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CME Review

Update on allergic fungal rhinosinusitis

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Key Messages

- The Bent and Kuhn criteria for allergic fungal rhinosinusitis (AFRS) serves to define classic presentations but individual criteria are non-specific, and the criteria is cumbersome in clinical research.
- The mucosal expression of histatin, an antimicrobial peptide with significant antifungal activity, is significantly downregulated in AFRS as compared to CRS and healthy patients.
- The etiology of downregulation of histatins in AFRS remains unclear.
- Cornerstone of AFRS treatment remains sinus surgery with complete removal of eosinophilic mucin and post-operative steroids to maintain disease quiescence.
- Novel insights into the pathophysiology of AFRS provides opportunities for new therapeutic strategies.

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ABSTRACT

Allergic fungal rhinosinusitis (AFRS) is a unique clinical entity that falls under the broader umbrella of chronic rhinosinusitis with nasal polyps with type 2 inflammation. It is characterized by nasal polyposis, production of characteristic thick eosinophilic mucin, and expansile change of involved sinus cavities.

The diagnosis is classically made using the Bent and Kuhn criteria. However, recent studies have indicated the lack of specificity of some major criteria. The need to fulfill all 5 criteria before diagnosing AFRS partially mitigates this but renders the criteria cumbersome to use, and highlights the need to develop more specific criteria.

Our understanding of AFRS pathophysiology has advanced significantly and has helped elucidate the lack of histatins contributing to the inability to clear fungal spores, consequently leading to fungi-induced disruption of the epithelial barrier and stimulation of sinonasal epithelial cells. These trigger a cascade of type 2 inflammatory cytokines driven by both the adaptive and innate immune system. Although more research is needed, these findings could hypothetically point to a limited type 3 immune response at the sinus mucosa, resulting in a compensatory overstimulation of type 2 inflammatory processes.

Treatment for AFRS remains centered on surgery and topical corticosteroids. Short courses of systemic corticosteroids may be used with caution, and fungal-specific immunotherapy and systemic antifungals are options in recalcitrant disease. Biologics show early promise, as we await data from randomized controlled trials under way. Finally, new insights into AFRS pathology provide opportunities for novel therapeutic strategies.

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- Evaluate the limitations of the Bent and Kuhn criteria for diagnosing AFRS.
- Illustrate key concepts in the pathophysiology of AFRS.

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Introduction

Allergic fungal rhinosinusitis (AFRS) is a chronic inflammatory disease of the sinuses that was first recognized approximately 40 years ago. Before that, there had been several reports describing patients with allergic bronchopulmonary aspergillosis (ABPA) who also produced nasal casts or plugs,[1,2] and Millar had a series of 5 patients with "allergic aspergillosis of the paranasal sinuses."[3] However, it was in 1983 that Katzenstein reported 7 cases of "allergic Aspergillus sinusitis,"[3,4] coined the term "allergic mucin," and tied together the key clinico-pathologic features of AFRS to distinguish it as a unique clinical entity.[5]

Since then, the understanding of AFRS has evolved significantly. Allergic fungal rhinosinusitis was initially believed to be a nasal manifestation of ABPA, on the basis of overlapping clinical features of type I hypersensitivity to *Aspergillus*, respiratory epithelial inflammation, and the production of thick, tenacious secretions. However, subsequent work has revealed that it is uncommon for AFRS to coexist in patients with ABPA[6,7] and that a similar sinusitis phenotype could arise in patients who had allergy to non-*Aspergillus* fungi.[8,9] These observations led investigators to move away from understanding AFRS as a simple extension of ABPA to the nasal cavity, and to recognize AFRS as a separate disease in its own right.[10]

Clinically, AFRS is characterized by chronic inflammation of the paranasal sinuses and is generally considered a unique subset within the broader umbrella of chronic rhinosinusitis with nasal polyposis (CRSwNP).[11,12] It is a noninvasive form of fungal sinusitis typically affecting adults often younger than 30 years.[13] These tend to be individuals with atopy, and immunocompetence with a type I hypersensitivity to fungi. Up to 24% of patients with AFRS also have asthma, which, although significant, is a weaker association than in other forms of CRSwNP in which asthma can coexist in up to 50% of patients.[14] The inflammation is driven primarily by a type 2 immune response, and extremely thick eosinophilic mucin is produced as a result. The mucin has a consistency often described as "rubbery" or "peanut butter–like,"[15] with a variety of colors ranging from green to black. The involved sinuses often undergo expansile changes, leading to erosion of bony boundaries such as the medial orbital wall or anterior skull base.[16] In some individuals, these can become so pronounced that facial or orbital deformities such as telecanthus and proptosis can be discerned externally. Despite these significant and occasionally dramatic physical findings, patients often report disproportionately minimal symptoms of nasal obstruction, drainage, or hyposmia. The discrepancy between these dramatic objective signs of severe sinus inflammation and expansion of involved sinus cavities corroborates with the slow tempo of disease progression over years (Fig 1A).

Imaging is useful in assessing patients suspected of having AFRS, and computed tomography (CT) scans frequently reveal opacified, expanded sinuses[17] with a "double-density" sign, arising from highly attenuated sinus contents juxtaposed against hypodense inflamed mucosa[18] (Fig 1A). Computed tomography is also useful in showing altered anatomy and areas of bony erosions, and fine-cut CTs are critical for surgical navigation. Magnetic resonance imaging usually indicates mucosal edema with hypointensities within the sinuses on T2 sequences, because of the presence of eosinophilic mucin (with high protein and low water content).[19]

Laboratory investigations typically reveal extremely high total serum immunoglobulin (Ig) E level (>500 IU/mL)[20] and elevated fungal-specific IgE levels. Peripheral eosinophilia may be present, but this is less common.

Histopathologic analysis of the thick mucin reveals inflammatory cells on a background of amorphous eosinophilic mucin and necrotic cellular debris.[21] Charcot-Leyden crystals from degranulated eosinophils may be seen,[22] and special stains such as Gomori Methenamine Silver may be required to reveal fungal elements[23] that can be hard to visualize on routine hematoxylin and eosin stains.

Despite the presence of many distinguishing features, making the diagnosis of AFRS is not always straightforward. The most widely accepted diagnostic criteria were developed by Bent and Kuhn in 1994.[24] Since then, technologic advances in diagnostic tools have enabled more accurate patient examination but have also highlighted gaps in which the criteria have suboptimal specificity.

In this review, we will examine these areas of controversy in diagnosing AFRS, provide an update on the latest understanding of its pathophysiology, and discuss its implications for treatment strategy.

Issues With Diagnostic Criteria

In 1994, Bent and Kuhn reviewed 15 of their most recent patients with AFRS and developed a set of major and minor criteria for the diagnosis of AFRS. A patient had to fulfill all 5 major features to receive the diagnosis, and these were (1) type I hypersensitivity to fungi confirmed by history, skin tests, or serology; (2) nasal

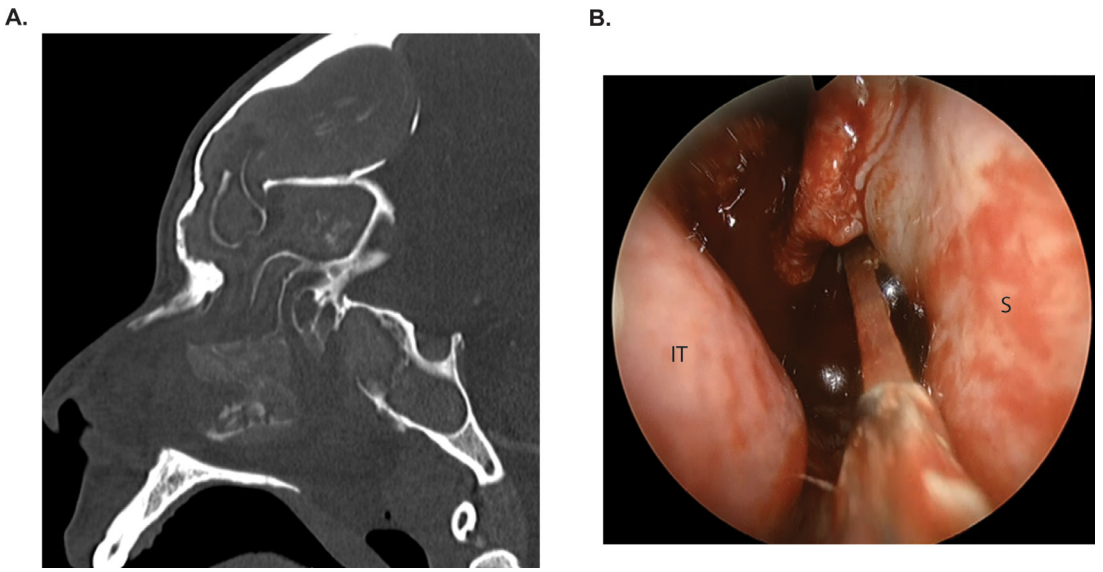

Figure 1. Characteristic computed tomography and nasal endoscopic image of allergic fungal rhinosinusitis. (A) Representative sagittal computed tomography sinus image highlighting expansion of frontal and ethmoid sinuses and "double-density" sign within affected sinus cavities. (B) Nasal endoscopic view of right nasal cavity revealing sticky nature of eosinophilic mucin found within diseased sinus cavities. IT, inferior turbinate; S, septum.

polyposis; (3) characteristic CT signs; (4) eosinophilic mucus without fungal invasion into sinus tissue; and (5) positive fungal stain of sinus contents removed during surgery. Minor features included (1) radiographic bone erosion; (2) positive fungal cultures; (3) unilateral disease predominance; (4) Charcot-Leyden crystals; and (5) peripheral eosinophilia.

A year after the Bent and Kuhn publication, DeShazo described another set of 5 criteria for the diagnosis of AFRS.[25] These excluded fungal type I hypersensitivity and nasal polyposis, including instead the absence of immunocompromise or immunosuppression and the absence of fungal invasion.

The Bent and Kuhn criteria are more widely used and accepted,[11] and have served well in accurately diagnosing patients presenting with classic AFRS. However, several limitations have recently been recognized in their application to both the clinical and research setting. These have been highlighted by advances in diagnostic technique, which suggest that there can be a spectrum of presentation arising from variations in environmental or host factors. As such, several of the major Bent and Kuhn features may lack specificity to AFRS, leading to possible overlap with other chronic rhinosinusitis (CRS) phenotypes.

Firstly, the value of fungal stains and cultures has been questioned. Ponikau et al,[26] treating collected nasal secretions with a reducing agent before analysis, reported that fungal elements were seen in 81% of histologic specimens taken from 101 patients with CRS, both with and without polyps. In that same study, 96% of patients had positive fungal culture test results, including all healthy controls. The specificity of identifying fungi within nasal secretions was thrown into further uncertainty when it was found that adding trypsin to surgically collected specimens before applying the Grocott Methenamine Silver (GMS) stain could increase the fungal detection rate 27% to 91%.[27] By incorporating both techniques, Porter et al found positive fungal culture results in 67.8% and 88.5% of surgical specimens from patients with CRSwNP and with AFRS, respectively.[28] These rates between CRSwNP and AFRS were closer than expected, suggesting that fungi were less specific to AFRS than previously thought.

Eosinophilic mucus is also found in other types of CRSwNP, including patients with aspirin-exacerbated respiratory disease (AERD). Our latest understanding now divides CRS into endotypes based on immunologic and molecular profiles. In the Western world, CRSwNP is predominantly driven by type 2 inflammation, characterized by innate and adaptive cells producing cytokines such as interleukin (IL)-4, IL-5, and IL-13, with increased numbers of eosinophils and mast cells.[12] Eosinophilic mucin is produced as a result, and because this pathway is shared across AFRS, CRSwNP, and most notably AERD, its mere presence is not specific for AFRS. This understanding has also superseded previous attempts to separate these disease subtypes using nomenclature such as “allergic fungal sinusitis-like syndrome”[29] or “eosinophilic mucin rhinosinusitis”[29,30] to describe patients with eosinophilic mucin without positive fungal studies.

From the above, it is evident that even a combination of positive fungal test result studies and the presence of eosinophilic mucin may not necessarily distinguish AFRS from other CRS subtypes. Nevertheless, AFRS clearly remains a unique disease entity because other CRS subtypes do not manifest other key features of AFRS such as expanded sinuses or bony erosions, among other differentiating factors.

Type I hypersensitivity to fungi is a major Bent and Kuhn criterion. However, elevated fungal-specific IgE has been shown in patients with allergic rhinitis with fungal sensitization. If such a patient also had CRSwNP (non-AFRS) with type 2 eosinophilic inflammation, the clinical picture could be confused with AFRS. Although the degree and number of different elevated fungal-specific IgE in AFRS are typically higher than in patients with non-AFRS CRS,[31] the current criterion lacks specific cut-off levels, diminishing its discriminatory ability.

These 3 major features were recognized in the European Position Paper on Rhinosinusitis and Nasal Polyps as being common in many cases of CRSwNP. On that basis, it was emphasized that the diagnosis of AFRS should be made only when all 5 criteria were met.[12] In so doing, the lack of specificity of an individual criterion could be mathematically mitigated by mandating the need to fulfill multiple criteria concurrently, at the cost of making the criteria unwieldy to apply.

This trade-off has been highlighted by recent challenges using the current Bent and Kuhn criteria in conducting clinical trials focused on patients with AFRS. For example, it is unclear how to show the lack of fungal invasion in a trial not requiring sinus tissue samples. Investigators are faced with the hard choice between designing a study that does involve sinus tissue collection (and thereby limits the study population to candidates for surgery) and having to face potential criticism about their disease definition not technically fulfilling all major features in the Bent and Kuhn criteria. As such, there remains an unmet need to develop criteria with greater specificity to AFRS but that are less cumbersome to use and yet have the flexibility to accommodate the possibility that AFRS can present on a spectrum based on various environmental factors (Table 1).

Update in Pathophysiology

Allergic fungal rhinosinusitis is a subset within a broader category of CRSwNP and therefore shares some pathophysiological pathways

Table 1
Diagnostic Criteria—Areas of Potential Research

Bent and Kuhn major criteria	Issues with current criteria
Type I fungal hypersensitivity	- Nonspecific, especially if patient has other coexisting type I hypersensitivity conditions, for example, allergic rhinitis or immunologic deficiencies
Nasal polyposis	- Not unique to AFRS - Nasal polyposis can be present in other subtypes of CRS conditions, for example, AERD
Characteristic CT findings	- Expansion and bony remodeling can occur with mucocele, thus not specific to AFRS - Bony erosion, definition of erosion lacking: full thickness vs bone thinning
Eosinophilic mucin without invasion	- Most specific diagnostic criterion - Limited reports of AFRS progression to invasive disease (typically in countries with barriers to healthcare access, such as India) - Present in other CRS subtypes (ie, AERD and eosinophilic CRS) - Need to define how to show noninvasion - Most challenging criterion to meet in clinical trials, especially in patients previously treated for AFRS
Positive fungal stain	- Variable yield based on location of collection (nasal vs surgically collected sinus secretions) and whether samples pretreated with reducing agent before analysis (100% of nasal secretions treated with DTT indicated presence of fungi) - Positive culture could fail to confirm diagnosis of AFRS, could just represent saprophytic fungal growth - Not all will stain positive, so cannot exclude absence of disease - Requires special stains: GMS

Abbreviations: AERD, aspirin-exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis; CRS, chronic rhinosinusitis; CT, computed tomography; DTT, dithiothreitol; GMS, Grocott's Methenamine Silver.

with other forms of CRS. This includes the overarching concept that there is a complex interplay between environmental and pathogenic factors, with a dysfunctional local immune response and a consequent perpetuation of inflammation.

A role for an environmental trigger such as fungi is suggested by a significant portion of patients with AFRS presenting with unilateral disease. Fungi are well known to produce a type 2 immune response as illustrated by murine models of eosinophilic CRS generated by intranasal challenge of *Aspergillus* conidia,[32] proteases, and ovalbumin.[33] *Staphylococcus aureus* is a common colonizer of nasal cavities and has been shown to coexist in eosinophilic mucin with fungi in patients.[34] With expression of superantigens, *S aureus* can amplify fungal-induced T_H2 activation, leading to the supranormal levels of total serum IgE levels characteristic of AFRS.[35]

Clinical similarities in AFRS to ABPA drew initial comparisons of the pathophysiology with a strong hypersensitive adaptive immune reaction in patients with fungal atopy as the central pathology leading to the cascade of type 2 inflammation characteristic of AFRS.[6] However, a growing understanding of the molecular details of the type 2 immune response resulted in a re-evaluation of the pathophysiology of AFRS.

One such critical advancement was appreciating the active role of respiratory epithelial cells in orchestrating the type 2 inflammatory cascade via production of epithelial cell derived cytokines IL-25, IL-33, and thymic stromal lymphopoetin. Initially, it was thought that the primary role of epithelial cells was limited to serving as a barrier from environmental factors. A defective mucosal barrier had been implicated in AFRS when in 2013, Den Beste et al studied the transepithelial resistance of cultured AFRS cells and found it less than in cells from healthy controls.[36] Similar loss of transepithelial resistance was noted when respiratory epithelial cells were exposed to type 2 cytokines IL-4 and IL-13.[37] Interleukin-33 and IL-25 are both alarmin molecules released when respiratory epithelial cells are damaged or stressed by environmental triggers such as allergens.[38,39] Elevated IL-33 levels and its receptor ST2 are associated with CRSwNP and recalcitrant disease.[40,41] Dietz et al[42] showed that sinonasal epithelial cells from patients with CRSwNP and patients with AFRS increased expression and release of IL-33 in response to challenge with *A fumigatus*, a common fungus associated with AFRS. The activation and release of IL-33 by fungi were dependent on its protease activity and stimulation of protease activated receptor-2 (PAR-2).[42] In addition to IL-33, IL-25 release can be stimulated from solitary chemosensory cells challenged with fungal extracts. Solitary chemosensory cells are a rare population of epithelial cells found within the respiratory epithelial barrier.[43] Taken together, these studies highlight the role of fungi in triggering the type 2 immunologic role of sinonasal epithelial cells.

As its name suggests, the adaptive immune response was the initial focus for driving the type 2 immune response characteristic of AFRS. However, in 2010, with the discovery of group 2 innate lymphoid cells (ILC2s), the focus on antigen-specific T-cell centered immune response was diverted toward the innate immunity. Representing a relatively small population of cells, ILC2s were identified and then isolated from inflamed sinus mucosa of patients with CRSwNP, which included AFRS.[41,44] In patients with CRSwNP, ILC2s appear to be the primary source of the type 2 cytokine IL-13 on stimulation with IL-33. These studies and others supported the close link of ILC2s and innate immunity to the pathophysiology of type 2 CRSwNP.

In an attempt to identify differentiating molecular pathways between patients with AFRS and other patients with CRSwNP, a microarray comparison of diseased sinonasal mucosa noted, as expected, a significant upregulation of adaptive T_H2 associated expression in AFRS.[45] In the same study, the expression of histatin, an antimicrobial peptide (AMP) characterized by its antifungal activity, was first identified in sinus tissue and found to be significantly reduced in AFRS mucosa compared with samples from patients with CRSwNP.[45] This observation re-establishes similarities between AFRS and ABPA in that ABPA occurs almost exclusively in patients with asthma and cystic fibrosis who are also unable to clear fungal spores before germination.[46] Although the etiology of the reduced histatin expression in AFRS remains unclear, AMP expression is regulated by type 3 cytokines IL-17 and IL-22.[47] Although more research is required, AFRS may represent a deficient type 3 sinonasal immune response with a compensating upregulation of type 2 immune response to control the fungi.

Taken as a whole, these findings support a hypothesis in which patients who develop AFRS have a pre-existing deficient type 3 immune response and hence inability of their innate immune response via AMPs such as histatin to clear fungal spores. On exposure to environments conducive to introducing fungal spores to sinus cavities, patients with AFRS are unable to clear the spores, which can then germinate into immunogenic fungal hyphae, leading to epithelial cell barrier dysfunction and release of epithelial cell derived cytokines IL-25, IL-33, and thymic stromal lymphopoetin. This leads to a compensatory overstimulation of the type 2 immune response, with the subsequent inflammatory cascade leading to eosinophilia, nasal polyposis, and mucus production (Fig 2). The mucosal swelling and mucin entrap additional fungal material, which serves to perpetually stimulate the dysfunctional response in a vicious cycle, ultimately manifesting clinically as AFRS. The proposed hypothesis of IL-17 deficiency in AFRS may also explain the decreased prevalence of asthma in AFRS compared with CRSwNP, given the role of IL-17 in severe asthma.[48]

Update in Treatment

Although much has been learned recently about the molecular profile of patients with AFRS, many of the elements of the above proposed hypothesis remain to be tested. In addition to the correlative human data, an animal or other model will be needed to provide more direct causation data. As such, the current mainstay of AFRS management remains sinus surgery followed by maintenance with sinus saline irrigation and nasal or oral steroid treatment.

Although sinus surgery is not curative, the goals of surgery are to clear the eosinophilic mucin that harbors the fungi triggering and perpetuating the sinonasal inflammation, to remove nasal polyps to improve symptoms of nasal congestion, and to open the sinus cavities, making them available for sinus irrigations and topical therapy. Unfortunately, in a meta-analysis that included 34,220 subjects with a mean follow-up of 89.6 months, patients with AFRS have higher rates of revision surgery at 28.7% than do other patients with CRSwNP at 18.6%.[49] As such, complete surgery with eradication of all present eosinophilic mucin followed by postoperative medical therapy remains the cornerstone for AFRS treatment. However, this surgical goal remains challenging because affected sinus cavities may expand beyond the reach of typical sinus surgery instruments, and the difficulty is compounded by the extremely sticky nature of the mucus itself (Fig 1B).

After surgery, the medical regimen includes daily saline irrigations to supplant the inability of patients with AFRS to clear fungal spores, and corticosteroids to nonspecifically minimize mucosal inflammation. Initially, extended courses of oral steroids over months postoperatively were recommended.[24] However, the recognition of risk associated with oral corticosteroids such as obesity, hypertension, osteoporosis, and worsening blood glucose levels has resulted in limiting the use of oral steroids to short courses for clinically significant recurrence of nasal polyps. As such, the current treatment paradigm emphasizes providing topical steroids instead. Metered dose sprays may be used, although nonstandard delivery methods are being explored. For instance, the addition of corticosteroids to nasal saline irrigations as a compounded mixture is now commonly prescribed with the aim of maximizing drug delivery to the sinuses,[50] despite being an off-label use. More recently, a fluticasone exhalation delivery device received US Food and Drug Administration approval for the treatment of nasal polyps and has been shown to penetrate

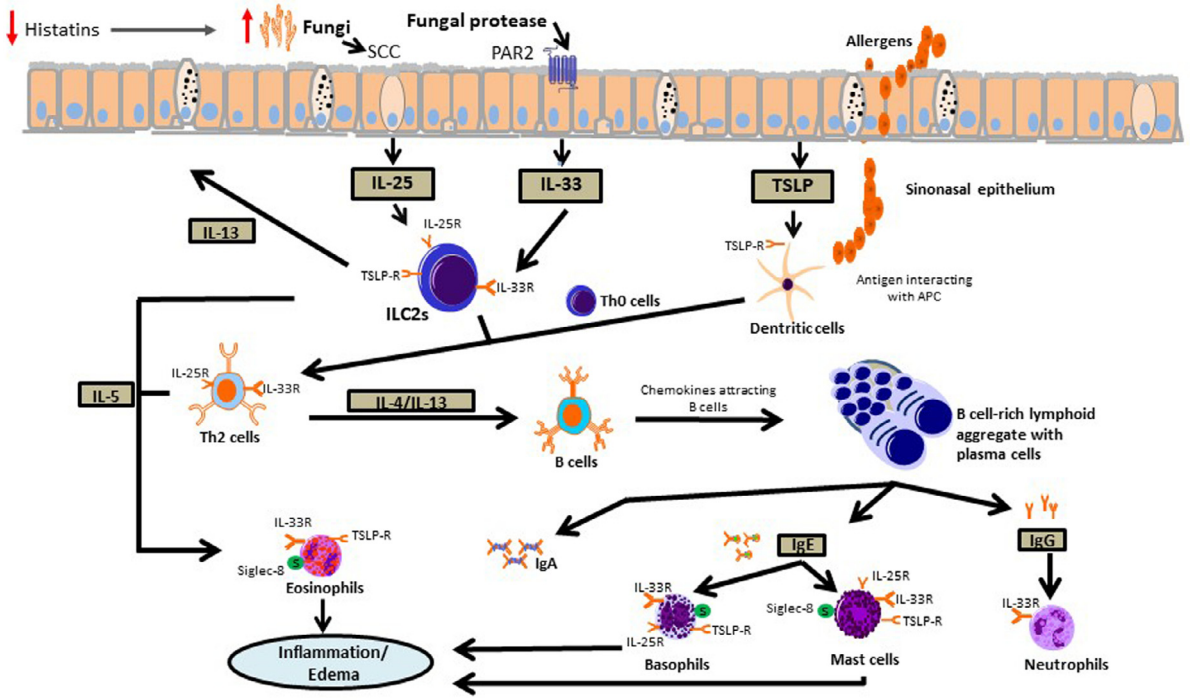

Figure 2. Schematic of proposed pathophysiology of allergic fungal rhinosinusitis. Significant decreased expression of histatins in allergic fungal rhinosinusitis compared with chronic rhinosinusitis with nasal polyposis and healthy controls. As such, fungal spores are able to germinate into fungal hyphae that ultimately induce expression of IL-25, thymic stromal lymphopoetin, and IL-33, orchestrating the type 2 immune response. IL, interleukin.

opened sinus cavities, including the frontal sinuses, more effectively than do conventional nasal spray bottles.[51]

The updated understanding that the T_H2 fungal hypersensitivity is not the critical factor in AFRS pathophysiology explains the recommendation for allergen immunotherapy to be only an option in patients with AFRS recalcitrant to surgery, saline irrigations, and corticosteroids.[11,52] In contrast, the proposed updated understanding that patients with AFRS may exhibit a local deficiency of type 3 cytokines such as IL-17 and IL-22 leading to limited antifungal activity would suggest that either oral or topical antifungals could be an effective treatment option. Topical formulations of antifungals have proven to have unstable antifungal activity and limited ability to access all diseased mucosa, even in surgically opened sinus cavities. As for oral antifungals, most clinical trials were not limited to patients with AFRS and were found to have limited treatment benefit. A Cochrane review of topical and systemic antifungals in CRS concluded that current studies provided very low quality of evidence, and their impact on patient outcomes was uncertain. In addition, it highlighted that studies specific to AFRS were lacking.[53] Indeed, although there have been clinical trials limited to patients with AFRS that have reported more encouraging treatment effects, these are small in number, and more trials are needed.[54-57] As such, the recommendation for antifungals is also only an option in patients with recalcitrant AFRS.[11]

Recently, the Food and Drug Administration approved 3 biologic agents for use in CRSwNP. In patients with severe polyps, dupilumab, omalizumab, and mepolizumab showed significant reduction in nasal polyp size, improvement in smell function, and need for sinus surgery compared with placebo.[58,59] However, these currently published trials specifically excluded patients with AFRS. To address this deficiency, a randomized controlled trial is ongoing evaluating the role of dupilumab for recurrent symptomatic nasal polyps in patients with AFRS who have undergone at least 1 sinus surgery (NCT04684524) and another as adjuvant therapy after sinus surgery (NCT05545072). Given these biologics target type 2 cytokines at the end of the common pathway shared with CRSwNP, it seems reasonable to predict that the current biologics will also show effectiveness in patients with AFRS. A recent review article published by Luong et al evaluated the role of biologics in AFRS disease,[60] and as our understanding of AFRS pathophysiology improves, we will be able to better rationalize the use of these biologics in the treatment of recalcitrant AFRS.

Conclusion

The body of knowledge surrounding AFRS continues to grow as advances in diagnostic, molecular, and quantification techniques begin to enable investigation of previously ill-defined pathophysiological pathways. In particular, the role of a deficiency in mounting a type 3 immune response to fungal antigens is a promising line of inquiry.

The time-honored major features in the Bent and Kuhn criteria have been useful in classifying patients presenting with classic AFRS. However, there are limitations in the specificity of each individual criterion when taken in isolation. The mandate that all 5 criteria need to be met before making a firm diagnosis of AFRS poses challenges to its clinical application and utility in research. Consequently, there is an unmet need to develop criteria that are more specific and easier to use. The mainstay of AFRS treatment remains meticulous and thorough surgery, complemented by the use of topical corticosteroids. Short courses of systemic steroids can be used with caution, and adjuncts such as fungal immunotherapy or systemic antifungals are options in recalcitrant disease. Biologics show promise in observational studies as we await results from double-blind randomized controlled trials. Future work is needed to further elucidate pathophysiological pathways and refine diagnostic criteria, and these will be critical in setting the stage for the development and testing of new therapeutic options.

Disclosures

Dr Chua serves as consultant for Acclarent, Inc (Irvine, California) and MicrogenDx (Lubbock, Texas). Dr Luong serves as a consultant

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