GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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Mucormycosis and role of clinical pharmacologist

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GSC Biological and Pharmaceutical Sciences, 2022, 19(03), 093–099

Publication history: Received on 26 November 2021; revised on 01 June 2022; accepted on 03 June 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.19.3.0344

Abstract

Mucormycosis (zygomycosis) is a fungal infection (serious but rare) caused by a group of molds called mucoromycetes and it is considered the third most common invasive fungal disease after candidiasis and aspergillosis (1) infection occurs by coming in contact with the fungal spores in the environment. There are several types such as Rhino cerebral (sinus and brain) Mucormycosis, Pulmonary (lung) mucormycosis, Gastrointestinal mucormycosis, Cutaneous (skin) Mucormycosis, Disseminated Mucormycosis. Diagnosis is done on the basis of biopsy, histological examination, CT scan or MRI.

With the help of Early diagnosis, Early administration of active antifungal agents, Reversal of underlying factor Complete removal of all infected tissues, use of various adjunctive therapies we can treat Mucormycosis.

In the era of Covid due to exposure of various immunosuppressant's Mucormycosis cases are hiked, and due to this there is key role of clinical pharmacologist to maintain drug therapy with accurate drug dosing regimen and correlate the drug therapy with other possible risk factors.

This review aims the detailed clinical information of Mucormycosis and Role of Clinical Pharmacologist in the management of Mucormycosis.

Keywords: Mucormycosis; Fungal infection; Diagnosis; Treatment; Clinical pharmacologist

1. Introduction

Mucormycosis (zygomycosis) is a fungal infection (serious but rare) caused by a group of molds called mucoromycetes and it is considered the third most common invasive fungal disease after candidiasis and aspergillosis infection occurs by coming in contact with the fungal spores in the environment. For example, the lung or sinus forms of the infection can occur after someone breathes in spores. These forms of Mucormycosis usually occur in people who have low immunity or on medication that lower the immunity. Fungus enters the skin through a cut, scrape, burn, or other type of skin trauma and causes Mucormycosis.

In this review we include information of Mucormycosis.

1.1. Types of fungi that most commonly cause Mucormycosis

- Rhizopus species
- Mucor species

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- Rhizomucor species
- Syncephalastrum species
- Cunninghamellaberthollетiae
- Apophysomyces species
- Lichtheimia (formerly Absidia) species

1.2. Types of mucormycosis

- Rhinocerebral (sinus and brain) mucormycosis
- Pulmonary (lung) mucormycosis
- Gastrointestinal mucormycosis
- Cutaneous (skin) mucormycosis
- Disseminated mucormycosis

2. Rhinocerbral Mucormycosis

- 50% of cases occur in patient with DM
- 50% of cases of total cases of mucormycosis

Usually occurs during an episode of DKA, with disruption of host defense mechanism, thereby permitting growth of Rhizopusoryzae. such growth is inhibited by correction of acidosis.

2.1. Clinical features

- Onset with nasal stuffiness, epistaxis and facial pain.
- Later, proptosis, chemosis, and ophthalmoplegia.
- Fever and confusion
- Black necrotic Escher on the nasal turbinates or palate; very characteristic

2.2. Complication

- Cavernous sinus thrombosis
- Multiple cranial nerve palsies
- Visual loss
- Frontal lobe abscess
- Carotid artery or jugular vein thrombosis causing hemi paresis

2.3. Diagnosis

- Punch biopsy of the lesion followed by fungal stains and culture
- Histological examination reveals the characteristic broad, branching hyphae of Rhizopus invading the tissue.
- CT or MRI of the head reveal air-fluid level in the sinuses and involvement of deep tissues

2.3.1. Pulmonary Mucormycosis

- Seen most commonly in neutropenia patients on chemotherapy, leukemia
- Dyspnea, cough and chest pain and fever
- Radiologically –consolidation, isolated masses, cavitation, wedge shaped infarcts.
- CT scan best method to detect the extent.

2.3.2. Cutaneous Mucormycosis

- Trauma is the predisposing factor
- Invasive locally
- May lead to necrotizing fascites& mortality up to 80%.
- Surgical debridement.

2.3.3. Gastrointesttnal Mucormycosis

- Rare, occurs in extremely malnourished, children.
- Stomach, colon and ileum are most commonly involved.
- Abdominal pain, nausea vomiting, may present as intraabdominal abscess, or perforation of the viscus. needs biopsy
- Prognosis very poor

2.3.4. Disseminated Mucormycosis

- Hematogenous
- Pulmonary Mucormycosis has highest incidence of dissemination
- Most common site of dissemination-brain spleen, heart, skin and other organs.
- Brain-100% other >90%

3. Epidemiology

The prevalence of Mucormycosis is lacking due to difficulties in clinical diagnosis. However, according to the current worldwide autopsy reports, it is the third most common cause of invasive fungal infections. Differences in the epidemiology of Mucormycosis seem to exist between developed and developing countries. While hematologic malignancies and hematopoietic stem cell transplantation (HSCT) are the leading causes of Mucormycosis in the developed countries, uncontrolled DM or trauma are the major causes in the developing countries, especially in India.

3.1. Risk Factors

- hematologic malignancies
- hematopoietic stem cell transplantation (HSTC)
- solid organ malignancies
- solid organ transplantation
- on high dose corticosteroids/immuno-suppression
- rheumatologic diseases
- uncontrolled diabetes mellitus with ketoacidosis
- metabolic acidosis
- on deferoxamine therapy
- multiple transfusions
- malnutrition, neonatal prematurity
- prophylaxis with voriconazole

3.2. Mode of Spread

The spores enter the body by

- inhalation
- ingestion of contaminated food
- implantation in injured skin by trauma/burns/surgery or percutaneous route by contaminated needles or catheters

3.3. Pathophysiology

- Rapid growth rates in the setting of neutropenia and diabetic ketoacidosis
- Acidity increases iron and hyperglycemia promotes organism growth
- Angioinvasion is common, resulting in thrombus formation and tissue necrosis
- Dead tissue nidus promotes additional growth

3.4. Treatment

3.4.1. General principles

- Early diagnosis (chamilos et al.)

- Early administration of active antifungal agents
- Reversal of underlying factor
- Complete removal of all infected tissues
- Use of various adjunctive therapies

3.5. Primary antifungal therapy

- liposomal amphotericin-B first line recommended agent
- fluconazole, voriconazole –no reliable activity,
- itraconazole –basidia species
- Posaconazole, isuvaconazole, can also be used as first line therapy

3.6. Liposomal amphotericin B

- 2016 ECIL& ESCMID/liposomal form as first line
- Can be given as 5mg /kg /day to 10mg /kg /day, if CNS involved
- Surgery + lip amp B increases survival rates and cure rates
- Use of amphotericin Deoxycholate is discouraged (ESCMID/ECMM)
- ABLC can also be used –if no CNS involvement(B)
- Alternate routes –ABLC aerolised with respigard 2 nebulizer, direct instillation of amphotericin B into pulmonary cavities or pleural space

3.7. Azoles

- Posaconazole 800 mg/day in 2or 4 divided doses –first line (SECMID/ECMM), salvage therapy (ECIL)
- Isuvaconazole (comely OA et al)-200mg OD. but VITAL study showed higher mortality rates and poor response

3.8. Duration of treatment

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

3.9. Surgery

- Removal of necrotic tissue –increases penetration of antifungal
- Lobectomy, pneumonectomy or wedge resection
- Surrounding infected healthy-looking tissues should be removed
- Groll A et al. mortality reduced by 79%

3.10. Salvage therapy

- If disease is refractory or intolerance towards previous antifungal therapy.
- Posaconazole(A)
- Polyenes+posaconazole (B)
- Lipid complex, liposomal, colbidal dispersion (b)
- Polyenes +caspofungin(c)

3.11. Adjunctive therapies

- Hyperbaric oxygen-100% O2 at 2atm pressure for 90 min twice day (c)
- Cytokine therapy in hematological malignancy-GCSF (A), granulocyte transfusion +/IFNY(C)
- Lovastatin
- VT- 1161(otesaconazole)-inhibits fungal CYP51
- Nivolumab and IFNY

3.12. Iron chelators –deferasirox

- Deferasirox -ambisome therapy for Mucormycosis (DEFEAT mucor) 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
- Hematological malignancy –ECIL-6and ESCMID/ECMM recommended against its use
- Ortho then hematological malignancy ESCMID/ECMM marginally supports its use (c)

4. Discussion

Mucormycosis is an extremely rare in healthy in- dividuals but several immunocompromised conditions predispose it.

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

Mucormycosis recovery depends greatly on early diagnosis and treatment. The infection has the potential to spread throughout the body. Death is a possibility with this type of severe infection.

4.1. Covid19

There are no specific studies till date that compared patients of mucor- mycosis in non-diabetic COVID-19 who did not receive steroids versus COVID-19 patients who received steroids and developed Mucormycosis; it is difficult to establish a promised relationship between COVID-19 and Mucormycosis in relation to corticosteroids.

Few studies show there is rise in Mucormycosis patients due to overuse of immunosuppressants and other drug abuse. With reference to this there is key role of clinical pharmacologist.

5. Role of Clinical Pharmacologist

5.1. Dose adjustment

Clinical pharmacologists are important role in the management of dose adjustment required in diabetic patient because during the administration of the steroid medication to cause increasing the blood sugar level. Presence of DM with or without DKA increasing the risk of contracting Mucormycosis & DM often associated increase the severity of COVID19. Deferasirox cannot be recommended as part of an initial combination regimen for the treatment of Mucormycosis

5.2. Antifungal

Amphotericin B formulation are not interchangeable ,including conventional amphotericin B, amphotericin B cholesteryl sulfate complex , amphotericin B lipid complex ,and amphotericin B liposome confusion between these product has led to fatal overdose as well as subtherapeutic dosing conventional formulation doses should not exceed 1.5 mg/kg/day , while lipid based products have much higher dosing recommendation .when communicating orders ,the institute for safe medication practice (ISMP)recommends the use of proprietary name (abelcet)(R) ,ambisome (R),amphotec (R) and inclusion of the indication ,mg per kg dose and final dosage calculation for the individual patient .extra precautionary measures are also recommended for the storage , preparation ,and administration of amphotericin B products.

Prior to administration administer an iv-test dose of 1mg in 20 ml OF D5W by slow infusion over 20 to 30 minutes. monitor and record temperature, pluse, respiratory and record temperature, pulse, respiratory rate, and blood pressure, pulse, respiratory rate, and blood pressure every 30 min for 2 to 4 hours.

5.3. Steroids

Prednisone treatment of >20mg /day or prior therapy with corticosteroids are risk factor in Mucormycosis. Depends on the infection should be steroid used.

5.4. Patient counseling

Avoid use of the iron overload & deferoxamine which are chelating both iron & aluminum increase the risk of Mucormycosis.

- Avoid self-medication
- Patient counseling with regard to amphotericin B
- This drug may cause weight loss, diarrhea, dyspepsia, loss of appetite, nausea, vomiting, malaise, thrombophlebitis, anaphylaxis, seizure, blurred vision, diplopia, or tachypnea instruct patient to repot sings/symptoms of cardiac dysrhythmia, hypotension, or nephrotoxicity. patient should report /symptoms of anemia or thrombocytopenia

6. Conclusion

Mucormycosis is serious fungal infection but with proper management of therapy and dose adjustment of medication it can cure with minimum complications thus its clearly shows the importance and key role of clinical pharmacologist in the treatment of Mucormycosis. Yet further studies with covid 19 patients are needed to be studied.

Compliance with ethical standards

Acknowledgments

I would like to express my very great appreciation to Mr. Visheveshwar Dharashive for his valuable and constructive suggestions during the planning and development of this review article work. His willingness to give his time so generously has been very much appreciated.

I would also like to thank the staff of the following organization for enabling me to visit their offices to observe their daily operations- Organization: Shivlingeshwar college of pharmacy latur, Maharashtra, India.

Disclosure of conflict of interest

No conflict of interest.

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