EDITORIAL COMMENTARY

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 tampered 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

[45]. However, reports of azole resistance in CAPA are emerging [46–48], and in those cases liposomal amphotericin B may be the treatment of choice [49]. New antifungal classes currently under development, namely fosmanogepix (phase 2b study currently enrolling CAPA patients) and olorofim [50], may have efficacy similar to triazoles without the same burden of drug–drug interactions and toxicity, and may therefore overcome the limitations of currently available antifungals and become the preferred treatment options in the near future.

When interpreted in conjunction with previous findings, the high fungal disease incidence and associated mortality rates reported in the study by White et al may open the door for trials evaluating antifungal prophylaxis in COVID-19 patients with ARDS. In an earlier single-center study, inhaled liposomal amphotericin B prophylaxis was effectively used to tackle high rates of CAPA in a Belgian ICU [19]. Although for prophylaxis trials isavuconazole or posaconazole may be preferable, given the better safety profiles, other new antifungals currently under development, namely rezafungin (a once-weekly echinocandin), ibrexafungerp (a triterpenoid, which is a novel class of structurally distinct glucan synthase inhibitors), and PC945e (an inhaled broad-spectrum azole with a favorable safety profile) may be viable options, once approved [50].

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

References

1. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis **2008**; 198:962–70.
2. Arastehfar A, Carvalho A, van de Veerdonk FL, et al. COVID-19 associated pulmonary aspergillosis (CAPA)—from immunology to treatment. J Fungi (Basel) **2020**; 6:91.
3. Tolle LB, Standiford TJ. Danger-associated molecular patterns (DAMPs) in acute lung injury. J Pathol **2013**; 229:145–56.
4. Cunha C, Carvalho A, Esposito A, Bistoni F, Romani L. DAMP signaling in fungal infections and diseases. Front Immunol **2012**; 3:286.
5. Alanio A, Dellière S, Fodil S, Bretagne S, Mégarbane B. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. Lancet Respir Med **2020**; 8:e48–9.
6. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: we should be prepared. J Mycol Med **2020**; 30:100971.
7. Koehler P Cornely OA, Böttiger BW, et al. COVID-19 associated pulmonary aspergillosis. Mycoses **2020**; 63:528–34.
8. van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19 associated pulmonary aspergillosis. Am J Respir Crit Care Med **2020**; 202:132–5.
9. Sharma A, Hofmeyr A, Bansal A, et al. COVID-19 associated pulmonary aspergillosis (CAPA): an Australian case report [manuscript published online ahead of print 18 June 2020]. Med Mycol Case Rep **2020**. doi:10.1016/j.mmcr.2020.06.002.
10. Fernandez NB, Caceres DH, Beer KD, et al. Ventilator-associated pneumonia involving *Aspergillus flavus* in a patient with coronavirus disease 2019 (COVID-19) from Argentina [manuscript published online ahead of print 5 July 2020]. Med Mycol Case Rep **2020**. doi:10.1016/j.mmcr.2020.07.001.
11. Abdalla S, Almaslamani MA, Hashim SM, Ibrahim AS, Omrani AS. Fatal coronavirus disease 2019-associated pulmonary aspergillosis; a report of two cases and review of the literature. IDCases **2020**; 22:e00935.
12. Gangneux JP, Reizine F, Guegan H, et al. Is the COVID-19 pandemic a good time to include *Aspergillus* molecular detection to categorize aspergillosis in ICU patients? A monocentric experience. J Fungi (Basel) **2020**; 6:E105.
13. Falces-Romero I, Ruiz-Bastián M, Díaz-Pollán B, Maseda E, García-Rodríguez J. Isolation of *Aspergillus* spp. in respiratory samples of patients with COVID-19 in a Spanish tertiary care hospital [manuscript published online ahead of print 4 August 2020]. Mycoses **2020**. doi:10.1111/myc.13155.
14. Bartoletti M, Pascale R, Cricca M, et al. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study [manuscript published online ahead of print 28 July 2020]. Clin infect Dis **2020**. doi:10.1093/cid/ciaa1065.
15. Lamoth F, Glampedakis E, Boillat-Blanco N, Oddo M, Pagani JL. Incidence of invasive pulmonary aspergillosis among critically ill COVID-19 patients [manuscript published online ahead of print 10 July 2020]. Clin Microbiol Infect **2020**. doi:10.1016/j.cmi.2020.07.010.
16. Nasir N, Farooqi J, Mahmood SF, Jabeen K. COVID-19-associated pulmonary aspergillosis (CAPA) in patients admitted with severe COVID-19 pneumonia: an observational study from Pakistan. Mycoses **2020**; 63:766–70.
17. Santana MF, Pivoto G, Alexandre MAA, et al. Confirmed invasive pulmonary aspergillosis and COVID-19: the value of postmortem findings to support antemortem management. Rev Soc Bras Med Trop **2020**; 53:e20200401.
18. Helleberg M, Steensen M, Arendrup MC. Invasive aspergillosis in patients with severe COVID-19 pneumonia [manuscript published online ahead of print 5 August 2020]. Clin Microbiol Infect **2020**. doi:10.1016/j.cmi.2020.07.047.
19. Rutsaert L, Steinfort N, Van Hunsel T, et al. COVID-19-associated invasive pulmonary aspergillosis. Ann Intensive Care **2020**; 10:71.
20. Antinori S, Rech R, Galimberti L, et al. Invasive pulmonary aspergillosis complicating SARS-CoV-2 pneumonia: a diagnostic challenge [manuscript published online ahead of print 26 May 2020]. Travel Med Infect Dis **2020**. doi:10.1016/j.tmaid.2020.101752.
21. Hoenigl M. Fungal translocation: a driving force behind the occurrence of non-AIDS events? Clin Infect Dis **2020**; 70:242–4.
22. Ventoulis I, Sarmourli T, Amoiridou P, et al. Bloodstream infection by *Saccharomyces cerevisiae* in two COVID-19 patients after receiving supplementation of *Saccharomyces* in the ICU. J Fungi **2020**; 6:98.
23. Garcia-Vidal C, Sanjuan G, Moreno-García E, et al. Incidence of co-infections and superinfections in hospitalised patients with COVID-19: a retrospective cohort study [manuscript published online ahead of print 31 July 2020]. Clin Microbiol Infect **2020**. doi:10.1016/j.cmi.2020.07.041.
24. Poignon C, Blaize M, Vezinet C, Lampros A, Monsel A, Fekkar A. Invasive pulmonary fusariosis in an immunocompetent critically ill patient with severe COVID-19 [manuscript published online ahead of print 30 June 2020]. Clin Microbiol Infect **2020**. doi:10.1016/j.cmi.2020.06.026.
25. White LP, Dhillon R, Cordey A, et al. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clin Infect Dis **2021**; 73:e1634–44.
26. Verweij PE, Gangneux JP, Bassetti M, et al; European Confederation of Medical Mycology; International Society for Human and Animal Mycology; European Society for Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; ESCMID Study Group for Infections in Critically Ill Patients. Diagnosing COVID-19-associated pulmonary aspergillosis. Lancet Microbe **2020**; 1:e53–5.
27. Jenks JD, Mehta SR, Taplitz R, Aslam S, Reed SL, Hoenigl M. Point-of-care diagnosis of invasive aspergillosis in non-neutropenic patients: *Aspergillus* galactomannan lateral flow assay versus *Aspergillus*-specific lateral flow device test in bronchoalveolar lavage. Mycoses **2019**; 62:230–6.
28. Flikweert AW, Grootenboers MJJH, Yick DCY, et al. Late histopathologic characteristics of critically ill

COVID-19 patients: different phenotypes without evidence of invasive aspergillosis, a case series. J Crit Care **2020**; 59:149–55.

29. Wahidi MM, Lamb C, Murgu S, et al. American Association for Bronchology and Interventional Pulmonology (AABIP) statement on the use of bronchoscopy and respiratory specimen collection in patients with suspected or confirmed COVID-19 infection [manuscript published online ahead of print 18 March 2020]. J Bronchology Interv Pulmonol **2020**. doi:10.1097/LBR.0000000000000681.

30. Rodrigues ML, Nosanchuk JD. Fungal diseases as neglected pathogens: a wake-up call to public health officials. PLoS Negl Trop Dis **2020**; 14:e0007964.

31. Rodrigues ML, Albuquerque PC. Searching for a change: the need for increased support for public health and research on fungal diseases. PLoS Negl Trop Dis **2018**; 12:e0006479.

32. D'Ordine RL, Garcia KA, Roy J, Zhang Y, Markley B, Finkelman MA. Performance characteristics of Fungitell STAT, a rapid $(1\rightarrow3)$-β-D-glucan single patient sample in vitro diagnostic assay [manuscript published online ahead of print 13 May 2020]. Med Mycol **2020**. doi:10.1093/mmy/myaa028.

33. Hoenigl M, Prattes J, Spiess B, et al. Performance of galactomannan, beta-d-glucan, *Aspergillus* lateral-flow device, conventional culture, and PCR tests with bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis. J Clin Microbiol **2014**; 52:2039–45.

34. Vergidis P, Moore CB, Novak-Frazer L, et al. High-volume culture and quantitative real-time PCR for the detection of *Aspergillus* in sputum. Clin Microbiol Infect **2020**; 26:935–40.

35. Jenks JD, Prattes J, Frank J, et al. Performance of the bronchoalveolar lavage fluid *Aspergillus* galactomannan lateral flow assay with Cube Reader for diagnosis of invasive pulmonary aspergillosis: a multicenter cohort study. Clin Infect Dis **2021**; 73:e1737–44.

36. Lewis RE, Kontoyiannis DP. Invasive aspergillosis in glucocorticoid-treated patients. Med Mycol **2009**; 47(Suppl 1):S271–81.

37. Thompson GR III, Cornely OA, Pappas PG, et al. Invasive aspergillosis as an underrecognized superinfection in COVID-19 [manuscript published online ahead of print 19 June 2020]. Open Forum Infect Dis **2020**. doi:10.1093/ofid/ofaa242.

38. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 63:e1–e60.

39. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect **2018**; 24(Suppl 1):e1–e38.

40. Baniasadi S, Farzanegan B, Alehashem M. Important drug classes associated with potential drug-drug interactions in critically ill patients: highlights for cardiothoracic intensivists. Ann Intensive Care **2015**; 5:44.

41. McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: a review of early and emerging options. Open Forum Infect Dis **2020**; 7:ofaa105.

42. Hoenigl M, Duettmann W, Raggam RB, et al. Potential factors for inadequate voriconazole plasma concentrations in intensive care unit patients and patients with hematological malignancies. Antimicrob Agents Chemother **2013**; 57:3262–7.

43. Jenks JD, Salzer HJ, Prattes J, Krause R, Buchheidt D, Hoenigl M. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design, development, and place in therapy. Drug Des Devel Ther **2018**; 12:1033–44.

44. Armstrong-James D, Koh M, Ostermann M, Cockwell P. Optimal management of acute kidney injury in critically ill patients with invasive fungal infections being treated with liposomal amphotericin B. BMJ Case Rep **2020**; 13:e233072.

45. Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med **2020**; 383:590–2.

46. Ghelfenstein-Ferreira T, Saade A, Alanio A, et al. Recovery of a triazole-resistant *Aspergillus fumigatus* in respiratory specimen of COVID-19 patient in ICU—a case report [manuscript published online ahead of print 2 July 2020]. Med Mycol Case Rep **2020**. doi:10.1016/j.mmcr.2020.06.006.

47. Mohamed A, Hassan T, Trzos-Grzybowska M, et al. Multi-triazole-resistant *Aspergillus fumigatus* and SARS-CoV-2 co-infection: a lethal combination [manuscript published online ahead of print 26 June 2020]. Med Mycol Case Rep **2020**. doi:10.1016/j.mmcr.2020.06.005.

48. Meijer EFJ, Dofferhoff ASM, Hoiting O, Buil JB, Meis JF. Azole-resistant COVID-19-associated pulmonary aspergillosis in an immunocompetent host: a case report. J Fungi (Basel) **2020**; 6:79.

49. Schauwvlieghe AFAD, de Jonge N, van Dijk K, et al. The diagnosis and treatment of invasive aspergillosis in Dutch haematology units facing a rapidly increasing prevalence of azole-resistance. A nationwide survey and rationale for the DB-MSG 002 study protocol. Mycoses **2018**; 61:656–64.

50. Kupferschmidt K. New drugs target growing threat of fatal fungi. Science **2019**; 366:407.