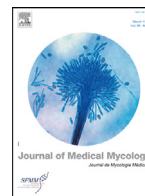




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Case report

COVID-19 and *Candida duobushaemulonii* superinfection: A case reportBassem Awada<sup>a,1</sup>, Walid Alam<sup>b,1,\*</sup>, Maria Chalfoun<sup>c</sup>, George Araj<sup>d</sup>, Abdul Rahman Bizri<sup>a</sup><sup>a</sup> Department of Internal Medicine, Division of Infectious Diseases, American University of Beirut Medical Center, Beirut, Lebanon<sup>b</sup> Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon<sup>c</sup> Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon<sup>d</sup> Department of Laboratory Medicine, American University of Beirut Medical Center, Beirut, Lebanon

## ARTICLE INFO

## Article History:

Received 1 March 2021

Revised 11 June 2021

Accepted 11 June 2021

Available online 16 June 2021

## Keywords:

COVID-19

*Candida duobushaemulonii*

ICU

Multidrug resistance

Mechanical ventilation

Broad-spectrum antibiotics

## ABSTRACT

**Introduction:** Critically ill COVID-19 patients are at high risk for nosocomial bacterial and fungal infections due to several predisposing factors such as intensive care unit stay, mechanical ventilation, and broad-spectrum antibiotics. Data regarding multidrug resistant (MDR) *Candida* species in COVID-19 patients is scarce, and nonexistent regarding *Candida duobushaemulonii* superinfections.

**Case description:** A 34-year-old male presented to our institution with acute respiratory distress syndrome (ARDS) due to COVID-19 infection and developed *Candida duobushaemulonii* fungemia after multiple courses of antibiotics and prolonged mechanical ventilation. He died after recurrent pneumothorax led to respiratory failure and cardiac arrest.

**Discussion:** Bacterial and fungal infections are common complications of viral pneumonia in critically ill patients. Data regarding these infections in COVID-19 patients has been poorly studied with only a few cases reporting secondary infection, mostly without identifying specific pathogens. Prolonged hospital stays, invasive interventions (central venous catheter, mechanical ventilation), and the use of broad-spectrum antibiotics in COVID-19 infections could carry a high risk of bacterial and/or fungal superinfections.

**Conclusion:** Strategies to improve outcome in COVID-19 ICU patients should include early recognition of candidemia and appropriate antifungal therapy.

© 2021 SFMM. Published by Elsevier Masson SAS. All rights reserved.

## Introduction

1.9 million deaths globally have been linked to the COVID-19 pandemic with 88 million cumulative cases reported as of January 12, 2021 [1]. Critically ill patients with COVID-19 are at high risk of developing acute respiratory distress syndrome (ARDS), requiring intensive care and mechanical ventilation, predisposing them to nosocomial bacterial and fungal infections [2,3]. In India, candidemia affected 15 critically ill coronavirus disease patients admitted to an intensive care unit (ICU), with two third of cases attributed to multidrug resistant *Candida auris* [4]. Data regarding multidrug resistant (MDR) *Candida* species in COVID-19 patients is scarce, and nonexistent regarding *Candida duobushaemulonii* superinfections. *Candida duobushaemulonii* is a yeast that is closely related to *Candida auris*

**Abbreviations:** rtPa, recombinant tissue plasminogen activator; DTA, deep tracheal aspirate; COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; *S. maltophilia*, *Stenotrophomonas maltophilia*; TMP-SMX, trimethoprim/sulfamethoxazole; MIC, minimum inhibitory concentration; CAUTI, catheter associated urinary tract infection; VAP, ventilator associated pneumonia

\* Corresponding author at: Department of Internal Medicine, American University of Beirut Medical Center, Hamra, Beirut, Lebanon.

E-mail address: [wa79@aub.edu.lb](mailto:wa79@aub.edu.lb) (W. Alam).

<sup>1</sup> Joint first authors.

and is emerging as a rare cause of invasive fungal infections with a multidrug resistant profile [5].

We report a case of *Candida duobushaemulonii* candidemia in a patient with prolonged ICU stay due to a complicated case of severe COVID-19 infection. To our knowledge, no data exists in the literature in this setting.

## Case description

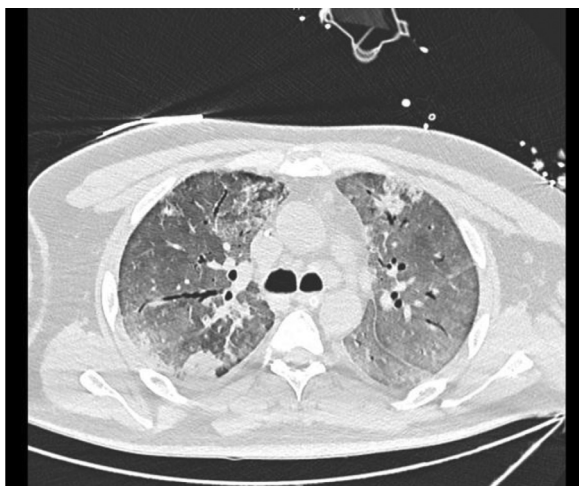
A 34-year-old male without a history of comorbidities presented to our tertiary care center in Beirut, Lebanon from Gabon, Central Africa with severe COVID-19 infection and ARDS. He was hospitalized in Gabon and his medical course was complicated by acute pulmonary embolism treated with recombinant tissue plasminogen activator (rtPA), with subarachnoid hemorrhage (SAH) developing as sequela, and a superimposed bacterial pneumonia for which he received levofloxacin and imipenem.

Patient presented 16 days post his COVID-19 infection to our institution. He was intubated, sedated and off vasopressors. His labs are reported and summarized in (Table 1) and were significant for elevated pro-inflammatory markers (d-dimer, ferritin, CRP, progressive thrombocytosis) and neutrophilia (80-90%). SARS-CoV-2 PCR was positive on admission. CT chest showed severe ARDS with typical

**Table 1**  
Brief summary of the lab results during the patient's stay.

	16/6/2020	20/6/2020	26/6/2020	4/7/2020	16/7/2020	26/7/2020	2/8/2020	10/8/2020
WBC (/cu.mm)	8,600	12,100	11,900	10,300	7,600	9,200	9,200	13,000
Neutrophils	93%	91%	85%	79%	82%	90%	90%	88%
Lymphocytes	4%	3%	6%	9%	10%	7%	6%	5%
Hb (g/dl)	10.6	10.8	10.3	9.5	8.5	8.5	8.4	9.4
Platelets (/cu.mm)	164,000	194,000	366,000	360,000	355,000	352,000	401,000	562,000
Cr (mg/l)	1	0.6	0.6	0.4	0.3	0.2	0.2	0.2
Na (mmol/L)	144	141	146	141	138	136	135	137
K (mmol/L)	4.8	5	5.3	4.4	4.1	4.8	4	4.5
Chloride (mmol/L)	100	102	106	92	90	92	90	93
SGPT (IU/L)	61							
SGOT (IU/L)	86							
Alkaline phosphate (IU/L)	96							
Bilirubin total (mg/dl)	0.7							
Bilirubin direct (mg/dl)	0.5							
Ferritin (ng/ml)	2,207	1109	820	667				
D dimer (ng/ml)	3,862			2,160				1,825
INR	1.9			1.2				
PTT (seconds)	29.6			27.1				
Procalcitonin (ng/ml)	6.9	0.7	0.06	0.16	0.32	0.07		
CRP (mg/L)	217.3	21.1	13.2	31	27.7	24.8	43.9	85.6
Troponin T (ng/ml)	0.06							
Blood parasite smear	Negative							
COVID-19 PCR	Positive							

picture of COVID-19 infection (Fig. 1). Due to the lack of data regarding local resistance in Gabon and the patient's recent history of multiple antibiotic use and long ICU stay, the decision was made to start meropenem for superimposed pneumonia. Blood, urine, and deep tracheal aspirate (DTA) cultures were taken beforehand. DTA cultures grew *Stenotrophomonas maltophilia* sensitive to levofloxacin and trimethoprim/sulfamethoxazole (TMP-SMX), and patient was subsequently started on levofloxacin. He was shifted to TMP-SMX after a new isolate of *S. maltophilia* from DTA was found to be resistant to levofloxacin. He developed catheter acquired urinary tract infection (CAUTI) and ventilator associated pneumonia (VAP) and progressed into septic shock. He was started on amikacin and tigecycline as his cultures grew carbapenem-resistant *Enterobacteriaceae* (CRE) *Enterobacter cloacae* with high minimal inhibitory concentrations (MICs) of ceftazidime/avibactam and carbapenems. Five days later, new DTA and urine cultures were taken and were positive for *Candida* non-albicans, mainly multi-sensitive *Candida parapsilosis* in the urine and *Candida lusitanae* in the DTA. He was subsequently started on intravenous fluconazole.



**Fig. 1.** CT chest showing diffuse ground gland abnormalities with peripheral consolidations. Findings suggestive of severe COVID-19 infection.

Antibiotics were discontinued following completion of fourteen days of therapy and clinical improvement. Antifungal therapy with fluconazole was kept. Patient initially improved clinically but he developed hypotension a week later with elevation of his inflammatory markers (Table 1). Blood cultures were taken from his central line and peripheral lines. He was started on inhaled colistin and tigecycline. Central line blood cultures grew *Candida* non-albicans, and caspofungin was started. Speciation and susceptibility testing revealed *Candida duobushaemulonii*, susceptible to flucytosine (Table 2). Susceptibility data for other anti-fungals is not available. His stay was again complicated by recurrent pneumothoraces leading to respiratory failure followed by cardiac arrest and death.

**Discussion**

Bacterial and fungal infections are common complications of viral pneumonia, especially in critically ill patients, leading to increased mortality rate [6]. Nosocomial fungal infections, particularly Candidiasis and Aspergillosis, are frequently seen in immunocompromised patients that exhibit predisposing risk factors such as neutropenia, compromised neutrophil function, cell-mediated immune dysfunction, and disruption of mucosal integrity [7,8]. In 2017, a team in France analyzed the proportion of fungemia associated with uncommon yeast species and the predisposing factors in 338 cases. The study demonstrated the existence of 35 species with different susceptibility profiles to antifungal drugs and a predisposition to patients who are immunocompromised or have received prior antifungal therapy [9]. COVID-19 has been found to cause immune dysregulation and hyperinflammation in severe cases potentially contributing to the development of nosocomial infections in severely ill patients [10–12]. Nevertheless, limited data regarding bacterial and fungal infections in COVID-19 patients has been published [6].

**Table 2**  
Fungal susceptibility of *Candida duobushaemulonii* based on Vitek testing and interpretation.

	<i>Candida duobushaemulonii</i>	Interpretation
Amphotericin B	8 ug/mL	Resistant
Flucytosine	≤ 1 ug/mL	Susceptible
Voriconazole	4 ug/mL	Resistant

Although the mechanism is still unclear, patients with severe COVID-19 are at similar risk of invasive fungal infections as patients with severe influenza [13]. However, a review of the literature showed that even when secondary infection data was available, the antibiotics use rate (94%–100%) was much higher than the reported incidence of secondary infection (10%–15%), potentially increasing the risk of fungal infections due to endogenous fungi such as *Candida* species [6,7]. A meta-analysis found three studies that reported four fungal pathogens in COVID-19 patients: *Candida albicans*, *Candida glabrata*, *Aspergillus flavus* and *Aspergillus fumigatus* [14].

No data in the literature currently exists regarding *Candida duobushaemulonii* superinfection in COVID-19 patients. A member of the *Candida haemulonii* species complex, *Candida duobushaemulonii* has been found to be invasive and resistant to drugs [15]. In 2018, a genomic study found that *Candida auris* and *Candida duobushaemulonii* were closely related phylogenetically [16]. Recently, a study found that six patients admitted to the ICU for severe COVID-19 were colonized by *Candida auris* and four of them developed candidemia. Testing showed resistance of all strains to amphotericin-B and azoles but susceptibility to echinocandins [17]. The increased reports of *Candida auris* co-infection in severely ill COVID-19 patients and the close phylogenetic relation between *Candida auris* and *Candida duobushaemulonii* could signify that *Candida duobushaemulonii* superinfection is underdiagnosed. In fact, in a study done by Jurado-Martin et al, 150 isolates were reanalyzed using novel PCR approaches to identify multidrug-resistant complex of uncommon *Candida* species that were missed by regular phenotypic testing [18]. The study found that the prevalence of *C. duobushaemulonii* was likely underestimated and that the species was initially associated with superficial infections before emerging as a cause of invasive candidiasis. The identified isolates also showed reduced susceptibility to fluconazole, itraconazole, and amphotericin B [18]. In our case, the pathogen was found to be susceptible to flucytosine with caspofungin already having been started empirically, but speciation and susceptibility results had come out after the patient had already died and were only available for flucytosine, voriconazole, and amphotericin B. Risk factors for invasive candidemia include prolonged hospital stay, invasive interventions (central venous catheter, mechanical ventilation), and the use of broad-spectrum antibiotics [19,20]. The wide use of empirical antibiotics in COVID-19 ICU patients could be a major cause of both bacterial and fungal superinfections and warrants additional evaluation. The reliance on clinical presentation, inflammatory markers, and radiological findings is insufficient to confirm secondary infections and may lead to overuse of antibiotics empirically, while current data on co-infections is limited [21].

Antimicrobial stewardship programs aim to optimize antimicrobial use, improve patient outcomes, and reduce harms from excess use, such as antimicrobial resistance [22]. However, due to the lack of stewardship programs targeted at pandemics such as COVID-19, inpatient antibiotic use may have proceeded unchecked for several months, potentially contributing to antimicrobial resistance and the development of secondary bacterial and/or fungal infections from unnecessary empirical use of broad-spectrum antibiotics [20,23,24].

## Conclusion

Severely ill COVID-19 are at high risk of developing nosocomial infections associated with mechanical ventilation and the use of broad-spectrum antibiotics. Medical and invasive procedures are potential routes of bacterial and fungal infections, with the latter though rare, is associated with considerable mortality in critically ill patients. Strategies to improve outcome in COVID-19 ICU patients should, therefore, include early recognition of candidemia and appropriate antifungal therapy.

## Authors' contribution

Dr. Bassem Awada contributed to the investigation and writing the original draft.

Dr. Walid Alam contributed to the investigation, writing the original draft, and review and editing.

Maria Chalfoun contributed to writing the original draft.

Dr. George Araj contributed to the investigation and formal analysis.

Dr. Abdul Rahman Bizri was responsible for conceptualization and contributed to the review and editing.

## Funding

No funding was received for this work.

## Ethics and patient consent

We acknowledge that approval from the American University of Beirut ethical committee was sought where necessary, and guidelines on consent were followed. Informed consent was obtained from the patient's family.

## Conflict of Interest

The authors have no conflict of interest.

## Acknowledgment

None

## References

- <https://www.who.int/publications/m/item/weekly-epidemiological-update—12-january-2021>.
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507–13. doi: [10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7).
- Arastehfar A, Carvalho A, Nguyen MH, et al. COVID-19-Associated Candidiasis (CAC): an underestimated complication in the absence of immunological predispositions? *J Fungi* 2020;6(4):211. Published Oct 8. doi: [10.3390/jof6040211](https://doi.org/10.3390/jof6040211).
- Chowdhary A, Tarai B, Singh A, Sharma A. Multidrug-resistant *Candida auris* infections in critically ill coronavirus disease patients, India, April–July 2020. *Emerg Infect Dis* 2020;26(11):2694–6 NovEpub 2020 Aug 27. PMID: 32852265; PMCID: PMC7588547. doi: [10.3201/eid2611.203504](https://doi.org/10.3201/eid2611.203504).
- Ramos R, Caceres DH, Perez M, et al. Emerging multidrug-resistant *Candida duobushaemulonii* infections in panama hospitals: importance of laboratory surveillance and accurate identification. *J Clin Microbiol* 2018;56(7):e00371–8 Published 2018 Jun 25. doi: [10.1128/JCM.00371-18](https://doi.org/10.1128/JCM.00371-18).
- Zhou P, Liu Z, Chen Y, Xiao Y, Huang X, Fan XG. Bacterial and fungal infections in COVID-19 patients: a matter of concern. *Infect Control Hosp Epidemiol* 2020;41(9):1124–5. doi: [10.1017/ice.2020.156](https://doi.org/10.1017/ice.2020.156).
- Vazquez JA, Miceli MH, Alangaden G. Invasive fungal infections in transplant recipients. *Ther Adv Infect Dis* 2013;1(3):85–105. doi: [10.1177/2049936113491936](https://doi.org/10.1177/2049936113491936).
- Suleyman G, Alangaden GJ. Nosocomial fungal infections: epidemiology, infection control, and prevention. *Infect Dis Clin North Am* 2016;30(4):1023–52. doi: [10.1016/j.idc.2016.07.008](https://doi.org/10.1016/j.idc.2016.07.008).
- Bretagne S, Renaudat C, Desnos-Ollivier M, et al. Predisposing factors and outcome of uncommon yeast species-related fungaemia based on an exhaustive surveillance programme (2002–14). *J Antimicrob Chemother* 2017;72(6):1784–93. doi: [10.1093/jac/dkx045](https://doi.org/10.1093/jac/dkx045).
- Bardi T, Pintado V, Gomez-Rojo M, et al. Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. *Eur J Clin Microbiol Infect Dis* 2021;40(3):495–502. doi: [10.1007/s10096-020-04142-w](https://doi.org/10.1007/s10096-020-04142-w).
- Alam W. Hypercoagulability in COVID-19: a review of the potential mechanisms underlying clotting disorders. *SAGE Open Med* 2021;9 20503121211002996. Published 2021 Mar 21. doi: [10.1177/20503121211002996](https://doi.org/10.1177/20503121211002996).
- Reusch N, De Domenico E, Bonaguro L, et al. Neutrophils in COVID-19. *Front Immunol* 2021;12:652470 Published 2021 Mar 25. doi: [10.3389/fimmu.2021.652470](https://doi.org/10.3389/fimmu.2021.652470).
- Gangneux JP, Bournoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: we should be prepared. *J Mycol Med* 2020;30(2):100971. doi: [10.1016/j.mycmed.2020.100971](https://doi.org/10.1016/j.mycmed.2020.100971).

- [14] 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(2):266–75. doi: [10.1016/j.jinf.2020.05.046](https://doi.org/10.1016/j.jinf.2020.05.046).
- [15] Hou X, Xiao M, Chen SC, Wang H, Cheng JW, Chen XX, Xu ZP, Fan X, Kong F, Xu YC. Identification and antifungal susceptibility profiles of *Candida haemulonii* species complex clinical isolates from a multicenter study in China. *J Clin Microbiol* 2016;54:2676–80. doi: [10.1128/JCM.01492-16](https://doi.org/10.1128/JCM.01492-16).
- [16] Muñoz JF, Gade L, Chow NA, et al. Genomic insights into multidrug-resistance, mating and virulence in *Candida auris* and related emerging species. *Nat Commun* 2018;9(1):5346. Published 2018 Dec 17. doi: [10.1038/s41467-018-07779-6](https://doi.org/10.1038/s41467-018-07779-6).
- [17] Magnasco L, Mikulska M, Giacobbe DR, et al. Spread of Carbapenem-resistant gram-negatives and *Candida auris* DURING the COVID-19 pandemic in critically ill patients: one step back in antimicrobial stewardship? *Microorganisms* 2021;9(1):95. Published 2021 Jan 3. doi: [10.3390/microorganisms9010095](https://doi.org/10.3390/microorganisms9010095).
- [18] Jurado-Martín I, Marcos-Arias C, Tamayo E, et al. *Candida duobushaemulonii*: an old but unreported pathogen. *J Fungi* 2020;6(4):374. Published 2020 Dec 17. doi: [10.3390/jof6040374](https://doi.org/10.3390/jof6040374).
- [19] Al-Hatmi AMS, Mohsin J, Al-Huraizi A, Khamis F. COVID-19 associated invasive candidiasis [published online ahead of print, 2020 Aug 7]. *J Infect* 2020 S0163-4453(20)30539-9. doi: [10.1016/j.jinf.2020.08.005](https://doi.org/10.1016/j.jinf.2020.08.005).
- [20] Ben-Ami R, Olshtain-Pops K, Krieger M, et al. Antibiotic exposure as a risk factor for fluconazole-resistant *Candida* bloodstream infection. *Antimicrob Agents Chemother* 2012;56(5):2518–23. doi: [10.1128/AAC.05947-11](https://doi.org/10.1128/AAC.05947-11).
- [21] Verroken A, Scohy A, Gérard L, et al. Co-infections in COVID-19 critically ill and antibiotic management: a prospective cohort analysis. *Crit Care* 2020;24:410. doi: [10.1186/s13054-020-03135-7](https://doi.org/10.1186/s13054-020-03135-7).
- [22] <https://www.cdc.gov/antibiotic-use/healthcare/evidence/asp-int-am-resistance.html>
- [23] Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect* 2020;26(12):1622–9. doi: [10.1016/j.cmi.2020.07.016](https://doi.org/10.1016/j.cmi.2020.07.016).
- [24] <https://www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations-complications/co-infection-and-Antimicrobial-Stewardship/>