EDITORIAL
INFECTIOUS DISEASE

Confronting and mitigating the risk of COVID-19 associated pulmonary aspergillosis

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Cases of COVID-19 associated pulmonary aspergillosis (CAPA) are being increasingly reported and physicians treating patients with COVID-19-related lung disease need to actively consider these fungal co-infections https://bit.ly/3feuGsQ

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The coronavirus disease 2019 (COVID-19) virus caused a wide spectrum of disease in healthy individuals, as well as those with common comorbidities [1]. Severe COVID-19 is characterised by acute respiratory distress syndrome (ARDS) secondary to viral pneumonitis, treatment of which may require mechanical ventilation or extracorporeal membrane oxygenation [2]. Clinicians are alert to the possibility of bacterial co-infection as a complication of lower respiratory tract viral infection; for example, a recent review found that 72% of patients with COVID-19 received antimicrobial therapy [3]. However, the risk of fungal co-infection, in particular COVID-19 associated pulmonary aspergillosis (CAPA), remains underappreciated.

Fungal disease consistent with invasive aspergillosis has been observed with other severe coronaviruses such as severe acute respiratory syndrome-coronavirus (SARS-CoV) 2003 [4, 5] and Middle East Respiratory Syndrome-coronavirus [6]. From the outset of the COVID-19 pandemic, there were warning

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signs of secondary invasive fungal infection. *Aspergillus flavus* was isolated from the respiratory tract in one out of 99 patients in the first COVID-19 cohort from Wuhan, China to be reported in any detail [2] and *Aspergillus* spp. were isolated from two (3.8%) out of 52 patients in a subsequent cohort of critically unwell patients from this region [7]. More recently, retrospective case series from Belgium [8], France [9], The Netherlands [10] and Germany [11] have reported evidence of CAPA in an alarming 20–35% of mechanically ventilated patients.

CAPA

Influenza-associated pulmonary aspergillosis (IAPA) presents a known risk to critically unwell patients with influenza [12–14] and the clinical course of COVID-19 shows many features that are shared with severe influenza infection. These include ARDS, lymphopenia, bilateral pulmonary infiltrates, systemic pro-inflammatory cytokine responses and sepsis leading to multiple organ failure [14, 15]. It is therefore reasonable to suspect that patients with severe COVID-19 may be similarly susceptible to invasive aspergillosis. Corticosteroid use is an important acquired immunological risk factor for IAPA [16] and, during the SARS-CoV 2003 epidemic, there were case reports of patients developing SARS-associated invasive aspergillosis after corticosteroid use [5]. Corticosteroid use has been reported in hospitalised patients with COVID-19 [1] and may further contribute to the risk of CAPA. Importantly, the recent finding by the UK RECOVERY trial (ISRCTN50189673) [17] of a one-third mortality reduction conferred by dexamethasone in ventilated patients with COVID-19, while leading to a crucial new therapeutic avenue, may increase the risk of patients acquiring CAPA and emphasises the need for enhanced fungal surveillance.

Table 1 summarises individual patient-level data in 33 cases of CAPA that have been reported to date. The median (interquartile range) age of cases is 70 (57–75) years, of whom only two (6%) had a European Organization for Research and Treatment of Cancer (EORTC) host factor. Of these 16 (48%) had exposure to inhaled or systemic corticosteroids, 10 (30%) had diabetes and nine (27%) had underlying chronic lung disease; COPD (n=5), asthma (n=3), bullous emphysema (n=1), pulmonary fibrosis (n=1) and post-radiotherapy for nonsmall-cell lung cancer (n=1). CAPA was diagnosed a median (interquartile range) 5.5 (4.3–9) days after intensive care unit (ICU) admission and 21 (63.6%) patients had died by the time of publication. This mortality is in excess of most cohorts of ventilated patients with COVID-19, as a comparison in the UK ISARIC cohort 618 (37%) out of 1658 ventilated patients had died by the time of publication (17% discharged and 46% still receiving care) [23].

Invasive aspergillosis is difficult to diagnose in critically unwell patients without traditional host factors because radiological changes are usually nonspecific (*e.g.* infiltrates, consolidation or nodules), with features such as halo sign, air-crescent sign or cavitation being rare [24]. For these reasons Schauwvlieghe *et al.* [13] developed the modified AspICU criteria to help diagnose IAPA which (in the absence of histology) essentially relies on mycological evidence of *Aspergillus* spp. in the form of a positive bronchoalveolar lavage (BAL) culture or positive galactomannan (GM) in serum/BAL. Applying these modified AspICU criteria, five cases of CAPA in table 1 were "proven", 11 "putative" and 17 might be considered putative but with caveats which have been described in the table. For example, in many cases a tracheal aspirate, rather than BAL, provided the only mycological evidence of invasive aspergillosis (in the absence of tracheobronchitis/cavitation). There should therefore be caution about over-estimating the incidence of CAPA from such case series, which may include some patients with aspergillus colonisation or contamination only. In the study by Alanio *et al.* [9] which reported evidence of CAPA in nine (33%) out of 27 ventilated patients who underwent BAL/tracheal aspirate, one case was defined based on a BAL GM of 0.89 (below the usual cut-off of 1.0), two based on tracheal aspirate rather than BAL culture, one based on a serum GM of 0.51 (cut-off being 0.50) and in four cases BAL culture was positive but BAL GM negative, which suggests a lack of tissue invasion. Indeed, out of seven cases that were not treated with antifungals, five survived. Accordingly, larger, prospective, multi-site studies are needed to refine the AspICU criteria for patients with COVID-19, as well as to estimate incidence and the impact of CAPA on survival [25, 26].

Diagnosis and risk of CAPA

Bearing these observations in mind, we argue that critically ill patients with COVID-19 and progressive features should be screened for CAPA. We acknowledge that acquiring and handling clinical samples for microbiology is very challenging given the Hazard Group 3 rating of the SARS-CoV-2 virus, alongside an overburdened critical care service [27].

Ideally, screening for CAPA entails using a combination of computed tomography chest imaging and *Aspergillus* antigen tests on BAL and serum including GM ELISA or lateral-flow tests [28], or aspergillus PCR [29]. Whilst characteristic CT features of invasive aspergillosis such as nodules with halo sign were

TABLE 1 Summary of reported cases of coronavirus disease 2019 (COVID-19) associated pulmonary aspergillosis in the intensive care unit (ICU) setting

Location [ref.]	Age years	Sex	IPA risk factors	Radiology	BAL culture	TA culture	BAL GM	Serum GM	Other diagnostics	Onset days post-ICU	EORTC status	Mod AspICU status	Treatment	Outcome
Cologne, Germany [11]	62	F	Ex-smoker, moderate COPD, inhaled steroids	Ground-glass opacities, crazy paving, peripheral nodular consolidation	*A. fumigatus*	NR	(+) >2.5	(-)	BAL PCR *A. fumigatus*	NR	No host factor[#]	Putative	V	Died
Cologne, Germany [11]	70	M	Ex-smoker	Ground-glass opacities, occasional nodules	(-)	NR	(+) >2.5	(+) 0.7	BAL PCR *A. fumigatus*	NR	No host factor	Putative	I	Died
Cologne, Germany [11]	54	M	Diabetes, systemic corticosteroids 0.4 mg·kg^{-1}·day^{-1}×13 days	Ground-glass opacities, nodular infiltrates with cavities, air crescent sign	(-)	*A. fumigatus*	(+) >2.5	(-)	BAL PCR *A. fumigatus*	NR	No host factor	Putative	C, V	Alive
Cologne, Germany [11]	73	M	Smoker, bullous emphysema, severe COPD, inhaled steroids	Ground-glass opacities, occasional nodules, known bullous emphysema	ND	*A. fumigatus*	ND	(-)	TA PCR *A. fumigatus*	NR	No host factor	Putative only if TA considered equivalent to BAL	V	Died
Cologne, Germany [11]	54	F	None	Ground-glass opacities, crazy paving, central and peripheral consolidation, smaller nodular infiltrates	ND	(-)	ND	(+) 2.7, 1.3	TA PCR (-)	NR	No host factor	Putative	C, V	Alive
Munich, Germany [18]	80	M	Pulmonary fibrosis	Typical signs for COVID-19 pneumonia but no specific signs for IPA	*A. fumigatus*	NR	(+) >6	(+) 1.5		5	No host factor	Putative	L-AmB	Died
Munich, Germany [18]	70	M	None	Typical signs for COVID-19 pneumonia but no specific signs for IPA	*A. fumigatus*	NR	(+) >6	(-)		6	No host factor	Putative	L-AmB	Died

Continued

TABLE 1 Continued

Location [ref.]	Age years	Sex	IPA risk factors	Radiology	BAL culture	TA culture	BAL GM	Serum GM	Other diagnostics	Onset days post-ICU	EORTC status	Mod AspICU status	Treatment	Outcome
Paris, France [19]	74	M	Myelodysplastic syndrome	NR	ND	*A. fumigatus*	ND	(-) x2	TA PCR *A. fumigatus* x2, TA GM (-)×1, BDG and serum PCR (-) x2	4	No host factor	Putative only if TA considered equivalent to BAL	None	Died
Paris, France [9]	53	M	Dexamethasone 20 mg·day^{-1} days 1–5, 10 mg·day^{-1} days 6–10	Typical COVID-19	(-)	NR	(-) 0.89	(-)	BAL PCR (-), Serum PCR (-), BDG (+) >500	NR	No host factor	Putative only if BAL GM cut-off lowered to >0.8	None	Alive
Paris, France [9]	59	F	Diabetes	Typical COVID-19	*A. fumigatus*	NR	(-)	(-)	BAL PCR (-), serum PCR (-)	NR	No host factor	Putative but note BAL culture (+) but BAL GM (-)	None	Alive
Paris, France [9]	69	F	Dexamethasone 20 mg·day^{-1} days 1–5, 10 mg·day^{-1} days 6–10	Typical COVID-19	ND	*A. fumigatus*	ND	(-)	TA PCR *A. fumigatus,* serum PCR (-), BDG (-)	NR	No host factor	Putative only if TA considered equivalent to BAL	None	Alive
Paris, France [9]	63	F	Diabetes, dexamethasone 20 mg·day^{-1} days 1–5, 10 mg·day^{-1} days 6–10	Typical COVID-19	(-)	NR	(-)	(+) 0.51	BAL PCR (-), BDG (+) 105	NR	No host factor	Putative but relies on serum GM of only 0.51	None	Died
Paris, France [9]	43	M	Asthma, corticosteroids	Typical COVID-19	*A. fumigatus*	NR	(-)	(-)	BAL PCR (-), serum PCR (-), BDG (-)	NR	No host factor	Putative but note BAL culture (+) but BAL GM (-)	None	Alive
Paris, France [9]	79	M	Diabetes, Dexamethasone 20 mg·d^{-1} days 1–5, 10 mg·d^{-1} days 6–10	Typical COVID-19, segmental lung atelectasis	*A. fumigatus*	NR	(-)	(-)	BAL PCR *A. fumigatus,* serum PCR (-), BDG (-)	NR	No host factor	Putative but note BAL culture (+) but BAL GM (-)	None	Alive
Paris, France [9]	77	M	Asthma, dexamethasone 20 mg·day^{-1} days 1–5, 10 mg·day^{-1} days 6–10	"Typical COVID-19", emphysema	*A. fumigatus*	NR	(+) 3.9	(-)	BAL PCR *A. fumigatus,* serum PCR (-), BDG (+) 135	NR	No host factor	Putative	V	Died
Paris, France [9]	75	F	Diabetes, dexamethasone 20 mg·day^{-1} days 1–5, 10 mg·day^{-1} days 6–10	Typical COVID-19	*A. fumigatus*	NR	(-)	(-)	BAL PCR, *A. fumigatus,* serum PCR (-), BDG (+) 450	NR	No host factor	Putative but note BAL culture (+) but BAL GM (-)	C	Died

Continued

TABLE 1 Continued

Location [ref.]	Age years	Sex	IPA risk factors	Radiology	BAL culture	TA culture	BAL GM	Serum GM	Other diagnostics	Onset days post-ICU	EORTC status	Mod AspICU status	Treatment	Outcome
Paris, France [9]	47	M	Myeloma, corticosteroids	Typical COVID-19, one peripheral nodule	ND	*A. fumigatus*	ND	(-)	TA PCR *A. fumigatus*, serum PCR (-), BDG (-)	NR	Probable	Putative only if TA considered equivalent to BAL	None	Died
Graz, Austria [20]	70	M	Moderate COPD, steroid inhaler, obstructive sleep apnoea, diabetes	Ground-glass opacities, crazy paving, reversed halo sign, progression of the bilateral infiltrates on day 2 chest radiography	ND	*A. fumigatus*	ND	(-)	TA LFD (+), BDG (-)	3	No host factor	Putative only if TA considered equivalent to BAL	V	Died
Antwerp, Belgium [8]	86	M	None	ND	ND	*A. flavus*	ND	(-)		9	No host factor	Putative only if TA considered equivalent to BAL	None	Died
Antwerp, Belgium [8]	38	M	None	(+)	*A. fumigatus*	NR	(+) >2.8	(-)	Histology from bronchoscopy (+)	6	Proven	Proven	V, I	Alive
Antwerp, Belgium [8]	62	M	Diabetes	ND	*A. fumigatus*	NR	(+) >2.0	(-)	Histology from bronchoscopy (+)	16	Proven	Proven	V	Died
Antwerp, Belgium [8]	73	M	Diabetes	ND	*A. fumigatus*	NR	(+) >2.8	(-)	Histology from bronchoscopy (+)	5	Proven	Proven	V	Alive
Antwerp, Belgium [8]	77	M	Diabetes, chronic corticosteroids for pemphigus foliaceous	ND	*A. fumigatus*	NR	(+) 2.79	(-)	Histology from bronchoscopy (+)	2	Proven	Proven	V	Alive
Antwerp, Belgium [8]	55	M	HIV (CD4 count >250, viral load <20) copies)	ND	(-)	NR	(-)	(+) 0.8	Histology from bronchoscopy (-)	13	No host factor	Putative but relies on serum GM of only 0.8	V, I	Died
Antwerp, Belgium [8]	75	M	AML with IPA 2012	ND	*A. fumigatus*	NR	(+) 2.63	ND		8	No host factor	Putative	V	Died
Breda, The Netherlands [10]	83	M	Prednisolone 0.13 $mg \cdot kg^{-1} \cdot day^{-1} \times 28$ days for cardiomyopathy	NR	ND	*A. fumigatus*	ND	(-)		3	Probable if steroid requirement reduced to $<0.3\ mg \cdot kg^{-1} \cdot day^{-1}$	Putative only if TA considered equivalent to BAL	V+A, or L-AmB	Died
Breda, The Netherlands [10]	67	M	Severe COPD, Post RT for NSCLC 2014, prednisolone 0.37 $mg \cdot kg^{-1} \cdot day^{-1} \times 2$ days	NR	ND	*A. fumigatus*	ND	ND		3	No host factor	Putative only if TA considered equivalent to BAL	V+A, or L-AmB	Died

Continued

TABLE 1 Continued

Location [ref.]	Age years	Sex	IPA risk factors	Radiology	BAL culture	TA culture	BAL GM	Serum GM	Other diagnostics	Onset days post-ICU	EORTC status	Mod AspICU status	Treatment	Outcome
Breda, The Netherlands [10]	75	M	Moderate COPD	NR	*A. fumigatus*	NR	(+) 4.0	ND	Mucoid white sputum left bronchus at bronchoscopy	5	No host factor	Putative	V+A, or L-AmB	Died
Breda, The Netherlands [10]	43	M	None	NR	(-)	NR	(+) 3.8	(-)		14	No host factor	Putative	V+A, or L-AmB	Alive
Breda, The Netherlands [10]	57	M	Asthma, inhaled steroids	NR	*A. fumigatus*	NR	(+) 1.6	(-)		5	No host factor	Putative	V+A, or L-AmB	Died
Breda, The Netherlands [10]	58	M	None	NR	ND	*A. fumigatus*	ND	ND		28	No host factor	Putative only if TA considered equivalent to BAL	V+A, or L-AmB	Alive
Paris, France [21]	80	M	None	Pleural effusions, alveolar condensation, ground-glass opacities, pulmonary cysts	ND	*A. flavus*	ND	ND		NR	No host factor	Putative only if TA considered equivalent to BAL	V, I	Died
Milan, Italy [22]	73	M	Diabetes	Interstitial opacities with right upper lobe focal consolidation which progressively worsened	*A. fumigatus*	NR	ND	(+) 8.6	Lung histology from PM (+), PM tissue PCR *Aspergillus* spp.	9	Proven	Proven	L-AmB	Died
Summary	Median (IQR) 70 (57–75)	M: 26 (79%) out of 33	EORTC host factor: n=2 (6%); inhaled/systemic steroid exposure: n=16 (48%); diabetes: n=10 (30%); chronic lung disease: n=9 (27%)	Nodules: n=6 (31.6%), cavity/ halo-sign: n=2 (10.5%)	16 (72.7%) out of 22 with BAL		14 (66.7%) out of 21 with BAL GM	6 (21.4%) out of 28 with serum GM		Median (IQR) 5.5 (4.3–9)	Proven: n=5; probable: n=1; no host factor: n=27	Proven: n=5; putative: n=11; putative with caveats: n=17	24 (72.7%) treated	21 (63.6%) died

IPA: invasive pulmonary aspergillosis; BAL: bronchoalveolar lavage; TA: tracheal aspirate; GM: galactomannan; EORTC: European Organization for Research and Treatment of Cancer; AspICU: clinical criteria to diagnose IPA; M: male; F: female; BDG: (1–3)-β-D-glucan; LFD: Aspergillus lateral-flow device; PM: post mortem; AML: acute myeloid leukaemia; RT: radiotherapy; NSCLC: nonsmall-cell lung cancer; NR: not recorded; V: voriconazole; I: isavuconazole; L-AmB: liposomal amphotericin B; C: caspofungin; A: anidulafungin; ND: no data; (+): positive result; (-): negative result. #: without histological evidence of "proven" IPA a patient host factor (*e.g.* recent neutropenia, haematological malignancy) is required to meet the probable/possible definition, corticosteroids must be given at ⩾0.3 mg·kg^{-1} for ⩾3 weeks to classify as a host factor result.

seen in 17.6% of severely ill COVID-19 patients, they were not confirmed to be IPA [30]. Given the lack of typical invasive aspergillosis features on CT in IAPA, the absence of classical findings such as cavitation should not be used to exclude CAPA; however, their presence can help support the diagnosis and reduce the burden of evidence placed on mycological investigations.

In a study of 26 ICU patients that were diagnosed with proven (non-CAPA/IAPA) IPA post mortem, serum GM had only 25% sensitivity in those that were not neutropenic (*versus* 70% in neutropenic patients) [31]. In contrast, BAL GM was 88–90% sensitive in both groups. In the IAPA study by Schauwvlieghe *et al.* [13] serum GM testing performed better with 20 (65%) out of 31 positive cases, however BAL GM remained superior at 67 (88%) out of 76 cases. In CAPA cases reported to date (table 1), BAL culture and GM had a sensitivity of 72.7% and 66.7%, respectively, but serum GM was positive in only six (21.4%) out of 28. Moreover, of the five cases of proven CAPA reported to date, four were serum GM negative (table 1) [8], indicating that serum GM test performance might be inferior in diagnosing CAPA. Therefore, bronchoscopy, including tracheobronchial inspection and BAL sampling for culture and GM should be the diagnostic gold standards whenever CAPA is suspected, providing this is compatible with local infection prevention and control guidance for aerosol-generating procedures. A positive BAL GM (index >1.0) would be indicative of CAPA, whereas if the index is <0.5 CAPA is much less likely [31]. A positive serum GM result ($\geqslant$ 0.5) would be highly suspicious for CAPA but a negative result should not be used to exclude the diagnosis. Novel lateral-flow antigen tests may represent a locally implementable alternative to GM ELISA in the CL3 laboratory, but currently require validation in ICU patients without EORTC host factors including COVID-19 [28]. An *Aspergillus*-specific PCR test [29] may also be helpful and if positive could also lead to the application of molecular testing for the recognised markers of clinically or environmentally derived azole resistance [32].

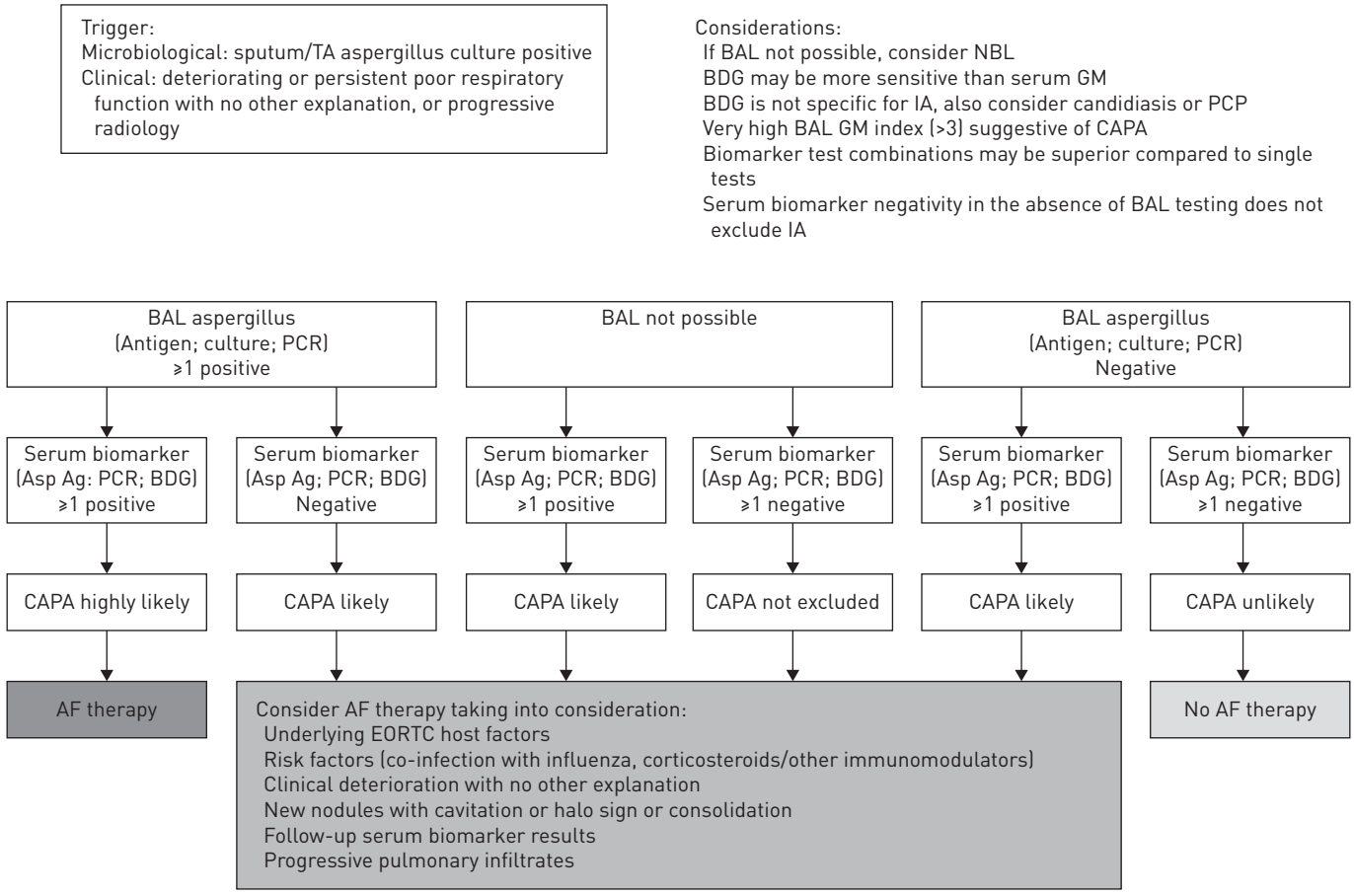

FIGURE 1 Proposed screening and diagnostic algorithm for coronavirus disease-2019 associated pulmonary aspergillosis (CAPA). BAL: bronchoalveolar lavage; BDG: (1–3)-β-D-glucan; TA: tracheal aspirate; Asp Ag: aspergillus antigen; AF: antifungal; IA: invasive aspergillosis; GM: galactomannan; EORTC: European Organization for Research and Treatment of Cancer; NBL: non-directed bronchoalveolar lavage; PCP: Pneumocystis pneumonia.

A (1–3)-β-D-glucan (BDG) test on a serum sample is an easily obtained, early screening test when there is a suspicion of IPA. Although performance might be superior to serum *Aspergillus* antigen testing for the detection of IPA in the ICU [33], BDG negativity cannot be used to rule out infection, with a 77% sensitivity determined across a heterogeneous population of invasive aspergillosis patients, and performance in CAPA as yet to be determined. BDG positivity can occur due to a number of reasons in this patient cohort, however serial positive tests increases specificity and should prompt a diagnostic work-up including computed tomography and bronchoscopy and testing for *Aspergillus* antigen as outlined above [34]. While initiating antifungal treatment pre-emptively based on BDG positivity may be an improvement on empirical therapy, every effort should be made to utilise other more specific diagnostic tests to complement the BDG result.

Current guidelines advise against routine diagnostic bronchoscopy due to the risk of aerosol generation; recommending it only in patients in whom nasopharyngeal cultures are negative and BAL sampling will change clinical management [35]. In practice many patients with suspected CAPA undergo endotracheal sampling or non-directed BAL sampling only, and it is important that any case definition proposed for CAPA reflects this reality. To acknowledge this, we propose a screening and diagnostic algorithm for CAPA, which has clinical (respiratory) deterioration and/or positive aspergillus sputum, or tracheal aspirate culture as its entry point (figure 1). Although the host risk factors and clinical characteristics of CAPA are not yet understood, those individuals fulfilling the criteria for proven or probable aspergillosis [13, 14] should then be treated according to current guidelines [36, 37]. Importantly, now that adjunctive use of dexamethasone is likely to become widespread in the treatment of patients with severe COVID-19 [17], intensified screening for invasive aspergillosis is indicated to study the possible association between corticosteroid usage and CAPA.

Finally, the use of immunomodulatory drugs such as anakinra (recombinant interleukin-1Ra), tocilizumab (anti-interleukin-6) and Janus kinase inhibitors, currently undergoing trials for COVID-19, may also predispose patients to CAPA. There is also an increased risk of *Aspergillus* exposure for patients who are treated in hospital wards or makeshift "hospital" facilities that do not meet ICU specifications for appropriate room ventilation and air changes. It is also worth bearing in mind that pulmonary aspergillosis could develop into a chronic cavitary disease in a subset of patients, perhaps in those developing post-COVID-19 pulmonary fibrosis. For these reasons, clinicians following up patients manifesting chronic respiratory problems following their primary COVID-19 infection should bear in mind longer term fungal complications.

Conclusion

Fungal infections present an additional threat in the challenging task of managing COVID-19 patients in outbreak conditions. The pandemic of SARS-CoV-2 virus will undoubtedly involve CAPA, and the use of immunomodulatory therapy and impact of overburdened critical care services during this pandemic may exaggerate its impact. More research is needed on the epidemiology and diagnosis of CAPA in patients with COVID-19, a need that is partially met as ongoing prospective multi-site clinical studies are extended to include this cohort (*e.g.* AspiFlu) [25] or are launched (CAPA) [26] in response to the COVID-19 pandemic.

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