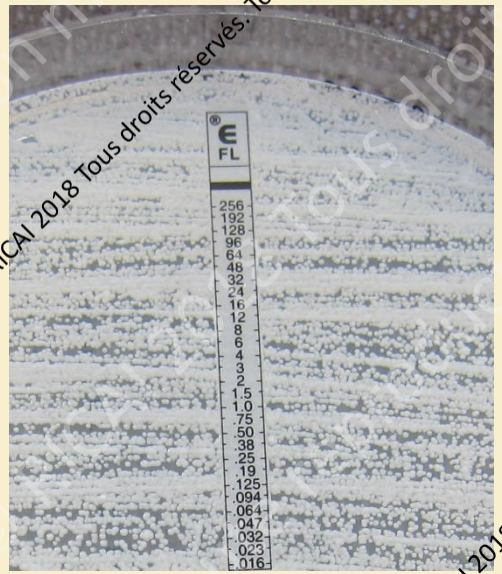
38e RÉUNION INTERDISCIPLINAIRE DE CHIMIOTHÉRAPIE ANTI-INFECTIEUSE

LUNDI 17 & MARDI 18 DÉCEMBRE 2018



Ces pathogènes méconnus: *Candida auris*

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Disclosures

DURING THE PAST 5 YEARS

- **RESEARCH GRANTS FROM MSD, GILEAD, AND ASTELLAS**
- **TRAVEL GRANTS FROM GILEAD, MSD, PFIZER, AND ASTELLAS**
- **SPEAKER'S FEE FROM GILEAD, MSD, AND ASTELLAS**

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Introduction

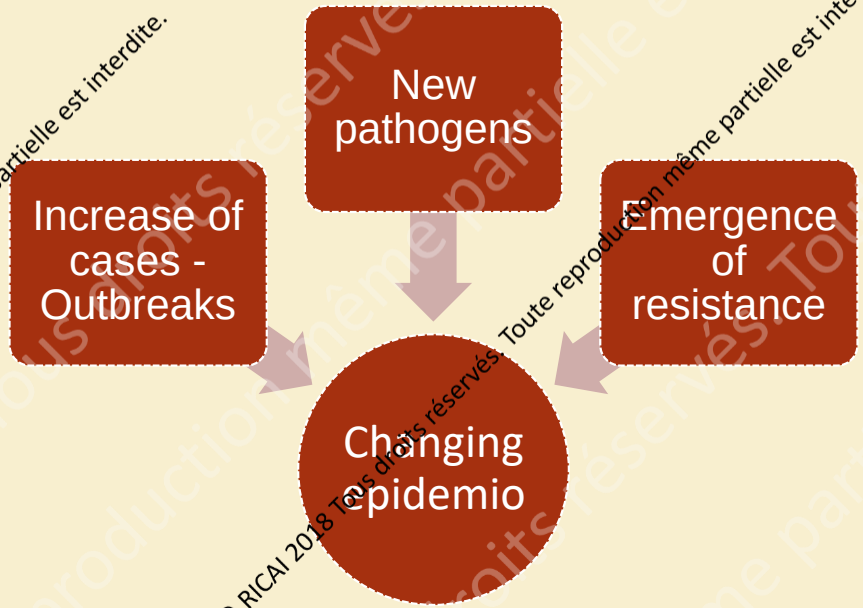
Statistics of the 10 most significant invasive fungal infections

Disease	Estimated life-threatening infections / year	Mortality rates
Aspergillosis	>200,000	30–95
Candidiasis	>400,000	46–75
Cryptococcosis	>1,000,000	20–70
Mucormycosis	>10,000	30–90
Pneumocystis	>400,000	20–80

IFI kill 1.5 million/year

≈ Tuberculosis, more than Malaria

Changing epidemiology



Brown GD, et al. 2012. Sci Transl Med 4:165rv113.

Introduction

Candida auris: an emerging pathogen

- First description 2009 (ear canal)
- Nosocomial fungemia caused by *C. auris* from South Korea in 2011
- Earliest isolate of *C. auris* found in 1996 (Korea)

Satoh K, et al. 2009. Microbiol Immunol 53:41-44.

Candida auris:
A drug-resistant germ that spreads in healthcare facilities

Candida auris (also called *C. auris)* is a fungus that causes serious infections. Patients with *C. auris* infection, their family members and other close contacts, public health officials, laboratory staff, and healthcare workers can all help stop it from spreading.

Why is *Candida auris* a problem?

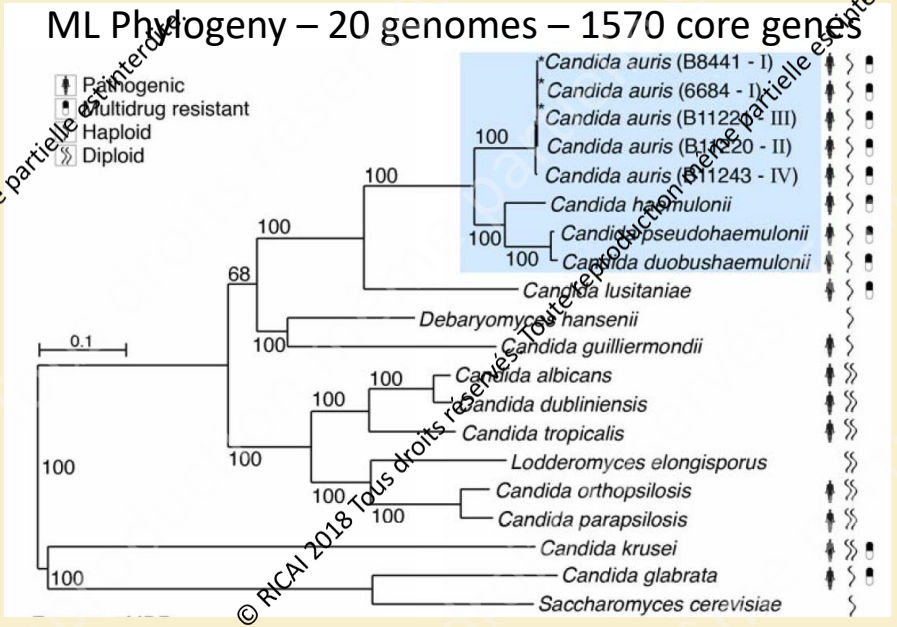
- **It causes serious infections**
- **It's often resistant to medicines**
- **It's becoming more common**
- **It's difficult to identify**
- **It can spread in hospitals and nursing homes**

CDC 2018, *Candida auris* factsheets.

Candida auris: Phylogenetics

- Distantly related to common species
  - ✓ *C. albicans* and *C. glabrata*
- Closely related to rarely observed and often multidrug-resistant species
  - ✓ *C. haemulonii*, *C. duobushaemulonii* and *C. pseudohaemulonii*

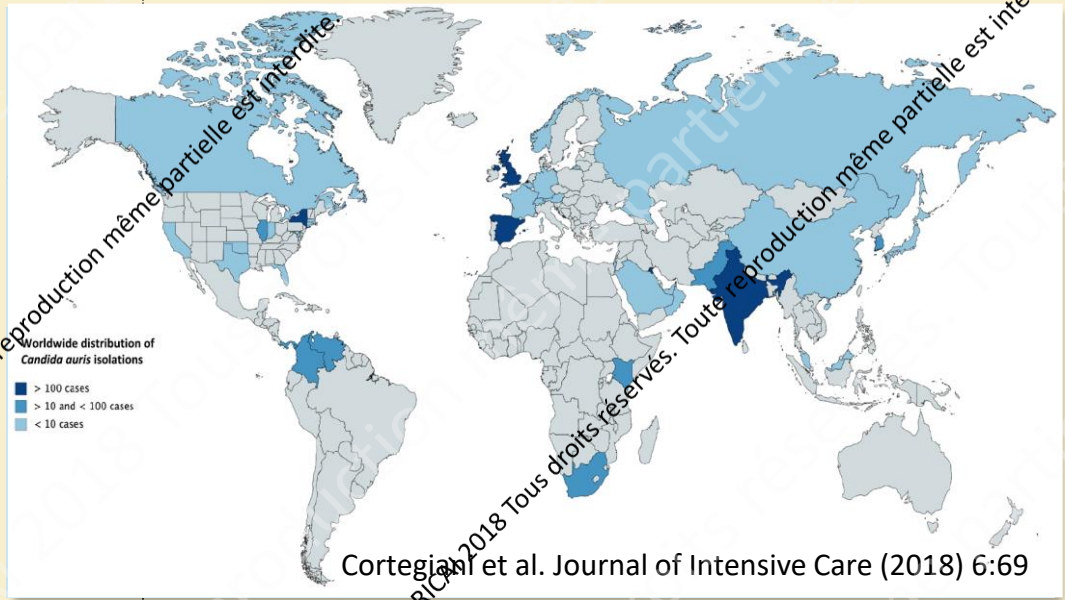
ML Phylogeny – 20 genomes – 1570 core genes



Munoz JF, et al. bioRxiv. 2018:299917

Candida auris: world-wide distribution

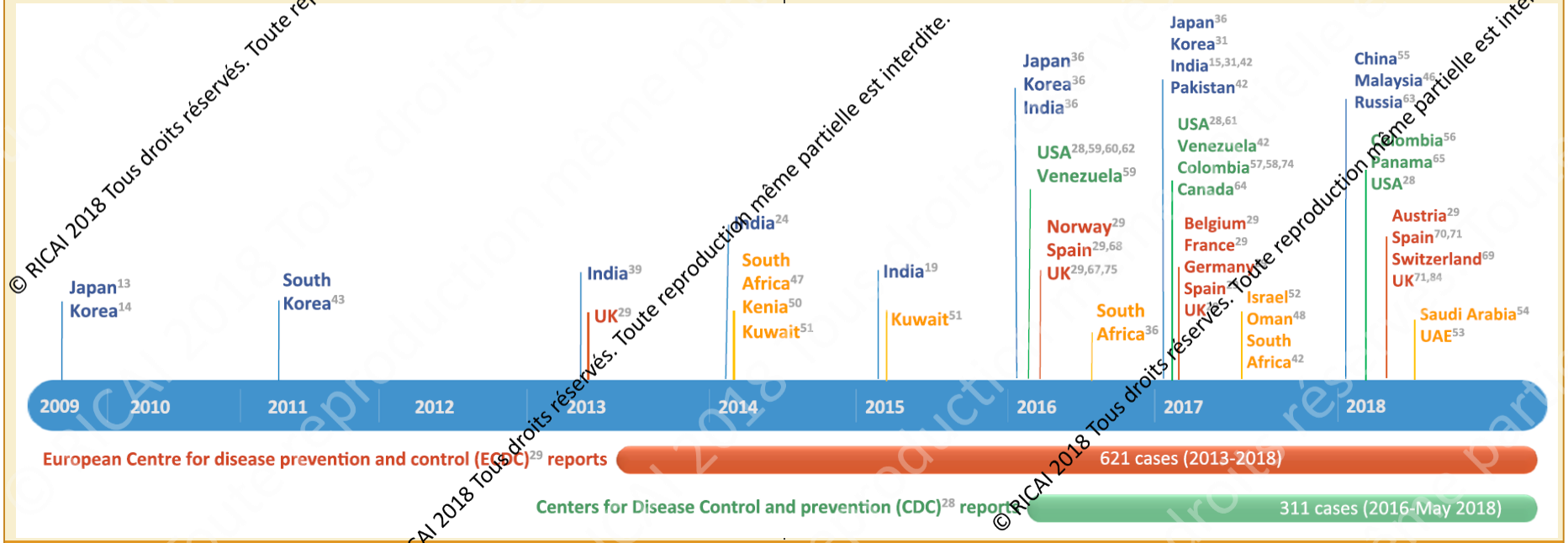
- First detection in Japan
- Increase
- Presence in many countries
- Epidemiology rapidly evolving



Cortegiani et al. Journal of Intensive Care (2018) 6:69

Chowdhary A, et al. 2017. PLoS Pathog 13:e1006290.
Arauz AB, et al. 2018. Mycoses 61:44-47.
Bidaud AL, et al. 2018. J Mycol Med. 2018, 28:568-573

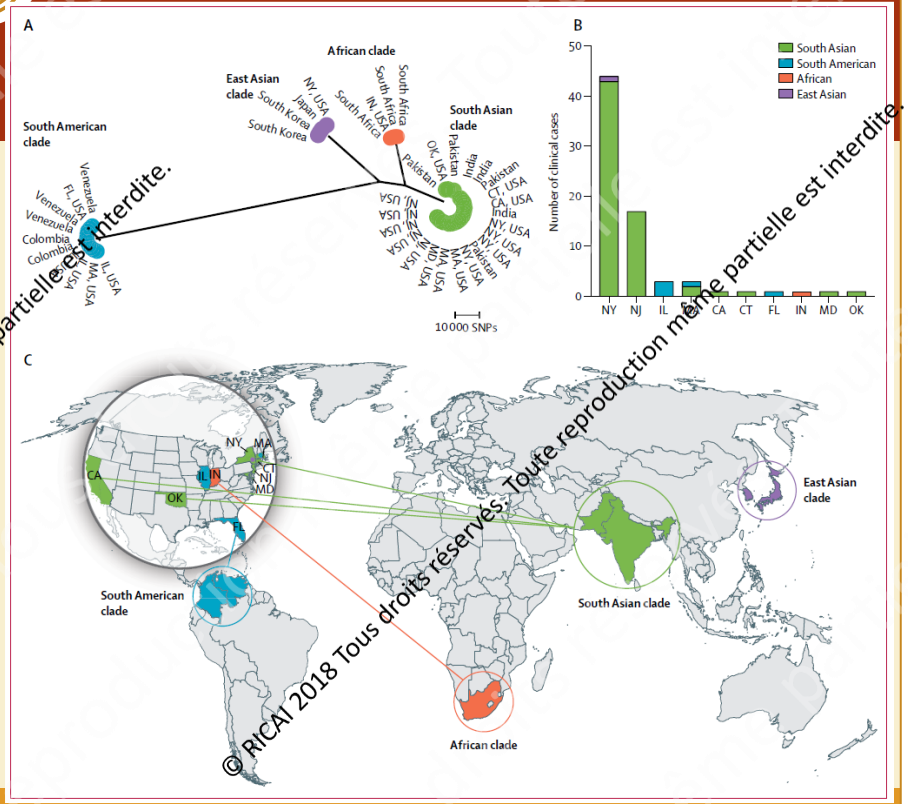
Candida auris: world-wide distribution



Candida auris: Molecular epidemiology - USA

- Molecular epidemiological survey
- 2013-2017, 133 cases
- Whole-genome sequencing
- Isolates from 10 US states

- *C. auris* was introduced several times into the USA.
- Local and ongoing transmission



Chow et al. 2018, *Lancet Infect Dis 18:1377-1384*

Candida auris: Epidemiology trends and world outbreaks

- Large healthcare-associated outbreaks in several countries
- Person-to-person transmission by direct contact
- Persistence in hospital environment
  - ✓ Surfaces
  - ✓ Shared equipment

Country	Ward	No. cases
UK - London	Cardio-Thor ICU	50
Spain	Surg ICU, other	41
India, Pakistan	several	multiple
Venezuela	ICU	18
Colombia	PICU	5
UK - Oxford	Neuro ICU	70
South Africa	several	multiple

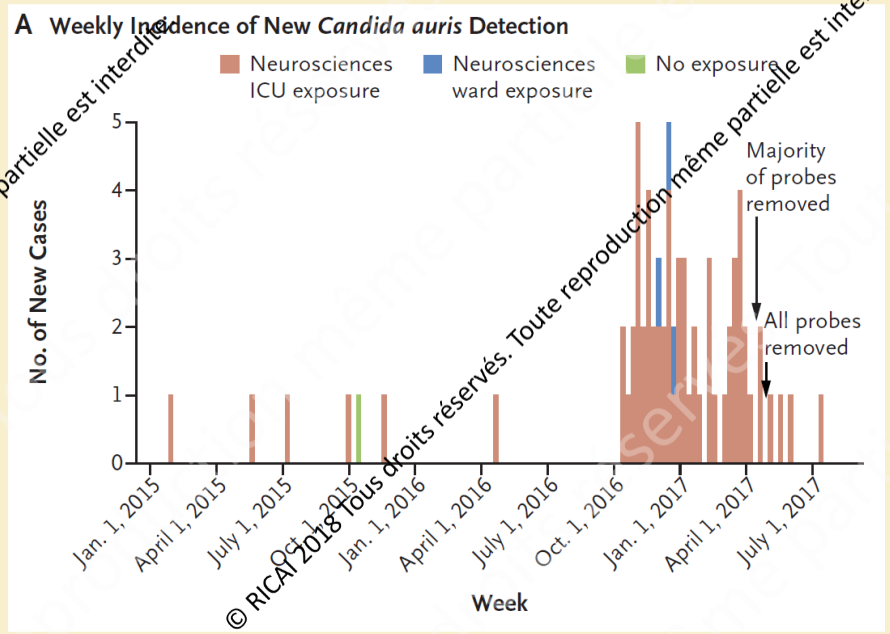
Ruiz-Gaitan A, et al. Mycoses 2018;61:498–505.
Chowdhary A, et al. 2017. PLoS Pathog 13:e1006290.
Schelenz S etal.. 2016. Antimicrob Resist Infect Control 5:35.

Govender NP, et al. Emerg Infect Dis. 2018;24(11):2036-2040.
Eyre DW et al. 2018, N Engl J Med 379:1322-31
PAHO/WHO Epidemiological Alert: 3 October 2016, Washington, D.C.

Candida auris: Epidemiology trends and world outbreaks

Hospital outbreak of *C. auris* colonization and infection – Oxford, UK

- Neurosciences ICU
- 2015-2017
- 70 patients colonized / infected with *C. auris*
- Use of reusable skin-surface axillary temperature probes



Eyre DW et al. 2018, N Engl J Med 379:1322-31.

C. auris: Clinical characteristics, risk factors, and outcome

Non-specific clinical presentation

- Bloodstream infections
- Other deep-seated infections: urinary tract, otitis, surgical wound, skin abscesses (related to catheter), myocarditis, meningitis, bone infections
- Frequent colonization (lung, urine, etc.)
  - Important++
  - Risk of transmission
  - Infection control

Risk factors not different from other *Candida* spp.

Crude in-hospital mortality range from 30 to 72%

Chowdhary A, et al. 2017. PLoS Pathog 13:e1006290

Jeffery-Smith A, et al. 2018. Clin Microbiol Rev 31:e00029

Candida auris: Infection prevention and control

Patients colonisés sans signe d'infection

- Non recommandé d'utiliser un traitement antifongique en systématique.
- Précautions standard et précautions contact (recommandation CDC)

Patients infectés ou colonisés ayant du matériel

- Surveillance des dispositifs (KT veineux centraux, urinaire, tubes de trachéotomie)
- Des qu'ils ne sont plus nécessaires les enlever.
- Précautions standard et précautions contact (recommandation CDC)

i.
Single room on contact precautions
ii.
Assess and enhance gown and glove use
iii.
Reinforce hand hygiene
iv.
Clean environment with a disinfectant that is effective against *C. auris* (i.e., those effective against *Clostridium difficile*)

Recommendations for treatment / prevention of *C. auris* | CDC 2017
Recommendations for infection control for *C. auris* | CDC 2017

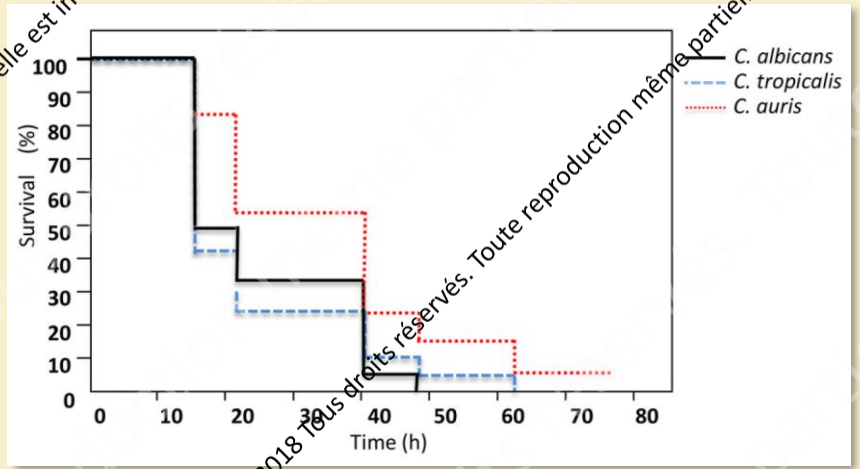
Candida auris: virulence

C. auris virulence factors

- Virulence genes for: Secreted aspartyl proteinases, secreted lipases, phosphatases, Hemolysin, …
- Adherence to surfaces and plastic (e.g., catheters)
- Biofilm formation
- Cellular morphology (aggregating and non-aggregating forms)

Chowdhary A, et al. 2017. PLoS Pathog 13:e1006290.

Virulence = *C. albicans*

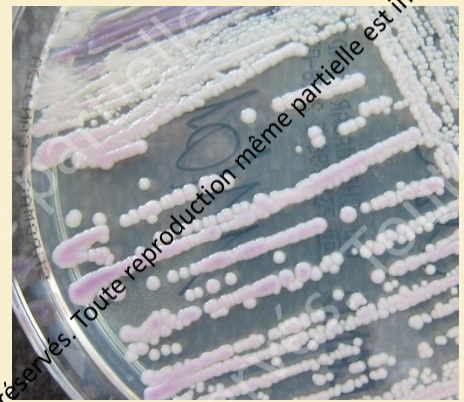


Borman AM, et al. mSphere 1:e00189-00116.

Candida auris: laboratory identification

- Smooth and white cream-colored on Sabouraud.
- Pale to dark pink on ChromAgar
- Germ-tube negative, no pseudo-hyphae
- Able to grow at 42 °C (≠ *C. haemulonii*)

Sabouraud



ChromAgar

Candida auris: laboratory identification

- Difficult identification by standard methods
- Misidentification with other *Candida* species, and even other genera
- ID by DNA sequencing (ITS, D1/D2, etc.)
- Specific PCR available

Identification Method	Organism *C. auris* can be misidentified as
Vitek 2 YST	*Candida haemulonii* *Candida duobushaemulonii*
API 20C	*Rhodotorula glutinis* *Candida sake*
BD Phoenix yeast ID system	*Candida haemulonii* *Candida catenulata*
MicroScan	*Candida famata* *Candida guilliermondii** *Candida lusitaniae** *Candida parapsilosis**
RapID Yeast Plus	*Candida parapsilosis**

Kathuria S, et al. 2015. JCM 53:1823-1830.
Mizusawa M, et al. 2017. JCM 55:638-640.

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

Candida auris: laboratory identification

- MALDI-TOF is a reliable identification method
- *C. auris* must be in the database
- Bruker Biotyper and Vitek-MS OK

Identification of 15 *C. auris* isolates by MALDI-TOF – routine technique – HEGP (Bruker)

Isolate	Identification	Score
CBS 12372	*Candida auris*	2,158
CBS 12773	*Candida auris*	2,001
CBS 12774	*Candida auris*	2,069
CBS 12775	*Candida auris*	2,093
CBS 12776	*Candida auris*	2,043
CBS 12777	*Candida auris*	1,989
CBS 10913	*Candida auris*	1,935
CBS 12373	*Candida auris*	2,063
CBS 12766	*Candida auris*	1,968
CBS 12767	*Candida auris*	1,897
CBS 12768	*Candida auris*	2,054
CBS 12769	*Candida auris*	2,028
CBS 12770	*Candida auris*	1,973
CBS 12771	*Candida auris*	1,95
CBS 12772	*Candida auris*	2,019

Mizusawa M, et al. 2017. JCM 55:638-640.

Bidaud AL, unpublished

Candida auris: antifungal resistance

- 90% of strains are resistant to FLU
- Elevated VRC MICs in 50% of isolates
- Posaconazole and isavuconazole show excellent in vitro activity
- Variable susceptibility to AMB: 15-30% of isolates exhibit high MIC (>2 µg/ml)
- Echinocandin resistance in fewer isolates (2-8%)
- Some isolates MDR

EUCAST

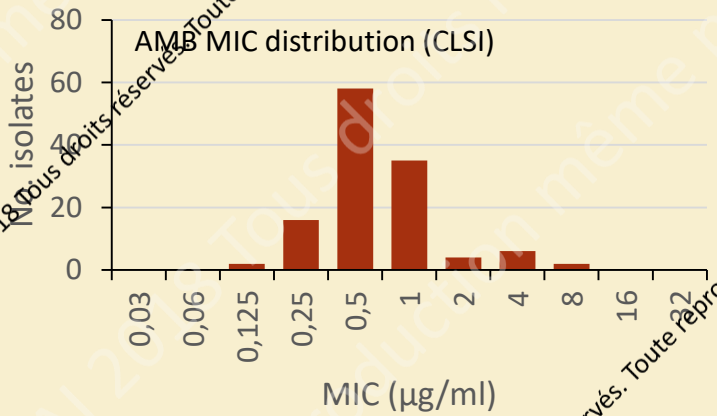
	MIC range	GM	MIC50	MIC90
FLU	0.5 to ≥64	53.74	≥64	≥64
ITC	≤0.008 to 1	0.13	0.125	0.5
VRC	≤0.008 to 4	0.54	0.5	2
ISA	≤0.008 to 2	0.090	0.125	0.5
PSC	≤0.008 to 0.5	0.033	0.032	0.125
AMB	0.25 to 1	0.92	1	1
AFG	0.002 to 2	0.17	0.125	1
MFG	0.002 to 4	0.13	0.125	0.25

Chowdhary A, et al. 2017. PLoS Pathog 13:e1006290.

Arendrup MC, et al. 2017. AAC 61:e00485

Candida auris: ECOFFs and tentative breakpoints

ECOFF determination



Several peaks for all compounds suggesting possible acquired resistance

Tentative breakpoints

Class/Drug	Tentative MIC Breakpoints (µg/mL)
Fluconazole	≥32
Voriconazole / 2nd gen. triazoles	N/A
Amphotericin B	≥2
Anidulafungin	≥ 4
Caspofungin	≥ 2
Micafungin	≥ 4

Arendrup MC, et al. 2017. AAC61:e00485-00417.

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

Candida auris

Mechanism of azole resistance

- WGS of 47 isolates (Pakistan, India, South Africa, and Venezuela)
- Decription of 9 mutations in ERG11 known to confer azole R in *C. albicans*
- substitutions strongly associated with geographic clades

→ indicative of acquired R

Lockhart SR, 2017. Clin Infect Dis 64:134-140.

Candida auris

Mechanism of echinocandin resistance

- Four isolates exhibited a S639F mutation, equivalent to the FKS1 HSI S645 position in *C. albicans*

Table 3. Amino acid substitutions in *FKS1* HSI in *C. auris* (n = 38) isolates

Isolate[a]	Site of isolation	Hospital	MIC (mg/L)				Amino acid substitution in *FKS1* HSI
			CAS	MFG	AFG	FLC	
VPCI 45/13	blood	D	16	16	8	64	S639F
VPCI 46/14	blood	C	8	16	8	64	S639F
VPCI 47/14	blood	C	8	16	8	64	S639F
VPCI 48/14	blood	C	4	16	8	64	S639F

- ✓ 34 *C. auris* isolates had low echinocandin MICs (range 0.125–1 mg/L) and presented WT genotype on FKS1 HSI sequencing

Chowdhary A, 2018. J Antimicrob Chemother 73:891-899.

Candida auris: treatment

No consensus exists for optimal treatment

Chowdhary A, et al. 2017. PLoS Pathog 13:e1006290

Jeffery-Smith A, et al. 2018. Clin Microbiol Rev 31:e00029

Candida auris: antifungal combination ?

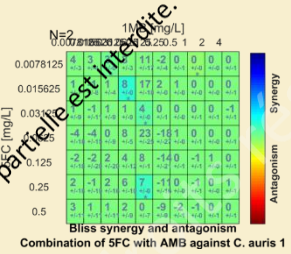
Echinocandins + Azoles

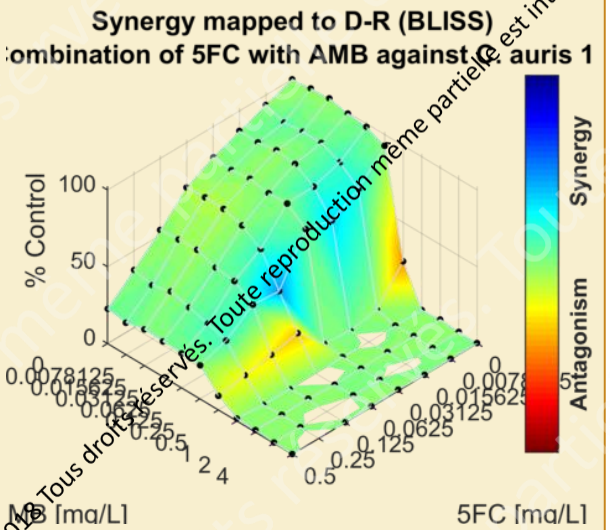
In vitro combination

- **SYN** for Mica+VRZ
- **IND** for
  - ✓ Mica+FCZ
  - ✓ CAS+FCZ
  - ✓ CAS+VRZ
- No antagonism

Fakhim H, et al. 2017 AAC. 61; e01056-17

Amphotercin B + Flucytosine





→Poster P193

Bidaud AL, unpublished

Candida auris: take-home messages

- Emerging pathogen, worldwide
- Often misidentified
- Responsible for invasive infections and outbreaks
- Multidrug resistance

Emerging fungal threats: a global challenge