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REVIEW ARTICLE

RHINO- ORBITAL-CEREBRAL MUCORMYCOSIS: CLINICAL PROFILE, POTENTIAL DIAGNOSIS AND RECENT TREATMENT ADVANCES IN COVID-19 ERA

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Abstract

Mucormycosis is a fungal infection which get worsens with time if not diagnosed and treated. The present COVID-19 pandemic has been associated with mucormycosis, an infection caused by fungi. Patients who possess impaired immune systems are easy targets for COVID-19 and mucormycosis. As COVID-19 infection results in a weakened immune system, COVID-19 patients have relatively high infection risk. Additionally, as we pointed out in case studies below, diabetes, corticosteroids, and a compromised immune system are the most common risk factors for this infection. Patients with COVID-19 who get steroids can experience adverse impacts on their health, and the condition frequently experiences diseases such mucormycosis.There are therapies, however they are less successful and not as optimistic. Therefore, the focus of study is to investigate potential treatments for mucormycosis. According to reports, mucormycosis has been successfully treated early on using liposomal amphotericin B (AmB), manogepix, echinocandinsisavuconazole, posaconazole, and other promising therapeutic agents. Due to their higher safety and efficacy, lipid formulations of AmB have replaced other treatments for mucormycosis as the norm. We included case reports involving mucormycosis infections in COVID-19 patients in the present study.For component of an immediate worldwide reaction to prevent and treat this deadly disease, particularly for individuals with documented risks, we also focused on anti-mucormycosis drugs including mechanisms of action of different therapeutics, including coverage of new antifungal medications under investigation.

Introduction:-

Infections with fungi have been more common during the past 20 years or more, and the number of persons who have acute immunosuppression has significantly increased in addition [1]. The fungus species Mucor spp., Rhizopus spp., Rhizomucor, Lichtheimia spp., and others in the order Mucorales are responsible for the fungal infection referred to as mucormycosis. The majority of people are exposed to these organisms every day since they are so common in the environment [2]. Due to the opportunistic nature of mucormycosis, those with weakened immune systems are more susceptible to contracting the infection. According to current studies, the number of immunocompromised people with diseases including diabetes, hematologic malignancies, hematopoietic stem

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cell/solid organ transplant, or trauma has significantly increased, which has led to an increase in mucormycosis [3]. Additionally, this was a mucormycosis outbreak in India among people who had the 2019 Coronavirus Disease (COVID-19), particularly in people with uncontrolled diabetes [4]. The widespread epidemic of mucormycosis is also caused by hypoxemia linked to COVID-19 and excessive glucocorticoid treatment.The risk of mucormycosis may have increased among COVID-19 individuals because of a high iron level brought on by hyperferritinaemia [5]. Subsequently, mucormycosis instances associated with COVID-19 emerged globally [6]. Mucormycosis can appear different clinically. The most serious symptoms is seen in diabetics with ketoacidosis, which frequently develop rhino-orbital-cerebral mucormycosis rather than pulmonary mucormycosis [7]. Despite having fewer instances than candidiasis, cryptococcosis, or aspergillosis among immunocompromised people, Mucorales infection nonetheless has serious effects because it is associated with an elevated death rate. Mucormycosis is additionally frequently incorrectly diagnosed and frequently only discovered after death. This review's focus is on the management and treatment of mucormycosis; it is not intended to cover the full spectrum of this disease. Mucormycosis management strategies generally complicated and depend on utilising of a number of therapies at once. These therapies range from surgical debridement of necrotic lesions to successful mono- or combination antifungal therapy, as well as early clinical detection and management of underlying health conditions (such as diabetes) [8]. Mucormycosis must be diagnosed and treated as soon as possible because it is nearly always fatal if left uncontrolled. Delaying therapy is not an option.

A brief taxonomy of black fungi

The Zygomycota are a subclass of lower fungi that have coenocytic, nonseptatethalli. One zygospore—a black, thick-walled, frequently ornamented sexual spore—is created after the fusion of isogamic sex organs (gametangia). In the host tissue, their broad, aseptate, hyaline, randomly branching hyphal components can be seen. Zygomycota are divided into two classes and eleven orders. The Entomophthorales, which have spores that are violently ejected, and the mucorales, whose spores develop from sporangial plasma cleavage and are passively released, being the only two of those that contain clinically significant fungus. The Mucorales family is among the most important in terms of medicine.Its members are widely dispersed and can be found in soil, food, and the air. Eleven genera with 22 species of medical importance have been named and illustrated by Dolatabadi and Guarro. The two of the most prevalent and significant mucoralean genera found in clinical laboratories are Rhizopus and Absidia [9, 10]. A variety of moulds in the fungal family "Mucorales" are the source of the uncommon, invasive, and opportunistic infection known as mucormycosis, which can occasionally be fatal. This fungus is pervasive and occurs naturally in soil, plants, manures, decaying fruits, and vegetables [11].

The etiology and epidemiology of black fungus

Only a dozen or so of the estimated 1.5 million fungal species that have been associated to human diseases are typically seen in clinical settings. Comparing to other infectious diseases, life-threatening fungal diseases are uncommon in populations of immunologically healthy humans, in spite of the lack of harmful fungal species. Human illness is rare, in contrast to a high rate of infection among people who live in fungus-rich environments. Because of this, only a small number of fungal species are pathogenic, and those that are rare causes of fatal sickness [12]. These epidemiological findings may have impacted the belief that fungi are less likely to be used as biological weapons. Fungal infections are usually divided into two categories, depending on whether the organism is acquired from a host or the environment. Pathogenic fungi that are obtained from the host include Candida spp., Malassessia furfur, and Dermatophytes [13]. These organisms are typically present in the host's flora and only result in disease when the balance between the host and the microbes is upset. For instance, a damaged integument, the use of antibacterial medications, the use of corticosteroids, and immune suppression are all associated with human candidiasis. Unless the host-microbe relationship is broken, fungi taken from other hosts, such as Candida spp., are typically low pathogenic organisms that rarely cause disease.

Pathogenic fungi that can be obtained from the environment include Cryptococcus neoformans, Aspergillus spp., and the dimorphic fungus. These microorganisms regularly infect humans who are exposed to them, although disease is rare unless the host's immunity is weakened [14]. As an illustration, previous to the creation of efficient antiretroviral drugs, the prevalence of cryptococcosis in AIDS patients was as high as 10%, although it is less common than one case per 100,000 in the general population. However, the introduction of antiretroviral drugs in areas with access to therapy greatly reduced the prevalence of cryptococcosis in HIV patients, underscoring the illness' dependency on the immunological health of the host population. Some of these organisms are able to remain in the host in a dormant state. Initial infection with environmentally acquired fungus is primarily acquired through inhalation, and the result is either asymptomatic or mild illness. The vast majority of first infections caused by

Coccidioides spp. are benign and cause no symptoms [15]. The disease that results from environmental fungi infecting the host is serious, challenging to cure, and frequently fatal. Few of the fungi that can be found in the environment can be passed from one host to another, and the main cause of illness clusters is specific exposures. For instance, pulmonary histoplasmosis outbreaks in individuals with a seemingly normal immune system have happened following tree-trimming and cave exploration. Environmentally acquired pathogenic fungi are not contagious, which restricts their potential for indiscriminate use as weapons but also makes them intriguing because they are unlikely to damage friendly soldiers who are not exposed [16].

Transmission method and related problems

The sinuses and lungs are frequently affected by fungal spores that are inhaled into the body. Infection of the skin can also occur when they pass through cuts or other open wounds. Patients who have severe COVID-19, especially those in the intensive care unit (ICU), require additional care and cleanliness since they are more susceptible to bacterial and fungal infection. Over the past few months, reports of various fungi illnesses besides black fungus have been made from all over the world. Other than black fungus, aspergillosis or invasive candidiasis is the most typical fungus infection found in COVID-19 patients [17]. Those infected fungal diseases are more frequently reported and have the potential to be fatal or seriously unwell. Recognizing the potential for bacterial and fungal co-infection is crucial for prompt diagnosis and treatment, which will help stop catastrophic disease and death brought on by these infections [18, 19], including COVID-19. Some medical professionals believe that this infection may be related to the use of steroid medications during the treatment of COVID-19 patients to lessen the patients' pulmonary inflammation, but regrettably this caused and pushed up sugar levels in both diabetic and non-diabetic patients in SARS-CoV-2 [20], consequently the patient's immunity was previously weakened.For example, "Diabetes lowers the body's immune system, coronavirus exacerbates it, steroids used to treat COVID-19 act like fuel to fire, and reductions in immunity may quickly lead to this black fungus infection." The next section goes into more detail regarding the unexpected black fungus outbreak, its signs and symptoms, and other COVID-19-related issues.

Current issues with black fungus in COVID-19 patients

A wide variety of opportunistic bacterial and fungal diseases have been connected to the coronavirus [21]. According to reports, the predominant fungal infections infecting COVID-19 patients and causing disease are aspergillosis or invasive candidiasis [22]. Variations in pathophysiology, diagnosis, and complications may be linked to a wide spectrum of illness types following the December 2019 outbreak in China. As rhino, orbital, and cerebral mucormycosis in COVID-19, the disease is present. During the COVID-19 sickness, several cases of this nature have been reported [23].Patients may have acquired immune deficiency syndrome, diabetes mellitus, haematological malignancies, or iatrogenic immunosuppression. Because of the breakdown of the endothelium barrier and reduced oxygen diffusion capacity in the COVID-19 state, hypoxic conditions developed [24]. The immunological response of COVID-19 individuals may be altered by severe lymphopenia with a decreased number of T lymphocytes (CD4+T and CD8+T cells), increasing the probability of invasive fungal infections. The COVID-19 virus and fungi both have symptoms that are very similar. Here are a few of them: heat, discomfort, headache, redness and periocularedoema, drooping eyelids, restrictions on ocular mobility, and excruciating vision loss [25]. It often only takes two days to advance, on average, from the beginning. Symptoms of exposure keratitis include edoema of the eyelids and periocular area, complete ptosis, total ophthalmoplegiaproptosis, relative afferent pupillary defect, unilateral facial or orbital pain, double vision or vision loss, chemosis, sinusitis, nasal discharge, and neurological signs and symptoms. a number of factors, including how severe the disease is, the clinical profile of coronavirus patients who have this fatal fungal infection varies.

Clinical profile and cases of mucormycosis infection in corona patients

This section will cover investigations carried out in various parts of the world as well as the clinical profile of mucormycosis. The nose, eyes, and brain are all impacted by fungus mucormycosis in rhino-orbito-cerebral mucormycosis (RCOM)[Figure-1.]. The bone cavity that surrounds the eye and brain gets infected by this fungal infection, which originates in the nose and spreads quickly. The patient initially experiences nasal discharge. This could hurt within the nose or be bloody or blocked. Following that, the patient develops facial pain and has numbness or swelling [26]. The patient has headache, orbital pain, periocularedoema, eyelid lowering, vision loss, and double vision with pain when the progression, as in the second stage, reaches the orbit. Typically, the passage only lasts two days on average after it starts. Additionally, there is impairment in jaw movement in the last stage. Lower jaw tooth begins to loosen, and there are changes in the skin's temperature, burning, or numbness. Near the eyes or nose, black eschar forms. The majority of patients with immunocompromising diseases develop pulmonary mucormycosis.The respiratory tract and lungs are both impacted by this infection. Haemoptysis is a condition

indicated by fever, shortness of breath, coughing up blood occasionally, and chest pain. Pleural effusion, in which fluid accumulates between the tissues lining the lungs and chest, was also noted in the patient as the infection progressed [27].

From August to December 2020, a retrospective investigation was conducted in the infectious disease department of Manipal Hospital in Bangalore, India.

10 patients with a 55-year-old median age.The COVID-19-related mucormycosis had been present for 8 years. Six of the ten patients who had diabetes and complained of significant eye pain, nasal obstruction, and face pain were given steroids. Tocilizumab was administered to one patient to treat COVID-19. Diabetes, hypertension, and chronic renal disease affected nine people. The remaining patients had mild to moderate illnesses, with the exception of one patient who had a severe COVID-19 infection. They administered COVID-19 therapy to AmB and local debridement of the necrotic and diseased tissue to all of the patients [28].

A further interesting study was conducted at Sawai Man Singh Medical Hospital in Jaipur, India, between August and December 2020, with a total of 23 patients. Eight women and fifteen men made up the group. Out of 23 patients, 19 had recovered and 4 were still COVID-19 positive at the time of treatment. 21 patients had diabetes, 12 had uncontrolled blood sugar, 9 had controlled diabetes, 14 had hypertension, and 1 had renal failure. Steroids were utilised to treat COVID-19 in all 23 cases. Now that they are all dealing with invasive mucormycosis, they all underwent surgery while keeping in mind thorough surgical dissection and intravenous amphotericin [29].

At the Department of Otorhinolaryngology and Head & Neck Surgery, KS Hegde Medical Academy, NITTE University, Mangalore, Karnataka, another case study was conducted on a 32-year-old woman with uncontrolled diabetes. She complained of left facial ache and full left eye ptosis. The left ethmoid was completely opaque on her CT scan of the nose and paranasal sinus, and the maxillary and frontal sinuses suggested fungal sinusitis. A COVID-19 test was performed and was positive; the doctor requested emergency endoscopic surgery; and after the surgery, AmB (25 mg/day) dose had been given. The patient was monitored for two months. Although there was less face pain, here was no improvement in eyesight [30].

Figure 1:- The nose, eyes, and brain infected by fungus mucormycosis in rhino-orbito-cerebral mucormycosis (RCOM).

Mucormycosis reasons in COVID-19 patients

The severe black fungal infection has been attributed to a number of factors. Multiple investigations have demonstrated that steroids decrease the capacity for fighting off other infections and help lower mortality in COVID-19 patients with low oxygen saturation levels. Patients with COVID-19 who had diabetes, chronic renal disease, or chronic liver disease who were already immunocompromised were taking steroids frequently for a long time and not at a set dose. They greatly increase the chance of developing mucormycosis as this condition affects persons with impaired immune systems and high blood sugar levels. Consequently, this increase is possibly related

to the incorrect treatment of diabetes and the wrong use of steroids to treat COVID-19 patients. Because steroids raise blood sugar levels, the blood becomes more acidic [31]. This fungus thrives in an acidic environment and high blood sugar levels. In filthy circumstances, this fungus has the ability to harm something. However, steroids are not just the bad guys in this fungus infection; they are also a contributing factor. Dr. Hegde claims that the virus is harmful and that it raises blood sugar levels to risky elevations. Surprisingly, a lot of young people are being harmed by the fungus. [32].Also linked to the pathophysiology of mucormycosis is the destruction of mononuclear and polymorphonuclear phagocytes in healthy hosts. Mucorales cause invasive mucormycosis in neutropenic people and those with damaged phagocytes by generating oxidative metabolites and defensins.In advanced infections, viral replication exacerbates the inflammatory response and the migration of neutrophils and monocytes into the circulation, and COVID-19 exhibits significant lymphopenia [33]. A systemic fungal infection is more likely to affect the patient as a result of this imbalance in neutrophil and lymphocyte activity. In addition to other causes, oxygen cylinders and environmental dampness can both be significant sources of mucormycosis infection because old oxygen cylinders can spread the disease. A shortage of pure water in the equipment, which has become standard in most towns dealing with the hospital bed scarcity, is one of the other possible reasons of the fungal infection [34]. Other possible reasons include inappropriate oxygen cylinder use, filthy masks, and unclean masks. The explanations listed above could be the main variables that lead to mucormycosis in COVID patients.

Diagnosis of mucormycosis

Mucormycosis has a high mortality rate and is challenging to diagnose in its early stages, especially in immunocompromised patients [35]. It is crucial to distinguish this sickness from invasive aspergillosis because antifungal treatment may vary and because the clinical appearance and underlying co-morbid diseases are frequently identical. Identification of possible mucormycosis necessitates a thorough medical history, physical examination, and imaging. In diabetes patients, bone degeneration is a frequent finding on a cranial CT. As the results will show any involvement of the brain, sinuses, or orbit, a cranial magnetic resonance imaging (MRI) is advised for increased sensitivity. Radiology will show the stage with relation to sinus and brain involvement. Planning should go into sending a biopsy for direct microscopy and standard media culture at 30/37 degrees Celsius. Susceptibility testing can then be required for a subsequent procedure [36]. Diagnostic methods for mucormycosis in most rural areas are based on insufficiently basic microbiology, which has caused delays in diagnosis. The diagnosis of mucormycosis is not helped by the detection of circulating antigens such galactomannan and D-1, 3-glucan, unlike invasive aspergillosis. As a result, samples from the anatomical site of infection are frequently needed in addition to culture and clinical aspects for the diagnosis of mucormycosis. The most recent molecular biology methods now make it possible to diagnose mucormycosis without using any invasive procedures [37]. In order to target Mucor/Rhizopus, Lichtheimia, and Rhizomucorxvi, Million et al. developed a qPCR based on the 18S rRNA of Mucor/Rhizopus, Lichtheimia, and Rhizomucorxvi. The PCR assay's objective is to identify Mucorales DNA in serum, which is the bloodstream [38]. In patients with haematological malignancies who had proved or suspected mucormycosis, a study examined the utility of Mucorales-targeting real-time PCR on tissue and respiratory samples. In order to detect pulmonary mucormycosis early in individuals with COVID-19 infections, reverse halo sign on computed tomography scans combined with serum qPCR targeting Mucorales are now necessary.

Antifungal drugs for treating mucormycosis

The promising treatment discovery against mucormycosis is a goal of research. In mice with disseminated mucormycosis, echinocandin and lipid polyene combinations improved survival rates [39]. Most often prescribed medication for the treatment of mucormycosis is AmB. It is crucial to monitor renal function closely when using AmB due to the increased risk of nephrotoxicity. Second-line medications may be tried if the condition is severe. Echinocandin and AmB combination therapy is advised as a secondary course of action. A polyene skeleton is added when echinocandin and AmB are combined, improving the likelihood that the treatment will be effective. Other renowned second-line antifungals include triazoles, posaconazole, and isoconazole.Triazoles prevent the process of 14-demethylation, which raises the dangerous 14-methyl sterol and alters the permeability of fungal membranes. When patients who are intolerant to AmB, posaconazole is used. Isaconazole has a wide-ranging impact. It is the only antifungal drug capable of cure invasive mucormycosis as a result [40]. Until clinical indications and symptoms, radiological signals, and underlying immunosuppression have all disappeared, the antifungal treatment should be continued. The best antifungal dosage for treating mucormycosis is uncertain and mostly depends on the patient's health and test findings. Additionally, whether suspected or confirmed, mucormycosis requires consultation with the surgical team. During surgical debridement, clear margins are crucial to halt the spread of the fungus. It is employed as an urgent treatment. Upon samples collected during surgery,

histopathology and microbiological diagnostics can be carried out. The dread of such fungi infections can significantly decrease thanks to the aforementioned methods and treatment plans.

Polyenes

The majority often used mycosaminepolyene macrolide in antifungal therapy is amphotericin B (1, AmB). Scientifically, this polyene binds to ergosterol (2) and creates ion channels in the fungal cell membrane. As a result, the membrane integrity is lost, and essential cytoplasmic components may leak through these channels and kill the fungal cell. Burke et al.'s research indicates that the mycosamine sugar is essential for promoting the direct binding contact between AmB and the hydroxyl group of ergosterol, which results in the creation of ion channels. Additionally, AmB attaches to the plasma membrane's surface and physically extracts ergosterol (ergosterol sequestration), which causes the membrane's essential component to be depleted and eventually leads to cell membrane malfunction. Reactive oxygen species (ROS) can damage proteins, lipids, and mitochondria when AmB is present [41, 42, 43, 44]. AmB has been successfully used as a fungicide against mucormycosis and multidrug-resistant fungus thanks to various formulations. These formulations have shown impressive and all-encompassing effectiveness against several fungi that cause mucormycosis. AmBdeoxycholate has a therapeutically recommended dose of 1-1.5 mg/kg/day [45, 46], which has been proven to be extremely harmful for patients with fungi illnesses.Interestingly, compared to AmB, the various lipid formulations of AmB were shown to be much less nephrotoxic. It is safe to use bigger doses for a longer period of time with this antifungal drug's lipid formulation. High-dose liposomal AmB (15 mg/kg/day) was discovered to be much more efficacious in vivo than AmB (1 mg/kg/day) in the treatment of diabetic ketoacidosis in murine mice infected with R. oryzae. When compared to AmBdeoxycholate, the liposomal AmB survival rate was found to be almost twice as high [47]. A clinically validated therapeutic alternative for the initial management of mucormycosis is lipid formulations of AmB. Preclinical and clinical studies have confirmed the efficacy of this AmB lipid formulation. Treatments for mucormycosis commonly involve different lipid formulations of AmB, such as lipid complex, colloidal dispersion, and liposomal AmB [48]. Another naturally occurring polyene antifungal drug is natamycin (3). Walther et al. compared the antifungal properties of natamycin to those of AmB, terbinafine, isavuconazole, itraconazole, and posaconazole when treating 101 mucoralean strains from the genus Mucor, the closely related species Cokeromycesrecurvatus, Rhizopus, Lichtheimia, and Rhizomucor. In comparison to AmB and posaconazole, natamycin was found to be less effective against a variety of fungi strains [49].

Azoles

Azoles are frequently employed as antifungal drugs in clinical settings. The fungal lanosterol 14-demethylase (LDM), which catalyses the synthesis of ergosterol in fungal cells, is inhibited with these medicinal compounds. The ERG11 gene's lanosterol 14-demethylase reacts differently to various triazoles. Ergosterol content in the fungal cell membrane is reduced as a result of LDM inhibition, which results in less fluidity, growth inhibition, and fungal pathogen death [50]. Fluconazole, Itraconazole, and Voriconazole were discovered to have little to no effect against the fungi that cause Mucormycosis. The clinical results of recently published azoles, such as posaconazole and isavuconazole, have shown dramatically increased in vitro antifungal activity against mucorales and propose their use for the treatment of mucormycosis.

Itraconazole

The commercially available antifungal azole-based medication itraconazole (4) has remarkable invitro action against mucormycosis [51]. Itraconazole is a successful treatment for mucormycosis, according to numerous case reports and investigations [52, 53]. While Rhizopus and Mucor spp. we’re not discovered to be responsive to itraconazole in in vivo experiments, itraconazole shown anti-fungal action against fungal isolates in in vitro investigations [54, 55]. Itraconazole, in contrast, demonstrated in vivo efficacy against a hypersusceptibleAbsidia fungal strain with a MIC of 0.03 g/mL.These results imply that itraconazole should not be used as the first line of defence against this fatal illness, but that it may be utilised in specific clinical situations as a supplementary therapy in the presence of highly vulnerable fungal pathogens that are itraconazole-resistant.

Posaconazole

Posaconazole (5) and ravuconazole (6) are two significant triazole-based medicinal compounds under research that have antifungal properties. Excellent in vitro action against the fungi that cause mucormycosis has been shown for these compounds [56]. In an in vivo study using animal models, posaconazole was found to be less efficacious than itraconazole but more effective than AmB [57]. Posaconazole has been proven to be an effective medication in a number of expanding case reports for the management of refractory mucormycosis. Posaconazole and AmB have

been used successfully to treat patients with rhino-orbital-cerebral mucormycosis [58] and kidney and heart transplant recipients [59] who had not responded to AmB treatment. Posaconazole has shown a range of in vitro efficacy against different Mucorales species. Posaconazole's median MICs for treating Mucorales species varied between 1.0 and 8.0 g/mL, according to a study of 131 clinical isolates of the organism [60]. Posaconazole was found to be most efficient against several species of mucorales in an in vivo experiment, but it was ineffective against infection brought on by Rhizopus spp. [61, 62]. In a different investigation by Lewis et al., it was found that posaconazole serum concentrations more than 4.00 mg/mL were necessary to inhibit the growth of Rhizopus spp. strains in a murine model of pulmonary mucormycosis in immunosuppressed mice [63]. These results raised concerns about the antifungal posaconazole's therapeutic efficacy against Rhizopus species, which cause mucormycosis, at least at the current recommended dose of 0.30 g/day of extended-release pills.

Isavuconazole

Isavuconazole (7), a new triazole-based medicine with broad-spectrum antifungal activity, is derived from the prodrugisavuconazoniumsulphate. For the treatment of mucormycosis, this antifungal compound has received approval in the US and Europe. Due of AmB's impossibility, isavuconazole was approved in Europe. This anti-fungal medication comes in oral and IV formulations, and the recommended dosage is 0.20 g/three times/day for the first two days and 0.20 g/day after that. Isavuconazole demonstrated a number of pharmacokinetic and safety advantages over other antifungal azole drugs against mucorales [64, 65], including linear pharmacokinetics, fewer P450 interactions leading to fewer drug-drug interactions, no liver failure, nephrotoxic cyclodextrin free in the intravenous formulation, and adjusting the dose in kidney was not necessary.Isavuconazole's differed, species-dependent in vitro anti-Mucorales efficacy was discovered to because isavuconazole's MIC values against mucorales were discovered to be two to four times higher than those of posaconazole, it should be taken into account in clinical practise [68, 69]. In the lungs and the brain of neutropenic mice with mucormycosis, isavuconazole was as effective at reducing tissue fungal burden as high-dose liposomal AmB. In terms of survival, isavuconazole was beneficial for 21 days [70]. Isavuconazole may be an effective therapy for mucormycosis in people with significant immunosuppression, including those who have failed posaconazole, according to a number of other studies. The FDA has approved the broad-spectrum antifungal medication isavuconazoniumsulphate (8) for the treatment of invasive aspergillosis and invasive mcormycosis. The prodrugisavuconazoniumsulphate is rapidly hydrolyzed into the active form of isavuconazole (BAL-4815) and a non-active cleavage product (BAL-8728) by the enzymatic action of butylcholinesterase [71].

Echinocandins

Echinocandins, that are involved in the synthesis of the vital component of the fungal cell wall, include caspofungin (9), micafungin (10), and anidulafungin (11), which are selective and noncompetitive inhibitors of (1, 3) - D-glucan synthase (GS). The GS complex, which is part of the fungal cell membrane, is essential for preserving the stability and strength of the cell wall. Echinocandins exhibit their antifungal effect by noncompetitively binding to the GS complex's Fks p subunit and preventing the production of (1, 3)-D-glucan [72]. Due to an absence of cell wall integrity and an imbalance in intracellular osmotic pressure, this inhibition leads to the lysis and death of fungal cells. The echinocandincaspofungin is the first antifungal medication to be sold in the US. With regard to the fungi that cause mucormycosis, capofungin had negligible in vitro action [73, 74]. For the treatment of disseminated mucormycosis in diabetic ketoacidotic (DKA) mice, caspofungin (1 mg/kg/day) and AmB lipid complex (5 mg/kg/day) combined therapy responded synergistically [75, 76].

Combination therapy

For patients who have significant immunosuppression, a combination of therapy modalities is frequently used. Clinical advantages of this approach include the medications' synergistic effects and a larger coverage of infections than monotherapy [77]. Echinocandins (such as caspofungin and micafungin) and other antifungals are frequently used with AMB. A crucial enzyme for maintaining the fungal cell wall, (1, 3)-D-glucan synthase, is inhibited by echinocandins as their mode of action. AMB and echinocandins appear to work in concert, according to a retrospective investigation. According to this study, which involved diabetic individuals with mucormycosis, patients who got combination treatment fared better than those who only received polyenemonotherapy [78].

AMB and triazoles make up another combination of drugs, but the evidence for this combination is conflicting. While posaconazole and polyenes have a synergistic impact in vitro, there is no benefit to this combination in murine models. In a mouse mucormycosis model, however, a combined therapy using LAMB and isavuconazole

exhibits synergistic benefit [79]. This variation might be caused by the various Mucorales species' varied reactions to antifungal medications.

Surgery

Antifungal medicine distribution may be compromised during mucormycosis due to necrosis and thrombosis.As a result, removing the damaged tissue may be a vital method of treatment to totally get rid of the infection [80]. It should be highlighted that selection biases make it impossible to forecast how surgery will turn out. The patient's condition will determine the best surgical strategy. When the condition is severe, open surgery is used; when the disease is mild, endoscopic surgery is used [81]. According to reports, surgical intervention provides better outcomes than non-surgical treatment for individuals with rhino-orbito-cerebral mucormycosis and results in local infection control [82].

Conclusions:-

Mucormycosis is a fatal fungal disease with a poorly understood aetiology that frequently affects immunocompromised patients. People who are on hemodialysis, using high doses of glucocorticoids, have severe burns, or have uncontrolled diabetes mellitus are more likely to have this. In those suffering from disseminated disease, brain infection, or prolonged neutropenia, the mortality rate for this condition exceeds 40% and reaches 100%. This article offers a thorough analysis of the urgent global efforts that are currently being made to find and create therapeutic medicines for the treatment of mucormycosis.This study focuses primarily on the different treatments' mechanisms of action, including new antifungal drugs under investigation as a component of the critical worldwide effort to contain and treat this deadly infection. Numerous antifungal medications, as mentioned in this study, may be effective in treating this potentially fatal condition. Although it is strongly advised that these issues be the subject of extensive clinical study.

Declaration of competing interest –

The authors declare that they have no known financial or interpersonal conflicts that would have appeared to have an impact on the research presented in this study.

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References:-

1. Hussain, M. K., Ahmed, S., Khan, A., Siddiqui, A. J., Khatoon, S., &Jahan, S. (2023). Mucormycosis: A hidden mystery of fungal infection, possible diagnosis, treatment and development of new therapeutic agents. European journal of medicinal chemistry, 246, 115010.
2. Gomes MZ, Lewis RE, Kontoyiannis DP. Mucormycosis caused by unusual mucormycetes, non-Rhizopus, -Mucor, and -Lichtheimia species. ClinMicrobiol Rev. 2011; 24(2):411–45. Epub 2011/04/13.
3. Kauffman CA. Zygomycosis: Reemergence of an Old Pathogen. Clin Infect Dis. 2004; 39(4):588–590.
4. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Multicenter Epidemiologic Study of Coronavirus Disease-Associated Mucormycosis, India. Emerg Infect Dis. 2021; 27(9):2349–Epub 20210604.
5. Prakash H, Skiada A, Paul RA, Chakrabarti A, Rudramurthy SM. Connecting the Dots: Interplay of Pathogenic Mechanisms between COVID-19 Disease and Mucormycosis. J Fungi (Basel). 2021; 7(8). Epub 20210729.
6. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, et al. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. Lancet Microbe. 2022; 3:e543–e52. Epub 20220125.
7. Lanternier F, Dannaoui E, Morizot G, Elie C, Garcia-Hermoso D, Huerre M, et al. A Global Analysis of Mucormycosis in France: The RetroZygo Study (2005–2007). Clin Infect Dis. 2012; 54(suppl_1):S35– S43.
8. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis. 2012; 54(Suppl 1):S55–60. Epub 2012/01/25.
9. S. Dolatabadi, et al., Virulence of Rhizopus species compared with two alternative model systems, MucoralesBetween Food Infect. (2015) 135.
10. J. Guarro, J. Gen´e, A.M. Stchigel, Developments in fungal taxonomy, Clin. Microbiol. Rev. 12 (3) (1999) 454–500.

11. T.O. India, Explained: Mucormycosis Aka Black Fungus in Covid-19 Patients; Symptoms, Treatment and How to Prevent it, 2021. https://timesofindia.indiat imes.com/.
12. G.D. Brown, et al., Hidden killers: human fungal infections, Sci. Transl. Med. 4 (165) (2012), 165rv13-165rv13.
13. A. Casadevall, L.-A. Pirofski, The weapon potential of human pathogenic fungi, Med. Mycol. 44 (8) (2006) 689–696.
14. J. Karkowska-Kuleta, M. Rapala-Kozik, A. Kozik, Fungi pathogenic to humans: molecular bases of virulence of Candida albicans, Cryptococcus neoformans and Aspergillusfumigatus, ActaBiochim. Pol. 56 (2) (2009).
15. S.T. Denham, M.A. Wambaugh, J.C. Brown, How environmental fungi cause a range of clinical outcomes in susceptible hosts, J. Mol. Biol. 431 (16) (2019) 2982–3009.
16. J. He, et al., Isolated pulmonary mucormycosis in an immunocompetent patient: a case report and systematic review of the literature, BMC Pulm. Med. 21 (1) (2021) 1–8.
17. M. Hoenigl, Invasive fungal disease complicating coronavirus disease 2019: when it Rains, it Spores, Clin. Infect. Dis. (2020).
18. K.D. Beer, et al., Does pulmonary aspergillosis complicate coronavirus disease 2019? Crit. Care Explor. 2 (9) (2020), e0211.
19. N. Stone, N. Gupta, I. Schwartz, Mucormycosis: time to address this deadly fungal infection, Lancet Microb. 2 (8) (2021) e343–e344.
20. A. Rodríguez-Molinero, et al., Association between high-dose steroid therapy, respiratory function, and time to discharge in patients with COVID-19: cohort study, Med. Clínica 156 (1) (2021) 7–12.
21. M. Salehi, et al., Opportunistic fungal infections in the epidemic area of COVID- 19: a clinical and diagnostic perspective from Iran, Mycopathologia 185 (4) (2020) 607–611.
22. C. Firacative, Invasive Fungal Disease in Humans: Are We Aware of the Real Impact? Mem´orias do Instituto Oswaldo Cruz, 2020, p. 115.
23. A. Werthman-Ehrenreich, Mucormycosis with orbital compartment syndrome in a patient with COVID-19, Am. J. Emerg. Med. 42 (2021) 264. e5–e264. e8.
24. S. Imam, et al., Fungus in a Viral Land-Orbital Mucormycosis in Patients with COVID-19 Infection, 2021.
25. A. Maini, et al., Sino-orbital mucormycosis in a COVID-19 patient: a case report, Int. J. Surg. Case Rep. 82 (2021), 105957.
26. F. Yasmin, et al., COVID-19 associated mucormycosis: a systematic review from diagnostic challenges to management, Diseases 9 (4) (2021) 65.
27. U. Rajoor, A. Mahabalshetti, M. Dhananjaya, Clinical profile of mucormycosis: a study from teaching hospital in North Karnataka, India, Int. J. Intg. Med. Sci. 3 (3) (2016) 253–256.
28. N. Mishra, et al., A case series of invasive mucormycosis in patients with COVID- 19 infection, Int. J. Otorhinolaryngol. Head Neck Surg. 7 (5) (2021) 867–870.
29. S. Sharma, et al., Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum, J. Laryngol. Otol. 135 (5) (2021) 442–447.
30. H.E. Tamez-P´erez, et al., Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review, World J. Diabetes 6 (8) (2015) 1073–1081.
31. Q. India, Why does India have so many cases of post-Covidmucormycosis?. https://qz.com/india/2012257/why-india-has-so-many-cases-of-mucormycosis-o r-black-fungus, 2021.
32. B. News, Mucormycosis: the 'black fungus' maiming Covid patients in India. https://www.bbc.com/news/world-asia-india-57027829 2021.
33. N. Mishra, et al., A case series of invasive mucormycosis in patients with COVID- 19 infection, Int. J. Otorhinolaryngol. Head Neck Surg. 7 (5) (2021) 867–870.
34. A. Mishra, et al., the rising Havoc of the black, white and yellow fungi in India, Biotica Res. Today 3 (5) (2021) 418–420.
35. A. Skiada, et al., Challenges in the diagnosis and treatment of mucormycosis, Med. Mycol. 56 (suppl_1) (2018) S93–S101.
36. K. Alekseyev, L. Didenko, B. Chaudhry, Rhinocerebralmucormycosis and COVID- 19 pneumonia, J. Med. Cases 12 (3) (2021) 85–89.
37. S.S. Dadwal, D.P. Kontoyiannis, Recent advances in the molecular diagnosis of mucormycosis, Expert Rev. Mol. Diagn. 18 (10) (2018) 845–854.
38. L. Millon, et al., Early diagnosis and monitoring of mucormycosis by detection of circulating DNA in serum: retrospective analysis of 44 cases collected through the French Surveillance Network of Invasive Fungal Infections (RESSIF), Clin. Microbiol. Infect. 22 (9) (2016) 810. e1–e810. e8.

39. B. Spellberg, et al., Combination therapy for mucormycosis: why, what, and how? Clin. Infect. Dis. 54 (suppl_1) (2012) S73–S78.
40. K. Alekseyev, L. Didenko, B. Chaudhry, Rhinocerebralmucormycosis and COVID- 19 pneumonia, J. Med. Cases 12 (3) (2021) 85–89.
41. D.M. Kami´nski, Recent progress in the study of the interactions of amphotericin B with cholesterol and ergosterol in lipid environments, Eur. Biophys. J. 43 (10–11) (2014) 453–467.
42. T.M. Anderson, et al., Amphotericin forms an extramembranous and fungicidal sterol sponge, Nat. Chem. Biol. 10 (5) (2014) 400–406.
43. K.C. Gray, et al., Amphotericin primarily kills yeast by simply binding ergosterol, Proc. Natl. Acad. Sci. USA 109 (7) (2012) 2234–2239.
44. D.S. Palacios, et al., Synthesis-enabled functional group deletions reveal key underpinnings of amphotericin B ion channel and antifungal activities, Proc. Natl. Acad. Sci. USA 108 (17) (2011) 6733–6738.
45. A. Ibrahim, et al., Clinical Mycology, Zygomycosis (2003) 241–251.
46. K. Kwan-Chung, R.C. Young, M. Orlando, Pulmonary mucormycosis caused by Cunninghamellaelegans in a patient with chronic myelogenous leukemia, Am. J. Clin. Pathol. 64 (4) (1975) 544–548.
47. A. Sugar, Agents of mucormycosis and related species, Princ. Pract. Infect. Dis. 2 (2005) 2973–2984.
48. B. Spellberg, J. Edwards Jr., A. Ibrahim, Novel perspectives on mucormycosis: pathophysiology, presentation, and management, Clin. Microbiol. Rev. 18 (3) (2005) 556–569.
49. L. Wagner, et al., A revised species concept for opportunistic Mucor species reveals species-specific antifungal susceptibility profiles, Antimicrob. Agents Chemother. 63 (8) (2019) e00653-19.
50. L.-J. Ma, et al., Genomic analysis of the basal lineage fungus Rhizopusoryzae reveals a whole-genome duplication, PLoS Genet. 5 (7) (2009), e1000549.
51. Q.N. Sun, et al., In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes, Antimicrob. Agents Chemother. 46 (5) (2002) 1581–1582.
52. D. Quinio, et al., Zygomycosis caused by Cunninghamellabertholletiae in a kidney transplant recipient, Med. Mycol. 42 (2) (2004) 177–180.
53. D. Eisen, J. Robson, Complete resolution of pulmonary Rhizopusoryzae infection with itraconazole treatment: more evidence of the utility of azoles for zygomycosis, Mycoses 47 (3–4) (2004) 159–162.
54. E. Dannaoui, et al., Activity of posaconazole in treatment of experimental disseminated zygomycosis, Antimicrob. Agents Chemother. 47 (11) (2003) 3647–3650.
55. E. Dannaoui, et al., In vitro susceptibilities of zygomycetes to conventional and new antifungals, J. Antimicrob. Chemother. 51 (1) (2003) 45–52.
56. J. Van Cutsem, et al., Treatment of experimental zygomycosis in Guinea pigs with azoles and with amphotericin B, Chemotherapy 35 (4) (1989) 267–272.
57. M. Pfaller, et al., Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000, Antimicrob. Agents Chemother. 46 (4) (2002) 1032–1037.
58. Q.N. Sun, et al., In vivo activity of posaconazole against Mucor spp. in an immunosuppressed-mouse model, Antimicrob. Agents Chemother. 46 (7) (2002) 2310–2312.
59. A.M. Tob´on, et al., Mucormycosis (zygomycosis) in a heart-kidney transplant recipient: recovery after posaconazole therapy, Clin. Infect. Dis. 36 (11) (2003) 1488–1491.
60. L. Ide, et al., Zygomycosis in neutropenic patients with past Aspergillus infection: a role for posaconazole? Clin. Microbiol. Infect. 10 (9) (2004) 862–863.
61. R. Caramalho, et al., Etest cannot be recommended for in vitro susceptibility testing of Mucorales, Antimicrob. Agents Chemother. 59 (6) (2015) 3663–3665.
62. R.E. Lewis, N.D. Albert, D.P. Kontoyiannis, Comparative pharmacodynamics of posaconazole in neutropenic murine models of invasive pulmonary aspergillosis and mucormycosis, Antimicrob. Agents Chemother. 58 (11) (2014) 6767–6772.
63. A.-P. Bellanger, et al., Effect of preexposure to triazoles on susceptibility and virulence of Rhizopusoryzae, Antimicrob. Agents Chemother. 59 (12) (2015) 7830–7832.
64. B. Dupont, Pulmonary mucormycosis (zygomycosis) in a lung transplant recipient: recovery after posaconazole therapy, Transplantation 80 (4) (2005) 544–545.
65. N.V. Sipsas, et al., Therapy of mucormycosis, J. Fungi 4 (3) (2018) 90.

66. M.C. Arendrup, R.H. Jensen, J. Meletiadis, In vitro activity of isavuconazole and comparators against clinical isolates of the Mucorales order, Antimicrob. Agents Chemother. 59 (12) (2015) 7735–7742.
67. M.A. Donnelley, E.S. Zhu, G.R. Thompson 3rd, Isavuconazole in the treatment of invasive aspergillosis and mucormycosis infections, Infect. Drug Resist. 9 (2016) 79.
68. G. Luo, et al., Isavuconazole therapy protects immunosuppressed mice from mucormycosis, Antimicrob. Agents Chemother. 58 (4) (2014) 2450–2453.
69. D. Peixoto, et al., Isavuconazole treatment of a patient with disseminated mucormycosis, J. Clin. Microbiol. 52 (3) (2014) 1016–1019.
70. J. Ervens, et al., Successful isavuconazole salvage therapy in a patient with invasive mucormycosis, Infection 42 (2) (2014) 429–432.
71. B. Graves, et al., Isavuconazole as salvage therapy for mucormycosis, Med. Mycol. Case Rep. 11 (2016) 36–39.
72. A.C. Flick, et al., Synthetic approaches to new drugs approved during 2018, J. Med. Chem. 63 (19) (2020) 10652–10704.
73. M. Kurtz, C. Douglas, Lipopeptide inhibitors of fungal glucan synthase, J. Med. Vet. Mycol. 35 (2) (1997) 79–86.
74. A. Espinel-Ingroff, Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts, J. Clin. Microbiol. 36 (10) (1998) 2950–2956.
75. M. Del Poeta, W.A. Schell, J.R. Perfect, In vitro antifungal activity of pneumocandin L-743,872 against a variety of clinically important molds, Antimicrob. Agents Chemother. 41 (8) (1997) 1835–1836.
76. B. Spellberg, et al., Combination therapy with amphotericin B lipid complex and caspofungin acetate of disseminated zygomycosis in diabetic ketoacidotic mice, Antimicrob. Agents Chemother. 49 (2) (2005) 830–832.
77. Schwarz P, Cornely OA, Dannaoui E. Antifungal combinations in Mucorales: A microbiological perspective.Mycoses. 2019; 62(9):746–60.
78. Reed C, Bryant R, Ibrahim AS, Edwards J Jr., Filler SG, Goldberg R, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2008; 47(3):364–71. Epub 2008/06/19.
79. Gebremariam T, Gu Y, Singh S, Kitt TM, Ibrahim AS. Combination treatment of liposomal amphotericin B and isavuconazole is synergistic in treating experimental mucormycosis. J AntimicrobChemother. 2021; 76(10):2636–2639.
80. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. ESCMID andECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. ClinMicrobiolInfect. 2014; 20 Suppl 3:5–26. Epub 2014/02/01.
81. Spellberg B, Ibrahim A, Roilides E, Lewis RE, Lortholary O, Petrikkos G, et al. Combination therapy formucormycosis: why, what, and how? Clin Infect Dis. 2012; 54 Suppl 1(Suppl 1):S73-8. Epub 2012/01
82. Vironneau P, Kania R, Morizot G, Elie C, Garcia-Hermoso D, Herman P, et al. Local control of rhinoorbito-cerebral mucormycosis dramatically impacts survival. ClinMicrobiol Infect. 2014; 20(5):O336–9.