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.
Letter to the Editor

Outbreak of Candida auris infection in a COVID-19 hospital in Mexico

Hiram Villanueva-Lozano 1, *, Rogelio de J. Treviño-Rangel 1, *, Gloria M. González 1, *, María Teresa Ramírez-Elizondo 2,3, Reynaldo Lara-Medrano 2, Mary Cruz Aleman-Bocanegra 2, Claudia E. Guajardo-Lara 4, Natalia Gaona-Chávez 2, Fernando Castilleja-Leal 3, Guillermo Torre-Amione 3, Michel F. Martínez-Reséndez 2,3,*

1) Universidad Autónoma de Nuevo León, School of Medicine, Department of Microbiology, Monterrey, Nuevo León, Mexico
2) Hospital San José-Tec Salud, Epidemiological Surveillance Unit, Monterrey, Nuevo León, Mexico
3) Instituto Tecnológico y de Estudios Superiores de Monterrey, School of Medicine and Health Sciences, Monterrey, Nuevo León, Mexico
4) Laboratory of Clinical Microbiology, Hospital San José-TecSalud, Monterrey, Nuevo León, Mexico

To the Editor,

Since its emergence in December 2019, the rapid spread of coronavirus disease 2019 (COVID-19) has necessitated the expansion and transformation of healthcare facilities worldwide to accommodate the constantly increasing numbers of patients. This situation has provided a potential ground for the transmission of nosocomial infections [1]. Candida auris is a multidrug-resistant fungal pathogen with the capability for nosocomial transmission. Some studies have suggested an increased risk for Candida sp. in COVID-19 patients, resulting in poor outcomes [2,3].

Here we describe an outbreak of C. auris which started in a non-COVID-19 patient at the end of May 2020 (reported previously [4]). This occurred during the transition of the hospital to an exclusive COVID-19 facility: the infection later spread to 12 patients in the intensive care unit (ICU).

We collected the clinical data of all the patients admitted to the hospital from April 2020 to the present date. Characteristics of the patients with a diagnosis of C. auris infection were analysed. This study was approved by the Research Ethics Committee of the Hospital San José Tec-Salud (registration number: P000353-COVID-19-TecSalud-CS001).

C. auris strains from 12 patients and three environmental isolates from their bedrooms were identified by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, MALDI Biotyper) and confirmed by multi-locus sequence typing of the ITS1-5.8S-ITS2, D1/D2, RPB1 and RPB2 regions. Sequences were aligned and analysed by MEGA v.7.0.26 and a dendrogram was delineated. Antifungal susceptibility testing for amphotericin B (AMB), fluconazole (FLU), voriconazole (VRC), posaconazole (POS), itraconazole (ITC), isavuconazole (ISA), anidulafungin (ANF) and caspofungin (CAS) was performed using the Clinical and Laboratory Standards Institute (CLSI) broth micro-dilution method M27-A3/54.

Our team reported the first case of C. auris infection in May 2020. At that time the hospital was transitioning from a general hospital to an exclusive COVID-19 facility which included expansion of the ICU to four areas with 60 beds; this was completed as the last non-COVID–19 patient was discharged.

Three months later an outbreak of COVID-19-associated Candida auris infections started in three of the ICUs, affecting 12 patients. All the affected patients were under mechanical ventilation, had peripherally inserted central lines (PICCs), urinary catheters and prolonged hospital stay (20–70 days). C. auris was isolated from blood in six patients (6/12; 50%), from urine in eight (8/12; 66.6%), and from both sites in two (2/12; 16.6%). Mortality was 83.3% (5/6) among the patients with candidaemia (Table 1A).

Sequences of the genes used for the 15 C. auris isolates clustered together in the dendrogram performed with the sequence previously reported from a non-COVID-19 patient, which belonged to the Clade IV (South American) [4], suggesting a very close relationship. Antifungal susceptibility testing showed that all the isolates (15/15) were resistant to AMB (MIC ≥4 μg/mL), just one isolate was resistant to ANF (MIC ≥4 μg/mL), one to CAS (MIC ≥2 μg/mL)

* Corresponding author. Michel F. Martínez-Reséndez, Hospital San José-Tec Salud, Epidemiological Surveillance Unit, Av. Morones Prieto #3000 Pte. Los Doctores, 64710, Monterrey, Nuevo León, Mexico.
E-mail address: drmichelfernando@gmail.com (M.F. Martínez-Reséndez).

* These authors contributed equally to this work as first authors.
Table 1
(A) Clinical characteristics of 12 patients with C. auris infection and COVID-19 pneumonia. (B) MLST and antifungal susceptibility results of the C. auris isolates from the patients and surface sampling from an infusion pump (13) and bed rails (14 and 15).

### A. Clinical characteristics of 12 patients with C. auris infection and COVID-19 pneumonia.

| No. | Patient | Age | Sex | Co-infections | Risk factors | Antibiotics | SARS-CoV-2 treatment | Steroids | Cumulative dose of steroids (mg prednisone) | Antifungals | Interleukin 6 (pg/mL) | D-dimer (ng/mL) | Ferritin (ng/mL) | Days to 1st. positive culture | Outcome |
|-----|---------|-----|-----|---------------|--------------|-------------|---------------------|----------|-------------------------------------------|-------------|----------------------|----------------|----------------|--------------------------|----------|
| 1   | 1       | 51  | M   | Pseudomonas    | HBP, DM2,    | CTR, CAZ,    | LPV/RTV, BARI,     | Dex 6mg QD | 1480mg                                    | CAS, ANF    | 270.5 NA              | 831 383       | 1563 Blood        | 37 17 29 36 13 | Died       |
| 2   | 2       | 54  | M   | Pseudomonas    | DM2, Obesity | MEM, LZD,    | BARI, PLASMA       | Dex 6mg QD | 1580                                      | ANF, ISA    | 89.56 192.2          | 254 1000      | 3187 Urine        | 71 29 36 13 | Survived  |
| 3   | 3       | 55  | M   | Pseudomonas    |             | MEM, LZD,    | Dex 6mg QD,       | Metil 40mg QD| 1360                                      | ASA, ANF    | 1556 11000           | 2000 2000    | 363 Blood and Urine | 10 31 16 27 22 | Died       |
| 4   | 4       | 51  | M   | Pseudomonas    |             | MEM, LZD,    | Dex 6mg QD,       | Metil 40mg QD| 1440                                      | ASA, ANF    | 9.29 44.13           | 5516 11000   | 4163 Blood and Urine | 10 31 16 27 22 | Died       |
| 5   | 5       | 64  | M   | Pseudomonas    |             | MEM, LZD,    | Dex 6mg QD,       | Metil 40mg QD| 1300                                      | ANF, ISA    | 1293 798.3           | 5516 11000   | 4163 Blood and Urine | 10 31 16 27 22 | Died       |
| 6   | 6       | 64  | M   | Candida glabrata|             | MEM, LZD,    | Dex 6mg QD,       | Metil 40mg QD| 1000                                      | ANF, ISA    | 2.92 44.13           | 150 11000    | 4163 Blood and Urine | 10 31 16 27 22 | Died       |
| 7   | 7       | 64  | M   | None          | Risk factors | AMB, FLC, VRC  | LPV/RTV, BARI     | Metil 125mg QD| 1240                                      | CAS, ANF    | 4.0 99.3             | 2117 10000   | 4163 Blood and Urine | 10 31 16 27 22 | Died       |
| 8   | 8       | 54  | M   | None          | Antibiotics  | AMB, FLC, VRC  | LPV/RTV, BARI     | Metil 125mg QD| 5000                                      | ANF, ISA    | 1.0 99.3             | 2117 10000   | 4163 Blood and Urine | 10 31 16 27 22 | Died       |
| 9   | 9       | 60  | F   | None          | Steroids     | AMB, FLC, VRC  | LPV/RTV, BARI     | Metil 125mg QD| 2500                                      | ANF, ISA    | 0.99 99.3            | 2117 10000   | 4163 Blood and Urine | 10 31 16 27 22 | Died       |
| 10  | 10      | 58  | F   | None          | Antifungals  | AMB, FLC, VRC  | LPV/RTV, BARI     | Metil 125mg QD| 2500                                      | ANF, ISA    | 0.99 99.3            | 2117 10000   | 4163 Blood and Urine | 10 31 16 27 22 | Died       |
| 11  | 11      | 36  | M   | None          | Dimer        | AMB, FLC, VRC  | LPV/RTV, BARI     | Metil 125mg QD| 2500                                      | ANF, ISA    | 0.99 99.3            | 2117 10000   | 4163 Blood and Urine | 10 31 16 27 22 | Died       |
| 12  | 12      | 66  | M   | None          | Ferritin     | AMB, FLC, VRC  | LPV/RTV, BARI     | Metil 125mg QD| 2500                                      | ANF, ISA    | 0.99 99.3            | 2117 10000   | 4163 Blood and Urine | 10 31 16 27 22 | Died       |

### B. MLST and antifungal susceptibility results of the C. auris isolates from the patients and surface sampling from an infusion pump (13) and bed rails (14 and 15).

| No. | Isolate | GenBank accession numbers (ITS-D1/D2-RPB1-RPB2) | ST cluster | MIC (µg/mL) | AMB | FLC | VRC | POS | ITC | ISA | ANF | CAS |
|-----|---------|-----------------------------------------------|------------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 1   | MW087107-MW089312-MW090140-MW113720          | IV         | 4           | 64          | 1   | 0.5 | 0.5 | 2   | 0.5 | 1   | 1   | 1   |
| 2   | MW087108-MW089313-MW090141-MW113721          | IV         | 4           | 16          | 0.25| <0.03| 0.06| 2   | 0.5 | 0.5 | 1   | 1   |
| 3   | MW087109-MW089314-MW090142-MW113722          | IV         | 4           | 2           | 16  | <0.03| <0.03| 2   | 0.5 | 0.5 | 1   | 1   |
| 4   | MW087110-MW089315-MW090143-MW113723          | IV         | 4           | 2           | 16  | 0.5  | 0.06| 2   | 0.5 | 1   | 1   | 1   |
| 5   | MW087111-MW089316-MW090144-MW113724          | IV         | 4           | 2           | 64  | 0.25 | 0.125| 0.125| 0.125| 0.125| 0.5 | 1 |
| 6   | MW087112-MW089317-MW090145-MW113725          | IV         | 4           | 2           | 16  | 0.125| 0.03 | 0.125| 0.125| 0.5 | 1   | 1   |
| 7   | MW087113-MW089318-MW090146-MW113726          | IV         | 4           | 4           | 64  | 0.5  | 0.5 | 1   | 0.5 | 0.5 | 1   | 1   |
| 8   | MW087115-MW089319-MW090147-MW113727          | IV         | 4           | 2           | 32  | 0.25 | 0.03 | 0.125| 0.125| 0.5 | 1   | 1   |
| 9   | MW087115-MW089320-MW090148-MW113728          | IV         | 4           | 4           | 64  | 0.125| 0.5  | 0.5  | 1   | 1   | 1   | 1   |
and eight isolates (8/15; 53.3%) were resistant to FLU (MIC ≥32 μg/mL). Eight isolates were multidrug-resistant (resistance to two major classes of antifungals) Table 1B).

Numerous reports have described COVID-19 co-infections by fungal pathogens, especially in critically ill patients. As stated in the work of Arasthefar et al. [5], classic risk factors commonly found in these patients include diabetes mellitus, use of multiple antibiotics, renal failure, and use of central venous catheters, but other factors specifically associated with COVID-19—such as excessive corticosteroid use, which has an immunosuppressive effect on neutrophils and macrophages—might also contribute to this problem. Nonetheless, a lot of interest still exists in elucidating a relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immune response and predisposition to Candida infection [2].

In our report 12 patients have presented COVID-19-associated C. auris infection, and so far only three environmental samples have yielded this pathogen. The prolonged lag between the first case 3 months ago and current cases is thought to be due to measures taken during the transformation process from a general hospital to a COVID-19-exclusive facility, such as reinforcement of hand washing compliance and use of personal protective equipment (PPE). Chowdhary et al. [6] theorized that transmission of COVID-19-associated C. auris by health personnel is unlikely because of the use of PPE. The 15 isolates of C. auris were non-susceptible to AMB and FLU, which are the main antifungal drugs used in most of the hospitals in Mexico.

This study has some limitations as it was conceived as a description of an outbreak; as such, there is no control group, and findings may not be generalizable to other populations. Nonetheless mortality in patients with COVID-19-associated C. auris bloodstream infection was exceedingly high, five of six patients died even with antifungal treatment; strict control of risk factors, such as central line care bundles, corticosteroids and antibiotic stewardship, must therefore be implemented to avoid the lethal combination of these two emergent infectious threats.

Author contributions

HV-L, RJT-R and GMG contributed to drafting and revising the article, as well as in the conception and design of the study. RL-M, MTR-E and NG-Ch contributed to the acquisition and interpretation of data. FC-L, MCA-B, CEG-L and GT-A contributed to revision and final approval of the report. MFM-R participated in the analysis and interpretation of data, drafting and final approval of the version to be submitted.

Transparency declaration

All authors declare no conflicts of interest. This work was supported by internal resources of the department.

Acknowledgements

We thank all the health personnel involved in the attention and care of these patients, specially to Mauricio Sánchez-Rodríguez MD and Alvaro E. Camero-Garza MD. We also thank Gerald Martin Rhoades-Torres MD for his review of the manuscript prior to submission.

References

[1] Auerbach A, O'Leary KJ, Greysen SR, Harrison JD, Krispalani S, Ruhnke GW, et al. Hospital ward adaptation during the covid-19 pandemic: a national survey of academic medical centers. J Hosp Med 2020;15:483–8.
[2] Al-Hatmi AM, Mohsin J, Al-Huraizi A, Khamis F. Covid-19 associated invasive candidiasis. J Infect 2020; 50:163–445:30539-9.
[3] Lone SA, Ahmad A. *Candida auris*—the growing menace to global health. Mycoses 2019;62:620–37.
[4] Ayala-Gaytan JJ, Montoya AM, Martinez-Resendez MF, Guajardo-Lara CE, Trevino-Rangel RdJ, Salazar-Cavazos L, et al. First case of *Candida auris* isolated from the bloodstream of a Mexican patient with serious gastrointestinal complications from severe endometriosis. Infection 2020:1–3.
[5] Arastehfar A, Carvalho A, Nguyen MH, Hedayati MT, Netea MG, Perlin DS, et al. Covid-19-associated candidiasis (CAC): an underestimated complication in the absence of immunological predispositions? J Fungi 2020;6:211.
[6] 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;26:2694–6.