

## ISSUES IN PUBLIC HEALTH

# Opportunistic pathogenic fungal co-infections are prevalent in critically ill COVID-19 patients: Are they risk factors for disease severity?

O T Ezeokoli, PhD; C H Pohl, PhD

*Pathogenic Yeast Research Group, Department of Microbial, Biochemical and Food Biotechnology, Faculty of Natural and Agricultural Sciences, University of the Free State, Bloemfontein, South Africa*

**Corresponding author:** C H Pohl ([pohlch@ufs.ac.za](mailto:pohlch@ufs.ac.za))

Fungal co-infections, especially with *Aspergillus* and *Candida* species, are prevalent in hospitalised COVID-19 patients, and could influence patient outcomes and hamper treatment efforts. However, information about and elucidation of the causal relationship between fungal co-infections and COVID-19 disease outcomes or severity in patients are still lacking. Such information, if and when available, will help facilitate appropriate case management.

*S Afr Med J* 2020;110(11):1081-1085. <https://doi.org/10.7196/SAMJ.2020.v110i11.15248>

The novel severe-acute respiratory coronavirus 2 (SARS-CoV-2) is the cause of COVID-19, a condition that was declared a global pandemic by the World Health Organization on 30 January 2020. As of 20 August, a total of 213 countries and territories were affected by the pandemic, with >22 256 219 confirmed cases globally.<sup>[1]</sup> The prognosis of the disease in patients with underlying conditions is dire, with comorbidities reported in a large number of hospitalised and severe cases.<sup>[2]</sup> Based on initial reports, older individuals and individuals with pre-existing conditions such as diabetes, heart disease, chronic obstructive pulmonary disease and cancer are more predisposed than others to severe COVID-19.<sup>[2,3]</sup> While the mechanistic links between the aforementioned pre-existing conditions and COVID-19 severity are being unravelled, reasons for severe COVID-19 in individuals without a known history of comorbidities (otherwise healthy individuals) are somewhat puzzling and may be compounded by genetics, such as the ABO blood group, and androgens, which may predispose a person to adverse COVID-19 outcomes.<sup>[4-6]</sup> While there is much we have yet to learn about the disease, it is therefore clear that an immunocompromising condition places the patient at a disadvantage against SARS-CoV-2.

The high incidence of severe infection and mortality in COVID-19 is thought to be due in part to a lack of natural immunity and to viral replication in the lower respiratory tract, as well as superinfections, secondary infections or co-infections (these terms are often used interchangeably), leading to severe lung injury and acute respiratory distress syndrome (ARDS).<sup>[7]</sup> Co-infections with respiratory viruses (other than SARS-CoV-2), bacteria and fungi have been reported in COVID-19 patients in Wuhan, China,<sup>[8-10]</sup> and secondary infections were identified as one of the predictors of a fatal outcome in COVID-19 cases.<sup>[11]</sup> An earlier report from China suggests that the mortality rate for COVID-19 patients on ventilators in intensive care units (ICUs) is ~60%, and indicated that invasive fungal co-infections may contribute to this high mortality.<sup>[2]</sup>

Invasive fungal infections, including aspergillosis and candidiasis,<sup>[12-14]</sup> are prevalent in hospitalised patients, and it is commonly established that acute respiratory disease, including invasive

pulmonary aspergillosis (IPA), is frequent in ICUs and among immunocompromised populations.<sup>[15-18]</sup> In addition, in some patients without a well-defined underlying immunocompromising disease, there is a high risk of secondary complications with IPA in ARDS due to viral infection.<sup>[19-22]</sup> However, few such co-infections are being reported in the current COVID-19 pandemic, especially in South Africa (SA).

## Fungal co-infections are prevalent in critically ill COVID-19 patients: Are they risk factors for severe outcomes?

Fungal infections, either pre or post COVID-19 exposure, can complicate diagnosis, treatment and progression of COVID-19.<sup>[10,23-25]</sup> At this stage, data on pre-existing fungal infections are mostly not reported. This is in part due to the likelihood of undiagnosed fungal infections in healthy individuals pre COVID-19 exposure, a lack of comprehensive descriptions of patients' clinical characteristics, and prioritisation of COVID-19 diagnosis over fungal infection diagnosis.<sup>[24,26-28]</sup> However, a retrospective study by Gao *et al.*<sup>[29]</sup> in China showed that the presence of a coexisting medical condition was the only independent risk factor for the ARDS in influenza A (H7N9) patients during the spring of 2013, with secondary bacterial or fungal infection being the cause of death in 3 out of 30 patients (10%) who died. Shortly before the outbreak of SARS-CoV-2, Gao *et al.*<sup>[29]</sup> showed that 25 of 528 patients (4.8%) with viral pneumonia had fungal co-infections. Of these patients, 12 survived while 13 died.<sup>[29]</sup> In addition, data from previous coronavirus outbreaks (SARS (severe acute respiratory syndrome)-CoV and MERS (Middle East respiratory syndrome)) have indicated that invasive aspergillosis and other systemic fungal infections contributed to severe outcomes for patients in ICUs.<sup>[19,30,31]</sup>

With regard to secondary infections or co-infection, data from several countries show prevalence of fungal co-infections in COVID-19 patients (Table 1). From these data, it is evident that the majority of these infections are caused by *Aspergillus* (mostly *A. fumigatus*) and *Candida* species. These infections are not

Table 1. Fungal co-infections reported in hospitalised COVID-19 patients

City, country, reference	Study nature/number of cases/cohorts	Study period	Fungal co-infection, %	Fungal species identified	Treatment/outcomes/notes
Paris, France <sup>[40]</sup>	Case study of a 74-year-old immunocompetent man with severe COVID-19	Mar 2020	n/a	<i>Aspergillus fumigatus</i>	Confirmed IPA. Fatal outcome due to severe respiratory failure.
Paris, France <sup>[41]</sup>	Case study of 27 mechanically ventilated COVID-19 patients in ICU	Mar 2020	33% with putative IPA	<i>A. fumigatus</i>	Mortality rate did not differ significantly between IPA and non-IPA patients. Testing deep lung specimens for <i>Aspergillus</i> is recommended.
Breda, Netherlands <sup>[42]</sup>	Case report of 31 ICU-requiring patients	Feb 2020	19.4% (6/31 patients) with presumed IPA	<i>A. fumigatus</i>	3 patients had pre-existing lung diseases. CAPA occurred after a median of 11.5 days post COVID-19 symptom onset at ~5 days after ICU admission. 4 patients (66.7%) died at ~12 ICU days.
Paris, France <sup>[43]</sup>	Case series involving 5 COVID-19 patients	Jan 2020	20% (1/5 patients)	<i>A. flavus</i>	The single patient with fungal coinfection had multiple organ failure despite antimicrobial treatment for <i>A. flavus</i> and <i>Acinetobacter baumannii</i> secondary infections.
New South Wales, Australia <sup>[44]</sup>	Case report of a 66-year-old woman	Apr 2020	n/a	<i>A. fumigatus</i>	Intravenous voriconazole (6 mg/kg loading followed by 3 mg/kg twice daily) was administered, with rapid improvement in patient's condition observed within 7 days.
Manaus, Brazil <sup>[45]</sup>	Postmortem analysis on a 71-year-old man who died due to COVID-19-related complications	NR	n/a	<i>A. penicillioides</i>	Aspergillosis was not considered antemortem, no sputum was collected for fungus culture and no antifungal drugs were used. The study points to the need for timely diagnosis of IPA during antemortem management of COVID-19.
Dublin, Ireland <sup>[46]</sup>	Case study of a 66-year-old man	NR	n/a	<i>Candida albicans</i> <i>A. fumigatus</i>	Amphotericin B was administered. Patient died on day 14 of hospitalisation (on day 22 of COVID-19 illness). The <i>A. fumigatus</i> isolate was resistant to multiple azoles including voriconazole, itraconazole and posaconazole.
Graz, Austria <sup>[13]</sup>	Case study of a 70-year-old man	Mar 2020	n/a	<i>A. fumigatus</i>	The patient had several underlying diseases, including type 2 diabetes and obesity. IPA was established with an <i>A. fumigatus</i> isolate obtained from endotracheal aspirates having a voriconazole MIC of 0.125 mg/L. Patient died despite intravenous treatment with voriconazole alongside treatment in the ICU.
Netherlands <sup>[47]</sup>	Case study of an 83-year-old woman	Mar 2020	n/a	<i>Pneumocystis jirovecii</i>	Patient had a history of mild intermittent asthma and ulcerative colitis among other comorbidities but no immunocompromising illness. The patient was treated with trimethoprim-sulfamethoxazole with improvements observed.
Wuhan, China <sup>[48]</sup>	41 COVID-19 patients	Onset of outbreak - 2 Jan 2020	10% (4/41 patients had either bacterial or fungal co-infection)	NR	75% of patients with secondary infection had procalcitonin >0.5 ng/mL (0.69 ng/mL, 1.46 ng/mL and 6.48 ng/mL).

Continued ...

Table 1. (continued) Fungal co-infections reported in hospitalised COVID-19 patients

City, country, reference	Study nature/number of cases/cohorts	Study period	Fungal co-infection, %	Fungal species identified	Treatment/outcomes/notes
Tehran, Iran <sup>[49]</sup>	53 hospitalised COVID-19 patients with oropharyngeal candidiasis	Mar - Apr 2020	5% (53/1 059 patients)	<i>C. albicans</i> <i>C. glabrata</i> <i>C. dubliniensis</i> <i>C. parapsilosis</i> sensu stricto <i>C. tropicalis</i> <i>C. krusei</i>	65 fungal isolates with prevalence distribution as follows: 70.7% <i>C. albicans</i> , 10.7% <i>C. glabrata</i> , 9.2% <i>C. dubliniensis</i> , 4.6% <i>C. parapsilosis</i> sensu stricto, 3% <i>C. tropicalis</i> and 1.5% <i>C. krusei</i> .
Nanjing, China <sup>[8]</sup>	Throat swabs from 257 COVID-19 patients	Jan - Feb 2020	23.3% (60/242 co-infected patients)	<i>Candida</i> <i>Cryptococcus</i> <i>Aspergillus</i> <i>Mucor</i>	Proportion of co-infections, including fungal co-infections, highest in severe COVID-19 cases.
Wuhan, China <sup>[9]</sup>	65 patients (of 918 COVID-19 cases) with nosocomial infection	Dec 2019 - Feb 2020	11.5% (5/65 patients with identified fungi)	<i>C. albicans</i> <i>Mucor</i>	The mortality of COVID-19 patients with nosocomial infection was 15.4%, significantly higher than that of COVID-19 patients without nosocomial infections.
London, UK <sup>[50]</sup>	836 COVID-19 patients	Feb - Apr 2020	10/14 respiratory cultures with CA/HCAI <i>Candida</i> spp. and 1/2 with CA/HCAI <i>Aspergillus</i> spp.	<i>Candida</i> <i>Aspergillus</i>	3 patients requiring critical care admission developed hospital-acquired <i>C. albicans</i> candidaemia. No evidence of concomitant fungal and bacterial infection in the early phase of COVID-19. Frequency of microbial co-infection was low.
Wuhan, China <sup>[51]</sup>	221 COVID-19 patients	Jan - Feb 2020	3.2% (7/221 patients)	NR	6 of the 7 patients with fungal co-infections had severe COVID-19. 4 of the 6 died in the ICU.
Wuhan, China <sup>[52]</sup>	21 COVID-19 patients	Dec 2019 - Jan 2020	27% secondary (bacterial and fungal) infection	NR	Secondary bacterial and fungal infection was particularly observed in severe cases.
Wuhan, China <sup>[53]</sup>	99 COVID-19 patients	Onset of outbreak - Jan 2020	4% (4/99 patients)	<i>A. fumigatus</i> <i>C. glabrata</i> <i>C. albicans</i>	Of the 4 patients with fungal infection, 1 case was infections with <i>A. fumigatus</i> and <i>C. glabrata</i> and the rest were <i>C. albicans</i> .
Wuhan, China <sup>[54]</sup>	13 COVID-19 patients hospitalised with haematological cancers	Jan - Feb 2020	69% (9/13 patients) fungal coinfections	NR	Of the 9 patients with fungal infection, 6 (66.7%) did not survive. No report on antifungal administration.
Cologne, Germany <sup>[50]</sup>	19 consecutive critically ill patients with moderate to severe ARDS	Mar - Apr 2020	5/19 patients had CAPA	<i>A. fumigatus</i>	Antifungals voriconazole, caspofungin or isavuconazole were administered. 3 of the 5 patients died.
Wuhan, China <sup>[55]</sup>	85 fatal cases of COVID-19	Jan - Feb 2020	33.3% (3/9 patients) with fungi detected in sputum culture	NR	Antifungals such as caspofungin (2.4% of patients), voriconazole (9.4%) and fluconazole (3.5%) were administered.

n/a = not applicable; IPA = invasive pulmonary aspergillosis; ICU = intensive care unit; CAPA = COVID-19-associated pulmonary aspergillosis; NR = not reported; MIC = minimum inhibitory concentration; CA = community acquired; HCAI = healthcare-associated infection; ARDS = acute respiratory disease syndrome.

COVID-19 exclusive, but are often observed in patients admitted to ICUs.<sup>[32]</sup> This finding complicates establishment of a causal relationship between fungal co-infection and COVID-19 disease severity, as there may be underlying conditions that predispose a patient to both infections. Interestingly, Zuo *et al.*<sup>[33]</sup> reported that the gastrointestinal mycobiomes of hospitalised COVID-19 patients were more heterogeneous, more enriched for *C. albicans* and contained higher levels of *C. auris* and *A. flavus* compared with controls, even after resolution of symptoms. This finding highlights the question whether fungal colonisation contributes to or results from SARS-CoV-2 infection.

## An SA perspective

Studies conducted before the current COVID-19 pandemic showed that fungal infections are highly prevalent in the SA population, partly owing to the high incidence of HIV.<sup>[34-36]</sup> It was observed that the *Candida* carrier rate is higher in the SA population than elsewhere and that HIV-positive patients carry more and a greater variety of pathogenic yeasts compared with HIV-negative subjects.<sup>[35,36]</sup> Similarly, cryptococcal meningitis, caused by *Cryptococcus neoformans* species complex, is one of the leading causes of HIV-related deaths in SA, with >135 900 deaths estimated for sub-Saharan Africa in 2014.<sup>[34,35,37]</sup> Other fungal infections, including invasive aspergillosis, *Pneumocystis pneumonia* and endemic mycoses, are also prevalent in SA.<sup>[34]</sup> Given the high prevalence of HIV/AIDS in SA as well as the high number of persons undergoing immunosuppressive therapies for other illnesses, co-infections with opportunistic fungal species may be affecting the current COVID-19 disease statistics in SA. Unfortunately, information on microbial co-infections in COVID-19 patients is lacking in currently published epidemiological and clinical reports on COVID-19 patients in SA.<sup>[38,39]</sup> The extent and contribution of such fungal co-infections (either pre-existing or nosocomial) on COVID-19 patient outcomes in SA are therefore unclear. In time, meta-analyses of case reports from COVID-19 patients may help provide such answers. However, this requires that patients' histories, disease characteristics and prognosis must be well documented and accessible for meta-analyses, both globally and in SA. Such information is vital for the full appreciation of factors contributing to the current COVID-19 statistics in SA.

**Declaration.** None.

**Acknowledgements.** None.

**Author contributions.** OTE wrote the initial draft of the manuscript. CHP conceptualised the article, added recently published information and edited the manuscript.

**Funding.** The work was financially supported by the National Research Foundation (NRF). CHP holds an NRF SARChI Research Chair in Pathogenic Yeasts (grant no. 115566).

**Conflicts of interest.** None.

- World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard 2020. <https://covid19.who.int/> (accessed 20 August 2020).
- Zhou F, Yu T, Du R, 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(10299):1054-1062. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)
- Erener S. Diabetes, infection risk and COVID-19. *Mol Metab* 2020;34:101044. <https://doi.org/10.1016/j.molmet.2020.101044>
- Williams FM, Freydn M, Mangino M, et al. Self-reported symptoms of covid-19 including symptoms most predictive of SARS-CoV-2 infection, are heritable. *MedRxiv* 2020 (epub 27 April 2020). <https://doi.org/10.1101/2020.04.22.20071214>
- Goren A, Vaño-Galván S, Wambier CG, et al. A preliminary observation: Male pattern hair loss among hospitalized COVID-19 patients in Spain – a potential clue to the role of androgens in COVID-19 severity. *J Cosmet Dermatol* 2020;19(7):1545-1547. <https://doi.org/10.1111/jocd.13443>
- Ellinghaus D, Degenhardt F, Bujanda L, et al. The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis. *MedRxiv* 2020 (epub 2 June 2020). <https://doi.org/10.1101/2020.05.31.20114991>
- Kwon WJ, Zheng M, Kaur H, Magbual N, Dalai S. Superinfections and coinfections in COVID-19 – separating the signal from the noise. *Medpage Today*, 28 April 2020. <https://www.medpagetoday.com/infectiousdisease/covid19/86192> (accessed 21 June 2020).
- Zhu X, Ge Y, Wu T, et al. Co-infection with respiratory pathogens among COVID-2019 cases. *Virus Res* 2020;285:198005. <https://doi.org/10.1016/j.virusres.2020.198005>
- He Y, Li W, Wang Z, Chen H, Tian L, Liu D. Nosocomial infection among patients with COVID-19: A retrospective data analysis of 918 cases from a single center in Wuhan, China. *Infect Control Hosp Epidemiol* 2020;41(8):982-983. <https://doi.org/10.1017/ice.2020.126>
- Chuang J, Chan D, Pada S, Tambyah PA. Coinfection with COVID-19 and coronavirus HKU1 – the critical need for repeat testing if clinically indicated. *J Med Virol* 2020;92(10):1785-1786. <https://doi.org/10.1002/jmv.25890>
- Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46(5):846-848. <https://doi.org/10.1007/s00134-020-05991-x>
- Terraneo S, Ferrer M, Torres A. *Candida* spp in the respiratory tract. A real causality with worse outcomes or just a marker of severity? *ICU Manage Pract* 2016;16(3):158-160.
- Pratters J, Valentin T, Hoenigl M, Reisinger AC, Eller P. Invasive pulmonary aspergillosis complicating COVID-19 in the ICU – a case report. *Med Mycol Case Rep* 2020 (epub 11 May 2020). <https://doi.org/10.1016/j.mmcr.2020.05.001>
- Pendleton KM, Huffnagle GB, Dickson RP. The significance of *Candida* in the human respiratory tract: Our evolving understanding. *Pathog Dis* 2017;75(3):fx029. <https://doi.org/10.1093/femspd/ftx029>
- Zhou P, Liu Z, Chen Y, Xiao Y, Huang X, Fan X-G. Bacterial and fungal infections in COVID-19 patients: A matter of concern. *Infect Control Hosp Epidemiol* 2020;41(9):1124-1125. <https://doi.org/10.1017/ice.2020.156>
- Rutsaert L, Steinfort N, van Hunsel T, et al. COVID-19-associated invasive pulmonary aspergillosis. *Ann Intensive Care* 2020;10(1):1-4. <https://doi.org/10.1186/s13613-020-00686-4>
- Mohamed A, Rogers TR, Talento AF. COVID-19 associated invasive pulmonary aspergillosis: Diagnostic and therapeutic challenges. *J Fungi* 2020;6(3):115. <https://doi.org/10.3390/jof6030115>
- Alp E, Voss A. Ventilator associated pneumonia and infection control. *Ann Clin Microbiol Antimicrob* 2006;5(1):7. <https://doi.org/10.1186/1476-0711-5-7>
- Schauwvlieghe AF, Rijnders BJ, Philips N, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: A retrospective cohort study. *Lancet Respir Med* 2018;6(10):782-792. [https://doi.org/10.1016/S2213-2600\(18\)30274-1](https://doi.org/10.1016/S2213-2600(18)30274-1)
- Koehler P, Cornely OA, Böttiger BW, et al. COVID-19 associated pulmonary aspergillosis. *Mycoses* 2020;63(6):528-534. <https://doi.org/10.1111/myc.13096>
- Koehler P, Bassetti M, Kochanek M, Shimabukuro-Vornhagen A, Cornely OA. Intensive care management of influenza-associated pulmonary aspergillosis. *Clin Microbiol Infect* 2019;25(12):1501-1509. <https://doi.org/10.1016/j.cmi.2019.04.031>
- Buil JB, Meijer EF, Denning DW, Verweij PE, Meis JF. Burden of serious fungal infections in the Netherlands. *Mycoses* 2020;63(6):625-631. <https://doi.org/10.1111/myc.13089>
- Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. *JAMA* 2020;323(20):2085-2086. <https://doi.org/10.1001/jama.2020.6266>
- Gangneux J-P, Bougnoux M-E, Dannaoui E, Cornet M, Ralph ZJ. Invasive fungal diseases during COVID-19: We should be prepared. *J Mycol Med* 2020;30(2):100971. <https://doi.org/10.1016/j.jmycmed.2020.100971>
- Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfecting with 2019 novel coronavirus and influenza virus in Wuhan, China. *J Med Virol* 2020;92(9):1549-1555. <https://doi.org/10.1002/jmv.25781>
- Verweij PE, Gangneux J-P, Bassetti M, et al. Diagnosing COVID-19-associated pulmonary aspergillosis. *Lancet* 2020;1(2):E53-E55. [https://doi.org/10.1016/S2666-5247\(20\)30027-6](https://doi.org/10.1016/S2666-5247(20)30027-6)
- NHS. Prioritisation/deferral of pathology laboratory work (in light of SARS-CoV-2 (COVID-19) epidemic). 2020. <https://www.rcpath.org/uploads/assets/f5123842-950f-49c5-bf69ed866a7ca3da/Prioritisation-deferral-of-pathology-laboratory-work.pdf> (accessed 18 August 2020).
- Govender NP. Why we should take fungal infections more seriously. National Institute for Communicable Diseases, 4 October 2018. <https://www.nicd.ac.za/we-should-take-fungal-infections-more-seriously-heres-why/> (accessed 30 June 2020).
- Gao H-N, Lu H-Z, Cao B, et al. Clinical findings in 111 cases of influenza A (H7N9) virus infection. *N Engl J Med* 2013;368(24):2277-2285. <https://doi.org/10.1056/NEJMoa1305584>
- Hwang DM, Chamberlain DW, Poutanen SM, Low DE, Asa SL, Butany J. Pulmonary pathology of severe acute respiratory syndrome in Toronto. *Mod Pathol* 2005;18(1):1-10. <https://doi.org/10.1038/modpathol.3800247>
- Ahmadi A, Ardehali SH, Beigmohammadi MT, et al. Invasive candidiasis in intensive care unit: Consensus statement from an Iranian panel of experts, July 2013. *JRSM Open* 2014;5(3):1-10. <https://doi.org/10.1177/2042533313517689>
- Bassetti M, Garnacho-Montero J, Calandra T, et al. Intensive care medicine research agenda on invasive fungal infection in critically ill patients. *Intensive Care Med* 2017;43(9):1225-1238. <https://doi.org/10.1007/s00134-017-4731-2>
- Zuo T, Zhan H, Zhang F, et al. Alterations in fecal fungal microbiome of patients with COVID-19 during time of hospitalization until discharge. *Gastroenterology* 2020 (epub 26 June 2020). <https://doi.org/10.1053/j.gastro.2020.06.048>
- Schwartz IS, Boyles TH, Kenyon CR, Hoving JC, Brown GD, Denning DW. The estimated burden of fungal disease in South Africa. *S Afr Med J* 2019;109(11):885-892. <https://doi.org/10.7196/SAMJ.2019.v109i11.13718>
- Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: An updated analysis. *Lancet Infect Dis* 2017;17(8):873-881. [https://doi.org/10.1016/S1473-3099\(17\)30243-8](https://doi.org/10.1016/S1473-3099(17)30243-8)
- Patel M, Shackleton JT, Coogan MM. Effect of antifungal treatment on the prevalence of yeasts in HIV-infected subjects. *J Med Microbiol* 2006;55(9):1279-1284. <https://doi.org/10.1099/jmm.0.46588-0>
- National Institute for Communicable Diseases. The impact of COVID-19 public health measures on diagnosis of advanced HIV disease, cryptococcal antigenaemia and cryptococcal meningitis in South Africa. 15 June 2020. [https://www.nicd.ac.za/wp-content/uploads/2020/06/COVIDImpact\\_CryptoScreening\\_2020-06\\_15-002.pdf](https://www.nicd.ac.za/wp-content/uploads/2020/06/COVIDImpact_CryptoScreening_2020-06_15-002.pdf) (accessed 20 August 2020).
- Zamparini J, Venturas J, Shaddock E, et al. Clinical characteristics of the first 100 COVID-19 patients admitted to a tertiary hospital in Johannesburg, South Africa. *Wits J Clin Med* 2020;2(2):105-114. <https://doi.org/10.18772/26180197.2020.v2n2a1>
- National Institute for Communicable Diseases. COVID-19 surveillance reports. 2020. <https://www.nicd.ac.za/diseases-a-z-index/covid-19/surveillance-reports/> (accessed 20 August 2020).
- Blaize M, Mayaux J, Nabet C, et al. Fatal invasive aspergillosis and coronavirus disease in an immunocompetent patient. *Emerg Infect Dis* 2020;26(7):1636-1637. <https://doi.org/10.3201/eid2607.201603>
- Alanio A, Delliere S, Fodil S, Bretagne S, Megarbane B. High prevalence of putative invasive pulmonary aspergillosis in critically ill COVID-19 patients. *Lancet Respir Med* 2020;8(6):e48-e49. [https://doi.org/10.1016/S2213-2600\(20\)30237-X](https://doi.org/10.1016/S2213-2600(20)30237-X)

42. Van Arkel AL, Rijpstra TA, Belderbos HN, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19-associated pulmonary aspergillosis. *Am J Respir Crit Care Med* 2020;202(1):132-135. <https://doi.org/10.1164/rccm.202004-1038LE>
43. Lescure F-X, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: A case series. *Lancet Infect Dis* 2020;20(6):697-706. [https://doi.org/10.1016/S1473-3099\(20\)30200-0](https://doi.org/10.1016/S1473-3099(20)30200-0)
44. Sharma A, Hofmeyr A, Bansal A, et al. COVID-19 associated pulmonary aspergillosis (CAPA): An Australian case report. *Med Mycol Case Rep* 2020 (epub 18 June 2020). <https://doi.org/10.1016/j.mmcr.2020.06.002>
45. Santana MF, Pivoto G, Alexandre MAA, et al. Confirmed invasive pulmonary aspergillosis and COVID-19: The value of postmortem findings to support antemortem management. *Rev Soc Bras Med Trop* 2020;53:e20200401. <https://doi.org/10.1590/0037-8682-0401-2020>
46. Mohamed A, Hassan T, Trzos-Gryzbowska M, et al. Multi-triazole-resistant *Aspergillus fumigatus* and SARS-CoV-2 co-infection: A lethal combination. *Med Mycol Case Rep* 2020 (epub 26 June 2020). <https://doi.org/10.1016/j.mmcr.2020.06.005>
47. Menon AA, Berg DD, Brea EJ, et al. A case of COVID-19 and *Pneumocystis jirovecii* co-infection. *Am J Respir Crit Care Med* 2020;202(1):136-138. <https://doi.org/10.1164/rccm.202003-0766LE>
48. Huang C, Wang Y, Li X, 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](https://doi.org/10.1016/S0140-6736(20)30183-5)
49. Salehi M, Ahmadi K, Mahmoudi S, et al. Oropharyngeal candidiasis in hospitalized COVID-19 patients from Iran: Species identification and antifungal susceptibility pattern. *Mycoses* 2020;63(8):771-778. <https://doi.org/10.1111/myc.13137>
50. Hughes S, Troise O, Donaldson H, Mughal N, Moore LS. Bacterial and fungal coinfection among hospitalised patients with COVID-19: A retrospective cohort study in a UK secondary care setting. *Clin Microbiol Infect* 2020;26(20):1395-1399. <https://doi.org/10.1016/j.cmi.2020.06.025>
51. Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *J Clin Virol* 2020;127:104364. <https://doi.org/10.1016/j.jcv.2020.104364>
52. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130(5):2620-2629. <https://doi.org/10.1172/JCI137244>
53. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020;395(10223):507-513. [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7)
54. He W, Chen L, Chen L, et al. COVID-19 in persons with haematological cancers. *Leukemia* 2020;34:1637-1645. <https://doi.org/10.1038/s41375-020-0836-7>
55. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: A retrospective observational study. *Am J Respir Crit Care Med* 2020;201(11):1372-1379. <https://doi.org/10.1164/rccm.202003-0543OC>

Accepted 27 September 2020.