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The Pivotal Role of Clinical Pharmacist in Management of Mucormycosis

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Abstract: Mucormycosis, or zygomycotic or black fungus, is a fungal infection caused by a group of molds called mucoromycetes. It is the third most common invasive fungal disease after candidiasis and aspergillosis. Mainly caused by contact in the environment with fungal spores. Types of mucormycosis are Disseminated Mucormycosis, Pulmonary (lung) mucormycosis, Rhino cerebral (sinus and brain) Mucormycosis, Cutaneous (skin) Mucormycosis, Gastrointestinal Mucormycosis, Diagnosis mainly depends on biopsy, histological examination, CT scan, or MRI. Early diagnosis, complete removal of infected tissues, and early administration of active antifungal agents allow us to treat Mucormycosis by using different adjunctive therapies. In the pandemic of COVID due to exposure to various irrational and immunosuppressant's, Mucormycosis cases are in great extent, and due to this, the main role of the clinical pharmacist is to maintain drug therapy through medication therapy management, which involves drug dosing regimens and the correlation of drug therapy with other risk factors. This review highlights the indispensable role that clinical pharmacists play in the early diagnosis, treatment, and overall management of mucormycosis, with a focus on rhino-cerebral mucormycosis.

Keywords: Mucormycosis, fungal infection, diagnosis, treatment, clinical pharmacist.

Review Paper

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1. INTRODUCTION

Mucormycosis (zygomycosis) is a fungal infection caused by a group of molds called mucoromycetes. It is the third most common invasive fungal disease, coming after candidiasis and aspergillosis infection. Mucormycosis is mainly caused by contact with the fungal spores in the environment. For example, Pulmonary (lung) mucormycosis or sinus type of infection, is mainly caused by the inhalation of spores. While low immunity or patients on immusuppresrent are play an important role.

The fungi responsible for causing Mucormycosis are Mucor species, Rhizopus species, Lichtheimia (formerly Absidia) species, Apophysomyces species, Cunninghamellaberthollетiae, Syncephalastrum species, and Rhizomucor species.

Cutaneous (skin) mucormycosis, Gastrointestinal mucormycosis, Pulmonary (lung) mucormycosis, Rhinocerebral (sinus and brain) mucormycosis, disseminated mucormycosis are the major types of mucomycosis.

50% of the total cases of mucormycosis are Rhino- cerebral Mucormycosis, while 50% of cases occur in patients with diabetes mellitus.

There is disruption of host defense mechanisms in diabetic ketoacidosis, allowing the growth of Rhizopusoryzae. While its growth is inhibited by the correction of acidosis,

The main clinical features are facial pain, epistaxis, nasal stiffness, ophthalmoplegia, chemosis, proptosis, and chemosis. Fever, confusion, black necrotic lesions on the palate, or nasal turbinates.

Jugular vein or carotid artery thrombosis causing hemiparesis, frontal lobe abscess, visual loss, multiple cranial nerve palsies, and cavernous sinus thrombosis are the main complications of mucormycosis.

The diagnosis of mucormycosis can be carried out by a biopsy of the lesion followed by fungal stains and culture. Histological examination reveals the characteristic broad, branching hyphae of Rhizopus invading the tissue, and CT or MRI of the head reveal air-fluid levels in the sinuses and involvement of deep tissues.

The risk factors for mucormycosis are multiple transfusions, malnutrition, neonatal prematurity, on deferoxamine therapy, metabolic acidosis, uncontrolled diabetes mellitus with ketoacidosis, rheumatologic diseases, high-dose corticosteroids and immunosuppression, solid organ transplantation, solid organ malignancies, hematopoietic stem cell transplantation (HSTC), hematologic malignancies, and prophylaxis with voriconazole.

The spores enter the body by implantation in injured skin by trauma, burns, surgery, or percutaneous route by contaminated needles or catheters, ingestion of contaminated food, or inhalation.

The pathophysiology of mucormycosis is rapid growth rates in the setting of neutropenia and diabetic ketoacidosis, and hence acidity increases iron and hyperglycemia promotes organism growth. Angioinvasion is common, resulting in thrombus formation and tissue necrosis. Dead tissue nidus promotes additional growth. The surge of COVID-19 has notably increased mucormycosis cases, predominantly due to the excessive use of immunosuppressants, thereby spotlighting the clinical pharmacist's pivotal role in medication management and risk mitigation.

1.1. Treatment

The general principles of mucormycosis treatment are early diagnosis, early administration of active antifungal agents, reversal of the underlying factor, complete removal of all infected tissues, and use of various adjunctive therapies.

1.2. Primary antifungal therapy

- Liposomal amphotericin-B first line recommended agent 5-10mg/kg/day (intra cranial involvement 10 mg/kg /day)
- Inj. Amphotericin B lipid complex (5mg /kg/day)
- Amphoteracin B deoxycholate (1.0 – 1.5mg/kg/day)
- Fluconazole, voriconazole –no reliable activity,
- Itraconazole –basidia species
- Posaconazole 800 mg/day in 2or 4 divided doses, Isuvaconazole 200mg OD can also be used as first line therapy

1.3. Duration of treatment

- Highly individualized
- Near normalization of radiograph, negative, biopsy, specimens and cultures, recovery from immunosuppression.

1.4. Surgery

- Removal of necrotic tissue –increases penetration of antifungal
- Surrounding infected healthy-looking tissues should be removed

1.5. Salvage therapy

- If disease is refractory or intolerance towards previous antifungal therapy.
- Posaconazole 800 mg/day in 2or 4 divided doses
- Isuvaconazole 200mg OD
- Polyenes+posaconazole
- Lipid complex, liposomal, colbidal dispersion
- Polyenes +caspofungin

1.6. Adjunctive therapies

- Hyperbaric oxygen-100% O2 at 2atm pressure for 90 min twice day
- Nivolumab and IFNY
- VT- 1161(otesaconazole)-inhibits fungal CYP5
- Lovastatin
- Cytokine therapy in hematological malignancy-GCSF, granulocyte transfusion +/IFNY

1.7. Iron chelators –deferasirox

- Deferasirox therapy for Mucormycosis study
- First randomized trial for any treatment of Mucormycosis
- 45% (5) mortality at 30 days, 82% (9) mortality at 90 days
- Deferasirox cannot be recommended as part of an initial combination regimen for the treatment of Mucormycosis

2. DISCUSSION

The occurrence of Mucormycosis is rare in healthy individuals, while it most commonly occurs in immunocompromised individuals.

Factors such as uncontrolled immunosuppressive and corticosteroid therapy, DM with or without DKA, hematomalogical and other malignancies, prolonged neutropenia, organ transplantation, malnutrition, and open wounds following trauma. acquired immunodeficiency syndrome (AIDS), severe burns, intravenous drug abusers, deferoxamine or desferrioxamine therapy, iron overload or hemochromatosis, and voriconazole prophylaxis for transplant recipients.

Mucormycosis recovery mainly depends on early diagnosis and treatment. It has the potential to

spread throughout the body, and with this type of infection death is a possibility.

Several studies are available to explain that overuse of immunosuppressants or other drug abuse can cause mucormycosis. Providing the key role of the clinical pharmacist.

3. Role of Clinical Pharmacist

3.1. Dose adjustment

A clinical pharmacist plays an important role in adjusting the dose of corticosteroids in diabetic patients to normalize blood sugar levels. DM, with or without DKA, increases the risk of mucormycosis.

3.2. Antifungal

The formulations of Amphotericin B are not interchangeable, including the amphotericin B liposome, conventional amphotericin B, amphotericin B lipid complex, and amphotericin B cholesteryl sulfate complex. Confusing these formulations can cause subtherapeutic dosing and fatal overdose. Storage, preparation, and administration of amphotericin B products require careful consideration.

A. Inj Liposomal amphotericin B:

Test dose: Inj. Liposomal Amphotericin- B 1 vial (50 mg) to be diluted in 12 ml of the diluent and 0.25ml (1 mg) of solution made, to be mixed in 100ml Dextrose and to be infused in 30 minutes.

Observe for fever and reactions

Pre- Hydration: 500 mL NS over 30 minutes

To reduce the risk of renal toxicity and hypokalaemia:- 500ml Normal Saline + 1 Amp (20mmol) KCL

Therapeutic dose: 5mg-10 mg /kg/day Amphotericin B in 500 mL D5 with 10 Units HIR over 3 hrs (To be covered in black sheet)

Post- Hydration: 500 mL NS over 30 minutes

Post- Dose: •KFT with Serum electrolytes after Every dose of Amphotericin B

Fill Amphotericin monitoring chart.

B. Inj Amphotericin B Deoxycholate:

Test dose: 1 mg in 100 mL D5 over 20 minutes

Pre- Hydration: 500 mL NS over 30 minutes

Therapeutic dose: 1.0-1.5 mg/kg/day Amphotericin B in 500 mL D5 with 10 Units HIR over 3 hrs (To be covered in black sheet)

Post- Hydration: 500 mL NS over 30 minutes

Post- Dose: Urine output, Renal function Test (pH, Blood Urea, S. Creatinine, Electrolytes)

Fill Amphotericin monitoring chart

Amphotericin Chart (To be filled daily)							**Patient Name:**							
S: No	Name of drug	Date	Starting Time	Ending Time	Dose Given	Cumulative Dose	Serum Electrolytes					Premedications	complications	K^+ corrections
							Urea	Creatinine	Na^+	K^+	Mg^+			

3.3. Steroids

Irrational use of corticosteroids (prednisone treatment of >20mg/day) increases the risk of mucormycosis. The use of steroids should be individualized according to infections.

3.4. Patient counseling

Mucormycosis risk can be increased by the use of aluminum, iron overload, and deferoxamine.

Avoid self-medication

- The patient should be counseled about the use of amphotericin B.
- Amphotericin B may cause blurred vision, weight loss, malaise, diarrhea, vomiting, nausea, dyspepsia, thrombophlebitis, anaphylaxis, seizure, loss of appetite, tachypnea, or diplopia. Patients should be counseled to repot symptoms of hypotension, nephrotoxicity, cardiac dysrhythmia, thrombocytopenia, or anemia.

4. CONCLUSION

Mucormycosis is a serious invasive fungal infection and requires proper medication therapy with dose adjustments to minimize complications. Thus, it shows the key role and importance of clinical pharmacists in the management of mucormycoses.

Conflict of Interest: The author has no conflict of interest.

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