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Fungal Infection during COVID-19: Does *Aspergillus* Mean Secondary Invasive Aspergillosis?

To the Editor:

We read with great interest the letter "COVID-19–associated Pulmonary Aspergillosis" by van Arkel and colleagues (1). The authors report a high incidence of presumed invasive pulmonary aspergillosis (6 of 31; 19.4%) among patients with coronavirus disease (COVID-19) admitted to intensive care.

In light of the recent studies revealing the high incidence of influenza-associated pulmonary aspergillosis (2), it seems natural to expect similar complications in severe forms of COVID-19 pneumonia. However, we would like to discuss some particular points.

Among the six patients presented by the authors, two had chronic obstructive pulmonary disease (COPD), another had asthma with inhaled corticoid therapy, and a fourth received oral prednisone. The association between aspergillosis and COPD is well known; in a recent prospective study, 14% of patients with COPD exacerbations had respiratory samples with *Aspergillus* spp. of unclear clinical significance (3). Corticosteroid therapy is also a known risk factor for *Aspergillus* colonization (4). Furthermore, these four patients had an *A. fumigatus*–positive culture on a single respiratory sample, and aspergillosis was diagnosed within 3–5 days after ICU admission. Because no previous negative respiratory sample was available, the preexisting presence of *Aspergillus* cannot be ruled out. Finally, the fifth patient had only a single positive galactomannan on a BAL.

Eight years ago, Blot and colleagues proposed criteria for defining invasive aspergillosis in critically ill patients using histopathology-controlled cases as references (5). For immunocompetent patients, the direct examination of hyphae in respiratory samples was mandatory to classify the case as putative, which would have excluded all the presented cases. Criteria have evolved since then and are now similar to those suggested by the authors for the diagnosis of COVID-19–related aspergillosis, that is, *Aspergillus* spp. cultured from BAL (without direct examination) or a galactomannan index of 1 or greater on BAL or 0.5 or greater on serum. However, diagnosing an invasive aspergillosis in an immunocompetent individual solely on a single positive respiratory specimen culture or a single galactomannan index might be adventuresome. Indeed, this generates a risk of artificially increasing the incidence of aspergillosis and the overuse of antifungal treatments.

To illustrate this point, we present two cases of patients hospitalized for severe COVID-19 in our institution. Following the same criteria, secondary invasive aspergillosis would have been diagnosed in them. Nevertheless, they presented favorable outcomes without any antifungal treatment, which from our point of view makes the diagnosis refutable.

The first patient was a 66-year-old immunocompetent man with type 2 diabetes who was hospitalized for 21 days in our ICU. A BAL performed on Day 7 was positive for galactomannan (index = 3.2). Antifungal treatment was not administered because the direct examination, the *A. fumigatus* PCR, and the culture were negative, as were the serum galactomannan and β-D-glucan. The patient presented a favorable outcome and was later discharged from the hospital.

The second patient was a 38-year-old woman with obesity, hypertension, type 2 diabetes, and rheumatoid arthritis treated with methotrexate. She required venovenous extracorporeal membrane oxygenation and was therefore hospitalized in our ICU for 11 days. Several colonies of *A. niger* were found on a protected distal respiratory sample performed on Day 4 but not on later samples. This patient did not receive any antifungal treatment, but her respiratory state improved nonetheless.

The diagnosis of invasive aspergillosis is difficult and based on a body of arguments. This is especially true for critically ill patients in whom clinical arguments are not discriminant and computed tomographic scan is either lacking or difficult to analyze. This is why mycological arguments play a crucial role in the diagnostic approach. Consequently, we ask ourselves whether the use of more stringent criteria that are not limited to a single mycological argument would be preferable.

Also, careful attention should be paid to clearly differentiate aspergillosis as a subsequent complication of severe COVID-19 pneumonia from aspergillosis in patients with underlying chronic respiratory diseases (that may be occult noninvasive forms preexisting COVID-19).

We acknowledge that COVID-19 might be an independent risk factor for subsequent aspergillosis. It is also possible that underlying pulmonary conditions may favor COVID-19–associated aspergillosis. We also fully agree with the authors that classifying aspergillosis cases is very challenging, especially in the ICU setting. Common efforts should therefore be made to further assess the pathogenic nature of the presence of *Aspergillus* in respiratory samples in ICU patients with severe COVID-19. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Author Contributions: A.F. and A.L. drafted the manuscript and revised the final version. C.P. and M.B. collected clinical and microbiological data. All authors revised and contributed to the final version.

Originally Published in Press as DOI: 10.1164/rccm.202005-1945LE on July 20, 2020

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Reply to Fekkar *et al.*

From the Authors:

We thank Fekkar and colleagues for their thoughtful comments on our case series of patients with coronavirus disease (COVID-19)–associated pulmonary aspergillosis (CAPA) (1). The main points that are raised include the distinction between *Aspergillus* colonization and invasive infection and the subsequent classification. The presented cases are all classified as possible or probable CAPA, and none are histologically proven invasive aspergillosis, implying colonization without infection is a possibility.

First, we acknowledge the association between chronic obstructive pulmonary disease and *Aspergillus* spp. colonization. In our letter, two patients with chronic obstructive pulmonary disease are presented; here, we cannot rule out prior colonization. In addition, one of these patients received systemic corticosteroids for 2 days before admission, and one other patient was on a weaning scheme of oral corticosteroids preadmission for rheumatoid arthritis. A fourth patient with underlying bronchial asthma was treated with inhalation fluticasone for 1 month before admission. The use of corticosteroids is a known risk factor for colonization and invasive aspergillosis. However, the patients described in our series received a low daily dosage or a short duration of corticosteroids.

Cohort studies in patients with influenza-associated pulmonary aspergillosis (IAPA) in the ICU demonstrated that any indication of *Aspergillus* through positive culture or galactomannan (GM) detection is highly indicative of invasive aspergillosis (2). In this specific setting, a single positive test, such as serum GM or BAL GM, is considered sufficient to classify probable IAPA according to an expert panel. Both influenza and treatment with corticosteroids are considered risk factors for IAPA (3).

The direct microscopy findings of respiratory samples for fungal hyphae have no additional diagnostic value to the presented workup according to the latest criteria for IAPA (3). Nor can the criteria presented by Schauwvlieghe and colleagues rule out invasive pulmonary aspergillosis in the presented cases (2).

Furthermore, we would like to state that the start of antifungal therapy was always in multidisciplinary consultation on the basis of clinical deterioration and after reasonably excluding other causes. Indeed, a sole positive culture for *Aspergillus* might simply indicate colonization. However, rapid clinical deterioration with positive mycological evidence could not be ignored after the first cases of presumed CAPA with high mortality. We emphasize that starting antifungal therapy should always be considered in the context of the clinical status and in consultation with the attending ICU physicians. The overuse of antifungal treatment should be limited, because of adverse events such as liver and renal damage as well as the financial costs and the selection of resistant isolates.

The pathogenesis of COVID-19 is different from that of influenza, both regarding the tropism of the virus as well as the effect of the virus on (fungal) host defenses (4). As a consequence, the risk of invasive aspergillosis in patients with COVID-19 infection may be lower than in patients with influenza. Reports of presumed CAPA cases that survive without antifungal therapy, such as those presented by Fekkar and Alanio, are very informative and suggest that in patients with COVID-19, *Aspergillus* colonization is more common compared with in patients with influenza (5). In patients with COVID-19, additional factors, such as corticosteroid therapy, might contribute to an increased risk for developing invasive aspergillosis.

We agree with Fekkar and colleagues that a more stringent classification may be required for CAPA cases compared with existing classifications. Ultimate proof of CAPA can only be obtained through showing invasive hyphal growth in tissue samples. A recent case series included four proven CAPA cases, all of which were BAL culture and GM positive (6). However, all four cases were serum GM negative, underscoring the need for a better understanding of the pathophysiology of CAPA and the performance of diagnostic tests. Facing this uncertainty, in critically ill patients with COVID-19, the risk of further diagnostic testing, including bronchoscopy and/or lung biopsy, should be carefully weighed against delaying the initiation of antifungal therapy.

In conclusion, one mycological argument on a respiratory sample does not prove invasive aspergillosis. However, clinical deterioration in critically ill patients with COVID-19 that is not due to other causes, such as thromboembolic complications,

Originally Published in Press as DOI: 10.1164/rccm.202006-2241LE on July 20, 2020