TITLE: THE CHALLENGE OF MANAGING COVID-19 ASSOCIATED PULMONARY ASPERGILLOSIS

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Dr. Bartoletti and colleagues are the first to perform a prospective study to determine the incidence and mortality of COVID-19 associated pulmonary aspergillosis (CAPA) by systematic bronchoalveolar lavage (BAL) sampling in 108 mechanically ventilated patients with proven COVID-19 and acute respiratory distress syndrome (ARDS). The results show a very high incidence of 27.7% of CAPA and a 25% lower survival in patients compared to those not fulfilling the criteria for aspergillosis (44% vs 19%, p= 0.002) [Bartoletti et al, CID accepted for publication]. The authors indicate that CAPA has similarities to influenza associated pulmonary aspergillosis (IAPA) including the high prevalence of aspergillosis cases, comparable timing of CAPA and IAPA following ICU-admission, and the presence of lymphopenia.

Diagnosing patients with CAPA has been subject of much debate (1, 2). Recent case series indicate that well known host factors for invasive pulmonary aspergillosis (IPA) are commonly absent in COVID-19 patients in the ICU, and that radiology is seldom specific for invasive fungal disease(3-6). Due to limited use of bronchoscopy, CAPA diagnosis commonly relies on detection of *Aspergillus* in upper respiratory tract specimens such as sputum or tracheal aspirates, which may represent airway colonization rather than IPA. Diagnostic uncertainty is further increased by frequent negative serum galactomannan (GM), even in patients with proven CAPA (4) as well as the observation of survival of *Aspergillus* positive patients who did not receive antifungal therapy (5). Although histopathology would be required to prove angio-invasive disease, the study of Bartoletti et al. provides important evidence that detection of *Aspergillus* in critically-ill COVID-19 patients should be taken seriously. Through systematic bronchoscopy with BAL in COVID-19 patients with ARDS admitted to the ICU, a significant association was observed between CAPA diagnosis and mortality. A possible causal relation is supported by the correlation between initial BAL GM-index and odds of death and the trend towards lower mortality and GM index reduction in CAPA-patients receiving voriconazole.

Despite the observed similarities between IAPA and CAPA and the independent association between CAPA and mortality, it remains unclear if COVID-19 infection itself predisposes for IPA.

The pathophysiology of SARS-CoV-2 infection is different to that of influenza, including viral tropism as well as the effects on the host defense. Thus, additional risk factors may be required to develop IPA in COVID-19 patients. In the cohort of Dr Bartoletti and colleagues, two immunosuppressant agents, corticosteroids and tocilizumab, were widely used. Three quarters of the patients received anti-IL-6 treatment with tocilizumab. IL-6 is an important inducer of STAT3 which in turn is essential for protective Th17 responses (7). Patients who are deficient in STAT3 are specifically susceptible for IPA (8). Therefore, the blockade of IL-6 might be a very specific risk factor for the development of CAPA. In addition, it is known that corticosteroids can impair a specific form of phagocytosis called LC3-associated phagocytosis (LAP), which is essential for host defense against aspergillosis (9). Chronic steroid treatment was significantly more frequent in CAPA patients, while corticosteroid use was more frequent in non-survivors. Recently the use of systemic corticosteroids has irrevocably demonstrated a benefit on survival in patients with COVID-19 [Horby et al; unpublished]. Dexamethasone was found to reduce mortality by one-third in seriously ill COVID-19 patients on ventilator support [World Health Organization . WHO welcomes preliminary results about dexamethasone use in treating critically ill COVID-19 patients], which might accelerate its use in this patient group. But this benefit may come at the costs of an increased mortality due to CAPA. Further clinical studies are needed to identify risk factors in CAPA, including the use of corticosteroids and blocking IL-6.

Such studies would require a CAPA case definition, which is currently lacking. Bartoletti et al. validated the IAPA expert consensus definitions for classifying patients with CAPA (10)]. The study from Bartoletti et al was the first to evaluate the IAPA case definition and this appeared to be appropriate for CAPA-patient classification and clinical management. Yet, one must note that the performance of serum fungal biomarkers in CAPA patients is different compared to those with IAPA. While circulating GM may be detected in up to 65% of IAPA-patients (10), the *Aspergillus* antigen was detected in serum of only one of 16 (6%) patients that fulfilled the CAPA criteria. The CAPA case classification therefore heavily depends on BAL-GM and may overestimate the number of CAPA cases, as BAL-GM may be positive in colonized patients. This

is exemplified in a recent case series that showed no histopathological evidence for *Aspergillus* in deceased COVID-19 patients with positive BAL-GM (2). Although this study relied on postmortem ultrasound and CT-guided biopsies rather than autopsy introducing the possibility of sampling error the observation underscores our limited ability to accurately diagnose CAPA.

Given these diagnostic challenges the question remains how best to manage critically-ill COVID-19 patients in order to prevent mortality associated with CAPA. In Bartoletti's study antifungal treatment with voriconazole was initiated in 11 of 19 patients whereas one would expect that all 30 CAPA patients would have been treated [Bartoletti et al, CID accepted for publication]. The authors argue that reluctance to initiate antifungal therapy was due to the microbiology results being interpreted as respiratory colonization. The observed excess mortality in CAPA-patients underscores the need for therapeutic interventions.

As many centers may not have rapid access to diagnostics test such as GM and beta-D-glucan, and bronchoscopy may not be performed due to the associated contamination risk, antifungal prophylaxis might be a feasible approach. The question remains, with which drug as currently no antifungal agent is licensed for prophylactic use in the ICU.

A prophylactic strategy has been proposed for the management of IAPA (10), and a pilot study with intravenous posaconazole is currently being conducted in patients admitted to the ICU with influenza (the POSAFLU trial; NCT03378479). Results from this study might help to further explore the feasibility and benefits of a prophylactic strategy in CAPA.

Regardless of the strategic choice made, all efforts should be put into improving our ability to reliably identify patients that may benefit from therapeutic interventions, which include host and risk factors, clinical factors and CAPA disease markers. The WHO recently published a minimal common outcome measure set for COVID-19 clinical research, aimed to routinely collect specific data elements of COVID-19 patients in order to facilitate pooling of data across

cohort studies and clinical trials (11). The initiative may help to gain better insights in the dilemmas surrounding CAPA diagnosis and management if fungal infections are added to the secondary infection outcome set (Verweij and Alanio, accepted for publication Lancet Infect Dis 2020). In the meantime the study from Bartoletti et al alerts the clinical audience to be aware of CAPA and take appropriate (and where needed repetitive) actions that fits their clinical setting.

NOTES

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