ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2010, p. 4020–4025 Vol. 54, No. 9
0066-4804/10/$12.00 doi:10.1128/AAC.01240-09

Successful Treatment for Carriage of Methicillin-Resistant *Staphylococcus aureus* and Importance of Follow-Up▽

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Received 1 September 2009/Returned for modification 30 November 2009/Accepted 9 June 2010

With this prospective observational follow-up study of 165 methicillin-resistant *Staphylococcus aureus* (MRSA)-positive individuals (23 health care workers and 142 patients), we determined that our MRSA eradication therapy protocol results in a high success rate (81%). Five or more negative culture sets give a predictive value for MRSA eradication therapy success of >90%. Furthermore, MRSA colonization, at least in the throat, and the presence of wounds just before the start of MRSA eradication therapy are associated with MRSA eradication therapy failure.

Carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) precedes endogenous MRSA infections (4, 11, 24, 34). MRSA prevalence in the Netherlands is among the lowest in the world (13) because of an active "search-and-destroy" policy (35, 38). The "destroy" part of this policy is important, because it eliminates two out of the three known reservoirs: carriage in patients and health care workers (HCWs). The third reservoir is the environment.

Different MRSA eradication therapies have been studied (1, 2, 7, 8, 10, 15, 17–19, 22, 26, 29, 31, 33, 36, 37). Failure of MRSA eradication therapy has often been attributed to colonization of extranasal sites (2, 17, 20). No consensus exists regarding the number of follow-up cultures that should be obtained after MRSA eradication therapy to assess the success of treatment. The Dutch national policy (WIP) suggests a minimum of three follow-up culture sets to declare a former MRSA carrier negative. However, this culture rule is based not on solid evidence but on expert opinion (40).

The aim of this observational study was threefold: first, to assess the success rate of our MRSA eradication therapy; second, to analyze determinants predicting the outcome of eradication therapy; and third, to assess the minimum number of follow-up screenings after eradication therapy that are necessary in order to determine its success.

(This work was presented in part at the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy—Infectious Diseases Society of America [ICAAC/IDSA], Washington, DC, 24 to 28 October 2008.)

We prospectively studied 165 newly detected MRSA carriers, either health care workers (*n*, 23) or patients (*n*, 142), at the Erasmus University Medical Center (Rotterdam, Netherlands) from 2005 until 2008. Of these carriers, 110 were eligible for MRSA eradication therapy and follow-up (Fig. 1). Baseline

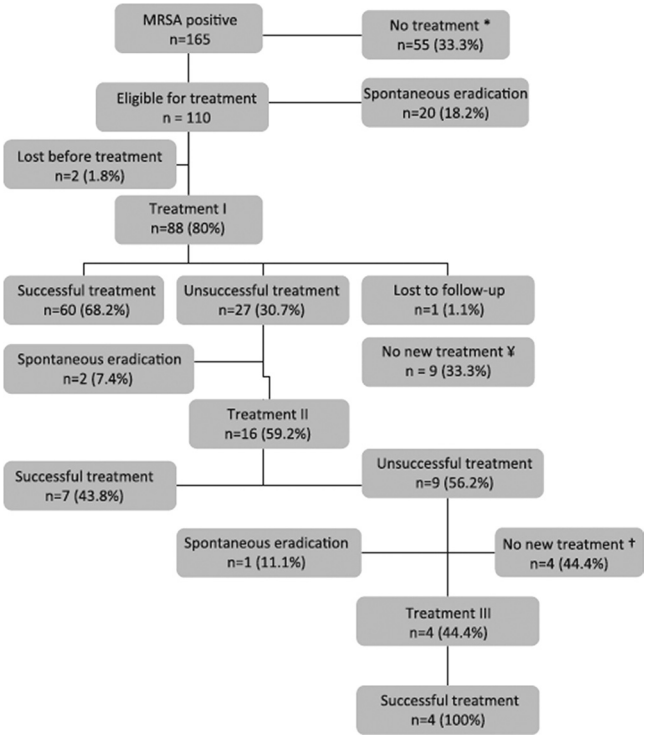

FIG. 1. Flowchart demonstrating the outcomes for MRSA-positive individuals after the first detection of MRSA. Unsuccessful treatment was defined as one or more cultures positive in one or more out of six consecutive follow-up culture sets (e.g., nose, throat, perineum, and any wounds or skin lesions present). *, patients not included because either (i) there was no treatment in our hospital (*n*, 26), (ii) they were not eligible for treatment (due to relative contraindications for eradication therapy, loss to follow-up after the first MRSA detection, or a high risk of noncompliance with treatment) (*n*, 17), or (iii) they died before treatment could be offered (*n*, 12). ¥, no new MRSA eradication therapy because of newly arisen relative contraindications for eradication therapy (*n*, 7), unavailability of new therapy in our hospital (*n*, 1); or loss to follow-up (*n*, 1). †, no new MRSA eradication therapy because of newly arisen relative contraindications for eradication therapy (*n*, 4). ‡, not included in the intention-to-treat analysis.

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▽ Published ahead of print on 14 June 2010.

TABLE 1. General baseline characteristics of MRSA-infected individuals as measured at the time of detection of the first MRSA-positive culture

Characteristic	Value for group[a]			*P* (patients with spontaneous clearance vs MRSA eradication therapy)
	Health care workers (*n* = 22)	Patients undergoing MRSA eradication therapy (*n* = 68)	Patients with spontaneous MRSA clearance (*n* = 20)	
Sex				0.43
Male	6 (27)	41 (60)	14 (70)	
Female	16 (73)	27 (40)	6 (30)	
Median (range) age (yr)	29 (22–53)	37.5 (1–82)	48 (1–76)	0.10[b]
Age category				
0–10 yr	0 (0)	16 (24)	2 (10)	0.30
11–20 yr	0 (0)	3 (4)	1 (5)	0.48
21–60 yr	22 (100)	40 (59)	11 (55)	0.34
>60 yr	0 (0)	9 (13)	6 (30)	0.07
Median (range) no. of sites colonized	1 (1–3)	2 (1–4)	1 (1–3)	0.005
MRSA colonization sites				
Nasal only	9 (41)	5 (7)	3 (15)	0.38
Extranasal only	7 (32)	17 (25)	11 (55)	0.01
Nasal and extranasal	6 (27)	46 (68)	6 (30)	0.003
Hospital admission in preceding yr		42 (62)	16 (80)	0.13
Nonintact skin	8 (38)[c]	44 (66)[d]	15 (75)	0.43
Wounds	4 (19)[c]	34 (52)[e]	14 (70)	0.15
Skin problems	8 (38)[c]	15 (22)[d]	4 (20)	0.82
Invasive devices (total)		23 (34)[d]	11 (55)	0.10
Catheter		19 (29)[f]	8 (40)	
Drain		11 (17)[f]	4 (20)	
Tracheostoma		2 (3)[e]	2 (10)	
Implant		9 (14)[e]	6 (30)	
Underlying disease (total)[g]	2 (10)[c]	11 (16)[d]	6 (30)	0.18
Diabetes mellitus	1 (5)[c]	2 (3)[d]	2 (10)	
COPD		3 (5)[d]	1 (5)	
Renal insufficiency	1 (5)[c]	3 (5)[d]	1 (5)	
Malignancy		5 (8)[d]	1 (5)	
HIV		1 (2)[d]	1 (5)	
Antibiotic use in the preceding mo	1 (5)[c]	20 (31)[h]	8 (42)[i]	0.38

[a] Except where otherwise stated, the value is the number (percentage) of individuals with the characteristic.
[b] Determined by the Mann-Whitney U test.
[c] A total of 21 individuals were evaluated.
[d] A total of 67 individuals were evaluated.
[e] A total of 66 individuals were evaluated.
[f] A total of 65 individuals were evaluated.
[g] COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.
[h] A total of 64 individuals were evaluated.
[i] A total of 19 individuals were evaluated.

characteristics are given in Table 1. Statistical analyses were done using SPSS, version 15.0 (SPSS Inc., Chicago, IL).

At the time of first detection of MRSA (baseline measurement), as well as before the start of MRSA eradication therapy (second measurement), swabs were taken from all defined culture sites: the anterior nares, the throat, the perineum, and, if present, skin lesions, wounds, or indwelling devices. All cultures were tested by a PCR method (23).

All MRSA-positive individuals, whether they received eradication therapy or took the "wait-and-see" option (see below), were followed up with screening of all culture sites. Six follow-up culture sets were taken, with a median interval of 7 days (range, 2 to 230 days) between sets. For individuals undergoing MRSA eradication therapy, the first follow-up culture set was taken 1 week after the completion of therapy. The median duration of all follow-up cultures for the individuals who became MRSA negative (20 individuals with spontaneous MRSA clearance, 71 with successful MRSA eradication therapy, and 3 with spontaneous clearance after MRSA eradication therapy failure) was 43 days (range, 17 to 366 days). The median duration of follow-up for individuals whose first eradication therapy failed (*n*, 27) was shorter, because they did not complete the six follow-up culture sets (median, 12 days; range, 4 to 137 days).

TABLE 2. MRSA eradication therapies offered to MRSA-positive individuals[a]

Therapy identification no.	Therapy description	No. (%) of MRSA-positive individuals receiving the therapy[b]
1	Mupirocin (2/day, 5 days) + chlorhexidine body wash (1/day, 5 days)[c]	18 (21)
2	1 + trimethoprim (2/day at 200 mg, 10 days) and rifampin (1/day at 600 mg, 10 days)[d]	23 (26)
3	2 + oral gentamicin solution (3/day at 80 mg, 10 days)[e]	3 (3)
4	1 + fusidic acid (3/day at 500 mg, 10 days) and rifampin (1/day at 600 mg, 10 days)[d]	13 (15)
5	Other[d]	31 (35)

[a] There were no significant differences between the success rates of the different MRSA eradication therapies offered.
[b] A total of 88 MRSA-positive individuals (20 health care workers and 68 patients) were studied.
[c] In case of nasal MRSA colonization (including 6 persons with extranasal MRSA colonization).
[d] In case of extranasal MRSA colonization with or without nasal MRSA colonization.
[e] In case of perineal MRSA colonization with or without nasal MRSA colonization (5).

Patients who had MRSA-negative cultures at all sites at the second measurement were offered the "wait-and-see" option (postponing eradication therapy and starting follow-up), and with this option, 20 patients (18%) spontaneously cleared their MRSA. The median number of colonized sites was significantly lower in patients with spontaneous MRSA clearance than in patients who needed MRSA eradication therapy (Table 1). Patients who received eradication therapy were more often colonized at both nasal and extranasal sites or at extranasal sites only than those with spontaneous MRSA clearance. This observation can be clarified by considering the findings of methicillin-susceptible *Staphylococcus aureus* (MSSA) studies showing that individuals with multiple-site colonization more often have high bacterial loads, which are associated with persistent carriage (8, 20, 27, 28, 39).

MRSA eradication therapies are listed in Table 2. These therapies were accompanied by hygienic instructions for daily life at home, such as washing bed linen, clothes, and towels. All health care workers (*n*, 20) received eradication therapy immediately after detection of MRSA (three HCWs were treated in another hospital). For MRSA-positive patients, the presence of indwelling devices, including drains, catheters, tracheostomas, and other implanted materials penetrating the skin, or nonintact skin was a relative contraindication for eradication therapy (14, 36), and MRSA eradication therapy was postponed if possible. Therefore, 68 patients received eradication therapy during the study period.

In total, 88 individuals received a mean of 1.5 MRSA eradication courses (range, 1 to 3 courses) per person. Seventy-one individuals (81% of those included in the intention-to-treat analysis) became MRSA negative (defined as six MRSA-negative follow-up culture sets). Eradication therapy has been studied in the past and has shown variable success rates (2, 6, 9, 12, 27, 28, 32, 36). Previous studies used definitions different from ours to ascertain the success of treatment; therefore, comparison of outcomes cannot yield robust conclusions.

Determinants for MRSA eradication therapy failure have been demonstrated in the past (6, 14, 16, 20, 21, 36), and our study confirmed several of these. Potential determinants of MRSA eradication therapy failure (MRSA-positive culture during follow-up) were colonization of the throat (74% compared to 53% with successful treatment; *P*, 0.06) and the presence of wounds (*P*, 0.05) at the second measurement (Table 3).

As is known (3, 6, 25, 30, 39), MRSA can survive in the throat despite eradication therapy. For this reason, it is essential to include throat swabs during follow-up.

When patients and HCWs were analyzed separately, colonization of the throat became statistically more significant for patients (*P*, 0.02; odds ratio [OR], 4.18 [95% confidence interval {95% CI}, 1.21 to 14.74]) and was nonsignificant for HCWs. In addition, the presence of wounds became a stronger determinant of MRSA eradication therapy failure (*P*, 0.02; OR, 8.27 [95% CI, 1.43 to 47.74]) for patients and nonsignificant for HCWs. For this reason, it seems preferable to have no wounds present at the time MRSA eradication therapy is started.

Other potential determinants could not be defined, probably due to our policy of postponing treatment for patients with relative contraindications for MRSA eradication therapy, which leaves only novel determinants of treatment failure to be revealed.

Seven (26%) of the individuals in our analysis whose first eradication therapy failed (*n*, 37) and 4 (44%) of the individuals whose second eradication therapy failed (*n*, 9) had MRSA-positive swabs after three consecutive negative culture sets taken more than 1 week after the end of treatment (Fig. 2). Eleven (31%) of the 36 individuals who failed to eradicate MRSA would, therefore, be incorrectly considered to have eradicated MRSA if only three follow-up culture sets had been obtained. When left untreated, this group can contribute to the spread of MRSA. Therefore, our study demonstrates that with five or more follow-up culture sets, the predictive value for eradication therapy success is >90%.

We do not know whether individuals who became MRSA free according to our culture rule will remain so in the foreseeable future. In 2007 we started to follow up individuals from whom MRSA was eradicated with one culture set every 1 to 2 months for 1 year. To date, we have encountered recolonization in one case only.

Our study may have some limitations. First, we studied the overall effect of MRSA eradication therapies and spontaneous MRSA loss. We did not analyze one specific MRSA eradication therapy, because the therapy that was offered depended on the MRSA-positive sites (nares, throat, perineum or other sites), and in some cases (resistance to one or more antibiotics of the regimen, adverse effects, allergies), another antibiotic

TABLE 3. Determinants of MRSA eradication therapy failure for individuals receiving their first MRSA eradication therapy

Determinant[a]	Value for group[b] with:		*P*	OR (95% CI)
	Successful treatment (*n* = 60)	Unsuccessful treatment (*n* = 27)		
Sex			0.36	1.53 (0.61–3.81)
Male	33 (55)	12 (44)		
Female	27 (45)	15 (56)		
Median (range) age (yr)	39 (1–82)	29 (1–73)	0.19[c]	
Age category				
0–10 yr	12 (20)	2 (7)	0.33	
11–20 yr	0 (0)	3 (11)	1.00	
21–60 yr	40 (67)	21 (78)	0.16	3.15 (0.64–15.41)
>60 yr	8 (13)	1 (4)	0.83	0.75 (0.06–9.72)
Median no. of colonized sites (range)	2 (1–4)	2 (1–4)	0.10[c]	
MRSA colonization sites[d]				
Nose (*n* = 87)	42 (70)	21 (78)	0.45	1.50 (0.52–4.34)
Throat (*n* = 86)	31 (53)	20 (74)	0.06	2.58 (0.95–7.02)
Perineum (*n* = 86)	18 (31)	12 (42)	0.21	1.82 (0.71–4.66)
Other (*n* = 87)[e]	21 (35)	9 (33)	0.88	0.93 (0.36–2.43)
Nasal only	10 (17)	4 (15)	1.00[c]	
Extranasal only	18 (30)	6 (22)	0.45	0.67 (0.23–1.93)
Nasal and extranasal	32 (53)	17 (63)	0.40	1.49 (0.59–3.78)
Hospital admission in preceding yr				
At baseline measurement (*n* = 86)	27 (46)	15 (56)	0.40	1.48 (0.59–3.76)
At second measurement (*n* = 86)	11 (18)	1 (4)	0.10[f]	0.18 (0.02–1.46)
Nonintact skin				
At baseline measurement (*n* = 85)	35 (59)	16 (62)	0.40	1.10 (0.43–2.82)
At second measurement (*n* = 84)	14 (24)	6 (23)	0.92	0.94 (0.32–2.81)
Wounds				
At baseline measurement (*n* = 84)	24 (41)	14 (56)	0.20	1.86 (0.72–4.78)
At second measurement (*n* = 83)	3 (5)	5 (20)	0.05[f]	4.58 (1.00–20.96)
Skin problems				
At baseline measurement (*n* = 85)	16 (27)	7 (27)	0.99	0.99 (0.35–2.80)
At second measurement (*n* = 84)	7 (12)	2 (8)	0.71[f]	0.61 (0.12–3.15)
Underlying disease				
At baseline measurement (*n* = 85)	9 (15)	4 (15)	1.00[f]	
At second measurement (*n* = 85)	8 (14)	2 (8)	0.72[f]	0.53 (0.11–2.69)
Antibiotic use in preceding mo				
At baseline measurement (*n* = 82)	12 (21)	8 (33)	0.23	1.92 (0.66–5.53)
At second measurement (*n* = 84)	2 (3)	0 (0)	1.00[f]	
Indwelling device				
At baseline measurement (*n* = 85)	15 (25)	7 (27)	0.88	1.08 (0.38–3.08)
At second measurement (*n* = 84)	5 (9)	3 (12)	0.69[f]	1.47 (0.32–6.70)

[a] *n*, number of individuals evaluated. The baseline measurement was taken at the time of MRSA detection. The second measurement was taken just before the start of MRSA eradication therapy.
[b] Except where otherwise stated, the value is the number (percentage) of individuals with the determinant.
[c] Determined by the Mann-Whitney U test.
[d] A combination of more than one colonization site is possible.
[e] Other colonization sites include sputum (4 individuals), urine (5 individuals), blood (2 individuals), wounds (16 individuals), and others (3 individuals).
[f] Determined by Fisher's exact test.

combination was used. Furthermore, when the different MRSA eradication therapies were analyzed separately, none of the regimens was demonstrated to be significantly superior with respect to the success rate of MRSA eradication. This is because our study was not designed for this purpose and probably also because of the relatively small population of individuals receiving MRSA eradication therapy (*n*, 88) that was studied. Second, infants, adults, and HCWs were included all together in this study, which assumes similar responses and epidemiology. As demonstrated in this study, patients have stronger determinants for MRSA eradication therapy failure than HCWs. In Table 1 we show that age (categorical or linear)

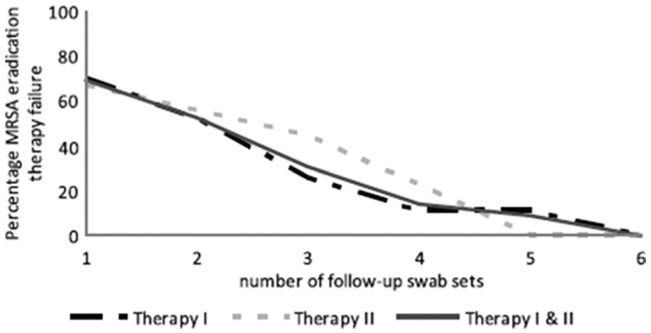

FIG. 2. Number of MRSA-negative swabs needed to predict the success of MRSA eradication therapy as measured with 36 individuals whose MRSA eradication therapy failed.

is not significantly associated with the success of MRSA eradication therapy; this finding may be realistic or may be related to the presence of too small numbers per category. To study the effect of age on outcome, we should perform a large prospective study with balanced age categories.

In conclusion, the present study suggests that with our MRSA eradication treatment policy, a large proportion of MRSA carriers successfully returned to MRSA noncarriage either by MRSA eradication therapy (81%) or by spontaneous MRSA clearance (18%).

Furthermore, we recommend that five or more complete follow-up culture sets be taken to ascertain the MRSA status of an individual. The application of this rule may be a step forward in reducing the spread of MRSA.

We thank all infection control practitioners for their diligent efforts to isolate MRSA-positive patients and health care workers and for their work during the follow-up period for individuals receiving MRSA eradication therapy.

All authors declare no conflict of interest.

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