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COVID-19 AND FUNGAL INFECTIONS (RPL KODIYANPLAKKAL, SECTION EDITOR)

# Overview of COVID-19-Associated Invasive Fungal Infection

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## Abstract

**Purpose of Review** Invasive fungal infections are a complication of COVID-19 disease. This article reviews literature characterizing invasive fungal infections associated with COVID-19.

**Recent Findings** Multiple invasive fungal infections including aspergillosis, candidiasis, pneumocystosis, other non-*Aspergillus* molds, and endemic fungi have been reported in patients with COVID-19. Risk factors for COVID-19-associated fungal disease include underlying lung disease, diabetes, steroid or immunomodulator use, leukopenia, and malignancy. COVID-19-associated pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM) are the most common fungal infections described. However, there is variability in the reported incidences related to use of differing diagnostic algorithms.

**Summary** Fungal pathogens are important cause of infection in patients with COVID-19, and the diagnostic strategies continue to evolve. Mortality in these patients is increased, and providers should operate with a high index of suspicion. Further studies will be required to elucidate the associations and pathogenesis of these diseases and best management and prevention strategies.

**Keywords** COVID-19 · SARS-CoV-2 · Aspergillosis · Pneumocystis · Endemic fungi · Candidiasis

## Introduction

Since the emergence of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in early 2020, there have been more than 500 million recorded cases and over 6 million deaths worldwide [1]. An important complication of COVID-19 in severely ill patients is superinfection, often caused by bacteria, fungi, or other viruses [2•, 3•, 4•, 5••, 6••, 7•].

Invasive fungal infections (IFIs), especially invasive pulmonary aspergillosis (IPA), are recognized as causing disease following viral respiratory infections with influenza, referred to as influenza-associated pulmonary aspergillosis (IAPA) [8–11]. Similarly, there has been an emergence of reported fungal infections complicating COVID-19. The pathophysiology of secondary fungal infections in COVID-19 is poorly understood. Analogous to IAPA, SARS-CoV-2 infection is thought to release danger-associated molecular patterns (DAMPs) that set into motion the hyperinflammatory cascade and cytokine storm leading to ARDS. This disrupts the lung epithelial barrier along with concomitant immune dysregulation, compromised host defenses, and impaired muco-ciliary clearance that aids in fungal invasion and pathogenesis (Fig. 1) [12•, 13–15].

Several predisposing risk factors for COVID-10-associated IFI have been identified, including the viral infection itself, underlying chronic structural lung disease, immunosuppressive therapies such as corticosteroids and immunomodulators, leukopenia, malignancy, longer duration (> 14 days) on mechanical ventilation, prior antibiotic use, cardiovascular disease, liver disease, and uncontrolled diabetes [16••, 17, 18••, 19].

COVID-19-associated pulmonary aspergillosis (CAPA) was initially reported to have high incidence comparable to IAPA and was associated with poor outcomes and prolonged hospital stays. However, the true incidence, associated risk factors, best diagnostic, prevention, and treatment strategies of COVID-19-associated fungal infections continue to

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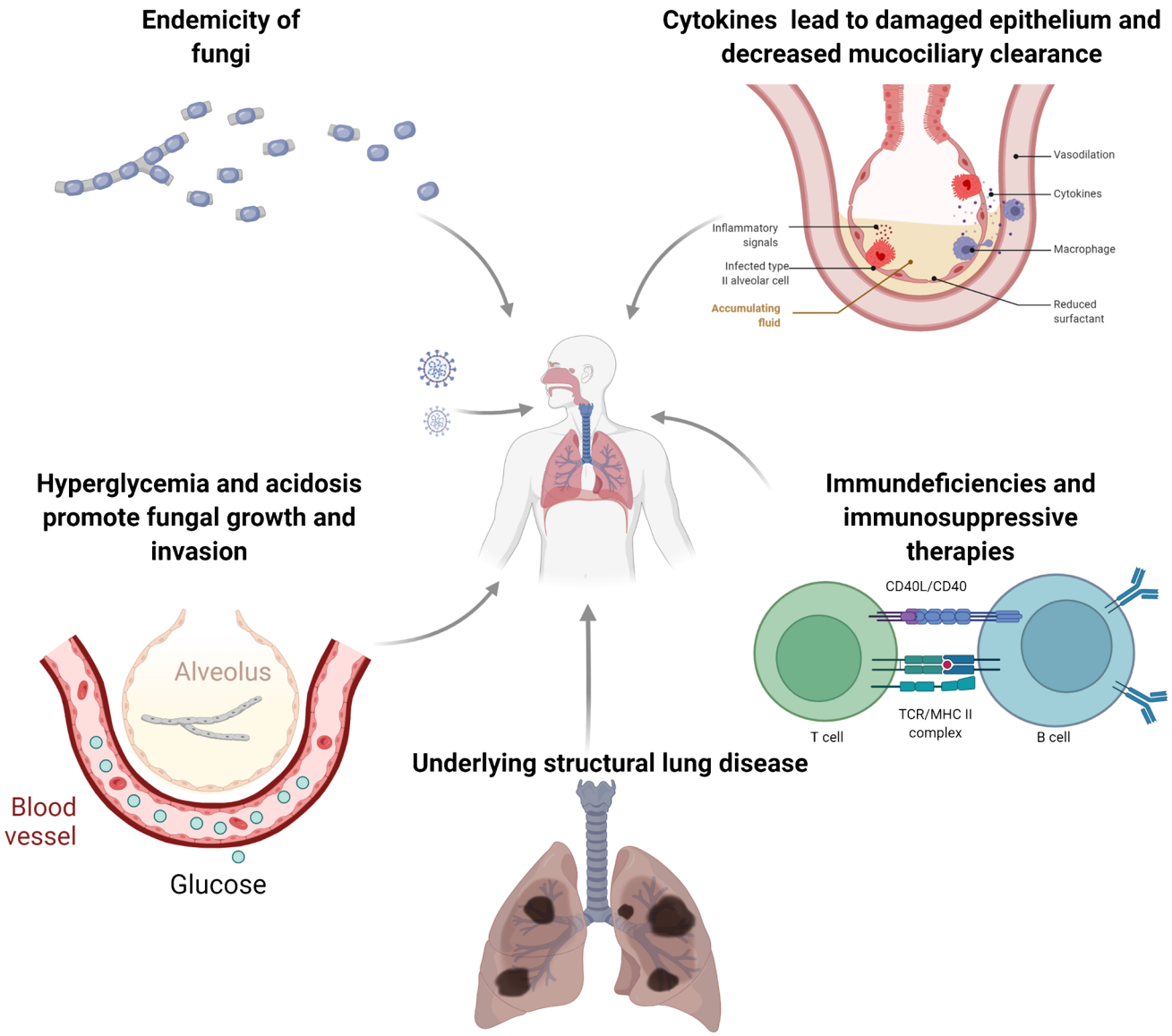


**Fig. 1** Proposed factors and mechanisms of invasive fungal disease in COVID-19 patients. Created with BioRender.com

evolve despite multiple observational studies and the recent consensus guidelines [20••]. Herein, we review current literature regarding incidence, diagnosis, and management of COVID-19-associated fungal infections (Table 1).

## CAPA

During the initial phase of the COVID-19 pandemic, several European centers reported an increased incidence of IPA, almost as high as IAPA rates ~ 20–30% [10, 11, 21–25]. However, subsequent studies have shown wide variability in CAPA incidence (2–33%), related in part to lack of consensus on case definition, poor understanding of diagnostic test performance, the clinical relevance of *Aspergillus* colonization of upper airways, limitations in obtaining lower respiratory samples/biopsies for proven disease, patient socioeconomic factors, and environmental burden of aspergillus spores [4•, 16••, 26, 27].

Neither the revised 2019 European Organization for Research and Treatment of Cancer and Mycosis Study Group Education and Research Consortium (EORTC/MSGERC) IPA guidelines [28] nor the AspICU algorithm formulated for IAPA[29] could appropriately classify cases given the absence of host factors and typical imaging findings for fungal pneumonia. This led the European Confederation for Medical Mycology and the International Society for Human and Animal Mycology (ECMM/ISHAM) to propose a new criteria for CAPA case definition, diagnosis and management. A new category of "possible CAPA" was proposed to include and manage COVID-19 patients with

**Table 1** COVID-19-associated fungal Infection

| Invasive fungal disease | Key points |
|---|---|
| COVID-19-associated pulmonary aspergillosis (CAPA) | • Disease pathogenesis not fully understood<br>• Knowledge gaps in true incidence, risk factors, and outcomes<br>• Wide variability in reported incidence due to lack of consensus on CAPA definition, differing diagnostic algorithms and surveillance practices<br>• Diagnoses are driven by isolation of *Aspergillus* species on culture or positive tests (Aspergillus galactomannan, Aspergillus PCR) from upper respiratory samples, which could reflect colonization<br>• Diagnostic tests currently used like serum and BAL Aspergillus galactomannan, Aspergillus PCR have not yet been validated in the COVID-19 population<br>• Most studies report an association of corticosteroids or IL-6 inhibitors with CAPA<br>• Role for prophylaxis or pre-emptive treatment needs to be further explored as it has been shown to reduce CAPA incidence rates but not overall mortality<br>• CAPA is associated with worse outcomes compared to non-CAPA patients |
| Mucormycosis | • Most commonly reported non-*Aspergillus* mold infection<br>• Uncontrolled diabetes and corticosteroid use appear associated with a higher risk<br>• Rhino-cerebral CAM is most common, but pulmonary CAM with the highest mortality<br>• Surgical intervention is an important part of management |
| Other non-*Aspergillus* molds | • Fusariosis reported in immunocompetent patients<br>• All cases involved lung parenchyma<br>• A single case of scedosporiosis reported in Chile<br>• Additional data are needed |
| Pneumocystosis | • More often in the elderly and immunocompromised (HIV, malignancy, chronic steroid use)<br>• Can be clinically indistinguishable from COVID-19 pneumonia<br>• Key features: elevated LDH, Beta-D Glucan, and lymphopenia |
| Candidiasis | • Suspected in patients who receive steroids, long ICU stays, indwelling central venous catheters<br>• Immunomodulators may increase risk |
| Cryptococcosis | • Patients older than 55 years of age with underlying comorbidities may be at risk<br>• High mortality |
| Endemic mycoses | • Limited data, but no clear association with COVID-19<br>• Endemicity is the greatest risk factor |

*Abbreviations*: *BAL* bronchoalveolar lavage, *CAM* COVID-19-associated mucormycosis, *CKD* chronic kidney disease, *IL-6* interleukin 6, *LDH* lactate dehydrogenase, *PCR* polymerase chain reaction, *ICU* intensive care unit

positive Aspergillus tests or culture on samples not yet validated in this patient population, such as upper respiratory samples (bronchial/tracheal aspirate) or non-directed Bronchioalveolar lavage fluid (NBL) [20••].

Fekkar and colleagues noted a significantly decreased probable/possible CAPA incidence of 6.1% after applying the 2021 ECMM/ISHAM consensus criteria to the cohorts cited by the expert panel in the same article [30•]. The results were closer to the incidence in proven autopsy studies early in the pandemic, as low as 0–3% [31, 32]. In contrast, another study from a single German ICU that evaluated autopsy findings after long-term treatment of COVID-19 patients found evidence of angioinvasive fungal infection in 7 out of 8 autopsies [33]. The variation in CAPA prevalence among different centers may be a result of the different diagnostic strategies that have been implemented.

The diagnosis of IPA remains challenging in the non-neutropenic and immunocompetent population. A number of diagnostic tests are currently being utilized for the diagnosis of CAPA, such as histopathology, fungal biomarkers (serum and BALF Aspergillus galactomannan, 1–3-Beta-D-glucan (BDG)) and Aspergillus polymerase chain reaction (PCR) [20••]. However, since test positivity is used to classify CAPA, the diagnostic accuracy of these tests can be overestimated. Additionally, these individual diagnostic test assays lack adequate sensitivity when used by themselves to make a diagnosis. Therefore, the recommendation is to use a more comprehensive screening algorithm that employs a combination of these tests to improve test characteristics like sensitivity to increase the likelihood of CAPA [16••, 20••].

A definitive diagnosis of CAPA requires invasive procedures such as bronchoscopy to show histopathological or direct microscopic evidence of *Aspergillus* species causing damage or invasion of the lung tissue. Bronchoscopy also aids in the visualization of plaques/eschars indicating Aspergillus tracheobronchitis [20••]. Early in the pandemic, the risk of aerosolization limited bronchoscopies at various centers. Tertiary care centers often made the diagnosis of probable/possible CAPA from suboptimal and unvalidated upper respiratory samples like bronchial or tracheal aspirates on routine surveillance [3•, 34, 35]. Use of NBL samples obtained via a closed-circuit suction

catheter reduces transmission risk of SARS-CoV-2; however, these samples are often not reflective of the lower respiratory tract microbiology and are yet to be validated for CAPA diagnosis [2•, 20••, 36, 37].

The clinical relevance of aspergillus PCR/culture from an upper respiratory sample has been questioned as it could reflect colonization [26, 31, 40–45]. While this should prompt a diagnostic workup in a patient with risk factors for CAPA, it may not always indicate invasive disease. Instead, it should be interpreted in conjunction with other mycological evidence, preferably from lower respiratory samples or serum. BALF galactomannan is highly indicative of IPA, particularly with high titers, but does not prove tissue invasion [15]. Invasive disease is more likely if circulating serum galactomannan is present. However, there are reports of proven IPA cases with negative serum galactomannan, supporting findings of the lower sensitivity of serum galactomannan in CAPA ~ 20%, compared to IAPA ~ 65% [2•, 44, 45]. Another recommendation has been to include serum BDG as part of the mycological evidence to increase the sensitivity of the serum *Aspergillus* galactomannan. Two consecutive positive tests were found to mount a specificity as high as 90% [41]. However, cautious interpretation in the appropriate clinical context after excluding an alternative etiology like candidemia is imperative due to non-specificity in IFI.

The non-specific radiological manifestations of SARS-CoV-2, with ground-glass opacities and nodular/cavitary lesions, are very similar to those seen in classic IPA. Moreover, findings of fungal pneumonia may be masked by the diffuse lung parenchymal damage caused by SARS-CoV-2. When these radiological manifestations are present, the ECMM/ISHAM panel recommends further investigation and workup for CAPA in a patient with high pretest probability, new fevers, or unclear cause of clinical deterioration [20••].

Several studies have investigated potentially modifiable risk factors that could help improve outcomes in patients with CAPA[2•, 17, 18••, 19]. Immunomodulatory agents are routinely administered in patients at risk of respiratory failure secondary to ARDS and cytokine storming. A significant association was established between dexamethasone and CAPA in multiple studies [2•, 3•, 17, 49, 50], while others failed to find an obvious correlation [51•, 52]. Although corticosteroids are known to suppress the body's natural immunity to fight invasive fungal infections, they might also simultaneously have a protective effect by decreasing the lung parenchymal damage (an independent IPA risk factor) caused by the hyperinflammatory syndrome [51•]. Corticosteroids have become the standard of care in severe COVID-19, given clear mortality benefits, making it difficult to compare to a control group that could have biased the analysis in a few of the studies mentioned above [46].

Additionally, tocilizumab has also been identified as a risk factor for CAPA [4•, 54–57]. One study reported a higher incidence of fungal infections, particularly when multiple doses were administered. CAPA was diagnosed in 2.5% of patients who did not receive tocilizumab, 20% in patients who received a single dose, and 50% in those who received two doses ($p < 0.01$) [51•]. Other cohorts, however found no increased risk of CAPA in tocilizumab versus non-tocilizumab groups [18••, 52, 53].

Compared to critically ill COVID-19 patients admitted to the ICU without invasive aspergillosis, patients with CAPA have been reported to have higher mortality (30–40% vs 50%), longer duration on mechanical ventilation, and hospital stay [2•, 3•, 4•, 5••, 6••, 7•, 12•, 17, 18••]. Most studies, however, did not see a decreased mortality with use of antifungal therapy [3•]. Of note, patients with possible CAPA in a few observational studies survived despite not receiving antifungal agents, raising the possibility of misclassification of infection, perhaps colonization or less invasive disease, and better outcomes in patients who are immunocompetent [54, 55].

Antifungal prophylaxis or pre-emptive treatment strategies have been suggested as management options in high-risk COVID-19 patients [2•]. Hatzl et al. observed a decrease in CAPA incidence without reducing overall mortality in patients who were on antifungal prophylaxis [61•]. In another study, mechanically ventilated COVID-19 patients who were started on prophylaxis with inhaled amphotericin because of a CAPA outbreak were noted to have reduced CAPA incidence rates [57]. A study of isavuconzole as fungal prophylaxis in COVID-19 patients is currently underway and will hopefully give much needed efficacy information [58].

As per current EORTC/MSGERC guidelines, a triazole antifungal has remained the mainstay therapeutic in the management of invasive aspergillosis [28]. The ECMM/ISHAM panel similarly recommends treatment of CAPA with voriconazole or isavuconazole as first-line treatment. Clinicians should keep in mind the local epidemiology of azole resistant *Aspergillus* species. Limitations of voriconazole include its narrow therapeutic window, drug-drug interactions, and the need for close therapeutic drug monitoring (TDM). COVID-19 patients with acute renal failure are often unable to receive liposomal amphotericin given its nephrotoxicity [20••].

## Non-*Aspergillus* Mold Infections

While *Aspergillus* is the most well-established fungal infection associated with COVID-19, many less common fungal infections have since been reported. In contrast to aspergillosis, mucormycosis is historically rare following viral

infection [59]. However, COVID-19-associated mucormycosis (CAM) is now the most widely reported non-*Aspergillus* mold infection [64•, 65••, 66, 67]. Most early cases were reported from India, although cases have since been reported from the Middle East, Australia, Asia, Europe, South America, and the USA [64•, 65••, 67, 68]. There has been much speculation regarding the clustering of cases in India. Though still unclear, the outbreak is suspected to be due to India's large diabetic population, environmental factors including the tropical and sub-tropical humid climates with the presence of *Mucorales* spores, and practice variations in use of corticosteroids [65••].

Uncontrolled diabetes and hyperglycemia appear to be key underlying risk factors for CAM. Analyses of CAM cases found that 83–94% of cases had diabetes, of which 67–83% were poorly controlled [68, 69•]. Acidemic states such as diabetic ketoacidosis (DKA) increase unbound iron supporting *Mucorales* growth [65••]. Hyperglycemia from diabetes and steroids also supports mold growth (Fig. 1) [69•]. Additionally, the by-products of DKA (B-hydroxybutyrate, glucose, and iron) increase both cell expression of GRP78, the receptor by which *Rhizopus* enters epithelial cells, and CotH, the fungal protein which binds GRP78 [65••]. Other risk factors for CAM include hematologic malignancy, organ and hematopoietic stem cell transplant, end-stage renal disease, and trauma [65••, 68].

CAM generally presents with fever and symptoms of rhino-orbital or rhino-orbital-cerebral mucormycosis (orbital swelling, nasal symptoms, discoloration, and necrosis) within 2 weeks of diagnosis of COVID-19 [64•, 65••, 67, 68]. Most cases of CAM are rhino-cerebral though lung; musculoskeletal, gastrointestinal, and disseminated cases have also been reported [65••, 68].

Diagnosis of CAM is challenging and requires a high index of suspicion. Nearly all cases of CAM are confirmed via biopsy with histopathology or RT-PCR [61•]. Additionally, up to 30% of cases have been reported to also have CAPA [62].

Treatment of CAM does not differ from previously established guidelines for mucormycosis [64•]. CAM patients require systemic antifungal treatment — most commonly amphotericin — and 78% require surgical debridement [61•, 62]. Mortality ranges from 37 to 80% with pulmonary CAM portending a worse prognosis than rhino-orbital [59, 61•, 62].

Several cases of COVID-19-associated fusariosis have been reported [65••, 66, 67]. Given the small number of case reports, broad conclusions cannot be drawn about the risk factors and presentation. However, in the cases reviewed, no patients had significant immunocompromising conditions other than COVID-19, and all involved lung parenchyma [65••, 66, 67]. All patients were diagnosed by cultures of either blood or sputum and were treated with systemic antifungal therapy; one patient died [65••, 66, 67]. One suspected case was never critically ill and treated on an outpatient basis [66].

COVID-associated *Scedosporium* or *Lomentaspora* infections appear rare. In a series of 16 cases of invasive mold infection among COVID-19 patients in Chile, only one had infection with *Scedosporium* [68]. The dearth of reports may stem from limitations in diagnostics [69•]. Nonetheless, *Scedosporium* or *Lomentaspora* are important opportunistic pathogens in immunocompromised patients and should be considered in such patients with COVID-19 [69•].

## Pneumocystosis

Several cases of COVID-19-associated *Pneumocystis jirovecii* have been reported [76, 77•]. Generally, cases have been in older patients (mean age 78) and have an underlying immunocompromising condition such as HIV, malignancy, or chronic steroid use [76, 77•]. The presentation of severe COVID-19 can be clinically indistinguishable from *Pneumocystis* pneumonia (PCP), as patients present with bilateral ground-glass opacities and lymphopenia [76, 77•]. All reported cases of PJP coinfection had increased lactate dehydrogenase levels and beta-D-glucan [76, 77•]. Lymphopenia is reportedly severe with absolute lymphocyte counts below 900 cells/mm and $CD4^+$ T-cell counts below 200 cells/mm [77•]. Patients are generally diagnosed via PCR of respiratory specimens from 2 to 21 days after initial COVID-19 presentation [77•]. A prospective study that tested all severe COVID-19 patients admitted to a single unit over 1 month found that 17% had positive respiratory samples for *Pneumocystis* [72]. However, given the clinical similarities between severe COVID-19 and PCP, it is speculated that contamination or colonization rather than true infection may contribute to this high prevalence [77•, 78, 79].

Treatment of PJP in COVID-19 is with use of use of the standard regimen of trimethoprim-sulfamethoxazole and steroids, with reported mortality ranging from 42 to 100% [76, 77•]. The use of prophylactic trimethoprim-sulfamethoxazole in patients with COVID-19 who have a positive *Pneumocystis* assay and unclear PJP diagnosis remains controversial [72, 73].

## Candidiasis

Comparative reports suggested a higher incidence of IC among COVID-19 patients vs non-COVID-19 patients, occurring earlier in hospitalization and associated with higher mortality rates [74–76]. No distinctive risk factors for COVID-19-associated IC have been identified, though generally, these patients appear more likely to have received

steroids, have longer ICU stays, and have longer central venous catheter dwell times [77•]. Additionally, steroid use, sepsis, and age over 65 were identified as independent risk factors for mortality in COVID-19 associated candidemia [75]. A COVID-19 predisposition to candidemia due to immune paralysis, intestinal translocation, and altered microbiota may also contribute [81•].

Early reports implicated immunomodulators such as tocilizumab as a risk factor for IC, particularly in the critically ill and those receiving renal replacement therapy [78, 79]. A recent meta-analysis examining IL-6 pathway inhibitors found that while sarilumab and anakinra did not affect the risk of secondary infections, tocilizumab specifically increased the risk of fungal infections [87••]. Additionally, baricitinib does not appear to be associated with increased risk fungal infections since being incorporated into the management of COVID-19 [81•].

COVID-19 patients particularly the elderly, critically ill, and those receiving immunomodulating therapy appear likely to be at increased risk for IC. Providers should maintain a high index of suspicion in such patients and obtain blood and site-specific cultures and start appropriate antifungal therapy per available guidelines [82].

## Cryptococcosis

Cryptococcosis is historically seen in patients with AIDS, malignancy, transplants, and other sources of immunosuppression. To date, several cases of COVID-19-associated cryptococcosis have been reported [83•, 84–86, 87••, 88–91]. Of the cases reported, all patients older than 55 years of age and had an underlying comorbidity (diabetes, hypertension, CKD). Only one had a history of organ transplant, and none had HIV [90]. All but one of the cases were male [83•]. Cryptococcosis was diagnosed from culture growth in blood, CSF, or bronchoalveolar lavage, and treated with amphotericin and flucytosine. All cases died, except one who remained in a vegetative state six weeks after appropriate therapy was initiated [84]. Traver et al. also reported a case of CAPA and cryptococcal coinfection [85]. Given the low number of reports, it is unclear if COVID-19 creates any specific predisposition to cryptococcal infection. However, clinicians should retain a high index of suspicion for cryptococcosis in patients with severe COVID-19 who have suspected meningitis.

## Endemic Fungi

There have been limited reports of COVID-19-associated infection with endemic fungi.

Several cases of histoplasmosis in COVID-19 patients have been reported [92–97]. However, three of these cases were diagnosed with COVID-19 after already being treated for histoplasmosis [92, 94, 95]. In one of these cases, the patient was on immunosuppressants [92] for a renal transplant, while two other had AIDS [94, 95]. Additionally, one case developed pulmonary histoplasmosis 4 months after recovering from COVID-19 [96]. These cases responded well to standard therapy of amphotericin and/or itraconazole. More information is needed to better understand the association of COVID-19 and histoplasmosis.

Like histoplasmosis, several cases of COVID-19 and coccidioidomycosis have been reported [98–104]. While one case was reportedly mild and did not require hospitalization, another case experienced rapid disease dissemination shortly after infection with SARS-CoV-2 [99, 100]. Additionally, one report describes a case of possible reactivation *Coccidiodes* from COVID-19 [98]. Other than geography, risk factors for coinfection appear to be older age, diabetes, immunosuppression, and minority status [101].

To date, only one case of COVID-19-associated blastomycosis has been reported in a 24-year-old pregnant woman with severe COVID-19, although additional cases have been noted anecdotally [105].

Overall, the association of endemic mycoses with COVID-19 needs is unclear; however, endemic mycoses should remain as a differential diagnosis in patients with severe COVID-19 who have symptoms consistent with endemic mycoses and appropriate geographic exposures. Management guidelines are available for these infections, and they are typically treated with triazole antifungals or amphotericin [106–108]

## Conclusion

Given the extensive pulmonary tissue damage and the immunosuppression related to SARS-CoV-2 infection and its management, fungal pathogens are important to consider in the assessment of suspected superinfection in COVID-19 patients. Aspergillosis, candidiasis, non-aspergillus mold infections, endemic fungi, and PJP have all been reported, and data will continue to emerge. Steroids and other immunomodulatory therapies appear to increase the risk for invasive fungal disease, as do pre-existing comorbidities such as diabetes, chronic kidney disease, and baseline immunosuppression. In many cases, the appropriate use of diagnostic studies and clinically similar syndromes has made diagnosis difficult, leading to a wide range of disease incidence or prevalence. Therefore, a high index of suspicion combined with selective diagnostics from a differential honed by clinical presentation and exposure history is necessary to best assess these patients. Further studies with larger cohorts will

be required to elucidate the true associations and pathogenesis of these diseases and best management and prevention strategies.

## Declarations

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Conflict of Interest** AAS: No conflicts.
MM: No conflicts.
JWB: has received consulting fees from Pfizer and Lilly for serving on data safety committees.

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