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Coronavirus Disease 2019–Associated Invasive Fungal Infection

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Coronavirus disease 2019 (COVID-19) can become complicated by secondary invasive fungal infections (IFIs), stemming primarily from severe lung damage and immunologic deficits associated with the virus or immunomodulatory therapy. Other risk factors include poorly controlled diabetes, structural lung disease and/or other comorbidities, and fungal colonization. Opportunistic IFI following severe respiratory viral illness has been increasingly recognized, most notably with severe influenza. There have been many reports of fungal infections associated with COVID-19, initially predominated by pulmonary aspergillosis, but with recent emergence of mucormycosis, candidiasis, and endemic mycoses. These infections can be challenging to diagnose and are associated with poor outcomes. The reported incidence of IFI has varied, often related to heterogeneity in patient populations, surveillance protocols, and definitions used for classification of fungal infections. Herein, we review IFI complicating COVID-19 and address knowledge gaps related to epidemiology, diagnosis, and management of COVID-19–associated fungal infections.

Keywords. *Aspergillus*; candidiasis; COVID-19; endemic fungi; *Pneumocystis*; SARS-CoV-2.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can cause critical illness with acute respiratory distress syndrome (ARDS) [1]. The severe lung damage and immunologic derangement resulting from SARS-CoV-2 infection or its treatment predispose to superinfections with multiple pathogens, including bacteria, other viruses, and fungi [2, 3].

Opportunistic invasive fungal infection (IFI) following severe respiratory viral illness has been described most frequently with influenza complicated by respiratory failure, with an incidence of invasive pulmonary aspergillosis ranging from 7% to 30% [4–6]. IFI has also been observed following severe parainfluenza and respiratory syncytial virus infections among patients with hematologic malignancy [7]. Invasive aspergillosis (IA) has similarly been recognized as an important complication in patients with severe COVID-19 pneumonia and is associated with poor outcomes [8–11]. Recently other non-*Aspergillus* fungal infections, including mucormycosis in India, have been described in those with severe COVID-19 pulmonary disease [12–15]. Risks for IFI in COVID-19 patients include leukopenia, neutropenia or lymphopenia, immune dysregulation and immunoparalysis secondary to SARS-CoV-2, poorly controlled diabetes, structural lung disease and/or other comorbidities, antibiotic use predisposing to fungal colonization, and therapies for COVID-19 such as corticosteroids or immunomodulators [10, 16–18].

Intensive care unit (ICU) cohort studies have described the incidence of COVID-19–associated pulmonary aspergillosis (CAPA) as ranging from 2% to 33%, while the incidence of other fungal infections has yet to be defined. Notably, a systematic review of autopsy studies examining patients with COVID-19 suggested the incidence is much lower, with invasive mold disease reported in <2% of autopsies [19, 20]. However, significant heterogeneity exists across centers, with an autopsy study from a single German ICU reporting CAPA or mucormycosis in 6 of 8 autopsies of decedents with COVID-19 [21]. Wide variability remains in publications citing the incidence of IFI due to the heterogeneity in patient populations,

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Table 1. Current Limitations Associated With Invasive Fungal Disease in the Coronavirus Disease 2019 Patient

Invasive Fungal Disease	Limitation and Gaps in Knowledge
Aspergillosis	Varied incidence of disease: dependent on diagnostic strategy and disease classification
	Varied confidence in classification of disease: disease classified using varying mycological, potentially associated with colonization, with prognosis not necessarily associated with or lack of antifungal treatment
	The impact of underlying disease and risk factors for disease, including immunosuppressive COVID-19 treatments: evidence can be conflicting, generally anecdotal or limited to single-center studies
	Limited proven disease: rates of autopsy-confirmed diagnosis are generally low, but variable—does this reflect overclassification of disease or disease pathogenesis?
	Limited understanding of disease pathogenesis: disease progression in the patient will affect optimal diagnostic test selection and clinical presentation and possibly prognosis
	Limited understanding of diagnostic test performance: when tests are used to define disease, it is not possible to define accurate performance and determine an optimal test or combination of tests. Even for tests previously established in ICU patients (eg, GM-EIA on BAL fluid), performance has generally been derived from the non–COVID-19 cohort
	Management of disease is based on existing knowledge among non–COVID-19 patients
Candidiasis	The impact of underlying disease and risk factors for disease, including immunosuppressive COVID-19 treatments, remains unclear
	Limited understanding of disease pathogenesis and relation to candidemia
	Management of disease is based on existing knowledge among non–COVID-19 patients
Mucormycosis	Varied incidence of disease: dependent on diagnostic strategy and risk factors/populations
	The true impact of underlying diseases (diabetes, etc) and risk factors for disease, including immunosuppressive COVID-19 treatments
	Management of disease is based on existing knowledge among non–COVID-19 patients
Pneumocystosis	Varied incidence of disease: dependent on diagnostic strategy and limitation of testing (ie, colonization vs infection)
	The impact of underlying disease (HIV, transplant) and risk factors for disease, including immunosuppressive COVID-19 treatments, are unclear
	Management of disease is based on existing knowledge among non–COVID-19 patients
Endemic mycoses	Varied incidence of disease, with few cases reported to date
	The impact of underlying disease (HIV, transplant) and risk factors for disease, including immunosuppressive COVID-19 treatments, are unclear
	Management of disease is based on existing knowledge among non–COVID-19 patients
Cryptococcosis	Few cases reported to date

Abbreviations: BAL, bronchoalveolar lavage; COVID-19, coronavirus disease 2019; GM-EIA, galactomannan enzyme immunoassay; HIV, human immunodeficiency virus; ICU, intensive care unit.

surveillance protocols, and definitions used for classification of fungal infections [11, 22, 23]. Despite improvements in the understanding of CAPA and other COVID-19–associated fungal infections since the beginning of the pandemic, knowledge gaps remain related to diagnosis, management, and prevention (Table 1). Herein, we review COVID-19–associated fungal infections and summarize current epidemiology and diagnosis.

PATHOPHYSIOLOGY OF COVID-19

Although incompletely understood, there are a number of pathophysiologic mechanisms by which COVID-19, and interventions to manage the disease, can predispose individuals to IFI. SARS-CoV-2 infection is mediated by angiotensin-converting enzyme 2 (ACE2)–containing respiratory epithelial cells, including in the airways and lungs. Infection subsequently leads to transient loss of ciliary motility from the trachea and inhibition of mucociliary clearance, an innate defense against airway pathogens [24]. Cellular entry and viral replication result in activation of the inflammasome and ignition of the inflammatory cascade. SARS-CoV-2 infection antagonizes the production of type I and type III interferon, the latter of which is a critical regulator of innate immunity against *Aspergillus* [25, 26]. Tissue damage leads to release of danger-associated molecular patterns, which, along with viral particles, stimulate alveolar macrophages to release proinflammatory cytokines leading to an influx of macrophages, monocytes, and T-cell lymphocytes, and ultimately the release of further proinflammatory cytokines. Local inflammation leads to further lung and airway damage, providing a portal of entry for hyphal invasion. In addition, systemic immune dysregulation ensues, characterized by high circulating proinflammatory cytokines, lymphopenia, and T-cell exhaustion, which may compromise defenses against fungal pathogens [27, 28]. Furthermore, hypoxia associated with severe COVID-19 may interfere with normal innate immunological control of *Aspergillus* [29]. Alterations in iron metabolism in COVID-19 increases iron levels and may predispose to mucormycosis [15].

Several immunotherapies recommended for COVID-19 management may increase the risk of IFIs, including corticosteroids, interleukin 6 (IL-6) inhibitors, and Janus kinase (JAK) inhibitors [30]. To date, corticosteroids such as dexamethasone are the cornerstone treatment in the later stages of COVID-19,

Table 2. Studies Describing Coronavirus Disease 2019 (COVID-19)–Associated Pulmonary Aspergillosis in Critical Care COVID-19 Patients

Reference	Study Design	Case/Total (%)	Certainty of Diagnosis[a]	Comments
Koehler et al [38]	Case series	5/19 (26.3)	4/5	One pt *Aspergillus fumigatus* detected in TA only
Van Arkel et al [40]	Case series	6/31 (19.4)	3/6	One pt *A fumigatus* detected in TA, serum GMI: 0.4; one pt *A fumigatus* detected in TA only; and one pt *A fumigatus* detected in sputum only
Zhu et al [42]	Prospective cohort	5/17 (29.4)	Unclear	Details not provided
Du et al [43]	Case series	3/9 (33.3)	0/3	All patients positive in sputum
Chen et al [44]	Case series	6/17 (35.3)	Unclear	Culture of various respiratory samples, details not provided
Machado et al [41]	Prospective cohort	8/239 (3.3)	7/8	Cases classified using EORTC/MSGERC and ASPICU definitions; 9 additional pts deemed to be colonized. One pt *A fumigatus* detected in TA
Bartoletti et al [9]	Prospective cohort	30/108 (27.8)	30/30	All cases had BAL GMI ≥1.0
Nasir et al [45]	Retrospective cohort	5/23 (21.7)	Unclear	4 additional pts deemed to be colonized
Rutsaert et al [46]	Case series	7/34 (20.6)	6/7	One pt *Aspergillus flavus* detected in TA
Alanio et al [39]	Case series	9/27 (33.3)	8/9	One pt BAL GMI <1.0
Helleberg et al [47]	Case series	2/8 (25.0)	1/2	One pt *A fumigatus* detected in TA
Dupont et al [48]	Prospective cohort	19/106 (17.9)	15/19	Four pts *A fumigatus* detected in TA
Segrelles-Calvo et al [49]	Prospective cohort	7/215 (3.2)	8/9	One pt had *Aspergillus* sp detected in sputum
Borman et al [50]	Prospective samples[b]	Proven/probable 36/719 (5.0) Possible 108/719 (15.0)	Unclear	Pts classified using modified ASPICU definitions
Van Biesen et al [51]	Case series	9/42 (21.4)	9/9	Nondirected bronchial lavage testing
Wang et al [52]	Retrospective cohort	8/104 (7.7)	4/8	Cases classified using the EORTC/MSGERC definitions. Four pts had *Aspergillus* sp detected in sputum
Flikweert et al [19]	Case series	6/7	6/6	Compares histology where 0/6 had evidence of IPA
White et al [11]	Prospective cohort	19/135 (14.1)	13/19	BDG testing incorporated into diagnostic strategy. Patients defined using local definitions
Delliere et al [53]	Retrospective cohort	21/108 (19.4)	Unclear	Cases classified using the EORTC/MSGERC definitions and revised IAPA definitions
Lamoth et al [54]	Prospective cohort	3/80 (3.8)	3/3	Cases classified using modified IAPA definitions
Gangneux et al [55]	Prospective cohort	7/45 (15.6)	Unclear	Cases classified using modified ASPICU definitions
Gouzien et al [56]	Retrospective cohort	2/53 (3.8)	2/2	One pt *Aspergillus* detected in TA. Limited testing of respiratory samples
Ripa et al [57]	Prospective cohort	10/86 (11.6)[c]	10/10	Includes secondary infections in all COVID-19 patients
Brown et al [58]	Prospective cohort	2/62 (3.2)	0/2	One patient meets EORTC/MSGERC classification
Ichai et al [59]	Case series	6/26 (23.1)	Unclear	Link with negative pressure rooms and CAPA, 2 further patients colonized with *Aspergillus*
Maes et al [60]	Retrospective cohort	3/23 (13.0)	3/3	IAPA classifications modified to include PCR
Razazi et al [61]	Retrospective cohort	7/90 (7.8)	7/7	Updated IAPA classification used IPA in COVID-19 less than non–COVID-19 pts
Meijer et al [62]	Case series	13/66 (19.7)	13/13	ECMM/ISHAM classification used. Data for both waves of the pandemic
Yusuf et al [63]	Case-control study	5/92 (5.4)	5/5	Comparison with IPA in influenza and bacterial infection
Fekkar et al [18]	Retrospective cohort	6/145 (4.1)	4/6	Used EORTC/MSGERC classification or negativity in follow-up testing in the absence of clinical deterioration or survival without antifungal treatment to classify CAPA
Versyck et al [64]	Retrospective cohort	2/54 (3.7)	2/2	Modified ASPICU definitions
Roman-Montes et al [65]	Prospective cohort	14/144 (9.7)	6/14	Modified ASPICU definitions, TA testing with GM-EIA and LFA
Van Grootveld et al [66]	Prospective cohort	11/63 (17.5)	11/11	Four additional patients considered colonized. Compares TA and BAL testing
Chauvet et al [10]	Retrospective cohort	6/46	3/6	Used EORTC/MSGERC, ASPICU, and modified ASPICU definitions
Heard et al [67]	Retrospective cohort	1/57	0/1	Highlights issues with empirical antifungal therapy
Permpalung et al [8]	Retrospective cohort	39/396	12/39	BDG testing incorporated into diagnostic strategy. Definitions based on proposed classifications and a local definition of possible CAPA
Total		353[d]/3519	195/273	

Abbreviations: ASPICU, Aspergillus in the Intensive Care Unit; BAL, bronchoalveolar lavage; BDG, (1–3)-β-D-glucan; CAPA, coronavirus disease 2019–associated pulmonary aspergillosis; COVID-19, coronavirus disease 2019; ECMM/ISHAM, European Confederation of Medical Mycology and International Society for Human and Animal Mycology; EORTC/MSGERC, European Organization for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium; GM-EIA, galactomannan enzyme immunoassay; GMI, galactomannan index; IAPA, influenza-associated pulmonary aspergillosis; IPA, invasive pulmonary aspergillosis; LFA, lateral flow assay; pt, patient; TA, tracheal aspirate.

[a]Meets ECMM/ISHAM definition of CAPA. Includes proven, probable, and possible CAPA, where possible CAPA permits nondirected bronchial lavage testing. For the purpose of this table, bronchial aspirates have been included, whereas sputum and tracheal aspirates are considered inadequate evidence.

[b]Samples referred from multiple centers to a specialist national mycology reference facility for testing.

[c]Intensive care unit patients only.

[d]Excludes 108 possible cases defined by Borman et al.

and these drugs modulate the systemic inflammatory response [31, 32]. IL-6 inhibitors such as tocilizumab and sarilumab are directed at reducing cytokine storm and its deleterious effects on multisystem organ function [33]. Kinase inhibitors, including the JAK inhibitor baricitinib, inhibit phosphorylation of proteins involved in signal transduction processes that lead to downstream immune activation effects [33]. Baricitinib may also exert direct effects on SARS-CoV-2 by inhibiting viral entry into cells. It has been shown to have higher affinity than several other kinase inhibitors for AP2-associated protein kinase 1 (AAK1), which regulates viral endocytosis [34]. Other kinase inhibitors may also modulate inflammatory responses through the JAK/STAT or other pathways. These immunotherapies may increase the risks of fungal infections via several mechanisms, including (1) cytopenias or additive effects with lymphopenia present in COVID-19 patients; (2) inhibition of cell signaling or function of either T cells, B cells, and/or phagocytes; and (3) increased growth and/or colonization of fungus [35–37].

COVID-19–ASSOCIATED PULMONARY ASPERGILLOSIS

A significant number of reports describing CAPA in the critically ill population have been published since the beginning of the pandemic. Initial case reports and case series indicated a high incidence (20%–30%), comparable with rates for influenza-associated pulmonary aspergillosis (IAPA) [5, 38–40]. However, there is considerable variability in the reported incidence (0–39%), likely influenced by various factors [17, 39, 41]. These include (1) study design (eg, small patient samples), selection bias, breadth of mycologic testing performed, retrospective evaluation of existing microbiological practice vs strategic, prospective screening; (2) patient host factors (eg, existing underlying condition; prior, continued, or subsequent use of immunosuppressive/immunomodulatory therapy; use of prophylactic/empirical antifungal therapy; use and duration of invasive mechanical ventilation and extracorporeal membrane oxygenation [ECMO]); (3) environmental conditions (levels of airborne conidia, local climate conditions and ecologic factors, ongoing local hospital construction, use of negative pressure rooms); (4) and variation in case definitions (which vary in incorporating different sample types, tests, and thresholds).

To date, 37 studies provide detail to permit CAPA frequency to be determined regardless of case definition and the variables described (Table 2; Supplementary Table 1). Combining these studies generates a pooled incidence of 10.0% (353/3519; 95% confidence interval [CI], 9.1%–11.1%). Thirty-one of the 37 studies provided sufficient detail to reclassify patients (n = 273) using European Confederation of Medical Mycology and International Society of Human and Animal Mycology (ECMM/ISHAM) CAPA definitions [23]. One-hundred ninety-five (71.4%) cases met ECMM/ISHAM definitions for probable or possible CAPA, generating an incidence of 7.6% (195/2575; 95% CI, 6.6%–8.7%). While this is lower than incidences reported in the initial small case series and for IAPA, given the worldwide number of COVID-19 cases requiring critical care management (approximately 5% of cases to date), it represents a significant burden of disease with considerable overall mortality (52%) [17].

Mortality in patients with CAPA summarized from 37 studies published to date is approximately 56% (151/268; 95% CI, 50.4%–62.2%). Survival benefits have been suggested with appropriate antifungal therapy, but delays in initiating, or lack of, treatment may reflect limited recognition/early diagnosis of CAPA and likely enhance mortality [9, 11]. Conversely, some cases have survived untreated, questioning the accuracy of the diagnosis or reflecting that CAPA may not be fatal in the immunocompetent patient successfully managed for COVID-19 [8, 39].

The pathophysiologic mechanisms responsible for CAPA remain incompletely understood and may not be unique to respiratory viral infections. One study demonstrated that mycologic positivity and rates of aspergillosis were similar in critical-care COVID-19 patients (5/92) and those diagnosed with pneumococcal pneumonia (3/65), compared to those with IAPA (9/48) [63]. These findings imply that aspergillosis may not necessarily be directly associated with COVID-19 but may be an underrecognized complication of critical illness with associated ARDS. While rates of aspergillosis in ICU patients lacking classic host factors have been greater during the pandemic, it is possible that this is not solely due to COVID-19. The cause of CAPA is primarily *Aspergillus fumigatus* (66%), but other species such as *Aspergillus niger* (7%), *Aspergillus flavus* (5%), *Aspergillus terreus* (3%) and cryptic species that may be resistant to primary azole therapy have been reported [17].

Across the various larger studies, numerous CAPA-associated factors have been identified. An evaluation of 186 CAPA cases showed that 97% of cases were admitted to the ICU for ARDS, 94% were mechanically ventilated, and 53% had documented corticosteroid use [17]. There was a wide range of underlying clinical conditions, many not considered traditional host factors for IA [68]. However, among patients with COVID-19 with traditional risk factors for IA, such as transplants or hematologic malignancies, it is unclear what factors are most important in risk of IA. A recent study did not find an association specifically between dexamethasone use and CAPA [8]. However, 3 studies have suggested a significant association between the use of corticosteroids in general and CAPA (combined rates across these studies: CAPA: 44/84 [52.4%; 95% CI, 41.8%–62.7%]; non-CAPA: 173/472 [36.7%; 95% CI, 32.4%–41.1%]; $P = .0076$) [8, 9, 11]. In these studies, corticosteroid use varied, including preexisting use, administration associated with ICU admission, or as management of underlying conditions (ie, chronic respiratory diseases), which themselves may be risk factors for aspergillosis. In an

observational study of outcome in 30 COVID-19 patients treated with tocilizumab, 3 patients developed CAPA; similar rates (3/39) were documented in another study, and significant associations with tocilizumab alone or combined with corticosteroid use and CAPA have been noted [8, 41, 49, 69].

Inhalation of airborne *Aspergillus* conidia are critical to infection; thus, local environmental conditions that increase exposure likely play a significant role. These factors include construction of new hospitals or units, repurposing of noncritical care areas for care of COVID-19 patients, and potentially the use of negative pressure rooms, which have been theorized to concentrate conidia in close proximity to patients [59, 70]. Contaminated respiratory equipment (humidifiers, nebulizers, oxygen cannisters) has also been investigated as potential sources of fungi in healthcare settings [71].

A variety of diagnostic tests have been used to diagnose CAPA, including cultures, histopathology, fungal biomarkers (*Aspergillus* galactomannan, 1–3-β-D-glucan [BDG]), and *Aspergillus* polymerase chain reaction (PCR), but no single test achieves the performance characteristics necessary for accurate diagnosis. Given test positivity is used to classify CAPA cases, incorporation bias makes it difficult to determine individual test performance. Most experts recommend the use of strategic, prospective, multimodal testing [23, 50, 70] (covidandfungus.org). This generally increases rates of detection over retrospective reviews of existing microbiological/mycological performance, appreciating that given the ubiquitous environmental dispersal of *Aspergillus*, increased testing rates will likely increase the chances of random, isolated test positivity [9, 11, 18]. The possibility of CAPA is likely increased when positive results are seen on multiple occasions, across multiple sample types and tests. Positivity in the preferred sample type, bronchoalveolar lavage fluid (BAL), is usually sufficient to confirm CAPA, especially if high fungal burdens are recorded. It is important to note that due to infection control concerns with potential spread of SARS-CoV-2, bronchoscopies and BAL sampling have been limited at many centers during the pandemic. Testing of upper respiratory tract specimens is common, but there is always concern for *Aspergillus* contamination or colonization. These tests may be more useful in resource-limited settings [70]. Nondirected bronchial lavage (NBL) fluid can be obtained using closed suction apparatus, which decreases transmission risk [51]. Testing of NBL samples, although not fully validated and not approved by manufacturers, may provide performance comparable to BAL [11, 51]. Positive *Aspergillus* galactomannan or PCR testing of blood is likely indicative of CAPA and while negativity is not sufficient to exclude CAPA, sensitivity may be improved by concurrent serum BDG testing, taking into account its broad detection range and various potential sources of false positivity [8, 11, 65]. The influence of prior antifungal therapy on test performance for CAPA is unclear but will likely impair sensitivity.

As is typical in the nonneutropenic patient, CAPA manifests as nonspecific findings on chest radiology, which complicates the diagnosis of secondary chest infections in patients with antecedent and often fibrotic underlying respiratory inflammatory conditions. The presence of tracheobronchitis, common in IAPA, has been occasionally documented in CAPA and the typical eschars/plaques/pseudomembranes should be considered evidence of CAPA [38, 52]. Given that COVID-19 binds to ACE2 receptors, which are more abundant in the smaller airways, this manifestation may be less evident in CAPA, but may also be underdiagnosed due to the reluctance to perform bronchoscopy. Cavitary lesions and nodules are also relatively common but may be a late finding [8, 11, 38].

A range of definitions to classify CAPA have been proposed, exploiting existing classifications for *Aspergillus* in critical care, prior experience from IAPA, and knowledge of CAPA (Supplementary Table 1) [5, 11, 18, 22, 38, 72]. Most definitions are a combination of clinical, radiological, and mycological evidence, with most excluding the use of upper respiratory tract specimens (ie, sputa and endotracheal aspirates) due to concerns over false positivity. The ECCM and ISHAM have proposed definitions involving a wide range of tests and specimen types, for use in clinical trials and routine practice [38]. Given the critical and changing situation, it was paramount that definitions are available in a timely manner and it is likely that these definitions will evolve as the evidence base grows and prospective validation occurs.

Guidelines for the treatment of CAPA have recommended voriconazole or isavuconazonium for 6–12 weeks; posaconazole may be an appropriate alternative [38, 73]. Drug-drug interactions (DDIs) may be problematic when using triazoles for the treatment of CAPA in the critically ill patient. Therapeutic drug monitoring is recommended for patients receiving triazoles to illuminate potentially toxic serum levels but also subtherapeutic levels that can arise due to DDIs or additional medical interventions (ECMO, hemodialysis). For cases of azole-resistant CAPA or in areas with known high levels of environmental azole resistance, treatment with a lipid preparation of amphotericin B (AmB) or combination therapy (ie, triazole plus an echinocandin) is recommended as initial therapy [38, 66, 74–76]. A lipid formulation of AmB would also be an option for patients with contraindications or treatment-related adverse events to azole therapy.

NON-*ASPERGILLUS* MOLD INFECTIONS ON THE SETTING OF COVID-19

Potential coinfections with less common mold pathogens should be considered given the aggressive nature of lung damage caused by SARS-CoV-2 and easy access of airborne fungi to the respiratory tract. When assessing a COVID-19 patient for coincident mold infection, additional mycological culture and non-culture-based analysis of respiratory tract specimens are

recommended [55]. The majority of infections are caused by the Mucorales [15, 77–79] and, notably, the number of case reports/small case series of COVID-19–associated mucormycosis (CAM) from India has increased substantially, with >20 000 cases reported [80–83]. In addition, fusariosis and mixed mold infections have been reported [84, 85].

Risk factors for acquisition of non-*Aspergillus* mold infections in COVID-19 patients are similar to those well established in other clinical contexts, including poorly controlled diabetes mellitus, hematologic malignancy, allogeneic hematopoietic stem cell transplant (HSCT), and trauma [86]. Diabetes mellitus with or without ketoacidosis has been a major underlying condition in patients with CAM, but many also had hypertension and/or end-stage kidney disease and received high-dose corticosteroid treatment for COVID-19. John and colleagues recently reviewed 41 cases of CAM where underlying diabetes was present in 94% of cases and associated with severe COVID-19 (95% of cases) [15]. Findings from another review identified similar risks [87]. Corticosteroid use is a key risk factor for mucormycosis from resulting hyperglycemia [35]. In addition, the high expression of ACE2 receptors in pancreatic islets leads to insulin resistance, the hyper-ferritinemic state of severe COVID-19 results in intracellular iron overload, and presence of endothelialitis pose further risks for mucormycosis [15]. Mucormycosis usually developed 10–14 days after hospitalization and in some cases, was diagnosed after recovery from COVID-19 or postmortem. Clinical presentation was mostly rhino-orbital/rhino-orbital cerebral, typical of that seen in diabetic patients. In contrast to CAPA, nearly all CAM infections were classified as proven [15]. Similar to CAPA, invasive mucormycosis and fusariosis share many common features in the critically ill with COVID-19 and awareness is the first step toward diagnosing these potentially devastating infections, where in the case of CAM, even in survivors, morbidity is high due to need for disfiguring surgery; in-hospital mortality is approximately 49% [15, 87].

Although no cases of coinfections with the *Scedosporium*/*Lomentospora* molds have yet been described, these pathogens are important in hospital epidemiology and should be considered in vulnerable at-risk immunocompromised patients such as those with hematological malignancy or HSCT and solid organ transplantation [88, 89].

Diagnostic approaches to Mucorales and other mold infections in COVID-19 follow similar principles to those in other populations and are detailed in recent guidelines [86, 90, 91]. A high index of suspicion in at-risk groups should prompt appropriate imaging and examination of clinical specimens (sputum, tracheal aspirates, BAL fluid, skin lesions) by histology, direct microscopy, culture for fungi, and employment of non-culture-based approaches, if available.

Antifungal therapy and the principles of surgical resection are similar to those in non–COVID-19 patients with these infections. Early surgical debridement is essential. Antifungal treatment recommendations are supported by 2 recent globally focused management guidelines [86, 90].

CANDIDIASIS

Information on invasive candidiasis (IC) complicating COVID-19 is limited, with reported incidence ranging from 0.8% to 14% and higher incidence found in ICU settings (Supplementary Table 2) [2, 3, 11, 92–106]. Several studies reported a 3- to 8-fold higher rate of candidemia associated with COVID-19 compared to the historical non–COVID-19 rate [92, 95, 99, 106]. Reasons for the higher disease frequency are unclear, and differences in underlying disease, disease severity at ICU admission, and classical risk factors for IC between patients with and without COVID-19 have not been identified. However, the higher rate of candidemia may reflect an accumulation of risk factors, such as prolonged ICU stays, protracted invasive mechanical ventilation, ECMO, broad-spectrum antimicrobial use, renal replacement therapy, and the presence and duration of central venous catheters [92, 95, 99, 101, 106, 107]. Breaches in routine infection prevention practices (eg, "bundles") during the pandemic may have also played a role, including crowded hospital rooms, decreased staff-to-patient ratios, the limited availability of personal protective equipment, and changes in cleaning and disinfection practices. Of note, breach in infection prevention practices are likely reasons leading to outbreaks of *Candida auris* in Florida (United States) and throughout the globe [93, 96, 104, 105, 108, 109].

The use of immunomodulating agents (eg, corticosteroids and tocilizumab) have been proposed as risk factors for candidemia [106, 110]. However, these reports were descriptive studies not involving control groups. Crude mortality in patients with COVID-19–associated candidemia has been reported between 40% and 70%; it is unclear if IC conferred increased risk of mortality among patients with COVID-19. Further studies are required to better understand the epidemiology of IC complicating COVID-19. In the interim, high suspicion for IC should be maintained among critically ill patients with COVID-19, as inflammatory responses (fever, C-reactive protein, etc) may be blunted following receipt of immunomodulating agents.

When candidiasis is suspected, cultures from blood and other sites suspected to be infected should be performed and rule-based empirical antifungal therapy may be started. Treatment of candidiasis is outlined in available guidelines [111].

PNEUMOCYSTOSIS

Compared with CAPA, few cases of coinfection by *Pnuemocystis jirovecii* have been described (Supplementary Table 3)

[112–118]. Many COVID-19 patients, especially those in ICU, have been reported to develop lymphopenia and ARDS, requiring adjunctive corticosteroids; these are established risks for *P jirovecii* pneumonia (PCP) [68].

In the first report describing an immunocompetent patient with COVID-19 who had ARDS, a high level of BDG detected in serum prompted the search for the coincident diagnosis, which included a positive qualitative PCR test for *P jirovecii* performed on a tracheal aspirate specimen [112, 119]. Additional cases of PCP/COVID-19 coinfections have been reported, largely in human immunodeficiency virus (HIV)–infected patients. Because of the focus on COVID-19, PCP diagnoses can be missed on first presentation, particularly given the similarity in radiological features [114, 120]. Indeed, this reminds us of the importance of HIV testing where appropriate in any patient presenting with otherwise explained pneumonia, regardless of COVID-19.

In addition, as *P jirovecii* can colonize the lung, detection by sensitive PCR-based tests in respiratory specimens may prove an interpretative challenge. In one study of consecutive COVID-19 patients admitted to a French ICU, *P jirovecii* DNA was detected by quantitative real-time PCR (qPCR) in sputum, tracheal aspirate, and BAL fluid specimens [121]. Unexpectedly, 10 of 108 (9.3%) patients tested positive for *P jirovecii*. Among these 10 patients, 5 also met criteria for CAPA. Four (40%) went on to receive trimethoprim-sulfamethoxazole treatment. Only low values of serum BDG were found, prompting suspicion that the patients were colonized with *P jirovecii* but did not develop PCP [121]. Whether a positive *P jirovecii* qPCR test should prompt consideration of treatment or at least prophylaxis is not known, but careful interpretation is required. It may also be prudent to search for *P jirovecii* in deep respiratory specimens to limit inadvertent *P jirovecii* transmission.

The approach to diagnosis of PCP in COVID-19 patients is similar to that in other clinical contexts and populations with the use of clinical findings, radiographic imaging, and laboratory-based tests. Although chest radiography may show diffuse ground glass opacity (GGO) with interstitial infiltrates, similar to that seen with COVID-19 pneumonia, it may also be normal [122]. Chest computed tomography (CT) is essential with extensive, mostly diffuse GGO on CT scans, which typically has an upper lobe and perihilar predominance, sometimes with peripheral sparing or a mosaic pattern typical of PCP [123]. Importantly, CT findings cannot distinguish PCP from COVID-19 pneumonia.

Definitive PCP diagnosis has traditionally relied on microscopic visualization of *P jirovecii* in respiratory tract specimens (eg, BAL fluid, lung and tracheal biopsy specimens, induced sputum and expectorated sputum), by various staining methods of which immunofluorescence is preferred due to its high sensitivity [124]. In many laboratories, quantitative PCR detection of *P jirovecii* DNA in respiratory tract specimens is the preferred approach. Serum BDG testing has been used for the diagnosis and exclusion of PCP. Its clinical utility is probably most useful in ruling out pneumocystosis because of its high negative predictive value.

With regard to antifungal therapy, the approach should be similar as in patients without COVID-19 [125]. Trimethoprim-sulfamethoxazole remains the preferred initial therapy for most patients. Although data are sparse in patients with COVID-19, the use of this agent has not been associated with adverse outcomes.

ENDEMIC MYCOSES

It is not clear to what extent endemic mycoses are associated with COVID-19. In the setting of the pandemic, diagnosis of endemic mycoses may be missed, given the overlapping symptoms between respiratory infection with an endemic mycosis and COVID-19. Patients with severe COVID-19 or those receiving immunosuppressive therapy may also experience reactivation of dormant/past infection with an endemic mycosis.

To date, a limited number of cases of *Coccidioides* and SARS-CoV-2 coinfection have been reported [14, 126, 127]. In one case, the infections were diagnosed simultaneously and did not result in hospitalization [126]. In another, the patient was hospitalized with severe COVID-19, and coccidioidomycosis was diagnosed by serologic testing during admission [14]. In a third case, a patient with subclinical coccidioidomycosis developed rapid disease dissemination shortly after a mild illness of COVID-19 [127]. Heaney et al provide a synopsis of possible social, demographic, and exposure risk factor interactions between coccidioidomycosis and COVID-19, focusing on racial and ethnic minorities and the role of geography [128]. The authors also suggest that chronic lung disease from coccidioidomycosis may increase risk of severe COVID-19 and that COVID-19 may increase the risk of reactivation of latent *Coccidioides* infection, which has been seen by several authors recently.

Four coinfections with *Histoplasma* and SARS-CoV-2 have been reported, all from South America [129–131]. Two reports from Argentina and one from Brazil describe positive SARS-CoV-2 tests in patients living with HIV who had disseminated histoplasmosis. In all 3 patients, histoplasmosis was the primary diagnosis, and the SARS-CoV-2 infection was thought to be less consequential. A fourth coinfection was reported from Brazil in an HIV-negative patient with persistent pulmonary histoplasmosis when pulmonary imaging prompted SARS-CoV-2 testing [132]. We did not identify reports of SARS-CoV-2 coinfections with *Blastomyces*, *Emergomyces*, *Paracoccidioides*, *Sporothrix*, or *Talaromyces,* although one of the authors has treated a case of *Blastomyces* complicating COVID-19 and other cases are likely to exist.

Wider use of corticosteroids, specifically dexamethasone, IL-6 inhibitors, and other immunosuppressants to treat severe COVID-19 might increase the risk of symptomatic endemic mycoses, although the impact is not yet known [133].

Endemic mycoses should remain on the differential diagnosis for patients presenting with acute respiratory symptoms, and the presence of SARS-CoV-2 infection should not exclude the possibility of a concomitant fungal infection. Several testing options are available for each of these diseases, including culture, microscopy, serologic antibody tests, antigen tests, and PCR. In patients with acute or subacute respiratory infection, noninvasive diagnostic testing for coccidioidomycosis typically begins with serologic antibody tests, with enzyme immunoassay being most widely available, and less commonly antigen testing [134]; antigen and antibody testing can be used for histoplasmosis [135], and antigen testing, and less reliably antibody testing, can be used for blastomycosis [136]. Treatment guidelines are available for the endemic mycoses [136–138]. Typically, mild or moderate illness can be treated with triazole antifungals and severe disease with AmB preparations followed by triazoles.

CRYPTOCOCCOSIS

Cryptococcosis is most commonly an opportunistic infection of meningoencephalitis in patients with AIDS, patients with malignancy, organ transplant recipients, and others receiving iatrogenic immunosuppression. The association of cryptococcosis and COVID-19 is unclear, although use of corticosteroids or immunomodulators could affect reactivation of cryptococcal infection. To date, only a few cases have been reported [139, 140].

CONCLUSIONS

During the COVID-19 pandemic there has been an increase in the reporting of fungal infections associated with COVID-19, most commonly CAPA; however, mucormycosis has become an important problem as of late, emerging in India, and rates of invasive candidiasis in the ICU are above pre–COVID-19 levels. In many cases, risk factors for IFI and appropriate diagnostic strategies have been challenging to define, which has led to a wide range of IFI incidence and reported outcomes. Our review, highlighting advances and knowledge gaps, supports the need for continued research and consensus to better define epidemiologic patterns and appropriate classification of infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The Centers for Disease Control and Prevention (CDC) is an agency within the Department of Health and Human Services (HHS). The contents of this manuscript do not necessarily represent the policy of CDC or HHS and should not be considered an endorsement by the federal government.

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