Invasive Fungal Disease Complicating Coronavirus Disease 2019: When It Rains, It Spores

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A century ago, the 1918 influenza pandemic changed the world, when one-third of the world’s population became infected and >50 million people died. By examining lung tissue samples preserved in paraffin blocks, Morens and colleagues from the National Institute of Allergy and Infectious Diseases found only out 80 years later that in fact the majority of deaths in the 1918 influenza pandemic resulted not from viral pneumonia, but from secondary bacterial pneumonia caused by common upper respiratory tract bacteria [1]. Now we are facing another devastating worldwide pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with to date >24 million individuals infected and a mortality rate >3%. Although superinfections were rarely reported in the beginning of the current pandemic, they are now on the rise, particularly reports about secondary fungal disease.

SARS-CoV-2–associated pulmonary aspergillosis (CAPA) has been the predominant fungal disease, adding insult to injury in coronavirus disease 2019 (COVID-19) patients with acute respiratory distress syndrome (ARDS), and although the pathogenesis is incompletely understood, there are several immunological mechanisms that may contribute to the development of CAPA and other fungal diseases. SARS-CoV-2 invasion results in the release of danger-associated molecular patterns (DAMPs) that act as endogenous signals that exacerbate the immune and inflammatory response leading to lung injury [2, 3]. Importantly, DAMPs are known to play a central role in the pathogenesis of fungal diseases [4]. Moreover, collateral effects of host recognition pathways required for the activation of antiviral immunity may, paradoxically, contribute to a highly permissive inflammatory environment that favors fungal pathogenesis [2].

To date, >100 cases of CAPA have been reported from many countries in Europe, Asia, Australia, and South America [2, 5–18], often occurring in patients with no other risk factor than COVID-19–associated ARDS [2], and multiple of them proven by autopsy [17, 19, 20]. In contrast, there are fewer reports on other fungal diseases complicating COVID-19, including 2 cases of Saccharomyces cerevisiae fungemia caused by fungal translocation [21] after administration of probiotic preparations containing Saccharomyces [22], cases of invasive Candida infections [23], and a case of invasive fusariosis [24].

Now, in this issue of Clinical Infectious Diseases, White and colleagues from the United Kingdom report a 26.7% incidence of invasive fungal disease in a multicenter prospective cohort of COVID-19 intensive care patients, including a 12.6% incidence of invasive yeast infections [25]. CAPA still accounted for the majority of fungal disease cases (14% of the cohort), although this was lower than the average incidence rate of 26% reported in previous studies.

Of note, CAPA incidence rates reported to date have varied widely, ranging from 4% [15] to 35% [19] in mechanically ventilated critically ill patients. Factors that may contribute to the differing incidence rates are 3-fold. First, fungal diseases and specifically CAPA are difficult to diagnose and are likely underestimated, particularly in the setting of COVID-19–associated ARDS, where the clinical picture and radiological findings of CAPA resemble those of severe COVID-19 [7, 26]; blood tests lack sensitivity due to the primarily airway invasive growth of Aspergillus in nonneutropenic patients [27]; and, most importantly, sampling of the primary site of infection is rarely performed, due to the risk of COVID-19 transmission through bronchoscopies with bronchoalveolar lavage (BAL) or autopsies (due to the overlap of imaging findings between CAPA and COVID-19, postmortem fine needle biopsies alone may not be sufficient to detect focal CAPA [28]), which are
both aerosol-creating procedures [29]. Random diagnosis of CAPA, without specifically and creatively searching for it, is therefore virtually impossible in this setting, and diagnosis requires specific expertise and awareness, which is rare given that fungi are neglected pathogens [30, 31]. Also, in many places around the world, clinical mycology remains a neglected subspecialty in the medical field, sometimes overlooked even within the specialty of infectious diseases where the focus is often laid on more common bacterial and viral infections. Funding for research on fungal diseases is limited compared to funding available for other infectious diseases that cause similar or lower mortality, a fact that is outlined by the Global Funding of Innovation for Neglected Diseases (G-Finder) Report [31].

Second, screening of critically ill COVID-19 patients for CAPA is necessary but serum galactomannan (GM), the screening standard in other high-risk settings, has limited utility because of a low sensitivity of only 21% for CAPA [2]. Screening with serum (1–3)-ß-D-glucan (BDG) might show better performance characteristics and also detect fungal diseases caused by Candida species, and as such BDG is also recommended as basic screening test in the present study by White and colleagues [25]. However, most hospitals do not have access to rapid in-house BDG test results, limiting the feasibility of BDG screening, something that may change in the near future with the introduction of the Fungitell STAT rapid test that allows for qualitative detection of BDG from serum, with results available in approximately 1 hour [32]. Also, BDG is a panfungal marker and not specific for CAPA or any other fungal disease, requiring further evaluations and testing of blood and BAL with, for example, culture, GM, polymerase chain reaction (PCR), or the Aspergillus lateral flow assay (LFA) in those who screen positive [33]. Given the difficulties to obtain BAL, nondirected bronchial lavage (NBL) and tracheal aspiration (TA) samples would be the logical alternatives for screening for CAPA and other pulmonary mold infections, but non-culture-based methods such as GM, PCR, or LFA are not validated for respiratory specimens other than BAL. Therefore, screening of NBL/TA would have to rely primarily on fungal culture, which would also require further workup given imperfect specificity. Taking into account feasibility and performance, screening of mechanically ventilated COVID-19 patients for fungal disease using serum BDG and/or screening for mold disease using direct microscopy and high-volume fungal culture [34, 35] of NBL/TA may be the preferable options with acceptable sensitivities, but positive screening results should always trigger further workup for fungal diseases.

Third, incidence of CAPA may differ depending on treatment modalities for severe COVID-19. In particular, dexamethasone treatment, as well as anti-interleukin 6 (IL-6) therapy, may result in an increasing rate of superinfections, including CAPA in critically ill COVID-19 patients [36]. Indeed most patients received anti-IL-6 treatment with tocilizumab, as well as corticosteroids, in some of the studies with high CAPA incidence [14]. While in other studies high incidence of CAPA was observed despite the absence of systemic corticosteroid use [19], the use of corticosteroids significantly increased the likelihood of CAPA in the present study by White et al [25]. Other environmental factors, such as construction activity for temporary facilities and hospitals that may not adhere to rigorous ventilation requirements present within permanent hospitals, may also increase fungal exposure beyond what would normally be encountered within hospitals and/or intensive care units (ICUs) [37].

CAPA-associated mortality rates have been devastating, with cohort studies consistently reporting mortality rates >40% [5, 7, 8, 14, 16, 19]. While it was shown recently that CAPA was significantly [14] associated with mortality among intubated patients with COVID-19 [7, 8, 19], it had remained unknown whether antifungal treatment could improve mortality rates. White et al now report significantly higher mortality rates in those with fungal disease (53% vs 32%; \( P = .04 \)), which was driven specifically by patients with fungal disease who were not receiving antifungal therapy (90% mortality), whereas mortality was significantly (\( P = .008 \)) reduced to 38.5% in those with fungal disease who received antifungal therapy [25]. These findings outline the utmost importance of early and appropriate antifungal therapy in order to improve CAPA survival. While in general, outside the hematologic malignancy setting voriconazole remains the recommended first-line treatment for invasive aspergillosis [38, 39], there are several drawbacks to using voriconazole in patients with severe COVID-19. Voriconazole is metabolized via CYP2C19, CYP2C9, and CYP3A4 and is among the drugs most frequently associated with major drug–drug interactions in the ICU setting [40]. Voriconazole also shows interactions with with some experimental COVID-19 therapies, including hydroxychloroquine, atazanavir, and lopinavir/ritonavir, although there seem to be no clinically relevant interactions with remdesivir and dexamethasone [41]. Enthusiasm for voriconazole is also tempered by its narrow therapeutic window [42]. While more limited data exist for isavuconazole outside the hematologic malignancy setting, isavuconazole, compared with voriconazole, showed a favorable pharmacokinetic profile and was associated with fewer toxicities and also fewer drug–drug interactions and may therefore be the treatment of choice [43]. Liposomal amphotericin B is the primary alternative option for treatment of invasive pulmonary aspergillosis in the ICU [38]; however, the drug is nephrotoxic and may thus result in a further decline of renal function [44], which is particularly relevant for patients infected by SARS-CoV-2, which has shown renal tropism and is a frequent cause of kidney injury.
for CAPA and other fungal diseases is screening of COVID-19 ARDS patients to facilitate the initiation of appropriate antifungal therapy. This is particularly important because the occurrence of fungal diseases, and particularly CAPA, add insult to injury during COVID-19: we should be prepared. J Mycol Med 2020; 30:100971.

In conclusion, fungal diseases, and particularly CAPA, add insult to injury in a significant proportion of critically ill COVID-19 patients and are associated with high mortality rates, which may be reduced by early diagnosis and initiation of appropriate antifungal therapy. In the absence of antifungal prophylaxis, screening of COVID-19 ARDS patients for CAPA and other fungal diseases is essential.

Notes

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