



Pediatric allergic fungal rhinosinusitis: optimizing outcomes

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Purpose of review

Allergic fungal rhinosinusitis (AFRS) is a debilitating condition for children. Despite there being several reviews on this topic in the adult population, there is a paucity of reviews of AFRS in the pediatric literature. This article reviews the recent evidence of pediatric AFRS with the aim to optimize outcomes of pediatric patients with this condition.

Recent findings

AFRS is clinically characterized by nasal polyposis, a type I hypersensitivity to fungal epitopes, very thick eosinophilic mucin, and peripheral eosinophilia. Pediatric AFRS has similar clinical characteristics to that in adults but is thought to have a more aggressive nature, with higher serum immunoglobulin E and more frequently bone erosion and malformation of facial bones. Diagnosis of pediatric AFRS is made by using the Bent and Kuhn's criteria developed for adult AFRS. The mainstay of treatment is surgery followed by postoperative corticosteroids. Adjunctive therapies, including topical/oral antifungal agents, allergen immunotherapy and biologics may improve outcomes in pediatric AFRS, but to date the current evidence is limited.

Summary

To optimize the outcome of pediatric AFRS, adequate and early diagnosis and treatment are essential. Appropriate and comprehensive endoscopic sinus surgery to open the sinuses, remove the fungal burden of disease and improve access of the sinuses to postoperative topical corticosteroid remains the standard of care.

Keywords

allergic fungal rhinosinusitis, chronic rhinosinusitis in children, budesonide, functional endoscopic sinus surgery, fungus, intranasal corticosteroid spray, pediatric sinusitis

INTRODUCTION

Allergic fungal rhinosinusitis (AFRS) is a subset of noninvasive chronic fungal sinusitis with unique clinical characteristics. AFRS is different from other phenotypes of chronic rhinosinusitis (CRS), with a higher rate of bony remodelling and recurrence. AFRS is most commonly diagnosed among adolescents and young adults but can occur in the pediatric population and should be diagnosed and treated in a timely fashion before irreversible changes to the bony anatomy occur. To date, there are only a few reviews of pediatric AFRS published [1–3]. Here we review the recent literature on this topic to provide otolaryngologists with information to optimize the outcomes of pediatric patients suffering from AFRS.

EPIDEMIOLOGY

Patients with AFRS typically present in the third decade of life, earlier than those with other

phenotypes of CRS [1,2,4]. The incidence of AFRS has been estimated to range between 1.3% and 10% of all CRS patients going to surgery [5,6,7]. It is more common in temperate regions with high humidity, such as India and the middle-east, and is also prevalent in south central USA which have a similar climate [8,9]. As per the new classification

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KEY POINTS

- Suspect AFRS in children with unilateral sinus disease, polyps and changes in facial structure/appearance.
- Diagnosis according to the Bent Kuhn criteria is made based on the presence of (1) type 1 hypersensitivity to fungi; (2) nasal polyposis; (3) characteristic radiographic finding of serpiginous areas of high attenuation; (4) eosinophilic mucin; and (5) positive fungal culture or microscopy.
- Endoscopic sinus surgery remains the mainstay of treatment to reduce the fungal burden and increase the access of the sinuses to postoperative topical treatments.
- Postoperative topical corticosteroid therapy may improve long-term outcomes but at present there is no consensus on treatment regimen.
- Life-long follow-up is necessary due to the high recurrence rate.

criteria of CRS set out in the most recent position paper of the European Academy of Allergy and Clinical Immunology (EPOS2020), AFRS is classified as a primary, localized or diffuse CRS with type 2 inflammation [6[•]].

The pathophysiology of allergic fungal rhinosinusitis

AFRS has a complex and incompletely defined pathogenesis. The primary established mechanism is exaggerated type 2 inflammation. Inciting factors that may propagate this include barrier dysfunction, defective innate immunity, direct effects of pathogenic fungi and superantigen stimulation.

Barrier dysfunction and defective innate immunity

In vitro studies identified reduced mucosal resistance and greater permeability in AFRS [10]. Expression of local antimicrobial peptides (lactoferrin, surface protein-D and histatin, a known antifungal) are reduced in AFRS [11]. AFRS derived CD8⁺ cells failed to activate and proliferate when sensitized to fungi in vitro [12]. These potentially defective antifungal mechanisms result in biofilm formation and overgrowth that incite perpetual innate and adaptive immune stimulation.

Direct role of fungi

Fungi have a direct pathogenic role in the allergic airway inflammation observed in AFRS. Fungal

molecules (including β -glucan, chitin and glycosidases) stimulate innate immune cells to secrete cytokines through epithelial activation and apoptosis [13,14]. These cytokines, including IL-25 and IL-33, induce Th2 polarization and type 2 inflammation. Fungal proteases are pro-inflammatory through the promotion of type 2 inflammation, eosinophilia and goblet cell hyperplasia [13]. Proteases also directly stimulate TLR4 pathways through the cleavage of fibrinogen, causing antifungal activity and allergic airway inflammation [15]. The mass effect of expansile fungal overgrowth and local cytokine release (TNF α and MMP9) can also induce bony deficiencies, which are commonly observed in paediatric AFRS [14,15].

Superantigen theory

A cross kingdom synergy between fungi and bacteria has been proposed, where both organisms benefit from alternative macrophage activation and weakened innate defences [16]. Fungal and bacterial superantigens drive an exaggerated inflammatory response through the stimulation of T cells, causing elaboration of epithelial cell-derived cytokines (IL-33, IL-25, and TSLP) and activation of group 2 innate lymphoid cells (ILC2) [11]. Activated ILC2 release IL-13, promoting a type 2 eosinophilic response and increased tissue and serum immunoglobulin E (IgE) [11,17,18]. *Staphylococcus aureus* enterotoxin (SE) has been proposed as a culprit superantigen with SE-specific IgE identified in AFRS patients [16].

Adaptive immunity and type 2 inflammation

Type 2 inflammation is the central mechanism underlying AFRS. Th2 activation releases IL4, IL5 and IL13, which promote B cell differentiation, IgE production, mast cell degranulation, and eosinophilia [14]. Whole-genome microarray studies identified upregulation of IgE loci, eosinophil pathways, Th2 signalling and specific cytokine expression as distinguishing molecular features in AFRS [19]. This manifests as elevated IgE, eosinophilic mucin and fungal specific hypersensitivity. Disease severity appears to be greater in children with significantly higher fungal biomass, serum IgE values and recalcitrant disease compared with adults [1].

CLINICAL PRESENTATION AND DIAGNOSIS

AFRS patients typically present with nasal obstruction secondary to nasal polyposis. Patients often also report thick mucinous discharge, that can be

Table 1. Diagnostic criteria for AFRS (by Bent and Kuhn) [6[■],19,53]

Criteria	Examination	Sample
Major		
Type I IgE-mediated hypersensitivity	Skin test and/or IgE immune CAP	Skin or blood
Nasal polyposis	Endoscope	N/A
Characteristic CT findings	CT	N/A
Eosinophilic mucin without invasion into the sinus tissue	Histology	Mucus and mucosa obtain during surgery
Positive fungal stain of sinus contents	Microbiology	Sinus contents obtain during surgery
Minor		
Radiographic bone erosion	CT	N/A
Unilateral disease	Endoscope/CT	N/A
Fungal cultures	Microbiology	Sinus contents obtain during surgery
Charcot-Leyden crystals	Histology	Mucus obtain during surgery
Peripheral eosinophilia	Blood examination	Blood
Asthma	Spirometry, CT, etc.	N/A

CT, computed tomography.

discoloured or malodorous. If disease is bilateral, complaints of hyposmia or anosmia may be reported. Pediatric patients often also have visible bony changes, usually the result of expansile pressure from the inflammation/trapped fungus on the developing facial skeleton. This may be manifested as proptosis, telecanthus, or malar flattening [1].

Local features of AFRS include thick eosinophilic mucin, often described as 'peanut butter' in nature because of its colour and high viscosity. This is in contrast to the 'chewing gum' description of mucin often described in CRSwNP patients [6[■]]. Unlike fungal balls, which simply reflect an overgrowth of mycelial elements, the mucin of AFRS is thought to be the product of these patient's local allergic hypersensitivity reaction to the fungi. Microscopic evaluation of the mucin not only demonstrated fungal elements but also commonly shows Charcot-Leyden crystals, which reflect severe eosinophilic inflammation. Evaluation of the mucosa sampled from these patients will demonstrate superficial fungus also, but unlike invasive fungal sinusitis, there is no submucosal or vascular invasion of the fungus.

Systemic characteristics of patients with AFRS include an atopic immune status, IgE-mediated hypersensitivity to fungi, and elevated peripheral eosinophilia. The hypersensitivity to fungi is confirmed by skin prick or serological allergy testing to specific IgE against fungal antigens. Patients with AFRS often also demonstrate an elevated total serum IgE [4,20], which has been proposed as one of the prognosis factors predicting recurrence [7]. Although peripheral eosinophilia is also found in patients with AFRS [7], this is not specific to AFRS and is also seen in allergic rhinitis and CRSwNP, [21].

Unlike other forms of CRS, the diagnosis is usually confirmed after surgery, from histopathological evaluation of surgical specimens of mucus and mucosa. Similar to adult AFRS, the diagnosis is based on the fulfilment of the criteria proposed by Bent and Kuhn (Table 1) [22]. The criteria are divided into major and minor, with the major 5 criteria being; (1) type 1 hypersensitivity to fungi; (2) nasal polyposis; (3) characteristic radiographic finding of serpiginous areas of high attenuation; (4) eosinophilic mucin; and (5) positive fungal culture or microscopy.

Characteristic imaging findings

CT sinus imaging is necessary for the diagnosis of AFRS as per the Bent and Kuhn criteria. Nonenhanced contrast the sinuses are typically opacified by centrally, often serpiginous hyperdense material with a peripheral rim of hypodense mucosa often referred to as the double density sign. Approximately 40% of children may show expansion of the involved sinus, remodelling, thinning or erosion of the bony sinus walls [6[■]]. On MRI hypointensity on T1WI and T2WI is the most common finding with the low T2 signal or signal void due to high concentration of various metals such as iron, magnesium and manganese concentrated by fungal organisms as well as high protein and low free water content in allergic mucin [6[■]].

Features specific to pediatric allergic fungal rhinosinusitis

Nasal polyposis is unusual in the pediatric population and if visualized AFRS should be considered in the differential along with antrochoanal polyps,

cystic fibrosis or other ciliary dysfunction disorders [3,8]. Studies have documented that up to 81.8% of pediatric patients with AFRS present with nasal polyps at initial clinical exam [23]. In AFRS, the sinus disease and polyposis are typically unilateral in children (up to 70%) whereas in cystic fibrosis and other forms of CRS, polyposis is more commonly bilateral [24]. Unilaterality of disease in children with AFRS is even more common than it is in adults with AFRS [25]. As discussed previously changes in the facial skeleton are also more common in the pediatric population with more than 50% of children presenting with changes manifesting as proptosis, telecanthus, or malar flattening due to bone erosion [23,24].

MANAGEMENT

The mainstay of the treatment for pediatric AFRS is surgery followed by postoperative corticosteroid therapy. Adjuvant therapies have been trialled to optimize outcomes but supporting their routine use remains limited.

Surgical management including the extent of surgery and postoperative management

Surgery is required for both diagnostic and therapeutic reasons. Although the diagnosis may be suspected through the clinical characteristics, diagnosis is ultimately achieved by confirmation of fungal presence on culture of tissue or mucin specimens obtained intra-operatively [2]. Surgery not only facilitates symptom relief through the removal of obstructing tissue but also serves to reduce the inflammatory burden of disease and remove the antigenic stimulation by the fungi as well as improve access of the sinuses to ventilation and topical drug delivery in the postoperative setting. For most phenotypes of pediatric CRS, surgery is generally reserved only for patients who fail appropriate medical therapy, and when performed is usually limited to an adenoidectomy in the first instance [26]. For pediatric AFRS, medical therapy is often futile, with a low threshold for surgery recommended when the diagnosis is suspected. Adenoid surgery does little to address the fungal disease load in the sinuses of children with AFRS, and so in this condition functional endoscopic sinus surgery to address the diseases sinuses is usually recommended as a first line procedure.

Although historical animal models raised concerns about the possible effect of FESS on pediatric facial development [27], this fear has been largely disbanded by more recent longitudinal human studies [28,29]. Furthermore, the study by Bothwell *et al.* reports that facial deformities are more likely to occur in untreated children with CRS than in those

treated in a timely fashion with appropriate surgery [29]. This is particularly pertinent to AFRS children who often present with facial abnormalities at diagnosis.

To date, due to the lack of available evidence, there is no consensus on the extent of FESS surgery that should be performed in the pediatric AFRS population. Interestingly in a study evaluating patients presenting with unilateral AFRS, 30% progressed to contralateral involvement at a later date with preemptive surgery on the unaffected side not delaying contralateral disease [29,30]. For this reason, and the added complexity of pediatric FESS due to the narrow operating confines, it is our opinion that FESS surgery should be targeted to the involved sinuses to remove the fungal disease and facilitate access for topical treatments.

Pediatric FESS is generally considered a relatively safe procedure with a low risk of significant comorbidity [26,31], but the surgeon must recognize the important differences between pediatric and adult patients when performing FESS. Pediatric patients have smaller nasal vestibule, underdevelopment of their turbinates, and relatively low vertical height of the nasal cavity [32]. This, coupled with the bone erosion and facial abnormalities in children with AFRS, does increase the risk of potential complications and so should be anticipated when planning for surgery. The use of image guidance and the involvement of a tertiary rhinologist is recommended if possible.

Medical treatment

Due to the ubiquitous nature of fungal aeroallergens and the patient's constitutional hypersensitivity to fungus, the recurrence rates of AFRS after surgery are high ranging between 10 and 100% in some studies [33,34]. Furthermore, the recurrence rates in children with AFRS have been shown to be higher than the adult population [1]. Recurrence rates can be improved with vigilant postoperative care and follow up.

Corticosteroid therapy

Corticosteroid treatment has been shown to reduce recurrence after surgery for AFRS [1,35,36]. Due to a paucity of studies in the pediatric population, there is no consensus on dosing or duration of steroid therapy for pediatric AFRS. Table 2 summarizes some of the dosing regimens used by various groups (Table 2). Caution should be exerted when using oral corticosteroids in children due to the possible adverse effects including those on the hypothalamus-pituitary-adrenal axis. A systematic review of the toxicity of oral corticosteroids in over 6817 children reported an

Table 2. Reported dose and duration of systemic corticosteroids for the treatment for AFRS

	Prednisolone	Adjuvant therapy
Younis <i>et al.</i> [31]	1 mg/kg for 7 days (max 60 mg/day), and 10 mg daily within 1 month.	Nasal rinsing Intranasal corticosteroid spray
Prasad <i>et al.</i> [36]	(Preoperatively) 1 mg/kg, for 1 week (Postoperatively) 0.5 mg/kg for 4 weeks, 0.4 mg/kg for 4 weeks, 0.2 mg/kg for 2 months, and 0.1 mg/kg for 2 months.	Intranasal corticosteroid spray
Patro <i>et al.</i> [1]	1.0 mg/kg for 7 days, 0.8 mg/kg for 7 days, 0.6 mg/kg for 7 days, 0.4 mg/kg for 7 days, and 0.2 mg/kg for 14 days.	Nasal rinsing

adverse event rate of 63.39%, with reported side effects including weight gain (21.1%), growth retardation (18.1%), and Cushingoid features (19.4%) [37]. The negative effect of steroids on growth is thought to be used to the suppression of chondrocyte maturation at the epiphyseal growth plate, which is essential for endochondral bone growth [38]. This has been shown to be dose dependent and usually occurs at doses at or more than 0.5 mg/kg/day, but can occur with lower doses [38,39]. For this reason, some authors recommend trailing alternate daily dosing or rapid titrations if corticosteroids are to be used in children. The evidence for topical steroid treatment for AFRS is limited with low-level evidence showing a possible benefit with intranasal corticoid sprays (INCS) [40] or nebulized steroids [41]. Given the long-term safety profile of INCS in children with rhinitis and CRS, and the very low rate of side effects, the EPOS2020 has recommended it as an option for the postop management of pediatric AFRS with evidence grade 3b [6[¶]]. In recent times the off-label use of budesonide irrigations (0.5 mg/2 ml in 240 ml saline) for CRS has become increasingly popular [42]. The advantage of budesonide irrigations over sprays and nebulizers is the increased delivery of the steroid to the sinuses after surgery. One study investigating its use in AFRS did show that it also may reduce the risk of both recurrence and delayed contralateral involvement in unilateral AFRS [30]. At some institutions, budesonide irrigation is already routinely used for pediatric AFRS once the patient has completed the oral corticosteroid taper [2,43]. But clearly further studies evaluating their safety and efficacy are required.

Immunotherapy

Given the role of fungal hypersensitivity in the disease process allergen immunotherapy may also improve the outcome of AFRS in adults and

children [43,44]. Several articles have reported the efficacy of subcutaneous immunotherapy in reducing the rate of recurrence of AFRS [42,43,45,46]. Bassichis *et al.* followed 60 patients with AFRS for at least one year after surgery and reported that the need for revision surgery was lower in patients treated with immunotherapy (11.1% vs. 33%) [45]. However, a follow-up study failed to demonstrate long-term efficacy 4–10 years later, although by the authors' own admissions the study was limited by a small sample size [46]. Sublingual immunotherapy has also been shown to be possibly effective in improving AFRS outcomes, although again the evidence is limited [47]. Given the small number of studies published on this topic to date and the lack of substantiating long term follow-up data, immunotherapy is currently considered as an adjunctive therapeutic option for AFRS, although a standardized protocol does not yet exist [42].

Antifungal therapy

Although several studies have shown the efficacy of both systemic and topical antifungal therapies for adult AFRS patients [48,49], a recently published meta-analysis failed to support their use [50]. Additionally, there is no currently available evidence for antifungal therapy in the pediatric AFRS population. At this stage, it is difficult to recommend the routine application of antifungals for pediatric AFRS patients. In cases of allergic bronchopulmonary aspergillosis, which has a similar pathophysiology to AFRS, antifungal therapies have been shown to reduce the dose of corticosteroid therapy [51], something that would no doubt be advantageous in the pediatric patients. Clearly further studies in this area are required.

Biologics

Antimonoclonal antibody or biological therapies have recently emerged as effective treatment for treatment resistance CRSwNP [52,53]. Several studies have also reported the efficacy of biologics, namely, omalizumab (anti-IgE) [54,55] and mepolizumab (anti-IL5) [56] for AFRS. Gan *et al.* observed in their small retrospective review, an improvement in symptomatic and endoscopic scores and a reduction in corticosteroid and antifungal use in AFRS patients receiving omalizumab for their asthma [55]. Karp *et al.* showed a similar benefit for AFRS patients treatment with mepolizumab for their asthma [56]. In their study, they showed improvements in SNOT 22, radiologic, and endoscopic scores with a reduction in eosinophil counts as well [56]. In another study, Mostafa *et al.* compared the efficacy of omalizumab to INCS for patients with AFRS [54]. They reported better SNOT-22 with omalizumab postoperatively than those with intranasal nasal steroid spray, whereas there were no significant differences in serum IgE or endoscopic scores between the two groups [54]. Although biologics may represent an important therapy for AFRS in the future, a lack of data and the expense associated with them, preclude their routine use for this condition in both the adult and pediatric populations. Clearly further studies are needed to not only document their efficacy but also their long-term safety in children, given a documented, albeit low risk of future malignancies with their use.

Author's recommended postoperative care

Given the severity of inflammation in children with AFRS, the authors typically prescribe a 3 weeks prednisolone taper immediately after surgery. Doing is 1 mg/kg for 1 week, 0.5 mg/kg for a week and then 0.5 mg/kg alternatively for 1 week. Patients are seen between 7 and 10 days postoperatively for an endoscopic debridement if tolerated. At this stage, budesonide irrigations (0.5 mg/2 ml dissolved in 120 ml of sinus irrigation) are commenced for a minimum of 4 weeks. Patients are typically then followed up at 4 weeks, 12 weeks and then 6 months with additional appointments if required. An assessment of the nasal mucosa is made at each appointment with endoscopic examination and the frequency of budesonide irrigations are adjusted according to clinical need. Referral to a pediatric allergist for consideration and discussion of desensitization is usually recommended, with the ultimate decision on immunotherapy made by the allergist and parents. Systemic antifungal medications and biologic

therapies are not routinely used in our pediatric patients given the lack of robust evidence supporting their use for this condition in this age group.

CONCLUSION

Although not a common condition, AFRS does occur in the pediatric population particularly in humid and temperate climates. It needs to be considered in children with polyps, unilateral sinus disease, particularly in the setting of facial bone malformations. Early diagnosis and management with FESS surgery are essential, as is long term follow-up and treatment with postoperative corticosteroid therapy, given its high rate of recurrence.

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