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Review Article

Invasive Fungal Disease Associated with COVID-19 Infection

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Abstract

While COVID-19 primarily attacks the lungs, its reach can extend to various organs. Patients battling severe cases, especially those in intensive care, face a heightened risk of secondary infections caused by fungi, bacteria, and even other viruses. This vulnerability stems from a weakened immune system due to the initial infection, extended hospital stays, and the use of medications that suppress the immune response. Fungal infections pose a significant threat, with aspergillosis, candidiasis, mucormycosis, Cryptococcus, pneumocystis, and even regional fungal strains being identified in COVID-19 patients. Weakened immunity and underlying lung issues make these patients particularly susceptible to aspergillosis. Prolonged hospitalization, broad-spectrum antibiotics, and a compromised immune system increase the risk of Candida infections. Additionally, diabetics receiving corticosteroids are more likely to develop mucormycosis. Diagnosing fungal infections in COVID-19 patients is challenging because symptoms often mimic those of the initial COVID-19 infection. However, accurate diagnosis is crucial for effective treatment. Doctors often rely on a combination of tests, including traditional microbiology, advanced molecular techniques, and tissue examination (histopathology). Improved monitoring of fungal infections, optimized treatment protocols, and the development of new antifungal therapies are all critical weapons in the fight against this global pandemic.

Keywords

COVID-19, Invasive, Fungal Infection

1. Introduction

COVID-19, caused by the novel coronavirus SARS-CoV-2, first emerged in Wuhan, China, in late 2019 and has since spread globally, leading to a pandemic of unprecedented scale in recent history [1]. The virus primarily affects the respiratory system, but its impact extends to multiple organ systems, leading to a wide range of clinical manifestations. The severity of COVID-19 varies, with some individuals remaining asymptomatic, while others develop severe disease requiring hospitalization and intensive care [2].

A significant concern in managing severe COVID-19 cases is the occurrence of coinfections and superinfections. Coinfections refer to the simultaneous infection of a host by multiple pathogenic species, while superinfections refer to secondary infections that occur during or after treatment of a primary infection [3]. These additional infections can complicate the clinical course, prolong hospital stays, and increase mortality rates.

COVID-19 patients aren't just battling the coronavirus alone. Coinfections with other respiratory viruses, like influenza, have been reported. These double threats can worsen

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breathing problems and potentially lead to more serious illness [4]. Bacterial co-infections are also a concern, especially with culprits like *Streptococcus pneumoniae* and *Haemophilus influenzae*, which can worsen the disease [5]. These secondary infections often strike patients in critical condition who require mechanical ventilation in hospitals [6].

Among the various pathogens contributing to coinfections and superinfections in COVID-19 patients, fungi have emerged as significant players. Fungal infections, particularly invasive infections, are a serious concern in immunocompromised individuals and those with severe illnesses, such as COVID-19 [7]. These infections can be caused by a variety of fungal species, including Aspergillus, Candida, and Mucorales, and can lead to conditions such as invasive aspergillosis, candidiasis, and mucormycosis, respectively [8].

In the following sections, the relationship between COVID-19 and fungal infections will be explored in greater depth, examining the pathophysiology, specific fungal pathogens, and implications for patient management and outcomes.

2. COVID-19 and Fungal Diseases

Fungal diseases are caused by fungi, a diverse group of microorganisms that can cause a wide range of infections, from superficial skin conditions to life-threatening systemic diseases. The most common types of fungal infections include candidiasis, aspergillosis, and cryptococcosis. The prevalence of fungal diseases varies widely depending on the specific type of infection and the population being studied. Risk factors for fungal diseases include immunosuppression, prolonged hospitalization, and the use of certain medications, such as corticosteroids and antibiotics [9].

COVID-19 has been associated with increased susceptibility to fungal infections. This is likely due to a combination of factors, including immune system dysregulation caused by the virus, prolonged hospitalization, and the use of immunosuppressive drugs in the treatment of severe COVID-19 [6]. A systematic review and meta-analysis by Musuuza et al. revealed that as many as 19% of patients with COVID-19 had coinfections, and 24% had superinfections. Of these fungal coinfections, 4% were coinfections, and 8% were superinfections. The presence of either coinfection or superinfection was associated with poor outcomes, including increased mortality [10].

3. Pathophysiology of Fungal Infections in COVID-19 Patients

The pathophysiology of fungal infections in COVID-19 patients is complex and multifactorial. Studies suggest several factors contribute to these patients' increased vulnerability to fungal infections. These factors include:

Immune System Dysregulation

COVID-19 can weaken the immune system, hindering the body's fight against fungal infections. This disruption is characterized by a hyperinflammatory state, often referred to as a "cytokine storm," and lymphopenia, which is a reduction in T cells (Figure 1). Cytokine storms can lead to tissue damage, creating an environment conducive to fungal invasion. Moreover, lymphopenia can weaken cell-mediated immunity, a crucial component in controlling fungal infections [11].

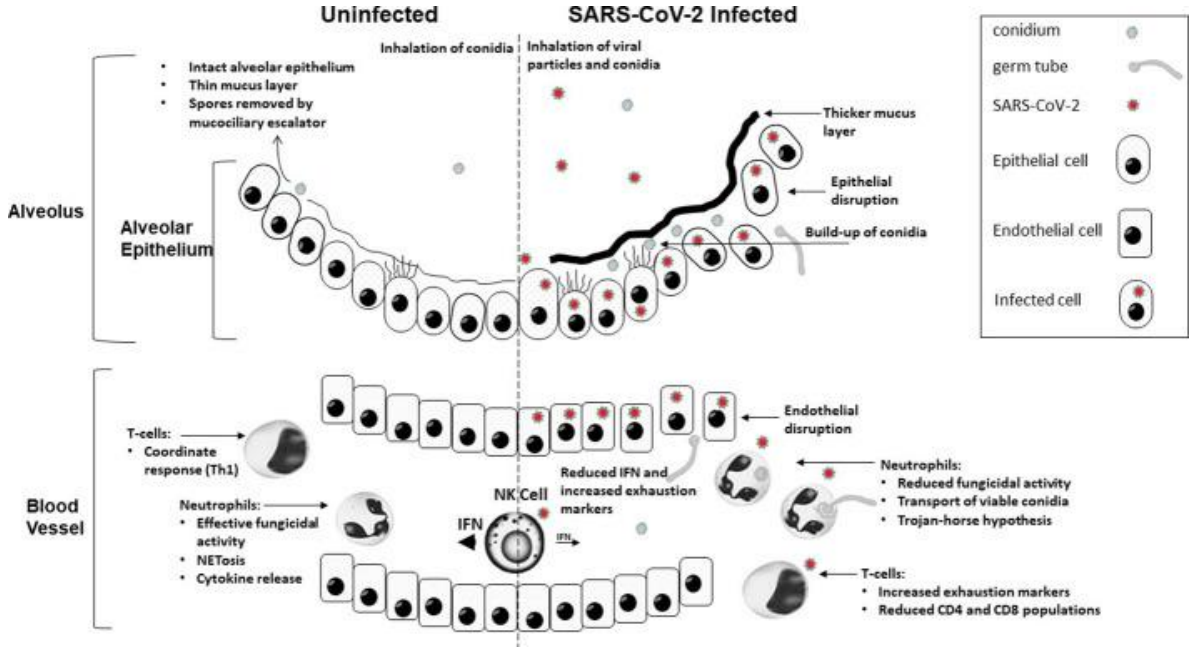

Figure 1. *The mechanisms of COVID-19 infection contribute to increased susceptibility to invasive fungal disease [12].*

COVID-19 punches a hole in the body's natural defenses against fungal infections in several ways. First, the virus can severely damage the lining of the lungs (epithelium) due to an overactive immune response. This damage, along with difficulty clearing mucus (limited mucociliary clearance), creates a perfect environment for fungal spores to invade. Next, the body's ability to engulf and destroy these spores (phagocytosis) weakens. This happens because genes involved in recognizing and preparing spores for destruction are downregulated. Finally, even if spores bypass these initial defenses, the body struggles to control the growth of fungal filaments due to a decrease in a type of white blood cell important for fighting infection (neutrophils). Essentially, COVID-19 weakens natural defenses at each step, increasing susceptibility to fungal infections [12].

Prolonged Hospitalization

A long hospital stay, particularly in intensive care units (ICUs), significantly increases the risk of fungal infections. These units become breeding grounds for fungus due to several factors. First, procedures that rely on invasive devices like ventilators and catheters can directly introduce fungus into the body [7]. Second, broad-spectrum antibiotics, while crucial for fighting bacterial infections, disrupt the natural balance of microbes in the body. This disruption creates an environment where fungus can flourish. Third, patients who rely on intravenous feeding (parenteral nutrition) bypass the body's natural defenses in the digestive system, making them more vulnerable to fungal invaders. Finally, some antibiotics, like azithromycin, have side effects that weaken the immune response, further amplifying the risk of fungal infections [13].

Use of Immunosuppressive Drugs

Medications used to calm the overactive immune system in severe COVID-19, like corticosteroids and tocilizumab, can also open the door to fungal infections. Corticosteroids, for example, can weaken the body's overall ability to fight off fungal invaders. Dexamethasone, a common corticosteroid used for severe COVID-19 because it reduces inflammation and lung damage, has been linked to an increased risk of secondary infections, including fungal ones [14].

4. Common Fungal Infections in COVID-19 Patients

Several types of fungal infections have been reported in COVID-19 patients, including aspergillosis, candidiasis, mucormycosis, endemic mycoses, pneumocytosis and cryptococcosis [8].

Aspergillus

The genus Aspergillus can cause a range of illnesses in humans, from allergic reactions to life-threatening invasive infections. *A. fumigatus* is the most common species causing disease in humans. Patients with severe COVID-19, especially those requiring intensive care, are at high risk of developing secondary Aspergillus infections, including invasive pulmonary aspergillosis (IPA), due to their immunocompromised state and underlying lung disease [8].

Aspergillus, a fungus commonly found in the environment, poses little threat to healthy individuals who breathe in its spores daily. However, people with weakened immune systems are susceptible to infection [15]. COVID-19 and other severe viral infections can cause a unique type of lung aspergillosis different from the classic form seen in patients with cancers or undergoing transplants. Classic IPA is most common in individuals with low white blood cell counts (neutropenia) and other immune deficiencies. Research suggests that damage to the lining of the respiratory system caused by the virus plays a role in this specific type of fungal infection seen with severe viral illnesses [16].

COVID-19 is associated with extensive lung damage, including diffuse alveolar injury, hyaline membrane formation, interstitial lymphocyte infiltration, and vascular microthrombi. These lung issues can take weeks to resolve, creating a conducive environment for fungal growth [16]. The initial cases of COVID-19-associated pulmonary aspergillosis (CAPA) were documented in China in early 2020. Since then, various case series and cohort studies have emphasized the significance of this potentially fatal secondary infection, which can sometimes be caused by azole-resistant Aspergillus species [17].

Research suggests steroid treatments and other therapies that alter the immune system raise the risk of a condition similar to severe COVID-19 [16]. This syndrome, called CAPA, typically starts with fungal growth in the airways for a few days before invading blood vessels. Unlike some fungal infections, CAPA can occur even in people with normal white blood cell counts. Unfortunately, once CAPA enters the bloodstream and a specific fungal test turns positive, the chance of death is very high, even with antifungal medication [17].

Van Arkel et al. reported Aspergillus species in 18% of samples from patients in the Netherlands, with 12% meeting the criteria for probable IPA [18]. Similarly, Alanio et al. reported Aspergillus species in 22% of COVID-19 patients in France, with 8% having proven or probable IPA [19]. Risk factors for developing IPA in COVID-19 patients include the use of corticosteroids, severe lymphopenia, chronic lung disease, older age and mechanical ventilation [20].

Candida

Candida is a genus of yeasts that can cause infections in humans, ranging from superficial to life-threatening invasive disease. *Candida albicans* is the most common species causing infection, although other species, such as *C. glabrata* and C. auris, are emerging as pathogens [21]. Patients with severe COVID-19, especially those requiring intensive care, are at high risk of developing secondary Candida infections due to prolonged hospitalization, the use of broad-spectrum antibiotics, and impaired immunity [8].

Candida is part of the normal human microbiota, colonizing

the gastrointestinal and genitourinary tracts, although overgrowth can lead to disease. Preventing candidiasis infections has long been a medical challenge, and COVID-19-associated candidiasis (CAC) is currently posing new challenges. The most common types of Candida infections in COVID-19 patients are invasive candidiasis and candidaemia [22].

The very beginning of the COVID-19 pandemic saw reports of ICU patients with COVID-19 also developing serious Candida infections, which significantly worsen their condition. Especially worrisome are outbreaks of a particularly dangerous type of Candida called C. auris. This strain is hard to tell apart from other Candida but often resists most or all antifungal medications. Unlike other fungal infections, C. auris can linger on surfaces in hospitals and spread among patients [17].

Several studies highlight the prevalence of Candida infections in COVID-19 patients. In India, Candida spp. ranked as the third most common cause (4.1%) of secondary bloodstream infections in COVID-19 patients, following bacterial infections like Klebsiella pneumoniae and Acinetobacter baumannii [23]. Similar trends were observed elsewhere. A study in Wuhan, China found Candida spp. in 5% of respiratory samples from ICU patients with COVID-19 [24], while another study in Italy reported a 9% infection rate with Candida spp. as secondary infections in COVID-19 patients [25]. These findings suggest Candida infections are a significant concern for COVID-19 patients, particularly those in ICUs.

Certain factors significantly increase the risk of Candida fungal infections. These include the use of central venous catheters, which are tubes inserted into large veins for medication or feeding. Additionally, people who rely on total parenteral nutrition (feeding through a vein) and those undergoing renal replacement therapy (dialysis) are more susceptible. Other risk factors include diabetes and the use of corticosteroid medications [7, 26]. For patients with COVID-19, the risk is further complicated by prior use of antifungal drugs or the medication Tocilizumab. These can increase the likelihood of developing serious bloodstream infections caused by the particularly dangerous fungus, C. auris [17].

Mucorales

Mucormycosis is an invasive fungal infection caused by fungi in the order Mucorales, including Rhizopus, Mucor, and Rhizomucor species. These fungi are ubiquitous in the environment, and infection occurs by the inhalation of spores. Patients with severe COVID-19, especially those with diabetes who are receiving corticosteroids, are at high risk of developing mucormycosis due to impaired immunity and hyperglycemia [27].

A scary fungal infection called "black fungus" (mucormycosis) became more common worldwide in people with COVID-19. India was hit especially hard, with cases skyrocketing compared to pre-pandemic times. This situation became so serious that the Indian government declared a mucormycosis epidemic in May 2021 [17]. Scientists suspect several reasons for this outbreak, including India's high number of diabetics, the hot and humid climate perfect for fungal spores to thrive, and the use of certain medications during COVID-19 treatment [28]. While data on overall mucormycosis rates is limited in other countries, cases linked to COVID-19 (CAM) have been reported across Asia, Europe, and the Americas [17].

In a multicenter epidemiologic study, Patel et al. compared mucormycosis cases from January to May in 2019, 2020, and during India's COVID-19 peak in 2021. They observed a 2.1-fold increase in cases in 2021, suggesting an association between the COVID-19 surge and the increased risk of mucormycosis [29]. Moorthy et al. reported that 8% of COVID-19 patients receiving oxygen therapy and 20% of those on mechanical ventilation in India developed mucormycosis [30]. Similarly, Ardehali et al. identified 12 cases of mucormycosis among 235 COVID-19 patients in Iran, with most of these patients having diabetes and receiving corticosteroids [31].

Risk factors for mucormycosis in COVID-19 patients include diabetes mellitus, hematological malignancies, organ transplants, corticosteroid use, severe lymphopenia, and mechanical ventilation [27]. In addition, COVID-19 can cause glucocorticoid-induced diabetes, and entry of the virus into pancreatic cells, which harbor angiotensin converting enzyme 2 (ACE 2), may damage beta cells, leading to insulin deficiency management and fueling the flames [28, 32]. The ability of the SARS-CoV-2 spike glycoprotein to mimic 'hepcidin' can lead to hyperferritinemia in patients with severe COVID-19, causing an accumulation of intracellular iron, tissue injury, and the release of free iron into the blood, potentially stimulating Mucorales fungal pathophysiology [28].

Mucormycosis in COVID-19 patients can affect different parts of the body, with varying degrees of severity. The most common form attacks the face and sinuses (rhino-orbital mucormycosis, ROM) causing facial swelling, bulging eyes (proptosis), and limited eye movement (ophthalmoplegia). If it spreads to the lungs (pulmonary mucormycosis), symptoms like cough, chest pain, and bleeding (hemoptysis) can occur. In the gut (gastrointestinal mucormycosis), patients experience abdominal pain, bleeding, and even perforation. Any of these forms can become disseminated, meaning it infects multiple organs throughout the body. The chance of death depends on the location of the infection. Mucormycosis affecting the face and sinuses (ROM) has a lower mortality rate (around 14%), while lung or disseminated infections have a much higher death rate (over 80%) [17, 28].

Other invasive fungal infections associated with COVID-19

Traditionally, cryptococcosis has been a fungal infection mainly affecting people with weakened immune systems due to conditions like AIDS, cancers, organ transplants, and others. However, recent reports have identified a growing number of cases where cryptococcosis occurs alongside COVID-19 infection [8]. COVID-19-associated Cryptococcus infections

typically present as meningoencephalitis and pneumonia. Patients often have underlying conditions such as HIV or use of corticosteroids [33]. Chastin D, et al,. Patients with COVID-19 and cryptococcosis were more likely to be male, have pulmonary involvement, and require ICU admission. COVID-19 patients also have increased rates of respiratory failure, acute kidney injury, and mortality [34].

Clinician have identified some cases where COVID-19 and a fungal infection called Pneumocystis jirovecii pneumonia (PCP) occur together. This can be a challenge because both illnesses can cause very similar symptoms, like cloudy patches on lung scans (bilateral ground-glass opacities) and a low white blood cell count (lymphopenia) [8]. Gentile I et al. identified five cases of PJP in non-HIV patients who recovered from COVID-19. They diagnosed PJP based on clinical symptoms, radiological findings, and the detection of P. jirovecii DNA in respiratory samples. All patients had severe COVID-19 and were treated with corticosteroids. The researchers concluded that PJP should be considered in the differential diagnosis of patients with severe COVID-19 and worsening respiratory symptoms during the recovery phase, especially if they receive prolonged corticosteroid therapy [35].

There is emerging evidence that COVID-19 patients may be at greater risk of coinfection or reactivation of dimorphic fungi. Borges et al. investigated the association between COVID-19 and dimorphic fungal coinfections in hospitalized patients in Brazil. This study reviewed the medical records of 673 patients hospitalized with COVID-19. Of these, 38 patients (5.7%) had positive fungal cultures, with the most common fungi being Paracoccidioides spp. (57.9%) and Histoplasma capsulatum (39.5%). The immunosuppression caused by COVID-19, the use of immunomodulatory drugs, and lung damage may increase susceptibility to dimorphic fungi in these patients [36].

5. Laboratory Diagnosis

The diagnosis of IFDs in COVID-19 patients can be challenging due to overlapping clinical features with COVID-19 pneumonia, but early diagnosis and treatment are critical for reducing morbidity and mortality [37-39]. Microbiological methods such as direct microscopy, culture, and antigen testing are commonly used for the diagnosis of major IFDs such as aspergillosis, candidiasis, and mucormycosis. Direct microscopic examination of respiratory samples, blood, and tissues using stains such as potassium hydroxide (KOH) and calcofluor white can detect fungal elements and provide a quick preliminary diagnosis. However, the sensitivity is low [40]. Culture using selective fungal media such as Sabouraud dextrose agar remains the gold standard but can take 2-3 weeks for slow-growing fungi such as Aspergillus. Antigen tests such as galactomannan (for Aspergillus) and 1,3-beta-D-glucan (for Candida and Aspergillus) have good sensitivity and specificity and provide results within a day. Molecular methods such as polymerase chain reaction (PCR) can also aid in diagnosis, especially for mucormycosis [41].

Pathological examination using stains such as Gomori methenamine silver (GMS), periodic acid–Schiff (PAS), and Fontana-Masson can detect fungal hyphae in tissue specimens. Histopathology provides a definitive diagnosis but requires invasive procedures to obtain specimens. Nonculture-based methods such as next-generation sequencing of respiratory samples show promise for the diagnosis of a range of fungi but require further validation [41].

Due to their low sensitivity and specificity, serological tests for identifying fungal antibodies are not helpful for diagnosis, but they may be useful in epidemiological studies. ELISA, western blot, and other methods are used to detect fungal antibodies; these methods are retrospective diagnostic methods that are unable to distinguish between present and past infections and are used for the diagnosis of aspergillosis, candidiasis, and cryptococcosis [40, 41]. Radiological features such as halo signs or reverse halo signs may suggest invasive aspergillosis but lack specificity. The use of bronchoalveolar lavage (BAL) to obtain respiratory samples for microbiological and pathological tests remains the most useful diagnostic procedure for detecting IFDs in COVID-19 patients [41].

6. Management and Treatment of Fungal Infection

The management of invasive fungal infections in COVID-19 patients requires aggressive diagnostic and treatment approaches given the high mortality associated with these secondary infections. For aspergillosis, voriconazole is the primary treatment, with liposomal amphotericin B as an alternative. Isavuconazole or itraconazole can also be used. For candidiasis, echinocandins (caspofungin, micafungin, and anidulafungin) are preferred, along with fluconazole for less ill patients or as a step-down therapy. However, only echinocandins treat multidrug-resistant Candida auris, which requires strict isolation and screening [23].

Mucormycosis requires early surgical debridement and antifungals. For neutropenic or high-risk patients, posaconazole prophylaxis may help. Amphotericin B, liposomal amphotericin B, and posaconazole were used to treat mucormycosis, and isavuconazole was used for salvage [17]. Pneumocystis jirovecii pneumonia can be treated with trimethoprim-sulfamethoxazole and steroids [8].

7. Conclusion

Fungal infections pose a major danger to people severely ill with COVID-19, significantly worsening their health and increasing their risk of death. Several factors make COVID-19 patients, especially those in intensive care, more vulnerable to these opportunistic fungal invaders. These factors include a weakened immune system (dysregulation),

extended hospital stays, and the use of medications that suppress the immune system. A wide range of fungi, including Aspergillus, Mucorales, Candida, Cryptococcus, Pneumocystis jirovecii, and even some that can transform between mold and yeast forms (dimorphic fungi), have been identified as culprits behind secondary infections in COVID-19 patients. These fungal infections can manifest in various ways, causing problems in the lungs (pneumonia), sinuses (sinusitis), brain and meninges (meningitis), and even spreading throughout the body (disseminated disease). Early detection and prompt treatment with antifungal medications are essential for improving the outcome for COVID-19 patients battling these fungal invaders. In some cases, doctors may need to be highly suspicious of fungal infection, conduct tests on respiratory and other samples, and even start antifungal treatment before a definitive diagnosis is confirmed (empirical therapy). Knowing the types of fungal infections commonly found in their area (local epidemiology) is crucial for doctors to choose the most effective antifungal medications. Improved monitoring of fungal infections, optimized treatment protocols, and the development of new antifungal therapies are all critical weapons in the fight against this global pandemic.

Abbreviations

CAC	COVID-19-Associated Candidiasis
CAPA	COVID-19-Associated Pulmonary Aspergillosis
ICUs	Intensive Care Units
IFIs	Invasive Fungal Infections
IPA	Invasive Pulmonary Aspergillosis
PCP	*Pneumocystis* Pneumonia
ROCM	Rhino-Orbital Cerebral Mucormycosis
ROM	Rhino-Orbital Mucormycosis

Author Contributions

Negeri Debela: Conceptualization, Writing – review & editing

Solome Nekahiwot: Resources, Writing – original draft

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020; 382(8): 727-33. https://doi.org/10.1056/NEJMoa2001017

[2] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

[3] Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. Clin Infect Dis. 2020; 71(9): 2459-68. https://doi.org/10.1093/cid/ciaa530

[4] Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Coinfection Between SARS-CoV-2 and Other Respiratory Pathogens. Jama. 2020; 323(20): 2085-6. https://doi.org/10.1001/jama.2020.6266

[5] Garcia-Vidal C, Sanjuan G, Moreno-Garc á E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of coinfections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2021; 27(1): 83-8. https://doi.org/10.1016/j.cmi.2020.07.041

[6] Arastehfar A, Carvalho A, van de Veerdonk FL, Jenks JD, Koehler P, Krause R, et al. COVID-19 Associated Pulmonary Aspergillosis (CAPA)-From Immunology to Treatment. J Fungi (Basel). 2020; 6(2). https://doi.org/10.3390/jof6020091

[7] Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis. 2021; 21(6): e149-e62. https://doi.org/10.1016/S1473-3099(20)30847-1

[8] Shishido AA, Mathew M, Baddley JW. Overview of COVID-19-Associated Invasive Fungal Infection. Curr Fungal Infect Rep. 2022; 16(3): 87-97. https://doi.org/10.1007/s12281-022-00434-0

[9] Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med. 2012; 4(165): 165rv13. https://doi.org/10.1126/scitranslmed.3004404

[10] Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of coinfection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. PloS one. 2021; 16(5): e0251170. https://doi.org/10.1371/journal.pone.0251170

[11] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395(10229): 1033-4. https://doi.org/10.1016/S0140-6736(20)30628-0

[12] Morton CO, Griffiths JS, Loeffler J, Orr S, White PL. Defective antifungal immunity in patients with COVID-19. Front Immunol. 2022; 13: 1080822. https://doi.org/10.3389/fimmu.2022.1080822

[13] Castro-Fuentes CA, Reyes-Montes MdR, Fr ás-De-Le ón MG, Valencia-Ledezma OE, Acosta-Altamirano G, Duarte-Escalante E. Aspergillus-SARS-CoV-2 Coinfection: What Is Known? Pathogens. 2022; 11(11): 1227. https://doi.org/10.3390/pathogens11111227

[14] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021; 384(8): 693-704. https://doi.org/10.1371/journal.pone.0275217

[15] Latgé JP. *Aspergillus fumigatus* and aspergillosis. Clin Microbiol Rev. 1999; 12(2): 310-50. https://doi.org/10.1128/cmr.12.2.310

[16] Dimopoulos G, Almyroudi M-P, Myrianthefs P, Rello J. COVID-19-Associated Pulmonary Aspergillosis (CAPA). Journal of Intensive Medicine. 2021; 1(2): 71-80. https://doi.org/10.1016/j.jointm.2021.07.001

[17] Hoenigl M, Seidel D, Sprute R, Cunha C, Oliverio M, Goldman GH, et al. COVID-19-associated fungal infections. Nat Microbiol. 2022; 7(8): 1127-40. https://doi.org/10.1038/s41564-022-01172-2

[18] van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19-associated Pulmonary Aspergillosis. Am J Respir Crit Care Med. 2020; 202(1): 132-5. https://doi.org/10.1164/rccm.202004-1038LE

[19] Alanio A, Delliè re S, Fodil S, Bretagne S, Mégarbane B. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. Lancet Respir Med. 2020; 8(6): e48-e9. https://doi.org/10.1016/S2213-2600(20)30237-X

[20] Bergmann F, Jorda A, Blaschke A, Gabler C, Bohdan S, Nussbaumer-Pröll A, et al. Pulmonary Aspergillosis in Critically Ill COVID-19 Patients Admitted to the Intensive Care Unit: A Retrospective Cohort Study. J Fungi (Basel). 2023; 9(3). https://doi.org/10.3390/jof9030315

[21] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016; 62(4): e1-50. https://doi.org/10.1093/cid/civ933

[22] Ahmed N, Mahmood MS, Ullah MA, Araf Y, Rahaman TI, Moin AT, et al. COVID-19-Associated Candidiasis: Possible Patho-Mechanism, Predisposing Factors, and Prevention Strategies. Curr Microbiol. 2022; 79(5): 127. https://doi.org/10.1007/s00284-022-02824-6

[23] Tsai CS, Lee SS, Chen WC, Tseng CH, Lee NY, Chen PL, et al. COVID-19-associated candidiasis and the emerging concern of Candida auris infections. J Microbiol Immunol Infect. 2022. https://doi.org/10.1016/j.jmii.2022.12.002

[24] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229): 1054-62. https://doi.org/10.1016/S0140-6736(20)30566-3

[25] Ripa M, Galli L, Poli A, Oltolini C, Spagnuolo V, Mastrangelo A, et al. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. Clin Microbiol Infect. 2021; 27(3): 451-7. https://doi.org/10.1016/j.cmi.2020.10.021

[26] Chowdhary A, Sharma C, Meis JF. Candida auris: A rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. PLoS Pathog. 2017; 13(5): e1006290. https://doi.org/10.1371/journal.ppat.1006290

[27] Chandley P, Subba P, Rohatgi S. COVID-19-Associated Mucormycosis: A Matter of Concern Amid the SARS-CoV-2 Pandemic. Vaccines (Basel). 2022; 10(8). https://doi.org/10.3390/vaccines10081266

[28] Dam P, Cardoso MH, Mandal S, Franco OL, Sağıroğlu P, Polat OA, et al. Surge of mucormycosis during the COVID-19 pandemic. Travel Med Infect Dis. 2023; 52: 102557. https://doi.org/10.1016/j.tmaid.2023.102557

[29] Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Multicenter Epidemiologic Study of Coronavirus Disease-Associated Mucormycosis, India. Emerg Infect Dis. 2021; 27(9): 2349-59. https://doi.org/10.3201/eid2709.210934

[30] Kumar R, Misra AK, Dutta S, Gupta A, Kumar B, Charan J. A systematic review of mucormycosis cases in COVID-19: Is it an unholy trilogy of COVID-19, diabetes mellitus, and corticosteroids? J Family Med Prim Care. 2022; 11(6): 2573-80. https://doi.org/10.4103/jfmpc.jfmpc_1934_21

[31] Pakdel F, Ahmadikia K, Salehi M, Tabari A, Jafari R, Mehrparvar G, et al. Mucormycosis in patients with COVID-19: A cross-sectional descriptive multicenter study from Iran. Mycoses. 2021; 64(10): 1238-52. https://doi.org/10.1111/myc.13334

[32] Choudhary NK, Jain AK, Soni R, Gahlot N. Mucormycosis: A deadly black fungus infection among COVID-19 patients in India. Clinical epidemiology and global health. 2021; 12: 100900. https://doi.org/10.1016/j.cegh.2021.100900

[33] Regalla D, VanNatta M, Alam M, Malek AE. COVID-19-associated Cryptococcus infection (CACI): a review of literature and clinical pearls. Infection. 2022; 50(4): 1007-12. https://doi.org/10.1007/s15010-022-01805-y

[34] Chastain DB, Kung VM, Vargas Barahona L, Jackson BT, Golpayegany S, Franco-Paredes C, et al. Characteristics and Outcomes of Cryptococcosis among Patients with and without COVID-19. J Fungi (Basel). 2022; 8(11). https://doi.org/10.3390/jof8111234

[35] Gentile I, Viceconte G, Lanzardo A, Zotta I, Zappulo E, Pinchera B, et al. Pneumocystis jirovecii Pneumonia in Non-HIV Patients Recovering from COVID-19: A Single-Center Experience. Int J Environ Res Public Health. 2021; 18(21). https://doi.org/10.3390/ijerph182111399

[36] Cighir A, Mare AD, Cighir T, Coșeriu RL, Vintilă C, Man A. Filamentous Fungi Infections: However, Another Victim of COVID-19? Life (Basel). 2023; 13(2). https://doi.org/10.3390/life13020546

[37] Hoenigl M. Invasive Fungal Disease Complicating Coronavirus Disease 2019: When It Rains, It Spores. Clin Infect Dis. 2021; 73(7): e1645-e8. https://doi.org/10.1093/cid/ciaa1342

[38] Raffaelli F, Tanzarella ES, De Pascale G, Tumbarello M. Invasive Respiratory Fungal Infections in COVID-19 Critically Ill Patients. J Fungi (Basel). 2022; 8(4). https://doi.org/10.3390/jof8040415

[39] Sasani E, Bahrami F, Salehi M, Aala F, Bakhtiari R, Abdollahi A, et al. Pneumocystis pneumonia in COVID-19 patients: A comprehensive review. Heliyon. 2023; 9(2): e13618. https://doi.org/10.1016/j.heliyon.2023.e13618

[40] White PL. Diagnosis of invasive fungal disease in coronavirus disease 2019: approaches and pitfalls. Curr Opin Infect Dis. 2021; 34(6): 573-80. https://doi.org/10.1097/QCO.0000000000000791

[41] Song G, Liang G, Liu W. Fungal Coinfections Associated with Global COVID-19 Pandemic: A Clinical and Diagnostic Perspective from China. Mycopathologia. 2020; 185(4): 599-606. https://doi.org/10.1007/s11046-020-00462-9