

Staphylococcus aureus prevalence in allergic fungal rhinosinusitis vs other subsets of chronic rhinosinusitis with nasal polyps

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Background: The pathogenesis of allergic fungal rhinosinusitis (AFRS) is thought to represent an immunological reaction to fungal antigens. Recent studies have implicated superantigens and non-immunoglobulin E (IgE)-mediated mechanisms in the development of AFRS. The objective of this study is to assess the prevalence of *Staphylococcus aureus* in AFRS vs other subsets of chronic rhinosinusitis with polyps (CRSwNP, also termed non-AFRS).

Methods: A case series with retrospective review of 19 patients with AFRS and 21 patients with CRSwNP was performed at a tertiary referral center. The diagnosis of AFRS required the presence of defined criteria described by Bent and Kuhn. Bacterial cultures and fungal cultures were analyzed for each group.

Results: *S. aureus* was significantly more prevalent in the AFRS group compared with the non-AFRS group (63.2% vs 24.1%, $p = 0.005$).

Conclusion: *S. aureus* has been implicated as a disease modifier in CRSwNP through superantigen-mediated mechanisms. This study demonstrates a higher prevalence of *S. aureus* in patients with AFRS vs patients with other subsets of CRSwNP (non-AFRS). These results support a potential role for *S. aureus* in the pathogenesis of AFRS. © 2012 ARS-AAOA, LLC.

Key Words:

allergic fungal sinusitis; chronic rhinosinusitis; fungal sinusitis; superantigen; paranasal sinus disease; rhinosinusitis

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Chronic rhinosinusitis (CRS) represents a broad spectrum of disease, with the term itself inclusive of a variety of subsets. Allergic fungal rhinosinusitis (AFRS) represents 1 of these subsets, with a reported prevalence of 4% to 24% of CRS nasal specimens evaluated by pathologic review in the United States, though there is significant geographic variation of disease, with the southern states demonstrating a higher propensity for the condition vs northern states.^{1–5}

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Initial description of the disease entity occurred in the early 1980s and was suggested to be the nasal analog of allergic bronchopulmonary aspergillosis.^{6,7} A framework put forth by Bent and Kuhn⁸ in 1994 provided the most commonly employed criteria for the diagnosis of the disease entity as we know it today. It suggested that the development of AFRS evolves from incitement of the immune system in response to fungal antigens through a type I hypersensitivity reaction leading to eosinophilic inflammation. This notion of fungal hypersensitivity was recently upheld at an international panel and was suggested as a diagnostic criterion for AFRS.⁹ Even so, considerable controversy still exists regarding the role of fungus and the pathogenesis of this condition. Regardless of the specific immune mechanisms fungal antigens play in the development of AFRS, the resultant inflammation consistently demonstrates eosinophilic features. This has led many authors to highlight this “eosinophilic” common denominator and propose descriptive terminology according to the presence or absence of fungus and/or fungal-specific immunoglobulin E (IgE). This is reflected in the consensus terminology used to describe various subsets of CRS such as: eosinophilic fungal

rhinosinusitis (EFRS), eosinophilic mucin rhinosinusitis (EMRS), AFRS, and AFRS-like groups.^{1,10–14}

Recent evidence implicates staphylococcal enterotoxins, acting as superantigens, in the development and maintenance of eosinophilic inflammation in nasal polyps.¹⁵ *Staphylococcus aureus* is a prototypical model for the superantigen response and has been shown to play a role in several chronic inflammatory and atopic conditions including bronchial asthma and atopic dermatitis.^{16–18} Superantigens elicit T-cell activation by binding directly to major histocompatibility complex class II molecules on antigen-presenting cells, therefore eliciting an exaggerated immune response outside of the classic antigen-receptor mechanism.^{16,19–22}

The role of *Staphylococcus* superantigen as immune activator and co-pathogen in AFRS has been previously hypothesized but not specifically assessed by microbial analysis.^{16,20} The objective of this study is to evaluate the prevalence of *S. aureus* in patients meeting criteria for AFRS vs those with other subsets of CRS with nasal polyps (CRSwNP) (non-AFRS).

Patients and methods

Following institutional review board (IRB) approval from the Committee for the Protection of Human Subjects Office of Research Support Committees at the University of Texas Health Science Center at Houston, a retrospective review of patients diagnosed with CRSwNP or AFRS over a 4-year period was systematically performed. The diagnosis of AFRS required: (1) the presence of eosinophilic mucin defined histologically by the presence of intact and degenerating eosinophils, Charcot-Leyden crystals, and cellular debris, along with (2) fungal hyphae on histopathology at the time of mucin sampling. Additional Bent and Kuhn criteria⁸ were employed to establish the diagnosis of AFRS. These include: (3) type I hypersensitivity to fungus based on serology; (4) nasal polyposis; and (5) characteristic imaging findings on computed tomography (CT) including bony expansion and areas of increased attenuation. Therefore, patients were included in the AFRS group if 5 of 5 of the described criteria were met, or if 4 of 5 criteria were met in the absence of characteristic CT findings.

All CRSwNP patients were also evaluated for the criteria listed above, including serology testing for hypersensitivity to fungus and evaluation for fungal elements on histopathology. Patients were included in the CRSwNP group if they fulfilled established diagnostic guidelines⁹ and did not meet the criteria of AFRS.

Patients were excluded from analysis if there was insufficient data to meet all previously described diagnostic criteria. Patients were also excluded if they presented with a history of immunodeficiency, cystic fibrosis, ciliary dysmotility syndromes, antral choanal polyps, CRS without nasal polyposis, or autoimmune inflammatory diseases such as Wegener's granulomatosis, sarcoidosis, or systemic lupus erythematosus. Also, patients who received antibiotics or

antifungals in the 2 weeks prior to the date of culture were excluded.

Per clinical protocol, all patients underwent rigid nasal endoscopy with a 3-mm or 4-mm 30-degree rigid telescope. Cultures were obtained under endoscopic guidance using a strict aseptic technique. Tami Sinus Secretion Collectors (Medtronic ENT, Jacksonville, FL) or standard 40-cc Kendall-Argyle suction traps (Tyco Healthcare Group LP, Mansfield, MA) were used to sample mucopus or mucin from any of the following areas: middle meatus, sphenoethmoidal recess, or ethmoid, frontal, maxillary, or sphenoid sinuses. Clear mucus was not considered pathologic and not sampled. Swabs were not employed to obtain specimens. Cultures were processed in routine fashion using standard handling protocols. Gram stain, fungal cultures, aerobic bacterial culture and sensitivity were routinely requested. The first recorded culture prior to antibiotic therapy and/or surgical intervention was considered for data analysis.

Bacterial culture results, specifically the presence of *S. aureus*, as well as fungal culture results, were analyzed and compared between groups. Additional demographic data were compared between the AFRS and CRSwNP groups. Statistical analysis was performed using STATA 11 software (StataCorp LP, College Station, TX).

Categorical data were analyzed using the Pearson chi-squared test. Continuous data employed the independent sample *t* test. A *p* value of less than 0.05 was considered statistically significant.

Results

Patient population

During the study time period, 132 patients with available cultures were identified according to diagnostic International Classification of Diseases, 9th edition (ICD-9) codes. Of these, 19 patients met the strict AFRS inclusion criteria described above. All 19 patients fulfilled Bent and Kuhn criteria⁸ and had fungal presence on histopathology, demonstrating fungal elements. Eosinophilic mucin, nasal polyposis, and type I hypersensitivity to fungal antigens were present in all AFRS patients. In the AFRS group, CT data could not be located in 3 patients (Table 1). Another 21 patients met the criteria for CRSwNP. All had nasal polyps on exam. Additionally, 15 patients were noted to have eosinophilic mucin on histopathologic examination.

Demographic information was compared between these 2 groups. There was a higher incidence in African Americans vs Caucasians with AFRS vs CRSwNP (*p* = 0.007). In addition, patients with AFRS were found to be younger than CRSwNP patients (*p* = 0.009). This is consistent with previously published data.²³ There was also a higher prevalence of asthma on the CRSwNP group vs the AFRS group (*p* = 0.038). There was no statistical difference between the AFRS and CRSwNP groups in the incidence of aspirin sensitivity, 20-item Sino-Nasal Outcomes Test (SNOT-20) scores, Lund-Mackay scores, or prior medical or surgical intervention over the course of the preceding year. Table 2 summarizes the population data.

TABLE 1. Inclusion criteria for the AFRS (n = 19) and CRSwNP (n = 21)

Variable	AFRS (%)	CRSwNP (%)
Fungal elements ^a	19 (100)	2 (9.5)
Fungal culture ^b	11 (61)	5 (29)
Eosinophilic mucin	19 (100)	15 (71)
Nasal polyposis	19 (100)	21 (100)
Type I hypersensitivity	19 (100)	9 (43)
Characteristic CT findings	15 (79)	9 (43)

^aFungal identification performed on histopathology.^bDenotes positive growth of fungus on culture, note that 18 fungal cultures were obtained in 19 patients in the AFRS group and 17 of 21 in the CRSwNP group. AFRS = allergic fungal rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography.

Microbiology

Staphylococcus aureus is more prevalent in the AFRS group

Bacterial cultures were obtained on pathologic secretions in all patients in the study (n = 40). A total of 21 cultures were obtained from the CRSwNP group and 19 from the AFRS group, yielding bacterial growth in 20 (95%), and 19 (100%) of the samples in the respective groups. *S. aureus* grew on 16 of 40 total cultures and was found to be statistically more prevalent in the AFRS group (12/19, 63%) compared to the CRSwNP (4/21, 24%, $p = 0.005$). Coagulase-negative *Staphylococcus* was the second most common isolate obtained, with growth on 6 (21%) of CRSwNP samples and 2 (11%, $p = 0.12$) AFRS samples. *Pseudomonas aeruginosa*

TABLE 3. Bacterial microbiology results

	AFRS	CRSwNP	p
Total samples obtained (n)	19	21	–
Total cultures yielding bacterial growth (n)	19	20	–
Specific bacterial isolates, n (%) ^a			
<i>Staphylococcus aureus</i>	12(63.2%)	4(19.0%)	0.005
<i>Pseudomonas aeruginosa</i>	0(0.0%)	5(23.8%)	–
Coagulase-negative <i>Staphylococcus</i>	2(10.5%)	6(28.5%)	0.12
Other	5(26.3%)	5(23.8%)	0.28
No growth	0	1	

^aNumber of cultures with corresponding isolate (% isolates per number of samples obtained).

AFRS = allergic fungal rhinosinusitis; CRSwNP = chronic rhinosinusitis with polyps.

inosa was the third most commonly recovered bacterium, growing in 5 of 21 cultures, all of which were in the CRSwNP group (24%). There was no *P. aeruginosa* isolated in the AFRS group. Table 3 summarizes bacterial culture results.

A total of 18 fungal cultures were obtained from the AFRS, yielding fungal growth in 11 (61%) of the samples. The CRSwNP group had 17 fungal cultures that yielded growth in 5 (29%) of the samples. This was statistically different between the 2 groups ($p = 0.049$). Concurrent presence of *S. aureus* with positive fungal cultures or hypersensitivity to fungus did not demonstrate a difference between the 2 groups (AFRS 7/12, CRSwNP 1/4, $p = 0.246$).

TABLE 2. Characteristics of patient population

Variable	Total (n = 40) (%)	AFRS (n = 19) (%)	CRSwNP (n = 21) (%)	p
Age (average)	43.9	38.4	48.8	0.029
Sex (male/female)	19/21(47.5/52.5)	10/8(55.6/44.4)	9/13(40.9/59.2)	0.369
African American	17(43.6)	10(52.6)	7(35)	0.007
Caucasian	19(48.7)	8(42.1)	11(55)	
Other ^a	3(7.7)	1(5.3)	2(10)	
Asthma ^b	16/38(42.1)	4/17(23.5)	12/21(57.1)	0.038
Aspirin sensitivity	4(10.0)	1(5.3)	3(14.3)	0.355
SNOT-20 (average)	35.6	37.4	33.9	0.611
Previous surgery	22/40(55.0)	10(52.6)	12(57.1)	0.781
Previous medical therapy ^c	36/40(90.0)	17(89.5)	19(90.1)	0.919
Eosinophilic mucin	34/40(85.0)	19(100)	15(71.4)	0.016
Lund-Mackay (average)	13.4	13.3	13.5	0.939

^aDesignation of "Other" included Asian, Hispanic, Indian, and Middle Eastern descents, ethnic data was unavailable for 1 CRSwNP patient.^bAsthma status was unavailable for 2 AFRS patients.^cPrevious medical therapy includes antibiotics, antifungals, or oral steroids within 1 year of presentation.

AFRS = allergic fungal rhinosinusitis; CRSwNP = chronic rhinosinusitis with polyps; SNOT-20 = 20-item Sino-Nasal Outcomes Test.

Discussion

The role of fungus in CRS still engenders significant controversy. The ubiquitous nature of fungal elements in patients with CRS and normal subjects has been used as an argument for and against the role of fungus in inflammatory CRS. Equally controversial are the specific immune mechanisms fungal antigens play in the development of AFRS. The role of a type I hypersensitivity to fungus in AFRS, suggested by many as a feature of this condition, has been disputed by others.¹¹ Furthermore, fungal allergy provides little insight into the development of the disease at hand, considering that many patients with fungal-specific IgE and a clinical picture similar to AFRS fail to demonstrate fungal presence on histopathology or culture.^{10,24} A recent study demonstrated paucity of antigen-specific IgE activation in the setting of CRSwNP when IgE sequences were amplified, questioning the role antigen-specific IgE (eg, fungal-specific IgE) plays in the pathogenesis of CRSwNP.²⁵ Thus, the specific role of antigen-specific IgE in CRS pathogenesis remains poorly understood. However, consensus exists among clinicians and investigators that eosinophilic inflammation is the common denominator in most subsets of CRS, including AFRS.

The data presented in this study demonstrate an increased prevalence of *S. aureus* in AFRS compared with non-AFRS patients. Several possibilities exist whereby *S. aureus* may have a more favorable environment in which to proliferate. For example, the severe eosinophilic inflammation and characteristic mucin found in AFRS may lead to a favorable milieu for *S. aureus* overgrowth, possibly altering the efficacy of the innate immune response in the local environment. The presence of *S. aureus* is well documented as a common organism in patients with CRS.^{26–29} It has also been observed in bacterial cultures taken from AFRS patients; however, the data was either not presented or was limited in sample size.^{30,31} The role of *S. aureus* in sinonasal inflammation has been shown to go beyond the traditional model of pathogenic induction of infectious neutrophilic inflammation. There is increasing evidence that *S. aureus* enterotoxins, known as superantigens, amplify eosinophilic inflammation in patients with CRSwNP.^{15,22} In fact, recent evidence suggests a higher prevalence of bacteria in eosinophilic mucin than previously thought. Ferguson et al.¹⁹ demonstrated that upon re-review of pathologic specimens of eosinophilic mucin 50% (34.5% to 62% upon re-review) of the samples initially negative for bacteria were found to have organisms. This was in the absence of positive bacterial cultures in a number of cases. In our study, the difference in *S. aureus* yield between the AFRS (61%) and the CRSwNP group (24%) is intriguing. AFRS is considered to fall on a higher spectrum of inflammation than most subsets of CRSwNP. The difference in *S. aureus* yield between the 2 groups in our study may therefore reflect the more severe eosinophilic inflammation augmented by the presence of *S. aureus*, possibly via induction of superantigen mechanisms.

We have recently reported an association between the sinonasal presence of *S. aureus* and elevated total serum IgE in patients with CRSwNP.³² Superantigen has also been implicated in the production of local IgE through direct effects on local plasma and B cells.³³ In addition, in vitro studies demonstrate that basophils armed with specific IgE to enterotoxin B degranulate rapidly when exposed to superantigens.¹⁷ Thus it is conceivable that superantigen, by direct effect on local cells, enables local inflammation against various inhalant allergens including fungus. This may potentially explain the asymmetric nature of inflammatory disease in AFRS in its nonadvanced state.

Our study did not demonstrate a higher association between *S. aureus* and fungus in AFRS. This may be attributed to the relatively small numbers showing concurrent growth. Ferguson et al.,¹⁹ in a noncontrolled study, also found a higher prevalence of bacteria in conjunction with fungal elements on histopathology, although *S. aureus* specifically was not evaluated. One potential explanation for this intriguing association is that *S. aureus*, releasing enterotoxins that can act as superantigens, activates a large percentage of T cells in the body and creates a favorable T-helper 2 (Th-2) milieu conducive to the production of IgE against otherwise colonizing fungus. This will eventually lead to the development of the clinical phenotype of classic AFRS. This concept has been previously put forth by Schubert,¹⁶ who hypothesized that superantigen-responsiveness is an essential but not exclusive driver of inflammation in AFRS.

Our study has several limitations. Tissue analysis for presence of enterotoxins was not available at the time of chart review. This data would strengthen the current study if *S. aureus* on culture correlated with superantigen presence in tissue. Therefore, no firm conclusions could be drawn on the mechanism of association between *S. aureus* and AFRS. This study also suffers from limitations common to retrospective reviews. Stringent diagnostic and inclusion criteria significantly limited the number of patients included in the study. This was done in order to limit selection bias that would naturally occur if patients had incomplete variables on data collection. Additionally, although we could not control for previous medical/surgical intervention due to the study design, analysis demonstrated no significant difference between the study groups in this area. A prospectively designed study would afford adequate patient stratification and systematic diagnostic evaluation.

Conclusion

S. aureus was more prevalent in patients with AFRS vs patients with other subsets of CRSwNP. These results support a potential role for *S. aureus* in the pathogenesis of AFRS. 

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