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.

pool preparation and the release of manufactured IVIG.

These results suggest that plasma pools for fractionation might mirror the immunogenic status of the general population regarding SARS-CoV-2. Consequently, anti SARS-CoV-2 antibodies are being increasingly integrated into therapeutic IVIG products and, presumably, into intramuscular and subcutaneous immunoglobulin products. Since these products are indicated for immunodeficient patients and other therapeutic or prophylactic approaches, a close follow-up of the progression of the presence of anti-SARS-CoV-2 antibodies in both plasma pools and IgG products is recommended.

All authors are employees of Grifols, a manufacturer of IVIG products and other blood plasma derivatives.

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Diagnostic dilemma in COVID-19-associated pulmonary aspergillosis

We thank the community for rapid recognition and characterisation of COVID-19-associated pulmonary aspergillosis (CAPA), increasingly observed in people with severe SARS-CoV-2 infection. Consistent with previous efforts to standardise definitions for invasive fungal infections,[1–3] Philipp Koehler and colleagues[4] propose new definitions for CAPA and provide management recommendations. We have questions and concerns for feedback.

Although we agree that standardised definitions are necessary to facilitate enrolment into clinical trials, consensus definitions for invasive fungal infections were historically supported by observational studies and not intended to guide clinical care.[1,2] As a newly recognised syndrome, we worry that the proposed definitions for CAPA are not adequately supported by evidence; premature confidence in definitions risks biasing outcomes of future research and directing inappropriate management, without first establishing a requisite level of evidence.

The proposed CAPA definitions are highly reliant on bronchoscopy, which is variably used, especially in surge conditions with strained infection control. A bronchoscopy-driven approach will inevitably underestimate the burden of CAPA and potentially skew trial enrolment towards people with more invasive disease.

Also, we have concerns with the biomarker cutoffs proposed. Whereas investigators have done detailed studies to determine cutoffs for galactomannan enzyme immunoassays using appropriate measures (ie, receiver operating characteristic curves) in other populations,[3,5] we are not aware of similar data to support recommendations for positivity at the multiple levels proposed by Koehler and colleagues, combined with requirements for repeated testing. This expert proposal is particularly problematic when cutoffs are not aligned with local regulatory recommendations. Should clinicians and investigators ignore their regulatory-cleared biomarker cutoffs in the absence of supportive evidence? Moreover, Koehler and colleagues proposed various cutoffs for non-bronchoalveolar lavage biomarkers, which have not been cleared or validated. Although this proposal is reasonable to generate data in early research settings, one can hardly say that we have enough evidence to derive consensus.

Multiple issues arise with using definitions in different clinical and research contexts. For instance, conservative definitions are not actionable for clinical care or prevention studies—settings where the earliest therapy is essential to improve clinical outcomes. We thank our colleagues for early efforts to understand and define this new entity, but fear that more caution is needed to acknowledge critical gaps in data. We believe that establishing consensus definitions for CAPA requires more efforts, especially those directed towards deriving biomarker performance characteristics.

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We read with interest the ECMM/ISHAM consensus criteria for COVID-19-associated pulmonary aspergillosis (CAPA), but noted with concern its limited applicability to resource-limited settings.[1] Multiple studies indicate that approximately 20% of severely ill patients with COVID-19 develop invasive aspergillosis if a diagnosis is actively sought.[2] Pakistan was among the first countries to report CAPA in critically ill patients with COVID-19 using AspICU criteria.[3] After an initial report of five putative CAPA cases from March to April, 2020, at our institute, within 2 months 12 more putative CAPA cases were identified. The largest series of CAPA cases include data from four low-income and middle-income countries (LMICs).[4] In these and other LMICs, very few clinical laboratories do fungal PCR or expensive serology-based tests such as galactomannan and β-D-glucan. Similarly, due to hazards related to aerosol production, bronchoscopic or non-bronchoscopic lavage procedures are rarely done. At our institute from July to December, 2020, 490 tracheal aspirates were sent for culture, compared with only two bronchial lavage samples from COVID-19 patients. Therefore, despite having substantial CAPA burden in our centre, none of the patients in retrospect could be categorised into any of the three grades of proven, probable, or possible, as suggested by Philipp Koehler and colleagues.[1]

A very restricted disease categorisation is concerning as it will lead to underrecognition of this important complication in patients with COVID-19, not only for surveillance but also for their management. On the basis of better inclusivity of patients too hypoxic to undergo bronchoscopy and applicability to low-resource settings, we propose that endotracheal aspirates be added to the appropriate specimens for diagnosis. These may be cultured in high volume (0·5–1·0 mL) for better fungal yield[5] and in settings where galactomannan is available be validated for detecting the aspergillus antigen. High-volume culture on Sabouraud dextrose agar in our laboratory increased yield of moulds from 15% to 72% in 133 lower respiratory samples (tracheal aspirates, bronchial lavages, and sputa). However, cultures positive for *Aspergillus* spp must be interpreted strictly within each clinical context to prevent overdiagnosis. We have begun to validate aspergillus galactomannan in endotracheal aspirates for patients with CAPA. So far, in 15 patients with CAPA and 15 without, we have found a sensitivity and specificity of 93·3% and 60·0%, respectively, at a galactomannan index of 1·414 (appendix). These data, and those from a study by Roman-Montes and colleagues,[6] highlight the need for expanded datasets.

More flexible diagnostic criteria might be warranted for a common complication of a pandemic, incorporating simpler approaches on difficult-to-obtain samples, including high-volume culture and aspergillus antigen on tracheal aspirates.

DWD reports holding founder shares in F2G; acting as a consultant to Pulmatrix, Pulmocide, Zambon, iCo Therapeutics, Mayne Pharma, Biosergen, Bright Angel Therapeutics, Cipla, and Metis; being paid for talks on behalf of Dynamiker, Hikma, Gilead, Merck, Mylan, and Pfizer; and being a longstanding member of the Infectious Diseases Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology, and Infectious Diseases Aspergillosis Guidelines group. All other authors declare no competing interests.

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Authors' reply

We thank Nitipong Permpalung and colleagues and Kauser Jabeen and colleagues for their thoughtful remarks on the 2020 ECMM/ISHAM consensus criteria on COVID-19-associated pulmonary aspergillosis (CAPA).[1] We acknowledge that the proposed definitions have shortcomings due to the recent and rapid emergence of CAPA limiting validation studies in this patient population. However, up to publication of these consensus definitions, CAPA cohort studies had used numerous case definitions, including EORTC/MSGERC (for immunocompromised patients), AspICU, modified AspICU, modified Influenza-Associated Pulmonary Aspergillosis (IAPA), and modified IAPA expert case definition, illustrating the urgent need for standardisation[2] and recognition of secondary fungal infections as an issue in future WHO COVID-19 clinical research recommendations.[3]

Despite reservations during the first COVID-19 wave about doing

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See **Online** for appendix