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Review Article

COVID-19 associated mold infections: Review of COVID-19 associated pulmonary aspergillosis and mucormycosis

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Abbreviations: ACE2, Angiotensin-converting enzyme 2; BALF, Bronchoalveolar lavage fluid; CAM, COVID-19 associated mucormycosis; CAPA, COVID-19 associated pulmonary aspergillosis; GM, Galactomannan; non-BALF, Fluid obtained from lower respiratory tract by non-BAL procedure; non-CAPA, Patients with SARS-CoV-2 virus infection who did not develop CAPA.

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Abstract COVID-19-associated mold infection (CAMI) is defined as development of mold infections in COVID-19 patients. Co-pathogenesis of viral and fungal infections include the disruption of tissue barrier following SARS CoV-2 infection with the damage in the alveolar space, respiratory epithelium and endothelium injury and overwhelming inflammation and immune dysregulation during severe COVID-19. Other predisposing risk factors permissive to fungal infections during COVID-19 include the administration of immune modulators such as corticosteroids and IL-6 antagonist. COVID-19-associated pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM) is increasingly reported during the COVID-19 pandemic. CAPA usually developed within the first month of COVID infection, and CAM frequently arose 10–15 days post diagnosis of COVID-19. Diagnosis is challenging and often indistinguishable during the cytokine storm in COVID-19, and several diagnostic criteria have been proposed. Development of CAPA and CAM is associated with a high mortality despite appropriate anti-mold therapy. Both isavuconazole and amphotericin B can be used for treatment of CAPA and CAM; voriconazole is the primary agent for CAPA and posaconazole is an alternative for CAM. Aggressive surgery is recommended for CAM to improve patient survival. A high index of suspicion and timely and appropriate treatment is crucial to improve patient outcome.

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Introduction

Invasive mold infections (IMI) associated with COVID-19 are emerging as severe complications with high mortality. Diagnosis and treatment of IMIs due to two common filamentous fungi, *Aspergillus* and *Mucorales*, respectively, are challenging. Typically, IMI develops in immunosuppressed patients, such as hematopoietic stem cell or organ transplant recipients, those who have prolonged agranulocytosis, in patients with severe lymphopenia during acute illness such as influenza associated respiratory distress, or in those with severe sepsis requiring intensive care unit (ICU) support.

COVID-19 is characterized by a profound inflammation initiated by damaged alveolar cells, and injury to respiratory epithelium and vascular endothelium, in which monocytes and neutrophils play a key role.^{1,2} In severe COVID-19 disease, delayed or poor induction of interferon (IFN) response or the presence of auto-IFN antibodies was associated with increased viral replication and induction of hyperinflammation.² Immunosuppressive therapy with corticosteroids or anti-interleukin-6 (IL-6) blockers can help to control the inflammation in COVID-19,^{3,4} but predisposes patients to fungal superinfection.^{5,6} The pathogenesis of

fungal super-infection in COVID-19 is facilitated by the loss of alveolar epithelium barrier and dysregulated innate and cellular immunity.⁷ Distinguishing COVID-19-associated pulmonary aspergillosis (CAPA) or COVID-19-associated mucormycosis (CAM) from a concurrent proinflammatory cytokine storm in COVID-19 is difficult. Timely identification and treatment of CAPA or CAM is important for improving patient outcome, especially in areas with a high prevalence of aspergillosis and mucormycosis.

To date, several diagnostic criteria for CAPA and CAM have been proposed by several groups.^{8–11} However, there is a lack of consensus on which criteria is more appropriate or applicable. In addition, in the setting of COVID-19, invasive diagnostic procedures are limited due to concerns with transmission of SARS-CoV-2. Herein, we reviewed studies of CAPA and CAM in COVID-19 patients regarding the epidemiological data, diagnostic laboratory indicators, clinical characteristics, risk factors, prognostic factors and treatment strategy from the published articles in PUBMED, MEDLINE, and Google Scholar databases during the period of January 2020 to March 2022. We also introduce the pathogenesis and role of SARS-CoV-2 in CAMI by a brief review.

Covid-19 associated pulmonary aspergillosis (CAPA)

Pathogenesis

A brief summary of the pathogenesis of CAPA is shown in Fig. 1. The first impact of COVID-19 virus is interruption of the respiratory ciliary¹² and epithelium system.¹ The damaged pneumocytes and disrupted lung epithelial barrier attract neutrophils and monocytes released extracellular trap, resulting in disjunction between endothelial cells.² SARS-CoV-2 infection also leads to endothelial cells activation, swelling, and destruction, then thrombus formation in endovascular systems.¹³ After SARS-CoV-2 infection, the disrupted lung epithelial barrier creates an environment conducive for fungus hyphae invasion into lung parenchyma.¹⁴ The link between the two pathogens is the sharing surface markers that recognize both the virus and *Aspergillus*. SARS-CoV-2 infection can activate Toll-like receptor 4 (TLR4) expression that further induces ACE2 expression.¹⁵ The *Aspergillus* molecules such as galactosaminogalactan (GAG), melanin, galactomannan (GM), and chitins¹⁶ have an affinity to bind or modify the function of lung epithelial cells, macrophages, T and B cells, C-C chemokine receptor

type 2 presenting (CCR2+) monocytes, and endothelial cells¹⁷ through pattern recognition receptors (PRRs) such as macrophage inducible Ca-dependent lectin receptor (Mincle), dectin-1, dectin-2, NOD-like receptors (NLRs), TLR2 and TLR4.¹⁸ The galactomannan and beta-glucan of *Aspergillus* further diminish the TLR4-mediated immunity, such as phagocytosis.¹⁹ *Aspergillus* is also known as a pathogen capable of both endothelium invasion and angiogenesis.^{20,21} Proteomic study suggests that proteins expressed by *Aspergillus*-infected endothelial model are involved in apoptosis and affects adaptive and innate immunity.²¹ In patients complicated with CAPA, the ACE2, hypoxia-inducible factor 1 α (HIF-1 α), cytokines including interleukin 1-beta (IL-1 β), tumor necrosis factor- α (TNF- α) were also significantly more expressed compared to those in non-CAPA patients.^{14,19} As a result, a vicious cycle between COVID-19 and *Aspergillus* increased the risk of mutual infection and aggravates the severity of disease.

The immunomodulatory effect of the SARS-CoV-2 associated with fungal infection was by both innate and adaptive immunity. Once entering the host cells, the virus can modulate the expression of type I and III interferon,²² decrease production of IFN- γ ,^{23,24} and affect the activation of antigen presenting cells who presented with PRRs,

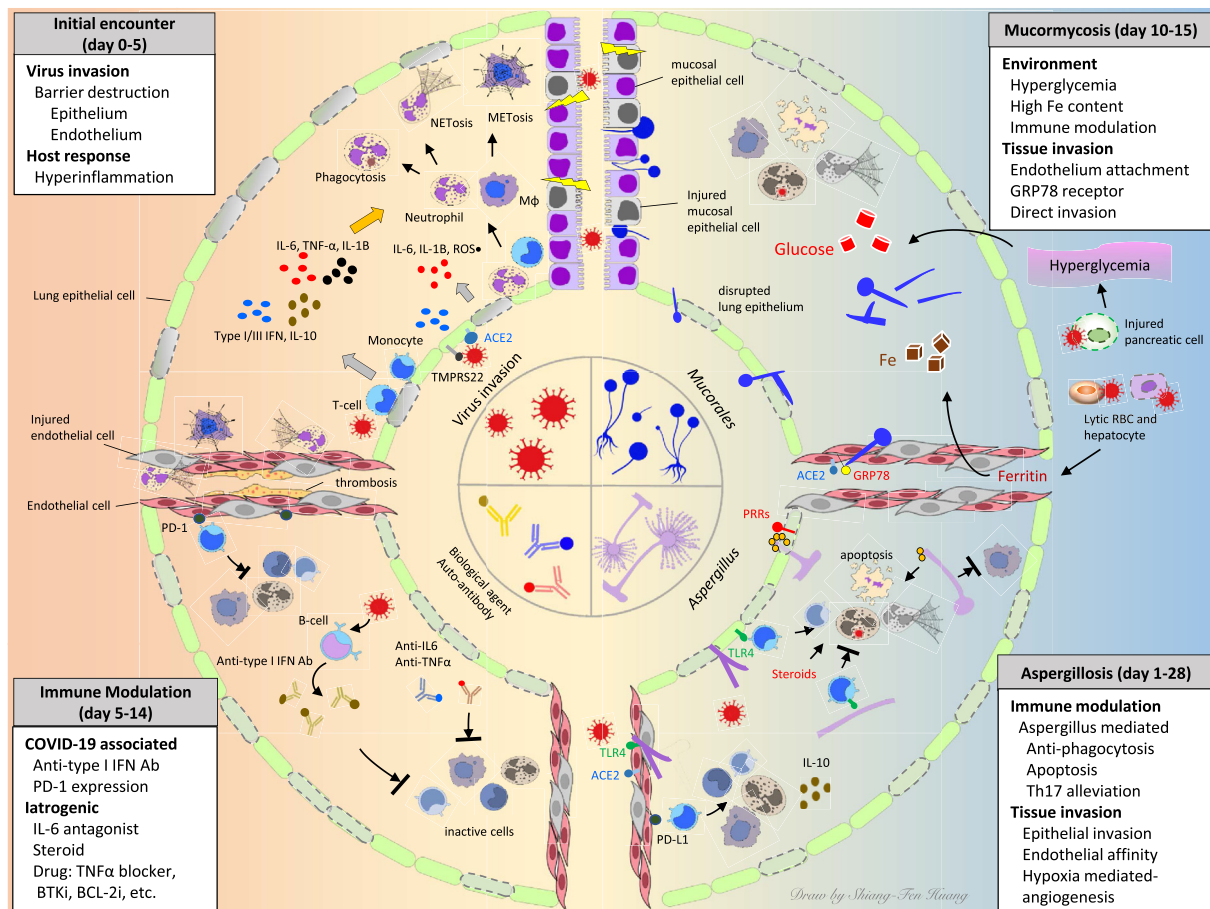


Figure 1. Pathogenesis of CAPA and CAM **Abbreviations:** ACE2: Angiotensin-converting enzyme 2, BCL-2i: B-Cell Lymphoma 2 inhibitors, BTKi: Bruton's Tyrosine Kinase inhibitors, GRP78: glucose-regulated protein 78, IFN: interferon, IL: interleukin, NETosis: macrophage extracellular trap generation, M ϕ : macrophage, NETosis: neutrophil extracellular trap generation, PD-1: program cell death protein 1; PD-L1: program cell death protein-ligand 1, TMPRSS22: transmembrane protease serine 22, ROS: reactive oxygen species, TLR4: Toll-like receptor 4, Th17: T-helper 17 cell immune cascade, TNF α : tumor necrosis factor α .

such as TLR4, TLR7, and TLR8²⁵. The SARS-CoV-2 resulted in increased NADPH cascades and ROS oxidative stress system^{26,27} related to overwhelmed inflammatory reaction. However, SARS-CoV-2 infection led to decreased protective cellular immunity through increased expression of programmed cell death protein 1 (PD-1) expression^{28–30} and IL-1B cascades.²⁵ The *Aspergillus* fungal wall alpha-(1,3)-Glucan also increases expression of ligand of PD-1 (PD-L1) on human endothelial cells.³¹ The use of PD-L1 blockade could improve anti-SARS-CoV immune abnormalities,³⁰ and showed beneficial effect when co-administered with anti-fungal agent in an invasive pulmonary aspergillosis model.³² Meanwhile, the B cells may produce neutralizing auto-antibody against type I IFN (IFN- α 2, IFN- ω , IFN- β)³³ especially in patients aged >70 and with higher mortality. Interestingly, the type I IFN (IFN- β)-mediated dendritic cell can stimulate protective T-cells with anti-*Aspergillus* ability³⁴; that type I IFN may be considered an adjuvant therapy for severe COVID-19 in the future.³⁵

Before the era of COVID-19, increased *Aspergillus* infections has been observed during treatment with target therapy, such as Bruton's Tyrosine Kinase inhibitors (BTKi),^{36,37} B-Cell Lymphoma 2 (BCL-2) inhibitors,^{38,39} medication those used for hematological malignancy,⁴⁰ and immune modulators for rheumatoid arthritis (RA).^{41,42} The Tocilizumab aimed to suppress inflammatory response in RA, sepsis, and COVID-19 by inhibiting overwhelmed inflammation activities,⁴³ phagocytosis,⁴⁴ restore endothelial dysfunction and abridged neutrophil extracellular trap (NET) generation,⁴⁵ which were essential for anti-*Aspergillus* infection.^{46,47} Theoretically, tocilizumab may increase the incidence of *Aspergillus* infection;^{42,48} however, large scale epidemiological report for increased aspergillosis in patients with RA who received Tocilizumab therapy was lacking. Methylprednisolone resulted in broad-spectrum effect on cellular and adaptive immunity, such as increasing ROS system with tissue destruction in IA.⁴⁹ Steroids also inhibit phagocytosis by increasing apoptosis of neutrophil,⁵⁰ alleviate CD4⁺, Th1⁺, Th17⁺ lineage T cells immunities, which are essential against *Aspergillus* infection.⁵¹ Beeke Tappe et al. demonstrated the recent corticosteroid exposure might predispose common COVID-19 and *Aspergillus* co-infection through diminished cellular immunity and exhausted T cells.⁵²

Epidemiology

The incidence of CAPA varied by countries, and most studies reported an observation period for 1 month to 6 months during the year 2020. In a meta-analysis including 28 studies with 3184 COVID-19 patients admitted to the ICU,⁵³ the cumulative incidence for CAPA was 12.3% (294/3184), and were the highest in central Europe and Asia countries (21–31.4%), followed by UK, Spain, south Europe,⁵⁴ and north American countries (<10%). Jon Salmanton-García et al. reported the incidence of CAPA in ICU patients to be 6.8% (131/1902) in 19 facilities across Europe, Mexico, Pakistan, Argentina, and the United Kingdom. Patients included those with suspected IA by literature review (160 patients) and reported in the FungiScope registry databases (129 patients), from March–August 2020.⁵⁵ The incidence of CAPA in those with ICU admission was 0.1% (2/163) in South America and 20% (3/15) in Ireland. Notably, seven cases of CAPA registered in

FungiScope databases were from South America, mid Asia, and Australia.⁵⁵

Risk factors for developing CAPA

Older age is the most common host factor for developing CAPA.^{56–58} In a multicenter study, requirement for respiratory support, anti-IL-6 monoclonal antibody (Tocilizumab),^{56,57} initial disease severity and respiratory distress were risk factors for developing CAPA.^{56–58}

In the subgroup analysis among patients with ICU stay, host factors for CAPA included underlying COPD, bronchiectasis, HIV infection, liver cirrhosis, cardiovascular disease, active malignancy status, older age, and solid organ transplant recipient^{57,58}. Iatrogenic risk factors included use of T or B cell immunosuppressants, dexamethasone plus anti-IL-6 therapy,⁵⁹ long-term corticosteroids⁶⁰ and renal replacement therapy (RRT) during ICU stay.⁵⁷

Clinical characteristics

The onset of CAPA ranged from the first day to the 28th day after ICU admission, with a mean of 7.3 days.^{53,61} Patients with CAPA had higher SOFA scores, shorter duration from illness to ICU admission (mean 11 $\pm$ 2.5 days),⁶⁰ a higher probability for ventilation support requirement, ECMO support,⁵⁶ and renal replacement therapy.^{57,60} Overall, patients with CAPA had a higher mortality than those without CAPA.^{56,57,62,63} The utility of laboratory biomarkers (such as C-reactive protein, ferritin, ESR, or creatinine) in the diagnosis of CAPA have not been evaluated. Current literature suggests that every patient with respiratory distress and without treatment response or deterioration are potentially at risk for CAPA.¹¹

Mycological evidence of *Aspergillus* spp.

Culture

The culture positivity rate of *Aspergillus* species in respiratory specimens varied widely across different studies and populations. The lowest rate was 42% in bronchoalveolar lavage fluid (BALF) or innon-BALF in a multicenter study,⁵⁷ and a higher positive rate of 90% was found in cases with a previous history of airway diseases⁶⁴ (Table 1). In a review of 28 published studies with 134 CAPA cases reported during Jan to Oct, 2020⁶³, 101 cases had cultures positive for *Aspergillus*. The most frequently identified species were *Aspergillus fumigatus* (86%), followed by *Aspergillus flavus* (5.9%), *Aspergillus niger* (4.9%), and other (3.9%). Less than 5% of patients with CAPA were confirmed by histology. Another review article summarized 85 patients with CAPA reported from Jan to April, 2020; 66% of them were culture positive with *A. fumigatus*, followed by *A. flavus* (9%), and 21% were un-identified *Aspergillus*.⁶⁵ There is a regional variation in the most commonly identified *Aspergillus* species.⁵⁸ In European countries, *A. fumigatus* was the most frequently isolated species. In Pakistan, a higher proportion of cultures isolated was *A. flavus* (60%). *A. flavus* accounted for 10–16% of identified species in Belgium, Netherlands, and 0–10% in other European countries such as in France, Germany, and Austria.⁶⁶ Non-*fumigatus* and non-*flavus*

Table 1 The positive rates of mycological examinations in the cases with and without COVID-19-associated pulmonary aspergillosis after SARS-CoV-2 infection.^{57,63,64,67,82}

Examination	Positive rate (%)	
	CAPA ^a	non-CAPA
Histopathology ^b	4.1	0
Growth of <i>Aspergillus</i> spp. ^c	42–90	0–67
Serum		
BDG (>80)	40.9–58	0
Galactomannan index (>0.5) ^d	11–33	0–19
PCR	30.7–56	0–15.8
Respiratory samples ^e		
Galactomannan index (>1.0)	38–100	53.3
PCR	66.6	42
BALF		
Galactomannan index (>1.0)	46–100	50–68
PCR	17–89	2–83
Other respiratory sample ^f		
BDG (+)	42	66
Galactomannan index (>1.0)	92.5	66
PCR	15–100	—

^a CAPA included proven, probable, possible, and putative CAPA according to different diagnostic algorithm.

^b Proven pulmonary aspergillosis with presence of filaments hyphae in lung tissue through bronchoscopy, concurrent with positive Galactomannan index or culture positive for *Aspergillus* spp. in BALF or bronchial aspiration.

^d With significant difference in the mortality rate, if serum galactomannan index is > 0.5 in the cases of CAPA.⁶³

^c Please see reference^{57,64,67,82} and the description in section Mycological evidence of *Aspergillus* spp..

^e Respiratory samples by any type of specimens, including BALF, non-BALF, trachea aspiration, and others.

^f Respiratory samples collected by method other than BAL, including tracheal aspiration and lower respiratory tract fluid by non-BAL procedure.

Abbreviations: BDG: Beta-D-glucan, BALF: bronchioalveolar lavage fluid; CAPA: Covid-19-associated pulmonary aspergillosis; PCR: polymerase chain reaction for *Aspergillus*. non-CAPA: Patients with SARS-CoV-2 virus infection who did not develop CAPA.

Aspergillus were frequently found in America and Spain, such as *Aspergillus citrinoterreus*, *Aspergillus lentulus*, and *Aspergillus nidulans*, which had been reported with >10% frequency in isolated *Aspergillus* in Spain.⁶⁷

The rate of azole resistance by detecting mutations in the TR34/L98H gene *cyp51A* in *A. fumigatus* was 3.4% (3/87) in a systemic review.⁶³ Another longitudinal survey of 27 *Aspergillus* strains from CAPA in a German ICU reference center reported 3.7% azole resistance with a TR34/L98H mutation.⁶⁸ Recently, a single center study of 329 ICU patients during March–April, 2020 in Austria,⁶⁹ found that all 22 *A. fumigatus* colonies from respiratory samples of CAPA patients were susceptible to caspofungin (CAS), isavuconazole (ISZ), voriconazole (VOR), posaconazole (POS), micafungin (MIC), and amphotericin B (AmphB) by E-test.

The source of *Aspergillus* has not been comprehensively investigated; however, a comparison of 35 *Aspergillus* isolates by genotyping for *cyp51A* gene from respiratory samples of CAPA patients and 8 strains from ICU environment found no

correlation. This suggested that CAPA was unlikely to be hospital acquired but rather may be due to pre-colonization in the host or may be community-acquired infection.⁷⁰

Current consensus for diagnosis of CAPA includes a positive culture for *Aspergillus* species, with compatible radiological imaging and clinical manifestations. Histological findings are not mandatory for diagnosis, considering the possible transmission risks of SARS-CoV-2 when performing invasive diagnostic procedures. Nearly 60–90% of patients with CAPA reported in the literature had a positive culture of *Aspergillus* from their respiratory tract specimens.^{63,64} Despite a low rate of antifungal resistance (<5%), treatment response was poor, and mortality remained high. In a small case series, a high mortality of 50%–71% was reported, even though appropriate antifungal therapy with documented susceptibility was administered.⁶⁹ A case report of an HIV-infected patient with CAPA due to infection with a multi-drug resistance *A. spp.* died despite use of combination anti-fungal regimen.⁷¹ In a meta-analysis enrolling 134 cases of CAPA,⁶³ none of the mycological factors were associated with mortality.

Biomarkers

Beta-D-glucan (BDG) is a biomarker for pan-fungal infection used for early diagnosis of invasive fungal disease (IFD). Although it is not specific for *Aspergillus* infection, several meta-analyses and reviews showed a higher positivity rate of BDG than serum galactomannan (GM) antigen in CAPA patients.⁶³

GM antigen test is used to detect invasive aspergillosis; however, it has cross reactivity with other fungal infections, such as *Penicillium* and *Fusarium* spp.⁷² GM index (>0.5) in serum may represent invasive aspergillosis and is associated with a higher mortality in CAPA.⁶³ GM index (>1.0) in BALF^{73–75} or non-BAL aspiration¹¹ were considered a biomarker for diagnosis of invasive pulmonary aspergillosis (IPA). The level of GM index in BALF decreases in response to voriconazole - based therapy in CAPA.⁷⁶

Rapid molecular detection methods using PCR to target internal transcribed spacer region (ITS1), 28S rRNA, and 18S rRNA genes⁷⁷ had been used for detection of *Aspergillus*⁷⁸ and diagnosis of IA.⁷⁹ AsperGenius® can identify *cyp51A* gene of *A. fumigatus* with TR34/L98H and TR46/Y121F/T289A⁸⁰ mutations; MycoGENIE® can detect TR34/L98H,⁸¹ and FungiPlex® can detect TR34/TR46⁸¹ mutation for azole resistance. Other commercial kits have additional benefits in identification of non-*fumigatus* *Aspergillus* species; for example, *Aspergillus* spp. ELITE MGB® Kit uses a quantitative qPCR method for 18S rRNA and had been used for diagnosis of CAPA.⁵⁴ Although an added benefit in PCR detection of *Aspergillus* directly from serum and BALF was described,⁶⁸ a comparison evaluating the accuracy of different kits to detect CAPA has not been published. There is currently no consensus on which commercial method is better for detection of CAPA or for non-COVID-associated invasive aspergillosis.

Currently, multi-model detection of CAPA by fungus culture, biomarkers in respiratory samples (PCR, GM, or BDG), and in serum (PCR, GM or BDG) is suggested to improve diagnostic sensitivity. A higher mortality has been associated with the number of positive mycological criteria in patients with CAPA. In patients with CAPA fulfilling four mycological criteria, a lower survival was found compared

to those with less than two mycological criteria.⁶⁴ Significant predictors of mortality in CAPA include positive biomarkers in blood, such as PCR (odds ratio (OR): 11.67, 95% confidence interval (CI): 3.06–55.5) or GM index (OR: 5.79, 95% CI: 1.98–16.9)⁶³, and a concordant positive culture and biomarker-based mycological evidence.⁶⁹ Giacobbe et al. compared different methods and found that a positive GM index concurrent with a positive culture of *Aspergillus* in BALF was a prognostic factor for 90-day mortality in CAPA.^{76,82}

Among various mycological examinations, the highest proportion with positive findings for CAPA was the fungus culture, followed by BDG, GM index in BALF and then in serum (Table 1). PCR methods provided an accurate and rapid identification for specific *Aspergillus*, and were included in the recent diagnostic criteria for CAPA.^{11,75} However, the sensitivity of the PCR method varies with the PCR kit and DNA extraction procedure used.

Diagnosis

A surveillance for CAPA is suggested in individuals with clinical deterioration and abnormal chest images.¹¹ To maximize the sensitivity and specificity, mycological evidence by fungus culture and biomarkers in serum or lower respiratory tract using BAL or non-BAL procedure were suggested in several guidelines.^{11,73–75,83} The BAL procedure was often unfeasible in patients with COVID-19, and alternative methods such as tracheal aspiration and non-BAL fluid (non-BALF) acquired from the lower respiratory tract were acceptable substitutes to aid in the diagnosis of CAPA.

In published articles regarding CAPA, commonly used criteria include revised EORTC/MSG criteria,⁷⁵ influenza-associated PA criteria (IAPA),⁷⁴ AspiCU algorithm,⁸³ BM-AspiCU algorithm,¹⁰ BM-AspiCU with severe influenza infection⁷³ and ECMM/ISHAM consensus criteria.¹¹ The host population constitute the major differences among them. For EORTC/MSG criteria, the invasive pulmonary aspergillosis (IPA) is defined in population with prolonged neutropenic fever or immunocompromised status. AspiCU is the earliest diagnostic algorithm to define patients in ICU and with host factors for developing IPA, and only consider *Aspergillus* culture from lower respiratory tract (LRT) as mycological evidence. The BM-AspiCU employed GM test as biomarker to increase the diagnostic sensitivities, and IAPA criteria is specific for patients with influenza co-infection. Diagnostic criteria for CAPA by ISHAM/ECMM¹¹ is specific for COVID-19 complication, which is similar to IAPA criteria⁷⁴ in the characteristics described on chest imaging. Due to the high accuracy and rapid detection by PCR method, this was introduced into the modified EORTC algorithm⁷⁵ and ISHAM/ECMM criteria for CAPA.¹¹ A summary and comparison for different algorithms to define IPA and CAPA is summarized in Table 2. Both BM-AspiCU and ISHAM/ECMM criteria consider the SARS-CoV-2 infection as host factor in the development of IPA and CAPA. Only the AspiCU and BM-AspiCU defined the condition of *Aspergillus* colonization, that were without indication for anti-fungal therapy; and the ECMM/ISHAM, EORTC/MSG and the IAPA criteria defined a new category *Aspergillus* tracheo-bronchitis, which also contributed to morbidity during COVID-19 infection.

Current antifungal therapy and predictors of clinical outcome

The overall mortality of patients with CAPA were from 43% to 71.4% and was higher than in patients without CAPA ($p < 0.05$).^{53,62} The mortality in CAPA patients without anti-mold therapy ranged from 59% to 90%, compared to 38%–66.7% among CAPA patients who had received anti-mold treatment.^{67,84} However, one meta-analysis including 20 studies demonstrated that none of the mycological factors affected mortality in CAPA.⁶²

Primary anti-mold regimens used in the treatment of CAPA were diverse. Currently, there are no RCTs regarding which regimen is the most appropriate treatment for CAPA. One prospective, observational study described 14 patients with CAPA who received voriconazole, resulting in a lower mortality compared with those who received other anti-mold agents, though not reaching statistical significance (46% vs 59%, $p = 0.30$).⁷⁶ According to recent publications, the most common regimens used for CAPA included voriconazole, isavuconazole, and amphotericin B. One meta-analysis demonstrated that case fatality rates of CAPA were not significantly different between different triazoles, but a marginally inferior survival was found for anidulafungin therapy compared to other triazoles.⁶³ A phase 3 clinical trial for isavuconazole-based therapy for CAPA was initiated since 2021 (*ClinicalTrials.gov*: NCT04707703).

There is no consensus whether anti-mold prophylaxis is necessary in COVID-19 infection. Two small observational studies found that the administration of posaconazole or inhaled liposomal amphotericin-B could decrease the incidence of CAPA,^{85,86} but the antifungal prophylaxis did not reduce the mortality.

COVID-19 associated mucormycosis (CAM)

Introduction

A rise in the incidence of mucormycosis was seen recently with the advent of the COVID-19 pandemic, and COVID-19 is increasingly regarded as a possible risk factor of mucormycosis. COVID-associated mucormycosis (CAM) cases are found worldwide, after a surge of cases reported in India with the second wave of COVID-19 epidemic after April 2021.

Mucormycosis is an uncommon but life-threatening invasive fungal infection caused by the mold in the order of Mucorales, which are rapidly growing saprophytic fungus that is ubiquitous in the environment. The most common genera causing human infections is *Rhizopus*, but also includes *Apophysomyces*, *Cunninghamella*, *Lichtheimia*, *Mucor*, and *Rhizomucor*.⁸ Mucormycosis results from the inhalation of sporangiospores, which colonize or infect the nasal turbinates, then spread into the sinuses and palate, and subsequently invade into the orbital or cerebral areas. Ingestion of fungi may cause gastrointestinal mucormycosis, while fungal contamination of wounds can cause cutaneous mucormycosis. In immunocompetent individuals, the host neutrophils can inhibit and kill fungal hyphae.⁸⁷ The host respiratory cilia clear inhaled fungus into the gastrointestinal tract. These defenses are impaired in

Table 2 Summary of diagnostic criteria for invasive pulmonary aspergillosis (IPA).

	Revised EORTC/MSG (2020)	ISHAM/ECMM for CAPA	IAPA	AspICU	BM-Asp ICU
Published year [Ref.]	2020 ⁷⁵	2021 ¹¹	2020 ⁷⁴	2012 ⁸³	2021 ¹⁰
Category	proven, probable, possible	TBs: proven, probable. PA: proven, probable, possible	TBs and IAPA: proven, probable	Proven, putative, colonization	Proven, Probable, possible, colonization
Host factors	immuno-compromised	COVID with ICU, temporal entering criteria	ICU with influenza	ICU with immuno-compromised	ICU, immuno-compromised
Particular pattern on chest image	Wedge shaped, consolidation, tracheobronchitis	Cavity, tracheo bronchitis, non-specific	Cavity, airway plaques, and others	Non-specific	Any infiltrations
<i>Aspergillus</i> culture				^g Entry criteria	
Lower respiratory tract, trachea	✓	✓	✓		
BALF	✓	✓	✓	a	✓
Hyphae (in LRT)	✓	✓	✓	b	
Tissue ^f					^h
Presence of hyphae					c
Culture +					d
Serum/plasma/blood					
Galactomannan index	≥0.5	>0.5	>0.5		≥0.5
PCR	Positive ^e	plus PCR+ in BALF			
BALF/non-BALF					
Galactomannan index	≥1.0, or serum ≥0.7 and BALF ≥0.8	≥1.0, or non-BALF >4.5 once, or non-BALF >1.2 for ≥2 times; or ≥1.0 plus GM index > 0.5 in blood	≥1.0		≥1.0
PCR	Positive ^e	Ct < 36			

^e : Two or more duplicate positive tests.

^f : Proven *Aspergillus* in modified EORTC, ISHAM/ECMM, and IAPA algorithm if the histopathology showed hyphae compatible with *Aspergillus* or with culture positive for *Aspergillus* spp. from tissue specimens.

^g : Mycological evidence for putative IPA: *Aspergillus* culture positive from LRT (entry criteria), and (a) semiquantitative culture from BALF without bacterial growth plus (b) cytological smear showing branching hyphae.

^h : Proven IPA by BM-AspICU criteria if (c) dichromats septate hyphae in histology concurrent with (d) culture positive in *Aspergillus* from tissue.

Abbreviations: BALF: bronchoalveolar lavage fluid; Ct: Cycle threshold of *Aspergillus* qPCR; TBs: tracheobronchitis; LRT: lower respiratory tract; PA: pulmonary aspergillosis.

immunocompromised hosts. Traditional predisposing conditions for mucormycosis include diabetes mellitus, immunosuppression, hematologic malignancies, allogeneic hematopoietic transplantation, and trauma.

Pathogenesis

A number of factors have been hypothesized to predispose COVID-19 patients to mucormycosis. Firstly, uncontrolled diabetes and corticosteroid therapy were found to be closely linked with the development of CAM. However, the exact causal relationship between COVID-19 and

mucormycosis in relation to diabetes and corticosteroid use remains unclear.⁸⁸ Hyperglycemia in COVID-19 may be caused by direct infection of the pancreatic islets cells, which express ACE2 entry receptors, by SARS-CoV-2 virus, leading to beta cell failure, and by systemic inflammation resulting in increased insulin resistance.⁸⁹ Moreover, corticosteroids used to treat severe COVID-19 infection requiring oxygen or invasive mechanical ventilation may exacerbate hyperglycemia by inducing insulin resistance and beta cell dysfunction. Under acidic and glucose-rich conditions⁹⁰ such as that during uncontrolled diabetes mellitus, diabetic ketoacidosis, COVID-19 infection and

with use of corticosteroids, *Rhizopus* hyphae can proliferate and thrive.^{91–99}

Secondly, COVID-19 results in dysregulation of the immune system and lymphopenia with decreased CD4⁺ and CD8⁺ T cells,¹⁰⁰ which lowers the innate immune defenses against mucormycosis. Use of corticosteroids and immunomodulatory agents, such as anti-IL-6 antagonists to counter COVID-19-induced hyperinflammation also results in immunosuppression. Finally, virus-induced impairment in ciliary function¹⁰¹ facilitate fungal spread.¹⁰²

Thirdly, COVID-19 may induce an inflammatory state with elevated ferritin levels which predisposes to mucormycosis by increasing serum iron level. Iron is required for the growth of the fungus. In a cross-sectional study involving 63 patients in India, significantly higher levels of ferritin were seen in patients with more severe extent of mucormycosis.¹⁰³ COVID-19-induced inflammatory reactions may result in apoptosis of hepatocytes and release of stored labile iron and serum ferritin. The virus may also attack hemoglobin causing dissociation of porphyrins from iron, and induce dysregulation of hepcidin, which is an iron regulatory hormone. All this results in elevated free iron levels in patients with COVID-19.¹⁰⁴ The upregulation of host glucose regulated protein 78 (GRP78), an endothelial co-receptor mediating entry of SARS-CoV-2, may play a role in the endothelial invasion by *Mucorales* in CAM.¹⁰⁵

Epidemiology and predisposing factors

The prevalence of mucormycosis in patients with COVID-19 admitted to the intensive care units (ICU) was 0.3%–0.8% in a national, multicenter, observational cohort study in France.¹⁰² The predominant co-morbidities associated with CAM included diabetes mellitus (77.1%), hypertension (29.5%), and renal disease (14.3%).¹⁰⁶ Risk factors for CAM in mechanically ventilated COVID-19 patients include older age, treatment with dexamethasone and anti-interleukin-6 (IL-6) antagonists, and long duration of mechanical ventilation (>14 days).^{102,106} More males (69.6%) than females (19.6%)¹⁰⁷ were affected, although this was reflective of the male predominance (65.39%) of COVID-19 cases in India.¹⁰⁸ The median time to diagnosis of mucormycosis after COVID-19 diagnosis was 10–15 days.^{102,109}

Clinical manifestations

In a recent review of 80 cases of CAM from 18 countries worldwide, rhino-orbital cerebral mucormycosis was the most frequent clinical syndrome (74%), followed by pulmonary mucormycosis (25%), while concomitant disseminated mucormycosis (4%) and gastrointestinal mucormycosis was rare (1%).¹⁰² The most common sites of involvement were the sinuses (79.4%), especially the maxillary sinus (47.4%); the orbits (56.7%) and the lungs (11.3%) were affected in another review of 99 cases.¹⁰⁶

The clinical manifestations of mucormycosis included fever, nasal passage dryness, periorbital or facial pain, ptosis, proptosis, toothache, loss of tooth, blurry or double vision, and shortness of breath.¹¹⁰ Neurological symptoms such as headache, confusion, and altered mental status can be found in the later stages.¹¹⁰

Diagnosis

Diagnosis of CAM is challenging since the clinical and radiologic findings may overlap with those of COVID-19.¹⁰² Currently, conventional culture and histopathological demonstration of typical *Mucorales* hyphae, which are broad (5–25 µm), aseptate, with ribbon-like, irregular branching, and wide-angle bifurcation up to 90°, remains the mainstay of diagnosis. Histopathology may show an acute suppurative inflammation with focal areas of granulomatous inflammation, although this may be absent in immunosuppressed patients.⁸ Invasion into the blood vessels with subsequent thrombosis and inflammation is hallmark for mucormycosis. The organism is very delicate; grinding or homogenization of tissues may destroy fungal hyphae, leading to negative culture results.¹¹¹ Blood cultures are rarely positive despite evidence of angioinvasion.

Imaging signs suggestive of pulmonary mucormycosis on computed tomography (CT) or magnetic resonance (MRI) include the halo sign, reversed halo sign, or a ring of ground glass opacity surrounding a nodular infiltrate that is indicative of focal ischemia. The “reverse halo sign” was suggestive of *Mucorales* infection and may be useful for the preemptive initiation of antifungal therapy but is not consistently detected (55%) and can be associated with other mold infections. Thrombosis may be seen on CT angiography.⁸ In a study involving 50 patients with rhino-orbital-cerebral CAM, the most common imaging features on MRI were the black turbinate sign/non enhancing sinonasal mucosa (82%), followed by peri-antral soft tissue inflammation (74%) and extra-ocular muscle involvement (76%).¹¹² MRI has is more sensitive than CT in detecting early angioinvasion of mucormycosis.^{113,114} Radiological changes may precede overt clinical symptoms.

Molecular diagnostic methods have a high potential for diagnosing fungal infections in early stages of the disease, though not clinically validated. Polymerase chain reaction (PCR)-based diagnostic methods on BAL fluid, biopsy specimens, and serum has been reported and appear promising. One study evaluated quantitative PCR of the serum in patients with non-COVID-associated mucormycosis with a sensitivity and specificity of 85.2% and 89.8% respectively.¹¹⁵

Treatment and prevention

Judicious use of corticosteroids and strict control of glucose in COVID-19 patients may prevent the development of CAM.¹¹⁶ Once diagnosed, prompt antifungal therapy must be administered. Aggressive surgical treatment has been shown to improve outcomes.¹⁰⁹ Currently, there is a lack of evidence to support the use of iron chelators and hyperbaric oxygen as standard or salvage therapy in the treatment of mucormycosis.

Pharmacologic treatment of COVID-associated mucormycosis is similar to that of mucormycosis in general. Evidence for the treatment of mucormycosis is limited by the rarity of the disease. Global guidelines for the antifungal management of mucormycosis are based on that established by the 2017 European Conference on Infections in Leukemia (ECIL), with an upgrade in 2019 by the European Confederation of Medical Mycology (ECMM).⁸ The first line

of treatment recommended is liposomal amphotericin B (L-AMB). A dosage of 5–10 mg/kg of L-AMB is suggested while a higher dose of 10 mg/kg is necessary in patients with central nervous system (CNS) involvement. ECIL guideline suggests that in the absence of CNS involvement, amphotericin B lipid complex (ABLC) may also be used.¹¹⁷ Amphotericin B deoxycholate has been shown to be effective but is limited by substantial nephrotoxicity, especially given the prolonged duration of treatment at high doses as required in the treatment of mucormycosis.

Isavuconazole was approved by the United States and Europe as an effective oral and intravenous formulation to treat mucormycosis in 2015, following the results of the VITAL study, which showed clinical response rates comparable to that of amphotericin B.¹¹⁸ Clinical success has been documented in a few patients treated with isavuconazole, either alone or in combination with amphotericin B.¹¹⁹

Posaconazole exhibits *in vitro* susceptibility against *Mucorales*. Both the tablet and intravenous forms are recommended by ECMM/ISHAM as an alternative treatment, combination treatment with amphotericin B, salvage therapy, or step-down therapy for mucormycosis. In the recent Indian epidemic of CAM, posaconazole was used as monotherapy in the treatment of a few cases of mucormycosis with varying success.¹²⁰

Although *Rhizopus oryzae* expresses the target enzyme for echinocandins, the echinocandins do not exhibit *in vitro* susceptibility against mucormycosis. The use of echinocandins is not supported in major guidelines including ECMM, ISHAM, ECIL. The impact of combination antifungal therapy with echinocandins in humans are uncertain.

Treatment duration

The optimal treatment duration is unknown.⁸ Guidelines from India generally recommend 4–6 weeks of amphotericin B therapy followed by consolidation therapy with posaconazole or isavuconazole for an additional 3–6 months.¹²¹

Prognosis

Mucormycosis is a grave disease which progresses rapidly and often have poor clinical outcome. Mortality is high for those with extensive involvement and nearly 100% die in cases of disseminated mucormycosis. For CAM, large case series revealed case fatality rates from 14%⁹⁴ to 45%.¹²⁰ No difference in mortality rates was reported between COVID and non-COVID cases of mucormycosis.¹²⁰

Conclusions

COVID-19 infection is associated with an increased risk of invasive mold infections. During the pandemic of COVID-19 from 2020 to 2021, accumulating evidence demonstrated that CAMI contributed to high morbidity and mortality despite anti-mold therapy; however, the relationship between treatment response and antifungal resistance remains under investigation. Clinicians must maintain high clinical suspicion for these fungal diseases in COVID-19 patients, especially in those who have severe COVID-19 and multiple risk factors. Early diagnosis and aggressive medical and surgical therapy are necessary to improve patient outcome.

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