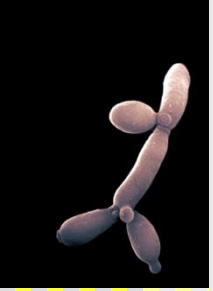
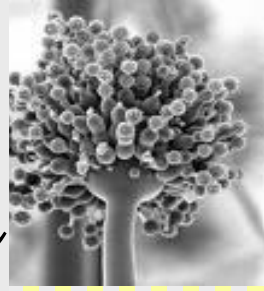


XX. Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Kongresi

13-16 Mart 2019, Antalya



2018'in Popüler Mikroorganizmaları

Candida auris: Risk Faktörleri, Olgu Grupları, Tedavi

Prof. Dr. Sevtap Arıkan Akdağlı, FESCMID, FECMM
Hacettepe Üniversitesi Tıp Fakültesi
Tıbbi Mikrobiyoloji Anabilim Dalı

SUNUM PLANI

- C. auris neden önemli?
- Tanımlama problemleri
- Olgular: Coğrafi dağılım, enfeksiyonlar
- Risk faktörleri
- Antifungal Direnç
- Tedavi
- Enfeksiyon Kontrol Önlemleri
- Sonuç

Özel konakta sık enfeksiyon etkeni mantarlar

- Yanık
- YBÜ
- Yabancı cisim
- DM
- Uç yaş grupları
- Anti-TNF ve diğer immünsupresan tedaviler
- SOT
- HIV
- Hematoonkolojik malignansi
- KİT, PKHT
- .....

CANDIDA
ASPERGILLUS

DİĞER
Mucorales
C. neoformans
Fusarium
P. jirovecii
Scedosporium
Dematisiyöz küfler.....

Scanning electron microscope image of ***Candida* yeast cells**
From: Science Photo Library

The world's ten most feared fungi

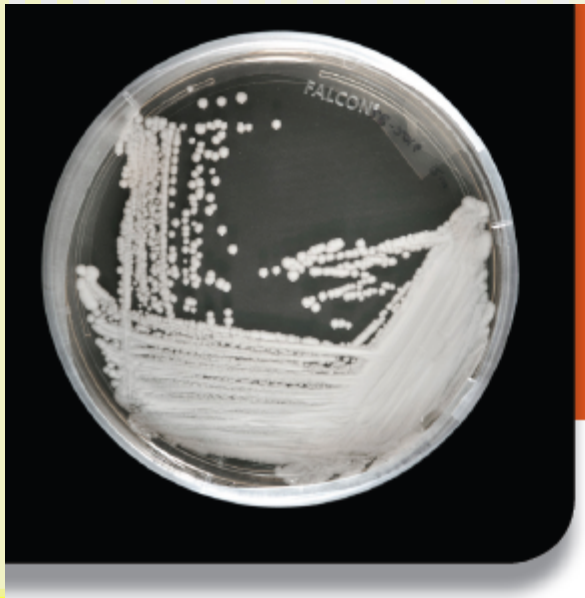
Kevin D. Hyde[1,2] · Abdullah M. S. Al-Hatmi[3,6] · Birgitte Andersen[4] · Teun Boekhout[5,6] · Walter Buzina[7] · Thomas L. Dawson Jr.[8,9] · Dan C. Eastwood[10] · E. B. Gareth Jones[12] · Sybren de Hoog[6,11] · Jingqian Kang[13] · Joyce E. Longcore[14] · Eric H. C. McKenzie[15] · Jacques F. Meis[11,16] · Laetitia Pinson-Gadais[17] · Achala R. Rathnayaka[2] · Florence Richard-Forget[17] · Marc Stadler[18] · Bart Theelen[6] · Benjarong Thongbai[18] · Clement K. M. Tsui[19,20]

Fungal Diversity

Published online: 10 November 2018

1. Cladophialophora bantiana: the brain-eating fungus
2. Candida auris: the ultra-fast emerging problem
3. Talaromyces marneffei—from HIV to everyone, the two-faced travel companion
4. Malassezia globosa: the dandruff fungus
5. Aspergillus flavus—the aflatoxin producing fungus
6. *Stachybotrys chartarum*: the uninvited lodger
7. Amanita phalloides: a deadly mushroom
8. Serpula lacrymans: wood decay basidiomycetes
9. Austropuccinia psidii: an invasive rust fungus with an extremely broad host range
10. Batrachochytrium dendrobatidis

Tsay et al. CID 2017; Aug 17



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.

www.cdc.gov/fungal/diseases/candidiasis/c-auris-drug-resistant.html

Simultaneous Emergence of Multidrug-Resistant *Candida auris* on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses

Shawn R. Lockhart,[1] Kizee A. Etienne,[1] Snigdha Vallabhaneni,[1] Joveria Farooqi,[4] Anuradha Chowdhary,[6] Nelesh P. Govender,[7] Arnaldo Lopes Colombo,[8] Belinda Calvo,[9] Christina A. Cuomo,[2] Christopher A. Desjardins,[2] Elizabeth L. Berkow,[1] Mariana Castanheira,[3] Rindidzani E. Magobo,[7] Kauser Jabeen,[4] Rana J. Asghar,[5] Jacques F. Meis,[10,11] Brendan Jackson,[1] Tom Chiller,[1] and Anastasia P. Litvintseva[1]

CID 2017:64 (15 January)

Methods. To understand the global emergence and epidemiology of *C. auris*, we obtained isolates from 54 patients with *C. auris* infection from Pakistan, India, South Africa, and Venezuela during 2012–2015 and the type specimen from Japan. Patient information was available for 41 of the isolates. We conducted antifungal susceptibility testing and whole-genome sequencing (WGS).

Results. Available clinical information revealed that 41% of patients had diabetes mellitus, 51% had undergone recent surgery, 73% had a central venous catheter, and 41% were receiving systemic antifungal therapy when *C. auris* was isolated. The median time from admission to infection was 19 days (interquartile range, 9–36 days), 61% of patients had bloodstream infection, and 59% died. Using stringent break points, 93% of isolates were resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins; 41% were resistant to 2 antifungal classes and 4% were resistant to 3 classes. WGS demonstrated that isolates were grouped into unique clades by geographic region. Clades were separated by thousands of single-nucleotide polymorphisms, but within each clade isolates were clonal. Different mutations in *ERG11* were associated with azole resistance in each geographic clade.

Conclusions. *C. auris* is an emerging healthcare-associated pathogen associated with high mortality. Treatment options are limited, due to antifungal resistance. WGS analysis suggests nearly simultaneous, and recent, independent emergence of different clonal populations on 3 continents. Risk factors and transmission mechanisms need to be elucidated to guide control measures.

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.

www.cdc.gov/fungal/diseases/candidiasis/c-auris-drug-resistant.html

Scientists are still learning about *Candida auris*

CDC and public health partners are working hard to better understand *C. auris* and answer the following questions so that we can continue to help protect people from this serious infection:

- Why is *C. auris* resistant to antifungal medicines?
- Why did *C. auris* start causing infections in recent years?
- Where did *C. auris* originally come from, and why has it appeared in many regions of the world at the same time?

What is CDC doing?

CDC is collaborating closely with partners to better respond, contain spread, and prevent future infections by:

- Advising healthcare workers and infection control staff on ways to stop the spread of *C. auris* and continually updating this guidance as we learn more about the infection.
- Working with state and local health agencies, healthcare facilities, and clinical microbiology laboratories to ensure that laboratories are using proper methods to detect *C. auris*.
- Testing *C. auris* strains to monitor for resistance to antifungal medicines.
- Examining the DNA of *C. auris* strains using whole genome sequencing to better understand how this germ is spreading in the United States and around the world.
- Working with public health partners in the United States and internationally to learn more about how *C. auris* spreads in healthcare facilities and to eliminate it from those facilities.

www.cdc.gov/fungal/diseases/candidiasis/c-auris-drug-resistant.html

"News from ESCMID-EFISG": Candida auris (January 2017)

- "… Due to the difficulty of the correct identification of *C. auris*, if proper identification methods are not available, we recommend the referral of suspected invasive isolates to a reference mycology laboratory.
- For more information you can visit the following links:
- · Risk Assessment of the European Center for Disease Control (ECDC)
- · Guidance for the laboratory investigation, management and infection prevention and control from cases of *Candida auris* elaborated by Public Health England (PHE)
- · CDC *Candida auris* website with links to Interim Recommendations, as well as links to papers on a global WGS analysis and investigation of the first seven US cases

This Newsletter is issued on behalf of EFISG by the ESCMID Executive Office. It contains announcements of EFISG-related matters and other information of interest to professionals in the infection field.

Candida auris

- Yıl 2009, Japonya (Avrupa: İngiltere, 2015)
- Çok ilaca dirençli
- Yüksek geçiş oranı, salgınlar
- İnvazif, (yara, kulak) enf.
- Tanımlama: MALDI-TOF / rDNA D1-D2 veya ITS sekans analizi
- Biyokimyasal stripler/VITEK-2 YST,…:

  C. haemulonii, C. famata, C. sake, S. cerevisiae, C. catenulata, R. glutinis,…

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Hangi sistemde hangi türler şüphe uyandırmalı?

Identification Method	Database/Software, if applicable	*C. auris* is confirmed if initial identification is *C. auris*.	*C. auris* is possible if the following initial identifications are given. Further work-up is needed to determine if the isolate is *C. auris*.
Bruker Biotyper MALDI-TOF	RUO libraries (Versions 2014 [5627] and more recent)	*C. auris*	n/a
	CA System library (Version Claim 4)	*C. auris*	n/a
bioMérieux VITEK MS MALDI-TOF	RUO library (with Saramis Version 4.14 database and Saccharomycetaceae update)	*C. auris*	*C. haemulonii* No identification
	IVD library	n/a	*C. haemulonii* No identification
VITEK 2 YST	Software version 8.01	*C. auris*	*C. haemulonii* *C. duobushaemulonii* *Candida* spp. not identified
	Older versions	n/a	*C. haemulonii* *C. duobushaemulonii* *Candida* spp. not identified
API 20C		n/a	*Rhodotorula glutinis* (with characteristic red color present) *C. sake* *Candida* spp. not identified
BD Phoenix		n/a	*C. catenulata* *C. haemulonii* *Candida* spp. not identified
MicroScan		n/a	*C. lusitaniae** *C. guilliermondii** *C. parapsilosis** *C. famata* *Candida* spp. not identified
RapID Yeast Plus		n/a	*C. parapsilosis** *Candida* spp. not identified

* *C. guilliermondii, C. lusitaniae,* and *C. parapsilosis* generally make hyphae or pseudohyphae on cornmeal agar. If hyphae or pseudohyphae are not present on cornmeal agar, the isolate should raise suspicions of being *C. auris* as *C. auris* typically does not make hyphae or pseudohyphae. However, some *C. auris* isolates have formed hyphae or pseudohyphae. Therefore, it would be prudent to consider any *C. guilliermondii, C. lusitaniae,* and *C. parapsilosis* isolates identified on MicroScan and any *C. parapsilosis* isolates identified on RapID Yeast Plus as possible *C. auris* isolates and further work-up should be considered.

If *C. auris* is confirmed: Place patient in transmission-based precautions, report to CDC (candidaauris@cdc.gov), and notify state and local health departments.

If *C. auris* is possible: Further work-up is needed to determine if actually *C. auris*. Send isolates to a reference lab, a state public health lab, a regional lab, or CDC for further identification. Place patient in transmission-based precautions and notify state and local health departments and CDC (candidaauris@cdc.gov).

Candida auris: a Review of the Literature

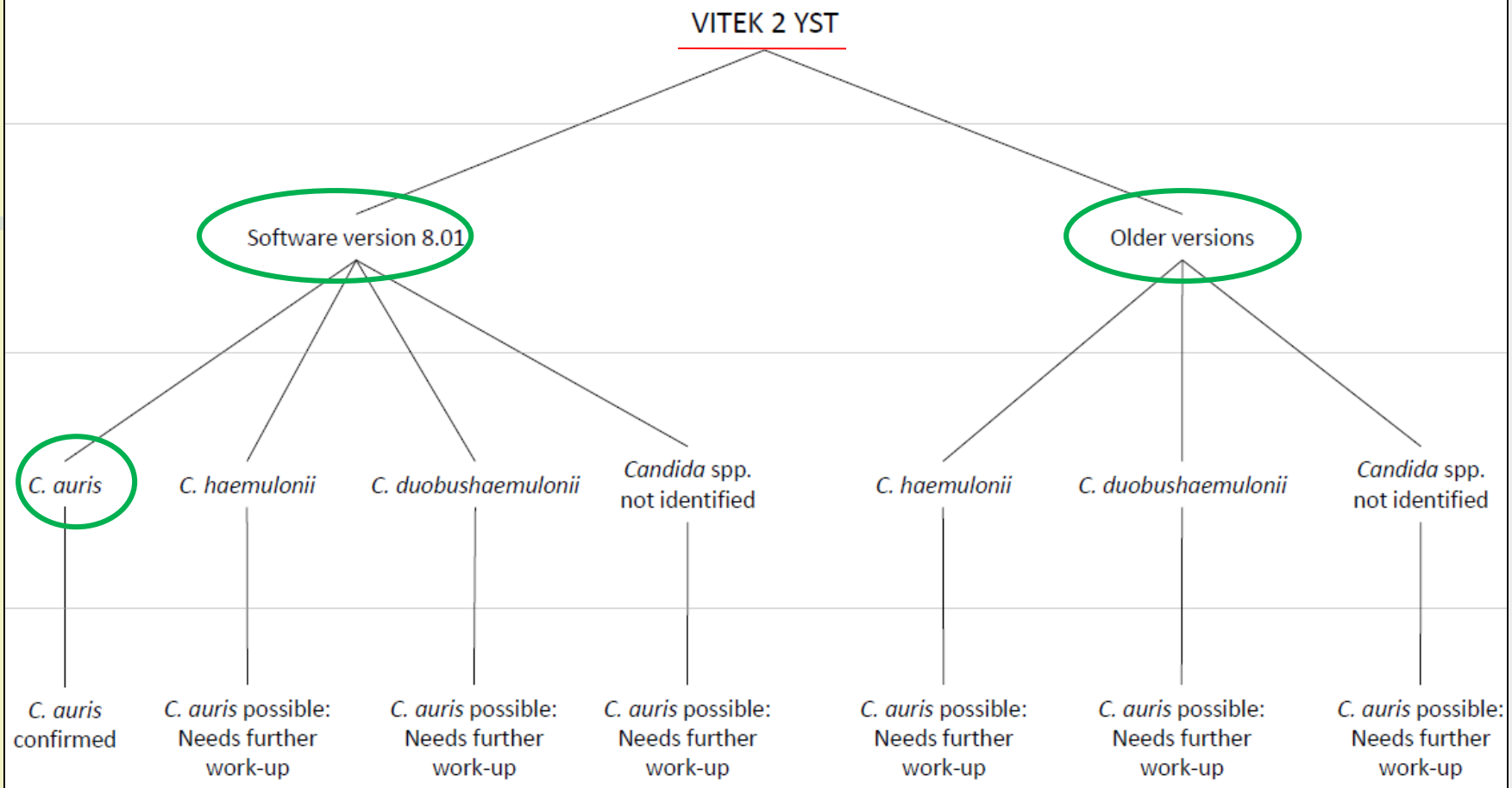
Anna Jeffery-Smith,[a,b] Surabhi K. Taori,[c] Silke Schelenz,[d] Katie Jeffery,[e] Elizabeth M. Johnson,[a] Andrew Borman,[a] *Candida auris* Incident Management Team, Rohini Manuel,[a] Colin S. Brown[a,f]

Clinical Microbiology Reviews January 2018 Volume 31 Issue 1 e00029-17

TABLE 2 Misidentification of *C. auris* by different diagnostic methods

Diagnostic method (manufacturer)	Misidentification example(s) (reference[s])
Biochemical	
API 20CAUX	*Rhodotorula glutinis* (5, 31, 33)
	C. sake (3, 15, 34)
	Unidentified (35)
API Candida	*C. famata* (12)
Phoenix (BD Diagnostics)	*C. haemulonii*, *C catenulate* (31)
Vitek	*C. haemulonii* (3–5, 7, 12, 14, 15, 26, 27, 33–36)
	C. lusitaniae (15)
	C. famata (3, 27)
MicroScan (Beckman Coulter)	*C. famata*, *C. lusitaniae*, *C. guilliermondii*, *C. parapsilosis*, *C. albicans*, *C. tropicalis* (12, 31)
MALDI-TOF MS	
Vitek MS (bioMérieux)	*C. albicans*, *C. haemulonii* (29)
	Not identified (28, 36)
MALDI Biotyper (Bruker Daltonics)	*Neisseria meningitides* serogroup A, *Pseudomonas rhizosphaerae* (29)[a]

[a]Subsequently, samples were identified as containing *C. auris* by ITS sequencing of ear swab samples; the bacteria isolated by MALDI-TOF MS likely represent colonizing bacteria.



***C. auris* confirmed:**
Place patient in transmission-based precautions, report to CDC (candidaauris@cdc.gov), and notify state and local health departments.

***C. auris* possible:**
Further work-up needed to determine if actually *C. auris*. Send isolates to a reference lab, a state public health lab, a regional lab, or CDC for further identification. Place patient in transmission-based precautions and notify state and local health departments and CDC (candidaauris@cdc.gov).

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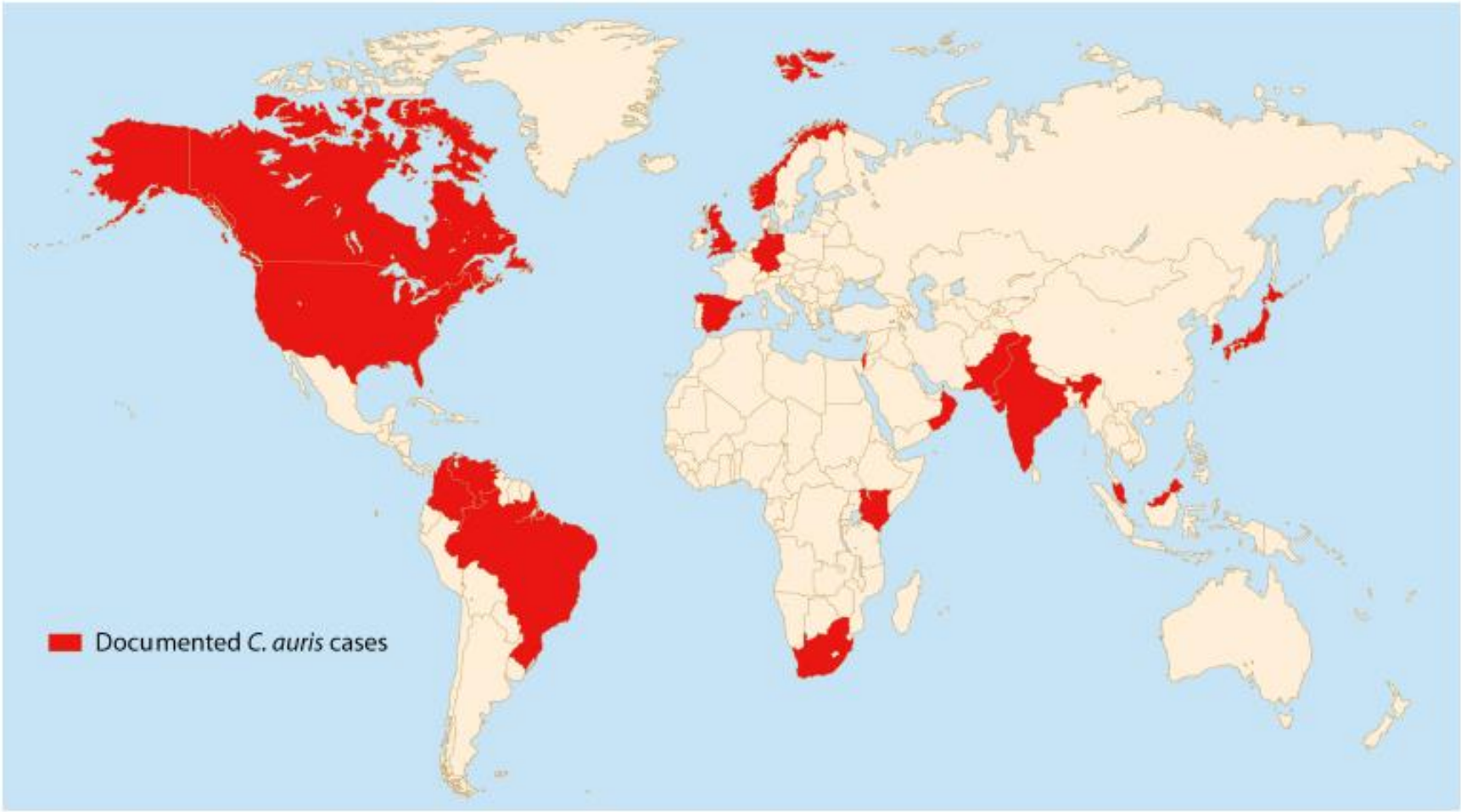

FIG 1 Countries that have reported detection of *C. auris* (shown in red). *C. auris* has been detected in mainland Norway and Canada, a single Brazilian hospital, and the continental United States, excluding Alaska.

Published 15 November 2017

OLGU GRUPLARI: Candida auris enfeksiyonları

TABLE 3 *Candida* auris infection cases by disease type reported in the literature

Type of disease or location of isolation[b]	No. of cases (reference[s])
Candidemia	291 (3–5, 7, 8, 10, 12, 14–16, 26, 27, 57, 58, 70, 71)
Central venous catheter tip	2 (70)
CNS	1 (12)
ENT	21[a] (1, 17, 58, 70, 72)
Respiratory tract	18 (26, 27, 36, 70)
Urogenital system	17 (12, 27, 56)
Abdominal	13 (12, 27, 70)
Skin and soft tissue, including surgical wounds	12 (3, 10, 27, 70)
Bone	2 (12, 70)

[a]Two associated with otomastoiditis and 19 from ear swabs of patients with otitis externa.
[b]CNS, central nervous system; ENT, ear, nose, and throat.

Clinical Microbiology Reviews January 2018 Volume 31 Issue 1 e00029-17

Atfedilen Mortalite ? Rapor edilmiş değişik oranlar (%28->50). Altta yatan hastalıktan bağımsız, kandidemi kaynaklı oranları söylemek zor…

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RİSK FAKTÖRLERİ 1

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

A CDC message to infection preventionists

Prepare for *C. auris* in your facility

3. Know which patients are at higher risk for *C. auris*. These include:
   i. Patients who have received healthcare in post-acute care facilities (e.g., nursing homes), especially those with ventilator units.
   ii. Patients with a recent history of receiving healthcare outside the United States in a country with known *C. auris* transmission (visit www.cdc.gov/fungal/candida-auris for a map of countries). These patients have a higher risk of *C. auris* infection or asymptomatic colonization.

RİSK FAKTÖRLERİ 2

İnvaziv enfeksiyon:

YBÜ'de olan, invaziv işlem yapılan, altta yatan ağır hastalık - hematolojik malignansi / diğer nedenlere bağlı immünsupresyon,….- olan olgularda
(-ciddi klinik tablo varlığında-) gelişiyor.

Kandidemi / SVK mevcudiyeti / perikardit / solunum yolu enf. / üriner sistem enf.

- Geniş spektrumlu antimikrobiyal kullanımı
- Antifungal ilaç kullanımı
- SVK, üriner kateter varlığı
- Düşük APACHE II skoru
- Vasküler cerrahi
- Diğer türlere bağlı kandidemilere oranla tanıdan önce daha uzun YBÜ'de kalma süresi

Jeffery-Smith et al. Clin Microbiol Rev 2018; 31: e00029; de Cássia Orlandi Sardi J et al. Microb Pathog 2018;125:116-121

Candida auris candidaemia in Indian ICUs: analysis of risk factors

Shivaprakash M. Rudramurthy[1], Arunaloke Chakrabarti[1]*, Raees A. Paul[1], Prashant Sood[1]†, Harsimran Kaur[1], Malini R. Capoor[2], Anupma J. Kindo[3], Rungmei S. K. Marak[4], Anita Arora[5], Raman Sardana[6], Shukla Das[7], Deepinder Chhina[8], Atul Patel[9], Immaculata Xess[10], Bansidhar Tarai[11], Pankaj Singh[1] and Anup Ghosh[1]

J Antimicrob Chemother 2017; **72**: 1794–1801

Table 2. Multivariate analysis of *C. auris* and non-*auris* candidaemia cases

Variables	OR (95% CI)	*P* value
C. auris and non-*C. auris* (model = AUC: 75.5%, accuracy: 93.6%, $R^2 = 0.137$, $P < 0.001$)		
public-sector hospital	2.2 (1.25–3.87)	0.006
northern India ICUs	2.1 (1.17–3.84)	0.012
underlying respiratory disease	2.1 (1.31–3.60)	0.002
urinary catheter	1.9 (1.11–3.42)	0.02
vascular surgery	2.3 (1.00–5.36)	0.048
prior antifungal exposure	2.8 (1.64–4.86)	<0.001
APACHE II at admission	0.8 (0.81–0.96)	0.007
C. auris and *C. tropicalis* (model = AUC: 74.1%, accuracy: 87.7%, $R^2 = 0.165$, $P < 0.001$)		
public-sector hospital	2.2 (1.25–4.07)	0.006
northern India ICUs	2.0 (1.09–3.73)	0.025
prior antifungal exposure	3.5 (1.95–6.52)	<0.001
APACHE II at admission	0.8 (0.81–0.96)	0.007
C. auris and *C. albicans* (model = AUC: 75.3%, accuracy: 79.8%, $R^2 = 0.188$, $P < 0.001$)		
public-sector hospital	2.7 (1.56–4.95)	0.001
underlying respiratory disease	2.1 (1.18–3.79)	0.011
prior antifungal exposure	3.3 (1.71–6.43)	<0.001
urinary catheter	2.3 (1.27–4.33)	0.006
APACHE II at admission	0.8 (0.82–0.97)	0.009
C. auris and *C. parapsilosis* (model = AUC: 69.5%, accuracy: 69.3%, $R^2 = 0.153$, $P < 0.001$)		
northern India ICU	3.9 (2.09–7.26)	<0.001
underlying respiratory disease	2.0 (1.08–3.82)	0.028
C. auris and *C. krusei* (model = AUC: 86.5%, accuracy: 77.3%, $R^2 = 0.558$, $P < 0.001$)		
northern India ICU	12 (4.8–34.1)	<0.001
urinary catheter	13 (4.93–35.5)	<0.001
broad-spectrum antibiotics	0.06 (0.009–0.475)	0.007
C. auris and *C. glabrata* (model = AUC: 62.2%, accuracy: 62.2%, $R^2 = 0.081$, $P < 0.011$)		
northern India ICU	2.8 (1.4–5.6)	0.003

Only those variables with *P* values ≤0.05 are included. The following variables were also assessed: gender, respiratory distress, postoperative, trauma, burn, total parenteral nutrition (TPN), central venous catheterization, drainage catheter, abdominal catheter, intraperitoneal catheter, thoracic catheter, urinary catheter, underlying respiratory disease, underlying cardiovascular disease, underlying renal disease, previous antifungal, broad-spectrum antibiotics, immunodeficiency, malignancy, transplantation, low-birthweight neonates, premature neonates, neutropenia.

1400 kandidemi;
74 C. auris kandidemisi

MAJOR RİSK FAKTÖRLERİ:

- YBÜ'de uzamış yatış
- Altta yatan solunum yolu hastalığı
- Vasküler cerrahi
- Tıbbi girişim
- Antifungal ilaç kullanımı

A *Candida auris* Outbreak and Its Control in an Intensive Care Setting

N Engl J Med 2018;379:1322-31.
DOI: 10.1056/NEJMoa1714373

Oxford Univ, UK

Table 1. Multivariable Predictors of *Candida auris* Colonization.*

Variable	Controls (N=361)	Case Patients (N=66)	Univariable Analysis		Multivariable Analysis	
			Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Median ICU stay before diagnosis (IQR) — days†	1.8 (0.7–6.6)	8.4 (4.6–13.4)				
Length of ICU stay before diagnosis				<0.001		0.001
1 day			Reference		Reference	
3 days			3.89 (2.38–6.36)		2.24 (1.30–3.86)	
5 days			7.37 (3.65–14.89)		2.97 (1.35–6.53)	
10 days			12.68 (5.38–29.88)		2.78 (1.02–7.54)	
20 days			6.75 (2.78–16.40)		0.69 (0.22–2.19)	
Axillary temperature monitoring — no. (%)	122 (34)	57 (86)	12.41 (5.94–25.90)	<0.001	6.80 (2.96–15.63)	<0.001
Median blood sodium level (IQR) — mmol/liter	139.3 (137.1–141.1)	141.4 (138.5–143.6)	1.20 (1.09–1.31)	<0.001	1.10 (0.99–1.22)	0.07
Median neutrophil count (IQR) — cells/mm^3†	8600 (6600–10,900)	9600 (7300–10,900)				
Neutrophil count				0.003		0.01
4000 cells/mm^3			Reference		Reference	
7000 cells/mm^3			2.18 (1.40– 3.41)		2.21 (1.30– 3.76)	
10,000 cells/mm^3			4.41 (1.84–10.59)		4.72 (1.64–13.59)	
15,000 cells/mm^3			1.17 (0.37–3.71)		1.69 (0.45–6.42)	
Median body temperature (IQR) — °C	36.5 (36.3–36.9)	36.9 (36.6–37.3)	2.44 (1.78–3.35)‡	<0.001	1.43 (0.96–2.14)‡	0.08
Any antifungal treatment — no. (%)§	3 (1)	3 (5)	5.68 (1.12–28.79)	0.04	10.34 (1.64–65.18)	0.01

Kolonizasyon ve Enfeksiyon için Risk Faktörleri: YBÜ'de kalış süresi, Yüksek nötrofil sayısı, Aksiller tekrar kullanılabilir ateş ölçüm problarının kullanımı (bu çalışmada salgın nedeninin bu problar olduğu saptanmış), Sistemik flukonazol tedavisi

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Simultaneous Emergence of Multidrug-Resistant *Candida auris* on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses

Clinical Infectious Diseases® 2017;64(2):134–40

Lockhart et al.

Table 2. Antifungal Susceptibility Data for 54 *Candida auris* Isolates

Antifungal	MIC Range, µg/mL	MIC_{50}, µg/mL	MIC_{90}, µg/mL
Fluconazole	4–256	128	256
Voriconazole	0.03–16	2	8
Itraconazole	0.125–2	0.5	1
Posaconazole	0.06–1	0.5	1
Caspofungin	0.03–16	0.25	1
Anidulafungin	0.125–16	0.5	1
Micafungin	0.06–4	0.25	2
Flucytosine	0.125–128	0.125	0.5
Amphotericin B	0.38–4	1	2

Abbreviations: MIC, minimum inhibitory concentration; MIC_{50}, MIC for 50% of isolates; MIC_{90}, MIC for 90% of isolates.

4 filogenik grup (Coğrafi):
Doğu Asya
Güney Asya
Afrika
Güney Amerika

Antifungal Susceptibility Testing

Antifungal susceptibility testing was performed on 54 isolates. The MIC range and the MICs for 50% and 90% of isolates are shown in Table 2, and the MIC distribution is shown in Supplemental Table 2. Using stringent break points, 50 isolates (93%) were resistant to fluconazole, 29 (54%) to voriconazole (≥2 µg/mL), 19 (35%) to amphotericin B (7 from Pakistan and 12 from India), 4 (7%) to echinocandins (2 from India and 2 from South Africa), and 3 (6%) (from India) were resistant to flucytosine. Two isolates, both from India, were resistant to fluconazole, voriconazole, echinocandins, and amphotericin B. In all, 22 (41%) isolates were resistant to ≥2 classes of antifungals.

Comparison of EUCAST and CLSI Reference Microdilution MICs of Eight Antifungal Compounds for *Candida auris* and Associated Tentative Epidemiological Cutoff Values

Antimicrobial Agents and Chemotherapy®

June 2017 Volume 61 Issue 6 e00485-17

M. C. Arendrup,[a,b,c] Anupam Prakash,[d] Joseph Meletiadis,[e,f] Cheshta Sharma,[d] Anuradha Chowdhary[d]

99% endpoints), and via the derivatization method (dECOFFs). The CLSI and EUCAST MIC distributions were wide, with several peaks for all compounds except amphotericin B, suggesting possible acquired resistance. Modal MIC, geometric MIC, MIC_{50}, and MIC_{90} values were ≤1 2-fold dilutions apart, and no significant differences were found. The quantitative agreement was best for amphotericin B (80%/97% within ±1/±2 dilutions) and lowest for isavuconazole and anidulafungin (58%/76% to 75% within ±1/±2 dilutions). We found that 90.2%/100% of the isolates were amphotericin B susceptible based on CLSI/EUCAST methods, respectively (i.e., with MICs of ≤1 mg/liter), and 100%/97.6% were fluconazole nonsusceptible by CLSI/EUCAST (MICs > 2). The ECOFFs (in milligrams per liter) were similar across the three different methods for itraconazole (ranges for CLSI/EUCAST, 0.25 to 0.5/0.5 to 1), posaconazole (0.125/0.125 to 0.25), amphotericin B (0.25 to 0.5/1 to 2), micafungin (0.25 to 0.5), and anidulafungin (0.25 to 0.5/0.25 to 1). In contrast, the estimated ECOFFs were dependent on the method applied for voriconazole (1 to 32) and isavuconazole (0.125 to 4). CLSI and EUCAST MICs were remarkably similar and confirmed uniform fluconazole resistance and variable acquired resistance to the other agents.

TABLE 1 MIC distributions of antifungal drugs for *C. auris* isolates (n = 123) tested by using the CLSI and EUCAST methods

Drug and AFST method	MIC (mg/liter)[a]																MIC range (no. of dilutions[b])	GM	MIC_{50}	MIC_{90}
	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				
FLU																				
CLSI											-	10		7	15	(91)	4 to ≥64 (5)	43.38	≥64	≥64
EUCAST	NT[c]	NT	NT	NT					1		2			2	10	(108)	0.5 to ≥64 (8)	53.74	≥64	≥64
ITC																				
CLSI					25	12	57	20	7	1	1						0.032 to 2 (7)	0.11	0.125	0.25
EUCAST	NT	NT	(4)	9	4	14	36	35	20	1							≤0.008 to 1 (8)	0.13	0.125	0.5
VRC																				
CLSI					1	11	14	10	27	19	24	13	1	3			0.032 to 16 (10)	0.66	0.5	4
EUCAST	NT	NT	(1)		2	1	17	12	35	37	13	5					≤0.008 to 4 (10)	0.54	0.5	2
ISA																				
CLSI				26	7	23	20	30	12		3	2					0.015 to 4 (9)	0.095	0.125	0.5
EUCAST	NT	NT	(22)	1	19	9	20	20	21	6	5						≤0.008 to 2 (9)	0.090	0.125	0.5
PSC																				
CLSI				73	4	26	9	7		1	1	1	1				0.015 to 8 (9)	0.035	0.016	0.125
EUCAST	NT	NT	(22)	19	33	33	12	3	1								≤0.008 to 0.5 (7)	0.033	0.032	0.125
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
AFG																				
CLSI				1		8	61	24	20	2		-	7				0.015 to 8 (10)	0.22	0.125	0.5
EUCAST	1			2	11	34	30	12	12	11	2	8					0.002 to 2 (12)	0.17	0.125	1
MFG																				
CLSI				4	4	47	49	9	2	1			7				0.015 to 8 (10)	0.12	0.125	0.25
EUCAST	1			1	5	29	69	9				8					0.002 to 4 (12)	0.13	0.125	0.25

[a]Modal MICs are indicated with underlined numbers and gray 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.

[b]The number of dilutions each MIC distribution spanned is given in parentheses.

[c]NT, not tested.

TABLE 3 CLSI and EUCAST tentative statistical, derivatization, and visual ECOFFs for *Candida auris*, using three different endpoints for the statistical methods

Drug and AFST method	Modal MIC (mg/liter)	Statistical ECOFF at indicated endpoint[a]						dECOFF via derivatization method	ECOFF via visual eyeball method[b]
		95%		97.5%		99%			
		ECOFF Finder	MicDat1.23 software	ECOFF Finder	MicDat1.23 software	ECOFF Finder	MicDat1.23 software		
FLC									
CLSI	64	NA	64	NA	64	NA	64	128	ND
EUCAST	64	NA	64	NA	64	NA	64	128	ND
ITC									
CLSI	0.125	0.5	0.5	0.5	0.5	1	1	0.25	0.5
EUCAST	0.125	1	1	1	1	2	2	1	0.5
VRC									
CLSI	0.5	8	8	16	16	32	16	1	ND
EUCAST	1	4	4	4	4	8	8	2	ND
ISA									
CLSI	0.25	1	1	2	1	2	2	0.5	ND
EUCAST	0.5	0.125	2	0.25	4	0.25	4	1	1
POS									
CLSI	0.016	0.125	0.125	0.125	0.125	0.25	0.25	0.125	ND
EUCAST	0.032/0.64	0.125	0.125	0.25	0.25	0.25	0.25	0.125	0.25
AMB									
CLSI	0.5	1	2	2	2	2	2	2	2
EUCAST	1	NA	1	NA	1	NA	1	2	1
AFG									
CLSI	0.125	0.25	0.5	0.25	0.5	0.25	1	0.25	0.5
EUCAST	0.06	0.25	1	0.25	1	0.5	2	0.25	1
MFG									
CLSI	0.125	0.25	0.25	0.25	0.25	0.25	0.5	0.25	0.5
EUCAST	0.125	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.5

[a]The statistical ECOFF determination method we used is described in reference 21, and the derivatization ECOFF determination method is described in reference 22. The ECOFF Finder program (21) will soon be freely available at the EUCAST website (www.eucast.org). NA, not available; the ECOFF Finder program could not provide an ECOFF.

[b]ND, not determined; an ECOFF could not be determined by the visual method when distributions were truncated or bi- or trimodal with no clear main wild-type population.

Multidrug-Resistant *Candida*: Epidemiology, Molecular Mechanisms, and Treatment

Maiken Cavling Arendrup[1,2,3] and Thomas F. Patterson[4]

JID 2017:216 (Suppl 3) • S445

Table 1. Intrinsic Susceptibility Patterns for *Candida* Species

Species	AMB	Echinocandins	Fluconazole	Comments
Common *Candida* species				
C. albicans	S	S	S	
C. dubliniensis	S	S	S	Closely related to *C. albicans;* fluconazole resistance easily acquired [13]
C. glabrata	S	S	I	Efflux pumps often induced during azole therapy [14]
C. krusei	S	S	R	
C. parapsilosis	S	S/I	S	Harbors an *FKS1* hot spot alteration responsible for elevated echinocandin MICs. Wild-type population is categorized as susceptible by CLSI and as intermediate by EUCAST [15]
C. tropicalis	S	S	S	
Uncommon *Candida* species				
C. auris	(X)	(X)	X	
C. bracharensis			X	
C. lusitaniae	X			
C. fermentati		X		
C. guilliermondii		S/X	X	Harbors an *FKS1* hot spot alteration responsible for elevated echinocandin MICs. Wild-type population is categorized as susceptible by CLSI but not by EUCAST due to insufficient evidence to indicate whether the wild-type population of this pathogen can be considered susceptible to echinocandins [17, 18]
C. metapsilosis		X		Closely related to *C. parapsilosis*
C. nivariensis			X	Closely related to *C. glabrata*
C. orthopsilosis		X		Closely related to *C. parapsilosis*
C. ciferrii			X	
C. inconspicua			X	
C. humicula			X	
C. lambica			X	
C. lipolytica			X	
C. norvegensis			X	
C. palmioleophila			X	
C. rugosa			X	
C. valida			X	
S. cerevisiae[a]			X	Closely related to *C. glabrata*

93% resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins; 41% resistant to 2 antifungal classes and 4% resistant to 3 classes [16]

X: elevated MICs as compared to those for C. albicans

ANTİFUNGAL DİRENÇ MEKANİZMALARI

Table 2. Summary of Molecular Resistance Mechanisms Described in *Candida*

Arendrup & Patterson JID 2017; 216: S445

	Drug Class			
	Amphotericin B	Echinocandins	Azoles	Flucytosine
Drug target	Ergosterol	Glucan synthase	P450 demethylase	DNA and RNA synthesis
Resistance mechanism				
Target gene mutation	*ERG2, 3, 5, 6* and *11* → less ergosterol	*FKS1* and *FKS2* → less binding	*ERG11* → less binding	
Target up-regulation			*UPC2*, Duplication of chromosome 5 Isochromosomes	
Efflux pumps			*CDR*[a], *MFS*[a] *CgSNQ2, PDH1* (*C. glabrata* specifically)	
Reduced drug uptake				Loss of permease
Reduced intracellular activation				*FCA1*[b] (*C. albicans*), *FCY1*[b] (*C. glabrata*) *FUR1*[c]

[a]ATP-binding cassette (ABC) transporters including *CDR1* and *CDR2* are regulated by a zinc cluster finger transcription regulator and major facilitator superfamily transporters by transcription factors *MMR1* in *C. albicans*. In *C. glabrata*, other transcription regulators are described including *PDR1* that regulates *CgCDR1*, *CgCDR2*, and *CgSNQ2* [40–42].

[b]*FCA1* and *FCY1* encodes cytosine deaminase, and mutations in these genes therefore inhibits the conversion of flucytosine into 5-F-fluorouridine [43].

[c]*FUR1* encodes uracil phosphoribosyltransferase, and mutations in this gene therefore inhibits the conversion of 5-F-fluorouridine into 5-fluorodeoxyuridylic acid monophosphate [44].

C. auris; antifungal direnç mekanizmaları:
Efluks pompaları-aşırı ekspresyon (ABC, MDR) (FLC)
ERG11 – mutasyonlar (FLC)

Arikan -Akdagli et al. J Fungi 2018; 4: 129

Primer ve Sekonder Antifungal direnç

Direnç türü	Örnek
PRİMER (DOĞAL)  	C. auris-flukonazol C. krusei-flukonazol C. glabrata-fukonazol C. norvegensis-flukonazol C. lusitaniae-amfoterisin B C. krusei-flusitozin Aspergillus-flukonazol Mucorales-vorikonazol
SEKONDER (EDİNİLMİŞ)	C. albicans (-orofaringiyal kandidoz-HIV)-flukonazol C. glabrata-ekinokandin Aspergillus-ITC/VCZ/POS …

www.nfid.org, Clinical Updates, National Foundation for Infectious Diseases

Antifungal direncin getirdiği sorunlar

- Tedavi başarısına olumsuz etki
  - Çapraz direnç olasılığı
- Tedavi seçeneklerinin kısıtlanması

  (Genel durumu, ilaç etkileşimleri, biyoyararlanım, mevcut formülasyon,... ve direnç ...)

SUNUM PLANI

- C. auris neden önemli?
- Tanımlama problemleri
- Olgular: Coğrafi dağılım, enfeksiyonlar
- Risk faktörleri
- Antifungal Direnç
- Tedavi
- Enfeksiyon Kontrol Önlemleri
- Sonuç

TEDAVİ 1

- Optimal tedavi?
- Empirik tedavi: Ekinokandin (Duyarlılık testleri sonuçlanana kadar)

(Ekinokandine duyarlılığı azalmış C. auris suşları da var!)

- Kolonize olduğu bilinen olguda klinik kötüleşme: Empirik antifungal tedavi

TEDAVİ 2
Ekinokandinlerin etkin olamadığı bölge enfeksiyonları

Üriner Sistem: AMB (+5-FC)

SSS: AMB+5-FC

(5-FC için yüksek MİK değeri olan suşlar da var.)

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

MULTİPL DİRENÇLİ SUŞLARDA ANTİFUNGAL KOMBİNASYONLARI ?

In Vitro Interactions of Echinocandins with Triazoles against Multidrug-Resistant *Candida auris*

Hamed Fakhim,[a,b] Anuradha Chowdhary,[c] Anupam Prakash,[c] Afsane Vaezi,[d] Eric Dannaoui,[e] Jacques F. Meis,[f,g] Hamid Badali[h,i]

November 2017 Volume 61 Issue 11 e01056-17 Antimicrobial Agents and Chemotherapy

n=10

TABLE 2 *In vitro* interactions of micafungin with fluconazole and voriconazole against *Candida auris*

	MFG + FLU[c]				MFG + VRC[c]			
	MIC (μg/ml)				MIC (μg/ml)			
Strain no.	MFG	FLU	MFG/FLU	FICI/INT	MFG	VRC	MFG/VRC	FICI/INT
VPCI 482/P/13[a]	0.25	≥64	0.25/64	1.5/IND	0.25	2	0.016/0.5	0.31/SYN
VPCI 1132/P/13[a]	0.5	32	0.25/4	0.62/IND	0.5	0.5	0.016/0.125	0.28/SYN
VPCI 1133/P/13[a,b]	8	≥64	4/32	0.75/IND	8	1	2/0.25	0.5/SYN
VPCI 265/P/14[a]	0.5	32	0.5/8	1.25/IND	0.5	8	0.063/1	0.25/SYN
VPCI 1510/P/14[a]	0.125	32	0.063/8	0.75/IND	0.125	4	0.016/0.25	0.19/SYN
VPCI 1514/P/14[a,b]	8	≥64	8/16	1.12/IND	8	0.5	1/0.125	0.37/SYN
VPCI 266/P/14[a]	0.25	≥64	0.25/32	1.25/IND	0.25	0.5	0.008/0.125	0.28/SYN
VPCI 267/P/14[a,b]	8	32	8/8	1.25/IND	8	0.5	1/0.125	0.37/SYN
VPCI 487/P/14[a]	4	≥64	4/32	1.25/IND	4	1	0.5/0.125	0.25/SYN
VPCI 518/P/14[a]	0.5	≥64	0.25/64	1/IND	0.5	1	0.016/0.125	0.15/SYN

[a]Fluconazole-resistant isolates (n = 10).
[b]Micafungin-resistant isolates (n = 3).
[c]MFG, micafungin; FLU, fluconazole; VRC, voriconazole; FICI, fractional inhibitory concentration index; IND, indifference; SYN, synergy; INT, interpretation.

MFG+VRC: Sinerji
MFG+FLC: Etkileşim yok
CAS+FLC: Etkileşim yok
CAS+ VRC: Etkileşim yok
Antagonizma Φ

Mikafungin + Vorikonazol ?
Öneri oluşturabilecek düzeyde veri yok

SUNUM PLANI

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ENFEKSİYON KONTROL ÖNLEMLERİ 1

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

What should I do if there is *C. auris* in my facility?

1. Check the CDC website for the most up-to-date guidance on identifying and managing *C. auris*: www.cdc.gov/fungal/candida-auris.
2. Report possible or confirmed *C. auris* immediately to your public health department.
3. Ensure adherence to CDC recommendations for infection control, including:
   i. Place patients infected or colonized with *C. auris* in a single room on contact precautions
   ii. Assess and enhance gown and glove use
   iii. Reinforce hand hygiene
   iv. Coordinate with environmental services to ensure the patient care environment is cleaned with a disinfectant that is effective against *C. auris* (i.e., those effective against *Clostridium difficile*) by searching "List K" at www.epa.gov. Work with the environmental services team to monitor the cleaning process.
4. After consulting with public health personnel, screen contacts of case-patients to identify patients with *C. auris* colonization. Use the same infection control measures for patients found to be colonized.
5. When a patient is being transferred from your facility (e.g., to a nursing home or other hospital), clearly communicate the patient's *C. auris* status to receiving healthcare providers.

ENFEKSİYON KONTROL ÖNLEMLERİ 2

TABLE 4 Reported infection prevention and control recommendations[a]

	Recommendation(s)					
Body	Patient screening	Contact precaution(s)	Contact screening	Decolonization procedure(s)	Environmental management	Community management
PHE (UK)	Recommended in units with ongoing cases or colonizations; those arriving from affected units (UK and abroad); screening sites such as groin, axilla, nose, throat, urine, perineal area, rectal area, and stool; consider screening, if indicated, LVS, sputum, endotracheal secretions, drain fluid, wounds, and cannula; rescreening of patients known to have been previously colonized; deisolation of screen-positive patients is not recommended apart from units with experience in managing *C. auris*	Side room with *en suite* facilities where possible; isolation of all patients from affected UK or international hospital until screening is available; strict adherence to hand hygiene using soap and water, followed by alcohol rub to dry hands; PPE with gloves and aprons or gowns if there is a high risk of body or body fluid contact; briefing of visitors regarding contact precautions; single-patient-use items such as blood pressure cuffs should be considered; for cleaning *C. auris*-exposed areas, glove and apron use with subsequent appropriate hand decontamination	If there is novel detection in a unit, close contacts should be screened and isolated or cohorted; if the index patient is isolated, identify all *Candida* species isolates from the same unit to the species level using a method able to detect *C. auris*; review *Candida* spp. detected in the same ward areas in the 4 wk prior to diagnosis of the index patient in case of unrecognized transmission; deisolation with 3 negative screens >24 h apart	Strict adherence to central and peripheral catheter care bundles, urinary catheter care bundle, care of the tracheostomy site; skin decontamination with chlorhexidine washes in critically ill patients; consider use of mouth gargles with chlorhexidine and use of topical nystatin and terbinafine for topical management of key sites	Use of chlorine-releasing agent at 1,000 ppm for cleaning contact environments; change privacy curtains; for equipment, consider single-use items or discarding less expensive items that are difficult to decontaminate; all equipment should be cleaned in accordance with the manufacturer's instructions; terminal cleaning when patient leaves the environment; schedule affected patients last for theater/procedures/ imaging; for waste and linen disposal, follow local policy as for other multiresistance organisms; training and supervision of cleaning staff until competent	Nurse in a single room with *en suite* facilities when possible; if single room is not possible, the colonized individual should not share a room with an immunocompromised individual; thorough environmental cleaning with a chlorine-releasing agent at 1,000 ppm of available chlorine; follow standard infection control precautions; ensure that staff are trained in the use of PPE and hand hygiene; special care should be taken with wound, catheter, and device care

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

ENFEKSİYON KONTROL ÖNLEMLERİ 3

TABLE 4 (Continued)

Body	Recommendation(s)					
	Patient screening	Contact precaution(s)	Contact screening	Decolonization procedure(s)	Environmental management	Community management
ECDC (Europe-wide)	All patients from in-country or internationally affected units transferred in; conduct active surveillance in accordance with specified protocol; screening sites include urine, feces, wounds, drain fluid, respiratory samples	Contact precautions, single room isolation; patient cohorting; dedicated nursing staff for colonized or infected patients; hand hygiene	Cross-sectional patient screening in outbreak setting		Terminal cleaning of rooms using disinfectants and methods with certified antifungal activity; environmental sampling in outbreak setting	
COTHI (South Africa)	Routine screening not advised	Single room with *en suite* or cohorting of patients; hand hygiene using soap and water or alcohol rub; gloves and aprons for patient contact; adherence to venous and urinary catheter and tracheostomy care bundles; advise visitors regarding contact precautions; notify receiving hospitals of positive status			Schedule affected patients last for theater/procedures/ imaging; regular cleaning with chlorine-releasing agent at 1,000 ppm; terminal cleaning and disinfection of bed space; consider terminal cleaning with hydrogen peroxide vapor; clean multiuse equipment thoroughly; cleaning of all contact areas	

[a]CDC, Centers for Disease Control and Prevention, USA; ECDC, European Centre for Disease Prevention and Control; COTHI, Centre for Opportunistic, Tropical, and Hospital Infections; LVS, low vaginal swab; PPE, personal protective equipment.

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

ENFEKSİYON KONTROL ÖNLEMLERİ 4

TABLE 4 Reported infection prevention and control recommendations[a]

Body	Recommendation(s)					
	Patient screening	Contact precaution(s)	Contact screening	Decolonization procedure(s)	Environmental management	Community management
CDC (USA)	Axilla and groin screening; additional sites as directed clinically or by previously positive sites; periodic reassessment for presence of colonization at 1- to 3-mo intervals; for deisolation, 2 or more assessments 1 wk apart with negative results (off antifungals)	Single room with standard and contact precautions; gown and gloves; hand hygiene precautions		Wait 48 h after administration of topical chlorhexidine prescreening	Thorough daily and terminal cleaning/ disinfection using Environmental Protection Agency-registered disinfectant effective against *C. difficile* spores	Do not restrict nursing home residents to rooms and perform hand hygiene; if receiving health input, gown and glove contact precautions; thorough cleaning of shared equipment

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

SUNUM PLANI

- C. auris neden önemli?
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- Sonuç

- C. auris, morbidite ve mortaliteyi önemli ölçüde etkileyebilecek, her an her merkezde izole edilebilecek özellikte bir Candida türüdür.
- Tanımlama ile ilgili şüpheler/veriler, laboratuvar-klinik işbirliği ile gereken yaklaşımı ve tedbirleri ivedilikle sağlamalıdır.
- Antifungal duyarlılık testlerinin uygulanması bu tür için de özel bir önem arz etmektedir.
- C.auris ile ilgili birçok soru henüz yanıt beklemektedir.
- Global bir sorun olarak mevcudiyetini koruyup korumayacağı da bilinmemektedir.

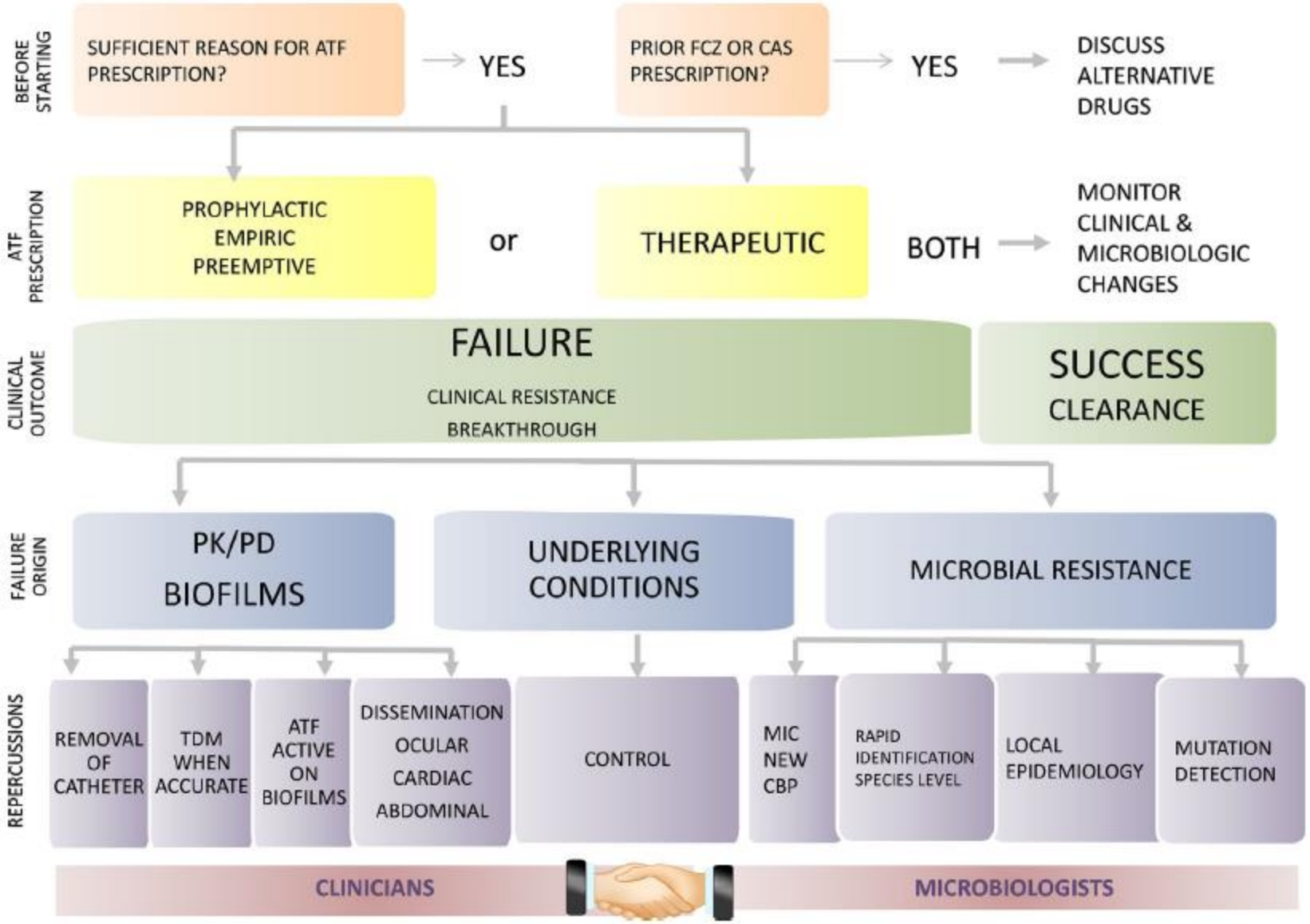

Fig. 3 Bedside strategy for circumventing antifungal drug resistance in 2014. *ATF* antifungal drug, *FCZ* fluconazole, *CAS* caspofungin, *PK/PD* pharmacokinetics and pharmacodynamics, *TDM* therapeutic drug monitoring, *MIC* minimal inhibitory concentration, *CBP* clinical breakpoint

Maubon et al. Inten Care Med 2014; 40: 1241

YENİ İLAÇLAR ?

Rezafungin (CD101)

Cidara Therapeutics CA, A.B.D.

Yapı	(Yeni nesil) ekinokandin Siklik hekzapeptid, lipofilik kuyruk yapısı. AFG'e benzer, ancak hemiaminal yapı yerine kolin aminal eter yapısının olması nedeniyle daha stabil ve t1/2 uzun - - insanda 130 sa.
Formülasyon	IV, s.c.
Hedef kullanım alanı	IC – Tedavi Antifungal proflaksi (Candida, Asp, P. jirovecii)
In vitro aktivite	Genelde diğer ekinokandinlere benzer
Hayvan çalışmaları	Fare – IC (IV, kaspofungin karşılaştırmalı) Fare - Aspergilloz proflaksisi (s.c., amfoterisin B karşılaştırmalı) Fare-PCP proflaksisi (TMP-SMX'e benzer, kist ve trofozoitlere etki)

Pharmacodynamic Evaluation of Rezafungin (CD101) Against *Candida auris* in the Neutropenic Mouse Invasive Candidiasis Model

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Rezafungin (CD101) is a novel echinocandin under development for once-weekly intravenous (IV) dosing. We evaluated the pharmacodynamics (PD) of rezafungin against four *Candida auris* strains using the neutropenic mouse invasive candidiasis model. AUC/MIC was a robust predictor of efficacy (R^2 0.76). The stasis free-drug 24-h AUC/MIC target exposure for the group was 1.88; whereas the 1-log kill free-drug 24-h AUC/MIC target exposure was 5.77. These values are very similar to previous rezafungin PD studies with other *Candida* spp. Based on recent surveillance susceptibility data, AUC/MIC targets are likely to be exceeded for >90% of *C. auris* isolates using the previously studied human dose of 400 mg IV once weekly.

İbreksafungerp (SCY-078)

Scynexis Inc., A.B.D.

ORAL ekinokandin

In Vitro Activity of a Novel Glucan Synthase Inhibitor, SCY-078, against Clinical Isolates of *Candida auris*

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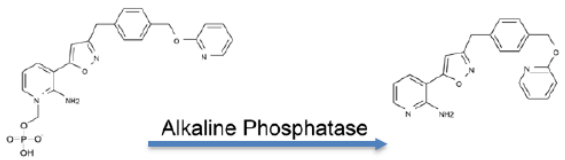
TABLE 2 SCY-078 MIC data compared to isolates with elevated echinocandin MICs

	MIC (μg/ml) of drug:			
Isolate	Anidulafungin	Caspofungin	Micafungin	SCY-078
1	8	1	4	1
2	16	1	4	1
3	1	16	1	1
4	2	16	2	1
5	4	0.5	0.5	0.5
6	>16	>16	>8	0.5
7	4	>16	1	1

APX001A (E1210)

Amplyx Pharmaceu., Inc., A.B.D.

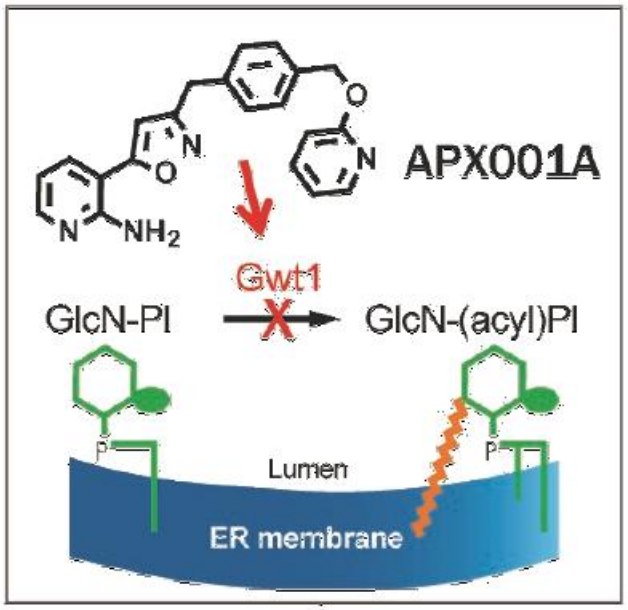
Yapı Etki mek.	Fungal Gwt1 (=«GPI-anchored wall transfer protein 1»= inositol açil transferaz enzimi) inhibitörü
Formülasyon	Oral, IV (1 sa. infüzyon)
In vitro aktivite	Geniş spektrum Candida {(C.auris dahil) ancak C. krusei MİK'leri yüksek} Asp, Mucorales, Fusarium, Scedosporium
Hayvan çalışmaları	Murine, immnünokompr. ve immünokomp. Pulmoner ve dissemine modeller (sağ kalım, organ yükü) C.alb, C.trop, C.glabr, C.auris, C. neo, A.fum, A.flav, F.solani, L.prolificans, R. arrhizus, C. immitis AUC/MIC (etkinlik)



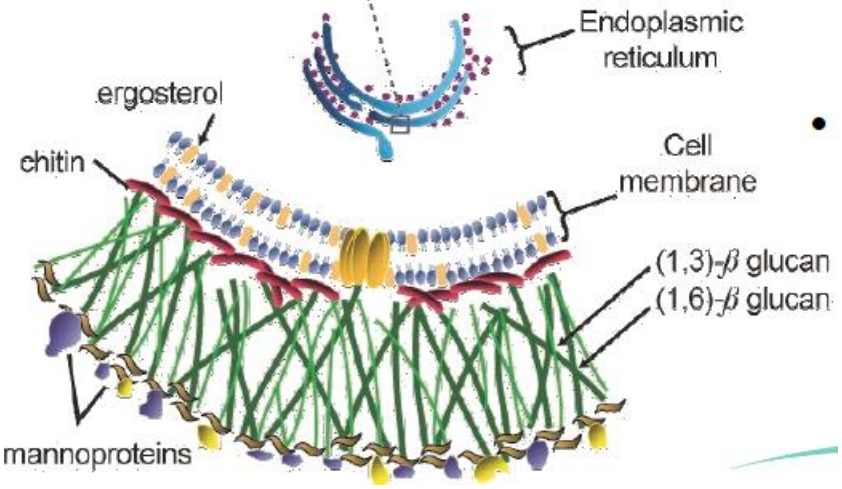
Aktif şekli

Dr. Michael Hodges, TIMM 2017 APX001 presentation

Etki mekanizması 1



İnositol açil transferaz enzimi inhibitörü



Dr. Michael Hodges, TIMM 2017 APX001 presentation

Etki mekanizması 2

- Glikozil fosfatidil inositole (GPI) bağlı proteinler (örn. mannoprt.ler) hücre duvarı bütünlüğü ve homeostazı, adezyon, patojenisite ve immün sistemden kaçışta rol alır. GPI, prt.lerin membrana bağlanmasında çapa görevi görür.

- «GPI-anchored wall transfer protein 1»= Gwt1, GPI'dan glukozaminil açil fosfatidil inositol oluşumunda gerekli açil transferaz enzimidir. Bu reaksiyon, GPI sentezinin erken basamaklarından birisidir. Bu enzimin inhibisyonu, GPI e bağlı proteinlerin matürasyonunu ve böylece fungal üremeyi önler.

- APX001A, fungal Gwt1 inhibitörüdür; memelide bulunan eşdeğer proteinlere etkinliği yoktur.

APX001A *In Vitro* Activity against Contemporary Blood Isolates and *Candida auris* Determined by the EUCAST Reference Method

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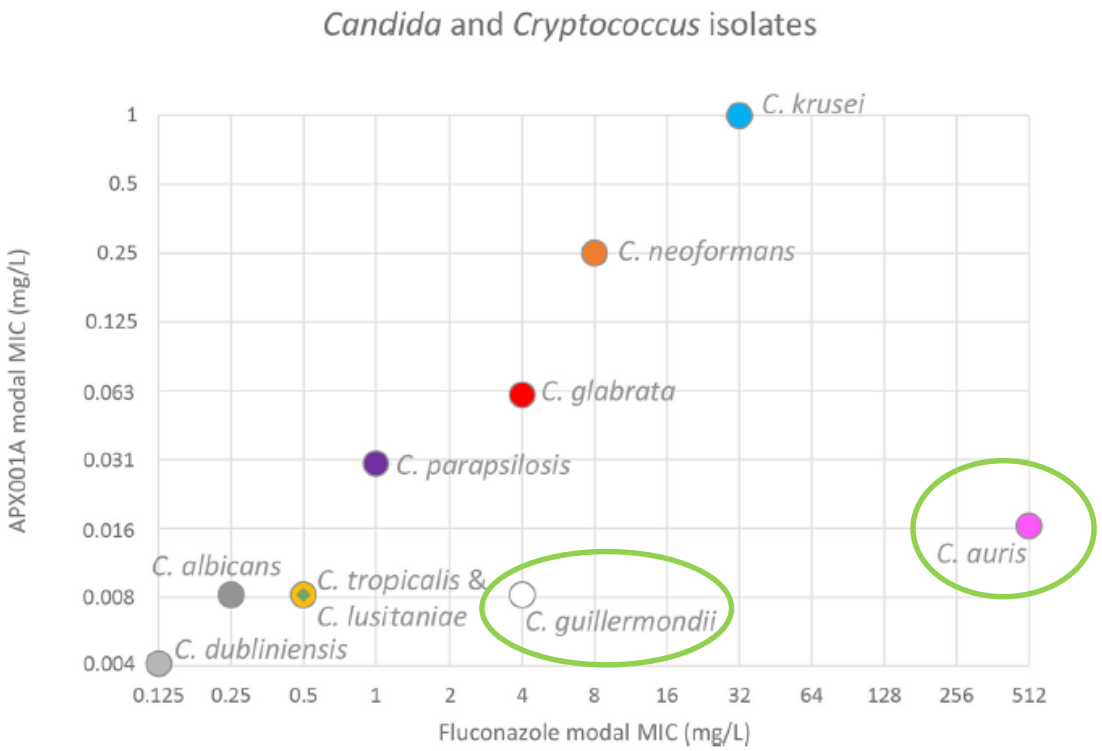

FIG 1 Correlation between APX001A and fluconazole modal MICs for bloodstream isolates represented by at least four isolates. *C. albicans* (dark gray circle), *C. auris* (pink), *C. dubliniensis* (light gray circle), *C. glabrata* (red circle), *C. guilliermondii* (white circle), *C. lusitaniae* (green diamond), *C. krusei* (turquoise circle), *C. parapsilosis* (purple circle), *C. tropicalis* (yellow circle), and *Cryptococcus neoformans* (orange circle).

FLC ile karşılaştırmalı in vitro etkide, APX001A ile FLC MİK'leri arasında korelasyon gözleniyor.
(Her ikisi de membran üzerinden etki sağlıyor.)
Nedeni? Ancak, FLC-R ve APX001A-WT suşlar var.