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Early View

Editorial

Confronting and mitigating the risk of COVID-19 Associated Pulmonary Aspergillosis (CAPA)

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Confronting and mitigating the risk of COVID-19 Associated Pulmonary Aspergillosis (CAPA)

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The SARS-CoV-2 (COVID-19) virus causes a wide spectrum of disease in healthy individuals as well as those with common comorbidities (1). Severe COVID-19 is characterised acute respiratory distress syndrome (ARDS) secondary to viral pneumonitis, treatment of which may require mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (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 (IA) has been observed with other severe Coronaviruses such as Severe Acute Respiratory Syndrome (SARS-CoV-2003) (4, 5) and Middle East Respiratory Syndrome (MERS-CoV) (6). From the outset of the COVID-19 pandemic, there were warning signs of secondary invasive fungal infection; *Aspergillus flavus* was isolated from the respiratory tract from one of 99 patients in the first COVID-19 cohort from Wuhan to be reported in any detail (2) and *Aspergillus* spp. were isolated from 2/52 (3.8%) of 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.

Coronavirus-associated pulmonary aspergillosis (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 IA. Corticosteroid use is an important acquired immunological risk factor for IAPA (16) and, during the SARS-2003 epidemic, there were case reports of patients developing SARS-associated IA 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 age of cases is 70 (IQR 57-75), of whom only 2 (6%) had an EORTC host factor. Of these 16 (48%) had exposure to inhaled or systemic corticosteroids, 10 (30%) diabetes and 9 (27%) underlying chronic lung disease; chronic obstructive pulmonary disease (n=5), asthma (n=3), bullous emphysema (n=1), pulmonary fibrosis (n=1) and post-radiotherapy for non-small-cell lung cancer (n=1). CAPA was diagnosed a median 5.5 days (IQR 4.3-9) after ICU admission and 21 (63.6%) of patients had died at 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 618/1658 (37%) of ventilated patients had died by the time of publication (17% discharged and 46% still receiving care) (18).

IA is difficult to diagnose in critically unwell patients without traditional host factors because radiological changes are usually non-specific (e.g. infiltrates, consolidation or nodules), with features such as halo sign, air-crescent sign or cavitation being rare (19). For these reasons Schauwvlieghe et al. 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 (13), 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 IA (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 9/27 (33%) of ventilated patients who underwent BAL/ tracheal aspirate (TA), one case was defined based on on a BAL GM of 0.89 (below the usual cut-off of 1.0), two based on TA 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, 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 (20, 21).

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 (HG3) rating of the SARS-CoV-2 virus, alongside an overburdened critical care service (22).

Ideally, screening for CAPA entails using a combination of CT chest imaging and *Aspergillus* antigen tests on BAL and serum including galactomannan (GM) ELISA or lateral-flow tests (23), or Aspergillus PCR (24). Whilst characteristic CT features of IA such as nodules with halo sign were seen in 17.6% of severely ill COVID-19 patients, they were not confirmed to be IPA (25). Given the lack of typical IA 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 (vs 70% in neutropenic patients) (26). 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 20/31 (65%) of cases positive, however BAL GM remained superior at 67/76 (88%). 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 6/28 (21.4%). 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 (26). A positive serum GM result (≥ 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 (23). An *Aspergillus*-specific PCR test (24) 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 (27).

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 (28), BDG negativity cannot be used to rule out infection, with a 77% sensitivity determined across a heterogeneous population of IA 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 CT and bronchoscopy and testing for *Aspergillus* antigen as outlined above (29). While initiating antifungal treatment pre-emptively based on of 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 (30). 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 (31, 32). 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 IA is indicated to study the possible association between corticosteroid usage and CAPA.

Finally, the use of immunomodulatory drugs such as Anakinra (recombinant IL-1Ra), Tocilizumab (anti-IL6) and Janus kinase (JAK) inhibitors, currently undergoing trials for COVID19, 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-COVID19 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.

Conclusions

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 (20)) or are launched (CAPA (21)) in response to pandemic COVID-19.

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Table 1. Summary of reported cases of COVID-19 associated pulmonary aspergillosis (CAPA)

Setting [ref]	Age	Sex	IA risk factors	Radiology	BAL culture	TA culture	BAL GM	Serum GM	Other diagnostics	Onset days post ICU	EORTC status	Mod AspICU status	Treatment	Outcome
ICU, Cologne, Germany [1]	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[a]	Putative	V	Died
ICU, Cologne, Germany [1]	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
ICU, Cologne, Germany [1]	54	M	Diabetes, systemic corticosteroids 0.4 mg/kg/d x 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
ICU, Cologne, Germany [1]	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
ICU, Cologne, Germany [1]	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
ICU, Munich, Germany [2]	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
ICU, Munich, Germany [2]	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
ICU, Paris, France [3]	74	M	Myelodysplastic syndrome	NR	ND	*A. fumigatus*	ND	(-) x2	TA PCR *A. fumigatus* x2, TA GM (-) x 1, BDG and serum PCR (-) x2	4	No host factor	Putative only if TA considered equivalent to BAL	None	Died
ICU, Paris, France [4]	53	M	Dexamethasone 20mg/d days 1-5, 10mg/d 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
ICU, Paris, France [4]	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
ICU, Paris, France [4]	69	F	Dexamethasone 20mg/d days 1-5, 10mg/d 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
ICU, Paris, France [4]	63	F	Diabetes, Dexamethasone 20mg/d days 1-5, 10mg/d 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
ICU, Paris, France [4]	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
ICU, Paris, France [4]	79	M	Diabetes, Dexamethasone 20mg/d days 1-5, 10mg/d 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
ICU, Paris, France [4]	77	M	Asthma, Dexamethasone 20mg/d days 1-5, 10mg/d 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
ICU, Paris, France [4]	75	F	Diabetes, Dexamethasone 20mg/d days 1-5, 10mg/d 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
ICU, Paris, France [4]	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
ICU, Graz, Austria [5]	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 CXR.	ND	*A. fumigatus*	ND	(-)	TA LFD (+), BDG (-)	3	No host factor	Putative only if TA considered equivalent to BAL	V	Died
ICU, Antwerp, Belgium [6]	86	M	None	ND	ND	*A. flavus*	ND	(-)		9	No host factor	Putative only if TA considered	None	Died

												equivalent to BAL		
ICU, Antwerp, Belgium [6]	38	M	None	"(+)"	*A. fumigatus*	NR	(+) > 2.8	(-)	Histology from bronchoscopy (+)	6	Proven	Proven	V, I	Alive
ICU, Antwerp, Belgium [6]	62	M	Diabetes	ND	*A. fumigatus*	NR	(+) > 2.0	(-)	Histology from bronchoscopy (+)	16	Proven	Proven	V	Died
ICU, Antwerp, Belgium [6]	73	M	Diabetes	ND	*A. fumigatus*	NR	(+) > 2.8	(-)	Histology from bronchoscopy (+)	5	Proven	Proven	V	Alive
ICU, Antwerp, Belgium [6]	77	M	Diabetes, chronic corticosteroids for pemphigus foliaceous	ND	*A. fumigatus*	NR	(+) 2.79	(-)	Histology from bronchoscopy (+)	2	Proven	Proven	V	Alive
ICU, Antwerp, Belgium [6]	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
ICU, Antwerp, Belgium [6]	75	M	AML with IPA 2012	ND	*A. fumigatus*	NR	(+) 2.63	ND		8	No host factor	Putative	V	Died
ICU, Breda, The Netherlands [7]	83	M	Prednisolone 0.13 mg/kg/d x 28 days for cardiomyopathy	NR	ND	*A. fumigatus*	ND	(-)		3	Probable if steroid requirement reduced to < 0.3mg/kg/d	Putative only if TA considered equivalent to BAL	V + A, or L-AmB	Died
ICU, Breda, The Netherlands [7]	67	M	Severe COPD, Post RT for NSCLC 2014, Prednisolone 0.37 mg/kg/d x 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
ICU, Breda, The Netherlands [7]	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
ICU, Breda, The Netherlands [7]	43	M	None	NR	(-)	NR	(+) 3.8	(-)		14	No host factor	Putative	V + A, or L-AmB	Alive
ICU, Breda, The Netherlands [7]	57	M	Asthma, inhaled steroids	NR	*A. fumigatus*	NR	(+) 1.6	(-)		5	No host factor	Putative	V + A, or L-AmB	Died
ICU, Breda, The Netherlands [7]	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
ICU, Paris, France [8]	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
ICU, Milan, Italy [9]	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)	N = M (%)		Of the 19 with details reported	Of the 22 with BAL n = (+), (%)		Of the 21 with BAL GM n = (+), (%)	Of the 28 with serum GM n = (+), (%)		Median (IQR)			N = treated (%)	N = died (%)
	70 (57-75)	26/33 (79)	EORTC Host factor 2(6%), inhaled/systemic steroid exposure 16(48%), diabetes 10(30%), chronic lung disease 9(27%)	Nodules 6 (31.6%), cavity/ halo-sign 2 (10.5%)	16 (72.7)		14 (66.7)	6 (21.4)		5.5 (4.3-9)	Proven (5), Probable (1), No host factor (27)	Proven (5), Putative (11), Putative with caveats (17)	24 (72.7)	21 (63.6)

A, Anidulafungin. *BAL*, Bronchoalveolar lavage. *BDG*, Beta-d-glucan. *C*, Caspofungin. *GM*, Galactomannan. *IA*, Invasive Aspergillosis. *I*, Isavuconazole. *L-AmB*, Liposomal Amphotericin B. *LFD*, Aspergillus lateral-flow device. *NSCLC*, non-small-cell lung cancer. *RT*, radiotherapy. *PCR* Polymerase chain reaction. *PM*, post-mortem. *TA*, Tracheal Aspirate. *V*, Voriconazole. *EORTC*, Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer. BAL GM (+) ≥1.0, Serum GM (+) ≥ 0.5.

a. Under EORTC criteria 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 for ≥3 weeks to classify as a host factor.

Table 1 References

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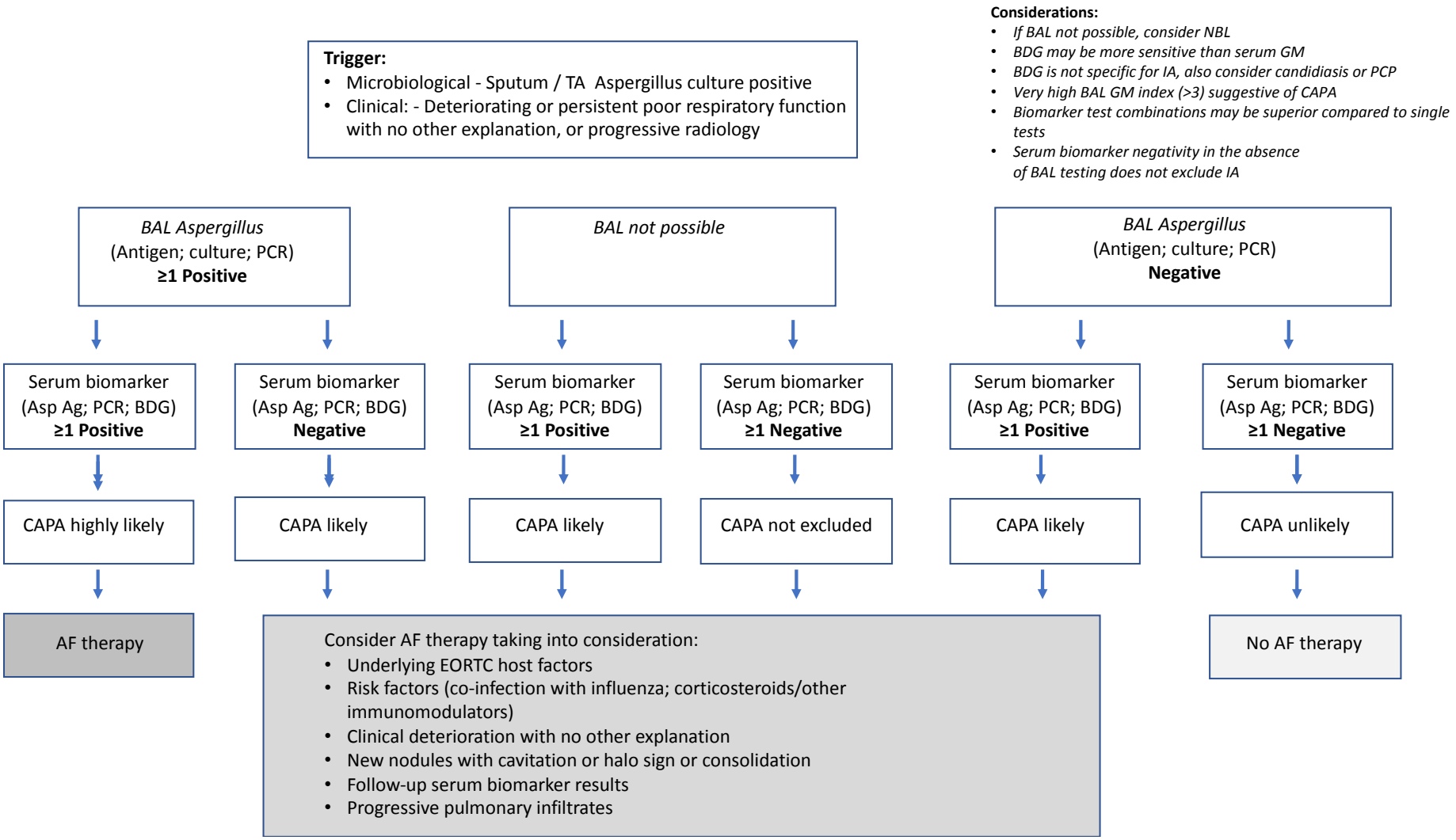
Figure 1: Proposed screening and diagnostic algorithm for COVID-19 Associated Pulmonary Aspergillosis (CAPA)



Notes: BAL- Bronchoalveolar lavage; BDG- (1-3)-β-D-glucan; TA- tracheal aspirate; Aspergillus antigen (Asp Ag)- GM ELISA or lateral-flow antigen; AF- Antifungal