ANVESHA-A Multidisciplinary E-Journal for all Researches Volume 2, Issue 1, june2021
Bi annual, Bi lingual, Peer reviewed, Referred Journal
Available online on: www.anveshaejournal.com e-ISSN 2582-6719

AN OVERVIEW OF FUNGAL CO-INFECTION EVENTS ASSOCIATED WITH COVID-19

Ruchika Yogesh[a], Noopur Srivastava[b*]

[a]ruchika77c@gmail.com, https://orcid.org/0000-0001-8017-0840

[b]Department of Chemistry and Biochemistry School of Basic Sciences & Research, Sharda University, Greater Noida, 201306,

noopursriv@gmail.com

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has recently emerged as a significant risk factor for now frequently reported severe co-infections in hospitalized and recovering patients. Microorganisms like bacteria, viruses, and fungi easily infect a person with weakened immunity. This article aims to review significant fungal co-infections associated with coronavirus disease 2019 (COVID-19) in terms of the disease-causing fungus type, favorable conditions, and associated severity, and diagnostic and treatment methods. This review includes the latest publications, based on fungal superinfections, available in PubMed, Google Scholar, Elsevier, Europe PMC, and Web of Science databases. We found that these opportunistic co-infections are of major concern in patients who are already under treatment for other diseases or being treated with immunosuppressant. Events of superinfections such as aspergillosis, candidiasis, mucormycosis, and miscellaneous fungal infections are emerging causes of concern in COVID-19 patients as they increase mortality rates in affected patients. A combination of effective and timely prognosis, correct diagnosis, and immediate treatment with available resources is an effective strategy to control fungal infections associated with COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic caused due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is nothing less than Pandora's Box. Within three months of its first reported case, the disease was declared a global pandemic by World Health Organization (WHO) on March 11, 2020 (Cucinotta and Vanelli, 2020). Since then, more than 16 billion people were infected, and 3.5 billion people have lost their lives worldwide (WHO COVID-19 Homepage, 2021). This pandemic presented a major setback to the overall economy and healthcare infrastructure across the world. Another matter of concern is the development of other health concerns acquired during or after COVID-19 infection. The major concerns are psychological effects, microbial co-infections (Soltani et al., 2021), ICU-acquired infections, making the situation burdensome and challenging (W. Song et al., 2021; Soriano et al., 2021). Unfortunately, these co-infections are challenging to diagnose (Lai, Wang, and Hsueh, 2020). Although superinfections or *opportunistic* infections were not reported in the earlier phase of the pandemic, several cases of infections caused by other viruses, bacteria, and fungi reported in COVID-19 patients of all age groups were reported later (Lansbury et al. 2020). Furthermore, the frequency of fungal co-infections is increasing currently and contributes to severe illness and death cases (G. Song, Liang, and Liu, 2020; Nori et al., 2021; SciDev.Net, 2021). Some fungal diseases show symptoms similar to COVID-19 disease, such as cough, fever, and shortness of breath (Hoenigl, 2020).

There are millions of fungal species present everywhere around us. Fungi live outdoors, indoors, within, and over our bodies. A few hundred species can make us sick by causing asthma, allergies, skin and nail rashes, skin infections, brain infections, blood infections, and lung infections that have symptoms similar to tuberculosis, pneumonia, and flu. Most of these infections occur in people with weakened immune systems due to medical conditions like an organ transplant, HIV, cancer, and prevailing medical treatment. It is reported that patients lacking any immunosuppressive condition are at low risk of invasive, secondary fungal infections (Fekkar et al., 2021). SARS-CoV-2

infection is known to deteriorate the immune system and hence a definite cause of accompanying fungal infection cases. SARS-CoV-2 infection dysregulates the immune system leading to reduced numbers of cells responsible of adaptive immune system, T lymphocytes, CD4+T, and CD8+T cells, altering the innate immunity and increasing chances of acquiring secondary infections. Studies related with COVID-19 clinical characteristics have reported that patients show lymphocytopenia (abnormal shortage of lymphocytes in blood) (Guan et al., 2020) and thrombocytopenia (low blood platelet count) (Lippi, Plebani, and Henry, 2020).

Fungal co-infections are rapidly becoming a matter of concern in COVID-19 patients (Ezeokoli and Pohl, 2020). This paper overviews the different fungal infections accompanying SARS-CoV-2 infection and the associated impact on disease burden.

PULMONARY ASPERGILLOSIS

Patients having severe COVID-19 infection often suffer from acute respiratory distress syndrome (ARDS). Many patients with ARDS are reported to get a fungal co-infection called SARS-CoV-2-associated pulmonary aspergillosis (CAPA), whose pathogenesis is yet uncertain (Hoenigl 2020). Aspergillosis is caused by a common mold *Aspergillus*, an omnipresent genus of fungus. Aspergillosis is manifested in the patients through lung infections, allergic reactions, and infections in other organs. Most of us are always exposed to this fungus but reduced and burdened immunity responses during COVID-19 infection easily led to fungal infection.

,

The symptoms of aspergillosis are non-specific and mostly similar to COVID-19, which makes it difficult to diagnose. Damage caused by SARS-CoV-2 infection interferes in the action of prominent antifungal medicines used to cure aspergillosis, thus making treatment difficult (Arastehfar et al., 2020). Severe COVID-19 infection results in the release of danger-associated molecular patterns (DAMPs), which causes inflammatory damage in lung epithelium giving way to pulmonary aspergillosis infection. Sometimes, host recognition pathways required to activate antiviral immunity also cause increased inflammation favouring fungal infection. COVID-19 patients receiving immunosuppressive treatment are more likely to experience life-threatening situation when infected with *Aspergillus* fungus (Machado et al., 2021). In COVID-19 patients, primary pulmonary immunity is already decreased, allowing fungal spores to grow and cause inflammation in the airways and finally spread into the lungs (Kuehn, 2020). Recent studies have demonstrated that CAPA co-infection may cause high mortality rates in COVID-19 patients (Lahmer et al., 2021). Several recent studies have reported invasive pulmonary aspergillosis as a cause of concern in infected- and post- COVID-19 patients (Fekkar et al. 2021; Kakamad et al. 2021). According to another study, *Aspergillus fumigatus* was the most common fungus causing secondary fungal pulmonary infections (Chong et al., 2021). Fungus culture and galactomannan test of samples taken from respiratory tract are used to diagnose pulmonary aspergillosis (Verweij et al., 2020). Drugs belonging to the azole family, such as voriconazole, are considered the best therapeutic for aspergillosis (Lai and Yu, 2021). Combating this situation needs antifungal drugs having better pharmacokinetic and pharmacodynamic profiles (Mohamed, Rogers, and Talento, 2020).

MUCORMYCOSIS

Mucormycosis is another severe secondary invasive fungal infection increasingly reported in patients with COVID-19 infection (Szarpak, 2021). Mucormycosis is a rare but severe infection caused by the filamentous fungus *Mucormycetes* or *Zygomycetes* (Ribes, Vanover-Sams, and Baker, 2000). It was also known as zygomycosis earlier (Roden et al., 2005). Mucormycosis does not spread between people or people and animals; people get the infection through fungal spores occurring in the environment. The recent COVID-19 outbreak is accompanied by an outbreak of mucormycosis, also known as black fungus disease, infections (Mehta and Pandey 2020; Revannavar et al. 2021; Sharma et al. 2021).

Mucormycetes are abundant in the environment and are primarily found in rotting or decomposing organic matter, such as decaying food and bread, decaying fruit and vegetables, rotten wood, rotten leaves, compost piles, and animal excreta. Other possible reservoirs are construction sites, contaminated air-conditioning filters, and contaminated air filled with fungal spores exhaled by infected humans (Richardson, 2009). Mucormycosis is known to affect people who are immunosuppressed, are diabetic, have undergone organ transplants (Farojov et al., 2016), or are suffering from blood disorders and

ketoacidosis (Lewis and Kontoyiannis, 2013). Mucormycosis co-infection is a potential reason for increased fatality in COVID-19 patients (Bhatt et al., 2021). Immune dysregulation and breach in personal hygiene in people affected with COVID-19 are the most likely factors behind the sudden outbreak of mucormycosis.

Depending upon anatomic localization, this disease has six major types: (1) rhinocerebral, (2) pulmonary, (3) gastrointestinal, (4) cutaneous, (5) disseminated, and (6) uncommon presentations (Petrikkos et al. 2012). Rhinocerebral mucormycosis is a sinus infection that may spread to the eyes, facial tissues, and brain later (Sarkar et al., 2021). Rhinocerebral type is also known as rhino-orbital-cerebral-mucormycosis (ROCM) (Nithyanandam et al., 2003). This type of mucormycosis is commonly found in people who have undergone a kidney transplant (Song et al., 2017) or have uncontrolled diabetes (Jacob and Chaney 2016; Gupta, Goyal, and Kaore 2020). Currently, ROCM is of utmost concern in India (Bala et al., 2015; Sen et al., 2021) and other countries worldwide.

Pulmonary mucormycosis happens in the lungs and is one of the most common types of mucormycosis. It is mostly observed in patients who have undergone an organ or a stem cell transplant and people suffering from cancer (Čolović et al., 2016). Gastrointestinal mucormycosis is generally found in young children who have had strong medications like antibiotics reducing the body's ability to fight infections (Francis et al., 2018). Cutaneous mucormycosis affects the skin and occurs when fungi enter the body through disrupted skin. This happens to people even when they do not have any weakened immune systems. Disseminated mucormycosis is the event of infection spread through the bloodstream affecting other body parts. The brain is affected maximum in this case; spleen, heart, and skin being the second most affected organs.

A health care provider diagnoses mucormycosis in a patient by evaluating the symptoms shown and a few diagnostic tests. Often a CT scan of lungs, sinuses, or other body parts (depending on the location of the suspected infection) is carried out in conjunction with affected tissue biopsy, where a small sample of affected tissue is put through fungal culture and later analyzed for the presence of fungus. Unfortunately, common antifungals like fluconazole, voriconazole, and echinocandins do not work against mucormycosis. However, antifungal medicines amphotericin B, posaconazole, and isavuconazole are effective against mucormycosis (Riley et al., 2016). Acute cases may need surgical removal or debridement of affected tissue (Gamaletsou et al., 2012). Early detection and immediate action using global guidelines are needed to prevent life-threatening situations in patients (Cornely et al., 2019).

CANDIDIASIS

Candida fungal species are a significant cause of invasive fungal infections in humans, with a high mortality rate. *Candida* yeast species are a significant component of the human mycobiome (Arendrup, 2013). COVID-19-associated candidiasis (CAC) is becoming a major concern as a co-infection with SARS-CoV-2 infection (Moser et al., 2021)(Chen et al., 2020). Some Candida species are always present inside the body or on the skin such as mouth, gut, throat, and vagina and do not cause any problem to the human body. However, when excessive growth of this yeast occurs, it enters our bloodstream or deep into the body and gives rise to candidiasis infection in the mouth, gut, throat, or invasive candidiasis in blood, kidney, heart, brain, or other internal organs. The challenged and compromised immune response of the patient's body is again the primary cause of infection here (Arastehfar, Carvalho, Nguyen, et al., 2020).

Many recent publications have reported Candidemia, a bloodstream infection, in COVID-19 patients (Mastrangelo et al., 2020; Garcia-Vidal et al., 2021). *Candida auris* is a resistant species and is believed to be the major one causing candidiasis in immunocompromised COVID-19 infected patients (Dyer, 2020). Some other publications have reported oropharyngeal candidiasis (Salehi et al., 2020) and oral candidiasis (Santosh et al., 2021; Santos et al., 2020) in COVID-19 patients.

Drugs belonging to echinocandins and azoles are the primary antifungal drugs used to treat candidiasis. However, more effective drugs need to be invented for drug-resistant species like *Candida auris* and *Candida glabrata.*

MISCELLANEOUS FUNGAL INFECTIONS

Apart from these major fungal co-infections described above, there are a few other co-infections observed in COVID-19 patients in the recent past (Shah et al., 2020; Goyal et al., 2020). People with severe disease conditions are more likely to get fungal infections that usually occur less frequently

(Rabagliati et al., 2021). One such respiratory infection is coccidioidomycosis or *Valley Fever*, which happens when spores of the fungus *Coccidioides* present in dust are inhaled (www.cdc.gov, 2020). *Coccidioides* is a dimorphic fungus dwelling in soil, and its spores spread through the air, mainly through the dusty environment due to soil erosion or construction activities. Symptoms like cough, fatigue, and difficulty in breathing are the common symptoms of coccidioidomycosis and COVID-19 (Heaney et al., 2021; Blair et al., 2014). Coccidioidomycosis causes pulmonary pneumonia; however, immunocompromised patients may develop severe pneumonia with added issues related to soft tissues, bone, joints, and the central nervous system (Chen et al., 2021)

Acute invasive fungal rhinosinusitis (AIFRS) (Deutsch, Whittaker, and Prasad, 2019) is another such secondary infection observed in immunocompromised patients of COVID-19, especially those with diabetes, renal, and liver dysfunction conditions (Ismaiel et al., 2021).

Another study reports a case of histoplasmosis fungal infection in an immunocompromised COVID-19 patient (Bertolini et al., 2020). Histoplasmosis fungal infection is caused by the dimorphic fungus *Histoplasma capsulatum*, and is an endemic usually found in central and south-central United States, and Latin America. Typical symptoms of this disease include cough, acute dyspnea, fever, night sweats, abdominal pain, and diarrhea.

Pneumocystis jirovecii is a fungal pathogen infecting patients with defected T-cell immunity. *Pneumocystis* infection causes pneumonia along with conditions of fever, headache, dry cough, and dyspnea. Several cases of *Pneumocystis jirovecii* infection have recently been reported in COVID-19 patients (Menon et al., 2020; Rubiano et al., 2020; Kelly et al., 2020). *Pneumocystis* infection is severe in immunocompromised COVID-19 patients already infected with HIV (Coleman et al., 2020). A recent study has reported post-recovery *Pneumocystis* infection (Viceconte et al., 2021). Considering the similarity of symptoms with COVID-19, a careful diagnosis is mandatory (Kelly et al., 2020; Jeican et al., 2021).

CONCLUSION

The already burdensome SARS-CoV-2 infection has given way to superinfections in patients leading to an increase in the mortality rate. Fungal infections such as pulmonary aspergillosis, candidiasis, rhino-orbital-cerebral mucormycosis, and pulmonary mucormycosis have emerged as the gravest of all opportunistic fungal co-infections affecting COVID-19 patients. Furthermore, fungal infection rates are higher and morbid in people having a condition of diabetes, organ transplant history, cancer, and other co-morbidities. Treatment with immunosuppressants and steroids increases the risk factor due to reduced immune response of the patients. Failure of routine infection avoiding practices—due to the enormous patient population in hospitals, limited availability of safety gloves and gowns, the inadequacy of disinfection and cleaning activities—can be attributed to the outbreak of yeast co-infections. Early prognosis by the health care provider, effective diagnosis with the help of available diagnostic tools, collaborative treatment involving different specialist physicians, and judicious usage of available medicines is the key to ensure recovery of patients. Nonetheless, such outbreaks call for invention of more effective antifungal medicines, preferably targeting each species separately.

REFERENCES

1. Arastehfar, Amir, Agostinho Carvalho, M Hong Nguyen, Mohammad Taghi Hedayati, Mihai G Netea, David S Perlin, and Martin Hoenigl. 2020. “COVID-19-Associated Candidiasis (CAC): An Underestimated Complication in the Absence of Immunological Predispositions?” *Journal of Fungi (Basel, Switzerland)* 6 (4). https://doi.org/10.3390/jof6040211.
2. Arastehfar, Amir, Agostinho Carvalho, Frank L van de Veerdonk, Jeffrey D Jenks, Philipp Koehler, Robert Krause, Oliver A Cornely, David S Perlin, Cornelia Lass-Flörl, and Martin Hoenigl. 2020. “COVID-19 Associated Pulmonary Aspergillosis (CAPA)-From Immunology to Treatment.” *Journal of Fungi (Basel, Switzerland)* 6 (2). https://doi.org/10.3390/jof6020091.
3. Arendrup, Maiken Cavling. 2013. “Candida and Candidaemia. Susceptibility and Epidemiology.” *Danish Medical Journal* 60 (11): B4698.
4. Bala, Kiran, Jagdish Chander, Uma Handa, Rajpal Singh Punia, and Ashok Kumar Attri. 2015. “A Prospective Study of

Mucormycosis in North India: Experience from a Tertiary Care Hospital." *Medical Mycology* 53 (3): 248–57. https://doi.org/10.1093/mmy/myu086.

5. Bertolini, Mauro, María Felicitas Mutti, José A E Barletta, Adriana Falak, Daniel Cuatz, Alicia Sisto, Martín A Ragusa, Nigel Osvaldo Fernandez Claros, and María José Rolón. 2020. "COVID-19 Associated with AIDS-Related Disseminated Histoplasmosis: A Case Report." *International Journal of STD \& AIDS* 31 (12): 1222–24. https://doi.org/10.1177/0956462420957518.
6. Bhatt, Kinal, Arjola Agolli, Mehrie H Patel, Radhika Garimella, Madhuri Devi, Efrain Garcia, Harshad Amin, Carlos Domingue, Roberto Guerra Del Castillo, and Marcos Sanchez-Gonzalez. 2021. "High Mortality Co-Infections of COVID-19 Patients: Mucormycosis and Other Fungal Infections." *Discoveries (Craiova, Romania)* 9 (1): e126. https://doi.org/10.15190/d.2021.5.
7. Blair, Janis E, Yu-Hui H Chang, Meng-Ru Cheng, Laszlo T Vaszar, Holenarasipur R Vikram, Robert Orenstein, Shimon Kusne, Stanford Ho, Maria T Seville, and James M Parish. 2014. "Characteristics of Patients with Mild to Moderate Primary Pulmonary Coccidioidomycosis." *Emerging Infectious Diseases* 20 (6): 983–90. https://doi.org/10.3201/eid2006.131842.
8. Chen, Joshua C, Darren Wong, Sina Rabi, Scott Worswick, Brittney DeClerck, and Gibb Jean. 2021. "All That Coughs Is Not Covid-19: A Delayed Diagnosis of Disseminated Coccidioidomycosis Following SARS-CoV-2." *Open Forum Infectious Diseases*. https://doi.org/10.1093/ofid/ofab246.
9. Chen, Nanshan, Min Zhou, Xuan Dong, Jieming Qu, Fengyun Gong, Yang Han, Yang Qiu, et al. 2020. "Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study." *Lancet (London, England)* 395 (10223): 507–13. https://doi.org/10.1016/S0140-6736(20)30211-7.
10. Chong, Woon H, Biplab K Saha, Ananthakrishnan Ramani, and Amit Chopra. 2021. "State-of-the-Art Review of Secondary Pulmonary Infections in Patients with COVID-19 Pneumonia." *Infection*, March, 1–15. https://doi.org/10.1007/s15010-021-01602-z.
11. Coleman, Harry, Luke B Snell, Rebecca Simons, Sam T Douthwaite, and Ming J Lee. 2020. "Coronavirus Disease 2019 and Pneumocystis Jirovecii Pneumonia: A Diagnostic Dilemma in HIV." *AIDS* 34 (8). https://journals.lww.com/aidsonline/Fulltext/2020/07010/Coronavirus_disease_2019_and_Pneumocystis.21.aspx.
12. Čolović, Nataša, Valentina Arsić-Arsenijević, Aleksandra Barać, Nada Suvajdžić, Danijela Leković, and Dragica Tomin. 2016. "Mucormycosis of the Paranasal Sinuses in a Patient with Acute Myeloid Leukemia." *Srpski Arhiv Za Celokupno Lekarstvo* 144 (11–12): 657–60.
13. Cornely, Oliver A, Ana Alastruey-Izquierdo, Dorothee Arenz, Sharon C A Chen, Eric Dannaoui, Bruno Hochhegger, Martin Hoenigl, et al. 2019. "Global Guideline for the Diagnosis and Management of Mucormycosis: An Initiative of the European Confederation of Medical Mycology in Cooperation with the Mycoses Study Group Education and Research Consortium." *The Lancet Infectious Diseases* 19 (12): e405–21. https://doi.org/10.1016/S1473-3099(19)30312-3.
14. Cucinotta, Domenico, and Maurizio Vanelli. 2020. "WHO Declares COVID-19 a Pandemic." *Acta Bio-Medica : Atenei Parmensis* 91 (1): 157–60. https://doi.org/10.23750/abm.v91i1.9397.
15. Deutsch, Peter George, Joshua Whittaker, and Shashi Prasad. 2019. "Invasive and Non-Invasive Fungal Rhinosinusitis-A Review and Update of the Evidence." *Medicina (Kaunas, Lithuania)* 55 (7). https://doi.org/10.3390/medicina55070319.
,
16. Dyer, Jan. 2020. "COVID Unleashes the 'Lurking Scourge' Candida Auris." 2020. https://www.infectioncontroltoday.com/view/covid-unleashes-the-lurking-scourge-candida-auris.
17. Ezeokoli, O T, and C H Pohl. 2020.

"Opportunistic Pathogenic Fungal Co-Infections Are Prevalent in Critically Ill COVID-19 Patients: Are They Risk Factors for Disease Severity?" *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 110 (11): 1081–85.

18. Farojov, R, O Aydın, C Yılmaz, Z Iakobadze, L Doğanay, D Camlı, A Demireller, S C Küçükgül, and M Kılıç. 2016. "Rhino-Orbita-Maxillary Mucormycosis After Liver Transplantation: A Case Report." *Transplantation Proceedings* 48 (9): 3210–13. https://doi.org/10.1016/j.transproceed.2016.08.016.
19. Fekkar, Arnaud, Alexandre Lampros, Julien Mayaux, Corentin Poignon, Sophie Demeret, Jean-Michel Constantin, Anne-Geneviève Marcelin, Antoine Monsel, Charles-Edouard Luyt, and Marion Blaize. 2021. "Occurrence of Invasive Pulmonary Fungal Infections in Patients with Severe COVID-19 Admitted to the ICU." *American Journal of Respiratory and Critical Care Medicine* 203 (3): 307–17. https://doi.org/10.1164/rccm.202009-3400OC.
20. Francis, Joshua R, Paola Villanueva, Penelope Bryant, and Christopher C Blyth. 2018. "Mucormycosis in Children: Review and Recommendations for Management." *Journal of the Pediatric Infectious Diseases Society* 7 (2): 159–64. https://doi.org/10.1093/jpids/pix107.
21. Gamaletsou, Maria N, Nikolaos V Sipsas, Emmanuel Roilides, and Thomas J Walsh. 2012. "Rhino-Orbital-Cerebral Mucormycosis." *Current Infectious Disease Reports* 14 (4): 423–34. https://doi.org/10.1007/s11908-012-0272-6.
22. Garcia-Vidal, Carolina, Gemma Sanjuan, Estela Moreno-García, Pedro Puerta-Alcalde, Nicole Garcia-Pouton, Mariana Chumbita, Mariana Fernandez-Pittol, et al. 2021. "Incidence of Co-Infections and Superinfections in Hospitalized Patients with COVID-19: A Retrospective Cohort Study." *Clinical Microbiology and Infection* 27 (1): 83–88. https://doi.org/10.1016/j.cmi.2020.07.041.
23. Goyal, Parag, Justin J Choi, Laura C Pinheiro, Edward J Schenck, Ruijun Chen, Assem Jabri, Michael J Satlin, et al. 2020. "Clinical Characteristics of Covid-19 in New York City." *The New England Journal of Medicine* 382 (24): 2372–74. https://doi.org/10.1056/NEJMc2010419.
24. Guan, Wei-Jie, Zheng-Yi Ni, Yu Hu, Wen-Hua Liang, Chun-Quan Ou, Jian-Xing He, Lei Liu, et al. 2020. "Clinical Characteristics of Coronavirus Disease 2019 in China." *The New England Journal of Medicine* 382 (18): 1708–20. https://doi.org/10.1056/NEJMoa2002032.
25. Gupta, Saroj, Rashmi Goyal, and Navinchandra M Kaore. 2020. "Rhino-Orbital-Cerebral Mucormycosis: Battle with the Deadly Enemy." *Indian Journal of Otolaryngology and Head and Neck Surgery : Official Publication of the Association of Otolaryngologists of India* 72 (1): 104–11. https://doi.org/10.1007/s12070-019-01774-z.
26. Heaney, Alexandra K, Jennifer R Head, Kelly Broen, Karen Click, John Taylor, John R Balmes, Jon Zelner, and Justin V Remais. 2021. "Coccidioidomycosis and COVID-19 Co-Infection, United States, 2020." *Emerging Infectious Diseases* 27 (5): 1266–73. https://doi.org/10.3201/eid2705.204661.
27. Hoenigl, Martin. 2020. "Invasive Fungal Disease Complicating COVID-19: When It Rains It Pours." *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, September, ciaa1342. https://doi.org/10.1093/cid/ciaa1342.
28. Ismaiel, Wael F, Mohamed H Abdelazim, Ibrahim Eldsoky, Ahmed A Ibrahim, Mahmoud E Alsobky, Ebtesam Zafan, and Abdulkarim Hasan. 2021. "The Impact of COVID-19 Outbreak on the Incidence of Acute Invasive Fungal Rhinosinusitis." *American Journal of Otolaryngology* 42 (6): 103080. https://doi.org/10.1016/j.amjoto.2021.103080.
29. Jacob, Nisha Bincent, and Susan Chaney. 2016. "Rhino Orbito Cerebral Mucormycosis: A Fatal Acute Invasive Fungal Infection in Uncontrolled Diabetes." *The Journal for Nurse Practitioners* 12 (10): 667–74.

https://doi.org/https://doi.org/10.1016/j.nurpra.2016.06.021.
30. Jeican, Ionuț Isaia, Patricia Inișca, Dan Gheban, Flaviu Tăbăran, Maria Aluaș, Veronica Trombitas, Victor Cristea, Carmen Crivii, Lia Monica Junie, and Silviu Albu. 2021. "COVID-19 and Pneumocystis Jirovecii Pulmonary Coinfection-The First Case Confirmed through Autopsy." *Medicina (Kaunas, Lithuania)* 57 (4): 302. https://doi.org/10.3390/medicina57040302.
31. Kakamad, Fahmi H, Safeen O Mahmood, Hawbash M Rahim, Berwn A Abdulla, Hiwa O Abdullah, Snur Othman, Shvan H Mohammed, Suhaib H Kakamad, Shevan M Mustafa, and Abdulwahid M Salih. 2021. "Post Covid-19 Invasive Pulmonary Aspergillosis: A Case Report." *International Journal of Surgery Case Reports*. https://doi.org/10.1016/j.ijscr.2021.105865.
32. Kelly, Sophie H, L Waters, M Cevik, S Collins, J Lewis, Meng-San Wu, T Blanchard, and A Geretti. 2020. "Pneumocystis Pneumonia, a COVID-19 Mimic, Reminds Us of the Importance of HIV Testing in COVID-19." *Clinical Medicine* 20 6: 590–92.
33. Kuehn, Bridget M. 2020. "Pulmonary Fungal Infections Affect Patients With COVID-19." *JAMA* 324 (22): 2248. https://doi.org/10.1001/jama.2020.22914.
34. Lahmer, Tobias, Silja Kriescher, Alexander Herner, Kathrin Rothe, Christoph D Spinner, Jochen Schneider, Ulrich Mayer, et al. 2021. "Invasive Pulmonary Aspergillosis in Critically Ill Patients with Severe COVID-19 Pneumonia: Results from the Prospective AspCOVID-19 Study." *PloS One* 16 (3): e0238825. https://doi.org/10.1371/journal.pone.0238825
35. Lai, Chih-Cheng, Cheng-Yi Wang, and Po-Ren Hsueh. 2020. "Co-Infections among Patients with COVID-19: The Need for Combination Therapy with Non-Anti-SARS-CoV-2 Agents?" *Journal of Microbiology, Immunology, and Infection = Wei Mian Yu Gan Ran Za Zhi* 53 (4): 505–12. https://doi.org/10.1016/j.jmii.2020.05.013.
36. Lai, Chih-Cheng, and Weng-Liang Yu. 2021. "COVID-19 Associated with Pulmonary Aspergillosis: A Literature Review." *Journal of Microbiology, Immunology, and Infection = Wei Mian Yu Gan Ran Za Zhi* 54 (1): 46–53. https://doi.org/10.1016/j.jmii.2020.09.004.
37. Lansbury, Louise, Benjamin Lim, Vadsala Baskaran, and Wei Shen Lim. 2020. "Co-Infections in People with COVID-19: A Systematic Review and Meta-Analysis." *The Journal of Infection* 81 (2): 266–75. https://doi.org/10.1016/j.jinf.2020.05.046.
38. Lewis, Russell E, and Dimitrios P Kontoyiannis. 2013. "Epidemiology and Treatment of Mucormycosis." *Future Microbiology* 8 (9): 1163–75. https://doi.org/10.2217/fmb.13.78.
39. Lippi, Giuseppe, Mario Plebani, and Brandon Michael Henry. 2020. "Thrombocytopenia Is Associated with Severe Coronavirus Disease 2019 (COVID-19) Infections: A Meta-Analysis." *Clinica Chimica Acta; International Journal of Clinical Chemistry* 506 (July): 145–48. https://doi.org/10.1016/j.cca.2020.03.022.
40. Machado, Marina, Maricela Valerio, Ana Álvarez-Uría, María Olmedo, Cristina Veintimilla, Belén Padilla, Sofía De la Villa, et al. 2021. "Invasive Pulmonary Aspergillosis in the COVID-19 Era: An Expected New Entity." *Mycoses* 64 (2): 132–43. https://doi.org/10.1111/myc.13213.
41. Mastrangelo, Andrea, Bruno Nicolò Germinario, Marica Ferrante, Claudia Frangi, Raffaele Li Voti, Camilla Muccini, Marco Ripa, and COVID-BioB Study Group. 2020. "Candidemia in Coronavirus Disease 2019 (COVID-19) Patients: Incidence and Characteristics in a Prospective Cohort Compared With Historical Non–COVID-19 Controls." *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciaa1594.
42. Mehta, Salil, and Abha Pandey. 2020. "Rhino-Orbital Mucormycosis Associated With COVID-19." *Cureus*. https://doi.org/10.7759/cureus.10726.
43. Menon, Aravind A, David D Berg, Elliot J Brea, Aaron J Deutsch, Khameer K Kidia, Emilia G Thurber, Sylvie B Polsky, et al. 2020. "A Case of COVID-19 and Pneumocystis Jirovecii Coinfection." *American Journal of Respiratory and*

Critical Care Medicine 202 (1): 136–38. https://doi.org/10.1164/rccm.202003-0766LE.

44. Mohamed, Aia, Thomas R Rogers, and Alida Fe Talento. 2020. "COVID-19 Associated Invasive Pulmonary Aspergillosis: Diagnostic and Therapeutic Challenges." *Journal of Fungi (Basel, Switzerland)* 6 (3). https://doi.org/10.3390/jof6030115.
45. Moser, Dominique, Katharina Biere, Bing Han, Marion Hoerl, Gustav Schelling, Alexander Choukér, and Tobias Woehrle. 2021. "COVID-19 Impairs Immune Response to Candida Albicans." *Frontiers in Immunology* 12: 640644. https://doi.org/10.3389/fimmu.2021.640644.
46. Nithyanandam, Suneetha, Moire S Jacob, Ravindra R Battu, Reji K Thomas, Majorie A Correa, and Ophelia D'Souza. 2003. "Rhino-Orbito-Cerebral Mucormycosis. A Retrospective Analysis of Clinical Features and Treatment Outcomes." *Indian Journal of Ophthalmology* 51 (3): 231–36.
47. Nori, Priya, Kelsie Cowman, Victor Chen, Rachel Bartash, Wendy Szymczak, Theresa Madaline, Chitra Punjabi Katiyar, et al. 2021. "Bacterial and Fungal Coinfections in COVID-19 Patients Hospitalized during the New York City Pandemic Surge." *Infection Control and Hospital Epidemiology* 42 (1): 84–88. https://doi.org/10.1017/ice.2020.368.
48. Petrikkos, George, Anna Skiada, Olivier Lortholary, Emmanuel Roilides, Thomas J Walsh, and Dimitrios P Kontoyiannis. 2012. "Epidemiology and Clinical Manifestations of Mucormycosis." *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America* 54 Suppl 1 (February): S23-34. https://doi.org/10.1093/cid/cir866.
49. Rabagliati, Ricardo, Nicolás Rodríguez, Carolina Núñez, Alvaro Huete, Sebastian Bravo, and Patricia Garcia. 2021. "COVID-19–Associated Mold Infection in Critically Ill Patients, Chile." *Emerging Infectious Disease Journal* 27 (5): 1454. https://doi.org/10.3201/eid2705.204412.
50. Revannavar, Shweta Mallikarjun, Supriya P S, Laxminarayana Samaga, and Vineeth V K. 2021. "COVID-19 Triggering Mucormycosis in a Susceptible Patient: A New Phenomenon in the Developing World?" *BMJ Case Reports CP* 14 (4). https://doi.org/10.1136/bcr-2021-241663.
51. Ribes, J A, C L Vanover-Sams, and D J Baker. 2000. "Zygomycetes in Human Disease." *Clinical Microbiology Reviews* 13 (2): 236–301. https://doi.org/10.1128/CMR.13.2.236.
52. Richardson, M. 2009. "The Ecology of the Zygomycetes and Its Impact on Environmental Exposure." *Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases* 15 Suppl 5 (October): 2–9. https://doi.org/10.1111/j.1469-0691.2009.02972.x.
53. Riley, Treavor T, Christina A Muzny, Edwin Swiatlo, and Davey P Legendre. 2016. "Breaking the Mold: A Review of Mucormycosis and Current Pharmacological Treatment Options." *The Annals of Pharmacotherapy* 50 (9): 747–57. https://doi.org/10.1177/1060028016655425.
54. Roden, Maureen M, Theoklis E Zaoutis, Wendy L Buchanan, Tena A Knudsen, Tatyana A Sarkisova, Robert L Schaufele, Michael Sein, et al. 2005. "Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases." *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America* 41 (5): 634–53. https://doi.org/10.1086/432579.
55. Rubiano, Carlos, Kathleen Tompkins, Subhashini A Sellers, Brian Bramson, Joseph Eron, Jonathan B Parr, and Asher J Schranz. 2020. "Pneumocystis and Severe Acute Respiratory Syndrome Coronavirus 2 Coinfection: A Case Report and Review of an Emerging Diagnostic Dilemma." *Open Forum Infectious Diseases* 8 (1). https://doi.org/10.1093/ofid/ofaa633.
56. Salehi, Mohammadreza, Kazem Ahmadikia, Shahram Mahmoudi, Saeed Kalantari, Saeidreza Jamalimoghadamsiahkali, Alireza Izadi, Mohammad Kord, et al. 2020. "Oropharyngeal Candidiasis in

Hospitalised COVID-19 Patients from Iran: Species Identification and Antifungal Susceptibility Pattern." *Mycoses* 63 (8): 771–78. https://doi.org/10.1111/myc.13137.

57. Santos, Amorim Dos, Julia Normando, Ana Gabriela Costa, Rainier Luiz Carvalho da Silva, Renata Monteiro De Paula, Allan Christian Cembranel, Alan Roger Santos-Silva, and Eliete Neves Silva Guerra. 2020. "Oral Mucosal Lesions in a COVID-19 Patient: New Signs or Secondary Manifestations?" *International Journal of Infectious Diseases : IJID : Official Publication of the International Society for Infectious Diseases* 97 (August): 326–28. https://doi.org/10.1016/j.ijid.2020.06.012.
58. Santosh, A. R., A. B. Muddana, K. Bakki, and S. Rani. 2021. "Fungal Infections of Oral Cavity: Diagnosis, Management, and Association with COVID-19." *SN Comprehensive Clinical Medicine*, March, 1–12. https://doi.org/10.1007/s42399-021-00873-9.
59. Sarkar, Sandip, Tanmay Gokhale, Sushmita Sana Choudhury, and Amit Kumar Deb. 2021. "COVID-19 and Orbital Mucormycosis." *Indian Journal of Ophthalmology*. https://doi.org/10.4103/ijo.IJO_3763_20.
60. SciDev.Net. 2021. "Fungal Disease Is Emerging among Hundreds of COVID-19 Patients in India, Shows Study." 2021. https://www.news-medical.net/news/20210512/Fungal-disease-is-emerging-among-hundreds-of-COVID-19-patients-in-India-shows-study.aspx.
61. Sen, Mrittika, Sumeet Lahane, Tatyarao P Lahane, Ragini Parekh, and Santosh G Honavar. 2021. "Mucor in a Viral Land: A Tale of Two Pathogens." *Indian Journal of Ophthalmology* 69 (2): 244–52. https://doi.org/10.4103/ijo.IJO_3774_20.
62. Shah, Amar S, Arash Heidari, Valerie F Civelli, Ritika Sharma, Charles S Clark, Augustine D Munoz, Alan Scott Ragland, and Royce H Johnson. 2020. "The Coincidence of 2 Epidemics, Coccidioidomycosis and SARS-CoV-2: A Case Report." *Journal of Investigative Medicine High Impact Case Reports* 8: 2324709620930540–2324709620930540. https://doi.org/10.1177/2324709620930540.
63. Sharma, S, M Grover, S Bhargava, S Samdani, and T Kataria. 2021. "Post Coronavirus Disease Mucormycosis: A Deadly Addition to the Pandemic Spectrum." *The Journal of Laryngology and Otology*, April, 1–6. https://doi.org/10.1017/S0022215121000992.
64. Soltani, Saber, Armin Zakeri, Milad Zandi, Mina Mobini Kesheh, Alireza Tabibzadeh, Mahsa Dastranj, Samireh Faramarzi, et al. 2021. "The Role of Bacterial and Fungal Human Respiratory Microbiota in COVID-19 Patients." *BioMed Research International* 2021 (February): 6670798. https://doi.org/10.1155/2021/6670798.
65. Song, Ge, Guanzhao Liang, and Weida Liu. 2020. "Fungal Co-Infections Associated with Global COVID-19 Pandemic: A Clinical and Diagnostic Perspective from China." *Mycopathologia*. https://doi.org/10.1007/s11046-020-00462-9.
66. Song, Wuhui, Xiaofang Jia, Xiaonan Zhang, Yun Ling, and Zhigang Yi. 2021. "Co-Infection in COVID-19, a Cohort Study." *The Journal of Infection*. https://doi.org/10.1016/j.jinf.2020.10.006.
67. Song, Yan, Jianjun Qiao, Gaffi Giovanni, Guangjun Liu, Hao Yang, Jianyong Wu, and Jianghua Chen. 2017. "Mucormycosis in Renal Transplant Recipients: Review of 174 Reported Cases." *BMC Infectious Diseases* 17 (1): 283. https://doi.org/10.1186/s12879-017-2381-1.
68. Soriano, María Cruz, Concepción Vaquero, Almudena Ortiz-Fernández, Alvaro Caballero, Aaron Blandino-Ortiz, and Raúl de Pablo. 2021. "Low Incidence of Co-Infection, but High Incidence of ICU-Acquired Infections in Critically Ill Patients with COVID-19." *The Journal of Infection*. https://doi.org/10.1016/j.jinf.2020.09.010.
69. Szarpak, Lukasz. 2021. "Mucormycosis - a Serious Threat in the COVID-19 Pandemic?" *The Journal of Infection*. https://doi.org/10.1016/j.jinf.2021.05.015.
70. Verweij, Paul E, Jean-Pierre Gangneux, Matteo Bassetti, Roger J M Brüggemann, Oliver A Cornely, Philipp Koehler, Cornelia

Lass-Flörl, Frank L van de Veerdonk, Arunaloke Chakrabarti, and Martin Hoenigl. 2020. "Diagnosing COVID-19-Associated Pulmonary Aspergillosis." *The Lancet Microbe* 1 (2): e53–55. https://doi.org/10.1016/S2666-5247(20)30027-6.

71. Viceconte, Giulio, Antonio Riccardo Buonomo, Amedeo Lanzardo, Biagio Pinchera, Emanuela Zappulo, Riccardo Scotto, Nicola Schiano Moriello, et al. 2021. "Pneumocystis Jirovecii Pneumonia in an Immunocompetent Patient Recovered from COVID-19." *Infectious Diseases* 53 (5): 382–85. https://doi.org/10.1080/23744235.2021.1890331.
72. WHO COVID-19 Homepage. 2021. "WHO Coronavirus (COVID-19) Dashboard." 2021. https://covid19.who.int/.
73. www.cdc.gov. 2020. "Valley Fever (Coccidioidomycosis) Statistics." 2020. https://www.cdc.gov/fungal/diseases/coccidioidomycosis/statistics.html.

.