Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

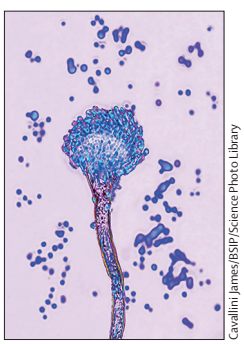
Managing secondary fungal infections in severe COVID-19: how to move forward?

The recent literature has been confusing regarding the frequency and clinical implications of COVID-19-associated pulmonary aspergillosis (CAPA).[1] This confusion has been due to the use of variable case definitions, infrequent histopathological confirmation of CAPA,[2] and reports of patients with CAPA surviving without receiving antifungal therapy.[3]

Using the 2020 CAPA consensus criteria of the European Confederation of Medical Mycology and International Society for Human and Animal Mycology (ECMM/ISHAM),[1] Jean-Pierre Gangneux and colleagues show that CAPA is a frequent and clinically relevant complication of severe COVID-19.[4] In their study in *The Lancet Respiratory Medicine*, 76 (15%) of 509 mechanically ventilated patients with COVID-19 fulfilled the ECMM/ISHAM criteria for proven or probable CAPA. In addition, 38 (7%) patients developed other fungal infections including invasive candidiasis (32 patients), mucormycosis (six patients), or fusariosis (one patient), or infection or colonisation with *Pneumocystis jirovecii* (four patients). Among secondary infections, only fungal co-infection (ie, pulmonary aspergillosis) was significantly associated with mortality, with patients with CAPA showing a significantly higher mortality (61·8% [95% CI 50·0–72·8]) than those without CAPA (32·1% [27·7–36·7]; p<0·0001).[4] Antifungal therapy did not modify mortality and was not associated with improved survival.

An important question is how best to manage secondary fungal infections in patients with severe COVID-19 in the intensive care unit (ICU). The 15% CAPA incidence and high mortality might justify antifungal prophylaxis, but no antifungal drugs are currently licensed for prophylaxis in the ICU. A recent study evaluated posaconazole prophylaxis in patients admitted to the ICU with severe influenza, with the aim of preventing cases of influenza-associated pulmonary aspergillosis (IAPA).[5] The study was unsuccessful because 15 (71%) of 21 IAPA cases were diagnosed at ICU admission, and required immediate antifungal therapy and were excluded. As a consequence, the study was underpowered to show a beneficial effect of posaconazole prophylaxis, although no IAPA cases were observed in patients on posaconazole.[5] Compared with IAPA, CAPA develops later in the course of ICU admission. Gangneux and colleagues report a median time to CAPA diagnosis of 8·0 days (IQR 4·0–14·0), which is in line with other studies.[4] This delay in onset might provide a period to allow patients with COVID-19 to benefit from antifungal prophylaxis. A small observational study involving 132 patients, of whom 75 (57%) received antifungal prophylaxis, predominantly posaconazole, showed a greater than 90% reduction in 30-day CAPA incidence estimates, from 17·5% (95% CI 9·6–31·4) in the group without prophylaxis to 1·4% (95% CI 0·2–9·7) in those patients receiving antifungal prophylaxis (p=0·002).[6] However, a survival benefit was not observed, which would require a randomised controlled trial. Posaconazole is regarded as the standard treatment for antimould prophylaxis in patients with haematological malignancy and might also help to prevent secondary fungal infections due to other fungi such as mucormycetes. However, primary prophylaxis depends on the anticipated frequency of secondary fungal infections. Although reported CAPA incidence is 10–17%,[4,6,7] most of these studies were performed during the first wave of COVID-19, whereas the current epidemiology is likely to have changed. Factors that might increase invasive fungal infection frequency include the standard use of dexamethasone combined with anti-IL-6 in severe COVID-19, emergence of new (more virulent) SARS-CoV-2 variants,[8] and a possible shift towards unvaccinated individuals and those who respond less well to vaccination. Conversely, COVID-19 vaccination has been shown to be highly effective in reducing hospitalisation and ICU admission,[9] with increasing vaccine coverages in most countries. The feasibility of a prophylaxis strategy will thus depend on characteristics of the population of patients with severe COVID-19 admitted to the ICU and their probability of developing opportunistic infections.

The current recommendation to perform bronchoscopy and bronchoalveolar lavage in patients with COVID-19 who are clinically deteriorating is challenged by the observation of Gangneux and colleagues that any positive *Aspergillus* culture or PCR from respiratory specimens



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See **Articles** page 180

was associated with increased mortality, regardless of the aspergillosis status.[4] This observation might prompt clinicians to start antifungal therapy as soon as *Aspergillus* is recovered, which will substantially increase the use of antifungal drugs in patients with COVID-19 in the ICU. Profiling of patients with severe COVID-19 needs to be improved with regard to their risk of developing opportunistic infections. We previously hypothesised that the risk of developing CAPA depends on the accumulation of factors related to the host, including age and risk factors defined by the European Organisation for Research and Treatment of Cancer and Mycoses Study Group Education and Research Consortium for invasive fungal diseases, factors related to viral infection, including lytic effects and immune dysregulation, and factors related to treatment interventions, including the administration of dexamethasone and tocilizumab.[10] However, the spectrum of secondary infections is broad, also including viral reactivations, such as herpes simplex virus (HSV) and cytomegalovirus (CMV).[4] In this respect, CAPA might also be seen as a reflection of a broader immunocompromised status and a sign of the severity of the weakened host status. Integrated risk profiling could involve analysing markers of opportunistic pathogens, including SARS-CoV-2, HSV, and CMV viral loads and biomarkers of opportunistic fungal infections, as well as systemic and local host parameters, including inflammatory cells and cytokines associated with inflammatory pathways, endothelial injury, and alveolar type 1 and 2 injury. Risk profiles could then be correlated with immunosuppressive treatments and outcome. Such an approach might help early identification of patients with severe COVID-19 who might benefit from tailored interventions such as pre-emptive antifungal therapy.

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Risk of COVID-19 hospital admission among children with asthma


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See **Articles** page 191

Throughout the COVID-19 pandemic it has been clear that children are at substantially lower risk of severe disease than adults.[1] Nevertheless, large groups of children with comorbidities have been asked to shield for long durations, forgoing their access to face-to-face education and reducing their social contact, with substantial potential detriment to their mental health and emotional wellbeing. Identification of subgroups of children with comorbidities at increased risk of severe disease compared with their counterparts has been much slower to become evident than in adults because of the low rates of severe disease. Asthma was recognised as a comorbidity that increases the risk of death and admission to hospital with COVID-19 in adults early in the pandemic.[2] Subsequently, asthma was identified as a comorbidity that increases the risk of severe disease (admission to critical care, receiving invasive ventilation, or death) in hospitalised children.[3,4] However, although deaths of children with asthma and SARS-CoV-2 infection have been reported, the deaths