Infectious Medicine 3 (2024) 100112

Contents lists available at ScienceDirect

Infectious Medicine

journal homepage: www.elsevier.com/locate/imj

Review

Mucormycosis during COVID-19 era: A retrospective assessment

Tuhin Mukherjee[a], Tanisha Das[b], Sourav Basak[c], Satyajit Mohanty[a], Krishnendu Adhikary[d], Prity Chatterjee[e], Rajkumar Maiti[f,*], Prithviraj Karak[f,*]

[a] Department of Advanced Pharmacology, Birla Institute of Technology, Mesra, Ranchi 835215, Jharkhand, India
[b] School of Pharmaceutical Sciences (SPS), Siksha 'O' Anusandhan University, Bhubaneswar 751003, Odisha, India
[c] Department of Pharmacy, Guru Ghasidas Central University, Bilaspur 495009, Chhattisgarh, India
[d] Department of Interdisciplinary Science, Centurion University of Technology & Management, Odisha 761211, India
[e] Department of Biotechnology, Paramedical College Durgapur, West Bengal 713212, India
[f] Department of Physiology, Bankura Christian College, Bankura, West Bengal 722101, India

ARTICLE INFO

Keywords:
COVID-19
Mucormycosis
Fungal agents
Pandemic

ABSTRACT

In a retrospective view, this review examines the impact of mucormycosis on health workers and researchers during the COVID era. The diagnostic and treatment challenges arising from unestablished underlying pathology and limited case studies add strain to healthcare systems. Mucormycosis, caused by environmental molds, poses a significant threat to COVID-19 patients, particularly those with comorbidities and compromised immune systems. Due to a variety of infectious Mucorales causes and regionally related risk factors, the disease's incidence is rising globally. Data on mucormycosis remains scarce in many countries, highlighting the urgent need for more extensive research on its epidemiology and prevalence. This review explores the associations between COVID-19 disease and mucormycosis pathology, shedding light on potential future diagnostic techniques based on the fungal agent's biochemical components. Medications used in ICUs and for life support in ventilated patients have been reported, revealing the challenge of managing this dual onslaught. To develop more effective treatment strategies, it is crucial to identify novel pharmacological targets through "pragmatic" multicenter trials and registries. In the absence of positive mycology culture data, early clinical detection, prompt treatment, and tissue biopsy are essential to confirm the specific morphologic features of the fungal agent. This review delves into the history, pathogens, and pathogenesis of mucormycosis, its opportunistic nature in COVID or immunocompromised individuals, and the latest advancements in therapeutics. Additionally, it offers a forward-looking perspective on potential pharmacological targets for future drug development.

1. Introduction

In the wake of the COVID-19 pandemic, mucormycosis, also known as "Zygomycosis," emerged as a unique fungal infection that posed significant challenges to healthcare systems worldwide [1]. As we reflect on the experiences of the past years, it became evident that certain groups of people, particularly those recovering from COVID-19, were at higher risk of contracting this aggressive fungal infection [2]. Among patients with COVID-19, a range of complications including heart disorders, arrhythmias, thromboembolic disorders, and secondary infections heightened the risk factors during their recovery [3]. Moreover, studies revealed that immune suppression or pre-existing chronic conditions played a crucial role in the development of mucormycosis [4]. The mechanisms of mucormycosis manifestation indicated that the mold often gained entry through the respiratory tract, particularly via the nose and sinuses in the head and neck regions, with the potential to progress to orbital and intracranial structures. Early diagnosis and intervention were crucial for improved prognosis and reduced morbidity [5]. With advances in diagnostic techniques, successful identification of mucormycosis became possible through

Abbreviations: PCR, polymerase chain reaction; DM, diabetes mellitus; DNA, deoxyribonucleic acid; IFI, invasive fungal infections; AMB, amphotericin-B.

* Corresponding author.
E-mail addresses: rajkumar@bankurachristiancollege.in (R. Maiti), prithviraj@bankurachristiancollege.in (P. Karak).

https://doi.org/10.1016/j.imj.2024.100112
Received 21 December 2023; Received in revised form 14 March 2024; Accepted 8 April 2024

direct microscopic analysis, histopathology, systemic culture [1,3], β-D-glucan, galactomannan, and polymerase chain reaction (PCR) based assays. This comprehensive diagnostic rationale played a significant role in improving patient outcomes. The mortality rate associated with mucormycosis remained a concern, with a notable impact on diverse populations [6]. While the exact cause of mucormycosis in COVID-19 patients remained uncertain, experts speculated that the use of steroids during COVID-19 treatment might lead to immunological compromise, increasing susceptibility to the fungal infection [7]. Researchers hypothesized that the coexistence of fungal infections with COVID-19 might have led to potential misdiagnoses, drawing lessons from previous severe acute respiratory syndrome (SARS) and influenza data [8]. Critically immune-compromised COVID-19 patients were particularly at risk of developing invasive mycoses [9]. As we move into the future, the lessons learned from the COVID-19 era underscore the importance of vigilance in managing infectious diseases. It is imperative to prioritize measures to reduce immunosuppression when treating COVID-19 patients to mitigate the risk of mucormycosis. Continuous research and vigilance will be essential to stay ahead of emerging infections. In 2023 and beyond, healthcare systems must continue to implement robust safety measures to protect patients, especially those recovering from improved strains of COVID-19. Improved infection control protocols and early detection methods can contribute to the prevention and management of mucormycosis [10]. The collaboration between experts, scientists, and healthcare professionals will be vital in facing future health challenges effectively.

1.1. History of mucormycosis

Nothing has changed in the diagnosis and outcome of mucormycosis in its history, from Paltauf's first case in humans in 1885, to the publication of the first observation of rhino-orbital cerebral mucormycosis in 1943, to another study in 1955 of the first confirmed survivor [11]. Mucormycosis in any form; cerebral, cutaneous, rhinocerebral, intestinal, or pulmonary is still uncommon, but it should be suspected in diabetic or immunocompromised patients [12]. The normal therapies include amphotericin-B administration, surgical debridement of contaminated tissue, correction of the underlying cause, and adjunctive hyperbaric oxygen (HBO) therapy [13]. The typical outcome of mucormycosis was usually fatal but when breakthrough occurred in 1953, Charles Smith and William Winn contributed with the discovery of amphotericin-B. This pivotal discovery originated from a soil sample collected in Venezuela's Orinoco Basin [14]. Mucormycosis is much less common than candidiasis or aspergillosis [15]. Its prevalence, on the other hand, has recently risen. According to Brown's pioneered review, zygomycosis has become more common in the United States over the last 14 years, with this fungal infection being found in up to 6.8% of patients at autopsy [16]. Another research found that the virus is spreading through Europe. Better diagnostic methods, increased diabetes mellitus (DM) occurrence, and the use of immunosuppressive agents in the modern therapeutic era all contribute to this rise [17]. Three prior retrospective studies, conducted in 1971, 1994, and 1999, revealed an unexplained male gender preference for zygomycosis. The male-to-female ratio ranged from 2.4:1 to 3:1 [18]. Roden and other research associates published a broader research report in 2005 that supported this finding: 65 percent of the cases studied were male. In previous review studies, the average age was in the 30s to 40s [19]. Nevertheless, invasive mycosis can afflict a remarkably broad spectrum of individuals, spanning from neonates to the elderly [20].

1.2. Mucormycosis and the microorganisms involved

Mucormycetes, the fungi that activate mucormycosis, can be included in soil and rotting organic matter such as leaves, compost piles, and sewage sludge across the world. It has been determined through numerous studies and reviews that they are more abundant in the soil than in the air, and that they are more prevalent in the summer and fall than in the winter and spring [21]. Mucormycetes are challenging to prevent, because most people regularly encounter microscopic fungal spores. These fungi typically have little impact on the majority of individuals [22]. However, individuals with compromised immune systems are at higher risk of developing infections if they inhale mucormycetes spores, leads to lung or sinus infections that may progress to other parts of the body. Mucormycosis can be caused by various fungi [23], with mucormycetes belonging to the scientific order Mucorales. The most common culprits responsible for mucormycosis are species of *Rhizopus* and *Mucor* [24]. Other fungal species known to cause these infections include *Rhizomucor*, *Syncephalastrum*, *Cunninghamella bertholletiae*, *Apophysomyces*, *Lichtheimia* (formerly *Absidia*), *Saksenaea*, and *Rhizomucor* [25].

1.3. Physical and historical impact

According to some peer-reviewed journals, mucormycosis can infect a variety of organ systems. It has a wide range of clinical symptoms, but it is characterized by rapid progression [26]. The clinical manifestations are primarily determined by the fungus's mode of entry and the underlying disease. Spores that are aspirated into the paranasal sinuses and then enter the blood vessels in the tissues cause rhino-cerebral mucormycosis [27]. It has been studied that nasal cough or mucous discharge is the most common symptom, but facial numbness, blurred vision, sinus drainage, nasofrontal discomfort, ocular pain,

fever, diplopia, and chemosis are all other possible side effects [28]. Intranasal lesions are characterized by painless ulcers with exudation and necrotic tissue that develop quickly over days. A low threshold for having a biopsy to rule out mucormycosis should be preserved in an immunocompromised patient who has persistent nasal symptoms (often called "invasive fungal sinusitis" or IFS) [29]. Pulmonary mucormycosis is a rapidly progressive infection that occurs after inhalation of spores into the bronchioles and alveoli [30]. Fever, hemoptysis, dyspnea, and cough are the most common symptoms. Patients with hematological disorders are more likely to develop this clinical type. Bronchitis, bronchopneumonia, and even pulmonary embolism are all symptoms of this pulmonary disease [31]. It can induce cavitary symptoms that resemble tuberculosis or a milder allergic fungal infection, and it can potentially spread to other tissues including the mediastinum and heart [32]. Cutaneous mucormycosis may occur as a primary or secondary infection. The skin infection occurs as a result of direct inoculation in the primary disease and as a result of transmission from other locations in the secondary disease [33]. People who have burn wounds and traumatic skin wounds are more likely to develop the primary kind, which often manifests as a single, indurated zone of cellulitis that develops into a necrotic lesion; other expressions include abscess formation, skin edema, and tissue necrosis [34]. Consuming infected food can result in gastrointestinal illness, while the utilization of contaminated herbal remedies has also been associated with the emergence of gastrointestinal disorders. Gradual discomforts of the gastric, esophageal, and intestinal mucosa can occur, along with diarrhoea, hematemesis, and melena as symptoms [35]. Necrotic ulcers can cause perforation and peritonitis. Bowel corruption and hemorrhagic shock are often associated with a poor prognosis [36]. Gastro intestinal (GI) symptoms are uncommon, but rescue is feasible in the most profoundly immunocompromised individuals, due to the large immune tissue present in the GI tract, including cases involving leukemia patients and intestine transplant recipients [37]. The disseminated form of mucormycosis can develop from any original location of infection and exhibit ill-defined symptoms that make diagnosis extremely difficult [38]. A metastatic skin lesion, however, unmistakably indicates widespread mucormycosis and a dismal prognosis [39].

2. Mucormycosis pathogenesis

Infections are caused by a group of fungi, zygomycetes which includes organisms like Mucorales and Entomophthorales [40]. They are known as zygomycoses. Entomophthorales are uncommon causes of entomophthoromycosis, a form of subcutaneous and mucocutaneous infection that primarily affects immunocompetent hosts in developing countries [41]. Mucormycosis is a lethal fungal infection that impacts highly immunocompromised hosts in developed countries [42]. Mucorales are fungi that can be found in abundance in soil and rotting matter [43]. *Rhizopus* is a fungus that can be found in moldy bread. Since these fungi are so common, most people come into contact with them on a regular or weekly basis [44]. Despite this, they seldom cause disease due to the low virulence of the organisms; instead, they only affect people who have compromised immune systems [45]. Immunocompetent hosts with poorly regulated diabetes mellitus (especially ketoacidosis), glucocorticoids, and thrombocytopenia in the setting of hematologic or solid malignant tumors, implantation, iron deficiency anemia, and burns are at risk [46] (Fig. 1).

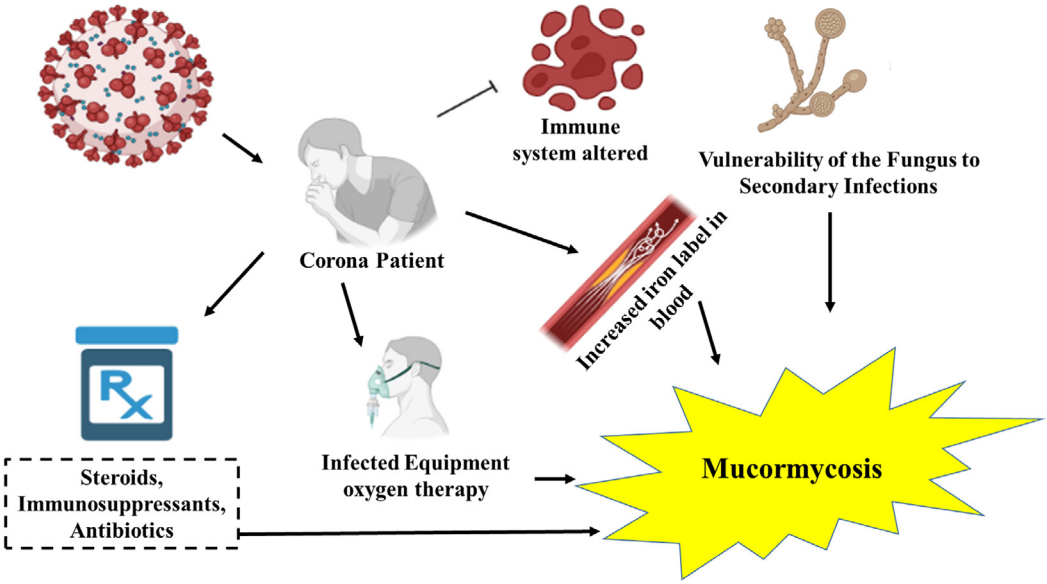

Fig. 1. Pathogenesis of mucormycosis.

2.1. Host defense mechanism

According to comprehensive research, mononuclear and polymorphonuclear phagocytes play a crucial role in eliminating Mucorales, utilizing oxidative metabolites and cationic peptides, in individuals with normal immune function [47]. These metabolites and peptides are collectively referred to as defensins [48]. Clinical evidence suggests that these phagocytes are instrumental in bolstering the host defense mechanism against mucormycosis. A review of multiple studies indicates that neutropenic patients are at heightened risk of developing mucormycosis [49]. Patients with phagocyte dysfunction are also at an elevated risk of getting affected by the invasive and opportunistic infection, mucormycosis [50]. Both oxidative and non-oxidative mechanisms, hyperglycemia and acidosis are acknowledged to inhibit the phagocytes from traveling forward and destroying organisms [51]. Furthermore, ketoacidosis, diabetes, and steroids all affect the function of these phagocytes, but the exact mechanisms are unclear [52].

2.2. Involvement of iron in the mechanism of pathogenesis

The susceptibility to mucormycosis is influenced by factors such as elevated usable serum iron, particularly in patients with conditions like diabetic ketoacidosis. Research indicates that conditions like acidosis can lead to higher levels of usable serum iron, potentially facilitating the growth of *Mucor* spp. Ferroptosis, a form of regulated cell death characterized by iron-dependent lipid peroxidation, may play a role in this process. Increased iron availability in conditions such as acidosis could contribute to cellular oxidative stress and promote ferroptosis, thereby exacerbating tissue damage and creating a conducive environment for mucormycosis infection according to the clinical features that have been recently reviewed by a few researchers. Thus, deferoxamine have a significantly higher risk of developing hostile mucormycosis [53]. Nevertheless, after achieving clarity in many studies it has been revised that deferoxamine does not activate mucormycosis infections by iron chelation [54]. *Rhizopus* spp. is reportedly found to use deferoxamine as a siderophore that is responsible for supplying previously inaccessible iron to the fungal organism, even though it serves as an iron chelator in the human host [55]. Deferoxamine can consume eight and forty times the iron of *Aspergillus fumigatus* and *Candida albicans* respectively, which is linearly related to serum growth of *Rhizopus* spp. [56]. A serious illness known as rhinocerebral mycosis can develop in people with diabetic ketoacidosis. Much evidence outlined the fact that individuals having systemic acidosis are vulnerable to having higher amounts of usable serum iron, which is most likely because of the iron released from the binding proteins in the occurrence of acidosis [57]. Few conducted studies have acknowledged the presence of sera in diabetic ketoacidosis patients, for example, for enhancing *Rhizopus oryzae* (*R. oryzae*) development in the presence of acidic pH [58]. It did not support the presence of alkaline pH. The availability of serum iron was found to be higher in acidic sera that supported *R. oryzae* growth [59]. It appears that acidosis temporarily impairs transferrin's ability to bind iron because simulating acidosis reduces the capacity of sera obtained from healthy executives (Fig. 2). As a result, patients with diabetic ketoacidosis are more susceptible to mucormycosis, which is possibly attributable to a rise in sufficient serum iron during the condition [60].

3. Interactions between fungi and endothelial cells

The nearly universal survival of extensive angioinvasion followed by the resulting vessel thrombosis and tissue necrosis is one of the most relevant outcomes of mucormycosis infections [61]. Angioinvasion is linked to the organism's inclination to spread hematogenously from the initial infection site to other target organs [62]. As a result, endothelial cell disruption and penetration into blood vessels is conceivably a crucial stage in the organism's pathogenetic approach [63]. *R. oryzae* spores *in vitro* can bind to proteins such as laminin and collagen type IV but not germlings (i.e., pregerminated spores) *R. oryzae* spores can attach them [64]. Likewise, *R. oryzae* spores marginally better bind to subendotheral matrix proteins than *R. oryzae* hyphae, but spores and hyphae bind to endothelial cells of the human umbilical vein conversely [65]. Since subendothelial matrix proteins bind to spores and germs but the adherence of spores and germs to endothelial cells is the same, endothelial cell adhesions from *R. oryzae* can be different from adhesins to the subendothelial matrix proteins [66]. *In vitro*, scientists discovered that *R. oryzae* germlings cause damage to endothelial cells [67]. Endothelial cells must phagocytose *R. oryzae* to cause this damage, which is independent of serum factors [68]. Surprisingly, endothelial cell damage was not dependent on *R. oryzae* viability, but dead *R. oryzae* allowed phagocytosis to inflict damage [69]. The exact mechanisms by which dead *R. oryzae* causes tissue damage are unknown [70].

A consistent increase in mucormycosis prevalence has also been shown in several studies, with several contributing causes recognized [71]. First, medical advancements have increased the number of people who are immunosuppressed as a result of the transplantation of solid organs and bone marrow [72]. Correspondingly, persistent acute neutropenia following intensive treatment in hematological patients and individuals having solid tumors jeopardize the lethal factors leading to mucormycosis [73]. Furthermore, invasive fungal infections (IFI) have been recorded in individuals receiving prophylaxis

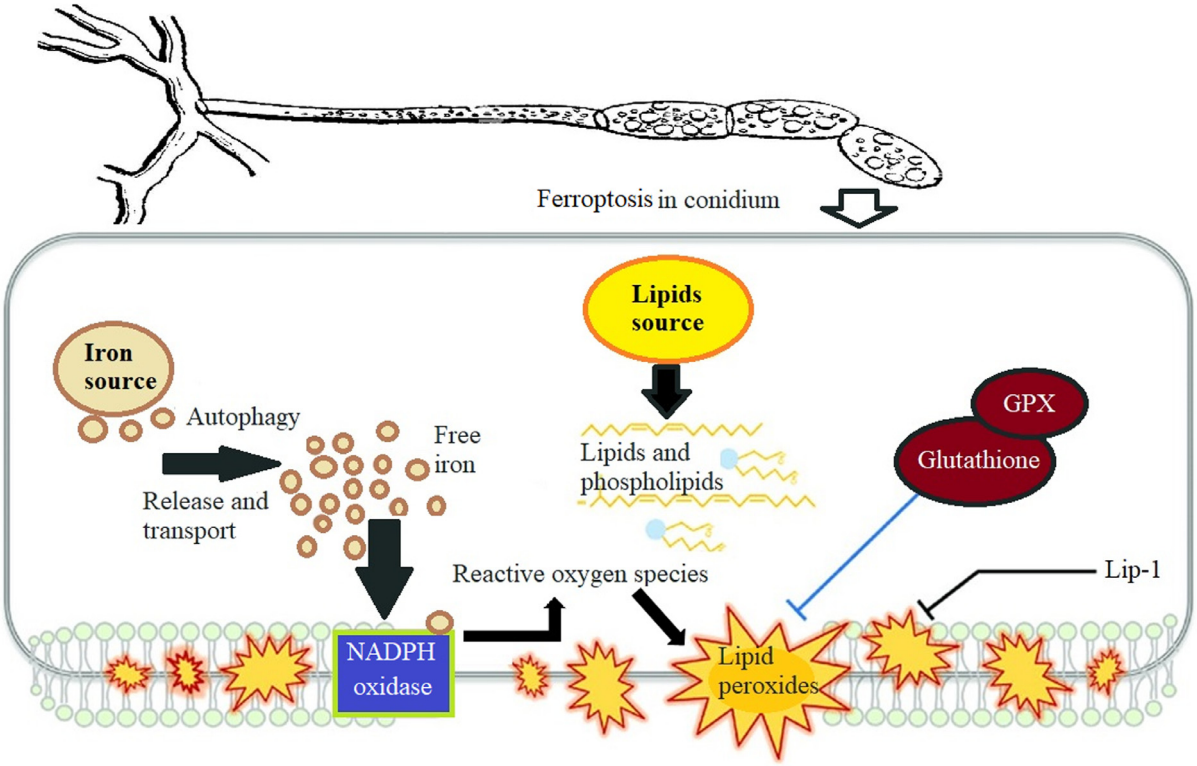

Fig. 2. Schematic representation of regulated cell death characterized by iron dependent lipid peroxidation.

antifungal therapy [74]. According to recent research, DM is becoming less of a primary mucormycosis risk factor in affluent countries. This development could be explained by better DM control and the widespread use of statins with antifungal effects. DM, on the other hand, continues to be the most predisposing condition in poorer nations because of a dearth of accessibility in healthcare sectors and poor control [75]. Hyperglycemia, whether with or without diabetic ketoacidosis, is linked to a reduction in neutrophil activity [76]. An endothelial cell receptor is responsible for upsurging an endocytic process. It notably permits the fungus to invade blood vessels and tissues. That endothelial cell is known as glucose-regulated protein 78 (GRP78) [77].

A cohort study in Arab countries was conducted and it was revealed that a database of all the patients suffering from mucormycosis has been compiled. The registry includes the details of the infectious disease, microbiological aspects of the invasive infection that has been diagnosed, and pathology laboratory studies. Histopathological confirmation and/or culture from sterile areas were used to diagnose eighteen (18) instances. The slides were examined by two pathologists. In the event of a disagreement, a third pathologist was consulted. Fungal culture was performed on all tissues. The samples are cultivated on Sabouraud dextrose agar, enrichment broth (brain heart infusion), and standard bacteria medium after tissue processing. The cultures are incubated for 8 weeks at 25–30 degrees Celsius. Every 48 h, the cultures are red. When growth was detected, colony morphology was used to make a macroscopic identification, while lactophenol stain was used to make a microscopic identification. The final identification of isolated species was done retrospectively in Riyadh and Saudi Arabia using molecular sequencing. Deoxyribonucleic acid (DNA) was isolated from paraffin-embedded tissue blocks that had been formalin-fixed. The segments were deparaffinized two times in xylene and then rinsed thrice in ethanol at various concentrations. After mechanical homogenization with a TissueLyser, DNA was extracted using a QIAamp DNA FFPE Tissue Kit (Qiagen) [78]. The internal transcribed spacer section of the fungal rDNA was amplified and then used to detect and identify *Mucor* species [79]. Demographic data, fundamental risk factors, clinical specifications and/or trials, infection site, laboratory constraints, radiological characteristics, microbiology outcomes, histopathology reports, type of treatments, and clinical outcomes were all examined and determined in all patient records. According to the researchers, instances were characterized as proven invasive mould infections (IMIs) in all categories of cases. Demographics, clinical symptoms, predisposing variables, microbiology, treatment regimens, and outcomes have all been examined. The patients' median age was 43.45 years (range: 13–72 years, with 72% of men) [80]. Mucormycosis was found in 18 individuals after microscopic testing. Both cultures and histological findings for mucormycosis were positive in 4 cases. Fungal isolates of *Apophysomyces variabilis* (5

instances), *Rhizopus oryzae* (3 cases), *Rhizopus microsporus* (2 cases), and *Lichtheimia corymbifera* (2 cases) were discovered using molecular testing (1 case). Seven of the isolates were found to be unclassifiable. *Aspergillus niger, Cochliobolus hawaiiensis, Penicillium* spp., and *Rhodotulla* spp. were found to be co-infected in five people. *R. oryzae* was found to be the causative factor in 42.9% of rhino-orbit-cerebral mucormycosis cases, whereas *A. variabilis* was shown to be the causative factor in 71% of cutaneous cases [81] (Fig. 2). The most common types of mucormycosis were cutaneous and rhino-cerebral mucormycosis (77.8%), gastrointestinal mucormycosis (2%), and disseminated and renal mucormycosis (2%) (1 patient each). Six of the patients had sinus or sino-orbital illness, and two of them had infections that spread to their brains. Overall, 33.3% and 38.9% of the cases had diabetes mellitus and trauma as underlying causes, respectively [82]. Motor vehicle collisions (MVCs) accounted for 43.0% of all trauma cases, resulting in cutaneous and soft-tissue mucormycosis in predominantly immunocompetent patients. Correspondingly, DM was the primary etiology of rhino-orbito-cerebral mucormycosis in 57.0% of patients. Diabetic ketoacidosis affected only one diabetic patient. The studies and research have revealed that in three of the patients, a hematological malignancy favored mucormycosis, and two of them had a neutrophil count of zero [83]. There was no evidence of a breakthrough infection in any of the individuals. Subsequently, extensive surgical debridement was paired with liposomal amphotericin-B (LAmB) treatment in all patients, in addition to any underlying etiology being controlled. Four patients were given an antifungal cocktail. Overall, there was a 27.8% mortality rate. The other research works also determined that DM was considered to be one of the most influencing factors in contrast to European countries, although, in other research, only 33% of patients were found to have presented with diabetic ketoacidosis. Even though acidosis promotes fungus development, uncontrolled diabetics' phagocytic activity can be impaired by hyperglycemia alone. Mucormycosis of the gastrointestinal tract is rare and difficult to detect antemortem. Furthermore, it has been related to about 85% of the mortality rate. In the same study, two out of the three gastrointestinal mucormycosis patients reportedly experienced intestinal ischemia and gangrene, while the third person only presented with stomach discomfort followed by multiple splenic infarctions; According to the reports, their fatality rate read 66.7% [84]. There was a paucity of randomized clinical efficacy trials that were significantly well-designed. Despite this fact, it is widely accepted that rigorous surgical debridement accompanied by efficient antifungal medicines is the keystone of the therapeutic approach. Infections of the skin and soft tissues, as well as rhino-orbits-cerebral illness, necessitate appropriate surgery. All of the patients in that research were given a high dose of LAmB (510 mg/kg/day), as well as repeated surgical debridement and therapy for diabetes if it was present. LAmB at a dose of 10 mg/kg/day has been demonstrated to be both efficacious and safe in the treatment and management of mucormycosis [85] (Fig. 3). Isavuconazole was recently approved as a first-line treatment for mucormycosis in the United States [86]. Posaconazole was utilized as a step-down therapy or when LAmB was not tolerated because the medicine was not available to us [87]. In the established mucormycosis, there is insufficient evidence to justify the use of a combination of olyenes and azoles or polyenes with echinocandins [88]. A combination of LAmB plus posaconazole or LAmB and voriconazole, on the other hand, was found to be effective and potent for trauma-related IFI. The established study found that the group had a low mortality rate of 27.8% [89]. Mortality rates vary between 40% and 80% depending on the underlying predisposing factors and infection site. Patients who are immunocompetent have a lower mortality rate than those who are immunocompromised. Localized sinus and skin infections may also have reduced fatality rates. This could be the reason for the study's lower fatality rate. The identification of infection down to the species level was strength of that study that was established [90]. While this information may not be useful in advising treatment, it can help with disease epidemiology. The retrospective approach of the study has some disadvantages, such as inaccurate case collecting. The hospital provides trauma and haemato-oncology services as a tertiary care facility. As a result, when compared to other centers, the respective findings may seem inflated [91].

Another study was reviewed broadly by recognized scientists and their backend team on the invasive mucormycosis after COVID-19 in transplanted hearts of some patients [92]. Mucormycosis is more common in patients with underlying co-morbidities, according to the findings of this study (including organ transplantation). During the ongoing impact of the novel Coronavirus pandemic, healthcare professionals presented with some generated relevant reports. The reports showed an increased number of bacterial and fungal co-infections in COVID-19 patients. One of the most significant and deadly co-infection was COVID-19-associated pulmonary aspergillosis (CAPA) that has been discovered at the same time [93]. Hematologic malignancies, solid organ transplant recipients (SOTRs), stem cell transplantation, sustained and chronic neutropenia, diabetes mellitus (DM), and iron overload deferoxamine were reportedly presented as the risk factors for mucormycosis [94]. Mucormycosis accounts for 2%–6% of IFIs [95]. The ongoing COVID-19 pandemic has resulted in more than 110 million illnesses and 2.4 million fatalities worldwide, thanks to the novel severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) [96]. The development of bacterial and fungal co-

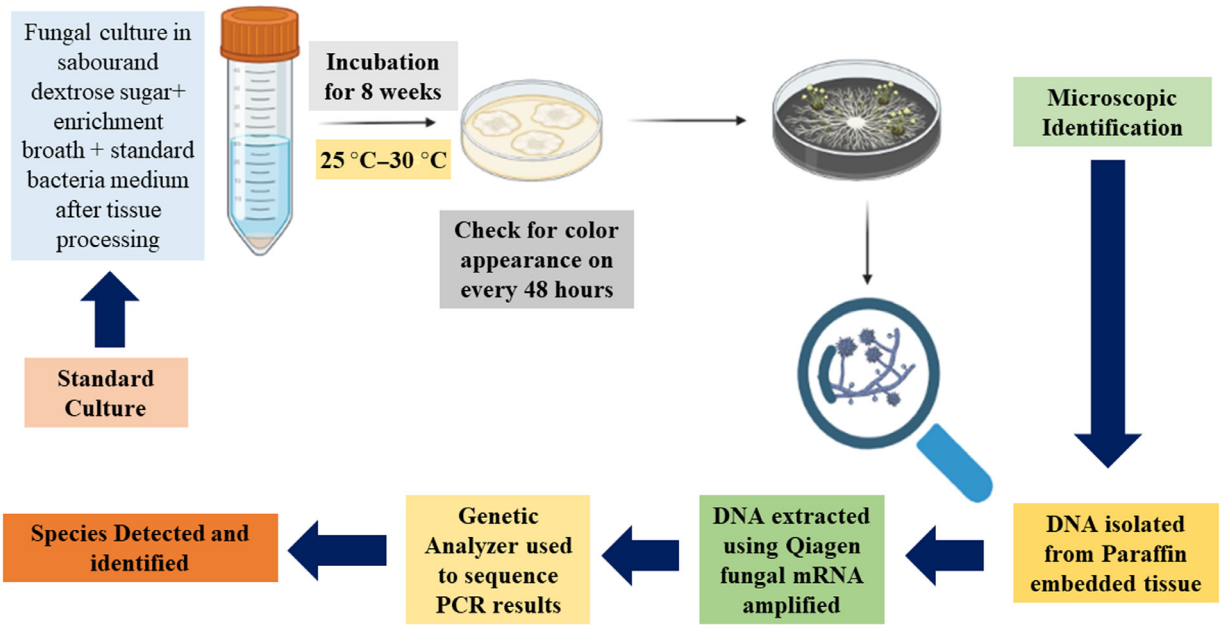

Fig. 3. Diagrammatic illustration of the key steps of molecular identification of pathogenic fungi.

infections in COVID-19 patients is becoming more common. In this study, the experience of a heart-transplanted recipient with cutaneous black fungus after COVID-19 was well documented, and the potential mechanisms around the manifestation of mucormycosis after COVID-19 were reported too [97]. Patients who have had their skin barrier disrupted (burns, trauma, catheter insertion, injections) or who have had continuous skin maceration are more likely to develop cutaneous mucormycosis. Secondary vascular invasion and hematogenous spread are less common, although the fungus can penetrate neighboring fat, muscle, fascia, and even bone. Cutaneous mucormycosis with hematogenous dissemination carries a high fatality rate [98]. Treatment strategies for mucormycosis typically encompass early detection, reversal of comorbid conditions (if feasible), surgical excision of infected tissue, and administration of appropriate antifungal agents [99]. Patients undergoing organ transplantation or implantation procedures are particularly susceptible to mucormycosis invasion [99].

After comprehensive review of multiple studies and research findings, esteemed teams of scientists conducted exploratory case studies to investigate the elevated risk factors associated with mucormycosis. In one retrospective and interventional study, six COVID-19 patients who developed rhino-orbital mucormycosis were treated at a tertiary ophthalmology center in India [100]. All patients had Type 2 diabetes and were male, with an average age of (60.5 ± 12) years. Systemic corticosteroids were administered for COVID-19 treatment in all patients except one. The average duration between COVID-19 diagnosis and onset of mucor symptoms was found to be (15.6 ± 9.6) days. Following endoscopic sinus debridement, only two of the six patients required ocular exenteration, but all six were alive at the latest follow-up. The researchers underscored the importance of maintaining a high index of suspicion, early diagnosis, and appropriate therapy for patient survival. In another report, a 56-year-old man admitted to the hospital with COVID-19 succumbed to mucormycosis while receiving hemodialysis for end-stage renal illness [101]. The patient was asymptomatic for four days before being admitted to the hospital for exhaustion and breathing problems [102]. Four days later, the patient tested positive for SARS-CoV-2 by Reverse transcription-PCR (RT-PCR). The patient was given methylprednisolone, tocilizumab, and a single dose of convalescent plasma upon arrival. Negative results were obtained from blood cultures used to identify bacterial and fungal infections. After being discharged home seven days later, the patient was readmitted five days later with nonspecific exhaustion, shortness of breath, and hemoptysis [102]. The patient started receiving empirical antibiotic medication for probable pneumonia related to healthcare. A chest X-ray taken later revealed both lung fields in both lung fields had increased airspace density and pleural effusion. The third day saw the start of an empirical treatment with liposomal amphotericin B after a repeat sputum investigation revealed the presence of filamentous fungus [103]. Despite continued pleural effusion drainage with a pigtail catheter over the next three days, the results of a repeat chest CT were unchanged. *Rhizopus azygosporous* was also diagnosed after repeated sample analysis, and the patient was given the necessary treatment [104]. The patient was hospitalized for 17 days before succumbing to cardiac arrest despite intensive treatment. Severe COVID-19 has

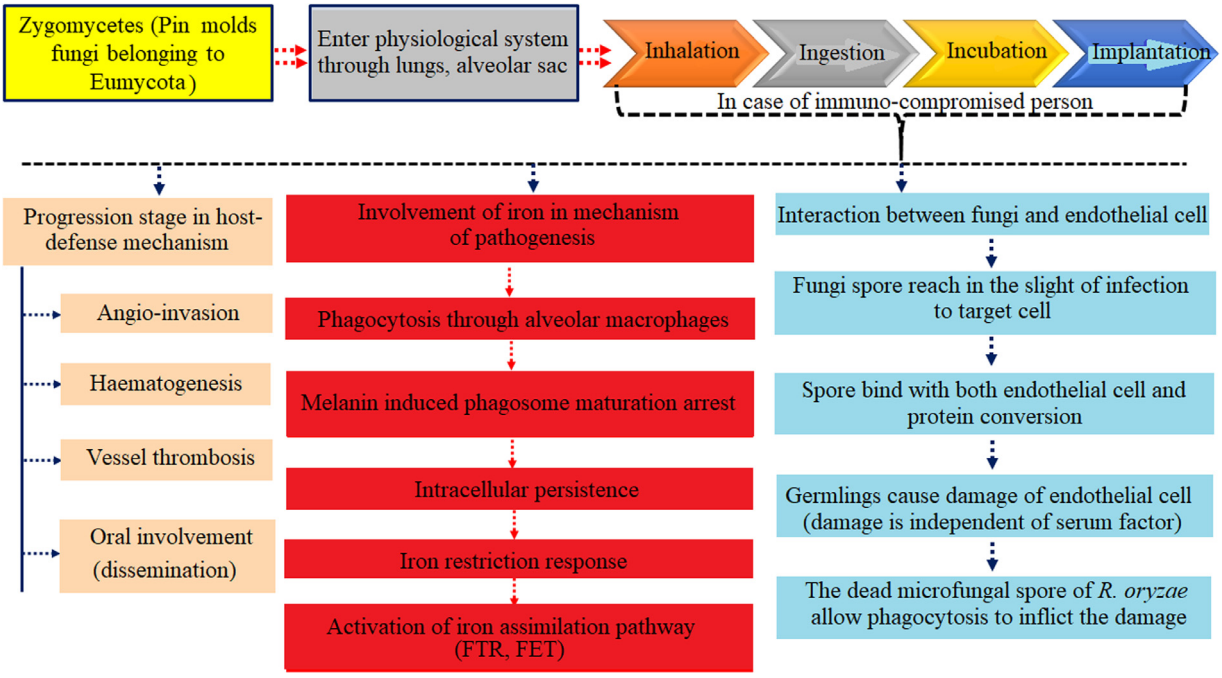

Fig. 4. Process of host defense mechanism and ferroptosis in zygomycetes infection.

been associated with an increased risk of invasive fungal infections, particularly in individuals receiving immunosuppressive drugs such as corticosteroids and IL-6 inhibitors like tocilizumab. The incidence of mucormycosis cases may be underestimated due to the lack of non-invasive diagnostic tools for invasive fungal diseases [105].

In another retrospective case study, a 61-year-old woman with no preexisting medical conditions was hospitalized for two weeks due to COVID-19 infection. She received remdesivir, interferon-alpha, and systemic corticosteroid treatment without requiring mechanical ventilation or intubation [106]. About a week after discharge, she developed right hemifacial pain, hemifacial numbness, decreased visual acuity, and chemosis. Upon readmission, diagnostic endoscopy, MRI, and subsequent CT scans confirmed invasive mucormycosis infection [107]. The patient, despite having no prior medical conditions, experienced hyperglycemia and immunosuppression due to corticosteroid injection administered by the researchers. COVID-19-induced immunological dysregulation further exacerbated the emergence of invasive mucormycosis, emphasizing the importance of early diagnosis by healthcare professionals [108].

In another case, a 24-year-old woman from Mexico City, with a history of obesity and COVID-19 positivity, presented with left midface pain persisting for at least six days. Within two days, she also developed left lid swelling and decreased sensation in the maxillary region, prompting her to seek emergency care. When oral amoxicillin-clavulanate failed to alleviate symptoms, an invasive fungal infection was suspected. Subsequent rhinoscopy and contrast-enhanced CT scans of the head and chest confirmed the diagnosis of rhino-orbital mucormycosis [109]. This patient experienced metabolic acidosis, lung issues, and acute renal injury due to disseminated intravascular coagulopathy, all compounded by septic shock, leading to multi-organ failure and eventual death. The researchers noted that the woman had an immunological state induced by diabetic ketoacidosis, rendering her susceptible to coinfections with COVID-19 and mucormycosis. Delayed diagnosis and treatment contributed to the unfavorable outcome [110].

In another case, a 60-year-old male patient with a decade-long history of diabetes presented with profound dyspnea, high fever, rapid breathing, and overall discomfort. On the 10th day of hospitalization for COVID-19 treatment, he developed bilateral eyelid swelling, particularly prominent in the right eye. Brain MRI revealed soft tissue enlargement in the orbital and paranasal sinus regions, along with mucosal thickening. A nasal swab cultured on Sabouraud's dextrose agar confirmed the presence of an invasive fungal infection, likely mucormycosis. Given diabetes' strong association with mucormycosis, it's plausible that the patient either had an undiagnosed mucor infection prior to contracting COVID-19 or that it exacerbated due to further immunological dysregulation. The risk of opportunistic infections such mucormycosis has been linked to the use of steroids and monoclonal antibodies in the treatment of COVID-19. Due to the serious consequences of opportunistic co-infections, particularly invasive fungal infections in the context of

Table 1
Diagnosis process and chemical used.

Method of diagnosis	Process of detection	Chemicals used for visualization
1. Histopathologic Test	It identifies the presence of fungus as well as any pathogens present in the specimen from a culture.	a) GMS highlights the fungal wall [116]. b) PAS provides a better view of surrounding tissue [116].
2. Direct Microscopic Test	Immunophenotyping with monoclonal antibodies against fungi has been found as aid of detection.	Blankophor or calcofluor white in combination with KOH provides a speculative visualization [117].
3. Molecular Methods of Diagnosis	It is the molecular approach to detecting ITS region. Most commonly sequenced is DNA region of fungi.	PCR-Based technique using Tris-HCl, KCl, $MgCl_2$, such as, Nested PCR, electrospray ionization, mass spectroscopy, HRMA has been developed for tissue visualization [100,119].

COVID-19, it is essential for healthcare professionals, especially physicians, to exercise caution, remain aware of the infection risk, and diligently implement necessary precautions [111] (Fig. 4).

4. Biochemical aspects of mucormycosis

The lack of a non-invasive, quick, and reliable diagnostic test has been a major stumbling block in treatment. A key unsolved need in modern mycology is the development of a culture-independent biomarker for the early detection of mucormycosis [112]. Several methodologies have been introduced, including immunohistochemistry (IHC) to validate the histopathologic diagnosis of obtrusive fungus infection, PCR on formalin fixed paraffin embedded (FFPE) or fresh tissue, body fluids like bronchoalveolar fluid (BAL), and intensity modulation from serum/blood [113]. Other emerging technologies include serologic testing, matrix-aided laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS), metabolomics, and metagenomic shotgun sequencing [114] (Table 1).

5. Histopathologic tests

In individuals with pulmonary mucormycosis, biopsies of damaged tissues or bronchoalveolar lavage (BAL) are used to confirm the diagnosis. Histopathology plays a pivotal role in diagnostics as it helps discern the presence of fungus as a potential antigen within a specimen, distinguishing it from culture contaminants. Additionally, it is indispensable in ascertaining the occurrence of blood vessel invasion, and it has the capacity to unveil fungal illnesses attributed to various other fungal species [115]. In contrast to *Aspergillus* species or other hyaline fungi, Mucorales typically produce unpigmented, broad, slender-walled, ribbon-like hyphae characterized by minimal septations (pauciseptate) and perpendicular branching. Hematoxylin and eosin (H&E) staining may only reveal the cell wall without internal structures or, occasionally, highly deteriorated hyphae. *Grocott methenamine*-silver (GMS) and periodic acid-schiff (PAS) stains can both help highlight the fungal wall, with PAS offering a clearer view of the surrounding tissue compared to GMS [116].

5.1. Direct microscopic method

Potassium hydroxide (KOH) wet mounts can serve as a rapid preliminary diagnostic method for mucormycosis via direct microscopy. This method is suitable for all samples submitted to the clinical laboratory, especially when fluorescent brighteners like Blankophor and Calcofluor White are utilized alongside KOH. This combination facilitates the improved detection of distinctive fungal hyphae, requiring the utilization of a fluorescent microscope within this particular context [117]. When dealing with invasive fungal infections during surgical operations, direct microscopy of fresh specimens is a beneficial and affordable way to quickly make an initial diagnosis and define precise surgical limits. A thorough diagnostic strategy should combine this procedure with histopathology, which is strongly recommended. These techniques, on the other hand, are unable to determine fungi down to the genus or species level. When negative cultures are established, another method, immunophenotyping with monoclonal antibodies against *R. arrhizus* has been found to aid in the diagnosis. It has been shown to be useful in distinguishing aspergillosis from mucormycosis and has been acknowledged as a moderate recommendation in the recent ECMM/MSGERC guidelines [118].

5.2. Recent molecular methods for the diagnosis

Molecular approaches have emerged to become an important tool for confirming infections and detecting the strains involved in invasive fungal infection. As a result, methods have been developed to properly recognize strains. Conversely, the previously grown strains in cultures explored various methods to detect mucoromycetes in tissues. In general, the ITS region is the most commonly sequenced DNA region in fungi. The most valuable tool for molecular systematics, at both the species level and within individual species. has historically been recognized as the dependable method of ITS sequencing. As a result, it is strongly advised to use it as the main technique for identifying Mucorales species. PCR-based methodologies, including nested PCR, real-time PCR (qPCR), nested PCR coupled with RFLP, PCR integrated with electrospray ionization mass spectrometry (PCR/ESI-MS), and PCR/high-resolution melt analysis (HRMA), have all been devised for the detection of tissue samples [119]. Nu-

merous methods have been shown to be effective when used on fresh or extremely frozen specimens rather than those embedded in paraffin. The success of the approach is largely due to the choice of PCR targets. Multiplex PCR techniques that use universal fungal primers developed for the ITS genomic region or custom primers created for a specific set of mucoralean genera or species, followed by sequencing of the amplified DNA, are widely available. Instances of such targets encompass the CotH gene, the cytochrome b gene, the rnl mitochondrial gene, and 28S rDNA, which is exclusive to Mucorales [120].

6. Updated therapeutics

This paper, has detailed in brief the current scenario regarding the treatment options and regimens that have been obtained from a few analytical studies followed by the clinical *in-vitro* and *in-vivo* experiments.

6.1. Complications in assessing treatment strategies in mucormycosis

Mucormycosis, being a rare disease, has no existing forthcoming and/or expected randomized outcomes from clinical studies. Scientists and researchers are continuously facing difficulties in determining and evaluating robust treatment strategies for the causes of mucormycosis. The current therapeutic approach focuses mainly on solitary, systematic reviews with a small number of patients with high diversity in their manifestation and risk factors, methodologically flawed databases, and "expert opinions." Inadequate diagnostic efforts were investigated, relying on mishandled tissue cultures and/or overlooked histology instances, which consequently introduced biases in treatment decisions, particularly steering towards culture and/or histology-positive cases associated with heightened disease risks, or specific patient cohorts like sinusitis or trauma patients, where tissue accessibility is more precarious. The obtained data of poor quality has been reflected in the recently issued European guidelines, which have a substandard scaling of evidence and, consequently, their utility raises controversies and debates on clinical practices [121].

6.2. Therapeutic principles for mucormycosis

Multiple therapies, either occurring concurrently or at different times and intensities, are used to treat mucormycosis. The core tenets underpinning the therapeutic management of mucormycosis encompass risk assessment for disease severity, informed by diverse analytical, clinical, and laboratory findings; timely commencement of effective antifungal treatment, whether through monotherapy or combination therapy; followed by vigorous surgical excision of necrotic lesions; and the reversal of immunosuppression, involving the cessation of chemotherapy and elevation of immunoglobulin levels [122]. It is expected that the tissue invasion and its sequelae progression can be prevented successfully if diagnosed earlier with proper intervention. Subsequently, the necessity of extensive surgery and successive distortion may be reduced, thereby improving the survival rate. Mucormycosis, if left untreated, can be invasively fatal. After going through a cohort study having 70 patients with hematological malignancies and mucormycosis, it has been found that when compared to early diagnosis, delaying antifungal therapy for 6 days after diagnosis resulted in a 2-fold increase in fatality rate. Another study of 929 confirmed cases of mucormycosis found that antifungal therapy followed by surgery was strongly related to higher survival rates (69%), but fatality was practically certain (97%) for individuals who did not receive any treatment [123].

6.3. Use of antifungal agents in the treatment and management of mucormycosis

After subsequent reviews and studies, only Amphotericin-B (AMB) and its lipid formulation has been confirmed as a first-line therapy for mucormycosis. Isavuconazole has also been studied and confirmed as a first-line therapy for mucormycosis along with AMB. The effectiveness of these drugs is based on minimal clinical data as well as preclinical *in vitro/in vivo* evidence of Mucorales' activity. It should be noted, however, that none of these drugs have any proven minimum inhibitory concentration (MIC) breakpoints. However, it has also been studied that posaconazole can be also used for the management of mucormycosis but, as a salvage therapy. Regardless of the lack of reliable clinical evidence, treating mucormycosis in immunocompromised individuals with a combination of antifungal agents is becoming more prevalent. Synergistic impact and expanded exposure are the benefits of such a therapeutic approach, whereas possible antagonistic activity, drug interactions, toxicity studies, and elevated price are the reported drawbacks. The data concerning the efficacy of the AMB + triazole combination in mucormycosis treatment remains inconclusive. The combination of a polyene with posaconazole has shown synergistic effects *in vitro*, but *in vivo* investigations in mouse models of mucormycosis exhibited no such notable improvements when the drugs were taken simultaneously [124]. In a study involving neutropenic mice infected with *R. oryzae,* it was noted that the combination of amphotericin B and posaconazole did not appear to enhance the survival rate or reduce the fungal load in organs beyond the results attained with AMB monotherapy. There have been a few human studies conducted, assessing the combination of polyene and triazole for the treatment of mucormycosis [125].

6.4. Surgical methods for the management of mucormycosis

At the heart of mucormycosis treatment lies the surgical removal of necrotic tissues. The fusion of surgical intervention with appropriate systemic antifungal treatment has been demonstrated to significantly boost survival rates in pulmonary mucormycosis, in contrast to relying solely on antifungal therapy. Hemoptysis owing to cavitation of lesions near hilar vessels is a marker that directs the lesion to be resected right away. Surgery may be curative in some cases with localized illness [126]. MRI may be useful in determining the respectability of lesions in individuals with rhino-orbital mucormycosis. Conversely, in the treatment of rhino-orbital-cerebral illness, surgical excision of contaminated tissues is critical. It must be noted, however, that attributable to selection biases, determining the influence of surgery on outcome is challenging. In patients with primary, limited illness or major medical comorbidities, an endoscopic approach is favored over open surgery [127].

6.5. Adjunctive therapeutically approaches

From a few studies, it has been reported that most of the deaths due to mucormycosis have been caused due to the low recovery status of the functioning of bone marrow. The individuals might have required prolonged immunosuppressive therapy. Immunosuppressive reversal has been considered as one of the most significant therapeutic approaches for the management of mucormycosis. Surgery and the administration of the prementioned antifungal agents have also contributed rationally to this novel therapeutic approach. Therefore, using hematopoietic growth factors or white cell transfusions can affordably put in the efforts to reverse neutropenia in hematologic patients [128]. Iron chelators have been recommended as a viable supplementary therapy, as they reduce accessible iron and hence prevent fungal development. In a mouse model, preclinical results demonstrated that Deferasirox, a novel iron chelator with no siderophore capacity, enhanced survival. Nonetheless, a subsequent prospective, randomized investigation conducted among patients with hematologic malignancies revealed an association between the use of LAMB in combination with Deferasirox and an elevated risk of mortality. While Deferasirox doesn't seem to be effective in patients with hematologic malignancies and mucormycosis, it remains a viable treatment choice for other high-risk individuals, such as those with diabetes [129]. Despite the limited availability of *in vitro* data and case reports, there has been endorsement of immune augmentation techniques, such as administering granulocyte (macrophage) colony-stimulating factor or interferon, as a supplementary therapy. Granulocyte infusions also have been undertaken, with mixed results and the possibility of inflammatory lung damage. Statins have exhibited anti-*Rhizopus* spp. efficacy *in vitro* and *in vivo*, but clinical data is insufficient. Due to the limited availability of data, the relative effectiveness of supplementary therapies must be weighed against the expense and risk of harm for each patient individually [130].

6.6. Novel antifungal agents to combat Mucorales

Even after receiving antifungal therapy, most of the hematological patients die from the invasive infection. These reports put up the evidence that mucormycosis is not like other fungal infections such as candidiasis and aspergillosis. Conversely, it can be highlighted readily that there is a need for novel antifungal agents that will target and effectively help combat the Mucorales. Mucorales, on the other hand, have a hard time finding unique targets [131]. In laboratory experiments, VT-1161, an experimental drug, displayed activity against Mucorales, including *R. oryzae, Lichtheimia*, and *Cunninghamella*. This new compound serves as an inhibitor of the fungus CYP 51. On the other hand, APX001A, an antifungal medication, targets Gwt1, a critical component in the conserved glycosyl phosphatidyl inositol (GPI) post-translational modification pathway responsible for surface protein alteration in eukaryotic cells [132]. Although it has only minor antimicrobial action against other Mucorales *in vitro*. Phase I clinical studies for APX001A have begun [133]. Finally, caspofungin, a new drug, has been discovered that has been further found to inhibit the growth of abundant fungi *in vitro*, including *Rhizopus* [134–137].

7. Conclusion

In retrospect, the importance of vigilance among clinicians in managing mucormycosis in COVID-19 infected individuals becomes evident. This rather uncommon condition demands further investigation to fully understand its potential and impact on global health. The rising prevalence of mucormycosis and its geographical links to diverse contagious Mucorales causes underscore the need for comprehensive epidemiological studies in various countries where data remains scarce. Diagnosing mucormycosis remains challenging, emphasizing the critical role of early suspicion and prompt intervention to improve prognostic outcomes. Limited data on treatment options adds to the complexity faced by healthcare professionals in managing this formidable illness. It is prudent to exercise caution when interpreting case reports and single-institution retrospective case series, given the potential for inherent biases. Managing mucormycosis necessitates a multifaceted strategy, considering a range of host-related, microbiological, surgical, and pharmaceutical elements that impact results and formulate tailored treatment scenarios. Future efforts must focus on identifying novel pharmacological targets through "pragmatic"

prospective, multicenter studies, and registries to develop more effective treatment strategies. Retrospective studies have highlighted the importance of early clinical detection and timely medication, alongside tissue biopsy, to accurately identify the unique morphologic features of the fungal agent in the absence of positive mycology culture results. Looking ahead to 2024 and beyond, healthcare systems worldwide must be prepared to tackle powerful strains of mucormycosis. Enhanced surveillance, research collaborations, and investment in healthcare infrastructure will be necessary to effectively manage the growing incidence of this disease. The interdisciplinary approach must be encouraged, as the involvement of dermatologists in diagnosing rhino-orbital-cerebral mucormycosis exemplifies the need for diverse expertise in combatting this condition. By embracing ongoing research, updated therapeutics, and coordinated efforts, we can strive to mitigate the impact of mucormycosis and enhance patient outcomes in the years to come.

Funding

The authors declare that this review article did not receive any funding from either government or non-government agencies.

Author contributions

T.M., T.D., S.B., and S.M.: Conceptualization, data curation, writing–original draft preparation, validation. K.A., P.C., R.M., and P.K.: Methodology, data curation, writing–original draft preparation, supervision of final review, visualization and editing.

Acknowledgments

The authors are thankful to the Department of Pharmaceutical Sciences & Technology, Birla Institute of Technology Mesra, Ranchi, India for providing a literature review facility and essential data for preparing the manuscript.

Declaration of competing interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Data available statement

Data sharing is not applicable to this review article as there are no databases were generated or analyzed during the present study.

Ethics statement

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not applicable.

References

[1] J.M. Steinbrink, M.H. Miceli, Mucormycosis, Infect. Dis. Clin. North Am. 35 (2) (2021) 435–452, doi:10.1016/j.idc.2021.03.009.
[2] A.S. Ibrahim, B. Spellberg, T.J. Walsh, et al., Pathogenesis of mucormycosis, Clin. Infect. Dis. 54 (2012) 16–22, doi:10.1093/cid/cir865.
[3] M. Madjid, P. Safavi-Naeini, S.D. Solomon, et al., Potential effects of coronaviruses on the cardiovascular system: a review, JAMA Cardiol. 5 (7) (2020) 831–840, doi:10.1001/jamacardio.2020.1286.
[4] I. Mahalaxmi, K. Jayaramayya, D. Venkatesan, et al., Mucormycosis: an opportunistic pathogen during COVID-19, Environ. Res. 201 (2021) 111643, doi:10.1016/j.envres.2021.111643.
[5] F. Lanternier, E. Dannaoui, G. Morizot, et al., A global analysis of mucormycosis in France: the RetroZygo Study (2005–2007), Clin. Infect. Dis. 54 (Suppl 1) (2012) S35–S43, doi:10.1093/cid/cir880.
[6] J.R. Köhler, A. Casadevall, J. Perfect, The spectrum of fungi that infects humans, Cold Spring Harb. Perspect. Med. 5 (1) (2014) a019273, doi:10.1101/cshperspect.a019273.
[7] R. Bhogireddy, V. Krishnamurthy, S. Sugin Jabaris, et al., Is Mucormycosis an inevitable complication of Covid-19 in India? Braz. J. Infect. Dis. 25 (3) (2021) 101597, doi:10.1016/j.bjid.2021.101597.
[8] K. Bhattacharya, L.D. Mukhopadhyay, R. Goswami, et al., SARS-CoV-2 infection and human semen: possible modes of contamination and transmission, Middle East Fertil. Soc. J 26 (1) (2021) 18, doi:10.1186/s43043-021-00063-6.
[9] A. Fekkar, A. Lampros, J. Mayaux, et al., Occurrence of invasive pulmonary fungal infections in patients with severe COVID-19 admitted to the ICU, Am. J. Respir. Crit. Care Med. 203 (3) (2021) 307–317, doi:10.1164/rccm.202009-3400OC.
[10] E.S. Theel, C.D. Doern, β-D-glucan testing is important for diagnosis of invasive fungal infections, J. Clin. Microbiol. 51 (11) (2013) 3478–3483, doi:10.1128/JCM.01737-13.
[11] S. Bell, L. Mahoney, Mucormycosis: a case study, Crit. Care Nurse 20 (1) (2000) 18–23.
[12] A. Ramadorai, P. Ravi, V. Narayanan, Rhinocerebral mucormycosis: a prospective analysis of an effective treatment protocol, Ann. Maxillofac. Surg. 9 (1) (2019) 192–196, doi:10.4103/ams.ams_231_18.
[13] A. Skiada, F. Lanternier, A.H. Groll, et al., Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3), Haematologica 98 (4) (2013) 492–504, doi:10.3324/haematol.2012.065110.
[14] A.J. Ullmann, M.A. Sanz, A. Tramarin, et al., Prospective study of amphotericin B formulations in immunocompromised patients in 4 European countries, Clin. Infect. Dis. 43 (4) (2006) e29–e38, doi:10.1086/505969.
[15] J.P. Latgé, G. Chamilos, *Aspergillus fumigatus* and aspergillosis in 2019, Clin. Microbiol. Rev. 33 (1) (2019) e00140–e00118, doi:10.1128/CMR.00140-18.
[16] J. Brown, Zygomycosis: an emerging fungal infection, Am. J. Health Syst. Pharm. 62 (24) (2005) 2593–2596, doi:10.2146/ajhp050188.
[17] A. Hussain, B. Bhowmik, N.C. do Vale Moreira, COVID-19 and diabetes: knowledge in progress, Diabetes Res. Clin. Pract. 162 (2020) 108142, doi:10.1016/j.diabres.2020.108142.
[18] S. Sharma, M. Grover, S. Bhargava, et al., Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum, J. Laryngol. Otol. 135 (5) (2021) 442–447, doi:10.1017/S0022215121000992.
[19] A. Waness, G.A. Dawsari, H. Al Jahdali, The Rise of an opportunistic infection called “Invasive Zygomycosis, J. Glob. Infect. Dis. 1 (2) (2009) 131–138, doi:10.4103/0974-777X.56256.
[20] M.A. Pfaller, D.J. Diekema, Epidemiology of invasive candidiasis: a persistent public health problem, Clin. Microbiol. Rev. 20 (1) (2007) 133–163, doi:10.1128/CMR.00029-06.
[21] B.C. West, A.D. Oberle, K.J. Kwon-Chung, Mucormycosis caused by *Rhizopus microsporus* var. microsporus: cellulitis in the leg of a diabetic patient cured by amputation, J. Clin. Microbiol. 33 (12) (1995) 3341–3344, doi:10.1128/jcm.33.12.3341-3344.1995.
[22] K.P. Hartnett, B.R. Jackson, K.M. Perkins, et al., A guide to investigating suspected outbreaks of mucormycosis in healthcare, J. Fungi 5 (3) (2019) 69, doi:10.3390/jof5030069.
[23] H. Prakash, A. Chakrabarti, Global epidemiology of mucormycosis, J. Fungi 5 (1) (2019) 26, doi:10.3390/jof5010026.
[24] U. Pamidimukkala, S. Sudhaharan, A. Kancharla, et al., Mucormycosis due to *Apophysomyces* species complex- 25 years’ experience at a tertiary care hospital in southern India, Med. Mycol. 58 (4) (2020) 425–433, doi:10.1093/mmy/myz081.
[25] J.M. Balaguer, E. Soto, D. Perry, et al., Postoperative intramyocardial abscess caused by mucormycosis, Ann. Thorac. Surg. 58 (6) (1994) 1760–1762, doi:10.1016/0003-4975(94)91684-5.

[26] A. Mertens, D. Barche, L. Scheinpflug, et al., Rhinocerebrale Mucormykose, Laryngorhinootologie 97 (2018) 550–554, doi:10.1055/a-0619-5143.
[27] Invasive mucormycosis: problems of diagnosis and treatment-medexpert. Available at: https://med-expert.com.ua/journals/en/invasive-mucormycosis-problems-diagnosis-treatment/. Accessed December 18, 2023.
[28] C.K. Tebbi, Mycoviruses in fungi: carcinogenesis of fungal agents may not always be mycotoxin related, J. Fungi 9 (3) (2023) 368, doi:10.3390/jof9030368.
[29] E. Lin, M. Teng, A.H. Limper, Pulmonary mucormycosis: clinical features and outcomes, Infection 45 (4) (2017) 443–448, doi:10.1007/s15010-017-0991-6.
[30] P. McCallion, A. De Soyza, Cough and bronchiectasis, Pulm. Pharmacol. Ther. 47 (2017) 77–83, doi:10.1016/j.pupt.2017.04.010.
[31] S. Ojha, J. Gaskin, Spontaneous pneumomediastinum, BMJ Case Rep. 2018 (2018) bcr2017222965, doi:10.1136/bcr-2017-222965.
[32] A.D. Castrejón-Pérez, E.C. Welsh, I. Miranda, et al., Cutaneous mucormycosis, An. Bras. Dermatol. 92 (3) (2017) 304–311, doi:10.1590/abd1806-4841.20176614.
[33] S. Menzinger, S. Sid'Amar, G. Kaya, Cutaneous mucormycosis resulting from hematogenous dissemination of *Rhizomucor pusillus* in an immunocompromised patient, Dermatopathology 6 (4) (2020) 275–278, doi:10.1159/000506272.
[34] B. Spellberg, Gastrointestinal mucormycosis, Gastroenterol. Hepatol. 8 (2) (2012) 140–142.
[35] M. Sedlacek, J.G. Cotter, A.A. Suriawinata, et al., Mucormycosis peritonitis: more than 2 years of disease-free follow-up after posaconazole salvage therapy after failure of liposomal amphotericin B, Am. J. Kidney Dis. 51 (2) (2008) 302–306, doi:10.1053/j.ajkd.2007.09.026.
[36] M.V. Dioverti, K.A. Cawcutt, M. Abidi, et al., Gastrointestinal mucormycosis in immunocompromised hosts, Mycoses 58 (12) (2015) 714–718, doi:10.1111/myc.12419.
[37] A.H. Sarrami, M. Setareh, M. Izadinejad, et al., Fatal disseminated mucormycosis in an immunocompotent patient: a case report and literature review, Int. J. Prev. Med. 4 (12) (2013) 1468–1471.
[38] V.S. Humphrey, X. Li, S. Choudhary, et al., Fatal disseminated mucormycosis in a hematological immunocompromised patient with extensive voriconazole exposure: a case report and review of the literature, Case Rep. Dermatol. 12 (3) (2020) 168–173, doi:10.1159/000508457.
[39] J.R. Köhler, B. Hube, R. Puccia, et al., Fungi that infect humans, Microbiol. Spectr. 5 (3) (2017), doi:10.1128/microbiolspec.funk-0014-2016.
[40] L. Mendoza, R. Vilela, K. Voelz, et al., Human fungal pathogens of mucorales and entomophthorales, Cold Spring Harb. Perspect. Med. 5 (4) (2014) a019562, doi:10.1101/cshperspect.a019562.
[41] B. Spellberg, J. Edwards Jr, A. Ibrahim, Novel perspectives on mucormycosis: pathophysiology, presentation, and management, Clin. Microbiol. Rev. 18 (3) (2005) 556–569, doi:10.1128/CMR.18.3.556-569.2005.
[42] F.E. Nicolás, L. Murcia, E. Navarro, et al., Mucorales species and macrophages, J. Fungi 6 (2) (2020) 94, doi:10.3390/jof6020094.
[43] A.P. Gryganskyi, J. Golan, S. Dolatabadi, et al., Phylogenetic and phylogenomic definition of *Rhizopus* species, G3 8 (6) (2018) 2007–2018, doi:10.1534/g3.118.200235.
[44] A. Aqsa, S. Droubi, A. Glaser, *Aspergillus* and *Rhizopus* fungal coinfection in a patient with multiple myeloma, Cureus 12 (5) (2020) e8050, doi:10.7759/cureus.8050.
[45] G. Tansir, N. Rastogi, P. Ramteke, et al., Disseminated mucormycosis: a sinister cause of neutropenic fever syndrome, Intractable Rare Dis. Res. 6 (4) (2017) 310–313, doi:10.5582/irdr.2017.01063.
[46] E. Roilides, M. Simitsopoulou, Immune responses to Mucorales growth forms: do we know everything? Virulence 8 (8) (2017) 1489–1491, doi:10.1080/21505594.2017.1368942.
[47] T. Ganz, M.E. Selsted, R.I. Lehrer, Defensins, Eur. J. Haematol. 44 (1990) 1–8, doi:10.1111/j.1600-0609.1990.tb00339.x.
[48] J.W. Park, J.S. Chung, S. Lee, et al., Neutropenic Enterocolitis due to mucormycosis in a patient with myelodysplastic syndrome, Infect. Chemother. 52 (1) (2020) 98–104, doi:10.3947/ic.2020.52.1.98.
[49] H. Ghuman, K. Voelz, Innate and adaptive immunity to mucorales, J. Fungi 3 (3) (2017) 48, doi:10.3390/jof3030048.
[50] K. Ramphul, J. Joynauth, An update on the incidence and burden of diabetic ketoacidosis in the U.S, Diabetes Care. 43 (12) (2020) e196–e197, doi:10.2337/dc20-1258.
[51] M. Fayfman, F.J. Pasquel, G.E. Umpierrez, Management of hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state, Med. Clin. North Am. 101 (3) (2017) 587–606, doi:10.1016/j.mcna.2016.12.011.
[52] A.S. Ibrahim, B. Spellberg, J.J. Edwards, Iron acquisition: a novel perspective on mucormycosis pathogenesis and treatment, Curr. Opin. Infect. Dis. 21 (6) (2008) 620–625, doi:10.1097/QCO.0b013e3283165fd1.
[53] F. Álvarez, M. Fernández-Ruiz, J.M. Aguado, Iron and invasive fungal infection, Rev. Iberoam. Micol. 30 (4) (2013) 217–225, doi:10.1016/j.riam.2013.04.002.
[54] M. Miethke, M.A. Marahiel, Siderophore-based iron acquisition and pathogen control, Microbiol. Mol. Biol. Rev. 71 (3) (2007) 413–451, doi:10.1128/MMBR.00012-07.
[55] F. Gerwien, V. Skrahina, L. Kasper, et al., Metals in fungal virulence, FEMS Microbiol. Rev 42 (1) (2018) fux050, doi:10.1093/femsre/fux050.
[56] S.M.S. Hosseini, P. Borghei, Rhinocerebral mucormycosis: pathways of spread, Eur. Arch. Otorhinolaryngol. 262 (2005) 932–938, doi:10.1007/s00405-005-0919-0.
[57] J.L. Chiasson, N. Aris-Jilwan, R. Bélanger, et al., Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state, CMAJ 168 (7) (2003) 859–866.
[58] W.M. Artis, J.A. Fountain, H.K. Delcher, et al., A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability, Diabetes 31 (12) (1982) 1109–1114, doi:10.2337/diacare.31.12.1109.
[59] A.E. Kitabchi, G.E. Umpierrez, M.B. Murphy, et al., Management of hyperglycemic crises in patients with diabetes, Diabetes Care 24 (1) (2001) 131–153, doi:10.2337/diacare.24.1.131.
[60] M. Sen, S. Lahane, T.P. Lahane, et al., *Mucor* in a viral land: a tale of two pathogens, Indian J. Ophthalmol. 69 (2) (2021) 244–252, doi:10.4103/ijo.IJO_3774_20.
[61] O. Mete, S.L. Asa, Pathological definition and clinical significance of vascular invasion in thyroid carcinomas of follicular epithelial derivation, Mod. Pathol. 24 (12) (2011) 1545–1552, doi:10.1038/modpathol.2011.119.
[62] K.J. Maeda, D.M. McClung, K.C. Showmaker, et al., Endothelial cell disruption drives increased blood-brain barrier permeability and cerebral edema in the Dahl SS/jr rat model of superimposed preeclampsia, Am. J. Physiol. Heart Circ. Physiol. 320 (2) (2021) H535–H548, doi:10.1152/ajpheart.00383.2020.
[63] J.P. Bouchara, N.A. Oumeziane, J.C. Lissitzky, et al., Attachment of spores of the human pathogenic fungus *Rhizopus oryzae* to extracellular matrix components, Eur. J. Cell Biol. 70 (1) (1996) 76–83.
[64] A.S. Ibrahim, B. Spellberg, V. Avanessian, et al., *Rhizopus oryzae* adheres to, is phagocytosed by, and damages endothelial cells *in vitro*, Infect. Immun. 73 (2) (2005) 778–783, doi:10.1128/IAI.73.2.778-783.2005.
[65] M. Liu, B. Spellberg, Q.T. Phan, et al., The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice, J. Clin. Invest. 120 (6) (2010) 1914–1924, doi:10.1172/JCI42164.
[66] T. Gebremariam, M. Liu, G. Luo, et al., CotH3 mediates fungal invasion of host cells during mucormycosis, J. Clin. Invest. 124 (1) (2014) 237–250, doi:10.1172/JCI71349.
[67] L.M. Lopes Bezerra, S.G. Filler, Interactions of *Aspergillus fumigatus* with endothelial cells: internalization, injury, and stimulation of tissue factor activity, Blood 103 (6) (2004) 2143–2149, doi:10.1182/blood-2003-06-2186.
[68] A.R. Waldorf, N. Ruderman, R.D. Diamond, Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against *Rhizopus*, J. Clin. Invest. 74 (1) (1984) 150–160, doi:10.1172/JCI111395.
[69] J. Fernandez, K. Orth, Rise of a cereal killer: the biology of Magnaporthe oryzae biotrophic growth, Trends Microbiol. 26 (7) (2018) 582–597, doi:10.1016/j.tim.2017.12.007.
[70] A. Chakrabarti, R. Singh, The emerging epidemiology of mould infections in developing countries, Curr. Opin. Infect. Dis. 24 (6) (2011) 521–526, doi:10.1097/QCO.0b013e32834ab21e.
[71] R. Kumar, M.G. Ison, Opportunistic infections in transplant patients, Infect. Dis. Clin. North Am. 33 (4) (2019) 1143–1157, doi:10.1016/j.idc.2019.05.008.
[72] P.E. Newburger, D.C. Dale, Evaluation and management of patients with isolated neutropenia, Semin. Hematol. 50 (3) (2013) 198–206, doi:10.1053/j.seminhematol.2013.06.010.
[73] M. von Lilienfeld-Toal, J. Wagener, H. Einsele, et al., Invasive fungal infection, Dtsch Arztebl. Int. 116 (16) (2019) 271–278, doi:10.3238/arztebl.2019.0271.
[74] M. Asif, The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern, J. Educ. Health Promot. 3 (2014) 1, doi:10.4103/2277-9531.127541.
[75] C. de Souza Ferreira, T.H. Araújo, M.L. Ângelo, et al., Neutrophil dysfunction induced by hyperglycemia: modulation of myeloperoxidase activity, Cell Biochem. Funct. 30 (7) (2012) 604–610, doi:10.1002/cbf.2840.
[76] A. Vuorio, P.T. Kovanen, Mucormycosis and glucose-regulated protein 78 in COVID-19: amenable to statin treatment? J. Intern. Med. 290 (4) (2021) 931–933, doi:10.1111/joim.13347.
[77] R. Maiti, Hypoglycemic and antioxidant potency of ethyl acetate fraction of hydromethanolic extract (60:40) of *Tamarindus indica* Linn. seed in streptozotocin-induced diabetic experimental animal, Int. J. Health Sci. (2022) 11164–11182, doi:10.53730/ijhs.v6ns5.10964.
[78] E. Bonnet, M.L. Moutet, C. Baulard, et al., Performance comparison of three DNA extraction kits on human whole-exome data from formalin-fixed paraffin-embedded normal and tumor samples, PLoS One 13 (4) (2018) e0195471, doi:10.1371/journal.pone.0195471.
[79] P. Rotjanapan, Y.C. Chen, A. Chakrabarti, Epidemiology and clinical characteristics of invasive mould infections: A multicenter, retrospective analysis in five Asian countries, Med. Mycol. 56 (2) (2018) 186–196, doi:10.1093/mmy/myx029.
[80] C. Mbarek, S. Zribi, K. Khamassi, et al., Rhinocerebral mucormycosis: five cases and a literature review, B-ENT 7 (3) (2011) 189–193.
[81] G. Reid, J.P. Lynch 3rd, M.C. Fishbein, et al., Mucormycosis, Semin. Respir. Crit. Care Med. 41 (1) (2020) 99–114, doi:10.1055/s-0039-3401992.
[82] S.N. Afroze, R. Korlepara, G.V. Rao, et al., Mucormycosis in a diabetic patient: a case report with an insight into its pathophysiology, Contemp. Clin. Dent. 8 (4) (2017) 662–666, doi:10.4103/ccd.ccd_558_17.
[83] R. Poyuran, B.S. Dharan, S. Sandhyamani, et al., Mucormycosis-induced ileocecal perforation: a case report and review of literature, J. Postgrad. Med. 66 (1) (2020) 48–50, doi:10.4103/jpgm.JPGM_420_19.
[84] G. Luo, T. Gebremariam, H. Lee, et al., Efficacy of liposomal amphotericin B and posaconazole in intratracheal models of murine mucormycosis, Antimicrob. Agents Chemother. 57 (7) (2013) 3340–3347, doi:10.1128/AAC.00313-13.
[85] F.M. Marty, L. Ostrosky-Zeichner, O.A. Cornely, et al., Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis, Lancet Infect. Dis. 16 (7) (2016) 828–837, doi:10.1016/S1473-3099(16)00071-2.
[86] J.J. Vehreschild, A. Birtel, M.J.G.T. Vehreschild, et al., Mucormycosis treated with posaconazole: review of 96 case reports, Crit. Rev. Microbiol. 39 (3) (2013) 310–324, doi:10.3109/1040841X.2012.711741.
[87] A.S. Ibrahim, T. Gebremariam, Y. Fu, et al., Combination echinocandin-polyene treatment of murine mucormycosis, Antimicrob. Agents Chemother. 52 (4) (2008) 1556–1558, doi:10.1128/AAC.01458-07.

[88] B. Spellberg, T.J. Walsh, D.P. Kontoyiannis, et al., Recent advances in the management of mucormycosis: from bench to bedside, Clin. Infect. Dis. 48 (12) (2009) 1743–1751, doi:10.1086/599105.
[89] B. Spellberg, A.S. Ibrahim, Recent advances in the treatment of mucormycosis, Curr. Infect. Dis. Rep. 12 (6) (2010) 423–429, doi:10.1007/s11908-010-0129-9.
[90] K.C. Lawson, D.H. Lawson, Insights into the psychology of trauma should inform the practice of oncology, Oncologist 23 (7) (2018) 750–751, doi:10.1634/theoncologist.2018-0091.
[91] D. Garg, V. Muthu, I.S. Sehgal, et al., Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature, Mycopathologia 186 (2) (2021) 289–298, doi:10.1007/s11046-021-00528-2.
[92] P. Koehler, O.A. Cornely, B.W. Böttiger, et al., COVID-19 associated pulmonary aspergillosis, Mycoses 63 (6) (2020) 528–534, doi:10.1111/myc.13096.
[93] N. Singh, A.P. Limaye, in: Infections in solid-organ transplant recipients. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Elsevier, Amsterdam, 2015, pp. 3440–3452, doi:10.1016/b978-1-4557-4801-3.00313-1.
[94] U. Binder, E. Maurer, C. Lass-Flörl, Mucormycosis: from the pathogens to the disease, Clin. Microbiol. Infect. 20 (Suppl 6) (2014) 60–66, doi:10.1111/1469-0691.12566.
[95] C.C. Lai, T.P. Shih, W.C. Ko, et al., Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges, Int. J. Antimicrob. Agents 55 (3) (2020) 105924, doi:10.1016/j.ijantimicag.2020.105924.
[96] K. Bhattacharya, S. Bhattacharya, P. Sengupta, et al., Coronavirus disease 2019 (COVID-19) and pregnancy, Biomed. Pharmacol. J. 14 (3) (2021), doi:10.13005/bpj/2219.
[97] E. Hadaschik, R. Koschny, B. Willinger, et al., Pulmonary, rhino-orbital and cutaneous mucormycosis caused by *Rhizomucor pusillus* in an immunocompromised patient, Clin. Exp. Dermatol. 37 (4) (2012) 355–357, doi:10.1111/j.1365-2230.2011.04235.x.
[98] N.V. Sipsas, M.N. Gamaletsou, A. Anastasopoulou, et al., Therapy of mucormycosis, J. Fungi 4 (3) (2018) 90, doi:10.3390/jof4030090.
[99] S. Mehta, A. Pandey, Rhino-orbital mucormycosis associated with COVID-19, Cureus 12 (9) (2020) e10726, doi:10.7759/cureus.10726.
[100] G. Mathew, V. Arumugam, S. Murugesan, et al., Renal mucormycosis: a rare cause of urinary tract infection leading to end-stage renal disease (ESRD), J. Trop. Pediatr. 65 (4) (2019) 405–408, doi:10.1093/tropej/fmy059.
[101] M. Mikulska, L.A. Nicolini, A. Signori, et al., Tocilizumab and steroid treatment in patients with COVID-19 pneumonia, PLoS One 15 (8) (2020) e0237831, doi:10.1371/journal.pone.0237831.
[102] M.D. Moen, K.A. Lyseng-Williamson, L.J. Scott, Liposomal amphotericin B: a review of its use as empirical therapy in febrile neutropenia and in the treatment of invasive fungal infections, Drugs 69 (3) (2009) 361–392, doi:10.2165/00003495-200969030-00010.
[103] M.A. Schipper, M.M. Maslen, G.G. Hogg, et al., Human infection by *Rhizopus azygosporus* and the occurrence of azygospores in Zygomycetes, J. Med. Vet. Mycol. 34 (3) (1996) 199–203.
[104] S. Atal, Z. Fatima, IL-6 inhibitors in the treatment of serious COVID-19: a promising therapy? Pharmaceut. Med. 34 (4) (2020) 223–231, doi:10.1007/s40290-020-00342-z.
[105] J.H. Beigel, K.M. Tomashek, L.E. Dodd, et al., Remdesivir for the treatment of covid-19 - final report, N. Engl. J. Med. 383 (19) (2020) 1813–1826, doi:10.1056/NEJMoa2007764.
[106] V.P. Singh, C. Bansal, M. Kaintura, Sinonasal mucormycosis: a to Z, Indian J. Otolaryngol. Head Neck Surg. 71 (3) (2019) 1962–1971, doi:10.1007/s12070-018-1384-6.
[107] H.E. Tamez-Pérez, D.L. Quintanilla-Flores, R. Rodríguez-Gutiérrez, et al., Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review, World J. Diabetes 6 (8) (2015) 1073–1081, doi:10.4239/wjd.v6.i8.1073.
[108] Z.K. Mekonnen, D.C. Ashraf, T. Jankowski, et al., Acute invasive rhino-orbital mucormycosis in a patient with COVID-19-associated acute respiratory distress syndrome, Ophthalmic Plast. Reconstr. Surg. 37 (2) (2021) e40–e80, doi:10.1097/IOP.0000000000001889.
[109] J. Yoshimura, K. Yamakawa, A. Kodate, et al., Prognostic accuracy of different disseminated intravascular coagulation criteria in critically ill adult patients: a protocol for a systematic review and meta-analysis, BMJ Open 8 (12) (2018) e024878, doi:10.1136/bmjopen-2018-024878.
[110] M. Sen, S.G. Honavar, N. Sharma, et al., COVID-19 and eye: a review of ophthalmic manifestations of COVID-19, Indian J. Ophthalmol. 69 (3) (2021) 488–509, doi:10.4103/ijo.IJO_297_21.
[111] C. Hoffmann, G. Guillerm, P. Le Pape, et al., Mucorales DNA detection in serum specimens for early diagnosis of mucormycosis, Diagn. Microbiol. Infect. Dis. 97 (2) (2020) 115004, doi:10.1016/j.diagmicrobio.2020.115004.
[112] M. Glazer, S. Nusair, R. Breuer, et al., The role of BAL in the diagnosis of pulmonary mucormycosis, Chest 117 (1) (2000) 279–282, doi:10.1378/chest.117.1.279.
[113] T.J. Sharpton, An introduction to the analysis of shotgun metagenomic data, Front. Plant Sci. 5 (2014) 209, doi:10.3389/fpls.2014.00209.
[114] P. Badiee, A. Arastefar, H. Jafarian, Comparison of histopathological analysis, culture and polymerase chain reaction assays to detect mucormycosis in biopsy and blood specimens, Iran. J. Microbiol. 5 (4) (2013) 406–410.
[115] J. Guarner, M.E. Brandt, Histopathologic diagnosis of fungal infections in the 21st century, Clin. Microbiol. Rev. 24 (2) (2011) 247–280, doi:10.1128/CMR.00053-10.
[116] A. Leclercq, E. Cinotti, B. Labeille, et al., *Ex vivo* confocal microscopy: a new diagnostic technique for mucormycosis, Skin Res. Technol. 22 (2) (2016) 203–207, doi:10.1111/srt.12251.
[117] A.S. Kelliher, D.W. Parent, D.C. Anderson, et al., Novel use of the BD FACS SPA to automate custom monoclonal antibody panel preparations for immunophenotyping, Cytometry B Clin. Cytom. 66 (1) (2005) 40–45, doi:10.1002/cyto.b.20055.
[118] M. Pandey, I. Xess, G. Singh, et al., Conventional PCR as a reliable method for diagnosing invasive mucormycosis in resource-limited settings, J. Med. Microbiol. 70 (5) (2021), doi:10.1099/jmm.0.001370.
[119] E. Scherer, X. Iriart, A.P. Bellanger, et al., Quantitative PCR (qPCR) detection of mucorales DNA in bronchoalveolar lavage fluid to diagnose pulmonary mucormycosis, J. Clin. Microbiol. 56 (8) (2018) e00289–e00218, doi:10.1128/JCM.00289-18.
[120] D. Tacke, P. Koehler, B. Markiefka, et al., Our 2014 approach to mucormycosis, Mycoses 57 (9) (2014) 519–524, doi:10.1111/myc.12203.
[121] F. Danion, C. Aguilar, E. Catherinot, et al., Mucormycosis: new developments into a persistently devastating infection, Semin. Respir. Crit. Care Med. 36 (5) (2015) 692–705, doi:10.1055/s-0035-1562896.
[122] L. Pagano, P. Ricci, A. Tonso, et al., Mucormycosis in patients with haematological malignancies: a retrospective clinical study of 37 cases. GIMEMA Infection Program (Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto), Br. J. Haematol. 99 (2) (1997) 331–336, doi:10.1046/j.1365-2141.1997.3983214.x.
[123] B. Spellberg, A. Ibrahim, E. Roilides, et al., Combination therapy for mucormycosis: why, what, and how? Clin. Infect. Dis. 54 (suppl_1) (2012) S73–S78, doi:10.1093/cid/cir885.
[124] S. Krishnan-Natesan, P.H. Chandrasekar, Current and future therapeutic options in the management of invasive aspergillosis, Drugs 68 (3) (2008) 265–282, doi:10.2165/00003495-200868030-00002.
[125] S.E.A. Mills, A.V. Yeldandi, D.D. Odell, Surgical treatment of multifocal pulmonary mucormycosis, Ann. Thorac. Surg. 106 (2) (2018) e93–e95, doi:10.1016/j.athoracsur.2017.12.033.
[126] B.A. Zahoor, J.E. Piercey, D.R. Wall, et al., A surgical approach in the management of mucormycosis in a trauma patient, Ann. R. Coll. Surg. Engl. 98 (8) (2016) e173–e177, doi:10.1308/rcsann.2016.0221.
[127] A. Sharma, A. Goel, Mucormycosis: risk factors, diagnosis, treatments, and challenges during COVID-19 pandemic, Folia Microbiol. 67 (3) (2022) 363–387, doi:10.1007/s12223-021-00934-5.
[128] C.F. Whitsett, The role of hematopoietic growth factors in transfusion medicine, Hematol. Oncol. Clin. North Am. 9 (1) (1995) 23–68.
[129] A.P. Bellanger, A.M. Tatara, F. Shirazi, et al., Statin concentrations below the minimum inhibitory concentration attenuate the virulence of *Rhizopus oryzae*, J. Infect. Dis. 214 (1) (2016) 114–121, doi:10.1093/infdis/jiw090.
[130] T.T. Riley, C.A. Muzny, E. Swiatlo, et al., Breaking the mold: a review of mucormycosis and current pharmacological treatment options, Ann. Pharmacother. 50 (9) (2016) 747–757, doi:10.1177/1060028016655425.
[131] A.G.S. Warrilow, C.M. Hull, J.E. Parker, et al., The clinical candidate VT-1161 is a highly potent inhibitor of *Candida albicans* CYP51 but fails to bind the human enzyme, Antimicrob. Agents Chemother. 58 (12) (2014) 7121–7127, doi:10.1128/AAC.03707-14.
[132] K. Adhikary, An updated review on nanomaterials for biomedical advancements: concepts and applications, Biosci. Biotechnol. Res. Commun. 14 (4) (2021) 1428–1434, doi:10.21786/bbrc/14.4.9.
[133] D. Ben Yaakov, A. Rivkin, G. Mircus, et al., Identification and characterization of haemofungin, a novel antifungal compound that inhibits the final step of haem biosynthesis, J. Antimicrob. Chemother. 71 (4) (2016) 946–952, doi:10.1093/jac/dkv446.
[134] K. Adhikary, P. Banerjee, S. Barman, et al., Nutritional aspects, chemistry profile, extraction techniques of lemongrass essential oil and it's physiological benefits, J. Am. Nutr. Assoc. 43 (2) (2024) 183–200, doi:10.1080/27697061.2023.2245435.
[135] H. Prakash, A. Chakrabarti, Epidemiology of mucormycosis in India, Microorganisms 9 (3) (2021) 523, doi:10.3390/microorganisms9030523.
[136] J. Chander, M. Kaur, N. Singla, et al., Mucormycosis: battle with the deadly enemy over a five-year period in India, J. Fungi 4 (2) (2018) 46, doi:10.3390/jof4020046.
[137] K. Adhikary, S. Mohanty, B. Bandyopadhyay, et al., β-Amyloid peptide modulates peripheral immune responses and neuroinflammation in rats, Biomol. Concepts 15 (1) (2024) 20220042, doi:10.1515/bmc-2022-0042.