KLIMIK
Antimikrobiyal Yönetim Sempozyumu
6-8 Ekim 2016 Istanbul

Antifungal Direnç Sorunu

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

Sunum Planı

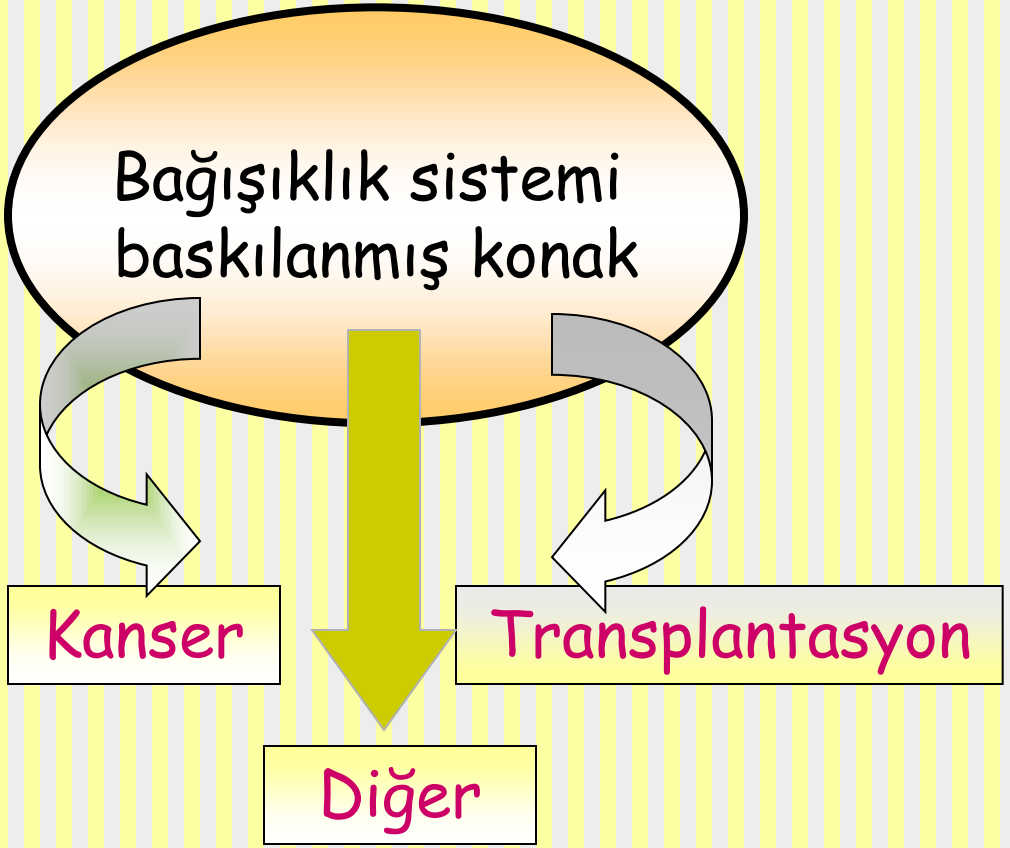
Temel bilgiler

YÖNTEM ve DEĞERLENDİRME

DİRENÇ VARLIĞI / ORANI

ÖNERİLER

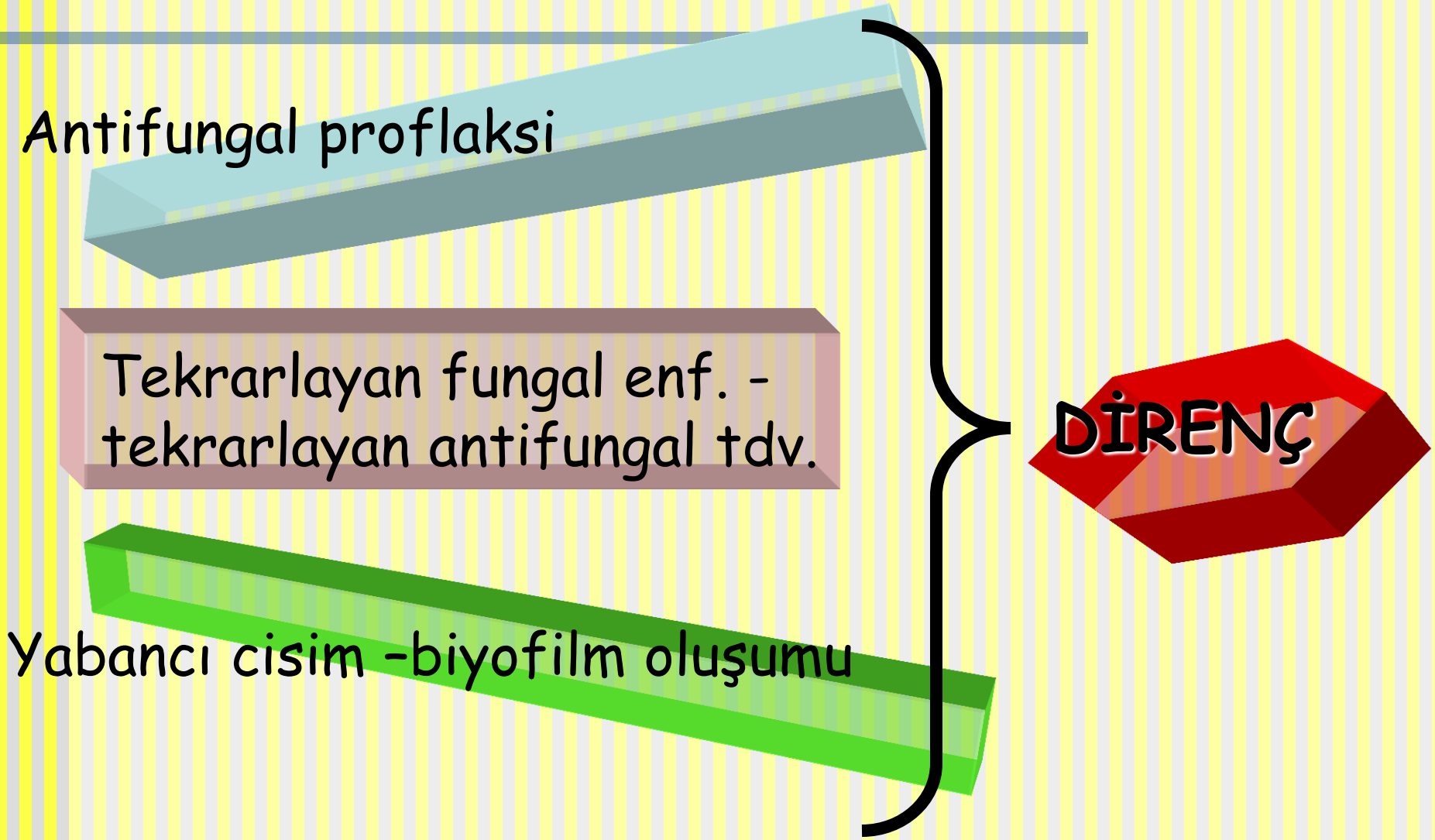
Fırsatçı mantar enfeksiyonları: KONAK



- Kritik, ağır hastalığı olan YBÜ olguları
- Düşkün, postop. olgular
- Kateterize olgular
- Diğer

Bille et al. Curr Opin Infect Dis 2005; 18: 314

"Özel konak" koşulları, antifungal direnç riskini beraberinde getirir



Özel konakta Hangi mantar?

SIK İZOLE EDİLEN ETKENLER

- 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.....

1950'lerden günümüze: Değişen antifungal ilaç spektrumu

1950'ler
Grizeofulvin
İlk azol

1960'lar
Amfoterisin B
Mikonazol
Klotrimazol
Flusitozin

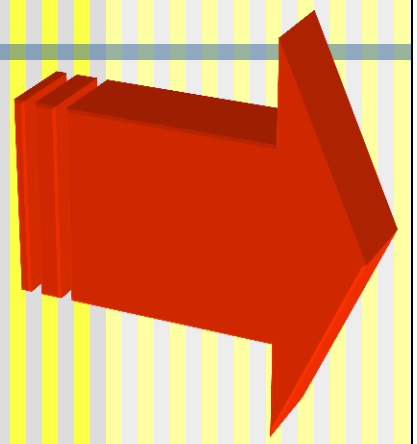
1970'ler
Ekonazol
Mikonazol (IV)

1980'ler
Ketokonazol
(po)

1990'lar
Flukonazol
Itrakonazol
Terbinafin
Lipid Amfo
bileşikleri

2000'ler
Kaspofungin
Vorikonazol

Mikafungin
Anidulafungin
Posakonazol
...



Candida ve Aspergillus

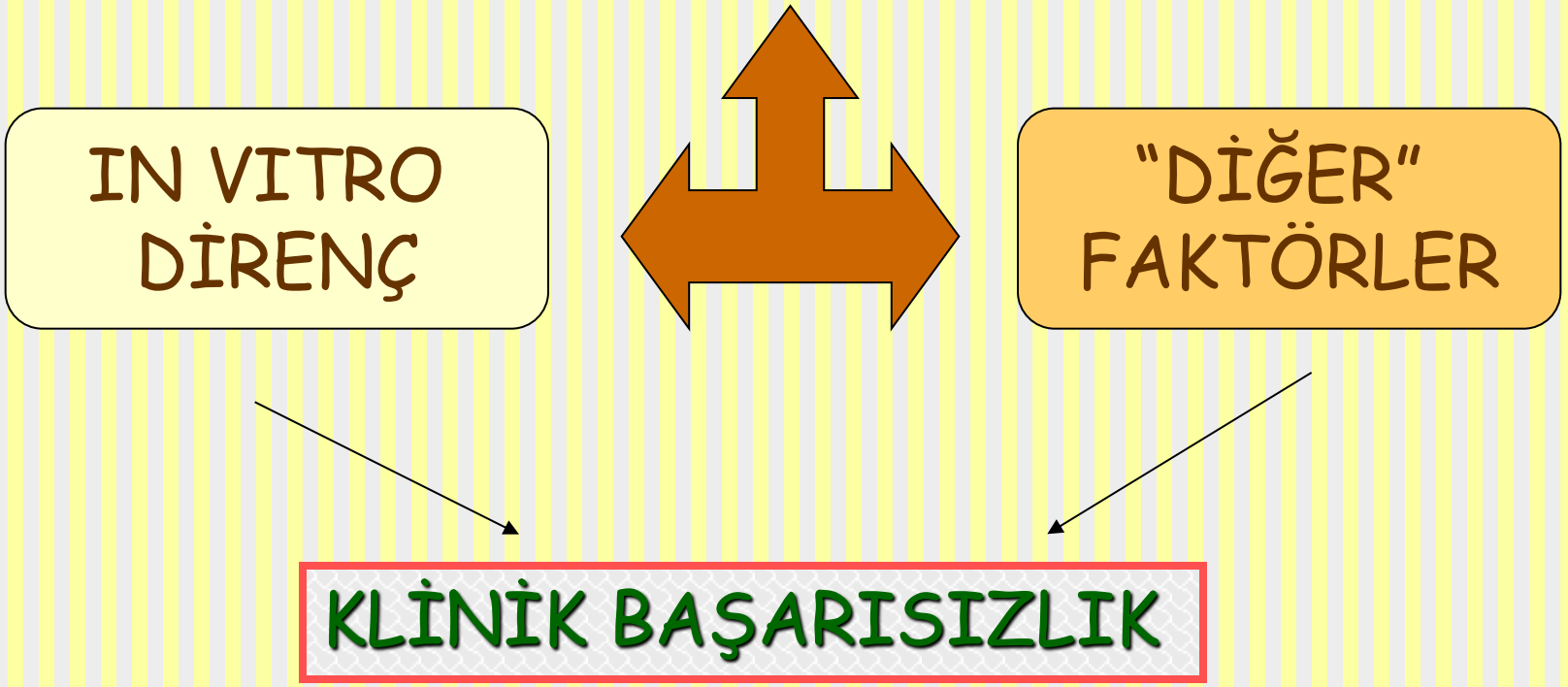
SUŞLARINDA

ANTİFUNGAL DİRENÇ

Candida
Ekinokandin

Aspergillus
Azol

Mantar Enfeksiyonlarında Klinik Başarısızlığın Nedenleri



"Diğer" faktörler…

MANTAR

- Direnç
- Hücre tipi
- İnokulum miktarı

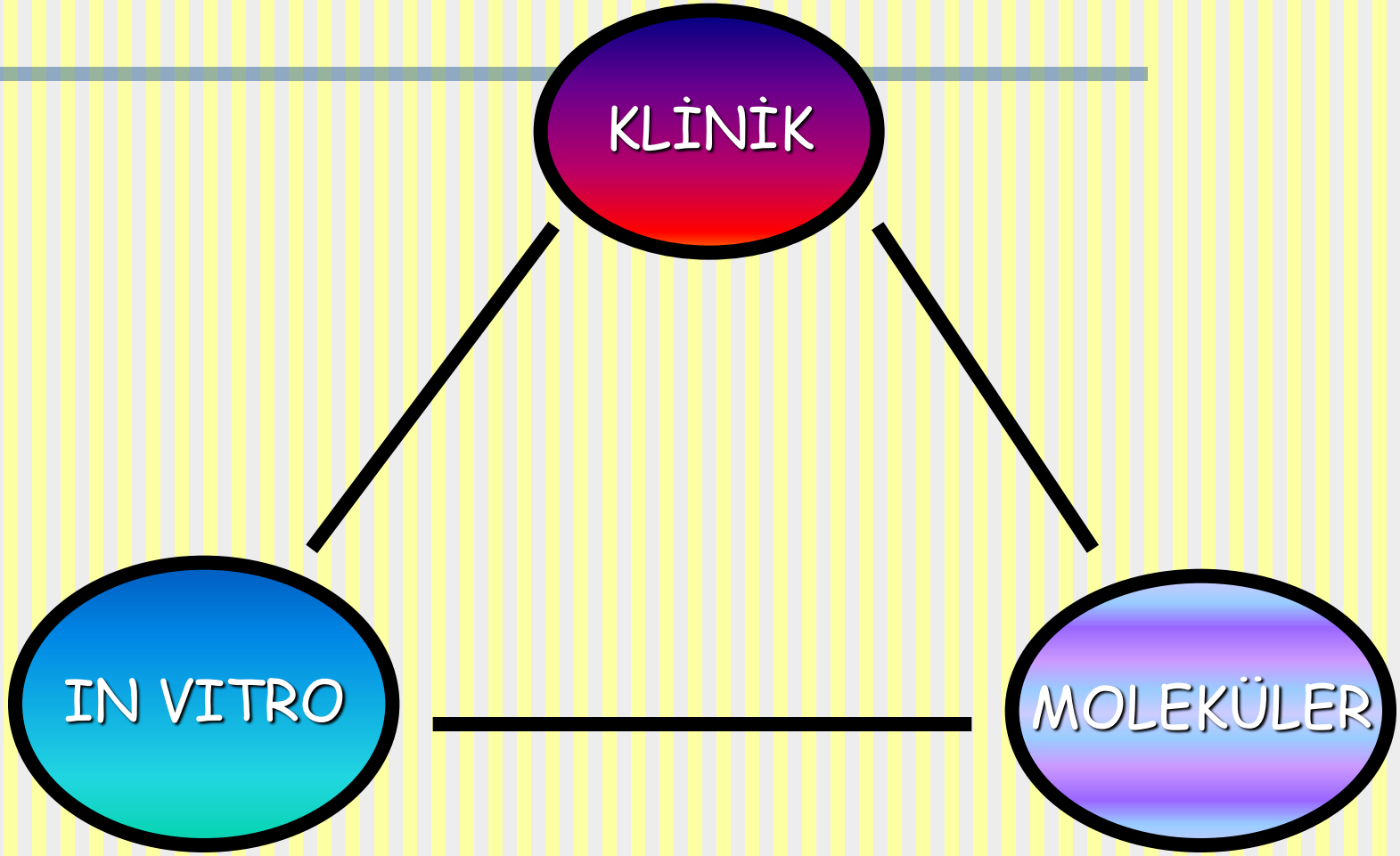
İLAÇ

- Yanlış doz
- Fungistatik etki
- Yetersiz emilim, dağılım ve metabolizma
- İlaç etkileşimleri

KONAK

- İmmün yanıt
- Yabancı cisim
- İnfeksiyon bölgesi
- Apse
- Tedaviye uyumsuzluk

DİRENÇ



Antifungal direncin getirdiği sorunlar

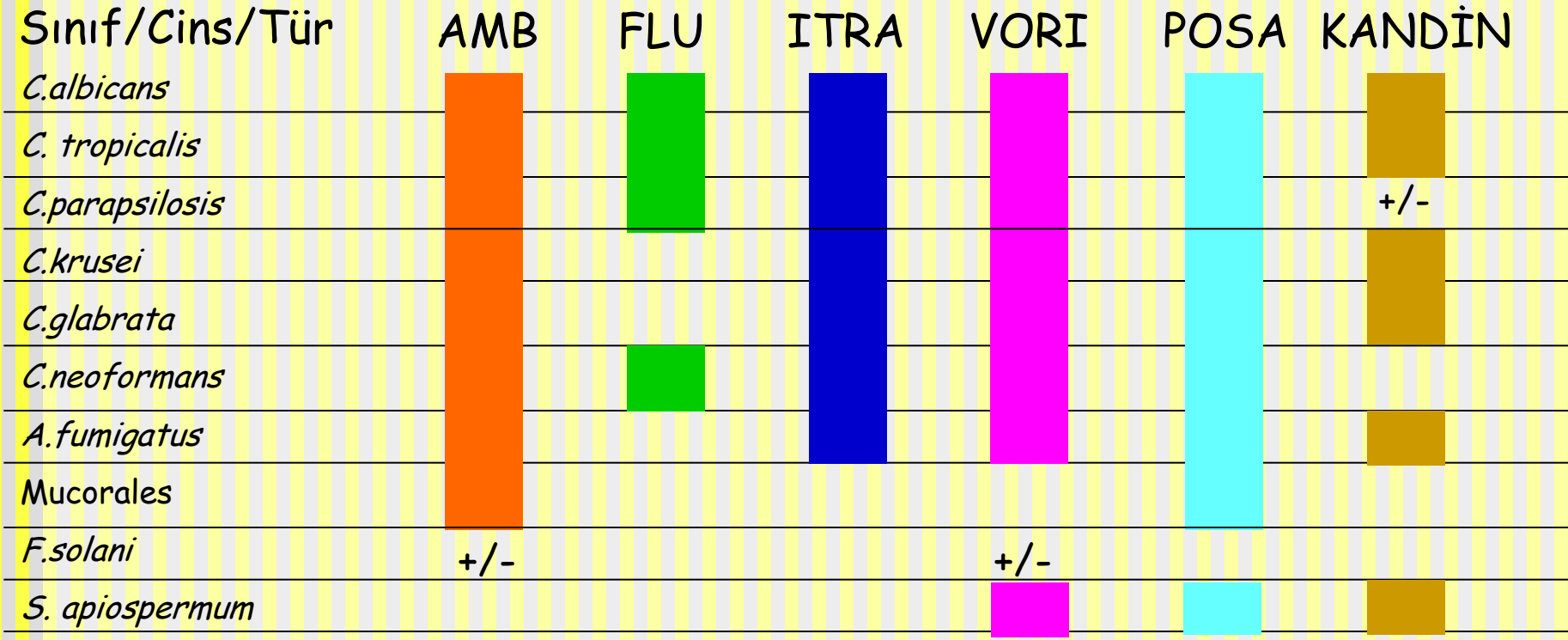
- Tedavi başarısına olumsuz etki
  - Çapraz direnç olasılığı
- Tedavi seçeneklerinin kısıtlanması

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

Ve direnç ...

Etki Spektrumu

Antifungal ilaçlar-sık etken olan mantarlar



Donnelly & de Pauw. CMI 2004, 10 (Suppl.1): 107

Primer ve Sekonder direnç

Direnç türü	Örnek
PRİMER (DOĞAL) 	C. krusei-flukonazol C. glabrata-flukonazol C. norvegensis-flukonazol C. lusitaniae-amfoterisin B C. krusei-flusitozin Aspergillus-flukonazol Mucorales-vorikonazol
SEKONDER (EDİNİLMİŞ)	C. albicans-orofaringiyal kandidoz-HIV C. dubliniensis...

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

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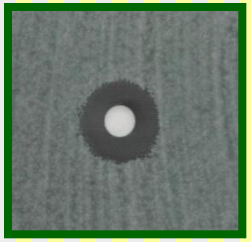
DİRENÇ VARLIĞI / ORANI

ÖNERİLER

Direncin in vitro saptanması: Antifungal duyarlılık testleri-I

CLSI M27-A3	Candida, Cryptococcus
CLSI M38-A2	Aspergillus, Rhizopus, Fusarium, P. boydii, S. schenckii-küf formu, dermatofitler
CLSI M44-A2	Candida
CLSI M51-A	Dermatofit dışı küfler



Direncin in vitro saptanması: Antifungal duyarlılık testleri-II

EUCAST E.Dis 7.3 — Candida

Aralık 2015

EUCAST E.Dis 9.3 — Konidyum oluşturan küfler

Aralık 2015

DIN-58940-84

Duyarlılık testlerinin rutin amaçlı uygulanma endikasyonları

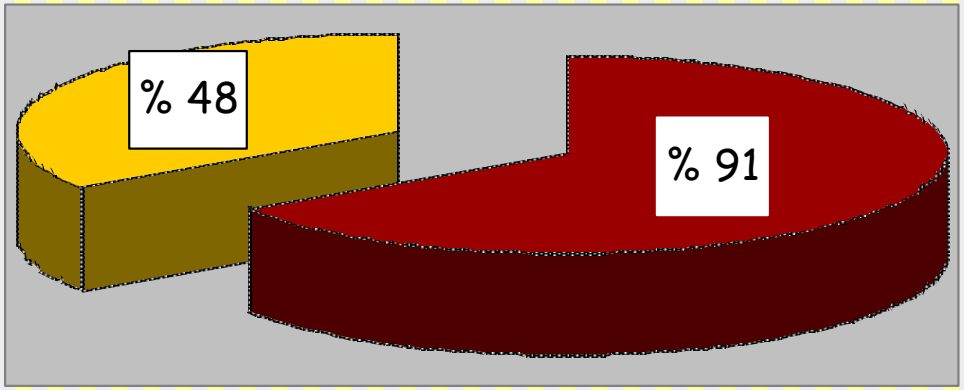
(Candida)

- İnvazif enfeksiyon; steril bölgeden izolasyon
- Direncin görülebildiği türler (örn. *C. glabrata* - flukonazol)
- (Beklenmeyen) klinik yanıtsızlık
- Tedaviye bağlı sekonder direnç gelişimi riski nedeniyle izlem için
- Epidemiyolojik veri (her merkez - periyodik)

ESCMID Guideline for the diagnosis and management of Candida diseases: Diagnostic procedures. CMI 2012; 18 (Suppl. 7): 9

Ancak... Duyarlılık testi sonucu klinik yanıtı ne kadar yansıtıyor??

Meta analiz



Candida -flukonazol

Candida - itrakonazol

Candida - ketokonazol

C. neoformans - flukonazol

Histoplasma - flukonazol

Rex et al. CID 2002; 35: 982

Duyarlılık testlerinin rutinde uygulanması -KÜFler

(Aspergillus)

- CLSI M38-A2

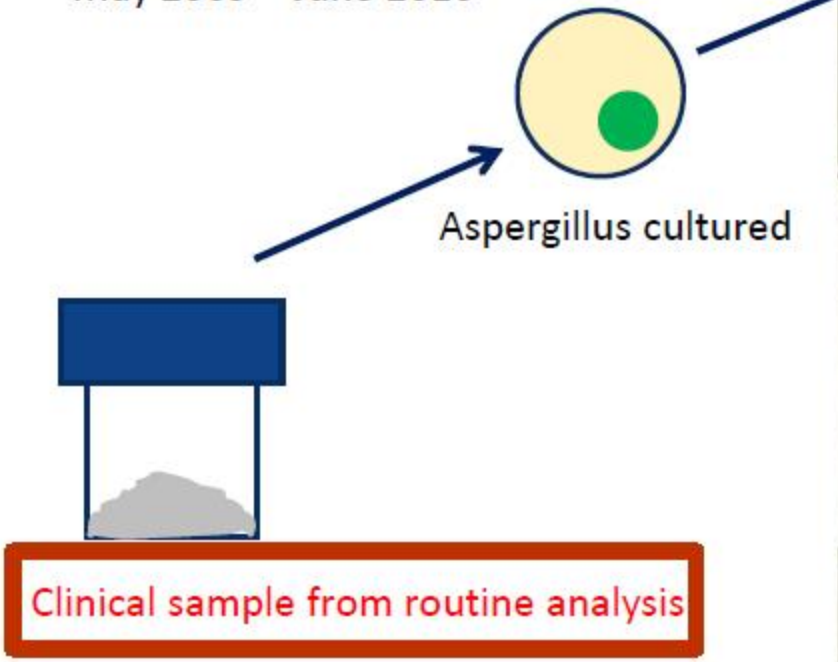
- EUCAST E.Dis 9.3

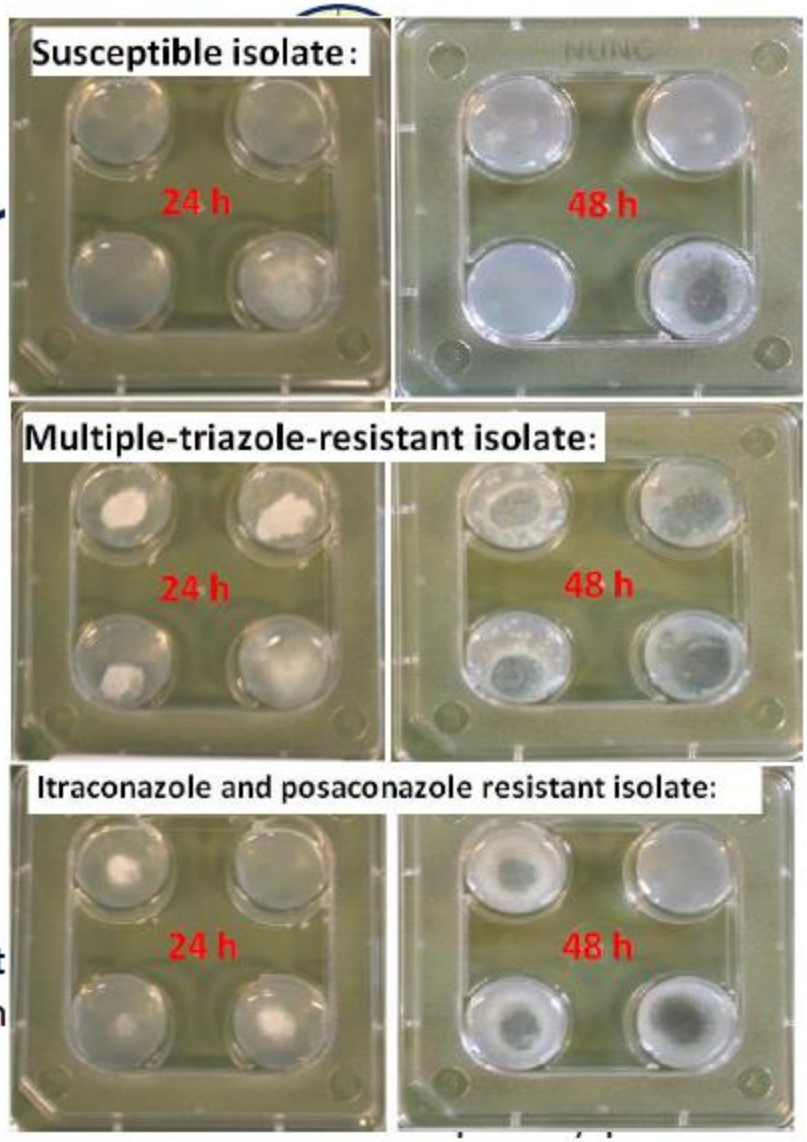
Aralık 2015

UMC St Radboud

Surveillance-method

Prospective, multicenter surveillance
May 2009 – June 2010





• Complet
questionn

• Cyp-sequencing

www.umcn.nl

Courtesy of Paul Verweij & Jan van der Linden

Aspergillus – Azol direnci

J.W.M. van der Linden, M.C. Arendrup, A. Warris, K. Lagrou, H. Pelloux, P.M. Hauser, E. Chryssanthou, E. Mellado, S.E. Kidd, A.M. Tortorano, E. Dannaoui, P. Gaustad, J.W. Baddley, A. Uekötter, C. Lass-Flörl, N. Klimko, C.B. Moore, D.W. Denning, A.C. Pasqualotto, C. Kibbler, S. Arikan-Akdagli, D. Andes, J. Meletiadis, L. Naumiuk, M. Nucci, W.J.G. Melchers, P.E. Verweij

Prospective Multicenter International Surveillance of Azole Resistance in *Aspergillus fumigatus*

To investigate azole resistance in clinical *Aspergillus* isolates, we conducted prospective multicenter international surveillance. A total of 3,788 *Aspergillus* isolates were screened in 22 centers from 19 countries. Azole-resistant *A. fumigatus* was more frequently found (3.2% prevalence) than previously acknowledged, causing resistant invasive and noninvasive aspergillosis and severely compromising clinical use of azoles.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 21, No. 6, June 2015

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5,b] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

Clinical Infectious Diseases® 2016;63(4):433–42

When Should Antifungal Susceptibility Testing Be Performed, and How Should Results Be Interpreted and Affect Management?

Recommendation.

24. Routine antifungal susceptibility testing (AFST) of isolates recovered during initial infection is not recommended. AFST of *Aspergillus* isolates using a reference method is reserved for patients suspected to have an azole-resistant isolate or who are unresponsive to antifungal agents, or for epidemiological purposes *(strong recommendation; moderate-quality evidence)*.

Aspergillus- AFDT

ESCMID-EFISG Aspergillus Guideline- Unpublished Preliminary

Population	Intention	Intervention	SoR	QoE	Comment
All clinically relevant *Aspergillus* isolates (in patient groups or regions with known azole resistance)	Identify azole resistance	MIC test (always and routine)	A	II	As the initial and only test in situations where rapid testing is not available
		Routine agar screening only	B	III	.If MIC is not available .No validated assays - Refer to reference lab. for MIC testing if growth observed on screening agar

Verweij, Arendrup, Denning, Kullberg, Meis, Arikan-Akdagli

Mucorales - AFDT

ESCMID† and ECMM‡ joint clinical guidelines for the diagnosis and management of mucormycosis 2013

O. A. Cornely[1,†,‡,§], S. Arikan-Akdagli[2,‡,§], E. Dannaoui[3,§], A. H. Groll[4,†,‡,§], K. Lagrou[5,‡,§], A. Chakrabarti[6,§], F. Lanternier[7,8], L. Pagano[9], A. Skiada[10], M. Akova[2], M. C. Arendrup[11], T. Boekhout[12,13,14], A. Chowdhary[15], M. Cuenca-Estrella[16,†,‡], T. Freiberger[17,18,†], J. Guinea[19,†,‡], J. Guarro[20,‡], S. de Hoog[12,‡], W. Hope[21,†], E. Johnson[22,‡], S. Kathuria[15], M. Lackner[23,‡], C. Lass-Flörl[23,†,‡], O. Lortholary[7,†,‡], J. F. Meis[24,25,†,‡], J. Meletiadis[26,‡], P. Muñoz[19,†], M. Richardson[27,28,†,‡], E. Roilides[29,†,‡], A. M. Tortorano[30,‡], A. J. Ullmann[31,†,‡], A. van Diepeningen[12], P. Verweij[25,32,†,‡] and G. Petrikkos[33,†,‡,§]

TABLE 5. Recommendations on susceptibility testing in mucormycosis

Population	Intention	Method/Finding	SoR	QoE	Comment	References
Any	To guide treatment	EUCAST/CLSI reference microdilution methods	C	IIu	Clinical relevance uncertain. No data available to correlate MIC and outcome	79,80,83
Any	To guide treatment	Correlation of MIC with *in vivo* outcome	C	IIu	For *Apophysomyces elegans*, limited retrospective data suggest correlation	83
Any	To guide treatment	Correlation of MIC/MFC with *in vivo* outcome	B	III	Animal, posaconazole better in *Rhizopus microsporus* and *Rhizopus oryzae* strains MIC 0.25 μg/mL than in those with MICs 2 μg/mL	82,84,85
Any	To establish epidemiological knowledge	Susceptibility testing	A	IIu	*n* = 37 *n* = 36 *n* = 217 *n* = 45 *n* = 77 *n* = 18, *Apophysomyces elegans* *n* = 21 *n* = 66 Review	86 88 87 21 92 83 91 90 195
Any	To establish epidemiological knowledge	MIC determined by reference method	A	III	e.g. Etest® not validated for Mucorales	79,80

MFC, minimum fungicidal concentration; QoE, quality of evidence; SoR, strength of recommendation.

Clin Microbiol Infect 2014; **20** (Suppl. 3): 5–26

Fusarium - AFDT

ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others

A. M. Tortorano[1,*,†], M. Richardson[2,3,*,†,‡], E. Roilides[4,*,†,‡], A. van Diepeningen[5,*], M. Caira[6,*], P. Munoz[7,*,‡], E. Johnson[8,*,†], J. Meletiadis[9,*,†], Z.-D. Pana[4,*], M. Lackner[10,*,†], P. Verweij[11,12,*,†,‡], T. Freiberger[13,*,‡], O. A. Cornely[14,†,‡], S. Arikan-Akdagli[15,†], E. Dannaoui[16,†], A. H. Groll[17,†,‡], K. Lagrou[18,†], A. Chakrabarti[19], F. Lanternier[20,21], L. Pagano[22,†], A. Skiada[23,‡], M. Akova[15,‡], M. C. Arendrup[24,†,‡], T. Boekhout[5,25,26,†], A. Chowdhary[27,‡], M. Cuenca-Estrella[28,†,‡], J. Guinea[7,†,‡], J. Guarro[29,†], S. de Hoog[5,†], W. Hope[30,‡], S. Kathuria[27], O. Lortholary[31,32,†,‡], J. F. Meis[11,33,†,‡], A. J. Ullmann[34,†,‡], G. Petrikkos[35,*,†,‡] and C. Lass-Flörl[10,*,†,‡]

TABLE 4. Summary of recommendations for diagnosis of *Fusarium* infection

Fusarium infection/ Population	Test	SoR	QoE	Comment	References
Any population	Direct microscopy	A	III	Essential investigation	[2]
	Culture (species identification)	A	III	Essential investigation Easily recovered on routine mycological media without cycloheximide Accurate species assignment is important for guiding clinical management	[2,190]
	Histopathology	A	IIu	Essential investigation Features of hyaline septate hyphae (with acute angle branching) are similar to those seen with aspergillosis	[120]
	Immunohistochemistry	C	III	Not yet evaluated	[120]
	β-D-Glucan test/ Galactomannan	B	III	Glucan usually positive in case of invasive fusariosis. *Aspergillus* galactomannan sometimes positive in patients with fusariosis	[46]
	Pan-fungal PCRs for identification[a]	C	II	In combination with conventional methods High negative predictive values	[36–38]
	Multiplex PCRs[a]	C	III	Not yet validated Cover limited number of species/genera	[30,37,39]
	In situ hybridization	C	III	Not yet evaluated In house tests	[191,192]
	Susceptibility testing	C	III	Gives an overview of drug activity and may be helpful in selecting antifungals	[2,181,182,193–195]
	Environmental sampling (and fungal typing)	A	III	In case of an outbreak situation	[33,76]
Haematological patients	Chest computed tomography (CT) scan	A	IIu	None of patients had normal CT Pulmonary nodules in 82% of patients	[26]

QoE, quality of evidence; SoR, strength of recommendation.
[a]Third-party appraisal of results and harmonization of PCR-based techniques are necessary before any clear recommendations can be made regarding clinical utility.

Clin Microbiol Infect 2014; **20** (Suppl. 3): 27–46

Scedosporium - AFDT

ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others

A. M. Tortorano[1,*,†], M. Richardson[2,3,*,†,‡], E. Roilides[4,*,†,‡], A. van Diepeningen[5,*], M. Caira[6,*], P. Munoz[7,*,‡], E. Johnson[8,*,†], J. Meletiadis[9,*,†], Z.-D. Pana[4,*], M. Lackner[10,*,†], P. Verweij[11,12,*,†,‡], T. Freiberger[13,*,‡], O. A. Cornely[14,†,‡], S. Arikan-Akdagli[15,†], E. Dannaoui[16,†], A. H. Groll[17,†,‡], K. Lagrou[18,†], A. Chakrabarti[19], F. Lanternier[20,21], L. Pagano[22,†], A. Skiada[23,‡], M. Akova[15,‡], M. C. Arendrup[24,†,‡], T. Boekhout[5,25,26,†], A. Chowdhary[27,‡], M. Cuenca-Estrella[28,†,‡], J. Guinea[7,†,‡], J. Guarro[29,†], S. de Hoog[5,†], W. Hope[30,‡], S. Kathuria[27], O. Lortholary[31,32,†,‡], J. F. Meis[11,33,†,‡], A. J. Ullmann[34,†,‡], G. Petrikkos[35,*,†,‡] and C. Lass-Flörl[10,*,†,‡]

TABLE 7. Summary of recommendations for diagnosis of *Scedosporium* infections

Population	Test	SoR	QoE	Comment	References
Any population	Direct microscopy	A	III	Essential investigation	[85]
	Culture (species identification by morphology and physiological characteristics)	A	III	Essential investigation Selective media supplemented with cycloheximide or benomyl (10 mg/L, Sce Sel[+]) allows growth of *Scedosporium* over other filamentous fungi from bronchial secretions.	[85,122,123,136,206–210]
	Molecular-based identification methods	C	III	Accurate species assignment is important for guiding clinical management	[121–123,211]
	Histopathology	A	III	Hyaline thin-walled septate hyphae, 2-5 μm wide similar to those seen with aspergillosis and other hyalohyphomycoses Irregular branching	[120,212,213]
	Pan-fungal PCR[a]	C	III	Molecular tests could be used in combination with conventional laboratory tests.	[36–38]
	Multiplex PCR[a]	C	III	Molecular tests could be used in combination with conventional laboratory tests.	[30,31,37,39]
	In situ hybridization	C	III	Low sensitivity Not yet validated	[191,192]
	Species identification (MALDI TOF and PCR)	C	III	Not yet validated	[124,214–219]
	Physiological typing	C	III	In case of an outbreak situation	[220]
	In vitro susceptibility testing	C	III	Gives an overview of drug activity and therefore may support choice of antifungals	[221–223]

MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; QoE, quality of evidence; SoR, strength of recommendation.
[a]Third-party appraisal of results and harmonization of PCR-based techniques are necessary before any clear recommendations can be made regarding clinical utility.

Clin Microbiol Infect 2014; **20** (Suppl. 3): 27–46

Klinik direnç sınır değerleri / "ECV" ("ECOFF")

GÜNCEL: Türe özgü
Yönteme özgü
İnkübasyon süresine özgü

CLSI M27-S4 2012

Progress in Antifungal Susceptibility Testing of *Candida* spp. by Use of Clinical and Laboratory Standards Institute Broth Microdilution Methods, 2010 to 2012

M. A. Pfaller[a,b] and D. J. Diekema[b]

JMI Laboratories, North Liberty, Iowa, USA,[a] University of Iowa Carver College of Medicine, Iowa City, Iowa, USA[b]

Journal of Clinical Microbiology p. 2846–2856 September 2012 Volume 50 Number 9

Wild-Type MIC Distributions and Epidemiological Cutoff Values for Amphotericin B and *Aspergillus* spp. for the CLSI Broth Microdilution Method (M38-A2 Document)[▽]

A. Espinel-Ingroff,[1]* M. Cuenca-Estrella,[2] A. Fothergill,[3] J. Fuller,[4] M. Ghannoum,[5] E. Johnson,[6] T. Pelaez,[7] M. A. Pfaller,[8] and J. Turnidge[9]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5150–5154 Vol. 55, No. 11

Wild-Type MIC Distributions and Epidemiological Cutoff Values for the Triazoles and Six *Aspergillus* spp. for the CLSI Broth Microdilution Method (M38-A2 Document)[▽]

A. Espinel-Ingroff,[1]* D. J. Diekema,[2] A. Fothergill,[3] E. Johnson,[4] T. Pelaez,[5] M. A. Pfaller,[2] M. G. Rinaldi,[3] E. Canton,[6] and J. Turnidge[7]

JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2010, p. 3251–3257 Vol. 48, No. 9

Multicenter Study of Isavuconazole MIC Distributions and Epidemiological Cutoff Values for *Aspergillus* spp. for the CLSI M38-A2 Broth Microdilution Method

A. Espinel-Ingroff,[a] A. Chowdhary,[b] G. M. Gonzalez,[c] C. Lass-Flörl,[d] E. Martin-Mazuelos,[e] J. Meis,[f,g] T. Peláez,[h] M. A. Pfaller,[i] J. Turnidge[j]

August 2013 Volume 57 Number 8 Antimicrobial Agents and Chemotherapy p. 3823–3828

Multicenter Evaluation of MIC Distributions for Epidemiologic Cutoff Value Definition To Detect Amphotericin B, Posaconazole, and Itraconazole Resistance among the Most Clinically Relevant Species of *Mucorales*

A. Espinel-Ingroff,[a] A. Chakrabarti,[b] A. Chowdhary,[c] S. Cordoba,[d] E. Dannaoui,[e] P. Dufresne,[f] A. Fothergill,[g] M. Ghannoum,[h] G. M. Gonzalez,[i] J. Guarro,[j] S. Kidd,[k] C. Lass-Flörl,[l] J. F. Meis,[m] T. Pelaez,[n] A. M. Tortorano,[o] J. Turnidge[p]

March 2015 Volume 59 Number 3 Antimicrobial Agents and Chemotherapy

International Evaluation of MIC Distributions and Epidemiological Cutoff Value (ECV) Definitions for *Fusarium* Species Identified by Molecular Methods for the CLSI Broth Microdilution Method

A. Espinel-Ingroff,[a] A. L. Colombo,[b] S. Cordoba,[c] P. J. Dufresne,[d] J. Fuller,[e] M. Ghannoum,[f] G. M. Gonzalez,[g] J. Guarro,[h] S. E. Kidd,[i] J. F. Meis,[j] T. M. S. C. Melhem,[k] T. Pelaez,[l] M. A. Pfaller,[m] M. W. Szeszs,[n] J. P. Takahaschi,[o] A. M. Tortorano,[p] N. P. Wiederhold,[q] J. Turnidge[r]

February 2016 Volume 60 Number 2 1079–1084. Antimicrobial Agents and Chemotherapy

AMB, Azoller, Kandin- Candida

EUCAST

***Candida* spp.**

EUCAST Antifungal Clinical Breakpoint Table v. 8.0 valid from 2015-11-16

MIC method (EUCAST standardised broth microdilution method)
Medium: RPMI1640-2% glucose, MOPS buffer
Inoculum: Final $0.5 \times 10^5 - 2.5 \times 10^5$ cfu/mL
Incubation: 18-24h
Reading: Spectrophotometric, complete (>90%) inhibition for amphotericin B but 50% growth inhibition for other compounds
Quality control: *C. parapsilosis* ATCC 22019 or *C. krusei* ATCC 6258

Antifungal agent	MIC breakpoint (mg/L)														Notes
	C. albicans		*C. glabrata*		*C. krusei*		*C. parapsilosis*		*C. tropicalis*		*C. guilliermondii*		Non-species related breakpoints[1]		
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	
Amphotericin B	1	1	1	1	1	1	1	1	1	1	IE	IE	IE	IE	**1.** Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.
Anidulafungin	0.03	0.03	0.06	0.06	0.06	0.06	0.002	4	0.06	0.06	IE[2]	IE[2]	IE	IE	**2.** The ECOFFs for these species are in general higher than for *C. albicans*.
Caspofungin	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	IE[2]	IE[2]	IE	IE	**3.** Isolates that are susceptible to anidulafungin as well as micafungin should be considered susceptible to caspofungin, until caspofungin breakpoints have been established. Similarly, *C. parapsilosis* isolates intermediate to anidulafungin and micafungin can be regarded intermediate to caspofungin. EUCAST breakpoints have not yet been established for caspofungin, due to significant inter-laboratory variation in MIC ranges for caspofungin.
Fluconazole	2	4	0.002	32	-	-	2	4	2	4	IE[2]	IE[2]	2	4	
Isavuconazole	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	**4.** MICs for *C. tropicalis* are 1-2 two-fold dilution steps higher than for *C. albicans* and *C. glabrata*. In the clinical study successful outcome was numerically slightly lower for *C. tropicalis* than for *C. albicans* at both dosages (100 and 150 mg daily). However, the difference was not significant and whether it translates into a relevant clinical difference is unknown. MICs for *C. krusei* are approximately three two-fold dilution steps higher than those for *C. albicans* and, similarly, those for *C. guilliermondii* are approximately eight two-fold dilutions higher. In addition, only a small number of cases involved these species in the clinical trials. This means there is insufficient evidence to indicate whether the wild-type population of these pathogens can be considered susceptible to micafungin.
Itraconazole	0.06	0.06	IE[2]	IE[2]	IE[2]	IE[2]	0.12	0.12	0.12	0.12	IE[2]	IE[2]	IE	IE	
Micafungin	0.016	0.016	0.03	0.03	IE[4]	IE[4]	0.002	2	IE[4]	IE[4]	IE[4]	IE[4]	IE	IE	
Posaconazole	0.06	0.06	IE[2]	IE[2]	IE[2]	IE[2]	0.06	0.06	0.06	0.06	IE[2]	IE[2]	IE	IE	**5.** Strains with MIC values above the S/I breakpoint are rare or not yet reported. The identification and antifungal susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.
Voriconazole	0.12[5]	0.12[5]	IE	IE	IE	IE	0.12[5]	0.12[5]	0.12[5]	0.12[5]	IE[2]	IE[2]	IE	IE	

Antimicrobial Agents and Chemotherapy p. 5836–5842

December 2013 Volume 57 Number 12

Interlaboratory variability of caspofungin MICs for *Candida* spp. using CLSI and EUCAST methods: Should the clinical laboratory be testing this agent?

A. Espinel-Ingroff[1*], M.C. Arendrup[2], M.A. Pfaller[3], L.X. Bonfietti[4], B. Bustamante[5], E. Canton[6], E. Chryssanthou[7], M. Cuenca-Estrella[8], E. Dannaoui[9], A. Fothergill[10], J. Fuller[11], P. Gaustad[12], G. M. Gonzalez[13], J. Guarro[14], C. Lass-Flörl[15], S.R. Lockhart[16], J.F. Meis[17], C.B. Moore[18], L. Ostrosky-Zeichner[19], T. Pelaez[20], S.R.B.S. Pukinskas[21], G. St-Germain[22], M.W. Szeszs[23], and J. Turnidge[24]

Although many factors (caspofungin powder source, stock solution solvent, powder storage time length and temperature, and MIC determination testing parameters) were examined as a potential cause of such unprecedented variability, a single specific cause was not identified. Therefore, it seems highly likely that the use of the CLSI species-specific caspofungin CBPs could lead to reporting an excessive number of wild-type [WT] (e.g., *C. glabrata* and *C. krusei*) as either non-WT or resistant isolates. Until this problem is resolved, routine testing or reporting of CLSI caspofungin MICs for *Candida* is not recommended; micafungin or anidulafungin data could be used instead.

AMB & Azoles -Asp

EUCAST

***Aspergillus* spp.**

EUCAST Antifungal Clinical Breakpoint Table v. 8.0 valid from 2015-11-16

MIC method (EUCAST standardised broth microdilution method)
Medium: RPMI1640-2% glucose, MOPS as buffer
Inoculum: Final 1x10(5) – 2.5x10(5) cfu/mL
Incubation: 48h
Reading: Visual, complete inhibition for amphotericin B and azoles (MIC), aberrant growth endpoint for echinocandins (MEC).
Quality control: *A. fumigatus* ATCC 204305, *A. flavus* ATCC 204304, *A. fumigatus* F 6919, *A. flavus* CM 1813, *C. parapsilosis* ATCC 22019 (read after 18-24 h) or *C. krusei* ATCC 6258 (read after 18-24 h)

Antifungal agent	MIC breakpoint (mg/L)												Notes
	A. flavus		*A. fumigatus*		*A. nidulans*		*A. niger*		*A. terreus*		Non-species related breakpoints[1]		
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	
Amphotericin B	IE[2]	IE[2]	1	2	Note[3]	Note[3]	1	2	-	-	IE	IE	**1.** Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. **2.** The ECOFFs for these species are in general one step higher than for *A. fumigatus*. **3.** There are too few MIC data to establish ECOFFs and hence to suggest any breakpoints. **4.** Monitoring of azole trough concentrations in patients treated for fungal infection is recommended. **5.** The MIC values for isolates of *A. niger* and *A. versicolor* are in general higher than those for *A. fumigatus*. Whether this translates into a poorer clinical response is unknown. **6.** Provided adequate drug exposure has been confirmed using therapeutic drug monitoring (TDM). There remains some uncertainty regarding cut-off values for posaconazole concentrations that separate patients with a high probability of clinical success from those with a low probability of clinical success. In some circumstances (e.g. patients with persistent and profound neutropenia, large lesions, or those with other features associated with a poor clinical outcome) a relatively high trough concentration should be sought. Preclinical and clinical data suggest this value should be >1 mg/L at steady state. For other patient groups a lower trough concentration may be acceptable. For prophylaxis a target concentration of >0.7 mg/L has been suggested.
Anidulafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	
Caspofungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	
Fluconazole	-	-	-	-	-	-	-	-	-	-	-	-	
Isavuconazole	IE[2]	IE[2]	1	1	0.25	0.25	IE[2]	IE[2]	1	1	IE	IE	
Itraconazole[4]	1	2	1	2	1	2	IE[2,5]	IE[2,5]	1	2	IE[5]	IE[5]	
Micafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	
Posaconazole[4]	IE[2]	IE[2]	0.12[6]	0.25[6]	IE[2]	IE[2]	IE[2]	IE[2]	0.12[6]	0.25[6]	IE	IE	
Voriconazole[4]	IE[2]	IE[2]	1	2	IE	IE	IE[2]	IE[2]	IE[2]	IE[2]	IE	IE	

Wild-type MIC distributions, epidemiological cutoff values and species-specific clinical breakpoints for fluconazole and *Candida*: Time for harmonization of CLSI and EUCAST broth microdilution methods

Drug Resistance Updates 13 (2010) 180–195

M.A. Pfaller[a,*], D. Andes[b], D.J. Diekema[a], A. Espinel-Ingroff[c], D. Sheehan[d], The CLSI Subcommittee for Antifungal Susceptibility Testing

Clinical breakpoints for voriconazole and *Candida* spp. revisited: review of microbiologic, molecular, pharmacodynamic, and clinical data as they pertain to the development of species-specific interpretive criteria ☆

Michael A. Pfaller[a,*,1], David Andes[b,1], Maiken C. Arendrup[c,1], Daniel J. Diekema[a,1], Ana Espinel-Ingroff[d,1], Barbara D. Alexander[e,1], Steven D. Brown[f,1], Vishnu Chaturvedi[g,1], Cynthia L. Fowler[h,1], Mahmoud A. Ghannoum[i,1], Elizabeth M. Johnson[j,1], Cynthia C. Knapp[k,1], Mary R. Motyl[l,1], Luis Ostrosky-Zeichner[m,1], Thomas J. Walsh[n,1]

Diagnostic Microbiology and Infectious Disease 70 (2011) 330–343

Evaluation of CLSI M44-A2 Disk Diffusion and Associated Breakpoint Testing of Caspofungin and Micafungin Using a Well-Characterized Panel of Wild-Type and *fks* Hot Spot Mutant *Candida* Isolates[▽]

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2011, p. 1891–1895

Sunum Planı

Temel bilgiler

YÖNTEM ve DEĞERLENDİRME

DİRENÇ VARLIĞI / ORANI

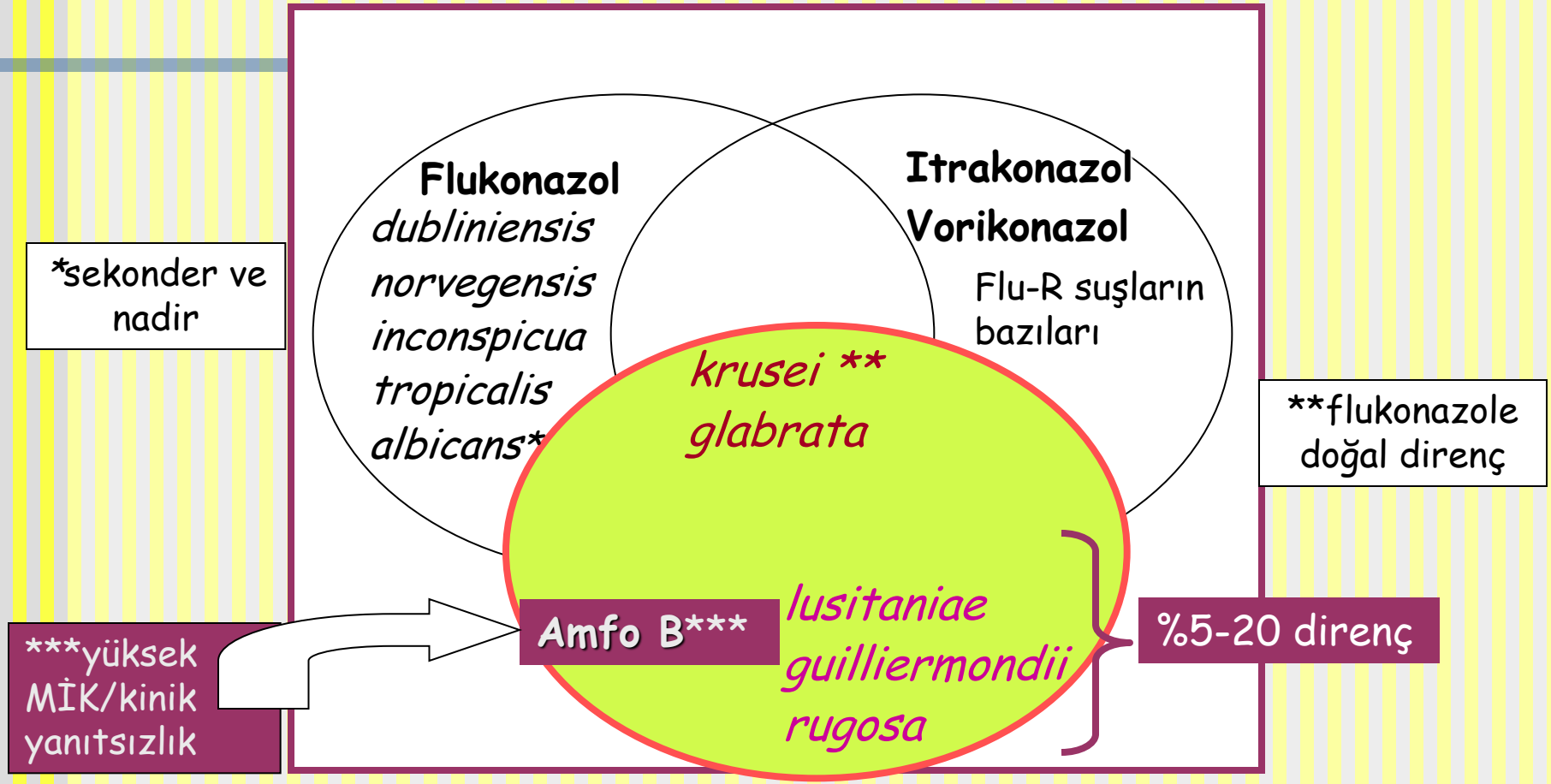
ÖNERİLER

Direnç

VE

Candida

AMB, Azol - Candida



Arikan et al. JCM 2002; 40: 1406; Martinez et al. JCM 2002; 40: 3135; Yoon et al. AAC 1999; 43: 836; Baily et al. CID 1997; 25: 161; Moran et al. AAC 1997; 41: 617; Sandven et al. AAC 1997; 41: 1375; Stevens et al. DMID 1996; 26: 145; Morgan et al. AAC 1998; 42: 1819; Krcymery & Barnes. J Hosp Infect 2002; 50: 243; Favel et al. JAC 1999; 43: 227

Echinocandin and Triazole Antifungal Susceptibility Profiles for Clinical Opportunistic Yeast and Mold Isolates Collected from 2010 to 2011: Application of New CLSI Clinical Breakpoints and Epidemiological Cutoff Values for Characterization of Geographic and Temporal Trends of Antifungal Resistance

JCM 2013; 51: 2571

Michael A. Pfaller, Shawn A. Messer, Leah N. Woosley, Ronald N. Jones, Mariana Castanheira
JMI Laboratories, North Liberty, Iowa, USA

SENTRY Antimicrobial Surveillance Program

34 countries, 98 centers
3418 strains
(2010-2011)

Low rates of triazole and echinocandin resistance
C. glabrata

Azol, Kandin - Candida

(Sensititre Yeast One)

Clin Microbiol Infect 2014; **20**: 698–705

Candida species distribution and antifungal susceptibility testing according to European Committee on Antimicrobial Susceptibility Testing and new vs. old Clinical and Laboratory Standards Institute clinical breakpoints: a 6-year prospective candidaemia survey from the fungal infection network of Switzerland

C. Orasch[1], O. Marchetti[1], J. Garbino[2], J. Schrenzel[3], S. Zimmerli[4], K. Mühlethaler[4], G. Pfyffer[5], C. Ruef[6], J. Fehr[6], R. Zbinden[7], T. Calandra[1], J. Bille[8] and the Fungal Infection Network of Switzerland (FUNGINOS)*

(*C. albicans*, *C. glabrata*, *C. tropicalis* and *C. parapsilosis*) represented >90% of all CBIs. *In vitro* resistance to fluconazole, voriconazole and caspofungin was rare among *C. albicans*, but an increase of non-susceptibile isolates was observed among *C. tropicalis*/*C. parapsilosis* for the azoles and *C. glabrata*/*C. krusei* for caspofungin according to EUCAST and new CLSI breakpoints compared with old CLSI breakpoints.

Using the revised breakpoints: Increase in azole-R C. tropicalis/ C.parapsilosis and caspofungin-R C. glabrata/C. krusei

Azol, Kandin - Candida

Antifungal susceptibility patterns of a global collection of fungal isolates: results of the SENTRY Antifungal Surveillance Program (2013)

Mariana Castanheira [a,*], Shawn A. Messer [a], Paul R. Rhomberg [a], Michael A. Pfaller [a,b]

Diagnostic Microbiology and Infectious Disease 85 (2016) 200–204

1846 suş (31 ülke)

C. glabrata, Flukonazol direnci: % 11.9

C. tropicalis, Flukonazol direnci: % 11.6

Candida (genel), Kandin direnci: % 0 – 2.8

Antifungal susceptibility patterns of a global collection of fungal isolates: results of the SENTRY Antifungal Surveillance Program (2013)

Mariana Castanheira [a,*], Shawn A. Messer [a], Paul R. Rhomberg [a], Michael A. Pfaller [a,b]

Diagnostic Microbiology and Infectious Disease 85 (2016) 200–204

Table 2
Summary of FKS alterations detected in *Candida* spp. strains displaying echinocandin MIC values greater than ECV as part of the 2013 international surveillance program.

Organism	State and/or country	CLSI method (μg/mL; CLSI interpretation):[a]			1,3-β-D-glucan synthase mutations:			
		Anidulafungin	Caspofungin	Micafungin	*fks1* HS1	fks1 HS2	*fks2* HS1	*fks2* HS2
C. glabrata	Canada	1 (R)	0.5 (I)	0.5 (R)	WT	WT	F659 deletion	WT
C. glabrata	Germany	0.25 (I)	0.12 (S)	0.03 (S)	WT	WT	WT	WT
C. glabrata	Germany	0.5 (R)	0.5 (I)	0.06 (S)	WT	WT	D666E, K753Q	WT
C. glabrata	Germany	0.5 (R)	0.12 (S)	0.03 (S)	WT	WT	WT	WT
C. glabrata	Turkey	0.5 (R)	0.5 (I)	0.06 (S)	WT	WT	WT	WT
C. glabrata	Brazil	0.25 (I)	0.06 (S)	0.03 (S)	WT	WT	WT	WT
C. glabrata	France	2 (R)	1 (R)	0.5 (R)	WT	WT	S663P	WT
C. glabrata	NY, USA	1 (R)	1 (R)	0.12 (I)	WT	WT	WT	WT
C. glabrata	NY, USA	0.25 (I)	0.12 (S)	0.03 (S)	WT	WT	WT	WT
C. glabrata	Australia	0.12 (S)	0.06 (S)	0.06 (S)	WT	WT	WT	WT
C. glabrata	Australia	0.25 (I)	0.06 (S)	0.015 (S)	WT	WT	WT	WT
C. guilliermondii	Belgium	4 (I)	0.5 (S)	1 (S)	WT	WT	WT	WT
C. guilliermondii	Argentina						VT	WT
C. tropicalis	IN, USA						IT	NT
C. tropicalis	CA, USA						IT	NT
C. tropicalis	Spain						IT	NT
C. tropicalis	Czech Repu						IT	NT
C. pelliculosa[b]	China						IT	NT

S = susceptible; I = intermediate; R
[a] According to the MS7-S4 docume
[b] Results were compared to those o

C. glabrata n=11

A total of 11 *C. glabrata* strains displayed echinocandin MIC values greater than the ECV, and amino acid alterations were detected in 3 (1.2%) isolates and were all in the *fks*2 HS1 (F659 deletion, D666E/K753Q, and S663P). Eight (72.7%) of the isolates screened displayed no *fks* mutations, and 7 of those had MIC values within 1–2 dilutions of the ECV for the echinocandins; however, 1 isolate displaying MIC values of 1 μg/mL for anidulafungin and caspofungin (MIC was confirmed) carried no mutations in the HS of *fks* genes.

(Türkiye, n=81)

Azol, C. glabrata Hacettepe Üniv.

Değişen sınır değerler ile değişen duyarlılık kategorileri (CLSI MD ve DD ile)

Klinik *Candida glabrata* İzolatlarında Flukonazol ve Vorikonazol Duyarlılığının Saptanmasında Mikrodilüsyon ve Disk Difüzyon Yöntemlerinin Karşılaştırılması ve Yeni CLSI Direnç Sınır Değerleri ile Duyarlılık Sonuçlarındaki Değişimin Belirlenmesi

Gülşen HAZIROLAN[1], Zeynep SARIBAŞ[2], Sevtap ARIKAN AKDAĞLI[2]

Tablo IV. Önceki ve yeni CLSI direnç sınır değerlerine göre flukonazol mikrodilüsyon ve disk difüzyon test sonuçları (%) (n= 70)

MİKRODİLÜSYON (24 saat)		Önceki CLSI			DİSK DİFÜZYON (24 saat)		Önceki CLSI		
		H	DBD	D			H	DBD	D
Yeni CLSI	DBD	94.3	5.7	-	Yeni CLSI	DBD	81.4	5.7	-
	D	-	-	-		D	-	-	12.9
MİKRODİLÜSYON *(48 saat)*		**Önceki CLSI**			**DİSK DİFÜZYON *(48 saat)***		**Önceki CLSI**		
		H	DBD	D			H	DBD	D
Yeni CLSI	DBD	80	15.7	-	Yeni CLSI	DBD	68.6	15.7	-
	D	-	-	4.3		D	-	-	15.7

H: Duyarlı; DBD: Doza bağlı duyarlı; D: Dirençli.

Mikrobiyol Bul 2016; 50(3): 428-437

Kan k. izolatları (n=361; 1999-2014)

Hacettepe Üniv.

CLSI M27-A3

	Önceki CBP	%	Şimdiki CBP
FLU			
C. glabrata, S-DD*	40		97
C. parapsilosis, R	1.8		8.8
C. albicans, 1 suş	(S-DD → R)		
VOR			
C. parapsilosis, S-DD	0		5.3

(*duyarlı kategorisinin kaldırılmış olması nedeniyle)

Azol, Candida YBÜleri kan k. izolatları n=140

Yeni sınır değerler ile duyarlılık kategorileri

Candida Türlerinin Triazol Antifungal Duyarlılık Profilleri: Antifungal Direncin Belirlenmesinde Yeni CLSI Türe Özgü Klinik Direnç Sınır Değerleri ve Epidemiyolojik Eşik Değerlerinin Uygulanması*

.....

Buna göre, 5 *Candida* izolatı (3 *C.albicans*, 1 *C.parapsilosis* ve 1 *C.glabrata*) flukonazole dirençli; birer *C.lusitaniae*, *C.dubliniensis* ve *C.kefyr* izolatı ise vahşi olmayan tip olarak saptanmıştır. Ayrıca 4 *Candida* izolatı (2 *C.albicans*, ve 2 *C.tropicalis*) vorikonazole dirençli ve 9 *Candida* izolatı (5 *C.glabrata*, 3 *C.lusitaniae*, ve 1 *C.kefyr*) vahşi olmayan tip olarak değerlendirilmiştir.

Nilgün KARABIÇAK, Nihal ALEM

Mikrobiyol Bul 2016; 50(1): 122-132

Direnç

VE

Aspergillus

Epidemiology and molecular mechanisms of antifungal resistance in *Candida* and *Aspergillus*

Sarah Santos Gonçalves,[1] Ana Carolina Remondi Souza,[1] Anuradha Chowdhary,[2] Jacques F. Meis[3,4] and Arnaldo Lopes Colombo[1]

Mycoses, 2016, **59**, 198–219

Table 3 Primary resistance among *Aspergillus* species.

Species	Invasive disease	Resistance profile	Section	References
A. lentulus	Relatively common	Primary resistance to AMB, azoles and varied resistance to CFG	*Fumigati*	[48, 301–304]
A. udagawae	Rare	Primary resistance to AMB and VRC	*Fumigati*	[66, 301, 302, 305, 306]
N. pseudofisheri	Rare	Varied susceptibility to AMB and lower susceptibility to azoles	*Fumigati*	[48, 302, 307]
A. fumigatiaffinis	Not reported	Primary resistance to AMB and lower resistance to azoles	*Fumigati*	[49]
A. viridinutans	Rare	Lower susceptibility to AMB and azoles	*Fumigati*	[48, 308]
A. flavus	Relatively common	Primary resistance to AMB and varied susceptibility to CFG	*Flavi*	[54, 66, 302, 309–313]
A. allilaceus	Relatively common	Lower susceptibility to AMB and CFG	*Flavi*	[302, 314–317]
A. terreus	Relatively common	Primary resistance to AMB	*Terrei*	[66,276,280,318–321]
A. alabamensis	Not reported	Primary resistance to AMB	*Terrei*	[322]
A. niger	Rare	Varied and lower susceptibility to azoles	*Nigri*	[60,310,323–325]
A. calidoustus	Rare	Primary resistance to AMB and azoles and varied susceptibility to CFG	*Ustis*	[77,302,326,327]
A. versicolor	Rare	Varied susceptibility to AMB and lower susceptibility to azoles	*Nidulantes*	[302,325,328]
A. sydowii	Rare	Varied susceptibility to AMB and lower susceptibility to azoles	*Nidulantes*	[60,302,328]

AMB, amphotericin B; CFG, caspofungin; IA, invasive aspergillosis; VRC, voriconazole.

Medical Mycology
2008, 1–7, iFirst article

informa
healthcare

Comparative *in vitro* activities of posaconazole, voriconazole, itraconazole, and amphotericin B against *Aspergillus* and *Rhizopus*, and synergy testing for *Rhizopus*

SEVTAP ARIKAN*, BANU SANCAK*, SEHNAZ ALP*, GULSEN HASCELIK* & PAUL MCNICHOLAS†

Table 1 MICs of posaconazole, voriconazole, itraconazole, and amphotericin B against clinical *Aspergillus* and *Rhizopus* isolates.

Test isolates (number tested) Incubation time	Posaconazole CLSI microdilution		Posaconazole Etest		Voriconazole CLSI microdilution		Itraconazole CLSI microdilution		Amphotericin B CLSI microdilution	
	GM	Range	GM	Range	GM	Range	GM	Range	GM	Range
Aspergillus (Total, *n* =82)										
24 h	0.96	0.5–1	0.02	0.002–0.03	0.49	0.125–1	0.93	0.25–2	1.82	0.5–4
48h	1.01	0.5–2	0.02	0.0075–0.125	0.80	0.125–2	1.13	0.25–2	2.51	1–8
A. fumigatus (43)										
24 h	0.94	0.5–1	0.01	0.002–0.03	0.45	0.125–1	1	0.5–2	1.73	1–4
48 h	0.97	0.5–2	0.03	0.0075–0.125	0.72	0.125–2	1.21	0.5–2	2.39	2–8
A. flavus (29)										
24 h	1	1	0.02	0.0075–0.03	0.65	0.25–1	0.83	0.25–1	2.2	1–4
48 h	1.02	1–2	0.06	0.03–0.125	1	0.5–2	0.98	0.25–2	2.93	2–4
A. niger (7)										
24 h	0.91	0.5–1	0.01	0.002–0.03	0.30	0.125–0.5	0.91	0.5–2	1.21	0.5–2
48 h	1.22	1–2	0.07	0.06–0.125	0.67	0.25–1	1.35	0.5–2	1.81	1–2
A. terreus (2)										
24 h	–	1	–	0.0075–0.03	–	0.5	–	1	–	2
48 h	–	1	–	0.015–0.125	–	1	–	1	–	2–4
A. nidulans (1)										
24 h	–	1	–	0.03	–	0.125	–	1	–	2
48 h	–	1	–	0.125	–	0.25	–	1	–	2
R.oryzae (*n* =11)										
24 h	1.13	1–2	ND	ND	15.02	8 →8	2	2	2.57	2–4
48h	1.55	1–2	ND	ND	15.02	8 →8	3.75	2–8	3.53	2–8

GM, Geometric mean; ND, not determined.

1997: İlk itrakonazol-R Aspergillus fumigatus :Yüksek (≥16 µg/ml) MİK, klinik yanıtsızlık, destekleyen hayvan modeli sonuçları

Denning et al. JAC 1997, 40: 401; Denning et al. AAC 1997, 41:1364

JOURNAL OF CLINICAL MICROBIOLOGY, July 2002, p. 2648–2650 Vol. 40, No. 7
0095-1137/02/$04.00+0 DOI: 10.1128/JCM.40.7.2648–2650.2002

Nationwide Survey of In Vitro Activities of Itraconazole and Voriconazole against Clinical *Aspergillus fumigatus* Isolates Cultured between 1945 and 1998

Paul E. Verweij,[1]* Debbie T. A. Te Dorsthorst,[1,2] Anthonius J. M. M. Rijs,[1] Hilly G. De Vries-Hospers,[3] Jacques F. G. M. Meis,[2] and the Dutch Interuniversity Working Party for Invasive Mycoses

The isolates in a collection of 170 *Aspergillus fumigatus* isolates recovered from 114 patients and 21 different medical centers in The Netherlands over a period of 53 years were tested for the presence of resistance to itraconazole and voriconazole according to the guidelines of NCCLS document M38-P and by the E-test. Three isolates were highly resistant to itraconazole, and voriconazole MICs were low for all isolates.

170 A. fumigatus

Çok merkezli, Hollanda

53 yıl, 1945-1998

MİK-1

- 3 izolatta itra MİK: 64
- Yüksek vori MİK'i olan suş yok

TABLE 1. Comparison of itraconazole and voriconazole MICs for 170 *A. fumigatus* isolates

Antifungal agent	Test method[a]	MIC (μg/ml)			
		Geometric mean	Range	50%	90%
Itraconazole	Broth micro (24 h)	1	0.5–64	1	1
	Broth micro (48 h)	1	0.5–64	1	1
	Etest (24 h)	0.6	0.03–64	0.5	0.75
	Etest (48 h)	0.7	0.13–64	0.5	0.75
Voriconazole	Broth micro (24 h)	0.17	0.06–0.5	0.13	0.25
	Broth micro (48 h)	0.25	0.06–1	0.25	0.5

PLoS Medicine November 2008 | Volume 5 | Issue 11 | e219

Emergence of Azole Resistance in *Aspergillus fumigatus* and Spread of a Single Resistance Mechanism

-I

Eveline Snelders[1,2], Henrich A. L. van der Lee[1,2], Judith Kuijpers[1,2], Anthonius J. M. M. Rijs[1,2], János Varga[3,4], Robert A. Samson[3], Emilia Mellado[5], A. Rogier T. Donders[6], Willem J. G. Melchers[1,2], Paul E. Verweij[1,2*]

ITRA DİRENCİ
1994-2007 izolatları
n=1912
Hollanda, tek merkez
Tarama testinde 8 µg/ml itra varlığında üreme,
MİK: ≥4 µg/ml

GENOTİPLENDİRME ve DİRENÇ EPİDEMİYOLOJİSİ ÇALIŞMALARI

n=464
Çok merkez; Hollanda ve ayrıca 6 Avrupa ülkesi

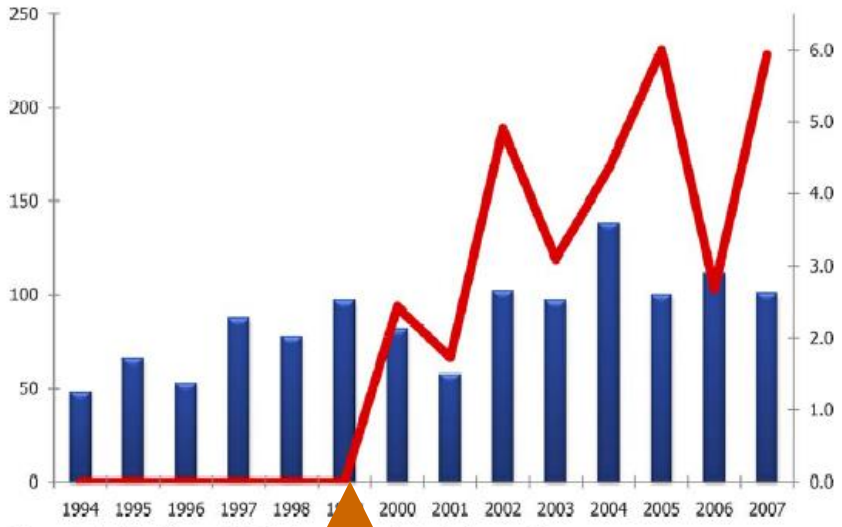


Figure 1. Epidemiology of ITZ Resistanc in the *A. fumigatus* Isolates

Blue bars represent the number of patie s with a positive *A. fumigatus* culture (left *y*-axis) and the red line represents the percentage of those patients with an ITZ+ isolate (right *y*-axis). The *x*-axis is the year.

doi:10.1371/

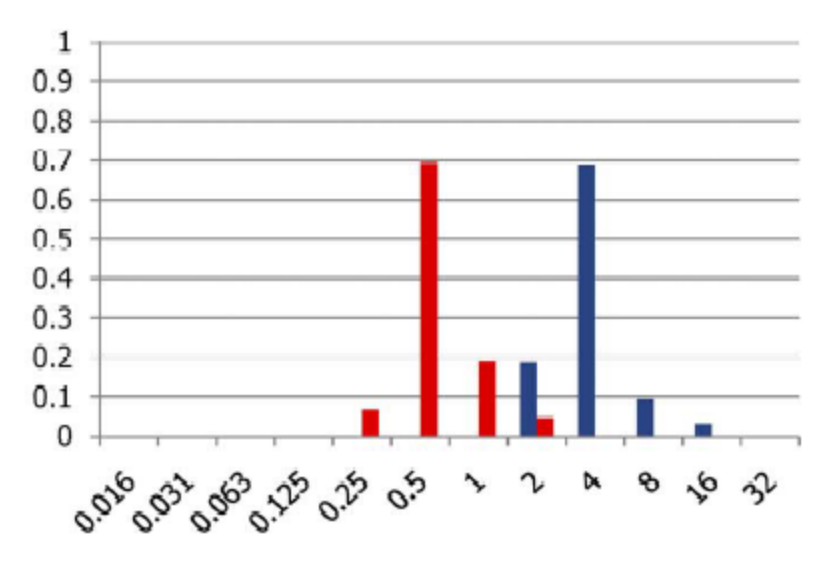
Itra R oranı: %1.7-6

1999'dan sonraki yıllarda izole edilen suşlarda itra direnci ortaya çıkıyor ve artarak devam ediyor.

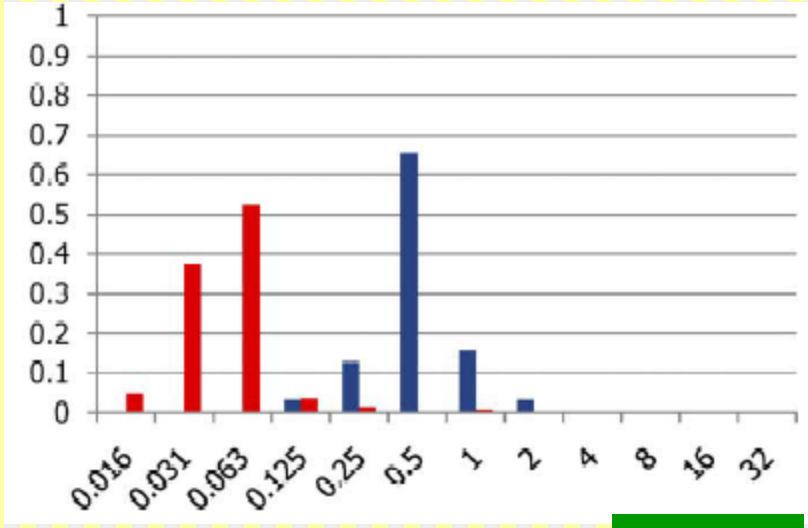
PLoS Medicine November 2008 | Volume 5 | Issue 11 | e219

Emergence of Azole Resistance in *Aspergillus fumigatus* and Spread of a Single Resistance Mechanism -II

Eveline Snelders[1,2], Henrich A. L. van der Lee[1,2], Judith Kuijpers[1,2], Anthonius J. M. M. Rijs[1,2], János Varga[3,4], Robert A. Samson[3], Emilia Mellado[5], A. Rogier T. Donders[6], Willem J. G. Melchers[1,2], Paul E. Verweij[1,2*]



VORİ



POSA

Itra MİK'i yüksek suşların (lacivert) vori ve posa MİK'leri de göreceli olarak yüksek

PLoS Medicine November 2008 | Volume 5 | Issue 11 | e219

Emergence of Azole Resistance in *Aspergillus fumigatus* and Spread of a Single Resistance Mechanism

-III

Eveline Snelders[1,2], Henrich A. L. van der Lee[1,2], Judith Kuijpers[1,2], Anthonius J. M. M. Rijs[1,2], János Varga[3,4], Robert A. Samson[3], Emilia Mellado[5], A. Rogier T. Donders[6], Willem J. G. Melchers[1,2], Paul E. Verweij[1,2*]

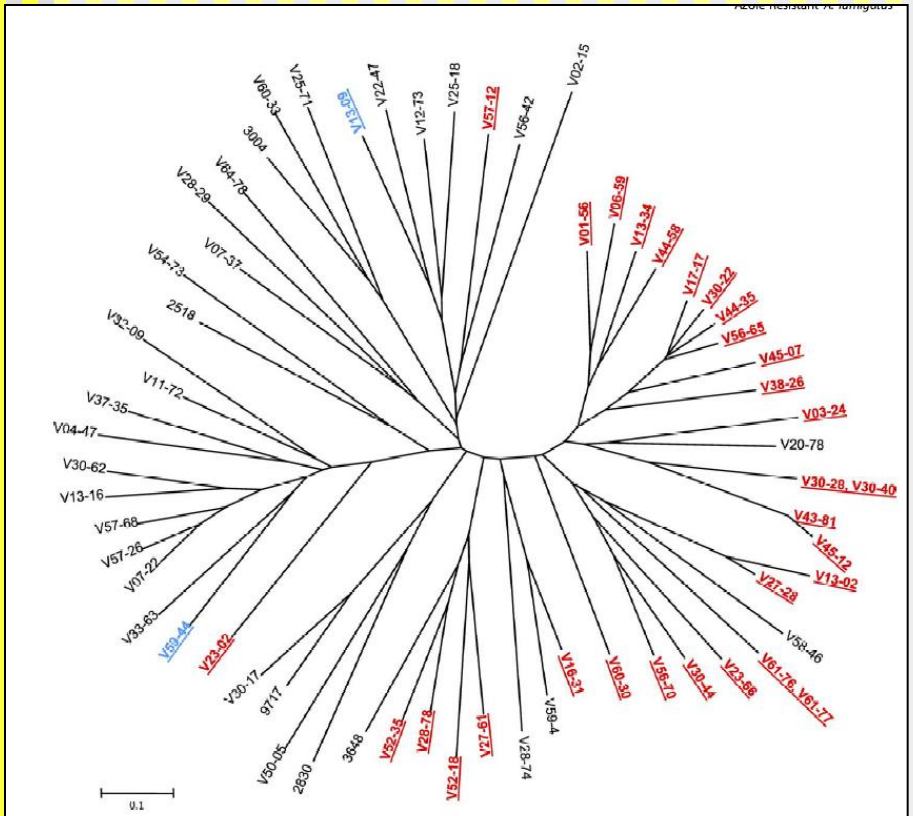


Figure 3. Genotypic Relatedness of 32 ITZ+ *A. fumigatus* Isolates and 32 ITZ− Controls

The numbers are the identification numbers of the individual isolates. The ITZ+ *A. fumigatus* with the L98H substitution and a tandem repeat in the promoter region of the *cyp51A* gene are underlined and printed in red. The ITZ+ isolates with other or unknown resistance mechanisms are underlined and printed in blue. The ITZ− isolates are printed in black.

doi:10.1371/journal.pmed.0050219.g003

Itra-R suşların genotipik ilişkileri:

Kırmızı: Cyp51A geninde L98H değişimi ile birlikte genin promoter bölgesinde 'tandem repeat' olan Itra-R suşlar

Suşların çoğunluğu. Bu suşlar, genotipik olarak birbiriyle ilişkili. Bir kısmı, daha önce hiç azol almamış hastalardan…

Aspergillus fumigatus suşlarında sekonder azol direnci

A.B.D.
Almanya
Avusturya
Avustralya
Belçika
Brezilya
Çek Cumhuriyeti
Çin
Danimarka
Fransa
Hindistan

Hollanda
İngiltere
İran
İspanya
İsveç
İsviçre
İtalya
Japonya
Kanada
Portekiz
Türkiye

Hematolojik malignansi / kistik fibroz / çevre örneklemesi

Vermeulen et al. Curr Opin Infect Dis 2013; 26: 493; Bueid et al. JAC 2010; 65: 2116; Snelders et al. PLoS Med 2008; 5: e219; van der Linden et al. CID 2013; 57: 513; Mortensen et al. JCM 2011; 49: 2243; Burgel et al. AAC 2012; 56: 869; van der Linden et al. Emerg Infect Dis 2011; 17: 1846; Morio et al. JAC 2012; 67: 1870; Alanio et al. JAC 2011; 66: 371; Escribano et al. AAC 2013; 57: 2815; Chowdhary et al. JAC 2012; 67: 362; Fischer et al. JAC 2014; 69: 1533

Worldwide map of azole resistance in Aspergillus fumigatus. Red highlighted countries have reported azole resistance.

Meis et al. Philos Trans R Soc Lond B Biol Sci, in press. Clinical implications of globally emerging azole resistance in A. fumigatus

A. fumigatus - itrakonazol direnç oranı

ÜLKE	SUŞUN KAYNAĞI	R %	REFERANS
Danimarka	Klinik	4.5	Mortensen JCM 2011
Fransa	Klinik	0.85-4.6	Alanio JAC 2011; Burgel AAC 2012;
Hindistan	Klinik	1.9	Chowdhary JAC 2012
Hollanda	Klinik	5.3-38	Van der Linden Emerg Infect Dis 2011,; van Ingen JAC 2015
İngiltere	Klinik	5	Howard Emerg Infect Dis 2009
Japonya	Klinik	7	Tashiro AAC 2012
Danimarka	Çevre	5.8-14.2	Mortensen AAC 2010
Hollanda	Çevre	12.2	Snelders Appl &Env Microbiol 2009
İran	Çevre	3.3	Badali Mycoses 2013

First determination of azole resistance in *Aspergillus fumigatus* strains carrying the TR34/L98H mutations in Turkey

Gülşah Ece Özmerdiven [a], Seçil Ak [b], Beyza Ener [a,*], Harun Ağca [a], Burcu Dalyan Cilo [a], Berrin Tunca [b], Halis Akalın [c]

J Infect Chemother 21 (2015) 581–586

exhibited good activity against all isolates whereas the azoles were resistant. Sequence analysis of the promoter region and *CYP51A* gene indicated the presence of TR34/L98H in 86.8% (n = 66) of isolates. This initial analysis of the resistance mechanism of *A. fumigatus* from Turkey revealed a common TR34/L98H mutation in the *cyp51A* gene.

Olgular azol-R *Aspergillus* suşlarını ne yolla alıyor olabilir? [1]

De novo acquisition of resistant strains from the environment

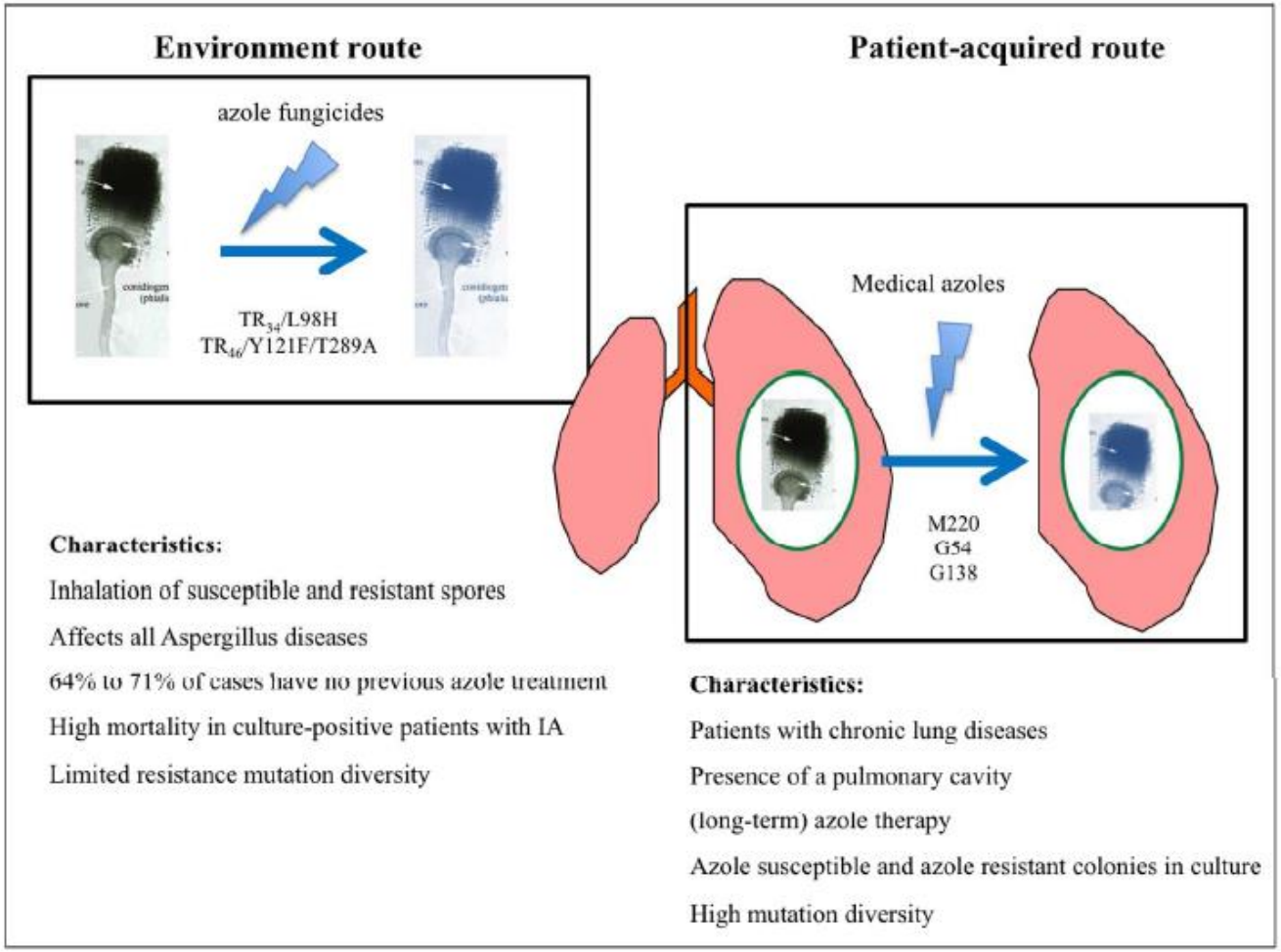
SOURCE: Agricultural use of azole compounds (metcunazole, tebuconazole,…; 25 azole fungicides in total)

Selection in the individual patient during azole therapy
- - Selection of resistance *in vivo*

RISK FACTORS : Azole exposure, Chronic *Aspergillus* inf.s, aspergilloma (high fungal burden)

Howard & Arendrup. Med Mycol 2011;49 (Suppl. 1): S90; Bowyer et al. Curr Infect Dis Rep. 2011;13: 485; Camps et al. AAC 2012; 56: 10; Arendrup et al. PLoS One 2010; 5: e10080

Olgular azol-R *Aspergillus* suşlarını ne yolla alıyor olabilir? [2]



Characteristics of azole resistant Aspergillus infections by the environmental- and patient route.

Meis et al. Philos Trans R Soc Lond B Biol Sci, in press. Clinical implications of globally emerging azole resistance in A. fumigatus

Hangi triazole direnç ?

TR* / cyp51A geninde nokta mutasyon sonucu a.a. değişikliği	DİRENÇ
TR34/L98H	Tüm triazoller
TR46/Y121F/T289A	VOR, ISV (ITR ve POS MİK'lerine etkisi değişken)
G54	ITR, POS
M220	ITR, POS

A-Alanin
F-Fenilalanin
G-Glisin
H-Histidin
L-Lösin
M-Metionin
T-Treonin
Y-Tirozin

*CYP51A geninin promoter kısmında 34 ya da 46 bp'lik bir diziden iki kopya ("tandem repeat") bulunması ve CYP51A ekspresyonunda artış

Meis et al. Philos Trans R Soc Lond B Biol Sci, in press. Clinical implications of globally emerging azole resistance in A. fumigatus

Table 1. Common resistance mechanisms reported in the *cyp51A* gene of clinical and environmental *Aspergillus fumigatus*

Promotor tandem repeat (TR) insertion and Point Mutation	Country	Medical azoles affected	Reference
TR34/L98H	Netherlands, UK, Germany, Belgium, France, Spain, Italy, Austria, Denmark, Poland, Ireland China, USA, India, Japan, Colombia, Taiwan, Turkey, Kuwait, Iran, Pakistan, Australia, Tanzania	Itraconazole, voriconazole, posaconazole, isavuconazole	24,55,56,57,59,60, 62,63,64,65,66,67, 68,69,70,71,72,73,74,76
TR46/Y121F/T289A	Netherlands, UK, Germany, Belgium, France, Spain, Denmark, Ireland China, USA, India, Japan, Colombia, Tanzania	Itraconazole (variable), voriconazole, posaconazole (variable), isavuconazole	24,55,56,58,61, 62,75,76,77
TR53	Netherlands, Colombia	Itraconazole, voriconazole, posaconazole, isavuconazole	24,77
G54	Netherlands, UK, Germany, France, Spain, India, Romania, China, USA, Tanzania	Itraconazole, posaconazole	24
M220	Netherlands, UK, Germany, Belgium, France, Spain, China, USA	Itraconazole, posaconazole	24
Y121F	France	Voriconazole	92

Meis et al. Philos Trans R Soc Lond B Biol Sci, in press. Clinical implications of globally emerging azole resistance in A. fumigatus

Sunum Planı

Temel bilgiler

YÖNTEM ve DEĞERLENDİRME

DİRENÇ VARLIĞI / ORANI

ÖNERİLER

CID 2016:62 (15 February)

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

Clinical Infectious Diseases® 2016;63(4):433–42

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5,b] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

ESCMID-EFISG Aspergillus Guideline- Unpublished Preliminary

Recommendations for identification of species by molecular methods for prediction of primary AMB resistance

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Clinically relevant *Asp* isolate	Predict primary AMB resistance according to the species	Species ID by using β tubulin or calmodulin sequencing	B	III	Alastruey-Izquierdo AAC 2013 Blum AAC 2013 Colozza Intl J Antimicrob Agents 2012 Escribano CMI 2012 Baddley JCM 2009 Lass-Flörl Br J Haem 2005 Arikan Med Mycol 2008 Barchiesi JAC2013 (murine) Hadrich Med Mycol 2012 Shivaprakash DMID 2011 Arendrup EUCAST-AFST CMI 2012 Espinel-Ingroff AAC 2011	A.terreus A. flavus

ESCMID-EFISG Aspergillus Guideline-Unpublished

Intrinsic resistance – Antifungal regimen

Intention	Intervention	SoR	QoE	Comment
Change tx. if AMB MIC ≥1 mg/L.	Replace AMB with azole, if azole-S	B	II	
Treat *Aspergillus* disease due to:	Voriconazole	A	II	Avoid polyenes
A. terreus	Isavuconazole	A	II	
	Posaconazole	B	III	Avoid polyenes
	Itraconazole	B	III	Avoid polyenes
A. calidoustus	Lipid AMB	A	II	Avoid azoles
A. tubingensis (*A. niger* complex) *A. lentulus* (*A. fumigatus* complex)	Avoid azole monotherapy	C	III	No data: higher azole MICs are common but clinical impact unknown
A. alliaceus (*A. flavus* complex)	Avoid AmB	C	III	
A. niger complex	Avoid itra & isavu	B	III	MICs are in general 1 step higher compared to *A. fumigatus* for ISAV, POS and VCZ and 2 steps higher for ITZ but limited clinical data.
A. nidulans	Prefer VCZ	C	IIIa	Elevated AmB MICs, poor clinical responses in CGD

Azol direnci klinik yanıtsızlığa yol açan bağımsız bir risk faktörü müdür?

Direnç oranı ?

Primer tedavi seçeneğinin değiştirilmesi gerekliliği ?

Impact of azole resistance on Aspergillus guidelines

Georgiadou and Kontoyiannis Ann NY Acad Sci **2012**; 1272: 15-22

Table 1. Variability of azole resistance prevalence in *Aspergillus* isolates among medical centers and published studies: a multifactorial issue

Parameters
Patient referral patterns (acute versus chronic aspergillosis)
Selected versus random specimens
Time factors (recent versus older series)
Small collections of isolates (e.g., <100 isolates)
Differences in screening methods (microdilution versus plate method)
Exclusion of cryptic *Aspergillus* species
Rates using different denominators (patient versus isolates)
Different susceptibility methods and inocula
Different breakpoints[a] and definitions of resistance
Differences in geographic location of the center

Conclusions

Resistance of *Aspergillus* spp. to azoles might be on the rise; nevertheless, inferences are drawn from incomplete observational data, and it is rather early to consider that azole resistance is becoming a menacing worldwide phenomenon. A better understanding of the epidemiology and the biologic plausibility of resistance would assist in the development of better diagnostic strategies (probably PCR-based assays) for both prevention and treatment. Currently, we need better field studies but not necessarily modification of guidelines.

ECDC - Technical Report

European Centre for Disease Prevention and Control

Risk assessment on the impact of environmental usage of triazoles on the development and spread of resistance to medical triazoles in Aspergillus species

Stockholm: ECDC; **2013**

www.ecdc.europa.eu/en/publications/publications/risk-assessment-impact-environmental-usage-of-triazoles-on-aspergillus-spp-resistance-to-medical-triazoles.pdf

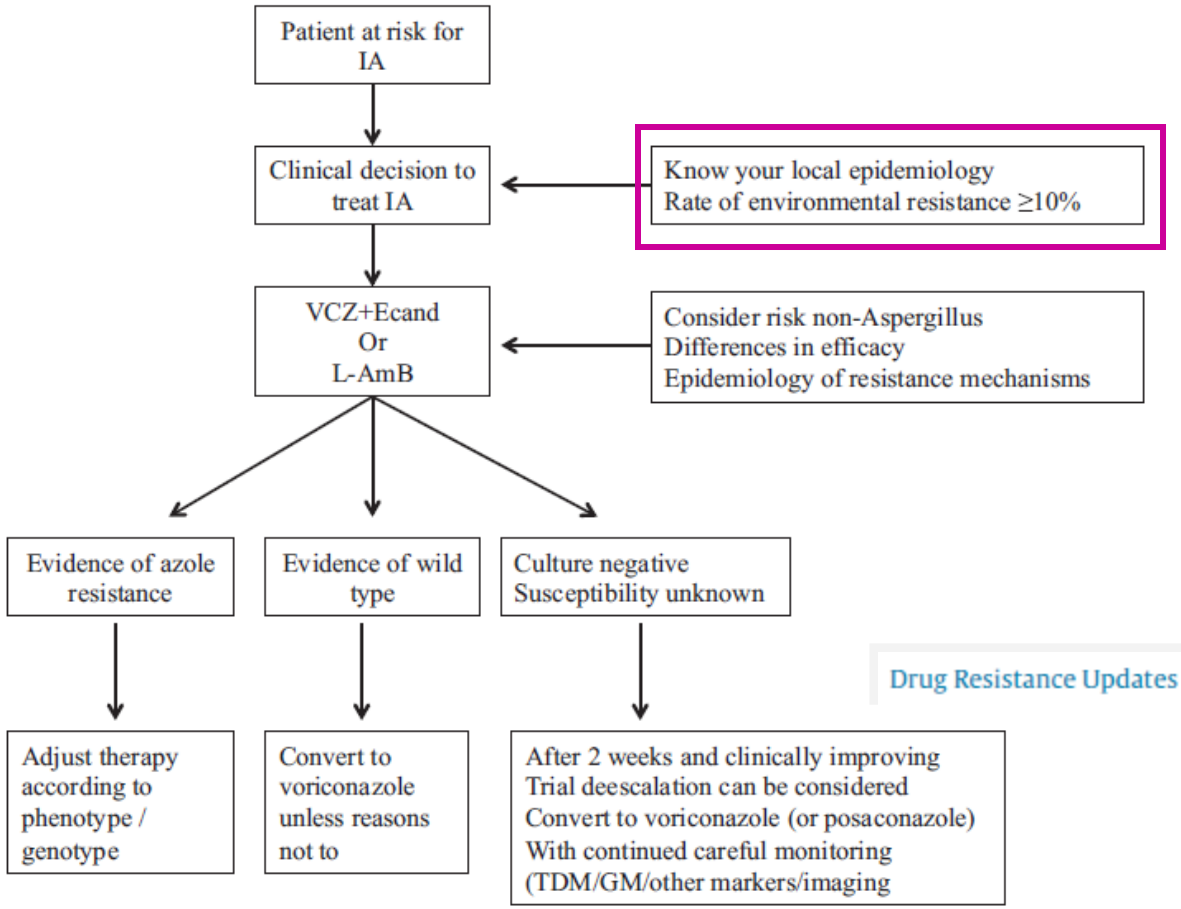
Direnç nasıl gelişiyor ?

"Çevre"de direnç: Klinik etki ? Ekonomik etki ?

("This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Niels Kleinkauf and Dominique Monnet. Contributing authors Niels Kleinkauf, Paul E. Verweij, Maiken C. Arendrup, Peter J. Donnelly, Manuel Cuenca-Estrella, Bart Fraaije, Willem J.G. Melchers, Niels Adriaenssens, Gert H.J. Kema, Andrew Ullmann, Paul Bowyer, David W. Denning This report was sent for consultation to the European Food Safety Authority - EFSA.")

International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*

Paul E. Verweij[a,*], Michelle Ananda-Rajah[b], David Andes[c], Maiken C. Arendrup[d], Roger J. Brüggemann[e], Anuradha Chowdhary[f], Oliver A. Cornely[g], David W. Denning[h], Andreas H. Groll[i], Koichi Izumikawa[j], Bart Jan Kullberg[k], Katrien Lagrou[l], Johan Maertens[m], Jacques F. Meis[a,n], Pippa Newton[h], Iain Page[h], Seyedmojtaba Seyedmousavi[a], Donald C. Sheppard[o], Claudio Viscoli[p], Adilia Warris[q], J. Peter Donnelly[r]



Drug Resistance Updates 21–22 (2015) 30–40

Fig. 3. Management of patients with clinical suspicion of IPA in regions with environmental resistance of ≥10%. IA, invasive aspergillosis; L-AmB, liposomal amphoptericin B, VCZ, voriconazole; Ecand, echinocandin; TDM, therapeutic drug monitoring; GM, galactomannan.

Azole resistance surveillance in *Aspergillus fumigatus*: beneficial or biased?

Paul E. Verweij[1,2]*, Pieter P. A. Lestrade[1], Willem J. G. Melchers[1,2] and Jacques F. Meis[2,3]

J Antimicrob Chemother 2016; **71**: 2079–2082

Table 1. Characteristics of three surveillance strategies for azole resistance

Surveillance strategy	Aim	Advantage	Disadvantage	Bias
Screening of unselected clinical *A. fumigatus* isolates	Trends in resistance frequency Trends in distribution of resistance mutations Detection of new resistance mutations	A substantial number of isolates may be screened Relatively straightforward to conduct	Includes isolates that are clinically not relevant or from colonized/ untreated patients May not correspond to resistance frequency in specific risk groups	Denominator bias Laboratory practice and procedure bias in multicentre design
Identify patients with IA based on a positive *Aspergillus* culture	Determine the frequency of resistance in patients with culture-positive IA	Provides a relatively high sample size, when patients are included independent of risk category	Includes only a minority of IA patients Variability in underlying diseases Variability in management/ sampling strategy	Case definition, case ascertainment and sampling bias Laboratory practice and procedure bias in multicentre design
Determine the frequency of IA within a cohort of patients	To determine the prevalence of azole resistance in a specific risk group	Gives an accurate indication of resistance prevalence Relatively uniform management and sampling strategy in single-centre design	Requires a substantial effort to evaluate and classify patients May take a long time to include a meaningful number of cases Variability in management/ sampling strategy in multicentre design	Case definition, case ascertainment and sampling bias Laboratory practice and procedure bias in multicentre design

Azole resistance surveillance in *Aspergillus fumigatus*: beneficial or biased?

Paul E. Verweij[1,2*], Pieter P. A. Lestrade[1], Willem J. G. Melchers[1,2] and Jacques F. Meis[2,3]

J Antimicrob Chemother 2016; **71**: 2079–2082

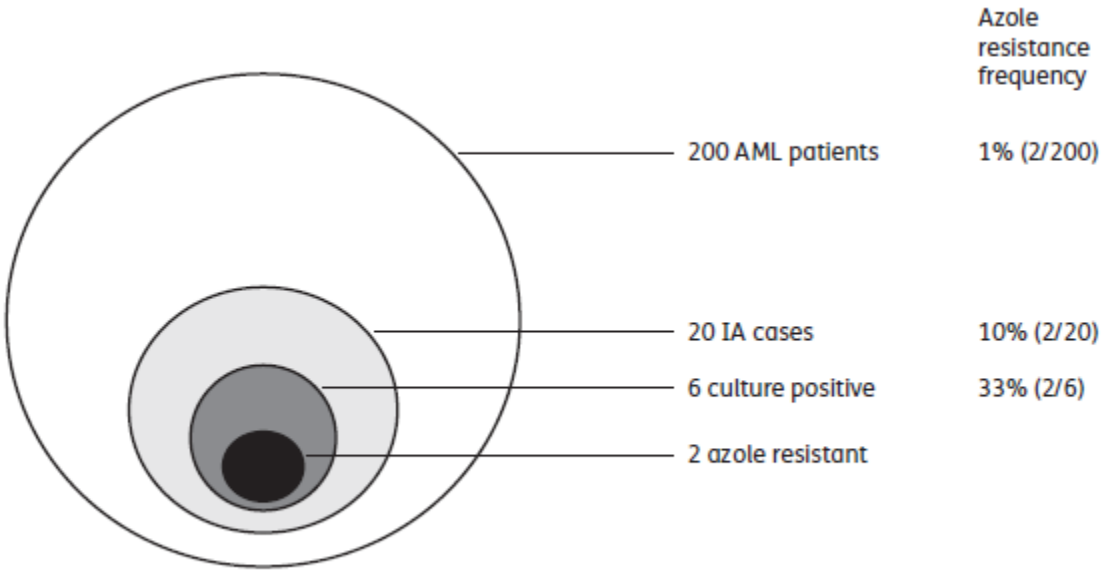


Figure 1. Impact of the denominator on the resistance frequency in azole resistance surveillance. Resistance rates are calculated for a theoretical population of 200 AML patients, with a 10% prevalence of IA and 33% culture positivity.

"…….**Azole resistance frequencies have been based on** screening of unselected A. fumigatus isolates, on the number of azole-resistant cases within a cohort of patients with a specific Aspergillus disease, or on analysis of patients within a specific risk group……."

SONUÇ ve ÖNERİLER

- Tanımlama: Primer direnç
- AFDT: Standart yöntem (endikasyonlar)
- Güncel direnç sınır değerleri; "ECV"
- Direnç oranı
- Multipl faktörler

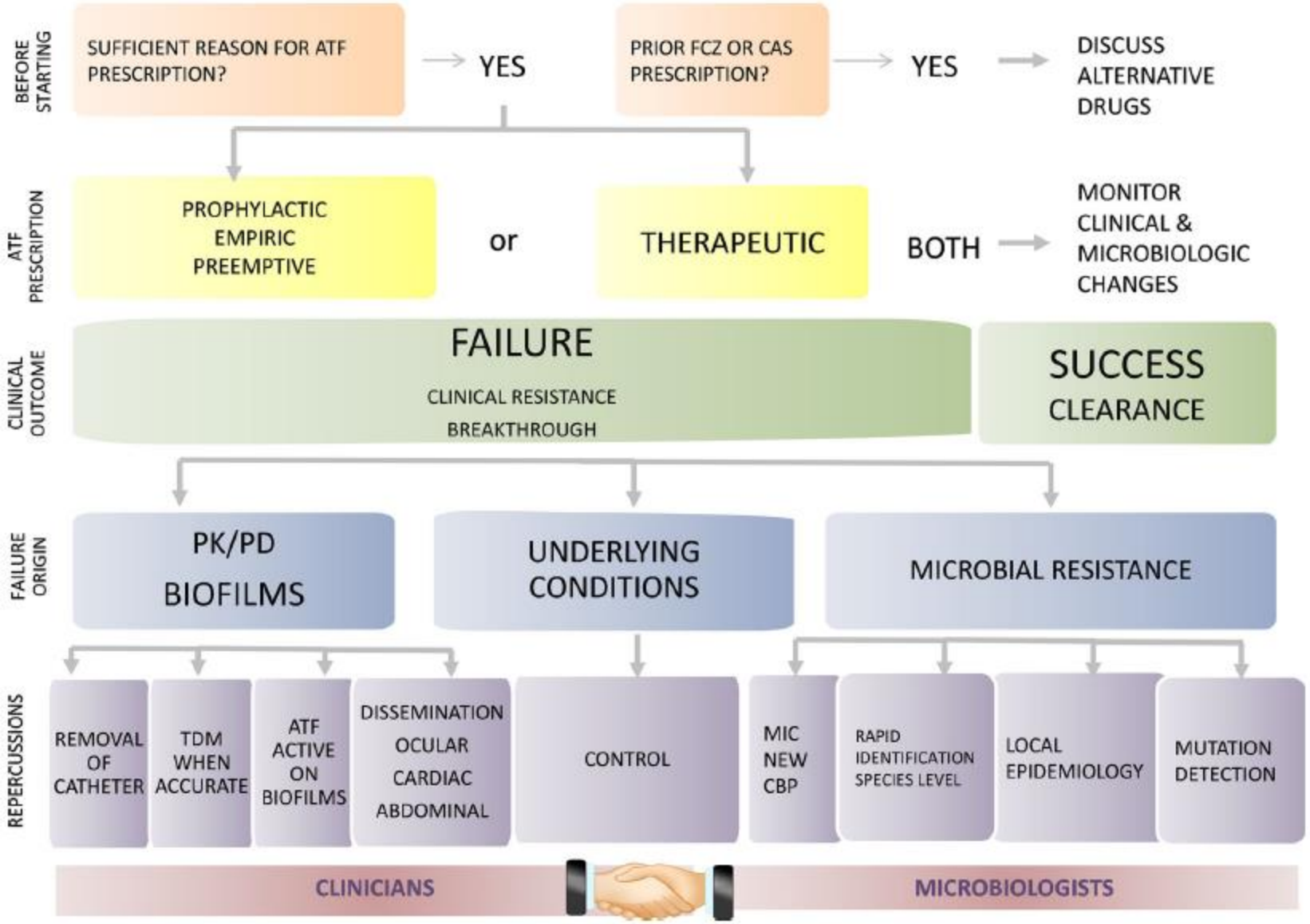


Fig. 3 Bedside strategy for circumventing antifungal drug resistance in 2014. *ATF* antifungal drug, *FCZ* fluconazole, *CAS* caspofungin, *PK/PD* pharmacokinetics and pharmacodynamics, *TDM* therapeutic drug monitoring, *MIC* minimal inhibitory concentration, *CBP* clinical breakpoint

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