STICHTING WERKGROEP ANTIBIOTICABELEID

Optimalization of the antibiotic policy in the Netherlands XI

Revision SWAB Guideline for the Treatment of MRSA Carriage

Dutch Working Party on Antibiotic Policy (SWAB), February 2012

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Changes in relation to the guideline dated March 2007 are indicated YELLOW.

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Introduction

The Dutch Working Party on Antibiotic Policy (SWAB) develops guidelines for the administration of antibiotics to hospitalized adults with the aim to optimize antibiotic policy and thus to contribute to the management of both costs and the development of resistance. The guidelines serve as a framework for the committees which formulate the antibiotic policy for each hospital.

Epidemiological data on the causative agent of a certain infection form an important starting point; the emphasis is on the principle that an antibiotic should only be prescribed when the correct indication is present.

Methicillin-resistant Staphylococcus aureus (MRSA) today is endemic in health care institutions almost everywhere in the world. In addition a strong increase in MRSA in the open population has been observed. Resistance percentages for invasive infections with *S. aureus* of 60% and more are now being observed in countries with a high prevalence.[1;2] MRSA infections are difficult to treat because only a limited arsenal of effective antibiotics remains. Moreover they are accompanied by an increase in morbidity and mortality. The mortality associated with MRSA bacteraemia has been estimated to be twice as high as that for a susceptible staphylococcus.[3] Furthermore the number of patients with invasive infections increases when MRSA is present.[4]

In the Netherlands the prevalence of MRSA is still exceptionally low despite the high prevalence in surrounding countries.[1;5;6] To keep the prevalence low a "Search and Destroy" (S&D) policy is followed. This means that there is an active search for MRSA. If MRSA is found, a policy consisting of transmission based precautions for colonized individuals is followed. The guidelines for detection in the microbiological laboratory were drawn up by the Dutch Society for Medical Microbiology (http://www.nvmm.nl). Measures to control the spread of MRSA within health care facilities are described in national guidelines drawn up by the Working party for Infection Control (http://www.wip.nl). The measures are for both patients and staff members in health care facilities.

This SWAB guideline concerns the treatment of MRSA carriage by both patients and health care workers. Effective treatment of MRSA carriage is an important pillar of the Dutch “search and destroy” policy. This guideline does not offer advice on infections with MRSA. For the treatment of MRSA infections one should consult an expert (medical

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microbiologist or a doctor of infectious diseases for children in combination with an internist or paediatrician).

Definition of MRSA carriage

The microbiological detection of MRSA depends on the one hand on the presence of the species S. aureus and on the other on the presence of the mec-A gene, which codes for the production of a modified penicillin-binding protein (PBP-2a). This PBP-2a has a decreased affinity for beta-lactam antibiotics so that this important group of antibiotics becomes inactive. Expression of the mec-A gene varies so that detection in the laboratory can be a problem. An individual whose skin, mucous membrane or foreign material contains MRSA is a carrier. This is independent of the localization on the body or the amount present.

Methods used to establish the guideline

This guideline was drawn up according to the so-called “evidence-based” principle. In addition to meta-analyses and guidelines collected via the Cochrane Library, relevant literature from the database Medline was consulted. Recommendations in the guideline were assigned a level of the strength of evidence according to the instructions drawn up by CBO (Table 1). In order to carry out a literature survey for this guideline, we focused on the following research question:

What is the best initial treatment of MRSA carriage?

The following search criteria were used for the literature survey: *Staphylococcus aureus*, methicillin (also searched without methicillin), MRSA, human, decolonization, decolonisation, eradication, elimination, treatment, clinical trial, and randomized controlled trial; period: up to and including January 2010.
Only articles with an abstract in Dutch or English were evaluated. In addition studies from the archives of *Staphylococcus aureus* investigators/experts in the Netherlands were selected.

The following studies were not included in the analysis: studies of beta-lactam antibiotics, studies of (experimental) drugs not available in the Netherlands, studies with a follow-up of less than one week, studies without a control group, and studies in which

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MRSA infections were treated but the presence of carriage was not determined. For situations in which there is no solid proof of the best way to eradicate MRSA, a temporary choice was made by those who drew up this guideline. According to the results of a Dutch cohort study conducted from October 2006 / October 2008 in which the effectiveness of the original guideline was evaluated, the guideline was further optimized.[7;8]

Consequences of carriage

Members of the staff of health care facilities

Staff members who are colonized with MRSA may not carry out patient-related activities. The motivation for this is the fact that they can infect patients and colleagues.[9-11] This is described in the guidelines of the WIP (http://www.wip.nl).

Patients

Patients who do not have an infection but are colonized with MRSA run an enhanced risk of developing an infection with MRSA. Investigation by Davis et al. showed that 19% of all patients who are colonized with MRSA at admission develop an infection with MRSA during hospitalization. For patients with a susceptible *S. aureus* this percentage was 1.5% and for those without *S. aureus* 2.0%.[12]

Patients who have an MRSA infection must be treated from a therapeutic standpoint. In such cases antibiotics may be necessary but this is certainly not always the case. For infections of the skin and soft tissues, surgical drainage and/or nettoyage often yields satisfactory results. The choice of antibiotics for the treatment of infections with MRSA demands specific expertise and must be carried out in consultation with a medical microbiologist, or an infectious disease specialist together with a paediatrician when it concerns a child. Carelessly chosen therapies can lead to treatment failure and the development of more extensive resistance. There is a British guideline for the treatment of MRSA infections.[13]

Healthy individuals outside of health care facilities

The greater risk of infection also applies for healthy individuals. For example, in a study of army recruits, an infection percentage of 38% was found for MRSA carriers whereas that for carriers of susceptible *S. aureus* was only 3%.[14] The increased morbidity in

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healthy individuals is partly due to the rapid increase in MRSA in the open population whereby specific virulence factors, such as Panton-Valentine leukocidin (PVL), are present in increased quantities.[15] How to handle MRSA carriers in the open population is described in an LCI handbook (http://www.rivm.nl/cib).

Treatment of MRSA carriage

Indications for treatment of MRSA carriage

The establishment of **indications** for the treatment of carriage depends on careful consideration of (1) the effects of MRSA carriage for the individual involved and those around him, (2) the chances and severity of side-effects of the treatment and (3) the estimated *a priori* chance of successful treatment in view of the characteristics of the *S. aureus* strain and the host.

For **staff members** of health care facilities an active policy to eradicate carriage is pursued as part of the S&D strategy. An important reason for this is the fact that the individual involved may not work due to the risk of contamination as long as MRSA carriage is present (see WIP guideline). In addition for healthy individuals (uncomplicated MRSA carrier, see below), the chance of successful treatment with a relatively safe drug is substantial.

For **healthy individuals** outside of the hospital, initiation of treatment for carriage should be approached with reservations. If the risk of infections with MRSA is present, treatment for carriage is recommended. Another indication could be when a (family) contact of the carrier works in a health care facility or is a patient. If the chance of recolonization of the MRSA carrier via external sources is pronounced, then treatment of carriage is rarely or never indicated. An example of this is a pig farmer who has acquired MRSA via his live stock.

For **patients** the fact that there are often risk factors for failure of therapy plays an important role (complicated MRSA carrier, see below). Such risk factors are skin lesions, presence of foreign materials, carriage at multiple sites on the body and antimicrobial therapy directed against other causative agents than MRSA.

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On the other hand the consideration must include the risk of the development of an infection with MRSA and the risk of spread to other patients. As long as carriage exists, the patient must be nursed in strict isolation; extensive measures apply for visits to outpatient clinics and so on, as described in the WIP guideline.
Without treatment carriage can be quite prolonged. In various observational studies among colonized patients half-life times of 8 to 40 months were found.[16-20] As mentioned previously, risk factors for persistent carriage include the presence of skin lesions and foreign materials. In addition, the presence of MRSA on multiple sites on the body is associated with persistent carriage which complicates treatment of MRSA carriage.[8;21] In this guideline therefore a distinction is made between uncomplicated and complicated MRSA carriage.

The patient has **uncomplicated MRSA carriage** when the criteria below are met:

- Individual without active infection with MRSA **and**
- MRSA is sensitive *in vitro* to the antibiotic to be prescribed **and**
- There are no active skin lesions **and**
- There is no foreign material that forms a connection between the internal environment and the external environment (for example urine catheter, external fixation) **and**
- Carriage is exclusively localized in the nose.

The patient has **complicated MRSA carriage** when at least one of the criteria below is met:

- Carriage is located in throat, perineum or skin lesions, independent of nasal carriage **and/or**
- There are active skin lesions and/or there is foreign material that forms a connection between the internal environment and the external environment **and/or**
- MRSA is *in vitro* resistant to mupirocin **and/or**
- Previous treatments according to the recommendations for uncomplicated carriage have failed.

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Literature analysis of treatment of carriage

(See also “selected studies” in the appendix)

For the literature survey 23 clinical studies were selected (see appendix)[22-44] plus one Cochrane review,[45] three international guidelines,[13;46;47] three national related guidelines (WIP, LCI and NVMM) and two reviews.[48;49] The Cochrane review concerns only studies in which MRSA eradication was investigated. The authors concluded on the basis of six selected studies that there is no proof that local or systemic therapy is effective for MRSA eradication. However, according to our opinion, it is worthwhile to analyze studies in which methicillin-susceptible *S. aureus* (MSSA) eradication by means of antibiotics other than beta-lactam antibiotics is investigated.

The 23 selected studies are summarized in Table 2. The average number of participants per study was 80. All included studies were randomized and more than half were blinded (n = 13). The populations studied vary: hospital staff (n = 6), hospital patients (n = 8), healthy volunteers (n = 5), nursing home patients (n = 2) and staff plus patients (n = 2). Within the selected studies MSSA (n = 12), MRSA (n = 9) and both (n = 2) were studied.

A variety of interventions was studied, both systemic (oral administration) and local. The local interventions studied were: mupirocin nasal ointment, bacitracin nasal ointment, fusidic acid nasal ointment, tea tree oil, oral vancomycin, and hygienic measures. The systemic interventions included macrolides, doxycycline, cotrimoxazole, chinolons, fusidic acid, rifampicin, and bacitracin. Often combinations of the above-mentioned drugs were used with an average duration of treatment of seven days (range 5-14 days). Mupirocin nasal ointment was investigated in the majority (14) of the studies.

In the selected studies there is no standardization with respect to culture methods used, body sites sampled, duration of follow-up period and/or typing in order to determine whether there really was treatment failure. In 12 studies only the nose was sampled for cultures. However, most carriers have MRSA at more than one site. In studies in which cultures were taken from more than one site, the effectiveness of the intervention investigated was lower than in studies of cultures only from the nose. In addition the effectiveness of the intervention studied is lower when follow-up is longer.

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Of the 14 studies which focused on mupirocin, seven studies were for MRSA. In eight studies only nasal cultures were taken during follow-up. From these studies one can conclude that 73% and 47% become *S. aureus*-free (nasal and extra nasal, respectively) versus 25% and 31% in the control group. Other topical remedies investigated are tea tree oil, oral vancomycin and bacitracin (with or without rifampicin). Oral vancomycin and bacitracin with or without rifampicin are not effective in eradicating carriage. Tea tree oil can probably be quite useful in the treatment of carriage but this therapy needs to be investigated in more detail.

Of the systemic therapies studied, most experience has been acquired with cotrimoxazole in combination with rifampicin or fusidic acid (three studies) and macrolide antibiotics (three studies). There us one study that compares combination treatment of doxycyclin, rifampicin and topical treatment to no treatment.[44] There are not enough data on the effectiveness of the chinolons. Combination therapy with cotrimoxazole yields eradication in half of the carriers. They were all MRSA carriers and multiple relevant sites were cultured during follow-up. Combination therapy with doxycyclin shows eradication in 74% of carriers, with multiple relevant sites cultured. Various types of macrolides were investigated, with claritromycin as the most effective drug. However this claritomycin study was not set up primarily to answer our research question. Systemic monotherapy is not recommended, especially not with fusidic acid or rifampicin because then one sees a very easy and rapid development of resistance.
The studies that focus on fusidic acid and rifampicin monotherapy will not be discussed further here. A study of the effect on the development of recurrent infections with S. aureus in carriers consisted of prolonged low-dose clindamycin (150 mg 1x daily for 3 months).[50] No development of resistance was observed and there was a marked decrease in the number of recurrences. The effect on carriage is not known.

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Recommendations

The recommendations for the treatment of MRSA carriage, together with the level of the strength of evidence, are presented below (Table 1). The recommendations differ for complicated and uncomplicated MRSA carriage (see also above).

Uncomplicated carriage

Recommendations:

Level 1	Mupirocin nasal ointment three times daily for five days
Level 3	During treatment skin and hair must be washed daily with a disinfecting soap (Chlorhexidine soap in a 40 mg/ml solution or beta dine shampoo 75 mg/ml), preferably in the shower (not the bathtub).
Level 4	Daily clean underwear, clean clothing, clean washcloth and towels. On days 1, 2 and 5 of the cure, put clean bedclothes on the bed. When the patient goes to bed at night, he must wear clean underwear or pyjamas during treatment.
Level 3	Find out whether there is a reservoir in the home environment (human or animal).
Level 3	If a reservoir is found in the home environment, it must be treated simultaneously.

Note: A recent study by Mollema et al. shows that MRSA transmission occurs in about half of the cases from an index person to housemates.[51] The study by Ammerlaan et al. shows that carriage among household members is associated with treatment failure in 66 of 162 cases where carriage has been demonstrated (adjusted OR of 2.9 (1.1-8.1)).[7;8] The advice to the treating physician is to evaluate the household in advance of the first treatment (through cultivating nose, throat, perineum and, if necessary, skin lesions of housemates). The household (housemates) can be defined as persons who remain in the same house, day and night, as the index person, and commonly use the same bedroom, bathroom, living room and/or kitchen. If a roommate is found to be a MRSA carrier, one will need to assess whether he/she is an (un)complicated carrier, so that he/she can be treated simultaneously as such.

When treatment fails, one speaks of complicated MRSA carriage (see below).

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Complicated carriage

Recommendations:

Level 4	If active skin lesions are present, treat them first – if necessary in consultation with a dermatologist.

If, at end of this treatment, it turns out to be (un)complicated carriage, then treatment as described over there can be initiated.

Level 4	If foreign material forms a connection between the internal environment and the external environment, it is preferable to wait until it can be removed.

In the event of osteosynthetic material and a closed wound, carriage can be treated, but when the material is removed, isolation measures and control cultures must be taken once again.
If, after removal of the foreign material, it turns out to be (un)complicated carriage, then treatment as described over there can be initiated.

Treatment of complicated carriage of a mupirocin-susceptible MRSA

Level 3	Systemic treatment for at least seven days with a combination of 2 drugs as listed in Table 3. The choice is determined primarily by the *in vitro* sensitivity of the cultured MRSA. In principle, oral treatment is preferred.

Systemic treatment is combined with:

Level 1	Mupirocin nasal ointment 3 times daily for five days
Level 3	During treatment skin and hair must be washed daily with a disinfecting soap (chlorhexidine soap in a 40mg/ml solution or beta dine shampoo 75 mg/ml), preferably in the shower (not the bathtub).
Level 4	Daily clean underwear, clean clothing and clean towels. On days one, two and five of the cure put clean bedclothes on the bed. Before

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	going to bed, during treatment, the patient must also put on clean underwear and/or pyjamas.
Level 3	Treat infected household members simultaneously. If they are considered uncomplicated carriers, they can be treated as described above and systemic drugs need not be administered.
Level 3	In the presence of wounds, treatment of carriage is delayed until the wound has healed, unless there are reasons for not delaying treatment. Local administration of mupirocin to the wound is not recommended because of the risk of the development of resistance.
Level 4	The use of disinfectants is preferred, possibly in combination with systemic antibiotic therapy.
Level 3	In the presence of intestinal or rectal carriage, experience with oral administration of aminoglycosides and glycopeptides is limited. Because of the risk of development of resistance against these important therapeutic drugs, this is not recommended.

When treatment fails, referral to a centre with specific expertise is recommended.

Treatment of complicated carriage of an (intermediate) mupirocin-resistant MRSA

Mupirocin sensitivity is determined for every individual colonized by MRSA and again after failure of treatment with mupirocin. Assessment takes place preferably by means of E-tests. There are MRSA strains with a decreased sensitivity for mupirocin (low-level or intermediate resistance) at a minimal inhibiting concentration (MIC) of 4-256 µg ml -1 and high-level resistance with MIC ≥512 µg ml -1. A patient with an (intermediate) mupirocin-resistant MRSA should be referred to a centre with specific expertise.

Control cultures

Control cultures are taken and further handled according to the guidelines of the Dutch Society for Medical Microbiology (http://www.nvmm.nl). The first cultures for evaluation of the effectiveness of the treatment are taken at least 48 hours after termination of the treatment. The frequency of subsequent cultures is amongst others dependent on the results for the individual involved. In the guidelines of the WIP, these results are described (http://www.wip.nl/).

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Table 1. CBO classification of literature and conclusions

Classification of the proof according to the strength of the evidence

	For publications on intervention
A1	Systematic reviews of at least several studies on the A2 level, whereby the results of the separate studies are consistent.
A2	Randomized comparative clinical investigation of good quality, sufficient size and consistent results.
B	Randomized clinical trials of moderate quality or insufficient size or other comparative study (not randomized, comparative cohort study, patient control study).
C	Non-comparative study.
D	Opinion of experts, for example members of the study group.

Level of evidence of the conclusions

1	At least 1 systematic review (A1) or 2 independently performed investigations at level A2.
2	At least 2 independently performed investigations at level B.
3	At least 1 investigation of level A2, B or C.
4	Opinion of an expert, for example a member of the study group.

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Table 2. Summary selected studies

Ref	Year	Study design	Patient population	Sample size	Treatment per studygroup	Duration of treatment (days)	Duration of follow up (days)	Culture sites	% Eradication Week 1 after treatment[a]	% Eradication End of follow up[a]
[40]	1977	DB-RCT	HV	77 MSSA	1. josamycin[b]	7	28	N	55	36
					2. erythromycin[b]	7			54	8
					3. placebo[b]	7			0	0
[41]	1979	DB-RCT	HV	87 MSSA	1. rosamycin[b]	7	28	N	43	23
					2. erythromycin[b]	7			74	22
					3. placebo[b]	7			7	7
[35]	1984	O-RCT	HCW	59 MSSA	1. rifampicin[b]	5	28	N	86	64
					2. bacitracin[c]	10			13	13
					3. bacitracin[c]/rifampicin[b]	10-5			58	75
					4. no treatment	0			12	12
[23]	1986	DB-RCT	HV	33 MSSA	1. mupirocin[c]	5	28	N	100	81
					2. placebo[c]	5			0	0
[38]	1986	O-RCT	Hemodialysis Outpts	60 MSSA	1. bacitracin[c]/rifampicin[b]	5	90	N	NA	67
					2. no treatment	5			NA	27
[22d]	1989	DB-RCT	HCW	69 MSSA	1. mupirocin[c]	5/3	365/28	N	96	83
					2. placebo[c]	5/3			0	43
[34]	1990	SB-RCT	Hosp pts	21 MRSA	1. ciprofloxacin[b]/rifampicin[b]	14	180	N G W	70	27
					2. co-trimoxazole[b]/rifampicin[b]	14			67	40
[24]	1993	DB-RCT	HCW	322 MSSA, 17 MRSA	1. mupirocin[c]	5	28	N	91	67
					2. placebo[c]	5			6	1
[29]	1993	O-RCT	HV	66 MSSA	1. mupirocin[c]/chlorhexidin[e]	7	91	N G S	95	57

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					2. chlorhexidin neomycin[c]/chlorhexidin[e]	7				11
[37]	1993	DB-RCT	HCW & Pts	94 MRSA	1. novamycin[b]/rifampicin[b]	7	14	N G W Sp	NA	67
					2. co-trimoxazole[b]/rifampicin[b]	7				53
[36]	1994	O-RCT	LTCF	35 MRSA	1. rifampicin[b]	5	90	N U W	60	67
					2. minocyclin[b]	5			13	38
					3. minocyclin[b]/rifampicin[b]	5			70	50
					4. no treatment	0			14	14
[25]	1994	DB-RCT	HCW	68 MSSA	1. mupirocin[c]	5	180	N S	NA	50
					2. placebo[c]	5				26
[27]	1995	DB-RCT	HCW	61 MSSA, 1 MRSA	1. mupirocin[c]	5	180	N	87	52
					2. placebo[c]	5			9	6
[32]	1995	O-RCT	HCW & Hosp pts	84 MRSA	1. mupirocin[c]/chlorhexidin[e]	5	28	N	100	96
					2. fusidic acid[c]/co-trimoxazole[b]/chlorhexidin[e]	5			100	95
[28]	1999	DB-RCT	Hosp pts	98 MRSA	1. mupirocin[c]/chlorhexidin[e]	5	26	N G U W	NA	25
					2. placebo[c]/chlorhexidin[e]	5				18
[30]	1999	DB-RCT	HIV Outpts	76 MSSA	1. mupirocin[c]	5	70	N	89	43
					2. placebo[c]	5			8	31
[33]	1999	SB-RCT	HCW	34 MSSA, 3 MRSA	1. mupirocin[c]	5	30	N	94	80
					2. bacitracin[c]	5			44	23
[42]	2000	O-RCT	Hosp pts (ICU)	16 MRSA	1. fusidic acid[b]	7	28	N T W Sp	50	40
					2. no treatment	0			0	30
[31]	2003	DB-RCT	LTCF	64 MSSA, 63 MRSA	1. mupirocin[c]	14	16	N W	93	88
					2. placebo[c]	14			15	18
[39]	2004	DB-RCT	Hosp pts	95 MSSA	1. clarithromycin[b]	14	56	N T	NA	88
					2. placebo[b]	14				7
[26]	2004	O-RCT	Hosp pts	224 MRSA	1. mupirocin[c]/chlorhexidin[e]	5	14	N T G S W	NA	49
					2. tea tree oil[c]/tea tree oil[e]	5				42

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[44]	2007	O-RCT	Hosp pts	146 MRSA	1. mupirocin[c]/rifampicin[b]/doxycyclin[b]/chlorhexidin[e]	7	90	N G W D	NA	74
					2. no treatment	0				32
[43]	2007	Cluster-DB-RCT	Healthy soldiers	134 CA-MRSA	1. mupirocin[c]	5	56	N	NA	88
					2. placebo[c]	5				65

Note: Ref – Reference number, MSSA – methicillin susceptible *Staphylococcus aureus*, MRSA – methicillin resistant *Staphylococcus aureus*, DB-RCT – double blind randomized controlled trial, SB-RCT – single blind randomized controlled trial, O-RCT – open randomized controlled trial, CT – controlled trial, HV – healthy volunteers, HCW – health care workers, Outpts – outpatients, Hosp pts – hospitalized patients, pts – patients, LTCF – long term care facility, HIV – human immunodeficiency virus, ICU – intensive care unit, N – nose, G – groin, W – wounds, T – throat, Sp – sputum, S – skin, U – urine, D – device exit site, NA – data not available, CA – community acquired. [a] Number of persons successfully decolonized is with exclusion of re-colonization with another strain. Recolonization with another strain is defined as failure of treatment. [b] Oral tablets. [c] Nasal ointment. [d] During the first halve of the study, included persons were treated for five days with a follow up of 365 days. During the second halve of study, persons were treated for three days with a follow up of 28 days. [e] Body washing.

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Table 3. Oral combination therapy for the treatment of MRSA carriage

Richtlijn	**Antibiotic 1**	**Antibiotic 2**
Recommended	Doxycyclin 200 mg 1 x daily **or** Trimethoprim 200 mg 2 x daily	Rifampicin 600 mg 2 x daily
Alternative[1]	Clindamycin 600 mg 3 x daily **or** Clarithromycin 500 mg 2 x daily **or** Ciprofloxacin 750 mg 2 x daily **or** Fusidic Acid 500 mg 3 x daily	Fusidic Acid 500 mg 3 x daily

All treatments are preferably oral. The dosage given is the recommended dosage for an adult weighing about 70 kg. Combination therapy is preferred because of a better efficacy and a lower risk of acquisition of resistance. [1]Alternative options should only be used if a contraindication exists (e.g. *in vitro* resistance, intolerance) for the recommended options.

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Appendix

SELECTED STUDIES

Mupirocin

Authors:	Bulanda M, Gruszka M, Heczko B.
Title:	Effect of mupirocin on nasal carriage of Staphylococcus aureau
Source:	J. Hosp Infect 1989; 14(2):117-24.
Type:	Randomized, placebo-controlled, double-blind
Participants:	Polish hospital staff, S. aureus nasal carriage (n = 69)
Intervention:	A: mupirocin, 3x daily, 3-5 days (n=
	B: placebo: 3x daily, 3-5 days
Culture:	nose
Follow-up:	4 days, 2 weeks, l month, 3 months, 6 months, 1 year (drop outs)
Results:	A: 60% nasal SA-free after 2 weeks
	B: 85% nasal SA-free after 2 weeks
Note:	MSSA

Authors:	Casewell MW, Hill RL
Title:	Elimination of nasal carriage of Staphylococcus aureus with mupirocin ('pseudomonic acid') – a controlled trial
Source:	J Antimicrob Chemother 1986; 17(3):365-72
Type:	Controlled study
Participants:	English, healthy volunteers; S. aureus carriage MSSA (n=32)
Intervention:	A: nasal mupirocin, 4x daily for 5 days (n=15)
	B: nasal placebo, 4x daily for 5 days (n=17)
Culture:	nose
Follow-up:	2-5 weeks
Results:	A: 90% nasal SA-free after 3 weeks
	B: 0% nasal SA-free
Note:	Only nose, allocation not clear, analysis not clear

Authors:	Doebbeling BN, Reagan DR, Pfaller MA, Houston AK, Hollis RJ, Wenzel RP.

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Title:	Long-term efficacy of intranasal mupirocin ointment. A prospective cohort study of Staphylococcus aureus carriage.
Source:	Arch Intern Med 1994; 154(13):1505-8
Type:	Randomized, placebo-controlled, blind
Participants:	USA, hospital staff, S. aureus nasal carriage (MSSA) (n=68)
Intervention:	A: nasal mupirocin 2x daily for 5 days B: nasal placebo 2x daily for 5 days
Cultures:	Nose, hand
Follow-up:	6 and 12 months
Results:	A: 52% nasal SA-free at 6 months (less hand carriage), 47% at 1 year (no difference more in hand carriage) B: 28% nasal SA-free at 6 months (no difference in hand carriage), 24% at 1 year (no difference in hand carriage).
Note:	MSSA. 87% nose-hand type identical. Baseline: significantly more hand carriers in placebo group. 34% recolonization with new strain at 1 year. See also Doebbeling J Chemother 1994

Authors:	Doebbeling NB, Freeman DL, Kneu HCA, et al.
Title:	Elimination of Staphylococcus aureus nasal carriage in health care workers: analysis of six clinical trials with calcium mupirocin ointment. The Mupirocin Collaborative Study Group.
Source:	Clin Infect Dis 1993; 17(3):466-74.
Type:	Randomized, placebo-controlled,? blind?
Participants:	USA, hospital staff (n=339)
Intervention	A: mupirocin, 2x daily for 5 days (n=170) B: nasal placebo 2x daily for 5 days (n=169)
Culture:	nose
Follow-up:	1-4 weeks
Result:	A: 82% nasal SA-free at week 4 B: 12% nasal SA-free at week 4
Note:	Only nose. 2/6 studies published (Reagan 1991, Scully 1992). Mainly MSSA

Authors:	Dryden MS, Dailly S, Crouch M.

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Title:	A randomized controlled trial of tea tree topical preparations versus a standard topical regimen for the clearance of MRSA colonization.
Source:	J Hosp Infect 2004; 56(4):283-6
Type:	randomized, controlled study, open label
Participants:	English hospitalized patients, MRSA carriers (n=224)
Intervention:	A: nasal mupirocin 3x daily + chlorhexidine for 5 days, silver sulfadiazine 1x daily for 5 days (wound) (n=114) B: 10% tea tree nasal cream 3 x daily for 5 days, 5% tea tree body wash for 5 days, 10% tea tree cream for wounds for 5 days (n=110)
Culture:	nose, throat, armpit, perineum, wounds
Follow-up:	2 and 14 days after end of cure
Results:	A: 49% MRSA-free all sites, 78% nose-free B: 41% MRSA-free all sites, 47% nose-free
Note:	Therapy compliance not measured (therefore real life)

Authors:	Ellis MW, Griffith ME, Dooley DP, et al.
Title:	Targeted intranasal mupirocin to prevent colonization and infection by community-associated methicillin-resistant *Staphylococcus aureus* strains in soldiers: a cluster randomized controlled trial.
Source:	Antimicrob Agents Chemother 2007;51:3591-8.
Type:	Cluster-randomized controlled study, double blind
Participants:	US, healthy soldiers, CA-MRSA carriers (n=134)
Intervention:	A: mupirocine nasal ointment 3 x daily for 5 days (n=64) B: placebo nasal ointment 3 x daily for 5 days (n=62)
Culture:	nose
Follow up:	56 days after end of cure
Results:	A: 88% nose-free B: 65% nose-free
Note:	

Authors:	Fernandez C, Gaspar C, Torrellas A, et al.
Title:	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.

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Source:	J Antimicrob Chemother 1995; 35(3):399-408.
Type:	Randomized, placebo-controlled, blind
Participants:	Spanish, hospital staff, S. aureus nasal carriage (MSSA)(n=68)
Intervention:	A: nasal mupirocin, 2x daily for 5 days (n=34)
	B: nasal placebo, 2x daily for 5 days (n=34)
Culture:	nose
Follow-up:	1-5 weeks, 2-6 months
Result:	A: 57% nasal SA-free at 1 month
	B: 9.4% nasal SA-free at ??
Note:	Only nose, 32% recolonization with same strain

Authors:	Harbarth S, Dharan S, Liassine N, Herrault P, Auckenthaler R, Pittet D.
Title:	Randomized, placebo-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant *Staphylococcus aureus.*
Source:	Antimicrob Agents Chemother 1999; 43(6):1412-6
Type:	Swiss, randomized placebo-controlled, double-blind
Participants:	hospitalized patients (>16 yrs), MSRA carriage somewhere (n=98)
Intervention:	A: mupirocin 2x daily for 5 days + chlorhexidine (n=48)
	B: placebo 2x daily for 5 days + chlorhexidine (n=50)
Culture:	nose, perineum, urine (catheter), lesions
Follow-up:	12, 19, 26 days
Results:	A: 25% MRSA-free at all sites together, 44% nasal free
	B: 18% MRSA-free all sites together, 23% nasal free
Note:	MRSA marginally effective when multiple body sites are colonized. Endemic but not epidemic setting. Usually 2 sites colonized: nose 58%, perineum 38%, skin 48%, and urine 20%. Failure due, among others, to mupirocin-resistance. Little exogenous recolonization.

Authors:	Leigh DA, Joy G.
Title:	Treatment of familial staphylococcal infection – comparison of mupirocin nasal ointment and chlorhexidine/neomycin (Naseptin) cream in eradication of nasal carriage.
Source:	J Antimicrob Chemother 1993; 31(6):909-17

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Type:	controlled study
Participants:	UK, families with staphylococcal infections (18 families, n=66)
Intervention:	A: nasal mupirocin, 7 days (n=32)
	B: chlorhexidine/nasal neomycin (Naseptin), 7 days (n=34)
Culture:	nose, armpit, perineum
Follow-up:	1 week, 2 weeks, 4 weeks, 13 weeks
Results:	A: 65% SA-free all sites together
	B: 17% SA-free all sites together
Note:	MSSA, allocation/blind not clear

Authors:	Martin JN, Perdreau-Remington F, Kartalija M, et al.
Title:	A randomized clinical trial of mupirocin in the eradication of *Staphylococcus aureus* nasal carriage in human immunodeficiency virus disease.
Source:	J Infect Dis 1999; 180(3):896-9
Type:	randomized, placebo-controlled
Participants:	USA, HIV patients, S. aureus nasal carriage (MSSA) (n=76)
Intervention:	A: nasal mupirocin 2x daily for 5 days
	B: nasal placebo, 2x daily for 5 days
Culture:	nose
Follow-up:	1, 2, 6, 10 weeks
Results:	A: 29% nasal SA-free at 10 weeks
	B: 3% nasal SA-free
Note:	MSSA, only nose. 84% recolonization with former strain

Authors:	Mody, L, Kauffman CA, McNeil SA, Garlicky AT, Bradley SF.
Title:	Mupirocin-based decolonization of Staphylococcus aueus carriers in residents of 2 long term care facilities: a randomized, double-blind, placebo-controlled trial.
Source:	Clin Infect Dis 2003; 37(11):1467-74
Type:	Randomized, placebo-controlled, blind
Participants:	USA, nursing home patients, S. aureus nasal carriage (MSSA and MSRA) (n=127)
Intervention:	A: nasal mupirocin 2x daily for 14 days (n=64)

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	B: nasal placebo 2x daily for 14 days (n=63).
Culture:	nasal wound
Follow-up:	2 weeks after end of cure
Results:	A: 88% nasal SA-free
	B: 13% nasal SA-free
Note:	Many with MRSA; 86 % recolonization with former strain

Authors:	Parras F, Guerrero MC, Bouza E, et al.
Title:	Comparative study of mupirocin and oral co-trimoxazole plus topical fusidic acid in eradication of nasal carriage of methicillin-resistant *Staphylococcus aureus.*
Source:	Antimicrob Agents Chemother 1995; 39(1):175-9
Type:	randomized, controlled, open label
Participants:	Spanish, hospitalized patients and hospital staff, MRSA nasal carriage (n=)
Intervention:	A: nasal mupirocin, 3x daily for 5 days + chlorhexidine
	B: nasal fusidic acid 3x daily, co-trimoxazole 960 mg 2x daily for 5 days + chlorhexidine
Culture:	nose, armpit, perineum
Follow-up:	1, 2, 3, 4, 13 weeks
Results:	A: 97% nasal MRSA-free at 2 weeks, 83% extra nasal MRSA-free
	B: 94% nasal MRSA-free at 2 weeks, 76% extra nasal MRSA-free
Note:	Baseline: significantly more extra nasal carriage in group B.

Authors:	Soto NE, Vaghjimal A, Stahl-Avicolli A, Protic JR, Lutwick LI, Chapnick EK.
Title:	Bacitracin versus mupirocin for Staphylococcus aureus nasal colonization.
Source:	Infect Control Hosp Epidemiol 1999; 20(5):351-3.
Type:	randomized, controlled
Participants:	USA, hospital staff, SA nasal carriage (MSSA and MSRA) (n=35)
Intervention:	A: nasal mupirocin, 5 days (n=16)
	B: nasal bacitracin, 5 days (n=19)
Culture:	nose

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Follow-up:	4 days, 1 month
Results:	A: 80% nasal SA-free at 1 month
	B: 23% nasal SA-free at 1 month
Note:	8% MRSA

Chinolons

Authors:	Peterson LR, Quick JN, Jensen B, et al.
Title:	Emergence of ciprofloxacin resistance in nosocomial methicillin-resistant *Staphylococcus aureus* isolates. Resistance during ciprofloxacin plus rifampin therapy for methicillin-resistant *S. aureus* colonization.
Source:	Arch Intern Med 1990; 150(10):2151-5
Type:	randomized, controlled, blind
Participants:	patients, MRSA-positive (n=21)
Intervention:	A: ciprofloxacin 750 mg po 2x daily + rifampicin 300 mg 2x daily for 14 days (n=11)
	B: cotrimoxazole 960 mg 2x daily + rifampicin 300 mg 2x daily po for 14 days, (n=10)
Culture:	nose, rectum lesions
Follow-up:	1 wk, 2-3 wk, 3 m and 6 m.
Results:	A: 37% MRSA-free at all sites at 2-3 weeks, 40% at 6 months
	B: 50% MRSA-free at all sites at 2-3 weeks, 27% at 6 months
Note:	Trial terminated prematurely due to cipro resistance (clonal), 36% also rifampin resistant.

Rifampicin

Authors:	McAnally TP, Lewis MR, Brown DR.
Title:	Effect of rifampin and bacitracin on nasal carriers of *Staphylococcus aureus.*
Source:	Antimicrob Agents Chemother 1984; 25(4):422-6
Type:	randomized, controlled
Participants:	hospital staff, S. aureus nasal carriage (MSSA) (n=59)
Intervention:	A: rifampicin 600 mg for 5 days (n=14)
	B: nasal bacitracin 3x daily for 10 days (n=16)
	C: combination therapy (n=12)

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	D: no therapy (n=17)
Culture:	nose
Follow-up:	2w, 4w
Results:	A: 57% nasal SA-free at 4 weeks
	B: 13% nasal SA-free
	C: 42% nasal SA-free
	D: 12% nasal SA-free
Note:	only nose

Authors:	Muder RR, Boldin M, Brennen C, et al.
Title:	A controlled trial of rifampicin, minocycline and rifampicin plus minocycline for eradication of methicillin-resistant *Staphylococcus aureus* in long-term care patients.
Source:	J Antimicrob Chemother 1994; 34(1):189-90
Type:	randomized, controlled study, open label
Participants:	MRSA-positive nursing home patients (n=35)
Intervention:	A: rifampicin 600 mg 2x daily po for 5 days (n=10)
	B: minocycline 100 mg 2x daily po for 5 days (n=8)
	C: rifampicin 600 mg 2x daily + minocycline 100 mg 2x daily (n=10)
	D: no treatment (n=7)
Culture:	nose, lesions, urine (catheter)
Follow-up:	1 w, 1 m, 3m
Results:	A: 70% MRSA-free at 1 month
	B: 12% MRSA-free
	C: 60% MRSA-free
	D: 0% MRSA-free
Note:	Small groups; marked development of resistance to both drugs (also in combination therapy).

Authors:	Simor AE, Phillips E, McGeer A, et al.
Title:	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.

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Source:	Clin Infect Dis 2007;44:178-85
Type:	Randomized, controlled, open label
Participants:	USA, patients with MRSA (n=146)
Intervention:	A: mupirocin/rifampicin/doxycyclin/chlorhexidin, 7 days
	B: no treatment
Culture:	nose, groin, wound, catheter site
Follow up:	90 d
Results:	A: 88% MRSA-free
	B: 65% MRSA-free
Note:	

Authors:	Walsh TJ, Standiford HC, Reboli AC, et al.
Title:	Randomized double-blind 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.
Source:	Antimicrob Agents Chemother 1993; 37(6):1334-42
Type:	randomized, controlled, blind
Participants:	USA, patients and hospital staff with MRSA (n=126)
Intervention:	A: novobiocin 500 mg po 2x daily + rifampicin 300 mg po 2x daily for 7 days
	B: cotrimoxazole 960 mg po 2x daily + rifampicin 300 mg po 2x daily for 7 days.
Culture:	nose, wounds, sputum
Follow-up:	14 days
Results:	A: 67% MRSA-free all sites together, 74% nose, 80 % rectum
	B: 53% MRSA-free all sites together, 68% nose, 67% rectum
Note:	none

Authors:	Yu VL, Goetz A, Wagener M, Smith PB, Rihs JD, Hanchett J, Zuravleff JJ.
Title:	Staphylococcus aureus nasal carriage and infection in patients on haemodialysis. Efficacy of antibiotic prophylaxis.
Source:	N Eng J Med 1986;315(2):91-6

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Type:	randomized, controlled, open label
Participants:	haemodialysis patients, S. aureus nasal carriage (MSSA) (n=60)
Intervention:	A: vancomycin 500 mg/week for 2 weeks (n=13)
	B: bacitracin 3x daily for 7 days (n=7)
	C: bacitracin + rifampicin 600 mg po 2x daily (n=22)
	D: no therapy (n=26)
Culture:	nose
Follow-up:	1w, 1m, 3m
Results:	A: 24% nasal SA-free at 1 month, 10% at 3 months
	B: 15% nasal SA-free at 1 month, 30% at 3 months
	C: 75% nasal SA-free at 1 month, 40% at 3 months
Note:	Only nose; rifampicin resistance – also together with bacitracin.

Macrolide

Authors:	Berg HF, Tjhie JH, Scheffer GJ, et al.
Title:	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.
Source:	Antimicrob Agents Chemother 2004; 48(11):4183-8
Type:	randomized, placebo-controlled, blind
Participants:	Dutch, heart patients with S aureus in the nose (MSSA) (n=95)
Intervention:	A: slow-release claritromycin 1x 500 mg po daily until surgery (n=49)
	B: placebo until surgery (n=46)
Culture:	nose, throat
Follow-up:	8 weeks
Results:	A: 88% nasal SA-free at 8 weeks
	B: 7% nasal SA-free at 8 weeks
Note:	only nose; length of cure not clear, monotherapy, considerable macrolide resistance after cure

Authors:	Wilson SZ, Martin RR, Putman M.
Title:	In vivo effects of josamycin, erythromycin and placebo therapy on nasal carriage of *Staphylococcus aureus*

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Source:	Antimicrob Agents Chemother 1977; 11(3):407-10
Type:	randomized, controlled, blind
Participants:	USA, volunteers, Nasal carriage S. aureus, (MSSA) (n=73)
Intervention:	A: josamycin 350 mg 4x daily for 7 days (n = 22)
	B: erythromycin 250 mg 4x daily for 7 days (n=26)
	C: placebo 4x daily for 7 days (n=25)
Culture:	nose
Follow-up:	1d, 9d, 30 d
Results:	A: 60% nasal SA-free at 9 days
	B: 35% nasal SA-free at 9 days
	C: 0% nasal SA-free
Note:	only nose, considerable recolonization after 30 days

Authors:	Wilson SZ, Martin RR, Putman M, Greenberg SB, Wallace RJ. Jr., Jemsek JG.
Title:	Quantitative nasal cultures from carriers of *Staphylococcus aureus*: effects of oral therapy with erythromycin, rosamicin and placebo.
Source:	Antimicrob Agents Chemother 1979;15(3):379-83
Type:	randomized, controlled, blind
Participants:	volunteers, nasal carriage S. aureus (n=87)
Intervention:	A: erythromycin, 250 mg 4 x daily po for 7 days
	B: rosamicin, 250 mg 4x daily po for 7 days
	C: placebo, 4x daily for 7 days
Culture:	nose
Follow-up:	1d, 4w
Results:	A: 22% nasal SA-free
	B: 23% nasal SA-free
	C: 7% nasal SA-free
Note:	only nose, monotherapy

Fusidic acid

Authors:	Chang SC, Hsieh SM, Chen ML, Sheng WH, Chen YC.

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Title:	Oral fusidic acid fails to eradicate methicillin-resistant *Staphylococcus aureus* colonization and results in emergence of fusidic acid-resistant strains.
Source:	Diagn Microbiol Inf Dis 2000; 36:131-6
Type:	randomized, controlled, blind
Participants:	Taiwan, IC patients, MRSA carriage (n=16)
Intervention:	A: fusidic acid 500mg 3x daily po for 7 days (n=6)
	B: no therapy (n=10)
Culture:	nose, sputum, throat, armpit, groin, skin lesions
Follow-up:	1, 2, 7, 8 weeks
Results:	A: 17% MRSA-free
	B: 50% MRSA-free
Note:	monotherapy, study prematurely discontinued due to development of resistance. Reason for difference in size of groups not clear.

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