Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

COVID-19-associated pulmonary aspergillosis (CAPA): how big a problem is it?

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To the Editor,

An international panel of experts has recently proposed criteria for defining a new clinical entity called CAPA—coronavirus disease 2019 (COVID-19)-associated pulmonary aspergillosis—and has made recommendations for its management [1]. The foundation for proposing CAPA as a distinct entity was the premise that pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection might promote fungal lung superinfections, particularly invasive pulmonary aspergillosis (IPA), as has been documented for influenza. The expert panel referred to articles that introduced the concept of CAPA, and raised concerns not only for a high incidence of this fungal superinfection but also a high rate of associated mortality. This literature included five case series [2–6] and two prospective studies [7,8] with a total of 94 CAPA cases (i.e. those considered as proven/probable or putative by the authors, according to different criteria). The overall incidence of CAPA was 22.6% (83/368). The association between CAPA and increased mortality was suggested by one study [7].

Such claims, however, have not been substantiated by other studies that were not considered in the expert panel publication; some of these studies reported a low incidence of CAPA and questioned the clinical relevance of colonization by *Aspergillus* spp. in patients with severe COVID-19 [9–14]. Furthermore, this contrasting view is supported by an autopsy series and a recent systematic review of an autopsy series showing that proven CAPA is uncommon (<3%) [10,15]. Moreover, a case series did not show a worse outcome in putative CAPA cases, even in the absence of antifungal therapy [2]. These discrepancies, and the lack of anatomical and pathological backing, fuel the controversy about whether CAPA represents a legitimate and unique entity.

Clearly, the diagnosis of IPA is challenging, especially in critically ill patients, as clinical and radiological presentations lack specificity, and the 'gold standard' of proof of fungal invasion by histology is rarely available [16]. The new CAPA definitions place heavy emphasis on mycological criteria, such as direct or indirect detection of *Aspergillus* in respiratory samples, including cut-offs for galactomannan antigen in non-bronchoalveolar lavage (BAL) samplings for which supportive data are lacking, as also noted by others [17]. Such findings do not allow clinicians to distinguish angioinvasion from airway colonization, particularly in patients with preexisting chronic respiratory diseases. Indeed, the rate of positive serum galactomannan antigen, a more objective evidence of invasive disease, is extremely low in CAPA, unlike the case in influenza-associated IPA.

The difficulty in establishing a diagnosis of aspergillosis in the ICU setting has been illustrated by the wide variety of criteria and definitions proposed and used in recent studies. If we focus only on patients with CAPA, there are almost as many criteria as there are publications. Although we fully recognize the desire to achieve a consensual framework for CAPA, such efforts need to stem from a sound scientific approach by dissecting first and foremost the pathophysiology of CAPA. Establishing non-validated criteria before demonstrating critical pathophysiological links and a specific association between COVID-19 and IPA may be premature.

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Table 1
Incidence of CAPA (COVID-19-associated pulmonary aspergillosis) among non-immunocompromised patients in published cohorts according to definition criteria

Consideration of publications in the paper by Koehler et al.	References	Date of online availability	Incidence of COVID-19-associated aspergillosis reported by the authors[a]	Incidence of proven/probable cases according to Koehler et al.	Incidence of possible cases according to Koehler et al.
Publications referenced in the paper by Koehler et al.	Koehler et al. [3]	15th May 2020	26.3% (5/19)	21.1% (4/19)	0% (0/19)
	Alanio et al. [2]	29th May 2020	30.8% (8/26)	19.2% (5/26)	3.8% (1/26)
	Rutsaert et al. [16]	1st June 2020	31.6% (6/19)	26.3% (5/19)	5.3% (1/19)
	Van Arkel et al. [4]	1st July 2020	19.4% (6/31)	9.7% (3/31)	6.5% (2/31)
	Heard et al. [13] [b]	3rd July 2020	0% (0/57)	0% (0/57)	1.8% (1/57)
	Gangneux et al. [6]	10th July 2020	20.0% (9/45)	Not calculable	Not calculable
	Nasir et al. [5]	18th July 2020	21.7% (5/23)	0% (0/23)	21.7% (5/23)
	Bartoletti et al. [7]	28th July 2020	28.2% (29/103)	28.2% (29/103)	0% (0/103)
	White et al. [8]	29th August 2020	14.1% (19/135)	2.2% (3/135)	8.1% (11/135)
	Subtotal		**19.0% (87/458)**	**11.9% (49/413)**	**5.1% (21/413)**
Publications not referenced in the paper by Koehler et al.	Wang et al. [14]	5th June 2020	7.7% (8/104)	3.8% (4/104)[c]	3.8% (4/104)
	Lamoth et al. [11]	10th July 2020	3.8% (3/80)	1.3% (1/80)	2.5% (2/80)
	Brown et al. [12]	6th August 2020	0% (0/60)	0% (0/60)	6.7% (4/60)
	Subtotal		**4.5% (11/244)**	**2.0% (5/244)**	**4.1% (10/244)**
Publications not available at the time the paper by Koehler et al. was written	Dupont et al. [19]	10th September 2020	17.9% (19/106)	8.5% (9/106)	7.5% (8/106)
	Chauvet et al. [18]	11th November 2020	9.8% (4/41)	4.9% (2/41)	0% (0/41)
	Roman-Montes et al. [21]	20th November 2020	9.7% (14/144)	3.5% (5/144)	6.3% (9/144)
	Fekkar et al. [20]	2nd December 2020	2.4% (3/125)	1.6% (2/125)[d]	0.8% (1/125)
	Segrelles-Calvo et al. [22]	3rd December 2020	3.3% (7/215)	2.8% (6/215)[c]	0.5% (1/215)
	Subtotal		**7.4% (47/631)**	**3.8% (24/631)**	**3.0% (19/631)**
All publications	**Total**		**10.9% (145/1333)**	**6.1% (78/1288)**	**3.9% (50/1288)**

[a] Incidence claimed by the authors using their case definitions.
[b] This publication reporting an incidence of 0% invasive aspergillosis among 57 patients is not discussed in the article by Koehler et al.
[c] Due to missing data in the original article, we include the high estimate here.
[d] A case of pulmonary fusariosis is counted with aspergillosis.

We retrospectively applied the CAPA definition criteria proposed by Koehler et al. [1] to all the published CAPA cohorts, especially the publications cited by the expert panel, to emphasize a high incidence of CAPA [2–8,16]. The latter reported a mean incidence of 19% for CAPA in non-immunocompromised patients, with incidence as high as 31.6% in individual studies (Table 1). When applying the proposed CAPA criteria to evaluable cases, the incidence of proven/probable and possible CAPA was only 11.9% and 5.1%, respectively. Moreover, after inclusion of omitted and more recent publications [11,12,14,18–22], incidence of proven/probable cases fell to 6.1%. Such comparison infers that CAPA incidence might be lower than initially supposed, although we recognize that important local epidemiological variations exist. Applying the criteria proposed by Koehler et al. brings the prevalence of proven/probable cases closer to that suggested by autopsy studies.

Intuitively, there is always justifiable concern about finding *Aspergillus* spp. in the respiratory tract, not only because it is not a commensal microorganism but also because its presence may reflect the severity of the underlying illness leading to a poor prognosis. It can be assumed that clearance of *Aspergillus* conidia may be difficult and the risk of subsequent lung invasion increased in patients whose respiratory tract is severely altered. Therefore, considerations to start pre-emptive antifungal therapy are legitimate in such situations. However, the benefits of this approach remain to be demonstrated.

The concept of CAPA was deduced largely from the association between influenza infection and *Aspergillus* superinfection, assuming similar pathophysiological features with SARS-CoV-2 which are as yet unconfirmed. Indeed, SARS-CoV-2 pneumonia seems to be associated with less extensive airway epithelium destruction and distinct host immune response profiles compared to influenza pneumonia. In sharp contrast to the reported CAPA cases, 93% of the 41 reported COVID-19-associated mucormycosis were proven [23].

In conclusion, it is debatable whether CAPA represents a distinct and novel entity of aspergillosis or should be integrated within the global problem of IPA among ICU patients in general. Validating criteria for case definitions is required to ascertain consistency in future clinical studies addressing the incidence and impact of IPA in COVID-19. However, until these goals are achieved, unvalidated conclusions and clinical recommendations might lead to unhelpful clinical and public health recommendations, additional confusion in the hot topic of aspergillosis in the ICU, and unproductive allocation of resources. Carefully designed prospective studies seeking to validate definitions of CAPA and to define its epidemiology and clinical features are required.

Author contributions

AF conceptualized the letter, performed analysis, and wrote the original draft. DN, MHN, CC and DPK participated in the design and writing. FL conceptualized the paper, performed analysis and wrote the original draft.

Transparency declaration

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