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## COVID-19 and fungal superinfection

The Comment by Paul Verweij and colleagues<sup>1</sup> on diagnosing COVID-19-associated pulmonary aspergillosis was insightful and much needed. We note some unanswered questions and review specific details of the studies cited. Zhang and colleagues<sup>2</sup> note that seven (3%) of 221 patients had co-infection with a fungus; however, there was no discussion regarding which fungi were isolated, nor any supporting evidence of invasive fungal infection (eg, by imaging or antigen testing) or treatment. Alanio and colleagues<sup>3</sup> described nine (33%) of 27 patients admitted to the intensive care unit (ICU) as having invasive aspergillosis. However, only one patient, with concurrent candidaemia (*Candida glabrata*), received antifungal treatment (voriconazole). Supportive diagnostic criteria, including serum galactomannan and bronchoalveolar lavage galactomannan, were negative in all patients, and no deaths were attributed to invasive fungal infection. Koehler and colleagues<sup>4</sup> described invasive aspergillosis in five (26%) of 19 patients admitted to the ICU; three patients were positive for *Aspergillus* spp by PCR and galactomannan from a bronchoalveolar lavage sample, one patient grew *Aspergillus* spp on a tracheal aspirate but was negative for serum galactomannan, and the final patient had positive serum galactomannan with no growth on a tracheal aspirate.

From our experience, if a patient does not respond to broad-spectrum

antibacterials in the ICU we suggest the addition of an antifungal, liposomal amphotericin B. This recommendation was extrapolated from seasonal influenza findings in the absence of available COVID-19 epidemiology data.<sup>5</sup> Of those patients admitted to the ICU, 24 (42%) of 57 received liposomal amphotericin B (median treatment of 6 days, range 1–16; Heard KL unpublished). No patients grew fungi from invasive samples, but 12 (50%) had fungi from superficial samples (rectal screening swabs, tracheal aspirates, or sputum); one of which had *Aspergillus fumigatus* in a sputum sample and 11 grew *Candida* spp from superficial swabs. 14 (58%) patients who started liposomal amphotericin B had a serum (1,3)- $\beta$ -D-glucan antigen test: all were negative. The one patient who grew *Aspergillus* spp had a bronchoalveolar lavage 1 day before the sputum sample, which did not grow a fungus and had negative serum (1, 3)- $\beta$ -D-glucan and galactomannan. Five (21%) patients developed acute kidney injury in the context of liposomal amphotericin B therapy.

Given our findings among patients with COVID-19, which include a notable incidence of *Candida* spp, minimal definitive invasive fungal infection, and a potential drug toxicity, we would like to add to the research questions posed by Verweij and colleagues.<sup>1</sup> We suggest COVID-19 fungal research should also explore invasive *Candida* spp as potential pathogens, the environmental factors (rapid changes to ICU capacity and infrastructure) that might increase the risk of COVID-19-associated pulmonary

aspergillosis, and the potential harm of treating unproven invasive aspergillosis.

LSPM has consulted for bioMerieux (2013–20), DNAelectronics (2015), Dairy Crest (2017–18), Pfizer (2018–20), and Umovis Lab (2020), received speaker fees from Profile Pharma (2018), received research grants from the National Institute for Health Research (2013–19), Leo Pharma (2016), and CW+ charity (2018–19), and received educational support from Eumedica (2016–17), outside of the submitted work. All other authors declare no competing interests.

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\*Katie L Heard, Stephen Hughes, Nabeela Mughal, Luke S P Moore  
katie.heard@nhs.net

Chelsea and Westminster NHS Foundation Trust, London SW10 9NH, UK (KLH, SH, NM, LSPM); North West London Pathology, Imperial College Healthcare NHS Trust, London, UK (NM, LSPM); and National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, London, UK (NM, LSPM)

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