of intermittent iNO therapy made this approach reasonable for our patient.

This patient was remotely managed by clinicians and was more amenable (as a physician herself) to self-monitoring and self-directed therapy than the ordinary patient would be. This is not a typical case, and although the clinical improvement she experienced may not be wholly generalizable, her care represents a first step toward support for outpatient use of iNO to treat exacerbation of PH symptoms due to COVID-19. This approach should not replace best clinical practices when patients present with more substantial symptoms and progressive worsening. Although this case may serve as a proof of concept, it does not prove the utility of iNO for treating respiratory manifestations of COVID-19. Well-designed clinical trials are needed to evaluate the effectiveness of iNO in the setting of COVID-19. If this approach is demonstrated to be effective, outpatient iNO may serve to not only improve clinical outcomes but also reduce the strain on inpatient resources in the current pandemic. ■

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COVID-19–associated Pulmonary Aspergillosis

To the Editor:

Late December 2019, China reported an outbreak of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This has become a global threat, with high attack rates, ICU admissions, and mortality. Initial cohort studies reported a substantial case fatality rate in patients admitted to the ICU, of whom half developed secondary infections (1). Late February, the Southern

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Table 1. Patient Characteristics, Clinical Course, and Outcome

Patient	Sex and Age in Years	Medical History	Days after Symptom Onset to CAPA Onset	APACHE-II at ICU Admission	Days after ICU Admission to CAPA Onset	Bronchoscopy Findings	Microbiological Findings (Days after Symptom Onset of Sample Acquisition)	CAPA Classification (10)	Outcome (Days after Symptom Onset)
1	M, 83	Cardiomyopathy; prednisolon 0.13 mg/kg/d for 28 d preadmission	10	16	3	Not performed	Tracheal aspirate–cultured *Aspergillus fumigatus* (7); serum GM index 0.4 (8)	Possible	Died (12)
2	M, 67	COPD GOLD III; Post-RTx NSCLC 2014; prednisolon 0.37 mg/kg/d for 2 d preadmission	10	16	3	Not performed	Tracheal aspirate–cultured *Aspergillus fumigatus* (5)	Possible	Died (11)
3	M, 75	COPD GOLD IIa	8	15	5	Mucoid white sputum left bronchus	BAL-cultured *Aspergillus fumigatus* (8); BAL GM index 4.0 (8)	Probable	Died (12)
4	M, 43	None	21	10	14	Unrevealing	BAL GM index 3.8 (18); serum GM index 0.1 (16)	Probable	Survived
5	M, 57	Bronchial asthma; fluticason 1.94 mcg/kg/d for 1 mo preadmission	13	15	5	Unrevealing	BAL-cultured *Aspergillus fumigatus* (11); BAL GM index 1.6 (11); serum GM index 0.1 (13)	Probable	Died (20)
6	M, 58	None	42	15	28	Not performed	Sputum-cultured *Aspergillus fumigatus* (36, 40, 43, 47, and 50)	Possible	Survived
Median	—	—	11.5	15	5	—	—	—	12 d

Definition of abbreviations: APACHE-II = Acute Physiology and Chronic Health Evaluation II; CAPA = COVID-19–associated pulmonary aspergillosis; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; GM = galactomannan; GOLD = Global Initiative for Chronic Obstructive Lung Disease; NSCLC = non–small-cell lung carcinoma; RTx = radiation therapy.

Netherlands emerged as a hotspot for COVID-19, and we noticed cases of invasive pulmonary aspergillosis (IPA) occurring in patients with COVID-19 admitted to the ICU. Here, we describe the clinical characteristics of COVID-19–associated pulmonary aspergillosis (CAPA) cases and the frequency in our ICU.

In the first 3 weeks of the outbreak, 135 adult patients with laboratory-confirmed COVID-19 were admitted to the Amphia Hospital Breda, a 700-bed teaching hospital. Of these patients, 31 (23%) required mechanical ventilation on ICU. Eleven ICU patients with COVID-19 developed a secondary infection, of whom six (19.4%) were presumed to have IPA. We identified *Aspergillus fumigatus* in five patients, and in three patients, the *Aspergillus* antigen galactomannan (GM) (Platelia *Aspergillus*; Biorad) was found positive on BAL fluid (Table 1). Three patients had preexisting lung diseases, but none were positive for the European Organisation for Research and Treatment of Cancer (EORTC) and Mycoses Study Group Education and Research Consortium (MSGERC) host factor (2). Three patients received corticosteroids before ICU admission; however, either the dose received was $<$0.3 mg/kg/d or the duration was $<$3 weeks. No other immunosuppressive medication was given before CAPA diagnosis, and all were treated for COVID-19 with chloroquine and lopinavir/ritonavir. There were no significant differences in clinical characteristics between ICU patients with COVID-19 with presumed CAPA and those without presumed CAPA (Table 2). CAPA occurred after a median of 11.5 days (range, 8–42) after COVID-19 symptom onset and at a median of 5 days (range, 3–28) after ICU admission. Chest computed tomographic scan was performed in one patient without apparent signs of fungal infection. In one patient, the bronchoscopy was abnormal, with mucoid white sputum in the left bronchus. Serum GM tested negative in three patients. Voriconazole and anidulafungin combination therapy was initiated in five patients, and one patient received liposomal amphotericin B. Four (66.7%) patients died at a median of 12 ICU days (11–20). Autopsies were not performed because of concerns for the risk of contamination.

Discussion

We observed a high incidence (19.4%) of presumed aspergillosis in our cohort of 31 ICU patients, which might indicate that patients with COVID-19 are at risk for developing IPA.

Secondary fungal infections are increasingly being reported in patients with COVID-19. Studies from Wuhan, China, reported secondary fungal infections in 3 of 9 (33.3%) patients and in 6 of 17 (35.3%) critically ill patients (3, 4). Subsequent reports from Europe indicate that IPA may be found in association with severe COVID-19. Lescure and colleagues described an ICU patient with COVID-19 with antifungal treatment for *A. flavus* who died on Day 24 after symptom onset (5). A research letter reports a fatal case of pulmonary aspergillosis coinfection in an immunocompetent patient (6). A case series from France reported presumed CAPA in 9 of 27 (33.3%) ICU patients with COVID-19, and a series from Germany reported CAPA in 5 of 19 (26.3%) ICU patients. All-cause mortality was three of nine (33.3%) in the French CAPA series and four of five (80%) in the German series (7, 8). This high incidence of secondary aspergillosis in COVID-19 cases resembles the high rates (16% and 23%) of influenza-associated pulmonary aspergillosis (IAPA) that have been reported in ICUs in the Netherlands and Belgium (9). One problem is that there is no case definition for CAPA. However, a case definition for IAPA was recently proposed by an expert panel, and this could be used to classify patients with CAPA (10). In the IAPA case definition, host factors are not used to classify patients because IAPA may develop in any patient with severe influenza. Diagnostic criteria include proven influenza infection with clinical symptoms and a GM index of $\geq$1 on BAL or $\geq$0.5 on serum, or *Aspergillus* spp. cultured from BAL (10). When we apply the IAPA case definition to our cases, three (Table 1) cases could be classified as probable CAPA on the basis of BAL GM detection. The remaining three patients might classify as possible CAPA, with clinical deterioration and *A. fumigatus* recovered from tracheal aspirates because bronchoscopy was not performed. However, recovery of *Aspergillus* from upper respiratory samples may represent colonization and not invasive pulmonary disease.

Table 2. Characteristics of Patients with versus without CAPA, Clinical Course, and Outcome

Parameter	Presumed CAPA (*n* = 6)	Non-CAPA (*n* = 25)	*P* Value
Age, yr, median (range)	62.5 (43–83)	67 (16–79)	0.942
Sex, M, *n* (%)	6/6 (100)	20/25 (80)	0.553
EORTC/MSGERC host risk factors, *n* (%)	0/6 (0)	3/25 (12)	1
Interval from symptom onset to ICU admission, median (range), d	7 (3–14)	9 (3–15)	0.268
Interval from ICU admission to ICU discharge, median (range), d	10.5 (4–47)	14 (2–42)	1
Interval from symptom onset to death, median (range), d	12 (11–20)	17.5 (9–37)	0.570
Systemic corticosteroid use, *n* (%)	2/6 (33.3)	3/25 (12)	0.241
BAL performed, *n* (%)	1/6 (16.7)	6/25 (24)	1
Mortality, *n* (%)	4/6 (66.7)	8/25 (32)	0.174

Definition of abbreviations: CAPA = COVID-19–associated pulmonary aspergillosis; COVID-19 = coronavirus disease; EORTC = European Organisation for Research and Treatment of Cancer; MSGERC = Mycoses Study Group Education and Research Consortium.
We used the Mann-Whitney *U* test or Fisher's exact test to compare differences between patients with and without CAPA when appropriate.

Although 94% of patients with IAPA had positive BAL GM and 71% had positive serum GM in a retrospective ICU study (9), the performance of GM in BAL and serum of patients with CAPA remains to be further evaluated, as it may differ from IAPA. Indeed, in three of our patients with CAPA, circulating GM was not detected in serum. In one patient, the serum GM index was 0.4, which is borderline negative. Including our case series, to date, 22 ICU patients have been reported with presumed CAPA (5–8). Only three patients tested GM-positive in serum. It is important to investigate the diagnostic value of serum GM in CAPA, as there is a general reluctance to perform bronchoscopy in patients with COVID-19 because of the risks for the patient and the pulmonologist.

For CAPA, some clinical characteristics are similar to those of IAPA, including early symptom onset after ICU admission, absence of EORTC/MSGERC host factors, and a high ICU mortality. Invasive *Aspergillus* tracheobronchitis (with plaque formation), which is a common manifestation of IAPA, was, however, not registered in these patients. Three patients were known to have chronic lung disease, which makes differentiation between IPA and *Aspergillus* colonization challenging.

The diagnosis of IAPA has controversies because varying frequencies of the infection have been reported in ICU influenza studies. Geographical differences may explain the observed variations, although differences in diagnostic approaches are also likely to contribute. IAPA may remain undiagnosed because respiratory deterioration is considered to be caused by bacterial coinfection rather than fungal infection, and appropriate fungal diagnostics are not performed (11).

SARS-CoV-2 infection might be a risk factor for IPA, and early diagnosis and prompt treatment for CAPA in ICU patients seems warranted because high mortality rates have been reported. In our center, on suspicion of CAPA, a diagnostic workup is performed that includes serum GM and, if feasible, bronchoscopy with BAL for fungal culture and GM. Antifungal therapy is started in patients highly suspected of having CAPA while awaiting results of fungal diagnostics. Until the risk of IPA in severe COVID-19 is better understood, infectious disease specialists, ICU physicians, pulmonologists, and clinical microbiologists should be aware of this secondary infection. ■

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