Viral-associated Pulmonary Aspergillosis: Have We Finally Overcome the Debate of Colonization versus Infection?

Invasive pulmonary aspergillosis (IPA) has emerged in the ICU setting following the recent influenza H1N1 and coronavirus disease (COVID-19) pandemics. Viral-associated IPA (VAPA) is quite different than classical IPA in terms of pathogenicity and clinical presentation in immunocompromised populations. An important matter of debate is the actual significance of mycological evidence of *Aspergillus* in a respiratory sample and the distinction between colonization and true infection (1).

This is the question Vanderbeke and colleagues (pp. 301–311) address in this issue of the *Journal* (2). They performed a retrospective case series of critically ill adult ICU patients from a single Belgian center with influenza or COVID-19 infection who underwent autopsy ($n = 44$) or who had an ante- or postmortem tracheobronchial biopsy ($n = 25$). They determined the proportion of patients with histologically proven VAPA and assessed the performance of current consensus criteria of antemortem probable VAPA (3, 4). They found high incidences of proven influenza-associated pulmonary aspergillosis (29%) and COVID-19–associated pulmonary aspergillosis (26%) in the autopsy cohort, in line with some autopsy series and considerably higher than in others (5–7). Probable antemortem VAPA was confirmed by histopathology in 55% of patients with influenza and in 50% of patients with COVID-19. Only one histopathologically proven VAPA was missed by the antemortem assessment. Positive findings for galactomannan in BAL had the best sensitivity (92%) for VAPA, with a high specificity, particularly in patients without prior mold-active therapy (94%).

Although there are previous studies showing the association between a clinical diagnosis of probable VAPA and poor outcome, the causality link may be unclear in some cases. Indeed, a positive mycological test could also indicate patients who are more severely ill and prone to fungal colonization (8–10). The study of Vanderbeke and colleagues strongly suggests that microbiological documentation of *Aspergillus* represents true VAPA rather than colonization in more than half of cases and therefore supports the use of the VAPA consensus criteria as reliable diagnostic tools (3, 4). Although histopathologically proven VAPA is considered the gold standard, it may also suffer from some biases. First, by focusing on nonsurviving patients, there is a selection bias in favor of the sickest patients. Therefore, the prevalence of VAPA may be overestimated, and we cannot deduce the actual proportions of proven VAPA versus *Aspergillus* colonization among the less severely ill patients who survived. The sensitivity of histopathologic analysis may also be questioned. The major histological pattern of VAPA, independent of viral etiology, was impeded growth, which may raise concern for sampling error even during autopsy. Moreover, previous antifungal therapy might have been a cause of false-negative autopsy results, as patients with probable unconfirmed VAPA had a longer time receiving mold-active therapy (15 d vs. 9 d) than those with proven VAPA.

Another important question concerns the reproducibility of these results in other ICU settings or regions with lower VAPA incidence. Vanderbeke and colleagues found a high VAPA incidence in an ICU cohort consisting of a substantial proportion of immunocompromised patients (27%) who also exhibited a high degree of use of systematic corticosteroids before admission (48% of patients). Other studies have reported much lower prevalences of antemortem or postmortem VAPA (i.e., <5%) (5, 11). Although Vanderbeke and colleagues showed a 68% specificity of VAPA consensus criteria to identify proven autopsy cases, the positive predictive value would vary from 55% to only 8% for VAPA prevalences ranging between 30% and 3%, respectively.

Nonetheless, the results of this study, in addition to previous data supporting the association of VAPA with increased mortality (10, 12), strongly support the prompt initiation of antifungal therapy, at least preemptively, in such patients at high risk in an ICU with severe viral infections. A randomized placebo-controlled trial might have provided definitive proof of the benefit of antifungal therapy in this setting, but this is no longer feasible because of ethical considerations.

What should be the next steps? The pandemic of severe COVID-19 has diminished, but seasonal influenza remains an issue, and other respiratory viruses may emerge or gain in virulence. The reasons why VAPA prevalence may exhibit such important variations across regions and even over time within a single center remain unclear (13). Although differential awareness and diagnostic algorithms likely play a role, environmental conditions and genetic predisposing factors should be investigated. The role of antifungal prophylaxis and the selection of patients at high risk qualifying for such an approach should be further investigated.

Until now, the core of the debate was about the distinction between true VAPA and colonization. The study by Vanderbeke and colleagues, despite its limitations, suggests that we should end this debate, as it showed that a substantial number of *Aspergillus* cases (with a positive mycological criterion) were in fact proven.

After a lot of efforts have been put into the elaboration of consensus definitions of VAPA, expert panels should now move to practical guidelines for the overall management of VAPA in terms of diagnostic and therapeutic approaches. Because the emergence of mold infections in the ICU has become a reality, increased awareness is also expected to lead to an increase in antifungal drug use, with possible epidemiological shifts toward more resistant fungi, including more resistant *Candida* spp. that remain a major issue in this setting. In addition to management guidelines, epidemiological surveillance programs and antifungal stewardship policies will be needed. ■

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Illuminating the Importance of Pulmonary Arterial Compliance in Pulmonary Hypertension

Pulmonary hypertension (PH) is an abnormal increase in pulmonary arterial pressure that is a hemodynamic consequence of a broad range of cardiopulmonary and systemic diseases. PH is an umbrella term that has been iteratively classified into five clinical groups according to similar hemodynamic profiles, pathophysiology, associated conditions, and management (1). Over time, with new and accumulating data from large cohorts, the hemodynamic definitions and classification of PH have evolved. For example, the threshold for PH has been lowered from a mean pulmonary arterial pressure (mPAP) of ⩾25 mm Hg to >20 mm Hg based on systematic reviews of normal hemodynamics and large studies analyzing the relationships between hemodynamic variables and clinical outcomes (2, 3). Similarly, the threshold for an abnormal pulmonary vascular resistance (PVR) has been lowered from >3 Wood units to >2 Wood units based on evidence that an increased mortality risk is present starting at >2.2 Wood units (4). Pulmonary arterial compliance (PAC) has gained increasing attention as a useful hemodynamic marker in PH, with several studies showing an association between PAC and outcomes (5). PAC is calculated from

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