Workshop on Fungal Sinusitis:

The working group on ‘Fungal Sinusitis’ organized a Workshop during 9 - 11 February 2008 at Chandigarh, India. Established by the International Society for Human and Animal Mycology (ISHAM), Fungal Sinusitis working group has been developed by inviting clinicians, scientists and workers of this field from all over the world to join the consortium. The focus areas of the network are: to assess the prevalence of fungal rhinosinusitis among patients with chronic rhinosinusitis; categorization; etiological agents; pathogenesis; and management. Sinusitis, or more accurately rhinosinusitis, is a common disorder affecting approximately 20% of the population at some times of their lives. Acute rhinosinusitis (ARS) is well categorized. However, controversies surround chronic rhinosinusitis (CRS) and the role of fungus in this condition. CRS accounts for > 90% of all cases of rhinosinusitis, and the correct diagnosis of each category of CRS is important for optimum therapy and predicting the course.

Recognizing the importance to resolve the controversies and to develop a systematic management protocol of fungal rhinosinusitis (FRS), the working group participated in this workshop at Chandigarh, India and deliberated on their experiences while handling patients with FRS and research aspects in the same area. From this workshop a consensus document was prepared through panel discussions.

Workshop Faculty: The following members of the network participated in the workshop symposia. Arunaloke Chakrabarti, Convener, Fungal sinusitis network (Medical Microbiology, PGI, Chandigarh), Annette Fothergill (San Antonio, USA), Ashim Das (Histopathology, PGI, Chandigarh), Ashok Gupta (Otolaryngology, PGI, Chandigarh), A. Serda Kantarcioğlu (Istanbul, Turkey), B. J. Ferguson (Pittsburgh, USA), Bradley Marple (Texas, USA), Catherine Kauffmann-Lacroix (Poitiers, France), David Denning (Manchester, UK), Hirohito Kita (Rochester, USA), Jens Ponikau (Buffalo, USA), K. K. Handa (Otolaryngology, AIIMS, New Delhi), Naresh Panda (Otolaryngology, PGI, Chandigarh), Paramjeet Singh (Radiodiagnosis,
Including the faculty there were 65 participants at the workshop. There were 16 poster presentations by the participants on their experiences and findings on fungal rhino sinusitis.

**Content of the Fungal Sinusitis Workshop**

The various aspects of fungal rhino sinusitis were covered under five symposia in the workshop. These topics were “Magnitude of the problem”, “Categorization of fungal sinusitis”, “Allergic fungal sinusitis”, “Colonizing fungal ball” and “The invasive disease”.

Under the “Magnitude of the problem”, the global prevalence of FR was related by David Denning. There are probably 1000-1200 cases/year of acute invasive aspergillosis (omitting zygomycosis) as opposed to difficult to estimate-prevalence of chronic and allergic fungal sinusitis. The prevalence figure of allergic fungal sinusitis for various countries include 13 million in US, 55 million in Europe, 19 million in Japan and the global figure could be roughly 900 million cases (15% of the world’s population). Arunaloke Chakrabarti described the Indian scenario. FRS is a common disorder in India, but no population-based data is available. The commonest category appears to be AFRS and *Aspergillus flavus* being the most common agent without any apparent strain clustering. More studies are needed to understand the Indian occurrence of FRS. A. Gupta described that fungal sinusitis cases in pediatric patients. The disease appears to be more aggressive in pediatric patients with rhinocranial and rhinorbital complications. Annette Fothergill narrated on the spectrum of causative agents.

The second symposium was centered on **Categorization of Fungal Sinusitis**. Arunaloke Chakrabarti enlisted the controversies surrounding fungal sinusitis. This topic was initially scheduled to be presented by Stammberger who could not make it in the last minute. A. Das enlightened role of histopathologists in the categorization of fungal rhinosinusitis. Paramjit Singh
illustrated the role of CT and MRI in diagnosis. He observed that CT scan is better investigation for diagnosis of FRS, high density contents and bone re-modeling are indices of suspicion for FRS and MRI is helpful in looking for intracranial extent of disease. Talking on AFRS, Bradley Marple defined that presence of mucin, presence of fungi in mucin and presence of fungal allergy are criteria for AFRS and he categorized it as IgE dependent (AFRS) and non-IgE dependent (EFRS). BJ Ferguson elaborating on the concept of EFRS, stressed that categorization of eosinophilic sinus disease by potential mechanism provides a framework which can allow us to discover potentially important differences in therapeutic responses. She described four potential mechanisms for EMRS- allergic fungal RS, non-allergic fungal ERS, super-antigen induced ERS and aspirin exacerbated ERS. Describing about the pathogenesis of CRS, Jens Ponikau explained that the infiltration and activation of eosinophils occur in response to fungal antigen and that the major basic protein secreted by eosinophils is a signature of CRS, which seems to have local toxic effects. He also stressed that presence of fungus in CRS could be demonstrated by improved processing of the specimen. Hirohito Kita elegantly described the use of animal model for study of fungal rhinosinusitis with particular emphasis on the role of immune system.

**Symposium 3** addressed issues of AFRS. Whether fungus is an allergen or bystander in AFRS was discussed by W. Buzina who emphasized the role of fungus, as fungal extracts can trigger the activation of eosinophils in chronic rhinosinusitis patients but not in healthy controls. DNA of *Alternaria* spp. was found in all CRS patients but not in controls and topical antifungal therapy seem to reduce symptoms of CRS patients. However, further studies are required to substantiate the facts. In the talk on novel biomarkers and newer techniques in fungal sinusitis, Kita revealed several potential biomarkers viz. local levels of major basic protein (MBP), Charcot Leyden crystals (CLC), PBMC production of IL-5 and IL-3 and IgG4, all based on his research findings.
Whether eosinophilic fungal rhinosinusitis (EFRS) is a distinct entity was discussed by S. Vlaminck. High prevalence of EFRS was noted in female during 5th decade of life. Bilateral disease was common and polyposis not mandatory. Typical radiological features may be present but not mandatory and he stressed that every CRS should be suspected for EFRS. In order to increase the diagnostic yield in AFRS, Rupa Vedantam recommended collection of both polyps and mucin for diagnosis.

The medical management of CRS in light of EMRS was taken up by B. Marple who detailed on the various aspects of pathogenesis of CRS before he reviewed the treatment strategies for CRS. The primary therapy for CRS remains broad-spectrum antibiotic with topical intra nasal steroid. The adjunctive therapy consists of oral decongestants, saline-irrigation and mucolytic agents, antihistamine to treat classic allergic symptoms and corticosteroids. According to FDA (2006), CRS is classified as an inflammatory disease and hence therapy should address the underlying inflammation. Macrolides bring about considerable reduction in cytokine production and appear to be effective and the antileukotriene therapy appears to reduce polyps (subjective polyp score). He discussed the contradictory views and findings in the Mayo clinic experience and Weschta experience in the management of CRS. Further, Ebbens experience with topical antifungal therapy with amphotericin B failed to reduce clinical signs and symptoms in patients with CRS. Possible anti inflammatory treatment strategies using anti IL-15, IL-12 and Cochrane were also discussed. However, the net conclusion was that reliable consistent forms of treatment for CRS are not yet available. J Ponikau emphasized the role of antifungal agents in the treatment of CRS. Antifungal therapy with amphotericin B decreased fungal load as well as inflammation in CRS patients. In the Phase III clinical trial, which is ongoing, intranasal itraconazole and voriconazole nasal spray have been used. The preliminary findings conclude-resolution of congestion and headache at week 16 is 60% and the time for 100% cure of the responders was 16 weeks as determined by endoscopy score.
The theme of **symposium 4** was **Colonizing Fungal ball**. Catherine Kauffman discussed her experiences on epidemiological aspects. The fungal ball appears to be prevalent among females (60%) and localized mainly in the maxillary sinus. Histopathological examination appeared to be more sensitive (93.1%) than culture (32.1%) for diagnosis and *A. fumigatus* was most frequently isolated from biopsied tissue in France. In the next lecture on the diagnosis and management of fungal ball, K. K Handa described that there has been a gross reduction of frequency of fungal ball from 60% to 3% at his center possibly due to inaccurate diagnosis of AFRS cases as fungal ball in earlier years. In India unilateral maxillary sinus fungal ball was common occurrence as in France. Fungal ball in sphenoid sinus lead to increased morbidity. Antifungal agents do not seem to have any effect except in cases with mucosal invasion. Included in the same session was a lecture by Thungapathra, who focused on the array-based techniques for identification of molecular mediators in the disease process. She emphasized on the need for homogenous samples for gene expression profiling and validation of biomarkers in large number of samples.

**Symposium 5** included three presentations on **The Invasive Disease**. Discussing on the invasive disease, Taj Aldeen emphasized on the proper identification of the agent as fungi respond differentially to antifungal agents. He also enlisted emerging and uncommon pathogens of invasive fungal rhinosinusitis and emphasized on the factors associated with poor prognosis. Talking on the diagnosis of the invasive disease, S. Kantarcioğlu listed the criteria for diagnosis and that include radiological, histopathological and mycological findings. Histopathologic and microbiological evaluations of biopsies are gold standard for diagnosis. N. Panda enlightened on the management of invasive disease. He stressed that diagnosis and management have been evolving over recent years. Standard therapy was surgical debridement followed by medication with systemic amphotericin B. Early recognition and aggressive management hold the key for
successful outcome. He also proposed that combinatorial chemotherapy would improve the outcome.

At the end of the symposia the following consensus opinions and definitions were made through a rigorous Panel discussion, which was moderated by David Denning. The other panelists present were Arunaloke Chakrabarti, Bradley Marple, Jens Ponikau, Walter Buzina and BJ Ferguson.

1. **Is it fungal rhinosinusitis or fungal sinusitis?**

   As most cases of nasal fungal sinusitis have a proceeding or concomitant involvement of nasal cavity except isolated fungal ball lesions, ‘fungal rhinosinusitis’ term was considered appropriate.

2. **Is it ‘acute invasive’ or ‘fulminant’ or ‘necrotizing’ fungal rhinosinusitis?**

   The characteristic of this life-threatening category in immunosuppressed patients is invasion of tissue and duration of illness below 4 weeks. Necrotizing lesion is not seen in all patients in this group and the term ‘fulminant’ occurs only in patients with severe immunosuppression or when untreated. Therefore, the consensus was to use the term ‘acute invasive fungal rhinosinusitis’

3. **Distinction between acute and chronic FRS**

   Acute disease is when the duration of illness is less than one month and that of chronic disease is greater than three months, though other factors like host immune status and vascular invasion also distinguish the two forms of disease. In the acute variety neutrophilic reaction and in chronic course eosinophilic reactions are usually seen. The term ‘sub-acute’
might be used in rare situation when the duration of illness is within one to three months period and the pathology is of mixed cellular reaction.

4. Are granulomatous and chronic FRS separate entities?

This was one of the unresolved issues. In the granulomatous type, a granulomatous response is seen with considerable fibrosis on histopathology; non-caseating granuloma with foreign body or Langhans’ type may be observed; sometimes vasculitis, vascular proliferation and perivascular fibrosis are seen in granulomatous type; hyphae in many occasions are scanty and *A. flavus* is consistently isolated. The disease is commonly seen in Sudan, India, Pakistan and Saudi Arabia. In contrast chronic invasive type is characterized by dense accumulation of hyphae, sometimes with vascular invasion, chronic or sparse inflammatory reaction, isolation of *A. fumigatus*, and association with orbital apex syndrome, diabetes mellitus, and corticosteroid therapy. The clinicopathological distinction between these two types is not sharp. It was agreed that chronic invasive and granulomatous FRS should be differentiated primarily on pathological grounds until more data are forthcoming. A fungal rhinosinusitis registry was proposed. The database would help in correlation between histopathology, behavior of the disease and the fungus in these two forms of FRS.

5. Is it ‘fungal ball’ or ‘mycetoma’ or ‘aspergilloma’?

The disease is defined as the presence of non-invasive dense accumulation of fungi in sinus cavities. The use of the term ‘mycetoma’ is not technically correct, as mycetoma is chronic local invasion of subcutaneous tissue by bacteria or fungi with the formation of sinus tract, swelling and granule. The term ‘aspergilloma’ is not appropriate since it is not always due to *Aspergillus* species. The consensus arrived was to describe it as ‘**localization** + fungal **ball ± causative fungus** (e.g. maxillary sinus fungal ball due to *A. flavus*).
6. **Is there any saprophytic fungal infestation of nasal mucosa?**

Simple colonization of nasal or paranasal sinuses without any symptoms has been described as saprophytic fungal infestation. The colonization occurs over mucous crust often in patients who had a history of previous sinus surgery and is detected upon endoscopic examination. It remains silent until it is detected or presents with foul odor. Further extension of the growth may lead to fungal ball formation. After deliberation, the consensus was to describe the condition as ‘**localized fungal colonization of nasal or paranasal mucosa**’.

7. **Distinction between AFRS/EFRS/EMRS**

The discussion initiated to find the relationship between the different forms of eosinophilic diseases of rhinosinusitis. In AFRS, there is so called ‘allergic mucin’ with lot of eosinophils and the presence of non-invasive fungi with raised fungal specific IgE. The EFRS and EMRS (EFRS-like) cases do not have specific IgE and they differ in the presence (EFRS) or absence of fungus (EMRS). The possibility of another group “AFRS-like” was also evoked in which the presence of fungus is not demonstrated though there is fungal specific IgE reaction.

The first consensus reached was to call the mucous in such conditions as ‘**eosinophilic mucin**’ rather than ‘allergic mucin’ irrespective of presence or absence of atopy, as ‘eosinophilic mucin’ describes the presence of eosinophil or eosinophil degraded products in mucus, which is present in all described conditions. The diseases with eosinophilic mucin may be broadly divided into ‘non-fungal’ and ‘fungal’ category. The ‘non-fungal’ side includes the ‘AFRS like’, the EMRS (EFRS Like) category and aspirin exacerbated RS (previously known as ‘aspirin sensitive RS’). The ‘fungal’ side includes AFRS, EFRS and a limited number of cases of aspirin exacerbated RS, which have presence of fungus.
After long deliberations, broad consensus was that there is no clear-cut evidence whether antifungal treatment is useful for eosinophilic diseases with fungus. In general, there are clusters of eosinophils and eosinophil degraded products with or without Charcot Leyden crystals in the mucus. Sometimes there is sensitivity to specific fungus (as IgE in AFRS) and sometimes there is presence of IgG antibodies to specific fungus. The disease is usually bilateral with the presence of polyps (unilateral disease during the early part of illness). Consensus arrived at the following figure to describe the relationship between the various forms of chronic (fungal) rhinosinusitis in immuno-competent hosts.
It was also decided to address the following areas in future research:

**Epidemiology**
- Setting up of an International registry of all fungal sinusitis.
- Autopsy survey of at-risk patients for invasive sinusitis to identify the missed cases of invasive sinusitis.
- Population autopsy study of sinuses in patients dying of any other reasons, which have nothing to do with sinuses to assess the frequency of rhinosinusitis.

**Clinical**
- Secretions/mucin and CT/MR correlation and the information regarding secretions in terms of protein content, DNA and water content and also compare the fungal load with CT and MR.
- Multivariate analysis of risk factors for fungal ball in terms of age and sex of patients, extent of obstruction, immune competence status etc.
- Management of Sphenoid sinusitis

**Diagnostic tests and biomarkers**
- Sample processing for histology/ cytology
- Diagnostic testing which can be used for monitoring response to treatment.
- Antibody testing for diagnosis for fungal genera / species
  - *Aspergillus flavus* specific antibody testing
- Molecular diagnosis versus culture based diagnosis
- Role of immunohistochemistry reagents for genus/ species identification

**Pathogenesis**
- Genetic basis of chronic/ granulomatous/ allergic/ eosinophilic disease.
- Study of Pediatric cases
- Polyp histology / Classification
• Charcot Leyden Crystals
• Animal model (To study chronic invasive, antigen stimulation, pressure effects, impact of blockage etc).
• Local production of cytokines versus systemic stimulation of expression in different diseases

Treatment
• Well-validated scoring system for rhinosinusitis
• Saline treatment efficacy study
• Outcomes for invasive fungal sinusitis
• Antifungal treatment – which patients, whether antifungal is required for the management of fungal ball in sphenoid sinus
• Immuno-modulator Therapy
• Multi-centre drug trials in chronic invasive patients

Outcome of the Fungal Sinusitis Workshop:

It was decided by the panel that it is important to create an International Registry by professionals working on fungal sinusitis. This will enable entry and dissemination of all the relevant information in the field. In this common registry, information regarding incidence and prevalence of fungal sinusitis in particular geographical areas, diagnosis, histopathological results, management details etc. may be registered so that it is possible to exchange views, suggestions and improvements in all of the above mentioned aspects. Several representatives from different countries were selected who would update the registry time to time with the upcoming information in fungal sinusitis from their respective countries and geographical localities.
The workshop stimulated interest among the participants to develop co-operative research in understanding the disease. Multi-center clinical trials are expected to be initiated soon which would help in developing the algorithm in management of fungal sinusitis. This direct meeting of the working group members has helped in the exchange of opinion based on their experience to resolve a number of controversies that exist and indeed consensus was arrived in many aspects of fungal sinusitis through rigorous panel discussions.