploratory subgroup analyses were performed for studies with similar study populations, methods, and targeted bacteria. The estimated pooled relative risk of treatment failure 1 week after short-term nasal mupirocin treatment, compared with placebo, was 0.10 (range, 0.07–0.14). There was low heterogeneity between study outcomes, and effects were similar for patients and healthy subjects, as well as in studies that included only methicillin-susceptible *S. aureus* carriers or both methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* carriers. The development of drug resistance during treatment was reported in 1% and 9% of patients receiving mupirocin and oral antibiotics, respectively. Short-term nasal application of mupirocin is the most effective treatment for eradicating methicillin-resistant *S. aureus* carriage, with an estimated success of rate of 90% 1 week after treatment and ~60% after a longer follow-up period.

Colonization is an important step in the pathogenesis of *Staphylococcus aureus* infection and is instrumental in the nosocomial epidemiology of these bacteria. Approximately 20% of the general population is persistently colonized with *S. aureus,* most frequently in the anterior nares, although other body sites, such as the perineum and throat, may also be colonized. Another 30% of the general population is intermittently colonized, and the remaining 50% appear not to be susceptible, for unknown reasons, to *S. aureus* carriage [1]. Methicillin-resistant *S. aureus* (MRSA) has become endemic in health care institutions worldwide, with up to 70% of invasive *S. aureus* infections having resistance [2–5], and most patients who develop drug-resistant *S. aureus* infection will have been colonized prior to infection. The half-life of MRSA carriage has been reported to be as long as 40 months in individuals who do not receive treatment [6].

Received 13 August 2008; accepted 27 November 2008; electronically published 20 February 2009.

Reprints or correspondence: Dr. H. S. M. Ammerlaan, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands (H.Ammerlaan@umcutrecht.nl).

Clinical Infectious Diseases 2009; 48:922–30
© 2009 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2009/4807-0013$15.00
DOI: 10.1086/597291

Eradication of *S. aureus* carriage may serve 2 purposes: prevention of infection and prevention of transmission. Several eradication strategies have been evaluated, but studies have differed markedly in their design, study population, targeted bacteria (methicillin-susceptible *S. aureus* [MSSA] and/or MRSA), and duration of follow-up. Furthermore, guidelines and reviews have differed in their selection of studies (only those evaluating mupirocin [7] or excluding studies that involved MSSA [8–11] or health care workers [8]), or they have been narrative rather than systematic [7, 10–12].

Therefore, we performed a systematic review to determine the most effective approach for eradicating MRSA carriage. Importantly, the literature search was not restricted to studies that addressed eradication of MRSA alone but included studies evaluating MSSA eradication, provided that eradication was pursued with agents that had presumed antibacterial activity against MRSA.

METHODS

Data sources. We searched PubMed from 1966 through October 2008, Embase from 1966 through October 2008, and Web of Science from 1988 through October 2008 using the terms

Downloaded from https://academic.oup.com/cid/article/48/7/922/326174 by guest on 30 September 2020

"*Staphylococcus aureus*," "eradication," "treatment," "decolonization," "decolonisation," "elimination," "carrier(s)," "carriage," "carriership," "colonization," and "colonisation" to identify articles reporting on the effectiveness of treatment of MRSA or MSSA carriage. In addition, the bibliographies of selected articles were searched in an attempt to identify additional studies. We established inclusion and exclusion criteria before reviewing abstracts and articles.

Study selection and data extraction. Three independent reviewers (H.S.M.A., H.W., and J.N.) performed the search and screened titles and abstracts for relevant studies. The identified titles and abstracts were screened without blinding to authors and journal. Potentially relevant studies were obtained, and the full text was examined. Studies were included if they were written in English or Dutch and involved human subjects. Studies were excluded for the following reasons: (1) intervention with β-lactam antibiotics, (2) duration of follow-up <1 week, (3) no randomization, and (4) evaluation of treatment of MRSA infections without evaluation of the effect on carriage. For each study, the following characteristics were extracted: year of study, study design, study size, total number of patients in the treatment and control groups with corresponding success rates, study population, MRSA or MSSA carriage, culture sites, and length of follow-up. The validity of the included studies was assessed by determining the following criteria: generation of allocation sequence, reporting of baseline imbalances, blinding, and follow-up (we defined adequate follow-up as including 80% of study participants) [8].

Data synthesis and analysis. The meta-analysis was performed using Review manager software, version 4.2.8 (The Cochrane Collaboration). We used the random-effects model to calculate pooled relative risks (RR_p) of failure of treatment versus placebo or no treatment and 95% CIs, because this model best accounts for statistical heterogeneity between study results. The pooled RRs at end of treatment (if available) and at end of follow-up are presented. I-squares (I^2) are provided, which describe the percentage of variability in point estimates that is attributable to statistical heterogeneity rather than to sampling error and which are defined to be low (<25%), moderate (25%–75%), or high (>75%) [13]. Because of clinical heterogeneity among study populations, culture methods, culture sites, interventions, and durations of follow-up, a quantitative analysis of all included studies by means of a random-effects model was deemed to be inappropriate. Therefore, exploratory subgroup analyses were performed of studies with similar study populations (healthy volunteers [including health care workers] vs. patients), methods (effectivity determined by nasal cultures only vs. cultures of multiple body sites), and targeted bacteria (MSSA vs. MRSA and MSSA vs. MRSA and MSSA combined).

RESULTS

Selected studies. Initially, 2388 articles were identified in PubMed, 1161 were identified in Embase, and 876 were identified in the Web of Science. Of these, 342 articles met the inclusion criteria, 319 of which were excluded on the basis of the defined exclusion criteria (the most common reasons being missing data on the effect of treatment on carriage, a follow-up duration of <1 week, or no control group). Five studies were excluded because β-lactam antibiotics were evaluated. Twenty-three studies, all of which were published from March 1977 through October 2008, remained; they involved a total of 2114 subjects, 1831 of whom were evaluated until the end of the follow-up period, with a mean of 80 subjects per study (table 1) [14–36].

Interventions. Different interventions were evaluated, including topically applied antimicrobial agents (mupirocin [17, 19, 21, 22, 25, 26, 28–30, 32, 34, 36], bacitracin nasal ointment [30], and tea tree oil [34]), systemic (orally administered) antibiotics (tetracyclines [24], fusidic acid [31], macrolides [14, 15, 33], ciprofloxacin [20], rifampin [20, 23, 24], and trimethoprim-sulfamethoxazole [20, 23]), and combinations of both [16, 18, 27, 35]. Interventions were most often used for 7 days (range, 3–14 days), with eradication rates determined for MSSA [14–19, 22, 25, 26, 29, 33], MRSA [20, 23, 24, 27, 28, 31, 34–36], or both [21, 30, 32].

Study quality. There was large variation in the methodological quality of included studies (tables 2 and 3; online only). The method of allocation was described in 12 studies only; there were no statistically significant differences in the baseline characteristics reported in 7 of these 12 studies [21, 23, 26, 28, 32, 35, 36], differences in baseline characteristics were not explicitly mentioned in 4 studies [18, 19, 33, 34], and there was a statistically significant difference in extranasal carriage between both study groups in 1 study [27]. Most studies were blinded. All studies that compared mupirocin with placebo were double-blinded [17, 19, 21, 25, 26, 28–30, 32, 36], as were 4 [14, 15, 23, 33] of 11 studies that compared systemic treatment with placebo or another treatment. One of these studies was single-blinded [20], and the remaining 6 studies were not blinded [16, 18, 24, 27, 31, 35]. Follow-up of >80% of study subjects was achieved in 16 studies; the percentage of subjects with follow-up could not be determined from the published data in 3 studies [22, 31, 33] and was <80% (range, 51%–77%) in 4 studies [18, 27, 32, 35].

Populations studied. Different populations were studied, including healthy carriers [14, 15, 17, 22, 36], health care workers [16, 19, 21, 25, 26, 30], hospitalized patients and patients visiting outpatient clinics [18, 20, 28, 29, 31, 33–35], nursing home patients [24, 32], and health care workers and patients combined [23, 27].

Topical treatment. The efficacy of topical mupirocin was

Downloaded from https://academic.oup.com/cid/article/48/7/922/326174 by guest on 30 September 2020

Table 1. Study characteristics of 23 selected studies.

Study	Year	Study design	Patient population	Sample size	Treatment per study group	Duration of treatment, days	Duration of follow-up, days	Culture site(s)	Eradication 1 week after treatment, % of patients[a]	Eradication at end of follow-up, % of patients[a]
Wilson et al. [14]	1977	DB-RCT	HVs	77 Patients with MSSA	1. Josamycin[b] 2. Erythromycin[b] 3. Placebo[b]	7 7 7	28	N	55 54 0	36 8 0
Wilson et al. [15]	1979	DB-RCT	HVs	87 Patients with MSSA	1. Rosamycin[b] 2. Erythromycin[b] 3. Placebo[b]	7 7 7	28	N	43 74 7	23 22 7
McAnally et al. [16]	1984	O-RCT	HCWs	59 Patients with MSSA	1. Rifampicin[b] 2. Bacitracin[c] 3. Bacitracin[c] and rifampicin[b] 4. No treatment	5 10 10–5 0	28	N	86 13 58 12	64 13 75 12
Casewell et al. [17]	1986	DB-RCT	HVs	33 Patients with MSSA	1. Mupirocin[c] 2. Placebo[c]	5 5	28	N	100 0	81 0
Yu et al. [18]	1986	O-RCT	Hemodialysis outpatients	60 Patients with MSSA	1. Bacitracin[c] and rifampicin[b] 2. No treatment	5 5	90	N	NA	67 27
Bulanda et al. [19][d]	1989	DB-RCT	HCWs	69 Patients with MSSA	1. Mupirocin[c] 2. Placebo[c]	5 3	365/28	N	96 0	83 43
Peterson et al. [20]	1990	SB-RCT	Hosp patients	21 Patients with MRSA	1. Ciprofloxacin[b] and rifampicin[b] 2. Trimethoprim-sulfamethoxazole[b] and rifampicin[b]	14 14	180	N, G, W	70 67	27 40
Doebbeling et al. [21]	1993	DB-RCT	HCWs	322 Patients with MSSA, 17 patients with MRSA	1. Mupirocin[c] 2. Placebo[c]	5 5	28	N	91 6	67 1
Leigh et al. [22]	1993	O-RCT	HVs	66 Patients with MSSA	1. Mupirocin[c] and chlorhexidin[e] 2. Chlorhexidin neomycin[c] and chlorhexidin[e]	7 7	91	N, G, S	95	57 11
Walsh et al. [23]	1993	DB-RCT	HCWs and patients	94 Patients with MRSA	1. Novamycin[b] and rifampicin[b] 2. Trimethoprim-sulfamethoxazole[b] and rifampicin[b]	7 7	14	N, G, W, Sp	NA	67 53
Muder et al. [24]	1994	O-RCT	LTCF	35 Patients with MRSA	1. Rifampicin[b] 2. Minocyclin[b] 3. Minocyclin[b] and rifampicin[b] 4. No treatment	5 5 5 0	90	N, U, W	60 13 70 14	67 38 50 14
Doebbeling et al. [25]	1994	DB-RCT	HCWs	68 Patients with MSSA	1. Mupirocin[c] 2. Placebo[c]	5 5	180	N, S	NA	50 14

Downloaded from https://academic.oup.com/cid/article/48/7/922/326174 by guest on 30 September 2020

Fernandez et al. [26]	1995	DB-RCT	HCWs	61 Patients with MSSA, 1 patient with MRSA	1. Mupirocin[c] 2. Placebo[c]	5 5	180	N	87 9	52 6
Parras et al. [27]	1995	O-RCT	HCWs and hosp patients	84 Patients with MRSA	1. Mupirocin[c] and chlorhexidin[e] 2. Fusidic acid,[c] trimetho-prim-sulfamethoxazole,[b] and chlorhexidin[e]	5 5	28	N	100 100	96 95
Harbarth et al. [28]	1999	DB-RCT	Hosp patients	98 Patients with MRSA	1. Mupirocin[c] and chlorhexidin[e] 2. Placebo[c] and chlorhexidin[e]	5 5	26	N, G, U, W	NA	25 18
Martin et al. [29]	1999	DB-RCT	HIV outpatients	76 Patients with MSSA	1. Mupirocin[c] 2. Placebo[c]	5 5	70	N	89 8	43 31
Soto et al. [30]	1999	SB-RCT	HCWs	34 Patients with MSSA, 3 pa-tients with MRSA	1. Mupirocin[c] 2. Bacitracin[c]	5 5	30	N	94 44	80 23
Chang et al. [31]	2000	O-RCT	Hosp patients (ICU)	16 Patients with MRSA	1. Fusidic acid[b] 2. No treatment	7 0	28	N, T, W, Sp	50 0	40 30
Mody et al. [32]	2003	DB-RCT	LTCF	64 Patients with MSSA, 63 pa-tients with MRSA	1. Mupirocin[c] 2. Placebo[c]	14 14	16	N, W	93 15	88 18
Berg et al. [33]	2004	DB-RCT	Hosp patients	95 Patients with MSSA	1. Clarithromycin[b] 2. Placebo[b]	14 14	56	N, T	NA	88 7
Dryden et al. [34]	2004	O-RCT	Hosp patients	224 Patients with MRSA	1. Mupirocin[c] and chlorhexidin[e] 2. Tea tree oil[c] and tea tree oil[e]	5 5	14	N, T, G, S, W	NA	49 42
Simor et al. [35]	2006	O-RCT	Hosp patients	146 Patients with MRSA	1. Mupirocin,[c] rifampicin,[b] doxycyclin,[b] and chlorhexidin[e] 2. No treatment	7 0	90	N, G, W, D	NA	74 32
Ellis et al. [36]	2008	Cluster-DB-RCT	Healthy soldiers	134 Patients with CA MRSA	1. Mupirocin[c] 2. Placebo[c]	5 5	56	N	NA	88 65

NOTE. CA, community acquired; CT, controlled trial; D, device exit site; DB-RCT, double-blind randomized controlled trial; G, groin; HCW, health care worker; hosp, hospitalized; HV, healthy volunteer; ICU, intensive care unit; LTCF, long-term care facility; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; N, nose; O-RCT, open randomized controlled trial; NA, not available; S, skin; SB-RCT, single-blind randomized controlled trial; Sp, sputum; T, throat; U, urine; W, wound.

[a] Number of persons successfully decolonized excludes recolonization with another strain. Recolonization with another strain is defined as treatment failure.

[b] Oral tablets.

[c] Nasal ointment.

[d] During the first half of the study, patients were treated for 5 days with a follow-up period of 365 days. During the second half of the study, patients were treated for 3 days with a follow-up period of 28 days.

[e] Body washing.

Downloaded from https://academic.oup.com/cid/article/48/7/922/326174 by guest on 30 September 2020

Table 2 (online only). Efficacy of studied treatments.

This table is available in its entirety in the online edition of *Clinical Infectious Diseases*

evaluated in 13 studies (table 1). Mupirocin was compared with placebo in 8 studies. In addition, mupirocin was compared with chlorhexidin-neomycin nasal ointment [22] and with fusidic acid nasal ointment combined with trimethoprim-sulfamethoxazole [27]. In 2 other studies, mupirocin was compared with bacitracin [30] and tea tree oil [34]. Chlorhexidin was part of the intervention in 3 studies; however, it was always administered to both groups, which allowed determination of the effect of mupirocin [22, 27, 28].

The effects of mupirocin, compared with placebo, on carriage 1 week after treatment could be quantified for 6 studies (total number of subjects studied, 626) (table 4) [17, 19, 21, 26, 29, 32]. The efficacy of mupirocin was comparable among studies that included only MSSA carriers or included both MRSA and MSSA carriers, and efficacy was also comparable among studies that included patients or healthy subjects. As a result, the estimated pooled RRs of treatment failure with mupirocin, based on these 6 studies, was 0.10 (range, 0.07–0.14; I^2, 0%). The absence of heterogeneity in outcomes, as represented by the low I^2 value, allowed us to conclude that mupirocin eradicates MRSA and MSSA carriage 11 times more effectively than no treatment, with successful eradication in 94% of carriers (424 of 453 carriers) 1 week after treatment.

The effects of mupirocin, compared with placebo, on carriage at the end of follow-up could be quantified for 8 studies (total number of subjects studied, 902) (table 4) [17, 19, 21, 25, 26, 28, 29, 32, 36]. The duration of follow-up ranged from 16 days through 365 days. In contrast with the results at 1 week of follow-up, there was considerable heterogeneity in the results of studies with longer follow-up periods, which reduced the accuracy of the effect size. In general, however, mupirocin appeared to be effective, with estimated pooled RRs of treatment failure of 0.44 (range, 0.39–0.50; I^2, 90.2%). Eradication had been successful in 65% (range, 25%–90%) of carriers (402 of 622 carriers) after a follow-up period of at least 14 days [17, 19, 21, 22, 25–30, 32, 34, 36]. Overall, the efficacy of mupirocin was comparable among studies that included only MSSA carriers and studies that included both MRSA and MSSA carriers (including the 2 studies that involved only patients with MRSA carriage), with pooled RRs at the end of follow-up of 0.52 (range, 0.43–0.64; I^2, 76.8%) [17, 19, 25, 26, 29] and 0.40 (range, 0.34–0.48; I^2, 95.6%) (data not shown) [21, 28, 32, 36], respectively. Efficacy of mupirocin nasal ointment appeared to be lower in studies that included multiple body sites for evaluation (pooled RRs, 0.60; range, 0.49–0.74; I^2, 92.3%) [25, 28, 32], compared with studies that only tested for nasal carriage (pooled RRs, 0.38; range, 0.32–0.45; I^2, 78.5%) (data not shown) [17, 19, 21, 26, 29, 36].

Acquisition of mupirocin resistance during treatment was reported in 3 studies [28, 32, 35] and was found in 6 (1%) of 714 total subjects evaluated in 12 studies [17, 19, 21, 22, 25–29, 32, 34–36]. Reported adverse events attributable to mupirocin use were mild and did not lead to discontinuation of therapy (table 3; online only).

Other topical agents were investigated less often. Bacitracin nasal ointment only eradicated carriage in 10 (29%) of 34 MRSA and MSSA carriers at 1 week after treatment (range, 13%–44%) [16, 30], and tea tree oil eliminated MRSA carriage in 46 (44%) of 110 carriers at 2 weeks after treatment [34]. Compared with mupirocin, estimated pooled RRs of treatment failure of bacitracin and tea tree oil at the end of treatment was 1.88 (range, 0.57–6.15; I^2, 79.9%) (data not shown). Fusidic acid nasal ointment and chlorhexidin washings have only been studied in combination with other topical or systemic medication, and the effectiveness of these components could not be determined.

Systemic treatment. The efficacy of oral antibiotics was evaluated in 11 studies (table 1). In all studies, eradication was evaluated for either MRSA or MSSA. Only 6 studies compared systemic treatment with receipt of placebo or no treatment; 3 of these studies involved patients [24, 31, 33], and 3 involved healthy subjects [14–16]. Of these 6 studies, 4 addressed MSSA carriage [14–16, 33], and 2 addressed MRSA carriage [24, 31]). The results were pooled in the random-effects model (table 4). Different regimens were compared in the other 5 studies. The overall pooled RRs of treatment failure of oral antibiotics, compared with placebo or no treatment, was 0.47 (range, 0.39–0.57; I^2, 3.2%) 1 week after treatment [14–16, 24, 31] and 0.54 (range, 0.33–0.87; I^2, 91.9%) at the end of the follow-up period [14–16, 24, 31, 33]. The high level of heterogeneity in the second analysis, however, indicates that the effect estimate should be interpreted with caution. Efficacies at the end of the follow-up period appeared to be comparable in studies that included only MSSA carriers [14–16, 33] or only MRSA carriers [24, 31]. In contrast with the results of mupirocin studies, the efficacy of systemic treatment, when compared with that of placebo or no treatment, was not higher in studies that determined eradication by means of nasal cultures only (pooled RRs, 0.74; range, 0.65–0.85; I^2, 57.9%) [14–16], compared with those

Table 3 (online only). Adverse events and quality assessment of studies included in the review.

This table is available in its entirety in the online edition of *Clinical Infectious Diseases*

Downloaded from https://academic.oup.com/cid/article/48/7/922/326174 by guest on 30 September 2020

Table 4. Pooled relative risks (RR_p) of treatment failure 1 week after treatment and at the end of the follow-up period.

Variable	MRSA carriage			MSSA carriage			MRSA and MSSA carriage			Overall		
	No. of studies	RR_p (95% CI)	I^2, %	No. of studies	RR_p (95% CI)	I^2, %	No. of studies	RR_p (95% CI)	I^2, %	No. of studies	RR_p (95% CI)	I^2, %
One week after treatment												
Mupirocin vs. placebo												
Patients	…	…	…	1	0.11 (0.05–0.29)	NA	1	0.09 (0.03–0.22)	NA	2	0.10 (0.05–0.19)	0
Healthy carriers	…	…	…	3	0.08 (0.03–0.22)	44.1	1	0.10 (0.06–0.16)	NA	4	0.09 (0.06–0.15)	12.7
Overall	…	…	…	4	0.09 (0.05–0.18)	18.2	2	0.09 (0.06–0.15)	0	6	0.10 (0.07–0.14)	0
Systemic treatment vs. placebo												
Patients	2	0.57 (0.38–0.85)	0	…	…	…	…	…	…	2	0.57 (0.38–0.85)	0
Healthy carriers	…	…	…	3	0.44 (0.32–0.59)	33.3	…	…	…	3	0.44 (0.32–0.59)	33.3
Overall	2	0.57 (0.38–0.85)	0	3	0.44 (0.32–0.59)	33.3	…	…	…	5	0.47 (0.39–0.57)	3.2
End of follow-up period												
Mupirocin vs. placebo												
Patients	1	0.91 (0.74–1.13)	NA	1	0.83 (0.58–1.20)	NA	1	0.15 (0.07–0.35)	NA	3	0.64 (0.53–0.78)	91.8
Healthy carriers	1	0.29 (0.13–0.68)	NA	4	0.44 (0.35–0.57)	72.6	1	0.33 (0.26–0.42)	NA	6	0.37 (0.31–0.44)	69.1
Overall	2	0.71 (0.55–0.90)	90.2	6	0.52 (0.43–0.64)	76.8	2	0.30 (0.24–0.38)	68.8	9	0.44 (0.39–0.50)	90.2
Systemic treatment vs. placebo												
Patients	2	0.63 (0.41–0.96)	0	1	0.13 (0.06–0.28)	NA	…	…	…	3	0.40 (0.11–1.42)	90.3
Healthy carriers	…	…	…	3	0.77 (0.62–0.95)	58.6	…	…	…	3	0.77 (0.62–0.95)	58.6
Overall	2	0.63 (0.41–0.96)	0	4	0.48 (0.25–0.92)	92.5	…	…	…	6	0.54 (0.33–0.87)	91.9

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus;* NA, not applicable.

Downloaded from https://academic.oup.com/cid/article/48/7/922/326174 by guest on 30 September 2020

using cultures samples from multiple body sites (pooled RRs, 0.40; range, 0.11–1.42; I^2, 90.3%) (data not shown) [24, 31, 33].

More specifically, trimethoprim-sulfamethoxazole in combination with rifampin or nasal fusidic acid eradicated MRSA carriage in 48 (62%) of 78 subjects (range, 40%–95%) in 3 studies [20, 23, 27]. Of the macrolides, monotherapy with clarithromycin reduced nasal MSSA carriage in 43 (88%) of 49 subjects at the end of 8 weeks of follow-up, but it was also associated with a rapid and prolonged increase in macrolide resistance in oropharyngeal nonstaphylococcal flora [33]. Combined treatment with doxycycline, rifampin, mupirocin, and chlorhexidin was associated with MRSA eradication in 64 (74%) of 87 patients after 3 months, with >50% of patients being MRSA free up to 8 months later [35]. In 1 study, ciprofloxacin was compared with trimethoprim-sulfamethoxazole (with rifampin added to the treatment regimen in both study groups), but this randomized trial was terminated prematurely because of clonal spread of a ciprofloxacin-resistant MRSA strain in the hospital [20]. Rifampin as part of combination therapy with other oral and/or topical antibiotics was associated with eradication of MRSA in 138 (62%) of 221 carriers (after a follow-up period of at least 14 days) [20, 23, 24, 35]. Acquisition of resistance to the oral antibiotics used for eradicating MSSA and MRSA carriage was reported in 5 studies [18, 20, 23, 24, 31], in 39 (9%) of 443 total subjects evaluated in 10 studies [14–16, 18, 20, 23, 24, 27, 31, 35]; acquisition of resistance was especially common among patients who received fusidic acid and rifampin monotherapy [18, 24, 31]. Reported adverse events were mild and led to discontinuation of therapy in 4 patients in 2 studies (table 3; online only) [20, 23].

DISCUSSION

Short-term (4–7 days in duration) topical nasal application of mupirocin is the most effective treatment for eradicating MRSA, with an estimated success probability of ~90% 1 week after treatment and ~60% after a longer follow-up period, ranging from 14 days through 365 days in different studies. The reported effectiveness of mupirocin is comparable amogn MSSA carriers and MRSA carriers, but it is higher among healthy carriers than among patients. Estimated successful eradication with oral antibiotics was achieved in ~60% of subjects 1 week after treatment and in ~50% of subjects after longer follow-up periods. For oral antibiotics, the reported effectiveness was comparable among MRSA carriers and MSSA carriers and among patients and healthy carriers. Of note, MSSA eradication efficacy at the end of follow-up was higher in the 1 study that involved patients [33] than it was in the 3 studies with healthy carriers [14–16]. No explanation could be found for this difference.

To include as much of the available evidence as possible, we decided not to restrict our literature search to studies of the eradication of MRSA alone but to also include studies that evaluated MSSA carriage, under the assumption that MSSA carriage has a similar response to eradication therapy if agents with activity against both MRSA and MSSA are used. On the basis of the fact that mupirocin has a similar effect on both pathogens, as indicated by our analyses, there is no reason to reject this assumption for studies that involve mupirocin. This increases the size of the included population from 718 subjects for studies including MRSA carriers alone to 2036 subjects in the current analysis. The analyses of oral antibiotics yielded similar results, although heterogeneity across studies was higher and reduced the accuracy of the effect sizes obtained.

MRSA frequently colonizes extranasal sites (e.g., throat and perineum) [6, 37, 38], which reduces the effectiveness of topical (intranasal) mupirocin treatment, as the findings of our study suggest. The estimated risk of eradication failure increased from 0.38 to 0.60 for studies that evaluated nasal colonization alone and studies that evaluated colonization of additional body sites, respectively. However, such reduced effectiveness was not found for systemic treatment. For these agents, the risk of eradication failure was actually higher in studies that evaluated nasal colonization alone (pooled RRs, 0.74), compared with studies that also evaluated extranasal sites (pooled RRs, 0.43), although the 95% CI of the latter estimate ranged from 0.14 through 1.27. In fact, reported determinants in patients who experience failure of MRSA eradication by topical treatment (mupirocin treatment, in particular) are skin lesions (e.g., wounds and eczema) [22, 23, 28] and mupirocin resistance [28, 35].

Mupirocin effectiveness decreased with a prolonged follow-up period. There are 3 biological explanations for this difference in effectiveness related to the duration of follow-up. First, this estimate was affected by the results of the 1 study that included only hospitalized MRSA carriers (98 subjects) and that failed to demonstrate a beneficial effect of mupirocin therapy [28]. Compared with patients in the other studies, patients in this study had a higher risk of comorbidity, were more likely to have multiple body sites evaluated, and had a higher risk of having a mupirocin-resistant strain at the start of treatment (found in 23 [24%] of 98 subjects). Second, a longer duration of follow-up after a short course of treatment increases the risk of recolonization from other sources, such as other patients, which may be especially relevant in hospitalized populations. Third, recolonization may also result if mupirocin therapy suppresses bacterial density, rather than completely eradicating carriage.

On the basis of the available evidence in this systematic review, intranasal administration of mupirocin ointment seems to be safe and is associated with a 1% risk of acquiring a drug-resistant strain during treatment. Recent surveillance studies, however, have reported mupirocin-resistant MRSA strains in

Downloaded from https://academic.oup.com/cid/article/48/7/922/326174 by guest on 30 September 2020

up to 13% of patients in institutions that do not practice routine use of mupirocin and in up to 65% of patients in areas with widespread mupirocin use [39]. In such settings, tea tree oil might be an alternative treatment, because it was found to be as effective as mupirocin in 1 study [34].

Short-term nasal eradication therapy with mupirocin is highly effective during the period immediately after it is administered and would serve the purpose of presurgical eradication, as has been suggested for presurgical eradication of MSSA carriage [40]. Furthermore, because the duration of hospital stay is <1 week for most patients, such an approach would also reduce the potential burden of transmission if it was applied to control disease spread. These findings corroborate the beneficial results of rapid detection of MRSA carriage and subsequent mupirocin treatment [41]. In patients with factors that are associated with treatment failure (e.g., skin lesions, mupirocin-resistant strains, and positive results of cultures from extra-nasal sites), systemic eradication treatment (e.g., rifampin administered in combination with another oral antibiotic), in addition to mupirocin nasal ointment, is the treatment of choice.

Acknowledgments

Financial support. The Netherlands Organization of Scientific Research (VICI NOW 918.76.611 to M.J.M.B.).

Potential conflicts of interest. M.J.M.B. has received research funding from Novartis and 3M, is a member of the speakers' bureau for Pfizer, and is a member of the advisory boards of 3M and Novartis. J.L.N. is a member of the advisory board of GlaxoSmithKline. J.A.J.W.K. has received consulting fees from 3M, Novabay, and Wyeth and has received honoraria from 3M and Becton Dickenson for lectures. H.S.M.A. and H.F.L.W.: no conflicts.

References

1. Wertheim HF, Melles DC, Vos MC, et al. The role of nasal carriage in *Staphylococcus aureus* infections. Lancet Infect Dis **2005**; 5:751–62.
2. European Antimicrobial Resistance Surveillance System. EARSS annual report 2005: ongoing surveillance of *S. pneumoniae, S. aureus, E. coli, E. faecium, E. faecalis.* Bilthoven, The Netherlands: Rijksinstituut voor Volksgezondheid en Milieu, **2006**.
3. Tiemersma EW, Bronzwaer SL, Lyytikainen O, et al. Methicillin-resistant *Staphylococcus aureus* in Europe, 1999–2002. Emerg Infect Dis **2004**; 10:1627–34.
4. National Nosocomial Infections Surveillance (NNIS) System Report: data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control **2004**; 32:470–85.
5. Hsueh PR, Chen ML, Sun CC, et al. Antimicrobial drug resistance in pathogens causing nosocomial infections at a university hospital in Taiwan, 1981–1999. Emerg Infect Dis **2002**; 8:63–8.
6. Sanford MD, Widmer AF, Bale MJ, Jones RN, Wenzel RP. Efficient detection and long-term persistence of the carriage of methicillin-resistant *Staphylococcus aureus.* Clin Infect Dis **1994**; 19:1123–8.
7. Laupland KB, Conly JM. Treatment of *Staphylococcus aureus* colonization and prophylaxis for infection with topical intranasal mupirocin: an evidence-based review. Clin Infect Dis **2003**; 37:933–8.
8. Loeb M, Main C, Walker-Dilks C, Eady A. Antimicrobial drugs for treating methicillin-resistant *Staphylococcus aureus* colonization. Cochrane Database Syst Rev **2003**;CD003340.
9. Loveday HP, Pellowe CM, Jones SR, Pratt RJ. A systematic review of the evidence for interventions for the prevention and control of methicillin-resistant *Staphylococcus aureus* (1996–2004): report to the Joint MRSA Working Party (Subgroup A). J Hosp Infect **2006**; 63(Suppl 1): S45–70.
10. Muto CA, Jernigan JA, Ostrowsky BE, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and enterococcus. Infect Control Hosp Epidemiol **2003**; 24:362–86.
11. Coia JE, Duckworth GJ, Edwards DI, et al. Guidelines for the control and prevention of meticillin-resistant *Staphylococcus aureus* (MRSA) in healthcare facilities. J Hosp Infect **2006**; 63(Suppl 1):S1–44.
12. Gemmell CG, Edwards DI, Fraise AP, Gould FK, Ridgway GL, Warren RE. Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK. J Antimicrob Chemother **2006**; 57:589–608.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ **2003**; 327:557–60.
14. Wilson SZ, Martin RR, Putman M. In vivo effects of josamycin, erythromycin, and placebo therapy on nasal carriage of *Staphylococcus aureus.* Antimicrob Agents Chemother **1977**; 11:407–10.
15. Wilson SZ, Martin RR, Putman M, Greenberg SB, Wallace RJ Jr, Jemsek JG. Quantitative nasal cultures from carriers of *Staphylococcus aureus;* effects of oral therapy with erythromycin, rosamicin, and placebo. Antimicrob Agents Chemother **1979**; 15:379–83.
16. McAnally TP, Lewis MR, Brown DR. Effect of rifampin and bacitracin on nasal carriers of *Staphylococcus aureus.* Antimicrob Agents Chemother **1984**; 25:422–6.
17. Casewell MW, Hill RL. Elimination of nasal carriage of *Staphylococcus aureus* with mupirocin ("pseudomonic acid"): a controlled trial. J Antimicrob Chemother **1986**; 17:365–72.
18. Yu VL, Goetz A, Wagener M, et al. *Staphylococcus aureus* nasal carriage and infection in patients on hemodialysis: efficacy of antibiotic prophylaxis. N Engl J Med **1986**; 315:91–6.
19. Bulanda M, Gruszka M, Heczko B. Effect of mupirocin on nasal carriage of *Staphylococcus aureus.* J Hosp Infect **1989**; 14:117–24.
20. Peterson LR, Quick JN, Jensen B, et al. Emergence of ciprofloxacin resistance in nosocomial methicillin-resistant *Staphylococcus aureus* isolates: resistance during ciprofloxacin plus rifampin therapy for methicillin-resistant *S. aureus* colonization. Arch Intern Med **1990**; 150: 2151–5.
21. Doebbeling BN, Breneman DL, Neu HC, et al. Elimination of *Staphylococcus aureus* nasal carriage in health care workers: analysis of six clinical trials with calcium mupirocin ointment. The Mupirocin Collaborative Study Group. Clin Infect Dis **1993**; 17:466–74.
22. Leigh DA, Joy G. Treatment of familial staphylococcal infection: comparison of mupirocin nasal ointment and chlorhexidine/neomycin (Naseptin) cream in eradication of nasal carriage. J Antimicrob Chemother **1993**; 31:909–17.
23. Walsh TJ, Standiford HC, Reboli AC, et al. Randomized double-blinded trial of rifampin with either novobiocin or trimethoprim-sulfamethoxazole against methicillin-resistant *Staphylococcus aureus* colonization: prevention of antimicrobial resistance and effect of host factors on outcome. Antimicrob Agents Chemother **1993**; 37:1334–42.
24. Muder RR, Boldin M, Brennen C, et al. A controlled trial of rifampicin, minocycline, and rifampicin plus minocycline for eradication of methicillin-resistant *Staphylococcus aureus* in long-term care patients. J Antimicrob Chemother **1994**; 34:189–90.
25. Doebbeling BN, Reagan DR, Pfaller MA, Houston AK, Hollis RJ, Wenzel RP. Long-term efficacy of intranasal mupirocin ointment: a prospective cohort study of *Staphylococcus aureus* carriage. Arch Intern Med **1994**; 154:1505–8.
26. Fernandez C, Gaspar C, Torrellas A, et al. A double-blind, randomized, placebo-controlled clinical trial to evaluate the safety and efficacy of mupirocin calcium ointment for eliminating nasal carriage of *Staphylococcus aureus* among hospital personnel. J Antimicrob Chemother **1995**; 35:399–408.
27. Parras F, Guerrero MC, Bouza E, et al. Comparative study of mupirocin

Downloaded from https://academic.oup.com/cid/article/48/7/922/326174 by guest on 30 September 2020

and oral co-trimoxazole plus topical fusidic acid in eradication of nasal carriage of methicillin-resistant *Staphylococcus aureus.* Antimicrob Agents Chemother **1995**; 39:175–9.
28. Harbarth S, Dharan S, Liassine N, Herrault P, Auckenthaler R, Pittet D. Randomized, placebo-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant *Staphylococcus aureus.* Antimicrob Agents Chemother **1999**; 43:1412–6.
29. Martin JN, Perdreau-Remington F, Kartalija M, et al. A randomized clinical trial of mupirocin in the eradication of *Staphylococcus aureus* nasal carriage in human immunodeficiency virus disease. J Infect Dis **1999**; 180:896–9.
30. Soto NE, Vaghjimal A, Stahl-Avicolli A, Protic JR, Lutwick LI, Chapnick EK. Bacitracin versus mupirocin for *Staphylococcus aureus* nasal colonization. Infect Control Hosp Epidemiol **1999**; 20:351–3.
31. Chang SC, Hsieh SM, Chen ML, Sheng WH, Chen YC. Oral fusidic acid fails to eradicate methicillin-resistant *Staphylococcus aureus* colonization and results in emergence of fusidic acid-resistant strains. Diagn Microbiol Infect Dis **2000**; 36:131–6.
32. Mody L, Kauffman CA, McNeil SA, Galecki AT, Bradley SF. Mupirocin-based decolonization of *Staphylococcus aureus* carriers in residents of 2 long-term care facilities: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis **2003**; 37:1467–74.
33. Berg HF, Tjhie JH, Scheffer GJ, et al. Emergence and persistence of macrolide resistance in oropharyngeal flora and elimination of nasal carriage of *Staphylococcus aureus* after therapy with slow-release clarithromycin: a randomized, double-blind, placebo-controlled study. Antimicrob Agents Chemother **2004**; 48:4183–8.
34. Dryden MS, Dailly S, Crouch M. A randomized, controlled trial of tea tree topical preparations versus a standard topical regimen for the clearance of MRSA colonization. J Hosp Infect **2004**; 56:283–6.
35. Simor AE, Phillips E, McGeer A, et al. Randomized controlled trial of chlorhexidine gluconate for washing, intranasal mupirocin, and rifampin and doxycycline versus no treatment for the eradication of methicillin-resistant *Staphylococcus aureus* colonization. Clin Infect Dis **2007**; 44:178–85.
36. Ellis MW, Griffith ME, Dooley DP, et al. Targeted intranasal mupirocin to prevent colonization and infection by community-associated methicillin-resistant *Staphylococcus aureus* strains in soldiers: a cluster randomized controlled trial. Antimicrob Agents Chemother **2007**; 51: 3591–8.
37. Mertz D, Frei R, Jaussi B, et al. Throat swabs are necessary to reliably detect carriers of *Staphylococcus aureus.* Clin Infect Dis **2007**; 45:475–7.
38. Rohr U, Wilhelm M, Muhr G, Gatermann S. Qualitative and (semi)quantitative characterization of nasal and skin methicillin-resistant *Staphylococcus aureus* carriage of hospitalized patients. Int J Hyg Environ Health **2004**; 207:51–5.
39. Jones JC, Rogers TJ, Brookmeyer P, et al. Mupirocin resistance in patients colonized with methicillin-resistant *Staphylococcus aureus* in a surgical intensive care unit. Clin Infect Dis **2007**; 45:541–7.
40. van Rijen MM, Bonten M, Wenzel RP, Kluytmans JA. Intranasal mupirocin for reduction of *Staphylococcus aureus* infections in surgical patients with nasal carriage: a systematic review. J Antimicrob Chemother **2008**; 61:254–61.
41. Robicsek A, Beaumont JL, Paule SM, et al. Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. Ann Intern Med **2008**; 148:409–18.

Downloaded from https://academic.oup.com/cid/article/48/7/922/326174 by guest on 30 September 2020