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REVIEW ARTICLE OPEN ACCESS

MANAGEMENT OF MUCORMYCOSIS IN AYURVEDA: AN EVIDENCE BASED REVIEW

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ABSTRACT

Mucormycosis represents a group of life-threatening infections caused by fungi of the order *Mucorales* of the subphylum *Mucoromycotina* (formerly known as the class Zygomycetes). Mucormycosis highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality than many other infections Mucormycosis is a severe emerging invasive fungal infection that occurs as a consequence of environmental exposure. Those infections are becoming increasingly common yet survival remains very poor. It is a rare disease but increasingly recognized in immune-compromised patients. Out of which 39% in the sinonasal form. In spite of aggressive treatment once detected or diagnosed overall increased mortality rate is reported. The treatment cost is also very high and needs a long course of treatment. *Ayurveda* has got cost-effective, potent, and broad-spectrum Anti-fungal agents. In this article, preventive guidelines and treatment protocol for mucormycosis are discussed based on the evidence-based data collected from experiential data, experimental and clinical research findings.

Keywords: *Ayurveda* medicine, Mucormycosis, COVID-19, Anti-fungal Ayurveda medicines

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INTRODUCTION:

The pandemic coronavirus disease 2019 (COVID-19) continues to be a significant problem worldwide. While several treatment options have been evaluated none except systemic glucocorticoids have been show to improve survival in COVID-19. Unfortunately, the widespread use of glucocorticoids can lead to secondary bacterial or fungal infections. Invasive pulmonary *Aspergillosis* complicating the course of COVID-19 is widely recognized; however, mucormycosis is uncommonly suspected or diagnosed. When lunges are damaged and immune system suppressed in treating the case of severe COVID-19, these spores can grow in airway or sinuses, and invade bodies' tissue. Mucormycosis can manifest in the lungs, but nose and sinuses is most common site. From there it can spread to the eyes, potentially causing blindness, or the brain, causing headache or seizures. It can occur in patient with diverse precipitating factors such as uncontrolled diabetes, renal failure, organ transplant etc. In diabetes patient it can be triggered even by minor tooth dental procedure such as tooth extraction.[1] Furthermore, patients with diabetic ketoacidosis are at high risk of developing rhino-cerebral mucormycosis.[2]

To treat this deadly infectious disease, Usually Amphotericine-B is used and the cost of treating the mucormycosis patient is expensive due to use of high cost anti-fungal medicines, lengthy hospital stays etc. As the complications include severe damage to the involved organs, it needs costly procedures for proper management.

As conventional medicine system involves high cost health approach and it is highly unaffordable for common patients. *Ayurveda* has got cost effective, potent and broad spectrum Anti-fungal agents which need to be included in the treatment protocol.

AIMS AND OBJECTIVES:

1. Understanding of disease Mucormycosis as per modern science and *Ayurvedic* science.
2. Role of *Ayurveda* in the prevention and treatment of Mucormycosis.

METHODS AND MATERIALS:

Brihatrayi (Charaka Samhita, Sushruta Samhita, Asthanga Hridaya) were screened to compile references of *Pratimarsha Nasya, Gandusha, Dhupana Karma* etc. Textbook of Harrison's, Davidsons were screened for the word Mucormycosis and online search was done using the keywords Mucormycosis in COVID 19 and Anti-fungal herbal medicines.

Diseases Review

Pathophysiology:

Rapid growth rates in the setting of neutropenia and diabetic ketoacidosis. Acidity increases iron and hyperglycemia promotes organism growth. Angio invasion is common, resulting in thrombus formation and tissue necrosis. Dead tissue nidus promotes additional growth.[3] GRP78- Cell receptors bind to Mucorale leading to tissue penetration. Diabetic - Acidosis leading to disassociation of iron; enhances fungal growth and virulence. Diabetic ketoacidosis – β hydroxy butyrate increases fungal and host receptors leading to fungal adherence

and penetration into tissue leading to mucormycosis.[4]

High risk patients

- COVID recovered
- COVID recovering
- COVID in diabetic patient
- Patients undergoing dialysis
- Patients taking chemotherapy
- Patients who underwent organ transplant taking immunosuppressive drugs

Clinical features

Mucormycosis can be divided into at least 6 clinical syndromes. They are [5]

1. Rhino-orbital-cerebral disease: It continues to be the most common form of the disease. Most cases occur in patients with diabetes, although such cases are increasingly being described in the transplantation setting, often along with glucocorticoid-induced diabetes.

The initial symptoms are nonspecific and include eye or facial pain, headache, blurry vision, One-sided facial swelling, nasal or sinus congestion, black lesions on nasal bridge or upper inside of mouth that quickly become more severe and fever. If untreated, infection usually spreads from ethmoid sinus to the orbit, resulting in compromise of extra ocular muscle function and proptosis, typically with chemosis. From the orbit, spread often takes place via hematogenous or contiguous dissemination to the frontal lobe of the brain and / or via venous drainage to the cavernous sinus.

2. Pulmonary disease: It is the second most common manifestation. Symptoms include fever, dyspnea, cough, and chest pain. Angio invasion results in necrosis, cavitation and/ or hemoptysis. Lobar consolidation, isolated mass, nodular disease, cavities or wedge-shaped infarcts may be seen on chest radiography. High resolution chest CT is the best method for determining the extent and may demonstrate evidence of infarction before it is seen on chest x-ray.

3. Cutaneous disease: It may result from external implantation of the fungus or from hematogenous dissemination. It can be highly invasive, penetrating muscle, fascia and even bone. It can look like blisters or ulcers, and the infected area may turn black. Other symptoms include pain, warmth, excessive redness, or swelling around a wound. Necrotic cutaneous lesion in the setting of hematogenous disseminations also associated with an extremely high mortality rate.

4. Gastrointestinal disease: It has been reported as a nosocomial process following administration of medications mixed with contaminated wooden applicator sticks. Nonspecific abdominal pain and distention associated with nausea and vomiting are the most common symptoms. Gastrointestinal bleeding is common, and fungating masses may be seen in the stomach endoscopy. The disease may progress to visceral perforation, with extremely high mortality rates.

5. Disseminated and Miscellaneous forms of disease: It may originate from primary site of infection. The most common site of dissemination is the brain, but metastatic lesions may also be found in any other organ. Miscellaneous forms may affect any body site, including bones, mediastinum, trachea, kidney and peritoneum;

even isolated infection of teeth has been reported. Patients with disseminated infection in the brain can develop mental status changes or coma.

Diagnosis:

Clinical features- as mentioned above.

Radiology-

Endobronchial lesions in diabetes Infiltrate wedge-shaped consolidation, multiple nodules (>10), cavitation, mycetoma, lobar collapse, and rarely pleural effusion. Halo sign and air crescent sign Reverse halo sign on HRCT

Sample collection: Tissue biopsy & deep nasopharyngeal swab

Biopsy with Histopathological changes: It reveals characteristic wide, thick walled, ribbon like a septate hyphal elements that branch at right angles.

Treatment:

Optimizing the chances for successful treatment of Mucormycosis requires three steps. 1 Early initiation of therapy; 2.Rapid reversal of underlying predisposing risk factors; 3. Surgical debridement

Prevention: Good hygiene, Strict sugar control, proper ward protocols and RBS charting

Antifungal:

Liposomal Amphotericin B 5-10mg/kg OD

Isavuconazole 200mg BD

Posaconazole 200mg QID

Surgical: Immediate debridement [6]

DISCUSSION

Role of Ayurvedic treatment

Preventive Guidelines

1. Maintenance of Personal hygiene
2. Environmental hygiene
3. Role of diet
4. Use of preventive medications
5. Use of single and compound herbal medications having antifungal medications
6. Use of *Rasayana* drugs (Respiratory Immuno modulators)
7. Yoga for mental health.
8. Use of Ayurvedic Anti-fungal medicines after consultation with Ayurvedic physician.

Maintenance of Personal hygiene:

COVID 19 infections may be associated with a wide range of bacterial and fungal infections, and most common is Mucormycosis infection- a life threatening invasive fungal infection and the common route of spread is through nose, oral cavity and eyes etc. without early diagnosis and treatment of the disease there may be rapid progression of the disease, so maintenance of nasal and oral hygiene is must. In *Ayurvedic* literature many concepts are described to maintain the oral and nasal health. It includes following points:

a. **Oral hygiene:** Tongue scraping has a significant improvement on eliminating anaerobic bacteria and prevents the growth of microbes within the oral cavity. Application of Use of *Neem* leaves is proven as a potent Antibacterial, Antifungal, Antiviral and Antioxidant in property.[7]
b. In the same way use of *Tulasi* leaves, Turmeric, *Lavanga*, *Nagvelli* leaves etc is explained for the maintenance of oral hygiene.
c. **Pratimarsha Nasya:** Commonly *Pratimarsha Nasya* with *Anu Taila* is advised, as instillation

of oil in the nasal route kills the micro-organisms and prevents the entry of spores in the respiratory tract.[8]

d. **Anjana:** Anjana is the procedure of applying medicated collyrium to the inner part of the eyelid with the help of *Shalakha* or fingertip. Daily use of *Srotanjana* and use of *Rasanjana* is explained in *Ayurvedic* literatures.[9]

Maintaining the Environmental hygiene:

Air borne diseases may spread through breathing, sneezing, coughing etc. which generates droplets in the air. For purification of environment Ayurveda has explained a unique concept of *Dhupana Karma*. Commonly Use of *Krimighna*, *Kusthahara* is explained in *Samhitas*. *Guggulu*, *Vacha*, *Neem, Haridra, Kustha, Jatamansi, Sarjarasa* etc are used as *Rakshoghna* and *Dhupana* drugs which are Antimicrobial and Antifungal in nature.

Vidanga and *Khadira* are advocated for *Dhupana* (fumigation) in skin diseases and the same can be used here[10]. *Aparajita Dhuma Churna* has been explained in the context of *Jwara Chikitsa* for fumigation. A study has been conducted and microbial flora was examined before and after fumigation. The study concluded that, flora before fumigation was rich in coliforms and many saprophytic fungi and after fumigation the data showed a considerable reduction in microbes. The *Churna* showed significantly higher inhabitation of various *Aspergillus* species.[11]

Principles of treatment

1. Proper maintenance of *Agni Dipana*: for proper maintenance of Homeostasis condition of *Agni* is very important. Use of *Laghu Ahara*, *Agni Dipaka* drugs etc. plays an important role in prevention of Post-Covid complications like Mucormycosis.
2. *Krimihara Chikitsa* is useful to prevent the spread of disease. When we analyze the *Ayurvedic* literature the concept of *Rakataja Krimi* can be compared with the pathogenesis of Mucormycosis.
3. *Shodhana* by *Shirovirechana* with *VidangaTaila*/*ShigruTaila* and *Vairechanika Dhooma* is highly effective.[12]
4. In case of eye involvement, eye drops prepared from *Tankana*, *Sphatika*, *Yashada*, *Panchavalkala* and *Shirisha* can be used effectively.
5. Use of *Yakritashodhaka* and *Raktaprasadaka* drugs are also necessary in treating this condition. As Liver is responsible for the production of immunoglobulins which are the main defense mechanism components of the body. The black fungus is considered under the *Raktaja Krimi*, and *Pupphusa* (lungs) are originated from *Rakta*, so *Raktaprasadaka* medicines are beneficial.
6. *Kapha Pitta Nashaka* and *Vata Avirodhi Chikitsa* is main line of management in Mucormycosis.

Management

Prevention

Favor

- Take *Gomutra Arka* 10-30ml 2 times on empty stomach
- Use *Neem, Guggulu, Karanja*, cow dung for fumigation of room

- Take nutritious food
- Wear mask in house
- Wash the mask every day , or use disposable masks
- Wear mask in house
- Maintain Blood Sugar Level.

Avoid

- Avoid excess of sour, salt and spicy substances.
- Avoid gardening and farm work upto 2-3 months after covid recovery. Fungal spores are richly present in soil
- Avoid fatty, heavy, curd, acidic foods (such as cabbage, cauli flower, beans, palak, mashroom etc.)

Recommended Formulations

Following medicines can be used according to the *Dosha Vikalpa* and *Rogi Bala* in Mucormycosis-

i. *Panchanimba Gulika* 500mg to1gm TID/*Panchanimba Churna* 3-6gm TID
ii. *Gandhaka Rasayana* 500mg to1gm TID
iii. *Madhusnuhi Rasayana* 6-12gm TID
iv. *Amrita Bhallataka Leha*6-12gm TID
v. *Talakeshwara Rasa* 125mg to 250mg TID
vi. *Rasamanikya* 50 to150mg TID
vii. *Talasindhura* 30mg-125mg TID
viii. *Mallasindhura* 30mg-65mg TID
ix. Cap Pentaphyte P-5 1-2 Caps TID[13]

Research Evidence on Antifungal preparations:

A review article has been published on medicinal plants having antifungal activities – It is concluded that the drugs like *Neem, Vasa, Vacha, Yastimadhu, Haridra* etc. are having potent antimicrobial and antifungal activity. [14]

Another study has been conducted on 14 Indian plants, selected based on their use in respiratory and other disorders in traditional systems of medicine, were analyzed for their potential activity against fungi. The antifungal activity was investigated by disc diffusion, microbroth dilution and percent spore germination inhibition tests against pathogenic *Aspergilli*. Results revealed that *Dattura metel* and *Solanum xanthocarpum* had significant activity against fungal infections.[15]

Medicinal Gargling with *Triphala Kvatha*[16, 17] or *Panchavalkal Kashaya* has significant effect against fungal infections. Triphala extract demonstrated antimicrobial property against *Lactobacilli* and *C. albicans* with maximum zone of inhibition of 22 mm at 6% and 20 mm at 9%[18].

Gandhaka Rasayana solution in higher concentration showed similar anti fungal activity compared to Fluconazole against *Candida albicans* and *Cryptococcus neoformans*, but it was more significant against *Trycophytum rubrum* and *Aspergillus Niger* than Fluconazole[19].

From the study results, we conclude that efficiency of both medications are at a par, but TTO (Tea Tree Oil), being nontoxic, economical, and compliable, remains a better alternative to allopathy in the treatment of oral fungal infections.

Cumin and fennel essential oils could be used as alternatives to conventional antifungal drugs for treating edentulous patients with oral candidiasis.

Use of Rasayana (Immunomodulators):

As Post Covid complications are common in patients with Post-steroid therapy, Immuno-compromised conditions, patients with Diabetes, chronic respiratory diseases etc. So Use of *Rasayana* drugs like *Amalaki*, *Guduchi*, *Vasa*, *Pippali*, *Ashwagandha*, *Haridra* etc. is beneficial to prevent the associated complications. As *Rasayana* drugs are helpful to repair the lung parenchyma and they will enhance the qualitative and quantitative production of T cells.

Common preparations which acts as Respiratory Immunomodulators are:

a. *Mahalaxmi Vilasa Rasa*
b. *Chyavanprasha Leha*
c. *Pippali Vardhamana Rasayana*
d. *Agastya Haritaki Rasayana*
e. *Amalaki Rasayana*

Treatment Protocol for mild cases

1. *Tab Panchanimba Gulika 2 BD*
2. *Tab Gandhaka Rasayana 500mg TID*
3. *Arogyavardhini Vati 500mg TID*
4. *Nasya* with *Vidanga Taila* or *Shigru Taila* if the condition is fit for *Shirovirechana.*

Note: In COVID recovering patients, refer the COVID 19 management protocol- http://jahm.co.in/index.php/jahm/article/view/419.[20]

Treatment Protocol for moderate and severe cases

1. *Tab Gandhaka Rasayana* 500mg-1gm TID
2. *Arogyavardhini Vati* 500mg TID
3. *Panchanimbadi Churna* 3gm+ *Talasindhoora* 125mg + *Chakramarda Churna*- 2gm +*Trivanga Bhasma* 100mg + *Shuddha Shilajatu* 200mg + *Trikatu Churna* 500mg - 6gm TID
4. *Tab Gomutraharitaki* 2 BD
5. *Nasya* with *Vidanga Taila* or *Shigru Taila* if the condition is fit for *Shirovirechana.*

Note: In COVID recovering patients, refer the COVID 19 management protocol- http://jahm.co.in/index.php/jahm/article/view/419.[20]

CONCLUSION

Ayurveda definitely offer evidence based treatment protocol for the effective management of mucormycosis. I strongly recommend the AYUSH Dept. to implement the *Ayurvedic* management either alone or along with conventional medicine.

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