# Fungal infection during COVID-19: does aspergillus mean secondary invasive aspergillosis? Reply

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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,



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inflammatory diseases, or secondary bacterial or viral infection, may indicate aspergillosis. However, radiological presentation can be atypical for invasive fungal disease in COVID-19 pneumonia, resembling influenza. The quantity of mycological arguments or the variety of assays is not decisive, although the quality of clinical specimens is conclusive for proving invasive aspergillosis. ■

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

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## TMEM16A Potentiation: Possible Drawbacks

*To the Editor*:

Dr. Danahay and colleagues present an interesting and timely study of TMEM16A potentiation to increase the epithelial fluid secretion and thereby enhance mucus clearance in cystic fibrosis (CF) (1). They report that the novel compound ETX001 potentiates the opening of TMEM16A channels and augments the magnitude of the chloride current. In human cell and animal models, the ETX001 effect was independent of CFTR function. The authors conclude that the novel potentiator could also be suitable for patients with CF without mutation in CFTR. However, when previous investigations of TMEM16A are considered, this approach may raise concerns with respect to safety.

TMEM16A, a protein encoded by the gene ANO1, is a calcium-activated chloride channel robustly expressed not only in epithelial cells but also in smooth muscle cells of airways, pulmonary and systemic vessels, gastrointestinal smooth muscle cells, and the endothelial cells of pulmonary arteries (2). The wide distribution of the channel indicates diversity in its physiological functions, such as secreting chloride and regulating vascular and gastrointestinal tone. In addition, in the pacemaker cells of the gut, TMEM16A is important for peristalsis generation. Under physiological conditions, TMEM16A is active at the resting membrane potential, and the open probability is dependent on the intracellular calcium concentration. The chloride current is voltage-dependent and exhibits a greater current amplitude in a depolarized state than at hyperpolarization.

In addition to its physiological function, TMEM16A can be upregulated by, for example, ET-1 (endothelin-1), the transcription factor HIF-1α, or IL, factors that have been found to be important players in the pathology of pulmonary arterial hypertension (PAH). We have recently reported that TMEM16A is strongly upregulated in remodeled pulmonary arteries from patients with idiopathic PAH and that this change causes the depolarization of pulmonary arterial smooth muscle cells as well as a contraction of small pulmonary arteries (3). These detrimental changes were reversed by TMEM16A silencing or its pharmacological inhibition. We have shown that such inhibition reduced the increased pulmonary vascular tone in both *ex vivo* and *in vivo* settings and reversed pulmonary arterial remodeling, causing amelioration of pulmonary hypertension and right ventricular strain in two independent PAH animal models (3). TMEM16A overactivation was observed in inflammatory lung diseases, in which it was strongly upregulated in secretory cells and airway smooth muscle cells, significantly contributing



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