INTRODUCTION

Fungal rhinosinusitis (FRS) can be categorized into two broad groups: (1) noninvasive and (2) invasive. This is based on the absence or presence of fungus in the tissue (mucosa, blood vessel or bone) respectively. To avoid confusion and to optimize management, the International Society for Human and Animal Mycology group convened a panel of experts and published a consensus document in 2009 on the categorization of FRS. Noninvasive conditions include (1) saprophytic fungal infection, (2) fungal ball and (3) fungus-related eosinophilic FRS, including allergic fungal rhinosinusitis (AFRS) or eosinophilic fungal rhinosinusitis (EFRS). Invasive FRS include (1) acute invasive (fulminant) FRS, (2) granulomatous invasive FRS and (3) chronic invasive FRS. The clinical manifestations may overlap between the different types of FRS and the disease may even progress from a noninvasive form to an invasive form with the change of immunologic status in a patient. Because fungus-related eosinophilic FRS forms the bulk of patients with FRS and is laden with controversies in the pathogenesis, diagnosis and management, it will be the main focus of this chapter.

NONINVASIVE FUNGAL RHINOSINUSITIS

SAPROPHYTIC FUNGAL INFECTION

Saprophytic fungal infection refers to visible fungal colonization of mucus crusts seen within the nose and paranasal sinuses on nasoendoscopy (Fig. 1). These patients are usually asymptomatic or may present with a foul smelling odor. They are likely to have had previous sinus surgery. The proposed mechanism is dysfunction in mucociliary transportation from surgery leading to crust formation. The crust then acts as a platform for growth of fungal spores. It has been suggested that saprophytic fungal infections may be precursors to fungal balls if left untreated. Endoscopic cleaning of the infected crust is usually the only treatment required. However, if the infection recurs, self-irrigation of the paranasal sinuses with normal saline solutions and regular endoscopic toileting may be required.
**Fungal Ball**

A fungal ball is a dense accumulation of extramucosal fungal hyphae, usually within one sinus, most commonly the maxillary sinus. The terms mycetoma, aspergillosis and aspergilloma have been previously used to describe fungal balls in the paranasal sinuses. These terms are misnomers and should be avoided. Mycetoma refers to a local chronic invasive infection of the subcutaneous tissue with potential spread to the surrounding fascia or bone. This condition is usually seen in the hand and feet. Aspergillosis and aspergilloma are terms that have been used to describe various entities of FRS caused by Aspergillus, including fungal balls, allergic fungal sinusitis and chronic and granulomatous invasive sinusitis. Although the most common organism in a fungal ball is Aspergillus, the cultures are often negative and other fungal species have also been identified. Hence, fungal ball is the most appropriate term for this disease entity.

Fungal balls are seen more commonly in immunocompetent, middle aged and elderly females, often with a history of previous dental procedure, especially dental fillings. The diagnosis of fungal ball is based on the following features: radiological findings of sinus opacification often with areas of hyperattenuation (Fig. 2A), cheesy or clay-like debris within the sinus (Fig. 2B), accumulation of fungal hyphae without evidence of tissue fungal invasion seen microscopically, nonspecific chronic inflammation of the sinus and the absence of eosinophil predominance, granuloma or allergic mucin.

The management involves a wide opening of the involved sinus and complete removal of the fungal debris. Examination of the involved sinuses with angled scopes is crucial to ensure complete surgical extirpation. For fungal balls in the maxillary sinus, a total uncinectomy with a middle meatus antrostomy is usually sufficient. The size of the antrostomy is debatable and some authors will include an inferior meatus antrostomy to facilitate total removal of the fungus. Subsequent regular surveillance in the clinic is necessary. Oral or topical antifungals are not necessary.

**Fungus-Related Eosinophilic FRS Including Allergic Fungal Rhinosinusitis**

**Historical Background**

Allergic fungal rhinosinusitis was first recognized as an upper airway manifestation of allergic bronchopulmonary aspergillosis (ABPA) in the 1970s. In 1983, the term allergic aspergillus sinusitis was proposed by Katzenstein et al. because of its histologic similarity to ABPA. They described the thick, inspissated mucoid material containing fungal hyphae in both the sinuses and the bronchi as “allergic mucin.” This is characterized by “aggregates of necrotic eosinophils, nuclear debris, free eosinophil granules, sloughed respiratory tract epithelial cells, and Charcot-Leyden crystals within an amorphous, pale eosinophilic or basophilic mucinous background.” Although no fungi were formally cultured from the first few case series of patients with allergic aspergillus sinusitis, the presumed pathogen...
was *Aspergillus* due to clinical and histologic similarities to ABPA.\textsuperscript{10-12} Subsequent case series with culture results found that *Aspergillus* was a less common cause of this disease than other dematiaceous fungi such as *Bipolaris*, *Curvularia* and *Alternaria*.\textsuperscript{13} Consequently, the disease has become known as AFRS. AFRS is simply defined as a noninvasive fungal sinusitis resulting from an allergic and immunologic response to the presence of fungal hyphae in the sinuses.

### Epidemiology

The prevalence of FRS amongst chronic rhinosinusitis (CRS) patients who undergo surgery is between 12% and 47%.\textsuperscript{14,15} Of this, AFRS is the most common form, accounting for between 56% and 72% of patients with FRS.\textsuperscript{14,15} In the United States, one study showed a geographical variation in AFRS with the highest percentage of cases occurring in the south and along the Mississippi basin.\textsuperscript{16} The varied incidence may be due to a warm and humid environment that promotes fungal growth and exposure although no relationship to mould counts have been established.\textsuperscript{16,17} One of the largest histological series of surgical specimens was reported in India with an incidence of 24% in patients with CRS.\textsuperscript{15}

The typical AFRS patients are young immunocompetent adults.\textsuperscript{18} The mean age at presentation is between 21 and 35 years old.\textsuperscript{13,19-23} There is a higher male to female ratio of between 1.5 and 2.6 to 1.\textsuperscript{13,19-23,26,27} Wise et al. found that AFRS patients also have a lower socioeconomic status and a higher African-American ratio compared to CRS patients.\textsuperscript{28} In addition, young African-American male AFRS patients tend to present with advanced disease and have a higher risk of developing bone erosion of their paranasal sinuses at presentation.\textsuperscript{21}

### Pathophysiology

Although it has been over 30 years since AFRS was first described, the underlying pathophysiology remains unknown and controversial. A number of popular theories have evolved. Manning et al. proposed a mechanism derived from the ABPA model.\textsuperscript{29} In a series of 17 *Bipolaris* positive AFRS patients, 82% of patients had serum *Bipolaris*-specific IgE antibodies by radioallergosorbent test (RAST) inhibition and 94% of patients had serum *Bipolaris*-specific IgG antibodies by enzyme linked immunosorbent assay (ELISA).\textsuperscript{20} Hence, it is believed that an atopic host exposed to fungi resulted in antigenic stimulation by a combination of Gel and Coomb type I and type III hypersensitivity, leading to an intense inflammatory response.\textsuperscript{20,21,23} Subsequent study by Steward and Hunsaker showed that AFRS or AFRS-like patients had significantly higher levels of serum fungal-specific IgE and IgG levels compared to non-AFRS polyp patients.\textsuperscript{20} The importance of IgE in the pathogenesis of AFRS is further demonstrated by the finding that changes in serum IgE over time reflect the patients’ clinical status.\textsuperscript{30,31} More recently, antigen-specific fungal and non-fungal IgE in sinus mucosa of AFRS patients have been shown to be more prevalent compared with controls.\textsuperscript{32} The local IgE appears to be upregulated throughout the sinonasal cavity, without predilection for polyp-forming tissues.\textsuperscript{33}

While the immunologic theory proposed by Mannings et al. is supported in the literature, many questions remain unanswered. As highlighted by Marple, the immunologic theory fails to explain the unilateral or asymmetric nature of AFRS, the persistence of a raised IgE level after prolonged fungal immunotherapy (when it is expected to drop) and the failure of a rise in specific IgG levels resulting from the formation of IgG-blocking antibodies following fungal immunotherapy.\textsuperscript{34} An alternative theory was later proposed by Panikou et al.\textsuperscript{35} Their landmark, but non-peer-reviewed, paper stated that fungi was present in the nasal secretions of 96% (202 patients) of consecutive CRS patients and 100% (14 patients) of healthy volunteers with no sinus disease. Of the 210 consecutive patients with CRS, 101 underwent surgery with AFRS diagnosed in 93% (94 patients) of patients based on histologic findings and culture results. Elevated total and specific IgE levels were not prevalent amongst the AFRS patients and not significantly different to that of the control group. Based on these findings and their work using scanning electron microscopy, they rejected the role of an IgE-mediated reaction in the pathogenesis of AFRS. They believed that eosinophilic chemotaxis in response to extramucosal fungi was the hallmark of the inflammatory reaction in AFRS. Hence they proposed the term EFRS instead. Similarly, the term eosinophilic mucin was suggested as replacement for allergic mucin to emphasize the importance of eosinophils in the pathophysiology of AFRS.

Like the immunologic theory, the eosinophilic theory by Panikou et al. raised several important questions. If fungus is ubiquitous in sinonasal mucosa, then what triggers the migration of eosinophils into the mucous in AFRS patients? Does fungi play any role in the mechanism of AFRS or CRS? Are the “AFRS” patients in Panikou’s group a different entity altogether or is CRS an early form of AFRS?\textsuperscript{36} In 2000, Ferguson performed a literature review and concluded that there may be two different disease processes in play—allergic and non-AFRS.\textsuperscript{36} The term eosinophilic mucin rhinosinusitis...
(EMRS) was used to describe nonallergic fungal sinusitis. These patients were felt to have histological features similar to AFRS but without the presence of fungus. The underlying mechanism was believed to be a systemic dysregulation of immunologic controls resulting in upper and lower airway eosinophilia. As EMRS was a systemic disease, bilateral disease would be the norm. On the other hand, AFRS resulting from a localized IgE-mediated type I hypersensitivity to germinated fungus can have unilateral (30% of the time) or bilateral disease, depending on the antigenic stimulation. Ferguson observed that EMRS patients had a higher incidence of asthma, ASA sensitivity and IgG1 deficiency and a lower incidence of allergic rhinitis compared to AFRS patients. EMRS patients were also significantly older (48 years old) compared to AFRS patients (30.1 years old). Both EMRS and AFRS patients had a slight male predominance, universal presence of nasal polyposis and demonstrated serum eosinophilia and eosinophilic nasal disease. By recognizing EMRS and AFRS as two separate entities with a similar phenotypic endpoint, the treatment strategies for these patients can be formulated according to their pathogenesis. Systemic steroid, a potent and indiscriminant anti-inflammatory agent should be beneficial in both groups of patients. However, antifungal agents and fungal immunotherapy should theoretically benefit only AFRS and not EMRS patients. The triggering event leading to an inflammatory eosinophilic cascade in EMRS patients is likely to be multifactorial and remains a mystery. It is likely that the physiology is even more complex and that there is more than one genotypic process resulting in a similar phenotypic disease process.

**Diagnostic Criteria**

In 1994, Bent and Kuhn described a diagnostic criteria for AFRS based on 15 consecutive AFRS patients. They found 11 important clinical features, 5 of which were present in all 15 patients. These 5 features were termed major criteria and the remaining 6 features as minor criteria. All 5 major criteria were necessary to define AFRS while the minor criteria were considered supporting features (Table 1).

The Bent and Kuhn criteria have set the benchmark for the diagnosis of AFRS for many years with some minor variations proposed over the years. In 2004, a standardized definitions for clinical research and patient care for rhinosinusitis was published by a panel of international experts. Amongst the consensus definition put forth was classic AFRS. AFRS was recognized as a distinct subset of patients with CRS based on classic clinical, radiographic, pathologic and immunologic features as suggested by Bent and Kuhn. The five main clinical characteristics were: “(1) gross production of eosinophilic mucin containing noninvasive fungal hyphae, (2) nasal polyposis, (3) characteristic radiographic findings, (4) immunocompetence, and (5) allergy to fungi”.

There exists a subgroup of patients who do not meet all five major criteria but behave like AFRS patients and respond to AFRS treatment strategies (previously known as atypical AFRS). We have therefore adopted the Bent and Kuhn criteria with minor modifications to be more inclusive. An elevated IgE level is not always present in all AFRS patients and may fluctuate within the normal range as the disease stage changes. We currently utilize the following five major criteria to diagnose patients with AFRS (Table 2).

**Clinical Presentation**

Although there are no pathognomonic symptoms for AFRS, clinical suspicion should be high when one encounters a young patient with uni- or bi-lateral nasal polyposis with thick, sticky yellow/green mucus, characteristic double density sign on CT and who responds to oral steroids. Often, the symptoms are subtle and similar to that of chronic sinusitis with nasal polyposis. Patients may present with a long-standing history of gradual nasal obstruction associated with thick or crusty nasal discharge for months to year. They may not seek treatment until complete obstruction,
severe headaches or facial pain, anosmia, visual disturbance or facial distortion occurs.\textsuperscript{17}

On nasoendoscopy, nasal polyposis is universal and can be unilateral or bilateral. In bilateral cases, the bulk of the disease is usually asymmetric.\textsuperscript{17} Inspissated thick yellow or brown peanut-butter like mucus may be seen among the polyps (Figs. 3A to D).

**Investigation**

**Immunologic Test**

Patients with AFRS have an elevated IgE level. In a long-term follow-up of AFRS patients by Marple et al., the total IgE levels were found to be between 50 and greater than 1,000 IU/ml. The average total IgE level was about 550 IU/mL. Because of the wide range of total serum IgE level in AFRS patient it is not useful as a screening tool.\textsuperscript{39} However, total serum IgE level may be useful in monitoring clinical activity in the management of AFRS. IgE levels seems to parallel patient mucosal stage and is usually elevated just prior to worsening of the clinical stage.\textsuperscript{30}

As the diagnosis of AFRS requires demonstration of a fungus specific IgE, this can be achieved by an in-vivo test (skin prick test) or in-vitro (RAST) test. Studies have shown good concordance between the two tests for fungal and nonfungal antigens in patients with AFRS.\textsuperscript{40,41}

**Radiologic Test**

Computed tomography (CT) and magnetic resonant imaging (MRI) scans: Allergic fungal rhinosinusitis patients have
Endoscopic Sinus Surgery

Table 3: Characteristic findings of allergic fungal rhinosinusitis (AFRS) on CT and MRI scans of the paranasal sinuses.

<table>
<thead>
<tr>
<th>CT features</th>
<th>MRI features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Heterogenous signal intensities within the paranasal sinuses filled with allergic mucin (Double density sign)</td>
<td>• T1-weighted images—central areas of hypointensity with peripheral enhancement</td>
</tr>
<tr>
<td>• Expansion of the paranasal sinuses/nasal cavity</td>
<td>• T2-weighted images—central areas of hypointensity or signal void with peripheral enhancement</td>
</tr>
<tr>
<td>• Unilateral or asymmetric disease load</td>
<td></td>
</tr>
<tr>
<td>• Bony erosion</td>
<td></td>
</tr>
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</table>

Figs. 4A to D: CT images of a patient with AFRS with extensive disease. (A) Coronal cut showing complete opacification and expansion of the maxillary and frontal sinuses with erosion of the bilateral skull base and lamina papyracea; (B) axial and (C) sagittal cuts of the frontal sinuses with expansion and erosion of the posterior table of the frontal sinuses by fungal disease; (D) Axial image of the maxillary sinuses showing complete sinus opacification with heterogeneity (double density sign).

typical features seen on an unenhanced CT paranasal sinus and an enhanced MRI paranasal sinus (Table 3). This results in a “double density” or rail-track sign (Figs. 4A to D). The double density sign is best appreciated by viewing the CT on soft tissue windows. The optimum setting in the bone protocol to accentuate this sign is a window width of ~2000 House Unit (HU) and centered at ~–250/–200. The consistency
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of the sinus secretions determines the signal level on CT scan. In a watery sinus secretion, the CT attenuation is less than fat. In contrast, thick sinus secretion can result in a CT attenuation higher than that of muscle.\textsuperscript{45,46}

MRI of the paranasal sinus with intravenous gadolinium contrast can be considered when the diagnosis of AFRS is uncertain or if there are concerns with rare intracranial or intraorbital complications. The protein content and viscosity of the secretion will determine the signal intensity seen on MRI. In watery secretions (less than 5% protein), there is low T1 signal and high T2 signal. In thick secretions (5–25% protein), T1 signal increases while T2 signal remains high. In mycetoma/sludge (25–40% protein), there is low T1 signal and low signal intensity to void on T2.\textsuperscript{47} In fungal infections, the consistency of the secretion usually results in a low intensity on T1 and a much lower intensity to signal void on T2 (Figs. 5A and B).\textsuperscript{26,42,45,46} This is due to higher concentration of iron and manganese as well as calcium deposits within the fungal concretions.\textsuperscript{47}

Radiologic Staging

The Lund-MacKay system\textsuperscript{49} is a simple, well-studied and validated radiographic staging system developed to assess the severity of CRS on CT scan. This staging system is recommended by the Task Force for Rhinosinusitis for outcome research. It is a 24-point system in which each sinus and the osteomeatal complexes are assessed individually (Table 4).

The Lund-MacKay system has also been used by otolaryngologists to assess the severity of sinus opacification on CT scan of AFRS patients. However, it does not assess bony erosion and expansion within the affected sinuses seen in advanced AFRS patients. Hence, in 2009, Wise et al. proposed a 24-point radiologic staging system to assess bony remodeling (defined as bony erosion or expansion). Each sinus wall that bounded obvious opacification is given a score of 1 if there is evidence of bony erosion or expansion. Each sinus is assessed separately and the maximum score per sinus is allocated. For simplicity, even though there are more than three possible locations of remodeling for the maxillary and sphenoid sinuses, the authors decided to cap the maximum score of 3 for these sinuses (Table 5). In their series of AFRS patients, Wise et al. found that males and African American AFRS patients had the highest scores. As this is a relatively new staging system for AFRS, studies to determine the inter- and intraobserver variability and the usefulness of this staging system in predicting long-term outcomes will be required.\textsuperscript{50}

Table 4: Lund-MacKay CT staging system for chronic rhinosinusitis (CRS).

<table>
<thead>
<tr>
<th>Sinus</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior ethmoid sinus</td>
<td>/2</td>
<td>/2</td>
</tr>
<tr>
<td>Posterior ethmoid sinus</td>
<td>/2</td>
<td>/2</td>
</tr>
<tr>
<td>Sphenoid sinus</td>
<td>/2</td>
<td>/2</td>
</tr>
<tr>
<td>Frontal sinus</td>
<td>/2</td>
<td>/2</td>
</tr>
<tr>
<td>Osteomeatal complex</td>
<td>/2</td>
<td>/2</td>
</tr>
<tr>
<td>Total score</td>
<td>/12</td>
<td>/12</td>
</tr>
</tbody>
</table>

For sinuses, 0 = no opacification, 1 = partial opacification, 2 = complete opacification. For osteomeatal complex, 0 = not obstructed, 2 = obstructed.

Figs. 5A and B: Radiographic imaging of a patient with a fungal ball in the sphenoid sinus. (A) Coronal cut of a CT scan showing near complete opacification of the sphenoid sinus; (B) Coronal cut of a T2-weighted MRI of the same patient showing a signal void in the sphenoid sinus.
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**Differentiation from invasive Fungal Rhinosinusitis**

As advanced AFRS can present with features suggestive of fungal invasion, it is important to note the radiologic differences between AFRS and invasive fungal rhinosinusitis (IFRS). Reddy et al. performed one of the largest prospective studies comparing the CT and MRI findings of chronic IFRS versus that of AFRS. The more prevalent features are summarized as follows (Table 6).\(^{42}\)

The presence of bone erosion is not pathognomonic for fungal invasion.\(^{26,42,48}\) In AFRS, the mechanism of bone erosion is similar to that of a mucocele.\(^{42}\) The constant high pressure from expansion of the sinuses in an inflamed environment probably accounts for thinning and erosion of bone.

**Histology**

The hallmark of AFRS is the presence of allergic mucin. Grossly, it is thick, tenacious and highly viscous in consistency. The color can range from yellow to brown or dark green.\(^{38,51}\) Hence, the terms “peanut butter” and “axle-grease” are commonly used to describe the characteristic appearance of the mucus. Histologically, allergic mucin consists of an eosinophilic mucin with necrotic eosinophils, inflammatory cells, Charcot-Leyden crystals (the byproduct of eosinophil) and fungal hyphae (Fig. 6A).\(^{37}\) Fungal hyphae are usually not stained by haematoxylin and eosin (H&E) but can be deduced from their negative image on a stained background. As fungal hyphae are infrequent and scattered within allergic mucin, their detection is difficult unless specific stain with a silver stain such as Grocott’s or Gomori’s methamine silver (GMS) stain are performed\(^{38}\) (Fig. 6B).

**Fungal Culture**

A positive fungal culture provides supporting evidence in the diagnosis of AFRS. However, its absence does not exclude the diagnosis of AFRS. The presence of a positive fungal culture in AFRS patients ranged from 49% and 100%, depending on the culture method used.\(^{20,35,52,53}\) In our institution, positive fungal cultures were obtained in 64% of AFRS patients using a modified Mayo Clinic fungal culture technique. Therefore, AFRS with a negative fungal culture is possible. Likewise, a positive fungal culture also does not confirm the diagnosis of AFRS but merely confirms the presence of saprophytic fungal growth. The histological

<table>
<thead>
<tr>
<th>Table 5: Allergic fungal rhinosinusitis (AFRS) radiologic staging.</th>
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</thead>
<tbody>
<tr>
<td>Sinus involved</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Frontal sinus</td>
</tr>
<tr>
<td>Maxillary sinus</td>
</tr>
<tr>
<td>Ethmoid sinus</td>
</tr>
<tr>
<td>Sphenoid sinus</td>
</tr>
<tr>
<td>Sphenoid inter sinus septum</td>
</tr>
<tr>
<td>Frontal inter sinus septum sinus</td>
</tr>
<tr>
<td>Maximum score</td>
</tr>
</tbody>
</table>

| Table 6: Radiologic difference between invasive fungal sinusitis and allergic fungal rhinosinusitis (AFRS). |
|---|---|---|
| Characteristic | IFRS | AFRS |
| CT opacification | Homogenous | Heterogenous |
| MRI opacification | Intermediate signal on T1 | Low to very low signal on T2 |
| Contrast enhancement | Intense and homogenous | Sinus mucosa (not mucus/fungal debris) |
| Laterality | Slight prevalence for unilateral disease | Slight prevalence for bilateral disease |
| Sinus involvement | Limited sinus disease (≤ 2 sinuses involved) | Multiple sinuses involved |
| Intraorbital or intracranial extension | More disease outside sinuses than within | Extension of disease due to sinus expansion into orbit or cranial cavity |
| Expansion of sinuses | Not present | Always present |
| Bone erosion | Localized | Widespread |
identification of allergic mucin is still the most reliable marker for the diagnosis of AFRS.38

**MANAGEMENT**

Although the management of AFRS has advanced tremendously with better understanding of the underlying pathogenesis, the optimal treatment strategy is still far from clear. Once a diagnosis of AFRS has been established, patients are enrolled into a committed long-term management program with regular and long-term follow-up considered critical to the success of the treatment. A combination of surgery with a comprehensive postoperative medical regimen to keep the disease under control is almost always required.

**Surgical Treatment**

Unlike the management of classical CRS, surgery is usually the first line treatment in the management of AFRS. External approaches with mucosal stripping have largely been abandoned and meticulous and complete endoscopic sinus surgery are now the gold standard in the surgical extirpation of polyposid disease and allergic mucin in an attempt to restore ventilation and drainage of the sinuses.18 Removal of allergic mucin and fungal debris eliminates the antigenic factor that incites the disease in an atopic host.

In advanced disease, expansion of the sinuses by inspissated mucus, polypoid disease and mucoceles often facilitates surgery.17 However, the extensive disease with resulting mucocele and bony erosion will also distort normal sinus anatomy and increase the risks of intracranial and intraocular complications.17 Therefore, in our center, functional endoscopic sinus surgery (FESS) for AFRS patients is routinely carried out with image-guided system. Image guidance also aids in complete removal of eosinophilic mucin and opening of drainage pathways, especially in revision cases when postoperative scarring, osteoneogenesis and loss of anatomical landmark can make surgery extremely difficult and challenging. Incomplete surgical resection with remnant cells filled with allergic mucin can be a risk factor for early disease recurrence.36 To prevent postoperative scarring, osteoneogenesis and restenosis of the sinuses, mucosal preservation during surgery is key.

Surgery not only drains, re-establishes ventilation and removes the antigenic stimulation for AFRS patients, but also provides wide access for surveillance, clinical debridement and application of topical medication. It is only the first critical step in a long-term treatment contract with the patient and often a combination of medical treatments will be required for the patient to remain disease free.

**Endoscopic Staging of Mucosal Disease Postsurgery**

Regular follow-up and accurate documentation of the sinonasal mucosa of AFRS patients after surgery is critical to monitor disease status and response to adjunctive medical treatments. Therefore, Kupferberg et al. devised a four-stage system for endoscopic follow-up in these patients postsurgery (Table 7).57 However, the Kupferberg staging system lacks sensitivity, often resulting in patients remaining in
the same endoscopic stage even when they have improved symptomatically and endoscopically. Hence in 2010, Philpott et al. introduced a new endoscopic staging system for AFRS. The Philpott-Javer system is a validated system that was derived from modifications made to the Kupferberg system. Each sinus cavity is scored independently on a scale from 0 to 9 based on the degree of mucosal inflammation. An additional 1-point is allocated for each sinus if allergic mucin is noted grossly. This allows for a maximum score of 10 points per sinus cavity, 40 points for each side of the nose and 80 points for the total maximum bilateral score. More recently, we have added the olfactory cleft on each side as an independent site thereby rounding out the total maximum bilateral score to 100 (50 on each side). Such a system is much more sensitive and allows for much better tracking of disease control postoperatively (Tables 8A and B, Fig. 7).

**Medical Treatment**

**Systemic Medications**

Corticosteroids: Oral steroids are useful in the perioperative period of patients with AFRS. In the preoperative period, a short course of corticosteroids have been shown to reduce intraoperative bleeding and size of the polyps. In the postoperative period, the corticosteroids regimen was initially derived from the protocol used in treatment of ABPA. In a four-year follow-up study of 11 AFRS patients by Kuhn and Javer, a reduction in IgE and mucosal disease postoperatively were seen in patients who were on steroids. They found that in order to prevent recurrence, a minimum of 6 months of normal sinus mucosa while on steroids is necessary before steroids can be slowly discontinued. The longest time to recurrence was noted to be up to 34 months, hence the need for long-term follow-up of at least 3 years, even after the patient is steroid-free. A postoperative corticosteroid regimen proposed by Kuhn and Javer was as follows: 40 mg daily for 4 days followed with 30 mg daily for 4 days, followed with 20 mg daily for 1 month after surgery, followed by 0.2 mg/kg daily for 4 months while maintaining

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**Table 7: Kupferberg postoperative endoscopic staging system for allergic fungal rhinosinusitis (AFRS).**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Endoscopic finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal mucosa</td>
</tr>
<tr>
<td>II</td>
<td>Mucosal edema/allergic mucin</td>
</tr>
<tr>
<td>III</td>
<td>Polypoid edema/allergic mucin</td>
</tr>
<tr>
<td>IV</td>
<td>Sinus polyps and fungal debris</td>
</tr>
</tbody>
</table>

**Tables 8A and B: Philpott-Javer endoscopic staging system for allergic fungal rhinosinusitis (AFRS).**

**Table 8A**

<table>
<thead>
<tr>
<th>Sinus cavity</th>
<th>Right</th>
<th>Mucin</th>
<th>Left</th>
<th>Mucin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>0–9</td>
<td>1</td>
<td>0–9</td>
<td>1</td>
</tr>
<tr>
<td>Ethmoid</td>
<td>0–9</td>
<td>1</td>
<td>0–9</td>
<td>1</td>
</tr>
<tr>
<td>Maxillary</td>
<td>0–9</td>
<td>1</td>
<td>0–9</td>
<td>1</td>
</tr>
<tr>
<td>Sphenoid</td>
<td>0–9</td>
<td>1</td>
<td>0–9</td>
<td>1</td>
</tr>
<tr>
<td>Olfactory cleft</td>
<td>0–9</td>
<td>1</td>
<td>0–9</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>50</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bilateral total</strong></td>
<td>100</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Table 8B**

<table>
<thead>
<tr>
<th>Grading</th>
<th>State of mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No edema</td>
</tr>
<tr>
<td>1–3</td>
<td>Mucosal edema (mild/moderate/severe)</td>
</tr>
<tr>
<td>4–6</td>
<td>Polypoid edema (mild/moderate/severe)</td>
</tr>
<tr>
<td>7–9</td>
<td>Frank polyps (mild/moderate/severe)</td>
</tr>
</tbody>
</table>

**Fig. 7:** A clinic poster for the Philpott-Javer endoscopic staging system for AFRS.
endoscopic stage 0 and finally 0.1 mg/kg daily for 2 months, including the use of intranasal corticosteroids.57

Despite the widespread use of steroids in patients with CRS with nasal polyposis, a Cochrane Review in 201159 found only three randomized controlled trials that met their stringent criteria in assessing the efficacy of nasal steroids in patients with nasal polyposis. Out of 166 patients in these three trials, only 96 patients (58%) showed improvement in nasal symptoms score, quality of life and nasal polyp size after 2–4 weeks course of steroids compared to no steroid treatment.60–62

Systemic steroids, although beneficial in the perioperative period, are not without adverse side effects. Among some of the early side effects include psychosis, insomnia, poorer control of blood glucose level (in diabetic patients) and blood pressure (in hypertensive patients) and gastric upset from peptic ulcer disease. The long-term adverse effects include accelerated osteoporosis, glaucoma, cataract formation and avascular necrosis of the hip.18 Although long-term oral corticosteroid may be necessary in some patients, its use should be judicious and limited to short courses in the perioperative period and in acute exacerbations of AFRS to suppress growth of recurrent polyps.17

Antifungals: Oral antifungals are considered as a treatment option in patients with recalcitrant chronic fungal sinusitis. It is also used as a steroid-sparing medication, allowing some patients to be weaned off from long-term oral corticosteroid therapy.63 Oral itraconazole, when used in steroid-dependant ABPA patients, was found to reduce the dosage of steroids required, improve pulmonary function and exercise tolerance, and decrease IgE levels.64 The presumed mechanism involved is a decrease in fungal load with subsequent reduction in antigenic stimulation for chronic inflammation.63 As such, AFRS, a disease considered similar to ABPA, is thought to respond similarly to antifungals.

There are no randomized controlled trials on the effectiveness of oral antifungals in AFRS patients. Early reports by Bent and Kuhn showed mixed to poor results.65 However, in a large retrospective study of 137 AFRS patients treated with high dose oral itraconazole by Rains et al., recurrence occurred in 69 patients (50.3%) at about 10.8 months post-surgery and revision surgery was required in 17 patients (20.5%).66 In their regimen, itraconazole was given at 400 mg/day for 1 month, followed by 300 mg/day for 1 month, followed by 200 mg/day for 1 month or until clear by endoscopy. As the revision surgery rates have been reported to be between 48% and 56%,36,52 Rains et al. concluded that high dose antifungals reduced the requirement for repeated surgical debridement. Subsequent retrospective studies63,67 with lower dosage of oral antifungals (200–300 mg daily) showed potential benefits as a steroid-sparing alternative and in prolonging time to disease recurrence. In our small series of recalcitrant AFRS patients at the St Paul’s Sinus Centre treated with oral itraconazole (300 mg/day for 1 month followed by 200 mg/day for 2 months), 56% of patients reported subjective improvement in symptoms score and 38% of patients showed endoscopic improvement.87

Oral itraconazole is associated with risk of elevated liver enzymes, congestive heart failure, nausea, rash, headache, malaise, fatigue, and edema (Janseen Pharmaceutica, Beerse, Belgium). The prevalence of transaminitis in AFRS patients on oral itraconazole has been reported to be between 4% and 19%.63,67 Asymptomatic transaminitis is not uncommon and cessation of treatment is usually sufficient for the elevated liver enzymes to revert back to normal. Hepatotoxicity including liver failure and death is rare but a serious complication of itraconazole. Hence, the role of antifungals in the management of AFRS patients has to be more clearly defined. It seems that a subset of AFRS patients seems to respond to antifungals and future randomized controlled trials will be required to identify the ideal candidate and to assess the efficacy, safety and optimal dosage and regimen for oral antifungals in the treatment of AFRS.

Topical Medication

Corticosteroid: Topical corticosteroids are used as the standard treatment of patients with AFRS. They are most effective in the postoperative period, when the open sinus cavities and middle meatus provide access to the drug. The benefit of topical over systemic steroid lies in the ability of topical steroid to achieve the highest drug concentration in the target tissue (sinonasal mucosa) without the unwanted systemic side effects.68 Although studies on the effectiveness of intranasal steroids in AFRS patients are lacking, their benefits have been well established in CRS patients with nasal polyposis.69,70 In the treatment of nasal polyp disease, recent meta-analyses showed that topical corticosteroids reduced polyp size and improved symptoms compared to control.69,70 For AFRS patients, Kuhn and Javer recommended using a dosage three times that used for allergic rhinitis in weaning patients off oral corticosteroid.80

Recently, the use of budesonide administered as drops, atomized sprays or through low volume saline rinses have gained popularity in the treatment of AFRS patients.17 Inhaled budesonide have been shown to be an effective and
safe treatment for asthma.\textsuperscript{71,72} The systemic bioavailability of aqueous intranasal budesonide is 34\% when absorbed by nasal mucosa and its oral bioavailability is only 10\% due to extensive first past metabolism.\textsuperscript{72} In asthmatic children, the total bioavailability of nebulized budesonide has been reported to be approximately 6\%.\textsuperscript{72} In addition, long-term 400 \mu g/day budesonide via turbuhaler in asthmatic children and adults have not been shown to have any clinically significant effect on the hypothalamic-pituitary-adrenal (HPA) axis.\textsuperscript{71,74} In postsurgical CRS patients, Sachananda\textsuperscript{n}i et al. demonstrated that budesonide nasal irrigation (2.5 mg of budesonide diluted in 5 mL of normal saline in each nasal cavity) for 30 days improved clinical symptoms of CRS without HPA suppression.\textsuperscript{75}

In the treatment of postoperative refractory CRS patients, topical budesonide (Pulmicort Respules) via the Mucosal Atomization Device (MAD; Wolfe-Tory Medical, Salt Lake City, UT) resulted in improvements in both physician and patient global assessments and also reduction in the use of oral prednisolone (Fig. 8). A prospective study is currently being conducted in our center to determine if application of high dose budesonide (up to 0.5 mg/mL of Pulmicort Respules per nostril three times a day) via the MAD causes HPA suppression and results in an increase in plasma cortisol and detection of plasma budesonide. The preliminary data of the first 10 patients neither showed any evidence of HPA suppression nor any elevation of plasma cortisol or presence of plasma budesonide. Hence, the use of topical budesonide delivered via the MAD looks promising as an effective and safe adjunct in the treatment of AFRS.

At our center, AFRS patients are instructed to use budesonide rinses (2 mL of 0.5 mg/mL Pulmicort Respules in 500 mL of normal saline) in the immediate postoperative period. After 3 weeks postoperatively, the budesonide is delivered through a MAD. Patients are taught to apply the spray in a Mygind position (Fig. 9). Specifically, patients are asked to insert the MAD in the nose and aim laterally (towards the ipsilateral medial canthus). 1 mL (0.5 mg/mL) is then sprayed into each nasal nostril. Patients are advised to remain in the Mygind position for 2–3 minutes after instilling the spray. We favor the Mygind position as it is supported by our recently completed (unpublished) study on post-FESS cadaveric heads. Our study showed superior distribution of fluorescein within the ethmoid and frontal sinuses and the frontal recess when the head was placed in the lateral-head-back (LHB) position compared to the vertex-to-floor (VTF) position.

\textit{Antifungals:} As discussed above, systemic antifungal can have significant adverse effects. Therefore, the use of topical antifungals has been explored extensively. Unfortunately, evidence on the effectiveness of topical antifungals (spray or lavage) in AFRS patients has been scarce. On the other hand, there are numerous studies in the literature on the use of topical antifungals in CRS patients. A recent meta-analysis of topical amphotericin B for the treatment of CRS found no significant difference between computed tomography, nasal endoscopy and symptom scores between the amphotericin B treated group compared to the control arm.\textsuperscript{76} A Cochrane review completed in 2011 of randomized placebo-controlled trials for both topical and oral antifungals in the management of CRS patients did not show any
benefit in the treatment group over the control group. In fact, the symptom scores favored the placebo group and adverse events were significantly more prevalent in the antifungal group. Therefore it was concluded that antifungals, whether topical or oral should not be used in the treatment of CRS. In view of the lack of effect of antifungals on CRS patients, the role of fungus in the pathogenesis of CRS has largely been rejected. However, the role of fungus in the pathophysiology of AFRS is more established, though still controversial. As topical antifungals have fewer side effects than their oral counterparts, future randomized controlled trials on their effectiveness on true AFRS patients should be conducted.

**Immunotherapy**

Specific immunotherapy (IT), also known as allergen IT, refers to a process of repetitive administration of an antigen (either subcutaneously or sublingually) in increasing dosage to reduce patient sensitivity to that allergen. The mechanism of action is believed to be a decrease in production of allergen-specific IgE and the production of IgG4 blocking antibodies that interfere with the IgE antigen reaction. In ABPA, IT has been avoided due to the possibility of an immune complex-mediated reaction developing from the IgE and the production of IgG4 blocking allergen-specific antibodies. As AFRS is considered pathophysiologically similar to ABPA, allergen IT in AFRS was not well studied until recently. As opposed to ABPA, the fungal antigenic stimulus can be removed surgically in AFRS patients. Surgical removal of fungal debris and allergic mucin in AFRS patients has also been shown to decrease allergen specific IgE levels for fungal antigen. Hence, it can be argued that fungal IT after surgery may potentially provide benefit rather than harm in the management of AFRS.

Antifungal IT in AFRS patients was first presented by Ferguson in 1993 at the American Academy of Otolaryngology Allergy Meeting. In her retrospective review of 7 AFRS patients receiving fungal IT, 5 patients who did not have surgery did not improve or appeared to have worsened after IT. The other 2 patients who received IT after surgery did improve clinically. Subsequently, in 1995, Quinn et al. published the first case report on successful IT in an AFRS patient with *Bipolaris*. The patient had surgery and was refractory to multiple polypectomies, nasal and oral steroids and antibiotics. However, after 18 months of Bipolaris IT, the patient had resolution of symptoms and polyposis as well as significant improvement on a repeat CT scan. The patient’s total IgE, *Bipolaris*-specific IgE and IgG and eosinophilic counts did not change significantly. Following this, the majority of studies on fungal IT in AFRS patients were conducted by Mabry and colleagues. In their experience, fungal IT proves to be safe and effective in the majority of postsurgical AFRS patients. In their review of eight AFRS patients who received fungal IT for at least 3 years (range of 36–52 months, average 40 months), none had recurrence of nasal polyps or allergic mucin or fungal debris after discontinuation if IT for 7–17 months (average 13 months). A literature review by Hall and deShazo in 2012 revealed 10 studies on fungal IT in AFRS patients (Table 9). In all studies, there were no major systemic reactions, nor evidence of worsening of disease in patients treated with fungal IT. The only side effects reported were minor local reaction. Although the results of fungal IT appeared promising, the lack of randomized controlled trial warrants better well-designed research to establish the efficacy and safety of fungal IT in the treatment of AFRS.

**Adjunctive Treatments**

**Manuka honey**

Honey has been used since ancient times for the treatment of infected wounds. It has been proven to be effective in the management of chronic wounds such as diabetic ulcers and wounds infected by antibiotic-resistant bacteria that have failed conventional therapies. The antimicrobial activity in honey is due to its high glucose content (80%), acidic nature (pH 3.2 to 4.5), and the production of hydrogen peroxide when diluted with water. The glucose in honey fuels vital cells like phagocytes that are in need of energy production in an environment that is often deficient in oxygen supply. The acidic environment inhibits bacterial growth while hydrogen peroxide is an anti-inflammatory and bacteriociidal agent.

Amongst the various types of honey available, Manuka (Leptospermum scoparium) Honey from New Zealand is the most therapeutically potent honey, with antibacterial and anti-inflammatory effects. It has been shown to be active against a broad spectrum of gram-positive and gram-negative bacteria. The principal active ingredient responsible for the antibacterial property in Manuka Honey is Methylglyoxal (MGO). MGO is present at a concentration of up to 100-fold that of conventional honey. In a recent in-vitro study by Alandejani et al., Manuka Honey at a concentration of 33% v/v was shown to be effective in eradicating Methicillin-susceptible *Staphylococcus Aureus* (MSSA), Methicillin-resistant *Staphylococcus Aureus* (MRSA) and *Pseudomonas Aeruginosa* (PA) biofilms. In fact, conditions that rapidly induced antibiotic resistance did not cause bacterial resistance to honey.
### Table 9: Studies on fungal immunotherapy (IT) in allergic fungal rhinosinusitis (AFRS) patients.

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Study design</th>
<th>No. of patients treated with IT</th>
<th>Average duration of treatment</th>
<th>Main findings</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferguson⁶⁰/1993</td>
<td>Retrospective</td>
<td>7</td>
<td>Unknown</td>
<td>5 patients did not improve (presurgery), 2 patients improved symptomatically (IT given postsurgery)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Quinn et al.⁵⁹/1995</td>
<td>Case report</td>
<td>1</td>
<td>18 months</td>
<td>Resolution of symptoms and nasal polyposis</td>
<td>None</td>
</tr>
<tr>
<td>Mabry et al.⁶⁴/1997*</td>
<td>Prospective</td>
<td>9</td>
<td>8.6 months</td>
<td>Decreased need for oral and topical corticosteroids</td>
<td>None</td>
</tr>
<tr>
<td>Mabry and Mabry⁶⁴/1997*</td>
<td>Prospective</td>
<td>10</td>
<td>20 months</td>
<td>7 patients symptoms free, 2 patients required revision surgery, 1 patient was on nasal irrigation</td>
<td>Infrequent minor reactions at injection site</td>
</tr>
<tr>
<td>Mabry et al.⁶⁶/1998*</td>
<td>Prospective</td>
<td>11</td>
<td>28 months</td>
<td>No revision surgery, 3 patients on topical nasal steroids</td>
<td>None</td>
</tr>
<tr>
<td>Folker et al.⁶⁷/1998*</td>
<td>Prospective case control</td>
<td>11</td>
<td>33 months</td>
<td>Improvement in endoscopic and symptom scores and reduction in oral and topical nasal corticosteroid use compared to control</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mabry et al.⁶⁸/2000*</td>
<td>Prospective</td>
<td>8</td>
<td>40</td>
<td>No recurrence of disease after 7–17 months cessation of IT</td>
<td>Not reported</td>
</tr>
<tr>
<td>Bassichis et al.⁶⁹/2001*</td>
<td>Retrospective</td>
<td>36</td>
<td>Unknown</td>
<td>Decreased rate of revision surgery (11% in IT group vs 33% in non-IT group), reduced postoperative office visits requiring medical therapy (3.17 in IT group vs 4.79 in non-IT group)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Marple et al.⁷⁰/2002*</td>
<td>Retrospective</td>
<td>10</td>
<td>Unknown (follow-up period of 46–138 months)</td>
<td>No significant impact on number of operations, endoscopic and quality of life scores but overall well</td>
<td>Not reported</td>
</tr>
<tr>
<td>Greenhaw et al.⁷¹/2011</td>
<td>Retrospective</td>
<td>14</td>
<td>21.8 months</td>
<td>No difference in adverse reactions between patients receiving high dose fungal IT in AFRS patients vs high-dose fungal IT in CRS patients.</td>
<td>Minor local reactions</td>
</tr>
</tbody>
</table>

*Study from the Department of Otorhinolaryngology, University of Texas Southwestern Medical Center.

**Fig. 10:** Manuka honey preparation and the power rinse bottle for sinus irrigation.
As biofilms are increasingly recognized as key players in perpetuating chronic inflammation and infection in patients with recalcitrant CRS, the use of honey irrigation as an adjunct in the treatment of AFRS patients postsurgery should be considered. At St Paul's Sinus Centre, our early experience with Manuka honey irrigation (Fig. 10) in AFRS patients refractory to surgery and postoperative oral and intranasal steroids showed clinical improvement. However, a subsequent prospective randomized controlled trial of 34 postsurgical AFRS patients treated with Manuka honey in one nostril did not show any significant difference in sinonasal mucosal score compared to the untreated nostril. In this study, the patients acted as their own control. In the treated nostril, patients were instructed to use the MAD to administer 2 mL of 50/50 mixture of Manuka honey saline solution every night for 30 days. Only 7 out of 34 patients showed mucosal improvement after treatment with Manuka honey irrigation in one nostril. It appears that there is a subgroup of AFRS patients who do respond well to Manuka honey irrigation. We therefore embarked on a study to identify the cytokine profiles in this population of patients. In our recently completed randomized controlled study (unpublished) comparing post-FESS patients treated with either Manuka honey or saline solution for 3 months, we found a cytokine signature of upregulated interleukin (IL)-1b, IL-4, IL-6 and IL-12 in the sinonasal mucosa of patients who responded to Manuka honey treatment. This preliminary result looks promising and larger studies to confirm the result of this study will be warranted. As Manuka honey has been proven effective against biofilms and have anti-inflammatory properties, further research should aim to determine the optimal concentration and regimen for irrigation of the sinuses in postsurgical AFRS patients.

**Future Treatment Strategies**

**Anti-Immunoglobulin E (IgE) therapy**

Omalizumab (Xolair) is a humanized monoclonal anti-IgE antibody that has been used as an adjunctive treatment in severe atopic asthma. It has also been shown to clinically improve patients with allergic rhinitis. In individuals with CRS with nasal polyposis and allergic rhinitis, local sinonasal IgE levels and often serum IgE levels are increased. Although the pathogenesis of nasal polyposis in CRS is unknown, like in AFRS, allergy has been implicated as one of the potential etiologic factors. Hence, the use of omalizumab in patients with CRS with nasal polyposis and asthma has been explored.

In a small pilot study by Penn and Mikula amongst post-FESS atopic asthma patients with nasal polyposis treated with omalizumab, there was a significant reduction in the size of the polyps in the anti-IgE group compared to control. In addition, they found that the severity of nasal polyposis correlated with total serum IgE levels in atopic asthmatics. In their study, omalizumab was administered by subcutaneous injection in 2- or 4-week intervals with a dose range of 150-375 mg (depending on patients’ weight and pretreatment IgE levels) for an average of 5.5 months (range 3-8 months). Apart from reduction in polyp size, omalizumab treatment in post-FESS CRS with nasal polyposis patients with asthma has also been shown to reduce dependence on intranasal steroids and avoid revision surgery. In the only randomized double-blind placebo-controlled trial on omalizumab therapy on nasal polyps and asthma patients, Gevaert et al. demonstrated that there was significant improvement in total nasal endoscopic polyp scores, CT findings, airway symptoms and quality of life scores after 16 weeks of omalizumab treatment. These improvements were seen irrespective of the presence of allergy.

Given the pathophysiological similarity between ABPA and AFRS, recent case reports and case series demonstrating improvement in the clinical outcome of omalizumab in ABPA patients provide additional support for its use in AFRS patients. Although there are currently no published data on the effects of anti-IgE therapy on AFRS patients, a study of this nature is currently ongoing in our institution. We have administered subcutaneous omalizumab in a small number of AFRS patients with raised IgE levels and the early results seem to be favorable. We are excited about the final outcome of this study which we hope will pave the way for a double blind randomized controlled trial to prove the efficacy of this drug.

**INVASIVE FUNGAL RHINOSINUSITIS**

**ACUTE (FULMINANT) INVASIVE FRS**

Acute or fulminant invasive FRS is a life-threatening disease present usually in immunocompromised patients with impaired neutrophilic response. These patients include those with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome (AIDS), aplastic anemia,
hemochromatosis, aplastic anemia, iatrogenic immunosuppression, organ transplantation and hematological malignancies. Histological features include mycotic infiltration of blood vessels, vasculitis with thrombosis, tissue infarction, hemorrhage and acute neutrophilic infiltrate. Aspergillus species and the fungi in the order of mucorale (e.g. Rhizopus, Rhizomucor and Mucor) are the most commonly implicated species.

The inability to mount a host response to invasive fungal disease in immunocompromised patients can make the diagnosis of this disease entity difficult, especially in the early stages. Although common reported clinical symptoms include fever, cough, crusting of the nasal mucosa, epistaxis and headaches, a high index of suspicion of this disease entity should be present in any immunosuppressed patients with localizing sinonasal symptoms. Often, fever of unknown origin that has failed to respond to 48 hours of broad-spectrum intravenous antibioitcs may be the initial presenting symptom.

In the early stages, nasoendoscopic findings may be as subtle as the presenting symptoms. Alteration in mucosal appearance such as a discoloration, granulation and ulceration are the most consistent physical findings. Mucosal discoloration seen include gray, green, white and black. A white mucosal discoloration suggests tissue ischemia while a black mucosal discoloration indicates tissue necrosis seen in late disease. In a case series by Gillepsie and O’Malley, the mucosal changes were most commonly seen on the middle turbinate (67% of patients) followed by the septum (24%), palate (17%) and inferior turbinate (10%). A middle turbinate biopsy in the confirmation of acute invasive FRS has been shown to have a sensitivity of 86% and a specificity of 100%. On radiology, there are no pathognomonic features for invasive FRS and a CT scan is the initial radiologic investigation of choice (Figs. 11A and B). The main radiologic features suggestive of invasive FRS are summarized in Table 6.

Without early treatment, rapid progression of disease with 50%–80% mortality rates from intraorbital and intracranial complications have been reported. Improvement of the host immune response is paramount for survival. Once a diagnosis is confirmed, early and aggressive endoscopic surgical debridement till “bleeding margins” are seen is necessary. Even if middle turbinate biopsy in the clinical setting is negative, a low threshold for intraoperative biopsy and surgical debridement should be considered in high risk patients with suggestive clinical and radiological findings. The aims of surgery are to halt or slow progression of the disease (allowing time for bone marrow recovery), to reduce fungal load and to provide a tissue culture. In neutropenic patients, the ability to respond to granulocyte colony stimulating factor (GCSF) can be used as a marker for disease survivor. In these patients, GCSF responders are more likely to be disease survivors compared to non-GCSF responders. The presence of a better bone marrow reserve and the increased in total white cell count in GCSF responders may account for the hosts’ ability to overcome the disease.

Prior to definitive identification of the causative fungi, empirical treatment with intravenous amphotericin B, a broad-spectrum antifungal agent, has been recommended. Recommended dosage ranged from 0.25 mg/kg/day to 1 mg/kg/day. A maximum of 1.2 mg/kg/day in adults and 1.5 mg/kg/day in children is reserved for severe invasive mycosis. The use of amphotericin B is limited by its side effects such as electrolyte imbalance, renal toxicity, bone marrow suppression and infusion related reactions. Liposomal form of amphotericin B has better efficacy and side effect profile compared to standard amphotericin B deoxycholate. However, it is considerably more expensive (up to 30 times more) than standard amphotericin B. Hence, liposomal amphotericin B is generally reserved for patients with renal impairment or those who have failed standard amphotericin B. Once a causative fungal species has been identified, the use of the triazoles (fluconazole, itraconazole and variconazole) can be considered. However, the triazoles lack effectiveness against the Mucorales species and their presence should be ruled out before its use is considered.

**GRANULOMATOUS INVASIVE FRS**

This disease entity is defined by invasive fungal infection lasting more than 12 weeks. It is usually of gradual onset and is seen more commonly in Sudan, India, Pakistan and Saudi Arabia. The causative agent is almost exclusively Aspergillus flavus. Patients are typically immunocompetent and the predominant clinical features include proptosis with an enlarging mass in the cheek, nose, paranasal sinus and orbit. CT findings are not different to that of chronic invasive FRS although they have a tendency for multiple sinus involvement. The distinguishing feature from chronic invasive FRS is histological findings of fungal tissue
Figs. 11A and B: Intraoperative IGS images of the sphenoid sinus of a patient with invasive FRS. (A) Extensive fungal disease is seen eroding through the superior, inferior, lateral and posterior walls of the right sphenoid sinus; (B) The right optic canal has also been eroded by fungal disease.
invasion and a granulomatous reaction with considerable fibrosis. This is evident from the presence of noncaseating granulomas with foreign body or Langerhans-type giant cells, occasional vasculitis and sparse hyphae.\textsuperscript{1,3,11} Treatment includes complete surgical removal and antifungal agents. For \textit{Aspergillus} species, voriconazole is the drug of choice although itraconazole and pascoconazole are viable alternatives.\textsuperscript{113} For non-\textit{Aspergillus} species, amphotericin B is the treatment of choice while awaiting the results of susceptibility testing. Consultation with an infectious disease physician should be made as long-term antifungal treatment for more than 1 year may be required to prevent disease recurrence.\textsuperscript{120}

**CHRONIC INVASIVE FRS**

Chronic invasive FRS is a slowly destructive disease with a time course of more than 12 weeks duration. Patients are usually immunocompetent or have subtle abnormalities in the immune system from diabetes mellitus, chronic low dose corticosteroid use and AIDS.\textsuperscript{3,117} The most common fungi implicated is \textit{Aspergillus Fumigatus}.\textsuperscript{3} The clinical picture of chronic invasive FRS is similar to that of granulomatous invasive FRS with both conditions presenting with frequent orbital involvement. The ethmoid and sphenoid sinuses are most commonly involved.\textsuperscript{3} On histology, chronic invasive FRS demonstrates invasion of fungi into the sinonasal mucosa with a dense accumulation of fungal hyphae, occasional vascular invasion, and chronic or sparse inflammatory reaction.\textsuperscript{1,3,14} There is no difference in the prognosis or the management of both chronic invasive and granulomatous invasive FRS.\textsuperscript{3} For the occasional patients with invasive FRS with a time line between 4 and 12 weeks, the term subacute invasive FRS has been recommended.\textsuperscript{3}

**CONCLUSION**

In summary, FRS is an uncommon but important part of the disease spectrum of CRS. Although there are certain clues from clinical and radiological findings, histology is key in distinguishing the different subtypes of FRS. Obtaining the correct diagnosis is crucial as each disease entity differs in the optimal management strategy. Antifungal agents are usually not required in the management of noninvasive FRS but are part of the first line treatment in invasive FRS.

Fungus-related eosinophilic FRS is the most common subtype of FRS and continues to be a fascinating but difficult disease to understand and manage. Although controversy still exists, recent evidence has supported an immunologic rather than an infectious process as the underlying mechanism in AFRS. Surgery is still the mainstay treatment although most agree that radical and destructive approaches are not necessary, and a more conservative yet complete approach with mucosal preservation is the key to achieving the desired outcome. The main challenge is preventing disease recurrence. This can be achieved with a combination of regular and long-term clinical follow-ups coupled with office-based endoscopic debridement and adjuvant medical treatments. While emerging new therapies such as Manuka honey irrigation and anti-IgE therapy appears promising, a complete cure continues to remain elusive at present.

**REFERENCES**