# Local Measures Protocol in Solving Rhinocerebral Mucormycosis Dilemma

## A Clinical Study

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### ABSTRACT

**Background:** Rhinocerebral mucormycosis is a life threatening opportunistic fungal infection usually affecting medical compromised patients like uncontrolled diabetic patient, renal failure and hematological malignancy. The disease is transmitted by inhalation, ingestion and wounds contamination. Early management of this disease improves patient prognosis. Microbiological culture and biopsy are crucial tools for diagnosis. Surgical debridement, correction of underlying cause, systemic antifungal therapy is the standard management protocol.

**Objectives:** To analyze the effectiveness of surgical debridement along with strategy of local irrigation protocol in management of rhinocerebral mucormycosis.

**Methods:** Forty patient referred to Al-Salaam Teaching Hospital in Mosul of Iraq from Jan. 2010 to Jan 2014 complaining from facial pain, swelling and nasal congestion not responding to routine medical treatment. The diagnosis of rhinocerebral mucormycosis established by clinical examination, radiological and laboratory investigation. The treatment plan consists of surgical debridement and placement of iodofoam gauze or bismuth iodofoam paraffin paste pack in the surgical defect followed by irrigation with 0.9% normal saline and 0.2% chlorohexidine for two weeks and the patients kept in follow up program for 4 months.

**Results:** Twenty-seven cases from 40 patients confirmed as cases of rhinocerebral mucormycosis and included in this study. All cases managed by surgical debridement along with post-surgical irrigation protocol. They show significant improvement within 1st week post-surgery. The survival rate is 100% and all patients left hospital without serious complications.

**Conclusion:** Early diagnosis and urgent surgical intervention followed by local irrigation program and correction of underlying cause may give better prognostic results in management of rhinocerebral mucormycosis.


**Keywords: Rhinocerebral mucormycosis, Antifungal drugs, Fungal infection.**

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Mucormycosis is a life threatening opportunistic fungal infection caused by a filament of mucorales order which is a class of zygomycetes[1]. This microorganism commonly found in soil, bread and decayed fruits and vegetables[2]. The disease usually affects medically compromised patients especially uncontrolled diabetic patients, haematological malignancy like leukemia, renal failure, burns and severe contaminated injuries[3].

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The mortality rate ranges between 35-80% in spite of aggressive treatment[4]. This disease usually transmitted by inhalation or ingestion of spores from environment[5]. The pathophysiology of this disease represented by invasion of blood vessel by microorganism resulting in thrombosis and tissue necrosis.

The initial presentation of the disease is like allergic rhinitis, sinusitis or dental infection. The patient usually complains from fever, headache, blurred vision, nasal and sinus congestion and seizure attacks in case of intracranial extension. On examination, there is facial edema with black discoloration (eschar) of nasal

turbinate, palatal perforation, facial paralysis, ptosis and ophthalmoplasia in advanced stage. Radiological analysis represented by CT scan and magnetic resonance image (MRI) show features of pansinusitis, vascular invasion, intracranial extension and destruction of bony component of paranasal sinuses and orbit [6]. The diagnosis of the disease usually depends on microbiological culture and histopathological examination of the biopsy. Recently, polymerase chain reaction (PCR) and immunohistochemistry (IMC) play important role in noninvasive early diagnosis of mucormycosis[7]. The traditional treatment consists of surgical debridement along with treatment of underlying cause and systemic antifungal therapy[8].

The aim of this study is to confirm the efficacy of local measures protocol (iodofoam gauze or bismuth iodofoam paraffin paste (BIPP) pack, 0.9% normal saline and chlorohexidine 0.2% as irrigation solution) combined by early surgical debridement and correction of general health condition of the patients in management of rhinocerebral mucormycosis irrespective of systemic antifungal therapy.

## Methods

This study is a retrospective case series include 40 patients referred from many medical centers to maxillofacial unit in Al-Salaam Teaching Hospital in Mosul of Iraq from Jan. 2010 to Jan. 2014 with clinical suspicion of rhinocerebral mucormycosis. Most patients treated as cases of odontogenic or sinonasal infection without success.

The inclusion criteria include patients with sino-naso-orbital mucormycosis where the disease clinically and radiographically confined to nose, maxillary sinus, palate and orbit, positive results of microbiological and histopathological examination. Exclusion criteria include those patients who were taking pre-surgical course of antifungal therapy, untreatable patients because of advanced stage disease extending to the cranium, inoperable cases due to high risk of mortality rate during general anesthesia as a result of deteriorating in general health condition.

The patients admitted to the hospital and special case sheet done for each patient including demographic information, medical history, investigation, treatment plan and follow up. Thorough assessment performed for all patients including clinical examination, nasal endoscope, radiological analysis represented by plain x-ray film such as orthopantomogram (OPG) and occipitomental views, CT-scan and MRI. Laboratory tests like random and fasting blood sugar level, HbA1c, complete blood counts, ESR, C-reactive protein, kidney and liver function tests were done for each patient. Medical consultation with the ophthalmologist, otolaryngologist and physician done when indicated. Swabs for microbiological culture and incisional biopsy were taken from the nose and maxillary sinus, which confirmed the presence of fungal hyphae.

Twenty-two patients treated through oral approach (Caldwell-Luc maxillary sinus approach) with transnasal antrostomy for later pack removal and five patients treated through lateral rhinotomy incision. Management protocol consisted of aggressive surgical debridement and removal of all dead and necrotic tissue until reaching healthy viable tissue. When there was extensive surgery for example partial or total maxillectomy, iodofoam gauze or BIPP pack was placed in the surgical defect and supported by presurgically fabricated surgical splint made from heat cure methyl methacrylate fixed by circumdental and circumzygomatic wiring. The pack was removed after 7-10 days when it became impregnated with blood and the patient show signs of infection like discomfort, pain and skin redness. Irrigation by normal saline 0.9% and chlorohexidine 0.2% was done by 50 ml syringe with wide bore needle and started after pack removal and performed four times daily for two weeks.

The evaluation of patient response was done by improvement of patient general

health and regression of fever, malaise, headache, facial and orbital edema and appearance of local clinical signs of healing like granulation tissue formation at the surgical defect.

Postoperatively, the patients were put on antibiotic regimen and nonsteroidal anti-inflammatory drugs and oral hygiene maintenance instructions (Amoxicillin 500mg/tab clavulanic acid 125mg/tab with brufen tab 200-400mg/tab three times daily for ten days and chlorohexidine 0.2 as a mouth wash. In case of penicillin allergy, the patients put on amikacin ampule 500mg/2ml two times daily for five days). A hollow type acrylic obturator fabricated by prosthodontics after two months of surgery as a measure of rehabilitation. The patients kept in follow up visits every two weeks for four months.

## Results

Over all 27 from 40 patients diagnosed as a cases of rhinocerebral mucormycosis. Thirteen patients excluded from this study because they did not match our criteria of patient selection. Twenty patients are males and seven patients are females, (Table 1).

The age of patients ranges from 12-60 years (mean 36). Past medical history reveal that 22 patients had diabetes mellitus, three patients had renal failure, one patient was leukemic and one patient was normal healthy person, (Table 2).

Fifteen of the referred patients were diagnosed in other medical center as allergic rhinitis and bacterial sinusitis, 12 patients were diagnosed as cases of dental infection and they were treated with antibacterial drugs and nasal decongestant without response. Nasal eschar and necrosis seen in 16 patients, palatal blackness and ulceration seen in five patients, maxillary sinus involvement detected in nine patients and orbital involvement seen in three patients, (Table 3).

Neutropenia was seen in a leukemic patient. The radiological evaluation represented by CT-scan and MRI show opacification of paranasal sinuses and signs of bone destruction and vascular invasion. The duration of treatment between 18-30 days and the average of hospital stay was about 5 days. The positive microbiological and biopsy results coincide with clinical and radiological features of the disease. Rhizopus species of mucormycosis was the causative microorganism in 18 patients while mucor species seen in nine patients, (Table 4).

**Table 1: Gender distribution.**

| Gender | No. of patients | % |
|---|---|---|
| **Male** | 20 | 74 |
| **Female** | 7 | 26 |
| **Total** | 27 | 100 |

**Table 2: Risk factors for rhinocerebral mucormycosis.**

| Risk factor | No. of patients | % |
|---|---|---|
| **Diabetes mellitus** | 22 | 81.5 |
| **Renal failure** | 3 | 11.1 |
| **Leukemia** | 1 | 3.7 |
| **Normal healthy person** | 1 | 3.7 |
| **Total** | 27 | 100 |

**Table 3: Anatomical site involvement by rhinocerebral mucormycosis.**

| Site of involvement | No. of patients | % |
|---|---|---|
| **Nasal cavity** | 10 | 37 |
| **Maxillary sinus** | 9 | 33.3 |
| **Palatal bone** | 5 | 18.5 |
| **Orbit** | 3 | 11.1 |
| **Total** | 27 | 100 |

**Table 4: Causative agents of rhinocerebral mucormycosis.**

| Microorganism | No. of patients | % |
|---|---|---|
| **Rhizopus species** | 18 | 66.6 |
| **Mucor species** | 9 | 33.3 |
| **Total** | 27 | 100 |

Improvement in patients' general health was detected within 1st week post-surgery. All patients responded to the treatment plan. The systemic and local signs of infection like fever, malaise, anorexia, headache, nasal congestion facial and orbital edema subsided and the patients left hospital without life threatening post-operative complication. The patients who presented with ophthalmological manifestation showed improvement in their visual status and no patient underwent eye surgery. Survival rate is 100% and four patients died after four years due to complication of systemic disease and deterioration of their general medical condition.

## Discussion

Rhinocerebral mucormycosis is a serious fungal infection affecting medically compromised patients like diabetic patients, renal failure, haematological malignancy, burns and major trauma[9]. Successful treatment is restricted due to delay diagnosis, fulminant nature of the disease, inaccessibility of the lesion, poor penetration of antifungal drugs due to tissue ischemia and necrosis and toxicity associated with long-term use of antifungal therapy[10]. Most of literatures consider surgical debridement along with systemic antifungal therapy, correction of underling condition is the main treatment modality in management of the disease[11]. Recent researches believe that extensive surgery like partial or total maxillectomy and orbital exenteration may be associated with severe morbidity therefore a new treatment modalities developed for better clinical outcomes like hyperbaric oxygen therapy that enhance tissue revascularization and perfusion, granulocyte colony-stimulating factors (G-CSF) that improve body immune system function[12]. The treatment policy in the present study illustrated by surgical debridement, correction of medical status of the patients and local measures protocol represented by iodofoam gauze or BIPP, 0.9% saline and 0.2% chlorohexidine as irrigation solutions. Many scientific medical concepts and economic factors encouraged us to adopt this treatment regimen, like idea of limited therapeutic dose of systemic antifungal drugs reaching the site of infection as a result of poor tissue perfusion[13], risk of nephrotoxicity specially in patients with renal impairment, unavailability of the drugs for purchase every time and low economic status of many patients making them unable to tolerate the high cost of the drugs and long course of treatment. The advantages of local measures along with surgery represented by reducing the morbidity and mortality rate of the patients through limitation of spreading of the disease to vital organs like eye and brain, reducing the course of treatment and monitoring time of the patients, helping the patients with limited financial support and reducing the hazard of nephrotoxicity of systemic antifungal therapy.

In table 1, there was male preponderance and the diabetic patients carry the highest rate of incidence (Table 2), this may be due to genetic background related to high incidence of these medical condition in males in comparison with females. The tissue necrosis in the anatomical area is recorded in table 3 may be explain by the fact that the nidus of infection located in the pterygomaxillary fissure which the area of terminal branches of internal maxillary artery like long and short sphenopalatine arteries, greater and lesser palatine arteries and superior alveolar artery so invasion of these small arteries resulted in tissue necrosis in the areas supplied by these vascular systems.

The high percentage of Rhizopus species (table 4), may be related to high proliferative capacity, virulence of the microorganism and small size of the spores make it easily penetrate the blood vessels looking for iron nourishment from the blood. Our results in this study coincides with a study done by Kumar N et al, in this study they manage a case of oro- antral fistula due to mucormycosis depending on surgical debridement, oral care instructions and chlorohexidine mouth wash with significant improvement[14].

In a study performed by Oliga P, et al, they were talking about using topical antifungal in association with surgical intervention and frequent irrigation with saline as a treatment option in management of rhinocerebral mucormycosis, they found significant outcome and reduction of opportunity of disease extension to orbit and cranium, their findings match the results in the present study[15].

The survival rate of patients in our study was 100% in comparison with a study done by Shikha G, et al, in which they reported that the survival rate between 50-80% in spite of using systemic antifungal drugs as adjunctive therapy to surgical debridement[16]. This may be attributed to the fact that systemic antifungal therapy has a limited action if used alone after surgery due to tissue ischemia that reduce the drug efficacy in comparison with direct action of local disinfectant and irrigation solutions used in our treatment protocol.

In conclusion; surgical debridement and local measures represented by iodofoam gauze or BIPP and irrigation solutions in management of rhinocerebral mucormycosis may establish a promising results in selected patients where the infection confined to sino-naso-orbital region.

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## References

1. Ellie JC, Brad S, Thomas JW, Dimitrios PK, John E, Ashraf SI. Recent advances in the management of mucormycosis from bench to bedside. J of Clinical Infectious Disease 2009; 48(12):1743-51.
2. Richardson M. The ecology of the Zygomycetes and its impact on environmental exposure. Clinical Microbiology and Infection 2009; 15(5):2-9.
3. Rammaert B, Lanternier F, Zahar JR, Dannaoui E, Bougnoux ME, Lecuit M, et al. Healthcare-associated mucormycosis. J of Clinical Infectious Disease 2012; 54(1): 44-54.
4. Kazak E, Aslan E, Akalın H, Hakyemez B, Erisen L, Yazici B, et al. A mucormycosis case treated with a combination of caspofungin and amphotericin B. Journal of Medical Mycology 2013; 23(3):179-84.
5. Lewis RE, Kontoyiannis DP. Epidemiology and treatment of Mucormycosis. Future Microbiology 2013; 8(9):1163-75.
6. Rama kA, Anunayi J, Vivek AN, Ashalate G. Fatal rhino-orbito-cerebral mucormycosis in a healthy individual. J of Oral and Maxillofacial Pathology 2014;18(3):460-3.
7. Sanjeet SD, Dimitrios PK. Recent advances in the molecular diagnosis of mucormycosis. J of Expert Review of Molecular Diagnostics 2018; 18(10):845-54.
8. Yan S, Jianjun Q, Gaffi G, Guangjun L, Hao Y, Jianyong WU, et al. Mucormycosis in renal transplant recipients: review of 174 reported cases. BMC Infectious Disease 2017; 17(1): 283.
9. Nagres N, Firoozeh K, Nahid GG, Seyed RA, Zahra S, Emmanuel R, et al. Fatal rhinocerebral mucormycosis in a patient with ulcerative colitis receiving azathioprine and corticosteroid. Current Medical Mycology 2019; 5(1):37-41.
10. Somnath S, Tapas KB, Atanu R, Kumarjyoti G. A review of ocular fungal infection other than keratomycosis: The global and Indian scenario. J of Evolution of Medical and Dental Sciences 2016; 5(49): 3168-72.
11. Anna S, Fanny L, Andreas HG, Livio P, Stephan Z, Raoul H, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Haematologica 2013; 98: 492-504.
12. Saedi B, Sadeghi M, Seilani P. Endoscopic management of rhinocerebral mucormycosis with topical and intravenous amphotericin B. J of Laryngology Otology 2011; 125: 807-10.
13. Fadi A, Labib D, Lina A, Leyla B, Victor M, Kenneth R, et al. Palatal mucormycosis in patients with hematologic malignancy and stem cell transplantation. Medical Mycology 2011; 49(4):400-405.
14. Kumar N, Neelima AM, Uzma B. Mucormycosis in a healthy elderly patient presenting as oro-antral fistula: Report of a rare incidence. J of

Clinical and Experimental Dentistry 2015; 7(2): 333-5.
15. Oliga PH, Hector MP, Galo SD, Andres SG. Rhino-orbito-cerebral mucormycosis. management strategies to avoid or limit intracraneal affection and improve survival. Acta Otorrinolaringológica Española 2015; 66(6): 348-52.
16. Shikha G, Sangeeta JP, Vishwa PS, Anju B. Rhinomaxillary mucormycosis with cerebral extension. J of Oral and Maxillofacial Pathology 2009;13(1):14-17.

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