

***Staphylococcus aureus* colonization is associated with increased inhaled corticosteroid requirements in patients with atopic dermatitis and asthma**



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Clinical Implications

- Given that *Staphylococcus aureus* colonization is associated with increased inhaled corticosteroid doses in patients with atopic dermatitis and asthma, targeted therapies to reduce or eliminate *S aureus* colonization may improve asthma outcomes, though prospective studies would be needed.

TO THE EDITOR:

Atopic dermatitis (AD) is a chronic inflammatory skin condition that has been associated with progression to food allergies and asthma. Disruptions in the skin barrier (eg, mutations in filaggrin, an important skin barrier protein) lead to increased risk for AD, asthma, and peanut allergy. Filaggrin mutations, however, are found in only a minority of patients with AD; therefore, additional factors must be involved. AD is commonly associated with skin colonization by *Staphylococcus aureus*, which can contribute to epithelial barrier dysfunction and corticosteroid insensitivity.¹ Clinically, *S aureus* colonization in patients has been associated with severe AD, food allergies, and asthma.^{2,3} In this report, we examined the association between *S aureus* colonization and specific features of asthma. Because staphylococcal enterotoxins are known to induce corticosteroid resistance, we were interested in whether patients with asthma colonized with *S aureus* have increased corticosteroid requirements.

In our study, we reviewed the National Jewish Health Research Database in Denver. Our inclusion criteria were children who were 18 years or younger, had previous physician diagnoses of AD and asthma, and had a previous *S aureus* culture. Data queried included total and allergen specific serum IgE levels, prick skin tests to aeroallergens, fractional exhaled nitric oxide (FENO), asthma control test (ACT) scores, FEV₁ percent predicted, and dose of inhaled corticosteroids (ICSs) prescribed.

We compared outcomes in the *S aureus* and no *S aureus* groups using 999,999 replications of an approximate 2-sample permutation test. Doses of different corticosteroids were converted to micrograms of budesonide equivalents. ICS doses and serum IgE levels were log-transformed for analysis and then back-transformed to their original units. Fisher exact test was performed for enterotoxins.

We identified 557 patients with diagnoses of AD and concomitant asthma who had been cultured for *S aureus*. Of these, 459 subjects had positive *S aureus* cultures (average age, 6.4 years; 60% males) and 98 subjects had negative *S aureus* cultures (average age, 5.3 years; 62% males). Patients with asthma colonized with *S aureus* had significantly higher total

serum IgE levels compared with patients with asthma not colonized with *S aureus* ($P < .0001$; Figure 1). Those with *S aureus* colonization also had a significantly higher prevalence of aeroallergen sensitization ($P = .003$; Figure 1). Patients with asthma colonized with *S aureus* had higher percentages of detectable specific IgE against Staphylococcal enterotoxin A, enterotoxin B, or toxic shock syndrome toxin (77% vs 38%; $P = .03$; Figure 1).

Patients with asthma colonized with *S aureus* required a higher daily dose of ICSs ($P = .01$; see Figure 2). The ICS daily dose between the 2 groups differed despite similar ACT scores ($P = .91$; Figure 2), similar FENO levels ($P = .82$; Figure 2), and similar FEV₁ percent predicted (94% predicted [SD 14.2] in those colonized with *S aureus* vs 95% predicted [SD 12.6] in those not colonized; $P = .92$). The relationship of *S aureus* colonization to daily dose of ICSs persisted when we included FEV₁ percent predicted, total IgE, FENO, and the proportion of positive responses to aeroallergens in a regression model of ICS dose. We did not find a clinically meaningful difference in the percentages of subjects using oral corticosteroids or ICSs with or without a long-acting beta agonist.

Our data demonstrate that *S aureus* colonization is associated with increased corticosteroid requirements in patients with asthma at similar levels of asthma control, FENO, and FEV₁ percent predicted. A recent study also showed an association between *S aureus* nasal colonization and worsened asthma-associated outcomes (emergency room visits for wheezing, asthma diagnoses, and asthma attack in the past year).³ *S aureus* has also been found to occur in increased numbers in bronchial airways of children with asthma.⁴ *S aureus* secretes various enterotoxins that induce corticosteroid resistance directly. The mechanisms include induction of increased expression of glucocorticoid receptor β , which interferes with transcription of corticosteroid-responsive genes.⁵ Analysis of T-cell receptor repertoire in the bronchoalveolar lavage of patients with poorly controlled asthma was consistent with effects of staphylococcal enterotoxins acting as superantigens.⁶ In murine models, superantigens have been shown to induce airway hyperresponsiveness and inflammation.⁷ Together, these studies suggest that *S aureus* can contribute to disease severity in asthma.

Furthermore, our study showed that *S aureus* colonization is associated with increased serum total IgE and increased sensitization to aeroallergens and staphylococcal enterotoxins. Other studies have shown that sensitization to enterotoxins is associated with worsened asthma outcomes.^{8,9} Enterotoxin-sensitized subjects had significantly lower FEV₁ percent predicted and increased risk for severe asthma, oral steroid use, and hospitalizations.⁸ Sensitization to *Staphylococcal* enterotoxin A was also associated with poor asthma control, higher FENO, and total IgE levels, lower ACT scores, and more hospitalizations despite higher ICS dose.⁹

In conclusion, our study demonstrates that in patients with asthma with AD, *S aureus* colonization is associated with increased corticosteroid requirement, total IgE, and sensitization to aeroallergens and staphylococcal enterotoxins. This suggests that *S aureus* colonization may increase local airway inflammation and corticosteroid resistance, contributing to worsened asthma. Future prospective studies are required to determine

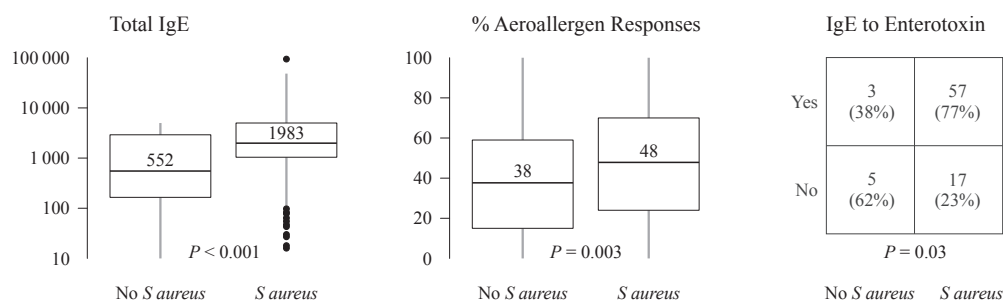


FIGURE 1. Patients with asthma colonized with *S aureus* had total IgE levels of $3.297 \pm \text{SD } 0.581$ in log-transformed units vs $2.742 \pm \text{SD } 0.802$ ($P < .0001$). When these log10 values were back-transformed to units of kU/L, the IgE values were 1983 kU/L vs 552 kU/L, respectively. Those with *S aureus* colonization also had higher percentages of testing positive for aeroallergen sensitization ($48\% \pm \text{SD } 29\%$ vs $38\% \pm \text{SD } 29\%$; $P = .003$) and sensitization to enterotoxin A, enterotoxin B, or toxic shock syndrome toxin (77% vs 38% ; $P = .03$). A positive test result was indicated by a detectable aeroallergen-specific serum IgE level of 0.35 kUA/L or more or skin wheal of 3×3 mm or more after accounting for any saline control positivity.

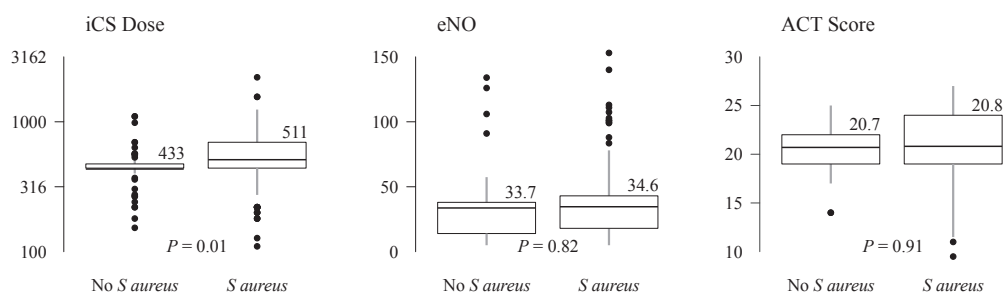


FIGURE 2. Patients with asthma colonized with *S aureus* required a higher daily dose of ICSs ($2.708 \pm \text{SD } 0.204$ in log10 [budesonide equivalents] vs $2.636 \pm \text{SD } 0.158$; $P = .01$). When these log10 values were back-transformed to units of μg , the values are 511 μg vs 433 μg , respectively. F_{ENO} values were similar ($34.6 \text{ ppb} \pm \text{SD } 24.9 \text{ ppb}$ in those with *S aureus* vs $33.7 \text{ ppb} \pm \text{SD } 34.8 \text{ ppb}$; $P = .82$). ACT scores were similar ($20.8 \pm \text{SD } 4.1$ in the *S aureus* group vs $20.7 \pm \text{SD } 2.7$; $P = .91$).

whether eradication of *S aureus* improves asthma control and reduces corticosteroid requirements.

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