room air between interventions, resulting in low probability of contamination between sequential experimental conditions. Sufficient time to ensure that the particle concentrations return to baseline is necessary between interventions in future studies, especially if frequent air exchange is not available.

Optimal respiratory management of patients suffering from COVID-19 pneumonia is debated; the potential benefits of early intubation, NIV, and HFNC, to be put into balance with the potential risk of bioaerosol generation and dispersion, are controversial; and practice is heterogeneous between units and over time during the pandemic spread (13, 14). As evidence is accumulating against a significantly increased bioaerosol generation associated with the use of HFNC and NIV, clinicians may consider those therapeutic options as they do when caring for patients with hypoxemia without COVID-19, not overemphasizing the potential theoretical risk of increased infectious transmission. In any case, personal protective equipment should be worn by professionals caring for patients with suspected or confirmed COVID-19.

Beyond bioaerosol generation and dispersion, the crucial question that needs to be answered remains the infectious potential of the virus carried by the bioaerosols generated by the patients or various procedures and its relative quantitative importance compared with other routes of viral dissemination such as surface contact. ■

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Jie Li, Ph.D., R.R.T., R.R.T.-A.C.C.S., R.R.T.-N.P.S.
Department of Cardiopulmonary Sciences
Rush University Medical Center
Chicago, Illinois

Stephan Ehrmann, M.D., Ph.D.
Médecine Intensive Réanimation
CHRU de Tours
Tours, France
and
Centre d'étude des pathologies respiratoires INSERM U1100
Université de Tours
Tours, France

ORCID IDs: 0000-0003-0121-1291 (J.L.); 0000-0001-6221-4467 (S.E.).

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Invasive Pulmonary Aspergillosis in Ventilator-associated Pneumonia: The Hidden Enemy?

Ventilator-associated pneumonia (VAP) is one of the most important hospital-acquired infections in mechanically ventilated patients. It has a major impact in terms of morbidity, mortality, and health costs.

The microbiology of bacterial VAP has been well established by studies using standard quantitative or semiquantitative microbiological techniques in either distal (BAL) or proximal samples (endotracheal aspirates) (1). The few studies to include rapid molecular techniques have demonstrated an increased rate of microbial diagnoses compared with standard methods (2).

Fungi, and especially *Aspergillus* species, are recognized as a potential cause of VAP in nonimmunosuppressed patients. However, the most recent guidelines do not provide recommendations for their suspicion and diagnosis (3, 4), nor do

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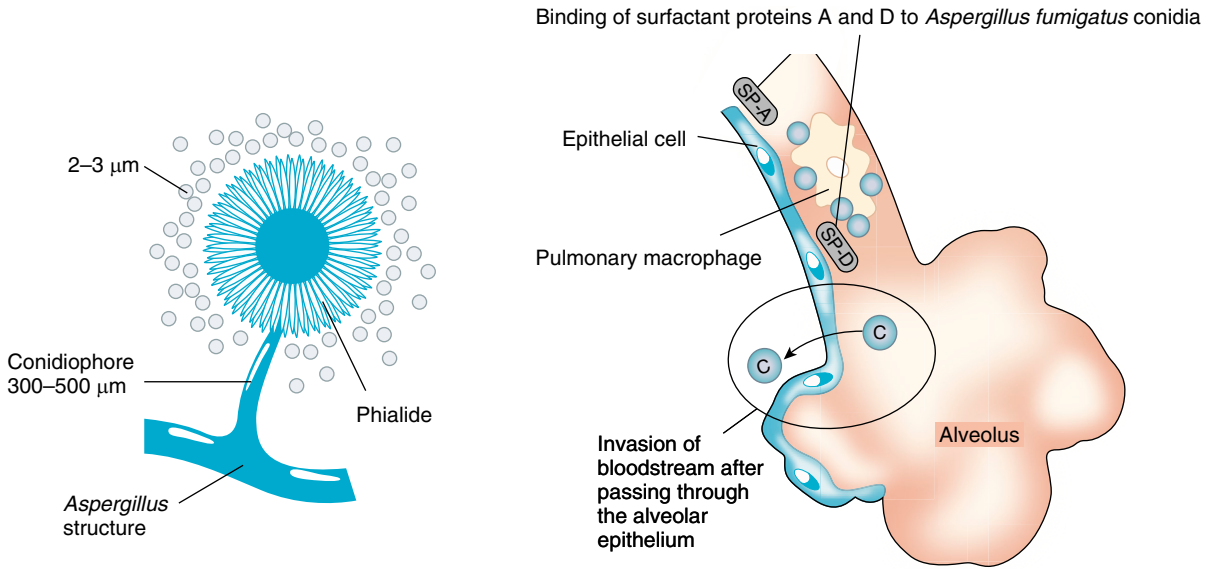

Figure 1. *Aspergillus* structure and mechanism of binding of pulmonary surfactant proteins A and D to *Aspergillus fumigatus* conidia enhances phagocytosis and killing by human neutrophils and alveolar macrophages. SP-A = surfactant protein A; SP-D = surfactant protein D.

clinicians include fungi in the differential diagnosis in the case of suspected VAP in nonimmunosuppressed patients. *Aspergillus* species have angioinvasive properties. It is well known that aspergillosis requires penetration of the spores after colonizing the upper respiratory tract, which is associated with tissue invasion (Figure 1). Understanding the pathophysiological mechanisms of fungal colonization is essential to develop strategies able to avert the disease.

The diagnosis of invasive pulmonary aspergillosis is based on cultures of clinical samples and on the detection of fungal elements (hyphae) in histopathological examination in primarily sterile specimens, independently of the culture results. Unfortunately, this is not possible in mechanically ventilated critically ill patients, which is why autopsy studies of mechanically ventilated patients have found aspergillosis to be the most frequently neglected potential cause of death (5). Additional tests may include nonculture methods, such as the detection of fungal cell wall components. Galactomannan antigens (GM) and 1,3-β-D-glucan circulating in serum and BAL are useful for the diagnosis of invasive aspergillosis. However, because of a variety of factors, there is a possibility of false-positive or false-negative results (6). False positives may be a consequence of using antibiotics such as β-lactams (piperacillin with tazobactam) and other drugs (immunoglobulin, cyclophosphamide, and plasma-like products). Patients infected with other fungal species (*Penicillium marneffei*, *Cryptococcus neoformans*, *Geotrichum capsulatum*, *Histoplasma capsulatum*, or *Lichtheimia ramosa*) or with *Bifidobacterium* species have also been reported as cases of cross reactions (7).

In this issue of the *Journal*, Loughlin and colleagues (pp. 1125–1132) (8) present the retrospective results of a multicenter UK study of two cohorts of patients with suspected VAP. The same methodology was applied in 194 nonimmunosuppressed patients, which included BAL with stains and semiquantitative standard cultures for bacteria and fungi. Significantly, the authors measured GM in BAL and in serum. The definition of probable *Aspergillus* infections required one of the following: positive microscopy or histology, a positive BAL fluid culture, and a GM optical index $\geq$1 in BAL or in serum. Using this systematic definition, the authors found a prevalence of *Aspergillus* VAP of 12.4%, a figure far higher than those reported in previous epidemiological studies in which the prevalence of the condition was anecdotal or very low.

How Can We Explain These Findings?

1) In previous studies, systematic searches for *Aspergillus* were not performed; investigators relied only on stains and cultures and on autopsy findings. Quantitative or semiquantitative cultures were also not performed.
2) Many studies were based only on endotracheal aspirates, which are not sensitive for detecting fungi in their cultures.
3) In nonsevere immunosuppressed patients, GM in BAL and serum is not measured and is not included in the diagnostic workup.
4) Clinicians do not include *Aspergillus* as a potential cause of VAP in nonsevere immunosuppressed patients.

The main lesson of this study is that *Aspergillus* is a more frequent cause of VAP in nonimmunosuppressed patients than clinicians may think. Second, applying nonculture methods such as GM in BAL and serum can diagnose some additional cases and thus save lives. The question that arises immediately is whether these procedures should be applied systematically in all cases of suspected VAP. The study under review was not designed to answer this question. The risk factors for *Aspergillus* VAP in nonimmunosuppressed patients are not well known but probably include long-term mechanical ventilation, previous antibiotic treatment, corticosteroid administration, and chronic lung comorbidities. In this study, corticosteroid treatment and chronic obstructive pulmonary disease were more frequent but nonsignificant in cases with presumptive diagnosis of *Aspergillus*.

Another point to establish is the extent to which rapid molecular techniques such as PCR might help in the diagnosis of *Aspergillus* VAP when added to cultures and GM in BAL. In the current study, PCR was positive in 10 out of the 24 patients in BAL and in 5 in serum, so it was not positive for *Aspergillus* in all 24 patients. This means that PCR should be performed together

with cultures and GM for the diagnosis of *Aspergillus* VAP in nonimmunosuppressed patients. In any case, both cultures and PCR need quantification to rule out colonization.

A burning subject is *Aspergillus* VAP in ventilated patients with coronavirus disease (COVID-19). In this issue of the *Journal*, Van Biesen and colleagues (pp. 1171–1173) report the performance of nondirected BAL in a cohort of 42 ventilated patients with COVD-19 (9). Based on clinical symptoms and a positive GM testing on directed BAL fluid, the proportion of putative aspergillosis was 21.4%. Fungal cultures of the nondirected BAL yielded positive results in seven of the patients with clinical symptoms and positive GM (cutoff 1 optical index) (77.8%). Bronchoscopic BAL is the preferred method to measure GM in BAL. However, because of the risk of aerosolization in patients with COVID-19, nonbronchoscopic methods should be the preferred ones given the results of this study. In fact, this is the current recommendation of the American Association for Bronchology and Interventional Pulmonology (10). Probably the use of nondirected BAL may increase the risk of false positives.

In summary, the manuscript published by Loughlin and colleagues provides some useful answers and poses interesting questions. On the one hand, the study warns us about the possibility of *Aspergillus* VAP in nonimmunosuppressed patients, a diagnosis that is frequently neglected. On the other, it draws attention to the matter of *Aspergillus* colonization, an issue that remains unresolved in this population. The second manuscript from Van Biesen and colleagues (9) recommends the use of nondirected BAL in mechanically ventilated patients with COVID-19 to minimize aerosolization but maintains a good performance for *Aspergillus* diagnosis (GM + cultures). ■

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Antoni Torres, M.D., Ph.D.
Hospital Clinic, IDIBAPS
Universitat de Barcelona
Barcelona, Spain
Universitat de Barcelona
Barcelona, Spain
CIBERes
Barcelona, Spain
and
ICREA, Institución Catalana de Investigación y Estudios Avanzados
Barcelona, Spain

Ignacio Martin-Loeches, M.D., Ph.D.
Hospital Clinic, IDIBAPS
Universitat de Barcelona
Barcelona, Spain
Universitat de Barcelona
Barcelona, Spain
CIBERes
Barcelona, Spain
Multidisciplinary Intensive Care Research Organization (MICRO)
Department of Intensive Care Medicine, St. James's University Hospital
Dublin, Ireland
and
Trinity Centre for Health Sciences
Dublin, Ireland

ORCID ID: 0000-0002-5834-4063 (I.M.-L.).

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