Review Article

Anti-fungal therapy: An overview for maxillofacial surgeons in post-covid-19 fungal infections

ABSTRACT

India is well known as the diabetes "capital" of the world but now it is also becoming the mucormycosis "capital" of the world. Indian Council of Medical Research has formed an "Evidence-Based Advisory in The Time of COVID-19 on Screening, Diagnosis, and Management of Mucormycosis." As per this advisory, an oral and maxillofacial surgeon forms an integral part of the team dedicated to fight this epidemic of mucormycosis. Also, there are other fungal infections such as aspergillosis which are getting reported in these patients affecting the paranasal sinuses and the jaws. Aggressive surgical debridement and a thorough knowledge of anti-fungal therapy are must in treating these fungal infections. The aim of this article is to give an overview on the available anti-fungal therapy required to manage the ever-increasing rise in fungal infections faced by maxillofacial surgeons in post-COVID-19 patients.

Keywords: Amphotericin B, anti-fungal therapy, aspergillosis, post-COVID-19 mucormycosis

INTRODUCTION

While our country is battling with an overwhelming second wave of the COVID-19 infections, the issue of post-COVID-19 mucormycosis has emerged as a significant problem. India is well known as the diabetes "capital" of the world but now it is also becoming the mucormycosis "capital" of the world.[1] According to the Center for Disease Control and Prevention (CDC), patients with severe COVID-19, such as those in an intensive care unit, are particularly vulnerable to bacterial and fungal infections. In the United States, the most common fungal infections in patients with COVID-19 include aspergillosis or invasive candidiasis. These fungal co-infections are associated with severe illness and death.[2] But in India, a change in the incidence of rhinocerebral mucormycosis infection has been observed, with more cases being diagnosed much more frequently. A lot of tertiary centers are overwhelmed and overburdened with the management of these patients.[1,3]

Indian Council of Medical Research has formed an "Evidence-Based Advisory in The Time of COVID-19 on Screening, Diagnosis, and Management of Mucormycosis." As per this advisory, an oral and maxillofacial surgeon forms an integral part of the team dedicated to fight this epidemic of mucormycosis.[4] Sharma *et al*.[3] in his study on 23 patients who presented with mucormycosis, found out that, all had an association with COVID-19 infection. The ethmoid sinuses were the most common sinuses affected (100% of the patients). There was an intra-orbital extension in 43.47% of cases, while the intracranial extension was only seen in 8.69% of cases. Diabetes mellitus was present in 21 of 23 cases and was of uncontrolled nature in 12 cases.

Abhay Datarkar, Amit Bhawalkar, Surendra Daware, Archana Deshpande, Damyanti Walkey

Department of Oral and Maxillofacial Surgery, Government Dental College and Hospital, Nagpur, Maharashtra, India

Address for correspondence: Dr. Amit Bhawalkar, 3rd Yr Resident, Department of Oral and Maxillofacial Surgery, Government Dental College and Hospital, Nagpur, Maharashtra, India.
E-mail: bhawalkaramit@yahoo.com

Received: 04 June 2021, **Revised:** 19 January 2022, **Accepted:** 22 August 2022, **Published:** 10 December 2022

Access this article online	
Website: www.njms.in	Quick Response Code
DOI: 10.4103/njms.njms_412_21	

How to cite this article: Datarkar A, Bhawalkar A, Daware S, Deshpande A, Walkey D. Anti-fungal therapy: An overview for maxillofacial surgeons in post-covid-19 fungal infections. Natl J Maxillofac Surg 2022;13:330-6.

A history of steroid use during their COVID-19 management was present in all the patients. Also, many surgeons are now seeing cases of post-COVID aspergillosis affecting the maxillofacial regions. Patients more vulnerable to these fungal infections can include those with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome, iatrogenic immunosuppression, and hematological malignancies, and those who have undergone organ transplants.

Awareness of the possibility of all this fungal co-infection is essential to reduce delays in diagnosis and treatment to prevent severe illness and death from these infections. We, maxillofacial surgeons being an integral part of managing these fungal infections affecting the paranasal sinuses, maxilla, zygoma, and even the mandible in some cases must be aware of the possible anti-fungal therapy available against the most common maxillofacial fungal infections.

The aim of this article is to give an overview on the available anti-fungal therapy required to manage the ever-increasing rise in fungal infections faced by maxillofacial surgeons in post-COVID-19 patients.

METHODOLOGY

Protocol

This is a review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist 2009.

Literature search strategy

A comprehensive electronic search was conducted by two review authors independently. Disagreements between the two review authors were solved by the third independent reviewer. PubMed, PubMed Central (PMC), Medline, and the Cochrane Central Register of Controlled Clinical Trials were searched to collect all published evidence from randomized and non-randomized clinical trials, retrospective studies from inception to May 2021 that assessed primary anti-fungal therapy in maxillofacial fungal infections. ClinicalTrials.gov (http://clinicaltrial.gov) and World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/en) were the other sources. Search terms that were used, singly and in combination, included "post-COVID-19 mucormycosis," "anti-fungal therapy," "post-COVID aspergillosis," "amphotericin B," "amphotericin B deoxycholate," "lipid-associated amphotericin B," "lipid complexed amphotericin B," "liposomal amphotericin B," "infusion-related reactions," "azoles," "echinocandins," "anti-metabolites," "fluconazole," "Itraconazole," "Voriconazole," "Posaconazole," "Isavuconazole." The exclusion was done for studies that were published in languages other than English and had incomplete texts, case series, case reports, and pilot studies. The selection process was charted down in the PRISMA flow chart [Figure 1].

Data extraction

From each relevant study, the following data were extracted: 1) classification of the important anti-fungal drugs, 2) important anti-fungal drugs in each class with the mechanism of action, indication, mode of administration, dose, and adverse reactions.

Classification of the important anti-fungal drugs and their indications

When we compare the number of anti-bacterial drugs available, there are far fewer anti-fungal compounds. There are four major families of compounds: the polyenes, the azoles, the allylamines, and the echinocandins. In addition, there is a miscellaneous group of compounds, such as flucytosine and griseofulvin, which do not belong to one of the major families [Figure 2].[5]

Detailed discussion on important anti-fungal drugs in each class

I. **Polyenes:**

Amphotericin B and Its derivatives

Amphotericin B is a macrocyclic polyene antibiotic derived from *Streptomyces nodosus*. It remains the drug of choice for many forms of deep fungal infection and is the drug of choice for post-COVID-19 mucormycosis. Parenteral administration of the conventional amphotericin B is often associated with unpleasant infusion-related reactions and has treatment-limiting toxic effects, in particular renal impairment. This problem has led to the development of three lipid-based formulations of the drug: liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion. These formulations appear to be less toxic than the micellar suspension because of their altered pharmacological distribution.[6,7]

- Mechanism of action: Amphotericin B binds to ergosterol, the principal sterol in the membrane of susceptible fungal cells, causing impairment of membrane barrier function, loss of cell constituents, metabolic disruption, and cell death. In addition to its membrane permeabilizing effects, the drug can cause oxidative damage to fungal cells.[6]
- Spectrum of action: It has a broad spectrum of action against many *Mucorales* and *Aspergillus* species, *Blastomyces dermatitidis, Candida* species, *Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum, Paracoccidioides* brasiliensis, and *Penicillium mameffei*.[6,7]

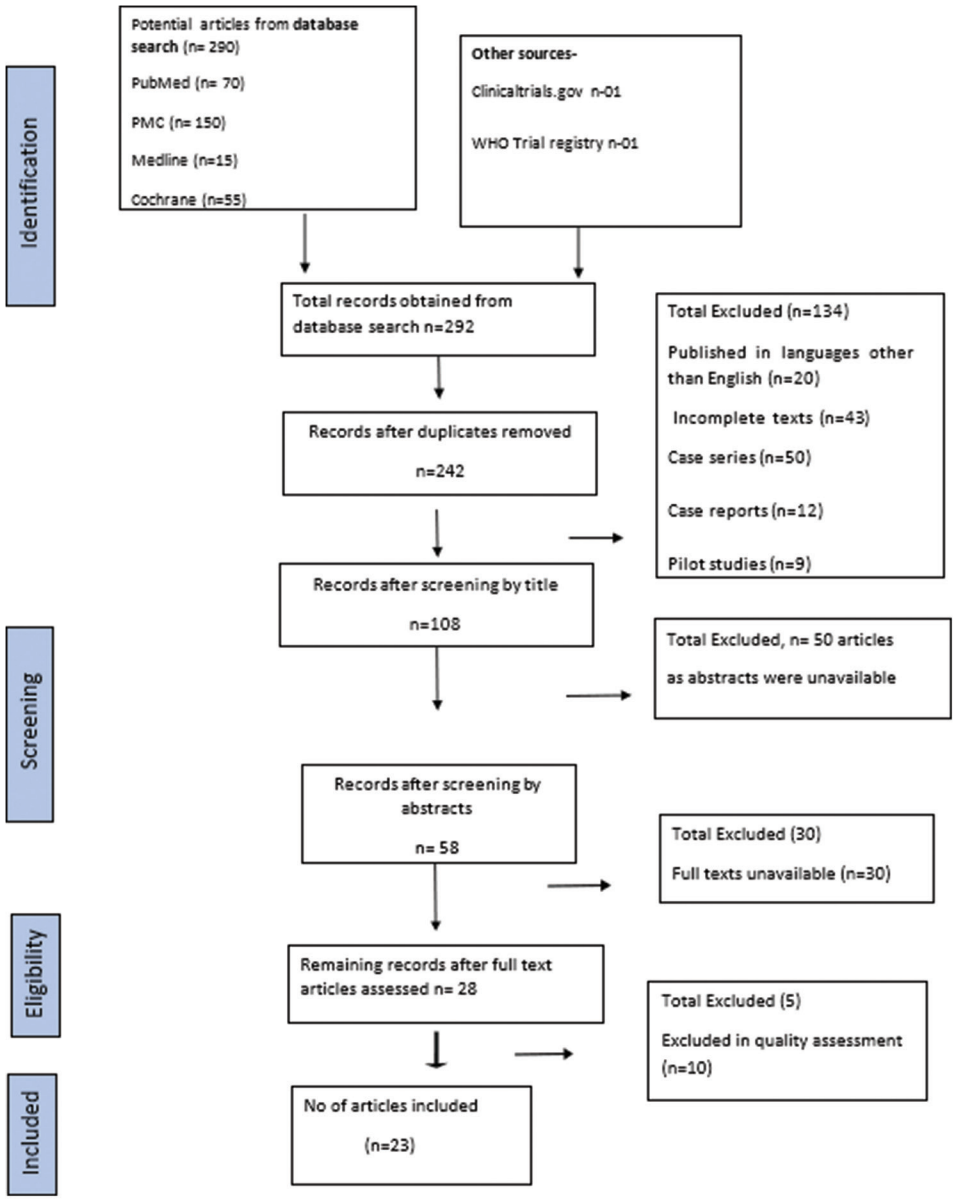

Figure 1: PRISMA flowchart

- Mode of administration: Amphotericin B is available in oral, topical, and parenteral forms.
  a. Topical and oral suspension: Topical dose and duration differ from patient to patient and are dependent on the nature and extent of the infection. The usual adult dose of the oral suspension for oral forms of candidiasis is 1–2 ml (100–200 mg) at 6 h intervals. The recommended dosage of the oral suspension for infants and children is 1 ml (100 mg) at 6 h intervals.[5,6]
  b. Parenteral forms:

i. Conventional formulation (with deoxycholate)
Amphotericin B is supplied for parenteral administration in lyophilized form in 50 mg amounts together with 41 mg sodium deoxycholate (which acts as a dispersing agent) and a sodium phosphate buffer. The addition of 10 ml sterile water gives a clear micellar suspension. This is further diluted with 490 ml of 5% dextrose solution before injection to give a final drug concentration of 100 mg/l. The dextrose solution should have a pH of 4.2 or greater to prevent the precipitation of the drug.[6]

Dose:

a. In adults with normal renal function, the usual dose is between 0.6 and 1.0 mg/kg. An initial test dose of 1 mg in adults and 0.5 mg in children of amphotericin B should be given in 50 ml dextrose solution over 1–2 h with general clinical observation and monitoring of temperature, pulse, and blood pressure of the patient at 30 min intervals.[7]

Figure 2: Approved anti-fungal drugs classification and indications[5]

b. In patients with suspected fungal meningitis, intracisternal injection is given. Injections should be given 2 or 3 times per week with the dose increased from 0.025 mg as tolerated to 0.25–1.0 mg.[6]

Advantages:

- Relatively affordable that the expensive lipid-based formulations.
- Concentration-dependent killing against a wide range of fungi.[7]

Disadvantages:

- Acute infusion-related reactions.
- Dose-dependent nephrotoxicity.
- Contraindicated in patients with acute or chronic renal problems.
- Hypokalemia can be aggravated if supplemental Potassium chloride (KCL) is not given.

ii. Lipid-based formulations

Alternative formulations of amphotericin B have been developed and incorporated into use to attenuate its toxicity and increase its therapeutic potential. As the molecular structure of amphotericin B deoxycholate has poor water solubility and excellent lipid solubility, it makes the drug an ideal candidate for incorporation into lipid-based preparations. There are three forms available

- Liposomal amphotericin B.
- Amphotericin B lipid complex.
- Amphotericin B colloidal suspension.

Dose:[6]

- It is usual to begin treatment with liposomal amphotericin B at a dose of 1.0 mg/kg, but this can be increased to 3.0–5.0 mg/kg, or even higher. This formulation should be infused over a 2 h period.
- The recommended dosage of amphotericin B lipid complex is 5 mg/kg and this should be infused at a rate of 2.5 mg/kg per hour.
- The recommended dosage of amphotericin B colloidal suspension is l mg/kg but can be increased to the dose of 3.0–4.0 mg/kg as required. This formulation is infused at a rate of 1 mg/kg per hour. It can be administered to individuals to a cumulative dosage of 3 g without significant toxic side effects.

Advantages:[6,7]

- Parenteral infusion can be prepared more easily if associated with lipids.
- Protection of the drug from destruction by enzymatic degradation and/or host immune factor inactivation.
- Slow release of amphotericin B.
- No nephrotoxicity.
- Preventing uncontrolled drug leakage.
- Targeted drug delivery to desired sites of infection.

Disadvantages:

- High-cost factor.
- Relative availability is less than the deoxycholate amphotericin B, especially in this pandemic.

- Adverse reactions of amphotericin B and its derivatives: The immediate side effects of the intravenous infusion of amphotericin B include fever, chills, and rigors and usually begin at 1–3 h after infusion and can last for 1 h.[7] Appropriate steps should be used to reduce or prevent this reaction: [Figure 3]

Adverse effects associated with conventional amphotericin B include as follows:[6-8]

- Nausea and vomiting.
- Local phlebitis from intravenous [Prevented by slowing the rate of the infusion or by adding a small amount of heparin (500–1000 units\l) to the solution.].
- Renal tubular damage (Reduced or prevented by careful monitoring during treatment and pre- and post-infusion hydration and sodium repletion with 500 ml saline, provided the clinical status of the patient will allow sodium loading.).
- Acute dyspnea, hypoxemia, and interstitial infiltrates.
- Also prolonged therapy may cause hypokalemia which can be prevented by simultaneous oral suspension of KCL and treated by properly regulated and calculated IV infusion of KCL.

Adverse effects associated with lipid-based formulations include as follows:[6,8]

- Infusion-related hypoxia.
- Elevations in liver transaminases.
- Alkaline phosphatase.
- Serum bilirubin concentrations.

II. Azoles and Triazoles

The most commonly used azoles for treating invasive fungal infections can be functionally divided between agents with primary activity against yeast-like fungi (yeast-active azoles), and those with expanded activity against fungi that grow as molds (mold-active azoles) [Figure 4].[5]

- **Mechanism of action:**
  These drugs cause the inhibition of the sterol 14α-demethylase (cytochrome P450 51 or CYP51), which catalyzes the final step in ergosterol biosynthesis thus leading to defects in fungal plasma membrane integrity and cellular integrity.[5,9]

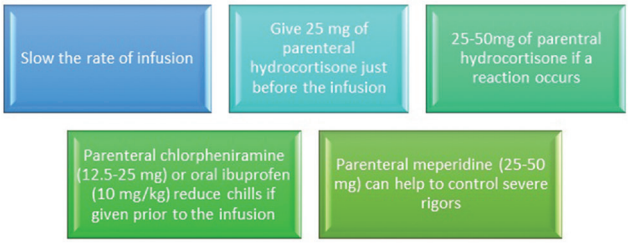

Figure 3: Steps to be taken to prevent or reduce the fever, chills, and rigors[6]

a. Fluconazole

- **Indication:** Invasive infections due to susceptible *Candida* species, cryptococcosis.[5]
- **Mode of administration:** Fluconazole is available in oral and parenteral forms as tablets, oral suspension, and an intravenous infusion. The drug is supplied for parenteral administration at a concentration of 2.0 mg/ml in 0.9% sodium chloride solution.[6,10]
- **Dose:**[6]
  a. Oropharyngeal candidiasis should be treated with an oral dose of 200 mg on the first day followed by 100 mg/day for 2 weeks.
  b. The recommended parenteral dose for adult patients with cryptococcosis or deep forms of candidiasis is 6 mg/kg for 6–8 weeks.
  c. For children, the dosage is 3 mg/kg.
- **Adverse reactions:** Nausea and abdominal discomfort, hepatitis, cholestasis, fulminant hepatic failure, and fatal exfoliative skin rashes.[6,10]

b. Itraconazole

- **Indication:** Blastomycosis, histoplasmosis, aspergillosis in patient's refractory to Amphotericin B.[5]
- **Mode of administration:** Itraconazole is available in oral and parenteral forms as oral capsules, oral solution, and intravenous infusion.[6]
- **Dose:**[6,11]
  a. In non-compromised individuals, oropharyngeal candidiasis can be treated with 100 mg/day for 2 weeks, but patients with Acquired

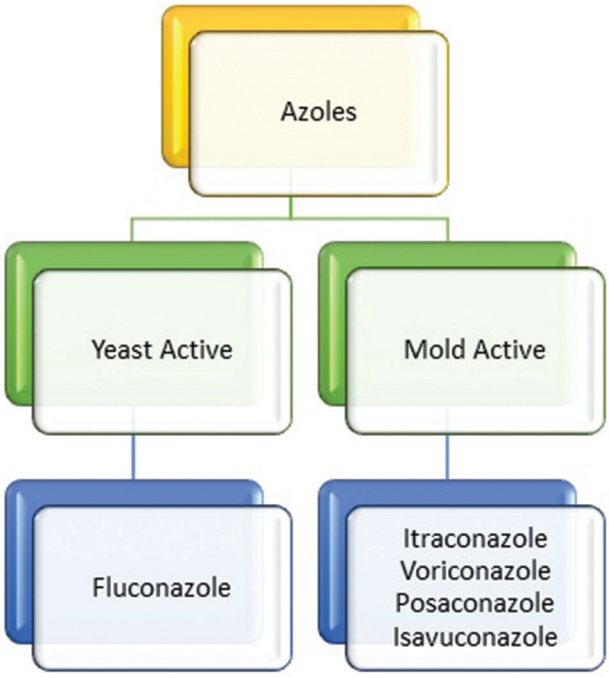

Figure 4: Functional classification of azoles group of anti-fungal drugs[5]

immunodeficiency syndrome and neutropenia often require 200–400 mg/day because of impaired oral absorption.

b. The recommended oral dosage of itraconazole for patients with deep fungal infections, such as aspergillosis, blastomycosis, and histoplasmosis, is 200–400 mg/day.

c. The recommended intravenous dose of itraconazole for patients with aspergillosis, blastomycosis, or histoplasmosis is 200 mg at 12 h intervals for four doses followed by 200 mg/day for up to 2 weeks.

- **Adverse reactions:** Nausea, abdominal discomfort and constipation, headache, dizziness, pruritus and allergic rashes, diarrhea, and hypokalemia.[6]

c. **Voriconazole**

- **Indication:** Invasive aspergillosis, non-neutropenic candidiasis, serious Scedosporium or Fusarium infections refractory to other agents. Voriconazole has been approved as a first-line agent for the treatment of acute invasive aspergillosis.[5]
- **Mode of administration:** Voriconazole is available in oral and parenteral forms.
- **Dose:**[6,12]

a. Intravenous treatment with voriconazole should be initiated with two loading doses of 6 mg/kg at 12 h apart, followed by 4 mg/kg at 12 h intervals.

b. Each dose should be infused at a maximum rate of 3 mg/kg per hour over a 1–2 h period.

c. Once the patient can tolerate oral medication, intravenous administration can be discontinued.

d. Patients who weigh more than 40 kg should receive two oral loading doses of 200 mg at 12 h intervals followed by the dose of 200 mg at 12 h intervals.

e. Adult patients who weigh less than 40 kg should receive two loading doses of 200 mg at 12 h intervals followed by the dose of 100 mg at 12 h intervals.

f. The duration of the treatment depends on the clinical response and the nature of the disease.

- **Adverse reactions:** Visual disturbances, fever rash, vomiting, nausea, diarrhea, headache, and abdominal pain.[6,12]

d. **Posaconazole-**

- Indication: Prevention of invasive fungal infections in neutropenic or transplant recipients.[5]
- Mode of administration: Posaconazole is available in oral tablets and parenteral forms.[6]
- Dose:

a. The prophylactic oral dosage is 200 mg three times daily.[13] The recommended oral dosage is given based on the clinical scenario [Figure 5].

b. For parenteral administration, administer by slow intravenous (IV) infusion. It must be diluted in a compatible diluent before IV infusion. Diluted posaconazole IV solutions must be administered through a 0.22-μm polyethersulfone or polyvinylidene difluoride filter. Administer by slow IV infusion into a central venous line [e.g. central venous catheter, peripherally inserted central catheter (PICC)].[13]

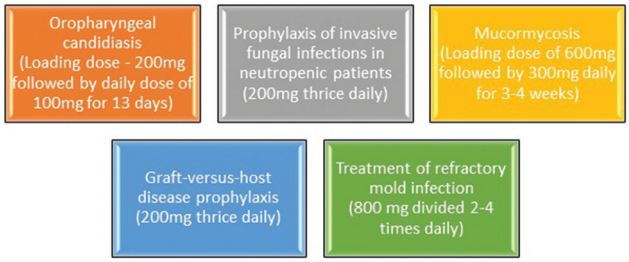

Figure 5: Recommended oral dosage of posaconazole[13]

- Adverse reactions: Nausea, vomiting, diarrhea, rash, hypokalemia, thrombocytopenia, abnormal liver function tests, and rarely Q-Tc interval prolongation.[5]

e. Isavuconazole

It is the most recently approved triazole anti-fungal drug. It differs from other approved azoles in several clinically relevant ways.[5]

- Indication: It has expanded *in vitro* activity that includes the *Mucorales* molds (Zygomycetes), such as *rhizopus*, *mucor*, and *cunninghamella* species, and it may, therefore, be an effective component of the complex, medical-surgical treatment of mucormycosis.[5,14]
- Mode of administration: It is available in oral and parenteral forms (Each oral capsule contains 100 mg of isavuconazole and each vial contains 200 mg of isavuconazole).[14]
- Dose:[6,14]

a. The loading dose is 200 mg every 8 hourly for the first 48 h

b. The maintenance dose is 200 mg daily.

- Adverse reactions: Nausea and vomiting, dyspnea, abdominal pain, diarrhea, injection site reaction, hypokalemia, rash, renal and respiratory failure, etc.[6]
- Importance of isavuconazole in post-COVID-19 mucormycosis patients:

a. It can be used in patients with renal insufficiency as its IV formulation lacks cyclodextrin, a solubilizing agent used with other triazoles that are associated with nephrotoxicity.[14]

b. Isavuconazole does not appear to exacerbate QT prolongation which is seen in many conventional azoles, and it may actually shorten the QT interval in some patients.[5]

c. But the biggest drawback of this drug is the high-cost factor which can cause quite a lot of

economic burden to the patients, especially those with post-COVID-19 mucormycosis.

III. Echinocandins

These are the newest class of anti-fungals. Currently, three drugs from this class are approved for clinical usage:[5]

a. Caspofungin.
b. Micafungin.
c. Anidulafungin.

- Indications: Treatment of invasive candidiasis and as an alternative therapy for the treatment of aspergillosis.[5,15]
- Mechanism of action: These drugs cause inhibition of β-1,3-glucan synthase, thus affecting cell wall biosynthesis through the non-competitive.[16]
- Advantages:[5]
  1. Low host toxicity.
  2. Few drug interactions.
- Disadvantages:[5,15]
  1. No activity against *Cryptococcus* species.
  2. Poor agents for the treatment of the endemic mycoses.
  3. Only available in IV form.
  4. They are not orally bioavailable.

IV. Anti-metabolites

Flucytosine

- **Indication:** Flucytosine has a limited spectrum of action including *Candida* species, *C. neoformans, Cladophialophora carrionii, Fonsecaea* species, and *Phialophora verrucosa*.[6]
- **Mechanism of action:** Inhibits DNA and RNA synthesis by incorporating them into the growing nucleic acid chain thus leading to impaired protein synthesis and cell division.[17]
- **Combination therapy:** Flucytosine is not used as a single drug but in combination with amphotericin B and other anti-fungal drugs.[5]
- **Mode of administration:** Oral as well as parenteral forms are available.
- **Dose:** In adults with normal renal function, the usual starting dose of flucytosine is 50–150 mg/kg given as four divided doses at 6 h intervals.[6]
- **Adverse reactions**: Nausea, vomiting, diarrhea, thrombocytopenia, leucopenia, bone marrow suppression, and liver necrosis.[5,6]

CONCLUSION

During this COVID-19 pandemic, many patients are suffering from post-COVID-19 complications. One of them is mucormycosis which is now becoming an epidemic in our country. The resources and manpower to fight this "black fungus" are getting stretched on a daily basis. Maxillofacial surgeons are an integral part of the team required to treat this fungal infection. Also, there are other fungal infections such as aspergillosis which are getting reported in these patients affecting the paranasal sinuses and the jaws. Aggressive surgical debridement and a thorough knowledge of anti-fungal therapy are must in treating these fungal infections.

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel) 2019;5:26.
2. Available from: https://www.cdc.gov/fungal/index.html. [Last accessed on 2021 June 04].
3. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: A deadly addition to the pandemic spectrum. J Laryngol Otol 2021;135:442-7.
4. Available from: https://www.icmr.gov.in/pdf/covid/techdoc/Mucormycosis ADVISORY FROM ICMR In COVID19 time.pdf. [Last accessed on 2021 Jun 04].
5. Pianalto KM, Alspaugh JA. New horizons in antifungal therapy. J Fungi 2016;2:26. doi: 10.3390/jof2040026.
6. Richardson MD, Warnock DW. Fungal Infection: Diagnosis and Management. John Wiley and Sons 111 River Street. Hoboken, NJ 07030 USA; 2012.
7. Hamill RJ. Amphotericin B formulations: A comparative review of efficacy and toxicity. Drugs 2013;73:919-34.
8. Rieger CT, Dittmer M, Ostermann H. Liposomal amphotericin B in the treatment of severe fungal infections. Results of a clinical cohort trial. Dtsch Med Wochenschr 2007;132:2062-6.
9. Hof H. A new, broad-spectrum azole antifungal: Posaconazole–mechanisms of action and resistance, spectrum of activity. Mycoses 2006;49:2-6.
10. Berkow EL, Lockhart SR. Fluconazole resistance in Candida species: A current perspective. Infect Drug Resist 2017;10:237-45.
11. Lestner J, Hope WW. Itraconazole: An update on pharmacology and clinical use for treatment of invasive and allergic fungal infections. Expert Opin Drug Metab Toxicol 2013;9:911-26.
12. Thompson III GR, Lewis JS. Pharmacology and clinical use of voriconazole. Expert Opin Drug Metab Toxicol 2010;6:83-94.
13. Morris MI. Posaconazole: A new oral antifungal agent with an expanded spectrum of activity. Am J Health Syst Pharm 2009;66:225-36.
14. Bose P, McCue D, Wiederhold NP, Kadia TM, Borthakur G, Ravandi F, *et al*. Isavuconazole (ISAV) as primary anti-fungal prophylaxis in acute myeloid leukemia or myelodysplastic syndrome: An open-label, prospective study. Blood 2018;132(Suppl 1):2674.
15. Van Daele R, Spriet I, Wauters J, Maertens J, Mercier T, Van Hecke S, *et al*. Antifungal drugs: what brings the future? Med Mycol 2019;57(Suppl 3):S328-43.
16. Maligie MA, Selitrennikoff CP. Cryptococcus neoformans resistance to echinocandins: (1, 3) β-glucan synthase activity is sensitive to echinocandins. Antimicrob Agents Chemother 2005;49:2851-6.
17. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O, French Cryptococcosis Study Group. Major role for amphotericin B–flucytosine combination in severe cryptococcosis. PloS One 2008;3:e2870.