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Fungal Infections in COVID-19 Intensive Care Patients

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A b s t r a c t

Opportunistic fungal infections increase morbidity and mortality in COVID-19 patients monitored in intensive care units (ICU). As patients' hospitalization days in the ICU and intubation period increase, opportunistic infections also increase, which prolongs hospital stay days and elevates costs. The study aimed to describe the profile of fungal infections and identify the risk factors associated with mortality in COVID-19 intensive care patients. The records of 627 patients hospitalized in ICU with the diagnosis of COVID-19 were investigated from electronic health records and hospitalization files. The demographic characteristics (age, gender), the number of ICU hospitalization days and mortality rates, APACHE II scores, accompanying diseases, antibiotic-steroid treatments taken during hospitalization, and microbiological results (blood, urine, tracheal aspirate samples) of the patients were recorded. Opportunistic fungal infection was detected in 32 patients (5.10%) of 627 patients monitored in ICU with a COVID-19 diagnosis. The average APACHE II score of the patients was 28 ± 6. While 25 of the patients (78.12%) died, seven (21.87%) were discharged from the ICU. *Candida parapsilosis* (43.7%) was the opportunistic fungal agent isolated from most blood samples taken from COVID-19 positive patients. The mortality rate of COVID-19 positive patients with candidemia was 80%. While two out of the three patients (66.6%) for whom fungi were grown from their tracheal aspirate died, one patient (33.3%) was transferred to the ward. Opportunistic fungal infections increase the mortality rate of COVID-19-positive patients. In addition to the risk factors that we cannot change, invasive procedures should be avoided, constant blood sugar regulation should be applied, and unnecessary antibiotics use should be avoided.

K e y w o r d s: COVID-19, fungal infections, intensive care

Introduction

Fungal infections, especially those whose incidence increases over time in ICU (Intensive Care Unit), have high mortality and morbidity. With a prolonged stay in ICU increase the cost of intensive care. In fungal infections, the limited sensitivity of diagnostic tests and the unresponsiveness of laboratory results hinder early diagnosis. Delayed and ineffective treatment is one of the major causes of mortality. Therefore, prompt diagnosis and treatment are imperative (Zaoutis et al. 2005; Armstrong-James 2007; Hassan et al. 2009). Previous studies have demonstrated a higher incidence of candidemia in the post-COVID-19 (Corona Virus Disease-19) period compared with the pre-COVID-19 period (Mastrangelo et al. 2020; Nucci et al. 2021).

Mortality due to fungal infections in ICU has been reported in a wide range of 5–70% (Gudlaugsson et al. 2003; Falagas et al. 2006). When we look at the international prevalence researches, it can be noticed that intensive care mortality increased twice in bacterial infection and approximately four times in fungal infections. In addition, in patients diagnosed with COVID-19, the mortality rate associated with candidemia is higher in ICUs (White et al. 2019; Mastrangelo et al. 2020; Al-Hatmi et al. 2021).

High APACHE II score, diabetes mellitus (DM), neutropenia, renal failure, abdominal surgery, use of broad-spectrum antibiotics, total parenteral nutrition, hemodialysis, mechanical ventilation, presence of a central venous catheter, and immunosuppressive treatments are important for the development of fungal infection in intensive care patients and are the risk factors that we frequently encounter (Pappas et al. 2016).

The aim of the present study was to evaluate fungal infections in intensive care patients after COVID-19 infection and to determine mortality and risk rates.

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Experimental

Materials and Methods

The records of 627 patients hospitalized in our hospital's intensive care unit (ICU), Antalya Kepez State Hospital/Turkey, with COVID-19 diagnosis between 13/03/2020 and 01/02/2021 were investigated from electronic health archives and hospitalization files. The diagnosis of COVID-19 was made by PCR (Polymerase Chain Reaction) test. Culture samples were taken from patients who were followed up in the ICU with the diagnosis of COVID-19 and had a high fever and clinic infections. Patients over the age of 18 were included in our study. Neutropenic patients using immunosuppressive drugs and receiving chemotherapy within one month were not included. The samples were sent to the central microbiology laboratory of our hospital. Patients with more than 48 hours between hospitalization date and positive blood culture were classified as those with hospital-acquired candidemia. Identification of fungal species was done with the VITEK 2 Compact System (Biomerieux, France) automated identification system. The definition of hospital infections was made according to the surveillance diagnosis criteria determined by the Centers for Diseases Control and Prevention (CDC) (Horan et al. 2008).

Patients were classified as being colonized when they had no clinical symptoms of infection, but the fungi were isolated from their clinical specimens. The study did not include the colonized patients or those whose samples demonstrated fungal growth in less than 48 hours. According to the CDC criteria, patients evaluated by an infectious diseases specialist and considered infected were included in the study.

In order to determine the possible risk factors in terms of the demographic characteristics (age, gender) of the patients as well as the infection development, the following data were recorded: the number of days of ICU hospitalization and mortality rates, Acute Physiology And Chronic Health Evaluation II (APACHE II) score, other diseases, antibiotics used within 30 days before *Candida* species isolation and the microbiological results (blood, urine, tracheal aspirate samples).

The Ethics Committee of Health Sciences University, Antalya Education and Research Hospital on 01/04/2021 approved this study under decision number 4/30.

All statistical analyzes were performed using IBM SPSS version 25.0 (SPSS Inc., Chicago, Illinois, USA). The tables present continuous variables as the mean ± SD, while categorical variables are presented as number (N) and percentage (%). Comparisons between groups were made using the Mann-Whitney U test for continuous variables and using Fisher's exact test for categorical variables. *P*-value ($p < 0.05$) was considered statistically significant (Rotondo et al. 2020).

Results

Fungal infection was detected in 32/627 patients (5.1%) who were followed up in ICU with a diagnosis of COVID-19. Twenty-eight patients were SARS-CoV-2 PCR positive, and four were considered positive with clinical and lung tomography findings. The average age of the patients was 73.5. The average APACHE II score of the patients was 28 ± 6. While 25 of the patients (78.12%) died, seven patients (21.87%) were discharged from the ICU. The demographic variables of the patients are presented in Table I.

Table I
Descriptive variables related to patients.

Demographic variables	N or X (Mean, min-max)	% or Mean ± SD
Gender		
Female	8	25.0
Male	24	75.0
Age (year)	73.50 (52–94)	73.43 ± 10.14
50–59	4	12.5
60–79	16	50.0
≥ 80	12	37.5
BMI* (kg/m²)		
Female	28.89 (20.41–44.44)	
Male	27.68 (20.76–44.98)	
Smoking status		
Female	2	25.0
Male	14	58.33

*BMI – Body Mass Index

A total of 57 separate fungal infection cases were detected in 32 COVID-19 patients treated in ICU. Totally 16 *Candida* sp. isolates were grown from blood samples, candidemia was confirmed, and antifungal treatment was started. *Candida* sp. growth in the urine samples was evaluated as candiduria. All patients had urinary catheterization. The culture of urine samples was repeated 24 hours after urinary catheter replacement in these patients. Since no urological surgical intervention was planned in any patient, patients with isolated candiduria were not treated. The presence of *Candida* sp. in urine was considered as colonization in these patients. Mechanical ventilator-induced colonization of *Candida* sp. was observed as their growth from tracheal aspirates and was very common as a poor predictor for the diagnosis of pneumonia. *Candida* sp. isolation from the aspirate cultures was not considered pneumonia and was treated as colonization. The presence of three *Aspergillus* sp. strains, obtained from the aspirate samples, was also considered the colonization because the radiological imaging and clinical findings

Table II
Isolation of fungi from the clinical specimens.

Specimen* (n = 57)	Fungal isolate (n)	%
Blood	16	23.2
Aspirate	12	17.4
Urine	29	42.1
Urine + blood	8	11.6
Aspirate + blood	3	4.4
Aspirate + urine	1	1.3

* – Since the categories were multiple-response,
N exceeded the sample size.

Table III
Distribution of candidemia cases by hospitalization days.

Mean ± SD 7.56 ± 25.62 (min-max: 1–136)	N	N (%)
1–30 days	4	25
> 30 days	12	75

Table IV
Distribution of fungal infection cases based on accompanying diseases.

Accompanying disease (n = 52)	Number of patients N (%)
Diabetes mellitus	11 (34.4)
Cardiovascular disease*	22 (68.8)
Respiratory disease	6 (18.8)
Neurological disease	11 (34.4)
Renal disease	1 (3.1)

* – Cardiovascular disease: coronary artery disease, hypertension,
heart failure

Table V
Distribution of fungal infection cases by risk factors.

	Number of Patients N (%)	Fungal Isolate N (%)
Parenteral nutrition		
No	25 (78.1)	45 (78.95)
Yes	7 (21.9)	12 (21.05)
Steroid use		
No	20 (62.5)	44 (77.19)
Yes	12 (37.5)	13 (22.81)
ICU insulin use		
No	12 (37.5)	24 (42.11)
Yes	20 (62.5)	33 (57.89)
Central venous catheter		
No	14 (43.75)	45 (78.95)
Yes	18 (56.25)	12 (21.05)

The accompanying comorbidities of the patients from whom the fungi were isolated from clinical specimens are given in Table IV. The most common cardiovascular disease (68%) and diabetes mellitus (34.4%) were detected.

The risk factors of cases with fungal infection are shown in Table V. Central venous catheter was used in all patients who developed candidemia.

Candida parapsilosis was the opportunistic fungal agent that was isolated from the most (43.7%) blood cultures of COVID-19 patients; *Candida tropicalis* (33.33%) was the most commonly isolated from tracheal aspirates, and *Candida albicans* (48.27%) was the most common in urine cultures (Table VI).

All patients were given carbapenem and glycopeptide simultaneously during the last month before fungal infection, and this period was even extended up to 30 days. Except for five patients, in the remaining 27 patients, carbapenem was combined with an antibiotic of the oxazolidinone group or glycopeptide type (Table VII).

Of the 15 patients with candidemia, 12 died (two fungal infection cases were detected in one patient), and

did not support the infection. Isolated zones and numbers are presented in Table II.

The distribution of candidemia cases by the number of hospitalization days is given in Table III. Candidemia was observed far more frequently in patients hospitalized for longer than 30 days.

Table VI
Distribution of fungal species in blood, tracheal aspirate, and urine cultures.

Fungus types	Fungal isolate N (%)	Blood N (%) Total: 16	Tracheal aspirate N (%) Total: 12	Urine N (%) Total: 29
Candida tropicalis	20 (35.08)	5 (31.25)	4 (33.33)	11 (37.93)
Candida albicans	18 (31.58)	4 (25.00)	0 (0.00)	14 (48.27)
Candida parapsilosis	14 (24.56)	7 (43.75)	3 (25)	4 (13.79)
Aspergillus spp.	3 (5.28)	0 (0.00)	3 (25)	0 (0.00)
Candida lusitaniae	1 (1.75)	0 (0.00)	1 (8.34)	0 (0.00)
Trichosporon mucoides	1 (1.75)	0 (0.00)	1 (8.34)	0 (0.00)

Table VII
Antibiotics used by patients with fungal infection and days.

Used antibiotics groups	Number of patients N (%)	Days of using antibiotic before fungal infection
Carbapenem	32 (100%)	17 ± 12.52
Glycopeptide	32 (100%)	13 ± 7.4
Linezolid	23 (71.87%)	10 ± 7.30
Quinolone	11 (33.3%)	14 ± 7.20
Tigecycline	8 (24.24%)	12 ± 5
Aminoglycoside	2 (6.06%)	10 ± 2.3

the mortality rate in candidemia was found to be 80%. Moreover, two of the three patients (66.6%), who had *Aspergillus* sp. grown in their tracheal aspirate died, one patient (33.3%) was transferred to the ward.

Discussion

In our study, 16 (2.6%) of 627 patients with COVID-19 followed in the ICU developed candidemia. Nori et al. (2021) found that eight (5%) of the 152 COVID-19 patients had developed candidemia. Similarly, in our study, this rate was found to be 2.6%.

In our study, *C. parapsilosis* was the leading agent of candidemia (n = 7, 43%), *C. tropicalis* at (n = 5, 31%) was the second, and *C. albicans* (n = 4, 25%) was the third. Similarly, Tokak et al. (2020) ranked *C. parapsilosis* (48.4%) the first and *C. albicans* (32.3%) the second in candidemia. Cortés et al. (2021) identified *C. parapsilosis* as the most common factor (38.5%) in their study.

In a study conducted by Segrelles-Calvo et al. (2021), *Aspergillus* sp. was detected in respiratory tract samples of seven (5.4%) out of 215 patients followed up in the ICU. The mortality rate of these patients was found to be 86%. Another study reported aspergillosis in 19 (17.9%) out of 106 patients with COVID-19 admitted to ICU. At the outcome of 42-day ICU admittance, seven patients died (Dupont et al. 2021). In our study, two out of three patients (66.6%) with aspergillosis died, one patient (33.3%) was transferred to the ward. Schauwvlieghe et al. (2018) defined invasive pulmonary aspergillosis in influenza as an independent risk factor associated with mortality (IPA). As in our study, aspergillosis was also associated with increased mortality for COVID-19 patients.

We found an 80% mortality rate in our patients who developed candidemia. It has been reported that candidemia mortality varies between 5–71% in ICUs (Patolia et al. 2013). Our high mortality rate can be explained by being tertiary ICU, high mean age of the patients, and the fact that the patients have multiple risk factors for candidemia.

In our study, hospitalized patients had high APACHE II scores and extensive use of antibiotics. Morrell et al. (2005) found that antimicrobial exposure and high APACHE II scores were independently associated with hospital mortality in patients with candidemia. The other study from Kansas City that included patients with diabetes mellitus and candidemia infections showed that mortality was related to the severity of illness, as measured by the Apache score, mechanical ventilation, and clinical appearance of the infection (Bader et al. 2004). In their study, Cortés et al. (2021) stated that diabetes mellitus accompanies candidemia with COVID-19 in 13 patients (11.9%) and that this comorbidity increased mortality and was an independent risk factor for mortality.

In our study, diabetes mellitus was present in 11 (34.4%) patients who developed fungal infection. Diabetes mellitus was the second most common comorbidity disease group in patients with COVID-19 fungal infection. The most common comorbidity was cardiovascular diseases. Similarly, Kaur and Chakrabarti (2017) also reported an increase in mortalities due to cardiovascular diseases, an increase in access to critical care units, and an increase in the incidence of candidemia in such units. This situation can be explained by the high mean age of the inpatients and the fact that the patients do not receive regular treatment.

Yang et al. (2020) emphasized the higher possibility of developing fungal co-infection in patients who were followed up in the ICU requiring mechanical ventilation and hospitalization longer than 50 days. Also, in our study, 75% of the patients with candidemia were hospitalized in the ICU for more than 30 days. Prolonged ICU stays increase the risk of candidemia.

Due to the severe cytokine release, COVID-19 steroid medication is applied. In a study investigating the use and effect of steroids, 226 hospitalized patients with COVID-19 were examined. Those who received steroid medication were found to have higher rates of bacterial infections (25% versus 13.1%, $p = 0.041$) and fungal infections (12.7% versus 0.7%, $p < 0.001$) (Obata et al. 2021). In our study, fungi were detected in 33 specimens from 12 patients (275%) who received steroid medication, while they were isolated from 44 samples from 20 patients (220%) who did not receive steroid medication. We determined that opportunistic fungal infection increased with the use of steroids.

It is known that the use of broad-spectrum antibiotics increases the patient's susceptibility to candidemia. Antibiotics are widely used in patients with COVID-19, especially those receiving treatment in ICU, and these antibiotics are started empirically. Recent World Health Organization guidelines recommend empiric antibiotics only for patients with severe COVID-19, using host factors and local epidemiology to drive antibiotic selection

(WHO 2020). Lai et al. (2020) reported that empirical antibiotics were prescribed for 90% of patients despite the low confirmation of secondary bacterial infections (10%). Similarly, in a study conducted by Rawson et al. (2020), 70% of COVID-19 patients received antimicrobial therapy, while only 10% had bacterial or fungal infections. In our ICU clinic, treatments with antibiotics started empirically for each patient, and during the treatment, combined antibiotics were used, and at least one of them was a broad-spectrum antibiotic. All of the patients used carbapenem and glycopeptide simultaneously during the last month before fungal infection, and this period was even extended up to 30 days. The rate of antibiotic use of patients in ICU was 98.7% during the days they were hospitalized. Such extensive use of antibiotics lays the groundwork for opportunistic infections. This situation indicates the necessity of using a new algorithm of antibiotics use for COVID-19 patients in intensive care units. One hundred sixty-six doctors from 23 countries and 82 different hospitals participated in a survey study conducted on antibiotics in COVID-19 patients. The study revealed the use of widespread broad-spectrum antibiotics in COVID-19 patients. In COVID-19 patients hospitalized in ICU, piperacillin/ tazobactam were the most frequently prescribed antibiotics, and the mean duration of antibiotic treatment was found to be 7.12 (SD = 2.44) days (Beović et al. 2020). Similar to our study, Sarı et al. (2018) found higher use of carbapenem in patients who developed candidemia. Rawson et al. (2020) summarized nine studies reporting data on co-infections in COVID-19 patients. A rate of 8% was found for bacterial and fungal co-infections in this study. It emphasized that bacterial co-infections are lower in patients with COVID 19, and it is necessary to avoid starting immediate treatment with antibiotics.

The small number of patient samples limited our study. The strength of our study is the conclusion that broad-spectrum and long-term antibiotics used in intensive care patients with a diagnosis of COVID-19 are a significant risk factor for fungal growth.

Conclusions

In patients with COVID-19, cell-mediated immunosuppression, widespread use of antibiotics, a steroid medication, and impaired glucose tolerance laid the foundations for opportunistic infections. Co-infections, especially fungal infections, increase the number of days and mortality of ICU patients. Given the high mortality, early recognition of candidemia and the need for appropriate antifungal therapy are key requirements to improve outcomes for COVID-19 patients in the ICU. In addition to the risk factors that we cannot

change, invasive procedures should be avoided, frequent blood sugar regulation should be applied, and unnecessary or inappropriate antibiotics use should be avoided. The antibiotic use guidelines should be established for COVID-19 patients.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Literature

Al-Hatmi AMS, Mohsin J, Al-Huraizi A, Khamis F. COVID-19 associated invasive candidiasis. J Infect. 2021 Feb;82(2):e45–e46. https://doi.org/10.1016/j.jinf.2020.08.005

Armstrong-James D. Invasive *Candida* species infection: the importance of adequate empirical antifungal therapy. Antimicrob Chemother. 2007 Sep;60(3):459–460. https://doi.org/10.1093/jac/dkm260

Bader MS, Lai SM, Kumar V, Hinthorn D. Candidemia in patients with diabetes mellitus: epidemiology and predictors of mortality. Scand J Infect Dis. 2004;36(11–12):860–864. https://doi.org/10.1080/00365540410021126

Beović B, Doušak M, Ferreira-Coimbra J, Nadrah K, Rubulotta F, Belliato M, Berger-Estilita J, Ayoade F, Rello J, Erdem H. Antibiotic use in patients with COVID-19: a 'snapshot' Infectious Diseases International Research Initiative (ID-IRI) survey. J Antimicrob Chemother. 2020 Nov 1;75(11):3386–3390. https://doi.org/10.1093/jac/dkaa326

Cortés JA, Montañez AM, Carreño-Gutiérrez AM, Reyes P, Gómez CH, Pescador A, Ariza B, Rosso F. Risk factors for mortality in Colombian patients with candidemia. J Fungi (Basel). 2021 May 31;7(6):442. https://doi.org/10.3390/jof7060442

Dupont D, Menotti J, Turc J, Miossec C, Wallet F, Richard JC, Argaud L, Paulus S, Wallon M, Ader F, et al. Pulmonary aspergillosis in critically ill patients with Coronavirus Disease 2019 (COVID-19). Med Mycol. 2021 Jan 4;59(1):110–114. https://doi.org/10.1093/mmy/myaa078

Falagas ME, Apostolou KE, Pappas VD. Attributable mortality of candidemia: a systematic review of matched cohort and case-control studies. Eur J Clin Microbiol Infect Dis. 2006 Jul;25(7):419–425. https://doi.org/10.1007/s10096-006-0159-2

Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, Herwaldt L, Pfaller M, Diekema D. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis. 2003 Nov 1;37(9): 1172–1177. https://doi.org/10.1086/378745

Hassan I, Powell G, Sidhu M, Hart WM, Denning DW. Excess mortality, length of stay and cost attributable to candidaemia. Infect. 2009 Nov;59(5):360–365. https://doi.org/10.1016/j.jinf.2009.08.020

Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008 Jun;36(5):309–332. https://doi.org/10.1016/j.ajic.2008.03.002

Kaur H, Chakrabarti A. Strategies to reduce mortality in adult and neonatal candidemia in developing countries. J Fungi (Basel). 2017 Jul 19;3(3):41. https://doi.org/10.3390/jof3030041

Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020 Mar;55(3):105924. https://doi.org/10.1016/j.ijantimicag.2020.105924

Mastrangelo A, Germinario BN, Ferrante M, Frangi C, Li Voti R, Muccini C, Ripa M; COVID-BioB Study Group. Candidemia in COVID-19 patients: incidence and characteristics in a prospective cohort compared to historical non-COVID-19 controls. Clin Infect Dis. 2020 Oct 30:ciaa1594.
https://doi.org/10.1093/cid/ciaa1594

Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother. 2005 Sep;49(9):3640–3645.
https://doi.org/10.1128/AAC.49.9.3640-3645.2005

Nori P, Cowman K, Chen V, Bartash R, Szymczak W, Madaline T, Punjabi Katiyar C, Jain R, Aldrich M, Weston G, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. Infect Control Hosp Epidemiol. 2021 Jan;42(1):84–88. https://doi.org/10.1017/ice.2020.368

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 Feb;64(2):152–156. https://doi.org/10.1111/myc.13225

Obata R, Maeda T, Rizk D, Kuno T. Increased secondary infection in COVID-19 patients treated with steroids in New York City. Jpn J Infect Dis. 2021 Jul 21;74(4):307–315.
https://doi.org/10.7883/yoken.JJID.2020.884

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1–e50.
https://doi.org/10.1093/cid/civ933

Patolia S, Kennedy E, Zahir M, Patolia S, Gulati N, Narendra D, Vadde R, Pokharel S, Schmidt FM, Enriquez D, et al. Risk factors for candida blood stream infection in medical ICU and role of colonization – A retrospective study. BJMP 2013;6(2):a618

Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, Satta G, Cooke G, Holmes A. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020 Dec 3;71(9):2459–2468. https://doi.org/10.1093/cid/ciaa530

Rotondo JC, Oton-Gonzalez L, Mazziotta C, Lanzillotti C, Iaquinta MR, Tognon M, Martini F. Simultaneous detection and viral DNA load quantification of different human papillomavirus types in clinical specimens by the high analytical droplet digital PCR method. Front Microbiol. 2020 Nov 19;11:591452.
https://doi.org/10.3389/fmicb.2020.591452

Sarı S, Dal HC, Mungan İ ,Tezcan B , Kazancı D, Turan S. [Retrospective evaluation of non-neutropenic candidemia cases in intensive care units] (in Turkish). J Medical Surg Intensive Care Med. 2018;9(3): 74–77. https://doi.org/10.5152/dcbybd.2018.1799

Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, Lagrou K, Verweij PE, Van de Veerdonk FL, Gommers D, et al.; Dutch-Belgian Mycosis study group. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med. 2018 Oct;6(10):782–792.
https://doi.org/10.1016/S2213-2600(18)30274-1

Segrelles-Calvo G, Araújo GRS, Llopis-Pastor E, Carrillo J, Hernández-Hernández M, Rey L, Rodríguez Melean N, Escribano I, Antón E, Zamarro C, et al. Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia. Mycoses. 2021 Feb;64(2):144–151.
https://doi.org/10.1111/myc.13219

Tokak S, Uğurcan D, Tekindal MA. [Determination of candidemia risk factors in inpatients in adult intensive care unit] (in Turkish). FLORA 2020;25(1):47–53. https://doi.org/10.5578/flora.68473

White PL, Dhillon R, Healy B, Wise MP, Backs M. Candidaemia in COVID-19, a link to disease pathology or increased clinical pressures? Clin Infect Dis. 2020 Oct 18:ciaa1597.
https://doi.org/10.1093/cid/ciaa1597

WHO. Clinical management of COVID-19: interim guidance, 27 May 2020 (No. WHO/2019-nCoV/clinical/2020.5) [Internet]. Geneva (Switzerland): World Health Organization; 2020 [cited 2021 May 17].
Available from https://apps.who.int/iris/handle/10665/332196

Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May; 8(5):475–481. https://doi.org/10.1016/S2213-2600(20)30079-5

Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis. 2005 Nov 1;41(9):1232–1239.
https://doi.org/10.1086/496922