



HAL
open science

Fungal Fog in Viral Storms: Necessity for Rigor in Aspergillosis Diagnosis and Research

Simon Feys, Martin Hoenigl, Jean-Pierre Gangneux, Paul Verweij, Joost Wauters

► **To cite this version:**

Simon Feys, Martin Hoenigl, Jean-Pierre Gangneux, Paul Verweij, Joost Wauters. Fungal Fog in Viral Storms: Necessity for Rigor in Aspergillosis Diagnosis and Research. *American Journal of Respiratory and Critical Care Medicine*, 2024, 209 (6), pp.631-633. 10.1164/rccm.202310-1815VP . hal-04467387

HAL Id: hal-04467387

<https://univ-rennes.hal.science/hal-04467387>

Submitted on 11 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Viewpoint: Turning the Air Blue

Fungal Fog in Viral Storms: Necessity for Rigor in Aspergillosis Diagnosis and Research

Simon Feys MD^{1,2}, Martin Hoenigl MD^{3,4,5}, Jean-Pierre Gangneux MD PhD^{6,7}, Paul E Verweij MD PhD^{8,9}, Joost Wauters MD PhD^{1,2}

Affiliations:

1: Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium

2: Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium

3: Division of Infectious Diseases, ECMM Excellence Center, Department of Internal Medicine, Medical University of Graz, Graz, Austria

4: Translational Medical Mycology Research Group, Medical University of Graz, Graz, Austria

5: Bio TechMed, Graz, Austria

6: Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail), UMR_S 1085, Rennes, France

7: Centre Hospitalier Universitaire de Rennes, Laboratoire de Parasitologie-Mycologie, ECMM Excellence Center in Medical Mycology, French National Reference Center on Mycoses and Antifungals (CNRMA LA-Asp C), Rennes, France

8: Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands

9: Center of Expertise for Mycology, Radboud University Medical Center-Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

Corresponding author: Joost Wauters

Herestraat 49, 3000 Leuven, BELGIUM

+32 16 34 03 85; joost.wauters@uzleuven.be

Running title: Fungal Fog in Viral Storms

Descriptor number: 10.4 Diagnosis of Infections

Total word count: 1000

Author contributions: Conceptualisation: SF, JW; Interpretation: SF, MH, JPG, PEV, JW;

Writing - Original draft: SF; Writing – Review & Editing: SF, MH, JPG, PEV, JW. All authors read and approved the final manuscript version.

ORCID IDs:

- Simon Feys: 0000-0002-7516-9471
- Martin Hoenigl: 0000-0002-1653-2824
- Jean-Pierre Gangneux: 0000-0002-4974-5607
- Paul Verweij: 0000-0002-8600-9860
- Joost Wauters: 0000-0002-5983-3897

Imagine reading a study that investigates the incidence of myocardial infarction among smokers hospitalized for acute chest pain. The authors report that only a minority of the patients received cardiovascular work-up with at least an electrocardiogram. They observe a low incidence of myocardial infarction, and consequently conclude that myocardial infarction is infrequent in that at-risk population.

We could even take it a step further: imagine the same study, but now the authors do not even mention how many patients received cardiovascular work-up, nonetheless their conclusion remains the same.

What would you think of the validity of such studies? Presumably, in many research fields, such studies would not survive peer review. Common sense would require to ask the authors to clearly report how many patients received the necessary work-up to establish a diagnosis, and to adapt their conclusions about disease incidence accordingly.

This common sense does not seem to apply to the research field of influenza- or COVID-19-associated pulmonary aspergillosis (IAPA or CAPA). Indeed, the extreme variation in reported incidences of these fungal superinfections in patients with severe viral pneumonia have partly been attributed to variations in diagnostic approaches (1). This is a major issue because mycological diagnosis of IAPA and CAPA relies heavily on bronchoalveolar lavage (BAL) sampling, given the limited sensitivity of serum galactomannan. Consequently, if one does not actively look for IAPA or CAPA, one will not find it. Not only the depth of fungal work-up differs, as we noted that in many observational studies essential information for calculating the incidence is missing, namely the proportion of patients that received BAL sampling.

The diligence of a physician to find a disease should not have to define whether you have a disease or not. Therefore, to substantiate these issues, we investigated all studies found in PubMed using the search terms “(“Aspergill*”) AND (“Influenza” OR “COVID-19”)” that reported observational data on IAPA or CAPA published online between January 1st, 2009 and October 1st, 2023. We identified 51 studies that included more than 100 patients requiring critical care for severe influenza or COVID-19, and which used the original or modified AspICU criteria for aspergillosis on ICU (2, 3), the criteria by Verweij et al for IAPA (4) or CAPA (5), the CAPA criteria of the European Confederation of Medical Mycology and the International Society for Human and Animal Mycology (6) or modifications based on these criteria. We excluded four studies that reported that no BAL samples were obtained. Two studies included both influenza and COVID-19 patients, these were counted as four separate studies. Only proven, putative or probable IAPA and CAPA were counted as cases. Strikingly, of the 49 included studies (with 22,381 inclusions and 1592 IAPA or CAPA cases), only 27% (13 studies with 3299 inclusions and 457 cases) reported the proportion of included patients that had BAL sampling performed during their ICU stay. IAPA and CAPA incidences were significantly higher in these studies compared to studies that did not report this proportion (median incidence 14% vs. 5%; $p = 0.0026$) (Figure 1A). Likewise, in studies reporting this proportion, those with high rates of sampled patients (arbitrarily defined as >50%) reported higher IAPA or CAPA incidences compared to studies with low rates (median incidence 19% vs. 9%; $p = 0.0062$) (Figure 1B).

Our results demonstrate that mentioning the rates of BAL sampling is essential for reporting IAPA and CAPA incidences, and discussions should interpret the reported incidences in this context. Our results imply that IAPA and CAPA are often underdiagnosed in studies, and that

researchers report the wrong denominator by assuming that non-sampled patients are IAPA or CAPA negative. In extension, IAPA and CAPA are probably underdiagnosed in daily clinical practice as well. Indeed, our results show that the sampling itself is probably underperformed, contributing negatively to the detected incidences.

We advise to have a low threshold to perform BAL sampling for culture and galactomannan testing. Importantly, instillation of a low volume of 2 x 20 mL saline bronchoscopically suffices for microbiological diagnostics and is usually safe (7). Ideally, every influenza patient should receive immediate BAL sampling when admitted to an ICU, given that IAPA typically is already present upon admission, and given that the admission profiles of influenza patients with or without IAPA are similar (3, 8). In COVID-19 patients (and influenza patients without IAPA upon admission), non-resolution or deterioration of the clinical picture should prompt BAL sampling, given that CAPA typically occurs later during ICU stay (1).

Our advice might seem to carry risk for overdiagnosing IAPA or CAPA instead of the present culture of underdiagnosis. Indeed, the current criteria for probable aspergillosis cannot always distinguish colonization from invasive disease, as both BAL culture and non-culture based tests are not 100% specific for invasive aspergillosis. Therefore, sampling more harbors risk of treating more false-positive results (9). However, we have three good reasons to favor a more aggressive, bronchoscopy-based diagnostic strategy. First, a recently published, thorough case series of biopsied and autopsied influenza and COVID-19 patients showed that a substantial number of IAPA and CAPA cases treated with systemic antifungals can be proven upon autopsy, making the debate on colonization or invasive disease less relevant (10, 11). Second, there is no good reason to justify the current mismatch between (extremely) low rates of BAL sampling and the substantial mortality rate

of severe influenza and COVID-19 patients. Indeed, the negative impact of a missed and therefore untreated diagnosis is probably higher than that of a treated colonization, which may have or may have not developed in an airway invasive infection in the absence of treatment. Third, BAL sampling should be preferred over non-bronchoscopic samples, as bronchoscopy allows to detect invasive *Aspergillus* tracheobronchitis (4, 5).

In conclusion, we urge clinicians to actively look for aspergillosis using BAL sampling whenever feasible in patients with severe influenza or COVID-19, and we urge researchers who publish observational studies on IAPA or CAPA to include details on the rates of BAL sampling and testing and interpret their results in the light of those diagnostic strategies.

Acknowledgment

SF acknowledges PhD-funding by Research Foundation Flanders (FWO, grant 11M6924N) for writing this Viewpoint. We thank Hanne Moon Lauwers and Cato Jacobs from University Hospitals Leuven, Belgium for assisting in the data collection for this Viewpoint.

References

1. Hoenigl M, Seidel D, Sprute R, Cunha C, Oliverio M, Goldman GH, *et al.* COVID-19-associated fungal infections. *Nat Microbiol* 2022;7:1127–1140.
2. Blot SI, Taccone FS, Van Den Abeele AM, Bulpa P, Meersseman W, Brusselaers N, *et al.* A Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients. *Am J Respir Crit Care Med* 2012;186:56–64.
3. Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, *et al.* Invasive Aspergillosis in Patients Admitted to the Intensive Care Unit with Severe Influenza: A Retrospective Cohort Study. *Lancet Respir Med* 2018;6:782–792.
4. Verweij P, Rijnders B, Brüggemann R, Azoulay E, Bassetti M, Blot S, *et al.* International Expert Review of Influenza-Associated Pulmonary Aspergillosis in ICU Patients and Recommendations for a Case Definition. *Intensive Care Med* 2020;46:1524–1535.
5. Verweij PE, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, Buil JB, *et al.* Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis. *Intensive Care Med* 2021;47:819–834.
6. Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, *et al.* Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis* 2021;21:e149–e162.
7. 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.
8. Vanderbeke L, Janssen NAF, Bergmans DCJJ, Bourgeois M, Buil JB, Debaveye Y, *et al.* Posaconazole for prevention of invasive pulmonary aspergillosis in critically ill influenza patients (POSA-FLU): a randomised, open-label, proof-of-concept trial. *Intensive Care Med* 2021;47:674–686.
9. Clancy CJ, Nguyen MH. Coronavirus Disease 2019-Associated Pulmonary Aspergillosis: Reframing the Debate. *Open Forum Infect Dis* 2022;9:ofac081.

10. Vanderbeke L, Jacobs C, Feys S, Reséndiz-Sharpe A, Debaveye Y, Hermans G, *et al.* A Pathology-based Case Series of Influenza- and COVID-19–associated Pulmonary Aspergillosis: The Proof Is in the Tissue. *Am J Respir Crit Care Med* 2023;208:301–311.
11. Albrich WC, Lamoth F. Viral-associated Pulmonary Aspergillosis: Have We Finally Overcome the Debate of Colonization versus Infection? *Am J Respir Crit Care Med* 208:230–231.

Figure legend

Figure 1. Panel (A): Boxplot showing differences in IAPA or CAPA incidence between observational studies that did not ($n = 36$) versus those that did ($n = 13$) report the number of all included patients that received BAL sampling. Blue and orange dots represent studies investigating COVID-19 and influenza patients respectively. P value calculated with Mann-Whitney U test. Panel (B): Boxplot showing the differences in IAPA or CAPA incidence between studies with less versus studies with more than 50% of all included patients having received a BAL sampling. Only observational studies that unequivocally reported the number of all included patients in whom at least one BAL sampling was performed were included in this analysis. Blue and orange dots represent studies investigating COVID-19 and influenza patients respectively. P value calculated with Mann-Whitney U test.

Figures**Figure 1**