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REVIEW

Invasive fungal infections in patients with COVID-19: a review on pathogenesis, epidemiology, clinical features, treatment, and outcomes

Matteo Chiurlo[+1], Andrea Mastrangelo[+1], Marco Ripa[1,2], Paolo Scarpellini[2]

[1]*Vita-Salute San Raffaele University, Milan, Italy;*
[2]*Unit of Infectious and Tropical Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy;*
[+]*These authors contributed equally to the work*

SUMMARY

COVID-19 is frequently associated with the onset of secondary infections, especially in severe cases treated in the intensive care unit. While bacterial pathogens are the most frequently encountered causative agents, several factors put SARS-CoV-2 infected patients at a heightened risk of invasive fungal infections, which have been recognized as a substantial cause of morbidity and mortality in this population. Moreover, the frequent occurrence of these complications in severely ill subjects and the absence of pathognomonic features, together with the emergence of fungal species with reduced susceptibility to first-line treatments and the difficult to manage safety profile of several antifungal drugs, demand an additional focus on these rare but challenging complications. In this review, we will summarize the currently available literature on fungal superinfections in COVID-19 patients, exploring the pathogenesis, epidemiology, clinical features, treatment, and outcomes.

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INTRODUCTION

SARS-CoV-2, the causative agent of COVID-19, emerged in late 2019 and since then has spread worldwide. COVID-19 patients could develop severe pneumonia requiring hospitalization and eventually intubation and transfer to the intensive care unit (Zhu *et al*., 2020). The respiratory failure associated with SARS-CoV-2 infection is the major driver of mortality in this population; nevertheless, several observations have pointed out that hospitalized patients with COVID-19 could also be at heightened risk of secondary infections.

While bacterial and viral co-infections at the time of SARS-CoV-2 diagnosis seem to be rare (Rawson *et al*., 2020), secondary infections arise commonly in hospitalized patients with COVID-19 (Langford *et al.*, 2020), and their frequency increases with the severity of the disease. A detailed pathological discussion of the mechanisms underlying the susceptibility to healthcare-associated infections in these subjects is beyond the scope of this review; however, several factors, such as comorbidities (Richardson *et al.*, 2020), immune-modulating therapies, widespread use of empirical antimicrobial drugs, and SARS-CoV-2-related pathological derangements of the immune system and epithelial barriers are likely to play a role (*Figure 1*).

Of note, several reports suggested that subjects with COVID-19 could be at higher risk of developing a secondary infection when compared to patients with either bacterial (Llitjos *et al*., 2021) or viral pneumonia (Rouzé *et al*., 2021; Shafran *et al*., 2021; Marcus *et al*., 2021; Brehm *et al*., 2021). Interestingly, this increased incidence of superinfections did not seem to be driven by pre-existing risk factors predisposing to healthcare-associated infections (e.g. diabetes, immune-suppression), suggesting that SARS-CoV-2 infection *per se* could be associated with a heightened risk of infectious complications.

The organisms most commonly involved in secondary infections are bacterial, (Langford *et al.*, 2020; Rawson *et al.*, 2020; Ripa *et al.*, 2021), while fungal pathogens are less frequently implicated.

Despite being encountered in a minority of patients, invasive fungal infections in COVID-19 are associated with a considerable burden of morbidity and mortality (Chowdhary *et al.*, 2020; Mastrangelo *et al.*,

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Corresponding author:
Marco Ripa, MD
E-mail: ripa.marco@hsr.it

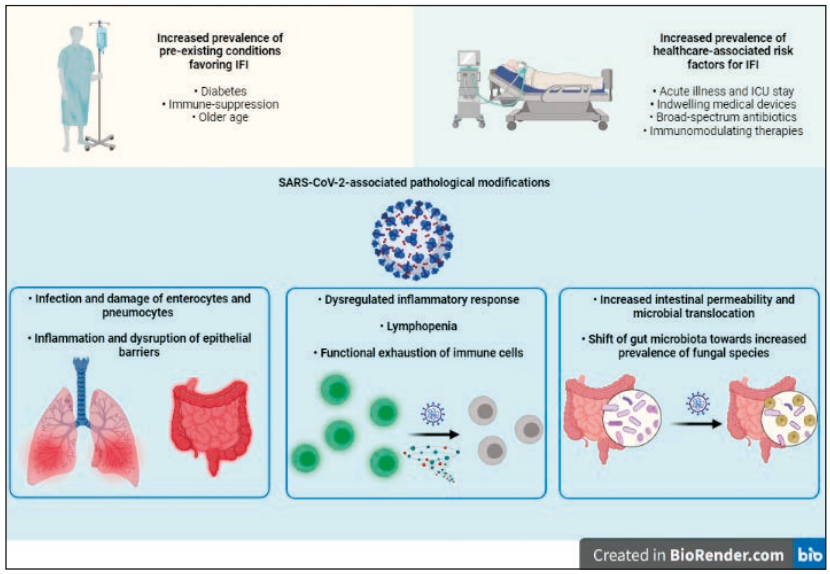

Figure 1 - *Overview on mechanisms associated with invasive fungal infections (IFI) in COVID-19 patients. Created with BioRender.com*

2020; Nucci *et al.*, 2021; Silva *et al.*, 2021; White *et al.*, 2020).

In addition, fungal pathogens with decreased susceptibility to the currently available antifungal therapies are emerging worldwide, and clusters of transmission have been documented in COVID-19 patients, representing a possible new severe threat to global health (Chowdhary *et al.*, 2020; Magnasco *et al.*, 2021).

The purpose of this article is to review the currently available literature on invasive fungal infections associated with COVID-19. Given the large number of studies investigating either invasive candidiasis or invasive aspergillosis in COVID-19, we will discuss these two pathogens separately, and we will provide a rapid overview of the published evidence on the others, less frequently encountered, fungal pathogens.

METHODS

We searched MEDLINE and Google Scholar databases for articles related to fungal infection in COVID-19 patients using the following keywords, included either in the title or in the abstract of the manuscript: "SARS-CoV-2" OR "COVID-19" AND "fungal infections"; "Candidemia"; "Invasive Candidiasis"; "Aspergillosis"; "Endemic mycoses"; "Secondary infections"; "Superinfections"; "Mucormycosis"; "Candida"; "Aspergillus"; "yeast"; "mold".

The title and abstract of the retrieved articles were screened by MC and AM. The studies investigating non-invasive manifestations of fungal infections were excluded. The full texts of those deemed significant for the purposes of this manuscript were further examined by all authors for final inclusion in the review.

The patients described in the studies included in this review were required to have a definite or presumptive diagnosis of COVID-19, on the basis of microbiological data (either real-time reverse transcriptase or antigen testing), clinical characteristics, and imaging features. All studies describing COVID-19 subjects were included, regardless of patients' severity.

INVASIVE CANDIDIASIS

Candida is a genus of yeasts broadly diffused worldwide. *Candida albicans*, the most frequently encountered representative of this species, could be a component of the common human enteric flora and is usually non-pathogenic for the healthy host. Other members of the *Candida* genus are instead not part of the human microbiota but are widely diffused in the hospital environment.

When immune responses are weakened, this organism could be associated with both localized and serious systemic infections (Pappas *et al.*, 2018). *Candida* spp. are among the most frequent isolates from severely ill patients, and a leading cause of healthcare-associated infections. In the intensive care unit (ICU), the burden of invasive candidiasis is substantial, and the incidence of this condition is rising in the last years (Calandra *et al.*, 2016). Due to the tendency to infect patients with severe illness or compromised immune system, invasive candidiasis is associated with considerable mortality (Pfaller and Diekema, 2007). Of note, this pathogen could also display different resistance patterns to several antifungal drugs, a condition that contributes to worsening the prognosis of infected patients. *Candida auris*, a recently described species of *Candida*, is frequently resistant to multiple classes of antifungal therapies, and is therefore a major threat to global health (Jeffery-Smith *et al.*, 2018).

Invasive candidiasis usually presents as fever and

worsening of clinical conditions in critically-ill and/or immune-suppressed patients. Signs and symptoms of candidiasis occurring at skin or mucosal surfaces could also be present, as well as signs suggesting a central-line associated infection (Cornely *et al.*, 2012). However, the majority of subjects do not show specific symptoms, and the diagnosis relies on the microbiological isolation of *Candida spp.* from a sterile site (typically blood cultures) or on the histopathological evidence of fungal infection in sterile tissue samples. Given the low sensitivity of these methods, additional approaches to diagnose *Candida spp.* infection have been proposed. The measurement of fungal cell wall component mannan, coupled to anti-mannan antibodies, and the detection of (1,3)-β-D-glucan in patients' body fluids could be useful to rule in and rule out the disease, and are currently recommended in the diagnostic workup for candidemia (Cuenca-Estrella *et al.*, 2012; Clancy *et al.*, 2018).

Classic risk factors for invasive candidiasis include alterations in hosts' physical barriers (e.g. indwelling vascular catheters, mucositis, recent gastrointestinal tract surgery), underlying immunosuppression (e.g. diabetes, renal failure, onco-hematological malignancies, and recent chemotherapy), or alterations in the healthy microbiota (e.g. use of broad-spectrum antibiotics) (Pappas *et al.*, 2018; Yapar, 2014).

Several cohort studies on secondary infection in COVID-19 reported variable rates of *Candida* bloodstream infection, ranging from 0.03 to 10% of patients admitted due to SARS-CoV-2 infection (*Table 1*) (Araste-

Table 1 - *Characteristics of studies investigating invasive candidiasis (IC) in COVID-19.*

Reference	*Number of cases in the cohort, N (%)*	*Patients diagnosed with IC in the ICU, N (%)*	*Patients diagnosed with IC treated with corticosteroids, N (%)*	*Patients diagnosed with IC treated with other Immuno-suppressants, N (%)*	*Patients diagnosed with IC with history of immune suppression, N (%)*	*Mortality among patients diagnosed with IC, N (%)*
Al-Hatmi *et al.*, (2021)*	5	5/5 (100%)¶	NA	NA	NA	3/5 (60.0%)
Antinori *et al.*, (2020)	3/43 (6.9%)	1/3 (33.3%)	1/3 (33.3%)	3/3 (100%)	0	0
Arastehfar *et al.*, (2021)	7/1988 (0.4%)	7/7 (100%)¶	0	0/7 (0%)	3/7 (42.3%)	7/7 (100%)
Bishburg *et al.*, (2021)	8/89 (8.9%)	8/8 (100%)¶	8/8 (100%)	4/8 (50.0%)	NA	3/8 (37.5%)
Chowdhary *et al.*, (2020)	15/596 (2.5%)	15/15 (100)¶	10/15 (66.7%)	NA	4/15 (26.7%)	8/15 (53.3%)
Denny *et al.*, (2021)*	11	10/11 (90.9%)	2/11 (18.2%)	NA	3/11 (27.3%)	6/11 (54.5%)
Falcone *et al.*, (2020)	8/315 (3.3%)	NA	NA	NA	NA	NA
Garcia-Vidal *et al.*, (2021)	4/989 (0.4%)	2/4 (50.0%)	NA	NA	NA	2/4 (50.0%)
Giacobbe *et al.*, (2020)	3/31 (9.7%)	3/3 (100%)¶	0	2/3 (66.7%)	NA	NA
Grasselli *et al.*, (2021)	17/813 (2.1%)	17/17 (100%)¶	NA	N	NA	NA
Hughes *et al.*, (2020)	3/836 (0.3%)	3/3 (100%)	NA	NA	NA	NA
Kokkoris *et al.*, (2021)	7/50 (14.0%)	7/7 (100%)¶	NA	NA	NA	NA
White *et al.*, (2020)	14/135 (10.3%)	14/14 (100%)¶	1/14 (7.1%)	NA	NA	5/14 (35.7%)
Mastrangelo *et al.*, (2020)*	21	14/21 (66.7%)	9/21 (42.9%)	13/21 (61.9%)	6/21 (28.6%)	12/21 (57.1%)
Nucci *et al.*, (2021)	9/608 (1.5%)	7/9 (77.8%)	NA	NA	6/9 (66.7%)	6/9 (66.7%)
Riche *et al.*, (2020)*	11	8/11 (72.7%)	11/11 (100%)	0	6/11 (54.5%)	8/11 (72.7%)
Ripa *et al.*, (2021)	7/731 (1.0%)	NA	NA	NA	NA	NA
Villanueva-Lozano *et al.*, (2021)*	12	12/12 (100%)¶	12/12 (100%)	12/12 (100%)	5/12 (41.7%)	8/12 (66.7%)

ICU: intensive care unit. N: number. NA: not available.
Only case-series and cohort studies with sample size >3 where considered for the inclusion in the table. *: case-series reporting data only of patients with IC; ¶: study considering only patients admitted to ICUs; ¦: refers to single episodes of IC

hfar *et al.*, 2021, 2020; Cuntrò *et al.*, 2021; Falcone *et al.*, 2020; Grasselli *et al.*, 2021; Nucci *et al.*, 2021). Invasive candidiasis developed late in the course of hospitalization (on average, >7 days since hospital admission) (Falcone *et al.*, 2020), and was associated with a markedly high rate of mortality (>50%). Some works have also suggested that SARS-CoV-2 infected subjects could be more prone to invasive candidiasis when compared to their uninfected counterpart (Mastrangelo *et al.*, 2020; Nucci *et al.*, 2021). The possible drivers of this increased incidence are currently under investigation.

On one hand, some of the risk factors usually associated with candidemia are strongly represented in SARS-CoV-2 infected population, especially if hospitalized due to severe pulmonary disease (e.g. diabetes, immune suppression, or older age) (Richardson *et al.*, 2020; Yapar, 2014). Nevertheless, other risk factors usually associated with invasive candidiasis, such as intestinal surgery, are on the contrary not frequent in SARS-CoV-2 infected patients (Arastehfar *et al.*, 2021; Mastrangelo *et al.*, 2020). A substantial proportion of the reported episodes were associated with the presence of intravascular catheters. *Candida* spp. is a notorious colonizer of central lines, and the pandemic context, with the subsequent high number of patients admitted simultaneously to COVID-19 wards and ICUs, could have led to suboptimal adherence to infection control measures and favored the occurrence of healthcare-associated infections (Grasselli *et al.*, 2021; Ripa *et al.*, 2021). Moreover, hospitalized patients with COVID-19, especially if severely ill, are almost invariably treated with antibiotics (Grasselli *et al.*, 2021; Langford *et al.*, 2020; Rawson *et al.*, 2020; Ripa *et al.*, 2021). The proportion of COVID-19 patients on empirical antimicrobial therapy has been reported to be around 70% (Rawson *et al.*, 2020), while the proportion of those with a documented secondary infection ranged between 10 and 1% (Rawson *et al.*, 2020; Grasselli *et al.*, 2021). Several works had noticed an increased consumption of antimicrobials during the surge of COVID-19 cases (Vaughn *et al.*, 2021; Abelenda-Alonso *et al.*, 2020; Guisado-Gil *et al.*, 2020), suggesting a low threshold for antibiotic prescribing in this population. The inappropriate use of broad-spectrum antibiotic drugs favors the selection of pathogens unaffected by ongoing antimicrobial treatment, such as *C. difficile* and *Candida* spp, possibly increasing the susceptibility to secondary infections due to fungal pathogens. Finally, the mainstay therapy of severe COVID-19 is currently represented by immunosuppressive drugs. Earlier reports suggested a possible association between the use of tocilizumab, an anti-IL-6-receptor agent, and the development of candidiasis (Antinori *et al.*, 2020; Kimmig *et al.*, 2020), while other small case series suggested an increased risk of candidemia in patients receiving corticosteroids (Riche *et al.*, 2020). However, the small number of patients included in these studies prevents from making any definitive conclusion; notably, the largest cohort study on critically ill patients with COVID-19 suggested that the use of immunosuppressive was not strongly associated with an increased risk of secondary infections, even though an analysis focused only on fungal infection was not performed (Grasselli *et al.*, 2021).

On the other hand, some observations found an increased incidence of invasive candidiasis in patients with COVID-19 even after adjustment for other common risk factors associated with *Candida* infection (Mastrangelo *et al.*, 2020; Nucci *et al.*, 2021). This observation led to the speculation that SARS-CoV-2 infection could be by itself associated with a heightened risk of candidiasis, through different pathogenic mechanisms. SARS-CoV-2 could infect enterocytes, thus leading to a decreased integrity of the intestinal barrier (Lamers *et al.*, 2020). Indeed, increased concentrations of plasmatic markers of microbial translocation have been reported in infected patients (Arunachalam *et al.*, 2020), and fungal microbiota of COVID-19 patients was found to be skewed toward an increased presence of *Candida* spp (Zuo *et al.*, 2020). These findings likely put this population at an increased risk of *Candida* translocation and subsequent candidemia. Moreover, the pathology of severe SARS-CoV-2 infection involves a profound dysregulation of the immune system. Based on cellular activation profile and cytokine secretion, different host immune phenotypes could be distinguished during COVID-19. These immunotypes range from a "hyper-inflamed" one, with increased T-lymphocytes and myeloid cell expression of activation markers, to an "exhausted" one, in which immune cells of the affected patient are enriched in immune-exhaustion markers and fail to respond to toll-like receptors engaging and to pathogen exposure *ex-vivo* (Diao *et al.*, 2020; Mathew *et al.*, 2020). Among this clinical and immunological spectrum of conditions, response to commensal pathogens, such as *Candida* spp, could be impaired, and invasive candidiasis could develop more frequently. Of note, a recent study reported a decreased response to ex-vivo stimulation with *Candida* lysate in whole-blood cells derived from COVID-19 infected patients. This impairment was not observed when the same cells were stimulated with either bacterial antigens or *Aspergillus fumigatus* lysate, suggesting a possible pathogen-specific weakening of immune response (Moser *et al.*, 2021). Although thought-provoking, these observations mostly derive from studies with small sample sizes and enrolling patients with different degrees of disease severity, two factors that impede a generalization of the described mechanisms.

The diagnosis of invasive candidiasis is notoriously challenging, as blood cultures have a low

yield (around 50%), and are frequently negative in deep-seated infections (Calandra *et al*., 2016; Pappas *et al*., 2018). The use of surrogate markers of fungal infection, such as detection in blood or other sterile samples of fungal wall products (such as β-D-glucan), even though non-specific for candidiasis, could reveal the presence of an invasive fungal infection. In several centers across Europe a surveillance strategy for high-risk patients admitted to the ICU, which includes the periodic measurement of these markers, has been proposed (Lei *et al*., 2020; White *et al*., 2020). This approach was associated with an increased likelihood of mycological positivity, suggesting that a thorough antifungal surveillance in COVID-19 patients admitted to the ICU could possibly be beneficial. However, β-D-glucan measurement, as well as other non-culture-based methods for addressing Candida positivity such as the research of fungal DNA by polymerase chain reaction (PCR), are not widely available outside tertiary-care hospitals. Given the substantial risk of mortality associated with untreated invasive candidiasis, a low threshold for the initiation of empirical antifungal therapies in COVID-19 patients hospitalized for >7 days and/or admitted to the ICU, who display clinical and laboratory features of sepsis or septic shock, could be associated with better outcomes.

The treatment of invasive candidiasis associated with COVID-19 infection should not differ from the current standard of care. The mainstay of antifungal treatment consists of azole drugs (Calandra *et al*., 2016). However, increased resistance to this class of medications is widely observed worldwide, especially among non-*albicans Candida* spp. For the isolates resistant to azoles, echinocandins or newer azoles (such as isavuconazole) could be used; amphotericin B and other agents under development such as rezafungin are possible second-line options (Ham *et al*., 2021; Pappas *et al*., 2004). In the context of an unstable patient in the ICU, given the substantial amount of non-albicans *Candida* spp isolates in hospital-acquired infections, initiating an echinocandin seems to be a reasonable choice. Moreover, the vast majority of reported cases of invasive candidiasis is represented by bloodstream and central-line associated infections, which could be optimally treated with this family of drugs, given the favorable pharmacokinetic profile (Pea and Lewis, 2018). On the contrary, for the rare cases of deep-seated candidiasis, and especially for central nervous system and/or ocular infections, echinocandins are not a good option, given the low penetration of these drugs in deep-seated abscess, cerebrospinal fluid, and vitreous (Felton *et al*., 2014). In these unfortunate cases, voriconazole or amphotericin B should be preferred, even though the latter has a less favorable safety profile (lipid formulations are therefore preferred in this context).

Candida auris deserves specific consideration as presents unique issues. This emerging pathogen, reported worldwide but more diffused in subtropical regions such as India and south-America, has been associated with invasive infection occurring in epidemic clusters in COVID-19 patients (Allaw *et al*., 2021; Magnasco *et al*., 2021). The extensive resistance pattern, almost invariably displaying non-susceptibility to azoles and amphotericin B, clearly narrows the therapeutic armamentarium. Moreover, the tendency to persist on medical supplies and to colonize severely ill patients make this organism a serious threat for ICUs. Given the potentially devastating consequences of the uncontrolled spread of this organism among severely ill patients infected with SARS-CoV-2, a surveillance strategy for prompt detection and isolation of colonized patients, as well as a strict adherence to contact precautions, must be implemented in all COVID-19 dedicated wards and ICUs.

INVASIVE ASPERGILLOSIS

Aspergillosis is a disease caused by *Aspergillus* spp., a ubiquitous environmental mold that grows on organic matter and aerosolizes conidia which are inhaled by humans, potentially leading to subsequent infection. The *Aspergillus* genus comprises numerous species, but among them, *Aspergillus fumigatus* is responsible for 90% of the aspergillosis syndromes when conidia are inhaled by non-immunocompetent hosts (Barnes and Marr, 2006). *Aspergillus* spp. can be associated with a variety of clinical manifestations, depending on the competence of the immune response of the host. Pulmonary aspergillosis and the progression to angioinvasive pulmonary aspergillosis are serious conditions leading to high mortality (up to 95% if not treated), often complicating critically hill patients (Barnes and Marr, 2006).

Risk factors that are known to increase the risk of invasive aspergillosis are hematopoietic stem cell transplant and solid organ transplant, neutropenia, primary and secondary immunodeficiencies, and immunosuppressive treatment (Baddley, 2011).

Among pathogens that have become a serious concern in COVID-19 infected patients, *Aspergillus* spp. should be carefully considered, being associated with high morbidity and mortality. Pulmonary aspergillosis is indeed difficult to diagnose and treat, leading to serious outcomes in critically ill patients. To our knowledge and to this date, a few hundred cases of COVID-19 associated pulmonary aspergillosis (CAPA) have been identified raising concerns about this infection as a contributing factor to mortality. Indeed, in a prospective cohort study, a higher 30-day mortality rate was observed among patients with CAPA compared to COVID-19 patients without invasive aspergillosis (Koehler *et al*., 2021).

Table 2 - *Characteristics of studies investigating COVID-19 Associated Pulmonary Aspergillosis (CAPA).*

Reference	*Number of cases in the cohort, N (%)*	*Patients diagnosed with CAPA in the ICU, N (%)*	*Patients with CAPA treated with corticosteroids, N (%)*	*Patients with CAPA treated with other immuno-suppressants, N (%)*	*Patient with CAPA with history of immune suppression, N (%)*	*Mortality among patients with CAPA, N (%)*
Alanio *et al.*, (2020)	9/27 (33.3%)	NA	6/9 (66.7%)	NA	0/9 (0%)	4/9 (44.4%)
Bartoletti *et al.*, (2020)	30/108 (27.7%)	NA	18/30 (60%)	22/30 (73.3%)	6/30 (20.0%)	13/30 (43.3%)
Chauvet *et al.*, (2020)	6/46 (13.0%)	6/6 (100%)	5/6 (83.3%)	NA	2/6 (33.3%)	4/6 (66.7%)
Dellière *et al.*, (2021)	21/366 (5.7%)	21/21 (100%)	6/21 (28.6%)	4/21 (19.0%)	5/21 (23.8%)	15/21 (71.4%)
Dupont *et al.*, (2021)	19/106 (17.9%)	19/19 (100%)	7/19 (36.8%)	NA	0/19 (0%)	7/19 (36.8%)
Fekkar *et al.*, (2021)	6/260 (2.3%)	6/6 (100%)	1/6 (16.7%)	NA	3/6 (50.0%)	4/6 (66.7%)
Gangneux *et al.*, (2020)	7/45 (15.6%)	7/7 (100%)	NA	NA	2/7 (28.6%)	2/7 (28.6%)
Gouzien *et al.*, (2021)	2/53 (3.8%)	2/2 (100%)	NA	NA	NA	NA
Grasselli *et al.*, (2021)	17/774 (2.1%)	17/17 (100%)	NA	NA	NA	NA
Helleberg *et al.*, (2021)	2/27 (7.4%)	2/2 (100%)	1/2 (50%)	0/2 (0%)	0/2 (0%)	2/2 (100%)
Koehler *et al.*, (2020)	5/19 (26.3%)	5/5 (100%)	NA	NA	0/5 (0%)	3/5 (60.0%)
Lahmer *et al.*, (2021)	11/32 (34.4%)	11/11 (100%)	NA	NA	0/11 (0%)	4/11 (36.4%)
Lamoth *et al.*, (2020)	3/80 (3.8%)	3/3 (100%)	NA	3/3 (100%)	0/3 (0%)	1/3 (33.3%)
Machado *et al.*, (2021)	8/239 (3.3%)	8/8 (100%)	8/8 (100%)	8/8 (100%)	2/8 (25.0%)	8/8 (100%)
Maes *et al.*, (2021)	3/81 (3.7%)	3/3 (100%)	0/3 (0%)	NA	NA	1/3 (33.3%)
Meijer *et al.*, (2021)	13/764 (1.7%)	13/13 (100%)	8/13 (61.5%)	0/13 (0%)	0/13 (0%)	6/13 (46.2%)
Nasir *et al.*, (2020)	5/147 (3.4%)	5/5 (100%)	4/5 (80.0%)	3/5 (60.0%)	0/5 (100%)	3/5 (60.0%)
Permpalung *et al.*, (2021)	39/396 (9.8%)	39/39 (100%)	26/39 (66.7%)	9/39 (23.1%)	3/39 (7.7%)	22/39 (56.4%)
Ripa *et al.*, (2021)	11/731 (1.5%)	10/11 (90.9%)	NA	1/11 (9.1%)	NA	NA
Roman-Montes *et al.*, (2021)	14/144 (9.7%)	14/14 (100%)	1/14 (7.1%)	4/14 (28.6%)	0/14 (0%)	8/14 (57.1%)
Rutsaert *et al.*, (2020)	4/34 (11.8%)	4/4 (100%)	NA	NA	NA	1/4 (25.0%)
Sarrazyn *et al.*, (2020)	4/131 (3.1%)	4/4 (100%)	NA	NA	0/4 (0%)	4/4 (100%)
Segrelles-Calvo *et al.*, (2021)	7/215 (3.3%)	7/7 (100%)	4/7 (57.1%)	5/7 (71.4%)	0/7 (0%)	5/7 (71.4%)
van Arkel *et al.*, (2020)	6/31 (19.3%)	6/6 (100%)	2/6 (33.3%)	NA	0/6 (0%)	4/6 (66.7%)
Van Biesen *et al.*, (2020)	9/53 (17.0%)	9/9 (100%)	1/9 (11.1%)	NA	2/9 (22.2%)	2/9 (22.2%)
van Grootveld *et al.*, (2021)	11/63 (17.5%)	11/11 (100%)	NA	NA	1/11 (9.1%)	7/11 (63.4%)
Vélez Pintado *et al.*, (2021)	16/83 (19.3%)	16/16 (100%)	2/16 (12.5%)	12/16 (75.0%)	3/16 (18.8%)	5/16 (31.2%)
Versyck *et al.*, (2021)	2/54 (3.7%)	2/2 (100%)	2/2 (100%)	1/2 (50%)	0/2 (0%)	2/2 (100%)
Wang *et al.*, (2020)	8/104 (7.7%)	8/8 (100%)	6/8 (75.0%)	NA	0/8 (0%)	NA
White *et al.*, (2020)	25/257 (9.7%)	25/25 (100%)	16/25 (64.0%)	NA	3/25 (12.0%)	13/25 (52.0%)

CAPA: COVID-19-associated invasive pulmonary aspergillosis; ICU: intensive care unit. N: number. NA: not available.

Several studies analyzed the occurrence of pulmonary aspergillosis associated with COVID-19 reporting an incidence ranging from 1.7% to 34.4% (*Table* 2). The largest case series has been described by Zhu *et al*. with 23.3% (60/243) of COVID-19 patients ranging from asymptomatic to critical showing *Aspergillus* superinfection. Nevertheless, in this work no distinction was made between colonization and infection, and the diagnosis was made on the basis of PCR only. Other studies also analyzed infections with *Aspergillus* in the subgroup of patients admitted to ICU or mechanically ventilated, with a broad variability in the reported incidence. The reasons behind this discrepancy may be related to the adoption of different diagnostic criteria, as well as to epidemiological variabilities between different centers (Garcia-Vidal *et al*., 2014; Schwartz *et al.*, 2020). Another explanation proposed by Lahmer *et al.* and Van Biesen *et al*. for the higher incidence of CAPA is related to the widespread use of non-direct BAL approach to reduce the risk of SARS-CoV-2 aerosolization, even though other Authors described a high incidence also with traditional BAL technique.(Lahmer *et al*., 2021; Rutsaert *et al*., 2020; Van Biesen *et al*., 2020) In two recent reviews by Chong *et al.* and Mitaka *et al*., the incidence of invasive aspergillosis was estimated to be 10-14%, with an overall mortality of 48-55% (Chong and Neu, 2021; Mitaka *et al*., 2021). Among the studies included in the reviews, the most commonly used diagnostic criteria were the modified AspICU-Dutch/Belgian Mycosis Study Group criteria (Schauwvlieghe *et al*., 2018). Interestingly, comparing patients colonized with *Aspergillus* with patients with CAPA, Machado et al. found that patients with invasive disease were ventilated significantly longer, were administered tocilizumab more frequently, and had longer courses of antibacterial treatment. Taken together, these findings suggest that COVID-19 patients that developed CAPA had a longer duration of ICU stay and worse outcomes compared to patients with Aspergillus colonization (Machado *et al*., 2021). In a variety of studies, different risk factors were identified to be correlated with invasive *Aspergillus* infection. COVID-19 associated lymphopenia might be a crucial factor, as it is a well-known risk for opportunistic infections (Salehi *et al*., 2020). Moreover, mechanical ventilation and admission to ICU greatly increase the risk of fungal colonization potentially leading to invasive pulmonary aspergillosis. Furthermore, corticosteroids currently represent the standard of care for patients hospitalized with COVID-19, and other immunosuppressive agents (such as tocilizumab) are employed in specific groups of subjects, potentially increasing the risk of opportunistic infections (The RECOVERY Collaborative Group, 2021). It is worth noting that conventional risk factors for aspergillosis such as immunodeficiency, long-term corticosteroid treatment, and chronic pulmonary diseases were not common in these specific populations.

A proposed pathogenetic mechanism involving the role of IL-10 and IL-6 interleukins can be considered when analyzing the association between aspergillosis and COVID-19. IL-10 has a key function in the regulation of cellular immune response being involved in a multitude of inflammatory diseases (Lai and Yu, 2020). In a rat model, aspergillosis was significantly associated with an increase of IL-10 levels correlating to increasing Th2 response and a decrease in Th1 response resulting in a down-regulation in macrophage activity and an increase in host susceptibility for *Aspergillus* infection (Clemons *et al*., 2000). On the other hand, IL-6 is a pleiotropic cytokine that can play a role in protective immunity against various pathogens, including *Aspergillus fumigatus* (Shen *et al*., 2016). However, IL-6 was also identified as being the leading cause of several biological processes contributing to ARDS and severe outcomes of COVID-19 patients, thus leading to the approval of IL-6 antagonists for the treatment of SARS-CoV-2 infection. All that considered, early intervention with IL-6 blockade target antagonists such as tocilizumab could prevent progression of COVID-19 but potentially expose to increased susceptibility to *Aspergillus* infection and other superinfections (Lai and Yu, 2020).

The early cases of presumed CAPA showed that the diagnosis could be challenging. While predisposing host factors should be considered to obtain a diagnosis of invasive fungal infection, along with clinical and mycological criteria, patients with CAPA often showed neither typical host factors nor typical radiological features. One major difficulty regarding the latter is that pathognomonic radiological features of pulmonary aspergillosis, such as the so-called "halo sign", are not sufficient to define CAPA without mycological evidence, since similar features can be caused by COVID-19 alone, being an expression of local infarction related to SARS-CoV-2-associated pulmonary thrombotic events (Koehler *et al*., 2021). Regarding mycological criteria, culture and tissue microscopy showing growth of *Aspergillus* hyphae still represent the gold standard for the diagnosis of aspergillosis. In addition, detection of galactomannan antigen in bronchoalveolar fluid is highly indicative of invasive aspergillosis, and PCR for *Aspergillus* spp. may be helpful in specific circumstances, especially in the case of positive results confirmed from separate specimens (Koehler *et al*., 2021). The lack of defining criteria for CAPA led to the proposal by the 2020 ECMM/ISHAM consensus of new criteria for proven, probable, and possible CAPA (*Table 3*), considered as invasive aspergillosis in temporal proximity to a preceding SARS-CoV-2 infection, depending on histological, microbiological, imaging and clinical criteria (Koehler *et al*., 2021).

Regarding the treatment of CAPA, there are no data

Table 3 - *Proposed case definition for CAPA (2020 ECMM/ISHAM consensus criteria).*

	Host factors	*Clinical factors*	*Mycological evidence*
Tracheobronchitis or other pulmonary form (proven)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)		At least one of the following: - histopathological or direct microscopic detection of fungal hyphae, showing invasive growth with associated tissue damage; - Aspergillus recovered by culture or microscopy or histology or PCR obtained by a sterile aspiration or biopsy from a pulmonary site, showing an infectious disease process.
Tracheobronchitis (probable)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Tracheobronchitis, indicated by tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis	At least one of the following: - microscopic detection of fungal elements in bronchoalveolar lavage, indicating a mold; - positive bronchoalveolar lavage culture or PCR; - serum galactomannan index >0.5 or serum LFA index >0.5; - bronchoalveolar lavage galactomannan index ≥1.0 or bronchoalveolar lavage LFA index ≥1.0.
Other pulmonary forms (probable)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Pulmonary infiltrate, preferably documented by chest CT, or cavitating infiltrate (not attributed to another cause)	At least one of the following: - microscopic detection of fungal elements in bronchoalveolar lavage, indicating a mold; - positive bronchoalveolar lavage culture; - serum galactomannan index >0.5 or serum LFA index >0.5; - bronchoalveolar lavage galactomannan index ≥1.0 or bronchoalveolar lavage LFA index ≥1.0; - two or more positive Aspergillus PCR tests in plasma, serum, or whole blood; - a single positive Aspergillus PCR in bronchoalveolar lavage fluid (<36 cycles); - a single positive Aspergillus PCR in plasma, serum, or whole blood, and a single positive in bronchoalveolar lavage fluid (any threshold cycle permitted).
Other pulmonary forms (possible)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Pulmonary infiltrate, preferably documented by chest CT, or cavitating infiltrate (not attributed to another cause)	At least one of the following: - microscopic detection of fungal elements in non-bronchoscopic lavage indicating a mold; - positive non-bronchoscopic lavage culture; - single non-bronchoscopic lavage galactomannan index >4.5; - non-bronchoscopic lavage galactomannan index >1.2 twice or more; - non-bronchoscopic lavage galactomannan index >1.2 plus another non-bronchoscopic lavage mycology test positive (non-bronchoscopic lavage PCR or LFA)

CAPA: COVID-19-associated invasive pulmonary aspergillosis; ICU: intensive care unit; LFA: lateral flow assay.

to suggest that the approach should be different than that for invasive pulmonary aspergillosis in patients without SARS-CoV-2 infection. Voriconazole should then be considered as first-line treatment, as recommended by international guidelines, and should be continued for a minimum of 6-12 weeks (Patterson *et al.*, 2016; Koehler *et al.*, 2021). Alternative regimens consider the use of liposomal amphotericin B, especially in documented azole-resistant aspergillus species, and isavuconazole, while echinocandins are not recommended as monotherapy but can be used as salvage therapy combined with azoles in case of suspected azole resistance (Patterson *et al.*, 2016; Ullmann *et al.*, 2018). However, there are several drawbacks to using voriconazole, such as its narrow therapeutic window, requiring adequate therapeutic drug monitoring, and the high frequency of drug-drug interactions. Indeed, being metabolized via CYP2C19, CYP2C9 and CYP3A4 voriconazole is among the azoles the one that presents the most interactions, especially in the ICU setting and with COVID-19 drugs such as remdesivir, which is also a substrate of CYP3A4 (Koehler *et al.*, 2021; Zonios *et al.*, 2014). Voriconazole is also associated with non-negligible acute adverse events, including photosensitivity, visual and auditory hallucinations, cardiac arrhythmias, and liver toxicity, alongside long-term toxicities such as skin carcinogenesis and fluorosis, that can lead to periostitis. Moreover, excipients like β-cyclodextrin can cause renal function impairment, raising concerns in COVID-19 infected patients as SARS-CoV-2 has been frequently associated with

acute kidney injury (possibly due to viral renal tropism) (Puelles *et al*., 2020). Given these concerns, isavuconazole, when compared to voriconazole, shows a more favorable pharmacokinetic profile and it is less prone to hepatotoxicity and neurotoxicity, and has a decreased risk of QT prolongation, having an overall non-inferior antifungal activity (Maertens *et al*., 2016). However, being metabolized via CYP3A4, isavuconazole could still be potentially problematic in COVID-19 patients. Lastly, posaconazole has been recently compared to voriconazole in a prospective randomized trial which demonstrated non-inferior efficacy for the treatment of invasive pulmonary aspergillosis, but with a more favorable safety profile. However, posaconazole is an inhibitor of CYP3A4 and therefore could increase concentrations of other substrates. In addition to that, serum electrolytes should be carefully monitored as hypokalemia was noted more often with posaconazole (Maertens *et al*., 2021).

In conclusion, severe COVID-19 pneumonia seems to be associated with invasive pulmonary aspergillosis and correlated to numerous risk factors, such as the use of immunosuppressants and corticosteroids, as well as the duration of mechanical ventilation and ICU stay. These findings led different authors to consider antifungal prophylaxis in selected high-risk patients (Koehler *et al*., 2021).

OTHER OPPORTUNISTIC FUNGAL PATHOGENS

Upon reviewing the literature on COVID-19 and associated invasive fungal infections, to this date, the main pathogens identified were *Aspergillus* and *Candida* species. However, as we gather more data regarding fungal superinfections in COVID-19 patients, less frequent opportunistic fungal pathogens are increasingly reported, such as *Mucormycetes*, *Histoplasma* spp, *Cryptococcus* spp., and *Pneumocystis jirovecii* (Song *et al*., 2020).

Mucormycosis is a rare fungal infection caused by a group of mycetes from the genus of *Rhizopus, Mucor, Rhizomucor,* and other *Zygomycetes*. Found in the environment, mucormycosis usually occurs in people presenting with immunocompromising factors such as diabetes mellitus, solid or hematological malignancies, solid organ and hematopoietic stem cells transplant, severe neutropenia, primary or acquired immunodeficiencies, and in patients treated with corticosteroids or other immunosuppressant agents. Mucormycosis can involve different sites ranging from cutaneous infection due to skin trauma, to pulmonary, rhinocerebral-sinus infection and disseminated visceral infection with fatal outcomes (Richardson, 2009). The infection is usually suspected on clinical grounds for its rapid progression in patients with relevant host factors, and the diagnosis is based on identification from clinical specimens of mucormycetes hyphae invasion on direct microscopy. Specimen cultures are recommended for the identification of species by morphological characteristics or via DNA sequencing and MALDI-TOF identification.

As noted above, COVID-19 patients are more vulnerable to fungal infections due to the decrease in CD4 and CD8 T-lymphocytes, and the use of corticosteroids and other immunosuppressants. Several cases of mucormycosis were reported to be associated with SARS-COV-2 infection, especially in severe COVID-19 patients requiring ICU admission or mechanical ventilation (Sen *et al*., 2021; Song *et al*., 2020). Song et al. indeed related fungal infections with the middle and later stages of COVID-19 infection, with an increase in mortality associated with longer hospital stay and the need for mechanical ventilation (Song *et al*., 2020). To this date there are multiple case reports of mucormycosis associated with COVID-19, the majority of them with sino-orbital localization (Johnson *et al*., 2021; Mehta and Pandey, 2020; Mekonnen *et al*., 2021; Pasero *et al*., 2020; Werthman-Ehrenreich, 2021). A recent review reported close to a hundred cases of mucormycosis in COVID-patients. Singh *et al.* identified 82/101 cases (81.2%) coming from India, reflecting the local epidemiology (with a prevalence 80 times higher than the rest of the World). Most of the reported cases involved sinus cavities (88.9%) and the rhino-orbital region (56.7%), while pulmonary involvement was reported in 7.9% of cases. Overall mortality was noted to be 30.7%, with higher mortality (up to 90%) associated with rhino-orbital-cerebral involvement. Most of the COVID-19 patients were also affected by diabetes and were treated with corticosteroids (Singh *et al*., 2021). However, cases in patients without known risk factors for mucormycosis or previous/concomitant corticosteroid treatment were reported. Alarmingly, recent reports from India highlighted a dramatic increase in the incidence of mucormycosis in patients with COVID-19, with about 15.000 cases as of May 28, 2021 (Raut A, 2021). Pasero *et al.* suggested that SARS-CoV-2 could indeed induce an immunosuppressive state by itself potentially exposing patients to the risk of developing opportunistic fungal infections (Pasero *et al*., 2020). On the other hand, the high incidence of mucormycosis in COVID-19 patients in India is in line with local epidemiology of diabetes, with India having the second largest population with this condition, with a prevalence of up to 14% (Anjana *et al*., 2017; "IDF Diabetes Atlas", n.d.). Furthermore, the high proportion of patients receiving corticosteroids constitutes another contributing factor, being responsible not only for an immunosuppressed state but also leading to uncontrolled diabetes and diabetic ketoacidosis, which are risk factors for mucormycosis per se (Singh *et al*., 2021). Taken together, diabetes-related risk factors

alongside COVID-19-associated lymphopenia, decrease of CD4 and CD8 T-cell counts and endothelial damage should be a matter of concern in this population, given that a delay in diagnosis could result in a fatal outcome. Historically, mucormycosis has indeed been diagnosed post-mortem in more than 50% of cases (Maartens and Wood, 1991).

Other opportunistic fungal pathogens were reported to be associated with COVID-19 patients. Song *et al.* raised a concern about *Cryptococcus* infections in COVID-19 in people living with HIV and a CD4 count of less than 200 cell/μL (Song *et al*., 2020). In this specific population, two cases of *Histoplasmosis* were also reported by Messina et al. from Argentina and by Basso *et al.* from Brazil (Basso *et al*., 2020; Messina *et al*., 2020). A troubling concern is also the evidence of other opportunistic fungal infections in non-immunocompromised patients with severe COVID-19 infection. Poignon *et al.* reported a case of invasive fusariosis in an immunocompetent patient with concurrent severe SARS-CoV-2 infection that underwent mechanical ventilation, albeit without corticosteroid treatment (Poignon *et al*., 2020). As fusariosis shares common characteristics with aspergillosis, the occurrence of this infection in critically ill patients should be considered. Finally, few cases of *Pneumocystis jirovecii* infection were also identified in patients with COVID-19. Bhat *et al.* reported a case of infection in a severely immunocompromised 25-year old man, with underlying HIV infection and a low CD4 count (Bhat *et al*., 2020). Conversely, two cases of immunocompetent, non-HIV patients with concomitant pneumocystosis and COVID-19 were reported by Menon *et al.* and by Jeican *et al*. In both cases, HIV serology tested negative and HIV-RNA was not detected, but patients presented with a low CD4 T-cell count, in one case <200 cell/μL (Jeican *et al*., 2021; Menon *et al*., 2020).

CONCLUSION

Invasive fungal infections are not uncommon in patients with SARS-CoV-2 infection, due to the interplay of predisposing pre-existing conditions, healthcare-associated risk factors, and COVID-19 associated pathological mechanisms (*Figure 1*). Physicians should maintain a high degree of suspicion and strive for an early diagnosis, as the occurrence of invasive fungal infections in critically ill patients may have a serious impact on morbidity and mortality. Moreover, treatment of these infections could be challenging due to the high prevalence of comorbidities and the risk of toxicities and drug-drug interactions. While evidence is growing regarding the epidemiology, pathogenesis, and management of invasive fungal infections in COVID-19, there is a crucial need for prospective studies to better characterize this dire complication.

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