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Abstract

Background. Secondary skin infection with *Staphylococcus aureus* is a significant problem in atopic dermatitis (AD) patients. **Objective.** This study evaluated antimicrobial resistance patterns of *S aureus* isolates from skin lesions in AD patients and empiric antimicrobial prescribing patterns. **Methods.** Resistance patterns from positive skin cultures obtained from AD patients in the Allergy/Immunology clinic from May 1, 2006, to December 31, 2008, were compared with all outpatient wound cultures over the same period. **Results.** Fifty-nine cultures were obtained from 38 AD patients. *S aureus* was the most common pathogen cultured from AD patients (53/59 cultures). *S aureus* resistance to clindamycin and methicillin differed significantly between the study group and the outpatient reference population (37.7% vs 9.4% and 45.3% vs 76.4%). Clindamycin was the most commonly prescribed antimicrobial (59%). Overall, 31.4% of organisms showed resistance to the antimicrobial prescribed. **Conclusions.** Susceptibility profiles of *S aureus* isolates from AD patients vary significantly from that of the general population.

Keywords

dermatitis, atopic, eczema, *Staphylococcus aureus*, antimicrobial agents, pediatrics, hypersensitivity

Introduction

Atopic dermatitis (AD) is a common and costly disease of childhood affecting 10% to 20% of children worldwide and costing third party payers an estimated \$0.9 to \$3.8 million yearly.^{1,2} More than 30 years ago, Leyden et al³ postulated that colonization and infection with *Staphylococcus aureus* played a significant role in this chronic, pruritic, inflammatory skin disorder. The unique skin environment of children with AD makes colonization with *S aureus* more likely.⁴ Many factors including a defective epidermal barrier, reduction in endogenous antimicrobial peptides, diminished neutrophil recruitment, defects in Toll-like receptors, and dysregulation in the adaptive immune response with increased total and specific IgE have been implicated in the pathogenesis of AD and the enhanced potential for secondary infection.⁵

It has been well documented that superantigens produced by *S aureus* play a major role in the pathogenesis of AD.^{6,7} Nineteen different staphylococcal superantigens have thus far been identified.⁸ Up to 80% of children with AD are colonized with *S aureus*, and more than 50% harbor at least 1 superantigen-producing strain

of *S aureus*.⁹ Colonization with superantigen-producing *S aureus* promotes the development of superantigen-specific IgE, which binds superantigen and activates mast cells and basophils.¹ Superantigens are also capable of stimulating up to 35% of T-cells, even at picogram concentrations, as compared with <0.1% stimulation with regular antigens, thus perpetuating the Th2-driven inflammation associated with AD.¹⁰ As the reasons behind the increased Th2 response are being elucidated, many of the disease promoting effects, such as upregulation of IgE receptors and reduced responsiveness of the skin to topical corticosteroids, have been described.^{1,11}

Although colonization with *S aureus* has been implicated as a major factor in the pathogenesis of AD, secondary skin infection with *S aureus* and other microbes poses a new set of challenges. Secondarily infected lesions can progress rapidly and can be potentially life

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threatening.¹² Oral antimicrobials are not typically recommended for long-term treatment of bacterial colonization in AD because of concerns over the promotion of resistant strains of bacteria; however, they are indicated in cases of secondary infection.¹³ In our institution, clindamycin is the primary empiric antibiotic chosen for skin and soft tissue infections (SSTI) in children in whom *S aureus* is the suspected causative agent, because of the increased prevalence of methicillin resistance. This is concordant with the latest recommendations of the Infectious Diseases Society of America for the treatment of SSTI in children.¹⁴ The purpose of our study was to examine microbial pathogens and their resistance patterns from secondarily infected skin lesions of children with AD presenting to the Arkansas Children's Hospital (ACH) Allergy/Immunology (A/I) clinic in comparison with resistance patterns of isolates obtained from other ACH outpatient settings during the same time period to ensure effective prescribing patterns among clinicians at our facility.

Methods

Study Design

We performed a retrospective chart review of all children with AD presenting to the ACH A/I clinic with positive skin cultures submitted between May 2006 and December 2008. Microbial pathogen data and antimicrobial susceptibility data were obtained from the hospital's microbiology laboratory. The accuracy of empirically prescribing an antibiotic to which the microbe was susceptible was also examined. In addition to culture results and susceptibility data, demographic and clinical characteristics were obtained via chart review. The susceptibility data of *S aureus* isolates from the A/I clinic were compared with microbial susceptibility data from *S aureus* isolates obtained from wound cultures at all outpatient locations at ACH during the same time period, including other outpatient clinics and the emergency department. A chart review was not conducted on the outpatient reference population.

Participants

Participants included in the study were patients (aged 4 months to 14 years 10 months) followed in the subspecialty A/I clinic at ACH, a tertiary care facility, for AD and other atopic disorders. Participants were identified based on receipt of wound cultures from the A/I clinic submitted to the microbiology lab during the specified time period. A total of 59 positive cultures from 38 A/I patients were examined. Cultures were obtained from

Table 1. Demographics of Study Group (n = 38)

Age	
Median (range)	3 y 9 mo (0 y 4 mo to 14 y 10 mo)
Gender	
Male	20
Female	18
Race	
White	21
Black	16
Other	1
Atopic characteristics	
Atopic dermatitis	100% (38/38)
Food allergy	82.4% (32/38)
Allergic rhinitis	63.2% (24/38)
Asthma	47.4% (18/38)
Antibiotic allergy	23.6% (9/38)
Penicillin	15.8% (6/38)
Trimethoprim/sulfamethoxazole	7.9% (3/38)
Cephalosporin	7.9% (3/38)
Clindamycin	2.6% (1/38)

AD lesions that appeared to be secondarily infected based on the clinical judgment of board-certified A/I faculty. The study was approved by the University of Arkansas for Medical Sciences Institutional Review Board.

Results

Participant Characteristics

Thirty-eight subjects (median age 3 years, 9 months) fulfilled criteria for inclusion in the study (Table 1). The study included 20 males and 18 females. Of the 38 participants, 21 were white, 16 were black, and 1 was classified as "other" in the medical record. The majority of participants (36/38) had at least 1 additional atopic disease other than AD. Food allergy was the most common concomitant atopic disease with 32/38 (84%) subjects having at least 1 documented food allergy. Allergic rhinitis and asthma were also common among study participants with 63.2% and 47.4% affected, respectively. Known antibiotic allergy limited antimicrobial treatment options in 9/38 (23%) cases.

Isolate Identification and Antimicrobial Susceptibility

Staphylococcus aureus was the most common isolate cultured from secondarily infected lesions (53/59, 90%), followed by *Streptococcus pyogenes* (5/59, 8%), and *Staphylococcus haemolyticus* (1/59, 2%). Susceptibility

Table 2. Antimicrobial Resistance of *Staphylococcus aureus* Isolates

Drug	Study Population	All Outpatients	P
Methicillin/oxacillin	45.3% (24/53)	76.4% (2274/2975)	<.001
Clindamycin	37.7% (20/53)	9.4% (280/2964)	<.001
Tetracycline	3.4% (2/53)	3.3% (97/2975)	.21
Trimethoprim/sulfamethoxazole	0% (0/53)	0.6% (19/2968)	.56

Table 3. Antimicrobial Prescribed at Time of Culture

Drug	Frequency Prescribed	Effective Based on Culture
Clindamycin	29/51 (56.9%)	19/29 (65.5%)
Trimethoprim/sulfamethoxazole	6/51 (11.7%)	5/6 (83.3%)
Cephalexin	5/51 (9.8%)	5/5 (100%)
Amoxicillin/clavulanic acid	4/51 (7.8%)	0/4 (0%)
Linezolid	3/51 (5.9%)	3/3 (100%)
Doxycycline	2/51 (3.9%)	2/2 (100%)
Amoxicillin	2/51 (3.9%)	1/2 (50%)

data of *S aureus* isolates from the A/I clinic as compared with isolates from the outpatient reference population are summarized in Table 2. Susceptibility to methicillin/oxacillin and clindamycin differed significantly ($P < .001$) between the study group and the outpatient reference population. Isolates from A/I patients were noted to be methicillin resistant in 45% of cases (24/53) as compared with 76% resistance in the outpatient reference population (2274/2975). Resistance to clindamycin was seen in 38% (20/53) of A/I patients compared with only 9% (280/2964) in the outpatient reference population. Resistance to other antibiotics (tetracycline and trimethoprim/sulfamethoxazole) did not differ significantly between the 2 groups.

Antibiotic Selection

On examination of the empiric antimicrobials prescribed at the time of culture, an appropriate antimicrobial was chosen in 35/59 (61%) of cases. In 16/59 (31%) of cases, an antimicrobial agent was empirically chosen to which the organism was resistant. Antimicrobials were not prescribed at the time of culture in 8/59 (14%) of cases. Antimicrobials prescribed at the time of culture are shown in Table 3. The most commonly prescribed antimicrobial agent was clindamycin, which was prescribed in 29/51 cases (57%).

Discussion

Few studies have examined the resistance patterns of microbes from secondarily infected skin lesions of AD patients in a region of the United States with a high

prevalence of methicillin-resistant *S aureus* (MRSA).^{9,15} Despite a modest number of patients, our data demonstrate 2 significant differences in resistance patterns between organisms isolated from children with AD when compared with isolates from a general outpatient population. First, *S aureus* isolates from our AD cohort were significantly less likely to be methicillin resistant than organisms isolated from the general outpatient population. Although the data from our microbiology lab do not include information on the type of lesion from which isolates were cultured, we assume abscess material was likely the most common source of wound cultures from our outpatient comparison group. Prior research suggests that abscesses and cellulitis are the most common SSTIs at the time of presentation to outpatient primary care clinics and emergency departments.¹⁶ Other studies suggest that cultures from abscesses are nearly twice as likely to involve MRSA as other types of SSTIs.^{17,18} Additionally, a study by Pallin et al¹⁹ showed no increase in the rate of office visits for dermatitis between 1993 and 2005, despite an increase in the prevalence of MRSA. The fact that no isolates in our study cohort were obtained from an abscess may explain the lower percentage of MRSA when compared with isolates from all outpatients. Another important finding from the current study includes the discovery of an almost 4-fold increase in resistance to clindamycin noted among *S aureus* isolates in the AD study group versus the outpatient reference group. The mechanism behind this finding is unclear. Since increased antibiotic use promotes development of antibiotic resistant bacteria, our findings among patients with AD may be because of the increased prescriptions for antimicrobials

in atopic patients as compared with the pediatric population as a whole.²⁰ Paul et al²¹ recently reported that antibiotics were prescribed during nearly 1 in 6 pediatric ambulatory care visits for asthma despite a lack of documented antibiotic need. In addition, a recent study by Fanelli et al²² found levels of clindamycin resistance in *S aureus* isolates from nasal swabs in children undergoing treatment with oral antimicrobials for acne that were similar to the rates reported in our study.

Because of the high prevalence of clindamycin-resistant *S aureus*, we have implemented several changes in the clinical management of secondary skin infections in our patients with AD in 2 notable ways. First, clinicians now obtain skin cultures from any secondarily infected lesion in AD patients at the initiation of antimicrobial therapy. Second, trimethoprim/sulfamethoxazole has been adopted as the first-line empiric antimicrobial therapy in children for whom there is no contraindication, with doxycycline as an alternative in older children. Two potential drawbacks of this change in therapeutic approach exist. First is the potential for treatment failure in patients who have secondary infection due to *Streptococcus pyogenes*, as trimethoprim/sulfamethoxazole is a poor agent for treatment of infections caused by this organism. Second, there is a potential for severe drug reaction caused by the use of trimethoprim/sulfamethoxazole.

Further research is needed to determine if *S aureus* isolates from children with AD have different virulence genes when compared with isolates from other types of SSTIs. Also, as resistance to commonly prescribed antimicrobials becomes more prevalent, a standardized monitoring system is critical to ensure that those patients empirically prescribed an antimicrobial agent that later proved to be ineffective based on susceptibility data are prescribed an appropriate therapeutic agent. Finally, as with any change in clinical practice parameters, this change in empiric antibiotic choice will need to be monitored to ensure continued effectiveness despite changes in antimicrobial susceptibility profiles.

One limitation of our study is the small sample size. AD participants in the study were from 1 subspecialty clinic in our hospital, despite the fact that these patients, including those with secondarily infected lesions, are treated in clinics throughout the hospital as well as in the emergency department. Second, because this was a retrospective study, a systematic set of guidelines involving when cultures are sent and which antimicrobials should be chosen as first line was not in place prior to beginning the study. Rationale for the decision to culture and the empiric antimicrobial chosen were solely based on the expertise of the clinician. Third, data regarding whether or not allergy to a specific antimicrobial played a role in

the empiric selection of a drug could not be adequately gleaned from the clinic notes used for this study. Finally, since data from our outpatient reference population were obtained from the microbiology lab, it was not possible to determine the source of lesions in this group.

In conclusion, secondarily infected lesions are a significant problem in patients with AD. Our study reveals 2 distinct differences in the antimicrobial susceptibility profiles of *S aureus* isolates between patients with AD when compared with all outpatients. Because of the increased clindamycin resistance noted among *S aureus* isolates in AD patients, we have made changes to the antimicrobial prescribing practices in AD patients with secondarily infected skin lesions, including adopting trimethoprim/sulfamethoxazole as our first-line empiric antimicrobial of choice in these patients and encouraging culture-driven antibiotic choices when feasible.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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