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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 spaciotemporal commonalities between patients with clinical isolates positive for *C. auris* (IRB 20200739). Spaciotemporal 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 $\geq$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 spaciotemporal 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 $\leq$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 spaciotemporal 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,

TABLE 1 Risk factors, clinical characteristics, and outcomes

| Parameter	Case[a]						
	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	F	M	F	M	F
Comorbidities	DLP	DM, HTN, DLP	MM, SCT	DM, HTN	SLE, HTN, DM, obesity	DM	DM
COVID-19 treatment	REM	REM	REM	REM	REM	None	REM
Notable COVID-19 complications	PE	DVT, PTX	No	PE	No	No	No
Antecedent treatment with steroids	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clinically relevant antecedent positive culture data	None	S. warneri (blood) E. faecalis (blood)	MRSA (blood, resp) VRE (blood)	C. pelliculosa (blood)	S. saprophyticus (blood) S. aureus (resp)	MRSA (resp, blood) E. coli (resp) E. faecalis (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[b]	Yes	No	No	Yes	No	No	No
Critically ill[c]	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 debridement	Blood	Blood
C. auris treatment	MIC, line removal	NA	MIC, AMB, line removal	NA	NA	NA	MIC, line removal
Candidemia duration (outcome)	Single episode, 13 days (resolved)	NA	First episode 2 days, second episode 3 days (resolved)	NA	NA	NA	Single episode, 3 days (resolved)
Disposition	DC	EXP	EXP	EXP	DC	EXP	DC
Connection in space and time to other clinical cases	No	Yes	Yes	Yes	Yes	Yes	Yes

[a]M, 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, pneumothorax; PE, pulmonary embolism; MRSA, methicillin-resistant S. aureus; VRE, vancomycin-resistant enterococcus; resp, respiratory culture. Antimicrobials: 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, levofloxacin; 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.
[b]Experimental trials include avaptadil, mesenchymal stem cell therapy, or convalescent plasma.
[c]"Critically ill" is signified by ICU admission, mechanical ventilation, and/or the use of vasopressor agents.

TABLE 1 (Continued)

Case[a]	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	F	M
	DM, bladder CA	HTN	HTN	HTN, ESRD	None	Obesity, OM	HTN, DM, chronic anoxic brain injury	Abdominal abscess, chronic anoxic brain injury
	REM	REM	REM	None	HCQ	NA	NA	NA
	No	No	No	No	Limb ischemia, PE	NA	NA	NA
	Yes	Yes	Yes	No	No	NA	NA	NA
	E. faecalis (urine)	K. pneumoniae (resp)	MRSA (resp)	S. hominis (blood)	E. cloacae (resp, blood)	S. lugdunensis (wound)	MRSA (resp)	P. mirabilis (wound)
			K. pneumoniae (resp)	VRE (resp)	S. maltophilia (resp)	P. aeruginosa (wound)	P. aeruginosa (resp, urine); K. pneumoniae (resp, urine, blood)	E. faecalis (wound)
	CFP, VAN, MER	CTX, CFP, AZI, LZD, MER	CTX, CFP, AZI, LZD, MER, VAN	CFP, VAN, LZD, LFN, MIC	P-T, LZD, MER, VAN, LFN	CFP, VAN	P-T, VAN, C-T, ERT, LFN, M-V	CFP, MET, P-T, VAN, ERT, DAP
	No	Yes	Yes	No	No	NA	NA	NA
	Yes	Yes	Yes	Yes	Yes	No	Yes	No
	32	12	28	20	33	0	123	55
	Urine	Resp	Blood	Blood	Wound	Catheter tip	Blood	Wound
	NA	NA	MIC, line removal	MIC	MIC	NA	MIC	NA
	NA	NA	Single episode, 5 days (resolved)	Single episode, 3 days (resolved)	NA	NA	Single episode, 2 days (resolved)	NA
	DC	EXP	EXP	DC	DC	DC	EXP	DC
	Yes	Yes	Yes	Yes	Yes	No	Yes	No

A)

B)
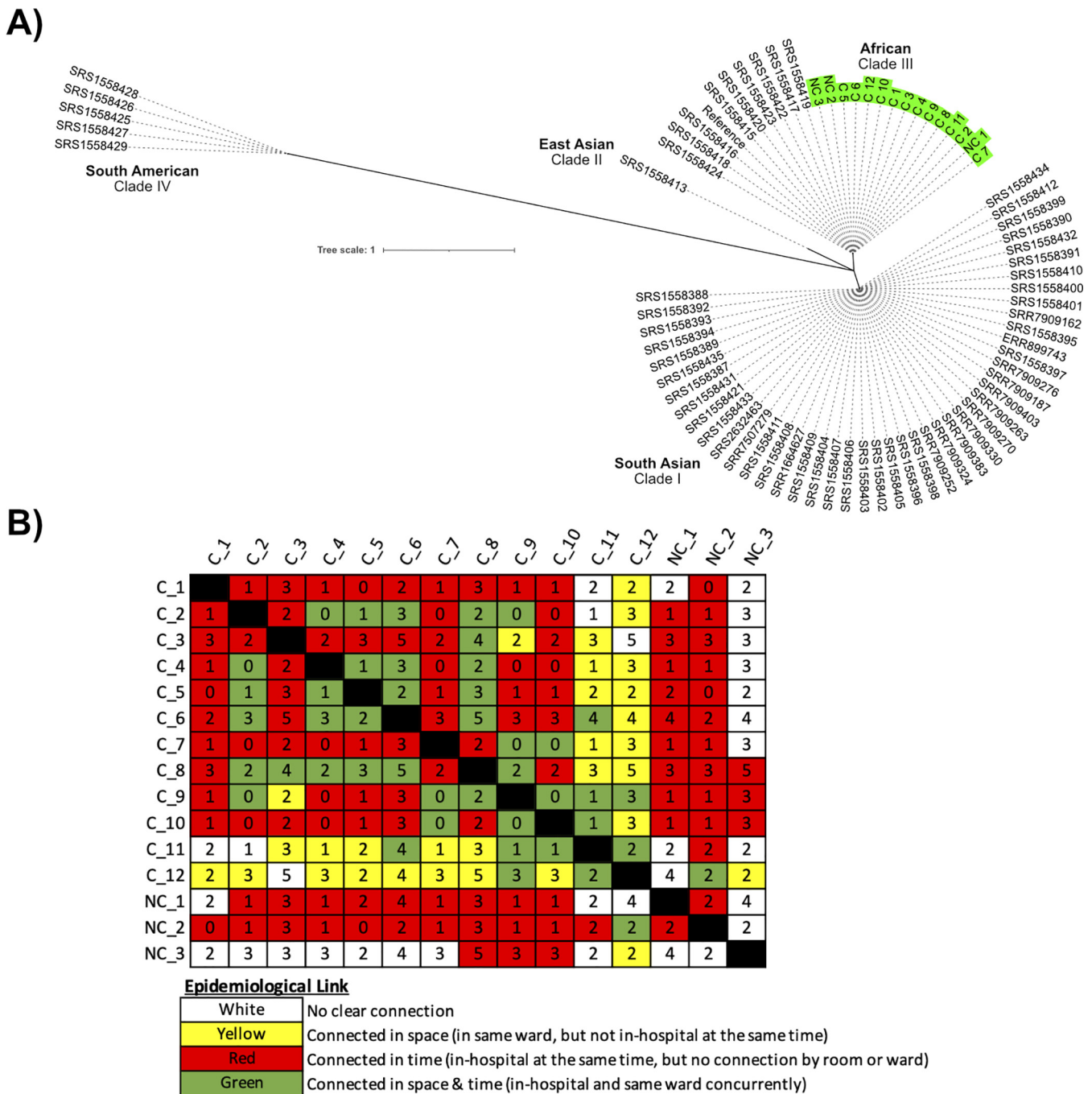
FIG 1 (A) Phylogenetic tree of *Candida auris* isolates (green) with 61 globally representative isolates demonstrating the four major *C. auris* clades. Outbreak isolates cluster with the African clade isolates. (B) Molecular epidemiological link between isolates and SNP distances between all isolates. The axes show a reciprocal list of the 15 outbreak isolates, and each cell represents the intersection between two isolates to show the epidemiological link (color) and the number of SNPs observed between the two isolates. Isolates demonstrating a common ancestor and putative transmission have either an epidemiologic link and/or a small number of SNPs. All isolates differ by ≤5 SNPs relative to the internal reference isolate NC_1, suggesting all isolates share a single common ancestor, and spread was due to either interpatient transmission or a point-source outbreak.

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*.

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