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Does Pulmonary Aspergillosis Complicate Coronavirus Disease 2019?

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Objectives: *Aspergillus* coinfection in coronavirus disease 2019 patients has rarely been described but may be occurring among coronavirus disease 2019 patients admitted to ICUs. Previous reports of viral coinfections with *Aspergillus*, including influenza-associated pulmonary aspergillosis, suggest that coronavirus disease 2019–associated aspergillosis is plausible. This report aims to summarize what is known about coronavirus disease 2019 complicated by *Aspergillus*, introduces coronavirus disease 2019–associated pulmonary aspergillosis as a possible clinical entity, and describes reasons clinical suspicion of *Aspergillus* is warranted in the critical care setting.

Data Sources: We summarize the available evidence suggesting the existence of *Aspergillus* coinfection among severe coronavirus disease 2019 patients. This includes published coronavirus disease 2019 patient case series, a case description, and a review of potential biologic mechanisms.

Study Selection: Reports of coronavirus disease 2019 patient attributes were selected if they included clinical, microbiologic, or radiologic signs of invasive fungal infection.

Data Extraction: Data included in summary tables were identified through a literature search for coronavirus disease 2019–associated pulmonary aspergillosis.

Data Synthesis: We present descriptive data extracted from coronavirus disease 2019–associated pulmonary aspergillosis case series current at the time of article submission.

Discussion: Pulmonary aspergillosis is known to occur among influenza patients requiring intensive care and is associated with increased mortality. If *Aspergillus* coinfections are occurring among coronavirus disease 2019 patients, early clinical suspicion and testing are needed to understand the epidemiology of these infections and prevent associated mortality. As the coronavirus disease 2019 pandemic unfolds, reports on the existence of this coinfection are needed, and opportunities to contribute cases of *Aspergillus* coinfection among coronavirus disease 2019 patients to an ongoing registry are described.

Key Words: aspergillosis; *Aspergillus* infection; coronavirus; coronavirus disease 2019; critical care; viral coinfection

Coinfections with viral and bacterial pathogens are associated with high mortality among influenza patients and account for an estimated 20–40% of influenza-associated deaths (1). Influenza-associated pulmonary aspergillosis (IAPA) is an emerging fungal complication of severe influenza, occurring in as many as 20% of ICU patients with influenza in some geographic locations, with high mortality compared with non-IAPA ICU influenza patients (51% vs 28%) (2–4). Characteristics of IAPA include the absence of conventional risk factors for invasive fungal disease (e.g., hematologic malignancy, prolonged neutropenia) and the frequent occurrence of invasive *Aspergillus* tracheobronchitis. Increased recognition of IAPA has led some centers to begin empiric antifungal treatment for some ICU patients with this syndrome. Importantly, the clinical and epidemiologic understanding of IAPA remains limited and some centers have detected much lower rates (6). Recently, an expert opinion, based on a conference report with 29 international experts, was published with a proposal for an IAPA case definition (7). This definition might further facilitate clinical research and is essential for surveillance.

Whether invasive aspergillosis complicates other severe viral respiratory infections, including coronavirus disease 2019 (COVID-19), in patients without immunosuppression remains unknown. One study reported five of 99 patients with confirmed COVID-19 treated in Wuhan, China, in January 2020 had positive fungal cultures or fungal coinfections caused by *Aspergillus*, *Candida glabrata*, and *C. albicans* (8). In the same study, 15% of patients had antifungal prophylaxis or treatment, suggesting clinician concern for COVID-19 patients' possibly elevated fungal infection risk. Yang et al (9) reviewed 52 severe COVID-19 patients, of whom 7 (14%) had additional infections; two of these

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had *Aspergillus* (*flavus* and *fumigatus*) cultured from respiratory specimens, although confirmation of invasive infection was not discussed. Radiologic signs characteristic of aspergillosis have also been reported. Among 51 confirmed COVID-19 patients, 18% had halo sign and 4% had reverse halo sign on CT (10), both of which represent clinical factors consistent with but not pathognomonic of invasive aspergillosis; mycological evidence was not presented. In April 2020, a series of 27 COVID-19 patients with acute respiratory distress syndrome (ARDS) requiring ICU admission and mechanical ventilation included nine patients (33%) with putative invasive pulmonary aspergillosis, having one or more of the following: positive *A. fumigatus* culture or quantitative polymerase chain reaction (PCR) result, or positive galactomannan and beta-D-glucan tests in serum or bronchoalveolar lavage (BAL). Six of nine met at least two of these criteria and one received antifungal treatment (11). Since this case series was published, four additional case series describing invasive aspergillosis among COVID-19 ICU patients ($n = 35$ among all five case series) revealed several common features among these patients (**Table 1**) (11–15). All had culture, serologic, or molecular evidence of *Aspergillus*, and hypertension, renal failure or replacement therapy, and abnormal chest radiology were common. Importantly, 18 of 35 received corticosteroids (51%) and 19 of 27 (70%) with reported medications received mold-active antifungal treatment. Given corticosteroids are a known risk factor for pulmonary aspergillosis among ICU patients (16), patients receiving these and antifungal treatment are likely to have had true invasive disease.

Although invasive aspergillosis was defined differently in each case series, severe COVID-19 (i.e., intensive care or ARDS) was common to all. ARDS develops in 15–30% of COVID-19 patients (17) and is also associated with development of invasive aspergillosis in the ICU. In a cohort of 423 non-COVID ARDS patients, 8% had *Aspergillus*-positive respiratory specimens (18). Similarly, 19% of ICU patients with influenza pneumonia and ARDS developed invasive aspergillosis (2). ARDS also occurs among invasive aspergillosis patients: a single-center study of 83 ICU patients with probable invasive aspergillosis found that 14% had radiologic signs of ARDS (19). That ARDS is an important feature of severe COVID-19 and influenza as well as invasive aspergillosis indicates suspicion of aspergillosis is warranted when COVID-19–associated ARDS is present.

Reports of aspergillosis among severe COVID-19 patients are still limited and often do not distinguish between colonization and infection. Of note, autopsy studies show that among patients who died in the ICU from any cause, invasive aspergillosis is among the most commonly missed diagnoses (20). In the setting of the ongoing outbreak of COVID-19 and considering the increased mortality associated with IAPA, aspergillosis coinfection may occur among severe COVID-19 patients. We urge clinicians to maintain a high index of suspicion for the possibility of this coinfection.

A recent PCR-confirmed COVID-19 case at one author's institution suggests that aspergillosis coinfections may exist; similar cases at this institution are under investigation. On March 21, 2020, a 65-year-old man with history of obesity, hypertension, intermittent atrial fibrillation, and gout was admitted to a Belgian hospital for progressive dyspnea; PCR on a nasopharyngeal swab at admission was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. The patient required increasing oxygen was admitted to the ICU on March 22 and was mechanically ventilated on March 23. During the following 4 days, the patient developed organ failure with refractory hypoxemia requiring extracorporeal membrane oxygenation (ECMO) and received piperacillin-tazobactam and vancomycin. Six days after ICU admission on March 27, bronchial aspirates were taken, revealing piperacillin-tazobactam resistant *Escherichia coli* and *A. fumigatus* on culture and positive galactomannan (result value 4.4). Serum galactomannan was 0.2. These findings prompted meropenem and amphotericin B therapy. Repeated positive BAL cultures and galactomannan were recorded during April 1–10; the patient was diagnosed with invasive pulmonary aspergillosis in the absence of classical risk factors and continued on ECMO as of April 17, 2020.

An elevated risk of pulmonary aspergillosis among COVID-19 patients is biologically plausible. Like influenza, SARS-CoV-2 has affinity for pulmonary epithelial cells, and the resulting viral binding can lead to alveolar injury and increased pulmonary epithelial and vascular permeability, which could create a permissive environment for fungal angioinvasion (21). This mechanism is similar to current hypotheses explaining the pathogenesis of IAPA (2, 3). Briefly, respiratory epithelial damage and mucociliary clearance dysfunction may potentiate *Aspergillus* tissue invasion (4). In addition, influenza-induced hypoxia and ARDS have been shown to attenuate the anti-*Aspergillus* immune response (22); ARDS and hypoxia are frequently reported complications of COVID-19, especially among ICU-admitted patients. In a report of 138 COVID-19 patients in Wuhan, China, 26% required ICU admission and 61% of those developed ARDS; all ICU-admitted patients required supplemental oxygen (23). Conceivably, COVID-19–associated ARDS and hypoxia might also act to attenuate antifungal innate immune responses as in IAPA.

COVID-19 differs from influenza in several ways, which could manifest as observed differences between *Aspergillus* coinfection in COVID-19 patients and IAPA. Specifically, influenza and COVID-19 have different cellular tropisms. SARS-CoV-2 binds to angiotensin-converting enzyme 2 which is expressed in type II pneumocytes and ciliated cells (21). Influenza, including H1N1, binds to sialic acids complexed with galactose, which are expressed on many more respiratory cells, including tracheal and bronchial epithelia (24). It is possible there is no association between COVID-19 and pulmonary aspergillosis or *Aspergillus* tracheobronchitis. In addition to epithelial damage, influenza can modulate the immune system by suppressing the nicotinamide adenine dinucleotide phosphate-oxidase complex, creating a chronic granulomatous disease (CGD)-like state, a condition highly associated with susceptibility to invasive aspergillosis and *Staphylococcus aureus* infection (25). Whether a CGD-like state occurs in COVID-19 remains to be elucidated. Therefore, it is important to determine whether *Aspergillus* coinfection occurs and if so, its extent and severity. Characterizing such coinfections can advance understanding of the mechanisms underlying differential susceptibility to viral-associated fungal infections.

Importantly, underreporting may be a concern for certain fungal infections, including IAPA. In the United States in 2019,

TABLE 1. Summary of Five Coronavirus Disease 2019–Associated Pulmonary Aspergillosis Case Series

References	Country	COVID-19–Associated Pulmonary Aspergillosis Definition	*n*	*Aspergillus* Culture+ (%)	Serum Galactomannan+ (%)[a]	Bronchoalveolar Lavage Galactomannan+ (%)[a]	Fungal PCR+ (%)[a]	Corticosteroid (%)	Antifungal Treatment (%)	Died (%)
Koehler et al (12)	Germany	SARS-CoV-2 positive PCR with acute respiratory distress syndrome and IPA by modified aspergillus ICU case definition algorithm (16)	5	3 (60)	2 (40)	3 (60)	4 (80)	3 (60)	5 (100)	3 (60)
Alanio et al (11)	France	COVID-19 and ICU admission, with IPA by MSG/EORTC or modified influenza-associated IPA criteria	9	7 (78)	1 (11)	2 (29)	4 (44)	6 (67)	2 (22)	4 (44)
van Arkel et al (13)	Netherlands	Laboratory-confirmed COVID-19 and ICU admission, with presumed IPA	6	5 (83)	0 (0)	2 (67)	Not done	2 (33)	6 (100)	4 (67)
Rutsaert et al (14)	Belgium	COVID-19 and ICU admission with invasive mechanical ventilation, with suspected IPA	7	6 (86)	1 (17)	6 (100)	Not done	1 (14)	6 (86)	4 (57)
Wang et al (15)	China	SARS-CoV-2 positive PCR with proven or probable IPA by MSG/EORTC criteria	8	8 (100)	Not done	Not done	Not done	6 (75)	Not described	Not described

COVID-19 = coronavirus disease 2019, IPA = invasive pulmonary aspergillosis, MSG/EORTC = Mycosis Study Group/European Organization for Research and Treatment of Cancer, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a]Denominators may vary as some patients did not receive each test.

only 26% of surveyed infectious disease physicians were familiar with the condition and less than 10% reported frequent use of *Aspergillus* galactomannan diagnostic tests among ICU patients with influenza (26), likely reflecting the absence of U.S. guidelines recommending *Aspergillus* diagnostics among severe influenza patients. For perspective, in a large IAPA study in the Netherlands and Belgium where fungal diagnostic testing of ICU influenza patients is recommended (5), 46% of 315 immunocompetent ICU influenza patients had a BAL fungal culture and 26% had a BAL galactomannan test (2). Early diagnosis is key: time from ICU admission or influenza diagnosis to IAPA diagnosis can be short (3–5 d), with 90-day mortality exceeding 50% (2). Should COVID-19–associated aspergillosis exist, it will be important to offer clinicians guidance on testing and treatment to optimize clinical outcomes and to characterize it clinically and epidemiologically.

Based on what is known of IAPA, testing for *Aspergillus* coinfection would be most appropriate for COVID-19 patients with severe pneumonia requiring ICU admission, especially those treated with immunomodulatory medication such as corticosteroids during the later phase of ARDS. Testing can include fungal cultures from BAL or sputum, and BAL and serum *Aspergillus* galactomannan antigen tests, although galactomannan sensitivity and specificity among COVID-19 patients have not been characterized. Findings from bronchoscopic visualization, biopsy, and autopsy data will be critical in assessing the presence and anatomic localization of fungal invasion. An important challenge in performing such testing in COVID-19 patients is that clinicians may wish to avoid aerosol-generating procedures, such as BAL, given concern for transmission; recommended guidance for healthcare workers on use of personal protective equipment should be consulted (27).

Although *Aspergillus* colonization without infection is possible, antifungal treatment should be considered if *Aspergillus* grows or galactomannan is detected in lower respiratory tract specimens, or when patients with COVID-19–associated ARDS or sepsis do not respond to antibacterial treatment. As manifestations of aspergillosis in COVID-19 patients are heterogeneous, ranging from upper respiratory tract colonization to acute invasive disease, decisions on initiation of antifungal therapy depend on assessment of the patients' condition and mycological evidence supporting invasive infection. Elevated suspicion of *Aspergillus* coinfection may be especially important during the second week of SARS-CoV-2 infection, as reported median time from onset to severe disease is relatively long, about 8 days (8). There is currently no evidence that supports antifungal prophylaxis in COVID-19 patients in the ICU.

To facilitate and expedite determination of whether aspergillosis coinfections are occurring in COVID-19 patients, ICU-based surveillance and registries are urgently needed. Toward that end, the Dutch-Belgian Mycosis Study Group has created a registry to report patients admitted to an ICU with suspected or proven COVID-19 infection, available to critical care clinicians worldwide at https://data.castoredc.com/. Clinicians interested in contributing cases should ensure compliance with their local institutional review board and then contact mycology@radboudumc.nl to be added as a registry contributor. Similarly, the U.S.-based Mycosis Study Group is developing an ICU-based surveillance network to identify and describe COVID-19–associated pulmonary aspergillosis (CAPA) coinfections in the United States. Should these

coinfections be detected and described in the United States, we suggest the nomenclature CAPA, which has been established in recent case studies (12).

In summary, it is important to consider secondary infections as a complication in critically ill COVID-19 patients, including whether coinfection with *Aspergillus* might be occurring without classical risk factors for aspergillosis. Critical care staff should consider fungal cultures or *Aspergillus* galactomannan testing in COVID-19 patients with severe disease or suspected secondary infection that does not respond to antibiotic treatment.

This work was performed at Centers for Disease Control and Prevention, Atlanta, GA; Center of Expertise in Mycology, Radboud University Medical Center/CWZ, Nijmegen, The Netherlands; and Medical ICU, UZLeuven, Leuven, Belgium.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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