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

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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.

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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.[1] The prognosis of the disease in patients with underlying conditions is dire, with comorbidities reported in a large number of hospitalised and severe cases.[2] 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.[2,3] 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.[4-6] 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).[7] Co-infections with respiratory viruses (other than SARS-CoV-2), bacteria and fungi have been reported in COVID-19 patients in Wuhan, China,[8-10] and secondary infections were identified as one of the predictors of a fatal outcome in COVID-19 cases.[11] 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.[2]

Invasive fungal infections, including aspergillosis and candidiasis,[12-14] 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.[15-18] 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.[19-22] 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.[10,23-25] 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.[24,26-28] However, a retrospective study by Gao *et al.*[29] 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.*[29] showed that 25 of 528 patients (4.8%) with viral pneumonia had fungal co-infections. Of these patients, 12 survived while 13 died.[29] 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.[19,30,31]

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[40]	Case study of a 74-year-old immunocompetent man with severe COVID-19	Mar 2020	n/a	*Aspergillus fumigatus*	Confirmed IPA. Fatal outcome due to severe respiratory failure.
Paris, France[41]	Case study of 27 mechanically ventilated COVID-19 patients in ICU	Mar 2020	33% with putative IPA	*A. fumigatus*	Mortality rate did not differ significantly between IPA and non-IPA patients. Testing deep lung specimens for *Aspergillus* is recommended.
Breda, Netherlands[42]	Case report of 31 ICU-requiring patients	Feb 2020	19.4% (6/31 patients) with presumed IPA	*A. fumigatus*	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[43]	Case series involving 5 COVID-19 patients	Jan 2020	20% (1/5 patients)	*A. flavus*	The single patient with fungal coinfection had multiple organ failure despite antimicrobial treatment for *A. flavus* and *Acinetobacter baumannii* secondary infections.
New South Wales, Australia[44]	Case report of a 66-year-old woman	Apr 2020	n/a	*A. fumigatus*	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[45]	Postmortem analysis on a 71-year-old man who died due to COVID-19-related complications	NR	n/a	*A. penicillioides*	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[46]	Case study of a 66-year-old-man	NR	n/a	*Candida albicans* *A. fumigatus*	Amphotericin B was administered. Patient died on day 14 of hospitalisation (on day 22 of COVID-19 illness). The *A. fumigatus* isolate was resistant to multiple azoles including voriconazole, itraconazole and posaconazole.
Graz, Austria[13]	Case study of a 70-year-old man	Mar 2020	n/a	*A. fumigatus*	The patient had several underlying diseases, including type 2 diabetes and obesity. IPA was established with an *A. fumigatus* 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[47]	Case study of an 83-year-old woman	Mar 2020	n/a	*Pneumocystis jirovecii*	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[48]	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[49]	53 hospitalised COVID-19 patients with oropharyngeal candidiasis	Mar - Apr 2020	5% (53/1 059 patients)	*C. albicans* *C. glabrata* *C. dubliniensis* *C. parapsilosis* sensu stricto *C. tropicalis* *C. krusei*	65 fungal isolates with prevalence distribution as follows: 70.7% *C. albicans*, 10.7% *C. glabrata*, 9.2% *C. dubliniensis*, 4.6% *C. parapsilosis* sensu stricto, 3% *C. tropicalis* and 1.5% *C. krusei*.
Nanjing, China[8]	Throat swabs from 257 COVID-19 patients	Jan - Feb 2020	23.3% (60/242 co-infected patients)	*Candida* *Cryptococcus* *Aspergillus* *Mucor*	Proportion of co-infections, including fungal co-infections, highest in severe COVID-19 cases.
Wuhan, China[9]	65 patients (of 918 COVID-19 cases) with nosocomial infection	Dec 2019 - Feb 2020	11.5% (5/65 patients with identified fungi)	*C. albicans* *Mucor*	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[50]	836 COVID-19 patients	Feb - Apr 2020	10/14 respiratory cultures with CA/HCAI *Candida* spp. and 1/2 with CA/HCAI *Aspergillus* spp.	*Candida* *Aspergillus*	3 patients requiring critical care admission developed hospital-acquired C. *albicans* 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[51]	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[52]	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[53]	99 COVID-19 patients	Onset of outbreak - Jan 2020	4% (4/99 patients)	*A. fumigatus* *C. glabrata* *C. albicans*	Of the 4 patients with fungal infection, 1 case was infections with *A. fumigatus* and *C. glabrata* and the rest were *C. albicans*.
Wuhan, China[54]	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[20]	19 consecutive critically ill patients with moderate to severe ARDS	Mar - Apr 2020	5/19 patients had CAPA	*A. fumigatus*	Antifungals voriconazole, caspofungin or isavuconazole were administered. 3 of the 5 patients died.
Wuhan, China[55]	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.[32] 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*.[33] 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.[34-36] 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.[35,36] 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.[34,35,37] Other fungal infections, including invasive aspergillosis, *Pneumocystis* pneumonia and endemic mycoses, are also prevalent in SA.[34] 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.[38,39] 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.

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