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Treatment of *Staphylococcus aureus* Colonization in Atopic Dermatitis Decreases Disease Severity

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What's Known on This Subject

Staphylococcus aureus infection is a major contributor to exacerbations of AD and resistance to therapy. However, suppression of *S aureus* has been poorly studied and is difficult to achieve.

What This Study Adds

This study provides an easy, safe, effective method for *S aureus* suppression on the skin of patients with AD.

ABSTRACT

OBJECTIVES. The goals were to determine the prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* colonization in patients with atopic dermatitis and to determine whether suppression of *S aureus* growth with sodium hypochlorite (bleach) baths and intranasal mupirocin treatment improves eczema severity.

METHODS. A randomized, investigator-blinded, placebo-controlled study was conducted with 31 patients, 6 months to 17 years of age, with moderate to severe atopic dermatitis and clinical signs of secondary bacterial infections. All patients received orally administered cephalexin for 14 days and were assigned randomly to receive intranasal mupirocin ointment treatment and sodium hypochlorite (bleach) baths (treatment arm) or intranasal petrolatum ointment treatment and plain water baths (placebo arm) for 3 months. The primary outcome measure was the Eczema Area and Severity Index score.

RESULTS. The prevalence of community-acquired methicillin-resistant *S aureus* in our study (7.4% of our *S aureus*-positive skin cultures and 4% of our *S aureus*-positive nasal cultures) was much lower than that in the general population with cultures at Children's Memorial Hospital (75%–85%). Patients in the group that received both the dilute bleach baths and intranasal mupirocin treatment showed significantly greater mean reductions from baseline in Eczema Area and Severity Index scores, compared with the placebo group, at the 1-month and 3-month visits. The mean Eczema Area and Severity Index scores for the head and neck did not decrease for patients in the treatment group, whereas scores for other body sites (submerged in the dilute bleach baths) decreased at 1 and 3 months, in comparison with placebo-treated patients.

CONCLUSIONS. Chronic use of dilute bleach baths with intermittent intranasal application of mupirocin ointment decreased the clinical severity of atopic dermatitis in patients with clinical signs of secondary bacterial infections. Patients with atopic dermatitis do not seem to have increased susceptibility to infection or colonization with resistant strains of *S aureus*. *Pediatrics* 2009;123:e808–e814

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Key Words

eczema, infection, bleach, sodium hypochlorite, mupirocin, community-acquired methicillin-resistant *Staphylococcus aureus*

Abbreviations

AD—atopic dermatitis
MRSA—methicillin-resistant *Staphylococcus aureus*
CA—community acquired
EASI—Eczema Area and Severity Index
IGA—Investigator's Global Assessment
BSA—body surface area
MSSA—methicillin-sensitive *Staphylococcus aureus*

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ATOPIC DERMATITIS (AD) is a chronic relapsing disease of pruritus and eczematous lesions that affects 15% to 20% of the childhood population.¹ *Staphylococcus aureus* infection is the most common complication of AD and also is involved in the worsening of this disease.² Individuals with AD carry *S aureus* on the skin and in the nares.³ Antibiotic therapy against *S aureus* is an important component of treatment for AD, because it improves both the secondary infections and severity of AD. However, the emergence of community-acquired methicillin-resistant *S aureus* (CA-MRSA) in the general population presents a new therapeutic challenge in this patient population.⁴ Continuing use of antibiotic therapy, whether systemic or topical, can increase the risk of bacterial resistance.

Given the high prevalence of *S aureus* nasal carriage, intranasal treatment with mupirocin ointment is a mainstay of treatment for *S aureus* colonization in healthy and hospitalized patients.⁵ Adjunctive therapy beyond intranasal mupirocin treatment, however, may be necessary for patients with AD, because of their inherent susceptibility for

both skin and nasal colonization. We and others have found anecdotally the addition of dilute sodium hypochlorite (bleach) baths to be helpful in decreasing infection rates and disease severity. However, no controlled studies have assessed objectively the efficacy of combined therapy with intranasal mupirocin ointment treatment and bleach baths for patients with AD. The primary goal of this investigation was to examine the possibility that this combination might decrease the severity of AD in patients prone to secondary bacterial infections, as well as addressing the frequency of CA-MRSA skin infections in our patient population with AD and secondary staphylococcal infections.

METHODS

Study Population

Patients were recruited from Children's Memorial Hospital pediatric dermatology clinic, a tertiary care center. Patients 6 months to 17 years of age with moderate/severe AD, as determined with the Investigator's Global Assessment (IGA), and signs of bacterial skin infection (weeping, crusting, and/or pustules) were eligible. Exclusion criteria included current or recent use (within the past 8 weeks) of topical or oral antibiotic preparations and allergy to cephalosporins or mupirocin.

Study Design

A 3-month, investigator-initiated, single-center, randomized, investigator-blinded, placebo-controlled, clinical trial was conducted. Patients were assigned randomly, through block randomization generated by the statistician, to the treatment or placebo study arm. All patients received cephalexin at 50 mg/kg per day (maximum of 2 g/day), divided into 3 daily doses, for 2 weeks to treat their staphylococcal infections. Patients were instructed to add either 0.5 cup of 6% bleach (final concentration: 0.005%; treatment arm) or water (placebo arm) to a full bathtub of water (40 gallons); the amount of administered bleach solution or water was adjusted by the family on the basis of the bathtub size and estimated height of bathtub water. Patients were instructed to bathe in the dilute bleach bath or placebo bath for 5 to 10 minutes twice weekly. The frequency and number of baths without bleach (or placebo) were not restricted. Patients and their household members also were instructed to apply mupirocin ointment (Centany [OrthoNeutrogena, Skillman, NJ]) (treatment arm) or petrolatum (placebo arm) intranasally twice daily for 5 consecutive days of each month. Each patient maintained a stable regimen of topical antiinflammatory medication and emollient therapy throughout the 3-month period.

Study Approval

The study protocol was approved by the Children's Memorial Hospital institutional review board. Each patient or legal guardian and all household members provided written informed consent before study-related procedures were initiated. A child assent form also was used for children 12 to 17 years of age.

Blinding

The randomization schedule and patient identification numbers were generated by the statistician. Mupirocin and petrolatum ointment were dispensed in identical white jars, labeled with the patient identification numbers. Bleach and water with patient identification numbers were dispensed in identical bleach bottles with the same brand-name labels. Investigators were blinded to the contents of the bottles and jars and dispensed these items sequentially, according to patient identification numbers. Neither patients nor clinicians knew the patients' assigned study arm. However, patients and/or family members were able to differentiate the pure bleach container from the water container on the basis of odor and were instructed at the beginning not to disclose their suspicions to the investigators. Bathing in the dilute bleach baths was not associated with an odor of bleach (in contrast to frequent pool exposure), and investigators were not able to distinguish study arms during examinations.

Assessments

Efficacy Assessments

The primary outcome was the Eczema Area and Severity Index (EASI).⁶ The proportion of affected body surface area (BSA) was estimated from 4 designated body regions (head/neck, upper limbs, trunk, and lower limbs), and the Physician's Assessment of Individual Signs was determined for each region. The Physician's Assessment of Individual Signs grades signs of AD (erythema, edema/induration/papulation, excoriation, oozing/weeping/crusting, scaling, and lichenification) on a 4-point scale, ranging from absent to severe. Both the proportion of affected BSA and the Physician's Assessment of Individual Signs score were used to calculate the EASI score, a validated composite score that ranges from 0 (clear) to 72 (very severe). The IGA score (clear = 0, almost clear = 1, mild = 2, moderate = 3, severe = 4, very severe = 5) also was assessed.

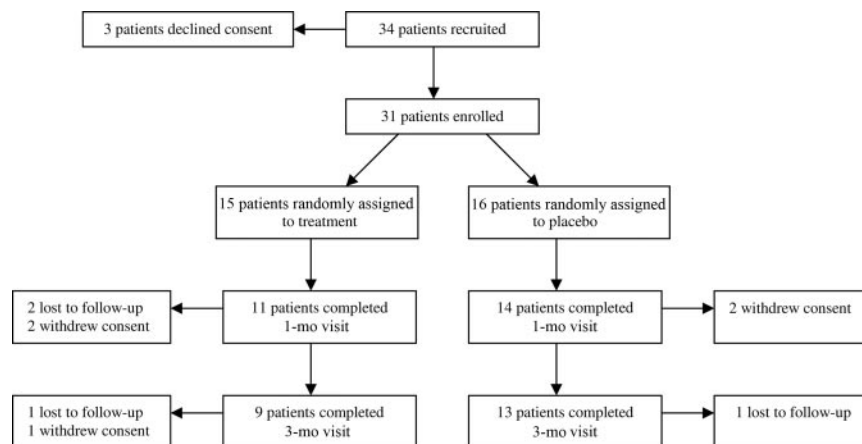
Bacteriologic Methods

Before intervention, qualitative bacterial cultures and culture sensitivities of the nares and the worst, overtly infected lesion were obtained. At 1 and 3 months after initiation of therapy, swabs of the nares and the most severely infected or eczematous lesions were obtained again. Antibiotic discs tested resistance to amoxicillin, amoxicillin-clavulanate, oxacillin, cephalexin, trimethoprim-sulfamethoxazole, erythromycin, clindamycin, and mupirocin.

Safety Assessments

Adverse events were assessed and recorded. Patients were removed from the study if they developed an allergic reaction (acute contact dermatitis, urticaria, or anaphylaxis) to an agent used during the study. Recurrence of infection did not preclude patients from continuing in the study.

FIGURE 1
Study enrollments and withdrawals.



Compliance

Compliance, measured as yes or no regarding completion of cephalixin therapy, frequency and concentration of bleach baths, and frequency and duration of intranasal mupirocin application, was assessed at 1-month and 3-month visits.

Statistical Analyses

We performed an intent-to-treat analysis. Fisher's exact test was used to compare study arms with respect to IGA scores. Independent-sample *t* tests were used to compare study arms with respect to baseline values and changes in EASI scores and proportions of affected BSA. Compliance was compared between arms by using Fisher's exact test. Values are expressed as mean \pm SEM, with significance set at $P < .05$.

The initial target sample size (40 patients) was determined by specifying 80% power to detect an estimated reduction of 14.2 EASI units in the treatment arm versus 7.1 units in the placebo arm, a net reduction of 7.1 units. We determined the desired reduction in EASI scores by using the results of a previous study that used EASI scores as the primary outcome measure for AD.⁷

RESULTS

Enrollment

Thirty-one patients were enrolled between January 2006 and January 2008 and had baseline cultures of nares and skin. Twenty-five patients (11 in the treatment arm and 14 in the placebo arm) returned for their first follow-up visit after 1 month and were included in the evaluation of treatment effects. Twenty-two patients (9 in the treatment arm and 13 in the placebo arm) completed the study (Fig 1). No patients withdrew because of adverse events. Noncompleters either were lost to follow-up monitoring or withdrew consent; parents withdrew consent for 3 patients receiving active treatment because of the inconvenience of study appointments and because their children had experienced great improvement. Despite the original intent to recruit 40 patients, we found it increasingly difficult to justify placebo therapy, given our anecdotal experiences with intranasal mupirocin treatment and bleach baths. With the

recognition that the effect size with a final sample size of 9 treatment group patients and 13 placebo group patients (as determined by the unblinded statistician) would still be 1.21, the study was closed to enrollment at 22 patients.

Baseline Comparisons

Patients 9 months to 17 years of age with moderate to very severe AD and infection were enrolled. The mean proportion of BSA affected was 33%, and the mean EASI score was 19.7. Demographic characteristics and disease activity showed no differences between the study arms (Table 1).

Efficacy

EASI Scores

Patients in the treatment arm showed greater mean reductions in EASI scores from baseline at both the

TABLE 1 Baseline Demographic Data

	Treatment	Placebo
All patients		
Sample size, <i>N</i>	15	16
Age, <i>y</i>		
Range	2.1–17.3	0.7–15.7
Mean \pm SD	8.0 \pm 5.0	6.3 \pm 4.5
Median	7.3	5.2
Gender, <i>n</i>		
Female	8	8
Male	7	8
EASI score, mean \pm SD	22.1 \pm 13.3	16.6 \pm 9.8
IGA score, mean \pm SD	3.67 \pm 0.82	3.50 \pm 0.63
Proportion of BSA affected, mean \pm SD, %	37.8 \pm 21.6	28.1 \pm 18.2
Patients treated for ≥ 1 mo ^a		
Sample size, <i>N</i>	11	14
Age, <i>y</i>		
Range	2.1–17.3	0.7–15.7
Mean \pm SD	8.2 \pm 5.7	6.3 \pm 4.8
Median	7.5	4.6
EASI score, mean \pm SD	26.9 \pm 8.2	17.7 \pm 9.9
IGA score, mean \pm SD	3.82 \pm 0.87	3.50 \pm 0.65
Proportion of BSA affected, mean \pm SD	44.6 \pm 20.8	29.1 \pm 18.5

^a Patients who completed only the baseline visit were excluded.

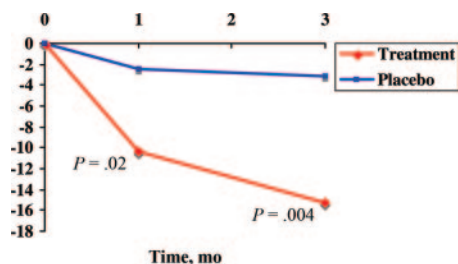


FIGURE 2
Changes in mean EASI scores over time.

1-month visit (-10.4 ± 2.8) and the 3-month visit (-15.3 ± 3.8), compared with the placebo arm (1-month visit: -2.5 ± 1.6 ; $P = .017$; 3-month visit: -3.2 ± 1.6 ; $P = .004$) (Fig 2). Because only the trunk and extremities were submerged in the bleach baths, we assessed the changes in EASI scores for these submerged areas, compared with the head and neck. At head and neck sites, no difference was found between the active and placebo arms at 1 or 3 months; in contrast, the submerged regions showed significant differences between placebo and active treatment at both 1 month ($P = .03$) and 3 months ($P = .0005$) (Table 2).

Because the final sample size at 3 months was a total of 22 patients, the net reduction in EASI scores detectable with 80% power increased to 9.7 units (see above). The actual net reduction in mean EASI scores at 3 months was 12.1 units, which indicates that there was sufficient power to detect the observed change in EASI scores.

Proportion of BSA Affected

Patients in the treatment arm showed greater mean reductions from baseline in the proportions of BSA affected by 1 month (-12.6 ± 3.4 ; placebo: -2.0 ± 3.7 ; $P = .049$) and 3 months (-23.7 ± 5.7 ; placebo: -3.0 ± 3.6 ; $P = .004$) (Fig 3).

TABLE 2 Changes in EASI Scores According to Location

Group	n	Change in EASI Score, Mean ± SE	P
Exposed sites: head and neck			
Change from baseline to 1 mo			
Treatment	11	-0.98 ± 0.86	.32
Placebo	14	-0.16 ± 0.80	
Change from baseline to 3 mo			
Treatment	9	-1.06 ± 1.04	.62
Placebo	13	-0.57 ± 0.86	
Bath-submerged sites: upper limbs, trunk, and lower limbs			
Change from baseline to 1 mo			
Treatment	11	-2.61 ± 0.60	.03
Placebo	14	-0.78 ± 0.55	
Change from baseline to 3 mo			
Treatment	9	-4.94 ± 0.74	.0005
Placebo	13	-0.88 ± 0.62	

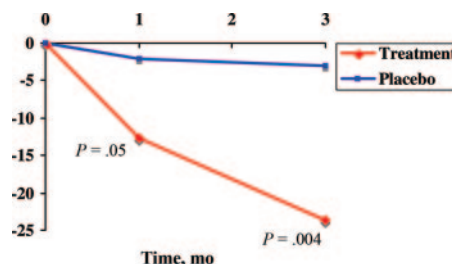


FIGURE 3
Changes in mean proportions of BSA affected over time.

IGA Scores

Patients in the treatment arm had significantly lower IGA scores, compared with patients in the placebo arm, at 1 month ($P = .024$) but demonstrated only a trend toward lower IGA scores at 3 months. A total of 67% of patients in the treatment arm showed decreases in IGA scores from baseline to 3 months, compared with 15% in the placebo arm; 70% of patients in the placebo arm showed no change at 3 months, and 15% demonstrated worsening.

Bacterial Cultures

At baseline, cultures yielded *S aureus* from lesional skin for 87.1% of patients and from the nares for 80.6% of patients. Of these positive cultures, 7.4% from lesional skin and 4% from the nares were resistant to methicillin. All methicillin-resistant *S aureus* (MRSA) strains were susceptible to both trimethoprim-sulfamethoxazole and clindamycin. No cultures showed resistance to mupirocin.

Cultures for all patients continued to yield *S aureus* from both skin and nares samples at 3 months (Fig 4). One patient in the treatment arm with CA-MRSA in both nares and lesional skin samples failed to attend the 1-month visit within the required time and was withdrawn from the study without follow-up evaluation. One patient in the placebo arm demonstrated CA-MRSA in lesional skin samples but methicillin-sensitive *S aureus* (MSSA) in nares samples at baseline. This patient was treated with cephalexin without switching, and subsequent cultures yielded MSSA from both skin and nares. Of patients with MSSA-positive skin cultures at baseline, 2 patients developed CA-MRSA-positive cultures at ≥ 1 of the subsequent visits; 1 of these patients was in the placebo arm (CA-MRSA found at 3 months) and 1 was in the treatment arm (CA-MRSA found at both 1 and 3 months). The switch to CA-MRSA was not associated with significant changes in EASI or IGA scores. Of note, all isolates in follow-up bacterial cultures at 1 and 3 months were susceptible to mupirocin.

Tolerance of the Bleach Baths

No significant difference in compliance was noted between the study arms. No patient withdrew from the study because of intolerance to the baths. One patient from the treatment arm (see above) reported itching and irritation of the skin with the use of bleach baths and failed to comply with the regimen. This patient subse-

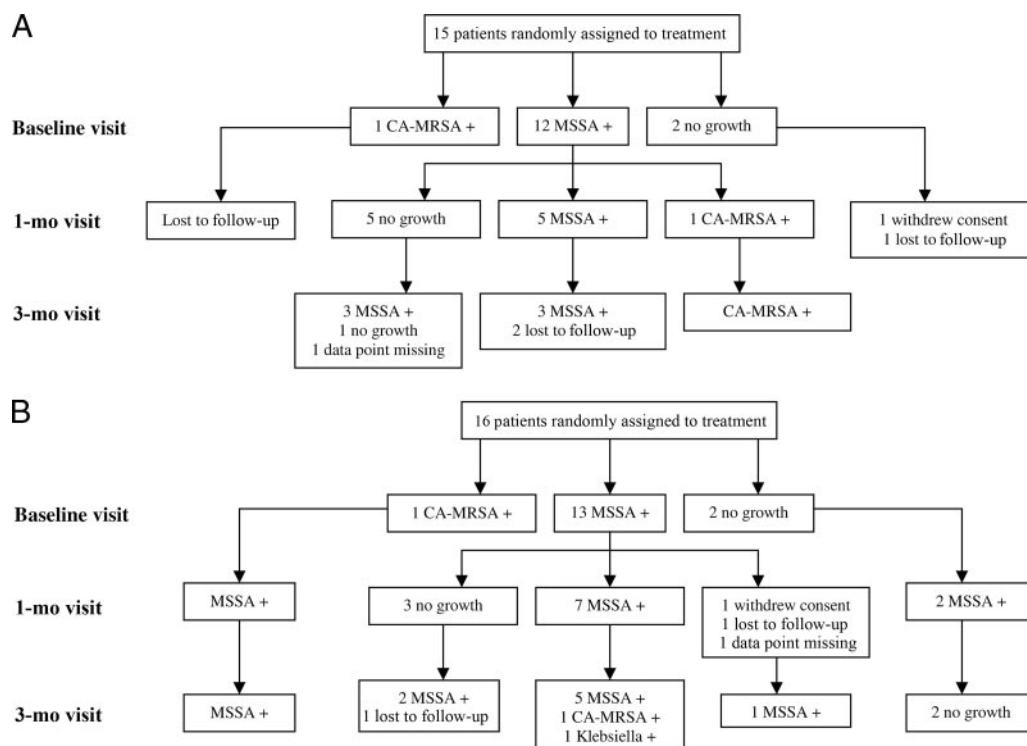


FIGURE 4
Bacterial skin culture results in the treatment (A) and placebo (B) arms. f/u indicates follow-up.

quently developed a CA-MRSA skin infection between the 1-month and 3-month study visits, which required hospitalization and intravenous antibiotic therapy. After discharge, the patient resumed the use of bleach baths without adverse effects. He remained in the study, with follow-up evaluation at 3 months.

DISCUSSION

S aureus skin infections in AD are linked to the high rates of *S aureus* colonization in the AD population (76%–100%, compared with 2%–25% for healthy control subjects).^{3,8,9} Several mechanisms have been suggested to account for the increased colonization. The defective epidermal barrier in patients with AD results from abnormalities in both lipids (ceramide and sphingosine deficiencies)^{10,11} and proteins (increased serum protease levels and decreased filaggrin expression).^{12–14} Levels of endogenously produced antimicrobial peptides also are reduced, in part because of local production of interleukins.¹⁵ In turn, *S aureus* superantigens activate keratinocytes, inducing the release of proinflammatory cytokines and exacerbating AD.

The deleterious effects of *S aureus* have led researchers to consider the suppression of bacterial growth as an important treatment for AD. The anterior nares and hands are important reservoirs for *S aureus* colonization and should be sites of *S aureus* decolonization.¹⁶ Although 2 reports suggested that topical antibiotic application to all affected areas could improve clinical severity,^{17,18} more-recent studies did not show an effect.^{19,20} Concomitant application of topical mupirocin and corti-

steroid preparations to lesional skin for 28 days did not decrease the clinical severity of AD more significantly than did topical corticosteroid administration alone.¹⁹ Similarly, adjunctive use of topical fusidic acid treatment for 8 weeks did not show greater improvement in AD than did the use of fluticasone propionate ointment or tacrolimus ointment alone.²⁰ Gentian violet decreases *S aureus* density and improves AD severity²¹ but is not cosmetically acceptable. In addition, the prolonged use of chlorhexidine has been found to cause irritant contact dermatitis.²² Skin exposure to silver-impregnated textiles and treatment with potent topical steroid preparations, calcineurin inhibitors, or phototherapy also have reduced the burden of *S aureus* on atopic skin, which may contribute to therapeutic potential.^{23–27}

Sodium hypochlorite has long been used for household and hospital cleaning and as a dental antiseptic.²⁸ Although no studies have addressed its efficacy against *S aureus* colonization, bleach has both in vitro and in vivo antimicrobial activity against *S aureus*, including MRSA.²⁹ Historically, Dakin's solution (0.025% bleach buffered with sodium bicarbonate) has been used as a wound disinfectant.³⁰ Bleach, in concentrations as low as 0.005%, has been shown to be effective specifically against *S aureus* in wounds and skin ulcers.^{31,32} We observed excellent tolerability of the dilute bleach baths in both our study and clinical practice, although some children complained early in the course, when sites of dermatitis were crusted or eroded as a result of secondary infections.

We show here that the concurrent use of intermittent

intranasal mupirocin treatment and dilute bleach baths led to significant improvement in the severity of moderate/severe AD. Decreased EASI scores at the 1-month visit, after a 2-week course of cephalixin therapy, might have been predicted. However, the continued improvement in EASI scores in the treatment arm at the 3-month visit, as well as the significant differences in the extent of involvement and severity of AD between the treatment and placebo groups despite the course of antibiotic therapy, supports the therapeutic benefits of sodium hypochlorite baths and intranasal mupirocin treatment in AD. Furthermore, the statistically significant reductions in EASI scores at 1 month and dramatically at 3 months for body sites exposed to the dilute bleach baths but not for the unexposed head and neck regions provide clear evidence that the addition of dilute bleach baths to intranasal mupirocin treatment decreased the severity of AD.

The prevalence of *S aureus* colonization among our patients with AD (81% in nares and 87% on lesional skin) is consistent with the previously described high frequency of colonization.^{3,7,8} The exposure to intranasal mupirocin treatment and sodium hypochlorite baths did not eradicate the organism, as demonstrated by the continued growth of *S aureus* from both the skin and the nares for each patient. The organism's persistence supports the need for long-term suppression. Quantitative bacterial culture assays will be needed to determine the degree of suppression of bacterial numbers with the topical therapy.

The proportion of baseline, *S aureus*-positive skin samples with CA-MRSA (7.4%) in our study population was markedly smaller than the 75% to 85% prevalence of CA-MRSA reported for the overall pediatric population with *S aureus* skin and soft-tissue infections at Children's Memorial Hospital during the study period (T. Tan, MD, written communication, 2008). This finding suggests that patients with AD are not at increased risk for developing CA-MRSA infections. Nevertheless, the increasing prevalence of CA-MRSA in the general population suggests that these more-resistant organisms will occur with increasing frequency in the population with AD. During the course of the study, patients exhibited transformation both from MRSA to MSSA and from MSSA to MRSA on their skin, without a time course to suggest that the use of the antibiotic influenced the transformation. The use of this easy nonantibiotic approach to inhibit overgrowth of organisms is preferable to the use of antibiotics, which may promote further *S aureus* resistance. The potential for development of bacterial resistance to mupirocin ointment, however, should not be neglected.³³

CONCLUSIONS

The concurrent use of intermittent intranasal mupirocin treatment and dilute bleach baths may improve the clinical condition of infection-prone patients with AD. Additional studies should assess the efficacy and long-term safety of bleach baths with greater numbers of patients, should compare the effects of dilute bleach baths alone with the effects of the combination of baths and intra-

nasal mupirocin treatment, and should measure quantitatively the reduction in bacterial numbers with this treatment regimen.

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