

## A Retrospective Review of Streptococcal Infections in Pediatric Atopic Dermatitis

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**Abstract:** In order to assess the clinical characteristics and impact of group A streptococcal infection in children with atopic dermatitis, a retrospective review was performed in children diagnosed with atopic dermatitis who had a skin culture. Culture results and clinical characteristics of those with group A *streptococcus* were compared with those with *Staphylococcus aureus*. Infection with group A streptococcus was present in 16%; infection with *Staphylococcus aureus* was present in 72%, and 14% had mixed cultures. Patients infected with group A *streptococcus* were more likely to be febrile, to have facial and periorbital involvement, and to be hospitalized compared with those infected with *Staphylococcus aureus* alone ( $p \leq 0.01$  for all comparisons). Bacteremia and cellulitis were significantly more common in those infected with group A *streptococcus* than in those infected with *Staphylococcus aureus*. Retrospective design and review of only those patients receiving bacterial cultures may select for greater severity than in the general atopic dermatitis population. Group A *streptococcus* appears to be a significant skin pathogen infecting children with atopic dermatitis. Children with atopic dermatitis and group A streptococcal infection are more likely to have invasive disease and complications than those infected with *Staphylococcus aureus* alone.

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Atopic dermatitis (AD) is an important and common cause of morbidity to children and their families, with a significant impairment of quality of life (1,2). It is the most common chronic inflammatory skin condition in pediatric practice, with an increasing prevalence

throughout the world (2,3). The association of *Staphylococcus aureus* (*S. aureus*) skin infections with AD is well recognized (4–6). The rate of bacterial colonization is higher during AD exacerbations than remissions and is correlated with the severity of skin lesions (7,8).

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Streptococcal skin infection complicating AD, although less well recognized, has also been documented as a pathogen in those with poorly controlled AD (9–11). Infection with *Streptococcus* may be facilitated through disruption of the disturbed epidermal barrier universal in atopic skin (12–14). Cutaneous group A streptococcal (GAS) infections may lead to more invasive GAS infections, which include bacteremia, toxic shock syndrome, osteomyelitis, and necrotizing fasciitis. Invasive GAS infections are a cause of significant morbidity and mortality (15–19) and have increased significantly in the past decade (20).

In the late 1990s, we noted an increasing number of children with AD who grew GAS from skin cultures. This prompted our retrospective review between June 1999 and September 2001 of all children seen in two practice settings (University of California, San Francisco [UCSF] and Children's Hospital Oakland [CHO]) with AD in whom a bacterial culture was positive (for *Streptococcus* or *S. aureus*) to determine the scope of GAS infection and compare the clinical characteristics of children with GAS (with or without *S. aureus*) to those children in whom *S. aureus* alone was recovered. Because of a time lapse of several years between this study and manuscript preparation, we also performed a second study, examining recent trends in GAS recovered from the skin of children with AD during a period from 2004 to 2008 at UCSF.

## METHODS

Following approval from the UCSF committee for human research, patient rosters were created from two clinical settings (community hospital practice [CHO] and university practice [UCSF]) using different laboratory databases. The UCSF patient roster was created by searching the University laboratory database (STOR) for culture results for the time period June 1999 through September 2001 for all patients 0 to 18 years old using the ICD9 code for atopic dermatitis (691.8). The CHO hospital database was searched using the Meditech system to generate a patient roster for all patients 0 to 18 years old with a culture and an ICD9 code for atopic dermatitis (691.8) for the same time period.

Within the UCSF patient roster, the output was limited to any microbiology data listed for those patients. Nonrelevant cultures (e.g., gram-negative urinary tract infections) were excluded. The great majority of microbiological data was generated from skin cultures (from areas of clinically infected AD). From the CHO hospital database, skin cultures (and cultures from other body sources where relevant) were tabulated. Patient records

(chart notes, hospital notes) for all 187 patients with relevant positive skin cultures on the combined rosters were then reviewed to assess the impact of *Streptococcus* and *S. aureus* infection in these children.

In order to determine whether GAS remained a commonly identified pathogen among patients with AD in more recent years, we reviewed the same UCSF laboratory database for the period 2004 to 2008. We searched for patients (0–18 yrs old) with a skin or wound culture that grew GAS and had a diagnosis of AD based on a previous or coincident ICD-9 code for AD. Because pediatric patients with AD are known to have a high prevalence of skin colonization with *S. aureus*, and because of the recent increasing incidence of methicillin-resistant *S. aureus* (MRSA) as a cause of skin and soft-tissue infections, information about the presence of *S. aureus* among patients with GAS was also recorded. Statistical comparisons made between groups were calculated using chi-square test.

## RESULTS

For the period from 1999 to 2001, a total of 245 skin bacterial culture results were seen. Of these, 187 (76%) were positive, and 24% were negative or grew a contaminant. Seventy-two percent of the total cultures grew *S. aureus* and 16% grew GAS. A mixed growth (*S. aureus* and *Streptococcus* species) occurred in 34 (14% of the total cultures). Of the 187 positive cultures, 95% (177/187) grew *S. aureus*, and 20% (38/187) grew GAS. A mixed growth occurred in 18% (34/187) of the positive cultures. Of the cultures that grew Streptococcal species, GAS was the predominant species recovered with all but six cultures growing GAS. Other  $\beta$ -hemolytic streptococcal species recovered included groups B and G. *Streptococcus viridans* was considered normal skin flora and was not counted as positive (Table 1).

Thick pustules and relatively thick crusts were noted (qualitatively) in many of the patients infected with GAS (Figs. 1 and 2). Patients infected with GAS were four times more likely to have facial and periorbital involvement (37% vs 9%,  $p < 0.0001$ ) compared with those infected with *S. aureus* alone. Those infected with GAS were 3.4 times more likely to have fever (47% vs 14%,  $p < 0.0001$ ) compared to those infected with *S. aureus* alone. The rates of hospitalization of those with GAS were three times greater compared to hospitalization of those with *S. aureus* alone (20% vs 6%,  $p < 0.001$ ). Overall, those infected with GAS were 3.7 times more likely to have invasive infections (37% vs 10%,  $p < 0.001$ ) compared to those infected with *S. aureus* alone. The most common invasive infections (defined as an infection of a normally sterile site) seen were

**TABLE 1.** Presence of *Staphylococcus* and *Streptococcus* in Cultures from Both Sites

|                          | Children's Hospital Oakland | University of California, San Francisco | Combined Groups |
|--------------------------|-----------------------------|-----------------------------------------|-----------------|
| Total cultures           | 97                          | 148                                     | 245             |
| Total positive cultures  | 77 (79%)                    | 110 (74%)                               | 187 (76%)       |
| Negative or contaminated | 20 (21%)                    | 38 (26%)                                | 58 (24%)        |
| Total SA                 | 74 (76%)                    | 103 (70%)                               | 177 (72%)       |
| Total Strep              | 20 (21%)                    | 24 (16%)                                | 44 (18%)        |
| Total GAS                | 18 (19%)                    | 20 (14%)                                | 38 (16%)        |
| SA alone                 | 57 (59%)                    | 86 (58%)                                | 143 (58%)       |
| Strep alone              | 3 (3%)                      | 7 (5%)                                  | 10 (4%)         |
| GAS alone                | 3 (3%)                      | 6 (4%)                                  | 9 (4%)          |
| Mixed (SA + Strep)       | 17 (18%)                    | 17 (11%)                                | 34 (14%)        |
| Mixed (SA + GAS)         | 15 (15%)                    | 14 (9%)                                 | 29 (12%)        |

SA, *S. aureus*; GAS, group A *Streptococcus*; Strep, Streptococcal species (including GAS and Groups B and G).

Total SA = SA with or without Strep.

Total Strep = Strep with or without SA.



**Figure 1.** 7-year-old girl with Group A *Streptococcus* complicating AD. Note thick periorbital crusting.



**Figure 2.** Thick, lichenified plaque cultured positive for group A *Streptococcus*.

bacteremia, which was four times more likely in those with GAS infection compared to those infected with *S. aureus* alone (13.2% vs 3.4%,  $p = 0.01$ ) and cellulitis, which was 2.7 times more likely in those infected with GAS compared to those infected with *S. aureus* alone (24% vs 9%,  $p = 0.01$ ) (Fig. 3). Other invasive complications of GAS infection included peritonitis, psoas muscle abscess, and toxic shock syndrome.

In reviewing the UCSF laboratory database between 2004 and 2008, GAS remained a commonly identified bacterium among patients with AD. A total of 74 unique pediatric patients (range 10–17 per year, mean 14.8) presented with AD and GAS from a skin culture. Among these, a total of 51 patients (69%) also had *S. aureus* growing in their culture, with methicillin resistant *S. aureus* (MRSA) accounting for 10% of the *S. aureus* recovered. Overall, patients with AD accounted for 60% of the total number of pediatric patients with GAS skin cultures during the study period.

## DISCUSSION

Children with AD are prone to recurrent cutaneous and occasional systemic bacterial infections. Despite the well recognized role of *S. aureus* in AD (21,22), GAS infection is emerging as an important pathogen causing skin and soft tissue infections in children with AD. In this review, GAS infection in children with AD was found frequently. Although *Streptococcus* (predominately GAS) was cultured less frequently in this study than *S. aureus*, and mixed infections were commonly present, children infected with GAS (with or without *S. aureus*) were more likely to be sicker and be hospitalized, have facial and periorbital involvement, and have invasive infection more often compared to those infected with *S. aureus* in the absence of GAS.

These findings emphasize the importance of considering GAS infection as a possible etiology of fever and worsening clinical appearance in patients with AD who appear to have a skin infection, in order to minimize

Comparison of clinical features, invasive infection and hospitalization between patients with *S. aureus* and GAS

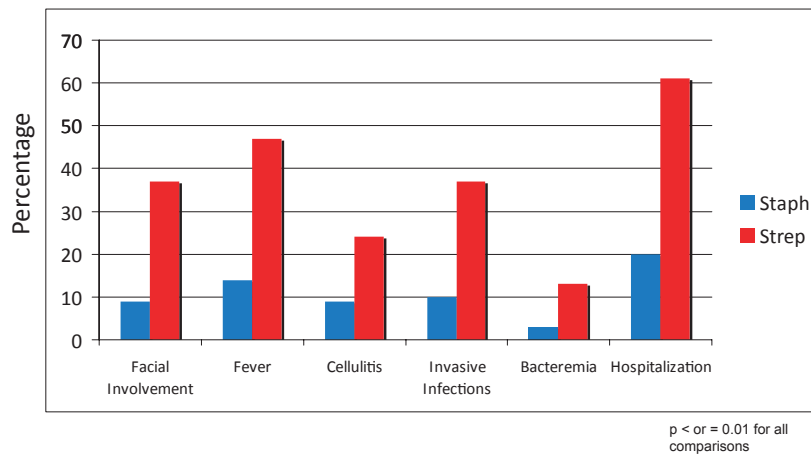


**Figure 3.** Comparison of clinical features, invasive disease, and hospitalization between patients with *Staphylococcus aureus* and Group A streptococcal diseases (*Streptococcus pyogenes*).



**Figure 4.** Herpetiform lesions cultured positive for group A *Streptococcus* and negative for HSV.

adverse outcomes from infection. Important clinical features that may aid the clinician in early detection of GAS include thick-walled pustules and heavy crusting, prominent facial and periorbital involvement, as well as fever and increased pain. Additionally, we noted several patients with small erosions mimicking eczema herpeticum (Fig. 4). Streptococcal infection mimicking herpes infection in AD has been reported recently (23) and may provide an additional important clinical clue alerting the clinician to the presence of GAS infection.

We acknowledge that the retrospective design and review of only those patients receiving bacterial cultures likely selects for more infections and greater severity than in the general AD population. Additionally, missing nonsuspected cases of infection may have introduced

bias in the analysis, preventing ascertainment of prevalence data for *Streptococcus* in children with AD. Hopefully, further prospective studies can address this issue more fully.

Further prospective studies examining the prevalence and role of GAS in AD are particularly important, because MRSA has become an important cause of purulent skin and soft-tissue infections, and AD can be a predisposing factor. In the most recent period of our study (2004–2008), MRSA prevalence was found to be relatively low, even within a community where MRSA is endemic, a finding similar to previous studies of MRSA in AD (24–26). This pattern more closely reflects expected rates of skin colonization (where methicillin-sensitive *S. aureus* is most common), rather than skin and soft-tissue infections (where MRSA is predominant). Because of the increased incidence of CA-MRSA, many physicians are now prescribing trimethoprim-sulfamethoxazole (TMP-SMX) in place of cephalosporins for empiric treatment of patients with skin infections (27,28), but trimethoprim-sulfamethoxazole is not reliably effective for GAS (29,30). The possibility of GAS infection and potential choices of antibiotics should be considered in patients with infected AD, particularly if clinical signs such as fever, toxicity, punctuate erosions resembling eczema herpeticum, or thick-walled pustules are present.

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