13th ACCP 2023

Meeting on Antimicrobial Chemotherapy in Clinical Practice (ACCP)

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DOBBIAMO AVER PAURA DI *CANDIDA AURIS* E CAMBIARE L'APPROCCIO TERAPEUTICO?

Dott.ssa Laura Magnasco

Clinica Malattie Infettive
Policlinico San Martino – IRCCS
Genova

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

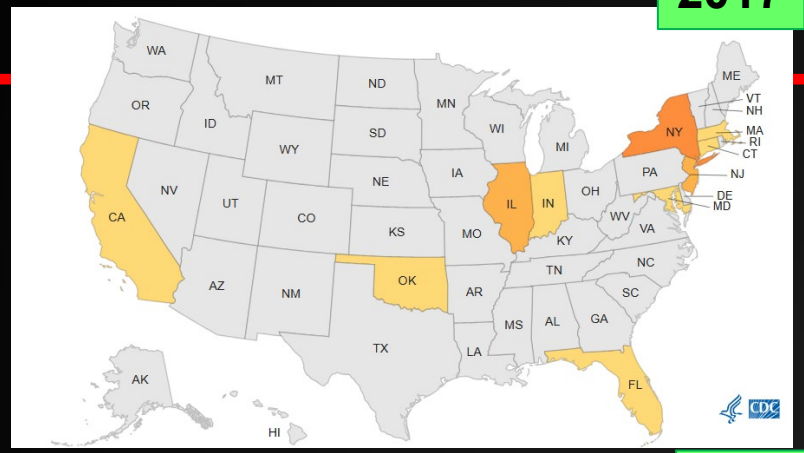
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Conflicts of interest

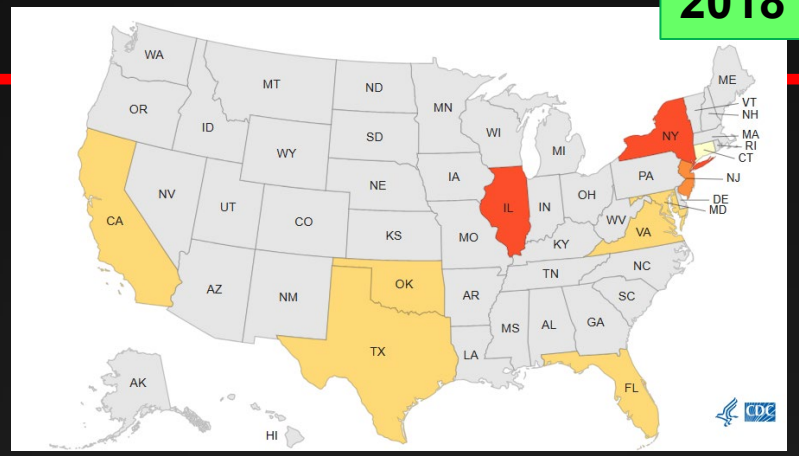
No conflicts of interest to disclose.

An already emerged pathogen

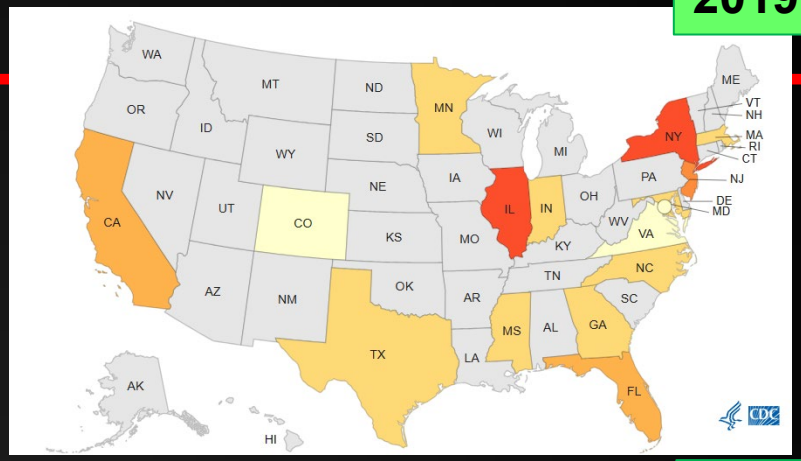
2017



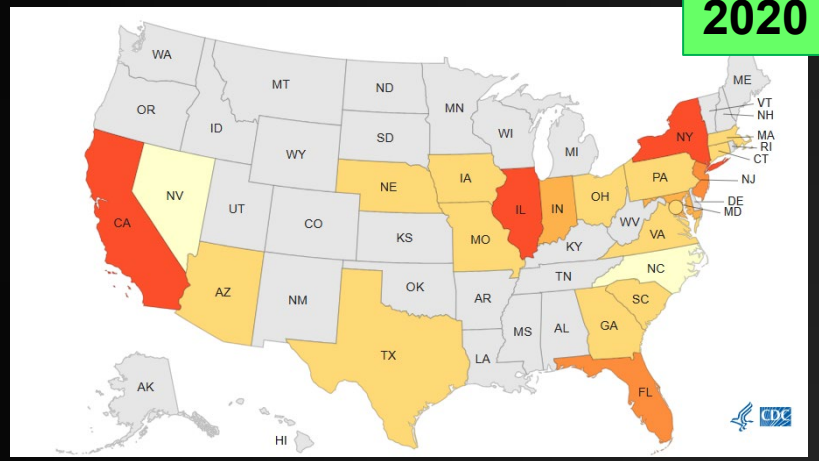
2018



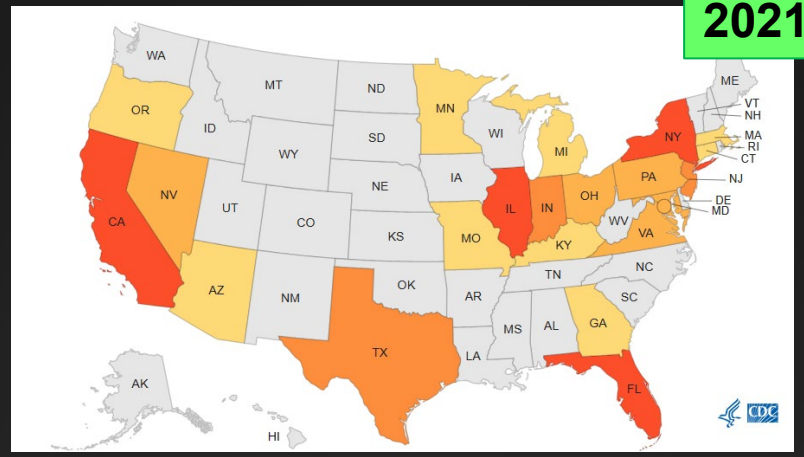
2019



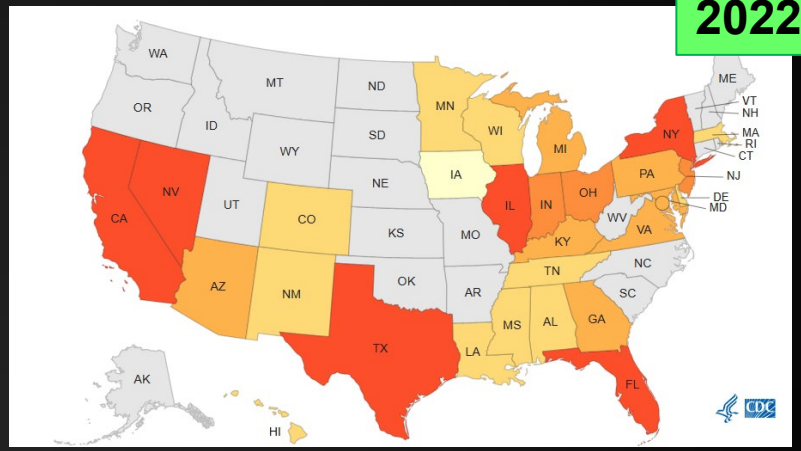
2020



2021



2022



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

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

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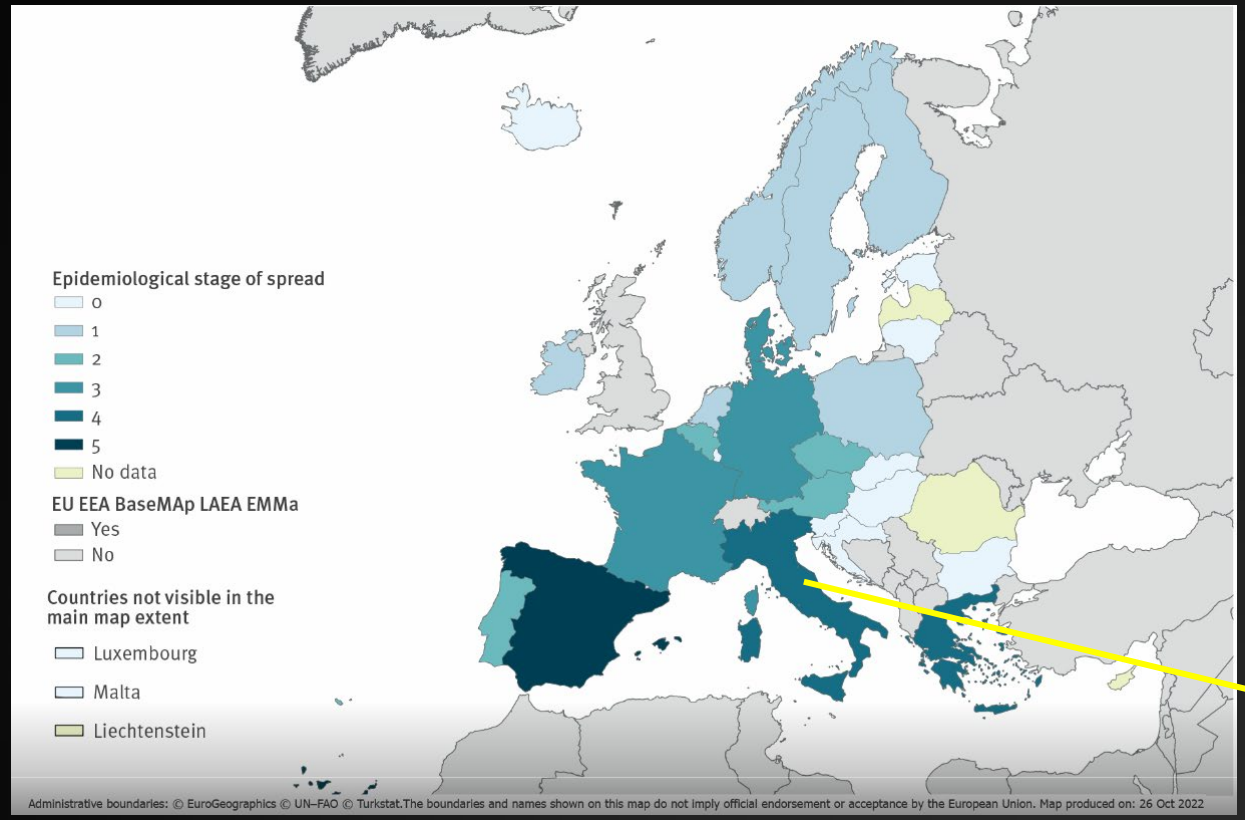
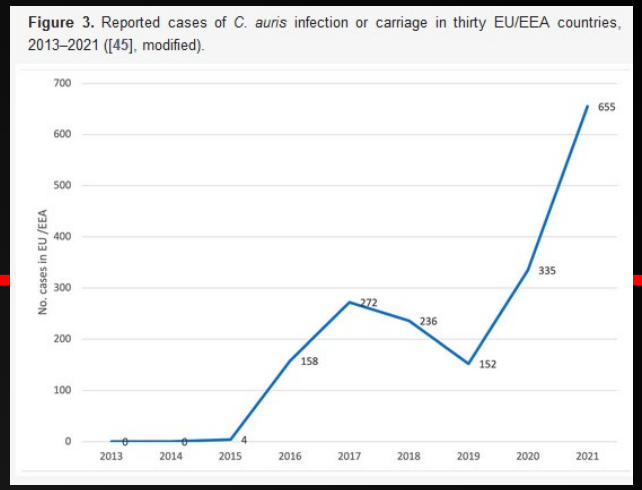
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

The European situation





- 2019 – 2021
- 5 countries (Denmark, France, Germany, Greece and Italy) reported 14 *C. auris* outbreaks, defined as ≥ 2 cases with an epidemiological link
- 3 outbreaks still ongoing at the time of survey publication
- Total of 327 affected patients

Stage 4: Multiple outbreaks of *C. auris* with verified or plausible inter-facility spread have occurred.
…WHAT ABOUT TODAY??

Kohlenberg Anke, Monnet Dominique L, Plachouras Diamantis, Candida auris survey collaborative group. Increasing number of cases and outbreaks caused by Candida auris in the EU/EEA, 2020 to 2021. Euro Surveill. 2022;27(46)

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Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Epidemiology in northern Italy – very confined

Aug 2021 – May 2023

23% of patients admitted to a single ICU in our Hospital became colonized with *C. auris*

Courtesy of Prof. Andrea Orsi, unpublished data

Abstract

Candida auris is a concerning pathogen in health care due to its ability to spread in medical settings. In this study, we characterized the genome of three *C. auris* clinical isolates collected in the Emilia-Romagna region of Northeastern Italy from January 2020 to May 2021. Whole-genome sequencing was performed using Illumina iSeq 100 and Oxford Nanopore MinION systems. Genomes were assembled with Flye. Phylogenetic analysis was carried out with RaxML. The ERG11, *TAC1b*, and *FKS1* genes were examined for known substitutions associated with resistance to azoles and caspofungin using Diamond. All three *C. auris* isolates belonged to clade I (South Asian lineage) and showed high minimum inhibitory concentrations for fluconazole. Two of the three isolates were closely related to the first Italian index case of *C. auris* occurred in the 2019 and carried similar mutations associated to azole resistance. The third isolate showed a greater phylogenetic distance from these strains and had a different genetic determinant not previously seen in Italy. Our data suggest that two *C. auris* clinical isolates may have been epidemiologically related to the first outbreak previously observed in Italy, while the remaining isolate may have originated from a different source. Further research is needed to understand *C. auris* transmission and resistance and to control its spread.

Amadesi S et al. Clonal Dissemination of *Candida auris* Clinical Isolates in Northern Italy, 2021. Microb Drug Resist. 2023 Oct 17

Table 1. Main demographic and clinical characteristics of confirmed *C. auris* cases, Liguria, Piedmont and Emilia-Romagna regions, Italy, July 2019–December 2022 (N = 360 out of 361 total cases).

Patients' Characteristics (%)	Liguria N = 297	Piedmont N = 48	Emilia-Romagna N = 15	Total N = 360

Figure 1. Map of the areas from where confirmed cases colonised with or infected by *C. auris* were reported, located in 4 neighbouring regions, North Italy, July 2019–December 2022 (N = 361). The size of the red circles represents the regional incidence rate per 1000 residents (N).

Sticchi C et al. Increasing Number of Cases Due to *Candida auris* in North Italy, July 2019-December 2022. J Clin Med. 2023 Feb 28;12(5):1912.

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Genova

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

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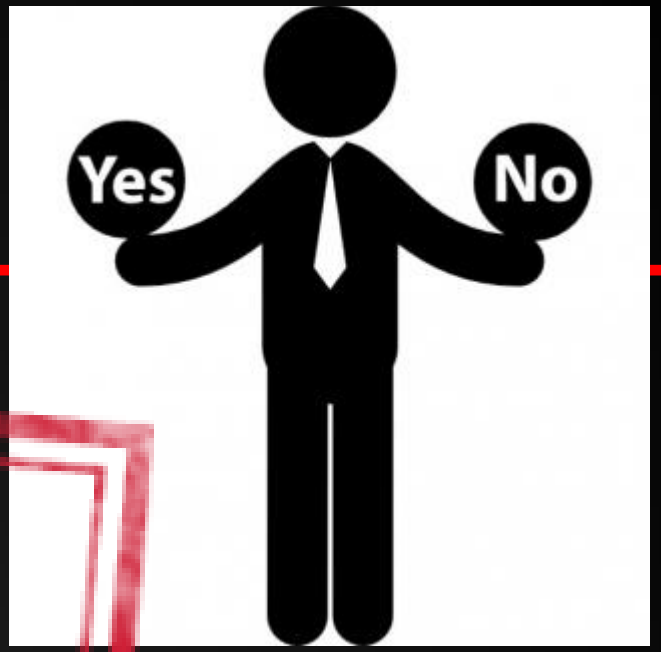

YES

SHOULD WE BE WORRIED?

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Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Environmental persistence

Medical device sources	Biological sources	Fomite sources	Period of persistence (median time)
Skin-surface temperature probes	ND	ND	61 days
Central venous catheters	Nose, axilla, groin, throat, rectum, and vascular line	Bedside trollies, radiators, windowsills, keypads, and equipment monitors	More than 4 h
Deep venous catheters	Rectum and nose	ND	18 months
ND	Nose, throat, axilla, groin, perineum, rectum, urine	ND	12 months
Bed railing, bed sheets, pillow, bedside trollies, floor, and air conditioner	Ear, nose, axilla, groin	Intravenous pole and oxygen mask were colonized by *C. auris*, while thermometer, blood pressure cuffs, nebulizer, ECG clip and sucker, and wheelchair had no *C. auris*	6 months
ND	Blood	Tunneled catheter	ND
Tables, beds, floors, walls, keyboards, and screens	Blood, vascular line, rectum,	ND	10 months and 3 weeks
Plastics	Groin, urine, stool, vagina, rectum, axilla, nares	ND	14 days
ND	Intraperitoneal cavity (intraperitoneal infection model), kidney	Catheter (mice subcutaneous model)	7 days for intraperitoneal cavity and 3 days for catheter
ND	ND	Central venous catheter (mice subcutaneous model)	2 days
Polymer, cellulose matrix, and steel	ND	ND	2 days
Hospital clothes	ND	ND	3 days

Is the control of possible environmental sources of *C. auris* relevant in limiting outbreaks?

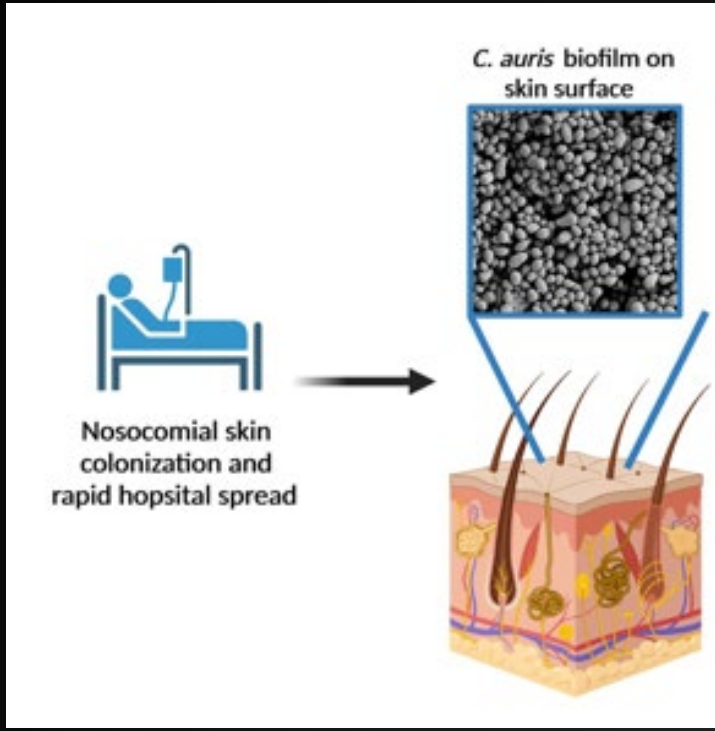
London (UK) – 70 patients over 30 months in a single ICU

Despite a bundle of infection-control interventions, the incidence of new cases was reduced only after removal of the skin-surface temperature probes

Eyre DW, A Candida auris Outbreak and Its Control in an Intensive Care Setting. N Engl J Med. 2018 Oct 4;379(14):1322-1331.

Nwachukwu KC, Nwarunma E, David Uchenna C, Chinyere Ugbogu O. Enablers of *Candida auris* persistence on medical devices and their mode of eradication. Curr Med Mycol. 2023 Mar;9(1):36-43.

Skin colonization



- In mouse and porcine skin models, *C. auris* proliferates to burdens 10- to 100-fold greater than *C. albicans.*
- In both murine and porcine models, *C. auris* appears to reside in deeper tissues, such as the hair follicles.
- While chlorhexidine can reduce the burden of *C. auris* on skin, it does not appear to eradicate the organism, allowing for fungal regrowth and persistent colonization.

Eix EF, Nett JE (2022) Modeling *Candida auris* skin colonization: Mice, swine, and humans. PLoS Pathog 18(9): e1010730

Skin colonization – for how long?

Unclear duration of colonization over time!

- When to start re-screening?
- Timing for repeated screning?
- How many negative samples?
- Which samples to screen?

Previous *C. auris*-positive patients should be placed in contact isolation and screened on three consecutive days. Contact precautions may be stopped if all three screens are negative. Weekly screening is recommended, as *C. auris* may resurface after antibiotic therapy or other interventions such as chemotherapy.

Liguria region: consider colonized for **24 months** after first detection

Kenters N et al. Control of Candida auris in healthcare institutions: Outcome of an International Society for Antimicrobial Chemotherapy expert meeting. Int J Antimicrob Agents. 2019 Oct;54(4):400-406

A.Li.Sa. Delibera 117 del 05/2023 Protocollo regionale di sorveglianza e controllo di infezioni e colonizzazioni da CRE e C. auris

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Dipartimento di Scienze della Salute (DISSAL)
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Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
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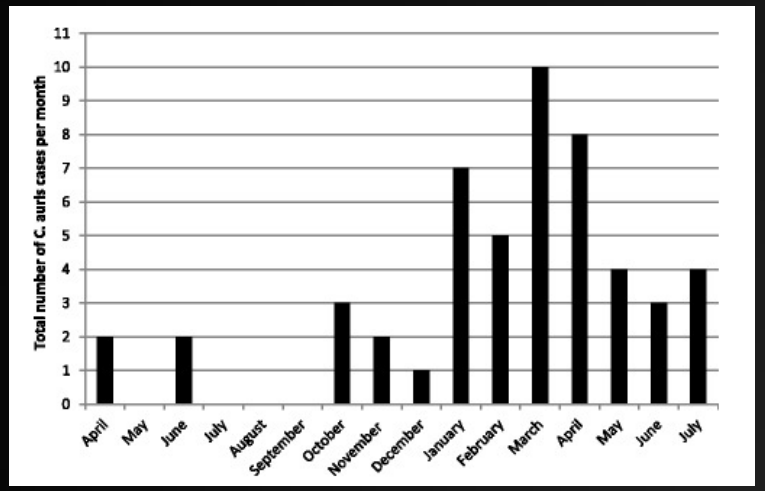
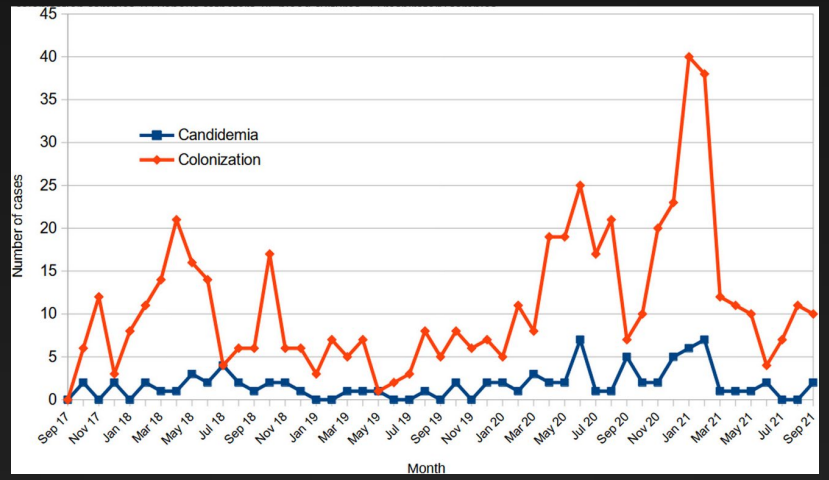
Invasive infection - candidemia

Candidemia 18%



Schelenz S et al. Antimicrob Resist Infect Control. 2016 Oct 19;5:35.
Garcia-Bustos V et al. Clin Microbiol Infect. 2020 Nov;26(11):1507-1513.

Candidemia 15,6%



Mulet Bayona JV et al. Candida auris from colonisation to candidemia: A four-year study. Mycoses. 2023 Oct;66(10):882-890.

Candidemia 17,6%

Codda G et al. In vivo evolution to echinocandin resistance and increasing clonal heterogeneity in *Candida auris* during a difficult-to-control hospital outbreak, Italy, 2019 to 2022. Euro Surveill. 2023 Apr;28(14):2300161.

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Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

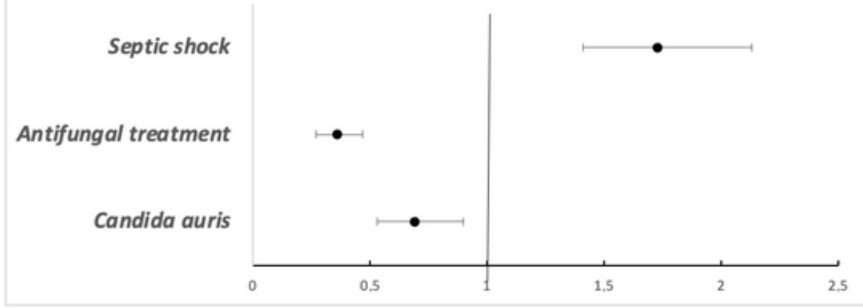
Mortality in *C. auris* candidemia

Table 1 Subgroup analyses of pooled mortality

Factors	Group	Number of studies	Pooled crude mortality (95%CI)	I^2 (%)	*p* value
Bloodstream infection	Yes	15	0.45 (0.39–0.51)	41	**0.002**
	No	5	0.21 (0.08–0.33)	40	Ref
Clade	Clade I	11	0.39 (0.31–0.47)	49	0.343
	Non- Clade I	4	0.31 (0.14–0.48)	83	Ref
FLC resistance	Higher	10	0.29 (0.21–0.38)	60	0.415
	Lower	3	0.49 (0.29–0.70)	70	Ref
AmB resistance	Higher	6	0.29 (0.19–0.40)	45	0.159
	Lower	6	0.43 (0.32–0.53)	62	Ref
Continent	Asia	9	0.44 (0.38–0.51)	0	**0.000**
	America	5	0.43 (0.27–0.59)	78	0.164
	Africa	2	0.37 (0.21–0.53)	81	0.303
	Europe	3	0.20 (0.04–037)	66	Ref
Publication Year	2018–2019	11	0.42 (0.31–0.53)	86	0.769
	2016–2017	5	0.39 (0.30–0.48)	0	0.415
	2013–2015	3	0.47 (0.31–0.63)	0	Ref

FLC fluconazole, *AmB* amphotericin B

Figure 2. The hazard ratios of variables affecting mortality in the cohort of patients with candidemia. *n* = 512, Robust 95% CI.



2016-2021 – 7 hospitals in Colombia

C. auris (n=134) vs non-*auris* (n=378)
30d-mortality 38% vs 51% (p=0,013)

Caspofungin 66% vs 31% !!

Chen J, Is the superbug fungus really so scary? A systematic review and meta-analysis of global epidemiology and mortality of Candida auris. BMC Infect Dis. 2020 Nov 11;20(1):827.

Ortiz-Roa C et al. Mortality Caused by *Candida auris* Bloodstream Infections in Comparison with Other Candida Species, a Multicentre Retrospective Cohort. J Fungi (Basel). 2023 Jun 29;9(7):715.

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Ospedale Policlinico San Martino IRCCS
Genoa, Italy

First line treatment for *C. auris* candidemia

- 93% resistance to fluconazole
- 35% resistance to amphotericin B
- 7% resistance to echinocandins
- 6% resistance to flucitosine
- **41% resistant to at least 2 antifungal classes**

Reference	Country (no. of isolates)	Method
(8)	India (350)	CLSI
(39)	United Kingdom[a] (119-128)	CLSI
(72)	India[*] (123)	CLSI
(11)	India (90)	CLSI
(14)	Colombia (87)	CLSI, Etest for AMB
(13)	United Kingdom[#] (73-79)	SYO
(32)	India (74)	CLSI
(10)	Spain (73)	EUCAST
(2)	Korea[#] (61)	CLSI
(9)	Kuwait (56)	Etest
(4)	Multiple[b] (54)	CLSI
(12)	Venezuela (18)	CLSI
(1)	Korea (15)	CLSI, Etest for AMB

Ryan Kean, Gordon Ramage, Combined Antifungal Resistance and Biofilm Tolerance: the Global Threat of *Candida auris,* mSphere, 2019
Shawn R. Lockhart et al, Simultaneous Emergence of Multidrug-Resistant *Candida auris* on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses, *Clinical Infectious Diseases*, January 2017

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Genoa, Italy

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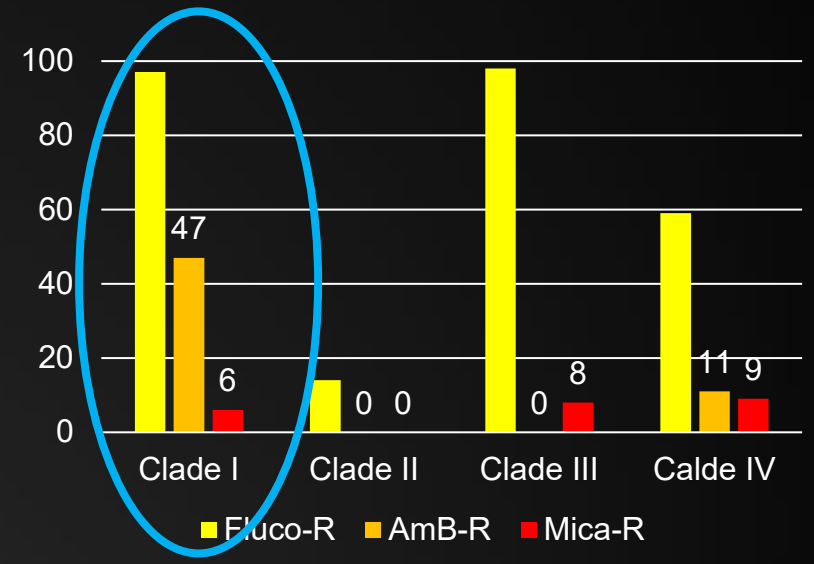
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Antifungal resistance – local data

Drug	MIC Range	Interpretation
Fluconazole	RESISTANT	**0%**
Caspofungin	0.06->8	**3 cases of resistance**
Anidulafungin	0.06-4	
Micafungin	0.06->8	
Amphotericin B	1-4	**Around 60%, most MICs on the breakpoint value**
Flucytosin* *available only for 2 patients with MDR strains	0.12	



Chow NA, et al. 2020. Tracing the evolutionary history and global expansion of Candida auris using population genomic analyses. mBio 11:e03364-19. https:// doi.org/10.1128/mBio.03364-19

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Genoa, Italy

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Ospedale Policlinico San Martino IRCCS
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Clinica Mal
Policlinico Sa

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Osp tie Infettive
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SHOULD CHA R TREATMENT POLICIES?

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Genoa, Italy

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Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Increasing resistance to echinocandins

Notes from the Field: Transmission of Pan-Resistant and Echinocandin-Resistant *Candida auris* in Health Care Facilities — Texas and the District of Columbia, January–April 2021

Weekly / July 23, 2021 / 70(29);1022–1023

The number of *C. auris* cases that were resistant to echinocandins in 2021 was about 3 times that in each of the previous 2 years

(7 isolates pan-R, 19 isolates echinocandin-R)

Table. Percentage Resistance of *Candida auris* Isolates Tested by the Antimicrobial Resistance Laboratory Network, 2018 to 2020*

Year or Region	Azoles†	Amphotericin B‡	Echinocandins§
Year			
2018 (*n* = 463)	372 (80.3)	151 (32.6)	2 (0.4)
2019 (*n* = 1006)	787 (78.2)	242 (24.1)	14 (1.4)
2020 (*n* = 1294)	1109 (85.7)	331 (25.6)	15 (1.2)
Region‖			
Mid-Atlantic (*n* = 135)	133 (98.5)	115 (85.2)	4 (3.0)
Midwest (*n* = 156)	17 (10.9)	2 (1.4)	0 (0.0)
Mountain (*n* = 25)	24 (96.0)	1 (4.0)	0 (0.0)
Northeast (*n* = 1051)	1046 (99.5)	468 (44.5)	22 (2.1)
Southeast (*n* = 172)	170 (99.4)	9 (5.2)	0 (0.0)
West (*n* = 556)	553 (99.5)	17 (3.1)	1 (0.2)

Lyman M, Forsberg K, Sexton DJ, Chow NA, Lockhart SR, Jackson BR, Chiller T. Worsening Spread of *Candida auris* in the United States, 2019 to 2021. Ann Intern Med. 2023 Apr;176(4):489-495.

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Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
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Resistance to echinocandins – local data

Emergence of pandrug resistance following independent selection of *FKS1* S639F and *FKS1* F635Y mutants

	Patient A		Patient B	
FKS1 genotype	WT	F635Y	WT	S639F
Antifungal agent	MIC			
Caspofungin	0.06	>8	0.25	2
Anidulafungin	0.125	2	0.5	4
Micafungin	0.125	2	0.125	>8
Days to candidaemia from hospital admission	29		95	
Days to candidaemia from first C. auris colonisation	23		74	
Previous echinocandin exposure[a]	Cumulative days			
Anidulafungin	19		23	
Caspofungin	None		58	

Successfully treated with
L-AmB + flucytosine (Patient A)
L-AmB alone (Patient B)

Codda G et al. In vivo evolution to echinocandin resistance and increasing clonal heterogeneity in *Candida auris* during a difficult-to-control hospital outbreak, Italy, 2019 to 2022. Euro Surveill. 2023 Apr;28(14):2300161.

Prior case or emergence of resistance to caspofungin after 6 months of admission to ICU in 2020 with need for prolonged antibiotic and antifungal treatment for complications

CASPOFUNGIN MIC 0,06 to 6 mg/L

More evidence…

Spain - another case of emergence of resistance to echinocandin

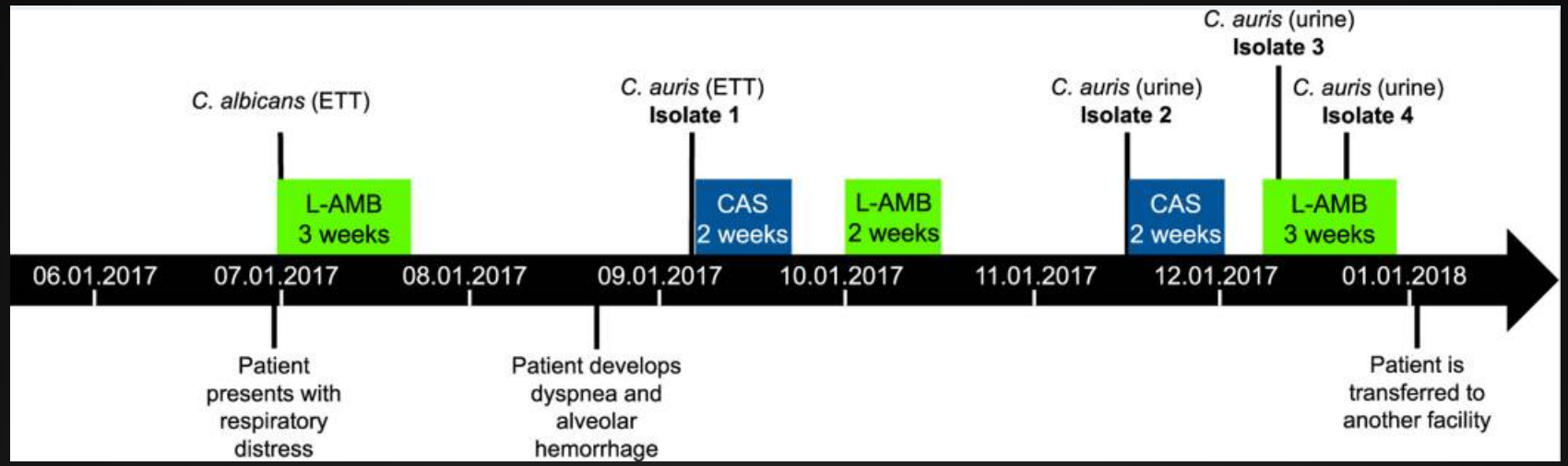
- CVC-related candidemia treated with anidulafungin for 28 days and antifungal lock of the catheter with anidulafungin until the catheter was replaced

Mulet Bayona JV, Tormo Palop N, Salvador García C, Herrero Rodríguez P, Abril López de Medrano V, Ferrer Gómez C, Gimeno Cardona C. Characteristics and Management of Candidaemia Episodes in an Established *Candida auris* Outbreak. Antibiotics (Basel). 2020 Aug 30;9(9):558.

PROLONGED TREATMENTS WITH ECHINOCANDINS and POSSIBLY INCOMPLETE SOURCE CONTROL

THE PERFECT COMBO FOR THE EMERGENCE OF RESISTANCE!

Worrisome news for AmB as well…



In vivo development of high-level AmB resistance **during therapy**

Novel mechanism mutation in the *C. auris* sterol-methyltransferase gene ERG6

Rybak JM et al. In vivo emergence of high-level resistance during treatment reveals the first identified mechanism of amphotericin B resistance in Candida auris. Clin Microbiol Infect. 2022 Jun;28(6):838-843.

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Should we change our treatment policies?

INVEST IN ANTIFUNGAL STEWARDSHIP!

Antimicrobial stewardship

Although there is no evidence for a specific beneficial effect of antimicrobial stewardship on the emergence and spread of *C. auris*, it is likely that an environment with a high use of broad-spectrum antibacterial and antifungal agents will favour the emergence of multidrug-resistant yeasts, such as *C. auris*. Therefore, the implementation of antimicrobial stewardship is likely to mitigate the risk of *C. auris* emergence and spread, in addition to being an essential component of strategies to reduce antimicrobial resistance in general. The need for antifungal prophylaxis should be reviewed in terms of risk-benefit analysis in settings with evidence of *C. auris* transmission.

European Centre for Disease Prevention and Control. Candida auris outbreak in healthcare in northern Italy, 2019-2021. ECDC: Stockholm; 2022.

Which options in case of multi-drug resistance?

1. Combinations of traditional antifungals
2. New antifungals

3. New formulations of traditional antifungals → encochleated amB
4. Repurposed drugs → miltefosine, sertraline…
5. Antifungals under development → new tetrazoles and triazoles

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Genoa, Italy

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Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Combination therapy

Synergism	Non-synergism
PK/PD simulations revealed that none of the combinations at standard or higher dosages would be effective!	
Micafungin + voriconazole	Anidulafungin + voriconazole Caspofunign + voriconazole
	Flucytosine + AmB/mica/vori
Micafungin + AmB	

Caballero U et al. PK/PD modeling and simulation of the in vitro activity of the combinations of isavuconazole with echinocandins against Candida auris. CPT Pharmacometrics Syst Pharmacol. 2023 Jun;12(6):770-782.

Caballero U, et al. In Vitro Synergistic Interactions of Isavuconazole and Echinocandins against *Candida auris*. Antibiotics (Basel). 2021 Mar 28;10(4):355
Fakhim H, et al. 2017. *In vitro* interactions of echinocandins with triazoles against multidrug-resistant *Candida auris*. Antimicrob Agents Chemother **61**:e01056-17
Bidaud AL, et al. Antimicrob Agents Chemother. 2019 Oct 7;63(12):e01393-19
O'Brien B, et al. V. *In Vitro* Evaluation of Antifungal Drug Combinations against Multidrug-Resistant Candida auris Isolates from New York Outbreak. Antimicrob Agents Chemother. 2020 Mar 24;64(4):e02195-19
Jaggavarapu S, Burd EM, Weiss DS. Micafungin and amphotericin B synergy against Candida auris. Lancet Microbe. 2020 Dec;1(8):e314-e315.

New antifungals – phase 2 and 3

New antifungal	Anfigungal Class	Activity against C. auris
Ibrexafungerp	Tripterenoid	
Rezafungin	Echinocandin with prolonged half-life	*fks1* mutations raised rezafungin MICs notably less than anidulafungin and micafungin MICs in *C. auris*
Fosmanogepix	Inhibitor of mannanoprotein production	
Oteseconazole	Novel tetrazole	
Olorofim	Orotomide	

Active against *C. auris* and already studied
Potentially active against *C. auris* but not yet studied
Not active against *C. auris*

Helleberg M et al. Rezafungin *In Vitro* Activity against Contemporary Nordic Clinical *Candida* Isolates and *Candida auris* Determined by the EUCAST Reference Method. Antimicrob Agents Chemother. 2020 Mar 24;64(4):e02438-19.

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Ibrexafungerp

New antifungal	Activity against C. auris
Ibrexafungerp	
Rezafungin	
Fosmanogepix	
Oteseconazole	
Olorofim	

- No cross-resistance expected for *fks1* mutations
- **CARES trial** for *C. auris*
  - 12 candidemia , 5 UTI, 1 IAI - partial/complete response in 80%
- **Good activity against *C. auris* biofilm**
- **Possible step-down therapy for *C. auris* infections?**

Larkin E et al. The Emerging Pathogen Candida auris: growth Phenotype, Virulence Factors, Activity of Antifungals, and Effect of SCY-078, a Novel Glucan Synthesis Inhibitor, on Growth Morphology and Biofilm Formation. Antimicrob Agents Chemother. 2017 May 61;(5): e02396–16
https://www.globenewswire.com/news-release

Fosmanogepix

New antifungal	Activity against C. auris
Ibrexafungerp	
Rezafungin	
Fosmanogepix	
Oteseconazole	
Olorofim	

- **Trial completed for the treatment of *C. auris* invasive infections with limited treatment options** (NCT04148287)
  - South Africa – 9 patients enrolled – treatment success at EOS 89%
- **Highly active against uncommon *Candida* spp, including *C. auris*** (MIC90 0,015 mg/L)

Pfaller MA et al. Activities of Manogepix and Comparators against 1,435 Recent Fungal Isolates Collected during an International Surveillance Program (2020). Antimicrob Agents Chemother. 2022 Nov 15;66(11):e0102822.
https://www.clinicaltrials.gov/study/NCT04148287

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Ospedale Policlinico San Martino IRCCS
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Take home messages

- *C. auris* is an already emerged pathogen – need to address the management of colonization in endemic situations
- The high environmental and skin persistance of *C. auris* are major challenges to limiting its spread
- To date echinocandins remain the first line therapy of *C. auris* invasive infections
- The emergence of resistance to echinocandins is worrisome – need to implement antifungal stewardship programs!

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ACCP 2023

Meeting on Antimicrobial Chemotherapy in Clinical Practice (ACCP)

ACCP 2023

THANK YOU FOR YOUR ATTENTION!

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Genoa, Italy

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Ospedale Policlinico San Martino IRCCS
Genoa, Italy