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.

Journal of Medical Mycology 31 (2021) 101175

Contents lists available at ScienceDirect

Journal of Medical Mycology

journal homepage: www.elsevier.com

Research Paper

COVID-19 and invasive fungal coinfections: A case series at a Brazilian referral hospital

Antonio Camargo Martins[a], Eliane Molina Psaltikidis[a], Tiago Cristiano de Lima[a], Renata Fagnani[a], Angelica Zaninelli Schreiber[a], Lucieni de Oliveira Conterno[a], Katsuhiko Kamei[b], Akira Watanabe[b], Plinio Trabasso[a], Mariângela Ribeiro Resende[a,*], Maria Luiza Moretti[a]

[a] School of Medical Sciences, University of Campinas, Campinas, São Paulo, Brazil
[b] Medical Mycology Research Center, Chiba University, Chiba, Japan

ARTICLE INFO

Article History:
Received 24 April 2021
Revised 20 June 2021
Accepted 13 July 2021
Available online 14 July 2021

Keywords:
COVID-19
Invasive fungal infection
Aspergillosis
Candidemia
Cryptococcosis

ABSTRACT

Background: COVID-19 co-infections have been described with different pathogens, including filamentous and yeast fungi.
Methodology: A retrospective case series study conducted from February to December 2020, at a Brazilian university hospital. Data were collected from two hospital surveillance systems: Invasive fungal infection (IFI) surveillance (Mycosis Resistance Program - MIRE) and COVID-19 surveillance. Data from both surveillance systems were cross-checked to identify individuals diagnosed with SARS-CoV-2 (by positive polymerase chain reaction (PCR)) and IFI during hospital stays within the study period.
Results: During the study period, 716 inpatients with COVID-19 and 55 cases of IFI were identified. Fungal co-infection with SARS-CoV-2 was observed in eight (1%) patients: three cases of aspergillosis; four candidemia and one cryptococcosis. The median age of patients was 66 years (IQR 58-71 years; range of 28-77 years) and 62.5% were men. Diagnosis of IFI occurred a median of 11.5 days (IQR 4.5-23 days) after admission and 11 days (IQR 6.5-16 days) after a positive PCR result for SARS-CoV-2. In 75% of cases, IFI was diagnosed in the intensive care unit (ICU). Cases of aspergillosis emerged earlier than those of candidemia: an average of 8.6 and 28.6 days after a positive PCR for SARS-CoV-2, respectively. All the patients with both infections ultimately died.
Conclusion: A low rate of COVID-19 co-infection with IFI was observed, with high mortality. Most cases were diagnosed in ICU patients. Aspergillosis diagnosis is highly complex in this context and requires different criteria.

Introduction

The COVID-19 pandemic has challenged surveillance systems around the world. In addition to COVID-19 *per se*, co-infections with different pathogens have also been described [1–3]. In this scenario, it is essential to gain a better understanding of aspects related to the host, intensive care unit admission and immunomodulation between SARS-CoV-2 and other microorganisms [4,5].

Bacterial co-infections are more frequently diagnosed than invasive fungal infections (IFI) [1]. IFI, particularly invasive aspergillosis (IA), requires a high level of suspicion from clinicians and robust laboratory investigation [6]. In this report, we describe the clinical presentation, diagnostic methods, therapeutic management and outcome of different invasive fungal infections associated with COVID-19.

Materials and methods

A retrospective case series study was carried out from February to December 2020. Setting: A Brazilian university hospital with 408 beds that operates as a referral facility for COVID-19. Patients with IFI and SARS-CoV-2 were identified via two surveillance systems used at the hospital: IFI surveillance (Mycosis Resistance Program – MIRE) and COVID-19 surveillance.

* Corresponding author.
E-mail addresses: antonio_camargo0@yahoo.com.br (A.C. Martins), emolina@hc.unicamp.br (E.M. Psaltikidis), tiagolima@hc.unicamp.br (T.C. de Lima), fagnani@hc.unicamp.br (R. Fagnani), zaninele@unicamp.br (A.Z. Schreiber), lucieniconterno@gmail.com (L.d.O. Conterno), kkamei-chiba@umin.ac.jp (K. Kamei), iron_wata@yahoo.co.jp (A. Watanabe), trabasso@hc.unicamp.br (P. Trabasso), mresende@unicamp.br (M.R. Resende), moretti.luiza@gmail.com (M.L. Moretti).

https://doi.org/10.1016/j.mycmed.2021.101175
1156-5233/

Active IFI surveillance has been in place at the hospital since 2018, with a special focus on resistance (Mycosis Resistance Program - MIRE). The healthcare team monitor IFIs by actively searching for positive IFI tests (cultures, serological tests, etc.), prescribing antifungals and reporting suspected infections. Cases are identified, compiled and analyzed by a multiprofessional team (infectologists, nurses, biologists etc.) at weekly meetings aimed at discussing and validating cases of IFI according to the criteria described below.

Case definition of IFI: the following three classifications were used. 1) Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) [7,8]; 2) Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients (AspICU) [9]; and 3) Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance (CAPA) [10].

With the emergence of SARS-CoV-2 infections in 2020, the hospital began to monitor the number of hospitalized cases of COVID-19 (patients whose clinical condition was indicative of infection or those who exhibited symptoms and were subsequently diagnosed with the disease). Thus, data were compiled on all the patients hospitalized from February to December 2020 who presented with a positive polymerase chain reaction (PCR) result for SARS-CoV-2 in respiratory sampling. Case definition of COVID-19: SARS-CoV-2 PCR detectable in respiratory specimens.

COVID-19 surveillance and MIRE databases were matched to identify patients with IFI and COVID-19 during the study period, which served as the inclusion criterion. The medical charts of the patients were examined to collect demographic, radiological, laboratory, clinical evolution and survival data. Patients already being treated for IFI who were subsequently diagnosed with SARS-CoV-2 were excluded from the study.

The categorical variables are expressed as absolute values and percentages and the continuous variables as mean, median and interquartile ranges (IQRs). The statistical analyses were performed using SPSS Statistics 20 software.

This study was approved by the Research Ethics Committee of the University of Campinas (protocol number 92692418.9.1001.5404 / 3.166.956).

Results

During the study period, 716 inpatients with COVID-19 confirmed by polymerase chain reaction (PCR) and 55 cases of IFI were identified. Eight patients met the inclusion criterion: positive PCR result for SARS-CoV-2 associated with IFI. Of the 716 cases of COVID-19, 44.1% required intensive care during hospitalization. Considering all the hospitalized cases of SARS-CoV-2, 21% ultimately died.

Fungal co-infection was observed in 8 patients (Table 1; Fig. 1). IFI consisted of three cases of aspergillosis, four candidemia and one cryptococcosis. The median age of these patients was 66 years (IQR 58-71 years; range of 28-77 years) and 62.5% were men. Diagnosis of IFI occurred a median of 11.5 days (IQR 4.5-23 days) after admission and 11 days (IQR 6.5-16 days) after a positive PCR result for SARS-CoV-2. A comparison of the diagnostic intervals showed that IFI was diagnosed a median of 11 days (IQR 6.5-16 days; range of -1 – 29 days) after a positive PCR result for SARS-CoV-2; the negative value (-1) resulted from a patient initially diagnosed with IFI on admission day (D0) of follow-up, who then tested positive (PCR) for COVID-19 on the first day (case 4). The median length of stay (LOS) was 25.5 days (IQR 13.5-40 days; range 13-82 days), not considering the period outside the hospital in case 4.

In most cases, IFI was diagnosed after admission to the ICU (75% of cases). The cases of aspergillosis (three patients) were diagnosed after ICU admission, as follows; an average of 7 days from ICU admission (3, 6 and 12 days after ICU admission), 8 days after implementing mechanical ventilation (3, 9 and 12 days after mechanical ventilation) and 8.6 days after testing positive (PCR) for SARS-CoV-2 (6, 7 and 13 days after PCR for SARS-CoV-2). Galactomannan was not collected from the respiratory specimens of these patients.

Of the four cases of candidemia, one was diagnosed on the admission day of hospitalization and the other three following intensive care treatment. The last three cases were diagnosed later than those of aspergillosis: an average of 18.6 days after ICU admission (13, 14 and 29 days after ICU admission), 18.3 after mechanical ventilation (13, 13 and 29 days after mechanical ventilation) and 28.6 days after receiving a positive PCR result for SARS-CoV-2 (13, 32 and 41 days after PCR for SARS-CoV-2).

In two cases, COVID-19 and IFI occurred simultaneously and outside the ICU: one patient with cryptococcosis (case 8) and the other with endocarditis (*Candida orthopsilosis*). In the first case, IFI and viral infection symptoms occurred at the same time, although cryptococcosis was diagnosed several days after COVID-19, with the patient exhibiting symptoms of both on admission. The patient diagnosed with endocarditis was hospitalized twice, with a 28-day interval between hospital stays. In this case the diagnosis of IFI occurred one day before that of COVID-19.

Antifungal therapy was used in all cases except two: in the first (case 3), the culture result was interpreted as colonization by the team caring for the patient (subsequently validated as a fungal infection by the IFI surveillance system), and in the second (case 6), the results were only available post mortem.

All eight patients described received corticosteroids; the doses used are presented in Table 1 in terms of prednisone equivalence. Case 5 and 8 were already using immunosuppressive medications (solid organ transplant). No specific SARS-CoV-2 medication was administered. All the patients progressed to intensive care treatment and death (including cases 4 and 8, who required ICU care during hospitalization).

Discussion

In the present study, the rate of fungal coinfection with COVID-19 was 1% among inpatients. Other studies have reported rates of 0.6 [11], 0.7 [3], 1.5 [12] and 5.5% [2]; however, the heterogenous populations assessed preclude an accurate comparison. In ICU patients with COVID-19, White et al. reported that 26.7% had IFI [13], Bartoletti et al. identified 27.7% with aspergillosis [14] and Salmanton-García et al. observed a cumulative incidence of 1.1–47.4% in patients under mechanical ventilation [15]. Premature ICU admission, respiratory failure and lymphopenia have been reported as risk factors for secondary infections among COVID-19 inpatients [12].

IFI can occur in two different COVID-19 scenarios. The first is in ICU patients with COVID-19, diagnosed with a fungal infection during hospitalization. In this scenario, factors such as mechanical ventilation, central venous access, broad-spectrum antibiotics and the Covid-19 infection itself seem to contribute to the fungal infection [4].

In the second scenario, both infections are diagnosed simultaneously, as described here in two cases. There are reports of this type of simultaneous diagnosis [16]. Garcia-Vidal et al. found that 3.1% of COVID-19 inpatients had a community coinfection, but none had IFI [3]. In our study, there were two cases of simultaneously diagnosed community coinfection with COVID-19 and fungal infection. One patient was a solid organ transplant recipient with cryptococcosis and the other had fungal endocarditis. Both exhibited symptoms of the two infections on admission and the target organ of the fungal infection was not the lung (central nervous system and heart, respectively), suggesting that co-infection was coincidental and had no cause-effect relationship. On the other hand, there are recent

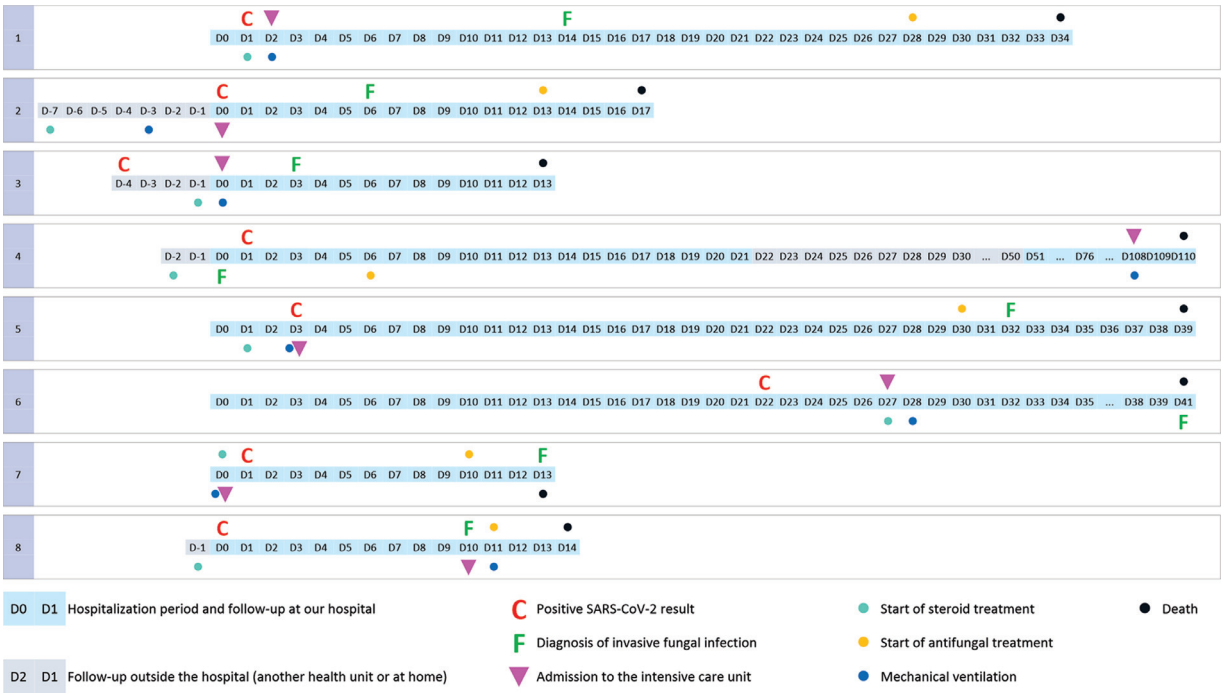

Fig. 1. - Timeline - Relationship between fungal infection and COVID-19.Subtext of Figure 1 – timeline: each line represents events related to the follow-up of each patient. Blue indicates follow-up for patients hospitalized at our hospital and gray the time period during which the patient was at another health unit or at home.

descriptions of cases of mucormycosis concomitant with COVID-19 (simultaneous diagnosis in 39% of cases, 16/41 patients), with researchers suggesting that the SARS-CoV-2 infection itself could predispose individuals to this IFI, particularly diabetic patients [17].

Analysis of the time between IFI diagnosis and the different variables demonstrated that aspergillosis was diagnosed earlier than candidemia. This finding is similar to that of White et al., who compared ICU admission times and PCR positive results for COVID-19 and found that *Aspergillus spp.* positivity occurred before confirmed yeast infections [13]. In the case of aspergillosis, a study with a larger sample indicated a median time of 10 days between a positive COVID-19 test and aspergillosis [15]. Bartoletti et al. reported a shorter interval between ICU admission and aspergillosis diagnosis (median 4 days) and a median of 14 days from the onset of COVID-19 symptoms and *Aspergillus spp* diagnosis [14].

Aspergillosis associated with COVID-19 can result in severe airway epithelial injury linked to other risk factors [10,18]. It is important to note that corticosteroid therapy is a classic risk factor that predisposes patients to invasive aspergillosis [13,14,18]. All the patients in the present study received steroid therapy in different doses and times. The characterization of invasive pulmonary aspergillosis in mechanically-ventilated COVID-19 patients is highly complex [14]. Recently, ECMM/ISHAM proposed criteria to diagnose COVID-19 associated with pulmonary aspergillosis (CAPA) [10].

CAPA diagnosis is more sensitive to IA when compared to previous criteria. Additionally, CAPA is associated with mortality risk, which is higher in patients with a positive CAPA result [14]. White et al. found that CAPA showed greater sensitivity than AspICU [13]. In our study, only one patient can be categorized as IA based on all the classifications (CAPA, AspICU and EORTC / MSG) and two in accordance with CAPA and AspICU. IA associated with COVID-19 poses different challenges in clinical practice, including the complex radiological results in both infections [13], poor access to biomarkers such as galactomannan [19], low sensitivity of serum galactomannan to COVID-19-associated pulmonary aspergillosis (CAPA) diagnosis [14] and difficulty differentiating between *Aspergillus spp* colonization and disease [18].

Possibly the greatest challenge in cases of aspergillosis is differentiating between colonization and infection. Taccone et al., studied ICU patients and found significantly lower mortality in those considered colonized by *Aspergullius spp* (38%) when compared to putative (67%) and proven infections (79%) [20]. The new diagnostic criteria proposed appear to be important tools in deciding whether to initiate antifungal treatment.

The reported mortality rate of COVID-19 patients in the ICU without fungal disease is greater than 30% [13]. Based on the CAPA or AspICU criteria, the mortality rate in patients with COVID-19 associated with *Aspergillus spp* is higher than that recorded in patients without aspergillosis [14]. All the patients in our study evolved to death. Mortality rate varies from 51.1% to 100% in aspergillosis cases and 43.7% to 97.0% for yeast infections [13]. Salmanton-García et al. reported a mortality rate of 52.2% in 186 patients with CAPA [15]. The clinical outcome can be improved with early antifungal therapy [3,13].

Candidemia is less complex to diagnose than aspergillosis and is based on blood culture. In an Italian cohort, a higher rate of candidemia was observed during the COVID-19 pandemic, likely due to the larger number of patients admitted to the ICU, resulting in immunosuppression [21]. Hughes et al. attributed the high number of candidemia cases to complications associated with hospitalization, such as central venous access [11]. The majority of hospital admission during the pandemic are related to COVID-19, resulting in limited beds for other comorbidities [22], overcrowding and failure in preventing healthcare-associated infections (HAIs).

The most frequent species reported is *Candida albicans* [3,11,21,22]. A larger number of *Candida non-albicans* cases were observed in our study. With respect to the time between the COVID-19 and candidemia diagnoses, in one case (*C. orthopsilosis*) they occurred simultaneously and three patients presented with candidemia an average of 28.6 days after a positive PCR result for COVID-19 and 18.6 days (average) after ICU admission. White et al. reported candidemia in COVID-19 patients ten days after the positive SARS-CoV-2 PCR diagnosis and nine days after ICU admission; all the patients required mechanical ventilation and a mortality rate of

Table 1
Description of coinfection cases.

Case	Age	Sex	Isolate fungus	Infection	Underlying disease	Sytemic steroid - (total days in use) - prednisone / kg / day	Diagnosis of COVID (PCR) related to the initial hospitalization date	Diagnosis of fungal infection related to the initial hospitalization date	Diagnosis of fungal infection related to ICU admission	Radiological Evidence fungal diseases	Mycological Evidence	Galactomannan (blood)	Antifungal Therapy	EORTC/MSG	AspICU	CAPA	Follow-up time	Outcome
1	68	F	*Aspergillus flavus / Aspergillus fumigatus*	Invasive Pulmonary Aspergillosis	DM / CKD / HYP	Yes (28) - 0.72	1	14	12	+	Blood galactomannan / Non-bronchoscopic lavage culture	1.42	Voriconazole	Probable	Putative	Probable	34	death
2	66	M	*Aspergillus fumigatus*	Invasive Pulmonary Aspergillosis	DM / HYP	Yes (5) - 0.49	0	6	6	+	Non-bronchoscopic lavage culture	0.21	Voriconazole	Not Classifiable	Putative	Possible	17	death
3	74	M	*Aspergillus fumigatus*	Invasive Pulmonary Aspergillosis	DM / RRT / HYP	Yes (9) - 0.87	-4	3	3	+	Non-bronchoscopic lavage culture	Unrealized	No	Not Classifiable	Putative	Possible	13	death
4	65	F	*Candida orthopsilosis*	Candidemia (with endocarditis)	DM / RRT / HYP	Yes (20) - 0.51	1	0	-	Not applicable	Blood culture	Not applicable	Micafungin / Amphotericin	Proven	Not applicable	Not applicable	110	death
5	50	M	*Candida albicans*	Candidemia	DM / KDT (everolimus)	Yes (1) - 0.48	3	32	29	Not applicable	Blood culture	Not applicable	Micafungin	Proven	Not applicable	Not applicable	39	death
6	77	F	*Candida krusei*	Candidemia	DM / RRT / HYP / OBE	Yes (6) - 0.98	22	41	14	Not applicable	Blood culture	Not applicable	No	Proven	Not applicable	Not applicable	41	death
7	66	M	*Candida lusitaniae*	Candidemia	DM / HYP / HF / STO	Yes (13) - 0.63	1	13	13	Not applicable	Blood culture	Not applicable	Fluconazole	Proven	Not applicable	Not applicable	13	death
8	28	M	*Cryptococcus neoformans*	Neurotoxoplasmosis	KDT (tacrolimus - mycophenolate)	Yes (14) - 0.70	0	10	-	Not applicable	CSF - microscopy / culture	Not applicable	Amphotericin / Fluconazole	Proven	Not applicable	Not applicable	14	death

DM: Diabetes Mellitus, CKD: Chronic Kidney Disease, RRT: Renal Replacement Therapy, HYP: Hypertension, OBE: Obesity, HF: Heart Failure, STO: Stroke, CH: Cirrhosis, KDT: Kidney
[a] not necessarily continuous use

47.1% was recorded [13]. In the present study, *Candida spp.* infection occurred later than *Aspergillus spp.* infection, which we believe may be related more to ICU care than the COVID-19 infection.

Few cases of cryptococcosis associated with COVID-19 have been reported. Heller et al., described a patient with a simultaneous diagnosis of HIV and cryptococcosis [23]. Another study reported cryptococcosis associated with COVID-19 and tocilizumab as a risk factor [24]. In our study, one patient (kidney transplant recipient) exhibited co-infection.

Limitations of the present study are its unicentric characteristic, descriptive design of the cases, the small number of cases and the failure to analyze denominators that make it possible to calculate the incidence density of IFI during the COVID-19 pandemic compared to the pre-pandemic period. Other limitations were related to SARS-CoV-2 data, since the number of patients tested for IFI and details on severity for the sample could not be characterized. However, we believe that the results obtained here, scarce in the literature to date, are highly relevant and consistent with emerging data in the context of the COVID-19 pandemic, with the potential to benefit other studies on the topic.

Low IFI and SARS-CoV-2 rates were recorded. It remains unclear whether COVID-19 infection is associated with IFI and as such, further research is needed to assess risk factors related to patients and intensive care, as well as the use of immunosuppressants. More robust prospective and multicenter studies are needed to determine the real impact of SARS-CoV-2 on the incidence of invasive fungal infection.

Declaration of Interest Statement

No potential conflict of interest has been reported by the author (s). All authors have reviewed and approved the manuscript. All authors have contributed significantly to the work. The manuscript has not been previously published nor is it being considered for publication elsewhere.

Acknowledgments

This collaborative research Project was assigned in UNICAMP as No.02-P-9427/2018, and supported by AMED (Japan Agency for Medical Research and Development) / JICA (Japan International Cooperation Agency), SATREPS (Science and Technology Research Partnership for Sustainable Development)

References

[1] Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020;71:2459–68. doi: 10.1093/cid/ciaa530.

[2] Falcone M, Tiseo G, Giordano C, Leonildi A, Menichini M, Vecchione A, et al. Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: a prospective observational study. J Antimicrob Chemother 2020. doi: 10.1093/jac/dkaa530.

[3] Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect 2021;27:83–8 https://doi.org/. doi: 10.1016/j.cmi.2020.07.041.

[4] Rawson TM, Wilson RC, Holmes A. Understanding the role of bacterial and fungal infection in COVID-19. Clin Microbiol Infect 2021;27:9–11. doi: 10.1016/j.cmi.2020.09.025.

[5] Chen X, Liao B, Cheng L, Peng X, Xu X, Li Y, et al. The microbial coinfection in COVID-19. Appl Microbiol Biotechnol 2020;104:7777–85. doi: 10.1007/s00253-020-10814-6.

[6] Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect 2020;81:266–75 https://doi.org/. doi: 10.1016/j.jinf.2020.05.046.

[7] De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) C. Clin Infect Dis 2008;46:1813–21. doi: 10.1086/588660.

[8] Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis 2020;71:1367–76. doi: 10.1093/cid/ciz1008.

[9] Blot SI, Taccone FS, Van den Abeele A-M, Bulpa P, Meersseman W, Brusselaers N, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 2012;186:56–64. doi: 10.1164/rccm.201111-1978OC.

[10] Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis 2020. doi: 10.1016/S1473-3099(20)30847-1.

[11] Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clin Microbiol Infect 2020;26:1395–9 https://doi.org/. doi: 10.1016/j.cmi.2020.06.025.

[12] Ripa M, Galli L, Poli A, Oltolini C, Spagnuolo V, Mastrangelo A, et al. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. Clin Microbiol Infect 2020 https://doi.org/. doi: 10.1016/j.cmi.2020.10.021.

[13] White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A national strategy to diagnose coronavirus disease 2019–associated invasive fungal disease in the intensive care unit. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa1298.

[14] Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, et al. Epidemiology of invasive pulmonary aspergillosis among intubated patients with COVID-19: a prospective study. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa1065.

[15] Salmanton-García J, Sprute R, Stemler J, Bartoletti M, Dupont D, Valerio M, et al. COVID-19-associated pulmonary aspergillosis, March-August 2020. Emerg Infect Dis 2021;27:1077–86. doi: 10.3201/eid2704.204895.

[16] Bassetti M, Kollef MH, Timsit J-F. Bacterial and fungal superinfections in critically ill patients with COVID-19. Intensive Care Med 2020;46:2071–4. doi: 10.1007/s00134-020-06219-8.

[17] John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. J Fungi 2021;7. doi: 10.3390/jof7040298.

[18] Marr K, Platt A, Tornheim J, Zhang S, Datta K, Cardozo C, et al. Aspergillosis complicating severe coronavirus disease. Emerg Infect Dis J 2021;27:18. doi: 10.3201/eid2701.202896.

[19] Salehi M, Ahmadikia K, Badali H, Khodavaisy S. Opportunistic fungal infections in the epidemic area of COVID-19: a clinical and diagnostic perspective from Iran. Mycopathologia 2020;185:607–11. doi: 10.1007/s11046-020-00472-7.

[20] Taccone FS, Van den Abeele A-M, Bulpa P, Misset B, Meersseman W, Cardoso T, et al. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit Care 2015;19:7. doi: 10.1186/s13054-014-0722-7.

[21] Mastrangelo A, Germinario BN, Ferrante M, Frangi C, Li Voti R, Muccini C, et al. Candidemia in coronavirus disease 2019 (COVID-19) patients: incidence and characteristics in a prospective cohort compared with historical non–COVID-19 controls. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa1594.

[22] Nucci M, Barreiros G, Guimarães LF, Deriquehem VAS, Castiñeiras AC, Nouér SA. Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. Mycoses 2021;64:152–6 https://doi.org/. doi: 10.1111/myc.13225.

[23] Heller HM, Gonzalez RG, Edlow BL, Ard KL, Gogakos T. Case 40-2020: a 24-year-old man with headache and COVID-19. N Engl J Med 2020;383:2572–80. doi: 10.1056/NEJMcpc2027083.

[24] Khatib MY, Ahmed AA, Shaat SB, Mohamed AS, Nashwan AJ. Cryptococcemia in a patient with COVID-19: a case report. Clin Case Rep 2021;9:853–5 https://doi.org/. doi: 10.1002/ccr3.3668.