Detection of Invasive Pulmonary Aspergillosis in COVID-19 with Nondirected BAL

To the Editor:

Invasive pulmonary aspergillosis (IPA) can complicate influenza pneumonia in critically ill patients owing to viral destruction of bronchial mucosa, facilitating invasion of *Aspergillus* species, and compromised host defenses to *Aspergillus* (1). Given the association between IPA and increased mortality in influenza, rapid diagnostic investigations and early (preemptive) treatment of IPA are recommended in critically ill patients with influenza (2). In ICU patients with coronavirus disease (COVID-19), the same principles may apply as in influenza. A high incidence of IPA in patients with COVID-19 admitted to the ICU has been reported in small cohorts of patients, some of which appeared online (3–7). However, in these studies, a bronchoscopy with BAL was not consistently applied, which may hamper estimation of the IPA incidence in COVID-19, as a BAL to obtain material for culture and for galactomannan (GM) measurement is generally recommended for IPA diagnosis in the critically ill. However, owing to risk of aerosolization, only a restricted role for bronchoscopy with BAL is recommended in patients with COVID-19 (8). We have applied a diagnostic approach by performing a nondirected BAL via a closed-circuit suction catheter, which we describe in this letter. Using this nondirected BAL technique as a standard approach, we aimed to determine the proportion of patients with IPA in a cohort of patients with COVID-19 (PCR confirmed) requiring mechanical ventilation who were consecutively admitted to the ICU of our teaching hospital during a 3-week time frame in April 2020. The institutional review board of the Amsterdam University Medical Center considered the study as not requiring informed consent. The clinical AspICU algorithm can be used to distinguish IPA from colonization in critically ill patients (9), but as viral infection is not a classified host risk factor in this definition, the host factor was omitted. The IPA definition used in this paper is based on nondirected BAL GM testing with a cutoff of 1 optical density index, for which sensitivity and specificity are 86% and 95%, respectively, combined with worsening clinical symptoms (i.e., increase in C-reactive protein, worsening Pa_{O_2}/Fi_{O_2} ratio, persistent or rising fever). Nondirected BAL was performed at a median of 2 days (range, 0–8 d) after ICU admission, in nonparalyzed patients, by advancing a 12-F suction catheter with a length of 54 cm via a closed circuit until bronchial wedging (Halyard Turbo-cleaning closed suction system for adults). Then, 2 × 20 ml of sterile NaCl 0.9% was given via the closed circuit and retrieved via the suction catheter. Samples were sent for GM (by ELISA, Platelia *Aspergillus* Ag from BIO-RAD) and culture only if it yielded nontransparent fluid. All patients received a 5-day course of hydroxychloroquine and lopinavir/ritonavir, either of which was stopped upon the emergence of side effects. Differences between IPA and non-IPA were tested with Student's *t* test or Mann-Whitney *U* or chi-square test/Fisher's exact test depending on data distribution. *P* value <0.05 was considered statistically significant.

Of 53 included patients, 2 patients died within 24 hours after admission and 9 patients were transferred to another hospital for logistical reasons shortly after admission. The remaining 42 patients underwent a nondirected BAL (patient characteristics in Table 1). A classical IPA risk factor was present in only one patient, who received immunosuppressive medication in the context of a renal transplant. None of the other patients received corticosteroid treatment before or during ICU admission. Patients with IPA more often had chronic obstructive pulmonary disease or asthma compared with those without IPA ($P < 0.05$), which may suggest a role for impaired ciliary clearance.

Based on clinical symptoms and a positive GM testing on nondirected BAL fluid, the proportion of putative IPA in the tested cohort was 21.4%,

Table 1. Characteristics of Included Patients

	IPA (*n* = 9)	Non-IPA (*n* = 33)	All Patients (*N* = 42)
Age, yr, mean (range)	68 (39–76)	60 (25–79)	62 (25–79)
Sex, M, *n* (%)	5 (55.6%)	28 (84.8%)	33 (78.6%)
BMI, kg/m^2	30 [26–34]	27 [27–29]	29 [28–30]
APACHE IV pred mort	19% [12–25]*	21% [17–26]	21% [17–25]
Lowest PF ratio	94 [74–114]	102 [91–114]	100 [91.2–110.2]
Galactomannan in BAL, ODI	3.33 [2.67–4.00]*	0.21 [0.17–0.27]	0.67 [0.39–0.95]
COPD, *n* (%)	4 (44.4%)*	4 (12.1%)	8 (19.0%)
DM, *n* (%)	1 (11.1%)	9 (27.3%)	10 (23.8%)
Chronic corticosteroid use, *n* (%)	1 (11.1%)	0	1 (2.4%)
Neutropenia, *n*	0	0	0
Stem cell transplant, *n*	0	0	0
Immunodeficiency (acquired/inherited), *n* (%)	1 (11.1%)	0	1 (2.4%)
Arterial hypertension, *n* (%)	3 (33.3%)	10 (30.3%)	13 (30.9%)
ICU LOS, d	37 [26–47]*	19 [15–23]	23 [18–27]
ICU mortality, *n* (%)	2 (22.2%)	5 (15.1%)	7 (16.6%)

Definition of abbreviations: APACHE IV = Acute Physiology and Chronic Health Evaluation IV; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; IPA = invasive pulmonary aspergillosis; LOS = length of stay; ODI = optical density index; PF = Pa_{O_2}/Fi_{O_2}; pred mort = predicted mortality.
Data are expressed as mean [95% confidence interval] unless stated otherwise.
*$P < 0.05$.

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Table 2. Diagnostic Variables of Patients with COVID-19 with Putative IPA

Patient No.	Sex	Age (*yr*)	APACHE IV Pred Mort. (%)	BMI (kg/m^2)	LOS at IPA Diagnosis (*d*)	GM in BAL at Diagnosis (*ODI*)	Fungal Culture	Comorbidity	Clinical Findings at Diagnosis	Radiological Findings
1	M	39	12.55	34.57	19	3.14	No growth	Obese, asthma	Persistent fever, increase in CRP	CT: GGO
2	F	76	25.73	39.34	4	>4.00	*A. fumigatus*	Obese, AHT, asthma	Persistent fever, increase in CRP, worsening PF ratio	CT: GGO, consolidations
3	F	73	14.73	29.78	3	>4.00	*A. fumigatus*	Obese, AHT, COPD	Persistent fever, increase in CRP	X-ray: patchy, peripheral consolidations
4	M	64	21.49	27.76	3	1.10	*A. fumigatus*	Overweight	Rising fever, increase in CRP, MOF	CT: GGO, basal consolidations
5	M	74	12.22	23.15	1	>4.00	*A. fumigatus*	None	Rising fever, increase in CRP, low PF ratio	X-ray: conglomerate alveolar consolidations
6	F	72	18.45	29.70	1	>4.00	*A. fumigatus*	Obese, COPD	Rising fever, increase in CRP, worsening PF ratio	CT: extensive peripheral consolidations, emphysema
7	M	76	30.67	27.78	1	>4.00	*A. flavus*	Overweight, AHT	Rising fever, increase CRP, MOF	CT: GGO, peripheral consolidations
8	M	64	12.80	31.46	6	2.60	No growth	Obese	Rising fever, increase in CRP, worsening PF ratio	X-ray: increasing consolidations
9	M	73	28.62	26.32	3	3.35	*A. terreus*	Overweight, DM II renal transplant	Rising fever, worsening PF ratio	X-ray: increasing consolidations, mainly peripheral

Definition of abbreviations: *A. flavus* = *Aspergillus flavus*; *A. fumigatus* = *Aspergillus fumigatus*; *A. terreus* = *Aspergillus terreus*; AHT = arterial hypertension; APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; CRP = C-reactive protein; CT = computed tomography; DM II = diabetes mellitus type 2; GGO = ground glass opacifications; GM = galactomannan; IPA = invasive pulmonary aspergillosis; LOS = length of stay; MOF = multiorgan failure; ODI = optical density index; PF = Pa_{O_2}/Fi_{O_2}; Pred Mort = predicted mortality.

with a 95% confidence interval of 9.0–33.8% (Table 2). Fungal cultures of the nondirected BAL yielded positive results in seven (77.8%) patients with IPA and only one (3%) patient without IPA, who, because of lack of clinical deterioration and lack of increased BAL GM levels, was ruled to be colonized with *Aspergillus*. At 30-day follow-up after inclusion cessation, ICU mortality in the IPA group was 22.2% and 15.1% in the non-IPA group ($P = 0.61$). Autopsies were not performed because of a perceived risk of contamination. Mean ICU length of stay was 37 days for patients with IPA versus 19 for those without IPA ($P < 0.05$).

A bronchoscopy with BAL is the preferred diagnostic approach because GM antigen detection and culture have a good sensitivity in influenza-associated IPA. However, given the risk of aerosolization, The American Association for Bronchology and Interventional Pulmonology issued a statement providing a limited role for bronchoscopy in patients with COVID-19, advocating the use of a nonbronchoscopic alveolar lavage (10). The technique we used in this study minimizes the risk for care providers while providing a diagnostic tool for our patients. However, the nondirected BAL technique is not validated for GM detection. As all patients had consolidations in all regions of the lung, the chances that a nondirected BAL may result in sampling of a lung region that was not affected by IPA may be low, although it is unclear to which extent consolidations are caused by the virus or by the fungus. More importantly, we cannot rule out overdiagnosis, as a nondirected sample may not always reflect microbiology of the lower airways. Therefore, instead of 0.5, a cutoff GM index of 1.0 was applied in this study. Nevertheless, sampling error cannot be ruled out. Of note, however, concordance between GM index >1.0 and positive *Aspergillus* cultures was high (77.8%).

Early detection and treatment of IPA improves outcome compared with delayed diagnosis. Therefore, we opted to treat all nine patients who were deemed to have putative IPA with antifungal therapy (with an empirical regimen consisting of amphotericin B and voriconazole). We noted a longer ICU length of stay for patients who developed IPA, although ICU mortality did not differ between groups. However, whether COVID-19–associated IPA contributes to mortality, or whether IPA therapy improves outcome, cannot be dissected from our study.

We conclude that the incidence of putative IPA may be high in patients with COVID-19 and that chronic obstructive pulmonary disease may be a particular risk factor. Implementation of surveillance of mechanically ventilated patients with COVID-19 using the nondirected BAL technique is feasible. As COVID-19–associated IPA appears to resemble influenza-associated IPA in many ways, and ICU length of stay was longer in those with IPA versus those without, it is our opinion that active surveillance and treatment may be beneficial in patients with COVID-19. ■

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Stefaan Van Biesen, M.D.
David Kwa, M.D., Ph.D.
Robert J. Bosman, M.D.
OLVG Hospital
Amsterdam, the Netherlands

Nicole P. Juffermans, M.D., Ph.D.*
OLVG Hospital
Amsterdam, the Netherlands
and
Amsterdam University Medical Center
Amsterdam, the Netherlands

*Corresponding author (e-mail: n.p.juffermans@amsterdamumc.nl).

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High Respiratory Drive and Excessive Respiratory Efforts Predict Relapse of Respiratory Failure in Critically Ill Patients with COVID-19

Since the first reported cases in December 2019 in Wuhan, China, coronavirus disease (COVID-19) outbreak has rapidly spread

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