

6. Fuchs O, Bahmer T, Rabe KF, von Mutius E. Asthma transition from childhood into adulthood. *Lancet Respir Med* 2017;5:224–234.
7. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemière C, *et al.*; Canadian Respiratory Research Network. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA* 2017; 317:269–279.
8. Psallidas I, Backer V, Kuna P, Palmér R, Necander S, Aurell M, *et al.* A phase 2a, double-blind, placebo-controlled randomized trial of inhaled TLR9 agonist AZD1419 in asthma. *Am J Respir Crit Care Med* 2021; 203:296–306.
9. Huang X, Yang Y. Targeting the TLR9-MyD88 pathway in the regulation of adaptive immune responses. *Expert Opin Ther Targets* 2010;14: 787–796.
10. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, *et al.*; American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602–615.
11. Petsky HL, Cates CJ, Kew KM, Chang AB. Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis. *Thorax* 2018; 73:1110–1119.
12. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–224.
13. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, *et al.*; National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315–323.

Copyright © 2021 by the American Thoracic Society



## ⊗ 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

⊗ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

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* trachea-bronchitis 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](http://www.atsjournals.org).

Joost Wauters, M.D., Ph.D.  
Department of Microbiology, Immunology and Transplantation  
Catholic University Leuven  
Leuven, Belgium  
and  
Medical Intensive Care Unit  
University Hospitals Leuven  
Leuven, Belgium

Frederic Lamothe, M.D.  
Institute of Microbiology  
and  
Infectious Diseases Service  
Lausanne University Hospital and University of Lausanne  
Lausanne, Switzerland

Bart J. A. Rijnders, M.D., Ph.D.  
Department of Internal Medicine  
Erasmus University Medical Center  
Rotterdam, the Netherlands

Thierry Calandra, M.D., Ph.D.  
Infectious Diseases Service  
Lausanne University Hospital and University of Lausanne  
Lausanne, Switzerland

ORCID IDs: 0000-0002-5983-3897 (J.W.); 0000-0002-1023-5597 (F.L.); 0000-0003-3051-1285 (T.C.).

## References

- Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, *et al.*; Dutch-Belgian Mycosis study group. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. *Lancet Respir Med* 2018;6: 782–792.
- van de Veerdonk FL, Kolwijck E, Lestrade PPA, Hodiament CJ, Rijnders BJ, van Paassen J, *et al.*; Dutch Mycoses Study Group. Influenza-associated aspergillosis in critically ill patients. *Am J Respir Crit Care Med* 2017;196:524–527.
- Verweij PE, Rijnders BJA, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, *et al.* Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. *Intensive Care Med* 2020;46:1524–1535.
- Meersseman W, Lagrou K, Maertens J, Wilmer A, Hermans G, Vanderschueren S, *et al.* Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. *Am J Respir Crit Care Med* 2008;177:27–34.
- Lamothe F, Glampedakis E, Boillat-Blanco N, Oddo M, Pagani JL. Incidence of invasive pulmonary aspergillosis among critically ill COVID-19 patients. *Clin Microbiol Infect* 2020;26:1706–1708.
- Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, *et al.*; PREDICO study group. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. *Clin Infect Dis* [online ahead of print] 28 Jul 2020; DOI: 10.1093/cid/ciaa1065.
- Fekkar A, Lampros A, Mayaux J, Poignon C, Demeret S, Constantin J-M, *et al.* Occurrence of invasive pulmonary fungal infections in patients with severe COVID-19 admitted to the ICU. *Am J Respir Crit Care Med* 2021;203:307–317.
- Yusuf E, Vonk A, van den Akker JPC, Bode L, Sips GJ, Rijnders BJA, *et al.* Frequency of positive *Aspergillus* tests in COVID-19 patients in comparison to other patients with pulmonary infections admitted to the ICU. *J Clin Microbiol* [online ahead of print] 4 Dec 2020; DOI: 10.1128/JCM.02278-20.
- Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, *et al.*; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19 - preliminary report. *N Engl J Med* [online ahead of print] 17 Jul 2020; DOI: 10.1056/NEJMoa2021436.
- Schwartz IS, Friedman DZP, Zapernick L, Dingle TC, Lee N, Sligl W, *et al.* High rates of influenza-associated invasive pulmonary aspergillosis may not be universal: a retrospective cohort study from Alberta, Canada. *Clin Infect Dis* 2020;71:1760–1763.
- White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, *et al.* A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. *Clin Infect Dis* [online ahead of print] 29 Aug 2020; DOI: 10.1093/cid/ciaa1298.
- Santana MF, Pivoto G, Alexandre MAA, Baía-da-Silva DC, Borba MGDs, Val FA, *et al.* Confirmed invasive pulmonary aspergillosis

and COVID-19: the value of postmortem findings to support antemortem management. *Rev Soc Bras Med Trop* 2020;53:e20200401.

13. Antinori S, Rech R, Galimberti L, Castelli A, Angeli E, Fossali T, et al. Invasive pulmonary aspergillosis complicating SARS-CoV-2 pneumonia: a diagnostic challenge. *Travel Med Infect Dis* [online ahead of print] 26 May 2020; DOI: 10.1016/j.tmaid.2020.101752.
14. Rutsaert L, Steinfurt N, Van Hunsel T, Bomans P, Naesens R, Mertes H, et al. COVID-19-associated invasive pulmonary aspergillosis. *Ann Intensive Care* 2020;10:71.
15. Flikweert AW, Grootenboers MJH, Yick DCY, du Mée AWF, van der Meer NJM, Rettig TCD, et al. Late histopathologic characteristics

of critically ill COVID-19 patients: different phenotypes without evidence of invasive aspergillosis, a case series. *J Crit Care* 2020;59:149–155.

16. De Michele S, Sun Y, Yilmaz MM, Katsyv I, Salvatore M, Dzierba AL, et al. Forty postmortem examinations in COVID-19 patients. *Am J Clin Pathol* 2020;154:748–760.
17. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020;20:1135–1140.

Copyright © 2021 by the American Thoracic Society



## ⊗ Rethinking Alveolar Ventilation and CO<sub>2</sub> 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<sub>2</sub>R) experiment in sheep. They showed that pulmonary ventilation progressively decreased until breathing ceased as CO<sub>2</sub> removal with ECCO<sub>2</sub>R approached metabolic CO<sub>2</sub> 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<sub>2</sub>. 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>R can increase CO<sub>2</sub> removal, but removing only the CO<sub>2</sub> dissolved in blood cannot permit long off-dialysis survival because stopping ECCO<sub>2</sub>R will cause CO<sub>2</sub> concentrations to immediately rise. This therapeutic approach

seems doomed to failure unless the CO<sub>2</sub> 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<sub>2</sub> kinetics, whole-body stores, and the impact of ventilation and ECCO<sub>2</sub>R on both (5). Using a porcine model, they measured exhaled CO<sub>2</sub> and  $\dot{V}O_2$  as they altered  $\dot{V}_E$  and ECCO<sub>2</sub>R. Armed with this information, they were able to use the respiratory quotient to determine metabolic  $\dot{V}_{CO_2}$  ( $\dot{V}_{mCO_2}$ ). Here lies a potential limitation of the work because it was necessary to make certain assumptions for  $\dot{V}_{mCO_2}$  calculations as the experiment progressed. The animals were subjected to different ventilatory conditions for 48 hours, and the difference between exhaled CO<sub>2</sub> and metabolically produced CO<sub>2</sub> was used to determine changes that had occurred in CO<sub>2</sub> stores. Animals were either hyperventilated or hypoventilated. After 24 hours, some of the hypoventilated animals received ECCO<sub>2</sub>R to supplement alveolar ventilation, and some had ventilation returned to baseline. A key observation of their work was that CO<sub>2</sub> changes occurred in two phases, as follows: a fast phase in which PCO<sub>2</sub> rapidly changed in blood, followed by a slow phase, which was revealed as a failure of measured PCO<sub>2</sub> 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<sub>2</sub> stores. Assuming relatively constant metabolism, conventional wisdom accepts that measured PCO<sub>2</sub> 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<sub>2</sub>R) are followed by a rapid change in PCO<sub>2</sub> 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 PCO<sub>2</sub> 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<sub>2</sub> slowly accumulating in the body exceeded the amount present (or stored) in the blood and interstitium. Similarly, during hyperventilation, the volume of expired CO<sub>2</sub> exceeded that which can be explained by the sum of the metabolically produced CO<sub>2</sub>

⊗This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

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