



Pharmacotherapy of Rhino-orbital- Cerebral Mucormycosis

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Received: 06-07-2021; Revised: 18-09-2021; Accepted: 25-09-2021; Published on: 15-10-2021.

ABSTRACT

The aim of this study is Recently there is an alarming increase in the incidence of mucormycosis in patients diagnosed with Covid -19. In this short review, we will discuss the basic principles of mucormycosis treatment, antifungal agents used along with update on pharmacotherapeutic guidelines recommended for management of mucormycosis. Searching the Pubmed with the key words "mucormycosis and covid 19", " Treatment of mucormycosis", " antifungal used in Mucormycosis revealed many articles, and the relevant articles were screened. Mucormycosis is an aggressive disease which is difficult to diagnose in early stage with high morbidity and mortality. Multimodal therapeutic approach consisting of early diagnosis, urgent surgical and medical intervention and elimination of predisposing factors is key to successful management of this condition. First-line antifungal agent is high-dose liposomal amphotericin B although amphotericin B deoxycholate may be the viable option in resource limited settings.

Keywords: Mucormycosis; COVID-19; Amphotericin B; Posaconazole; Pharmacotherapy.

QUICK RESPONSE CODE →

DOI:

10.47583/ijpsrr.2021.v70i02.007



DOI link: <http://dx.doi.org/10.47583/ijpsrr.2021.v70i02.007>

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported from Wuhan, China in December 2019 and eventually affected all the other parts of the world leading to global pandemic.¹ The clinical spectrum of COVID-19 infection can range from asymptomatic disease to life-threatening severe acute respiratory syndrome.² High risk category patients having associated comorbidities like diabetes mellitus, chronic obstructive pulmonary disease, post-transplant/malignancy are more susceptible to develop severe opportunistic infections. Certain predisposing factors like corticosteroid therapy, prolong use of ventilation, intensive care unit stay, recent use of voriconazole therapy have increased the risk of opportunistic infection in the patients. There are reports of oropharyngeal candidiasis, pulmonary aspergillosis, pneumocystis jiroveci pneumonia, rhino-orbital mucormycosis and systemic candida infections in patients affected with COVID-19 disease.^{3,4} Recently there are reports of increasing cases of rhino-orbital-cerebral mucormycosis in patient with second wave covid -19 disease in India leading to increased morbidity and mortality.

In this article, we will discuss the basic principles of mucormycosis treatment, antifungal agents used along

with recent pharmacotherapeutic guidelines recommended for management of mucormycosis.

Basic Principles of Treatment of Mucormycosis

The therapeutic approach to mucormycosis is multimodal. The four basic principles of mucormycosis management are early diagnosis, prompt initiation of an effective antifungal therapy, surgical debridement of necrotic lesions and elimination of predisposing factors.

Early diagnosis and prompt therapeutic intervention of mucormycosis is critical for improving the prognosis.⁵ Aggressive surgical debridement of involved tissues is an independent variable for favourable outcome in mucormycosis patients.⁶ Blood vessel thrombosis and extensive tissue necrosis during mucormycosis can hinder the penetration of antifungal agents to the site of infection.⁷ Therefore, adequate surgical debridement is indispensable for complete eradication of mucormycosis.⁸

Elimination of underlying predisposing factors is critical in mucormycosis. Correction of metabolic abnormalities and hyperglycemia in diabetics, reduction of neutropenia, discontinuation of deferoxamine administration and modulation of corticosteroids and immunosuppressive drugs is required.⁸

Antifungal Therapy

Prompt initiation of antifungal therapy improves the outcome of infection with mucormycosis. A study demonstrated that delay of ≥ 6 days of antifungal therapy resulted in an approximately 34% increase in mortality at 12 weeks after diagnosis.⁹ The antifungal agents effective against mucormycosis are amphotericin B, Isavuconazole and Posaconazole.



Current recommendations

The most recent guidelines for mucormycosis management was given by European Conference on Infections in Leukemia (ECIL) in 2017 and the European

Confederation of Medical Mycology (ECMM) provided an update in 2019.^{10,11} The recommendation regarding antifungal therapy in these guidelines are summarised in figure 1.

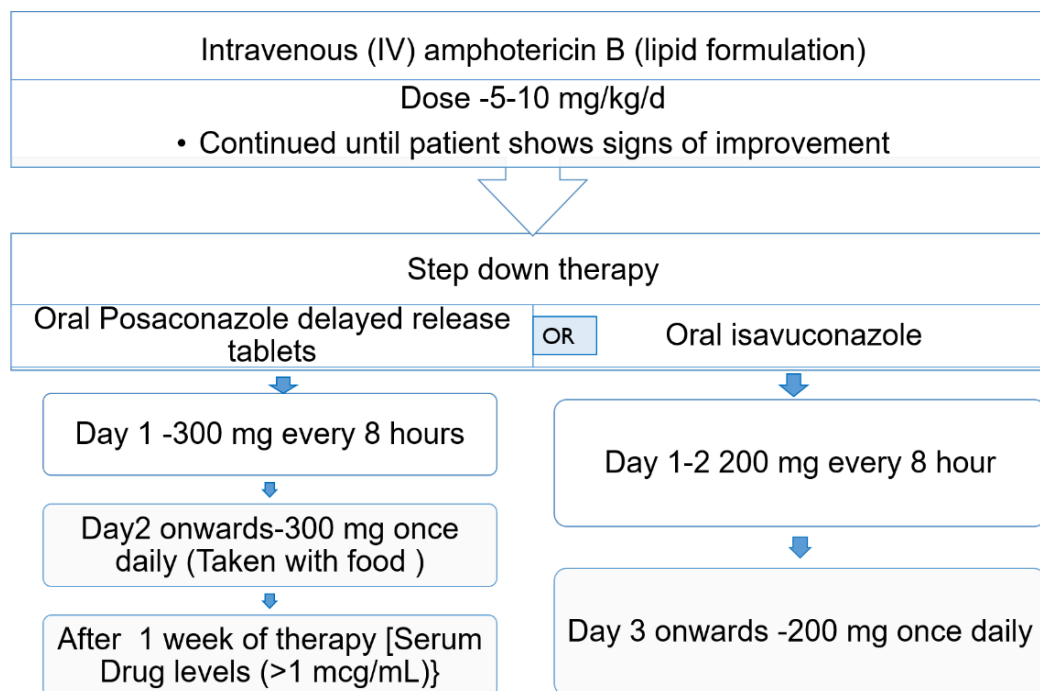


Figure 1: Summary of Pharmacotherapy of Mucormycosis

Initial therapy

Both the societies have recommended Amphotericin B (AmB) as drug of choice for initial therapy of mucormycosis. Lipid formulation of amphotericin B is preferred formulation as it facilitates the delivery of high dose with less nephrotoxicity. The usual starting dose of liposomal amphotericin B or amphotericin B lipid complex is 5 mg/kg daily and can be increased as high as 10 mg/kg daily in an attempt to control this infection. Amphotericin B is continued usually for several weeks until the patient shows signs of clinical and radiological improvement.

Step down therapy

The posaconazole or isavuconazole are recommended as stepdown therapy after response has been achieved with AmB.

When using posaconazole, delayed-release tablets are preferred over oral suspension, as they have more reliable absorption independent of gastric pH with fewer drug-drug interactions.¹² The dose of posaconazole is 300 mg every 12 hours on the first day followed by 300 mg once daily, taken preferably with food. Therapeutic drug monitoring (TDM) of posaconazole is recommended, serum trough concentration should be estimated after one week of therapy with a goal trough concentration >1 mcg/mL.¹³

When switching to oral isavuconazole, loading doses are required for first two days. Initial dosing is isavuconazole 200 mg (isavuconazonium sulfate 372 mg) every 8 hours for 2 days, followed by maintenance with 200 mg orally once daily.

Salvage therapy

Salvage therapy is indicated for patients who do not respond to or cannot tolerate amphotericin B. Both intravenous (IV) and oral formulation of posaconazole or isavuconazole can be used for salvage therapy.

Duration of Therapy

The duration of antifungal therapy is not clearly defined and is highly personalized to the clinical circumstances of patient. The antifungal treatment should continue until there is clinical resolution of associated symptoms, as well as resolution of radiographic signs of active disease.¹⁰ Duration of therapy often ranges from months to years, course of amphotericin B typically last 4-6 weeks and primary or salvage isavuconazole therapy may be continued for several months.

Drug Information

Polyenes (amphotericin formulations) and triazoles (isavuconazole and posaconazole) are two main classes of antifungal medications used to treat mucormycosis. Table 1 summarises the characteristic of antifungal drugs used in mucormycosis.

Table 1: Antifungal drugs used in mucormycosis

Agent	Antifungal activity	Formulation and dosage	Dosage	Adverse effect	Monitoring of therapy	Interaction	Approximate cost of treatment per day
Amphotericin B (AmB-D)	Fungicidal	AmB – deoxycholate (AmB-D):	IV 0.5–1 mg/kg/d	Infusion reactions, Phlebitis, Acute kidney injury, Electrolyte imbalance, Hypokalemia and Hypomagnesemia, Anemia	Temperature, input and output, Signs of hypokalemia, Renal functions and electrolytes (Cr, Na, K, Mg) CBC, LFTs at baseline, ECG monitoring if electrolyte disturbances present (hypokalemia	Increased nephrotoxicity with other nephrotoxic agents	Rs 300-34000 (depending upon type of drug formulation)
		Liposomal (AmB) - (L-Amp B):	IV 5–10 mg/kg/d				
		AmB colloidal dispersion (ABCD):	IV 5–10 mg/kg/d				
		AmB lipid complex (ABLC):	IV 5–10 mg/kg/d				
Posaconazole	Fungistatic	Oral suspension	Day 1-200 mg four times daily, followed by 400 mg twice daily	Nausea, vomiting, diarrhea, and headache QTc prolongation Hepatotoxicity	Hepatic function, Renal function, especially in patients on IV therapy if eGFR <50 ml/minute/1.73 m ² ; serum electrolytes (eg, calcium, magnesium, sodium, potassium) Therapeutic drug monitoring	CYP450 interactions Cause QTc prolongation	Rs 36000
		Delayed-release tablets:	Day 1- 300 mg twice daily, followed by 300 mg daily				Rs 1600
		IV formulation :	Same as DR tablets				Rs 4100
Isavuconazole	Fungistatic	IV formulation	First 48 hours: isavuconazole 200 mg (isavuconazonium sulfate 372 mg) every 8 h, followed by 200 mg once daily Same as IV	Nausea, vomiting, diarrhea, headache, and rash Edema, hypokalemia Hepatotoxicity Shortened QTc interval Infusion reactions	Hypersensitivity reactions Hepatic function	CYP450 interactions	Rs 8500
		Oral tablets	Same as IV				Rs 43000

Amphotericin B

Amphotericin B (AmB) is the most active drug in vitro against Mucorales and is therefore drug of choice for initial therapy.¹⁴ Amphotericin B exerts its fungicidal effect by binding to ergosterol and causing disruption in fungal cell wall leading leakage of cellular components. This affinity to ergosterol may also account for its toxic effects against select human cells.

Conventional form of Amphotericin B is AmB deoxycholate (AmB-D), which is still most affordable agent available for

the treatment of mucormycosis. Though, safety concerns are the major limiting factors for its use.

Method of administration

IV infusions are prepared by combining 5 percent dextrose in water (D5W) with amphotericin B at a final concentration of 0.1 mg/mL. Amphotericin B should be administered by intravenous infusion over four to six hours depending on the patient tolerability. The constituted solution for IV infusion should be protected from light during administration. Shorter time periods (eg, 45 to 60 minutes), for infusion is not recommended due to frequent



infusion-related reactions. (such as fever) may be more frequent.¹⁵ Direct or local instillation of amphotericin B deoxycholate has been used in several clinical circumstances.¹⁶

Pharmacokinetics

The drug is poorly absorbed orally hence requires intravenous (IV) administration. The drug is highly protein bound (up to 95 percent), primarily to lipoproteins. Its volume of distribution is approximately 4 L/kg representing its extensive distribution in body. Drug elimination is biphasic, with a terminal half-life of up to 15 days. The primary route of elimination of amphotericin B is not known. Hepatic or renal impairment doesn't influence the plasma amphotericin levels.

Adverse effects

Infusion-related reactions like nausea, vomiting, chills, and rigors, are common with IV amphotericin B deoxycholate administration, usually occurring either during infusion (within 15 minutes to 3 hours following initiation) or immediately following administration of the dose. Phlebitis is a complication that primarily occurs in patients receiving infusions via a small peripheral vein. Drug-induced fever, chills, and headache can also be seen. These symptoms can be minimized or prevented by premedication with acetaminophen (650 to 1000 mg) and/or diphenhydramine (25 to 50 mg).

Nephrotoxicity can occur in upto 80 percent of patients. It can manifest commonly as reversible and often transient decline in glomerular filtration rate (GFR) resulting in increased serum creatinine concentration. Risk of severe renal failure increase with diuretic-induced volume

depletion or the concurrent administration of another nephrotoxin. Amphotericin B deoxycholate is substantially more nephrotoxic than the lipid-based formulations of amphotericin B. Sodium loading i.e . administration of 1 L of normal saline intravenously may ameliorate the decline in GFR and therefore recommended for adults who are able to tolerate the Na⁺ load. Increase in distal tubular membrane permeability following amphotericin B administration lead to electrolyte abnormalities like Hypokalemia, hypomagnesemia, and hyperchloremic acidosis. A reversible, normochromic, normocytic anemia occurs in most patients receiving IV amphotericin B, but the onset may be delayed for as long as 10 weeks after the initiation of therapy.

Patient monitoring

Patients receiving amphotericin B should be monitored closely for infusion-related reactions. Measurements of renal function should be performed daily during initiation of therapy (up to two weeks) and at least weekly thereafter. In case, the plasma creatinine concentration exceeds 2.5 mg/dL, Amphotericin B administration should be withheld or substituted with lipid formulation. Serum electrolytes (potassium and magnesium) should be assessed at baseline and at least twice weekly throughout therapy. Complete blood counts should be measured weekly throughout therapy.

Lipid formulations of Amphotericin B

Lipid formulations of AmB were developed to reduce the toxicity associated with AmB-D. Table 2 compares four different formulations of amphotericin B that are available in market.

Table 2: Comparative features of different formulation of Amphotericin B

	Shape & Size of lipid preparation (µm)	Dose (mg/kg)	Blood levels (compared to AmB-D)	Nephrotoxicity	Infusion related reaction	Approximate cost per day (Rs)
L-AMB	Unilaminar 0.08	3-5	↑↑	±	+	31,000
ABCD	Disk-like 0.12-0.14	3-4	↓	±	++	18,000
ABLC	Ribbon like 1.6-11	5	↓	±	++	34,000
AMB-D	Micelles <0.4	0.5-1	-	+++	++++	300

Amphotericin B colloidal dispersion (ABCD)

It contains disc like structures equimolar amounts of amphotericin B and cholesteryl sulfate. ABCD is less nephrotoxic than C-AMB but cause more fever and chills.¹⁷

Liposomal amphotericin B (L-AMB)

It encompasses AmB within small, unilamellar spherical liposomes. Since L-AMB can be given at higher doses, higher blood levels can be achieved as compared to AmB-D.¹⁸

AmB lipid complex (ABLC)

It is composed of large ribbon like complexes of two phospholipids. Blood levels of amphotericin B are much lower with ABLC than with the same dose of C-AMB.

The efficacy of lipid formulations of AmB appears to be comparable but they are substantially less nephrotoxic than amphotericin B deoxycholate.¹⁹ The use of lipid formulation AmB allows for prolonged therapy and higher daily doses with less toxicity.

Posaconazole

Posaconazole is a synthetic structural analogue of itraconazole. It acts by inhibition of sterol 14- α -demethylase causing impairment in biosynthesis of ergosterol and thereby leading to growth arrest.

Pharmacokinetics

Posaconazole is available as a flavored suspension containing 40 mg/mL. Oral suspension requires oral intake with a high-fat meal for effective absorption may be impaired in the cases of gastrointestinal tract disruption.^{20,21} The drug has a long half-life (25–31 h), a large volume of distribution and extensive protein binding. Renal impairment does not alter plasma concentrations but hepatic impairment causes a modest increase in the drug concentration. Posaconazole is primarily metabolized via UDP glucuronosyltransferase and is a substrate of P glycoprotein (P-gp) efflux. Delayed released tablet and intravenous (IV) solution rectify the pharmacokinetic disadvantage associated with use of oral solution. The advantages of the tablet and IV formulation over the suspension include better bioavailability allowing once-daily dosage, no food requirements, absorption unaffected by changes in gastric pH or motility; less interpatient variability and more predictable plasma concentrations than the suspension.²² IV formulation contains betadex sulfobutyl ether sodium (SBECD) vehicle which can accumulate in patients with moderate or severe renal and therefore avoided in these patients. Posaconazole is a potent inhibitor of CYP3A4.

Dosage

The intravenous dose is 300 mg twice on day 1 and 300 mg daily thereafter. The same dose is used for the delayed-release tablets. The dose for the oral suspension is 200 mg (5 mL) three times daily.

Method of administration

Suspension should be shake well before use and administered within 20 minutes following a full meal or an acidic carbonated beverage. Delayed-release tablet should be swallowed as a whole tablet preferably with food. Intravenous injection should infuse over 90 minutes.

Adverse Effects

Thrombophlebitis can occur in up to 60% patient with IV administration. Other common adverse effects include rash, pruritus, Gastrointestinal intolerance like nausea, diarrhoea, vomiting and hepatic enzyme elevation.

Drug Interactions

Drugs that reduce gastric acid like cimetidine and esomeprazole decrease posaconazole exposure by 32%–50%. Coadministration with rifabutin or phenytoin increases the plasma concentration of these drugs and decreases posaconazole exposure by 2-fold.¹⁶ Posaconazole increases the plasma levels of CYP3A4 substrates like cyclosporine, tacrolimus, sirolimus,

midazolam etc.²¹ Posaconazole should not be coadministered with CYP3A4 substrates that prolong the QTc interval, such as methadone, haloperidol, quinidine, risperidone, tacrolimus, and halofantrine etc

Monitoring

Hepatic function test should be done prior to initiation and during treatment. Renal function test, especially in patients on IV therapy if eGFR <50 ml/minute/1.73 m² and serum electrolytes (eg, calcium, magnesium, sodium, potassium) should be done prior to initiation and during therapy. Routine therapeutic drug monitoring (TDM) is strongly recommended for patients treated by posaconazole.⁶ A serum trough posaconazole concentration of should be checked after steady state has been reached i.e after one week of therapy and concentrations of 1 mg/L or higher are recommended.

Isavuconazole

Isavuconazole is a novel triazole antifungal agent with mechanism of action similar to posaconazole but with additional pharmacokinetic advantages and broader spectrum of antifungal activity

Pharmacokinetics

It is available as an IV and oral formulation. It is formulated as the prodrug, isavuconazonium sulfate which is rapidly and almost completely converted to isavuconazole by plasma esterases. It is highly bioavailable (98%), is more than 99% protein bound and has a prolonged half-life of 130 hours, which enables once-daily dosing following loading dose for initial two days. Isavuconazole is eliminated by hepatic metabolism, predominantly by CYP3A4 and CYP3A5. No renal dose adjustments are needed.¹⁶

Dosage

Isavuconazole is dosed as 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 h for six doses followed by 372 mg isavuconazonium sulfate by mouth or intravenously once daily starting 12 to 24 h after the last loading dose.

Method of Administration

Intravenous formulation is infused over a minimum of 1 hour. Oral formulation can be administered as a whole without crushing with or without food.

Adverse Effects

Isavuconazole is generally well tolerated. Gastrointestinal disorders, pyrexia, hypokalemia, headache, constipation, and cough are the most frequently reported adverse effects.

Drug Interactions

Isavuconazole is both a substrate and an inhibitor of CYP3A4.¹⁶ CYP3A4 inhibitors or inducers may alter the plasma concentrations of isavuconazole. Coadministration with strong CYP inhibitors like



ketoconazole leads to increase in isavuconazole levels. Substantial reductions in isavuconazole levels occur with coadministration with CYP inducers like rifampin. Isavuconazole increases the plasma levels of CYP3A4 substrates like sirolimus and midazolam etc. Appropriate therapeutic drug monitoring and dose adjustment of immunosuppressants (i.e., tacrolimus, sirolimus, and cyclosporine) may be necessary when co-administered with isavuconazole. Importantly, isavuconazole does not appear to prolong QTc. Drugs with a narrow therapeutic window that are P-gp substrates, such as digoxin, may require dose adjustment when administered concomitantly with Isavuconazole.

Monitoring

Hypersensitivity reactions with initial doses should be monitored and LFTs at baseline and periodically during therapy.

Safety of Antifungals in Pregnancy and Lactation

Amphotericin B belongs to US FDA fetal risk category B. Hence it can be used if the potential benefit to the mother outweighs the potential risk to the fetus. Posaconazole and Isavuconazole belong to US FDA fetal risk category C and used only if the potential benefit to the patient outweighs the risk to the fetus.

CONCLUSIONS

Mucormycosis is an aggressive invasive fungal infection with high morbidity and mortality, particularly in patients with associated covid infections. High level of suspicion of infection is important, as early diagnosis and rapid initiation of surgical and antifungal therapy are key to improve survival. The basic principles of mucormycosis management are early diagnosis, prompt initiation of an effective antifungal therapy, surgical debridement of necrotic lesions and elimination of predisposing factors. The drug of choice for initial therapy of mucormycosis is a lipid formulation of amphotericin B. Amphotericin B is continued until the patient has shown signs of improvement which usually takes several weeks. Posaconazole or isavuconazole can be used for oral step-down therapy.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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