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The Pathogenesis of Fungal Coinfections in COVID-19 Cases

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Penyakit virus corona tahun 2019 (COVID-19), yang menyerang sistem pernapasan manusia, disebabkan oleh virus SARS-CoV2. Pasien yang sakit kritis lebih mungkin mengalami koinfeksi jamur jika mereka dirawat di rumah sakit dalam waktu lama, memerlukan ventilator, atau dirawat di ICU. Banyak jamur, seperti spesies Candida, spesies Aspergillus, spesies Mucor, dan spesies Cryptococcus, telah dikaitkan dengan koinfeksi COVID-19. Penelitian tentang mekanisme koinfeksi jamur pada pasien COVID-19 masih memerlukan penelitian lebih lanjut, namun ada beberapa kemungkinan yang dapat mengaitkan keduanya. Penggunaan kortikosteroid, ventilator dan masker oksigen pada pasien COVID-19 dapat menjadi salah satu jalan terjadinya koinfeksi fungal. Kondisi disregulasi imun pada pasien COVID-19 menyebabkan tubuh pasien tidak mampu melawan infeksi fungal. Beberapa pencegahan yang dapat dilakukan yaitu dengan mengkordinasikan deteksi dini infeksi fungal pada pasien COVID-19 secara rutin untuk mengurangi faktor resiko dan meningkatkan protokol perawatan rutin. Apabila pasien sudah terkena koinfeksi fungal dapat dilakukan pengobatan dengan menggunakan beberapa kombinasi obat yang disarankan. Selain itu, dalam upaya menjaga kebersihan alat kesehatan khususnya ventilator, kebersihan bangsal rumah sakit dan proses penanganan limbah pasien COVID-19, perlu juga memperhatikan pencegahan penularan jamur pada pasien COVID-19 yang dirawat di rumah sakit.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory disease carriedon by the SARS-CoV2 virus1, and is responsible for lower respiratorytract infections called Acute Respiratory Distress Syndromes (ARDS).2The first case of COVID-19 reportedly happened in the traditional marketlocated in Wuhan, South China. The cause of several pneumonia cases withan unknown cause in December 2019 has been identified as a novelcoronavirus, according to reports. WHO designated these respiratorytract infections Coronavirus disease-2019 (COVID-19) in February 2020.The significant rise in cases made WHO state the novel coronavirus as anemergency case for international concerns until March 11, 2020, andCOVID-19 was officially stated as a pandemic.3,4 The earliest time ofthe COVID-19 outbreak, Wenzhou, one of the busiest cities in China, havethe highest number of reported cases, with 499 of 1162 cases reported inChina on February 15, 2020.2 Wenzhou's worst cases and death ratecompared to Hubei are 2,6% vs 0% (1457/54.406 vs 0/499) and 15,2% vs5,2% (8276/64.406 vs 26/499), respectively. This stark contrasthighlights the significant difference. 3

Many problems can occur in COVID-19 patients, including complicationsdue to fungal coinfection that can aggravate and even cause death inpatients infected with COVID-19. Several fungal coinfections in COVID-19patients, such as Aspergillosis, Candidiasis, and Mucormycosis, havebeen found in patients with COVID-19 infections. Forty-onecases ofCOVID-19 associated with mucormycosis (CAM) were reported in March 2021,and 70% of them come from India.5 Telangana disclosed 50 cases per day6,and 1196 cases were reported until June 9th, 2011, in TamilNadu.7Another finding states that until June 2021, in a total of 275cases of CAM, 223 cases

were found in India and the other 42 cases fromother countries.8 Studies in the United Kingdom and Spain reported 12.6%and 0.4% of patients experienced an incidence of COVID-19-associatedcandidiasis (CAC), respectively.9,10 Furthermore, 23.3% of Aspergilluscoinfection with COVID-19 (CAPA) was reported in China.11 However,research on the invasive mechanism and fungal coinfections in COVID-19patients, especially CAPA and Mucormycosis, is still limited.8Nevertheless,researchers have revealed several possible mechanisms offungal coinfections in COVID-19 patients.

This review aimed to summarize these several possibilities of therelated mechanisms. The recognition of finding the pathway is crucialfor the specific management of affected patients.

METHOD

This article was compiled using a literature search approach fromseveral kinds of literature, such as books and articles that publishesin english. Pubmed and Google scholar searches were performed fromAugust 2021 until November 2022. The keywords were ‘COVID-19’, ‘fungalcoinfection’, ‘COVID-19’ AND ‘coinfection fungal’, ‘mucormycosis’ AND‘COVID-19’, ‘aspergillosis’ AND ‘ COVID-19’, ‘candidiasis’ AND‘COVID-19’, ‘invasive fungal infection’. All the studies related to thepathogenesis of fungal co-infection in COVID-19 patients were used. Theinformation was explained as text and figures.

RESULT AND DISCUSSION

SARS-COV2 andCovid-19

One of the -CoVs, Severe Acute Respiratory Syndrome Coronavirus 2(SARS-COV-2), has a 79% genomic sequence identity with SARS-CoV and a50% genomic sequence identity with MERS CoV.12 The virion of SARS-COV-2has a 29.9 genome size, and the nucleocapsid contains RNA genomic andphosphorylated nucleocapsid (N).13 The coronavirus genome (ORF) presentsnumerous open reading frames. 16 non-structural proteins (NSP-16) werecreated after a protease digested the 5′ ORF (ORF1a/b) that wastranslated by the host endoplasmic reticulum into pp1a and pp1b. The 3′ORF, which comprises one-third of the genome, is responsible fordecoding the structural and auxiliary proteins. One of the fouressential structural proteins is the surface spike protein (S), whichrecognizes the angiotensin-converting enzyme 2 (ACE2) receptor on thehost cell, binds to it, and helps the virus enter the host cell. Thebinding of the RNA by the envelope protein (E), matrix protein (M), andnucleocapsid protein (N) is the basis for virion formation.12

The six accessory proteins that are encoded by ORF3a, ORF6, ORF7a,ORF7b, ORF8, and ORF10, and whose functions are still unknown, areanother characteristic of SARS-COV-2.14 Most of the proteins that ORF1aand OF1ab encode are necessary for virus replication and, at the veryleast, host adaptation.15 The SARS-COV-2 genome's 5′ and 3′ untranslatedregions (UTR) have also been discovered.NSP 12 is a dependent RNApolymerase that replicates the viral RNA as part of a complexreplica/transcriptase formed by some NSPs. But for it to work properly,NSP 7 and NSP 8 are needed. More than 85% of the amino acid sequences inthe 12 structural proteins of SARS-COV-2 are identical to those ofSARS-CoV.12,16 The board receptor of SARS-COV-2, angiotensin-convertingenzyme 2 (ACE 2) could be recognized in various types of animals apartfrom humans, which emphasizes the wide range of infections.17

The pathogenesis of COVID-19 could be started from the transmissionof the virus, which occurs through respiratory droplets, directcontacts, and the fecal-oral route.18 The first suspected primer viralmultiplication occurred on the upper tract mucosal epithelium andcontinued to the lower tract and gastrointestinal tract, which caneventually lead to mild viremia. Some patients would show asymptomaticsymptoms,19 while others show non-respiratory signs such as diarrhea,kidney failures, and other symptoms involving several organs in thebody.16,20

Once SARS-COV-2 invaded the lower lungs, various cells, includingvascular endothelial cells, alveolar airway epithelial cells, andalveolar cell macrophages, would get infected. When this virus entersthe body, it will be detected by the innate immune sensor cytosolic andToll-like receptor (TLR) on endosomes signaling the production ofinterferon type I/III (IFN) and proinflammatory mediators.21,22 Theincreasing seven inflammatory cytokines amplify tissue damage throughendothelial dysfunction and vasodilatation, causing the presence ofmacrophages and neutrophils.22 The vascular leakage and the barrierfunction disruption increase endothelin and lung edema, restricting thegas exchange and causing hypoxia that eventually led to respiratoryfailures.23,24 The lung's hyperinflammation further inducestranscriptional alterations in neutrophils and macrophages, which makesthe tissue damage permanent and leads to irreversible lung damage.25 Thelatest report shows that systemic inflammation inducts a long-termeffect on the heart.26

The cytokine storm is reputed as the leading cause of death inCOVID-19 patients. Patients with older age (>60) and pre-existingdisease (comorbid) have a higher risk of developing ARDS and death.13The deathly symptoms of ARDS prevent oxygen from entering the lung andcirculating in the body, causing grave harm to respiratory tractdisorder and lung disease. Many things are associated with ARDS, namelygenetic susceptibility and inflammatory cytokines, as well as severalrelated genes such as ACE2, Interleukin 10 (IL-10), tumour necrosisfactor (TNF), and vascular endothelial growth factor (VEGF).13,27

The Mechanism of Fungal Infection

Less than 500 species of fungi are responsible for human and animalinfections. The more days passed, the more opportunistic fungi mixed up,causing severe disease in the host with a compromised immune system. Thegenus Candida is currently included in the order Saccharomycetales ofAscomycetes.28 This genus is commensals to humans and often isolatedfrom urine, skin, and gastrointestinal tract, which opportunisticallycauses candidiasis. Candida is pathogenic due to many virulence factorsthat help in adhesion to the mucosa, the ability to elude host defences,and the production of tissue-damaging hydrolytic enzymes. One ofCandida's important virulence factors is its ability to produce mucosaladherence and biofilms.29 By preventing the drug from penetrating thematrix and shielding it from the human immune response, it offersexcellent resistance to antifungal treatment. Additionally, the abilityof Candida to switch between yeast and hyphal growth is strongly linkedto its virulence.28,29 Aspergillus, the genera of the Trichomaceaefamily, secrete enzymes with various functions, such as protease,hydrolase, and catalase. For instance, these enzymes directly influencethe expression of virulence-related attributes in Aspergillus fumigatusby activating various pathways. Aspergillus's virulence is influenced bya combination of biological traits unique to the fungus and the immunehealth of the host..29 Another genus Cryptococcus, are one of theBasidiomycetes with capsuled oval yeast-like fungus. One ofthe Cryptococcus genera, C. neoformans has degradation enzymes such asprotease and lipase as its virulence factor. C. neoformans are infamousfor expressing two virulence factors that abrupt the host immune system:capsule and melanin. The prominent of these components is the doublefunction not only as virulence factors, but also responsible forprotecting the fungus from several immune response attacks.28,30

Mucorales is responsible for rhinocerebral infections, pulmonary,skin, or disseminated infections characterized by angioinvasion,necrosis, and severe prognosis despite antifungal therapy and surgerytoday.28 Mucorales are commonly found in soil, spoiled food, manure anddust.31 In the fungus, high-affinity iron permease (FTR1) plays a rolein iron absorption and transport, particularly in an environment withlow ferritin levels. Another virulence factor of Mucorales is the sporemantel (CotH) detected in all of Mucorales fungus but absent in otherspecies, playing the role ofinvasion agent and disrupting the hostimmune.32 Mucormycosis is distinguished by the development of hyphae onand around blood vessels that lead to disrupting the blood vessel,tissue damage, thrombosis and necrosis.33

Innate immune cells play a role in the host's response after fungiinvade the mucosa. The innate immune defense is quite specific. Thepattern recognition receptor (PRR) activates the response because it canrecognize the microorganism's conserved structure. The most importantPPRs in the immune response are C-type lectin receptors (CLRs) that isDectin-1, pentraxin-3, toll-like receptor, and Nod-like receptor(inflammasome).29 In the patient with the immunocompromised, theabundance of Fe creates a favorable environment for fungal growth.Mucorales use its high iron affinity permease and use it for theirgrowth.31 The spore coat protein (CotH) in the spore surface penetrates,interferes, and damages the immune cells.34

The epithelial cells are the front barrier that contacts the fungus,especially Mucorales, which disrupts the cells with the increasedsignaling of platelet-derived growth factor receptor B (PDGFRB) andserve as a proper environment to grow.31 The neutrophils are the firstbarrier against fungi that activate the innate immune defense andregulate the adaptive immune systems.35 In diabetes mellitus patients orwith steroid usage caused by ketoacidosis or hyperglycaemic, thechemotactic released by the neutrophil is decreased, causing hyphaegrowth increase. After entering the host cells, Mucorales produces theMucorales-specific T-cells, which produce the proinflammatory cytokinessuch as interleukin (IL4, IL-10, and IL-17) and IFN-γ that stimulateT-cell CD4+ to disrupt the host's cells. Additionally, the hyphaeprevent the release of some immunomodulatory molecules secreted by NKcells in the early stages of infections, including RANTES (regulatedupon activation, normal T-cells expressed and secreted) and IFN- γ.These mechanisms explain why immunocompromised patients are susceptibleto mucormycosis and the potential in the host's cell mechanism ofaction.31

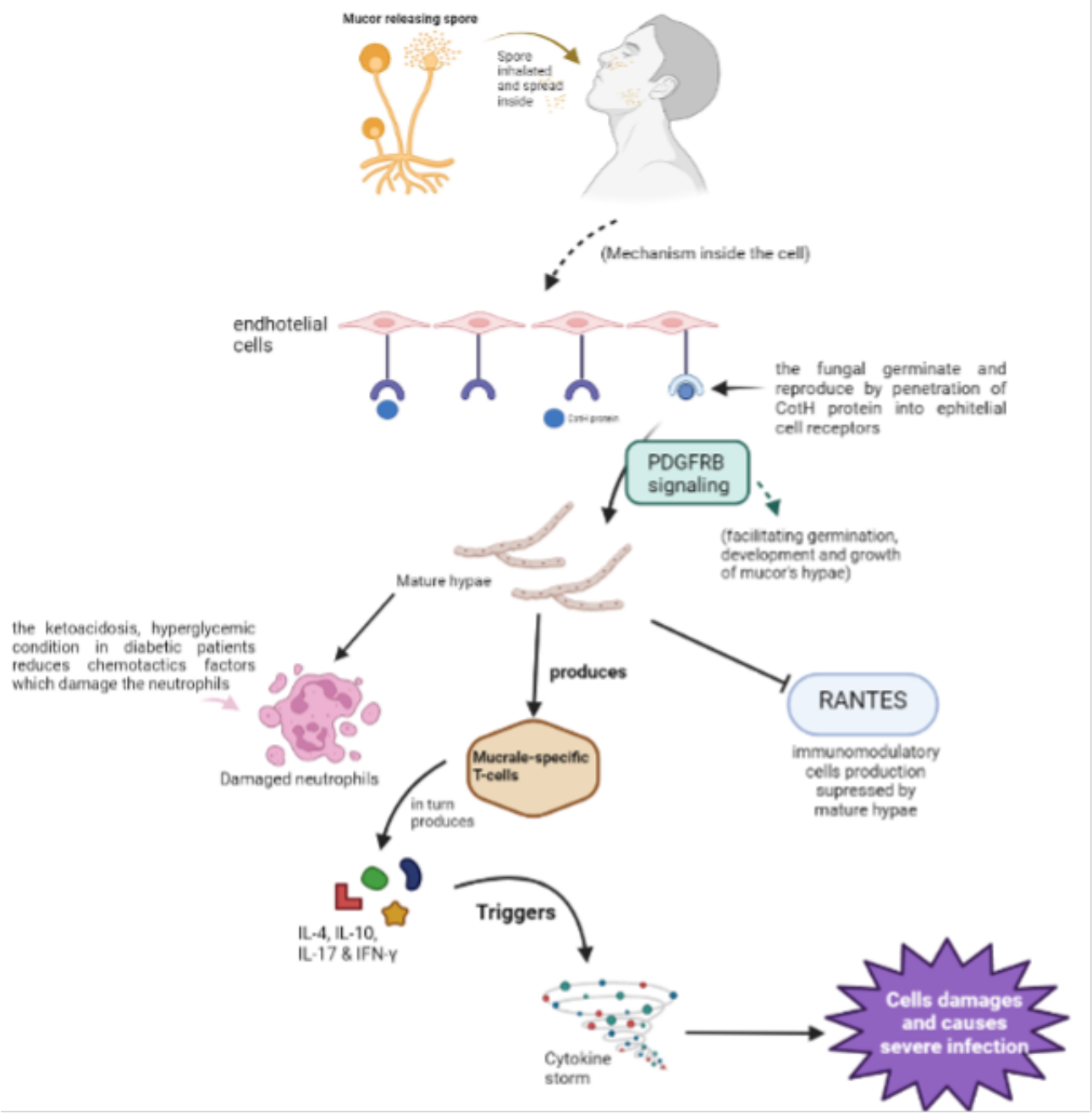

Figure 1. *Mucormycosis Mode of Action: Spores that enterimmunocompromised patients through the respiratory route will attach toepithelial receptors and be detected by CotH receptors, then the thingsneeded for the growth and development of fungal hyphae will be providedthrough the PDGFRB signaling pathway. When the fungus develops, the bodywill produce Mucorales-specific T cells with various proinflammatorycells, triggering a cytokine storm that causes cell damage.31*

Fungal coinfection in COVID-19 cases

There are numerous potential causes of mucormycosis in COVID-19patients, one of which is a variety of changes in the patient's lungcondition, which is suspected to be a focal point for fungalinitiation.1,8,31,36 Furthermore, COVID-19 is linked to weakenedimmunity.2,22,31,37 Patients with heavy symptoms who have beenhospitalized for a long time tend to use a ventilator, another way forspores to enter. On the other hand, high ferritin levels cause therelease of ROS (Reactive Oxygen Species) that damages the surroundingtissues.8 The cytokines released while infected also increase thelikelihood of intracellular iron entering circulation, increasing therisk of

developing mucormycosis.31

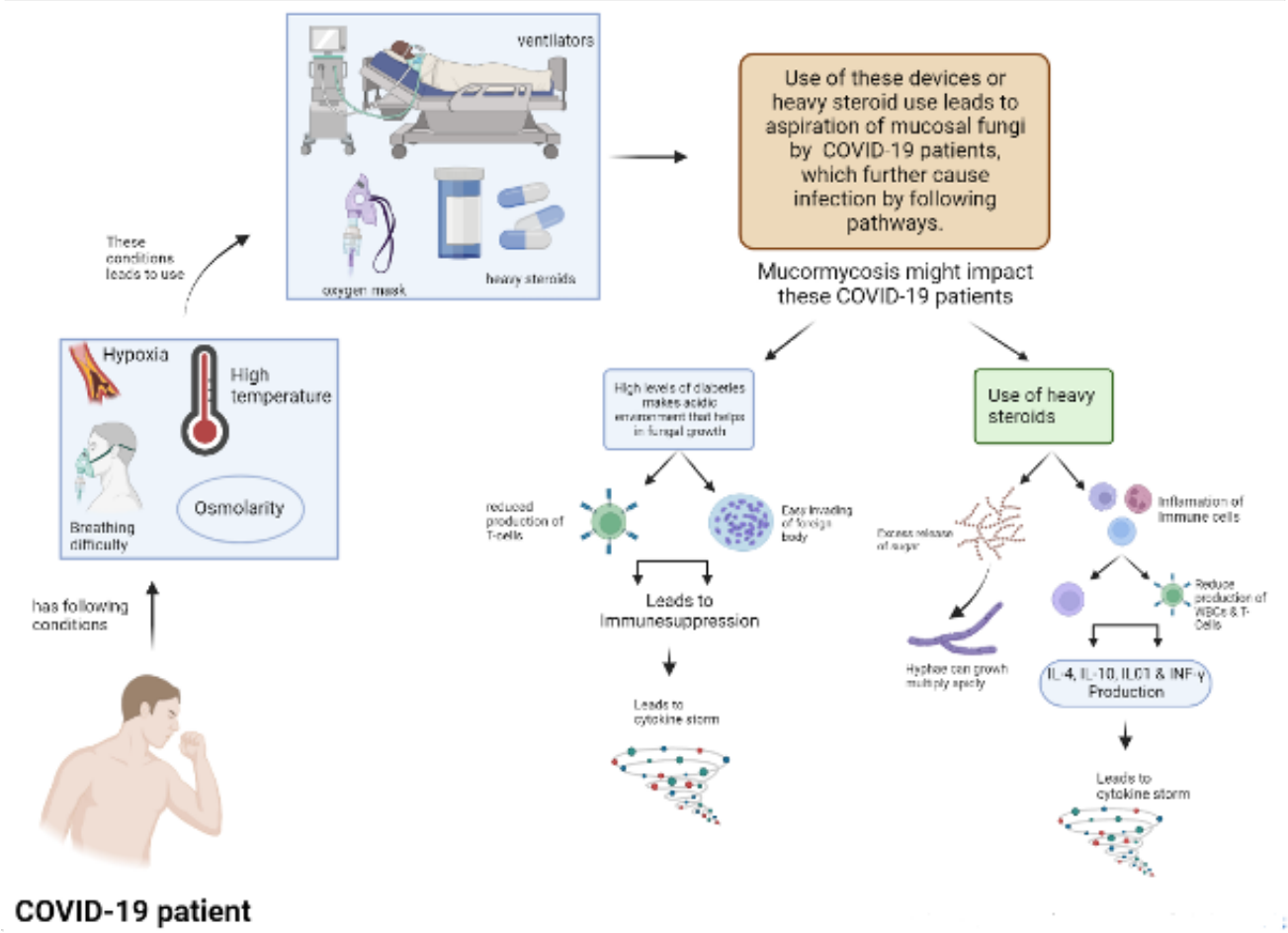

Figure 2. *Potential mechanism of mucormycosis in COVID-19 patients:Common symptoms in COVID-19 patients can be one of the causes ofmucormycosis. Especially in patients who use steroids in largequantities, the use of masks and ventilators in COVID-19 patients can bean entry point for Mucorales fungus. Mucormycosis can occur in two ways:1) In the condition of a diabetic COVID-19 patient. 2) Use of largeamounts of steroids which can eventually cause a cytokine storm anddamage cellular organs.31*

Viewed from the patient's immune response, the failure of the initialinflammation response could cause tissue damage and the spread ofinfections. The function of macrophages and neutrophils that directlyact as a barrier against the entry of pathogenic fungi, killed andphagocytize spores and hyphae by producing and releasing perforins,antimicrobial enzymes, reactive oxygen metabolites, and cationicpeptides are disrupted. The decrease of proinflammatory cytokines allowsthe spreading of fungal infections.36 Like the CAPA mechanism and itsrelation with COVID-19, mucormycosis also requires further research andunderstanding. A severe COVID-19 high-risk factor related to COVID-19death risk is diabetes mellitus. Diabetes significantly increasesglycemic control, disrupts phagocytic function, and delays theactivation of the adaptive immune response, all of which severely damagethe innate immune system. COVID-19 receptor (ACE2) was discovered in thelungs and pancreas. These proteins allow the entry of SARS-COV-2 andharm the pancreatic islet cells. Severe symptoms may increase insulinresistance by secreting stress hormones (cortisol and others) andcytokines.8,38,39

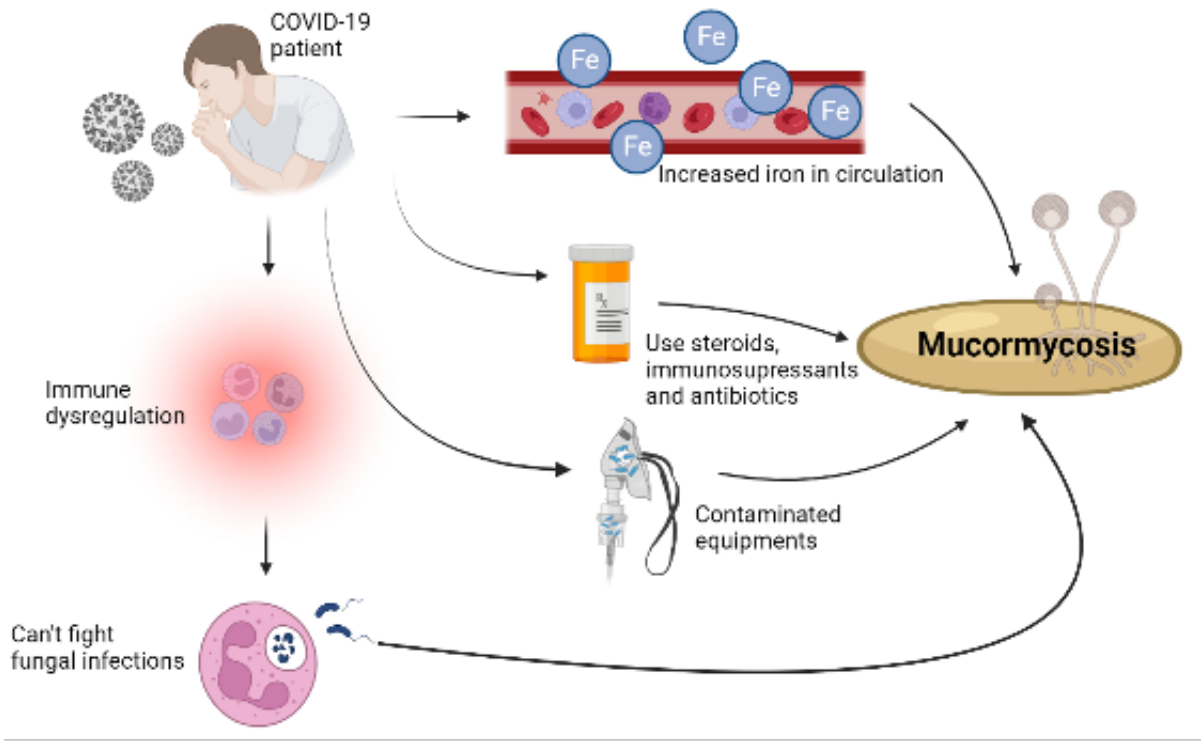

Figure 3. *Mucormycosis and COVID-19: COVID-19 patients are consideredmore susceptible to mucormycosis because their weakened immune conditionand the use of suppressants as therapy will reduce the ability ofphagocytic cells to fight fungi as foreign objects in the body.31*

An important predisposition for CAM is corticosteroid. They arestrong immunosuppressants with various effects on innate and adaptiveimmunity. The short-term glucocorticoid can trigger hyperglycemia and isproven as a predisposition to mucormycosis. Dexamethasone completelyinhibits Aspergillus and Rhizopus phagocytosis in Drosophilamelanogaster models. Dexamethasone and corticosteroids are commonly usedto treat COVID-19, and their contributions to CAM pathogenesis appearundeniable.8

Prevention and therapy

Fungal coinfections in COVID-19 patients can trigger due to variousthings, such as the length of hospitalization and the severity of thepatient's illness, errors in treating patients, and the lack ofsupervision and early diagnosis of infection.40 Therefore, variouspreventive measures are recommended to reduce the chance of fungalinfection in COVID-19 patients. One way to detect invasive aspergillosisin the body of COVID-19 is by detecting galactomannan, a polysaccharideantigen on the cell wall of Aspergillus spp., from bronchoalveolarlavage fluid (BALF). This method is known as precise and rapid detectionto see IA in patients.29,41–46 In addition, PCR testing can be analternative for early diagnosing fungal infections.47 Another way ofprevention is screening for Candida spp. Routinely to reduce riskfactors and improve routine treatment protocols.48

The treatment for fungi infection has been a broad topic mainlyrelated to COVID-19. The Infectious Disease Society of America's 2016update guidelines discussed the treatment of Invasive Aspergillosis (IA)using alternative medicines or drugs. Despite the azole interactioneffect, most patients treated with thiazole group drugs still needfurther observation. Amphotericin B is also commonly used as one of theIA treatments, as well as invasive candidiasis (IC). Another therapyuses echinocandins, liposomes, and monitoring for azole use for itseffect optimation and

reducing its toxicity.1 Treatment options forinvasive mucormycosis (IM) include (i) an induction phase ofamphotericin B deoxycholate + flucytosine, followed by fluconazole (orfluconazole + flucytosine or amphotericin B deoxycholate + fluconazole),(ii) a consolidation phase for fluconazole, and (iii) a maintenancephase (secondary prophylaxis) for fluconazole. A study that associatedbetter survival with medical combination treatment using amphotericin bfollowed by isavuconazole or posaconazole reported a lower mortalityrate in India, 36,5% lower than non-COVID-19 cases before, and to thelatest study of CAM, 45,7%.1,39

In addition to the antifungal combination, maintaining environmentalconditions such as air circulation in hospital wards and oxygen therapymachines must be considered. The recovering patient was also advised toremain in the hospital for a few weeks to revive the immunity andprevent further complications. Waste disposal from patients is also oneof the essential things to notice. The importance of fungal coinfectionsshould be considered a priority to prevent further fungal transmissionin COVID-19 patients.31

CONCLUSSION

The critically ill patients who are mainly admitted to ICU andrequire ventilators or are treated in the hospital for a long time aresusceptible to fungal coinfection and have added up a worrying mortalityrate in COVID-19 cases. The ability of fungi to evade host defenses, theadhesion sites in mucosa, and the production of tissue-damaginghydrolytic enzymes all contribute to their pathogenicity. Theinflammatory mechanism is essential in the immune defense system andvirulence agent from the fungus. Antifungal combinations, such asamphotericin B, fluconazole, flucytosine etc, should be considered forCOVID-19 patients, especially those with immunity deficiency. Inaddition, the cleanliness of the medical equipment, especially theventilators, the hospital ward, and the handling waste of COVID-19patients are necessary to prevent fungal transmission in COVID-19patients.

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CONFLICT OF INTEREST

There are no conflicts of interest, according to the authors.

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