The value of using post-operative systemic anti-fungal therapy in treatment of Allergic Fungal Sinusitis

A SYSTEMATIC REVIEW SUBMITTED FOR PARTIAL FULFILLMENT OF MASTER DEGREE IN OTORHINOLARYNGOLOY

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بسم الله الرحمن الرحيم

وَهُوَ الَّذِي أَنشَأَ لَكُمُ السَّمْعَ وَالْأَبْصَارَ وَالْأَفْئِدَةَ
قَلِيلاً مَّا تَشْكُرُون

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Introduction

Over the past 2 decades, allergic fungal rhinosinusitis (AFRS) has become increasingly prevalent. It is now believed to be an allergic reaction to aerosolized environmental fungi, usually of the dematiaceous species in an immunocompetent host. Most patients with AFRS have history of allergic rhinosinusitis, approximately 5-10% of patients affected by chronic rhinosinusitis actually carry a diagnosis of allergic fungal rhinosinusitis **(Corey et al., 1995 ; Thompson, 2011).**

The incidence of AFRS appears to be impacted by geographic factors. Review of the world's literature reveals the majority of sites reporting cases of AFRS to be located in temperate regions with relatively high humidity **(Gungor et al., 1998).**

Allergic fungal rhinosinusitisis generally recognized as a disease distinct from other fungal forms of sinusitis. Most common among adolescents and young adults (mean age at diagnosis 21.9 y), it is invariably associated with nasal polyposis and the presence of allergic fungal mucin. It is estimated that approximately 5% to 10% of those patients with chronic rhinosinusitis actually carries a diagnosis of AFRS **(Manning and Holman, 1998).**

The exact pathophysiology of AFRS remains a matter of conjecture for which several theories have been offered. One popular theory proposed by Manning and colleagues is based on the assumption that AFRS exists as the nasal correlate of allergic broncho-pulmonary aspergillosis, and suggests that several interrelated factors and events lead

to the development and perpetuation of the disease **(Bradley and Marple, 2001).**

Patients typically have gradual nasal airway obstruction and production of semisolid nasal crusts that, on inquiry, match the gross description of allergic fungal mucin. The development of nasal airway obstruction may have been so gradual that the patient is unaware of its presence. Likewise, if facial dysmorphia is present, its progression is often so slow that its identification escapes the patient and family members. Pain is uncommon among patients with AFRS and suggests the concomitant presence of a bacterial rhinosinusitis **(Marple, 1999)**.

The accumulation of allergic fungal mucin eventually leads to the increasingly well-recognized radiographic findings characteristic of AFRS (**Nussenbaum et al., 2001).**

Bone erosion and extension of disease into adjacent anatomic areas was encountered in 20% of the patients and was more likely to occur in the presence of bilateral advanced disease (**Mukherjig et al., 1998).**

Fungal cultures of allergic fungal mucin may provide some supportive evidence helpful in the diagnosis and subsequent treatment of AFRS, but must be interpreted with caution. It is important to realize that the diagnosis of AFRS is not established or eliminated based on the results of these cultures **(Manning and Holman, 1998).**

Histopathologically, it is impossible to definitively identify the species of various fungi that can be associated with the disease process, and concomitant fungal cultures are required to determine the particular fungus **(Ferguson, 1998)**.

Medical control of the disease has made use of various combinations of antifungal medications, corticosteroids, and immunotherapy with varying degrees of disease control. Successful treatment of AFRS requires that the treatment plan account for each factor responsible for the propagation of the disease. This comprehensive approach to management depends on complete removal of all fungal mucin (usually requiring surgery), and long-term prevention of recurrence through either immunomodulation (immunotherapy and/or corticosteroids) or fungistatic antimicrobials **(Marple and Mabry, 1998).**

Systemic antifungal therapy for AFRS was initially proposed to control the theoretical potential for progression to invasive forms of fungal sinusitis. As the potential for AFRS recidivism is well recognized and ranges from 10% to nearly 100%. AFRS recidivism appears to be influenced by long-term post-operative therapy. It is important to realize that AFRS recidivism remains high despite appropriate surgery and also post-operative medical therapy **(Marple and Mabry, 2000).**

Antifungal therapy was often used in an attempt to provide some degree of control over recurrence of AFRS. The early use of amphotericin B yielded to the use of less toxic agents, such as ketoconazole, itraconazole, and fluconazole, but the poor in vivo activity of these agents against dematiaceous fungi was soon discovered **(Bradley and Marple, 2001).**

Aim of the work

This study aimed to systemically review the literature for better clarifying the role of systemic antifungal therapy in the post-operative treatment of AFRS. This in turn will help clinicians to take more informed clinical decision when considering the use of post-operative oral antifungal agents in AFRS patients.

Review of Literature

Definitions:

Chronic rhinosinusitis: represents a common chronic disorder characterized by persistent inflammation of the nose and paranasal sinuses for 3 months or longer. The pathophysiology still poorly understood due to the variety of causes **(Khaled et al., 2004; Fokkens et al., 2007)**.

Fungal sinusitis: is an umbrella term which encompasses a wide range of diseases caused by different fungi. The type of infection depends upon the immune status of the host **(Gupta et al., 2007).**

Millar et al. (1981) were the first to describe allergic aspergillus sinusitis (AAS) due to its histopathological similarity to allergic broncho-pulmonary aspergillosis (ABPA) described by **Hinson et al. (1952).** Subsequently, it was recognized that other fungi can be grown from the mucin secretions in the sinuses in addition to aspergillus species and the term was changed to allergic fungal sinusitis (AFS) to reflect this finding **(Goldstien et al., 1994).**

Ponikau et al. (1999) suggested the term eosinophilic fungal rhinsosinusitis (EFRS) because of the striking role of the eosinophils in this disease which are probably triggered by the extramucosal fungi.

Chakrabarti et al. (2009) reported that the International Society for Human and Animal Mycology convened a working group to attempt consensus on terminology, so rhinosinusitis is preferred to sinusitis**,** and the term was changed to allergic fungal rhinosinusitis (AFRS).

Classification of chronic sinusitis and its subtypes:

The earlier classification of fungal sinusitis subtypes was described by **Schubert (2004)** as the following: Three invasive types: Acute necrotizing, chronic invasive and granulomatous invasive. Tow non-invasive types: Fungal ball (sinus mycetoma) and allergic fungal sinusitis (AFS).

A new classification by **Chakrabarti et al. (2009)** was based on the fact that the fungal rhinosinusitis encompasses a wide spectrum of immune and pathological responses, including invasive, chronic, granulomatous, and allergic disease. However, consensus on terminology, pathogenesis, and optimal management is lacking. The International Society for Human and Animal Mycology convened a working group to attempt consensus on terminology and disease classification.

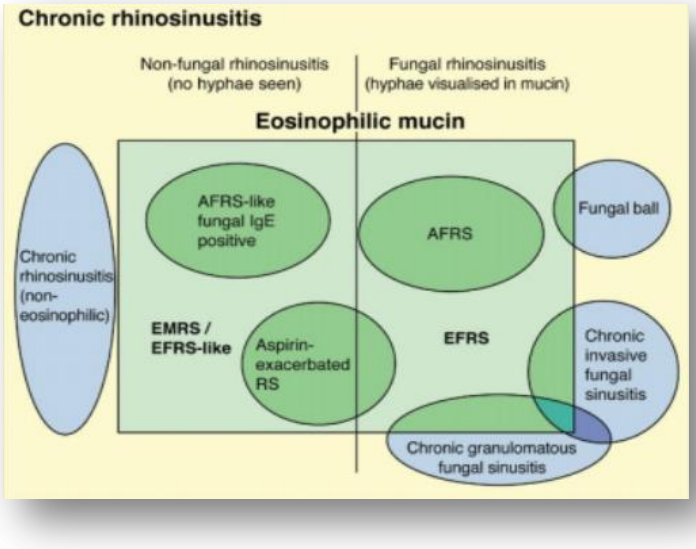

Fig: 1 Classification of chronic rhinosinusitis **(Chakrabarti et al., 2009).**

Key conclusions reached were:

Rhinosinusitis is preferred to sinusitis; acute invasive fungal rhinosinusitis is preferred to fulminant, or necrotizing and should refer to disease of <4 weeks duration in immunocompromised patients; both chronic invasive rhinosinusitis and granulomatous rhinosinusitis were useful terms encompassing locally invasive disease over at least 3 months duration, with differing pathology and clinical settings; fungal ball of the sinus is preferred to either mycetoma or aspergilloma of the sinuses; localized fungal colonization of nasal or paranasal mucosa should be introduced to refer to localized infection visualized endoscopically; eosinophilic mucin is preferred to allergic mucin; and allergic fungal rhinosinusitis (AFRS), eosinophilic fungal rhinosinusitis, and eosinophilic mucin rhinosinusitis (EMRS) are imprecise and require better definition. In particular, to implicate fungi (as in AFRS and EMRS), hyphae must be visualized in eosinophilic mucin, but this is often not processed or examined carefully enough by histologists, reducing the universality of the disease classification **(Chakrabarti et al., 2009).**

Table 1: Classification by **Chakrabarti et al., (2009).**

TABLE I.
Consensus Developed During Panel Discussion About the Controversies.

Sl No.	Controversy	Consensus
1	Fungal rhinosinusitis or fungal sinusitis?	Fungal rhinosinusitis
2	Acute invasive, fulminant, or necrotizing fungal rhinosinusitis?	Acute invasive fungal rhinosinusitis (when etiological agent is known, e.g., acute invasive *Aspergillus* rhinosinusitis)
3	Distinction between acute and chronic FRS	Acute when duration is <1 month
		Chronic when duration is >3 months
		Subacute when duration 1–3 months
4	Are granulomatous and chronic FRS separate entities?	Keep the entities separate until more data clarify the facts
5	Fungal ball, mycetoma, or aspergilloma?	Fungal ball with the description localization + fungal ball ± causative fungus (e.g., maxillary sinus fungal ball due to *Aspergillus flavus*)
6	Saprophytic fungal infestation of nasal mucosa?	Localized fungal colonization of nasal or paranasal sinus mucosa
7	Allergic mucin or eosinophilic mucin?	Eosinophilic mucin
8	Distinction between AFRS/EFRS/EMRS?	See Fig. 7

FRS = fungal rhinosinusitis; AFRS = allergic fungal rhinosinusitis; EFRS = eosinophilic fungal rhinosinusitis; EMRS = eosinophilic mucin rhinosinusitis.

Etiology:

It's now believed that AFRS is an immunologic reaction (Gell and coombs type I and possibility type III) to fungal spore deposition in the sinonasal cavity **(Rains and Mineck, 2003)**.

This allergic reaction to aerosolized environmental fungi, in an immunocompetent host, in which fungal debris, allergic mucin, and nasal polyposis are formed in the nasal cavity and paranasal sinuses. It may be microbial T-cell super antigen driven disorder. T-cells super antigens are microbial toxins that activate T cells through the t-cell receptor but bypass antigen specificity. T-cell receptors for foreign antigens dictate the specificity of the antigen recognition by the T-cells; they also have heritable elements, including the V beta component of the T-cell receptor that carries the super antigen bending motif. Super antigens bend the side of the HLA class II molecule on the antigen presenting cell, and the side of the T-cell receptor at the V beta motif on the responding T-cell simultaneously, bridging the two and activating the T-cell inappropriately. Whereas antigen-specific T-cells have a base line (preimmunised) frequency of about 0.01%, a given super antigen is potentially capable of activating up to 30% of all T-cells. Microbial T-cells super antigens are theoretically capable of amplifying T-cells activity inappropriately into a chronic sever inflammatory process, in patients who carry the proper T-cell receptor V beta motifs for the relevant super antigens **(Schubert, 2004).** This is in contrast to invasive fungal infections that affect immunocompromised hosts. Most patients have a history of allergic rhinitis, and the exact timing of AFRS development can be difficult to discern (**Thompson, 2011**)**.**

In a recent study done by **Mohindra et al. (2011)**, they put the innocence of the allergic theory of the AFRS under suspicion. Co-existent AFRS and invasive intracranial aspergellosis (InIA) in some of their patients (8 of them died), supports the hypothesis that the two entities representing the extremes of same disease. Numerous published case series have indicated the non invasive nature of AFRS, despite massive bony destruction associated with AFRS which is shown to be completely benign, so patients were placed in the category of AFRS, which may not be totally correct. The neglected or poorly followed cases of AFRS tend to contribute to poor outcomes by conversion into InIA. Many studies proved a pathological invasion in cases with AFRS such as **Shubert and Goetz (1998).**

Mohindra et al. (2011) propose the hypothesis that invasive fungal infection may fall within the same disease spectrum as allergic fungal rhinosinusitis rather than representing two separate disease processes. So, they recommend long term follow up post-operatively as AFRS tends to behave aggressively (InIA) in the later part of life.

Prevalence:

AFRS among Saudi patients with nasal polyps is 12.1% (**Telmesani, 2009).** Retrospective reviews of chronic sinusitis estimates that up to 10% of chronic sinusitis requiring surgical therapy is caused by AFRS **(Bent and Kuhn, 1994; Corey et al., 1995; Peric et al., 2011).**

Fungal colonization was detected in 50% of patients with massive nasal polyps; while fungal allergy was found in 38.8% of allergic patients with nasal polyps**.** Cases of this disorder were described from different parts of the world but the condition appears to be more prevalent in warm