



## REVIEW ARTICLE

# Medical treatment options available for mucormycosis

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### ARTICLE INFO ABSTRACT



Received 15 September 2021;  
Revised 28 October 2021;  
Accepted 27 December 2021.

**Keywords:**  
Mucormycosis,  
Medical Treatment

**Introduction:** Mucormycosis is known as a rapidly progressive and invasive lethal fungal infection. The predisposing factors known to potentiate this fungal infection are diabetes mellitus, primary or secondary immunodeficiency, etc. The clinical presentation of these cases may vary from involvement of localized skin infection to disseminated systemic infection.

**Methods:** In this article, an attempt was made to review the therapeutic guidelines released by European Committee for Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI).

**Results:** In addition to this, efforts were made to briefly review the evidence available on various formulations of accepted treatment methods including Amphotericin B (AmB), Posaconazole (PSZ), and Isavuconazole (ISZ), and other newer anti-fungal agents such as Voriconazole (VCZ), Echinocandins, etc.

**Conclusions:** An attempt was also made to discuss the various drugs that can be used as a single agent or combinations considered to be synergistically active and beneficial for the treatment/ prophylaxis of Mucormycosis.

An official publication of Global Pharmacovigilance Society.

## Introduction

Mucormycosis is a fatal fungal infection (Gupta *et al.*, 2019). It is an angioinvasive fungal infection with a high prevalence in poor-resource settings (Gupta *et al.*, 2019; Honavar *et al.*, 2021). This fungal infection generally finds a suitable environment to grow in tropical countries and especially in India due to the high prevalence of Diabetes Mellitus (Gupta *et al.*, 2019). Other factors known to potentiate the growth of this fungus are immunodeficiency (either primary or secondary), stem cell and solid organ transplantation, solid organ and blood cancer, and use of drugs that suppress immunity such as corticosteroids and immunosuppressive drugs, and iron overload (Gupta *et al.*, 2019; Honavar *et al.*, 2021).

Mucormycosis term generally can be interchanged with zygomycosis. Mucormycosis depicts the infection caused by Mucorales. But zygomycosis represents a group of infections caused by Mucorales, Entomophthorales, and other fungi. The term is now an obsolete one due to phylogenetic reanalysis of the kingdom Fungi (Brunet *et al.*, 2020; Cornely *et al.*, 2019). Mucorales are saprophytes and their spores are present abundantly in nature. They can survive in dead material, air, soil, and food. In normal healthy individuals, they may live longer in a commensal relationship in nasal mucosa due to their low virulence potential (Sharma *et al.*, 2021).

Pathogenic mucormycosis is generally caused by *Rhizopus* spp, *Mucor* spp, and *Lichtheimia* spp. Also frequently by *Rhizomucor* spp, *Cunninghamella* spp, *Apophysomyces*



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Available online 1 December 2021

spp, and *Saksenaea* spp. It is important to know the epidemiology and prevalence of the strains involved in causing mucormycosis due to possible geographical variations (Cornely et al., 2019).

Mucormycosis can produce life-threatening invasive fungal disease (IFD). The invasion of the fungus may manifest into localized infection to disseminated one. Patients with Immunosuppression, hematopoietic stem cell transplantation, and hematological malignancy are more susceptible to developing pulmonary infection and other forms of disseminated diseases. Those with diabetes are more prone to a rhino-orbital-cerebral form of infection. Trauma patients may develop a cutaneous form of the infection. Other localized fungal infections such as gastrointestinal, endocarditis, osteoarticular or isolated cerebral infections are less frequent (Brunet et al., 2020; Sun et al., 2011)

The objective of this article is to discuss the medical treatment options available for Mucormycosis.

### Medical treatment options for Mucormycosis

Successful management of Mucormycosis demands quick diagnosis, understanding of predisposing factors and reversal of the same, excision of infected tissues through appropriate surgical procedures, and medical management using appropriate antifungal agents (Sun et al., 2011; Spellberg et al., 2005). Detailed discussions on options available for medical management are given below.

The in-vitro and clinical efficacy of the antifungals is established by EUCAST (European Committee for Antimicrobial Susceptibility Testing) or CLSI (Clinical and Laboratory Standards Institute) standards. According to this Amphotericin B (AmB), Posaconazole (PSZ), and Isavuconazole (ISZ) are shown to have in-vitro and clinical efficacy against Mucormycosis. But Voriconazole (VCZ) and Echinocandins were not efficient in this fungal infection.

Monotherapy was found to have superior results clinically when compared to the combined regimen. Combined drugs show better results In-vitro. But failed to replicate the same clinically. Adjuvant therapy, surgery, correction of underlying factors, and other aggressive steps may be considered based on clinical condition and expected prognosis of the disease. Mortality due to Mucormycosis remains as high as 32 to 70 % according to organ involvement (Honavar et al., 2021; Brunet et al., 2020; Cornely et al., 2019)

### Amphotericin B (AmB)

AmB is found to be effective in both in-vivo and in-vitro studies. Two types of AmB are widely used. Liposomal Amphotericin B (L-AmB) and Amphotericin B Deoxycholate (AmBd). Sufficient evidence is now available to show a higher safety profile of L-AmB for nephrotoxicity on comparing with AmBd. Due to this

reason, L-AmB is preferred as the first line of treatment for mucormycosis. Various types of Mucorales were isolated and more than 524 species were found to be sensitive to Amphotericin B with epidemiologic cutoff values (ECVs) of at least 97.5 % at 2 mg/mL for *L. corymbifera*, *M. circinelloides*, *R. microspores*. On the other hand, it was at 4mg/ml for *R. arrhizus*. In-vitro studies revealed the need for higher minimum inhibitory concentrations (MICs) for AmB for Mucorale clearance. Due to this reason, a high dose of AmB is given to clear Mucorales from tissues. It has been shown that L-AmB of dose 5-10 mg/kg/day is more effective when given for 1 month. Indications included mucormycosis involving lung, rhino-orbital-cerebral, and/or skin. Medical management was supplemented with surgery. While treating, one should watch for serum creatinine level and it may double in 40 %-60 % of patients. In such cases dose of L-AmB dose may be adjusted to 7.5 mg/kg/day, and further reduction may be considered to 5 mg/kg/day to avoid toxic effects due to the sustained higher serum creatinine level. The overall response rate may range from 36 % after treating for week 4. After treating for 12 weeks, it may raise to 45 %. The overall mortality may range from 38 % to 53 % (Chitasombat et al., 2016; Hamill et al., 2013).

### Posaconazole (PSZ)

Posaconazole is another antifungal that is found to be effective against a good number of Mucorales isolates. The in-vitro studies suggested that the median minimum inhibitory concentration for 131 species of Mucorales isolates was between 1.0 and 8.0 mg/mL. But some species required different MIC values. MIC for *L. corymbifera* is between 0.5–2 mg/mL, for *M. circinelloides* it is 0.5–32.0 mg/mL. For *Mucor racemosus* the MIC is 0.125–32.0 mg/mL. While testing in animals, it was found that Mucorales with higher MICs were found to be less responsive in preclinical models. When Monotherapy was compared with combined use, high-dose of PSZ was considered to have better efficacy than the use of L-AmB or caspofungin, or deferasirox with a regular dose of PSZ (Chitasombat et al., 2016; Moore et al., 2015).

Three types of PSZ formulations are available. Conventional oral formulations delayed-release oral formulation and an intravenous formulation. Frequent dosing is required for the conventional oral formulation of PSZ due to its low bioavailability. This aspect is corrected in a newly developed delayed-release formulation which is having improved bioavailability. Its pharmacokinetic profile is more consistent irrespective of gastric motility in gastric pH. The intravenous formulation is recently made available and its safety and efficacy are still under evaluation especially concerning the patients with compromised renal function (Chitasombat et al., 2016; Moore et al., 2015).

### Isavuconazole (ISZ)

ISZ is available as a conventional oral formulation and an intravenous formulation. ISZ is approved for the management of invasive mucormycosis. In-vitro sensitivity pattern for ISZ varies depending on the species of Mucorales. When compared to the MIC requirement, it was understood that ISZ is less potent than PSZ. ISZ needs to be given in two to four times higher MIC than PSZ to achieve better cure rates. When ISZ and L-AmB were evaluated in animal models infected with *Rhizopus*, they were found to have similar efficacy in clearing tissue fungal burden in lung and brain tissues. Also after exposing a higher dose of ISZ and L-AmB for 21 days, survival benefits in the same model is found to be comparable (Chitasombat et al., 2016; Ellsworth et al., 2020).

### First-line treatment

Liposomal formulation of Amphotericin B at dose  $\geq 5$  mg/kg is considered as the first-line treatment of mucormycosis. If needed, surgery may be indicated in addition based on the invasiveness of the fungal infection (Brunet et al., 2020; Chitasombat et al., 2016; Hamill et al., 2013).

As per the European Conference on Infections in Leukemia (ECIL) 2017 and the European Confederation of Medical Mycology (ECMM) 2019 guidelines (Brunet et al., 2020; Cornely et al., 2019; Tissot et al., 2017).

- Adults: L-AmB remains as the first-line treatment of Mucormycosis in adult patients especially if the central nervous system (CNS) is

involved. Amphotericin B lipid complex (ABLC), another lipid formulation, may be used if no central nervous system (CNS) involvement.

- Newborns and pediatric patients: Even in pediatric patients and newborns, L-AmB and ABLC are recommended as the first-line treatment.

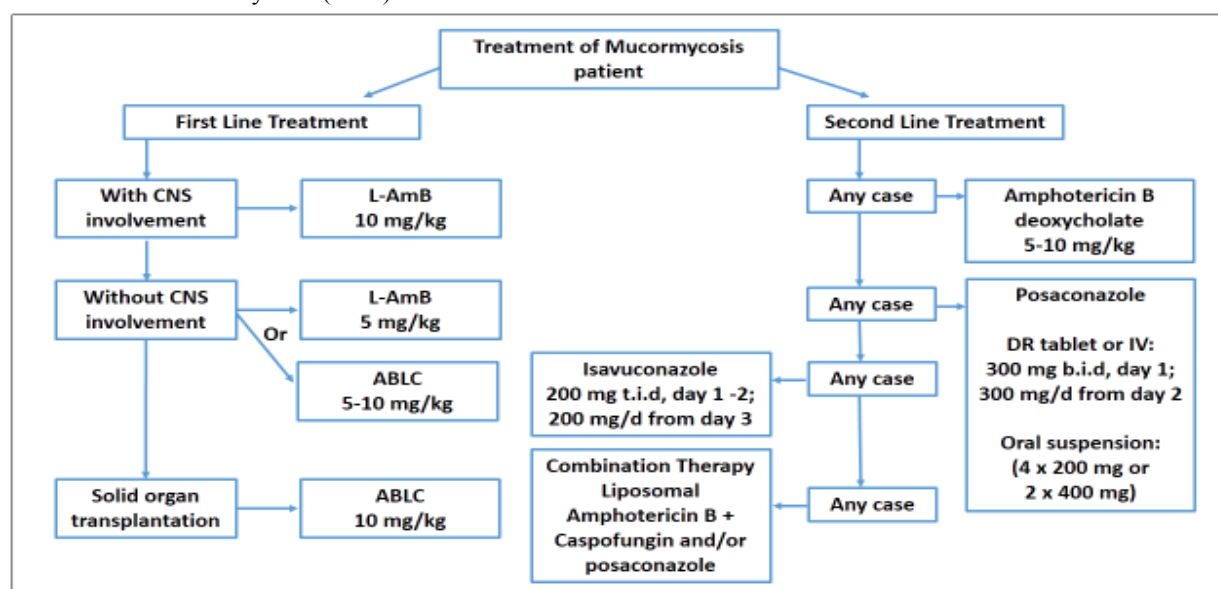
See **Figure 1** for detailed recommendations (based on poor to strong evidence-based recommendations).

### Second-line treatment

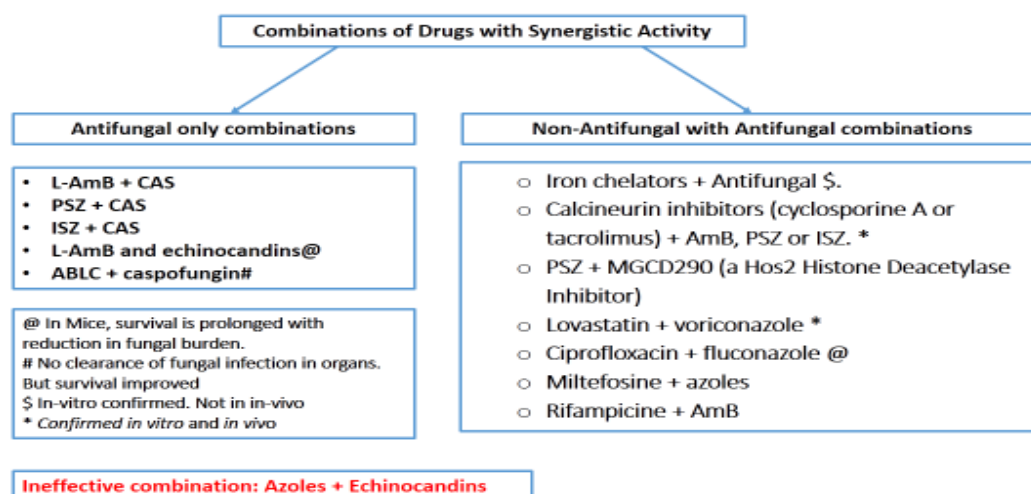
Select the most appropriate second-line treatment from the options given in **Figure 1** for treating mucormycosis. Either single-drug therapy method or combination of drugs used together method may be used based on clinician's decision. The drugs recommended are Amphotericin B deoxycholate, Isavuconazole oral tablets, Posaconazole intravenous injection or delayed-release tablet, and Combination Therapy including Liposomal Amphotericin B + Caspofungin and/or Posaconazole (Brunet et al., 2020; Cornely et al., 2019; Tissot et al., 2017; Schwarz et al., 2020).

### Combination of Drugs

The details of the drugs combinations found to be effective against mucormycosis are given in **Figure 2** (Brunet et al., 2020; Cornely et al., 2019; Tissot et al., 2017; Schwarz et al., 2020; Spellberg et al., 2012; Spellberg et al., 2012).



**Figure 1: Drugs and Doses for Mucormycosis**



**Figure 2: Drugs Combinations Effective Against Mucormycosis**

#### New Antifungals

Some new antifungal drugs are under clinical evaluation.

Some of them are also evaluated against Mucorales (see **Table 1** (Brunet *et al.*, 2020; Spellberg *et al.*, 2010; Spellberg *et al.*, 2009)).

**Table 1: Newer Antifungal drugs under evaluation against Mucormycosis**

| Sl No | Name of the Drug           | Class                                                                                                        | Important feature                                                                                                                                                                                                                                                                          |
|-------|----------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | Rezafungin                 | Echinocandin                                                                                                 | A newer member of this class. Not yet confirmed about its antifungal activity                                                                                                                                                                                                              |
| 2     | SCY-078                    | Inhibitor of Glucan synthase                                                                                 | It is a new subclass of drugs. None of the drugs from this class are proved to be active against Mucormycosis.                                                                                                                                                                             |
| 3     | Orolofin                   | Orotomides<br>(inhibitor of dihydro-orotate dehydrogenase (DHODH) - a key enzyme in pyrimidine biosynthesis) | The new antifungal drug is found to have poor activity against Mucormycosis.                                                                                                                                                                                                               |
| 4     | Enochleated Amphotericin B | A new oral formulation of Amphotericin B                                                                     | This oral formulation is expected to be well-tolerated and is still under trial. It is currently evaluated in cryptococcosis treatment (clinical trial NCT04031833). Not yet evaluated in Mucormycosis.                                                                                    |
| 5     | VT-1161                    | Inhibitor of fungal CYP 51                                                                                   | This is a new drug found to have <i>in-vitro</i> activity in the Mice <i>R. arrhizus</i> model having neutropenia. According to this evaluation, this drug is expected to be useful in curative or prophylactic treatment. It has been shown to prolong the survival of the infected mice. |

|   |                             |                                                                                                                                       |                                                                                                                                                                                                                                                   |
|---|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6 | SCH 42427                   | Broad-spectrum Triazole                                                                                                               | This drug is evaluated in the murine model and found to be effective.                                                                                                                                                                             |
| 7 | APX001A<br>(formerly E1210) | This molecule is targeted to act on Surface protein Gwt1 of the glycosyl phosphatidylinositol post-translational modification pathway | The antifungal activity of this molecule is considered to be as effective as Amphotericin B. Its protective effects are shown in mice in an <i>R. delamar</i> model. But the required minimum inhibitory concentration against Mucorales is high. |
| 8 | PC1244                      | Fungicidal Azole                                                                                                                      | This drug is evaluated in in-vitro against Mucorales and is found to be a long-acting antifungal drug with the minimum inhibitory concentration of 0.25 to 2 mg/L. Its in-vivo activity is not yet tested.                                        |
| 9 | Colistin                    | Antibiotic                                                                                                                            | Its antifungal activity is tested and found modest antifungal activity in both in-vitro and in-vivo models.                                                                                                                                       |

## Adjunctive Agents

### Iron chelators

Iron chelators are expected to reduce iron availability. By doing this, they will reduce fungal growth. Two drugs are found to be beneficial in the category. They are Deferiprone and Deferasirox.

When L-AmB is combined with Deferasirox, both are found to have a synergistic action. On the contrary, on comparing the mortality of patients with mucormycosis when treated with L-AmB alone Vs combined Deferasirox plus L-AmB, survival was found to be better in L-AmB alone arm.

When Deferasirox and L-AmB are given along with Micafungin as a triple therapy improved efficacy in antifungal activity was observed.

When Deferasirox was combined with PSZ, potentiation of antifungal activity is observed in the neutropenic mouse model (Brunet *et al.*, 2020; Sipsas *et al.*, 2018; Ibrahim *et al.*, 2008).

### Hyperbaric oxygen (HBO<sub>2</sub>) treatment

When antimicrobial drugs are combined with Hyperbaric oxygen (HBO<sub>2</sub>), they have been shown to have synergistic activity. Enhanced cellular immunity and the ability to repair tissue damage in infectious diseases may be the reason for this synergistic activity. However this is yet to be proved through a randomized clinical trial (Honavar *et al.*, 2021; Brunet *et al.*, 2020; Ferguson *et al.*, 1988).

### Adjunctive treatment

Patients suffering from Mucormycosis require a wholesome approach. The treating physician needs to do a quick global assessment and understand the general condition of the patient. Invasiveness of the fungal infection also needs to be assessed. Additional measures like the use of hyperbaric oxygen especially in diabetic patients should be considered. Surgical excision of the infected parts of the body needs to be done at the earliest to avoid further extension of the fungal infection. In addition, electrolyte balance, management of hyperglycemia, correction of ketoacidosis, especially in diabetic patients is very important. Generally,

fungal infections grow faster in immunocompromised patients. Therefore, it is important to optimize the use of corticosteroids and immunosuppressive drugs. Correction of neutropenia through use of hematopoietic growth factor, G-CSF is expected to improve the recovery. The physician should consider a complete assessment of the patient to bring the underlying disease and fungal invasion under control. Iron chelators may be avoided and considered only in suitable conditions (Brunet *et al.*, 2020; Spellberg *et al.*, 2012; Spellberg *et al.*, 2010; Spellberg *et al.*, 2009; Sipsas *et al.*, 2018; Ibrahim *et al.*, 2008; Ferguson *et al.*, 1988).

### New Therapeutic strategies under research

Research continues to identify innovative methods of drug delivery and therapeutic methods in Mucormycosis. Below mentioned three methods are considered promising for further development.

*Drug-loaded cells:* HL-60 Leukemia cell line-derived Neutrophil phenotypic cells loaded with PSZ are under development. This is a new strategy to reach infections site directly and deliver PSZ through drug-loaded cells.

**Antibodies acting synergistically to Antifungal drugs:** Research done in neutropenic and diabetic mice has shown to protect them from Mucormycosis when Anti-CoTH3 antibodies are used along with antifungal drugs. Anti-CoTH3 antibodies protected the mice synergistically on using along with antifungal drugs.

**Immune Serum to block Receptor:** Specific receptor interaction can be maximized to modulate the immune system and improve susceptibility to Mucormycosis. Modulation peptide-receptor interaction of GRP78 cells using GRP78-specific immune serum has been shown to protect diabetic mice from Mucormycosis (Brunet *et al.*,

2020; Spellberg *et al.*, 2012; Spellberg *et al.*, 2010; Spellberg *et al.*, 2009; Sipsas *et al.*, 2018; Ibrahim *et al.*, 2008; Ferguson *et al.*, 1988).

#### New routes of administration of AmB

Amphotericin B is the most preferred drug for Mucormycosis. Due to limitations posed by its adverse events, research is going on to develop new formulations to make it convenient to deliver this drug (Brunet *et al.*, 2020; Spellberg *et al.*, 2010; Spellberg *et al.*, 2009).

**Table 2** gives more details about the new formulations under evaluation.

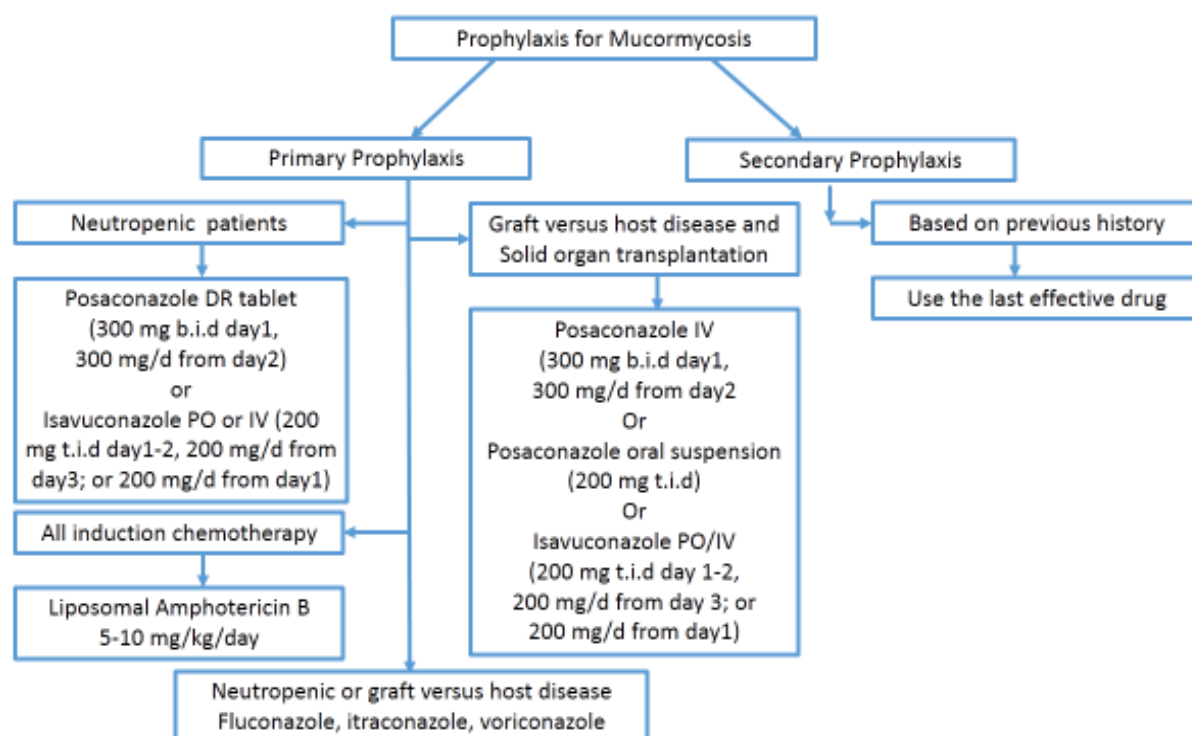
**Table 2: List of new Amphotericin B formulations under development**

| Sl No | Formulation          | Features                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | Nebulization         | Nebulization of AmB is expected to increase the lung concentration locally. This intrapulmonary drug delivery bypasses systemic passage and a lower dose helps to achieve better concentration in the lungs.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 2     | Aerosol              | Aerosol of L-AmB is considered to be effective in decreasing fungal burden. It is also expected to improve survival on administration from day 1 to 5. Further studies are expected to provide more evidence on the efficacy of aerosol alone or in combination with systemic treatment.                                                                                                                                                                                                                                                                                                                                                                                                           |
| 3     | Topical AmB for skin | Topical formulations are especially useful in patients with burns. There are several formulations are under consideration. Skin washes, pre-medicated dressings like 5% sulfamylon – AmB 2 mg/mL.<br><br>Topical infusion through skin dressings using 1 liter of sterile water with 50 mg L-AmB<br><br>Skin soaks or gauze soaked in AmB 0.2 % solutions<br><br>Nanoemulsion of AmB containing surfactant is expected to disrupt the microbial membranes mechanically. An example of Nanoemulsion is NB-201, which is having refined soybean oil, water, glycerol, EDTA, Tween 20, and the surfactant benzalkonium chloride.<br><br>Percutaneous injection of AmB is useful in cutaneous lesions. |
| 4     | Eye Drops of AmB     | Useful in Fungal infection of the cornea.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 5     | Oral AmB             | Useful in infection of parts of Gastrointestinal system.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 6     | AmB Cement beads     | Cement beads incorporated with AmB for Intra diaphyseal implantation is useful in bone marrow infections and osteomyelitis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 7     | AmB intrathecal      | Useful in the treatment of cerebral abscesses due to fungal infections                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

#### Prophylaxis

The details of the drugs suggested for preventing mucormycosis in special conditions are given in **Figure 3**

(Brunet *et al.*, 2020; Gebremariam *et al.*, 2017; Skiada *et al.*, 2020).



**Figure 3: Drugs for Prophylaxis Against Mucormycosis**

## Conclusions

Mucormycosis is a quickly progressing invasive fungal disease. AmB remains the main drug in the management of this disease and should be initiated as early as possible after the diagnosis. Delay in the initiation of treatment of more than 6 days after diagnosis of Mucormycosis may double the risk of mortality at 12 weeks. Surgical excision of the infected parts at the earliest plays a very important role in saving the life of the patient. Involvement of multiple medical and surgical specialties is a very important requirement and all the required professionals should be involved at the earliest. The integrated approach is required to save the patient's vital organs. Early rehabilitation can reduce inconvenience to the patient. Risk factors should be reversed at the earliest. Consider reduction of hyperglycemia and ketoacidosis, reduction of corticosteroids use, reversal of immunosuppression, reduction of zinc and iron concentrations.

Optimal use of a combination of drugs and newer formulations/newer routes of administration of the drugs should be considered. Many drugs are under development. Further research should continue and guidelines should be revised from time to time to ensure the quality of life is improved with the addition of years to the lives of those patients who survived from Mucormycosis.

## Acknowledgments

We acknowledge the support extended by CDSIMER, Harohalli management, and staff of the Pharmacology department.

## Funding

Nil

## Conflict of interest

None.

## Ethical approval

Not applicable

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