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Invasive pulmonary aspergillosis in critically ill patients with COVID-19 in Australia: implications for screening and treatment

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Brief Communication

The risk for invasive pulmonary aspergillosis (IPA) is increased in immunocompromised patients. There are also increasing reports of immunocompetent patients with respiratory viral and IPA co-infection, particularly in patients admitted to intensive care units (ICU) with severe influenza [1], and more recently in patients with coronavirus disease-19 (COVID-19) [2-7]. We report the emergence, clinical characteristics and outcomes of patients with COVID-19 associated pulmonary aspergillosis (CAPA), together with a recommended approach for screening and management in the Australian setting.

Between March and August 2020, 50 patients with laboratory-proven severe adult respiratory syndrome coronavirus-2 (SARS-CoV-2) infection required ICU admission at our facility. Of these, four patients (8%) had concurrent possible IPA (Table 1). All four patients required mechanical ventilation and were administered intravenous dexamethasone; one patient also received intravenous remdesivir. Chest computed tomography (CT) performed in three patients revealed ground-glass opacity and bilateral consolidation without nodules, halo-sign or cavitation (Figure 1). After a median of 5 days in ICU (range 2-9 days), *Aspergillus spp.* were isolated in tracheal aspirates of three patients (*A. fumigatus*, *n*=2; *A. terreus*, *n*=1), while patient 4 had two tracheal samples with positive *Aspergillus* PCR and negative fungal culture. Voriconazole treatment was commenced in the setting of declining respiratory function in 3 patients. Patient 2 was palliated before initiation of antifungal treatment.

All-cause mortality among COVID-19 patients admitted to ICU was 22% (11/50 patients). In contrast, in those with CAPA all-cause mortality occurred in 3 of 4 patients, compared with 8 of 46 patients in those without aspergillus co-infection.

To estimate relative disease burden of IPA in ICU patients during the COVID-19 pandemic, a baseline period (January 2017 to February 2020) was compared with the pandemic period (Mar-Aug 2020). In the pre-COVID period, 13 cases of IPA were identified in 9277 ICU-admitted patients, corresponding to an IPA rate of 1.4/1000 admitted patients (46% of cases had respiratory virus co-infection). In contrast, 7 cases of IPA were identified in 1171 ICU-admitted patients during the pandemic period,

corresponding to a rate of 6.0/1000 admitted patients (71% with respiratory virus co-infection, and majority of these (4/5) associated with SARS-CoV-2 infection).

Discussion

Internationally, variable but significant rates (3.2-35%) of CAPA have been reported in patients with acute respiratory distress syndrome (ARDS) complicating severe SARS-CoV-2 infection, with mortality as high as 65% [2-7]. We observed an 8% rate of CAPA in critically ill COVID-19 patients with ARDS admitted to our ICU, with mortality in 3 of 4 patients. Median time between ICU admission and CAPA diagnosis has been reported as 6 days [2], consistent with our observation of early-onset infection.

Damage to the lung epithelium by SARS-CoV-2, and defective fungal host responses secondary to hyperinflammatory response to the virus are thought to predispose to *Aspergillus* infection [2]. Other proposed risk factors include corticosteroid use in patients with ARDS, broad-spectrum antibiotics and underlying structural lung disease [2]. In particular there has been increased use of dexamethasone since publication of RECOVERY trial [8]. Concomitant use of corticosteroids with interleukin-6 receptor antagonist such as Tocilizumab may also increase patients' susceptibility to pulmonary *Aspergillus* infection [9, 10].

It can be difficult to differentiate *Aspergillus* colonisation from infection in non-neutropenic ICU patients who do not have underlying immunocompromised states and in whom typical radiological findings of invasive fungal disease may be absent. This highlights the need for an agreed consensus definition for CAPA, which was recently proposed, relying on entry criteria of ICU admission for respiratory distress with a positive COVID-19 test temporally related to ICU admission. Proven, probable or possible CAPA have been proposed based on sample validity and diagnostic certainty [11]. Despite this, there is ongoing debate if CAPA is actually represents an invasive disease post SARS-CoV-2 infection as seen in influenza-associated pulmonary aspergillosis, or whether it represents only colonisation of patients' airways [12, 13]. Understandably it has been challenging to prove the association between COVID-19 and IPA, even in the setting of post mortem evaluation [14] hence the majority of the reported cases to date were categorised as probable or putative CAPA [13].

The authors of the consensus regarded bronchoscopy as the cornerstone of CAPA diagnosis, however due to resource constraint in ICU, coupled with the need to reduce transmission risk related to aerosolization, bronchoscopy is not routinely performed in many institutions including ours. Jabeen et al criticized this emphasis on bronchoscopy samples as such strict criteria may lead to under recognition of this complication in critically ill patients with COVID-19, and proposed endotracheal aspirates be

incorporated into the diagnostic algorithm [15]. However, as pointed out in response to this, biomarkers such as galactomannan or *Aspergillus* PCR are not validated in tracheal aspirate specimens [16].

In view of this, at our institution we have adopted the following approach for ventilated ICU patients with new or worsening pulmonary infiltrates on chest imaging and laboratory-proven SARS-CoV-2:

- *Screening:* Twice-weekly fungal culture and if feasible, *Aspergillus* PCR from tracheal aspirate specimens. We do not recommend serum galactomannan as a routine screening test, as the sensitivity was reported to be only 20% [2, 11]. Nonetheless serum galactomannan has a role in predicting prognosis of suspected invasive pulmonary aspergillosis as emerging data suggests it is indicative of advanced CAPA infection and a positive result is associated with poor outcomes [17]. Hence it can be considered if *Aspergillus spp* is cultured or positive by PCR from tracheal aspirates.
- *Antifungal therapy:* If patients have persistent fevers for more than 3 days, or recurrence of fevers after at least 48 hours of defervescence (despite appropriate antibiotics), with increasing ventilator support, haemoptysis, pleural friction rub or chest pain [11], AND positive *Aspergillus spp* culture and/or *Aspergillus* detected on PCR on two separate occasions from tracheal aspirate specimens, this should then trigger a discussion between the multidisciplinary team of infectious diseases physicians, microbiologists and ICU physicians, to determine if bronchoscopy can be practically and safely performed to further confirm the diagnosis; or if empiric therapy should be commenced should bronchoscopy not be feasible. As per published criteria, a positive *Aspergillus spp* culture, *Aspergillus* PCR or galactomannan ≥ 1.0 on bronchoalveolar lavage is considered consistent with CAPA in this setting. A serum galactomannan ≥ 0.5 also supports the diagnosis of CAPA [11].

Voriconazole is the recommended first-line treatment for CAPA, however there are significant drug-drug interactions including interactions with common COVID-19 treatment such as remdesivir [18]. Its narrow therapeutic window and toxicity may worsen the clinical and biochemical status of these ICU patients. Liposomal amphotericin B is the alternative agent but it is nephrotoxic and is often not suitable as patients already have acute kidney injury. Posaconazole has recently been shown to be non-inferior to voriconazole in treatment of invasive aspergillosis [19] and it should be considered as the salvage therapy in patients who are not able to tolerate voriconazole or Liposomal amphotericin B. Isavuconazole can be considered if QTc prolongation is of concern with voriconazole or posaconazole [20].

We acknowledged the descriptive nature of our cases and that that our case series constitutes a small sample size only. In addition, given that only tracheal aspirates were examined twice weekly, we could only classify these cases as possible CAPA. Nonetheless, we believe that our real-world experience poses several learning points for other institutions across Australia. As demonstrated by Jabeen et al,

our experience highlights the challenges and diagnostic dilemma encountered by the clinicians working in environments with varied resources and access to diagnostic tests.

In conclusion, clinicians should be aware of IPA co-infection in ICU patients with COVID-19 infection, particularly those receiving dexamethasone. Given high mortality, treatment should be considered in deteriorating patients who have new or worsening pulmonary infiltrates and mycological evidence of *Aspergillus* infection.

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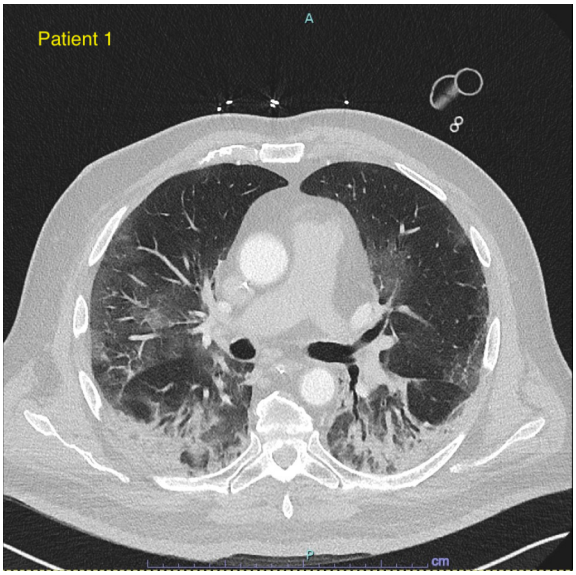
Table 1. Clinical characteristics of ICU patients with COVID-19 and pulmonary aspergillosis

Figure 1. Computed tomography (CT) images of chest of patient 1, 2 and 3, showing ground glass opacities in both lung fields, with no evidence of nodules, halo signs or cavitation.

	Patient 1	Patient 2	Patient 3	Patient 4
Comorbidities	Asthma, poorly controlled type 2 diabetes mellitus, hypertension	Child Pugh C liver cirrhosis from chronic hepatitis B	End stage renal failure from type 2 diabetes, renal transplant, myeloma, hypertension, obstructive sleep apnea	Hypertension, renal cell carcinoma (previous nephrectomy), ischemic heart disease, ex-smoker
Time between COVID-19 symptom onset and presentation to hospital	6 days	9 days	Already in hospital for 4 days for other reason before symptom onset	5 days
CT chest changes	Widespread bilateral ground glass opacity and consolidation at bilateral lower lobes. No definite evidence of pulmonary nodules or cavitation.	Patchy ground glass opacities and smooth interlobular septal thickening within both lungs with upper zone predominance. No halo signs or cavitation.	Extensive ground glass changes throughout both lungs with bibasal consolidation. No evidence of nodules, halo signs or cavitation.	Not done
Species isolated from tracheal aspirates (culture)	*Aspergillus fumigatus* complex	*Aspergillus fumigatus* complex	*Aspergillus terreus* complex	Culture negative
Time between ICU admission & positive *Aspergillus* test	2 days	9 days	6 days	3 days
COVID-19 specific therapy	Intravenous dexamethasone 6mg/ day (7 days)	Intravenous dexamethasone 6mg/ day (7 days)	Intravenous dexamethasone 6mg/ day (10 days)	Dexamethasone (oral) 6mg/day (10 days) and Remdesivir (6 days)
Time between dexamethasone and positive *Aspergillus* test	2 days	9 days	8 days	6 days
Serum Galactomannan (GM)/ *Aspergillus* PCR (subsequent tracheal aspirates)	Done only after treatment initiated – negative for both GM and *Aspergillus* PCR	Not done	Done only after treatment initiated – negative for both GM and *Aspergillus* PCR	Done prior to treatment – 2 x tracheal aspirate samples positive for *Aspergillus* PCR; 2 x serum GM negative
Treatment	Voriconazole (23 days)	No	Voriconazole (13 days)	Voriconazole (9 days)
Response to treatment	Improvement in pulmonary infiltrates on repeat CT chest	-	Unclear	Unclear
Outcome	Alive	Died	Died	Died



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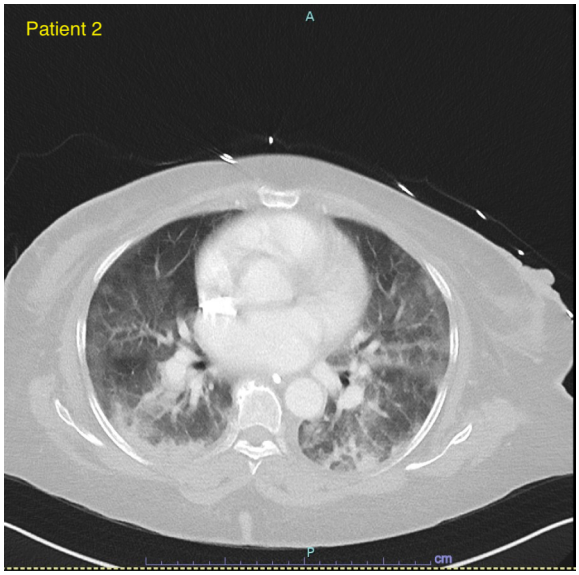

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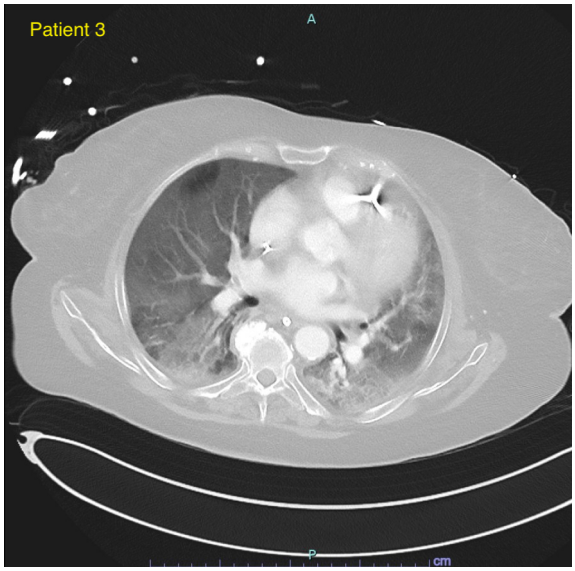

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Abstract

We report four cases of invasive pulmonary aspergillus co-infection in patients with COVID-19 infection and acute respiratory distress syndrome requiring ICU admission. *Aspergillus fumigatus* and *A. terreus* were isolated, with early infection onset following ICU admission. Clinicians should be aware of invasive pulmonary aspergillosis in ICU patients with COVID-19 infection, particularly those receiving dexamethasone. We propose screening of these high-risk patients with twice weekly fungal culture from tracheal aspirate and if feasible, *Aspergillus* PCR. Diagnosis is challenging and antifungal treatment should be considered in critically ill patients who have new or worsening pulmonary changes on chest imaging and mycological evidence of infection.

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