Intensive Care Med (2021) 47:1158–1160
https://doi.org/10.1007/s00134-021-06471-6

LETTER

Diagnosis and treatment of COVID-19 associated pulmonary apergillosis in critically ill patients: results from a European confederation of medical mycology registry

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Dear Editor,

Coronavirus disease 2019 (COVID-19)-associated pulmonary aspergillosis (CAPA) has emerged as an important complication among patients with acute respiratory failure caused by SARS-CoV-2 [1–3]. A cornerstone in CAPA diagnosis is microbiology, including culture from lower respiratory tract samples, and bronchoalveolar lavage fluid (BALF) galactomannan (GM) [4, 5].

We performed a multinational cohort study including 20 centers in 9 countries with the aim to evaluate diagnostic approaches and treatment of CAPA as well as CAPA prevalence. All participating centers were invited to provide data on diagnostic work-up, treatment and outcome on prospective cohorts of consecutive COVID-19 ICU patients (inclusion criteria: SARS-CoV-2-positive polymerase chain reaction, admission to intensive care unit (ICU) due to respiratory failure) with and without CAPA via an online case report form between 03/2020 and 05/2021. Cases were then classified according to the 2020 ECMM/ISHAM consensus criteria [4]. The study protocol was approved by the Medical University of Graz (EC #32–296 ex 19/20) and the other participating centers.

A total of 592 cases were entered (98.5% from Europe; for demographics see Supplementary Table 1) of whom 11 (1.9%) had proven CAPA, 80 (13.5%) probable CAPA and 18 (3%) possible CAPA. Table 1 displays diagnostic characteristics of those with CAPA. Median BALF-GM optical density index (ODI) in 83 CAPA patients was 2.74 (IQR 1.70–5.78). BALF-GM ODI > 1.0 was also reported in 4/170 (2.4%) patients without CAPA. BALF culture growing *Aspergillus* was detected exclusively among CAPA patients (0/184 non-CAPA patients). Serum GM was positive (> 0.5 ODI) in 1/192 patients without CAPA (0.5%). Antifungal treatment details are depicted in Table 1. Among those receiving systemic antifungal treatment, 52% were alive at ICU discharge.

During a median observation time of 32 days, 261 ICU deaths were observed. This corresponded to an − 30, − 60 and − 90 day ICU mortality of 36% (95% CI 33–40), 46% (95% CI 42–51) and 49% (95% CI 44–53). By applying a Fine-Gray competing risk model the 109 diagnosed CAPA cases (i.e., possible, probable or proven) on ICU corresponded to an − 1, − 15- and − 90 day ICU CAPA rate of 1% (95% CI 1–3), 16% (95% CI 13–20) and 20% (95% CI 16–32) (Supplementary Fig. 1).

Overall CAPA prevalence in our cohort was 15.4% and, therefore, within the range that has been previously reported in the literature [5], although prevalence varied widely between centers. Several factors such as awareness, diagnostic algorithms, local epidemiology and socioeconomic factors may explain these differences.

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Table 1 Diagnostic and treatment characteristics among CAPA patients

	Positivity in cases with possible/probable/proven CAPA ($n=109$)*
Diagnosis	
BALF galactomannan > 1.0 ODI	64/83 (77%)
Serum galactomannan > 0.5 ODI	16/85 (19%)
Tracheal aspirate galactomannan > 1.2 ODI	16/21 (76%)
BALF-positive *Aspergillus* spp. culture	45/85 (53%)
Bronchial aspiration positive *Aspergillus* spp. culture	14/32 (44%)
Tracheal aspiration positive *Aspergillus* spp. culture	42/68 (62%)
Sputum-positive *Aspergillus* spp. culture	4/29 (14%)
BALF-positive *Aspergillus* PCR	24/33 (73%)
Tracheal aspiration positive *Aspergillus* PCR	7/32 (22%)
Treatment	
Systemic antifungal treatment initiated for CAPA	99/109 (91%)
Voriconazole	52/99 (53%)
Isavuconazole	36/99 (36%)
Lipid formulations of amphotericin B	17/99 (17%)
Echinocandins	13/99 (13%)
Deoxycholate amphotericin B	3/99 (3%)
Posaconazole	4/99 (4%)
Antifungal combination therapy (voriconazole or isavuconazole based with echinocandin or liposomal amphotericin B)	18/99 (18%)

BALF bronchoalveolar lavage fluid, *CAPA* COVID-19-associated pulmonary aspergillosis, *ODI* optical density index, *PCR* polymerase chain reaction

*CAPA cases: Leuven, Belgium ($n=9$); Genoa, Italy ($n=5$); Graz, Austria (2 centers, $n=13$); Cologne, Germany ($n=19$); Manchester, UK ($n=2$); Antwerp, Belgium ($n=12$); Bruges, Belgium ($n=2$); Roeselare, Belgium ($n=1$); Munich, Germany ($n=13$); Madrid, Spain ($n=12$); Nuernberg, Germany ($n=5$); Stuttgart, Germany ($n=2$); Bordeaux, France ($n=5$); Karachi, Pakistan ($n=4$); Ann Arbor, USA ($n=3$); Besancon, France ($n=1$); Modena, Italy ($n=1$)

Our results confirm that diagnosis of CAPA remains a challenge with limited sensitivity of serum GM (19%) for CAPA and the need for a lower respiratory sample or tracheal/bronchial/lung biopsy to confirm diagnosis. Early diagnosis is considered a cornerstone in successful CAPA management, as ICU mortality rate is high in CAPA patients (52% versus 39% in non-CAPA COVID-19 patients on ICU; $p=0.027$). Voriconazole and isavuconazole were most frequently used for antifungal monotherapy, following current treatment recommendations for CAPA [4]. Even though > 90% of CAPA patients received antifungal treatment, there was also one CAPA case not receiving antifungal therapy among the survivors, indicating that not all patients who are diagnosed with CAPA based on consensus definitions may in fact have invasive fungal disease.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06471-6.

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Acknowledgements

We thank Marisa H. Miceli, Jean-Jacques Tudesq, Gregor Paul, Robert Krause, Marina Linhofer, Jonas Frost, Peter Zechner, Matthias Kochanek, Philipp Eller, Jeffrey D. Jenks, Sara Volpi, Anne-Pauline Bellanger, P Lewis White, Gustavo H. Goldman, Paul Bowyer, Antonis Rokas, Sara Gago, Paolo Pelosi, Chiara Robba, Jean-Pierre Gangneux, Cornelia Lass-Floerl, Marina Machado, and Patricia Muñoz. ECMM-CAPA Study Group Authors: Philipp Koehler, Jon Salmanton-García, Riina Rautemaa-Richardson, Stefan Hatzl, Johan Maertens, Yves Debaveye, Marc Bourgeois, Marijke Reynders, Lynn Rutsaert, Niels Van Regenmortel, Piet Lormans, Simon Feys, Alexander Christian Reisinger, Oliver A. Cornely, Tobias Lahmer, Maricela Valerio, Laurence Delhaes, Kauser Jabeen, Joerg Steinmann, Mathilde Chamula, Matteo Bassetti.

Author contributions

Substantial contribution to study concept and design: JP, JW, DRG, KL, MH. Substantial contribution to the acquisition of data for the work: JP, JW, DRG, JS-G, MB, MR, LR, NvR, PL, YD, JM, SF, ACR, TL, MV, LD, KJ, JS, SH, AR, MC, MH. Substantial contribution to the statistical analysis or interpretation of data: JP, JW, DRG, SH, KL, MH. Drafting the manuscript: JP, MH. Critical review of the manuscript and final approval for publication: all authors.

Funding
MH is supported by NIH and investigator initiated grants from Astellas, Gilead and Pfizer. No specific funding obtained for this study.

Declarations

Conflicts of interest
JP has received personal fees from Gilead Sciences and Pfizer, research funding from MSD and is stoke holder of AbbVie Inc and Novo Nordisk. JW reports grants and personal fees from Gilead and Pfizer: investigator-initiated grants, personal fees and also on-financial support from MSD. DRG reports an unconditional grant from Correvio Italia and a grant for his institution by Pfizer Inc. KL received consultancy fees from SMB Laboratories Brussels, MSD and Gilead, travel support from Pfizer, speaker fees from FUJIFILM WAKO, Pfizer and Gilead and a service fee from Thermo fisher Scientific. MH received research funding from Gilead Sciences, Astellas, Scynexis, F2G and Pfizer.

Ethics approval
The study protocol and all study-related procedures were approved by the Medical University of Graz (EC #32–296 ex 19/20) and the other participating centers which all followed the local ethical requirements.

Publisher's Note

Received: 18 June 2021 Accepted: 30 June 2021
Published online: 16 July 2021

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