COVID-19 Associated Pulmonary Aspergillosis: Do We Have the CAPAcity to Improve Outcomes?

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The diagnosis of invasive pulmonary aspergillosis remains challenging. Diagnostic guidelines are available for classical immunocompromised patients and also for non-traditional groups, where varying diagnostic approaches are warranted.[1-3] The SARS-CoV-2 pandemic and critically ill COVID-19 patients with pneumonia have provided a new opportunity to characterize patients with invasive fungal infections. Analogous to post-influenza opportunistic fungal infection, invasive aspergillosis has become an important superimposed infection among COVID-19 patients with pneumonia and is associated with poor outcomes[4-6]. However, risks for IA in COVID-19 patients are likely quite different[7]. Factors that may predispose to CAPA include leukopenia or lymphopenia, immune response dysregulation, lung damage or other chronic diseases, antibiotic use, or therapies for COVID-19 such as corticosteroids or immunomodulators.[4, 7-9]

COVID-19 associated pulmonary aspergillosis (CAPA) has become an emerging and well-described problem, yet it remains a challenge to find a definition that is applicable to clinical care worldwide. Recent cohorts have described CAPA disease incidence ranging from 2 to 33%.[6, 10-13] This variability is partly related to the heterogenous populations, with differing underlying co-morbidities; but, more importantly variability is related to the criteria employed for definition of CAPA. Indeed, there are now at multiple guidelines described and consensus criteria are available[1, 2, 14]. Current challenges in diagnosis include non-classical risk factors (fewer immunocompromised patients) in COVID-19 patients, non-specific radiographic presentations, decreased ability to obtain bronchoalveolar lavage testing due to SARS-CoV-2 transmission precautions, and decreased sensitivity of fungal biomarkers (serum galactomannan, β-D-glucan) in this population.

In this issue of *Clinical Infectious Diseases*, Permpalung and colleagues describe a large cohort of mechanically ventilated patients with COVID-19, focusing on risk factors and outcomes of patients with CAPA. This was a retrospective cohort study involving 5 hospitals in the Johns Hopkins University system during March through August 2020. A total of 396 patients were included, of whom 20 were classified as "probable" CAPA and 19 others as "possible" CAPA. Probable CAPA was defined as having one of the following: presence of new cavitary lesion(s) on chest CT without alternative explanation, positive serum galactomannan (GM) index ≥0.5, positive bronchoalveolar lavage (BAL) GM index ≥1.0, or positive culture for *Aspergillus* on BAL. Possible CAPA included at least one of the following: positive BAL GM index 0.5-1.0; positive Beta-D-glucan (BDG)>80 pg/ml without alternative explanation; or non-BAL respiratory culture with growth of *Aspergillus* species. The incidence of CAPA ranged from 5-10% depending on definition used. The authors identified several risk factors for CAPA, including pulmonary vascular diseases, liver disease, coagulopathy and solid tumor malignancy, among others. Importantly, they confirmed poor outcomes such as duration of oxygen use, duration on a ventilator or ECMO, and hospital length-of-stay, when compared to controls. These poorer outcomes were observed regardless of the CAPA definition used. There was not a significant mortality difference.

An important strength is that the cohort was a large, well-defined population using patient-level data from multiple hospitals. Beyond using standard, more restrictive criteria for probable CAPA, they included a definition for possible CAPA, which was relevant to clinical care during the study period, as a standardized surveillance process for invasive fungal infection was not instituted during the entirety of the cohort duration. Another important finding is that poor outcomes were associated with both definitions of CAPA. However, there

is an important limitation in outcome assessment, likely related to the retrospective nature of the study: among 39 patients classified as CAPA, only 48.7% received antifungal therapy. This potentially had an impact on differences in outcomes, including mortality. The reasons for lack of antifungal therapy may be multi-factorial, but underscores the challenges of identification of aspergillosis in a pandemic setting, where we continue to learn best practices and limitations of diagnostic testing.

Given these findings, how can this study inform clinical practice and elucidate current knowledge gaps? First, the definition of CAPA is a moving target, and may be different for research vs clinical care purposes, similar to pre-COVID-19 fungal diagnostic guidelines[1]. Traditionally, fungal diagnostic guidelines have relied on host (immunocompromise) factors, radiologic criteria, and fungal microbiologic tests to assign a proven, probable or possible certainty of infection[1]. Among patients with COVID-19, fewer have underlying immunocompromising conditions, although steroids and other biologic therapies for COVID-19 may increase risk. Interpretation of radiologic findings as a criterion for risk remains problematic and less helpful with the background of diffuse lung damage and infiltrates related to COVID-19 or bacterial superinfections. Traditional radiologic findings observed in IA patients with hematologic malignancies, such as nodules, cavities, and the "halo" sign are less frequent or may be hidden.[3] Microbiologic studies from BAL samples, although ideal, are less feasible in the pandemic setting due to risk of for transmission of SARS-CoV-2 from bronchoscopy procedures. There is still much to learn of the value of fungal biomarkers in non-BAL respiratory samples and predictive value of *Aspergillus* growing from respiratory cultures. [14, 15] Barriers persist for availability of fungal biomarkers and PCR testing in low-income countries, making a restrictive definition of CAPA poorly applicable.

Second, risk factors for CAPA require further investigation. As COVID-19 care is evolving, so must our cohorts and analyses. Many of these patients are critically ill, and larger cohorts with multivariable analyses will be necessary to identify confounding variables. As treatment practices are evolving, we must also adapt. As an example, Permpalung et al. identified that glucocorticoteroids (mostly hydrocortisone) increased the odds for CAPA, but among the whole cohort just over 50% received corticosteroids. With recent guidelines recommending 10-days of dexamethasone use for most critically ill patients with COVID-19, there will now be a large background of steroid use among COVID-19 patients, so it will be necessary to identify novel factors associated with CAPA to guide diagnosis, prevention and treatment[16].

Third, although most reports of COVID-19 associated fungal infections have focused on CAPA, there are an increasing number of reports describing other opportunistic fungal infections, such as candidiasis, pneumocystosis, endemic mycoses and non-Aspergillus molds.[17-20] These infections appear to be less common than CAPA among COVID-19 patients, but additional cohort data are required to better understand diagnostic limitations, disease frequency, risk factors and management.

Finally, as we continue to study CAPA, we must concurrently focus on prevention of CAPA and other COVID-19-associated fungal infections. Once an appropriate at-risk population is defined, is antifungal prophylaxis, preemptive or empiric antifungal therapy indicated, and for what duration? What factors should trigger antifungal administration? Antifungal agents have been safe and effective as prophylaxis in some populations, but safety, drug-interactions, drug levels and costs are always of concern, especially in critically ill patients. Hopefully ongoing prophylaxis strategies will be informative and applicable to COVID-19

patients (clincaltrials,gov; NCT03378479). As much progress has been made in the past year with COVID-19 and CAPA and its classification, we look forward to additional research like that published by Permpalung and colleagues to inform diagnostic and management strategies and improve patient outcomes.

Potential Conflicts of interest:

Dr Baddley reports consultation for Pfizer, Eli Lilly, R-Pharm and Viela Bio

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