


# Invasive Sino-orbito-cerebral mycosis- An Overview

Sushil Kumar Aggarwal,<sup>1\*</sup> Rajendra P Maurya<sup>2</sup>

<sup>1,2</sup>Assistant Professor (ENT), <sup>2</sup>Dept. of Ophthalmology, IMS, BHU, Varanasi-221005, India  
E-mail: doc.sushil.pgi@gmail.com

Access this article online	
Quick Response Code:	Website: www.innovativepublication.com
	DOI: 10.5958/2395-1451.2015.00006.2

## INTRODUCTION

Although fungal rhinosinusitis is a rare disorder but number of cases on record has increased manifold during the last decades worldwide.<sup>1,2</sup> There are two basic types of fungal rhinosinusitis- invasive and non-invasive. The invasive form may be of acute invasive and chronic invasive. The non-invasive fungal rhinosinusitis can be of three types- fungus balls or mycetomas, saprophytic colonization and allergic fungal rhinosinusitis.<sup>3,4</sup> Invasive fungal sinusitis (IFS) is one of the important cause of morbidity and mortality in immunocompromised patients.<sup>5,6</sup> Invasive fungal sinusitis (IFS) is commonly seen in uncontrolled diabetics, debilitated, chronic renal failure, haematological dyscrasias, immunocompromised patients such as those receiving high doses of chemotherapy for malignancy, using long term immuno-suppressive drug after organ transplantation and those suffering from immuno-suppressive diseases such as AIDS.<sup>7,13</sup> Invasive fungal sinusitis is caused by predominantly two classes of fungi *Mucor* and *Aspergillus*. The literature has only 12 reported cases of mucormycosis for all organs in AIDS patients.<sup>14,15,16</sup>

The yeast such as *Candida albicans* may cause this disease, and *Aspergillus flavus* and *Aspergillus fumigatus* being most widely isolated molds. IFS caused by *Zygomycetes* like *Rhizomucor*, *Rhizopus* and *Mucor*, has also been observed.<sup>8-10, 12, 13, 17-20</sup> Moreover, IFS can be characterized by a rapid vascular spread from the nasal and sinus mucosa into the orbit, skull base and brain. In comparison to the non-invasive type which usually has a good prognosis, IFS is considered to be a potentially lethal condition.<sup>19</sup> In India, initially the disease was prevalent only in north India<sup>21-24</sup> but now reported from other parts of the country as well.<sup>25-27</sup> Though species of *Aspergillus* is isolated from majority of such cases, *Dematiaceous* hyphomycetes, *Pseudallescheria boydii*, *Candida* species, *Fusarium* species are also reported from some cases.<sup>22,28</sup> Chronic indolent

invasive sinusitis is more slowly destructive, usually occurring in more immunologically normal patients.<sup>26</sup>

Mucormycosis refers to a spectrum of diseases caused by order of mucorales, disease was first described by Meyer 1815. In humans the most common causative agent being of the *rhizopus* species. Mucorales are predominantly found on decaying organic material and also act as opportunistic pathogens causing an acute angioinvasive infection seen primarily in the immunocompromised.<sup>29</sup> Baker introduced the term "rhinocerebral mucormycosis" as a malignant form of cephalic mucormycosis with a high mortality rate. Mucormycosis is an infrequent disease with an annual incidence of 0.4–1.7 cases/ 1,000,000 population and worldwide distribution.<sup>30</sup>

## Pathophysiology:

Various literature have shown a seasonal variation in concentration of airborne fungal spores in outdoor and indoor air during the summer period. Several authors<sup>31-39</sup> have found a positive correlation between average temperatures and airborne spore concentration. Epidemiological studies<sup>37,40</sup> confirmed an increased seasonal rate of occurrence of IFS during the summer caused by the *Mucor* species. Finally, a relationship between environmental fungal concentration and incidence of invasive fungal infections in hematologic patients has been noted.<sup>41-43</sup>

**Function** of nose consists of humidifying and warming the air during inspiration and also in filtering the larger particles, such as airborne fungal spores.<sup>44</sup> Some anatomical abnormalities, such as anterior septum deviation, could create or increase an airflow turbulence facilitating fungal spore deposition.<sup>46,47</sup> Nasal obstruction may leads to impaired ventilation with consequent inflammation and alteration of mucociliary clearance.<sup>44, 45</sup>

Invasive aspergillosis with intra-orbital and intra-cranial spread usually is fatal and necessitates prompt diagnosis and treatment.<sup>48</sup> It usually involves the species *Aspergillus fumigatus* and *Aspergillus flavus*. The maxillary sinus is the most common sinus to be affected. Invasive cranio-orbital aspergillosis originating in the sphenoid sinus is rare and associated with poor outcomes.<sup>49</sup> Invasive aspergillosis originating from the paranasal sinuses can cause an intra-cranial growth mainly along the skull base and larger vessels.<sup>50</sup> Orbital invasion readily occurs due to breach of thin bony partition of

lamina papyracea leading to proptosis and gradual loss of vision.

Paultauf in 1885 reported a case of mucormycosis with cerebral involvement.<sup>51</sup> The main route of fungal infection is inhalation. However, there may be traumatic transmission in polytraumatized patients mainly with the *Apophysomyces elegans*. There are no reports of person-to-person transmission.<sup>52, 53</sup>

Several clinical forms are described such as rhino-orbito-cerebral, pulmonary, disseminated, cutaneous and gastrointestinal<sup>54,55</sup>. Rhino-orbito-cerebral is the most common form in diabetic patients.<sup>56</sup> Initially majority of patients complaint about the typical symptoms of acute bacterial rhinosinusitis but they deteriorate rapidly and do not respond to conventional treatment. Such patients are usually associated with diabetic ketoacidosis (DKA). Acidosis inhibits iron binding of transferrin, resulting in an increased proportion of unbound iron, which may promote the growth of the fungus or it may also be due to decreased neutrophil chemotaxis and phagocytosis.<sup>56,57</sup> Jung et al, in their case series, reported 100% mortality with DKA, hence proving to be the single most important detrimental factor.<sup>58</sup>

Rhino-orbito-cerebral mucormycosis (ROCM) is an aggressive form of disease causing a very high residual morbidity and mortality due to the angioinvasive property of the fungus. After infection of nose and paranasal sinuses, organism causing blood vessel invasion and leading to vascular thrombosis with ischemic infarction and, haemorrhage necrosis and causing local destruction of the affected organs. In addition, the resulting hypoxic environment promotes fungal proliferation.<sup>57</sup> The disease in the nasal or sinus mucosa takes a rapidly progressive course extending to neighbouring tissues, including the orbit and sometimes to the brain.

A comprehensive review of patients with mucormycosis showed that dissemination developed in 23% of cases and was associated with 96% mortality.<sup>59</sup> Thus, early recognition of this disease along with aggressive management and appropriate antifungal treatment is critical for optimal outcomes.<sup>60,61</sup> Zygomycosis commonly presents as either acute invasive or chronic invasive form. Cases reported as fungus balls, saprophytic colonization and allergic fungal sinusitis associated with zygomycosis are quite rare.<sup>62</sup> The probable reason for the high incidence (61%) of zygomycosis from June to September can be the high degree of humidity with an optimal temperature range of 28-30°C during these months in tropical areas, which is well suited for the growth of mucorales. The extent of involvement by zygomycosis determines the prognosis of the disease significantly. As the fungal load in the tissue increases, the survival rate decreases. The cases where the patients had florid granulomatous

inflammation had a better prognosis. Castillo et al<sup>63</sup> have found that multinucleate giant cell granulomas may be correlated with the disease with better prognosis. Microscopically, all the cases of zygomycosis show varying amounts of necrosis and the necrotic tissue must be well sampled to identify the fungal elements. Also, as the degree of angioinvasion increases, the survival decreases.<sup>64</sup> The prognosis of patients with chronic rhino-orbito-cerebral zygomycosis is significantly better than that of acute rhino-orbito-cerebral zygomycosis. The extent of involvement by zygomycosis also determines the prognosis significantly. Using the above variables, the histopathologists can help the clinician in assessing the prognosis at the time of tissue diagnosis and considering the risk/benefit ratio, the clinicians can optimize the treatment accordingly.

In ROCM, the organisms spread by direct extension along the injured vessels. Infection typically originates in the nasal or oral mucosa, spreads to the paranasal sinuses, and enters the orbit via the ethmoid and maxillary sinuses or via the nasolacrimal duct.<sup>67</sup> Intracerebral extension may occur from the orbit via orbital apex, orbital vessels, or via cribriform plate.<sup>67</sup> Diabetes predisposes to this infection, as is seen in the majority of instances of ROCM (60%–81%) in different series.<sup>31, 65, 66, 68</sup>

Factors associated with poor survival in ROCM include (i) delay in diagnosis and treatment, (ii) hemiparesis, (iii) bilateral sinus involvement and (iv) facial necrosis.<sup>31</sup> Yohai et al reported survival of 63% of patients with a lag time from 7 to 12 days and 44% in those with a lag time of 13 to 30 days.<sup>31</sup>

### Clinical presentation:

It is believed that in most cases, the fungi enter the body by inhalation of aerosolized spores (3–11 mm) through the sinuses with infiltration and spread along neurovascular structures. The infection can progress rapidly and erode through the bony walls of the sinuses into the orbit, retro-orbital area, skull base and extending into the brain. Thrombosis of the cavernous sinus, carotid arteries and jugular vein indicate a very poor prognosis. In patients with intracranial involvement, fatality rates can exceed 80% with death occurring in less than 2 weeks from initial onset if mucormycosis cannot be successfully treated. Mucormycosis has various clinical presentations and may appear in pulmonary, cutaneous, disseminated, gastrointestinal and rhino-orbito-cerebral forms, but the latter is the most common one.<sup>69</sup> The term rhino-orbito-cerebral zygomycosis (ROCM) refers to the entire spectrum of the disease, which usually starts in the sinonasal tissue (limited sinonasal disease), progresses to the orbits (limited rhino-orbital disease) and finally affects central nervous system (rhinocerebral disease).<sup>65,70</sup> Black eschar and necrotic debris in the nasal cavity

are the usual endoscopic findings<sup>69</sup> but its absence does not rule out the disease. The mucormycosis is a more fatal acute fungal infection for mankind, with mortality rate from 15 to 34%.<sup>71</sup>

The rhino-orbito-cerebral form is clinically confirmed with low fever, unilateral or bilateral rhinorrhea, unilateral facial pain, change in the visual accuracy and in the ocular movements. Through nasal cavity or paranasal sinuses, the mucormycosis may spread to the orbit through the nasolacrimal duct, natural dehiscences in the lamina papyracea or through arteries and veins in the orbital wall. The orbital involvement may produce chemosis and proptosis.<sup>70</sup> When there is orbital involvement, the complaints are of blepharoptosis, diplopia and visual impairment. On physical examination, there may appear unilateral or bilateral rhinorrhea, proptosis, chemosis, periorbital cellulitis, alteration of the intrinsic and extrinsic ocular movements and amaurosis. The nasal endoscope may show necrotic lesions in the nasal mucosa.<sup>69</sup> The infection may get disseminated to the central nervous system (CNS) through the orbital apex, the cribriform plate or through thrombosis of arteries that irrigate the central nervous system. The CNS involvement is characterized by a change in the conscious level, convulsions and/or hemiplegia with a worse prognosis.<sup>70</sup> A potential intracranial complication of mucormycosis is the cavernous sinus thrombosis (CST). Complete cavernous sinus thrombosis occurs after carotid artery occlusion. Once this condition reaches cerebral ischemia and death ensue. The first description of this affection was made by Duncan in 1821.<sup>72</sup> The initial complaints of the cavernous sinus thrombosis are of retro-orbital pain, periorbital edema, chemosis, proptosis, palpebral ptosis and diplopia. Such symptoms are not specific and may be present in other affections as in the orbital cellulitis. However, the presence of sepsis, paralysis of cranial nerves and bilateral ocular involvement are important signs for the CST. The CST diagnosis is made with the help of clinical signs and computerized tomography and/or the nuclear magnetic resonance (NMR), and the latter is more sensitive to the diagnosis. This examination may reveal direct signs of CST such as changes in the signal intensity, the size and contour of the cavernous sinus and indirect signs like the thickening and enhancement of the contrast on the lateral wall of the cavernous sinus.<sup>73</sup> The CST occurs mostly due to the infections of the paranasal sinuses, mainly the ethmoid and the sphenoid.<sup>74</sup> The agent that most commonly causes the CST is the staphylococcus aureus, but this affection may also be caused by other bacteria or fungi.<sup>72</sup> Thus to prevent CST, the diagnosis must be early with aggressive therapy.

### Laboratory diagnosis:

Immediate diagnosis and treatment are essential. Diagnosis of aspergillosis is reached by histopathology, fungal mount and culture, which allows species identification.<sup>75</sup> Histopathology shows acute angled branching septate fungal hyphae with tissue invasion. *A. fumigatus* is the most common organism in immunocompetent patients.<sup>75</sup> Fungal cultures are essential to know the sensitivity of various anti-fungal agents for various species. Newer diagnostic markers, including *Aspergillus* galactomanan (GM) and  $\beta$ -glucan, are also available nowadays along with polymerase chain reaction (PCR) based assay in high risk patients having neutropenia or bone marrow transplant recipients.

The diagnosis of mucormycosis can be made by direct microscopy, histopathological examination or by culture on sabaroud's agar. Cultures are often negative and positive results alone are not sufficient to diagnose zygomycetes as these fungi can be grown from specimens taken from uninfected mucosal and skin surfaces. Demonstration of tissue invasion on histopathology is mandatory for diagnosis.<sup>65, 76</sup> Infected tissue biopsy can reveal the distinctive hyphae characteristics like broad, ribbon-like, irregularly shaped aseptate, and in many cases, with non-dichotomous and right-angle branching, pathognomonic for zygomycetes. The diagnostic confirmation, even if there is a negative imaging study, is the histopathological report, which demonstrates angioinvasion by the irregular broad aseptate hyphae that branch at right angles.<sup>77</sup>

### Radiological diagnosis:

Computed tomography (CT) and MRI usually show extensive sino-orbital and skull base lesions.<sup>78</sup> Only small series of patients with zygomycetes have been described. The gold standard imaging method is contrast-enhanced computed tomography (CECT) which shows opacification of sinuses, edema of the mucosa, bone destruction, soft tissue swelling and swelling of extraocular muscles.<sup>79</sup> Initial CT imaging is generally not impressive and shows nonspecific, sinus mucoperiosteal thickening or fluid collection. Perisinus soft tissue infiltration may be an early CT finding in patients with rhinocerebral mucormycosis.<sup>80</sup> CT scan is able to demonstrate the extent of disease in paranasal sinuses, orbit and intracranially accurately. Patients with cerebral aspergillosis have multiple lesions, an irregular ring of contrast enhancement, and hypointensity of the ring on T2- weighted MR images. Abnormal enhancement of the optic nerve and sheath with infiltrating enhancing soft tissue within the intra-orbital fat is seen in intraorbital lesions.<sup>80</sup> Clinicians should not forget that bone destruction can be a late finding and patients with early rhino-orbito-cerebral mucormycosis may have

normal CT and MRI picture. Also, surgical exploration with biopsy of the areas should always be performed to confirm invasive mycosis in high-risk patients.<sup>81</sup>

#### Differential diagnosis:

The differential diagnosis of invasive fungal sinusitis includes benign and malignant neoplasms, syphilis, tuberculosis, sarcoidosis, Wegner's granulomatosis, lymphoma, mucopycocele, allergic fungal sinusitis and rhinoscleroma.<sup>82</sup>

#### Follow-up:

Regular post-operative follow-up is recommended in all the cases. Contrast CT scan and nasal endoscopy is recommended to look for recurrent disease every 3–4 months. Early diagnosis of recurrent disease requires prolonged systemic antifungal chemotherapy.<sup>82</sup>

#### Treatment:

Therapy guidelines have been recently published.<sup>83</sup> The disease requires extensive and urgent surgical debridement and immediate first-line antifungal treatment with liposomal or lipid-complex Amphotericin B with a minimum dose of 5mg/kg/day for a protracted period of 4–6 weeks. In-vitro and in-vivo evidence support rapid institution of liposomal Amphotericin B as the main efficacious pharmacotherapeutic intervention.<sup>84</sup> Impaired delivery of the antifungal drugs to the site of infection because of vascular thrombosis and limited aggressive surgery because of the complex anatomy of the rhino-orbital region cautions for early diagnosis and aggressive management in such patients. Radical surgical debridement is also required as pharmacological agents are only fungostatic. Washburn has noted that invasive fungal sinusitis frequently recurs despite surgical debridement and recommended a prolonged course of Amphotericin B exceeding 2 g for adults after surgery.<sup>85, 86</sup> If persistent or recurrent disease develops, itraconazole 200–400 mg per day may be added.<sup>87</sup> Radical procedures like orbital exenteration must be considered in all cases.<sup>87</sup> Dhiwakar et al<sup>88</sup> reported that orbital exenteration appears to be justified for posterior orbital (retrobulbar, apical) diseases regardless of the functional status of the eye, but is not appropriate for anterior orbital (inferomedial) diseases.

Although not currently used as first line treatment, the concurrent use of Posaconazole, a triazole antifungal drug has been shown to be effective against mucormycosis and use has been increasingly reported when Amphotericin B has had to be discontinued due to adverse side effects.<sup>89</sup> The European guidelines strongly recommend Posaconazole for salvage therapy and support with moderate strength combination of lipid formulations

of Amphotericin B with Posaconazole. Posaconazole has been suggested for secondary prophylaxis in patients at high risk of relapse. But the utility of Posaconazole is limited by the need for a high fat diet and side effects like hepatotoxicity. Local irrigation with antifungal agents has been advocated by some authors.

Amphotericin B has a broad spectrum of activity against *Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., *Fusarium* spp., *Mucorales*, and endemic fungi.<sup>90, 91</sup> Triazoles are the only fungicidal drugs against *Aspergillus* spp., and echinocandins against *Candida*.<sup>91</sup> In contrast to other triazoles, posaconazole has activity against *Zygomycetes* including *Mucor* spp., *Rhizopus* spp., and *Cunninghamella* spp. The lipid complex and liposomal form of amphotericin are alternative drugs used in cases with impaired renal function.

The value of hyperbaric oxygen therapy (HBOT) has been related to direct antifungal activity mediated through increased oxygen-based free radicals, reversal of fungal growth promoting lactic acidosis, restoration of phagocytosis and oxidative burst of polymorphonuclear leukocytes, and enhanced healing.<sup>89</sup>

An alternative treatment option that has been used in cases where disease has spread intracranially despite surgical and medical management has been iron-chelating agents like Deferasirox. The use of iron chelators as a salvage agent has been an area of controversy as studies, which used iron chelators to treat iron and aluminium overload in renal dialysis patients reported an increase rate of mucormycosis and therefore cited iron chelators as a risk factor for angioinvasive mucormycosis.<sup>89</sup> The rise in risk of developing mucormycosis appears to be specific to the use of Deferoxamine, which acts as an iron siderophore for *Mucorales*. Iron is required by virtually all microbial pathogens for growth. Deferoxamine enables the supply of previously unavailable iron to the fungi enhancing virulence.<sup>89</sup> In contrast, other iron chelators like Deferiprone and Deferasirox do not supply iron to the fungus and were shown to be fungicidal in-vitro.

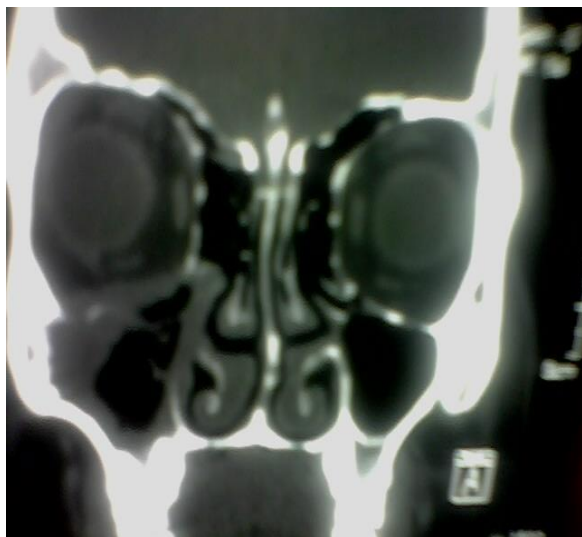
Reversal of predisposing conditions is also strongly recommended, like using granulocyte colony-stimulating factor in hematological patients with ongoing neutropenia, controlling hyperglycemia and ketoacidosis in diabetic patients, and limiting glucocorticosteroids to the minimum dose required.

Thus, treatment of rhinocerebral mucormycosis requires a multifaceted approach which includes antifungal agents, surgical debridement including exenteration of involved orbits and correction of the underlying disease which predisposes the individual to infection.<sup>85, 86</sup> However, long-term complications like loss of oral and visual function, disfigurement, diminished quality of life

and psychosocial consequences together with their impact on survival, force us to continue to redefine management strategies for mucormycosis. Another potential endpoint for clinical studies that needs to be spotlighted is the duration and dosage of antifungal therapy using single-drug or combination strategies.



**Figure 1:** Coronal cut of contrast enhanced computed tomography (CECT) showing left ethmoidal sinusitis eroding lamina papyracea



**Figure 2:** Coronal cut of contrast enhanced computed tomography (CECT) showing right maxillary sinusitis

## CONCLUSION

Early aggressive sinonasal debridement should be performed in all patients with IFS. The mainstays of treatment for IFS is repeated surgical debridement, prolonged use of antifungal agents (Echinocandins with increasing doses of Amphotericin B), exposure to hyperbaric oxygen

therapy unit, salvage therapy with Posaconazole along with reversal of predisposing factors is the best treatment for invasive mycosis followed worldwide.

## Bibliography:

- Holt GR, Standefel JA, Brown WE. Gates Ga. Infectious diseases of the sphenoid sinus Laryngoscope 1984, 94 330-335
- Stammberger H, Jakse R, Beanfort F Aspergilllosis of paranasal sinuses Ann Otol Rhinol Laryngol 1984, 93 251-256
- Ferguson BJ. Definitions of fungal rhinosinusitis. Otolaryngol Clin North Am 2000; 33: 22735.
- Granville L, Chirala M, Cernoch P, Ostrowski M, Truong LD. Fungal sinusitis: Histologic spectrum and correlation with culture. Hum Pathol 2004; 35: 47481.
- Chopra H, Dua K, Malhotra V, et al. Invasive fungal sinusitis of isolated sphenoid sinus in immunocompetent subjects. Mycoses 49: 30 –36, 2006.
- Gupta AK, Ghosh S, and Gupta AK. Sinonasal aspergilliosis in immunocompetent Indian children: An eight-year experience. Mycoses 46: 455– 461, 2003.
- Drakos PE, Nagler A, Or R, et al. Invasive fungal sinusitis in patients undergoing bone marrow transplantation. Bone Marrow Transplant 1993; 12: 203–8.
- Kameswaran M, Al-Wadei A, Khurana P, Okafor BC. Rhinocerebral aspergilliosis. J Laryngol Otol 1992; 106: 981–5.
- Lansford BK, Bower CM, Seibert RW. Invasive fungal sinusitis in the immunocompromised pediatric patient. Ear Nose Throat J 1995; 74: 566–73.
- Meyer RD, Gaultier CR, Yamashita JT, Babapour R, Pitchon HE, Wolfe PR. Fungal sinusitis in patients with AIDS: report of 4 cases and review of the literature. Medicine (Baltimore) 1994; 73: 69–78.
- Saah D, Braverman I, Drakos PE, Or R, Elidan J, Nagler A. Rhinocerebral aspergilliosis in patients undergoing bone marrow transplantation. Ann Otol Rhinol Laryngol 1994; 103: 306–10.
- Talbot GH, Huang A, Provencher M. Invasive aspergillus rhinosinusitis in patients with acute leukemia. Rev Infect Dis 1991; 13: 219–32.
- Waitzman AA, Birt BD. Fungal sinusitis. J Otolaryngol 1994; 23: 244–9.
- Lee BL, Holland GN, Glasgow BJ. Chiasmal infarction and sudden blindness caused by mucormycosis in AIDS and diabetes mellitus. Am J Ophthalmol. 1996; 122:89596.
- Sanchez MR, PongeWilson I, Moy JA, Rosenthal S. Zygomycosis and HIV infection. J Am Acad Dermatol 1994; 30: 9048.
- Blatt SP, Lucey DR, Dehoff D, Zellmer RB, Rhinocerebral zygomycosis in a patient with AIDS [letter]. J Infect Dis 1991; 164: 21516.
- Drakos PE, Nagler A, Or R, et al. Invasive fungal sinusitis in patients undergoing bone marrow transplantation. Bone Marrow Transplant 1993; 12: 203–8.
- Corey JP, Romberger CF, Shaw GY. Fungal diseases of the sinuses. Otolaryngol Head Neck Surg 1990; 103: 1012–5.

19. De Carpentier JP, Ramamurthy L, Denning DW, Taylor PH. An algorithmic approach to aspergillus sinusitis. *J Laryngol Otol* **1994**; 108: 314–8.
20. Zieske LA, Kopke RD, Hamill R. Dematiaceous fungal sinusitis. *Otolaryngol Head Neck Surg* **1991**; 105: 567–77.
21. Grewal RS, Khurana S, Aujla KS, Goyal SC. Incidence of fungal infections in chronic maxillary sinusitis. *Indian J Pathol Microbiol* 1990, 33: 339-343
22. Chakrabarti A, Sharma SC, Chandel J. Epidemiology and pathogenesis of paranasal sinus mycoses. *Otolaryngol Head Neck Surg* 1992, 107:745-750
23. Panda NK, Sharma SC, Chakrabarti A, Mann SBS. Paranasal sinus mycoses in north India. *Mycoses* 1998, 41: 281-286
24. Thakar A, Sarkar C, Dhiwakar M, Bahadur S, Dahlyia S. Allergic fungal sinusitis expanding the clinicopathologic spectrum. *Otolaryngol head Neck Surg* 2004, 130 209-216
25. Murthy JM, Sundaram C, Prasad VS, Purohlt AK, Rammam S, Laxmr V. Sinocranial aspergillosis, a form of central nervous system aspergillosis in south India. *Mycoses* 2001, 44 141-145
26. Rupa V, Jacob M, Mathews MS, Job A, Kunen M, Chan SM. Clinicopathological and mycological spectrum of allergic fungal sinusitis in south India. *Mycoses* 2002, 45 364-367
27. Rane S, Jayaraman A, Holla VV. Allergic fungal sinusitis - a case report. *Indian J Pathol Microbiol* 2003, 46 450-451
28. Washburn RG, Kennedy DW, Begley MG, Henderson DK, Bennett JE. Chronic fungal sinusitis in apparently normal hosts. *Medicine* 1988, 67 231-247
29. M.T.Yen, W.P.Baugh. Rhinocerebral Mucormycosis [Internet],[Placeun- known]: Medline, 2011. Available from: (<http://emedicine.medscape.com/article/227586-overview>)
30. G. Petrikkos, A.Skiada, O.Lortholary, E.Roilides, J.T.Walsh, D.P.Kontoyiannis, Epidemiology and clinical manifestations of mucormycosis. *Clin.Infect. Dis.*54 (1) (2012)23–34.
31. R.A. Yohai, J.D. Bullock,A. A.Aziz, R.J.Markert. Survival factors in rhino-orbital - cerebral mucormycosis. *Surg.Ophthalmol.* 39(1) (1994); 3–22.
32. VandenBergh MFQ, Verweij PE, and Voss A. Epidemiology of nosocomial fungal infections: Invasive aspergillosis and the environment. *Diagn Microbiol Infect Dis* 34: 221–227, 1999.
33. Aydogdu H, and Asan A. Airborne fungi in child day care centers in Edirne City, Turkey. *Environ Monit Assess* 147: 423–444, 2008.
34. Fang ZG, Ouyang ZY, Hu LF, et al. Culturable airborne fungi in outdoor environments in Beijing, China. *Sci Total Environ* 350: 47–58, 2005
35. Lee T, Grinshpun SA, Kim KY, et al. Relationship between indoor and outdoor airborne fungal spores, pollen, and (1 $\beta$ 3)-b-d-glucan in homes without visible mold growth. *Aerobiologia* 22: 227–236, 2006.
36. Herbarth O, Schlink U, Muller A, et al. Spatiotemporal distribution of airborne mould spores in apartments. *Mycol Res* 107: 1361–1371, 2003.
37. Al-Ajam MR, Bizri AR, Mokhbat J, et al. Mucormycosis in the Eastern Mediterranean: A seasonal disease. *Epidemiol Infect* 134: 341–346, 2006.
38. Ren P, Jankun TM, Belanger K, et al. The relation between fungal propagules in indoor air and home characteristics. *Allergy* 56: 419–424, 2001.
39. Kalyoncu F. Relationship between airborne fungal allergens and meteorological factors in Manisa City, Turkey. *Environ Monit Assess* 165: 553–558, 2010.
40. Shpitzer T, Keller N, Wolf M, et al. Seasonal variations in rhino-cerebral mucor infections. *Ann Otol Rhinol Laryngol* 114: 695–698, 2005.
41. Alberti C, Bouakline A, Ribaud P, et al. Relationship between environmental fungal contamination and the incidence of invasive aspergillosis in haematology patients. *J Hosp Infect* 48: 198–206, 2001.
42. Leenders A, Van Belkum A, Behrendt M, et al. Density and molecular epidemiology of *Aspergillus* in air and relationship to outbreaks of *Aspergillus* infection. *J Clin Microbiol* 37: 1752–1757, 1999.
43. Pini G, Donato R, Faggi E, et al. Two years of a fungal aerobic contamination survey in a Florentine haematology ward. *Eur J Epidemiol* 19: 693–698, 2004.
44. Wolf M, Naftali S, Schroter RC, et al. Air-conditioning characteristics of the human nose. *J Laryngol Otol* 118: 87–92, 2004.
45. Zhao K, and Dalton P. The way the wind blows: Implications of modelling of the nasal airflow. *Curr Allergy Asthma Rep* 7: 117–125, 2007.
46. Gru` tzenmacher S, Robinson DM, Gra` fe K, et al. First findings concerning airflow in noses with septal deviation and compensatory turbinate hypertrophy—A model study. *ORL J Otorhinolaryngol Relat Spec* 68: 199–205, 2006.
47. Garcia GJ, Tewksbury EW, Wong BA, et al. Interindividual variability in nasal filtration as a function of nasal cavity geometry. *J Aerosol Med Pulm Drug Deliv* 22: 139–155, 2009
48. Yoon JS, Park HK, Cho NH, Lee SY (2007) Outcomes of three patients with intra-cranially invasive sino-orbital aspergillosis. *Ophthal Plast Reconstr Surg* 23(5): 400–406
49. Akhaddar A, Gazzaz M, Albouzidi A, Lmimouni B, Elmostarchid B, Boucetta M (2008) Invasive *Aspergillus terreus* sinusitis with orbitocranial extension: case report. *Surg Neurol* 69(5):490–495
50. Knipping S, Holzhausen HJ, Koesling S, Bloching M (2008) Invasive aspergillosis of the paranasal sinuses and the skull base. *Pneumonol Alergol Pol* 76(5): 400–406
51. Paulltauf A. *Mycosis mucorina*. *Virchows Arch [A]*. 1885, 102-543.
52. Bray WH, Giangiacomo J, Ide CH. Orbital apex syndrome. *Surv Ophthalmol.* 1987, 32(2): 136-40.
53. Garcia-Covarrubias, L., R. Bartlett, D. M. Barratt, and R. J. Wassermann. Rhino-orbitocerebral mucormycosis attributable to *Apophysomyces elegans* in an immunocompetent individual: case report and review of the literature. *J. Trauma.* 2001, 50: 353-7
54. Pereira VG, Pereira MAA, Cruz JOB, Haron ES. Mucormicose rino-orbitária: Relato de um caso. *Rev Hosp Clin Fac Med S. Paulo.* 1982, 37(3): 140-6
55. Cuadrado LM, Guerrero A, Lopez Garcia Asenjo JA, et al. Cerebral mucormycosis in two cases of acquired immunodeficiency syndrome. *Arch Neurol.* 1988, 45: 109.
56. Dökmetas HS, Canbay E, Yilmaz S, Elaldi N, Topalkara A, Oztoprak I, et al. Diabetic ketoacidosis and rhinoorbital mucormycosis. *Diabetes Res Clin Pract* 2002; 57:13942.
57. Scheckenbach K, Cornely O, Hoffmann TK, Engers R, Bier H, Chaker A, et al. Emerging therapeutic options

- in fulminant invasive rhinocerebral mucormycosis. *Auris Nasus Larynx* 2010; 37: 3228.
58. Jung SH, Kim SW, Park CS, Song CE, Cho JH, Lee JH, et al. Rhinocerebral Mucormycosis: Consideration of prognostic factors and treatment modality. *Auris Nasus Larynx* 2009; 36: 2749
  59. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. 2005. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin. Infect. Dis.* 41: 634–653.
  60. Spellberg B, Edwards J, Jr, Ibrahim A. 2005. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin. Microbiol. Rev.* 18:556–569.
  61. Hammond SP, Baden LR, Marty FM. 2011. Mortality in hematologic malignancy and hematopoietic stem cell transplant patients with mucormycosis, 2001 to 2009. *Antimicrob. Agents Chemother.* 55: 5018–5021.
  62. Ferguson BJ. Definitions of fungal rhinosinusitis. *Otolaryngol Clin North Am* 2000; 33: 22735
  63. Castillo L, Hofman V, Betis F, Piche M, Roger PM, Santini J, et al. Long term survival in acute rhinocerebral mucormycosis with giant cell arteritis and foreign body granulomas. *Pathol Res Pract* 2001; 197: 199203.
  64. Frater JL, Hall GS, Procop GW. Histologic features of zygomycosis: emphasis on perineural invasion and fungal morphology. *Arch Pathol Lab Med* 2001; 125: 3758
  65. Ferry AP, Abedi S. Diagnosis and management of rhino-orbito-cerebral mucormycosis (phycomycosis): a report of 16 personally observed cases. *Ophthalmology* 1983; 90: 1096–104.
  66. Blitzer A, Lawson W, Meyers BR, et al. Patient survival factors in paranasal sinus mucormycosis. *Laryngoscope* 1980; 90: 635–648.
  67. Abramson E, Wilson D, Arky RA. Rhinocerebral phycomycosis in association with diabetic ketoacidosis. *Ann Intern Med* 1984: 1060–2.
  68. Pillsbury HC, Fischer ND. Rhinocerebral mucormycosis. *Arch Otolaryngol* 1977; 103: 600–4.
  69. Prabhu RM, Patel R. Mucormycosis and entomophthoromycosis: a review of the clinical manifestations, diagnosis and treatment. *Clin Microbiol Infect.* 2004, 10 (suppl 1): 31.
  70. Nithyanandam S, Jacob MS, Battu RR, Thomas RK, Correa MA, D'Souza O. Rhinoorbitocerebral Mucormycosis. A retrospective analysis of clinical features and treatment outcomes. *Indian J Ophthalmol* 2003; 51: 2316.
  71. Fairley C, Sullivan TJ, Bartley P, et al. Survival after rhino-orbitocerebral mucormycosis in an immunocompetent patient. *Ophthalmology.* 2000, 107:555.
  72. Duncan A. Contributions to morbid anatomy. *Edinburgh Med Surg J.* 1821, 17:321-36.
  73. Schuknecht B, Simmen D, Yuksel C, et al. Tributary venous occlusion and septic cavernous sinus thrombosis: CT and MR findings. *Am J Neuroradiol.* 1998, 19: 617-26.
  74. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med.* 2005, 352: 1791-8.
  75. T. J. Walsh, M. N. Gamaletsou, M. R. McGinnis, R. T. Hayden, and D. P. Kontoyiannis, "Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis)," *Clinical Infectious Diseases*, vol. 54, no. 1, pp. S55–S60, 2012.
  76. Parfrey NA. Improved diagnosis and prognosis of mucormycosis. A clinicopathologic study of 33 cases. *Medicine* 1986; 65: 11323.
  77. Munir N, Jones NS. Rhinocerebral mucormycosis with orbital and Intracranial extension: A case report and review of optimum management. *J Laryngol Otol* 2007;121:1925
  78. A. S. Ibrahim, B. Spellberg, T. J. Walsh, and D. P. Kontoyiannis, "Pathogenesis of mucormycosis," *Clinical Infectious Diseases*, vol. 54, supplement 1, pp. S16–S22, 2012
  79. Prasad K, LalithaRM, ReddyEK, RanganathK, SrinivasDR, SinghJ. Role of early diagnosis and multimodal treatment in rhinocerebral mucormycosis: experience of 4 cases. *J Oral Maxillofac Surg* 2012; 70(2): 354–62.
  80. Silverman CS, Mancuso AA. Periantral soft tissue infiltration and its relevance to the early detection of invasive fungal sinusitis: CT and MR findings. *AJNR Am J Neuroradiol* 1998; 19: 3215.
  81. Rapidis AD. Orbitomaxillary mucormycosis (zygomycosis) and the surgical approach to treatment: perspectives from a maxillofacial surgeon. *Clin Microbiol Infect* 2009; 15(Suppl.5): 98–102.
  82. C. Reed, R. Bryant, A. S. Ibrahim et al., "Combination polyene caspofungin treatment of rhino-orbital-cerebral mucormycosis," *Clinical Infectious Diseases*, vol. 47, no. 3, pp. 364–371, 2008.
  83. Cornely OA, Arikan- AkdagliS, DannaouiE, GrollAH, LagrouK, ChakrabartiA, et al. ESCMID and ECMM Joint Clinical Guidelines for the Diagnosis and Management of Mucormycosis 2013. *Clin Microbiol Infect* 2014; 20(Suppl. S3): 5–26.
  84. E.J.C. Goldstein, B. Spellberg, T.J. Walsh, D.P. Kontoyiannis, J. Edwards Jr, A. Ibrahim, Recent advances in the management of mucormycosis: from bench to bedside, *Clin. Infect. Dis.* 48(12)(2009)1743–1751.
  85. Ochi JW, Harris JP, Feldman JI, Press GA. Rhinocerebral mucormycosis: Results of aggressive surgical debridement and amphotericin B. *Laryngoscope* 1988; 98: 133942.
  86. Rangel Guerra R, Martinez HR, Saenz C. Mucormycosis. Report of 11 cases. *Arch Neurol* 1985; 42: 547881
  87. Kohn R, Hepler R. Management of limited rhino-orbital mucormycosis without exenteration. *Ophthalmology* 1985; 92: 144043.
  88. Dhiwakar M, Thakar A, Bahadur S. Invasive sino-orbital aspergillosis: surgical decisions and dilemmas. *J Laryngol Otol.* 2003 Apr; 117(4): 280-5.
  89. TragiannidisA, Groll AH. Hyperbaric oxygen therapy and other adjunctive treatments for zygomycosis. *Clin Microbiol Infect* 2009; 15(Suppl.5): 82–6.
  90. Leventakos K, Lewis RE, Kontoyiannis DP. Fungal infections in leukemia patients: how do we prevent and treat them? *Clin Infect Dis.* 2010 Feb; 50(3): 405-15.
  91. Vallejo C, Barberán J. Empirical antifungal treatment: a valid alternative for invasive fungal infection. *Rev Esp Quimioter.* 2011.