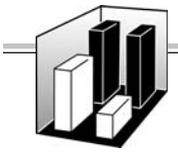
CLINICAL TRIALS REPORT



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Decontamination Strategies for MRSA-Colonized Patients

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:**178–185.

Rating: • Of importance.

Introduction: The first step in the pathogenesis of most skin and soft tissue infections is the colonization of the host by a potential pathogen or pathogens. *Staphylococcus aureus* has long been an important pathogen, but the dissemination of community-associated methicillin-resistant *S. aureus* (MRSA) over the past decade, superimposed on the gradually increasing carriage rates of hospital-associated MRSA, have made beta-lactam–resistant *S. aureus* isolates the dominant etiology of skin and soft tissue infections in many locations across the United States [1]. The costs of established MRSA infection with regard to prolonged hospital stay, increased mortality, and increased expense have been widely reported [2], and it is only natural that growing attention has been focused on preventing MRSA infection. Although the anterior nares are the most commonly reported site of MRSA carriage, MRSA may persist in additional sites (eg, skin, chronic wounds, and perianal/rectal carriage) in some individuals or may reside exclusively in sites other than the nares in others. The dynamic aspects of *S. aureus* carriage are complex: most individuals are transiently colonized for varying intervals, some are persistently colonized at one or more sites when studied longitudinally and a modest fraction of individuals remain persistently culture negative for *S. aureus* colonization.

Several interventional studies have explored the eradication of MRSA carriage. Eradication strategies have tended to use topical agents directed at nares and/or skin decontamination or systemic antibiotics. In general, these studies have been limited by enrollment size, duration of monitoring, and inherent study limitations regarding the distinction in culture-positive patients between decontamination failures and effective eradication followed by acquisition of a distinct MRSA strain.

Aims: To determine the efficacy of a 7-day combination decontamination regimen versus no treatment in eradicating MRSA colonization among inpatients identified at hospital admission, and to identify parameters associated with treatment failure.

Methods: A multicenter, randomized, prospective open-label study was performed comparing topical chlorhexidine 2% washes combined with intranasal mupirocin 2% ointment and twice-daily oral rifampin (300 mg/dose) and doxycycline (100 mg/dose) for 7 days versus no treatment in a 3:1 randomization scheme among patients identified as MRSA carriers at the time of hospital admission or outbreak investigation. Patients were subjected to screening cultures of the anterior nares, perianal skin, observed skin lesions, and any catheter or transcutaneous medical device exit site. Follow-up cultures were obtained weekly from these sites for 4 weeks and then monthly for another 7 months. Demographic and clinical information was collated for analysis. MRSA isolates were tested for drug susceptibility by broth microdilution cultures, and pulsed field gel electrophoresis (PFGE) was used to analyze strain heterogeneity. The primary outcome test was MRSA eradication at all sites 3 months after therapy or randomization.

Results: One hundred and forty-six patients were recruited into the study, and 112 were available for primary outcome analysis. The treatment and observational groups were well-matched elderly populations (mean age ~ 77 years) with expected high rates of chronic illness, recent hospitalization, surgery, antibiotic use, and significant short-term mortality rates. At 3 months, 74% of the treated patients had eradicated MRSA carriage in all cultures, compared with 32% in the untreated cohort. Mupirocin resistance at study entry was seen in 19% of patients. Only one MRSA isolate was documented to acquire mupirocin resistance during the course of the study, but the presence of mupirocin resistance at baseline was associated with a high rate of failure. In general, failure to eradicate MRSA was due to clonal relapse; this occurred in 82% of patients with persistent MRSA carriage, whereas reinfection by distinct strains occurred in 18%. Compliance with this complex regimen was good, with more than 90% of treated patients completing at least 6 days of therapy, although adverse gastrointestinal reactions were common.

Editor's comments

From a conceptual perspective, eradicating MRSA colonization among hospitalized patients would seem to be a desirable goal; it is somewhat surprising that the utility of decontaminating patients colonized with MRSA at the time of admission to the hospital remains controversial [3,4]. One might imagine that screening and treating colonized

individuals before elective admission to the hospital, particularly for device implantation procedures or high-risk myeloablative or immunosuppressive procedures (eg, bone marrow or solid-organ transplantation) would benefit from preadmission MRSA eradication. However, the rate of catastrophic MRSA infection in even these selected populations is low, challenging the cost effectiveness of large-scale, intensive decontamination programs. The Simor et al. study provides several valuable observations.

An intensive and comprehensive approach to eradicating MRSA using skin disinfection, topical nasal antibiotics, and systemic therapy with two oral antibiotics has good but not spectacular (~ 80%) efficacy. Among these patients, roughly 5% will be recolonized de novo by a distinct MRSA strain, so that about 75% of an initial cohort of treated MRSA-colonized patients remains MRSA free at 3 months.

About 20% of individuals will fail even this intensive therapy. It is difficult to parse out strictly how many of these failures were due solely to mupirocin resistance among the MRSA isolates but, interestingly, 18% of the MRSA isolates in the treated group were mupirocin resistant at outset. This suggests that mupirocin resistance plays a major role in decontamination failure, and multivariable analysis demonstrated that the relative risk of persistent MRSA carriage at 3 months was nearly 10-fold higher among patients carrying mupirocin-resistant strains within the treated group. Thus, although a three-pronged effort was used for patient decontamination, nares decontamination using topical antibiotic therapy was likely to be the dominant mechanism in successful decontamination. Although mupirocin testing was part of this investigation, routine disk testing for mupirocin resistance is not available, and resistance rates may vary in different populations.

The use of two study populations (either untreated control patients or patients subjected to comprehensive decontamination for 7 days) raises interesting questions about more limited decontamination strategies. It is difficult to assess the independent contributions that chlorhexidine cleansing and combination oral rifampin and doxycycline therapy made to the study outcomes. Among treated patients, 25% reported possible drug-associated side effects, mostly gastrointestinal. In an elderly and often chronically ill population, it is likely that rifampin might have interactions with other administered medications, possibly limiting its use in a decontamination regimen; however, this was not discussed in detail in the study. Similarly, the use of doxycycline in patients with renal insufficiency might be problematic. It would be of interest to know if shorter courses of oral antibiotic therapy were equally effective when combined with nasal and skin decontamination.

In this study of limited duration, the incidence of acquired drug resistance was reassuringly very low. It is not clear whether the MRSA resistance rates to doxycycline, rifampin, and/or mupirocin at the time of hospital entry might rise in a community where this intensive topical and systemic antibiotic decontamination regimen was applied over prolonged periods. In such a situation, the efficacy of continued decontamination might be expected to fall further.

This report provides a useful comparative framework for addressing the microbiologic efficacy of novel decontamination strategies for MRSA-positive patients entering the hospital. Ideally, a shorter, simpler, and more efficacious regimen would reliably accomplish this goal. The challenge will be identifying such a regimen.

References

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