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# Invasive Pulmonary Aspergillosis Goes Viral Again?

In the last decade, influenza emerged as a risk factor for invasive pulmonary aspergillosis (IPA) in patients admitted to an ICU for respiratory failure (1, 2). A case definition for influenza-associated pulmonary aspergillosis (IAPA) was recently proposed by an expert panel (3). However, the diagnosis of IPA in critically ill patients remains challenging, and the current EORTC-MSG criteria were not validated in immunocompetent ICU patients. Given that the specificity of a positive *Aspergillus* culture of an upper airway sample is low, measurement of galactomannan (GM) in BAL has become an important diagnostic tool in ICU patients (4). The increased awareness and the high mortality of IAPA has generated worldwide concerns that IPA may also occur in critically ill patients with coronavirus disease (COVID-19). Recently, studies of COVID-19–associated pulmonary aspergillosis (CAPA) reported incidences in the range of 3–33% (5, 6).

In this issue of the *Journal*, Fekkar and colleagues (pp. 307–317) report on a retrospective study on the incidence of invasive pulmonary fungal infections in 145 mechanically ventilated patients with COVID-19 (54% on extracorporeal membrane oxygenation) admitted to a large ICU in a 1,850-bed tertiary care center in France (7). A probable or putative invasive pulmonary mold infection was diagnosed in seven patients (4.8%), and four died. The authors used stringent definitions and did not consider an isolated positive non–culture-based fungal diagnostic test or an isolated positive fungal culture with negative follow-up cultures to be proof of infection. This occurred in 25 patients (17.2%). Multivariate analysis found solid organ transplantation and use of corticosteroids to be risk factors for CAPA. The authors should be commended for the careful assessment of CAPA and for providing detailed clinical and microbiological information that helps in distinguishing infection from colonization or a false-positive test result. Yet, as in previous CAPA publications, there was no control group. This precludes definite conclusions on severe COVID-19 being an independent risk factor for IPA. A recent elegant study by Yusuf and colleagues compared the rate of any positive *Aspergillus* test (culture, GM, or PCR) in patients admitted to the ICU for influenza, pneumococcal pneumonia, or COVID-19 (8). A positive *Aspergillus* test on BAL was observed in 18.8% of the patients with influenza, 5.4% of the patients with COVID-19, and 4.6% of the patients with pneumococcal pneumonia. Together with the data provided by Fekkar and colleagues, this study suggests that COVID-19 may not pose a high risk for IPA.

Several possible reasons may explain why the incidence of CAPA varies across studies. First, various definitions were used with a heterogeneity of diagnostic criteria, including BAL and other respiratory samples, such as tracheal aspirates or nonbronchoscopic lavages. In contrast to the definition of IPA in classically immunocompromised patients, the definition of IPA in critically ill patients is associated with much more uncertainty. Second, during the first wave of the pandemic, physicians were reluctant to do aerosol-forming procedures including bronchoscopies in critically ill patients with COVID-19. This explains why GM testing on BAL was often unavailable. Third, the use of immune modulating therapies and, in particular, corticosteroids, known to be associated with an increased risk for IPA, varied substantially between centers. In the study by Fekkar and colleagues, only 17% of the patients received corticosteroid therapy, possibly leading to an underestimation of the CAPA incidence. Now that dexamethasone has become the standard of care for critically ill patients with COVID-19, data on IPA in patients with COVID-19 collected later into the pandemic will be required to take this into account (9).

IAPA has also been reported with variable incidences (1, 10). The time window between ICU admission and diagnosis of IAPA tends to be very short (median, 3 d), whereas CAPA seems to occur later during ICU stay (median, 8–10 d) (11). From a pathophysiological standpoint, severe influenza causes destruction of the respiratory epithelium and of the associated ciliary function necessary to brush out *Aspergillus* conidia, leading to extensive



Supported by the European Union's Horizon 2020 research and innovation program under grant agreement no. 847507, HDM-FUN.

Originally Published in Press as DOI: 10.1164/rccm.202012-4413ED on December 22, 2020

damage of the protective epithelial barrier against invasive aspergillosis. Although COVID-19 enters the respiratory epithelium via the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *ACE2* receptor, it does not cause epithelial damage to the same extent as influenza but instead primarily leads to diffuse alveolar and endothelial vascular cell damage with increased capillary permeability and fluid leakage, resulting in congestion, edema, and diffuse inflammatory infiltrates. These observations raise a number of questions regarding the association between COVID-19 and IPA. Most importantly, the demonstration of invasiveness of the infection is lacking in most CAPA cases with some exceptions, such as the study by Rutsaert and colleagues, in which *Aspergillus* tracheobronchitis was documented on biopsy in 3 of 34 patients (12–14). On the other hand, Flikweert and colleagues found no histopathological prove of CAPA in postmortem needle core lung biopsies in six critically ill patients with COVID-19 with a GM index on BAL between 1.7 and 5.7 optical density index (15). Another argument against angioinvasion is the observation that serum GM was positive in up to 60% of IAPA cases (1), but this seems to be exceptional in CAPA. Furthermore, in the growing number of publications with an ever-increasing number of COVID-19 autopsies, CAPA has been remarkably absent (16, 17). However, the absence of hyphal invasion at autopsy may also be due to prolonged antifungal therapy in the weeks preceding death. However hard this may be, more autopsy data are needed, particularly from patients in whom *Aspergillus* was detected in the week preceding death.

Overall, these data strongly suggest that the incidence of CAPA is lower than that of IAPA. Indeed, the distinction between colonization and angioinvasive disease may be more difficult in CAPA because serum fungal infection markers are often negative. It also underscores the limitations of IPA definitions that rely almost solely on microbiological data with direct or indirect detection of *Aspergillus* in respiratory samples, particularly in clinical conditions with a low pretest probability of IPA. Taking into account host factors, clinical risk and radiological findings may help rise the pretest probability of IPA.

Apart from the uncertain diagnostic criteria and, as such, the incidence of CAPA, other questions need to be addressed as well. Is CAPA an independent risk factor for ICU mortality? Is the use of corticosteroids for COVID-19 a risk factor? And if so, is it high enough to start thinking about antifungal prophylaxis? Or will we be able to use more targeted immune-modulation agents in the future, such as anti–IL-6 drugs that may not pose a risk for IPA? Future research will need to answer these questions and many others, hopefully before a new virus appears and again leads to a new type of viral-associated pulmonary aspergillosis in critically ill patients, with or without corticosteroids. But the best scenario would be that, as of 2022, COVID-19 has become part of 21st century history. ■

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

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# Rethinking Alveolar Ventilation and $CO_2$ Removal

*"Yea, all things live forever, though at times they sleep and are forgotten."*
*H. Rider Haggard, She: A History of Adventure, 1887*

I recall my mentor and coauthor (M.R.P.) sharing a personal story from the 1970s. He had heard that Drs. Ted Kolobow and Luciano Gattinoni had performed an extracorporeal carbon dioxide removal ($ECCO_2R$) experiment in sheep. They showed that pulmonary ventilation progressively decreased until breathing ceased as $CO_2$ removal with $ECCO_2R$ approached metabolic $CO_2$ production (1). This innovative work confirmed important principles of respiratory drive and was groundbreaking enough for my mentor (a young man at the time) to travel from Johns Hopkins in Baltimore to the National Heart Institute in Bethesda and see it for himself. Fast forward to the 21st century, and it is hard to imagine my fellows showing such avid interest in $CO_2$. In fact, clinicians today appear to have a greater interest in oxygen physiology. This state of affairs is entirely understandable; noninvasive bedside monitoring provides us with regular information on oxygen status, whereas acquisition of information on $CO_2$ status generally demands more commitment.

The current pandemic has exposed the impact of our knowledge imbalance in this regard, because the mysterious "happy hypoxia" reported in patients with coronavirus disease (COVID-19) (2) is not nearly so mysterious when one considers the role of $CO_2$ in determining respiratory drive (3). Along similar lines, patients with end-stage chronic obstructive pulmonary disease are not so much limited by hypoxia but by dyspnea from hypercapnia caused by impaired alveolar ventilation (4). Under these circumstances, respiratory dialysis with $ECCO_2R$ can increase $CO_2$ removal, but removing only the $CO_2$ dissolved in blood cannot permit long off-dialysis survival because stopping $ECCO_2R$ will cause $CO_2$ concentrations to immediately rise. This therapeutic approach seems doomed to failure unless the $CO_2$ removed is not only that stored in the blood and interstitium but from the entire body.

Relative to this concept, in this issue of the *Journal*, Giosa and colleagues (pp. 318–327) report the findings of a physiology study exploring $CO_2$ kinetics, whole-body stores, and the impact of ventilation and $ECCO_2R$ on both (5). Using a porcine model, they measured exhaled $CO_2$ and $\dot{V}_{O_2}$ as they altered $V_E$ and $ECCO_2R$. Armed with this information, they were able to use the respiratory quotient to determine metabolic $\dot{V}_{CO_2}$ ($\dot{V}m_{CO_2}$). Here lies a potential limitation of the work because it was necessary to make certain assumptions for $\dot{V}m_{CO_2}$ calculations as the experiment progressed. The animals were subjected to different ventilatory conditions for 48 hours, and the difference between exhaled $CO_2$ and metabolically produced $CO_2$ was used to determine changes that had occurred in $CO_2$ stores. Animals were either hyperventilated or hypoventilated. After 24 hours, some of the hypoventilated animals received $ECCO_2R$ to supplement alveolar ventilation, and some had ventilation returned to baseline. A key observation of their work was that $CO_2$ changes occurred in two phases, as follows: a fast phase in which $P_{CO_2}$ rapidly changed in blood, followed by a slow phase, which was revealed as a failure of measured $P_{CO_2}$ to reach equilibrium even after 24 or 48 hours. So, how do we interpret these two phases?

Perhaps the simplest data to understand is the fast phase, in which blood and interstitial fluid quickly load or unload their $CO_2$ stores. Assuming relatively constant metabolism, conventional wisdom accepts that measured $P_{CO_2}$ reaches a new equilibrium within 45 minutes of ventilatory changes (6). A quick glance at the kinetics reported by Giosa and colleagues supports this; changes in ventilation (or $ECCO_2R$) are followed by a rapid change in $P_{CO_2}$ that plateaus within 15 minutes and changes little between 15 and 60 minutes. However, by continuing experimental conditions for 24 or 48 hours, the authors showed that $P_{CO_2}$ steadily increases or decreases at 0.002–0.003 mm Hg/minute depending on whether hypoventilation or hyperventilation is continued.

Importantly, during prolonged hypoventilation, the volume of $CO_2$ slowly accumulating in the body exceeded the amount present (or stored) in the blood and interstitium. Similarly, during hyperventilation, the volume of expired $CO_2$ exceeded that which can be explained by the sum of the metabolically produced $CO_2$



Originally Published in Press as DOI: 10.1164/rccm.202008-3306ED on September 11, 2020