

Methicillin-Resistant *Staphylococcus aureus* Colonization in Children with Atopic Dermatitis

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Abstract: Children with atopic dermatitis are more frequently colonized with *Staphylococcus aureus* than children without atopic dermatitis. However, little epidemiological data exist regarding the prevalence of methicillin-resistant *S. aureus* among children with atopic dermatitis. Recent studies have revealed an increasing prevalence of community-associated methicillin-resistant *S. aureus* among patients presenting to hospitals with serious bacterial infections, particularly those with cutaneous and soft tissue infections. As many atopic dermatitis patients are treated empirically with antibiotics for secondary skin infections, an understanding of the epidemiology of bacterial colonization and superinfection is essential for directing proper treatment in the atopic patient population. This study investigates the prevalence of risk factors for community-associated, methicillin-resistant *S. aureus* colonization among pediatric atopic dermatitis patients encountered at an academic pediatric dermatology clinic. An observational cross-sectional study was conducted at the Children's Hospital of Philadelphia in which 54 patients previously diagnosed with atopic dermatitis were enrolled. A detailed patient questionnaire, a complete cutaneous examination, and an evaluation of eczema severity according to the Eczema Area and Severity Index were completed at the time of enrollment. Bacterial cultures from the skin and nares were obtained to determine the frequency of colonization with either methicillin-sensitive *S. aureus* or methicillin-resistant *S. aureus*. Although most atopic dermatitis patients studied were colonized with *S. aureus* (43/54 [80%]), methicillin-resistant *S. aureus* was isolated from only seven atopic dermatitis patients (7/43 [16%]). Patients colonized with *S. aureus* were more likely to be male, to have been previously hospitalized, to have used a topical calcineurin inhibitor in combination with a topical steroid, and less likely to have used topical antibiotics. Bivariable analysis, however, revealed that only previous hospitalization was independently

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associated with an increased risk of methicillin-resistant *S. aureus* colonization. We observed that 80% of atopic dermatitis patients were colonized with *S. aureus*, and that of these patients, 16% of colonized patients were colonized with a methicillin-resistant strain. Methicillin-resistant *S. aureus* colonization was found to be significantly associated with previous hospitalization. Evidence also indicates that topical calcineurin inhibitors used in conjunction with topical steroids is associated with increased *S. aureus* colonization, while topical antibiotic use appears to decrease *S. aureus* colonization.

Atopic dermatitis (AD) is a common, chronic, relapsing skin condition related to impaired skin barrier function and associated inflammatory skin changes that are clinically characterized by pruritus, erythematous patches, plaques with a typical morphology and distribution (1). The majority of patients with AD manifest the disease during infancy, and despite its chronicity, the condition generally improves in severity and may remit by adolescence or young adulthood (2,3). Although rates vary depending on the study, the prevalence of AD among children in the United States is estimated to be approximately 17% (4,5). Initial treatment plans usually involve patient and family education regarding atopic skin care, avoidance of irritants and allergens, the use of emollients, topical corticosteroids, topical calcineurin inhibitors (TCI), and when concomitant secondary infection is present, topical and systemic antibiotics.

Atopic dermatitis patients are more frequently colonized by *Staphylococcus aureus* (SA) when compared with healthy children. While approximately 30% of nonatopic patients carry SA (6), 93% of AD patients have positive bacterial cultures for SA taken from affected skin (7,8). Little is known about the prevalence of methicillin-resistant *S. aureus* (MRSA) among pediatric AD patients who are colonized with SA, but available information suggests that MRSA colonization is infrequent among general AD patients (9).

Approximately 40–66% of AD patients may experience significant staphylococcal infections during their lifetimes (10). Typically, empiric therapy with anti-staphylococcal antibiotics is initiated when an AD patient develops superinfection. Because recent data point to an increasing level of community-associated MRSA (CA-MRSA) among patients presenting to hospitals with serious bacterial infections, particularly skin and soft tissue infections, hospitals including ours have had to review and revise their infectious disease policies regarding the empiric management of these infections to adapt to the recent rise in CA-MRSA infections. Preliminary data from our hospital indicates that approximately 50% of previously healthy patients presenting with community-associated SA infections are infected

with MRSA (11). However, little is known about the prevalence of MRSA colonization and infection among pediatric patients with AD. In addition, risk factors for MRSA infection or colonization have not been identified for AD patients.

The objectives of this study were to determine the prevalence of MRSA in the pediatric AD population and to identify possible AD-specific risk factors for MRSA. These findings could inform the development of a rational approach to antibiotic therapy among pediatric patients with AD.

METHODS

We conducted an observational cross-sectional study involving 54 patients with atopic dermatitis between 3 months and 17 years of age seen in the outpatient dermatology clinic of the Children's Hospital of Philadelphia during the months of November and December 2004. A convenience sample of patients was consecutively enrolled from all three dermatologists working in the clinic, but some qualified patients were missed randomly during this period if the study coordinator was unavailable. A single observer (L.S.) completed all the physical examinations including the evaluation of eczema severity according to the Eczema Area and Severity Index (EASI) scoring guidelines, and obtained separate bacterial swabs of lesional skin (typically the antecubital space) and nares. Patients were excluded if they had symptoms of an acute illness or had current viral, fungal, or untreated bacterial skin infections ($n = 3$). Patients' families provided information on medical histories, medication use, and other identifying risk factors for healthcare-associated MRSA (HCA-MRSA) by completing a detailed self-administered questionnaire with verification of recorded responses by a single investigator (L.S.). Culture swabs (BBL CultureSwab; Becton, Dickinson and Company, Sparks, MD) were used and sent to the hospital laboratory for routine processing. All cultures were plated for up to 5 days for the growth of SA and methicillin-sensitivity tests were performed on positive SA cultures.

Informed consent was obtained from patients and parents for participation in this study which was approved by the Institutional Review Board of the Children's Hospital of Philadelphia.

STATISTICAL ANALYSIS

A commercially available statistical package, SAS version 9.1 (SAS Corp., Cary, NC), was used for data analysis. Subjects were divided according to presence or absence of SA, with those positive for SA further subdivided into methicillin sensitive (MSSA) and resistant (MRSA) groups. Analyses of patients positive for SA were performed using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Prevalence data is reported with 95% confidence intervals. Multivariable analysis of MRSA outcome was performed using a logistic regression model. Variables with a p-value < 0.1 on univariable analysis were considered for inclusion in the model.

RESULTS

Of the 54 patients enrolled, 80% ($n = 43$; 95% CI: 66–89) were carriers of SA and 13% of the total number or

16% of those colonized with SA ($n = 7$; 95% CI: 5–25) were colonized with MRSA. Overall, patients colonized with MRSA, as compared with MSSA were similar (Table 1) with the exception that males were more likely to be colonized with MRSA—six of seven patients (86%; $p = 0.03$). Analysis of risk factors associated with HCA-MRSA (Table 2) revealed that three of seven were previously hospitalized (43%; OR = 26.2; 95% CI: 2.1–316.0). When controlling for gender, previous hospitalization was independently associated with MRSA infection with an adjusted odds ratio of 24.3 (95% CI: 1.4–418.8). When controlling for previous hospitalization, males were more likely to be colonized than females; however, the association did not achieve conventional levels of statistical significance (adjusted OR = 9.9; 95% CI: 0.8–119.8). The trend, however, might be validated with a larger number of patients.

Our data indicated that the use of TCI affects both SA carriage and MRSA colonization in patients already using topical steroids. As seen in Table 3, only one patient had used a topical calcineurin inhibitor as monotherapy and in this instance, there was insufficient data to suggest any statistically significant differences in either SA carriage or MRSA colonization. Of the patients who used topical steroids alone, 17 of 24 (71%)

TABLE 1. Demographic Characteristics of Patients with AD

Demographic characteristics	No. SA ($n = 11$)	All SA ($n = 43$)	MSSA ($n = 36$)	MRSA ($n = 7$)	p-value
Gender					
Male	5 (45%)	19 (44%)	13 (36%)	6 (86%)	0.03
Female	6 (55%)	24 (56%)	23 (64%)	1 (14%)	
Age					
Median (IQR)	3 (1–5)	5 (3–10)	6.5 (3–10)	4 (2–13)	0.6
Age at parental diagnosis					
Median (IQR)	0 (0–1)	1 (0–2)	1 (0–2)	0 (0–1)	0.3
Age at physician diagnosis					
Median (IQR)	1 (0–1)	1 (0–2)	1 (0–2)	0 (0–2)	0.4
No. MD visits					
Median (IQR)	4 (1–10)	3 (1–4)	2.5 (1.0–4.5)	3 (2–4)	0.3

SA, *Staphylococcus aureus*; MSSA, MRSA, methicillin-sensitive *S. aureus*; methicillin-resistant *S. aureus*. Values in bold are statistically significant.

TABLE 2. Known Risk Factors for MRSA*

Known risk factors	No. SA ($n = 11$)	All SA ($n = 43$)	MSSA ($n = 36$)	MRSA ($n = 7$)	p-value
Health worker in household	0	10 (23%)	9 (25%)	1 (14%)	0.9
Previous hospitalization**	3 (27%)	4 (9%)	1 (3%)	3 (43%)	0.01
Oral antibiotics**	7 (64%)	16 (37%)	12 (33%)	4 (57%)	0.3
Previous skin infection	5 (45%)	13 (30%)	9 (25%)	4 (57%)	0.1
History of MRSA	0	2 (5%)	1 (3%)	1 (14%)	0.3

SA, *Staphylococcus aureus*; MSSA, MRSA, methicillin-sensitive *S. aureus*; methicillin-resistant *S. aureus*.

*Other known risk factors, such as nonambulatory status, requirement of chronic hemodialysis, presence of a central venous catheter, diabetes mellitus, endotracheal intubation, and household member with risk factors were seen in too small numbers to delineate separately.

**Previous hospitalization was defined as admission to hospital in the last 6 months; oral antibiotic use was defined as use within the last 6 months; previous infection was defined as history of cellulitis, impetigo, boils, furuncles, or pus bumps.

Bold indicates that the value is not statistically significant

TABLE 3. AD-Specific Risk Factors for Bacterial Colonization

AD-specific risk factors	No. SA (n = 11)	All SA (n = 43)	p-value	MSSA (n = 36)	MRSA (n = 7)	p-value
EASI score	2.7 (1.4–16.1)	6.0 (3–15.2)	0.5	5.5 (2.9–10.7)	15.2 (3.3–52.2)	0.3
Calcineurin inhibitors alone	1 (9%)	0		0	0	NA
Topical steroids alone	7 (64%)	17 (40%)	0.1	16 (44%)	1 (14%)	0.2
Calcineurin inhibitors and topical steroids	2 (18%)	24 (56%)	0.04	18 (50%)	6 (86%)	0.1
Other medication use						
Steroids (oral or i.v.)	1 (9%)	9 (21%)	0.6	7 (19%)	2 (28%)	0.6
Topical antibiotics	5 (45%)	7 (16%)	0.03	5 (14%)	2 (28%)	0.3

SA, *Staphylococcus aureus*; MSSA, MRSA, methicillin-sensitive *S. aureus*; methicillin-resistant *S. aureus*.

Note: The number of those in each subcategory when added together may at times exceed the total number of patients in that category because some patients may have been managed with more than one therapeutic modality (such as topical steroids + topical antibiotics). Values in bold are statistically significant.

TABLE 4. Adjusted Odds Ratios for Major Risk Factors for Staphylococcal Bacterial Colonization

AD-specific risk factors	Odds ratio	95% CI
Prior hospitalization	24.3*	1.4–418.8
Calcineurin inhibitors + topical steroids	5.6	1.1–29.4
Topical antibiotics	0.23	0.05–0.98

*Odds ratio specific to MRSA

were colonized with SA. However, those patients who used TCI in combination with topical steroids were significantly more likely to be colonized with SA than patients who used only topical steroids (OR = 5.6; 95% CI: 1.1–29.4) (Table 4). Of the 24 patients using topical steroids alone, 17 (71%) were colonized while 24 of 26 (93%) patients using both topical steroids and calcineurin inhibitors were colonized. Most notable is that six of seven (71%) MRSA patients were using both types of topical medications concomitantly.

As might be expected, concurrent use of topical antibiotics was associated with decreased SA colonization (OR = 0.23; 95% CI: 0.05–0.98). A logistic model involving topical antibiotics as well as calcineurin inhibitors in combination with topical steroids revealed that these factors are independently associated (Table 4). It might be presumed that those AD patients using both topical steroids and TCI had a higher rate of SA colonization as a result of increased eczema severity. Further analysis to identify an association with calcineurin inhibitors and EASI score was conducted, but no such association was noted.

DISCUSSION

This study provides further evidence that SA colonization among AD patients is extremely common. Despite mounting concern over the increasing incidence of

CA-MRSA, colonization by MRSA affected only a relatively small proportion of atopic dermatitis patients in our population.

We observed that 80% of AD patients were colonized with SA, which is consistent with previously published data (7). Although there appears to be an increase in MRSA colonization (13%) compared with published MRSA prevalence data on the general population, colonization rates did not appear to adequately reflect the share of CA-MRSA infection seen in our hospital epidemiologic data. Because the confidence interval was wide, a larger sample size would likely have helped to clarify this issue. While about 20–30% of the general population is colonized with various species of SA (12), the prevalence among AD patients is three to four times higher with reported SA carriage rates of 70–100%. There has been much speculation as to exactly why staphylococcal colonization is so prevalent among AD patients. Recent evidence suggests that production of endogenous human antimicrobial peptides such as cathelicidins and defensins is decreased in patients with atopic dermatitis (13). These antimicrobial peptides show activity against a broad array of organisms including SA, and their deficiency contribute to the SA colonization seen in AD patients. Several recent studies have documented a role for antimicrobial peptides associated with skin, skin structures as well as the respiratory, urinary, and intestinal tracts in reducing colonization by an array of potential pathogens (14–18). Fibronectin and fibrinogen may also play a role in enhancing SA binding in AD. With the increased amount of excoriated, exposed skin, a greater amount of fibronectin is redistributed to the cornified layer than in normal skin (19). Presumably, MRSA is more prevalent among AD patients in part because of the extent of inflamed skin and exposed fibronectin and fibrinogen. Limited data are available regarding MRSA colonization among pediatric AD patients and they too have not

documented a higher MRSA carriage in atopic patients (8). By contrast, our data revealed a proportionate increase in MRSA colonization in AD patients. Among nonatopic patients, about 1–3% demonstrate CA-MRSA colonization (20), and in our population, MRSA carriage among AD patients is about 4 to 13 times higher at 13%. Recent evidence has documented the development of stronger adherence among current MRSA strains (21), which we hypothesize may explain some of this increase from previous studies.

We evaluated the significance of factors that might predispose to SA and MRSA colonization. Among these, male gender and previous hospitalization were significantly associated with MRSA colonization. Use of a logistic regression model revealed that male gender no longer achieved conventional levels of statistical significance, while previous hospitalization remained independently associated with MRSA colonization.

The use of TCI was associated with an increased prevalence of general SA colonization [2/11 (18%) non-SA and 24/43 (56%) SA; $p = 0.04$]. To our surprise, the use of TCI when used in combination with topical steroids was associated with a nearly sixfold increase in SA colonization. Although a similar trend in MRSA colonization was observed, this observation did not achieve statistical significance in the bivariable analysis and may have been due to the low numbers of patients evaluated in this pilot study.

As might be expected, the use of topical antibiotics decreased SA colonization. Multivariate analysis confirmed that these factors—TCI use in combination with topical steroids as well as concurrent use of topical antibiotics—were found to be independently associated and statistically significant factors in the rates of SA colonization among AD patients.

A possibility that might explain the strong association of SA colonization among patients using both TCI and topical steroids might have been that those AD patients requiring use of these combinations had more severe AD, and would suggest that TCI + topical corticosteroid use would simply be a proxy for severe AD. However, the rate of SA colonization among those patients with lower EASI scores was not significantly different than that those with higher EASI scores indicating that TCI + topical steroid use was an independent risk factor for SA colonization. However, we could not entirely account for the possibility of bias introduced through confounding by indication. As those patients treated with both TCI and topical steroid had high EASI scores at some point, our assessments could have occurred at a time when the patients were under better control. Until these issues are resolved, we continue to advise that patients with AD using both TCI

and topical steroid be monitored closely for SA superinfection.

Calcineurin inhibitors, such as pimecrolimus and tacrolimus, had gained wide acceptance, particularly for mild to moderate eczema, as effective steroid-sparing creams although use of these agents has decreased with the advent of revised Food and Drug Administration guidelines in the form of a Public Health Advisory (22), boxed warning (23), and medication guide (24,25). This is primarily due to concerns about possible side effects of prolonged steroid use including skin atrophy and systemic absorption, which can cause growth retardation and hypothalamic-pituitary-adrenal axis suppression. Corticosteroids have been shown to reduce bacterial counts in AD patients, and it has been proposed that this observation confirms the critical role of inflammation in bacterial colonization (26). Similar data have been published documenting that topical tacrolimus may also by itself reduce bacterial colonization in inflamed skin, albeit to a lesser degree than topical steroids (27–30). However, if limiting bacterial colonization were simply matter of controlling inflammation, then calcineurin inhibitors—either alone and especially in combination with topical steroids—should likewise have a similar effect in reduction of bacterial colonization, which it did not have in this study. In any case, the mechanism for this difference is not clear and requires further investigation.

Although MRSA has been associated with greater mortality in hospitals and has increased drug-resistance, it is unclear if the organism is truly more virulent (31). It has been speculated that part of the organism's energy expenditure is devoted to its ability for antibiotic resistance, leaving less capacity to devote to other virulence mechanisms. Thus the epidemiologic data showing higher mortality with MRSA may be due to other factors such as delayed recognition and inappropriate treatment. However, recent studies suggest that in fact, MRSA appears to be inherently more virulent. Certain virulence factors such as Panton-Valentine leukocidin appear to be linked with resistance factors on the CA-MRSA genome (32). In addition, other studies in the non-AD population show that a greater percentage of MRSA colonized patients go on to develop cutaneous skin infections in general compared with those colonized with MSSA (33). This would be consistent with our findings in that the MRSA colonization rate was only 13%, while MRSA is responsible for about 50% of hospital infections. MRSA involvement in AD-related infections is likely even higher than 50%, given that most MRSA is highly correlated with skin and soft tissue infections, which is a frequent complication in eczema.

A variety of risk factors have been previously identified in association with healthcare-associated strains,

including nonambulatory status, hospitalizations in the previous 6 months, requirement of chronic hemodialysis, presence of a central venous catheter, prior MRSA infection or colonization, diabetes mellitus, recent oral antibiotic exposure, endotracheal intubation, and household contacts with identified risk factors (34). In our study, we found a significant association with previous hospitalization and MRSA colonization (OR = 26.2; 95% CI: 2.1–316.0). However, the MRSA isolates found in our study were not typed. This information could have provided further insight as to how the MRSA was acquired and its relation to community-associated or healthcare associated strains. This is particularly important given that previous hospitalization was shown to have a significant association with MRSA colonization even when controlled for gender (adjusted OR = 24.3; 95% CI: 1.4–418.8).

According to our study data, topical antibiotic use appeared to be protective of SA colonization (OR = 0.23; 95% CI: 0.05–0.98). Mupirocin cream was the most commonly used antibiotic in AD patients. Antibiotic cream was typically prescribed for superficial bacterial infections, but AD patients often use it in areas of broken skin regardless of signs of symptoms of a bacterial infection. In addition, mupirocin has been shown to be effective in clearing bacterial colonization in asymptomatic healthy individuals to control for outbreaks (35). However, after discontinuation of the topical antibiotic, eventual bacterial recolonization is likely. Although patients' families were asked to relay information about topical medication use within the last 6 months, there may be recall bias in that those who used topical antibiotics more recently would be more likely to remember using these short courses of topical creams. Thus, topical antibiotic use may indicate effects of recent therapeutic use rather than a true lasting protective effect. Also, most patients used topical antibiotics for short periods of time, and so it is possible that long-term use may actually induce resistance and thus diminish any potential protective attributes. In addition, none of the patients had had prior dilute bleach baths used as part of their routine atopic skin care. The current popular practice of using diluted bleach baths (0.005% or 0.01% sodium hypochlorite, the equivalent of ¼ to ½ cup of bleach per tub of water) once or twice weekly to reduce cutaneous staphylococcal colonization may also in the future alter the prevalence of MRSA and SA in atopic dermatitis patients.

Although we have indicated possible trends in MRSA and SA colonization in atopic patients, the pilot study is limited statistically by the relatively small sample size. In addition, we are limited in our conclusions by the use of historical controls rather than concurrent nonatopic

controls. As colonization rates do not appear to account for the proportion of MRSA infection seen in hospitals, it seems that a more important strategy in selecting empiric antibiotic therapy would be based on information of the MRSA infection rates rather than MRSA colonization prevalence in AD patients. In addition, further investigation regarding the use of TCI, particularly when used in combination with topical corticosteroids, as well as the use of topical antibiotics with SA and MRSA colonization is clearly warranted.

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