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Tıbbi Mikoloji Çalışma Grubu

KLİMUD 2009 KLİNİK MİKROBİYOLOJİ UZMANLIK DERNEĞİ

APPROVED

Rezafungin: Yepyeni Bir Ekinokandin mi?

Uzm. Dr. Ali Korhan SIĞ

Tıbbi Mikoloji Uzmanı

Balıkesir Atatürk Şehir Hastanesi

İnvazif Fungal Enfeksiyonlar

- IFI sıklığı artıyor
  - Bağışıklığı baskılayıcı tedaviler
  - Ortalama yaş artışı?
  - Profilaksi sonucu “breakthrough” vakalar
  - IFI konusundaki farkındalığın artışı
    - Tanısal tekniklerdeki gelişmeler
    - Laboratuvar kapasitesi?
- Nadir görülen suşlar
- Hiç etken olarak görülmemiş suşlar

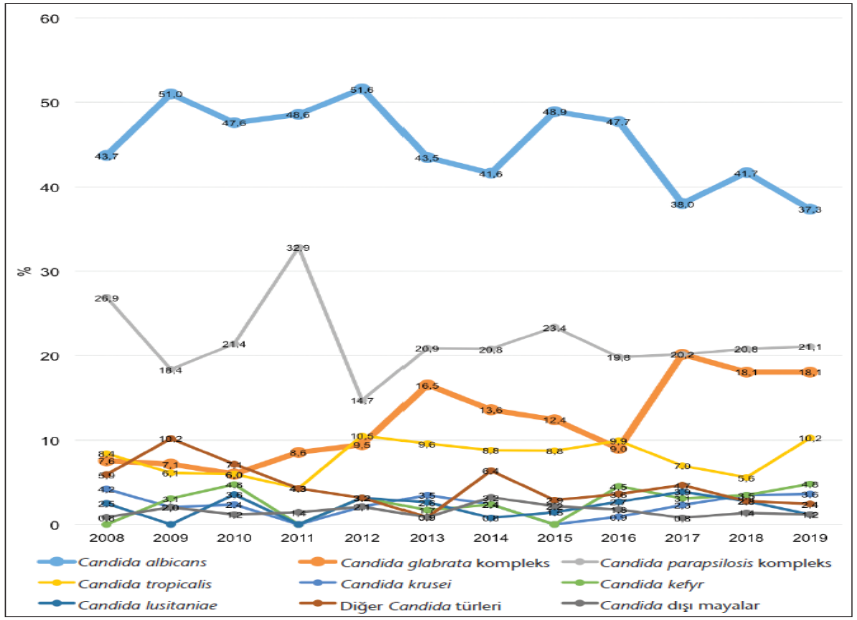
1. Sig AK, Arikan-Akdagli S. Yoğun Bakımlarda İnvazif Küf Enfeksiyonları: Epidemiyoloji, Mikrobiyolojik Tanı ve Antifungal Direnç. Yoğun Bakım Derg 2019;10(2):63−69.
2. Espinel-Ingroff A, Canton E, Peman J. Antifungal Resistance among Less Prevalent Candida Non-albicans and Other Yeasts versus Established and under Development Agents: A Literature Review. J Fungi, 2021; 7.1: 24.
3. Gulmez D, Sig AK, Akar N, Duyan S, Arikan-Akdagli S. Enfeksiyon Etkeni Mantarların Zamana Göre Sıklık ve Tür Dağılımlarındaki Değişimler: 12 Yıllık (2008-2019) Mikoloji Laboratuvarı Verileri Ne Söylüyor? Mikrobiyol Bul 2021;55(1):53-66.

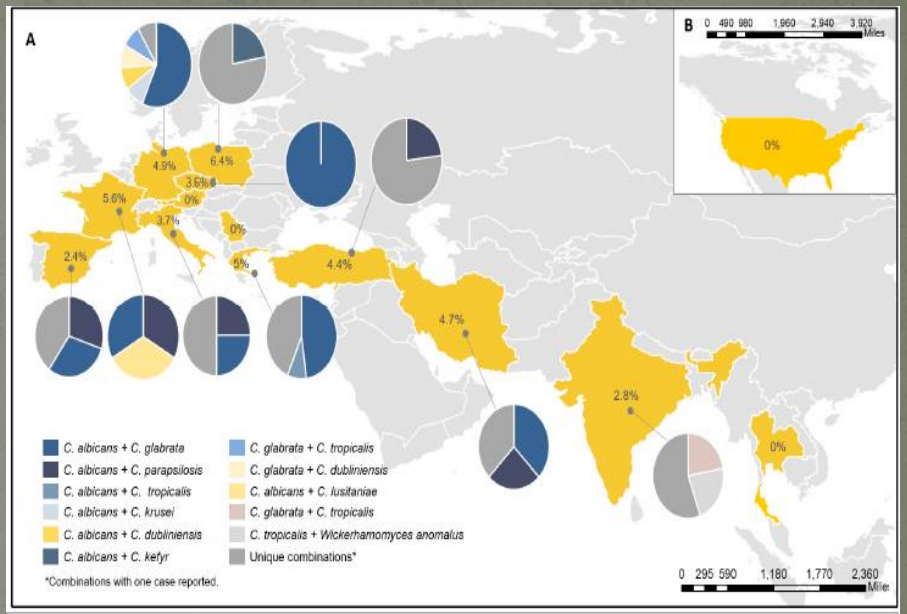
İnvazif Fungal Enfeksiyonlar

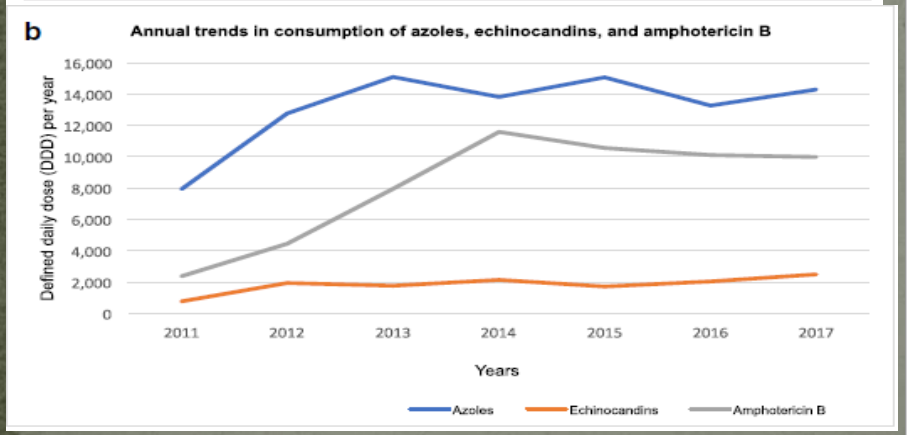
- Mortalite ve morbidite yüksek
- İnvazif maya enfeksiyonlarında %32-45 mortalite
  - Tedavi başarısı genel olarak %70'in altında
- Erken tanı ve tedavi: Prognozla doğrudan ilişkili
  - Profilaksi
  - Preemptif
  - Ampirik

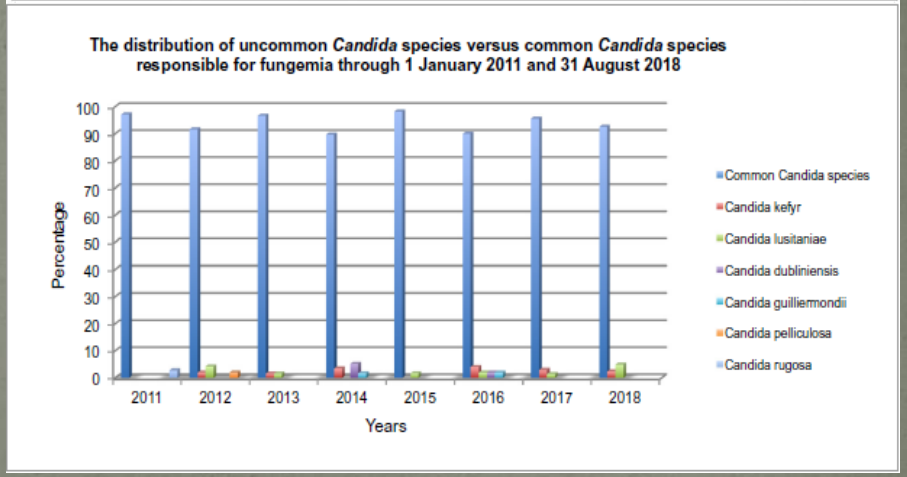
1. Sig AK, Arikan-Akdagli S. Yoğun Bakımlarda İnvazif Küf Enfeksiyonları: Epidemiyoloji, Mikrobiyolojik Tanı ve Antifungal Direnç. Yoğun Bakım Derg 2019;10(2):63−69..
2. Espinel-Ingroff A, Canton E, Peman J. Antifungal Resistance among Less Prevalent Candida Non-albicans and Other Yeasts versus Established and under Development Agents: A Literature Review. J Fungi, 2021; 7.1: 24.

İnvazif Etkenler Yer mi Değiştiriyor?









1. Gulmez D, Sig AK, Akar N, Duyan S, Arikan-Akdagli S. Enfeksiyon Etkeni Mantarların Zamana Göre Sıklık ve Tür Dağılımlarındaki Değişimler: 12 Yıllık (2008-2019) Mikoloji Laboratuvarı Verileri Ne Söylüyor? Mikrobiyol Bul 2021;55(1):53-66.
2. Medina N, Soto-Debrán JC, Seidel D, et al. MixInYeast: A Multicenter Study on Mixed Yeast Infections. J. Fungi 2021; 7, 13.
3. Alp, S., Gulmez, D., Kardas, R.C. et al. Expect the unexpected: fungemia caused by uncommon Candida species in a Turkish University Hospital. Eur J Clin Microbiol Infect Dis 2021; https://doi.org/10.1007/s10096-020-04147-5

Rehberlere Bakış

TABLE 5. Recommendations on initial targeted treatment of candidaemia and invasive candidiasis in adult patients

Intervention	SoR	QoE	References	Comment
Anidulafungin 200/100 mg	A	I	[64]	Consider local epidemiology (*Candida parapsilosis*, *Candida krusei*), less drug–drug interactions than caspofungin
Caspofungin 70/50 mg	A	I	[67] [55] [63]	Consider local epidemiology (*C. parapsilosis*)
Micafungin 100 mg	A	I	[61] [63]	Consider local epidemiology (*C. parapsilosis*), less drug–drug interactions than caspofungin, consider EMA warning label
Amphotericin B liposomal 3 mg/kg	B	I	[61] [62]	Similar efficacy as micafungin, higher renal toxicity than micafungin
Voriconazole 6/3 mg/kg/day[a,b]	B	I	[43] [78] [77]	Limited spectrum compared to echinocandins, drug–drug interactions, limitation of IV formulation in renal impairment, consider therapeutic drug monitoring
Fluconazole 400–800 mg[a]	C	I	[165] [53] [74] [54] [64] [76] [75] [73] [72]	Limited spectrum, inferiority to anidulafungin (especially in the subgroup with high APACHE scores), may be better than echinocandins against *C. parapsilosis*
Amphotericin B lipid complex 5 mg/kg	C	II_a	[57] [58]	
Amphotericin B deoxycholate 0.7–1.0 mg/kg	D	I	[50] [51] [165] [53] [54] [55]	Substantial renal and infusion-related toxicity
Amphotericin B deoxycholate plus fluconazole	D	I	[74]	Efficacious, but increased risk of toxicity in ICU patients No survival benefit
Amphotericin B deoxycholate plus 5-fluorocytosine	D	II	[75]	
Efungumab plus lipid-associated amphotericin B	D	II	[166]	
Amphotericin B colloidal dispersion	D	II_a	[60]	
Itraconazole	D	II_a	[76]	
Posaconazole	D	III	No reference found	

EMA, European Medicines Agency.
Comparative clinical trials did not prove a survival benefit of one treatment over another. Primary intention of treating candidaemia is clearing the blood stream.
[a]Not all experts agreed, SoR results from a majority vote.
[b]The licensed maintenance dosing is 4 mg/kg/day.

1. Cornely OA, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. CMI 2012; 18: 19-37.

Antifungal Duyarlılık Ne Zaman?

- CLSI ve EUCAST
  - Farklılıkları mevcut
  - Sonuçları denk
  - Mikrodilüsyon-Disk Difüzyon
  - Gradient Test?
  - YeastOne, Micronaut? Vitek 2?
  - Azol agar tarama testi

1. Berkow, E. L., Lockhart, S. R., Ostrosky-Zeichner, L. Antifungal susceptibility testing: current approaches. Clin Microbiol Rev 2020, 33.3. DOI: 10.1128/CMR .00069-19.

Antifungal Duyarlılık Ne Zaman?

	Reference Methods		Shortening of the turn-around-time				Novel techniques	
	CLSI	**EUCAST**	**Colorimetric BMD** (Sensititre™YeastOne™)	**Epsilometer test**	**Spectrophoto-meter** (VitekTM)	**Disk-diffusion**	**MALDI-TOF MS**	**Molecular detection**
Suitability	yeasts, molds	yeasts, molds	yeasts, molds	yeasts, molds	yeasts	yeasts, molds	*Candida* sp. *Aspergillus* sp.	*Candida* sp., *Aspergillus* sp.*
Format	BMD	BMD	colorimetric BMD	agar-based method	BMD	agar-based	mass-spectrometry	DNA-based detection**
Inoculum	culture	culture	culture, PBC	culture, PBC	culture, PBC	culture, PBC	culture, PBC	culture, PBC, BAL*
Turnaround time	24-48 h	24-48 h	24-48 h PBC, direct inoculation methods: 12h	24-48 h PBC, direct inoculation methods: 12h	12-24 h PBC, direct inoculation methods: 12h	24-48 h PBC, direct inoculation methods:12h	3-15 h (MALDI-TOF MS AFST) 6h (MBT ASTRA)	4–12h
Reading	visually	visually/ spectrophoto-metrically	visually	visually	automatically	visually	visually, automation	automatically
Antifungal drugs	customized selection: AMB, FC, azoles, ECH	customized selection: AMB, azoles, ECH	customized selection: AMB, azoles, ECH	customized selection: AMB, FC, azoles, ECH	AFST cards (customized selection)	validated: CAS, MICA, FLU, VOR	CAS, ANI, azoles	targets for ECH and azoles
Application Endpoint	specialized labs MIC, MEC (ECH)	specialized labs MIC, MEC (ECH)	routine MIC, MEC (ECH)	routine MIC	routine MIC	routine zone diameter no MICs	specialized labs CCI-measured spectral comparison	specialized labs resistance genes: FKS, multifaceted with azoles
Comments	detecting resistant isolates, but restricted to specialized laboratories AMB: narrow concentration range limit discriminatory potential	not all compounds are easy available AMB: narrow concentration range limit discriminatory potential	CLSI breakpoints are recommended direct inoculation methods: limited data, few antifungals tested	MIC ranges do not mirror those of the reference methods CLSI breakpoints are recommended direct inoculation methods: limited data, few antifungals tested ECH: CLSI breakpoints may bisect *C. glabrata* and *C. krusei*	interlaboratory variation CLSI breakpoints are recommended direct inoculation methods: limited data, few antifungals tested AMB: same concerns as for CLSI and EUCAST AMB: contrary data with *C. auris*	Lab to lab variations direct inoculation methods: limited data, few antifungals tested AMB: small zones	rapid detection of antifungal resistance for some drug-bug combinations	rapid detection of antifungal resistance for specific fungi **various platforms: real-time PCR, Sanger sequencing, pyrosequencing, Luminex technology and NGS initiatives

1. Berkow, E. L., Lockhart, S. R., Ostrosky-Zeichner, L. Antifungal susceptibility testing: current approaches. Clin Microbiol Rev 2020, 33.3. DOI: 10.1128/CMR .00069-19.
2. Bassetti, M., Vena, A., Bouza, E.,, et al. Antifungal susceptibility testing in Candida, Aspergillus and Cryptococcus infections: are the MICs useful for clinicians?. CMI 2020; 26.8:1024-1033.
3. Knabl, L., Lass-Flörl, C. Antifungal susceptibility testing in Candida species: Current methods and promising new tools for shortening the turnaround time. Expert review of anti-infective therapy 2020; 18.8: 779-787

Antifungal Duyarlılık Ne Zaman?

Clinical setting	Recommendation
Routine	• Species level identification of all *Candida* isolates from deep sites (eg, blood, normally sterile fluids, tissues, abscesses).
	• Species level identification of *Aspergillus*, genus level for all other molds.
	• Species level (if possible) identification of non-candidal yeast isolates from deep sites (eg, blood, normally sterile fluids, tissues, abscesses).
	• Selection of therapy is generally based on published consensus guidelines and review of survey data on the organism-drug combination in question.
	• Routine susceptibility testing of fluconazole, voriconazole, and an echinocandin against *C. glabrata* and fluconazole against non-candidal yeast isolates from deep sites (eg, blood, normally sterile fluids, tissues, abscesses).
	• Susceptibility testing of fluconazole, voriconazole, an echinocandin, and flucytosine against other species of *Candida* may be helpful in special circumstances, but not routinely, since susceptibility is usually predictable.
	• Susceptibility of *Candida* spp other than *C. glabrata* to echinocandins may be assumed unless initial response is suboptimal. Susceptibility testing of isolates to an echinocandin should be considered if there is a prior history of exposure to this class of agents.
Mucosal candidiasis	• Susceptibility testing may be useful for patients unresponsive to therapy.
Invasive disease with clinical failure of initial therapy	• Consider susceptibility testing.
	- *Candida* spp: amphotericin B, flucytosine, fluconazole, voriconazole, echinocandins
	- *C. neoformans*: fluconazole, amphotericin B, flucytosine
	- *Aspergillus* species: amphotericin B, posaconazole, itraconazole, voriconazole
	• Consultation with an experienced microbiologist recommended
Infection with species with high rates of intrinsic or acquired resistance	• Susceptibility testing not necessary when intrinsic resistance is known.
	- *A. terreus*: amphotericin B
	- *C. krusei*: fluconazole, flucytosine
	- *Cryptococcus* and *Trichosporon*: echinocandins
	- *Rhodotorula*: azoles, echinocandins
	- *Mucorales*: voriconazole, echinocandins
	• For species with significant rates of acquired resistance, monitor closely for signs of failure and perform susceptibility testing as needed.
	- *C. glabrata*: fluconazole, voriconazole, amphotericin B, echinocandins
	- *C. auris*: fluconazole, voriconazole, amphotericin B, echinocandins
	- *C. krusei*: amphotericin B
	- *C. lusitaniae*: amphotericin B
	- *C. rugosa*: amphotericin B, fluconazole
	- *Candida* spp: flucytosine, when used for endocarditis
Unusual organisms	• Susceptibility testing may be helpful when treating patients infected with unusual organisms for which susceptibility patterns have not been well established or are unpredictable.
Mold infections	• Species level identification of *Aspergillus*, genus level for all other molds.
	• Routine susceptibility testing not recommended.
	• Susceptibility of *Aspergillus* species to itraconazole, voriconazole, isavuconazole, and posaconazole may help to determine cross-resistance.
	• Clinical interpretive criteria have not been established for any agents.

1. https://www.uptodate.com/contents/image?csi=ea2fe15b-d805-4099-a52c-d554066975cb&source=contentShare&imageKey=ID%2F52140

Antifungal Duyarlılık Ne Zaman?

- **Mantar steril vücut alanlarından izole edildiyse**
- Direnç potansiyeli taşıyan bir suş ise
- Nadir rastlanan bir suş ise
- Sorumlu hekim bir gerekçeyle talep ediyor ise;
  - Klinik laboratuvar ilişkisi
  - Tedaviye rağmen yanıt alınamıyorsa
  - Etken olduğu konusunda klinik uyum var ise

1. Berkow, E. L., Lockhart, S. R., Ostrosky-Zeichner, L. Antifungal susceptibility testing: current approaches. Clin Microbiol Rev 2020, 33.3. DOI: 10.1128/CMR .00069-19.

Nereye Gidiyoruz?

- DD: Kaspofungin, Mikafungin, Vorikonazol, Flukonazol
  - *Candida albicans*
  - *Candida guilliermondii*
  - *Candida krusei*
  - *Candida parapsilosis*
  - *Candida glabrata*
  - *Candida tropicalis*
- BMD: Anidulafungin

1. CLSI. Performance Standards Susceptibility Testing For Antifungal M60 1st Ed.

Nereye Gidiyoruz?

ANTIFUNGAL	BODY SITE	REPORTING	COMMENT	RATIONALE	CLSI Antifungal Subcommittee Recommendations and Comments
Amphotericin B	-	No restrictions	-		No restrictions recommended by the committee
5 –Flucytosine (5-FC)	-	No restrictions	5-Flucytosine should not be used as monotherapy for severe Candida infections due to rapid development of resistance. It should be rarely used in neonates.		No restrictions recommended and committee supported the use of comment
Echinocandins	CNS (brain tissue, abscess material), CSF	**Option 1:** No restriction, append comment **Option 2:** Do not report, do not append comment **Option 3:** Do not report, append comment	The echnocandins have suboptimal penetration in CSF and CNS tissues. Consult pharmacy/infectious disease service for further guidance.	The echinocandindins have suboptimal penetration into CSF and CNS tissues, however the concentrations in the various CNS sub-compartments may achieve a significant anti-*Candida* effect based on animal models.	Committee to vote on options
Echinocandins	Urine	**DO NOT REPORT**		<1% of active echinocandin drug is excreted into the urine and echinocandins are generally not recommended for treating candiduria.	Committee to finalize vote on restriction
Echinocandins	Ocular (cornea, aqueous, vitreous)	**DO NOT REPORT**		Systemic administration of Echinocandins are not recommended for ocular infections given minimal tissue penetration. Consult ophthalmology, pharmacy or infectious disease service for further guidance.	Committee to vote on restriction
AZOLES	CNS (brain tissue, abscess material), CSF	Report fluconazole and voriconazole only.		Given more limited clinical data for itraconazole, posaconazole and isavuconazole, suppress these results and report by request.	Committee to vote
AZOLES	Ocular (cornea, aqueous, vitreous)	Report fluconazole and voriconazole only.		Given more limited clinical data for itraconazole, posaconazole and isavuconazole, suppress these results and report by request.	Committee to vote
AZOLES	Urine	Routinely test and report fluconazole only.		Other drugs could be reported by request, as these agents will get into kidney tissue.	Committee to vote

1. CLSI Winter 2021 Susceptibility Testing Meeting Series, 25 Jan-24 Feb 2021.

Antifungal Direnci-İntrensek Direnç

Organizma/Antifungal	Flukonazol	Isavukonazol	Itrakonazol	Posakonazol	Vorikonazol	Ekinokandinler[1]	Flusitozin	Amfoterisin B
Candida krusei	IR							
Candida lusitaniae								*
Cryptococcus spp.						IR		
Rhodotorula spp.						IR		
Trichosporon spp.						IR		
Mucorales takımı	IR				IR	IR**		
L.prolificans	IR	ÇA	IR	IR	***	ÇA		IR
Fusarium spp.						ÇA		
Purpureocillium lilacinum								IR
Aspergillus terreus kompleks								NR****
Aspergillus spp.	IR						NR*****	

IR: İntrensek direnç; NR: Raporlamayınız; ÇA: Çalışma aşamasında; 1. Mikafungin, Anidulafungin ve Kaspofungin

* *C.lusitaniae*, amfoterisin B'ye IR değildir, ancak tedavi sırasında direnç geliştirebilir. Çalışmalarda fenotipik dirençli olarak belirtildiğinde, dirençli fenotip mikrodilüsyonda gözlenmez ama agar gradient striplerinde gözlenir.

** Mucorales takımı ekinokandinlere in vitro intrensek dirençli kabul edilir. Ancak kombinasyon terapilerinde etkin olabilir. Monoterapi olarak tavsiye edilmez.

*** *L.prolificans*, vorikonazol hariç azol grubu antifungallere IR'dir. MİK ve doz düzenlemesi değerlendirilerek vorikonazol monoterapisi veya kombinasyon terapisi kullanılabilir.

**** MİK sonuçları klinik sonuçlar ile korelasyon sağlamamaktadır, antifungal duyarlılık testi önerilmez.

***** *Aspergillus* spp. için flusitozin direnci tespit edilememektedir, in vitro testlerdeki pH sorunu ciddi MİK varyasyonlarına sebep olmaktadır. MİK-klinik ilişkisine dair çalışmalar kısıtlıdır. Flusitozin sadece kombinasyon tedavilerde kullanılmalıdır.

Antifungal Direnci

Fungus	Inherent resistance	Acquired resistance
	Yeasts	
***Candida* spp.**		
C. albicans	None	Fluconazole, echinocandins
C. parapsilosis	Echinocandins (?)	Fluconazole
C. tropicalis	None	Fluconazole, echinocandins
C. glabrata	Triazoles	Echinocandins
C. krusei	Triazoles	Echinocandins
C. lusitaniae	Amphotericin B	Fluconazole, echinocandins
C. guilliermondii	Fluconazole, echinocandins	
C. auris	Azoles, amphotericin B	Echinocandins
Non-*Candida* yeasts		
Trichosporon spp.	Echinocandins amphotericin B None	Fluconazole
Saccharomyces Malassezia spp.	Echinocandins	Fluconazole
Geotrichum	Echinocandins	
Rhodotorula	Triazoles	
Pichia	Fluconazole	
	Molds	
Aspergillus spp.		
A. fumigatus	Fluconazole	Voriconazole, isavuconazole
A. terreus	Fluconazole, amphotericin B	Voriconazole, isavuconazole
A. flavus	Fluconazole, amphotericin B	Voriconazole, isavuconazole
A. nidulans	Fluconazole, amphotericin B	Voriconazole, isavuconazole
Mucorales	Fluconazole, voriconazole	
Hyalohyphomycetes *Fusarium solani* *Scedosporium* spp. *Lomentospora prolificans*	Echinocandins and variably resistant to amphotericin B and triazoles Panresistant*	

*Panresistant: Consistently resistant to all 4 major classes of systemic antifungal agents: triazoles, polyenes, echinocandins, and fluoropyrimidines.

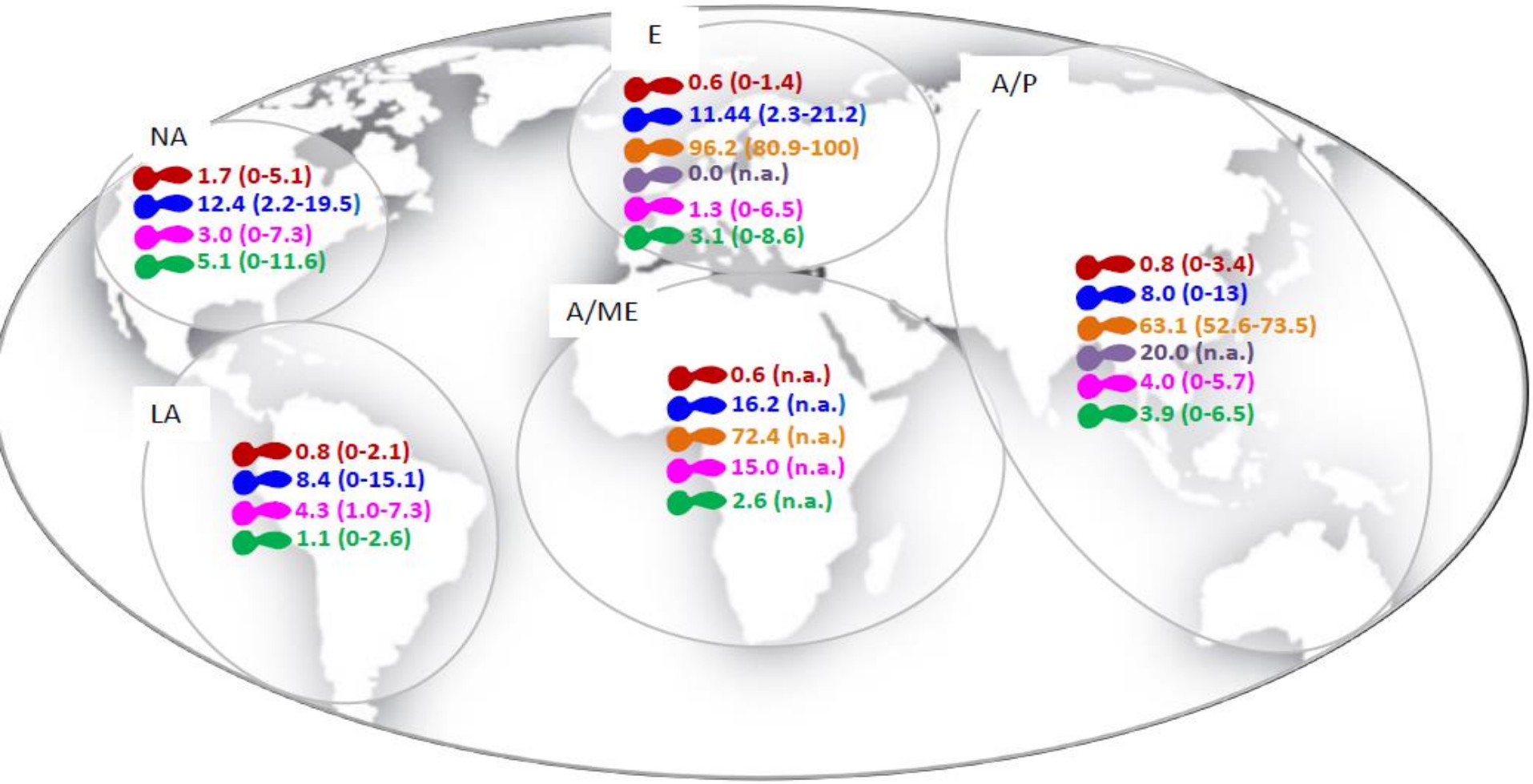
1. Gamaletsou MN, Walsh TJ, Sipsas NV. Invasive Fungal Infections in Patients with Hematological Malignancies: Emergence of Resistant Pathogens and New Antifungal Therapies. Turkish Journal of Hematology 2018; 35(1): 1.

Genre	Species	Antifungal	Antifungal resistance rates	Area	References
Candida	*C. glabrata*	Fluconazole	20.9%	Tunisia Hedi chaker (UH, Sfax-Tunisia)	Abbes S et al., 2014; Abbes S et al., 2013
	C. albicans	Fluconazole	0.54%	Habib Thameur	Eddouzi J et al., 2013
	C. tropicalis	Fluconazole	2.08%	Hospital, La Rabta	
	C. glabrata	Fluconazole	4.28%	Hospital (Tunis) and Ibn El Jazzar Hospital of Kairouan in central Tunisia	
	C. glabrata	Fluconazole	6.8%	Asia and western pacific region	Pfaller MA et al., 2015
	C. parapsilosis	Fluconazole	5.7%		
	C. tropicalis	Fluconazole	3.6%		
	C. albicans	Amphotericin B	1.1%	China and Korea	Zhang L et al., 2015
	C. krusei	Amphotericin B	3.4%		
	C. albicans	Caspofungin	6.67%	India	Wanjare S. et al., 2016
	Candida. spp	Amphotericin B	11.2%	German–Austrian multi-centre study	Schmalreck AF et al., 2012
	C. albicans	Fluconazole	1.5%	Spain	Nieto MC et al., 2015
	C. parapsilosis	Fluconazole	0.6%		
	C. glabrata	Fluconazole	1.1%		
	C. albicans	Voriconazole	3.4%		
	C. albicans	Fluconazole	0.5%	USA	Pfaller M.A. et al., 2015
	C. glabrata		11.1%		
	C. parapsilosis		2.5%		
	C. tropicalis		4.5%		
	C. guilliermondii		20.0%		
	C. glabrata	Echinocandins	1.3–2.1%		
	C. tropicalis		0.9–1.8%		
	C. auris	Fluconazole	93%	Colombia, India, Israel,	W.G. Lee, 2011;
		Amphotericin B	35%	Kenya, Kuwait, Pakistan,	Chowdhary A.
		Echinocandins	7%	South Africa,	et al., 2014;
				South Korea,	Magobo R.E.
				Venezuela,	et al., 2014; B.
				the United Kingdom	Calvo et al., 2016
				and in United States	
Cyptococcus	*C. neoformans*	Fluconazole	2.9%	European countries	Gago S et al., 2017,
		5-fluorocytosine	5.8%	Serbia	Arsenijevic A V et al., 2014
	C. neoformans	Azole	Resistance was not detected	Asia and western pacific region	Pfaller M.A. et al., 2015
Malassezia	*M. pachydermatis*	Amphotericin B terbinafine	High in vitro	European Area	Alvarez-Perez S et al., 2016
		All azoles except fluconazole	susceptibility	Spain	
	M. pachydermatis	Thiabendazole	13.7%	Brazil	Nascente Pda S et al., 2009
Trichosporon	*T. asahii*	Voriconazole	resistance was	Tunisia	Sellami H et al., 2017
	T. asahii	fluconazole voriconazole	not detected	Japan	Yang YL et al., 2013
			resistance was not detected		Sun W et al., 2012
Aspergillus	A. flavus	Amphotericin B	66.6%	Tunisia-Sousse	Gheith S et al., 2014
	A. flavus	Amphotericin B	84%	Tunisia-Sfax	Hadrich I et al., 2012
	A. flavus	Amphotericin B	67%	Austria	Lass-Florl C. et al., 1998
	A. flavus	Amphotericin B	14.8%	European countries	Alastruey-Izquierdo A et al., 2013
	A. terreus	Amphotericin B	27%	European countries	Oz Y et al., 2016
	A. lentulus	Itraconazole	100%	European countries	
	A. calidoustus	voriconazole-posaconazole	100%	European countries	
		Voriconazole and posaconazole			
Dermatophytes	*T. rubrum*	Amphotericin B, clotrimazole, itraconazole, ketoconazole, miconazole	Resistance was not detected	Malaysia	Mohd Nizam T et al., 2016
	Dermatophyte	Voriconazole and itraconazole	Resistance was not detected	Brazil	Aktas A.E. et al., 2014
	Dermatophyte	Fluconazole	100%	Iran	Afshari MA et al., 2016
Penicillium	*P. marneffei*	Amphotericin B echinocandins	Resistance was not detected	Spain	Alastruey-Izquierdo A et al., 2013
Mucorales	Mucorales	Posaconazole and amphotericin B	Resistance was not detected	Australia	Halliday CL et al., 2016
	A. variabilis	Posaconazole and terbinafine	Resistance was not detected	European countries	Chander J et al., 2015
	A. elegans		100%		

Genre	Species	Antifungal	Antifungal resistance rates	Area	References
	Rhizopus arrhizus, Rhizopus microsporus, Mucor sp., Rhizomucor pusillus, Cunninghamella bertholletiae, Mycocladus corymbifera and *Apophysomyces elegans*	Caspofungin	Showed lower MECs	USA	Thakur M et al., 2011
	R. oryzae	Caspofungin, voriconazole, and itraconazole	Poor in vitro activity	Western Asia countries	Kachuei R et al., 2016
Fusarium	*Fusarium spp.*	Amphotericin B	Resistance was not detected	American countries	Guevara-Suarez M et al., 2016
	Fusarium spp.	Azoles and caspofungin	Elevated MICs	India	Gupta C et al., 2016 Tupaki-Sreepurna A et al., 2017

1. Hadrich, I., Ayadi, A. Epidemiology of antifungal susceptibility: Review of literature. Journal de mycologie medicale 2018; 28.3: 574-584.

Fluconazole resistance (in %)



Candida albicans
Candida glabrata
Candida krusei
Candida lusitaniae
Candida parapsilosis
Candida tropicalis

1. Bassetti, M., Vena, A., Bouza, E.,, et al. Antifungal susceptibility testing in Candida, Aspergillus and Cryptococcus infections: are the MICs useful for clinicians?. CMI 2020; 26.8:1024-1033..

Türkiye'de Antifungal Direnç

Minimum inhibitory concentrations (MICs) following 24 h of incubation and resistance/non-wild-type (non-WT) rates obtained for all *Candida* spp. isolates included in the study ($n = 1991$).

Candida spp. (n)	Antifungal drug	MIC (μg/mL)				Rate of resistance/non–WT (%)			
		MIC_{50}	MIC_{90}	GM	Range	S	S-DD/I	R	Non-WT[a]
C. albicans (851)	AMB	1	2	0.95	0.125–2				0
	FLU	0.25	0.5	0.26	<0.125–4	99.8	0.2	0	
	ITR	0.06	0.125	0.04	≤0.015–0.5	99.4	0.6	0	
	MFG	≤0.03	≤0.03	0.03	≤0.03–0.06	100	0	0	
	POS	≤0.03	0.06	0.03	≤0.03–1				0
	VRC	≤0.015	≤0.015	0.02	≤0.015–0.06	100	0	0	
C. parapsilosis SC (575)	AMB	1	2	0.89	0.125–2				0
	FLU	1	4	0.95	≤0.125 to >64	89	3.3	7.7	
	ITR	0.06	0.25	0.07	≤0.015–1				0.2
	MFG	1	1	0.83	0.125–4	99.8	0.2	0	
	POS	≤0.03	0.25	0.05	≤0.03–0.5				3.5
	VRC	≤0.015	0.03	0.02	≤0.015–0.5	97.9	2.1	0	
C. glabrata SC (216)	AMB	1	2	1.13	0.125–2				0
	FLU	4	16	4.17	0.5–64	–	99.1	0.9	
	ITR	0.25	0.5	0.23	≤0.015–2				0
	MFG	≤0.03	≤0.03	0.03	≤0.03–0.06	100	0	0	
	POS	0.25	1	0.23	<0.03–2				0
	VRC	0.03	0.125	0.03	≤0.015–1				0.5
C. tropicalis (203)	AMB	1	2	1.17	0.25–2				0
	FLU	0.5	1	0.45	≤0.125–2	100	0	0	
	ITR	0.6	0.25	0.08	≤0.015–0.5				0
	MFG	≤0.03	≤0.03	0.03	≤0.03–0.06	100	0	0	
	POS	≤0.03	0.125	0.04	≤0.03–0.125				0
	VRC	≤0.015	≤0.015	0.02	≤0.015–0.06	100	0	0	
C. krusei (52)	AMB	2	2	1.32	0.5–2				0
	FLU	32	64	27.64	8 to >64	–	–	100[b]	
	ITR	0.25	0.5	0.17	≤0.015–0.5				0
	MFG	0.06	0.25	0.08	≤0.03–0.25	100	0	0	
	POS	0.25	0.5	0.14	≤0.03–1				1.9
	VRC	0.06	0.125	0.07	0.03–0.125	100	0	0	
C. kefyr (33)	AMB	2	2	1.37	0.5–2			[c]	[c]
	FLU	0.25	0.5	0.28	≤0.125–1				0
	ITR	0.06	0.125	0.07	≤0.015–0.5			[c]	[c]
	MFG	≤0.03	≤0.03	0.03	≤0.03–0.06				0
	POS	≤0.03	0.125	0.05	≤0.03–0.25				0
	VRC	≤0.015	≤0.015	0.02	≤0.015				0
C. lusitaniae (23)	AMB	1	1	1	0.5–2				0
	FLU	0.25	1	0.3	≤0.125–4				4.3
	ITR	0.06	0.125	0.06	0.03–0.125				0
	MFG	≤0.03	0.125	0.04	≤0.03–0.25				0
	POS	≤0.03	0.06	0.04	≤0.03–0.125				0
	VRC	≤0.015	≤0.015	0.02	≤0.015				0
C. guilliermondii SC (16)	AMB	1	1	0.81	0.25–1				0
	FLU	2	8	2.18	0.5–8				0
	ITR	0.125	0.25	0.14	0.03–0.5				0
	MFG	0.125	1	0.15	≤0.03–1	100	0	0	
	POS	0.125	0.5	0.13	≤0.03–0.5				0
	VRC	≤0.015	0.03	0.02	≤0.015–0.03				0
Other *Candida* spp. (22)[d]	AMB	–	–	–	0.25–2				
	FLU	–	–	–	≤0.125–32				
	ITR	–	–	–	0.03–0.125				
	MFG	–	–	–	≤0.03–0.25				
	POS	–	–	–	≤0.03–0.25				
	VRC	–	–	–	≤0.015–0.125				

$MIC_{50/90}$, MIC for 50% and 90% of the isolates, respectively; GM, geometric mean; S, susceptible; S-DD, susceptible dose-dependent (for FLU and ITR); I, intermediate (for echinocandins, i.e. MFG); R, resistant; AMB, amphotericin B; FLU, fluconazole; ITR, itraconazole; MFG, micafungin; POS, posaconazole; VRC, voriconazole; SC, species complex; ECV, epidemiological cut-off value.

[a] Rate of resistance could not be determined for these drug–species combinations owing to lack of determined clinical breakpoints.

[b] Intrinsic resistance to FLU.

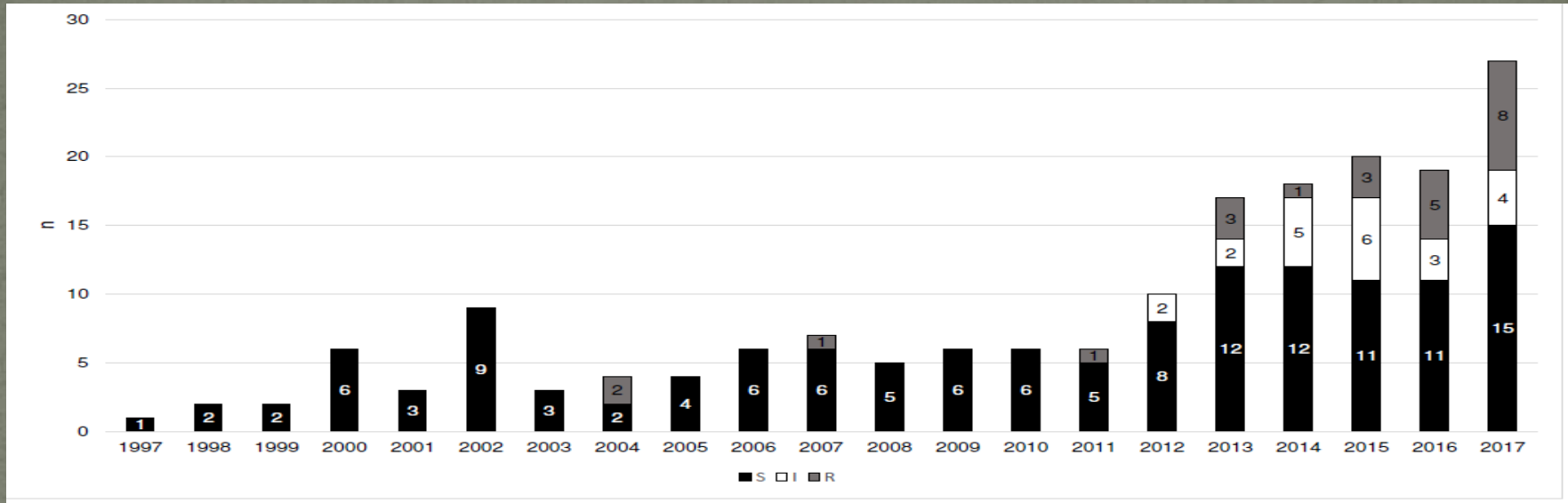
[c] Not determined owing to lack of established clinical breakpoints and ECVs.

[d] Includes *C. inconspicua/norvegensis* (7), *C. dubliniensis* (6), *C. pelliculosa* (3), *C. rugosa* (2), *C. utilis* (2), *C. lipolytica* (1) and *C. sake* (1). Among these, ECVs are available for FLU, VRC and POS against *C. dubliniensis* and *C. pelliculosa* and for AMB, ITR and MRG only against *C. dubliniensis*. All isolates of these species with available ECVs are wild-type for the denoted antifungal drugs.

FKS Mutasyonu

1. Arikan-Akdagli S, Gulmez D, Dogan O, et al. First multicentre report of in vitro resistance rates in candidaemia isolates in Turkey. J Glob Antimicrob Resist 2019; 18: 230-234.
2. Arastehfar, A., Daneshnia, F., Salehi, M., et al. Low level of antifungal resistance of Candida glabrata blood isolates in Turkey: fluconazole minimum inhibitory concentration and FKS mutations can predict therapeutic failure. Mycoses 2020; 63.9: 911-920.

Türkiye'de Antifungal Direnç



Antifungal	MIC Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Susceptibility n (%) S	I	R	Breakpoints (mg/L)** S	R
Fluconazole	≤0.125 - >64	1	8	135 (74.6)	22 (12.1)	24 (13.3)	≤2	>4
Voriconazole	≤0.008 - 2	0.015	0.25	160 (88.4)	12 (6.6)	9 (5.0)	≤0.125	>0.25
Posaconazole	≤0.008 – 0,5	0.03	0.06	174 (96.1)	-	7 (3.9)	≤0.06	>0.06

MIC: Minimum inhibitory concentration

S: Susceptible

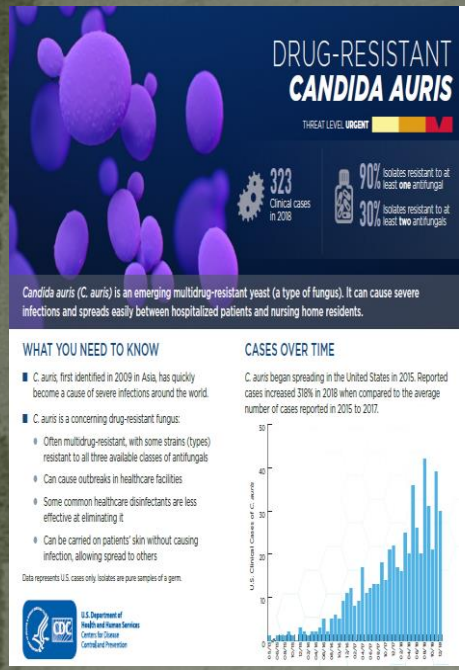
I: Susceptible, increased exposure

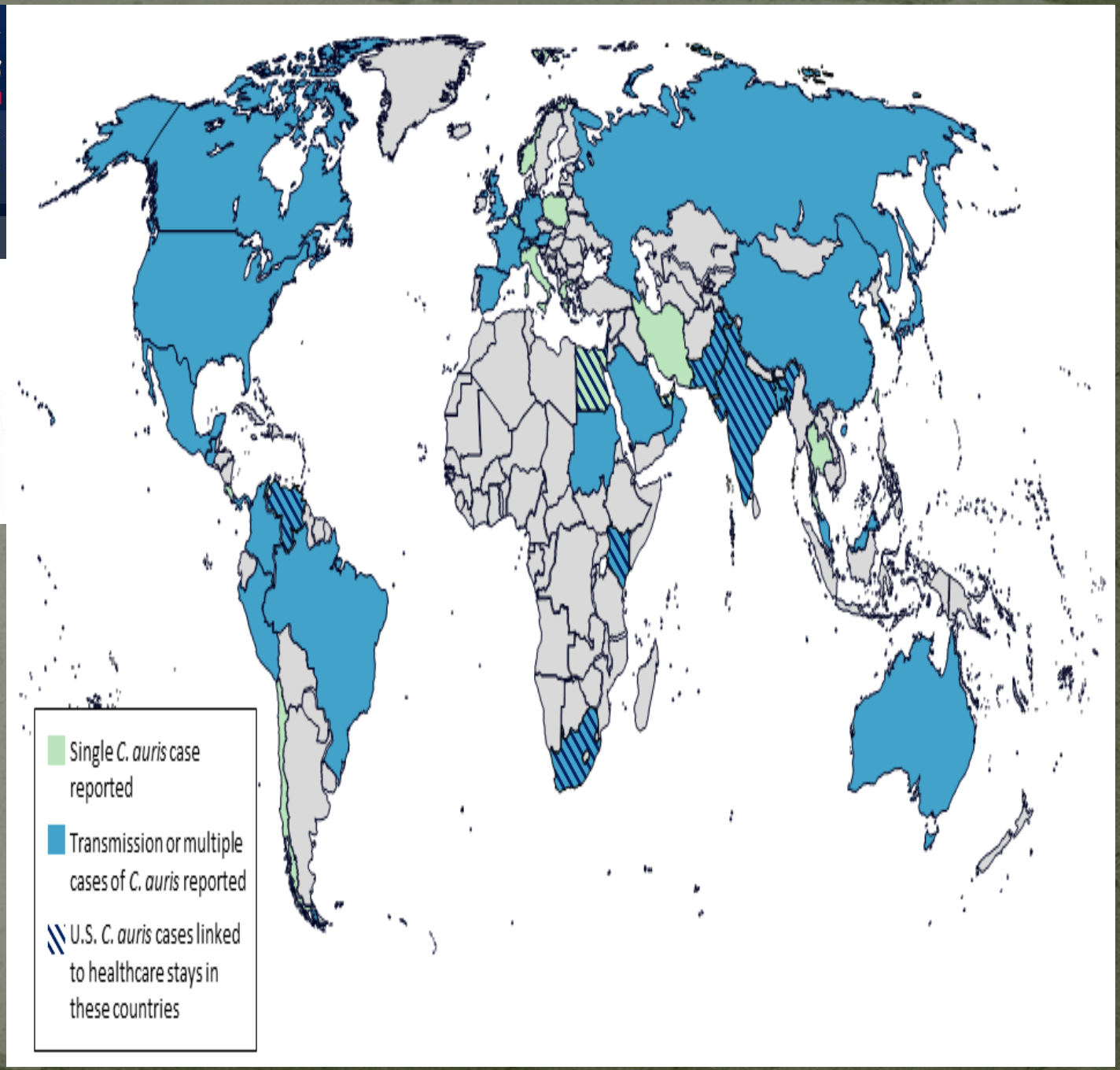
R: Resistant

*: Results represent the first isolate from each patient.

**:Reference no. 36; EUCAST Breakpoint Table v. 10.0.

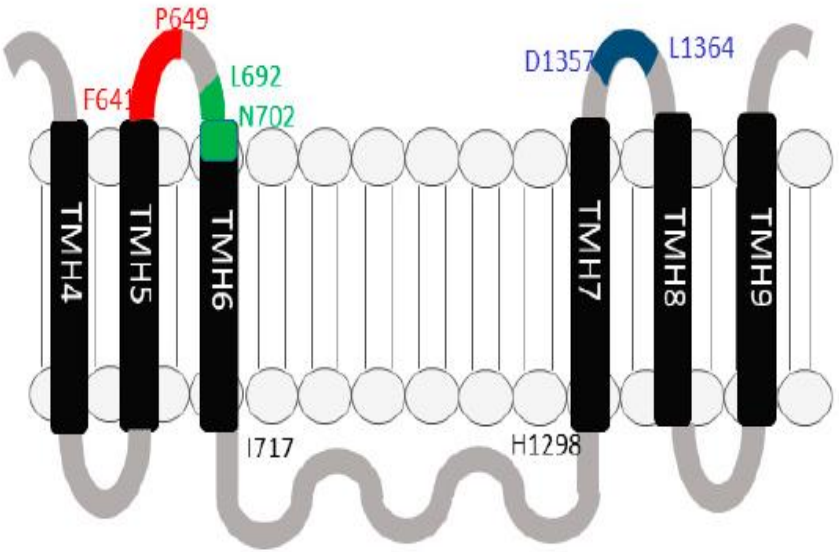
1. Demirci-Duarte S, Arikan-Akdagli S, Gülmez D. Species Distribution, Azole Resistance and Related Molecular Mechanisms in Invasive Candida parapsilosis Complex Isolates: Increase of Fluconazole Resistance in 21 Years. Mycoses 2021; DOI: https://doi.org/10.1111/myc.13296


DRUG-RESISTANT
CANDIDA AURIS
THREAT LEVEL URGENT
323
Clinical cases in 2018
90% Isolates resistant to at least one antifungal
30% Isolates resistant to at least two antifungals
Candida auris (C. auris) is an emerging multidrug-resistant yeast (a type of fungus). It can cause severe infections and spreads easily between hospitalized patients and nursing home residents.
WHAT YOU NEED TO KNOW
C. auris, first identified in 2009 in Asia, has quickly become a cause of severe infections around the world.
C. auris is a concerning drug-resistant fungus:
Often multidrug-resistant, with some strains (types) resistant to all three available classes of antifungals
Can cause outbreaks in healthcare facilities
Some common healthcare disinfectants are less effective at eliminating it
Can be carried on patients' skin without causing infection, allowing spread to others
Data represents U.S. cases only. Isolates are pure samples of a germ.
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
CASES OVER TIME
C. auris began spreading in the United States in 2015. Reported cases increased 318% in 2018 when compared to the average number of cases reported in 2015 to 2017.
U.S. Clinical Cases of C. auris
50
40
30
20
10
0


Single C. auris case reported
Transmission or multiple cases of C. auris reported
U.S. C. auris cases linked to healthcare stays in these countries

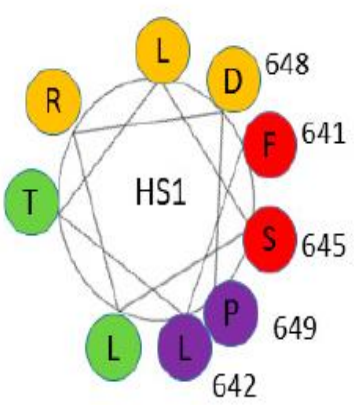
FKS Mutasyonları

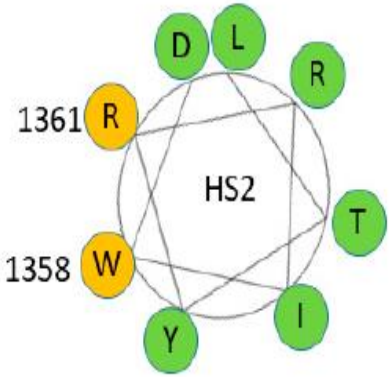
A



B

C. albicans Fks1p	FLTLSLRDP	DWIRRYTL
C. glabrata Fks1p	FLILSLRDP	DWVRRYTL
C. glabrata Fks2p	FLILSLRDP	DWIRRYTL
C. krusei Fks1p	FLILSIRDP	DWIRRYTL
C. tropicalis Fks1p	FLTLSLRDP	DWIRRYTL
C. auris Fks1p	FLTLSLRDP	DWIRRYTL
C. parapsilosis S.S. Fks1p	FLTLSLRDA	DWIRRYTL
C. guilliermondii Fks1p	FMALSLRDP	DWIRRYTL





F---S--DP HS2

- > Frequency
- > MIC / IC_{50}
- Better fitness
- > Vmax

1. Garcia-Effron, G. Rezafungin—Mechanisms of Action, Susceptibility and Resistance: Similarities and Differences with the Other Echinocandins. J Fungi 2020; 6.4: 262.

Antifungal Duyarlılık & Klinik İlişkisi

- Antifungal Duyarlılık Testleri:
  - Farmakolojik ilişki çok net
  - Bazı olgularda klinik korelasyonu açık
  - Rehberlere yönlendirici oluyor

  - Çalışmalar yetersiz; etik sorunlar, hasta sayısı kısıtlı (evreni temsiliyet?)
  - Terapötik başarısızlığı doğrudan MİK'e bağlamak zor
  - Klinik direnç oluşturan çok faktör var

MİK-Mortalite İlişkisi

- Kandidoz olgularında; AIDS varlığı MİK önemini arttırıyor
- *C.glabrata* kompleks
  - Ekinokandin MİKleri ile mortalite yükseliyor ya da enfeksiyon tekrarlıyor
- *A.terreus* ve *A.flavus* kompleks; amfoterisin B MİKleri ile korelasyon var

1. Kanafani ZA, Perfect JR. Resistance to antifungal agents: mechanisms and clinical impact. Clinical Infectious Diseases 2008; 46(1): 120-8.

2. Alexander BD, et al. Increasing echinocandin resistance in *Candida glabrata*: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clinical infectious diseases 2013; 56(12): 1724-32.

3. Hadrich I, et al. Amphotericin B in vitro resistance is associated with fatal *Aspergillus flavus* infection. Medical mycology 2012 50(8): 829-34.

4. Lionakis MS, et al. *Aspergillus* susceptibility testing in patients with cancer and invasive aspergillosis: difficulties in establishing correlation between in vitro susceptibility data and the outcome of initial amphotericin B therapy. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2005; 25(9): 1174-80.

5. Ullmann AJ, et al. Ullmann AJ, et al. Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clinical Microbiology and Infection 2018; DOI: https://doi.org/10.1016/j.cmi.2018.01.002

MİK-Mortalite İlişkisi

- *C.parapsilosis* kompleks ile ekinokandinler?

- Etkeni *A.fumigatus* kompleks olan invaziv aspergilloz olgularında;
  - Azol duyarlılığı var ise; %48
  - Azol direnci var ise; %53
  - Azol direnci ile ilişki var ancak veri yetersiz, istatistiksel anlamlı değil, in vivo çalışmalar sınırlı

1. Cornely OA, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. Clinical Microbiology and Infection 2012; 18: 19-37.

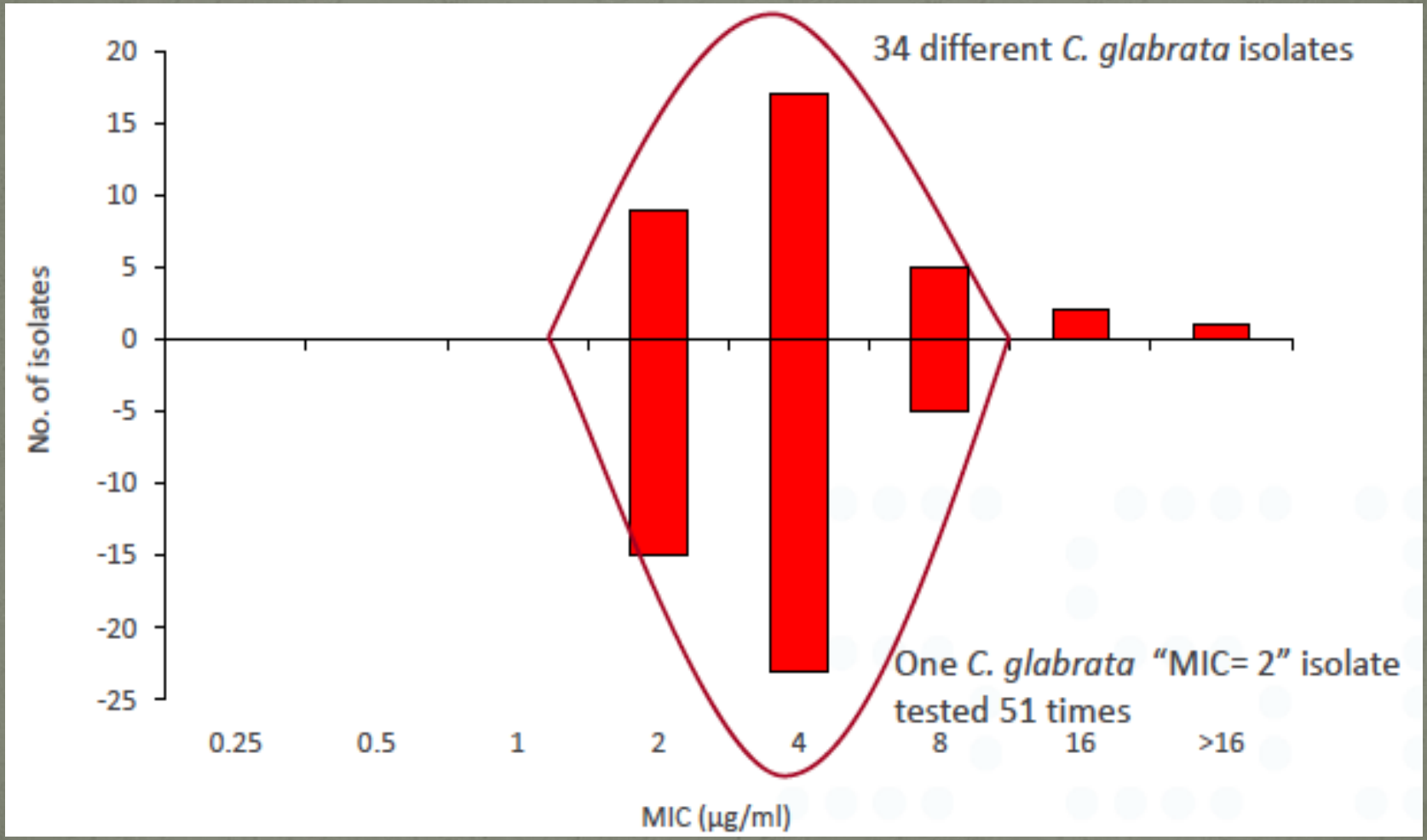
2. van der Linden JW, et al. Clinical implications of azole resistance in *Aspergillus fumigatus*, The Netherlands, 2007–2009. Emerging infectious diseases 2011; 17(10): 1846.

Klinik Eşik Değer (CBP)

- İlaç Dozu Uygulaması
- MİK Dağılımı
- Epidemiyolojik Eşik Değer (ECOFF, ECV) Belirleme
- PK/PD Hayvan ve İnsan Çalışmaları
- Monte Carlo Simulasyonu
- Klinik Verilerin Değerlendirilmesi

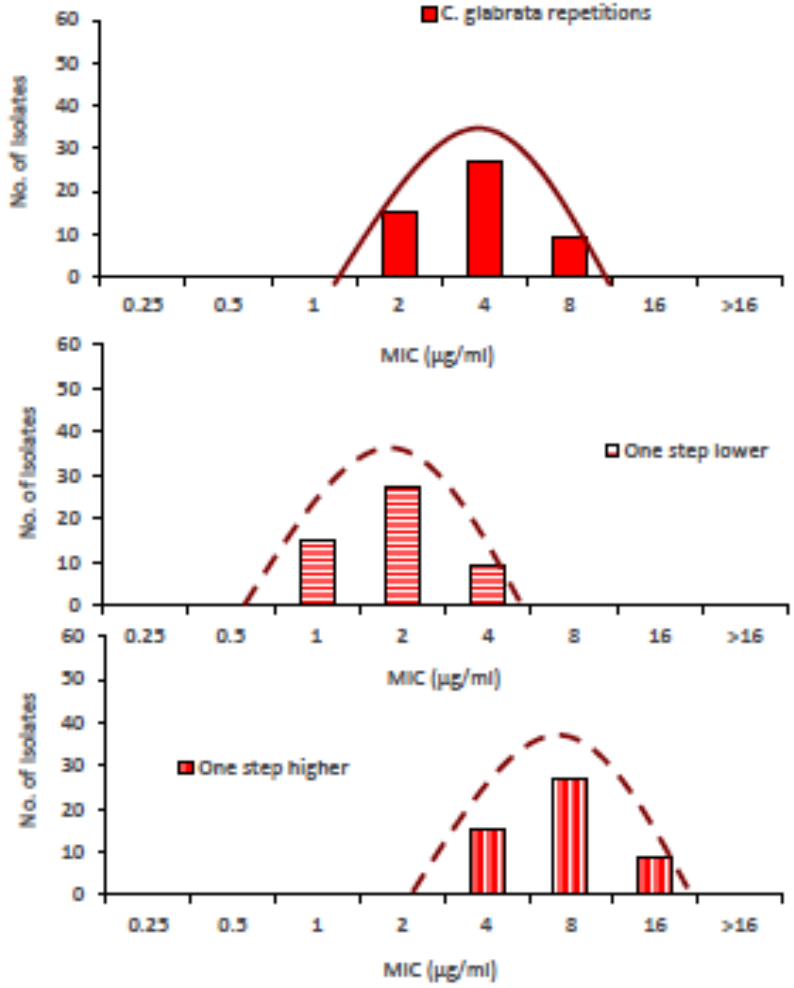
1. Arendrup MC, et al. Breakpoints for antifungal agents: An update from EUCAST focusing on echinocandins against *Candida* spp. And triazoles against *Aspergillus* spp.. Drug Resistance Updates2013; 16:81-95

MİK Dağılımı



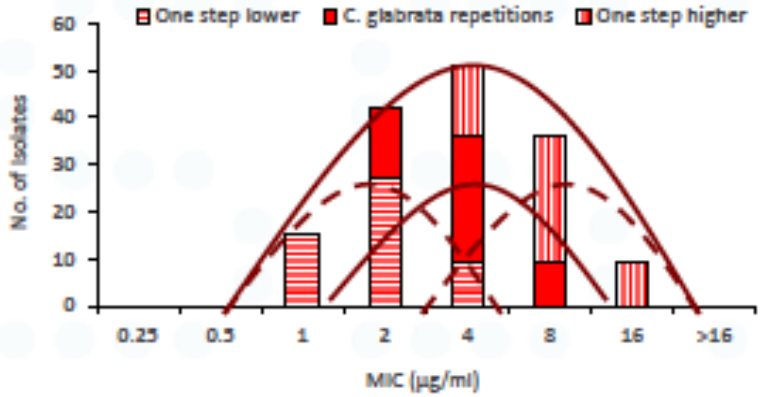
1. Arendrup MC. 2nd Mycology Masterclass, İzmir, Türkiye

MİK Dağılımı



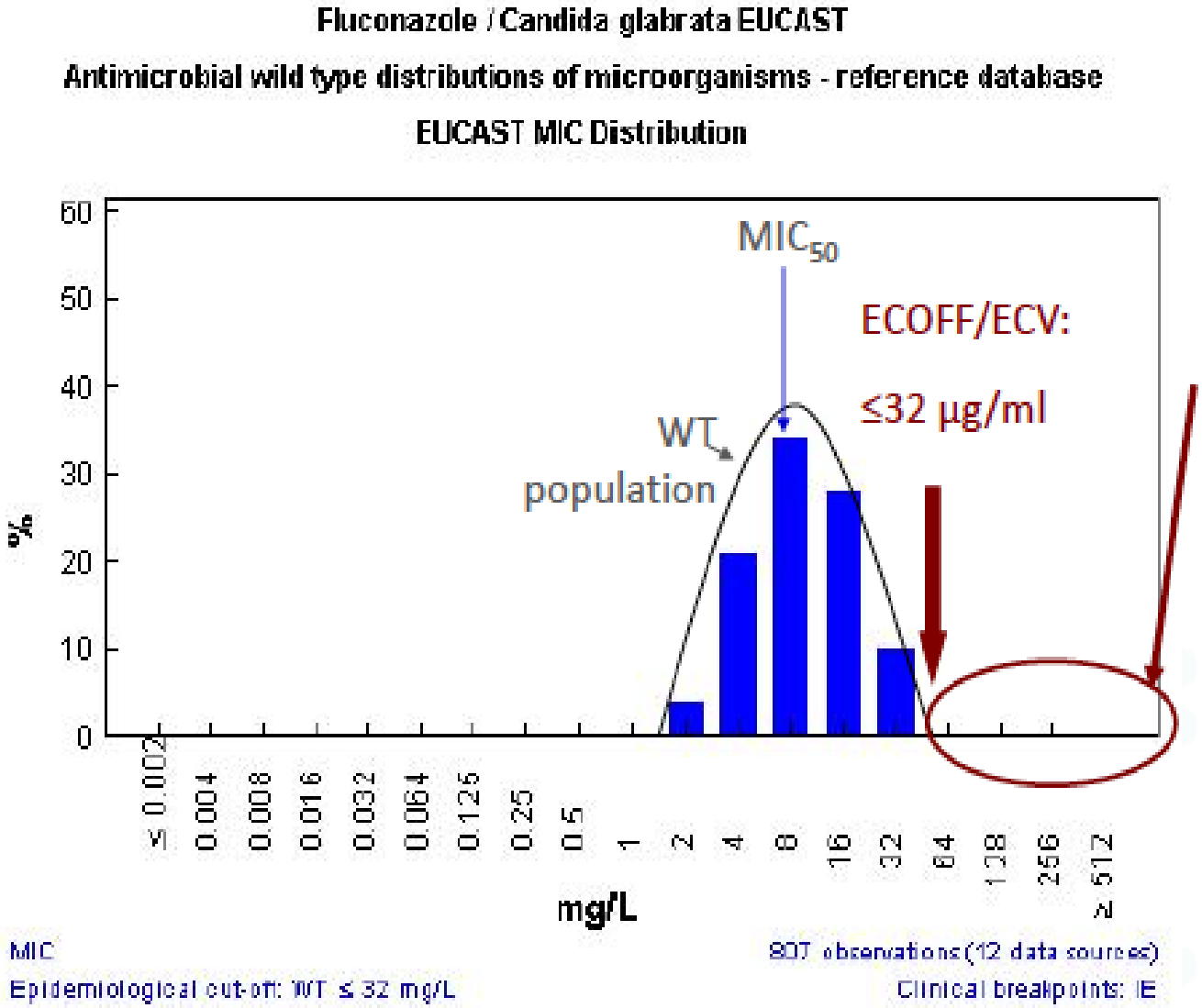
Modal MIC / MIC_{50}

Reflects the inherent susceptibility of the WT population



1. Arendrup MC. 2nd Mycology Masterclass, İzmir, Türkiye

Epidemiyolojik Eşik Değer (ECV, ECOFF)

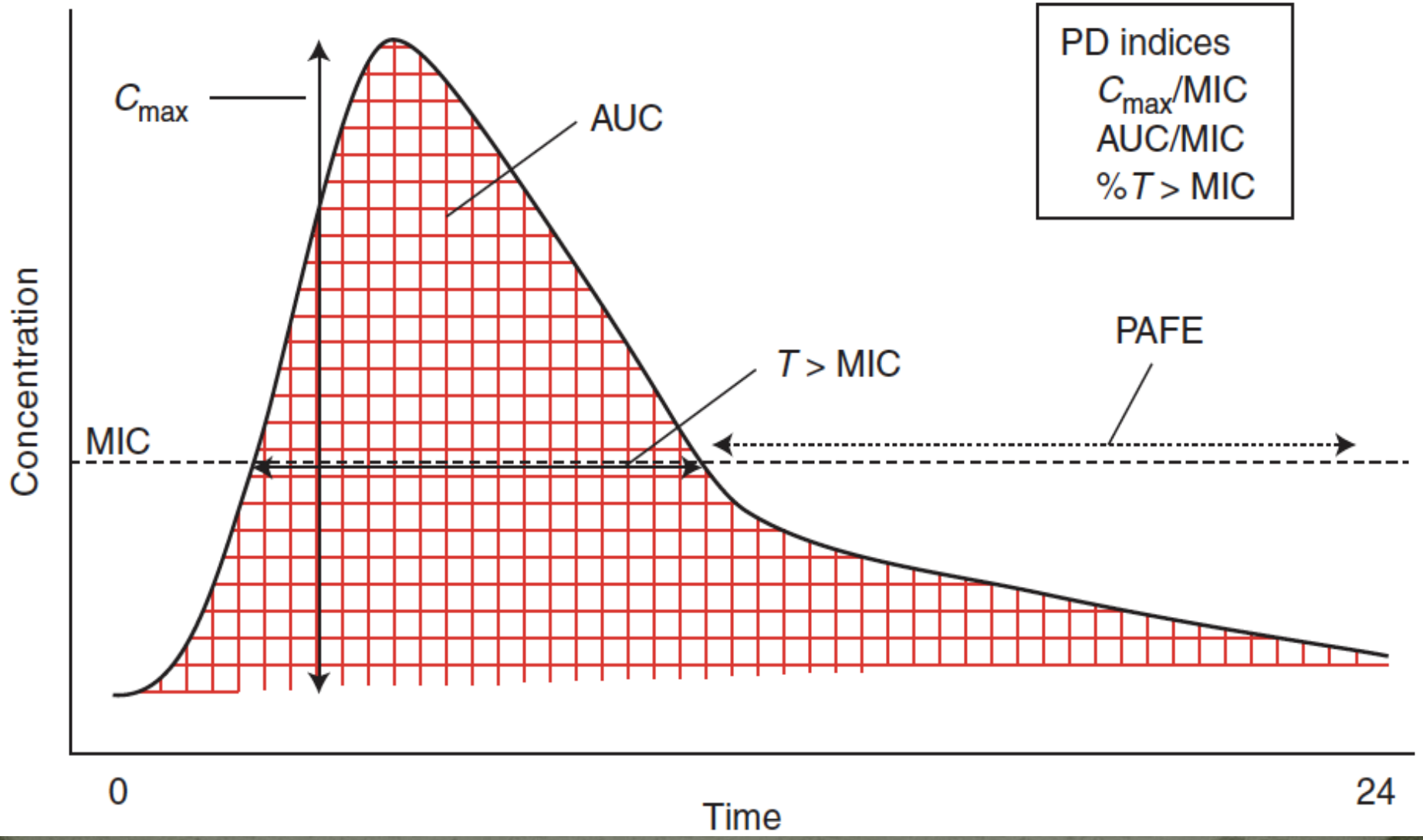


Non-WT

- MICs outside the WT population **cannot** be explained by test variation
- Microbiological resistance
- Outcome may be different than for WT isolates

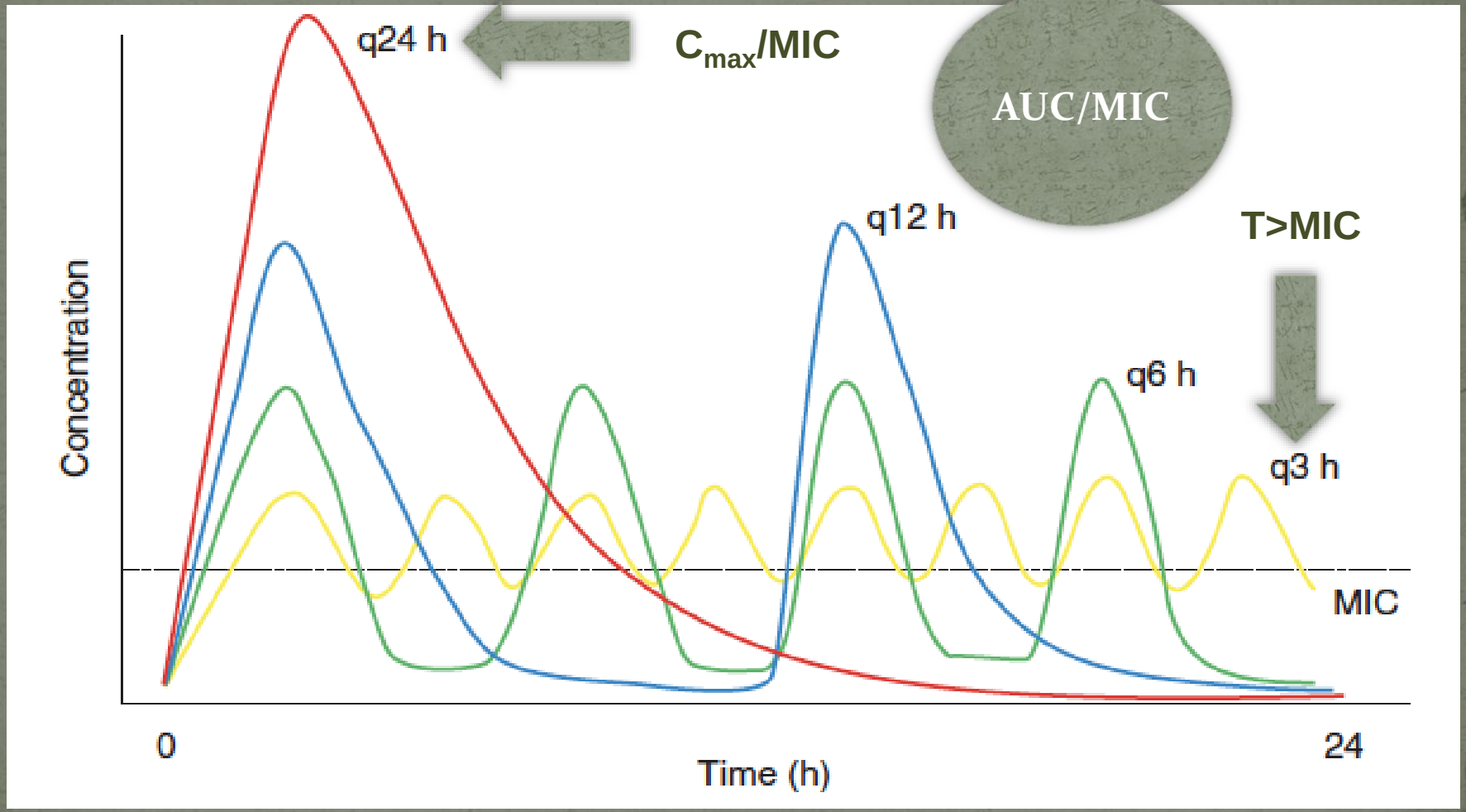
1. Arendrup MC. 2nd Mycology Masterclass, İzmir, Türkiye

PK/PD: Konsantrasyon-Zaman Eğrisi



1. Lepak AJ, Andes DR. Antifungal pharmacokinetics and pharmacodynamics. Cold Spring Harbor Prespectives in Medicine 2015; 5(5): a019653

PK/PD: Konsantrasyon-Zaman Eğrisi



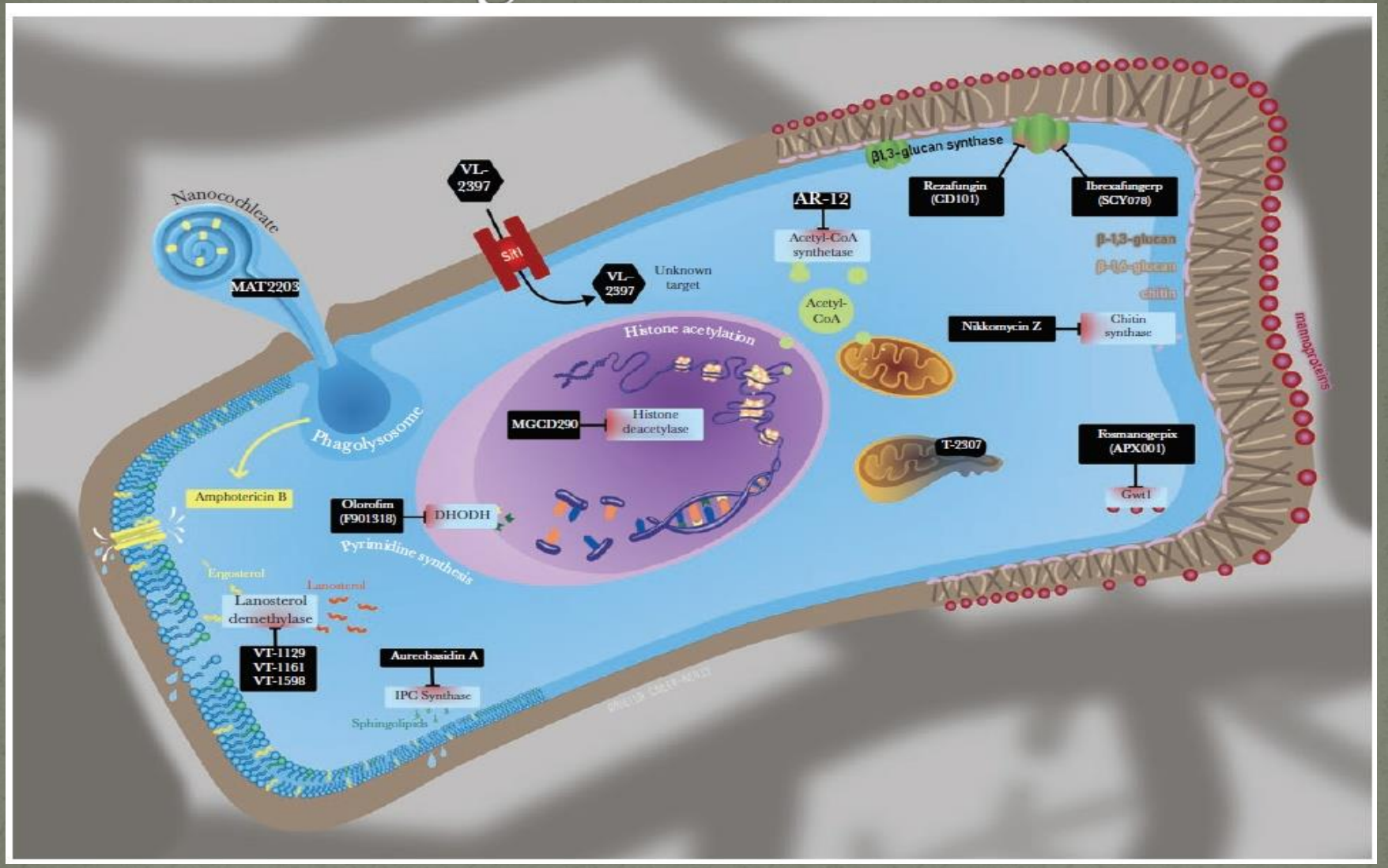
1. Lepak AJ, Andes DR. Antifungal pharmacokinetics and pharmacodynamics. Cold Spring Harbor Prespectives in Medicine 2015; 5(5): a019653

PD İndeksleri

Drug class	Concentration dependent	Prolonged PAFE	PD index predictive of efficacy
Polyene	Yes	Yes	C_{max}/MIC
Flucytosine	No	No	$T > MIC$
Azoles	No	Yes	AUC/MIC
Echinocandins	Yes	Yes	C_{max}/MIC or AUC/MIC

1. Lepak AJ, Andes DR. Antifungal pharmacokinetics and pharmacodynamics. Cold Spring Harbor Prespectives in Medicine 2015; 5(5): a019653

Yeni Antifungaller



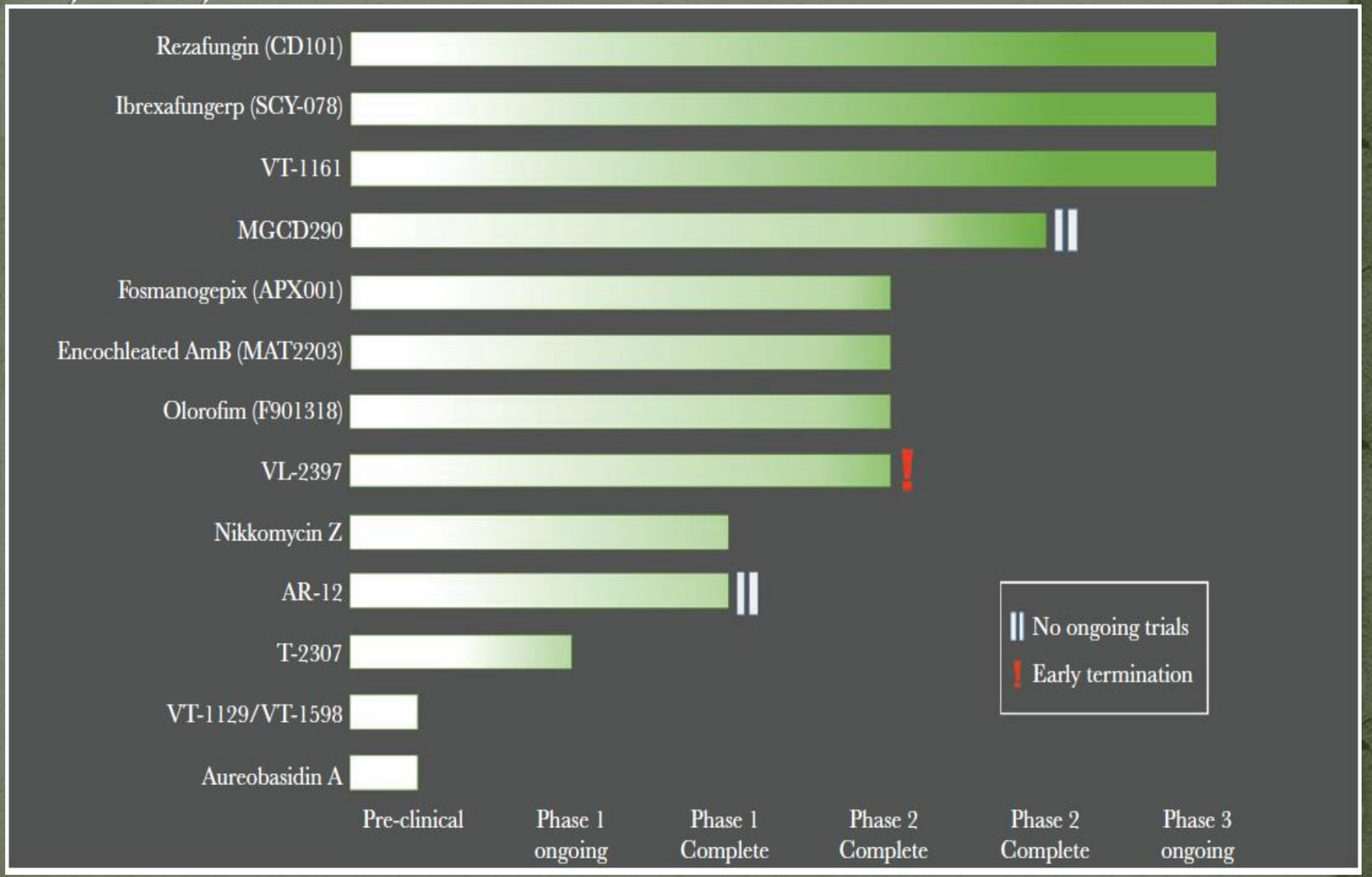
1. Gintjee, T. J., Donnelley, M. A., Thompson, G. R. Aspiring antifungals: review of current antifungal pipeline developments. J Fungi 2020; 6.1: 28.
2. Cotner, S. E., Dawson, K. L. New Options in Antifungal Therapy: New Drugs, Inhaled Antifungals, and Management of Resistant Pathogens. Current Treatment Options in Infectious Diseases, 2019, 11.4: 418-432.
3. Rauseo, A. M., Coler-Reilly, A., Larson, L., Spec, A.Hope on the horizon: Novel Fungal treatments in development. Open Forum Infectious Diseases 2020; DOI: 10.1093/ofid/ofaa016

Yeni Antifungaller

Class	Antifungal Agent	Mechanism of Action	Spectrum of Activity	Clinical Phase and Company	Clinical Advantages
Azole	SUBA-itraconazole	Interferes with cytochrome P450 activity, decreasing ergosterol synthesis, inhibiting cell membrane formation	blastomycosis, histoplasmosis, and aspergillosis	FDA approved Mayne Pharma Ltd.	Increased bioavailability compared to itraconazole
Echinocandin	Rezafungin	Inhibition of 1,3-β-D-glucan synthesis	*Candida albicans*, *Candida auris* *Candida krusei*, *Candida tropicalis*, *Aspergillus* spp. *Pneumocystis* spp.	Phase III Cidara Therapeutics, Inc.	Once-weekly dosing regimen. Treatment and potential role for prophylaxis
Terpenoid	Ibrexafungerp	Triterpenoid enfumafungin derivative that inhibits 1,3-β-D-glucan synthesis	*Candida* spp. including *Candida glabrata and Candida auris* *Aspergillus* spp.	Phase III SCYNEXIS Inc.	Oral and IV formulation Maintains activity against echinocandin-resistant *Candida* spp. and *Aspergillus* spp.
Orotomides	Olorofim	Inhibition of dihydroorotate dehydrogenase, thereby inhibiting pyrimidine production which negatively affects fungal nucleic acid, cell wall, and phospholipid synthesis, as well as cell regulation and protein production	*Aspergillus fumigatus*, *Aspergillus nidulans*, *Aspergillus terreus*, *and Aspergillus niger* and multidrug resistant strains of *Aspergillus* spp. Uncommon moulds such as *Lomentospora prolificans* and *Scedosporium* spp. Endemic Fungi	Phase II F2G Ltd.	Oral and IV formulation Activity against *Aspergillus* spp. including multidrug resistant and uncommon moulds
HDAC Inhibitor	MGCD290	Fungal histone deacetylase (HDAC) inhibitor	*Candida* spp. *Aspergillus* spp.	Phase II Mirati Therapeutics, Inc.	Possible role as an adjunctive antifungal in combination with an azole or echinocandin
Polyene	Amphotericin B Cochleate	Cochleate are a multilayered structure that forms a solid, lipid bilayer, configured into a spiral. Following oral administration, the cochleate is absorbed from the GI tract, enters circulation, and once calcium concentrations in cochleates are decreased, the spiral formation opens and releases the encapsulated drug into the cell.	*Candida* spp.	Phase II Matinas BioPharma	Oral formulation of amphotericin delivered via cochleate
Tetrazole	VT-1129	Interferes with cytochrome P450 activity, decreasing ergosterol synthesis, inhibiting cell membrane formation	*Cryptococcus* spp. *Candida* spp.	Pre-clinical Viamet Pharmaceuticals, Inc.	May have reduced P450 drug interactions
	VT-1161	Interferes with cytochrome P450 activity, decreasing ergosterol synthesis, inhibiting cell membrane formation	*Candida* spp. Coccidioides spp. Rhizopus spp.	Phase III Mycovia Pharmaceuticals	May have reduced P450 drug interactions
	VT-1598	Interferes with cytochrome P450 activity, decreasing ergosterol synthesis, inhibiting cell membrane formation	*Candida* spp. including *C. auris* *Aspergillus* spp. *Cryptococcus* spp.	Phase I Mycovia Pharmaceuticals	May have reduced P450 drug interactions
Glycosylphosphatidylinositol inhibitor	Fosmanogepix (APX001)	Inhibits fungal Gwt1 GPI anchor protein. Low affinity for human GPI anchor proteins	*Candida* spp. including C. auris *Cryptococcus* *Coccidioides* *Aspergillus* and hyaline moulds Mucorales Not active against *C. krusei*	Phase II Amplyx Pharmaceuticals	Broad spectrum, oral formulation little toxicity in human studies thus far
Siderophore	VL-2397	Uptake via siderophore iron transporter	*Aspergillus* Some *Candida* spp. and *Aspergillus* spp. Mucorales	No current development plans – phase II trial terminated early	Activity against triazole resistant Aspergillus isolates
Arylamidine	T-2307	Thought to inhibit fungal mitochondrial synthesis	*Candida* spp. *Aspergillus* and some hyaline moulds	Phase I Toyama Chemical Company Ltd.	Structurally similar to pentamidine

1. Gintjee, T. J., Donnelley, M. A., Thompson, G. R. Aspiring antifungals: review of current antifungal pipeline developments. J Fungi 2020; 6.1: 28.
2. Cotner, S. E., Dawson, K. L. New Options in Antifungal Therapy: New Drugs, Inhaled Antifungals, and Management of Resistant Pathogens. Current Treatment Options in Infectious Diseases, 2019, 11.4: 418-432.
3. Rauseo, A. M., Coler-Reilly, A., Larson, L., Spec, A. Open Forum Infectious Diseases 2020; DOI: 10.1093/ofid/ofaa016

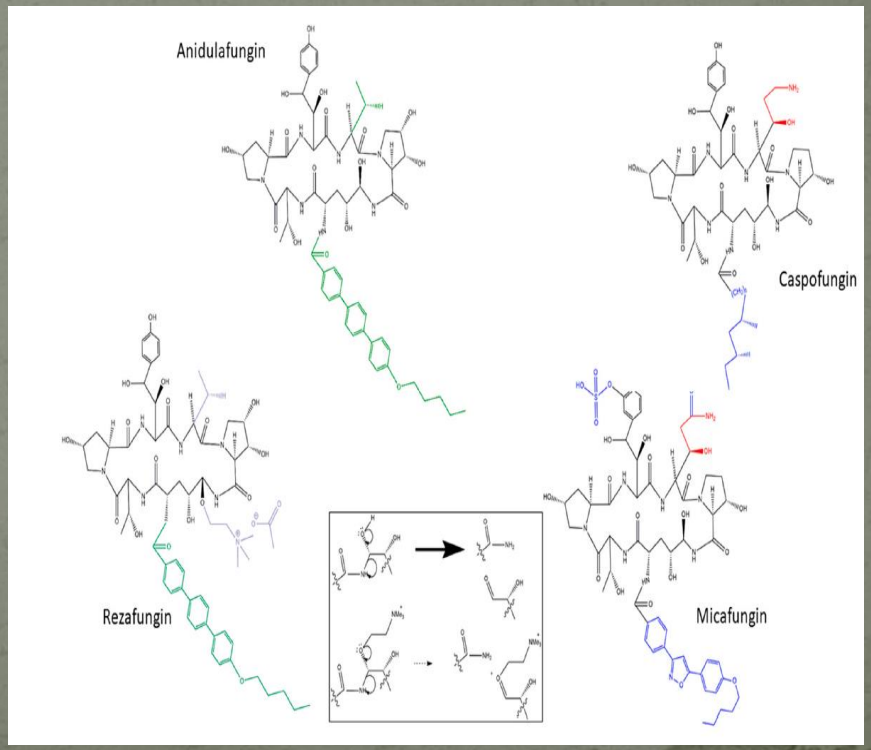
Çalışmaların Durumu



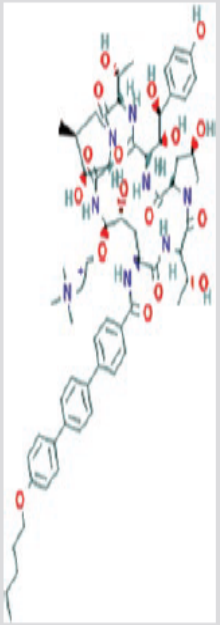
1. Rauseo, A. M., Coler-Reilly, A., Larson, L., Spec, A.Hope on the horizon: Novel Fungal treatments in development. Open Forum Infectious Diseases 2020; DOI: 10.1093/ofid/ofaa016

Rezafungin (RZF)

- CD101, biafungin, SP3025
- Yaklaşık 130 saat yarı ömür
- Anidulafungin analoğu



Rezafungin

Class	Novel Therapy	Chemical Structure	Mechanism of Action	Spectrum of Activity	Expected Benefits
Glucan synthesis inhibitors	Rezafungin (CD101)		Inhibition of β-1,3-glucan synthesis	*Candida* spp (including *Candida auris*), *Aspergillus* spp, and *Pneumocystis* spp	• Not hepatotoxic • Longer half-life (weekly dosing) • Better penetration (IAC) • Less risk of resistance • Active against resistant strains • SQ and IV formulation • Better adherence, less hospital costs

1. Garcia-Effron, G. Rezafungin—Mechanisms of Action, Susceptibility and Resistance: Similarities and Differences with the Other Echinocandins. J Fungi 2020; 6.4: 262.
2. Zhao, Y., Perlin, D. S. Review of the Novel Echinocandin Antifungal Rezafungin: Animal Studies and Clinical Data. Journal of Fungi, 2020, 6.4: 192.
3. Rauseo, A. M., Coler-Reilly, A., Larson, L., Spec, A.Hope on the horizon: Novel Fungal treatments in development. Open Forum Infectious Diseases 2020; DOI: 10.1093/ofid/ofaa016

Rezafungin – Geniş Çaplı Çalışmalar

- CLSI – Rehberine eklemek üzere
- EUCAST
  - Plak?

1. Pfaller, M. A., Carvalhaes, C., Messer, S. A.,et al. Activity of a long-acting echinocandin, rezafungin, and comparator antifungal agents tested against contemporary invasive fungal isolates (SENTRY Program, 2016 to 2018). Antimicrobial agents and chemotherapy, 2020, 64.4.
2. Arendrup, M. C., Meletiadis, J., Zaragoza, O., et al. Multicentre determination of rezafungin (CD101) susceptibility of Candida species by the EUCAST method. CMI 2018; 24.11: 1200-1204.
3. Arendrup, M. C., Jørgensen, K. M., Hare, R. K., et al. EUCAST reference testing of rezafungin susceptibility and impact of choice of plastic plates. Antimicrob Agent Chemother 2019; 63.9.
4. Zhao, Y., Perlin, D. S. Review of the Novel Echinocandin Antifungal Rezafungin: Animal Studies and Clinical Data. Journal of Fungi, 2020, 6.4: 192.
5. Cota, J. M., Giancola, S. E., Benavides, T. M., Wiederhold, N. Implications of Evolving and Emerging Pharmacokinetic-Pharmacodynamic Research for Triazoles and Echinocandins. Curr Fungal Infect Rep 2020; 14: 258-267.

Rezafungin - EUCAST

Summary of rezafungin *in vitro* activity against *Candida* species determined at four mycology reference laboratories[a]

Species centre	MIC (mg/L)													Total	MIC range	GM	MIC_{50}	MIC_{90}	WT-UL Visual	WT-UL statistical 97.5% endpoint	WT-UL statistical 99% endpoint	Derivatization WT-UL
	0.002	0.004	0.008	0.016	0.031	0.063	0.125	0.25	0.5	1	2	4	>4									
C. albicans																						
Laboratory 1			5	33	**41**	17	7							103	0.008–0.125	0.029	0.031	0.063	0.125	0.063	0.125	0.063
Laboratory 2			1	44	**48**	7								100	0.008–0.063	0.024	0.031	0.031	0.063	0.063	0.063	0.063
Laboratory 3	5	12	**77**	6										100	0.002–0.016	0.007	0.008	0.008	0.016	0.016	0.016	0.016
Laboratory 4	1	47	**47**	5										100	0.002–0.016	0.006	0.008	0.008	0.016	0.016	0.016	0.016
All	6	59	**130**	88	89	24	7							403	0.002–0.125	0.016	0.016	0.031	ND	0.063	0.125	0.063
C. glabrata																						
Laboratory 1					24	**58**	29	1						112	0.031–0.25	0.065	0.063	0.125	0.125	0.125	0.25	0.125
Laboratory 2					4	**69**	27							100	0.031–0.125	0.071	0.063	0.125	0.125	0.125	0.125	0.125
Laboratory 3				16	**72**	11	1							100	0.016–0.125	0.030	0.031	0.063	0.063	0.063	0.063	0.063
Laboratory 4				32	**69**									101	0.016–0.031	0.025	0.031	0.031	0.063	NP[b]	NP	0.063
All				48	**169**	138	57	1						413	0.016–0.25	0.048	0.031	0.125	0.125	0.125	0.125	0.125
C. krusei																						
Laboratory 1					17	40	**41**	1						99	0.031–0.25	0.075	0.063	0.125	0.25	0.25	0.25	0.25
Laboratory 2					29	**59**	12							100	0.031–0.125	0.054	0.063	0.125	0.125	0.125	0.125	0.125
Laboratory 3				7	25	**68**								100	0.016–0.063	0.047	0.063	0.063	0.125	NP	NP	0.125
Laboratory 4				4	**51**	46	2							103	0.016–0.125	0.043	0.031	0.063	0.125	0.125	0.125	0.125
All				11	122	**213**	55	1						402	0.016–0.25	0.055	0.063	0.125	0.125	0.125	0.125	0.125
C. parapsilosis																						
Laboratory 1						1			1	**52**	35	8	1	98	0.063->4	1.414	1.000	2.000	4	2	2	4
Laboratory 2										1	**87**	12		100	1–4	2.158	2.000	4.000	>4	NP	NP	4
Laboratory 3										29	**67**	4		100	1–4	1.682	2.000	2.000	4	4	4	4
Laboratory 4									5	44	**51**			100	0.5–2	1.376	2.000	2.000	4	NP	NP	4
All						1			6	126	**240**	24	1	398	0.063->4	1.657	2.000	2.000	4	4	4	4
C. tropicalis																						
Laboratory 1		1	1		17	29	**42**	11	1					102	0.004–0.5	0.084	0.125	0.250	0.25	0.25	0.5	0.25
Laboratory 2					7	**51**	41	1						100	0.031–0.25	0.078	0.063	0.125	0.25	0.25	0.25	0.25
Laboratory 3		1	2	30	**55**	12								100	0.004–0.063	0.026	0.031	0.063	0.063	0.063	0.063	0.063
Laboratory 4			2	41	**44**	13								100	0.008–0.063	0.025	0.031	0.063	0.063	0.063	0.063	0.063
All		2	5	71	**123**	105	83	12	1					402	0.002–0.5	0.053	0.031	0.125	0.25	0.25	0.25	0.25

WT-UL values determined visually and statistically with two endpoints (97.5% and 99%, respectively) are shown for individual MIC distributions and for the collated datasets.

[a] The MIC_{50} value is highlighted in bold for each MIC distribution.

[b] NP = not possible to estimate using the ECOFF finder programme.

Tissue treated?

1. Arendrup, M. C., Meletiadis, J., Zaragoza, O., et al. Multicentre determination of rezafungin (CD101) susceptibility of Candida species by the EUCAST method. CMI 2018; 24.11: 1200-1204.
2. Arendrup, M. C., Jørgensen, K. M., Hare, R. K., et al. EUCAST reference testing of rezafungin susceptibility and impact of choice of plastic plates. Antimicrob Agent Chemother 2019; 63.9.

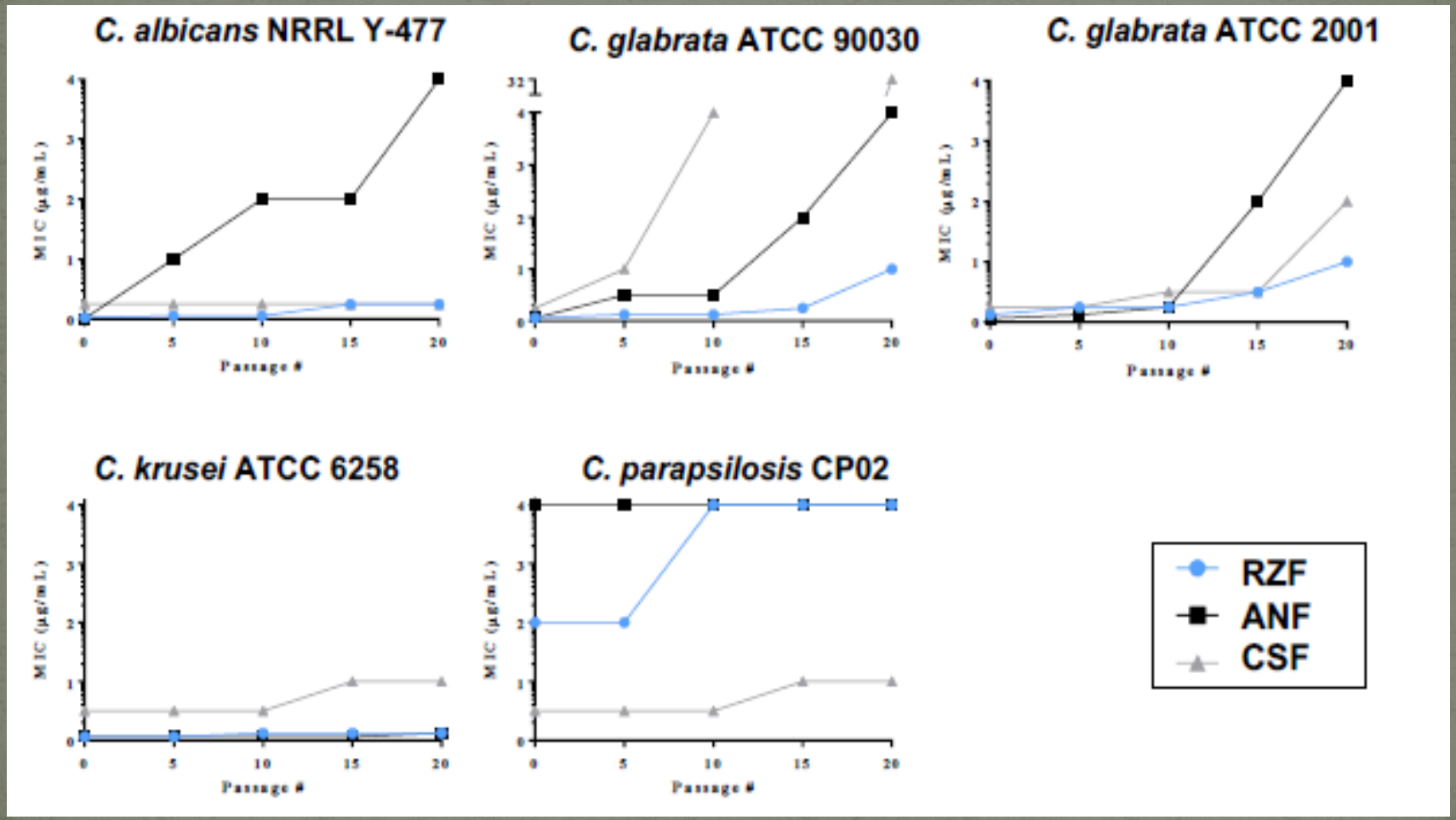
Rezafungin – CLSI / Şubat 2021

Format	QC strain	QC range
BMD (M27-Ed4)	*C. krusei* ATCC 6258	0.015 – 0.125 µg/mL (24 hr) 0.015 – 0.125 µg/mL (48 hr)
	C. parapsilosis ATCC 22019	0.25 – 2 µg/mL (24 hr)* 0.25 – 2 µg/mL (48 hr)
Disk diffusion (M44-A3)	*C. krusei* ATCC 6258	14 – 20 mm
	C. parapsilosis ATCC 22019	9 – 16 mm
	C. albicans ATCC 90028	13 – 20 mm
	C. tropicalis ATCC 750	14 – 20 mm

1. CLSI Winter 2021 Susceptibility Testing Meeting Series, 25 Jan-24 Feb 2021.

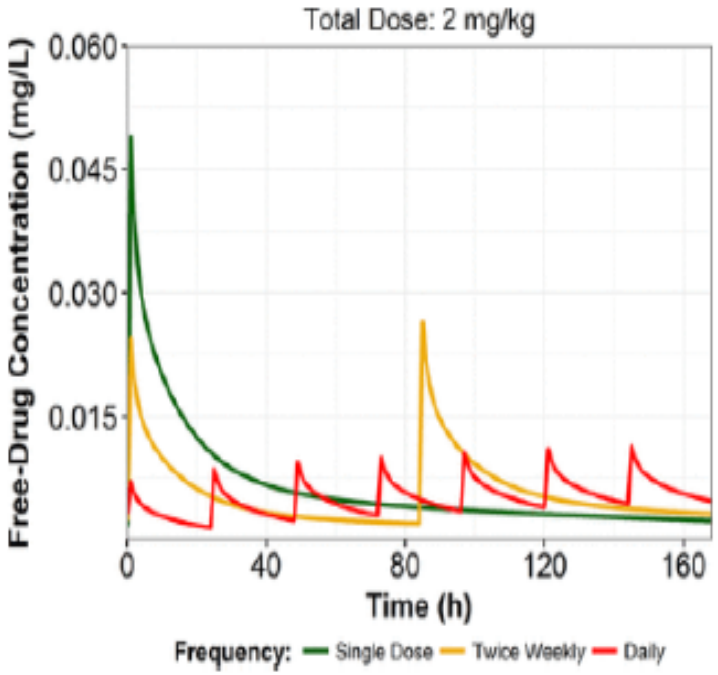
Rezafungin Direnç

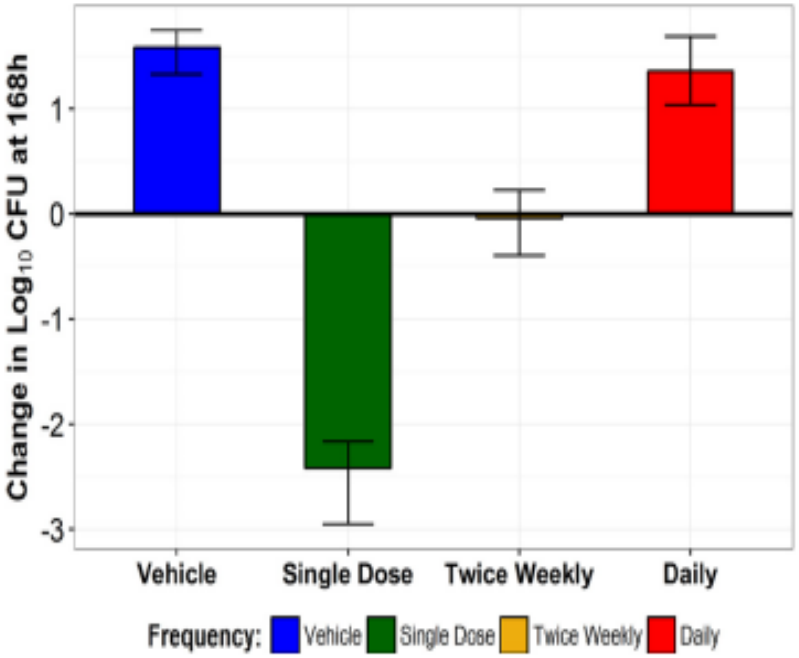
FKS HS mutasyonları RZF dahil tüm ekinokandinler için çapraz dirence neden oluyor. RZF kendine has bir mutasyona yol açmıyor



1. CLSI Winter 2021 Susceptibility Testing Meeting Series, 25 Jan-24 Feb 2021.

Rezafungin dose fractionation (2 mg/kg total dose)





REZAFUNGIN

Concentration-dependent killing

Long half-life

Safety

Supports Front-Loaded Dosing

- Once-weekly dosing of rezafungin demonstrated greater fungal killing than divided doses
- A higher degree of fungal killing achieved with the same amount of weekly exposure

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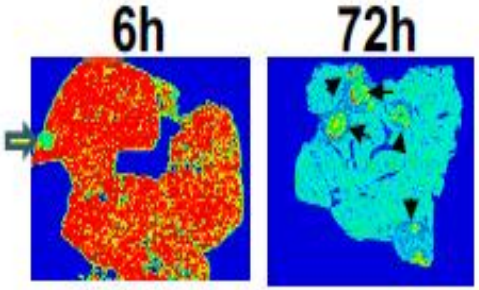
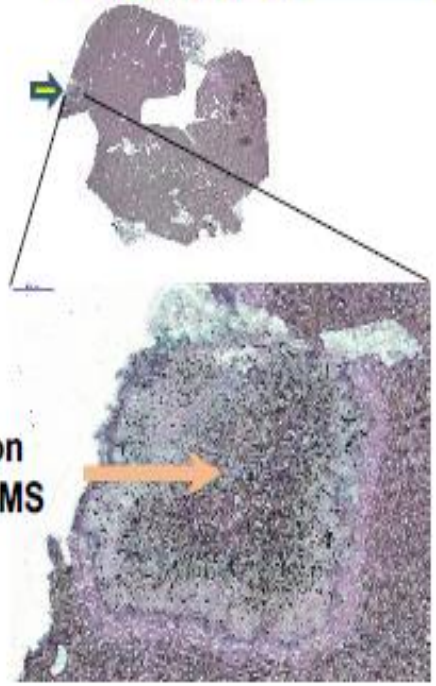
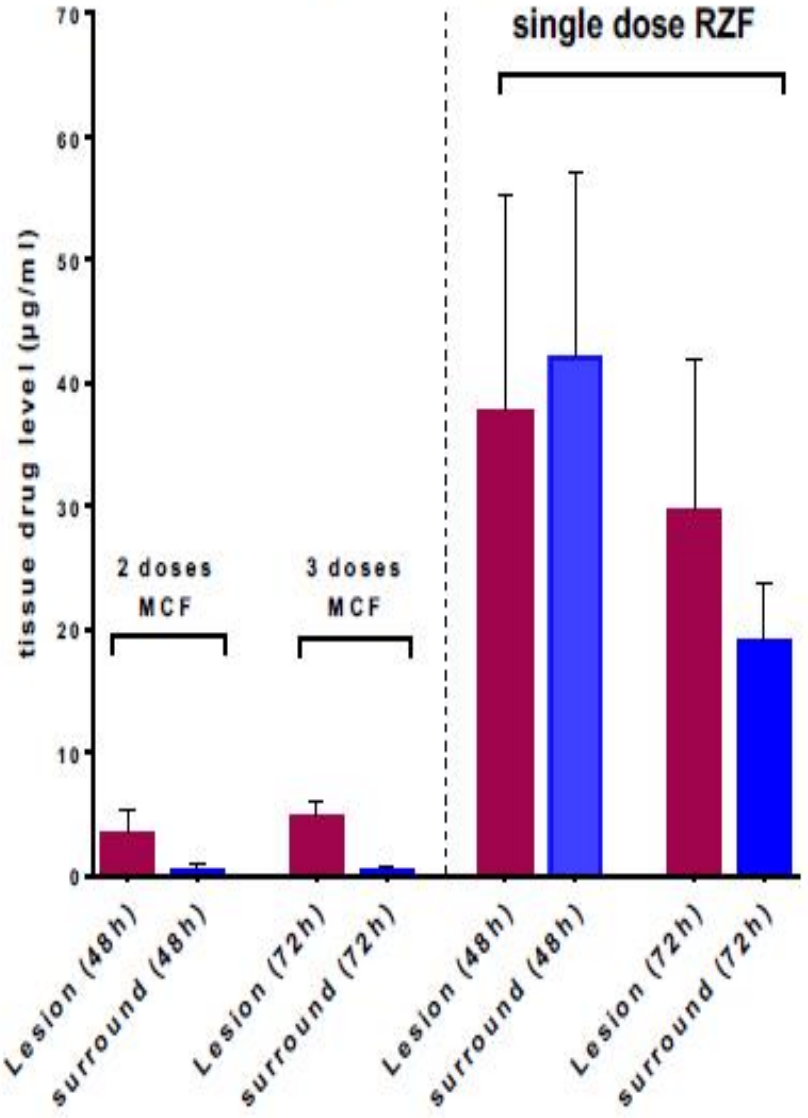
Drug distribution in liver after single dose RZF at 20 mg/kg determined by MALDI MS imaging





Fungi location stained by GMS

Multidose micafungin vs. single dose rezafungin



1. CLSI Winter 2021 Susceptibility Testing Meeting Series, 25 Jan-24 Feb 2021.

ECOFF

Agent	Species	No. of Distributions	No. of Isolates	Modal MIC	ECV 97.5% (only in range distributions)	ECV 99%
Rezafungin	*C. albicans*	9	1620	0.03	0.06	0.12
Rezafungin	*C. glabrata*	9	742	0.06	0.12 (0.25)	0.25
Rezafungin	*C. tropicalis*	9	406	0.03	0.12	0.12
Rezafungin	*C. krusei*	9	295	0.03	0.12	0.12
Rezafungin	*C. parapsilosis*	10	707	1	4	4
Rezafungin	*C. dubliniensis*	7	140	0.06	0.12	0.12
Rezafungin	*A. fumigatus*	7	401	0.015	0.03 (0.06)	0.03
Anidulafungin	*C. albicans*	7	1475	0.015	0.06	0.06
Anidulafungin	*C. glabrata*	9	822	0.06	0.25	0.25
Anidulafungin	*C. tropicalis*	8	387	0.03	0.06	0.12
Anidulafungin	*C. krusei*	8	280	0.03	0.12	0.12
Anidulafungin	*C. parapsilosis*	8	678	2	4	8
Anidulafungin	*C. dubliniensis*	6	138	0.03	0.12	0.12
Anidulafungin	*A. fumigatus*	6	356	0.008	0.03	0.03

1. CLSI Winter 2021 Susceptibility Testing Meeting Series, 25 Jan-24 Feb 2021.

Species (N)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
C. albicans (835)	0.03	0.06
C. glabrata (374)	0.06	0.12
C. auris (100)	0.125	0.5
C. tropicalis (196)	0.03	0.06
C. parapsilosis (329)	1	2
C. dubliniensis (93)	0.06	0.12

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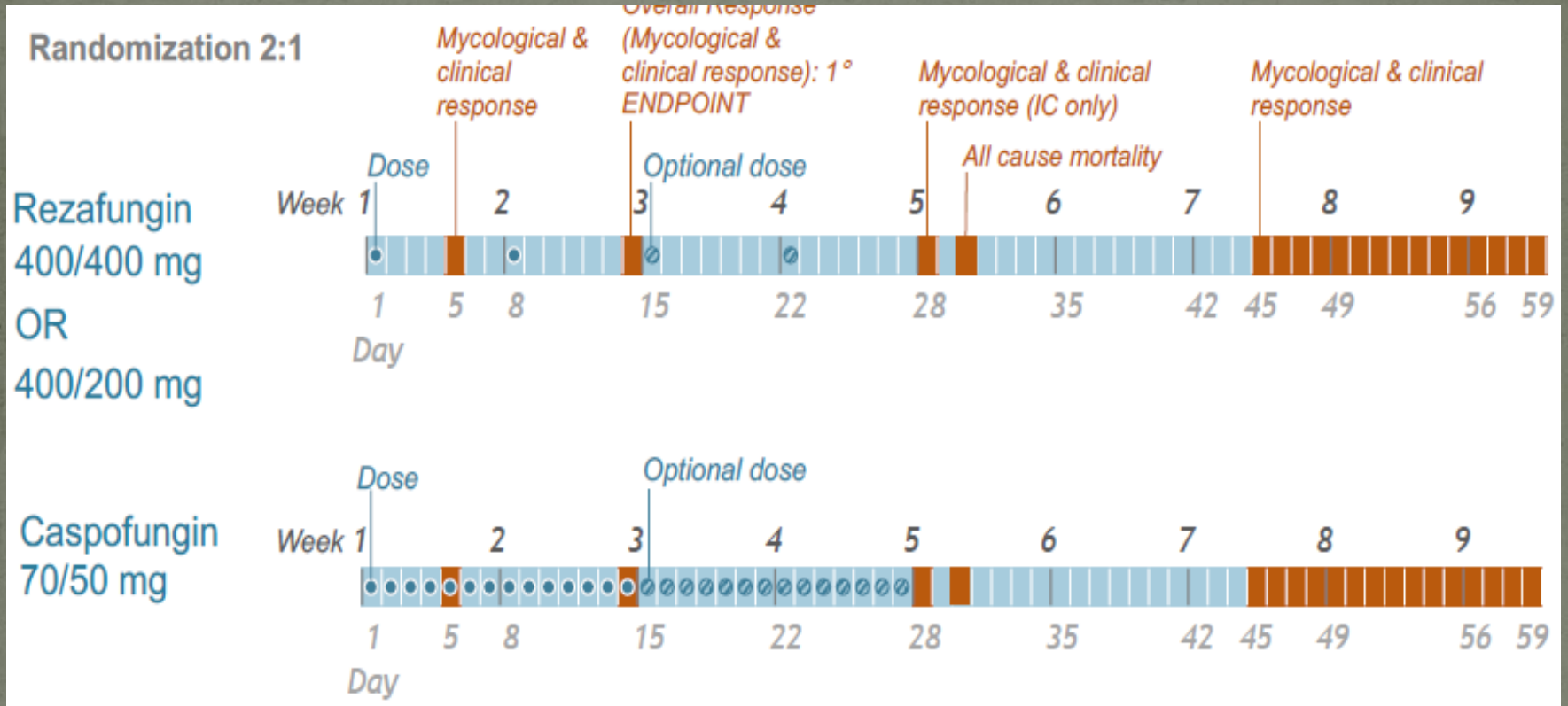
SENTRY

Species (n)	MIC_{90}/MEC_{90} (µg/mL)							
	RZF	ANF	CSF	MCF	FLU	POS	VOR	AMB
C. albicans (292)	0.06	0.03	0.03	0.03	0.25	0.06	0.015	1
C. glabrata (118)	0.06	0.12	0.06	0.03	32	1	1	1
C. parapsilosis (117)	2	2	0.5	2	32	0.25	0.5	1
C. tropicalis (78)	0.06	0.06	0.06	0.06	1	0.12	0.06	1
C. krusei (16)	0.12	0.12	0.25	0.25	64	0.5	0.5	1
C. dubliniensis (35)	0.12	0.06	0.06	0.03	0.25	0.06	0.015	0.5
A. fumigatus (75)	0.03	0.03	0.06	0.015	ND	0.5	0.5	2
A. flavus (15)	0.008	0.008	0.03	0.015	ND	0.5	1	2

1. Phaller, M. A., Carvalhaes, C., Messer, S. A., et al. Activity of a long-acting echinocandin, rezafungin, and comparator antifungal agents tested against contemporary invasive fungal isolates (SENTRY Program, 2016 to 2018). Antimicrob Agents Chemother 2020; 64.4.

STRIVE

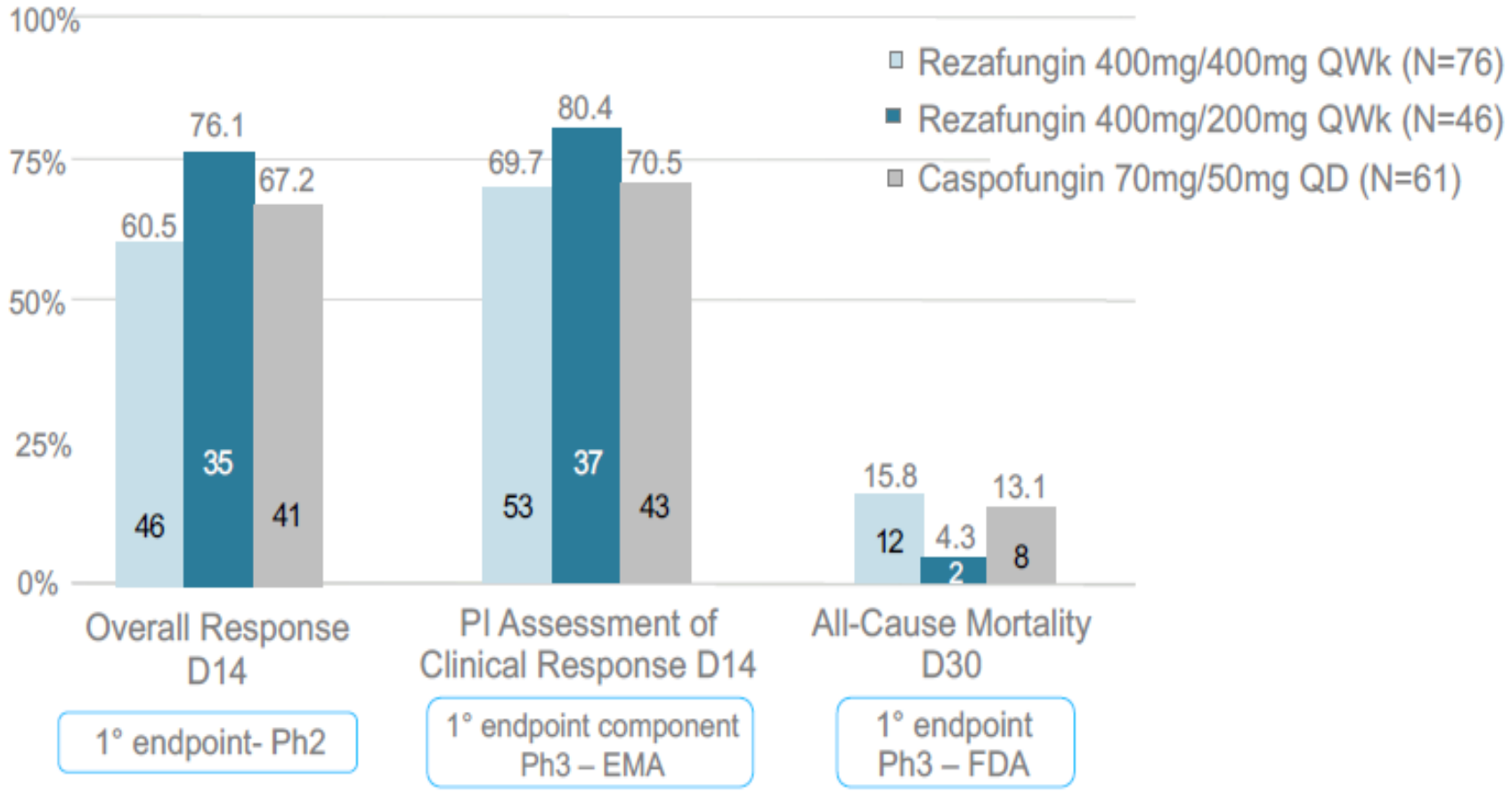


Analysis Populations:

- The Intent-to-treat (ITT) population: all randomized subjects
- The Safety population: all subjects who received any amount of study drug
- The Microbiological Intent-to-treat population (mITT): all subjects in safety population who had documented *Candida* infection
- The Microbiological Intent-to-treat population 2 (mITT2): all subjects in safety population who had documented *Candida* infection at or around the time of enrollment

1. Thompson, G. R., Soriano, A., Skoutelis, A., et al. Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial. Clinical Infectious Diseases 2021; https://doi.org/10.1093/cid/ciaa1380

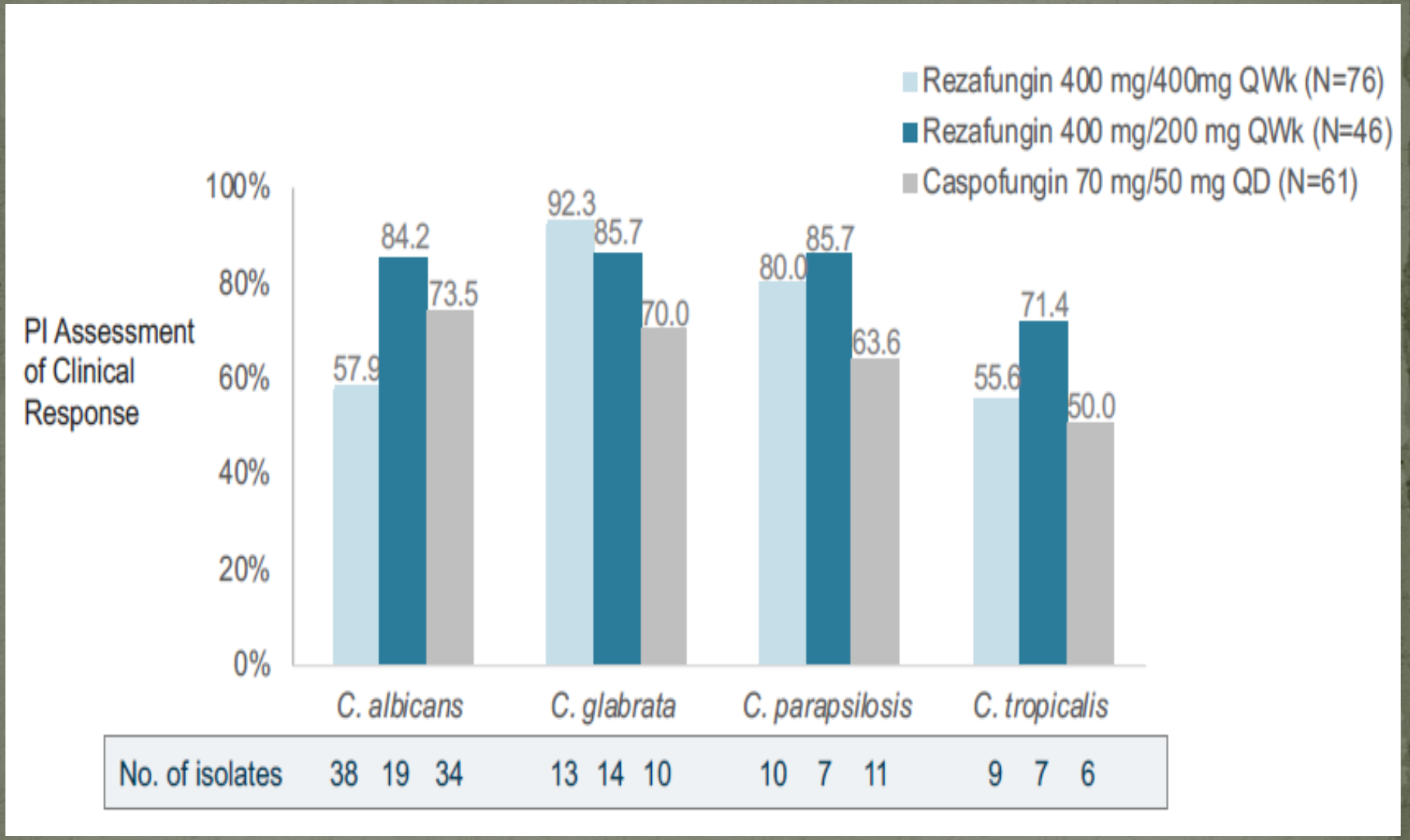
STRIVE



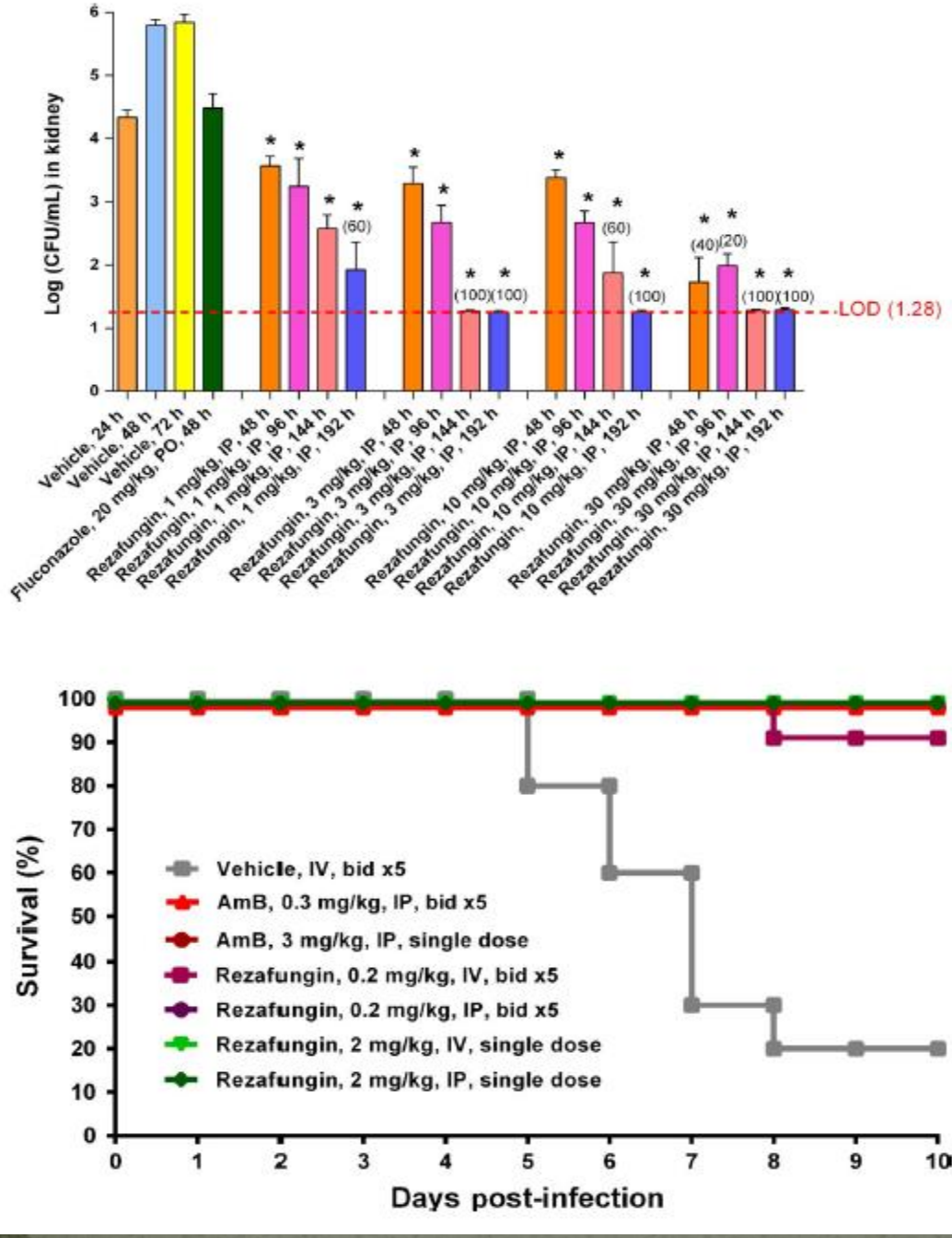
- Overall Response: resolution of all signs of candidemia/IC AND clearance of cultures from blood or other normally sterile sites
- PI Assessment of Clinical Response: determination of clinical response by PI with cure defined as: resolution of signs/symptoms of candidemia/IC, no new signs/symptoms of candidemia/IC, no new systemic antifungal therapy, and subject is alive

1. Thompson, G. R., Soriano, A., Skoutelis, A., et al. Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial. Clinical Infectious Diseases 2021; https://doi.org/10.1093/cid/ciaa1380

STRIVE



1. Thompson, G. R., Soriano, A., Skoutelis, A., et al. THOMPSON, George R., et al. Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial. Clinical Infectious Diseases 2021; https://doi.org/10.1093/cid/ciaa1380



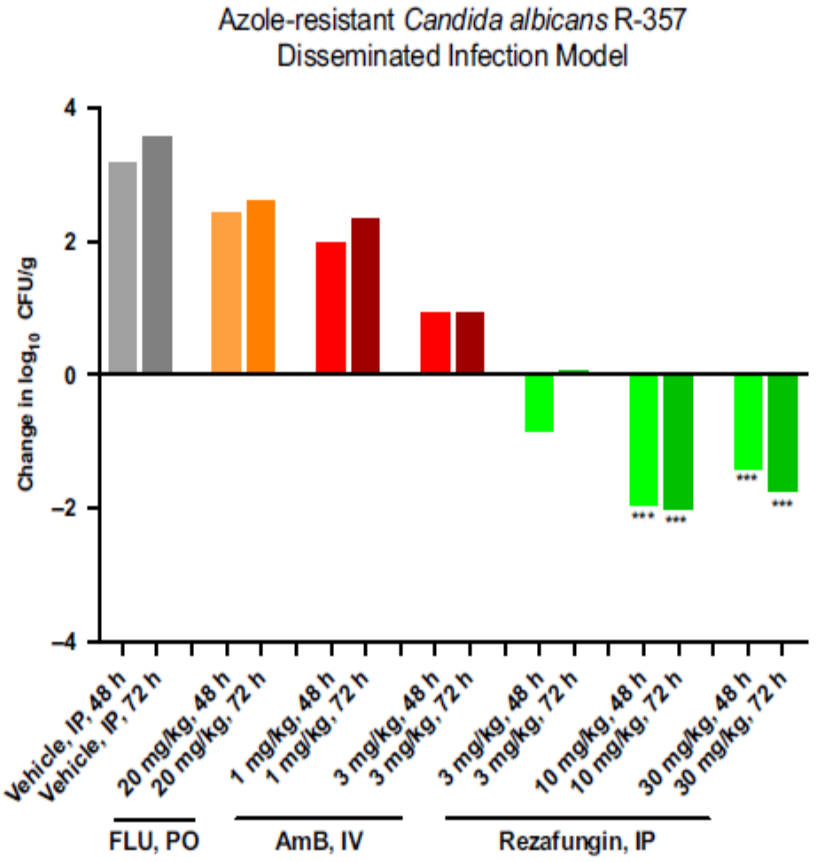


FIGURE 1 Efficacy against azole-resistant *Candida*: change in log counts in kidneys of fluconazole (FLU)-, amphotericin B (AmB)-, and rezafungin-treated mice at 48 and 72 h post-infection in an azole-resistant *Candida albicans* (R357) disseminated infection model. IP, intraperitoneal. *** $P < .001$ (reduction)

1. Miesel L, Lin KY, Ong V. Rezafungin treatment in mouse models of invasive candidiasis and aspergillosis: Insights on the PK/PD pharmacometrics of rezafungin efficacy. Pharmacology research & perspectives, 2019, 7.6: e00546.

TABLE 1 Summary of rezafungin in vivo efficacy

Reference	Objective	Preclinical model/ Pathogen	Materials and methods	Results and conclusions
Ong et al[6]	To evaluate RZF efficacy in pre-clinical models of systemic infection	Neutropenic mouse/ disseminated *Candida albicans* (R303)	• RZF 0.2, 0.4, 0.6 and 0.8 mg/kg (MIC, 0.12 μg/mL) • ANF 0.6 mg/kg (MIC, 0.03 μg/mL) • Vehicle By single IV injection 2 h post-infection --- • Reference: FLU 20 mg/kg (MIC, 2 μg/mL) by oral gavage	Significant efficacy (≥99%, 2-log reduction in CFU/g) with RZF 0.6 and 0.8 mg/kg at 24, 48, and 72 h and with ANF 0.6 mg/kg at 24 and 48 h *One dose of RZF demonstrated potent antifungal efficacy in a neutropenic mouse model of C. albicans infection, up to 72 h after a single dose*
		Neutropenic mouse/ disseminated *Aspergillus fumigatus* (ATCC 13073)	• RZF 0.2, 1, and 5 mg/kg (MEC, 0.004 μg/mL) • ANF 1 and 5 mg/kg (MEC, 0.004 μg/mL) • Vehicle By IV injection BID for 5 days, started 1 and 7 hr post-infection --- • Reference: AmB 0.3 mg/kg (MIC, 0.125 μg/mL) by IP injection BID for 5 days, started 1 and 7 h post-infection	Significant increase in 10-day survival rate compared with vehicle ($P < .05$) with all RZF groups (0.2, 1, and 5 mg/kg) and with ANF 1 and 5 mg/kg at 24 and 48 h *RZF administered BID for 5 days demonstrated potent antifungal efficacy in a neutropenic mouse model of A. fumigatus infection*
Lakota et al[14]	To evaluate the effects of front-loaded dosing regimens on RZF efficacy	Neutropenic mouse/ disseminated *C. albicans* (R303)	RZF total doses (0.7, 2, and 7 mg/kg) administered on 3 dosing schedules: single dose, twice weekly, and daily (eg, RZF 2 mg/kg total was evaluated as a single administration of 2 mg/kg, as 1 mg/kg given twice weekly, and as 0.29 mg/kg given daily for 7 days). (MIC, 0.125 μg/mL) By IP injection starting 24 h post-infection	A higher degree of fungal killing was achieved when RZF 2 mg/kg (total) was front-loaded - ie, delivered entirely in one dose versus divided into daily or twice weekly doses. There was a > 2 $\log_{10}$ CFU reduction from baseline at 168 h, whereas twice-weekly and daily regimens resulted in net stasis or log CFU similar to no-treatment controls. *RZF PK/PD produces beneficial effects on efficacy due to front-loaded dosing and the associated exposure shape of RZF (ie, high drug exposures achieved early in the course of therapy)*
Zhao et al[15]	To evaluate the effects of tissue drug exposure on RZF efficacy	Mouse/ intraabdominal *C. albicans* (SC5314)	• RZF 5 and 20 mg/kg • MCF 5 mg/kg. (MIC, 0.03 μg/mL) By single IP injection on day 3 post-infection	RZF demonstrated extensive tissue distribution and rapid penetration into abscesses. At 24 h after a single dose, the mean drug concentration within lesions was ~ 4-fold higher for RZF than for MCF at the same dosage, indicating superior lesion penetration by RZF. Four of 5 mouse livers were sterilized by RZF 20 mg/kg, and liver infection resolved in one of the 5 mice. No liver sterilization was observed in MCF-treated mice. *RZF demonstrated higher tissue exposure and lesion penetration compared with MCF.*
Hager et al[33]	To evaluate the efficacy of RZF in treatment of disseminated infection caused by *Candida auris*	Immunosuppressed mouse/ disseminated *C. auris* (MRL35368)	• RZF 20 mg/kg on Days 1, 3, and 6. (MIC, 0.063 μg/mL) • AMB 0.3 mg/kg QD × 7 days. (MIC, 4 μg/mL) • MCF 5 mg/kg QD × 7 days. (MIC, 1 μg/mL) • Vehicle QD × 7 days By IP injection starting 2 h post-infection	Mice treated with RZF had significantly lower average $\log_{10}$ CFU compared with AMB- and vehicle-treated mice on all days when kidneys were harvested and compared with the MCF-treated group on Day 10. *RZF demonstrated in vivo efficacy against C. auris.*

Abbreviations: AMB, amphotericin B; ANF, anidulafungin; CFU, colony-forming units; IP, intraperitoneal; IV, intravenous; MCF, micafungin; MEC, minimum effective concentration; MIC, minimum inhibitory concentration; RZF, rezafungin.

1. Miesel L, Lin KY, Ong V. Rezafungin treatment in mouse models of invasive candidiasis and aspergillosis: Insights on the PK/PD pharmacometrics of rezafungin efficacy. Pharmacology research & perspectives, 2019, 7.6: e00546.

Faz 3'e kadar neler oldu?

Clinical Status	Trial (ClinicalTrials.gov Identifier)	Objective	Key Finding
Phase 1 (completed)	Single-ascending-dose study (NCT02516904)	Safety, tolerability, and PK	No safety issues were noted; Dose-proportional plasma exposures (AUC and C_{max}) and low clearance; Long half-life (~80 h after first dose and ~150 h following addition dose)
	Multiple-ascending-dose study (NCT02551549)		
Phase 2 (completed)	STRIVE (NCT02734862)	Efficacy to treat candidemia and invasive candidiasis	Rezafungin IV 400 mg first week followed by 200 mg once weekly regimen showed greater efficacy than caspofungin
	RADIANT (NCT02733432)	Efficacy to treat vulvovaginitis	Topical formulations of rezafungin were safe and well tolerated; Cure rates of topical rezafungin were lower than those achieved with fluconazole
Phase 3 (ongoing)	ReSTORE (NCT03667690)	Efficacy to treat candidemia and invasive candidiasis	To be determined
	ReSPECT (NCT04368559)	Efficacy to prevent invasive fungal infections due to *Candida*, *Aspergillus*, and *Pneumocystis*	To be determined

1. Zhao, Y., Perlin, D. S. Review of the Novel Echinocandin Antifungal Rezafungin: Animal Studies and Clinical Data. Journal of Fungi, 2020, 6.4: 192.

Rezafungin – Avantajı ne?

- Uzamış yarı ömür ve çok iyi PK, Uygulama kolaylığı
- Diğer ekinokandinler ile benzer etkinlik
- Diğer ekinokandinlere göre direnç geliştirme potansiyeli daha düşük
- Terapötik indeksi geniş
- *Pneumocystis* pnömonisinde etkili
- Paketleme ve Transport, topikal uygulama
- Rezafungin vs *C.auris? FKS?*
- Asıl fayda kime?

1. Helleberg, M., Jørgensen, K. M., Hare, R. K., et al. Rezafungin in vitro activity against contemporary nordic clinical Candida isolates and Candida auris determined by the EUCAST reference method. Antimicrob Agent Chemother 2020; 64.4.
2. Lepak, A. J., Zhao, M., Andes, D. R. Pharmacodynamic evaluation of rezafungin (CD101) against Candida auris in the neutropenic mouse invasive candidiasis model. Antimicrob Agent Chemother 2018; 62.11.
3. Hager, C. L., Larkin, E. L., Long, L. A., Ghannoum, M. A. Evaluation of the efficacy of rezafungin, a novel echinocandin, in the treatment of disseminated Candida auris infection using an immunocompromised mouse model. J Antimicrob Chemother 2018; 73.8: 2085-2088.
4. Sofjan, A. K., Mitchell, A., Shah, D. N., et al. Rezafungin (CD101), a next-generation echinocandin: a systematic literature review and assessment of possible place in therapy. J Glob Antimicrob Resist 2018,;14: 58-64.

Human pharmacokinetics of rezafungin: results from two phase 1 single-dose and multiple-dose studies [33].

Study	Single dose	Multidose, Day 1	Multidose, Day 8	Single dose	Multidose, Day 1	Multidose, Day 8	Single dose	Multidose, Day 1	Multidose, Day 8
Dose (mg)	100	100	100	200	200	200	400	400	400
C_{max} (μg/mL)	4.86 ± 0.56	5.67 ± 0.89	6.49 ± 0.65	10.9 ± 2.17	10.6 ± 1.93	12.4 ± 3.45	22.7 ± 3.59	22.7 ± 4.87	30.5 ± 13.1
AUC_{0-168} (μg·h/mL)	254 ± 22.9	299 ± 27.4	390 ± 44.1	592 ± 66.8	570 ± 125	813 ± 225	1160 ± 170	1190 ± 229	1840 ± 323
$t_{1/2}$ (h)	146 ± 3.82	79.1 ± 4.04	158 ± 15.5	125 ± 13.0	81.3 ± 4.30	140 ± 13.2	129 ± 18.6	81.0 ± 7.92	152 ± 29.5
CL (L/h)	0.240 ± 0.02	0.258 ± 0.02	0.149 ± 0.02	0.219 ± 0.02	0.279 ± 0.07	0.155 ± 0.04	0.226 ± 0.04	0.268 ± 0.06	0.126 ± 0.02
V_{ss} (L)	42.9 ± 4.07	28.8 ± 3.59	29.3 ± 3.70	34.4 ± 4.99	31.7 ± 7.72	28.5 ± 7.18	35.9 ± 5.59	29.6 ± 6.35	25.4 ± 7.08
V_z (L)	50.6 ± 4.96	29.5 ± 3.23	33.8 ± 4.34	39.7 ± 6.99	32.8 ± 9.18	30.9 ± 7.35	41.6 ± 7.59	31.2 ± 6.33	27.9 ± 8.78

C_{max}, maximum plasma concentration; AUC_{0-168}, area under the concentration–time curve from time 0 to 168 h; $t_{1/2}$, half-life; CL, total body clearance; V_{ss}, volume of distribution at steady state; V_z, apparent volume of distribution during terminal phase.

1. Sofjan, A. K., Mitchell, A., Shah, D. N., et al. Rezafungin (CD101), a next-generation echinocandin: a systematic literature review and assessment of possible place in therapy. J Glob Antimicrob Resist 2018,;14: 58-64.

Table 2 Echinocandin total AUC_{24}/MIC_{90} ratios achieved with recommended dosing

	Anidulafungin	Caspofungin		Micafungin		Rezafungin
	200 mg × 1; 100 mg q24	70 mg × 1; 50 mg q24	150 mg q24	100 mg q24	150 mg q24	400 mg × 1; 200 mg weekly × 2
Candida spp.						
C. albicans	2500–4300	3300–4600	> 10,000	2000–4000	3300–6000	> 30,000
C. glabrata	625–1100	1700–2300	> 5000	2000–4000	3300–6000	> 7000
C. parapsilosis[a]	20–35	200–300	600–800	30–60	50–90	450–600
C. tropicalis	2500–4300	1700–2300	> 5000	1000–2000	1700–3000	> 7000
C. krusei	625–1100	400–600	1200–1600	500–1000	800–1400	> 7000
C. auris[b]	75–130	–	–	240–480	400–700	3600–4800
Aspergillus spp.[c]						
A. fumigates	2500–4300	3300–4600	> 10,000	4000–8000	> 7500	> 7000
A. niger	2500–4300	3300–4600	> 10,000	4000–8000	> 7500	–
A. terreus	2500–4300	3300–4600	> 10,000	4000–8000	> 7500	–

Derived from population pharmacokinetic studies [52–55]

Based on MIC_{90} values reported [27–29, 56, 57]

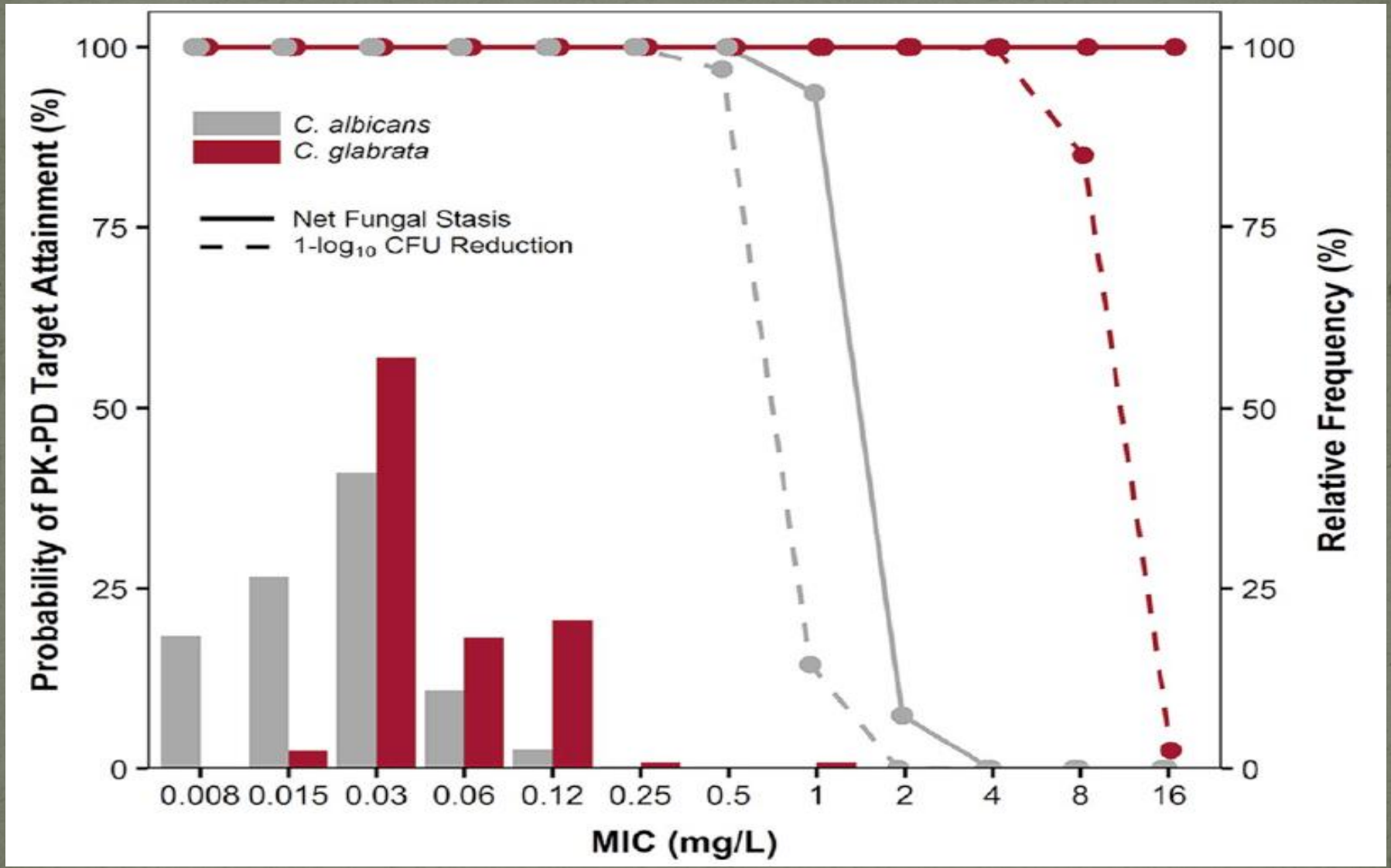
[a] Clinical PK-PD target of total $AUC_{24}/MIC > 285$

[b] Animal PK-PD target for 1-log kill of $AUC_{24}/MIC > 130$

[c] Echinocandin monotherapy is not recommended for invasive aspergillosis

1. Cota, J. M., Giancola, S. E., Benavides, T. M., Wiederhold, N. Implications of Evolving and Emerging Pharmacokinetic-Pharmacodynamic Research for Triazoles and Echinocandins. Curr Fungal Infect Rep 2020; 14: 258-267.

PK/PD Hedefi



1. CLSI Winter 2021 Susceptibility Testing Meeting Series, 25 Jan-24 Feb 2021.

Candida spp.	*n*	RZF [a]		ANF [a]		CSF [a]		MCF [a]		References
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	
C. albicans	2612	0.022	0.050	0.012	0.027	0.053	0.069	0.022	0.021	[100–107,109–111]
C. glabrata	1541	0.044	0.085	0.045	0.085	0.080	0.140	0.027	0.030	[100–107,109–111]
C. krusei	773	0.033	0.078	0.045	0.085	0.280	0.248	0.108	0.153	[100–107,109–111]
C. parapsilosis sensu stricto	1156	1.260	2.000	1.219	2.245	0.435	0.758	1.122	1.414	[100–107,109–111]
C. tropicalis	959	0.030	0.072	0.012	0.034	0.046	0.092	0.030	0.050	[100–107,109–111]
C. dubliniensis	207	0.060	1.360	0.034	0.270	0.036	0.370	0.030	0.105	[100–105,107,109,110]
C. auris	237	0.153	0.500	0.391	0.250	0.707	1.000	0.630	0.500	[105,107,109,110]
C. lusitaniae	66	0.120	0.250	0.042	0.060	0.500	1.000	0.038	0.250	[107,110]
C. kefyr	52	0.06	0.12	0.03	0.06	0.25	0.50	0.06	0.12	[107]
C. guilliermondii	27	1.00	1.00	1.00	2.00	0.50	1.00	1.00	2.00	[107]
C. orthopsilosis	25	0.500	1.000	0.707	1.000	0.354	0.707	0.500	1.000	[107,109]
C. metapsilosis	15	0.50	0.50	0.25	0.50	0.25	0.50	0.25	0.50	[107]
C. fabianii	15	0.06	0.12	0.06	0.12	1.00	1.00	0.06	0.12	[107]
C. insconspicua	41	0.06	0.06	0.008	0.015	0.25	0.50	0.03	0.06	[107]
C. sojae	10	0.06	0.06	0.015	0.03	0.25	0.50	0.03	0.06	[107]
C. lipolytica	10	0.06	0.06	0.06	0.12	0.25	0.50	0.25	1.00	[107]
C. pulcherrima	10	0.03	0.06	0.015	0.06	0.50	1.00	0.06	0.25	[107]

RZF: rezafungin, ANF: anidulafungin, CSF: caspofungin, MCF: micafungin. [a] Geometric means of the data published in the cited references expressed in µg/mL. ND: no data available.

Table 2. Rezafungin and FDA-approved echinocandin MIC values for *Candida* spp. with mutant *FKS* genes determined by CLSI microdilution reference methods.

Candida spp. *FKS* Mutants	*n*	RZF [a]		ANF [a]		CSF [a]		MCF [a]		References
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	
C. albicans	20	0.71	1.00	0.50	1.00	0.50	1.00	1.00	ND	[100,104]
C. glabrata	21	0.50	1.00	0.25	1.00	0.50	1.00	1.00	ND	[100,104]
C. krusei	6	0.35	1.00	0.50	2.00	1.00	16.00	1.00	ND	[100,104]
C. tropicalis	9	0.71	1.00	0.50	1.00	1.00	2.00	2.00	ND	[100,104]
C. dubliniensis	1	0.03	ND	ND	ND	ND	ND	0.03	ND	[100]
C. auris	4	8.00	8.00	8.00	ND	4.00	ND	4.00	ND	[105]

RZF: rezafungin, ANF: anidulafungin, CSF: caspofungin, MCF: micafungin. [a] Geometric means of the data published in the cited references expressed in µg/mL. ND: no data available.

1. Garcia-Effron, G. Rezafungin—Mechanisms of Action, Susceptibility and Resistance: Similarities and Differences with the Other Echinocandins. J Fungi 2020; 6.4: 262.

In vitro susceptibility of rezafungin and comparators as determined by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method[a].

Species	No. of isolates	Rezafungin		Anidulafungin		Caspofungin		Micafungin	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Candida albicans [15]	251	0.03	0.06	0.015	0.06	0.03	0.06	0.015	0.03
C. albicans [16]	25	0.06	0.5	0.03	1	0.12	1		
C. albicans [17]	10	<0.03						<0.03	
FKS mutant *C. albicans* [17]	10	2						1	
FKS mutant C. albicans [16]	9	0.12–1		0.12–2		0.5–2			
Candida glabrata [15]	100	0.03	0.06	0.06	0.12	0.06	0.12	0.015	0.03
C. glabrata [16]	25	0.06	1	0.12	1	0.25	1		
FKS mutant *C. glabrata* [17]	11	1						0.06	
FKS mutant *C. glabrata* [16]	9	0.06–2		0.06–4		0.25–> 8			
C. glabrata [17]	9	0.06						<0.03	
Candida parapsilosis [15]	92	1	2	2	4	0.5	1	1	2
C. parapsilosis [17]	19	2						4	
C. parapsilosis [16]	15	1	2	1	2	0.5	0.5		
Candida tropicalis [15]	51	0.015	0.06	0.015	0.03	0.03	0.06	0.03	0.06
C. tropicalis [16]	21	0.03	0.25	0.03	0.5	0.12	1		
C. tropicalis [17]	15	0.03						0.03	
FKS mutant *C. tropicalis* [17]	4	2						2	
FKS mutant *C. tropicalis* [16]	2	0.25–0.5		0.25–1		0.25–2			
Candida krusei [16]	20	0.06	0.06	0.06	0.12	0.12	0.12		
C. krusei [15]	16	0.03	0.06	0.06	0.06	0.12	0.25	0.06	0.12
C. krusei [17]	11	<0.03						0.12	
FKS mutant *C. krusei* [17]	4	<0.03						0.03	
FKS mutant C. krusei [16]	2	0.25–1		0.5–2		1–8			
Candida dubliniensis [15]	11	0.03	0.06	0.06	0.06	0.03	0.06	0.03	0.03
C. dubliniensis [17]	1	0.03						0.03	
FKS mutant *C. dubliniensis* [17]	1	0.03						0.03	
Candida orthopsilosis [15]	10	0.5	1	0.5	1	0.25	0.5	0.5	1
Cryptococcus neoformans var. *grubii* [15]	19	>8	>8	>8	>8	>8	>8	>8	>8
Aspergillus fumigatus [15]	56	0.015	0.015	<0.0016	0.015	0.03	0.03	0.015	0.015
A. fumigatus [16]	20	<0.008	0.015	<0.008	0.015	0.06	0.12		
Aspergillus terreus [16]	19	0.015	0.015	<0.008	0.015	0.06	0.12		
Aspergillus flavus [16]	12	<0.008	<0.008	<0.008	<0.008	0.06	0.06		
Aspergillus niger [16]	16	<0.008	<0.008	<0.008	<0.008	0.06	0.12		

[a] Minimum inhibitory concentrations (in μg/mL) for 50% (MIC_{50}) and 90% (MIC_{90}) of the isolates. For *Aspergillus*, susceptibility testing indicates the minimum effective concentration (MEC).

1. Sofjan, A. K., Mitchell, A., Shah, D. N., et al. Rezafungin (CD101), a next-generation echinocandin: a systematic literature review and assessment of possible place in therapy. J Glob Antimicrob Resist 2018,;14: 58-64.

TABLE 3 *In vitro* activities of rezafungin and comparators against 122 clinical *C. auris* isolates as determined by EUCAST E.Def 7.3.1[a]

Drug	Value for MIC (mg/liter): ≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	≥64	MIC range (mg/liter)	Modal MIC (mg/liter)	MIC_{50} (mg/liter)	WT-UL (mg/liter) Visual	97.5%	99%
Rezafungin					3	22	**63**	16	7	3		6	2			0.06 to 16	0.25	0.25	0.5	0.5	0.5
Anidulafungin[b]			1	11	35	**30**	12	12	11	2	1			7		0.016 to >32	0.06	0.125	0.25	0.25	0.5
Micafungin[b]				5	30	**70**	9							8		0.03 to >32	0.125	0.125	0.25	0.25	0.25
Amphotericin B[b]								14	**108**							0.5 to 1	1	1	2	NP	NP
Fluconazole[b]								1					2	10	**109**	0.5 to ≥64	≥64	≥64	NP	NP	NP
Voriconazole[b]	1			1	1	16	13	**34**	38	13	5					≤0.004 to 4	Bimodal	0.5	4	4	8
Isavuconazole[b]	20	1	1	19	9	**19**	21	21	6	5						≤0.004 to 2	Trimodal	0.125	0.016 or 2	NP	NP

[a]The shaded areas indicate that concentrations were not tested for the compound. MIC_{50}s are in boldface. The underlined values are the modal MICs for unimodal distributions but the lowest MIC peak for multimodal distributions, thus illustrating the modal MIC of the presumed wild-type distribution.
[b]The MIC distributions for comparator antifungals against *C. auris* were compiled from reference 20.

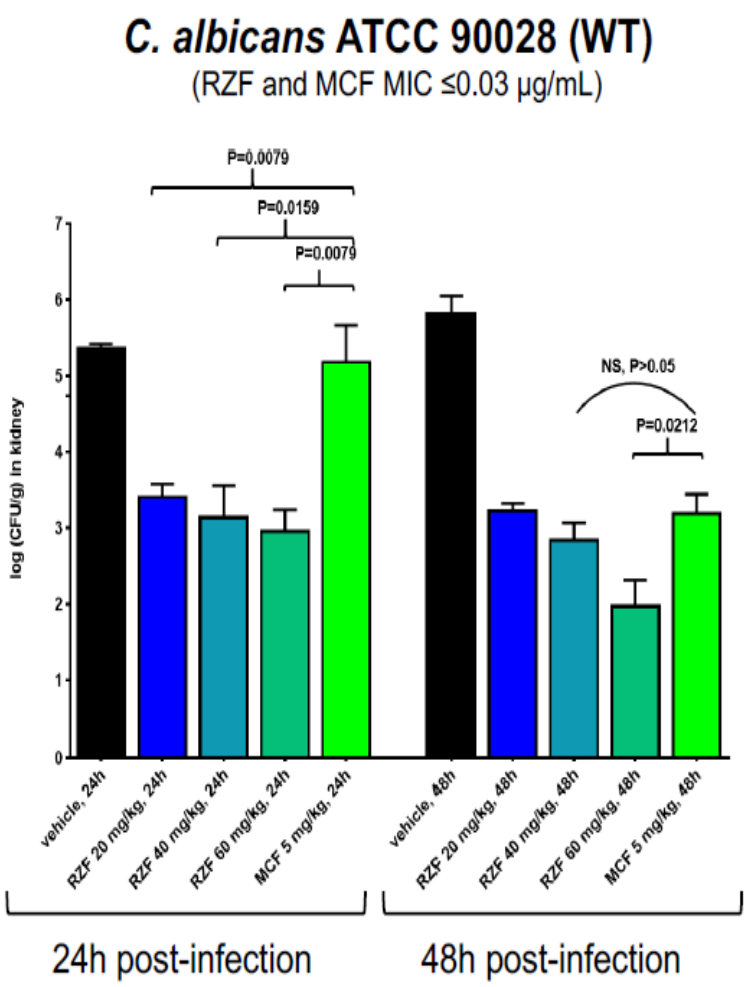
Organism	Mutation[a] Fks1	Fks2	MIC[b] (mg/liter) RZF	ANF	MCF	AMB	FLU	Increase in MIC[c] RZF	ANF	MCF
C. albicans	S645P	NT	**1**	**0.25**	**2**	0.25	0.25	4	6	7
	D648Y	NT	**0.5**	**0.06**	**0.125**	0.25	0.125	3	4	3
	P1354S	NT	**0.5**	**0.06**	**0.125**	0.5	**>64**	3	4	3
	P1354S	NT	**0.25**	0.016	**0.06**	0.5	**>32**	2	2	2
	P1354S	NT	**0.25**	0.016	**0.06**	0.5	**64**	2	2	2
	P1354S	NT	**0.25**	0.016	**0.06**	0.5	**64**	2	2	2
	P1354P/S	NT	**0.25**	0.03	**0.06**	0.5	**>64**	2	3	2
	P1354P/S	NT	**0.25**	**0.06**	**0.06**	0.5	**>64**	2	4	2
	R1361R/S	NT	**0.25**	**0.06**	**0.125**	0.125	0.125	2	4	3
	R1361G	NT	**0.25**	**0.06**	**0.125**	0.125	0.25	2	4	3
	R1361G	NT	**0.25**	0.016	**0.06**	0.5	**64**	2	2	2
C. glabrata	L630Q	S663F	**2**	**1**	**0.5**	0.5	1	4	5	5
	L630Q	S663F	**2**	**1**	**0.5**	0.5	32	4	5	5
	WT	S663F	**2**	**1**	**0.5**	0.5	2	4	5	5
	WT	S663F	**1**	**0.25**	**0.125**	0.125	2	3	3	3
	WT	S663F	**0.5**	**0.25**	**0.125**	0.5	2	2	3	3
	WT	S663F	**0.5**	0.06	**0.06**	0.5	2	2	1	2
	WT	S663P	**2**	**1**	**0.5**	0.125	2	4	5	5
	WT	S663P	**0.5**	**0.125**	**0.125**	0.25	4	2	2	3
	Y1429X	Y658N/L664Q	**0.5**	**0.125**	**0.06**	0.125	**>32**	2	2	2
	WT	F659del	**0.5**	0.06	**0.06**	0.25	**>64**	2	1	2
C. tropicalis	F650S	NT	**1**	**0.25**	**1**	0.25	0.5	3	3	5
	S654P	NT	**2**	**2**	**2**	0.5	0.5	4	6	6
C. dubliniensis	S645P	NT	**2**	**0.25**	**2**	0.03	0.125	4	3	6
	S645P	NT	**1**	**0.25**	**2**	0.03	0.125	3	3	6
C. krusei	S659F	NT	**1**	**0.25**	**4**	0.5	32	3	3	7
C. auris	S639F	NT	**16**	**4**	**>32**	1	**>256**	6	6	>8
	S639F	NT	**16**	**>32**	**>32**	1	**>256**	6	>9	>8
	S639F	NT	**8**	**>32**	**>32**	1	**>256**	5	>9	>8
	S639F	NT	**8**	**>32**	**>32**	1	**>256**	5	>9	>8
	S639F	NT	**8**	**>32**	**>32**	1	**>256**	5	>9	>8
	S639F	NT	**8**	**>32**	**>32**	1	**>256**	5	>9	>8
	S639F	NT	**8**	**>32**	**>32**	1	**>256**	5	>9	>8
	S639F	NT	**8**	**>32**	**>32**	1	**>256**	5	>9	>8
	WT	NT	**2**	**2**	0.25	1	**>256**	3	5	1
	WT	NT	**2**	**1**	0.25	1	**256**	3	4	1
	WT	NT	**2**	0.03	0.03	0.5	**256**	3	−1	−2

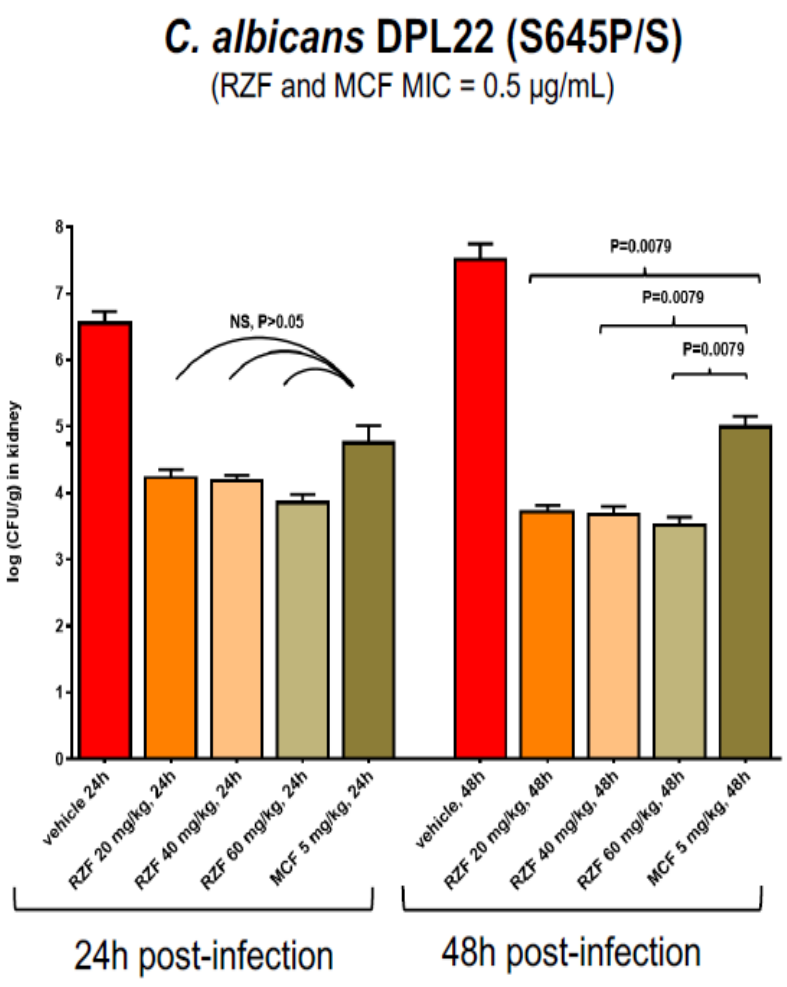
[a]NT, not tested.
[b]MICs above the wild-type upper limit/ECOFF are in boldface. RZF, rezafungin; ANF, anidulafungin; MCF, micafungin; AMB, amphotericin B; FLU, fluconazole.
[c]The number of two-fold dilution increases in the MIC compared to the modal MIC.

1. Helleberg, M., Jørgensen, K. M., Hare, R. K.,et al. Rezafungin in vitro activity against contemporary nordic clinical Candida isolates and Candida auris determined by the EUCAST reference method. Antimicrob Agents Chemother 2020; 64.4.

Rezafungin vs *FKS* mutant

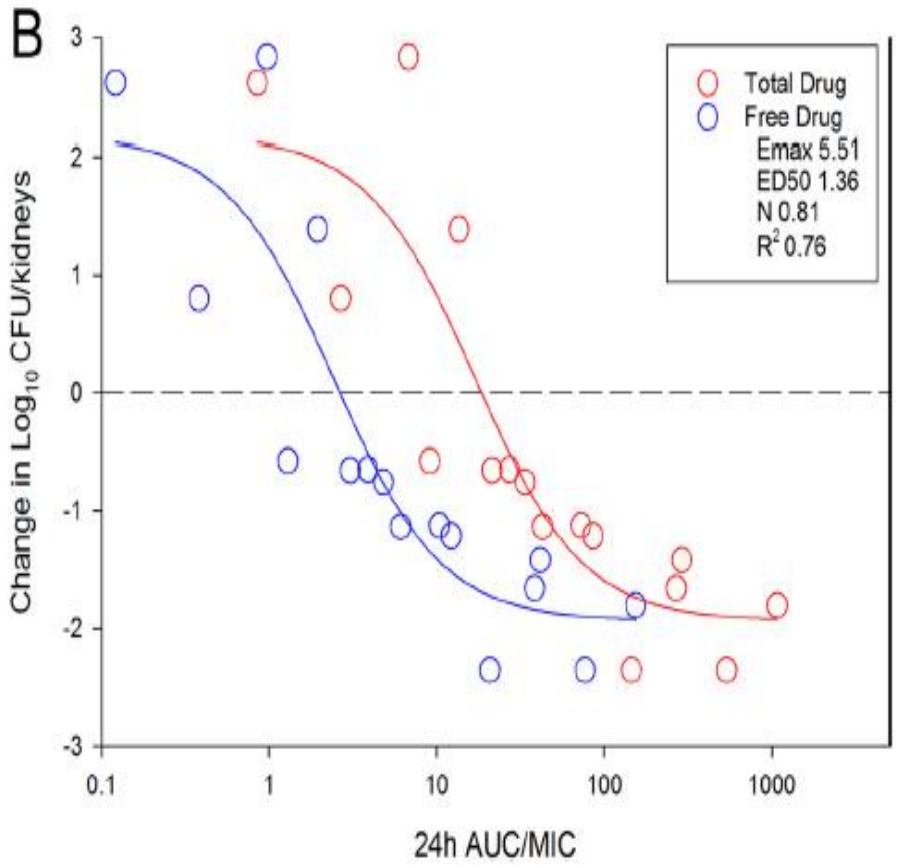
- Neutropenic mouse model of invasive candidiasis

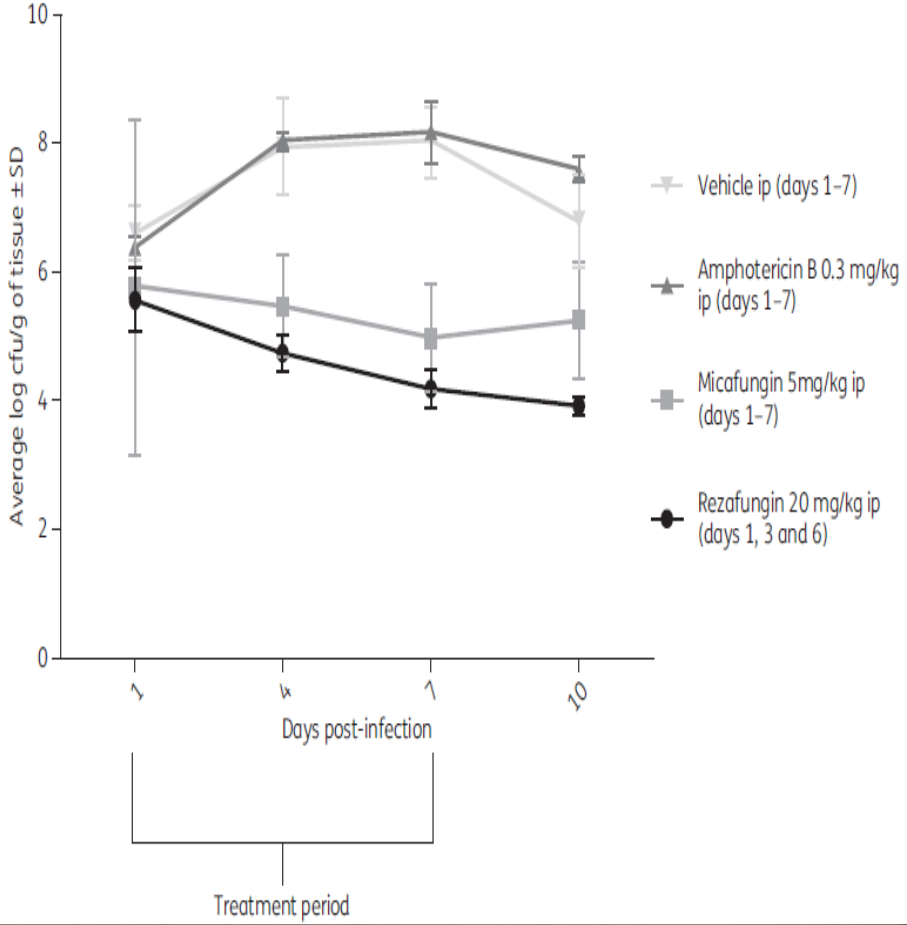




1. CLSI Winter 2021 Susceptibility Testing Meeting Series, 25 Jan-24 Feb 2021.

Rezafungin vs *Candida auris*





1. Lepak, A. J., Zhao, M., Andes, D. R. Pharmacodynamic evaluation of rezafungin (CD101) against Candida auris in the neutropenic mouse invasive candidiasis model. Antimicrob Agent Chemother 2018; 62.11.
2. Hager, C. L., Larkin, E. L., Long, L. A., Ghannoum, M. A. Evaluation of the efficacy of rezafungin, a novel echinocandin, in the treatment of disseminated Candida auris infection using an immunocompromised mouse model. J Antimicrobi Chemother 2018; 73.8: 2085-2088.

Rezafungin – Dezavantajı ne?

- Yepyeni mi?
- Türkiye'de henüz yok
- Faz çalışmaları devam ediyor
- Direnç potansiyeli ?
  - FKS mutasyonlarından etkileniyor?
- EUCAST test ederken plak seçimi !

Sonuç

- Yeni ama yepyeni değil
- MİK ile terapötik başarı ilişkisi gösterilemedi*
- Dokuya ulaşabilme yeteneği çok iyi
  - Direnç gelişimine engel olur mu?
  - *Candida auris* enfeksiyonlarında potansiyel yarar?

* Cidara therapeutics, ABD

Genel Bakış

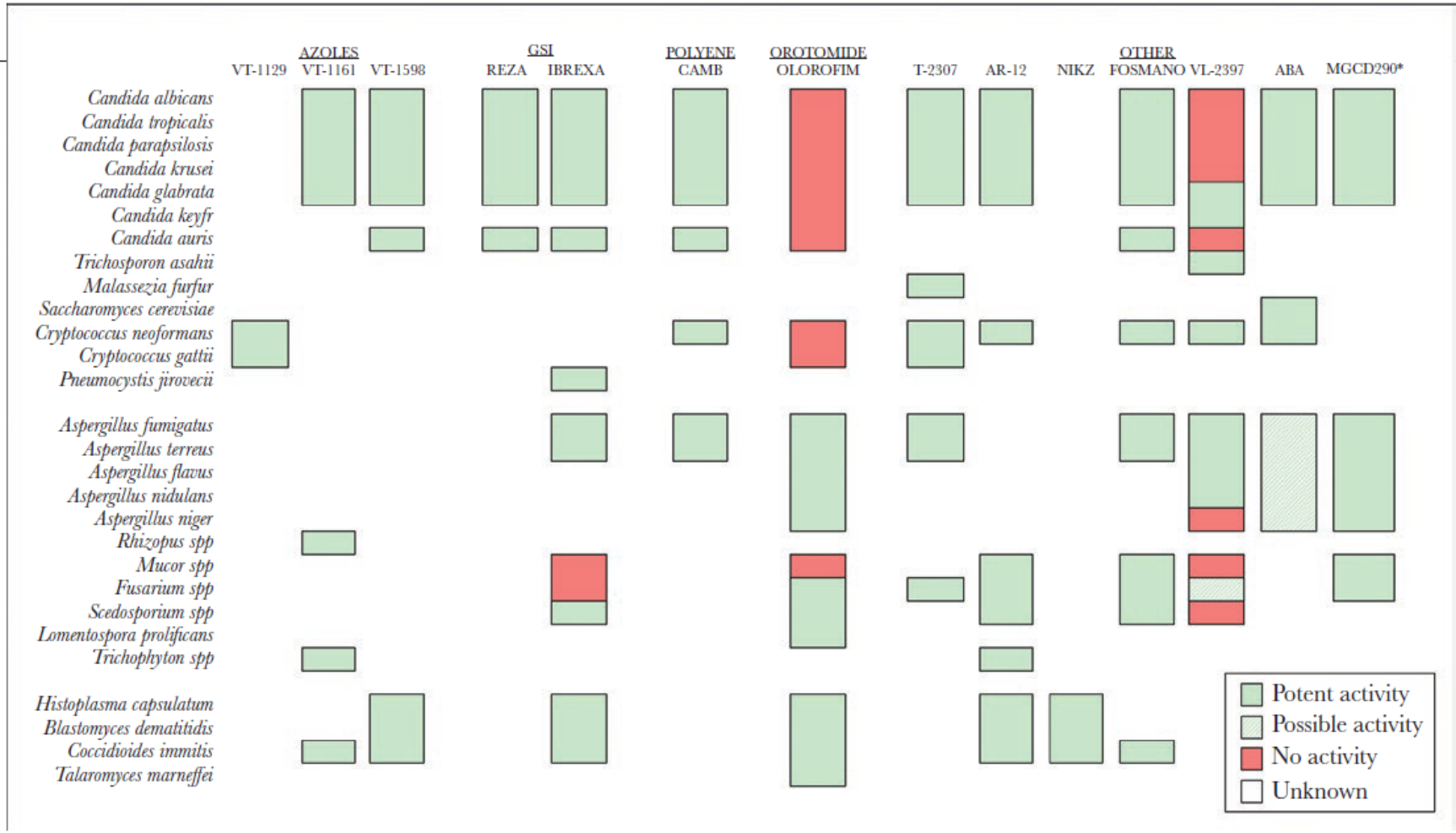


Figure 2. Novel antifungals with spectrum of activity. New antifungal compounds show extensive spectrum of activity to overcome resistant fungi; however, several gaps still remain. *MGCD290: Potent activity in combination with azoles and/or echinocandins. ABA, aureobasidin A; CAMB, encochleated amphotericin B; FOSMANO, fosmanogepix; GSI, glucan synthase inhibitor; IBREXA, ibrexafungerp; NIKZ, nikkomycin Z; REZA, rezafungin.

1. Rauseo, A. M., Coler-Reilly, A., Larson, L., Spec, A.Hope on the horizon: Novel Fungal treatments in development. Open Forum Infectious Diseases 2020; DOI: 10.1093/ofid/ofaa016

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