EMERGING INFECTIOUS DISEASES: CANDIDA AURIS

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BASIC CONCEPTS IN DISEASE EMERGENCE

- Emergence of infectious diseases is complex
- Infectious diseases are dynamic
- Most new infections are not caused by genuinely new pathogens
- Agents involved in new and reemergent infections cross taxonomic lines
- The concept of the microbe as the cause of disease is inadequate and incomplete
- Human activities are the most potent factors driving disease emergence
- Social, economic, political, climatic, technologic, and environmental factors shape disease patterns and influence emergence
- Understanding and responding to disease emergence require a global prospective, conceptually and geographically
- The current global situation favors disease emergence



WHO LIST OF PRIORITY DISEASES, 2015 CDC BACTERIA AND FUNGI LISTED IN 2019 AR THREAT REPORT

- Arenaviral hemorrhagic fevers (including Lassa Fever)
- Crimean Congo Haemorrhagic Fever (CCHF)
- Filoviral diseases (including Ebola and Marburg)
- Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
- Other highly pathogenic coronaviral diseases (such as Severe Acute Respiratory Syndrome, (SARS)
- Nipah and related henipaviral diseases
- Rift Valley Fever (RVF)
- Severe Fever with Thrombocytopenia Syndrome (SFTS)
- Zika

- Urgent Threats: Carabpenem-resistant *Acinetobacter, Candida auris*, *Clostridioides difficile*, CRE, Drug resistant N. *gonorrhoeae*
- Serious Threats: Drug resistant Campylobacter, drug resistant Candida, ESBL producing Enterobacterales, VRE, MDR-P. aeruginosa, drug resistant Salmonella, drug resistant Salmonella serotype Typhi, drug resistant Shigella, MRSA, drug resistant S. pneumoniae, drug resistant M. tuberculosis
- Concerning Threats: Erythromycin resistant Group A
 Streptococcus, Clindamycin resistant Group B *streptococcus*
- Watch List: Azole resistant *Aspergillus fumigatus*, drug resistant Mycoplasma genitalium, drug resistant *Bordetella pertussis*

CANDIDA AURIS: AN OVERVIEW, CDC

- Candida auris is an emerging fungus that presents a serious global health threat for the following reasons:
 - *C. auris* is spreading geographically and increasing in incidence.
 - C. auris may colonize patients for months to years (no method of decolonization). Infection (usually candidemia) has a high mortality (~60%).
 - It is often multidrug-resistant (e.g., echinocandins, triazoles, polyene {amphotericin B}). Some strains are resistant to all three available classes of antifungals.
 - It is difficult to identify with standard laboratory methods, and it can be misidentified in labs without specific technology. Misidentification may lead to inappropriate management.
 - It has caused multiple outbreaks in healthcare settings. For this reason, it is important to quickly identify *C. auris* in a hospitalized patient so that healthcare facilities can take special precautions to stop its spread.
- May 11, 2021: Updated Tracking *C. auris* to include historical and current U.S. interactive maps and downloadable datasets
- July 19, 2021: Environmental Protection Agency (EPA) has created List P, a list of EPA-registered disinfectants effective against C. auris
- Current needs: (1) rapid diagnostics; (2) new drugs; (3) decolonization methods; (4) registered, easy to use and effective disinfectants;
 (5) other tools or protocols for treatment and prevention

https://www.cdc.gov/fungal/candida-auris/index.html https://www.cdc.gov/fungal/candida-auris/researchers-and-industry-professionals.html



CANDIDA AURIS: EPIDEMIOLOGY



Fig 2. Countries with reported cases of *C. auris* infection or colonization from January 2009 to June 2020. (A) Number of countries belonging to each continent that have reported infection or colonization with *C. auris*. (B) Countries with reported cases from January 2009 to June 2020. The first reported case from each country is denoted in red text. ARE, United Arab Emirates; AUS, Australia; AUT, Austria; BEL, Belgium; BGD, Bangladesh; CAN, Canada; CHE, Switzerland; CHL, Chile; CHN, China; COL, Colombia; CRI, Costa Rica; DEU, Germany; EGY, Egypt; ESP, Spain; FRA, France; GBR, United Kingdom; GRC, Greece; IND, India; IRN, Iran; ISR, Israel; ITA, Italy; JPN, Japan; KEN, Kenya; KOR, Korea (South); KWT, Kuwait; MYS, Malaysia; NLD, the Netherlands; NOR, Norway; OMN, Oman; PAK, Pakistan; PAN, Panama; POL, Poland; RUS, Russia; SAU, Saudi Arabia; SDN, Sudan; SGP, Singapore; THA, Thailand; USA, United States of America; VEN, Venezuela; ZAF, South Africa.

https://doi.org/10.1371/journal.ppat.1008921.g002





Fig 4. Five clades of C. auris. The phylogenic tree was generated with the program RAxML v7.3.2 using SNPs. The GTR model, gamma distribution, and 1,000 bootstraps were used to construct the phylogenetic relationships. The MTL are also included for each clade. CHN, China; COL, Colombia; DEU, Germany; GBR, United Kingdom; GTR, generalized time reversible; IND, India; IRN, Iran; JPN, Japan; KOR, Korea (South); MTL, mating type loci; NLD, the Netherlands; PAK, Pakistan; RUS, Russia; SGP, Singapore; SNPs, single-nucleotide polymorphisms; USA, United States of America; VEN, Venezuela describe the country where the strain was first isolated; ZAF, South Africa.

On the emergence, spread and resistance of *Candida auris*: host, pathogen and environmental tipping points



Chakrabarti A, Sood P. J Med Microbiol 2021;70:001318

Potential host-pathogen-environmental factors driving the emergence and spread of *C. auris*. (a) Environmental degradation caused by deforestation, expanded land use, industrial farming, aquaculture, human travel and climate change have probably disrupted and amplified the environmental niche of C. auris, bringing it closer to humans. An exponential increase in antimicrobial use in medicine, agriculture, animal husbandry and industry (white arrows) have also likely induced C. auris to acquire multiple resistance mechanisms. (b) Critically ill patients exposed to multiple invasive procedures and broad spectrum antimicrobials are increasing in our hospitals and are susceptible to C. auris. Within hospitals C. auris contaminates and persists on inanimate surfaces and medical equipment, causing horizontal spread and outbreaks. (c) As a pathogen, C. auris exhibits high-level resistance to antifungals and hospital disinfectants, tolerates temperatures up to 42 °C, resists desiccation, thrives in high-salt environments like human skin and sweat, forms robust biofilms, and switches into azole-resistant aggregative forms. These properties make C. auris a hardy nosocomial pathogen.

CANDIDA AURIS: EPIDEMIOLOGY

- First isolated in 2009 from ear discharge of a female patient in Japan; now reported in >45 countries worldwide
- Healthcare-associated outbreaks common
- Mortality ~65%-70%
- Primarily infects the usual spectrum of compromised individuals including those with uncontrolled diabetes mellitus, chronic renal diseases, neutropenia, and those on immunosuppressive therapy, broad-spectrum antimicrobials, and those with indwelling medical devices, or at extremes of age.
- Causes an array of human diseases ranging from fungemias, surgical/nonsurgical wound infections, urinary tract infections, meningitis, myocarditis, skin abscesses, to bone infections.





TRANSMISSION AND PERSISTENCE OF CANDIDA AURIS

- Colonization of patients
 - Colonization of patients is common; multiple sites involved (Biswal 2017)
- Role of HCP
 - HCP may be colonized; uncommon (Schelenz 2017)
 - HCP hands may transiently carry *C. auris* (Biswal 2017)
- Role of environment
 - Environmental contamination common (Lesho 2018, Biswal 2017, Schelenz 2017, Valladhaneni 2016): mattresses, furniture, sinks, and medical equipment
 - Prolonged environmental survival on environmental surfaces; >14 days (Piedrahita 2017, Welsh 2017)
 - Prolonged survival (>7 days) on contaminated bedding (Biswal 2017)



Hallmarks Making Candida auris a Major Public Health Issue and Proposed Interventions

Hallmark	Threat	Control/Prevention
Increased prevalence, unknown origin	Continuous increase in the future leads to emergence of <i>C. auris</i> as a frequent cause of nosocomial infections	Investigate potential sources/reservoirs, conduct epidemiological surveys in large prospective cohorts
Simultaneous emergence on different continents	Worldwide dissemination leads to pandemics of <i>C. auris</i> infection	Investigate environmental sources/reservoirs
Misidentification by diagnostic laboratories	Lack or delayed recognition of clinical cases leads to occult outbreaks	Improve development and access to new diagnostic tools (MALDI-TOF mass spectrometry, molecular techniques), improve training of laboratory personnel
Biofilm formation, persistence/survival in the environment	Interhuman transmission leads to nosocomial outbreaks	Screen patients, create hospital hygiene plans (isolation/disinfection), improve decontamination of surfaces (sporicidal agents)
Antifungal resistance (intrinsic or rapidly inducible)	Emergence of multidrug- or pan-drug-resistant strains leads to outbreaks with high mortality rate	Limit antifungal drug overuse, develop of novel antifungal therapies

Abbreviation: MALDI-TOF, matrix-assisted laser desorption ionization-time of flight.

Lamoth F, Kontoyiannis DP. JID 2018;217:516



C. auris SURVEILLANCE, WORLDWIDE & US (CDC)



Chakravbarti A, Sood P. J Med Microbiol 2021;70:001318

C. auris tracking data

Filters



Cases through 31 December 2022



Number of C. auris clinical cases through December 31, 2022

In the most recent 12 months, there were 2,377 clinical cases and 5,754 screening cases (January 2022 - December 2022).

\bigcirc 0 clincial cases and at least 1 screening case	💛 1 to 10
0 11 to 50	😑 51 to 100
0 101 to 500	🛑 501 to 1000
1001 or more	

International Multicentre Study of Candida auris Infections

- Retrospective observational multicentre study, 10 centers, 5 countries
- Significant risk factors for *C. auris* infection include the age group of 61–70 years (39%), recent history of ICU admission (63%), diabetes (63%), renal failure (52%), presence of CVC (91%) and previous history of antibiotic treatment (96%). *C. auris* was commonly isolated from blood (76%).
- All-cause crude mortality rate after 30 days was 37%. Antifungal therapy was associated with a reduction in mortality (OR:0.27) and so was source removal (OR:0.74). Contact isolation precautions were followed in 87% patients.

Risk Factor	Group-1 (Expired Patients)	Group-2 (Patients with Other Outcome)	Odds Ratio
Renal failure	67%	40%	3.0
Congestive Heart Failure	46%	17%	4.23
Invasive ventilator	75%	63%	1.74
Haemodialysis	63%	17%	8.33
Total parenteral Nutrition	33%	13%	3.25
Central Venous Catheter	100%	83%	4.60
Candidemia	88%	67%	3.5
Bacterial co-infection	58%	40%	2.1

Table 4. Analysis to determine the risk factors for mortality among C. auris cases.



Table 2. Time from admission to positive culture.

No. of Days	Patient No.	Patient %
≤2 days	5	9%
3–7 days	8	15%
8–14 days	8	15%
15–30 days	17	31%
>1 month	16	30%

Pandya N, et al. J Fungi 2021;7:878

CANDIDA AURIS: COLONIZATION SITES

Extended Data



Extended Data Fig. 1 |. Map of sample sites. We surveyed 10 body sites per subject, including the anterior nares (N), tracheostomy site (Tc), anterior neck (Ne), palms/fingertips (Fg), buccal mucosa/tongue (Bu/To), inguinal crease (Ic), axilla (Ax), toe web (Tw), external auditory canal (Ea), and peri-anal skin (An)



Extended Data Fig. 2 |. Patterns of body site colonization visualized with UpSetR. Colors map to degree, a measure of the number of co-colonized sizes. A total of 36 distinct co-colonization patterns were observed, each arranged from the left to the right as a function of decreasing degree. The intersection size is the number of subjects whose body-site colonization matches the points connecting sites for each of the 36 unique co-colonization patterns. For example, the nares (N) and fingertips/palm (Fg) are more frequently monocolonized than any of the other sites while the buccal mucosa/tongue (Bu/To), neck (Ne), tracheostomy site (Tc), and external auditory canal (Ea) are never mono-colonized. Most patients have a distinct pattern of co-colonization with the most frequent pattern being singular colonization for each site for the first time point.

Proctor DM, et al. Nat Med 2021:27:1401-1409

CANDIDA AURIS: COLONIZATION SITES

TABLE 1

Hospital ICU	Start	End month	Total days screened	Admissions screened	No	se	Thre	oat	Axi	lla	Gro	oin	Perin	eum	Rect	um	Uri	ne
	month		n	n	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Hospital A	May 2017	July 2017	55	154	142	92	142	92	146	95	141	92	137	89	137	89	124	81
Hospital B	June 2017	Mar 2018	284	97	90	93	0	0	90	93	80	82	80	82	80	82	46	47
Hospital C	July 2017	Sep 2017	65	76	58	76	54	71	25	33	10	13	18	24	58	76	46	61
Hospital D	July 2017	Sep 2017	64	169	133	79	133	79	135	80	28	17	134	79	129	76	112	66
Hospital E	Aug 2017	Apr 2018	267	98	76	78	0	0	76	78	72	73	72	73	72	73	55	56
Hospital F	Oct 2017	Jan 2018	92	168	143	85	0	0	143	85	135	80	135	80	135	80	116	69
Hospital G	Dec 2017	Mar 2018	81	191	180	94	177	93	177	93	172	90	169	88	0	0	163	85
Hospital H	Jan 2018	Feb 2018	23	45	28	62	28	62	27	60	0	0	28	62	27	60	22	49
Total	NA	NA	NA	998	850	85	534	54	819	82	638	64	773	77	638	64	684	69

Candida auris screening activity by hospital and body site tested, England, 2017–2018 (n = 998)

ICU: intensive care unit; NA: not applicable.



ENVIRONMENTAL SURVIVAL OF CANDIDA AURIS



Piedrahita C, et al. ICHE 2017;38:1107-1109

Welsh RM, et al. J Clin Microbiol 2017;55:2996-3005

NOSOOCOMIAL OUTBREAK OF C. auris

(Biswal M, et al. JHI 2017;97:363-370)



Figure 3. Time to Candida auris acquisition after intensive care unit admission.

Colonization rate by Candida auris of different body sites

Contamination of Candida auris on environmental samples and carriage on healthcare workers' hands

Samples	MICU	CCU	Trauma ICU	NSW
Environmental				
No. of samples	68	10	189	37
C. auris-positive	7	0	17	0
samples				
Handwash samples (H	ICWs)			
No. of samples	41	13	79	12
C. auris-positive	2	0	2	0
samples				

MICU, medical intensive care unit; CCU, cardiac care unit; ICU, intensive care unit; NSW, neurosurgical ward; HCW, healthcare worker.

Site	Oral	Rectal	Axilla	Groin	
Trauma ICU					
No. of samples	89	83	158	168	
Growth of C. auris	4 (4.4%)	15 (18%)	62 (39.2%)	34 (20.2%)	
MICU					
No. of samples	38	35	38	38	
Growth of C. auris	6 (15.7%)	3 (8.5%)	10 (26.3%)	2 (5.2%)	
Total	10/95 (10.5%)	18/118 (15.2%)	72/196 (36.7%)	36/206 (17.4%)	

ICU, intensive care unit; MICU, medical intensive care unit.

First hospital outbreak of the globally emerging *Candida auris* in a European hospital



CDC

- The risk of *C. auris* infection to otherwise healthy people, including healthcare personnel, is very low.
- At this time, HCP do not need to be tested for *C. auris* unless they are identified as a possible source of transmission to patients

https://www.cdc.gov/fungal/candida-auris/c-auris-health-qa.html

• As healthcare workers (HCW) have been implemented in the transmission of other Candida species in the past we have undertaken an extensive staff screening program involving doctors, nurses, physiotherapists, catering and cleaning staff, dieticians, a Chaplin and ward administrators. Staff hands (agar impression plates), nose, axilla, groin and throat swabs were analyzed for the presence of Candida. Only one out of 258 HCW screened were found to have a C. auris positive nose swab (all other samples were negative). This nurse had been caring for a heavily C. auris colonized patient. After a five day decolonization protocol with chlorhexidine washes, nasal ointment and oral nystatin medication (as described below) repeat microbiology samples were negative suggesting transient carriage only

Schelenz S, et al. Antimicrob Resistant Infect Control 2016;5:35

Characteristics of clade-III *Candida auris* colonization and infection in southern California, 2019–2022

- Background: 5 clades clade 1 = highest frequency of antifungal resistance; clades I, III, and IV = frequency associated with outbreaks
- 45 patients identified from late 2019 to early 2022 in CA (mortality = 18%)
- Most had tracheostomy or were from facility with known outbreak, 15% identified through passive surveillance
- 8 (18%) had a history of COVID-19
- 13 (29%) had bloodstream infection (likely to have central line)



Fig. 2. Timeline and positive C. auris cases identified by either active or passive surveillance

De St. Maurice A, et al. ICHE 2022;1-9

Table 2. Characteristics of Patients (n=13) with Invasive C. auris

Characteristic	No. (%)
Comorbidities	13 (100)
Chronic respiratory failure	8 (61)
End-stage renal disease	4 (31)
Diabetes	9 (69)
Cirrhosis	1 (8)
Malignancy	1 (8)
Known history of C. auris prior to infection	8 (62)
Received treatment for C. auris infection	12 (92) ^a
C. auris antifungal treatment	
Caspofungin	11 (85)
Anidulafungin	1 (8)
Liposomal amphotericin ^b	1 (8)
Site of infection	
Blood	9 (69)
Urine	3 (23)
Pleural fluid	3 (23)
Tracheal aspirate	2 (15)
Wound	2 (15)

^aFor 1 patient, the blood culture grew C. *auris* after the patient died; therefore, the patient did not receive treatment.

^bOne patient received combination therapy with caspofungin and liposomal amphotericin.

C. auris and COVID-19

Systematic review of *C. auris* in COVID-19 infections, 1/20/20 to 31/12/21

Prevalence = 14%; Mortality = 44.4% (candidemia = 64.7%)





FIGURE 3 Forest plot of pooled prevalence of *Candida auris* infections in COVID-19 patients. "Frequency" denotes total number of *C. auris* cases and "Total" denotes total number of COVID-19 infected patients. References are given in square brackets. Abbreviations: C.I, Confidence Interval



FIGURE 4 Forest plot of pooled survival estimates of (A) Candida auris non-candidemia/colonised (CANC) and (B) Candida auris candidemia (CAC) cases in COVID-19 patients. "Frequency" denotes total number of patients survived with C. auris infections and "Total" denotes total number of C. auris cases reported in each study. References are given in square brackets. Abbreviations: C.I, Confidence Interval

TABLE 3 Underlying disease and iatrogenic risk factors associated with mortality in Candida auris non-candidemia/colonised (CANC) and Candida auris candidemia (CAC) cases

Underlying disease ^a and latrogenic risk factors	Candida auris non- candidemia (CANC) ^b (n)	Candida auris candidemia (CAC) ^b (n)	Death in CANC group (n)	Death in CAC group (n)	p value
Diabetes mellitus	11	12	2	9	.012*
Hypertension	10	17	3	12	.056
Central venous catheter	19	27	3	18	.0009
Intensive care unit (ICU) stay	27	33	6	22	.0008
Broad spectrum antibiotics	26	34	5	22	.0000
Mechanical ventilation	22	24	5	18	.0009*
Steroid therapy	24	27	5	20	.0002
Urinary catheter	17	19	3	13	.0031
Co-infections along with C. auris	13	20	5	15	.067
Previous antifungal therapy	12	7	0	4	.009*

Note: The values in the table are expressed in numbers (n). 'n' denotes the total number of patients. ^{*} 'p' values <.05 were considered significant. Abbreviations: CAC, *Candida auris* candidemia; CANC, *Candida auris* non-candidemia/colonised.

^aUnderlying disease and mortality association was statistically analysed for diabetes mellitus and hypertension alone. The number of cases for in other underlying diseases were less (refer Table 1), hence no statistical analysis was performed.

^bThe data for underlying diseases and iatrogenic risk factors of CANC and CAC cases were extracted from 10 studies.^{13,14,16,22-28}

Vinayagamoorthy K, et al. Mycoses 2022;65:631-624

DIAGNOSIS AND TREATMENT: OVERVIEW

- Sites for screening cultures = Axilla and groin
 - Screening recommended in healthcare facilities is index patient not isolated of patients in close proximity
 - Patients hospitalized abroad of \geq 1 day within past 12 months
- *C. auris* grows on bacterial media (chocolate and blood); *C. auris* grows on most fungal media (Sabouraud dextrose agar preferred), with the exception of mycobiotic agar (inhibited by cycloheximide)
- Fungitell assay, which looks for β-D-Glucan in serum, has a lower sensitivity for *C. auris* candidemia than other *Candida* species in limited studies(43-60%)
- Isolates of C. auris can be readily identified by MALDI-TOF but may be misidentified by Vitek 2 YST, API 20C, API ID 32C, BD Phoenix yeast identification system, MicroScan, and RapID yeast Plus
- Antifungal Susceptibility Testing
 - There are currently no established *C. auris* specific breakpoints
 - CDC has suggested MIC breakpoints based on previous data and interpretations from other related Candida spp.
 - Caspofungin may display an "Eagle effect," which may lead to false resistance interpretations, especially if other echinocandins
 are not tested
- Echinocandin = drug of choice (but resistance possible)







Eagle effect

https://doi.org/10.1016/j.tim.2018.10.007

Tools for Detecting a "Superbug": Updates on *Candida auris* Testing

TABLE 1 Methods for identification or isolation of Candida auris

Test type and details	Notes ^a	Reference(s)
Culture		
Original enrichment broth	Valuable reference method for diagnostic development	30
Chromogenic medium	Aids visual identification to the species level of the common Candida spp.	24, 26, 27
Other differential media	Use of Pal's medium, ferrous sulfate, and crystal violet	25, 28, 29
Biochemical tests		
API 20C AUX	Cannot currently identify C. auris; see CDC follow-up algorithm	12, 15, 16
API ID 32C	Cannot currently identify C. auris; see CDC follow-up algorithm	12
BD Phoenix	Cannot currently identify C. auris; see CDC follow-up algorithm	12
MicroScan	Cannot currently identify C. auris; see CDC follow-up algorithm	12
RapID yeast plus	Cannot currently identify C. auris; see CDC follow-up algorithm	
Vitek 2 YST	Can ID some but not all C. auris; see CDC follow-up algorithm	17
MALDI-TOF MS		
Bruker Biotyper 2.0 Microflex LT	FDA approved for isolate ID with CA System library (v4)	20
bioMérieux Vitek MS	FDA approved for isolate ID with IVD library v3.2	19
Blood culture, molecular		
BioFire BCID2	FDA approved for positive blood culture	
GenMark Dx ePlex BCID-FP panel	FDA approved for positive blood culture	58
RT-PCR		
TaqMan chemistry	Most common LDT for colonization screening in U.S. PHL	41, 52
SYBR green chemistry	Evaluated for skin and anterior nares	39, 42
Commercial RT-PCR kits		
AurisID, OLM Diagnostics	CE-IVD reagents for C. auris RT-PCR	47
BioGX Candida auris	RUO reagents supporting RT-PCR and extraction on BD Max platform	
Fungiplex Candida auris	RUO reagents for C. auris RT-PCR	47
Other		
LAMP	Unique molecular method for C. auris detection	40
T2MR C. auris	RUO test for C. auris using T2 magnetic resonance technology	50
Conventional PCR with GPI target	C. auris specific and multiplex tests feasible in low-resource settings	36-38

^oID, identification; LDT, laboratory-developed test; RUO, research use only; PHL, public health laboratories; CE-IVD, *in vitro* diagnostic approved for sale in the European Union; RT-PCR, real-time PCR.



FIG 1 *Candida auris* after 48 h of growth on CHROMagar Candida plus showing light blue colonies with a blue halo around the colonies. The combination of the color and the halo are distinct for *C. auris* (also see reference 22).

Lockhart SR, et al J Clin Microbiol 2022;60:1



Antifungal Susceptibility Testing and Interpretation

Antifungal Susceptibility Testing and Interpretation

All *Candida auris* isolates should undergo antifungal susceptibility testing according to CLSI guidelines. Although *C. auris* is commonly multidrug resistant, levels of antifungal resistance can vary widely across isolates.

There are currently no established *C. auris*-specific susceptibility breakpoints. Therefore, breakpoints are defined based on those established for closely related *Candida* species and on expert opinion. Correlation between microbiologic breakpoints and clinical outcomes is not known at this time. For this reason, the information below should be considered as a general guide and not as definitive breakpoints for resistance. Please note that a finding of an elevated minimum inhibitory concentration (MIC) for an antifungal drug should not necessarily preclude its use, especially if the use of other antifungal drugs for the patient has been ineffective.

Triazole Class Drugs	Tentative MIC Breakpoints (µg/mL)	Comment
Fluconazole	≥32	Modal minimum inhibitory concentration (MIC) to fluconazole among isolates tested at CDC was \geq 256; isolates with MICs \geq 32 were shown to have a resistance mutation in the <i>Erg11</i> gene, making them unlikely to respond to fluconazole.
Voriconazole and other second generation triazoles	N/A	Consider using fluconazole susceptibility as a surrogate for second generation triazole susceptibility assessment. However, isolates that are resistant to fluconazole may respond to other triazoles occasionally. The decision to treat with another triazole will need to be made on case-by- case basis.

Polyene Class Drug	Tentative MIC Breakpoints (µg/mL)	Comment
Amphotericin B	≥2	Recent pharmacokinetic/pharmacodynamic analysis of <i>C. auris</i> in a mouse model of infection indicates that under standard dosing, the breakpoint for amphotericin B should be 1 or 1.5, similar to what has been determined for other <i>Candida</i> species. Therefore, isolates with an MIC of \geq 2 should now be considered resistant. If using Etest for amphotericin B and an MIC of 1.5 is determined, that value should be rounded up to 2.

Echinocandin Class Drugs	Tentative MIC Breakpoints (µg/mL)	Comment
Anidulafungin	≥ 4	Tentative breakpoints are based on the modal distribution of echinocandin MICs of approximately 100 isolates from diverse geographic locations.
Caspofungin	≥ 2	
Micafungin	≥ 4	

Based on these MIC breakpoints, many isolates are resistant to multiple classes of drugs. Some U.S. *C. auris* isolates have been found to be resistant to all three classes of antifungal drugs. We have received reports of pan-resistance found in other countries as well. In the United States, about 90% of *C. auris* isolates have been resistant to fluconazole, about 30% have been resistant to amphotericin B, and less than 5% have been resistant to echinocandins. These proportions may include multiple isolates from the same individuals and may change as more isolates are tested.

https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html

Notes from the Field: Transmission of Pan-Resistant and Echinocandin-Resistant *Candida auris* in Health Care Facilities; TX and the DC, January–April 2021

- Candida auris is an emerging, often multidrug-resistant yeast that is highly transmissible, resulting in health care-associated outbreaks, especially in long-term care facilities. Skin colonization with *C. auris* allows spread and leads to invasive infections, including bloodstream infections, in 5%–10% of colonized patients. Three major classes of antifungal medications exist for treating invasive infections: azoles (e.g., fluconazole), polyenes (e.g., amphotericin B), and echinocandins. ~85% of *C. auris* isolates in the US are resistant to azoles, 33% to amphotericin B, and 1% to echinocandins, based on tentative susceptibility breakpoints.
- Pan-resistant *C. auris* isolates have been reported previously, although rarely, from the US and other countries. 3 pan-resistant *C. auris* cases reported in NY developed resistance following echinocandin treatment and lacked epidemiologic links or common health care, suggesting that resistance resulted from antifungal pressure rather than via person-to-person transmission. Since January 2021, however, the Antibiotic Resistance Laboratory Network has detected independent clusters of pan-resistant or echinocandin-resistant cases in Texas and the District of Columbia (DC). Each cluster involved common health care encounters and no known previous echinocandin exposure, suggesting transmission of pan- and echinocandin-resistant strains for the first time in the US.
- Among 101 clinical and screening cases of *C. auris* in DC during Jan–April 2021, 3 had an isolate that was pan-resistant.
- Among 22 clinical and screening cases of *C. auris* in TX during the same period, two were pan-resistant and five were resistant to both echinocandins and fluconazole.
- C. auris plus COVID-19 patients (N=41): resistance was noted in 33 isolates (80.5%) to fluconazole (MIC ≥ 32 mg/L), followed by 19 (46.3%) to amphotericin B (MIC ≥ 2 mg/L), 5 (12.8%) to caspofungin (MIC ≥ 2 mg/L), 2 (5.1%) to anidulafungin (MIC ≥ 4 mg/L), 1 (3.7%) to micafungin (MIC ≥ 4 mg/L), and 7 (43.8%) to 5-flucytosine (MIC ≥ 32 mg/L). Voriconazole non-susceptibility (MIC ≥ 2 mg/L) was observed in 12 (29.3%) C. auris isolates*

Lyman M, et al. MMWWR 2021;70:1022-1023; *Vinayagamoorthy K, et al. Mycoses 2022;65:613



Treatment and Management of *C. auris* Infections and Colonization, CDC

- Consultation with an infectious disease specialist is highly recommended when caring for patients with *C. auris* infection.
- Even after treatment for invasive infections, patients generally remain colonized with C. auris for long periods, and perhaps indefinitely.
- Adults and children ≥ 2 months of age: Based on the limited data available to date, an echinocandin drug at a dose listed below is
 recommended initial therapy for treatment of *C. auris* infections. Most strains of *C. auris* found in the US have been susceptible to
 echinocandins although reports of echinocandin or pan-resistant cases are increasing. This organism appears to develop resistance
 quickly. Patients on antifungal treatment should be carefully monitored for clinical improvement. Follow-up cultures and repeat
 susceptibility testing should be conducted. Both recurrent and persistent *C. auris* bloodstream infections have been documented.
- Switching to a liposomal amphotericin B (5 mg/kg daily) could be considered if the patient is clinically unresponsive to echinocandin treatment or has persistent fungemia for >5 days. Data are lacking about the most appropriate therapy for pan-resistant strains. Combination antifungal treatment yielded promising results in laboratory testing but has not been evaluated in clinical settings. Investigational drugs (Fosmanogepix, Ibrexafungerp) have been tried against *C. au*ris and may be considered for patients with echinocandin-resistant isolates

https://www.cdc.gov/fungal/candida-auris/c-auristreatment.html

Adult dosing	Pediatric dosing
loading dose 200 mg IV, then 100 mg IV daily	not approved for use in children
loading dose 70 mg IV, then 50 mg IV daily	loading dose 70mg/m²/day IV, then 50mg/m²/day IV (based on body surface area)
100 mg IV daily	2mg/kg/day IV with option to increase to 4mg/kg/day IV in children at least 40 kg
	loading dose 200 mg IV, then 100 mg IV daily loading dose 70 mg IV, then 50 mg IV daily

Susceptibility of *C. auris* and *C. albicans* to 21 germicides used in healthcare facilities

- Goal: Assess susceptibility of *C. auris* to germicides
- Methods: Disc-based quantitative carrier testing
- Results: All of the FDA-cleared high-level disinfectants have a registration claim >1 minute (e.g., 8–45 minutes). In summary, with the exception of a water-based QAC and a 1:50 dilution of sodium hypochlorite, our data demonstrate that most disinfectants (10 of 13, 77%) used in healthcare facilities are effective (>3-log₁₀ reduction) against *C. auris*.

Rutala WA, et al.	ICHE 2019;40:380-382

Germicide name	Manufacturer, Location	Active Ingredient	Formulation Tested	Classification	C. auris ^a	C. albicansª
Purell Advanced instant hand sanitizer	GOJO, Akron, OH	70% ethanol	Undiluted	Antiseptic	4.0	2.5
Betadine solution	Purdue Products, Stamford, CT	10% povidone-iodine/1% iodine	Undiluted	Antiseptic	2.5	2.3
Medicated Soft 'N Sure	Steris, St. Louis, MO	0.5% triclosan	Undiluted	Antiseptic/Handwash	1.4	1.7
Soft Care Defend	Diversey, Charlotte, NC	1% chloroxylenol	Undiluted	Antiseptic/Handwash	2.8	3.9
Avagard	3M, St Paul, MN	1% chlorhexidine gluconate solution, 61% ethyl alcohol	Undiluted	Antiseptic/Surgical hand scrub	2.0	1.9
Scrub-Stat 2%	Ecolab, St Paul, MN	2% chlorhexidine gluconate solution	Undiluted	Antiseptic/Surgical hand scrub/handwash	1.6	2.8
Scrub-Stat 4%	Ecolab, St Paul, MN	4% chlorhexidine gluconate solution	Undiluted	Antiseptic/Surgical hand scrub/handwash	1.9	3.5
Isopropyl rubbing alcohol 70% USP	Medichoice, Mechanicsville, VA	70% isopropyl alcohol	Undiluted	Antiseptic/Disinfectant	3.8	4.1
Solution of hydrogen peroxide 3% USP	Medichoice, Mechanicsville, VA	3% hydrogen peroxide	Undiluted	Antiseptic	1.4	1.8
Austin's A-1 bleach 1:10	James Austin Co, Mars, PA	5.25% sodium hypochlorite (~6,100–6,700 ppm)	1:10 dilution	Disinfectant	4.1	4.0
Austin's A-1 bleach 1:50	James Austin Co, Mars, PA	5.25% sodium hypochlorite (~1,245 ppm)	1:50 dilution	Disinfectant	1.6	1.5
Vesphene IIse	Steris, St Louis, MO	9.09% o-phenylphenol, 7.66% p-tertiary amylphenol	1:128 dilution	Disinfectant	4.1	3.6
Hydrogen peroxide cleaner disinfectant	Clorox, Oakland, CA	1.4% hydrogen peroxide	Undiluted	Disinfectant	4.1	4.1
Lysol disinfectant spray	Reckitt Benckiser, Parsippany, NJ	58% ethanol, 0.1% QAC ^b	Undiluted	Disinfectant	3.8	4.1
A-456 II disinfectant cleaner	Ecolab, St Paul, MN	21.7% QAC ^c	1:256 dilution	Disinfectant	1.7	1.5
Super Sani-Cloth wipe	PDI, Orangeburg, NY	55% isopropyl alcohol, 0.5% QAC ^d	Undiluted ^f	Disinfectant	3.9	4.1
Prime Sani-Cloth wipe	PDI, Orangeburg, NY	28.7% isopropyl alcohol, 27.3% ethyl alcohol, 0.61% QAC ^e	Undiluted ^f	Disinfectant	4.1	4.1

EFFICACY OF ANTISEPTICS AND DISINFECTANTS AGAINST C. AURIS

- Effectiveness of surface disinfectants (level of evidence)
 - Effective: Chlorine <a>1000 ppm (good); hydrogen peroxide 1.4% (moderate); phenolics 5%? (low); alcohols 29.4% (low); peracetic acid 2000 ppm (low)
 - Ineffective: Quats 2% didecyldimethyl ammonium chloride; alkyl dimethyl ammonium chlorides; didecyldimethyl ammonium chloride

Disinfectant	Concentrations tested (contact time in minutes used)	Effective	Level of Evidence	Comments	Reference
Chlorhexidine gluconate	<0.02% (1440), 0.5% (0.5), 2% (2), 4% (3, 180, 1800)	Yes	Good	Most studied antiseptic. Limited clinical evaluation.	Schelenz et al., 2016; Abdolrasouli et al., 2017; Moore et al., 2017; Sherry et al., 2017
Chlorhexidine gluconate in isopropyl alcohol	2%/70% (2)	Yes	Low	In vitro testing only.	Moore et al., 2017
Povidone-iodine	10% (2, 3, 180, 1800)	Yes	Moderate	In vitro testing only.	Abdolrasouli et al., 2017; Moore et al., 2017;
Alcohol	70%	Yes	Low	Limited clinical evaluation.	Biswal et al., 2017

 TABLE 3 | Antiseptics tested against C. auris.

Ku TSN, et al. Frontiers in Microbiol 2018;9:726



List P: Antimicrobial Products Registered with EPA for Claims Against Candida auris (contact times, product dependent)

- Sodium Hypochlorite (1-3 min)
- Hydrogen peroxide and peracetic acid (1-3 min)
- Hydrogen Peroxide, Peracetic Acid and Octoanoic Acid (4 min)
- Dodecylbenzenesulfonic acid (1-1.25 min)
- Isopropyl Alcohol and Quaternary Ammonium Compound (1 min)
- Isopropyl Alcohol, DDAC and ADBAC (2 min)
- Hydrogen Peroxide (1-5 min)
- Quaternary Ammonium Compounds (10 min)
- Sodium dichloro-s-triazinetrione (2 min)
- Ethanol, Isopropyl Alcohol and DDAC (1 min)
- Isopropyl Alcohol and Quaternary Ammonium Compounds (2 min)

Caveats

- List P displays 30 approved products
- All products are ONLY approved for "hard nonporous surfaces"
- Contact times vary by class and specific product
- Products include sprays, wipes and liquids
- Some products are ready to use; others may require dilution
- Per CDC, if products on List P are not accessible or otherwise suitable, interim guidance permits use of an EPA-registered disinfectant active against *C. difficile* (List K)
- Follow manufacturer's use recommendations

https://www.epa.gov/pesticide-registration/list-p-antimicrobial-products-registered-epa-claims-against-candida-auris https://www.cdc.gov/fungal/candida-auris/c-auris-infection-control.html

Key interventions recommended (or to be considered) by select governmental agencies to prevent transmission of *Candida auris*

Agency (country/ region)	Active surveillance population	Hand hygiene	Isolation	Transmission- based precautions	Environmental disinfection	Additional special measures	Reference
Centers for Disease Control and Prevention (USA)	Contacts of newly identified case patients. Patients with an overnight stay in a healthcare facility outside of the USA in the previous year	Alcohol-based hand rub, or soap and water if hands are visibly soiled	Single room or cohorting with another patient with C. auris	Standard and contact precautions, for the duration of colonization, perhaps indefinitely	Use a disinfectant active against <i>Clostridioides</i> <i>difficile</i> spores	Minimize the number of care providers	[91]
Public Health England (UK)	Patients admitted from affected hospitals within the UK or from hospitals in countries reporting outbreaks. Close contacts in intensive care settings or contacts of patients prior to implementation of isolation procedures	Soap and water followed by alcohol-based hand rub	Single room or cohorting for colonized or infected patients or pending screening from high-risk areas		Post-discharge terminal cleaning with sodium hypochlorite disinfectant, with or without no-touch disinfection	Single-use medical equipment; chlorhexidine skin washes for critically ill patients, mouth gargle with chlorhexidine, and topical nystatin and terbinafine at key sites	[92]
European Centre for Disease Prevention and Control (Europe)		-	Single room or cohorting	Contact precautions	Post-discharge terminal cleaning with chlorine-based disinfectants, hydrogen peroxide or other disinfectants with fungicidal activity	Staff cohorting. Single-use equipment or cohorting of equipment among cases	[<mark>61•</mark>]
Centre for Opportunistic, Tropical and Hospital Infections (South Africa)	Routine screening on admission not recommended	Soap and water followed by alcohol-based hand rub	Single room or cohorting	Standard and contact precautions	Environmental cleaning with a chlorine-based disinfectant and consider hydrogen peroxide vapor for no-touch disinfection after terminal cleaning	Off-unit procedures should be scheduled for last case of the day, followed by thorough cleaning	[93]

SUSCEPTIBILITY OF C. auris TO UV

- UV-C efficacy assessed against MRSA, C. auris, Candida sp., and MRSA¹
 - C. auris less susceptible to UV-C than MRSA; similar but slight less susceptible than C. difficile
 - Increasing exposure time (10 to 20 to 30 min) resulted in enhanced killing; at 20 min, >4.5 log₁₀; at 30 min >6 log₁₀
- Pulsed xenon efficacy assess against C. auris²
 - 99.4% reduction in C. auris CFU after 5min at 1m and 99.6% after 10min at 2m
- Killing of *C. auris* by UV-C: Importance of exposure time and distance³
 - Maximal effect of *C. auris* killing found at 30min exposure at 2m (maximal killing, >5 log₁₀). With half the time or twice the distance, efficacy diminished to ~10 and ~50-fold, respectively. At suboptimal exposure times and distance, strains from Japan/Korea more sensitive to UV-C killing than from Venezuela, Spain and India.
- Clade-specific variation in susceptibility of C. auris to UV-C⁴
 - Increased susceptibility of *C. auris* belonging to clades I, II and IV with increasing UV exposure time. *C. auris* isolates susceptible to UV-C were
 mostly nonaggregating, but the isolates that were more resistant to UV exposure formed aggregates.
- Efficacy of relatively low-cost UV-C devices against C. auris⁵
 - Some low-cost devices provided effective decontamination. C. auris from clades III and IV were less susceptible that from clades I and II.
- Inactivation of C. *auris* by UV-C⁶
 - With an organic load (FCS), *C. auris* reduction (log₁₀) were; 4.57 direct line of sight, 2.41 indirect line of sight
- UV-C disinfection using a robot for routine cleaning⁷
 - UV-C inhibited growth of C. auris in the lag phase, but not in the presence of rim shadows; C. auris not effectively killed by standard UV cycle

¹Cadnum JL, et al. ICHE 2018;39:94; ²Maslo C, et al. BMC ID 2019;19:540; 3 de Groot T, et al. Mycoses 2019;62:408; ⁴Chatterjee P, et al. ICHE 2020;41: 1384; ⁵Pearlmutter BS, et al. ICHE 2021, 1-5; ⁶Rutala WA, et al. ICHE 2021, 1-3; 7 Astrid F, et al. Antimicrob Resist Infect Control 2021;10:84



Infection Prevention and Control for Candida auris

- Hand Hygiene: HCP should follow standard hand hygiene practices. Alcohol-based hand sanitizer (ABHS) is the preferred hand hygiene method for *C. auris* when hands are not visibly soiled. If hands are visibly soiled, wash with soap and water.
- Transmission Based Precautions: Private room with bathroom, contact isolation (gloves & gown)
 - Duration of precautions: Patients often remain colonized with *C. auris* for many months, perhaps indefinitely, even after an acute infection (if present) has been treated and resolves. Continue precautions for entire duration of stay.
 - CDC does not recommend routine reassessments for *C. auris* colonization. At this time, no specific intervention is known to reduce or eliminate *C. auris* colonization.
- Disinfection: *C. auris* can persist on surfaces in healthcare environments for days to months.
 - Perform thorough routine (at least daily) and terminal cleaning and disinfection of patients' rooms and other areas where patients receive care (e.g., radiology, physical therapy) using an appropriate disinfectant. Clean and disinfect shared or reusable equipment (e.g., ventilators, physical therapy equipment) after each use. Label cleaned and disinfected equipment as such and store it away from dirty equipment. Data indicate that products solely dependent on quaternary ammonia compounds (QACs) are NOT effective. Use an EPA-registered hospital-grade disinfectant effective against *C. auris* (List P). Consider a "no touch" method (e.g., UV-C) as a supplement to standard disinfection.
- Other: 1) Educate HCP about appropriate precautions; 2) Ensure adequate supplies are available; 3) Monitor compliance with HH & disinfection (provide feedback); 4) Ensure proper signage on door; 5) Flag the patient's record; 6) Consider patient screening and lab surveillance.

https://www.cdc.gov/fungal/candida-auris/c-auris-infection-control.html



UNC Medical Center strategy for control:

- Patient's chart flagged before arrival to UNC Medical Center.
- Service lines caring for the patient have been communicated with directly.
- Infection Prevention has partnered with nursing staff, environmental services, patient transport, ICU transport, house supervisors, patient logistics center and ancillary areas the patient may visit.
- Patient placed on Enteric Precautions to ensure proper room cleaning daily with bleach and bleach + UV upon discharge.
- Alcohol based hand rubs are effective.
- Microbiology lab has been notified and has developed algorithm for identification.



PUBLIC HEALTH SCREENING FOR C. AURIS

- CDC recommendations Consider screening patients who are at high risk for C. auris including:
 - Close healthcare contacts of patients with newly identified *C. auris* infection or colonization.
 - Patients who have had an overnight stay in a healthcare facility outside the US in the previous one year, especially if in a country with documented *C. auris* cases. Strongly consider screening when patients have had such inpatient healthcare exposures outside the US and have infection or colonization with CRE. *C. auris* co-colonization has been observed regularly.
 - Screen roommates at healthcare facilities, including nursing homes, where the index patient resided in the previous month. Ideally, identify and screen roommates of the index patient even if they were discharged from the facility. Consider also screening patients who require higher levels of care (e.g., mechanical ventilation) and who overlapped on the ward or unit with the index patient for 3 or more days, as these patients are also at substantial risk for colonization
 - Screen for *C. auris* colonization using a composite swab of the patient's bilateral axilla and groin. Although patients have been colonized with *C. auris* in the nose, mouth, external ear canals, urine, wounds, and rectum, these sites are usually less sensitive for colonization screening.
- NC DHHS, 2/24/23
 - Screen any inpatient who have had an overnight stay in a healthcare facility outside the U.S. in the past 12mo for *C. auris*.

https://www.cdc.gov/fungal/candida-auris/c-auris-screening.html





C. auris Surveillance



CS316981A

C. auris Surveillance

- PCR testing is available to detect *C. auris* in axilla/groin swabs (colonization screening)
 - Commercial testing is limited at this time
 - AurisID (OLM Diagnostics), BioGX Candida auris, and Fungiplex Candida auris¹
- Currently, colonization screening is performed by public health laboratories in the US
 - NC State Public Health Laboratory does not currently do colonization screening, but our regional Antimicrobial Resistance Laboratory (Maryland) does



Nationally Notifiable Disease Case Definition Changes: C. auris

- Removes presumptive laboratory criteria (e.g., organisms commonly misclassified as *C. auris*), probable/suspect case classifications
- C. auris screening cases nationally notifiable
- Laboratory Criteria for Reporting
 - Detection of *C. auris* in a specimen using either culture or a culture independent diagnostic test (CIDT) (e.g., Polymerase Chain Reaction [PCR])
- Timeframe for 'new' case
 - Screening and clinical cases and only be counted one time per classification
 - An individual can be counted as a clinical case after being counted as a screening case (only one time)

CDC FACT SHEET

Why is *Candida auris* a problem?



It causes serious infections. C. auris can cause bloodstream infections and even death, particularly in hospital and nursing home patients with serious medical problems. More than 1 in 3 patients with invasive C. auris infection (for example, an infection that affects the blood, heart, or brain) die.



It's often resistant to medicines. Antifungal medicines commonly used to treat Candida infections often don't work for Candida auris. Some C. auris infections have been resistant to all three types of antifungal medicines.



It's becoming more common. Although C. auris was just discovered in 2009, it has spread quickly and caused infections in more than a dozen countries.



It's difficult to identify. C. auris can be misidentified as other types of fungi unless specialized laboratory technology is used. This misidentification might lead to a patient getting the wrong treatment.



It can spread in hospitals and nursing homes. C. auris has caused outbreaks in healthcare facilities and can spread through contact with affected patients and contaminated surfaces or equipment. Good hand hygiene and cleaning in healthcare facilities is important because C. auris can live on surfaces for several weeks.

Stopping the spread of *Candida auris*

CDC is working with public health partners, healthcare workers, and laboratories to stop the spread of C. auris in healthcare settings. Here's how CDC is asking everyone to help:



Family members and other close contacts of patients with C. auris

- » Clean your hands with hand sanitizer or soap and water before and after touching a patient with C. auris or equipment in his or her room.
- » Remind healthcare workers to clean their hands.

Laboratory staff, healthcare workers, and public health officials

- » Know when to suspect C. auris and how to properly identify it.
 - » Report cases quickly to public health departments.
 - » For healthcare workers, clean hands correctly and use precautions like wearing gowns and gloves to prevent spread.
 - » Clean patient rooms thoroughly with a disinfectant that works against C. auris.
 - » Investigate C. auris cases quickly and determine additional ways to prevent spread.
 - » Check the CDC website for the most up-to-date guidance on identifying and managing C. auris: https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html.

https://www.cdc.gov/fungal/diseases/candidiasis/pdf/Candida_auris_508.pdf

CONCLUSIONS: CANDIDA AURIS

- *C. auris* is a growing worldwide threat due to high mortality, resistance to many antifungals, and difficulties in laboratory identification
- *C. auris* is capable of prolonged environmental survival; contamination of hospital surfaces is common
- *C. auris* killed by high-level disinfectants but has reduced susceptibility to some low-level disinfectants disinfectants (QACs) and to UV-C (use settings for *C. difficile*); *C. auris* is susceptible to alcohol based antiseptics
- References
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