

Allergic Fungal Sinusitis in Children

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KEYWORDS

- Pediatric sinusitis • Pediatric rhinosinusitis • Allergic fungal sinusitis
- Management of rhinosinusitis • Chronic rhinosinusitis

KEY POINTS

- Allergic fungal sinusitis (AFS) is a distinct subtype of eosinophilic CRS marked by type I hypersensitivity (by history, skin tests, or serology), nasal polyposis, characteristic computed tomography findings, eosinophilic mucus, and the presence of fungal elements of the tissue removed during surgery without evidence of fungal tissue invasion.
- AFS is most common among adolescents and young adults.
- The treatment of AFS is both medical and surgical.
- Functional endoscopic sinus surgery is the intervention of choice in this patient population, as nearly all cases of AFS will require some form of surgical management.
- Active postoperative care is crucial to the successful management of these patients, and can reduce the need for further surgical procedures.

 TWO VIDEOS ACCOMPANY THIS ARTICLE: ONE VIDEO DEMONSTRATES AFS NASAL POLY REMOVAL AND THE OTHER DEMONSTRATES FESS for AFS AT <http://www.oto.theclinics.com/>.

Chronic rhinosinusitis (CRS) is a complex, heterogeneous disease process that affects nearly 37 million people in the United States each year and accounts for approximately \$6 billion in direct and indirect health care costs.¹ Estimates indicate that sinusitis is more widespread than arthritis or hypertension, and its effects on quality of life are comparable to that of many chronic debilitating diseases.² Despite its substantial impact on quality of life and financial burden to the health care system, little is known about the etiology and pathophysiology. Moreover, controversy regarding appropriate treatment options remains. This lack of consensus pertains to the adult population but

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also extends into the pediatric realm, leaving a significant deficit in the understanding of pediatric sinonasal disease.³

Pediatric rhinosinusitis remains one of the most common diseases of childhood. Upper respiratory tract infections represent the most significant predisposing factor, with children averaging 6 to 8 infections annually. Of these infections, 0.5% to 5% progress to acute rhinosinusitis with an unknown percentage progressing to CRS.³ Recent estimates indicate that patients diagnosed with CRS account for nearly 6 million pediatrician visits annually, with a substantial proportion of these being referred to subspecialty practitioners.²

CLASSIFICATION OF CRS

Rhinosinusitis is a group of disorders characterized by concurrent inflammatory and infectious processes that affect the nasal passages and the contiguous paranasal sinuses.⁴ Traditionally, symptom duration has dictated the rhinosinusitis classification schema as follows: acute (>4 weeks), subacute (4–12 weeks), and chronic (more than 12 weeks, with or without acute exacerbations).

Acute rhinosinusitis may be further subdivided by symptom pattern into:

- Acute bacterial rhinosinusitis, characterized by symptoms lasting 10 or more days beyond the onset of upper respiratory symptoms or symptomatic worsening within 10 days after initial improvement, termed double-worsening
- Acute viral rhinosinusitis.

When there are 4 or more episodes of acute bacterial rhinosinusitis per year without persistent intervening symptoms, the term recurrent acute rhinosinusitis is applied.⁵ Despite the ease and clinical applicability of the temporal scheme, classifications intended to guide clinical research have been described and include:

- Infectious etiology
- Complications
- Inflammatory markers
- Radiographic findings
- Endoscopic findings.

These systems of increased complexity allow for further patient subclassification and comparison of treatment modalities, which is of particular importance in the CRS population.

Clinical Diagnosis of Chronic Rhinosinusitis

CRS, as previously defined, is an inflammatory condition of the nasal passages and paranasal sinuses lasting 12 weeks or longer.⁴ This heterogeneous and multifactorial disease process is clinically characterized by purulent drainage, polyps, and polypoid mucosa consistent with inflammation. Although nasal endoscopy is recommended and may reveal mucosal abnormalities of the middle meatus or sphenoethmoid recess, visual confirmation of these findings is not a required criterion. The diagnosis remains clinical, owing to the multitude of health care professionals caring for these patients.² The clinical diagnosis in children is often more challenging, with radiographic studies reserved for those being considered for surgery, rather than for diagnostic purposes.⁶ In children, recurrent cough is a consistent sign and symptom of rhinosinusitis, and there is evidence to suggest that rhinosinusitis is an independent risk factor for the development of recurrent cough with wheezing.⁷ Moreover, the diagnosis of CRS is rarely made in isolation and common comorbidities may

include asthma, allergy, dental disease, polyposis, cystic fibrosis, and immunodeficiency syndromes.²

Detailed Classification of Chronic Rhinosinusitis

The heterogeneity of CRS has made classification challenging, and numerous schemes have been developed to further divide patients into more detailed groups.

One such scheme proposed by Meltzer divided rhinosinusitis into 4 categories⁸:

1. Acute presumed bacterial rhinosinusitis
2. CRS without polyps
3. CRS with polyps
4. Classic allergic fungal rhinosinusitis (AFS).

An alternative classification scheme proposed by Chan and Kuhn (F.A. Kuhn FA, MD, Savannah, GA, personal communication, 2009) divides CRS into 2 large categories based on the type of inflammatory response.⁴

1. Noneosinophilic chronic rhinosinusitis (NECRS)
2. Eosinophilic chronic rhinosinusitis (ECRS).

NECRS is marked by neutrophilic inflammation and T-helper (Th)-1 cell predominance. Pathologic subtypes of this designation include:

- Mechanical obstruction
- Chronic bacterial sinusitis without mucin or tissue eosinophilia
- Cystic fibrosis
- Primary ciliary dyskinesia
- Noneosinophilic rhinosinusitis with nasal polyps.

The latter example has recently been described by Borish,⁹ who reported that non-eosinophilic polyps tend to display more profound glandular hypertrophy, fibrosis, and mononuclear and mast cell infiltrates than eosinophilic counterparts.

ECRS is marked by eosinophilic inflammation in the setting of Th-2 and interleukin-5 predominance, and is extremely difficult to control. It is hypothesized that some external trigger activates and upregulates these pathways in the setting of a genetic predisposition toward the characteristic eosinophilic response. Pathologic subtypes of ECRS include:

- Aspirin-sensitive asthma with nasal polyps
- AFS
- AFS without fungus
- *Staphylococcus aureus*-induced superantigen rhinosinusitis
- Chronic gram-negative rhinosinusitis with nasal polyps
- Eosinophilic CRS of unknown etiology.

FUNGAL SINUSITIS

There are 4 distinct types of fungal sinusitis with varying clinical presentations and physical examination findings:

1. Acute fulminant invasive fungal sinusitis
2. Chronic indolent invasive fungal sinusitis
3. Mycetoma or fungus ball sinusitis
4. AFS.

Invasive sinusitis is often a life-threatening condition that uniformly requires surgical debridement and aggressive antifungal therapy. The subtypes are distinguished from each other based on the course of onset and the populations affected.

Acute fulminant invasive fungal sinusitis is a life-threatening condition that is rapidly progressive and affects immunocompromised patients.

Chronic indolent invasive fungal sinusitis generally affects the immunocompetent population, and is marked by fungal invasion into the sinonasal mucosa.

Mycetoma or fungus ball sinusitis is characterized by noninvasive, fungal proliferation and expansion within a sinus in a nonatopic, immunocompetent patient, and can be definitively treated by debridement.

AFS represents the final type of allergic sinusitis and is the topic of the remainder of this discussion.¹⁰

ALLERGIC FUNGAL SINUSITIS

AFS is a distinct subtype of eosinophilic CRS marked by^{10,11}:

- Type I hypersensitivity (by history, skin tests, or serology)
- Nasal polyposis
- Characteristic computed tomography findings (**Fig. 1**)
- Eosinophilic mucus (**Fig. 2**)
- Presence of fungal elements of the tissue removed during surgery without evidence of fungal tissue invasion (**Fig. 3**).

This entity was first recognized by Millar and colleagues,¹² who reported histopathologic similarities between materials obtained from the maxillary sinuses of 5 patients and pathologically diagnosed specimens of allergic bronchopulmonary aspergillosis. These findings were further described by Katzenstein and colleagues¹³ who, following a retrospective review of 113 consecutive cases, identified 7 patients with a newly recognized form of chronic sinusitis termed allergic *Aspergillus* sinusitis. These patients were mostly young adults with a history of asthma and nasal polyposis. Radiographic findings revealed opacification of multiple sinuses. Histopathologic analysis of tissue resected from the paranasal sinuses demonstrated distinct mucinous material containing eosinophils, Charcot-Leyden crystals, and fungal hyphae (**Fig. 4**). This mucinous material was likened to the mucoid impaction seen

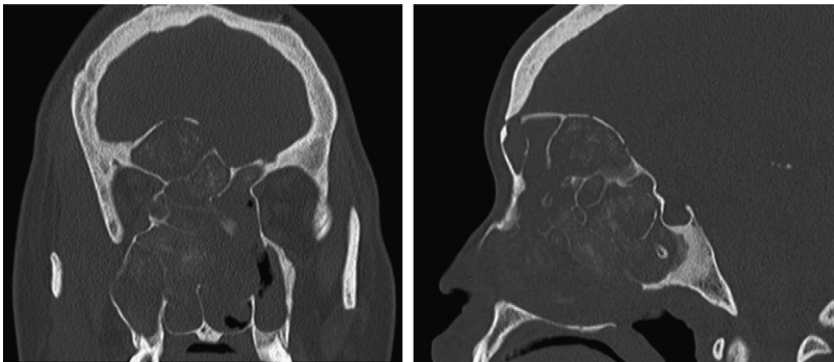


Fig. 1. Coronal and sagittal noncontrasted computed tomography maxillofacial scans from a pediatric patient with documented allergic fungal sinusitis. There is opacification of the bilateral paranasal sinuses with characteristic bony expansion and erosion.



Fig. 2. Endonasal endoscopic view of allergic mucin within the paranasal sinuses of a pediatric patient with documented allergic fungal sinusitis.

in bronchopulmonary aspergillosis and shared similar histopathologic features, prompting the aforementioned terminology and providing evidence to support a pathophysiologic relationship between the 2 entities.¹³ Bent and Kuhn¹¹ ultimately developed the diagnostic criteria for AFS in 1994 (**Box 1**). Numerous efforts have been made to modify the criteria for AFS, to clarify some inconsistencies in the clinical characteristics of cases.¹⁴ However, the Bent-Kuhn criteria have remained the most widely accepted diagnostic method.

Further investigation into this distinct entity revealed a myriad of other dematiaceous fungi resulting in similar clinical manifestations. To avoid confusion, a change in terminology was made to the clinical term allergic fungal sinusitis.¹⁴ In a recent study by (Melroy and colleagues, unpublished data, 2009) of 723 positive fungal cultures in 231 patients, the most common encountered genera in AFS were *Aspergillus*. However, other histologically similar dematiaceous fungi such as *Curvularia*, *Penicillium*, *Alternaria*, *Bipolaris*, and *Fusarium* have also been implicated. These data

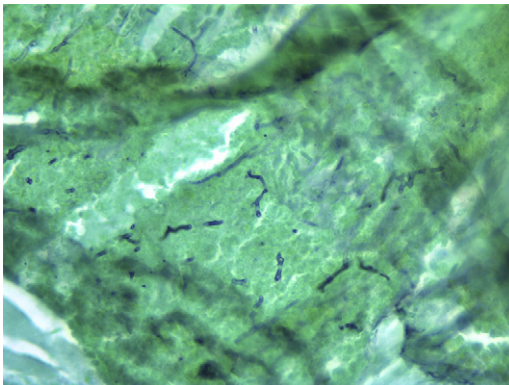


Fig. 3. Fungal elements displayed on a smear of paranasal sinus contents using Grocott's methenamine silver (GMS) stain.

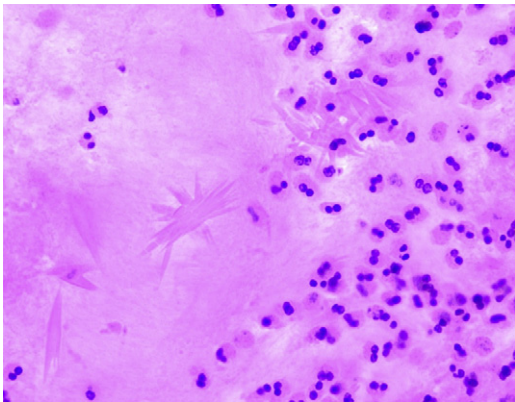


Fig. 4. Charcot-Leyden crystal displayed on a hematoxylin and eosin stain of allergic mucin.

suggest that the incidence of isolated fungal genera is likely related to the species distribution in the local environment, and that more than one fungal genera have a role in the disease process.

Epidemiology of Allergic Fungal Sinusitis

There are scant epidemiologic data on AFS in general, and even fewer in children. Nevertheless, AFS accounts for 7% to 12% of patients with chronic rhinosinusitis who undergo sinus surgery in the United States.^{15,16} In addition, there appears to be a clear geographic pattern of distribution focused in temperate climates. Specifically, an increased incidence in the southern United States and the Mississippi Basin likely represents the influence of climatic factors on the fungal milieu.¹⁷

AFS is most common among adolescents and young adults: the mean age at diagnosis is 21.9 years. Although reports differ on the male-to-female (M/F) ratio of AFS, the ratio is relatively equal when accounting for the different age distributions of disease between the genders.¹⁸ For example, McClay and colleagues¹⁹ reviewed 151 patients with ages ranging from 5 to 75 years and found nearly a 1:1 M/F ratio. However, there may be an age-related difference in the M/F ratio when comparing children and adults. A review of children with AFS at University of Texas Southwestern revealed a distinct male predominance, with a 2.1:1 M/F ratio and an average age at diagnosis of 13 years.¹⁸ Conversely, the adult population showed a female predominance, with an M/F ratio of 1:1.4 and an average age at diagnosis of 36 years.¹⁸ One

Box 1
Diagnostic criteria for AFS

Type I hypersensitivity confirmed by history, skin testing, or serology
Characteristic computed tomography findings
Nasal polyposis
Histologic evidence of eosinophilic mucus without evidence of fungal invasion into sinus tissue
Positive fungal stain of sinus contents

Data from Bent JP, Kuhn FA. Diagnosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 1994;111(5):580–8.

other series of children with AFS also reported an M/F ratio of 1.5:1 with a mean age at diagnosis of 13.6 years.

There is scant data to indicate whether ethnicity portends any significant risk for developing AFS. However, at our institution, we have found a clear racial predominance: African Americans represent the vast majority of our patients, outnumbering all other races combined by a ratio of 4:1. Whether this trend is generalizable to the entire population of AFS patients remains unknown.

Diagnosis of Allergic Fungal Sinusitis

The etiologic basis of AFS is the abnormally robust immunologic response elicited by an allergy to ubiquitous fungal species. Therefore, it is not surprising that the criteria defining this disease include documented atopy and the presence of fungus (see **Box 1**). Minor diagnostic criteria also exist, and include the concurrent presence of:

- Asthma
- Charcot-Leyden crystals
- Eosinophilia
- Unilaterality of disease
- Evidence of osseous erosion
- Positive sinonasal fungal culture.

A review of 178 pediatric and adult patients diagnosed with AFS found that the average time to diagnosis from the initial visit was 11 months, with patients undergoing an average of 2.4 surgeries before diagnosis. Moreover, the earliest documented clinical feature was most frequently a computed tomography finding (5.15 months), and the latest criterion was a positive fungal smear (8.63 months). While characteristic computed tomography findings were often the earliest documented signs of disease in patients with AFS, 65% of patients did not display these findings at any point during the course of their disease (Melroy and colleagues, unpublished data, 2009).

Radiographic findings

Characteristic radiographic findings are clearly important for diagnosis and planning of surgical treatment. Computed tomography plays a key role in diagnosis in this patient population. Findings invariably include multiple opacified sinuses and a combination of osseous expansion and/or erosion. AFS displays significantly more osseous expansion and thinning of the bony confines of the sinonasal cavities than other forms of CRS, with 56% of cases presenting with radiographic evidence of skull-base erosion or intraorbital extension. By contrast, bony erosion/expansion was noticed in only 5% of other causes of CRS.²⁰ In children asymmetric disease predominates, with 70% of pediatric patients presenting with unilateral disease, compared with only 37% of adults.¹⁹ Despite this increased propensity toward unilaterality, pediatric patients display comparable incidences of osseous erosion, especially of the intracranial anterior cranial fossa and orbit.¹⁸

Initial clinical diagnosis

The initial diagnosis of AFS is largely clinical and will likely be broadly termed CRS. This holds especially true for the pediatric population, where diagnostic radiographic studies may be less frequently used to minimize radiation exposure and are typically reserved for only those patients in whom surgical intervention is planned.³ A detailed history coupled with a complete examination is necessary to elucidate the diagnosis. Concurrent comorbidities such as asthma and atopy must be elicited to reach an

appropriate presumptive diagnosis. Atopy is a hallmark of the disease, with nearly 66% of patients reporting a history of allergic rhinitis (AR) and about 90% of patients demonstrating elevated specific immunoglobulin E (IgE) to 1 or more fungal antigens.¹⁸ Furthermore, in a study by Manning and Holman,²¹ roughly 50% of AFS patients were noted to have asthma.

Symptomatically, most children with AFS typically present with:

- Nasal airway obstruction
- Nasal discharge (at times purulent)
- Loss of smell/taste
- Headaches.

However, the presentation of AFS in children may be quite subtle.¹⁹ The onset of AFS is typically a protracted, indolent process. Children report a slow onset of nasal airway obstruction and production of large, dark-colored nasal debris. Because of this gradual onset and progression, patients may develop facial dysmorphism with proptosis and/or telecanthus.^{19,22–24} If pain is a presenting symptom, it generally indicates a concomitant bacterial infection.¹⁸

Endoscopy is the best method to adequately assess the nasal cavities. However, in children this may be neither feasible nor well tolerated. Therefore, a comprehensive history, noninvasive physical examination, and radiographic imaging are paramount. If endoscopy is tolerated, the examiner should interrogate the bilateral nasal cavities for evidence of allergic mucin, polypoid edema, or polyposis. Findings that include any of these in a patient with atopy necessitate further inquiry into the possibility of AFS. Although history and findings of physical examination are crucial, the definitive diagnosis of AFS relies on a combination of factors including histopathologic findings. Therefore, although one may be highly suspicious, the definitive diagnosis of AFS cannot be made until after surgical intervention.²⁵

Management of Allergic Fungal Sinusitis

The treatment of AFS is both medical and surgical. With increasing awareness of the pathogenesis of the disease and its relationship with the eosinophilic inflammatory cascade, a paradigm shift has led to medical therapies aimed at suppressing inflammation rather than eradicating fungal pathogens. In addition, as with other forms of sinusitis, medical therapy is not simply an initial treatment whose failure results in surgery, but rather a concurrent and adjuvant measure given to enhance the effects of surgical intervention and increase the symptom-free interval.

Functional endoscopic sinus surgery is the intervention of choice in this patient population, as nearly all cases of AFS will require some form of surgical management. Management should focus on tissue preservation to maintain sinonasal mucociliary clearance and relief of mechanical obstruction. Clearance of the sinus contents is also paramount and typically yields substantial amounts of thick allergic mucin and/or fungal debris, which should be sent for histopathologic review for the presence of fungal elements and eosinophils. Retention of cells filled with allergic mucin appears to be a risk factor for early recurrence, and every effort should be made to safely minimize residual disease ([Videos 1 and 2](#)).²⁶ Meticulous preoperative planning and intraoperative care must be taken in these patients, as osseous expansion and erosion often distorts the normal sinonasal anatomy and obliterates bony barriers, thus placing adjacent structures at an increased risk of iatrogenic injury. Image guidance is critical for orientation and anatomic confirmation (see [Fig. 1](#)).

PEARLS & PITFALLS: *It should be noted that normal anatomic surgical landmarks may be altered because of the expansive nature of allergic fungal disease.*

The goals of surgical management for primary and recurrent disease remain the same and include removal of mechanical obstruction, clearance of sinus contents, and creation of adequate outflow tracts while maintaining the functional capacity of the lining mucosa.

Surgery, while representing an important arm in the treatment of AFS, does not obviate the need for adjuvant medical therapy.¹¹ The pathophysiology of AFS and diagnostic criteria clearly indicate that it is not simply the presence of fungus but also the patient's response to this allergen that define the disease. Systemic steroids decrease the inflammatory response including sinonasal mucosal edema and polyp formation, and are typically used in an initial burst preoperatively and with a taper in the postoperative period.

PEARLS & PITFALLS: *A course of systemic corticosteroids preoperatively can significantly reduce inflammation, improving both patient symptoms and endoscopic visualization at the time of surgery.*

Serial examinations guide the need for continued systemic therapy. In the pediatric population, early efforts are made to transition from a systemic regimen to intranasal topical steroid therapy. The importance of adjuvant medical therapy was clearly displayed by Kupferberg and colleagues¹⁰ in their retrospective review of 26 pediatric and adult patients undergoing functional endoscopic sinus surgery for AFS. Using a novel endoscopic staging system, the success of various postoperative medication regimens were compared (Table 1). The results indicated that a significantly higher number of patients in the steroid-treatment group were maintained in stages 0 and I compared with patients in other groups who did not receive steroids. Moreover, once patients progressed to stage II or III disease it was unlikely that medical management could reverse the process, and repeat surgical management was universally necessary. These findings demonstrate the need for long-term suppressive therapy and serial endoscopic evaluations in postoperative AFS patients.¹¹ At the authors' institution, children who have completed the taper of oral corticosteroid therapy are transitioned to topical steroid treatment, typically with budesonide (0.5 mg) in 1 L of isotonic buffered saline. Patients irrigate, if possible, with 120 mL per nostril 2 times per day.

A wide range of other medical therapies may be used in children with AFS to target the intense eosinophilic response that results in polypoid inflammation. Immunotherapy with specific attention to the fungal-specific antigens is thought to decrease recurrence rates after surgery when combined with other medical treatments.²⁷ In addition, leukotriene

Table 1
Kupferberg, Bent, Kuhn novel endoscopic grading system

Stage	Criteria
0	No evidence of disease
I	Edematous mucosa/allergic mucin
II	Polypoid mucosa/allergic mucin
III	Polyps and fungal debris

Data from Kupferberg SB, Bent JP, Kuhn FA. Prognosis for allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 1997;117:35–41.

receptor antagonists, monoclonal antibody selectively binding IgE, macrolide antibiotics, and steroid-impregnated antibiotic gels may have a place in the long-term management of the disease process, although data are lacking.¹⁴ Some investigators have postulated that decreasing the fungal antigen load in the sinonasal cavities with either systemic or topical antifungal agents may be useful. However, these data have not demonstrated efficacy in controlling AFS.²⁸ In addition, it should be noted that neither surgical nor medical management is curative: every patient has the potential for recurrence, and therefore requires long-term follow-up and continuous management.

Future Directions for Allergic Fungal Sinusitis

To date, there continues to be some controversy regarding the diagnostic criteria because of temporal variations in the clinical features required to make the diagnosis of AFS. In lieu of systemic medical therapy, which entails known side effects, long-term treatment of AFS is being transitioned to topical therapies. Topical application of steroids, antibiotics, and/or antifungals via nebulized formulations or mixed-in irrigants have shown some promise anecdotally. However, there are no data currently demonstrating efficacies of these therapies. As our understanding of the pathophysiology of AFS deepens, particularly from a genetic standpoint, immunomodulation will likely be a mainstay of long-term medical management. Nevertheless, surgical intervention will continue to be an essential part of the overall treatment plan of the child with AFS. For this reason, it is imperative to integrate all of the tools in our armamentarium, both medical and surgical, to provide children with the greatest possibility of long-term control. Unfortunately, the exact proportions of medical or surgical management that should be used are not yet fully understood.¹⁸

SUMMARY

CRS in the pediatric population remains an area of great importance because of its high prevalence and the diversity of disease presentations. An understanding of the classification schema is critical to the appropriate management of each disease subtype. The most useful clinical delineation is between NECRS, characterized by upregulation of the Th-1 pathway, and ECRS, with an enhanced Th-2 response. AFS is a refractory subtype of ECRS, defined by an intense inflammatory response to fungal antigens that are ubiquitous in the environment. Although the pathogenic mechanisms that create this condition are largely unknown, early diagnosis during childhood is often possible through a comprehensive understanding of the risk factors of this disease and thorough history and physical examination. Clinically, this is useful in guiding the decision to pursue computed tomography scanning and medical and surgical interventions that could potentially provide earlier symptomatic relief.

From a surgical standpoint, the goals of therapy are to remove the physical obstruction of the sinus outflow tracts, debride polyps and debris that are filling the sinuses, and maintain the patency of the sinuses to restore that mucociliary function of the uninvolved sinonasal mucosa. In doing so, great care must be taken to avoid causing iatrogenic damage to the structures surrounding the sinonasal airspaces, particularly because of the remarkable anatomic deformities associated with this condition. Image guidance is a helpful tool in this regard, and should be universally used during these procedures.

Medical therapies remain a useful adjuvant to surgical intervention. Evidence indicates that oral and topical corticosteroids may be effectively used to control the underlying inflammatory process. Because of the risks associated with steroid use in children, sustained systemic courses should be avoided, and early transition to

topical regimens is advocated because of their lower systemic bioavailability. As more research reveals the underlying pathogenic mechanisms of AFS, there will likely be a shift toward immunomodulation of the robust Th-2 response that is present in this disease process.

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