Online Groenendael
Robbert Bentvelsen

NL-UNB-0734 Date of preparation: May 2024

Disclaimer

- De inhoud van deze presentatie is ontwikkeld door Robbert Bentvelsen en onafhankelijk van Gilead tot stand gekomen.

- De presentatie bevat educatieve informatie over een ziektebeeld en/of medische aandoening en is uitsluitend bedoeld voor beroepsbeoefenaren. Gilead beoogt geen behandeladvies te geven.

ESCMID GLOBAL 2024

Fungal highlights

Candida auris

Robbert Bentvelsen
Arts-microbioloog

Disclosure belangen

Geen (potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties	*Bedrijfsnaam en omschrijving*
- Sponsoring of onderzoeksgeld - Honorarium of andere (financiële) vergoeding - Aandeelhouder - Andere relatie, namelijk	- Gilead: gastspreker Online Groenendael - Janssen-Cilag: gastspreker Dermatology@C

ESCMID GLOBAL 2024

Fungal highlights

Candida auris

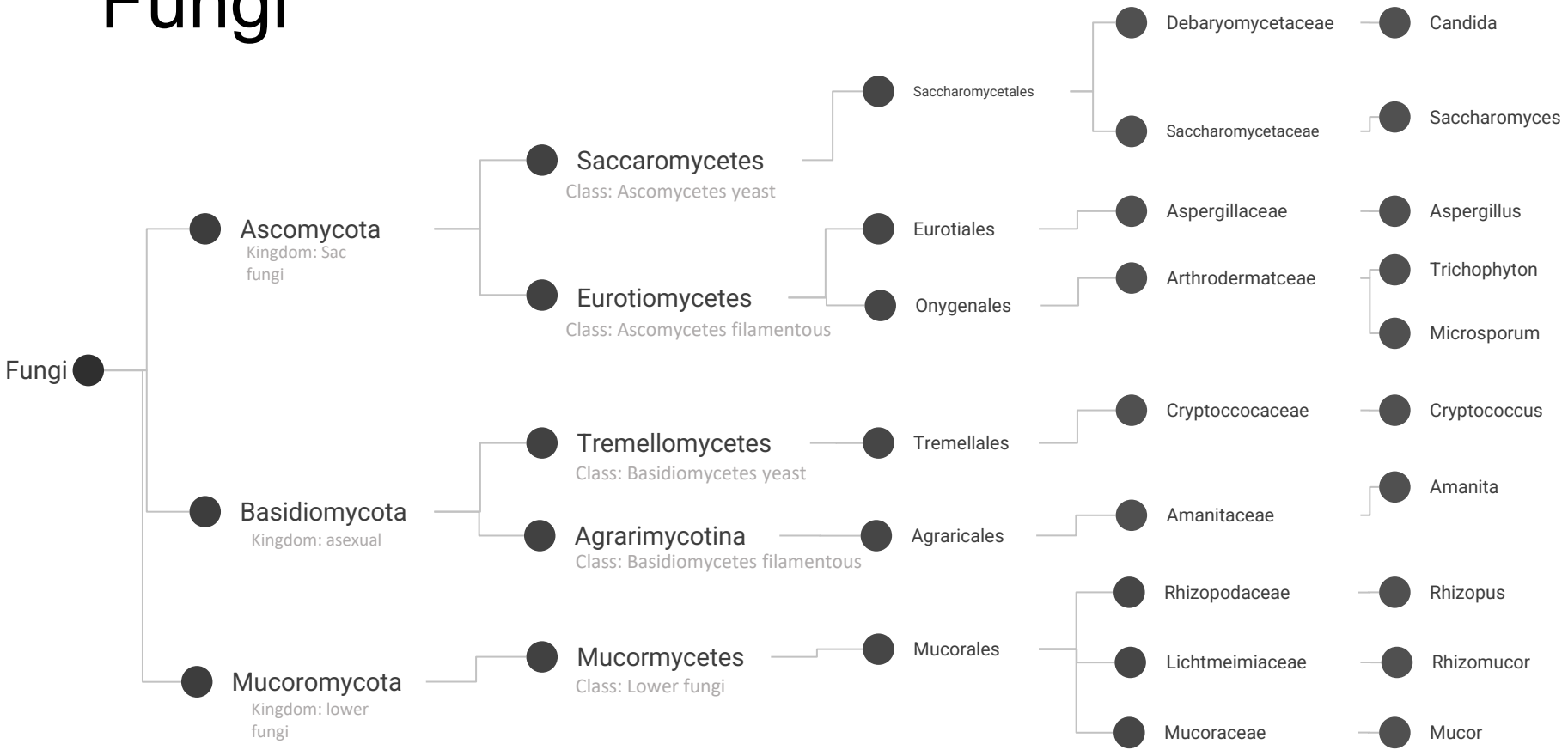
SESSION	REFERENTIE - TITEL - SPREKER
The changing faces of fungi	Referentie [1] Candida auris: a growing threat (A. CHOWDHARY), ESCMID GLOBAL 2024 Barcelona
Fungal infections from a One Health perspective	Referentie [2] Candida auris: current epidemiology and battle plan (V. DI PILATO), ESCMID GLOBAL 2024 Barcelona
Traditional and genomic epidemiology of fungal.	Referentie [3] Discovery of the sixth Candida auris clade: molecular epidemiology in Singapore (Kwan Ki Karrie KO), E1035 ESCMID GLOBAL 2024 Barcelona
The changing landscape of antifungal treatment.	Referentie [4] Candida auris, how to treat and do the old susceptibility methods apply? (J. MELETIADIS), ESCMID GLOBAL 2024 Barcelona

Schimmels

- Saprofyt
- Genera
  - Aspergillus
  - Candida
  - Cryptococcus
  - Histoplasma
  - Trichophyton
  - …
  - Zygomycetes - Mucorales

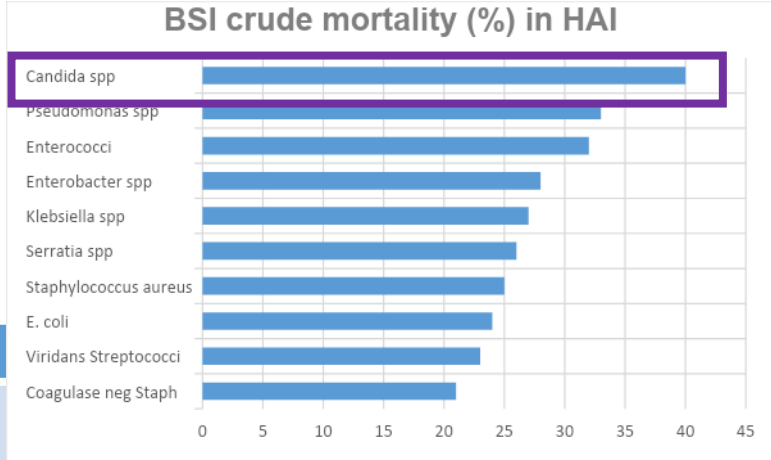
Schoch CL, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford). 2020: baaa062.
Image https://commons.wikimedia.org/wiki/File:Fungi_collage.jpg

Fungi



Schoch CL, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford). 2020: baaa062.

Candida



EUCAST en klinisch bekend als	Alternatieve namen
Candida albicans **(current)**	=
Candida glabrata (homotypic)	***Nakaseomyces glabratus***
Candida dubliniensis **(current)**	=
Candida krusei (heterotypic)	***Pichia kudriavzevii*** **(current)** *Issatchenkia orientalis* en *Candida acidothermophilum* (hetero)
Candida parapsilosis **(current)**	=
Candida tropicalis **(current)**	*Candida albicans* var. tropicalis (homotypic)
Candida kefyr (hetero)	***Kluyveromyces marxianus*** **(current)**; *Candida pseudotropicalis (heterotypic)*
Candida infanticola (basionym)	***Wickerhamiella infanticola*** **(current)**
Candida lusitaniae (heterotypic)	***Clavispora lusitaniae*** **(current)**
Candida guilliermondii (heterotypic)	***Meyerozyma guilliermondii*** **(current)**
Candida auris	***Candidozyma auris*** **(current)**

Microvida afspraak: als EUCAST/klinisch bekend (niet taxonomisch). Dikgedrukt is huidige wetenschappelijke taxonomische indeling.

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

NCBI taxonomy database; Edmond CID 1999; Liu F. doi.org/10.3767/persoonia.2024.52.02

Candida auris: reported cases

Speaker's own image based on: Kim, M. CID 2009; Satoh K. M&I 2009

Candida auris: reported cases

Speaker's own image based on: Chowdhary A. 2017; Kohlenberg 2022

Candida auris: reported cases

2009 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023+

Speaker's own image based on: Chowdhary A. 2017; Kohlenberg 2022

Candida auris

WHO Fungal Priority pathogens list
to guide research, development and public health action

CDC Antibiotic Resistance threats
in the United States 2019

- Tends to be resistance to multiple classes of antifungal agents
- Substantial pathogenicity
- Limited treatment options
- Transmitted nosocomial (skin scales)
- Persistence in the environment

Table 3. WHO fungal priority pathogens list

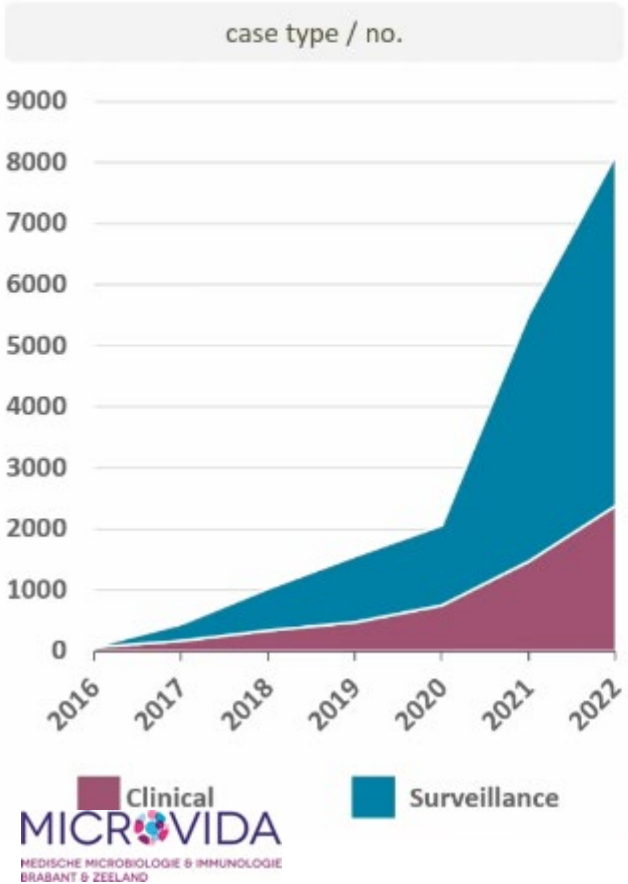
Critical group	High group	Medium group
Cryptococcus neoformans	*Nakaseomyces glabrata (Candida glabrata)*	*Scedosporium* spp.
Candida auris	*Histoplasma* spp.	*Lomentospora prolificans*
Aspergillus fumigatus	Eumycetoma causative agents	*Coccidioides* spp.
Candida albicans	Mucorales	*Pichia kudriavzeveii (Candida krusei)*
	Fusarium spp.	*Cryptococcus gattii*
	Candida tropicalis	*Talaromyces marneffei*
	Candida parapsilosis	*Pneumocystis jirovecii*
		Paracoccidioides spp.

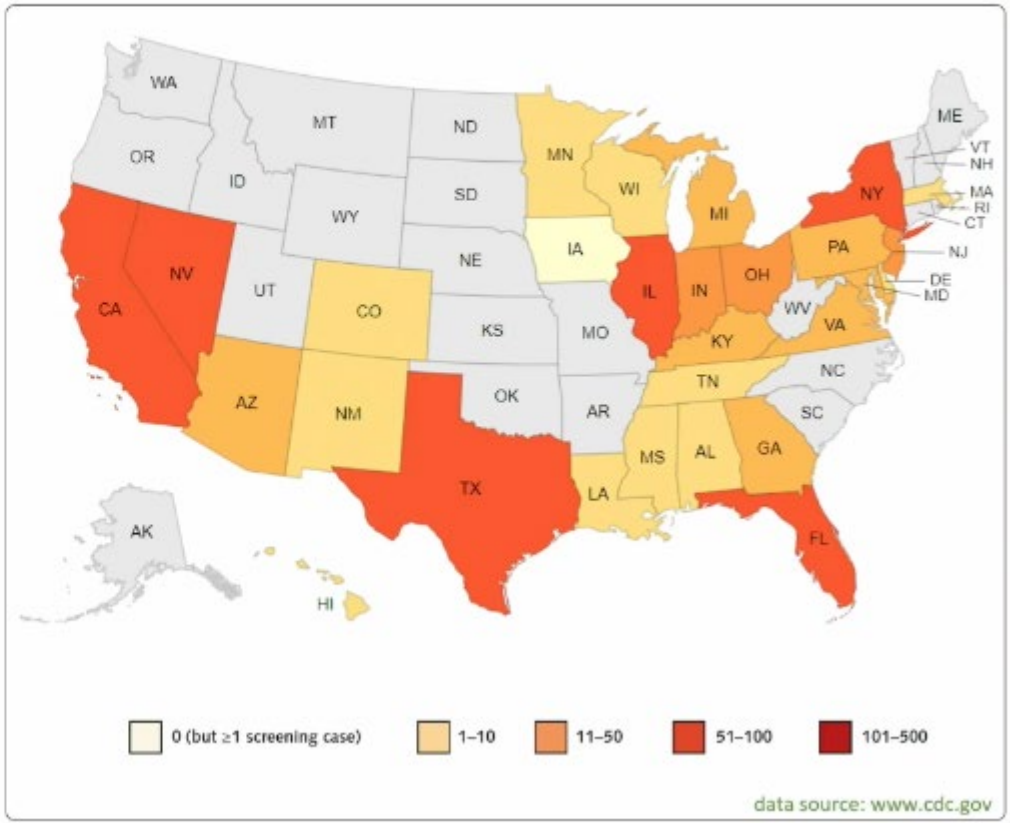
MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

[1]; cdc.gov/antimicrobial-resistance/media/pdfs/candida-auris-508.pdf who.int/publications/i/item/9789240060241

Global epidemiology of *Candida auris*

THE RAPIDLY EVOLVING SCENARIO IN THE U.S.





Candida auris

Clinical Manifestations

Candidaemia, urinary tract infections, wound infections, otitis and skin abscesses are the most common infection types. *C. auris* can also cause disseminated disease.

Risk factors for colonization and invasive infections by C. auris

Similar to those of other *Candida* species and those of multidrug resistant microorganisms, such as carbapenemase-producing enteric bacteria

Crude case fatality rates ranging between 30% and 60%

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

[1]

Candida auris

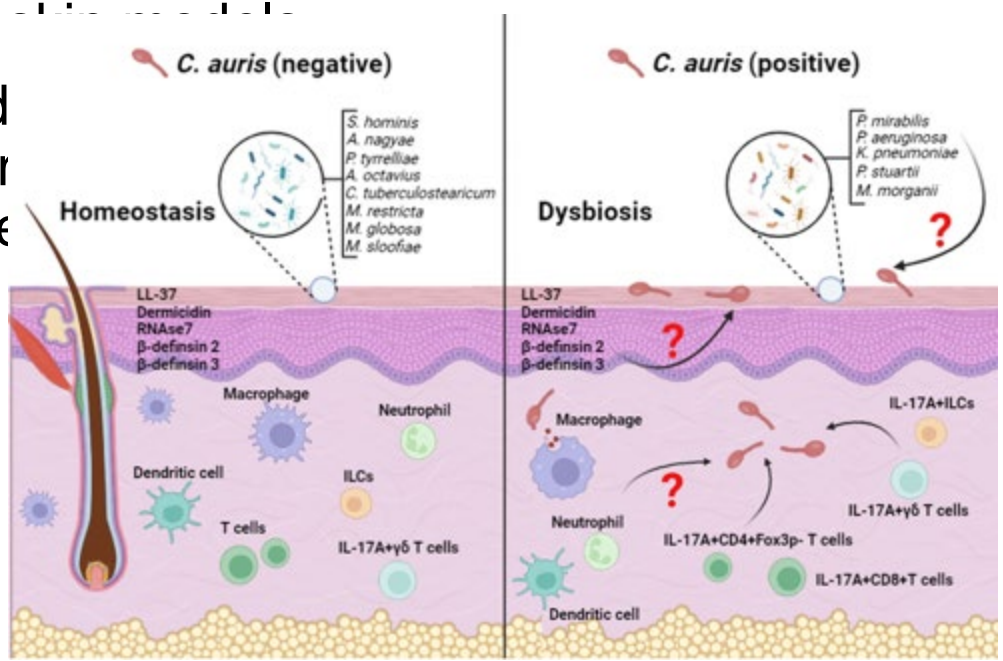
A *Candida auris*–specific adhesin, Scf1, governs surface association, colonization, and virulence

DARIAN J. SANTANA, JULIET A. E. ANKU, GUOLEI ZHAO, ROBERT ZARNOWSKI, CHAD J. JOHNSON, HALEY HAUTAU, NOELLE D. VISSER, ASHRAF S. IBRAHIM, DAVID ANDES, [...] AND TERESA R. O'MEARA +2 authors Authors Info & Affiliations

SCIENCE • 28 Sep 2023 • Vol 381, Issue 6665 • pp. 1461-1467 • DOI: 10.1126/science.adf8972

Porcine and human ex vivo skin models

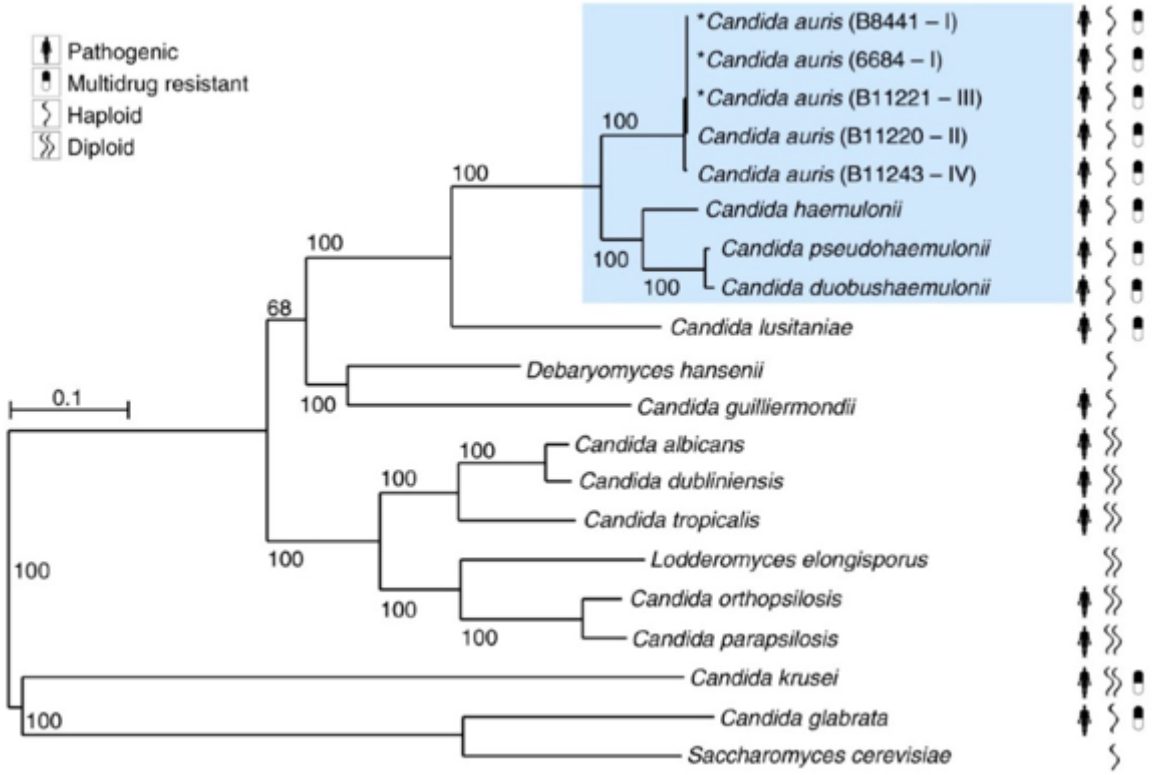
- *C.auris* cause sustained
- Multilayer biofilms under
- Reside within hair follicle



MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

[1]; DOI: 10.1126/science.adf8972 doi.org/10.1128/msphere.00623-22

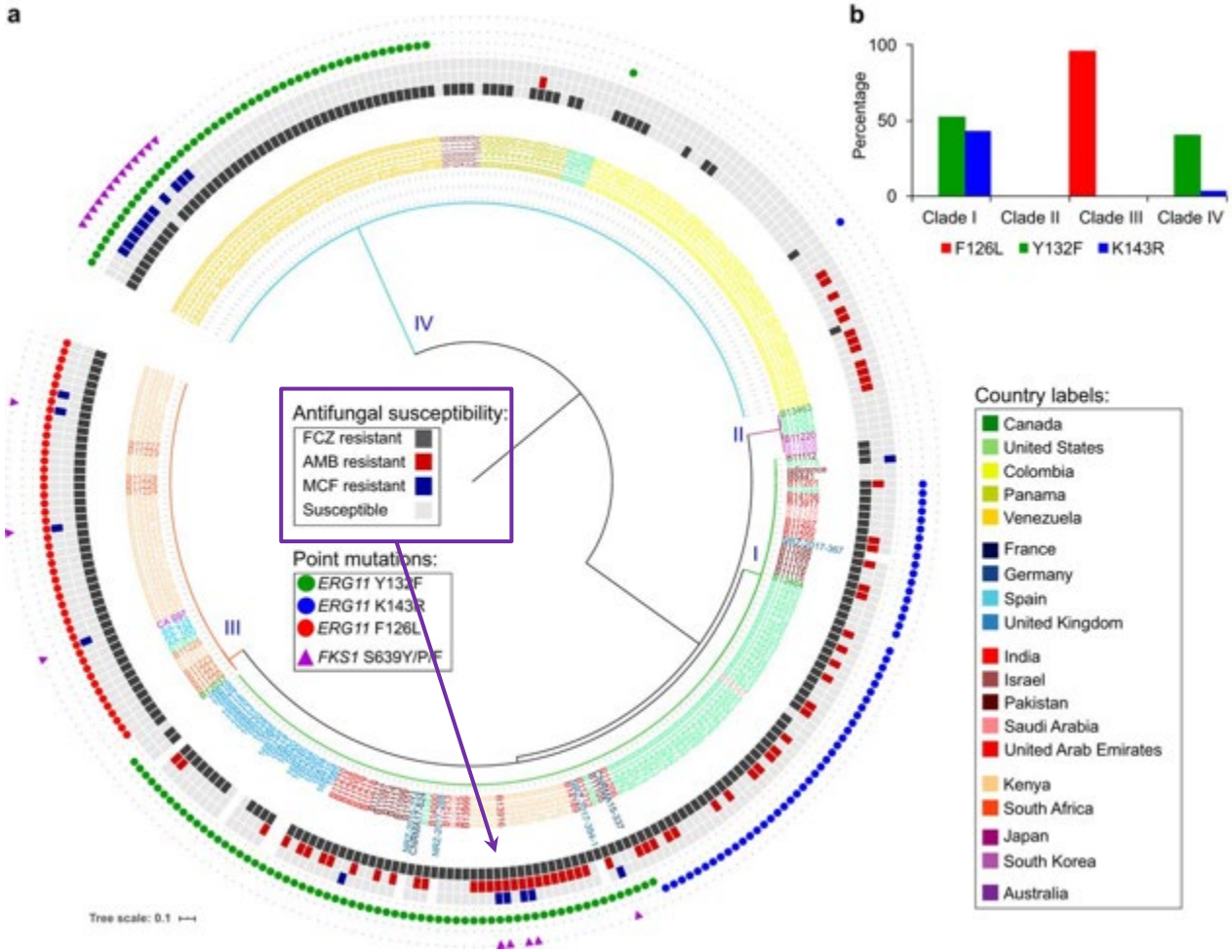
Candida auris



MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

Arastehfar JoF 2020 doi.org/10.3390/jof6030138

C. auris



Clade IV emerged 30-40 years ago
Clade II emerged 317-400 years ago

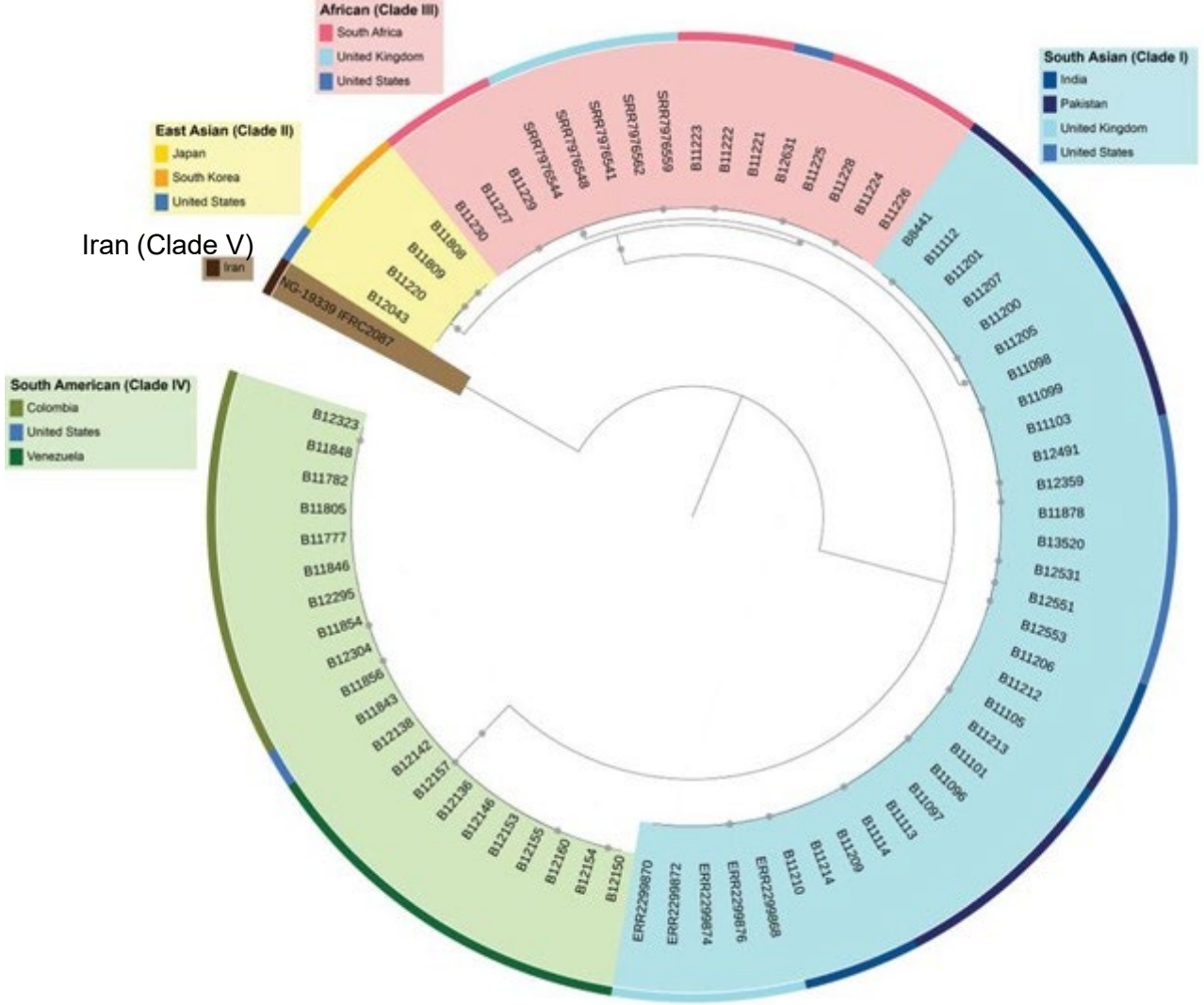
Global: 80% FLUC-R, 23% AmB-R, 7% MCF-R

Clade II (E.Asia) 86% FLUC-S

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

Chow NA mBio 2020 https://doi.org/10.1128/mbio.03364-19

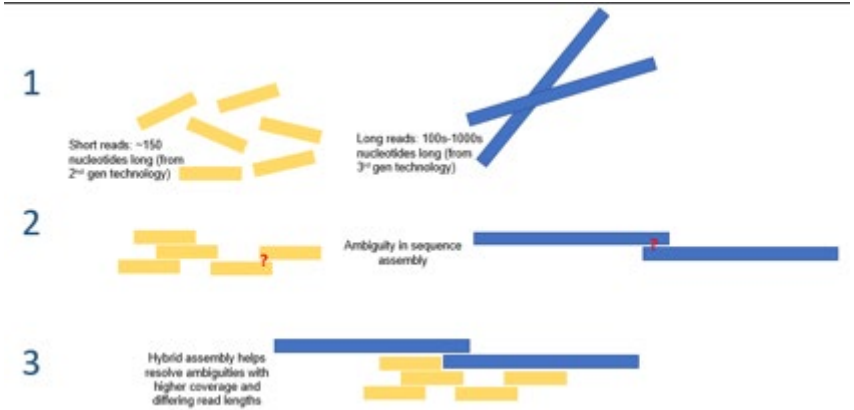
C. auris



MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

Chow NA EID 2019 https://doi.org/10.3201/eid2509.190686

Candida auris



Candida auris (CAU) is a serious threat to global public health due to its worldwide distribution, multidrug resistance, high transmissibility, proven outbreak potential, and high mortality rates. We report the molecular epidemiology of the largest CAU collection in Southeast Asia (SEA) to date, along with the discovery of a novel sixth CAU clade.

- 73 clinical CAU isolates (unique clinical specimens from 35 patients, collected 2012-2023) were identified using MALDI-TOF.
- Whole-genome sequencing (WGS) using MinION. Additional Illumina sequencing was performed on either HiSeq X Five or MiniSeq, for a subset of isolates.
- **De novo hybrid genome assembly** was performed by assembling nanopore reads and further polishing using Illumina reads. Phylogenetic analysis and SNP distances calculated. Clades were determined by inspecting SNP distances and the sixth clade was detected as the genomes formed a new cluster.

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

Candida auris

- Clade VI isolates separated > 37,000 SNPs
  - P1: 2018* fungemia from Bangladesh - cured
  - P2: Indonesia, intraoperative tissue - cured
  - P3: Singapore, surveillance nasal colonisation
- This genomic surveillance study represents the largest collection of CAU from SEA to date and provides evidence for the discovery of the sixth major CAU clade.
- Our findings underscore the need to e epres

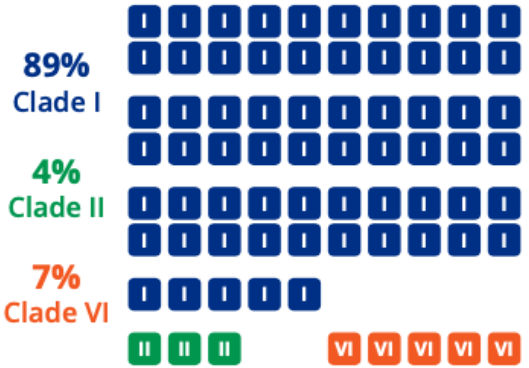


Fig. 2: Distribution of clades in our collection. 65/73 (89%) isolates from 30 unique patients belong to Clade I (blue). 3/73 (4%) isolates from 2 unique patients belong to Clade II (green). 5/73 (7%) isolates from 3 unique patients were found to be genetically distinct from all known clades, and likely constitute a new sixth clade (Clade VI, orange).

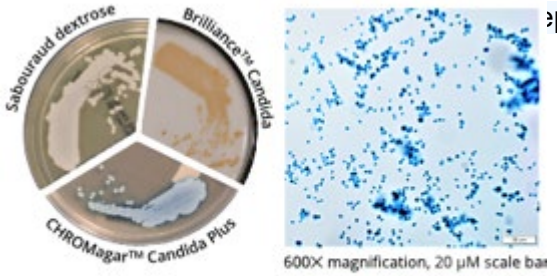


Fig. 3. Morphology of Clade VI isolates on various agar plates (left), and under microscope (right). Further clade-specific features are summarised in Table 2.

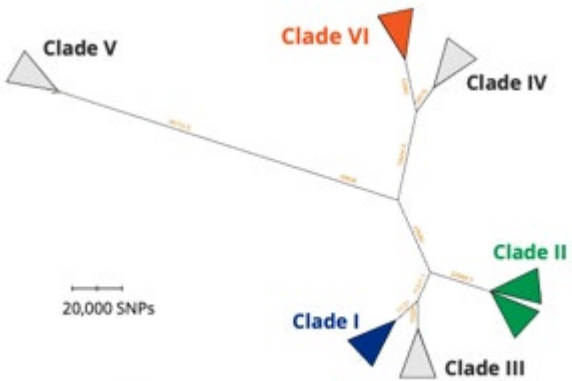


Fig. 4: Clade VI isolates (orange) were separated by ≥37,000 SNPs (up to 235,700 SNPs) from all known clades.

I. S.Asia
II. E.Asia
III. Africa
IV. S.America
V. Iran
VI. Indomalayan

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE BRABANT & ZEELAND

Candida auris

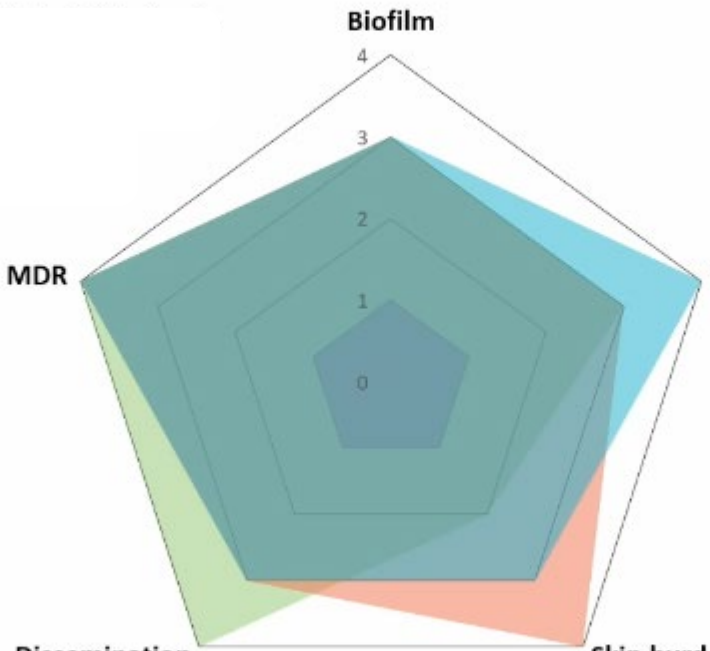
Table 2: Summary of features across clades. Clade VI was found to have unique features from other clades.

Clade	Geography	Outbreak-associated	Clinical relevance	Growth at 42°C	AMR pattern	Mating type
I	South Asian	✓	Invasive	✓	Resistant	*MTLa*
II	East Asian	✗	Otomycosis	✗	Susceptible	*MTLalpha*
III	African	✓	Invasive	✓	Resistant	*MTLalpha*
IV	South American	✓	Invasive	✓	Resistant	*MTLa*
V	Iran	✗	Otomycosis	?	Susceptible	*MTLa*
VI	Indomalayan	?	Suspected invasive	✓	Suspected susceptible	*MTLalpha*

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

Global epidemiology of *Candida auris*

FEATURES OF THE MAJOR EPIDEMIC CLADES



1982
(TMRCA)

Clade IV
South American

ERG11
Y132F, K143R,
K177R,N335S

TAC1B
F214S, K247E,
M635V, A615T,
P595H
F862_N866del

1983
(TMRCA)

Clade I
South Asian

ERG11
Y132F, K143R

TAC1B
A640V, R495G
A675V, A15T,
S195C, P595L

1984
(TMRCA)

Clade III
South African

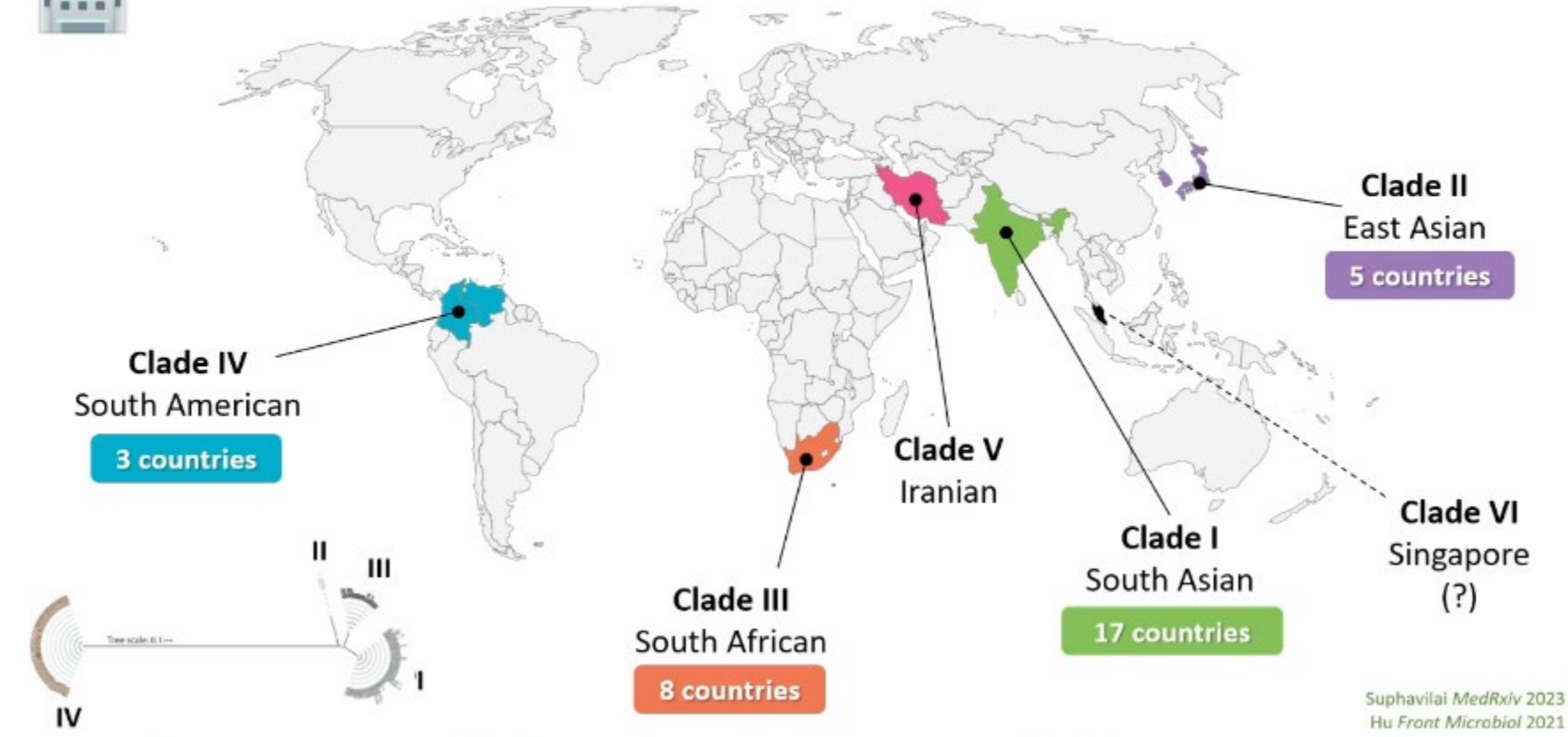
ERG11
VF126AL
(F126L)

Chow *mBio* 2020
Carty *Plos Path* 2023
Horton *Plos Path* 2023
Santana *Plos Path* 2023
Rybak *Curr Opin Microbiol* 2023
Chowdhary *Ann Rev Microbiol* 2023

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

Global epidemiology of *Candida auris*

SUDDEN EMERGENCE WITH A CHARACTERISTIC POPULATION STRUCTURE



Suphavilai *MedRxiv* 2023
Hu *Front Microbiol* 2021

MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

Candida auris

Morbidity and Mortality Weekly Report

***Candida auris* Isolates Resistant to Three Classes of Antifungal Medications — New York, 2019**

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

Pan-resistant strains

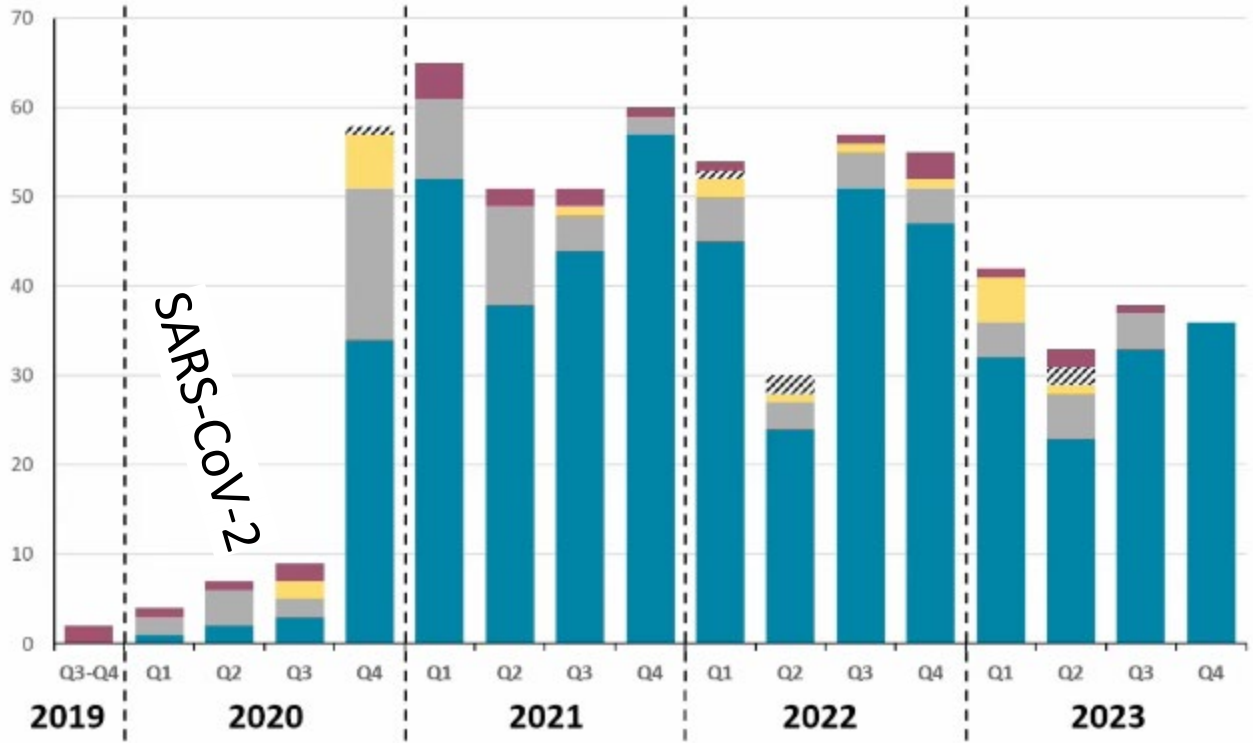
- 3 patients after treatment, no transmission
- Significant increase of transmission in ICU's 2020

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

[1]; cdc.gov/mmwr/volumes/69/wr/mm6901a2.htm?s_cid=mm6901a2_w cdc.gov/mmwr/volumes/70/wr/pdfs/mm7029a2-H.pdf

Emergence of *Candida auris* in Italy

Carriage/infection cases at HSM, Genoa (Liguria – IT), 2019-2023



Tot. cases: 652

Candidemia among carriers: **16%**

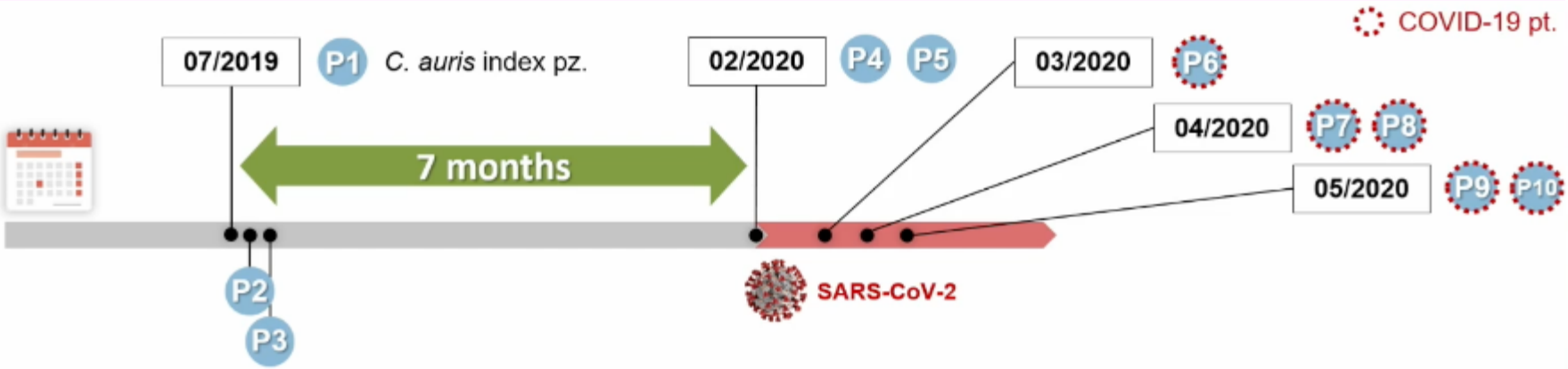
Carriage
- Skin
- Respiratory tract
- Urine
- Other

Infection
- Blood

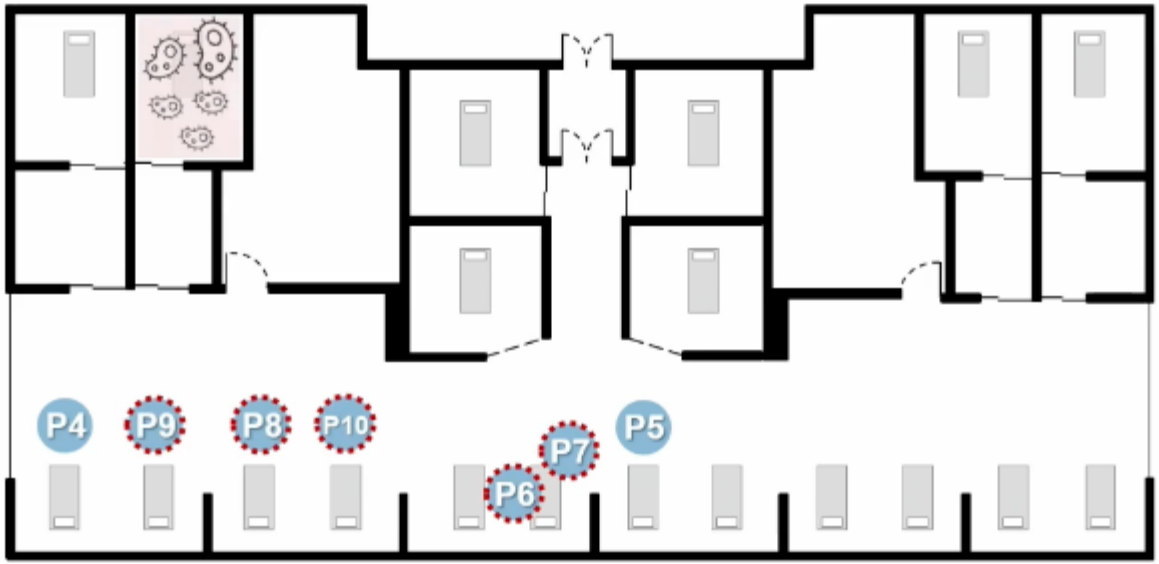
Codda *Eurosurv* 2023
Di Pilato V., data on file

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE BRABANT & ZEELAND

Emergence of *Candida auris* in Italy

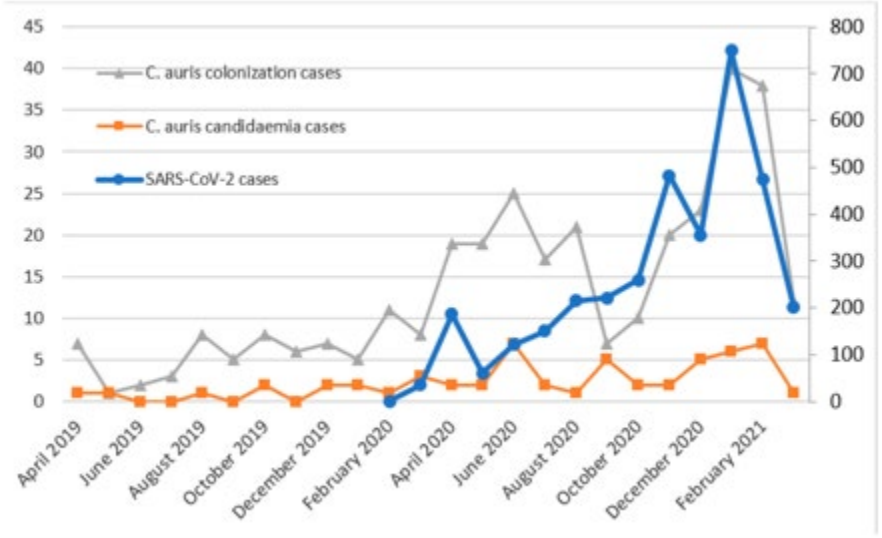


ICU converted to COVID-19 ward



Di Pilato *J Fungi* 2021

Impact of SARS-CoV-2 pandemic: Candidaemia and *C. auris*



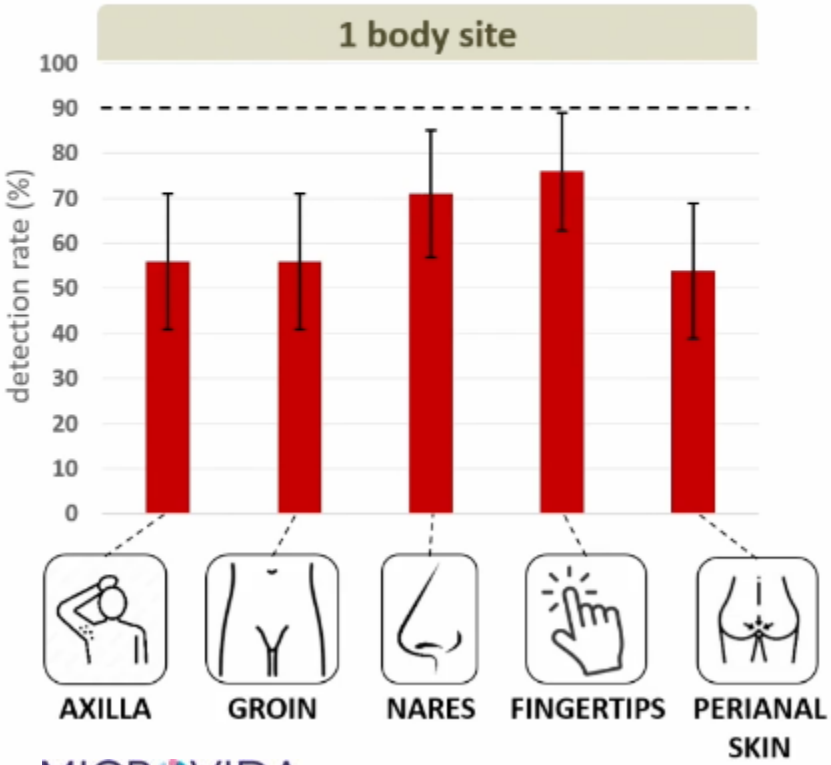
	2019 *n* (%)	2020 *n* (%)	2021 (Until March) *n* (%)
Candida albicans	18 (40.9)	15 (19.2)	11 (36.7)
Candida auris	9 (20.5)	33 (42.3)	14 (46.7)
Candida glabrata	8 (18.2)	9 (11.5)	1(3.3)
Candida parapsilosis	4 (9.1)	14 (17.9)	3 (1.0)
Candida tropicalis	3 (6.8)	4 (5.2)	1 (3.3)
Other species	2 (4.5)	3 (3.9)	0 (0.0)
Total	44	78	30

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

[1]; Mulet-Bayona JV JoF 2021 https://doi.org/10.3390/jof7060440

HIGH-YIELD BODY SITES CAN MAXIMIZE THE SENSITIVITY OF THE SCREENING

41 known *C. auris* carriers

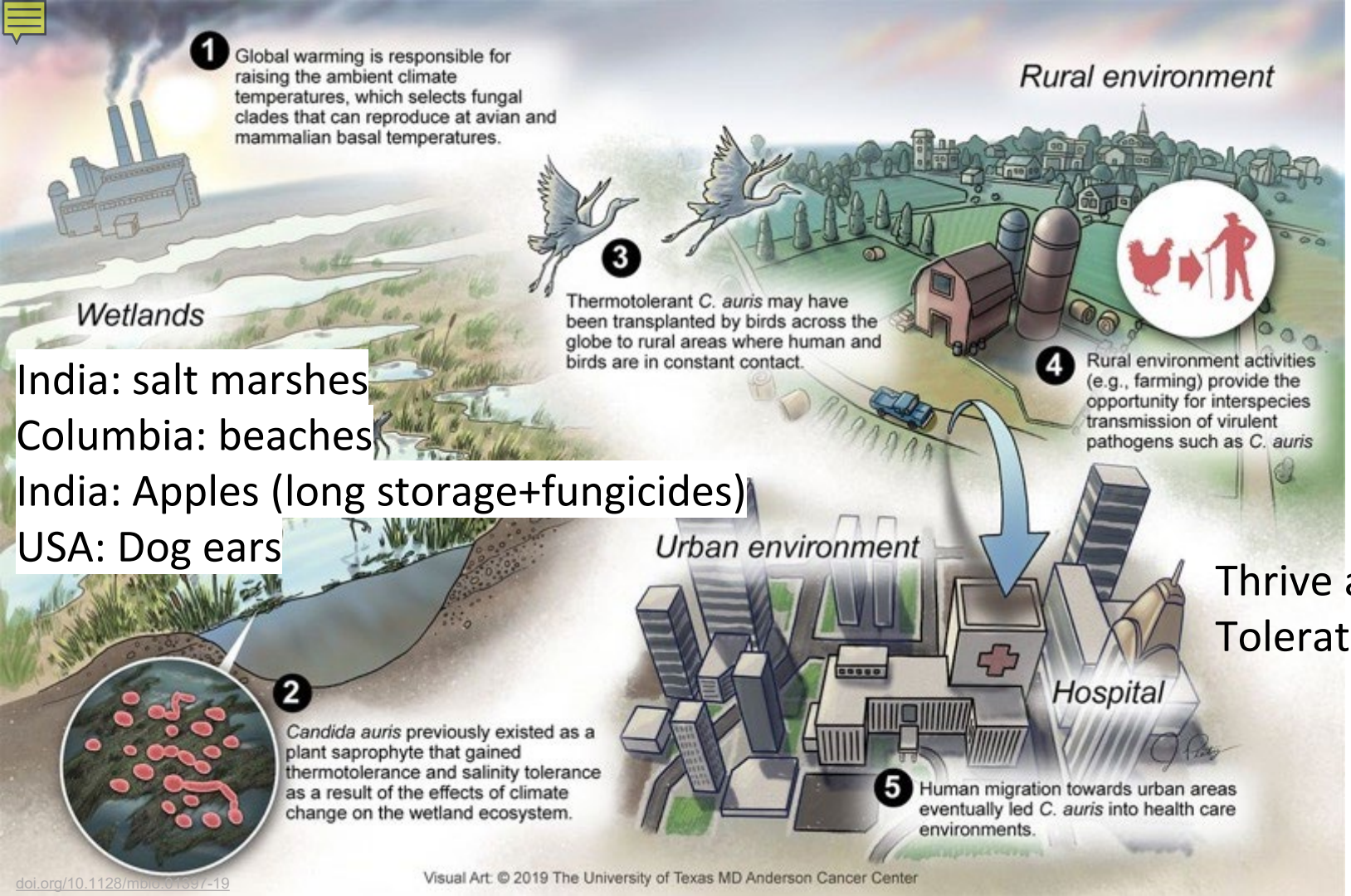


Sansom *CID* 2023

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE BRABANT & ZEELAND

Test name	Manufacturer	Test type	Specimen	TAT	Cost[a]	Detectable fungal pathogens	Regulatory status
ePlex BCID FP	GenMark	DNA hybridization/ electrochemical detection	Blood culture	90 min	High	11 *Candida* species[b] *Cryptococcus neoformans* *Cryptococcus gattii* *Fusarium* spp.[c] *Rhodotorula* spp.[d]	CE-IVD marked FDA-cleared
FilmArray BCID2	BioFire	Multiplex PCR	Blood culture	60 min	High	*C. albicans* *C. auris* *C. glabrata* *C. krusei* *C. parapsilosis* *C. tropicalis* *Cryptococcus neoformans/gattii*	CE-IVD marked FDA-cleared
Accelerate Pheno	Accelerate	FISH	Blood culture	90 min	High	*C. albicans* *C. glabrata*	CE-IVD marked FDA-cleared
MBT Sepsityper with Bruker Biotyper	Bruker	MALDI-TOF MS	Blood Culture	75 min	Low	Any validated fungal pathogens	CE-IVD marked FDA-cleared
Qvella Fast PBC with Bruker Biotyper	Qvella/Bruker	MALDI-TOF MS	Blood Culture	45 min	Low	Any validated fungal pathogens	CE-IVD marked FDA-cleared
T2Candida	T2 Biosystems	PCR with DNA hybridization/T2 MR detection	Direct EDTA blood	3 - 5 h	High	*C. albicans/C. tropicalis* *C. krusei/C. glabrata* *C. parapsilosis*	CE-IVD marked FDA-cleared
MagicPlex Sepsis Real-time Test	Seegene	Multiplex PCR	Direct whole blood	3 - 6 h	High	*C. albicans* *C. glabrata* *C. krusei* *C. parapsilosis* *C. tropicalis* *A. fumigatus*	CE-IVD marked
FungiPlex Candida IVD PCR	Bruker	Multiplex PCR	Direct whole blood, serum, plasma	3 h	High	*Candida* spp. *(C. albicans, C. parapsilosis, C. dubliniensis, C. tropicalis)* *C. glabrata* *C. krusei*	CE-IVD marked
SeptiTest-UMD	Molzym	Broad-range 16S/18S rRNA PCR/sequencing	Direct whole blood	8 - 12 h	High	Fungal pathogens from 40 genera	CE-IVD marked
Hybcell Pathogens DNA xB	CubeDx	Broad-range 16S/28S rDNA PCR/sequencing	Direct whole blood	3 h	High	19 fungal species and 5 fungal genera	CE-IVD marked
Karius Test	Karius	Metagenomic NGS	Direct plasma	1 - 3d	High	412 fungal species	LDT

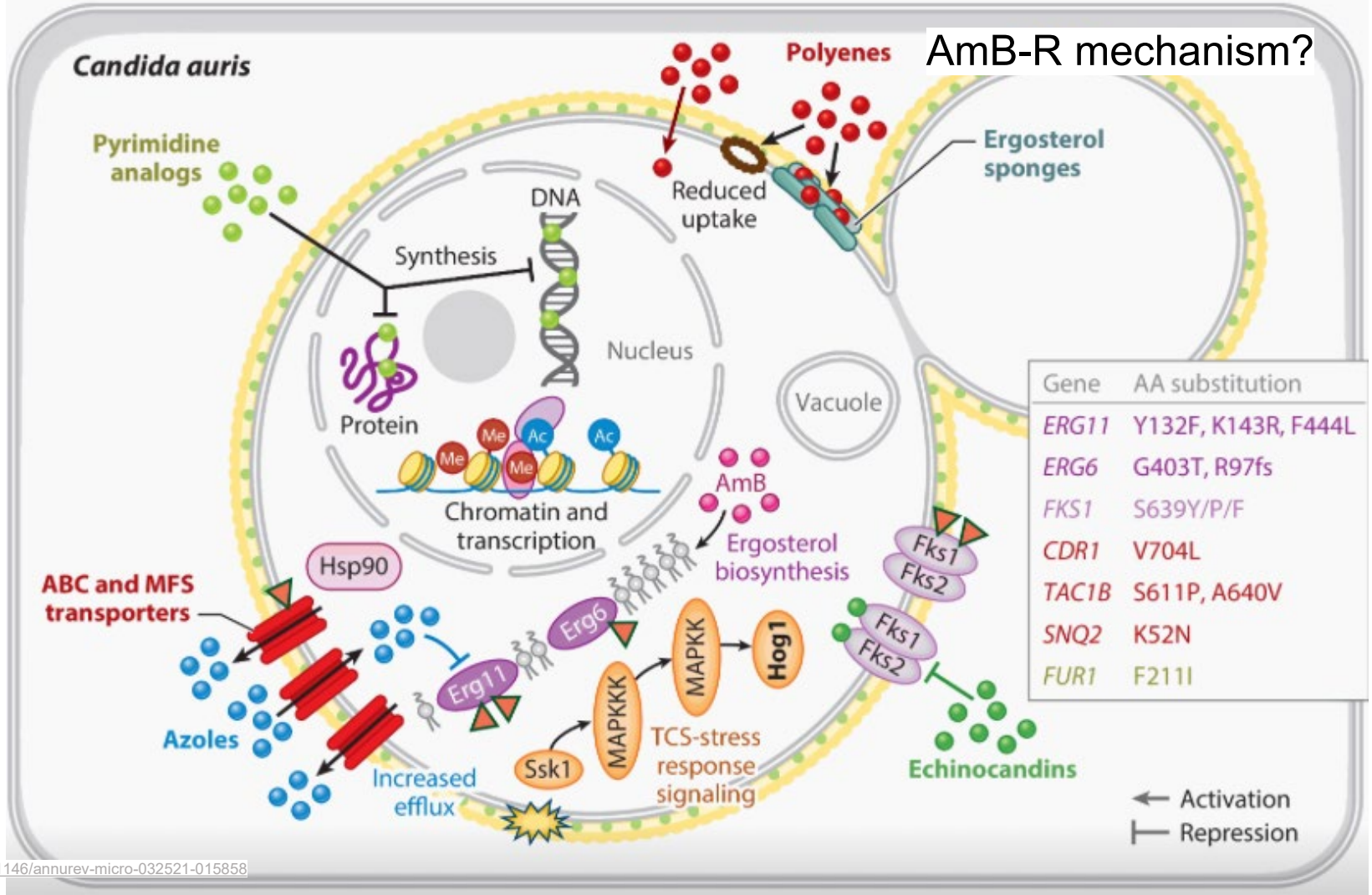
doi.org/10.1080/14737159.2023.2215929



Thrive at 42C
Tolerates 10% NaCl

doi.org/10.1128/mbio.01397-19

AmB-R mechanism?



Gene	AA substitution
ERG11	Y132F, K143R, F444L
ERG6	G403T, R97fs
FKS1	S639Y/P/F
CDR1	V704L
TAC1B	S611P, A640V
SNQ2	K52N
FUR1	F211I

doi.org/10.1146/annurev-micro-032521-015858

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

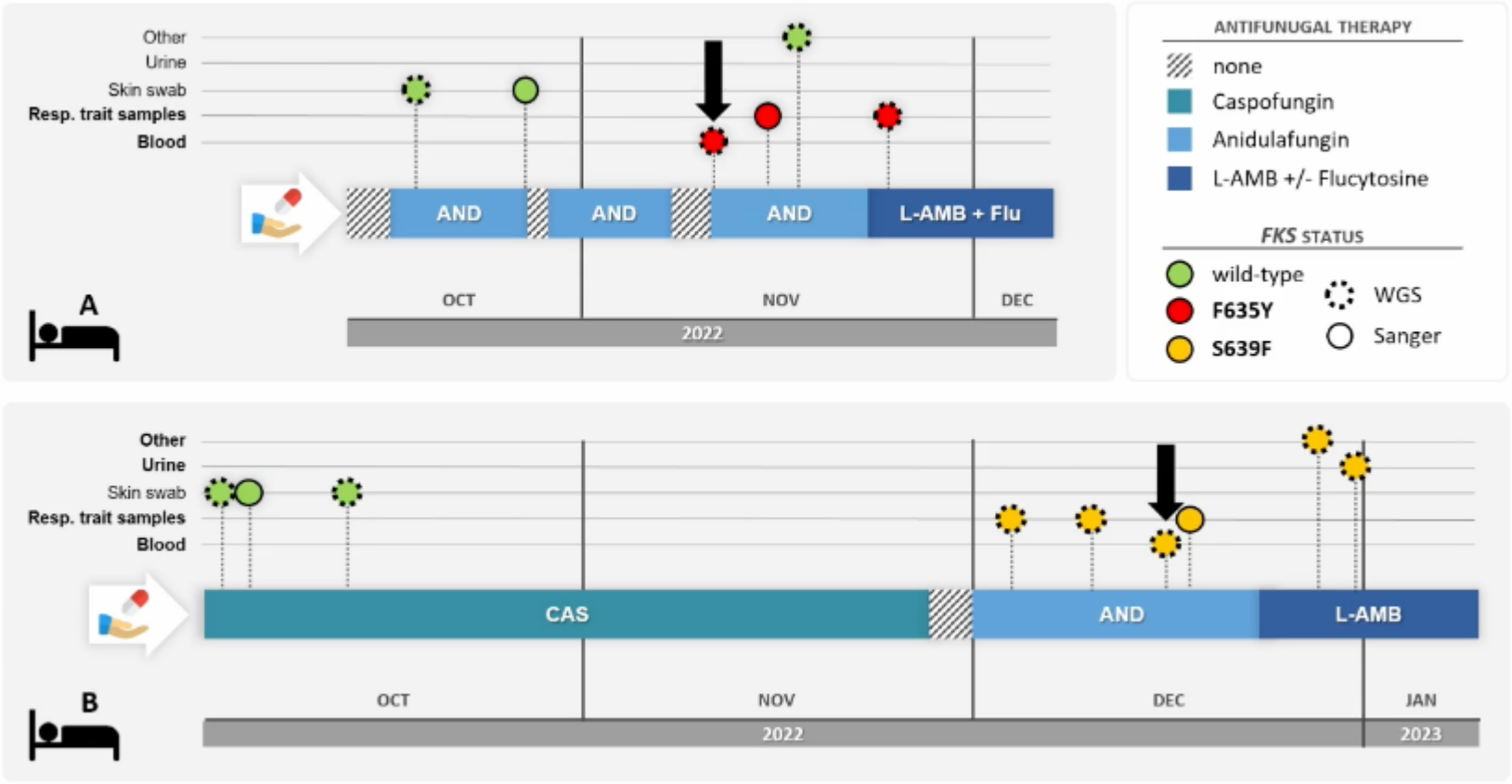
Anti-Fungal Susceptibility Testing Subcommittee

2024-04-19:
EUCAST has so far **not defined breakpoints for *C. auris***, due to the lack of clinical outcome data and the high degree of clonality of this species. Thus, there is currently insufficient evidence to set breakpoints, but EUCAST are aware of other provisional cut-offs which are being used elsewhere, and in some commercial systems.

Antifungal susceptibility testing of **amphotericin B** against *C. auris* has been associated with **overestimation of resistance** due to greater variability and wider MIC distributions and/or higher MICs in several studies, which are briefly summarised below. Consequently, **EUCAST warns against the use of the following tests for amphotericin B MIC testing of C. auris with S/R breakpoints of S ≤ 1 mg/L / R > 1 mg/L**

- Etest, (Etest, bioMerieux), gradient strip
- Mic Test Strip (MTS, Liofilchem), gradient strip
- Vitek 2 system (bioMerieux)
- Sensititre Yeast One (Thermofisher)

Antifungal Resistance: a pathognomonic sign of *C. auris*



Di Pilato *et al.* - *manuscript in preparation*

CDC guidelines for therapy of *C. auris* infections

Initial therapy

- An echinocandin is recommended

Echinocandin drug	Adult dosing	Paediatric dosing
Anidulafungin	Loading dose 200 mg IV, then 100 mg IV daily	Loading dose of 3.0 mg/kg/day (not to exceed 200 mg) then 1.5 mg/kg/day (not to exceed 100 mg) thereafter. [1 month to < 18 years]
Caspofungin	Loading dose 70 mg IV, then 50 mg IV daily	Loading dose 70 mg/m^2/day IV, then 50 mg/m^2/day IV (based on body surface area) [1–17 years]
Micafungin	100 mg IV daily	2mg/kg/day IV with option to increase to 200 mg/ day in children weighing over 40 kg or 4 mg/kg/day in children weighing ≤40 kg

Adapted from CDC

Clinically unresponsive or persistent fungemia for >5 days

- Switch to a liposomal amphotericin B (5 mg/kg daily)

For pan-resistant strains

- Combination antifungal treatment (in vitro data)

CDC, Centers for Disease Control and Prevention; IV, intravenous.

Centers for Disease Control and Prevention. Treatment and management of *C. auris* infections and colonization. https://www.cdc.gov/fungal/candida-auris/c-auris-treatment.html [accessed Mar 2024].

[4]

MIC interpretation

Polyene Class Drugs
Echinocandin Class Drugs
Triazole Class Drugs

Resistant breakpoints (FDA, CLSI)

Drug[1]	Tentative MIC Breakpoints (µg/ml)
Amphotericin B	≥2
Anidulafungin	≥4
Micafungin	≥4
Caspofungin	≥2
Fluconazole	≥32
Voriconazole	Fluconazole as surrogate
Itraconazole	
Posaconazole	
Isavuconazole	

Epidemiological cutoff values (proposed, 97.5%)

Drug[2]	CLSI	EUCAST
Amphotericin B	2	1
Anidulafungin	0.5	1
Micafungin	0.25	0.25
Caspofungin	-	-
Fluconazole	≥64	≥64
Voriconazole	16	4
Itraconazole	0.5	1
Posaconazole	0.125	0.25
Isavuconazole	1	4

Taken from CDC

CDC, Centers for Disease Control and Prevention; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee for Antimicrobial Susceptibility Testing; MIC, minimal inhibitory concentration.

1. Centers for Disease Control and Prevention. Antifungal susceptibility testing and interpretation. https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html [accessed Mar 2024]; 2. Arendrup MC et al. *Antimicrob Agents Chemother*. 2017;61:e00485-17

Reference methods CLSI vs EUCAST

Essential agreement (±1 twofold dilution) - 100 isolates, different clades[1]

Drug	% EA
Amphotericin B, fluconazole, flucytosine*	90–100%
Echinocandins	83–90%
Voriconazole and isavuconazole	71%
Posaconazole and itraconazole	40–50%

Taken from Siopi M et al. 2024[1] with the author's permission

Drug and AFST method	MIC (mg/liter)† 0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	≥64	MIC range (no. of dilutions‡)	GM	MIC_{50}	MIC_{90}
AMB																				
CLSI							2	16	58	35	4	6	2				0.125 to 8 (7)	0.66	0.5	2
EUCAST	NT		NT					1	15	107							0.25 to 1 (3)	0.91	1	1

Taken from Arendrup MC et al. 2017[2]
Reproduced with permission from American Society for Microbiology. Antimicrobial Agents and Chemotherapy, 2017, volume 24, pages e00485-17, DOI 10.1128/AAC.00485-17

Proposed ECOFFs

CLSI	EUCAST
2 mg/l	1 mg/l

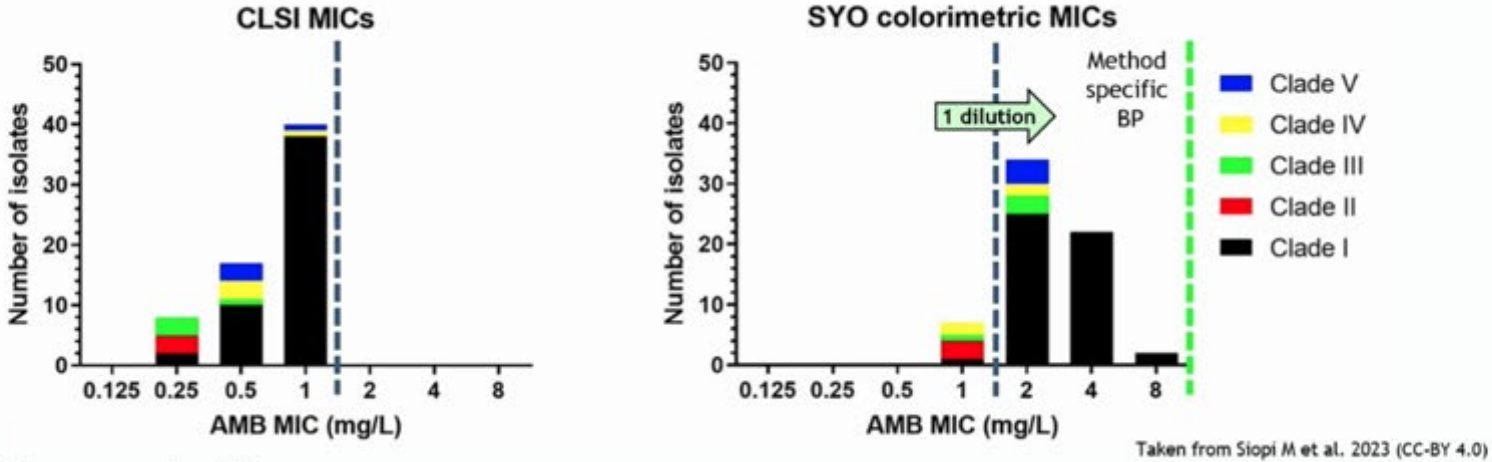
Resistance:

CLSI	EUCAST
6.5%	0%

* Flucytosine is not available in Spain. †Modal MICs are indicated with underlined numbers and grey shading, and values in parentheses represent the number of isolates with an MIC equal or less than the MIC indicated due to truncation. Additional peaks are illustrated by underlining. ‡The number of dilutions each MIC distribution spanned is given in parentheses.
AFST, Antifungal susceptibility testing; AMB, Amphotericin B; CLSI, Clinical and Laboratory Standards Institute; ECOFF, epidemiological cut-off value; EUCAST, European Committee for Antimicrobial Susceptibility Testing; GM, geometric mean; MIC, minimal inhibitory concentration; NT, not tested; WT, wild type.

1. Siopi M et al. ECCMID. 2024. Abstract 04843; 2. Arendrup MC et al. *Antimicrob Agents Chemother*. 2017;61:e00485-17.

Overestimation of amphotericin B resistance with Sensititre YeastOne™ method



- Essential agreement = 29%
- Categorical agreement = 11% (89% major errors; MaE)
- MaE were reduced when the SYO ECV of 8 mg/l was used (0% MaE)

AMB, amphotericin B; CLSI, Clinical and Laboratory Standards Institute; ECV, epidemiological cut-off value; MaE, mean absolute error; MIC, minimal inhibitory concentration; SYO, Sensititre YeastOne™.

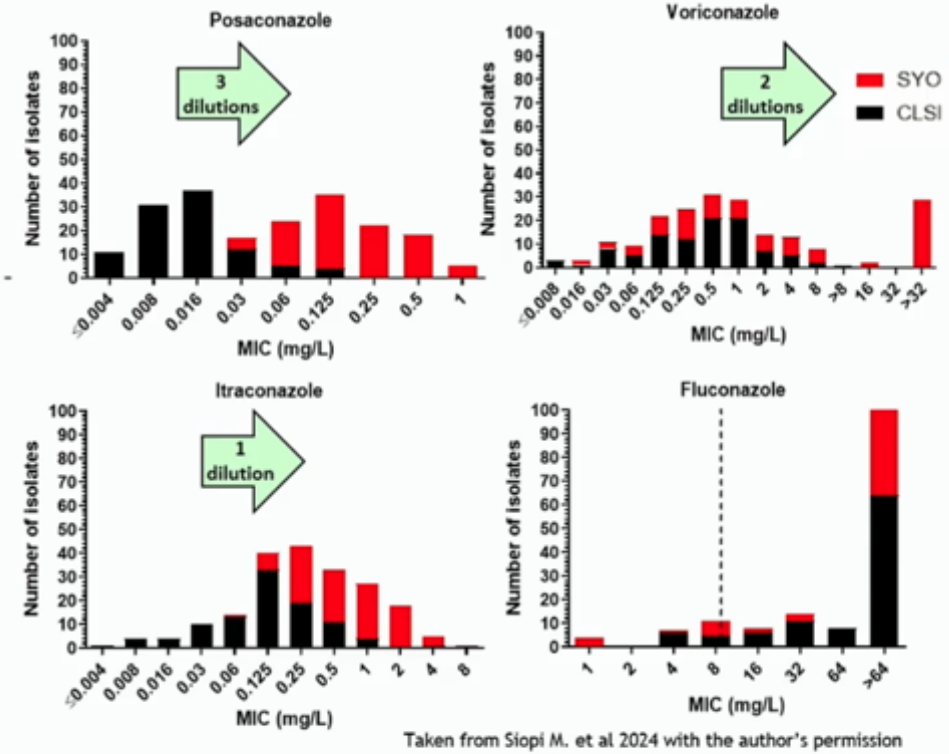
12 Siopi M et al. Microbiol Spectr. 2023;11:e0443122.

Sensititre YeastOne™

Azoles and *C. auris*

EA ±1/±2 two-fold dilutions[1]

- **Poor**
  - posaconazole (13%/24%)
  - fluconazole (27%/85%)
- **Moderate**
  - voriconazole (48%/74%)
  - itraconazole (63%/77%)
- **Based on CDC breakpoint**
  - fluconazole
  - (96% CA,1% VmE, 4% MaE)



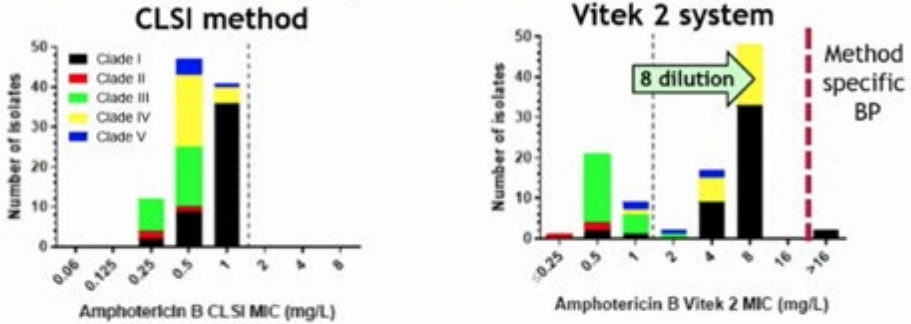
Taken from Siopi M. et al 2024 with the author's permission

CA, categorical agreement; CDC, Centres of Disease Control and Prevention; CLSI, Clinical and Laboratory Standards Institute; EA, essential agreement; MaE, mean absolute error; MIC, minimal inhibitory concentration; SYO, Sensititre YeastOne™; VmE, very major errors.

1. Leventaki S *et al*. 11th TIMM Conference. 2023. Poster P059; 2. Siopi M et al. ECCMID. 2024. Poster 2936.

Vitek® 2 system

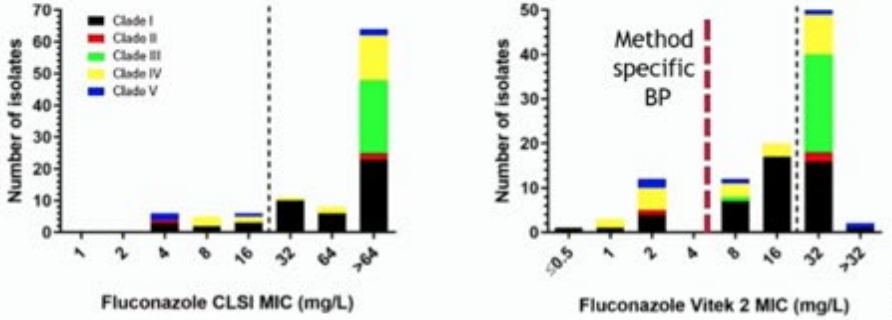
✓ Overestimation of amphotericin B resistance



Amphotericin B

- CA = 31%
- MaE = 69%
- MaE reduced using Vitek2 ECV 16 mg/l

✓ Underestimation of fluconazole resistance



Fluconazole

- CA = 69%
- VmE = 31%
- VmE reduced using Vitek2 ECV 4 mg/l

method specific breakpoint 4 mg/l?

Taken from Siopi M et al. 2024
With permission from American Society for Microbiology. Journal of Clinical Microbiology, 2024, Volume 62, page e0152823, DOI 10.1128/jcm.01528-23

CA, categorical agreement; CLSI, Clinical and Laboratory Standards Institute; ECV, epidemiological cut-off value; MaE, mean absolute error; MIC, minimal inhibitory concentration; VmE, very major errors.

Siopi M et al. *J Clin Microbiol*. 2024;e0152823.

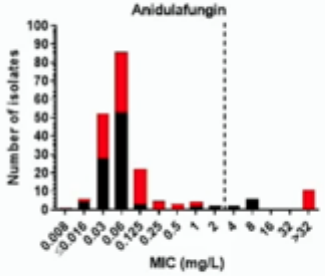
Gradient concentrations test strips

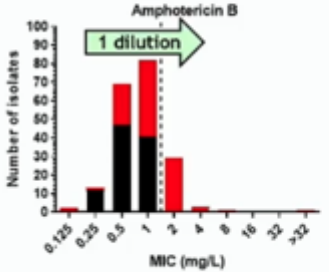
- ✓ Accurately predict fluconazole and echinocandin resistance
  - Fluconazole 98% CA, 1% MaEs, 1% VmEs
  - Echinocandins 99-95% CA, 1-5% MaEs

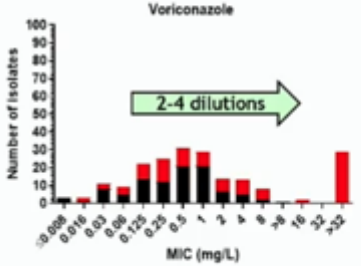
- ✓ Amphotericin B MTS™ MICs were 1 twofold dilution higher than CLSI
  - 66% CA, 34% MaEs
  - MaE reduced with MTS™ ECV 2 mg/l

method specific breakpoint 2 mg/l?

- ✓ MTS™ generated 2-4 twofold dilutions higher MICs than CLSI for azoles and 5-flucytosine







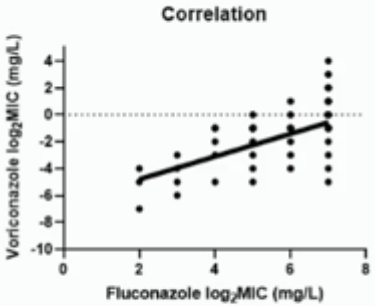
CA, categorical agreement; CLSI, Clinical and Laboratory Standards Institute; ECV, epidemiological cut-off value; MaE, mean absolute error; MIC, minimal inhibitory concentration; VmE, very major errors.

15 Siopi M et al. ECCMID. 2024. Poster 2936.

Taken from Siopi M et al. 2024 with the author's permission

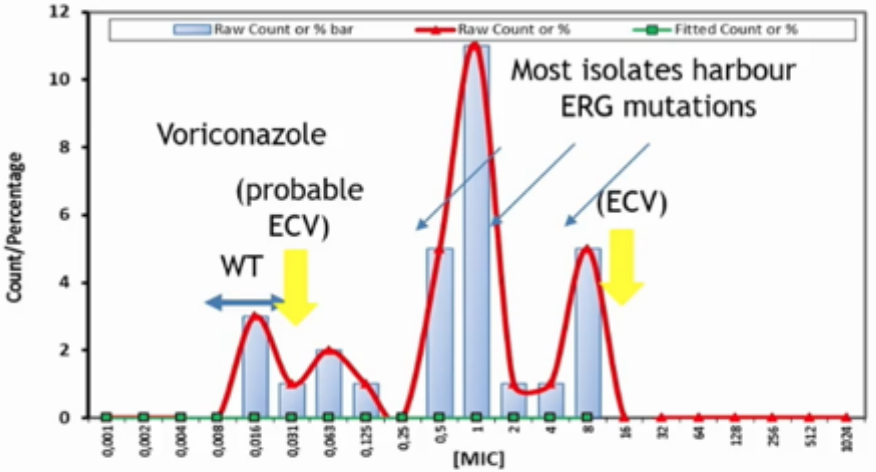
Other azoles and *C. auris*

Significant correlation with fluconazole MICs



Pearson r=0.59-0.92, P<0.0001

Cross resistance



method specific breakpoint 2 mg/l?

Categorical agreement

Between Fluconazole resistant and azole non-WT

Previous ECVs → <20% for all azoles

New cut-offs → >95% for all azoles

Drug	Proposed resistance breakpoints correlated with fluconazole resistance (mg/L)
Itraconazole	≥0.008
Voriconazole	≥0.06
Isavuconazole	≥0.008
Posaconazole	≥0.004

Taken from Paranos P et al. 2024 with the author's permission

ECV, epidemiological cut-off value; MIC, minimal inhibitory concentration; WT, wild type.

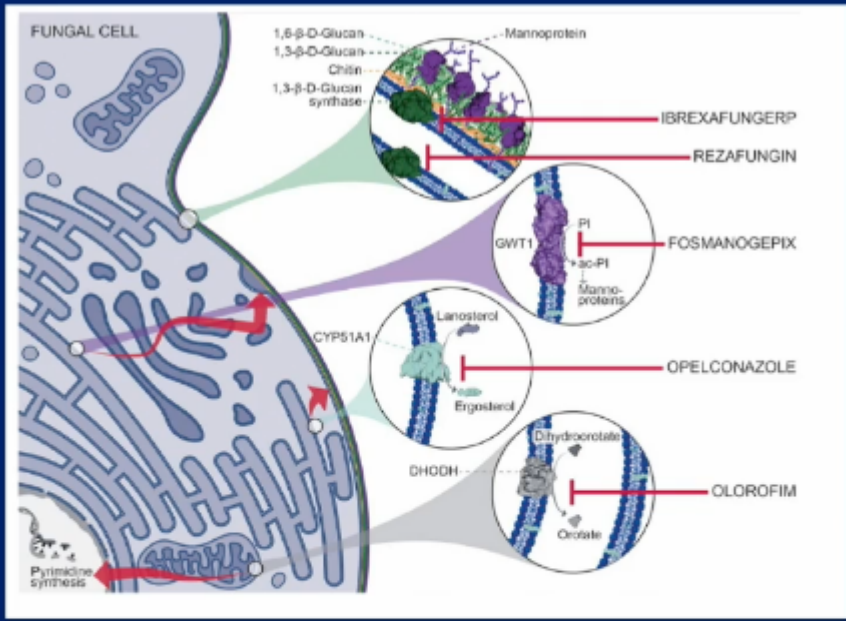
16 Paranos P et al. ECCMID. 2024. Poster 2967.

Conclusions

- **Problem: Different MIC distributions with each test**
  - Amphotericin B: Sensititre™ YeastOne, VITEK® 2 and GCS overestimate resistance
  - Fluconazole: VITEK® 2 underestimates resistance
  - Caspofungin: Sensititre™ YeastOne overestimates resistance
  - Other azoles: Commercial tests result in higher MICs than reference methods. Low categorical agreement with current ECV
- **Solutions: Method-specific ECVs can increase CA**
  - Amphotericin → Sensititre™ YeastOne/VITEK® 2 system AMB ECV 16 mg/l, GCS 2 mg/l
  - Fluconazole → VITEK® 2 system ECV 4 mg/l
  - Caspofungin → Check susceptibility to other echinocandins
  - Other azoles → ECV towards the lower end of MIC distribution
- **No problems**
  - Micafungin/anidulafungin with all methods
  - Fluconazole with Sensititre™ YeastOne and GCS

AMB, Amphotericin B; CA, categorical agreement; ECV, epidemiological cut-off value; GCS, gradient concentration strips; MIC, minimal inhibitory concentration.

- Echinocandins are the preferred treatment for *C. auris* infections.
- For a central nervous system infection, when echinocandins are unavailable, amphotericin B is the recommended treatment.
- Susceptibility testing is recommended for all isolates for which treatment is intended
- Rezafungin, a newly approved long acting echinocandin, and ibrexafungerp, a newly approved oral triterpenoid compound.



Mechanism of action of novel antifungal drugs

Antimicrob Agents Chemother. 2021; 65: e02694-20

Ibrexafungerp Demonstrates *In Vitro* Activity against Fluconazole-Resistant *Candida auris* and *In Vivo* Efficacy with Delayed Initiation of Therapy in an Experimental Model of Invasive Candidiasis

Nathan P. Wiederhold,[a] Laura K. Najvar,[a,b] Marcos Olivo,[a,b] Kelsey N. Morris,[a,b] Hoja P. Patterson,[a] Gabriel Catano,[a,b] Thomas F. Patterson[a,b]

Antimicrob Agents Chemother. 2023; 67: e0141922

Clinical Efficacy and Safety of a Novel Antifungal, Fosmanogepix, in Patients with Candidemia Caused by *Candida auris:* Results from a Phase 2 Trial

Jose A. Vazquez,[a] Peter G. Pappas,[b] Kenneth Boffard,[c] Fathima Paruk,[d] Paul A. Bien,[e] Margaret Tawadrous,[f] Eric Ople,[e] Pamela Wedel,[e] Iwona Oborska,[e] Michael R. Hodges[e]

Lancet. 2023; 401: 49-59.

Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

George R Thompson 3rd [1], Alex Soriano [2], Oliver A Cornely [3], Bart Jan Kullberg [4], Marin Kollef [5], Jose Vazquez [6], Patrick M Honore [7], Matteo Bassetti [8], John Pullman [9], Methee Chayakulkeeree [10], Ivan Poromanski [11], Cecilia Dignani [12], Anita F Das [13], Taylor Sandison [14], Peter G Pappas [15], ReSTORE trial investigators

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE BRABANT & ZEELAND

Skin colonization by *C. auris* is a risk factor for invasive infections, with candidemia developing in up to 25% of critically ill individuals.

Early detection and infection control can limit the spread of *C. auris*.

- Admission screening is a valuable tool in identifying and controlling new introductions of *C. auris*.
- Regular point prevalence surveys to control the spread of *C. auris*.
- Transmission-Based Precautions and, whenever possible, in a single room.
- Dedicated medical equipment and switching to single-use
- Disinfectants such as quaternary ammonia compounds are not effective against *C. auris*. chlorhexidine
- CDC recommends use of an EPA-registered, hospital-grade disinfectant effective against Clostridioides difficile spores.

Int J Antimicrob Agents. 2019; 54: 400-406

Control of *Candida auris* in healthcare institutions: Outcome of an International Society for Antimicrobial Chemotherapy expert meeting

Nikki Kenters[A,*], Martin Kiernan[B], Anuradha Chowdhary[C], David W. Denning[D], Javier Pemán[E], Katja Saris[A,F], Silke Schelenz[G], Ermira Tartari[H], Andreas Widmer[I], Jacques F. Meis[A,J], Andreas Voss[A,G,K]

Intern Med J. 2019; 49:1229-1243.

Diagnosis, management and prevention of Candida auris in hospitals: position statement of the Australasian Society for Infectious Diseases

Chong W Ong [1 2], Sharon C-A Chen [3 4], Julia E Clark [5 6], Catriona L Halliday [3 4], Sarah E Kidd [7], Deborah J Marriott [8], Caroline L Marshall [9], Arthur J Morris [10], C Orla Morrissey [11], Rita Roy [12], Monica A Slavin [13 14 15 16], Andrew J Stewardson [11], Leon J Worth [13 15 17 18 19], Christopher H Heath [20 21 22 23].

CDC Centers for Disease Control and Prevention

Infection Prevention and Control for *Candida auris*

Español (Spanish) Print

The primary infection control measures for prevention of *C. auris* transmission in healthcare settings are:

- Adherence to hand hygiene.
- Appropriate use of Transmission-Based Precautions based on setting.
- Cleaning and disinfecting the patient care environment (daily and terminal cleaning) and reusable equipment with recommended products, including focus on shared mobile equipment (e.g., glucometers, blood pressure cuffs).
- Communication about patient's *C. auris* status when patient is transferred.
- Screening contacts of newly identified case patients to identify *C. auris* colonization.
- Laboratory surveillance of clinical specimens to detect additional cases.

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

Take Home

- *C. auris* is primarily associated with the skin rather than the gut or mucosal surfaces.
- It spreads rapidly in health-care environments leading to frequent outbreaks of nosocomial blood stream infections.
- Resistance seems to be clade specific- clades I and III being almost universally resistant to fluconazole, clade II being almost universally susceptible.
- Spread of drug-resistant clones in health-care settings are concerning.

MICROVIDA
MEDISCHE MICROBIOLOGIE & IMMUNOLOGIE
BRABANT & ZEELAND

[1]

ESCMID GLOBAL 2024

Fungal highlights

Candida auris

Robbert Bentvelsen
Arts-microbioloog

Referentie [1] Candida auris: a growing threat (A. CHOWDHARY), ESCMID GLOBAL 2024 Barcelona

Referentie [2] Candida auris: current epidemiology and battle plan (V. DI PILATO), ESCMID GLOBAL 2024 Barcelona

Referentie [3] Discovery of the sixth Candida auris clade: molecular epidemiology in Singapore (Kwan Ki Karrie KO), E1035 ESCMID GLOBAL 2024 Barcelona

Referentie [4] Candida auris, how to treat and do the old susceptibility methods apply? (J. MELETIADIS), ESCMID GLOBAL 2024 Barcelona