



# COVID-19-Associated Pulmonary Aspergillosis at an Academic Medical Center in the Midwestern United States

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Received: 22 January 2021 / Accepted: 15 May 2021  
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**Abstract** Pulmonary aspergillosis has been reported at high rates in patients with coronavirus disease 2019 (COVID-19) and is associated with high morbidity and mortality. We retrospectively assessed all patients admitted to an intensive care unit during the early COVID-19 surge (3/17/20–5/10/20) at our medical center in the midwestern USA for the presence of COVID-19-associated pulmonary aspergillosis (CAPA). Patients were not routinely screened for CAPA; diagnostic work-up for fungal infections was pursued when clinically indicated. Among 256 patients admitted to the ICU with severe COVID-19, 188 (73%) were intubated and 62 (24%) ultimately expired within 30 days of admission to the ICU. Only three patients (1%) were found to have CAPA; diagnosis was made by tracheal aspirate cultures in two cases and by bronchoalveolar lavage fluid

*Aspergillus* galactomannan in one case. None of the patients who developed CAPA had classic risk factors for invasive fungal infection. The occurrence of CAPA was much lower than that reported at other centers, likely reflecting the local epidemiology.

**Keywords** Aspergillosis · Pneumonia · COVID-19 · CAPA

## Introduction

Invasive pulmonary aspergillosis (IPA) is a severe disease that causes high morbidity and mortality. IPA most commonly occurs in the immunocompromised, and classic host factors for this disease include prolonged neutropenia, hematologic malignancy, receipt of an allogeneic hematopoietic cell transplant or solid organ transplant, and prolonged use of high dose corticosteroids or T-cell immunosuppressive agents [1]. Growing evidence demonstrates that IPA also occurs in patients admitted to the intensive care unit (ICU) with other comorbidities such as diabetes, heart disease, and structural lung damage, but without classic risk factors [2, 3]. In ICU patients, the diagnosis of IPA is particularly challenging as the clinical and radiological presentation of IPA can be indistinguishable from other infectious processes. A diagnostic algorithm has been proposed to identify

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Handling Editor: Jean-Pierre Gangneux

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cases of putative IPA in this patient population [3]. Of particular interest are critically ill patients with respiratory viral infections, who are thought to be at increased risk of IPA. Recent studies have shown that severe influenza infection is an independent risk factor for IPA in critically ill patients and is associated with high mortality [4, 5].

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19), caused by the novel SARS-CoV-2 virus, was identified in Wuhan, China. The World Health Organization classified this as a public health emergency of international concern in January 2020. Shortly thereafter, reports of patients with COVID-19 who subsequently developed IPA emerged, particularly from European medical centers [6–9]. Early studies reported up to one-third of critically ill patients with COVID-19 developed IPA, suggesting that these patients may be at increased risk [6, 7]. As the COVID-19 pandemic continues to unfold, expert consensus definition criteria for COVID-19-associated pulmonary aspergillosis (CAPA) have been published [10]. Although not clinically validated, the CAPA definition criteria were developed to optimize clinical management and patient characterization for research purposes.

We sought to report our experience on CAPA among patients with severe COVID-19 illness admitted to our hospital during the early peak of the pandemic in the state of Michigan, USA.

## Materials and Methods

### Patients and Setting

This is a single-center retrospective cohort study of patients  $\geq 18$  years of age who were hospitalized for the management of COVID-19 from March 17, 2020 through May 10, 2020 at the University of Michigan Health System, a 1000-bed tertiary care center, located in the State of Michigan, USA. This study was approved by the institutional review board (IRB reference number HUM00180694).

Patients were included in the study if they were admitted to an ICU for the management of COVID-19 infection, including the existing medical and surgical ICUs as well as several additional ICUs opened to treat a surplus of critically ill patients during the initial local surge of COVID-19 cases.

Patients were identified as having COVID-19 by the presence of a positive polymerase chain reaction (PCR) for SARS-CoV-2 via nasopharyngeal swab. Patients with presumed COVID-19 but without a positive PCR result were excluded from this study. The COVID-19 testing process changed throughout the study; the initial SARS-CoV-2 PCR was conducted by the Michigan Department of Health and Human Services, but other assays were utilized (including an in-house PCR and assays by Abbott [Des Plaines, IL, USA] and DiaSorin [Stillwater, MN, USA]) as commercially available SARS-CoV-2 PCR testing became widely available.

Routine screening for CAPA was not conducted and testing for fungal infection was done only when clinically indicated.

### Data Collection and Definitions

Patients' electronic medical records were reviewed to obtain information regarding underlying comorbidities; classic host factors for invasive fungal infections (IFI) as defined by EORTC/MSGERC [1]; need for extracorporeal membrane oxygenation (ECMO) therapy; mechanical ventilation; acute renal replacement therapy; imaging, microbiologic data, and laboratory data while admitted to the ICU; occurrence and type of CAPA; and overall mortality at 30 days from admission. Patients who were diagnosed with CAPA were followed for an additional 3 months. Proven, probable and possible CAPA were defined by the 2020 ECMM/ISHAM consensus criteria [10].

### Statistical Analysis

We conducted descriptive data analyses for all variables. These values were reported as frequencies, means ( $\pm$  SD), medians (with ranges), and proportions. All statistical analyses were completed using SPSS software, version 27.0 (SPSS, Inc., Chicago, IL).

## Results

A total of 256 patients admitted to the ICU for management of COVID-19 were included in the study. The median age was 61, (range 20–90), and 167 (65%) were men. The most common comorbidities were obesity (BMI  $\geq 30$ ), hypertension, and diabetes.

Twenty (8%) patients in our cohort had no comorbidities (Table 1).

**Table 1** Demographics of patients admitted to the intensive care unit with COVID-19

Demographics	n (%)
Total	256 (100)
<i>Demographics</i>	
Gender (male)	167 (65)
Age (years) median; range	61; 20–90
IQR 25 (years)	50
IQR 50 (years)	61
IQR 75 (years)	71
<i>Comorbidities</i>	
None	20 (8)
Obesity (BMI > 30)	139 (54)
Hypertension	165 (64)
Coronary artery disease	49 (19)
Diabetes Mellitus	125(49)
Malignancy (solid tumor) <sup>§</sup>	17 (7)
Chronic obstructive pulmonary disease	31 (12)
Solid organ transplantation*	13 (5)
<i>Organ support</i>	
Mechanical ventilation	188 (73)
Extracorporeal membrane oxygenation	12 (5)
Acute renal replacement therapy	64 (25)
<i>Treatment for viral infection **</i>	
Tocilizumab	94 (37)
Sarilumab***	32 (13)
Remdesivir***	11 (4)
Hydroxychloroquine	137 (54)
Convalescent plasma	11 (4)
Invasive pulmonary aspergillosis	3 (1)
30-day all-cause mortality	62 (24)

\*Kidney transplantation ( $n = 6$ ), heart transplantation ( $n = 4$ ), lung transplantation ( $n = 2$ ), liver transplantation ( $n = 1$ )

\*\*Patients may have received more than one antiviral therapy for COVID-19

\*\*\*These drugs were administered as part of a randomized controlled trial; patient may have received study drug or placebo

<sup>§</sup>4 of 17 patients had > 1 solid tumor at time of COVID diagnosis; prostate ( $n = 7$ ), melanoma ( $n = 5$ ), breast ( $n = 4$ ), colon ( $n = 3$ ), gastric ( $n = 1$ ), bladder ( $n = 1$ ), and kidney ( $n = 1$ )

Among the 256 patients, 188 (73%) required intubation and mechanical ventilation, 12 (5%) required veno-venous ECMO, and 64 (25%) required acute renal replacement therapy.

A total of 205 patients received antiviral therapies for COVID-19, and 51 did not. Forty-three patients (17%) were participants in a randomized clinical trial (11 patients received either remdesivir or placebo, and 32 received either sarilumab or placebo). Outside of clinical trials, 94 (37%) received tocilizumab and 137 (54%) received hydroxychloroquine.

Outcomes were poor in patients admitted to the ICU with COVID-19. A total of 62 patients (24%) died within 30 days of admission.

### COVID-19-Associated Pulmonary Aspergillosis

Among the 256 patients, three (1%) had CAPA. None of these three patients had classic host factors for IFI (Table 2). All three patients with CAPA required mechanical ventilation, two required acute renal replacement therapy, and one required veno-venous ECMO. All three patients with CAPA had received tocilizumab for critical illness due to COVID-19. A chest computed tomography (CT) was obtained as part of the infectious work-up performed in the setting of worsening respiratory status in all three patients; cavitary lesions were observed in the chest CT of two patients and all three chest CT showed consolidations and ground glass opacities (Fig. 1). Tracheal aspirate cultures were performed in all three patients and cultures yielded *Aspergillus fumigatus* from two patients. The patient with a negative tracheal aspirate culture also underwent bronchoscopy and bronchoalveolar lavage (BAL) *Aspergillus* galactomannan (GM) was positive (1.4 ODI). Two of the three patients received antifungal therapy and remained alive at 12 weeks. In one patient, the diagnosis of CAPA was made post-mortem and, therefore, this patient never received antifungals.

### Discussion

In this study, we present a large cohort of critically ill patients with COVID-19 from a medical center located in the midwestern USA. We found that CAPA was uncommon and occurred in only 1% of patients. Our findings contrast with data from several European

**Table 2** Characteristics of three patients with COVID-19-associated pulmonary aspergillosis

Characteristics	Patient 1	Patient 2	Patient 3
Sex	Female	Male	Male
Age (years)	67	49	77
Comorbidities	Epilepsy, HTN, prediabetes, obesity	Hyperlipidemia, obesity	HTN, osteoarthritis
Classic host factors for IFI*	None	None	None
ICU requirements			
Mechanical ventilation	Yes	yes	yes
vvECMO	No	yes	no
Acute renal replacement therapy	Yes	yes	no
COVID therapy	Tocilizumab, convalescent plasma	Tocilizumab, HCQ	Tocilizumab
Mycological diagnosis			
Serum GM (ODI)	3.1	N/A	< 0.5
BAL GM**	N/A	1.4	Not obtained
Tracheal aspirate culture	<i>Aspergillus fumigatus</i>	No growth	<i>Aspergillus fumigatus</i>
Susceptibility testing <sup>#</sup>	Voriconazole MIC 0.5mcg/mL, isavuconazole MIC 1 mcg/ml, micafungin ≤ 0.015 mcg/ml, amphotericin B 1mcg/mL	N/A	N/A
CT imaging	Confluent peribronchial consolidations with cavitation, bilateral ground glass opacities	Peripheral patchy opacities with central cavitation	Peripheral ground glass opacities and peribronchovascular consolidations
CAPA classification***	Probable	Probable	Possible
Time to IPA diagnosis from time of COVID diagnosis	13 days	36 days	7 days
IPA therapy and outcomes			
Antifungal therapy	IV Voriconazole × 2 weeks, followed by combination of micafungin and liposomal amphotericin B <sup>§</sup>	N/A	PO Voriconazole × 2 days then PO isavuconazole daily <sup>§§</sup>
Duration of antifungal therapy	12 weeks	N/A	3 weeks <sup>§§§</sup>
12-week outcome	Alive	Deceased <sup>###</sup>	Alive

*BID* twice daily, *CAPA* COVID-19-associated pulmonary aspergillosis, *CT* computed tomography, *GM* galactomannan, *HCQ* hydroxychloroquine, *HTN* hypertension, *IFI* invasive fungal infection, *IV* intravenous, *N/A* not available, *PO* oral, *vvECMO* veno-venous extracorporeal membrane oxygenation

\*Classic host factors defined as per EORTC/MSG [1]

\*\*Done with IMMY

\*\*\*CAPA classification as per Koehler et al. [6]

§Patient required change in antifungal treatment drugs due to voriconazole liver toxicity

§§Patient required change in antifungal therapy due to QT prolongation and liver toxicity

§§§Antifungal treatment was discontinued due to liver toxicity in the setting of clinical and radiographic improvement

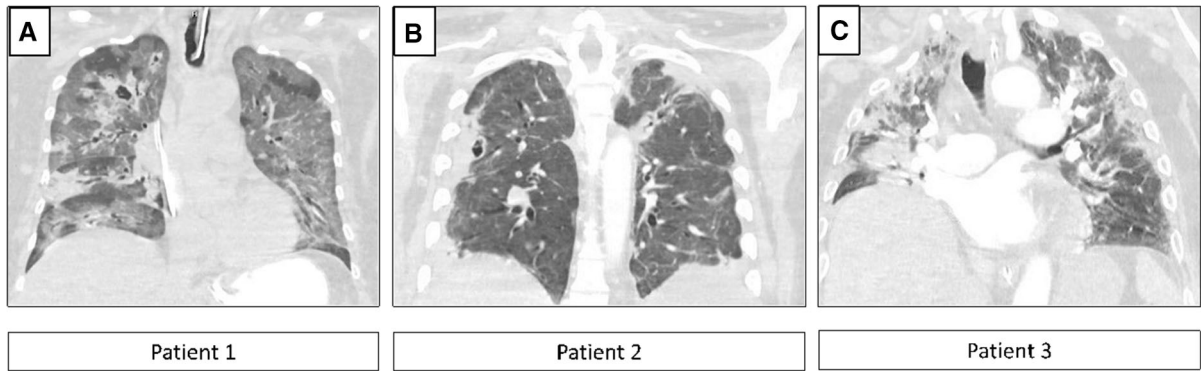
<sup>#</sup>*Aspergillus* susceptibility testing was performed according to CLSI M38-A2

<sup>###</sup>The diagnosis of CAPA was made post-mortem

studies, which have noted an alarming number of CAPA cases complicating critically ill patients with COVID-19, with rates of 19–33% [6–9, 11]. Outside of Europe, a study from Pakistan noted a cumulative incidence of CAPA of 22% in mechanically ventilated

patients [12]. Similar to our findings, one Swiss study reported only three cases of CAPA (2.5%) among 118 critically ill patients with COVID-19 [13].

The exact incidence and risk factors for CAPA in critically ill patients with COVID-19 are not well



**Fig. 1** Chest CT images of three patients with COVID-19-associated pulmonary aspergillosis at time of diagnosis. **a** (Patient 1): CT chest demonstrates bilateral ground glass opacities and confluent peribronchial consolidations with cavitation, notably in the right upper lobe lung field. **b** (Patient

2): CT chest demonstrates peripheral patchy opacities with central cavitation in the right peripheral mid-lung. **c** (Patient 3): CT chest demonstrates peripheral ground glass opacities and peribronchovascular consolidations in the setting of elevated right hemidiaphragm

understood. Other respiratory viral infections, particularly influenza, have been shown to be independent risk factors for IPA and increase mortality [4, 5]. Patients with influenza-associated aspergillosis (IAPA) typically do not have classic risk factors like neutropenia or T-cell immunosuppression [1, 14, 15]. Rather, influenza infection itself leads to disruption of the respiratory epithelium and destruction of mucociliary clearance [4, 15]. This allows for easier invasion by fungal organisms that are already colonizing the respiratory tree. Influenza may also impair the local immune response by impairing phagocytosis and reducing natural killer cell function via cytokine imbalance. [15] As the pathophysiology of IAPA is different than traditional IPA, which relies heavily on underlying immunocompromise, patients with IAPA are more likely to have atypical findings on imaging and, since angioinvasion is uncommon, may not present with positive biomarkers like  $\beta$ -D-glucan or GM [14–16].

As critically ill patients with COVID-19 may have similar clinical and radiological presentations as patients with severe influenza, it is possible that a similar process may be at play regarding susceptibility to fungal disease. Indeed, recognition of the similarities between influenza and COVID-19 related lung disease may have led to rapid recognition of aspergillosis in patients with COVID-19 early in the SARS-CoV-2 pandemic [17]. Autopsies of patients with the closely related epidemic coronavirus SARS-CoV-1 have demonstrated lung findings consistent

with aspergillosis, albeit in the setting of high dose steroid administration [18, 19]. Patients with COVID-19 have been shown to have activation of the innate immune system in the lungs, leading to localized inflammation and presumably similar damage to the respiratory epithelium similar to that seen in IAPA [14, 20]. Patients with severe COVID-19 also have lymphopenia and altered cytokine levels, likely leading to impaired immune cell function as is seen in IAPA [15]. Based on its similarity to IAPA, patients with CAPA may also present atypically, as did all three patients in our study (Table 2).

As the pathophysiology of severe COVID-19 pneumonia is universal and does not differ based on geographic location, one wonders why multiple European centers have much higher rates than our center located in the USA. Rates of *Aspergillus* infection vary around the world, and rates of *Aspergillus* infection may be lower in North America as compared to Europe; this has been specifically demonstrated for IAPA in a large Canadian series [5]. The reason for this difference in incidence is unknown, but speculation is that both genetic and environmental factors (including the local *Aspergillus* spore composition and distribution) are at play [21]. In addition, European centers may have higher rates than our center due to increased detection of IPA in patients with COVID-19. European centers have demonstrated awareness of and experience with secondary *Aspergillus* infections, as evidenced by the bulk of literature on IAPA, as well as the early reports of COVID-

associated secondary aspergillosis [6–9, 11, 22]. Several European centers have established screening protocols for CAPA in patients with severe COVID-19 [11, 13, 22]. This strategy may have led to early identification of a larger number of patients with CAPA. Our center did not standardize screening for CAPA in patients with severe COVID-19, but providers often obtained tracheal aspirate cultures, serum GM, and beta-D-glucan assay when clinically indicated. Similar to practice in other institutions, BAL fluid was uncommonly obtained as bronchoscopies were often deferred in patients with COVID-19 to minimize aerosol-generating procedures [13, 20].

The use of tocilizumab, which inhibits interleukin-6 (IL-6) and presumably halts the cytokine cascade, has been proposed as a predisposing factor for CAPA. IL-6 plays an important role in the immune system response to *Aspergillus*, and animal models suggest that decreased IL-6 levels increase susceptibility for *Aspergillus* infection [20, 23]. As per our institutional guidelines, 94 of our patients received tocilizumab for the treatment of COVID 19; only three of them developed CAPA [24]. In a retrospective review from our institution, tocilizumab use was associated with an increase in bacterial pneumonia but not with fungal infections [24].

Another proposed risk factor for CAPA is the widespread use of negative pressure rooms in patients with COVID-19. Data from observational studies support the use of positive pressure in the immunocompromised to prevent IPA; under normal circumstances, positive air pressure is used in ICU rooms [25]. However, during the height of the COVID-19 pandemic, a large portion of our ICU rooms were converted to negative air pressure rooms as recommended to protect patients and health care workers [26, 27]. In this setting, air could have been pulled from the outside environment, increasing the risk of fungal infection through the spread of aerosols, even in the setting of HEPA filtration [25, 28, 29]. Outbreaks of IPA have been linked to the use of negative pressure rooms for COVID-19 patients and switching to neutral or positive pressure ameliorated the outbreak in one instance [29].

Our study was limited by its retrospective and single-center nature. Importantly, the use of corticosteroids in the management of COVID-19 was not standardized at our center. In the early pandemic,

steroid use was not recommended under our institutional guidelines. A subsequent large multi-center study demonstrated a survival benefit of dexamethasone in patients with severe COVID-19, and guidelines were later changed to recommend steroid use; this occurred after the completion of our study period [30]. Our patients were followed for 30 days from the time of their ICU admission for COVID-19 and thus, cases of CAPA occurring beyond that period were not captured.

Our findings contrast with previous reports and highlight the significant variability in the rates of CAPA at different centers. Collaborative efforts are needed to further understand the specific geographic and environmental factors that may determine the risk of CAPA in critically ill patients with COVID-19.

## Disclosures

**Conflict of interest** M.H.M. has received research support and consulting honoraria from Astellas US, Scynexis, Inc. and Mayne Pharma A.I.W., G.R.W. and K.A.L. have nothing to disclose.

**CRedit Author Statement** Anastasia I. Wasylyshyn contributed to data collection, methodology, data curation, writing—original draft preparation. G. Rostyslaw Wasylyshyn contributed to data collection, writing—original draft preparation. Kathleen A. Linder contributed to validation, writing—reviewing and editing. Marisa H. Miceli contributed to conceptualization, methodology, writing—reviewing and editing.

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