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SYNERGISTIC EFFECT OF COMBINATION ANTIFUNGAL THERAPY FOR MUCORMYCOSIS IN CONTEXT TO COVID-19 INFECTION; A SYSTEMIC REVIEW

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Mucormycosis is an invasive fungal infection that may cause significant morbidity and mortality. The main target organs of mucormycosis infection are the parental sinusitis, orbital cavity and the brain tissue. It has come to focus during the last few years in context of COVID-19 infection. COVID-19 patients are highly susceptible to fungal infections as they are always immunosuppressed. Prompt eradication of mucormycosis infection by means of anti-fungal therapy in addition to surgical debridement is the standard of care. We questioned if combination antifungal therapy may offer a more effective, yet less toxic, therapy for mucormycosis. We reviewed the literature covering antifungal agents for mucormycosis, whether as monotherapy or in combination. We concluded that combination therapy could be a promising treatment for mucormycosis, particularly in cases associated with COVID-19 infection. This combination could decrease the nephrotoxicity caused by amphotericin B, the main choice in treating mucormycosis, and, on other hand, enhance its therapeutic efficacy

Keywords: *COVID-19 associated mucormycosis, Antifungal, Combination therapy*

INTRODUCTION

During the global epidemic, mucromycosis is widely observed in COVID-19 patients with predisposing conditions[1]. It is an uncommon, offensive, invasive, and fatal fungal infection. It may lead to thrombosis and tissue necrosis due to blood vessel invasion and infarction[2,3,4]. Mucormycosis is sourced from the Mucorales fungus, which belongs to the Zygomycetes class and is found mainly in organic substrates and soil[5,6,7]. Although it is not pathogenic for immunocompetent individuals, it may cause significant morbidity and mortality in an immunocompromised patient. Mucormycosis is caused by Rhizopus oryzae and Aspergillus oryzae. COVID-19-associated mucormycosis cases have been rising globally since the beginning of 2021[8]. Therefore, immunocompromised patients are highly sensitive to mucormycosis[9,10]. Infection with mucormycosis can appear in one of six forms based on localization: (1) rhinocerebral, (2) pulmonary, (3) cutaneous, (4) GIT, (5) disseminated, and (6) rare presentations[11,12]. Invasive mucormycosis has been commonly observed in the lungs (24%), sinuses (39%), and skin (19%). The predisposing conditions influence the mortality rate include hyperglycaemia (in 44% of patients) and malignant tumour (in 66%), however, no predisposing conditions could be observed in 35% of patients. Furthermore, the mortality rate correlated with site of infection where found to be 96% for patients with spread infections, 85% for those with GIT disorder, and 76% with pulmonary disorder. Moreover, children were infected with mucromycosis have (16%)

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pulmonary infections, (27%) cutaneous infections, (18%) rhinocerebral infections, and (21%) GIT infections. In children, the skin is influenced more frequently than in adults[13]. The patients who suffered from malignancy, transplantation of haematopoietic stem cells, or transplantation of solid organs were more susceptible to mucormycosis[14]. There is a relationship between the predisposing conditions and the site of infection, as shown in **Table 1**[15]. Furthermore, patients with diabetes mellitus, malnutrition, severe prematurity, iron overload, diabetic ketoacidosis, prolonged time therapy with high-dose corticosteroids, penetrating trauma, and burns are at high risk for mucormycosis[14,16].

Many reports show that significant COVID-19 patients are highly amenable to mucormycosis during hospitalisation or after discharge. Patients who are exposed to fungal infection with COVID-19 are always immunosuppressed with a decrease in lymphocytes, which is essential for maintaining immunity. Moreover, the long-term administration of glucocorticoids for managing COVID-19 has suppressed immunity[17].

Pathogenesis of Mucormycosis

Clinical evidence demonstrates the major host defence mechanism against mucormycosis. In the case of a normal host, the defence mechanism against mucormycosis was the confiscation of iron in the serum by expert iron-binding proteins. But in the case of susceptible hosts, this defence mechanisms collapses. Such as in diabetic ketoacidosis (DKA), the serum pH was acidic, which lead to the separation of free iron from confiscating proteins. The release of free iron causes fungi to grow faster. Furthermore, disorders in the phagocytic defence mechanisms, such as neutropenia (insufficiency in cell count) allow the growth of fungus. Moreover, functional disorders produced by corticosteroids, or DKA, permit the reproduction of the fungus. Furthermore, iron-loaded deferoxamine, which chelates both aluminium and iron, promotes the growth of fungi and increases the hazard of mucormycosis[17]. By adherence of the fungus to endothelial cell debris, thrombosis of vessels, tissue necrosis, dissemination of fungal infection, and fungal angio-invasion were observed as well[15]. Further, a potent inflammatory response in healthy hosts was obtained by inoculating or inhaling Mucorales spores. The infection is obtained by the spores, which are escaped by resident mononuclear phagocytes and then constructed into hyphae. Moreover, the angio-invasive growth in tissue with haemorrhage, thrombosis, and necrosis disseminates to other organs, as shown in **(Fig. 1,2)**[18].

Table 1: Relationship between predisposing factors and infectious sites**.**

Predisposing factors	Infectious sites
Diabetic ketoacidosis	Rhinocerebral
Neutropenia	Pulmonary and disseminated
Corticosteroids	Rhinocerebral, disseminated, or pulmonary
Iron overload	Disseminated
Nutrition deficiency	GIT
Trauma, injection site, skin maceration	Cutaneous/subcutaneous

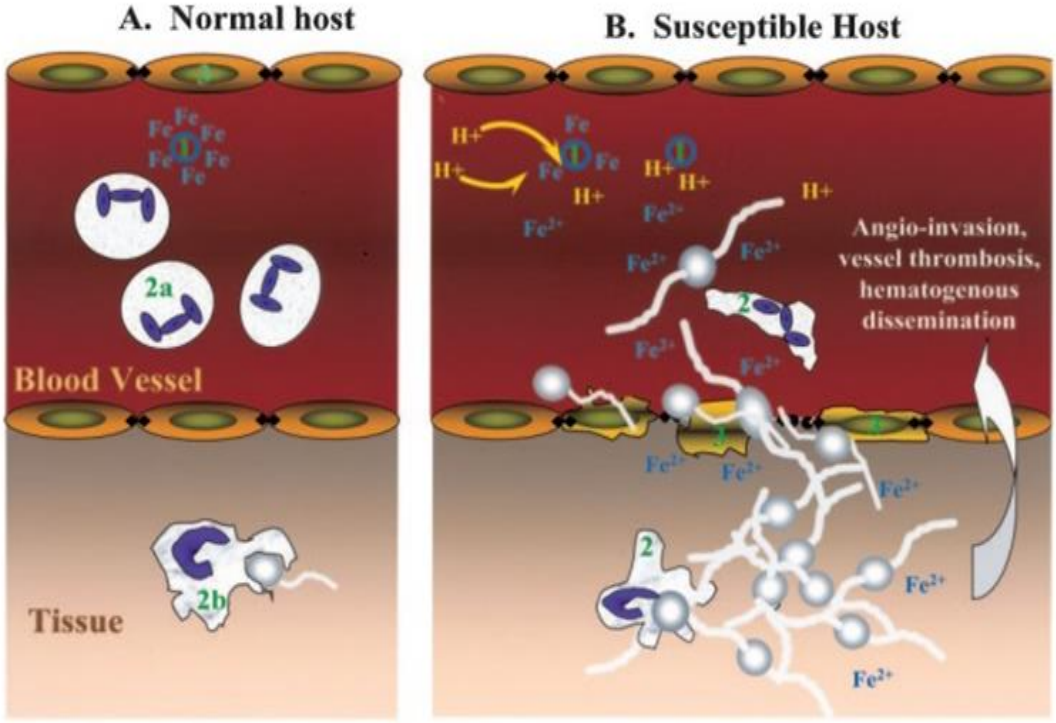

Fig. 1: Mechanisms of pathogenesis of host defence against mucormycosis.

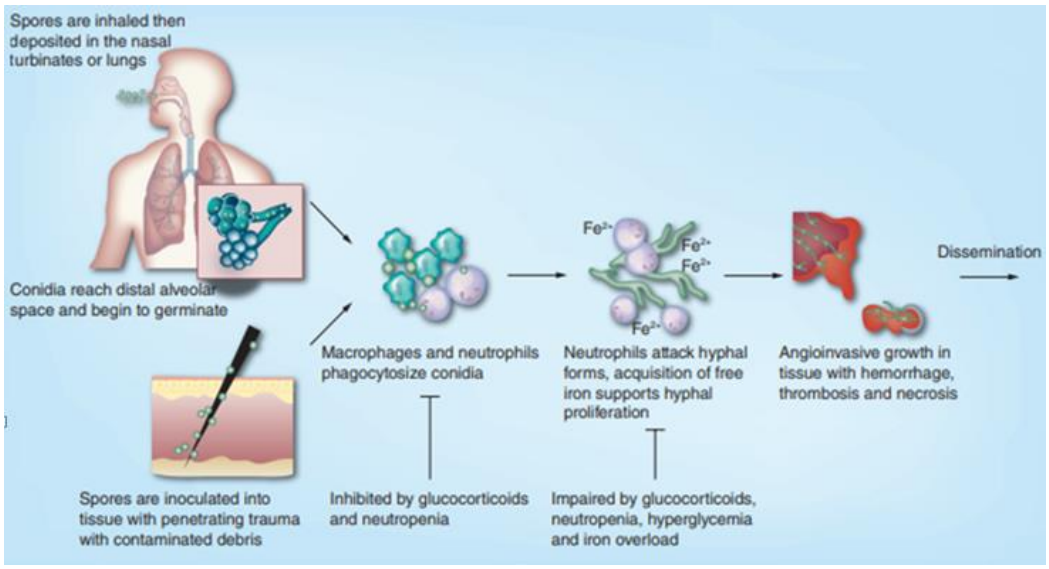

Fig. 2: Pathogenesis of mucormycosis.

Diagnosis of mucormycosis

There are no specified antigen tests for mucormycosis[16]. Although molecular technology is being used continuously as a traditional method, histopathology and culture are still the primary means of identifying mucromycosis[19]. The direct microscopic examination used to diagnose mucromycosis revealed branching at right angles with hyphae. Despite that computed tomography and magnetic resonance imaging (MRI) are non-specified techniques, however, it is helpful differentiate mucromycosis from sinusitis, which resulted from a bacterial infection. In the case of mucromycosis, non-enhancing mucosal tissue appeared in the sinuses and turbinates on contrast MRI (the "black turbinate" sign), as shown in **Fig. 3**[20]. Small-vessel occlusion and mucosal ischemia are the main reasons for this phenomena[13,19].

Cutaneous tissue necrosis caused by mucormycosis is shown in **Fig.4**[18]. In most

cases, unless treated with a surgical excision and immediate antifungal therapy, the infection is relentlessly progressive and may lead to death[17,21].

Recovery of mucormycosis

The basic essentials of treatment for mucormycosis include limiting the aggressiveness of the disease[6]. Four pillars of management are required for the successful recovery of mucormycosis: 1) early diagnosis; 2) limitation of risk factors, 3) instant antifungal therapy; and 4) surgical eradication[16].

Rapid diagnosis and immediate therapeutic intrusion may hinder the progression of the infection. Moreover, they may reduce the need for surgery and increase survival.[22]. A delay in the identification of the disease and convenient therapy might be related to increased mortality[23]. The researchers observed the benefits of rapidly initiation of polyene antifungal therapy (**nystatin, amphotericin B, and pimaricin)**. They also discovered that survival was significantly improved when the patient began treatment within 5 days of disease identification rather than 6 days after diagnosis[24].

Early diagnosis

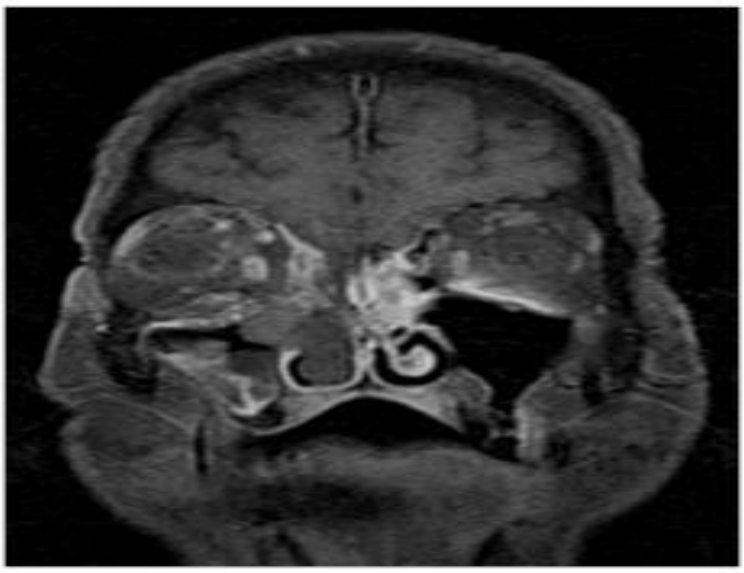

Fig. 3: MRI coronal post-contrast showed the ("Black Turbinate") of the enlarged right inferior nasal turbinate.

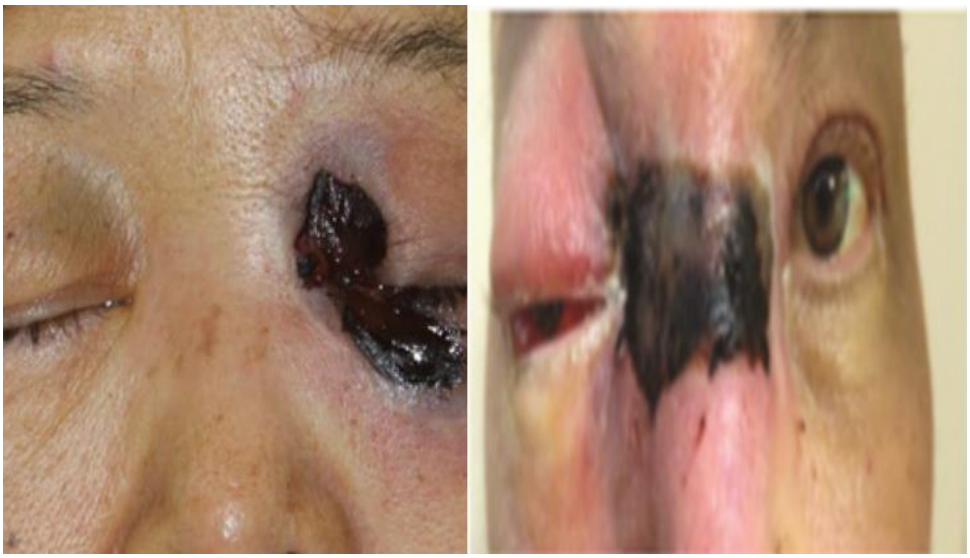

Fig. 4: The tissue necrosis of mucormycosis.

Elimination of risk factors

When recovering patients have mucormycosis, it is critical to have an adverse implied disorder in host defence. In this case, doses of immunosuppressive medications such as corticosteroids could be reduced or stopped. Further, the administration of iron should be limited or minimised in blood transfusions because it exacerbates the aggressiveness of the infection. Because voriconazole has the potential to increase Mucorales pathogenicity, it must be used in conjunction with other drugs to break down the infection[16].

Antifungal Therapy

First-Line Monotherapy Options (polyene)

Amphotericin B (AmB) is an antifungal obtained from the strain *Streptomyces nodosus*. The activity of AmB is based on the formation of transmembrane channels by the binding of the cell membrane of the fungi's ergosterol moiety to the hydrophobic moiety of the AmB molecule[25,26,27]. Several lipid-based drug delivery systems, such as amphotericin B deoxycholate, were the mainstay for the recovery of mucormycosis, although it is nephrotoxic. The lipid modifications of AmB, such as liposomal AmB (L-AmB) and AmB lipid complex (ABLC), are safer and less nephrotoxic. Furthermore, the incorporation of AmB with suitable lipid carriers such as phospholipid and cholesterol complexes has been enhanced to minimise the toxicity, maximise the therapeutic index, and promote the solubilization of AmB[28,29,30]. Interestingly, the researchers discovered that L-AmB improved survival (67%) compared to AmB, which had a (39%) survival rate[23].

Second-line azole deriv atives (Step Down or Salvage Therapy)

New Triazoles

Triazoles are implemented by exhausting ergosterol, which is considered the essential form of the fungal cell membrane. Such drugs as voriconazole, fluconazole, and itraconazole have minimal or no effectiveness against Mucorales. Posaconazole and isavuconazole, two newer triazoles, on the other hand, have superior *in vitro* activity against Mucorales, and an *in vivo* study supports mucormycosis recovery[31].

Step-down therapy

Posaconazole and isavuconazole, which are broad-spectrum azoles, are available in both oral and parenteral formulae. They can be given to patients who have completed AmB for oral step-down therapy. AmB should be continued until the patient has improved; this takes several weeks[32].

Salvage therapy

The salvage therapy was obtained for patients who did not respond to AmB. Posaconazole or isavuconazole may be administered as salvage therapy. Patients who need to turn over AmB but are unable to absorb oral medications should receive an IV injection of them[32].

Isavuconazole

Isavuconazole is a novel broad-spectrum triazole, and the prodrug isavuconazonium sulfate is the biologically active agent. Recently, isavuconazole was approved for the treatment of mucromycosis by the US Food and Drug Administration and the European Medicines Agency[33]. Isavuconazole should be administered as a loading dose of 200 mg IV or orally every 8 hours for the first six doses, followed by 200 mg IV or orally every 24 hours (equivalent to 372 mg of the prodrug isavuconazonium sulfate). Because the IV injection of isavuconazole is highly soluble in water, there are no concerns about it being administered to patients with renal impairment[34]. Isavuconazole advantages include fewer drug-drug interactions, minimal toxicity, minimal hepatotoxicity, linear pharmacokinetics, fewer skin and ocular side effects, and superior oral bioavailability with no food introduction[33].

Posaconazole

Posaconazole is considered a salvage option for cases of mucormycosis intolerant to polyene therapy[23,35]. Until recently, to enhance the bioavailability of posaconazole, it was taken with heavy meals as an oral suspension (3-4 times per day). These dosage forms make it difficult to use, and it might be nauseating. Moreover, there is a lack of absorption that leads to therapeutic insufficiencies. To control the pharmacokinetic restrictions of the oral solution, GIT tablets and IV injection solutions have been developed[35].

A survived tissue infected with mucromucosis fungi was used to measure the *in vivo* performance of posaconazole. Posaconazole at high doses improved survival and reduced tissue burden in neutropenic mice with disseminated Mucor infection. In non-immunocompromised mice, no beneficial effects were observed against R. Oryza, which is the fungus responsible for mucromycosis[36]. Otherwise, Jo-Anne H et al. published the results of a study of 91 patients with mucormycosis who recovered with posaconazole as salvage therapy. Oral posaconazole suspension was used as 200 mg taken 4 times daily or 400 mg taken twice daily, orally with meals. They showed that this drug is recommended for patients with mucromycosis who are not interrogated for IV AmB products[37].

Combination Therapy for Recovery Mucormycosis

Antifungal monotherapy treatments for mucromycosis remain unacceptable due to increasing mortality rates[38]. In recent years, combination therapy strategies have been described in preclinical studies to maintain the survival rate. The harmony between preclinical and clinical studies gives hope for improving the survival rate in patients suffering from mucromycosis[39,6]. The purpose of combination antifungal therapy is to avoid toxicity to the patient and to achieve increased clinical efficacy. There are several advantages for considering combination therapy, such as the synergistic effect of the fungal death, a broader spectrum of activity, targeting potentially resistant pathogens with antifungal drugs, and minimising toxicity. This review focused on combination therapy with a view to increase strength and limiting fungal growth. The interactions of antifungals in combination therapy *in vitro* and *in vivo* studies are optimally depicted in terms of synergy, antagonism, addictiveness, and difference[40].

Research Question

We questioned if combination antifungal therapy may offer a more effective, yet less toxic, therapy for mucormycosis.

MATERIALS AND METHODS

We reviewed works of literature published in PubMed, Cochrane, Science direct data bases using the keywords (mucormycosis, anti-fungal, COVID-19, and combination therapy) till 2023. This review article revealed 21 studies; 15 of them were in the COVID-19 era, and the rest were in the pre-COVID era **(Table 2**). We also considered researches published before COVID-19 era for historical comparison and for comprehensive coverage of available antifungal therapy against mucormycosis.

Table 2: Summary of different studies of combination therapy in the recovery of mucormycosis.

	Year	Type	No.	Tested intervention	Tested outcome	Results and comment
A.Kyvernitakis et al., [41]	2016	Retrospective study 1994-2014	106	44% monotherapy of L-AmB. 56% combination treatment of posaconazole and L-AmB.	6 weeks mortality	-Non-significant differences exist in mortality between monotherapy and combination therapy. -Lymphopenia and ICU admission at diagnosis were associated with increased mortality. -The infectious sites have an impact on the outcome.

Table 2: continued

Poonam Kumar Saidha et al., [42]	2021	Case Series	6	Six cases of mucormycosis in the context of COVID-19 and uncontrolled diabetes were identified. **Case 1-** AmB solution douching was applied twice daily. IV L-AmB was started at a dose of 1 mg/kg /day to a cumulative dose of 2 g after FESS surgical debridement with an uneventful post-operative period. **Case 2-** FESS, then postoperative nasal and antral douching. AmB was started with an oral suspension of posaconazole as salvage therapy for 14 days. **Case 3-** Patient didn't complete therapy against medical advice. **Case 4-** The patient died before beginning therapy. **Case 5-** AmB was administered intravenously at 1 mg/kg with nasal douching, resulting in adequate healing. **Case 6-** Following surgery, the patient was given IV AmB as well as a topical AmB solution for nasal douche.		- Early diagnosis and management including surgical removal of damaged tissue along with pharmacologic therapy may result in a quick recovery. -In addition to L-AmB, other antifungal agents such as posaconazole and itraconazole are recommended for treatment. -In cases of controlled blood sugar, antifungal therapy and surgical treatment are effective.

Table 2: continued

Salehi MR. et al., [22]	2020	case report	1	Surgical excision and a combination of L-AmB and posaconazole were obtained. The patient refused enucleation.	3 months	Surgical debridement with a combination of L-AmB and posaconazole may improve the survival rate of patients suffering from ROCM.
Muhammad Adnan et al., [43]	2022	A case series	20	COVID-19 was found to have a significant relationship with sino-orbital mucormycosis (p = 0.03).	Not observed treatment	-Early initiation of anti-fungal treatment and surgical excision was essentially intended to decrease both the mortality and morbidity of the disease.
Tamer Roushdy and Eman Hamid [44]	2021	A case series	4	**Case 1 and Case 2**-Broad-spectrum antibiotics and systemic AmB were administered, then surgery. **Case 3**- The patient was treated with systemic and topical eye antibiotics and IV L-AmB at a dose of 0.7 mg/kg once daily over 6 hours for 14 days; drainage and a biopsy for the sinuses were performed. **Case 4**- IV AmB (0.7 mg/kg) was given once daily/14 days, and amikacin antibiotic was given based on maxillary sinus culture & sensitivity of recovery.		-The mortality rate was 25%, with a 75% recovery rate.
Teclegiorgis Gebremariam et al., [45]	2021	Pre clinical study (mice)		L-AMB or isavuconazonium sulphate, or a combination of both used for recovery.	4 days	- The combination treatment resulted in an 80% increase in survival. - In mice treated with antifungal drugs, infection load in the brain and lungs was reduced by 1-2 fold compared to placebo. -Treatment with combination therapy recorded a 2–3.5 fold limitation of the infection rather than placebo, and a 1.0 fold limitation rather than monodrug therapy.

Table 2: continued

YK Yoon, et al., [23]	2009	Case Report	1	The treatment consisted of 61 days of IV AmB followed by 26 days of oral Posaconazole.	15 months	- After 15 months of treatment, the case returned to a normal life.
Karla Ojeda-Diezbarroso et al., [35]	2019	Case report	1	-Cefepime and deoxycholate AmB were initiated. The response was unsatisfactory. Antifungal therapy was turned into ABCL and extensive surgery; however, the disease progressed. -Oral posaconazole suspension as salvage therapy at 800 mg/day (30 mg/kg/day) was added. The patient was discharged from the hospital and remains treated with oral posaconazole as compassionate therapy.	-	- The patient showed healthy nasal and maxillary sinus mucosa after being treated with posaconazole for five months. -After six months of treatment, posacoazole was turned off. -Four years after diagnosis, the patient is still free of mucormycosis and leukemiaia.
Karthik Shamanna et al., [12]	2019	Case series	20	75% AMB+ debridement 25 % AMB only	Outcomes observed: Complications Disease clearance Mortality	-Patients treated with conventional Inj AmB without surgical debridement had more complications such as, hypokalemia, acute kidney disease, hypomagnesemia, etc. -Three (15%) patients died in the follow-up period. - Treatment with IV L-AmB and surgical debridement of necrotic tissue led to clearance of the disease.
Andrew M. Taylor et al., [20]	2020	Case report	1	After surgery, ceftriaxone, vancomycin, and L-AmB were obtained.		- The disease became aggressive, and the patient developed intracranial diffusion of mucormycosis. After ICU admission, a fatal pulmonary embolism was obtained. - A non-enhancing black turbinate (diagnosed by MRI) was observed in a mucromycosis patient.

Table 2: continued

P. K. Pandilwar et al., [2]	2020	Case report	2	**Case 1-**Systemic antifungal therapy (IV AmB) was administered to the patient. After the control of glucose levels, the maxillary surgical excision was done. **Case 2-** For three weeks, IV L-AmB (250 mg every 12 hours) was administered. The levels of blood glucose were adjusted. Following surgery, there was a significant improvement. There was no clinical evidence of persistence of disease after 2 months of follow-up.		**Case 1-**The patient´s healing was uneventful. **Case 2-**The case had improved, and vital signs were within normal limits.
L. Millon et al., [19]	2016	retrospective analysis	44	-Prediction & monitoring of mucormycosis by PCR. - L-AmB monotherapy	19 days	-Survival rate observed with patients with mucormycosis PCR – positive cases who became negative after treatment was significantly higher than those who remain positive (a ratio of 48% versus 4% respectively). - PCR would enable earlier start of treatment. - Patients treated with L-AmB showed 27 percent survival rate by the end of observation period. -The time required for a complete conversion to negative PCR was 3-19 days after the initiation of L-AmB treatment.

Table 2: continued

K. Rothe, K. Braitsch, R. Okrojek et al., [46]	2021	A retrospective case series	15	-Six (40%) of all patients had received antifungal prophylaxis (posaconazole) prior to mucormycosis due to underlying haematological malignancy, suggesting that these infections could be considered breakthrough. -Antifungal therapy was administered in 12 cases (80%) for duration of 16 days (the rest of the cases died before starting anti-fungal therapy). - Four patients received L-AmB and isavuconazole combination therapy. -Two-thirds (10 patients) of the patients received L-AmB, but in the remaining two cases (with previous posaconazole prophylaxis), primary initial therapy with isavuconazole was started. However, a change in antifungal substance class is required for empirical antifungal therapy. -L-AmB and echinocandins or posaconazole as combination therapy were beneficial in the case of a severe form of mucromycosis.		- The mortality rate was 100%. - In critically ill patients, combination therapy (at higher doses) or surgical debridement must be determined through additional research. -Excision surgery for infectious site local mucormycosis appears to be beneficial. .

Table 2: continued

Antonio Mastroianni et al., [47]	2004	Case reports	1	A case of maxillary paranasal sinus mucormycosis treated with surgery and combination therapy with L-AmB (3 mg/kg/day, cumulative dose of 2.5 g), and subcutaneous rHuGM-CSF (Mielogen®, 150 µg daily for five consecutive days).	5 days	During a 24-month follow-up period, the patient had no relapses of invasive murcormycosis.
Srinivas et al., [48]	2020	Case Series	3	**Case1**- A 12 years-old girl presented with DKA, sepsis, and cutaneous mucormycosis. Debridement was done; dressing with gauze soaked in diluted AmB was applied over the wound daily for 3 weeks. Intravenous L-AmB was infused over four weeks (a cumulative dose of 61 mg/kg). **Case 2**- A 7 years-old child with ALL and renal mucormycosis. The nephrectomy was done with an uneventful recovery. IV AMB was administered for 12 weeks, followed by eight weeks of oral Posaconazole (20 mg/kg/day). **Case 3**- Repeated debridement and parenteral therapy with L-AmB continued for four weeks. Fulfillment of antifungal therapy and secondary suturing of the residual wound were carried out with good results.		-Antifungals commonly in use are AmB, posaconazole, and isavuconazole, of which L-AmB is the most effective. -Combination therapy with both AmB and posaconazole or caspofungin has been examined; the drugs together exhibit synergy, but their efficacy is unclear. -The case fatality rate (CFR) with a combination of AmB and surgery is 18.5% and rises to 60% when AmB is used alone.

Table 2: continued

Thompson el al., [49]	2021	A retrospective study	204	-104 patient received ISAVUSULF (isavuconazonium sulfat): - 74 as a primary therapy: o 24 monotherapy o 50 combination with other antifungal therapies (AFT) - 30 as non-primary: o 11 monotherapy o 19 combinations with other anti-fungal therapy. -100 patient received other AFT: o 30 as monotherapy o 70 as combination therapy.	All cases of mortality at days 42 and 84.	-This study supports the effectiveness and tolerability of ISAVUSULF in clinical practice. -This study confirmed the benefit of ISAVUSULF combination therapy rather than monotherapy.
Sreehari, et al., [50]	2022	A retrospective analysis	350	Not observed the treatment after surgery		-discharged 91.7%, death 8.3%
P Pranave et al., [51]	2021	Case Series	7	**Functional Endoscopic Sinus Surgery (FESS) was done for all cases.** **Case 1**- I.V. AmB (2 mg/kg/day) was given to the patient for eight days, and then posaconazole (200 mg) was given twice a day for the next 28 days, one tablet twice daily. **Case 2**- Started on IV L-AmB (2 mg/kg/day) and I.V. ciprofloxacin as broad-spectrum antibiotics (400 mg). **Case 3**- AmB was administered for three weeks at 1.5 mg/kg/day, then 3 mg/kg/day for two weeks. **Case 4**- AmB was administered at 1.5 mg/kg/day for three weeks, followed by 3 mg/kg/day for 18 days. **Case 5**- The maxillary sinuses were surgically debrided after one week of treatment with IV AmB (2-3 mg/kg/day). **Case 6**- Chlorhexidine antiseptic mouthwash (0.2%) and 3% hydrogen peroxide solutions were administered for three weeks. Following that, monocef 1 g/12 hourly was administered according to the previous protocol. **Case 7**- IV AmB was administered at 1 mg/kg/day as an infusion in 100 mL of 5% dextrose (1-2 h).		**Case 1**-Two weeks later, the patient was discharged from the hospital. **Case 2**-the patient died. **Case 3**- Two weeks later, the patient was discharged from the hospital. **Case 4**- the patient was discharged after 28 days with an improved condition. **Case 5**-He was discharged after 14 days with satisfactory wound healing. **Case 6**- The patient was discharged from the hospital after healing the wound. He developed a respiratory disorder and extensive pneumonia, and he expired after one month of treatment. **Case 7**- The patient was discharged one month postoperatively (after wound healing).

Table 2: continued

-Anne H. van Burik et al., [37]	2006	Retrospective	91	-Patients had mucromycosis (69 proven cases; 22 probable cases) which was refractory to prior antifungal treatment or were intolerant to such treatment.	Activity of posaconazole for treatment of mucormycosis for at least 30 days.	-Twenty weeks later, all cases had responded to medication (partial or complete response); the overall response rate following the initiation of posaconazole treatment was 60% (14% complete response, 46% partial response, 21% had stable disease, 17% recovery insufficiency, and 2% were impotent to determine the consequence). - The immunocompromised patients treated with posaconazole monotherapy or in combination with L-AmB showed no statically significant difference. - Whether patients underwent adjunctive surgical procedures or not, the success rate was significant. -After being treated with posaconazole for 30 days, the patient died, inverting the effect of posaconazole therapy but not overcoming the aggressive nature of the disease. -After posaconazole was received for one month, 38% of the patients died.

Table 2: continued

Caitlin Reed et al., [38]	2008	Retrospective review	41	AmB + caspofungin AmB monotherapy L-AmB monotherapy L-AmB +caspofungin		-Patients treated with AmB + caspofungin ***had superior success*** (100% vs. 45%; *P* = 0.02) and Kaplan-Meier survival time (*P* = 0.02), rather than patients´ recovery with AmB monotherapy. - L-AmB monotherapy had inferior success (37% vs. 72%; *P* = 0.03) and a ***higher clinical failure rate*** (45% vs. 21%; *P* = 0.04), than patients treated with AmB monotherapy. - L-AmB and caspofungin combination therapy had better outcomes (100% vs. 20%; P =.009) and survival times (Pp =.001) than patients treated with L-AmB monotherapy. - When compared to monotherapy, the synergistic effect of combination therapy was most pronounced with cerebral disease (success rate, 100% vs. 25%; P =.01). -The combination therapy was significantly associated with enhanced recovery.
Belinda Shao et al., [52]	2022	Case Report	1	Autopsy revealed a cerebral mucormycosis infection.	-The starting dose for L-AmB is 5mg/day (24-26) although some literature supports a doses closer to 10 mg/day. -Removal of the affected necrotic and infracted tissue can improved the survival rate.	- The patients with mucormycosis and COVID-19 coinfection, surgery appears to decrease mortality and disease progression.

Surgical management

In the case of the patient with pulmonary infections and multifocal disease, the surgery was less effective. Endoscopic approaches were recommended for early and extensive disease[17]. Surgical intervention has been reduced because of the deformed function and possible disfigurement after radical surgery[23]. Furthermore, antifungal agents did not reach the infectious site due to tissue necrosis and thrombosis of blood vessel, which were the results of mucormycosis. Therefore, the eradication of tissue necrosis may be significant for the overall eradication of mucormycosis[23].

Caitlin Reed et al. reported a study of 41 patients with rhino-orbital mucormycosis exposed to surgical eradication. They observed that 25% (10 of 41 patients) revealed no necrosis after surgical procedures. Patients underwent two surgical procedures (ranging from one to six). Furthermore, complete orbital exenteration (surgical removal) was performed in 59% of cases (24 of 41 patients) but was not associated with improved survival. Survival was not altered on the basis of whether exenteration was performed during several surgical procedures[38].

On the other hand, Vetriselvan Subramaniyan et al.[1] observed that the most effective method for radical amputation was endoscopic sinus surgery (ESS). ESS helped in the recovery of nine rhinocerebral mucormycosis patients, of which six patients underwent only ESS, whereas the remaining three patients underwent ESS in addition to the transantral procedure. Studies have shown that the recovery of rhinocerebral mucormycosis with ESS alone or in combination with traditional surgical procedures offers the benefit of lower operative morbidity and higher operative accuracy. As soon as the patient was diagnosed with rhinocerebral mucormycosis (ROCM), surgical excision is recommended. Because of its high mortality rate, ROCM remains a difficult disease to treat. So the treatment includes a combination of eradication of the tissue necrosis and antifungal therapy[17,53].

Adjunctive therapies for mucormycosis

Immunosuppression with corticosteroids should be restricted to proper indications. Moreover, patients with HIV/AIDS should receive antiretroviral therapy to restore their immunity. Furthermore, uncontrolled hyperglycemia should be managed, preferably via insulin therapy. In addition, administration of sodium bicarbonate hinders overrunning endothelial cells and retrieving host iron chelation and neutrophil function[1]. The recovery with hyperbaric oxygen (HBO), which increased oxygen pressure, improved the neutrophil function. Inhibition of fungal growth and improved wound healing are obtained by high oxygen pressure. Furthermore, HBO treatment for mucormycosis includes surgical and antifungal therapy as adjunctive therapies. However, this treatment was sophisticated. In the absence of systematic clinical studies evaluating the role of HBO for mucormycosis, it's not recommended for the treatment strategy[54].

Future perspective

Improvements in prevention, recovery, and diagnosis of mucormycosis remain challenges. To enhance detection and therapeutic monitoring, new radiographic, molecular, and antigenic tools are demanded. Clinical trials are the remaining challenge that will be required to improve mucromycosis treatment. Furthermore, prospective randomized studies (clinical data) are also required to perfect therapeutic management. Finally, comprehension of the metabolism, molecular, and immunological properties of these organisms is essential for treatment[39].

Conclusion

A large international trial combining the new extended-spectrum triazole with other antifungal therapies (AmB) for mucromycosis treatment is currently underway. AmB, a lipid modification, is still essentially for mucormycosis treatment**.** Posaconazole is considered the second drug of choice against these fungi. It gives promising results *in vitro*, *in vivo* (in animal studies), and in clinical trials in humans. Combination therapies with new triazoles may also be considered alternatives to enhance the permanence of patients suffering from mucormycosis. So, combination therapy could be a promising solution for recovery, especially in many cases of mucormycosis associated with COVID-19 syndrome. This combination might decrease the nephrotoxicity caused by AmB and enhance the therapeutic efficacy of the therapy. Novel drug purposes, the development of a "pragmatic" perspective, multicenter studies, and registries are all necessary for developing more effective treatment strategies.

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التأثير التآزري للعلاج المركب المضاد للفطريات لداء الغشاء المخاطي في سياق عدوى كوفيد-١٩ ؛ مراجعة منهجية

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داء الغشاء المخاطي هو عدوى فطرية نافذه تم التركيز عليها خلال السنوات القليلة الماضية في سياق عدوى. COVID-19 مرضى COVID 19 معرضون بشدة للعدوى الفطرية لأنهم دائما ما يعانون من نقص المناعة. تساءلنا عما إذا كان العلاج المركب المضاد للفطريات قد يقدم بديلا أكثر فعالية، وأقل سمية، لداء الغشاء المخاطي. استعرضنا الأبحاث التي تغطي العوامل المضادة للفطريات لداء الغشاء المخاطي، سواء كعلاج وحيد أو مجتمعة. استنتجنا أن العلاج المركب يمكن أن يكون علاجا واعدا لداء الغشـــاء المخاطي، خاصـــة في الحالات المرتبطة بعدوى. COVID-19 هذا المزيج يمكن أن يقلل من السمية الكلوية التي يسببها الأمفوتريسين B ، الخيار الرئيسي في علاج داء الغشاء المخاطي ، ويعزز فعاليته العلاجية.