**Candida auris** Invasive Infections during a COVID-19 Case Surge

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**ABSTRACT**

Clinical cases of *C. auris* noted during a COVID-19 surge led to an epidemiological, clinical, and genomic investigation. Evaluation identified a close genetic relationship but inconclusive epidemiologic link between all cases. Prolonged hospitalization due to critical illness from COVID-19 and use of antimicrobials may have contributed to clinical infections.

**KEYWORDS** COVID-19, Candida auris, whole-genome sequencing, outbreak investigation

A major concern of the COVID-19 pandemic is the indiscriminate use of broad-spectrum antimicrobials to empirically treat suspected bacterial infections in patients with moderate to severe disease. This undiscerning use is likely to drive the selection of multidrug-resistant organisms. Thus, a convergence of COVID-19 with a surge of antimicrobial-resistant pathogens is likely to strain hospital capacity and the ability to treat critically ill patients. Furthermore, the use of immunomodulatory drugs for the treatment of COVID-19 may drive health care acquisition of multidrug-resistant superinfections (1). Of particular concern is the potential emergence of *Candida auris*, an organism designated a U.S. Centers for Disease Control and Prevention (CDC) “urgent threat” (2) due to its resistance to multiple antifungals and its propensity to cause infections in critically ill patients who have been subjected to broad-spectrum antimicrobials (3). According to the CDC, a growing number of clinical cases of *C. auris* have been reported in Florida over the past several years (https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html).

At our institution, an academic medical center in Miami, the first clinical case of *C. auris* was identified in 2019. Based on recommendations from the local health department, an emergency room screening program was implemented at that time in patients with the following risk factors: ventilator dependence, tracheostomy, and arrival from high-incidence post-acute care facilities in the area. Screening included identification of these risk factors and PCR-based testing using axillary and groin swabs (BD Eswab in 1 ml of liquid AMIES Medium, catalog no. 220245; BD Diagnostics). During a local surge of COVID-19 cases in which close to 40% of the hospital capacity was occupied by COVID-19 patients over the course of several months in the summer of 2020, *C. auris* was noted to be isolated from multiple clinical specimens in patients not meeting screening criteria, prompting an epidemiological, clinical, and genomic investigation.

An epidemiological investigation was conducted to identify spatiotemporal commonalities between patients with clinical isolates positive for *C. auris* (IRB 20200739). Spatiotemporal relationships were defined as concurrent admission time frame and
occupation of a room in the same ward in the hospital. We were unable to conduct environmental sampling as our institutional and health department laboratory capacities were limited by the pandemic. Clinical isolates from the cohort were identified using matrix-assisted laser desorption/ionization time of flight (MALDI-ToF), while antifungal susceptibility testing was completed using Vitek2 by the clinical microbiology laboratory. Relevant clinical data, including demographics, comorbidities, prior antibiotic and steroid administration, and level of care, were abstracted from medical records. C. auris isolates were subjected to whole-genome sequencing on an Illumina MiSeq and a single isolate (index isolate, NC_1) was sequenced using an Oxford Nanopore MinION sequencer. Illumina-based assemblies were generated as previously described (4), and the hybrid-assembly of NC_1 was generated using a bespoke pipeline (https://github.com/wshropshire/flye_hybrid_assembly_pipeline). A core gene phylogenetic tree using a representative set of reference genomes was generated to assess phylogenetic clustering and confirm species identification, as previously described (5). Single nucleotide polymorphisms (SNPs) were identified with GATK v4.1.9.0 (6) using the best practices workflow and NC_1 as an internal reference.

A total of 15 clinical C. auris isolates, 12 from COVID-19 (C) patients and 3 from non-COVID-19 (NC) patients on separate wards, were recovered from blood and nonsterile sites (Table 1). Only isolate C_1 displayed nonsusceptibility to all tested echinocandins. Antifungal susceptibility testing revealed that all isolates had amphotericin B MICs ranging from 0.5 to 1 μg/ml and were not susceptible to fluconazole (MIC ≥ 128 μg/ml). Isolation of C. auris followed a median hospital stay of 28 days from admission (interquartile range, 0 to 123 days), with 80% of patients in the cohort having critical illness requiring intensive care, mechanical ventilation, or use of vasopressor agents. All patients in the cohort received antibiotics, and all but one of the patients suffered from clinically relevant bacterial infections prior to isolation of C. auris. Steroids were administered as treatment in 83% of patients with COVID-19. Of the 15 patients in the cohort, C. auris was isolated from the bloodstream of 8 patients, and 6 patients had negative follow-up cultures after appropriate treatment. C. auris was identified for two of the patients posthumously.

We established spatiotemporal epidemiological relationships in 12 cases between each patient and at least one other. Phylogenetic analyses revealed that all clinical isolates belonged to the South African lineage and were closely clustered, with every isolate differing by ≤ 5 SNPs relative to NC_1 (Fig. 1), suggesting that this cluster originated from a single source and was disseminated by interpatient transmission or a point-source outbreak. However, no clear spatiotemporal link was identified in three of the cases, suggesting the possibility of community transmission or transmission between local health care or long-term-care facilities. Based on recently published known risk factors for C. auris acquisition (7), none of the cases in this cohort would have met screening criteria. To enhance disinfection, terminal cleaning, including ultraviolet C light (UV-C), was used in COVID-19 care wards. Of note, recent data suggest that UV-C may be less effective against decolonization of the environment by C. auris belonging to the South African clade (8).

Stresses during the surge and mixed messaging from local and national public health authorities led to changes in prescribing practices and perceptions of appropriate personal protective equipment (PPE) use, including extended and—at times—excessive use. This practice was compounded by the increase in use of agency nurses and staff with varied levels of training and experience in use of PPE and care of COVID-19 patients. Following the identification of the cluster, aggressive mitigation strategies were implemented, including expansion of C. auris screening to all patients arriving from any long-term-care facility, implementation of cleaning with hydrogen peroxide-based chemical and fogging disinfectants, repainting walls in rooms previously occupied by patients with C. auris, cohorting of patients and staff, standardization of COVID-19 PPE use aimed at minimizing potentially harmful overuse, removal of shared equipment, and enhanced guidance for antimicrobial use limited to defined indications. Once the local COVID-19 surge subsided,
| Parameter | Case | C.1 | C.2 | C.3 | C.4 | C.5 | C.6 | C.7 |
|-----------|------|-----|-----|-----|-----|-----|-----|-----|
| Age (yr)  |      | 72  | 77  | 71  | 71  | 38  | 71  | 75  |
| Sex       |      | M   | M   | M   | M   | M   | M   | F   |
| Comorbidities |     | DLP | DLP | MM, SCT | DM, HTN | DM, HTN | DM | DM |
| COVID-19 treatment | | REM | REM | REM | REM | REM | REM | REM |
| Notable COVID-19 complications | | PE | No | No | No | No | No | No |
| Antecedent treatment with steroids | | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Clinically relevant antecedent positive culture data | | None | S. warneri (blood) | MRSA (blood, resp) | C. pelliculosa (blood) | S. saprophyticus (blood) | S. epidermidis (blood) |
| Previous antimicrobials | | CTX, CFP, AZI | CTX, AZI, LZD, CFZ, AMP | CTX, CFP, AZI, LZD, VAN, T-S, ACY | CTX, CFP, AZI, MIC | AZT, AZI, MIC, LZD, MER | CTX, CFP, AZI, VAN, MER, LZD | AZI, CFP, VAN |
| Experimental COVID-19 treatment trial | | Yes | No | No | Yes | No | No | No |
| Critically ill | | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Days from admission to collection of C. auris isolate | | 14 | 28 | 24 | 24 | 32 | 30 | 12 |
| C. auris Source | | Blood | Urine | Blood | Blood | Wound | Blood | Blood |
| C. auris treatment | | MIC, line removal | NA | MIC, AMB, line removal | NA | debridement | NA | MIC, line removal |
| Candidemia duration (outcome) | | Single episode, 13 days (resolved) | NA | First episode 2 days, second episode 3 days (resolved) | NA | NA | Single episode, 3 days (resolved) |
| Disposition | | DC | EXP | EXP | EXP | DC | EXP | DC |
| Connection in space and time to other clinical cases | | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

*a* Male; F, female; DLP, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; MM, multiple myeloma; SCT, stem cell transplantation; SLE, systemic lupus erythematosus; CA, cancer; ESRD, end stage renal disease; OM, osteomyelitis; REM, remdesivir; HCQ, hydroxychloroquine; NA, not applicable; DVT, deep venous thrombosis; PTX, pneumo-thorax; PE, pulmonary embolism; MRSA, methicillin-resistant S. aureus; VRE, vancomycin-resistant enterococcus; resp, respiratory culture. Antimicrobial: CTX, ceftriaxone; CFP, cefepime; AZI, azithromycin; LZD, linezolid; CFZ, cefazolin; AMP, ampicillin; VAN, vancomycin; T-S, trimethoprim-sulfamethoxazole; ACY, acyclovir; MIC, micafungin; AZT, aztreonam; MER, meropenem; LFN, levofoxacin; P-T, piperacillin-tazobactam; C-T, ceftolozane-tazobactam; ERT, ertapenem; M-V, meropenem-vaborbactam; MET, metronidazole; DAP, daptomycin; MIC, micafungin; AMB, amphotericin B. Other abbreviations: DC, discharged; EXP, expired; NA, not applicable.

*Experimental trials include avapritil, mesenchymal stem cell therapy, or convalescent plasma.*

"Critically ill" is signified by ICU admission, mechanical ventilation, and/or the use of vasopressor agents.
| Case | C_8 | C_9 | C_10 | C_11 | C_12 | NC_1 | NC_2 | NC_3 |
|------|-----|-----|------|------|------|------|------|------|
|      |     |     |      |      |      |      |      |      |
| 68   | 65  | 69  | 41   | 68   | 34   | 42   | 51   |      |
| F    | M   | M   | M    | M    | M    | M    | M    | M    |
| DM, bladder CA | HTN, HTN, ESRD | None | Obesity, OM | HTN, DM, chronic anoxic brain injury | Abdominal abscess, chronic anoxic brain injury |
| REM  | REM | REM | None | HCO  | NA   | NA   | NA   | NA   |
| No   | No  | No  | No   | Limb ischemia, PE | NA   | NA   | NA   | NA   |
| Yes  | Yes | Yes | Yes  | No   | No   | No   | No   | No   |
| E. faecalis (urine) | K. pneumoniae (resp) | S. hominis (blood) | E. cloacae (resp, blood) | S. lugdunensis (wound) | MRSA (resp) | P. mirabilis (wound) |
| CFP, VAN, MER | CFP, VAN, AZI, LZD, MER, VAN | CFP, VAN, LZD, LFN, MIC | P-T, LZD, MER, VAN, LFN | CFP, VAN | CFP, VAN | CFP, VAN, ERT, LFN, M-V | CFP, MET, P-T, VAN, ERT, DAP |
| Yes  | Yes | Yes | Yes  | Yes  | No   | Yes  | No   | No   |
| 32   | 12  | 28  | 20   | 33   | 0    | 123  | 55   |
| Urine | Resp | Blood | Blood | Wound | Catheter tip | Blood | Wound |
| NA   | NA  | NA  | NA   | NA   | NA   | NA   | NA   |
| NA   | NA  | NA  | NA   | NA   | NA   | NA   | NA   |
| DC   | EXP | EXP | EXP  | DC   | DC   | DC   | EXP  | DC   |
| Yes  | Yes | Yes | Yes  | Yes  | No   | Yes  | No   | No   |

**Note:**
- **Case 68** was a 65-year-old female with DM and bladder cancer (bladder CA) who presented with HTN, HTN, and ESRD. She was admitted with obesity, OM and had a history of HTN, DM, chronic anoxic brain injury.
- **Case 69** was a 68-year-old male with DM, bladder CA who presented with HTN, HTN, and ESRD. He was admitted with obesity, OM and had a history of HTN, DM, chronic anoxic brain injury.
- **Case 41** was a 41-year-old female with DM, bladder CA who presented with HTN, HTN, and ESRD. She was admitted with obesity, OM and had a history of HTN, DM, chronic anoxic brain injury.
- **Case 68** was a 68-year-old male with DM, bladder CA who presented with HTN, HTN, and ESRD. He was admitted with obesity, OM and had a history of HTN, DM, chronic anoxic brain injury.
- **Case 34** was a 34-year-old female with DM, bladder CA who presented with HTN, HTN, and ESRD. She was admitted with obesity, OM and had a history of HTN, DM, chronic anoxic brain injury.
- **Case 42** was a 42-year-old male with DM, bladder CA who presented with HTN, HTN, and ESRD. He was admitted with obesity, OM and had a history of HTN, DM, chronic anoxic brain injury.
- **Case 51** was a 51-year-old female with DM, bladder CA who presented with HTN, HTN, and ESRD. She was admitted with obesity, OM and had a history of HTN, DM, chronic anoxic brain injury.

**Table Legend:**
- **CFP, VAN, MER** indicates the use of combination therapy including cefepime, vancomycin, and meropenem.
- **CFP, VAN, AZI, LZD, MER, VAN** indicates the use of combination therapy including cefepime, vancomycin, aztreonam, levofloxacin, meropenem, and vancomycin.
- **P-T, LZD, MER, VAN, LFN** indicates the use of combination therapy including piperacillin-tazobactam, levofloxacin, meropenem, vancomycin, and linezolid.
- **CFP, VAN** indicates the use of cefepime and vancomycin.
- **CFP, VAN, ERT, LFN, M-V** indicates the use of cefepime, vancomycin, ertapenem, linezolid, and meropenem.
- **CFP, MET, P-T, VAN, ERT, DAP** indicates the use of cefepime, metronidazole, piperacillin-tazobactam, vancomycin, ertapenem, and daptomycin.

**Microorganisms:**
- **E. faecalis (urine)**
- **K. pneumoniae (resp)**
- **S. hominis (blood)**
- **E. cloacae (resp, blood)**
- **S. lugdunensis (wound)**
- **MRSA (resp)**
- **P. mirabilis (wound)**
- **K. pneumoniae (resp, urine, blood)**
- **P. aeruginosa (resp, urine)**
- **P. aeruginosa (resp, urine, blood)**
- **E. faecalis (wound)**

**Antibiotics:**
- **CFP, VAN**
- **CFP, VAN, AZI, LZD, MER, VAN**
- **CFP, VAN, LZD, LFN, MIC**
- **P-T, LZD, MER, VAN, LFN**
- **CFP, VAN**
- **CFP, VAN, ERT, LFN, M-V**
- **CFP, MET, P-T, VAN, ERT, DAP**

**Other Information:**
- **Yes** indicates a positive result.
- **No** indicates a negative result.
- **32** indicates 32 days.
- **12** indicates 12 days.
- **28** indicates 28 days.
- **20** indicates 20 days.
- **33** indicates 33 days.
- **0** indicates 0 days.
- **55** indicates 55 days.
- **DC** indicates discharge.
- **EXP** indicates exacerbation.
- **MIC** indicates minimum inhibitory concentration.
- **Line removal** indicates catheter line removal.
- **Single episode** indicates a single episode of infection.
- **Single episode, 5 days** indicates a single episode of infection lasting 5 days.
- **Single episode, 3 days** indicates a single episode of infection lasting 3 days.
- **Single episode, 2 days** indicates a single episode of infection lasting 2 days.
- **Single episode, 5 days (resolved)** indicates a single episode of infection lasting 5 days (resolved).
- **Single episode, 3 days (resolved)** indicates a single episode of infection lasting 3 days (resolved).
- **Single episode, 2 days (resolved)** indicates a single episode of infection lasting 2 days (resolved).
a cessation of *C. auris* infections was observed. In summary, our results highlight the impending epidemic of multidrug-resistant organisms likely to emerge in the subsequent waves of the COVID-19 pandemic. As COVID-19 cases surge in different parts of the world, we urge a more judicious use of antimicrobials and steroids, as well as enhanced screening, surveillance, and isolation of patients colonized or infected with multidrug-resistant organisms, including *C. auris*.
SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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