

Frequency and Clinical Role of *Staphylococcus aureus* Overinfection in Atopic Dermatitis in Children

Giampaolo Ricci, M.D.,* Annalisa Patrizi, M.D.,† Iria Neri, M.D.,† Barbara Bendandi, M.D.,* and Massimo Masi, M.D.*

Departments of *Pediatrics and †Clinical and Experimental Medicine, Division of Dermatology, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy

Abstract: The goal of this study was to evaluate the frequency and role of *Staphylococcus aureus* infection in patients with atopic dermatitis (AD). In 81 children, ages 2 months to 9 years, affected with moderate to severe AD, 308 samples from the cutaneous lesions were obtained and analyzed. *S. aureus* was isolated in 52 children (64.2%). Five of these were also colonized by *Streptococcus pyogenes* and one by *Candida albicans*. In 61 patients, total IgE serum level and specific IgE were tested to evaluate their allergic status: in 43 children a diagnosis of extrinsic AD was made, while 18 were affected by intrinsic AD. A higher presence of the bacterium was observed in allergic (71%) versus nonallergic children (49%). Our data demonstrate the importance of *S. aureus* in the clinical manifestation of AD and, in particular, its role in worsening the eczematous lesions of the face, neck, and perineum in children less than 1 year of age.

Atopic dermatitis (AD) is a pruritic, chronically relapsing inflammatory cutaneous disease frequently associated with asthma and allergic rhinoconjunctivitis (1). The skin of AD patients exhibits a striking susceptibility to colonization with *Staphylococcus aureus* and the prominent role of *S. aureus* skin colonization as a factor contributing to the exacerbation of AD has been well established (2). In 1974, in a study by Leyden et al. (3), *S. aureus* was isolated from lesional skin in more than 90% of AD patients, and subsequent studies revealed that up to 80% of AD patients have skin colonization with *S. aureus* (2). Moreover, a relationship between *S. aureus* levels and AD extent and severity has been noted (4).

An attractive concept is that *S. aureus*-released proinflammatory products may gain access to the

dermis because of the disruption of the skin barrier. In addition to the various well-described molecules secreted by most strains of *S. aureus*, such as α -toxin, protein A, and other less known pyrogenic exoproteins (2), some strains of *S. aureus* produce exotoxins with T-cell superantigen activity (2) which are able to worsen AD. Some AD patients may therefore benefit from eradication of *S. aureus* by antimicrobial therapy. However, repeated courses of antibiotic therapy may lead to development of antibiotic-resistant strains of *S. aureus* (1,5).

The goal of this study was to determine the frequency of *S. aureus* colonization and its impact on the severity of AD in young children with moderate or severe disease.

Address correspondence to Giampaolo Ricci, M.D., Department of Pediatrics, University of Bologna, Via Massarenti 11, 40138 Bologna, Italy, or e-mail: ricci@med.unibo.it.

METHODS

Study Population

Our study was performed on a group of children with AD diagnosed according to the Hanifin and Rajika criteria (6) and consecutively referred to our Pediatric Department between October 2000 and May 2002. A clinical evaluation of AD was performed using the SCORAD index (7) as follows: severe AD > 40, moderate AD 20–40, mild AD < 20. A total of 81 patients showing moderate to severe AD with exudative lesions were selected for this study. They consisted of 46 boys and 35 girls, ages 2 months to 9 years (mean 2 years). Informed parental consent was obtained.

At the time of examination, all patients were in an acute phase of the disease; 48 children had a family history of atopy, and in all of the older children, AD had begun before 2 years of age.

Allergologic Assessment

An allergologic study was performed in 61 patients and consisted of total IgE serum level evaluation and circulating specific IgE antibody determination using the RAST CAP-System (Pharmacia, Uppsala, Sweden) for food allergens (cow's milk, hen's egg, wheat, soybean, fish, tomato, peanut) and inhalant allergens (grass pollen, cat, dog, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*). The specific IgE antibodies were considered to be present when the level was higher than 0.35 kU/L. Statistical analysis was performed using the square test.

Microbial Isolation from Skin Lesions

In order to isolate bacteria and fungi, samples from the cutaneous lesions were obtained and analyzed in our microbiology laboratory. From 1 to a maximum of 10 cutaneous samples (mean 4) were obtained from each patient. A total of 308 samples taken from areas affected by acute exudative eczema were obtained and analyzed: 89 samples from the face and neck, 55 samples from the

trunk, 81 samples from the arms, 75 samples from the legs, and 8 samples from the groin, genital area, and/or the perineum.

Treatment and Follow-Up

Patients with localized infected lesions were treated only with topical antimicrobial therapy associated with topical steroids, while patients with extended infected lesions were treated with systemic antimicrobial therapy and reevaluated after the end of this treatment.

RESULTS

Forty-seven of the 81 children had severe AD (SCORAD > 40) and 34 had moderate AD (SCORAD 20–40). The average SCORAD value was 43.3.

Skin lesions were colonized by *S. aureus* in 52 children (64.2%). Five of these were also colonized by *Streptococcus pyogenes* and one by *Candida albicans*. Of the 43 patients age 1–12 months, 34 (79%) tested positive for *S. aureus*, while only 18 (47.3%) of the 38 older children tested positive ($p < 0.006$) (Table 1). Of the 89 samples obtained from eczematous lesions of the face and neck, 53 (59.5%) were positive for *S. aureus*, 21 of the 55 samples (38.2%) from the trunk were positive, 31 of the 81 samples (38.3%) from the arms were positive, 32 of the 75 samples (42.6%) from the legs were positive, and 5 of the 8 samples (62%) from the groin, genital area, and/or perineum were positive. A prominent prevalence of positive samples were taken from the face and neck and from the groin, genital area, and/or perineum ($p < 0.02$). Moreover, the percentage of samples positive for *S. aureus* isolated from the face and neck was particularly high in the younger age group: 37 of the 57 samples (65%) obtained from the face and neck in children younger than 12 months were positive for *S. aureus*, as opposed to only 16 of the 32 samples (50%) obtained from the same area in older children ($p = 0.25$). Thirty-three of the 47 patients with severe AD (SCORAD > 40) were colonized with *S. aureus*, showing a higher percentage (70.2%) of *S. aureus* overinfection

TABLE 1. Relationship Between Clinical Evaluation with the SCORAD Index and *S. aureus* Positivity

	No. of cases SCORAD			Patients with cutaneous samples positive for <i>S. aureus</i> SCORAD			Patients with cutaneous samples negative for <i>S. aureus</i> SCORAD		
	Moderate	Severe	Total	Moderate	Severe	Total	Moderate	Severe	Total
0–12 months	43	15 (35%)	28 (65%)	34 (79%) ^a	9 (21%) ^a	11	23	4	5
> 12 months	38	19 (50%)	19 (50%)	18 (47.3%) ^a	20 (32.7%) ^a	8	10	11	9
Total	81	34	47	52	19	33	29	15	14

^a $p < 0.006$.

than in children with moderate AD (19 of the 34 children colonized; 55.8%) ($p = 0.27$).

Antimicrobial therapy was suggested for the 52 infected children, and good clinical results were obtained with good clinical control of AD in the following months. In 17 patients treated with systemic antimicrobial therapy, the SCORAD index was calculated not only before but also after treatment. In 16 children (94.1%) the SCORAD index showed a reduction; 9 of these patients (56.2%) showed a decrease of more than 20 points and only 1 patient showed no improvement. The other four patients treated with systemic antimicrobial therapy were contacted by phone to verify the clinical course of the disease after treatment and all of them reported good clinical improvement. The same procedure was followed for all 31 patients undergoing topical treatment, and positive results were again reported.

Allergologic Assessment

On the basis of the allergologic study results, we were able to divide the 61 patients studied into two groups: 43 affected by "extrinsic" AD (34 with a high IgE serum level and the presence of specific IgE and 9 with only specific IgE) and 18 by "intrinsic" AD (without allergologic test positivity). Of the 43 children with allergic AD, 30 (70%) were colonized by *S. aureus*, as opposed to only 9 of the 18 children (50%) with intrinsic AD ($p = 0.24$) (Fig. 1).

DISCUSSION

Several factors have been suggested to trigger AD, including irritants, foods, aeroallergens, and infections. There has been widespread interest in the potential role

of *S. aureus* in the pathogenesis of AD because most patients are colonized by this bacterium; *S. aureus* secretes potent toxins that trigger skin inflammation, worsening the eczema (8). Despite the relatively small number of patients involved in this study, some results are of considerable interest, particularly because of the very young age of the children (all but seven of the patients were younger than 5 years of age).

In our study, *S. aureus* was present in 64.2% of analyzed patients. This percentage is quite different from data reported in some previous studies (9), although our result is in line with more recent data reported by Patel et al. (10), where 57% of patients were infected, and by Breneman et al. (5), where 50% of patients were infected.

The overinfection by *S. aureus* in our study showed a statistically significant ($p < 0.006$) difference regarding the age of the children. The younger children (less than 12 months of age) had samples positive for *S. aureus* more often than the older group. Furthermore, a statistically significant prevalence of positivity ($p < 0.02$) was observed for samples taken from the face and neck and from the groin, genital area, and/or the perineum. Samples obtained from the lesions on the face and neck in children younger than 12 months of age showed a higher prevalence of the bacterium than those taken from the same areas in older children. This may be due in part to the high involvement of these areas by AD in younger children; in addition, we cannot exclude the possibility that the higher percentage of infection in these children may be related to the prevalence of exudative lesions at this age. The eight children with involvement of the diaper area showed relapsing rhagadized lesions or erythematous and exudative lesions on the folds associated with erosions due to intense itching. In all these children, an allergologic evaluation was performed because of a diagnosis of diaper eczema.

Moreover, in our study, the skin of "allergic" children was more often, although not significantly, colonized by *S. aureus*. Allergic status may in fact play a role in promoting skin colonization by the bacterium. Furthermore, in our patients, the majority of those less than 1 year old showed positivity to food allergens (Table 2).

The mechanism by which *S. aureus* is able to colonize the skin of AD patients is largely unknown. It has been reported that acute skin inflammation in AD is primarily mediated by type 2 helper T (Th2) cells (11). The reduction of skin colonization after antibacterial and corticosteroid therapy suggests that it is the inflammatory process that drives the attachment of *S. aureus* to atopic skin. A study by Cho et al. (11) reports a novel action of interleukin (IL)-4: the induction of *S. aureus* binding to the skin. In fact, *S. aureus* expresses an array of adhesions that allow it to bind extracellular matrix (ECM)

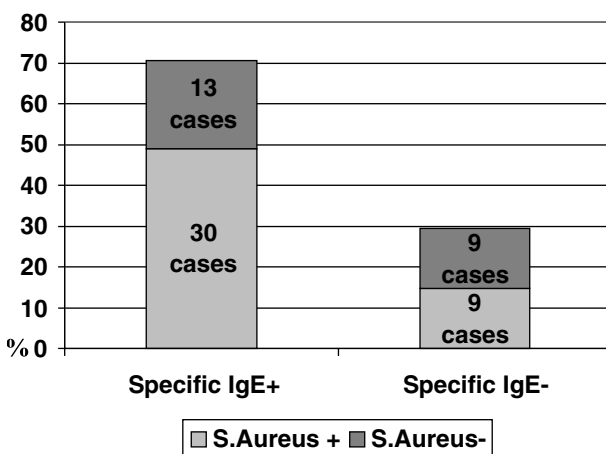


Figure 1. Relationship between IgE sensitization determined by RAST test and *S. aureus* overinfection in 61 children with AD.

TABLE 2. Relationship Between Two Groups of Children, IgE Serum Levels, and Specific IgE Sensitization

	Allergologic assessment	RAST negative	RAST positive	RAST positive (food only)	RAST positive (food and inhalant or inhalant only)
0–12 months	32	7 (22%)	25 (78%)	20 (80%)	5 (20%)
> 12 months	29	11 (38%)	18 (62%)	7 (38.9%)	11 (61.1%)
Total cases	61	18	43	27	16

components and also certain plasma proteins that can exude into sites of skin inflammation. By utilizing these adhesions, initial adherence to the skin occurs and the colonization process can begin. Thus IL-4-induced fibronectin synthesis, in combination with plasma exudation of fibrinogen, could provide a mechanism by which the atopic/inflammatory environment mediates enhanced *S. aureus* attachment to the skin (11). Another study (12) reports a direct link between Th2-mediated cutaneous inflammation and increased colonization of the skin by *S. aureus*.

S. aureus colonization and infection of the skin are thought to play an important role in the pathogenesis of AD. Many studies show that the extent of *S. aureus* colonization of the skin of AD patients correlates with disease severity (12), and in our study the infection rate of AD was higher in patients with severe AD (SCOR-AD > 40, 70.2% of infected patients) than in patients with moderate AD (55.8%).

Clinical studies have shown that all antimicrobial treatments result in an improvement in the clinical severity of AD (5). Recent studies (8) also suggest the important role of antibiotics in the treatment of *S. aureus* overinfection in AD. The observation that combined topical treatment of AD with antibiotics and corticosteroids is more effective than corticosteroids alone has been confirmed by experimental studies showing that *S. aureus* secretes products that can induce insensitivity to topical corticosteroids: when T cells are stimulated with superantigens they become insensitive to the immunosuppressive effects of corticosteroids (8,13). This may be clinically important because the use of antibiotics is known to inhibit superantigen production by *S. aureus* (8). However, prolonged use of antibiotics can be complicated by the development of bacterial resistance (1,5). In our study, children with severe skin lesions and positive skin samples for *S. aureus* were treated with systemic antimicrobial therapy: in all cases (with only one exception) we obtained a good clinical reaction with an improvement of the clinical status in the following months.

REFERENCES

- Taskapan MO, Kumar P. Role of staphylococcal superantigens in atopic dermatitis: from colonization to inflammation. *Ann Allergy Asthma Immunol* 2000;84:3–12.
- Bunikowski R, Mielke MEA, Skarabis H, et al. Evidence for a disease-promoting effect of *Staphylococcus aureus*-derived exotoxins in atopic dermatitis. *J Allergy Clin Immunol* 2000;105:814–818.
- Leyden JJ, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. *Br J Dermatol* 1974;90:525–530.
- Ghura HS, Graham Brown RAC, Johnston G, et al. Traitement des infections à Staphylocoques dorés Méthicilline résistants chez les enfants atteints de dermatite atopique. *Ann Dermatol Venereol* 2001;128:818.
- Breneman DL, Hanifin JM, Berge CA, Keswick BH, Neumann PB. The effect of antibacterial soap with 1.5% triclocarban on *Staphylococcus aureus* in patients with atopic dermatitis. *Cutis* 2000;66:296–300.
- Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venereol (Stockh)* 1980;92(suppl):44–47.
- Kunz B, Oranje A, Labreze L, et al. Clinical validation and guidelines for the Scord index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997;195:10–19.
- Leung DYM. Atopic dermatitis and the immune system: the role of superantigens and bacteria. *J Am Acad Dermatol* 2001;45:S13–S16.
- Thestrup-Pedersen K. Clinical aspects of atopic dermatitis. *Clin Exp Dermatol* 2000;25:535–543.
- Patel GK, Wyatt H, Kubiak EM, Clark SM, Mills CM. *Staphylococcus aureus* colonization of children with atopic eczema and their parents. *Acta Derm Venereol* 2001;81:366–367.
- Cho S-H, Strickland I, Tomkinson A, et al. Preferential binding of *Staphylococcus aureus* to skin sites of Th2-mediated inflammation in a murine model. *J Invest Dermatol* 2001;116:658–663.
- Cho S-H, Strickland I, Boguniewicz M, et al. Fibronectin and fibrinogen contribute to the enhanced binding of *Staphylococcus aureus* to atopic skin. *J Allergy Clin Immunol* 2001;108:269–274.
- Hauk PJ, Hamid QA, Chrousos GP, Leung DY. Induction of corticosteroid insensitivity in human PMBCs by microbial superantigens. *J Allergy Clin Immunol* 2000;105:782–787.