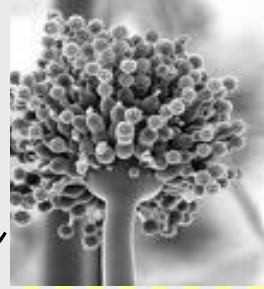
XIX. Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Kongresi

28-31 Mart 2018, Antalya



# Antifungal Direnç Ne Kadar Sorun?

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

# Sunum Planı

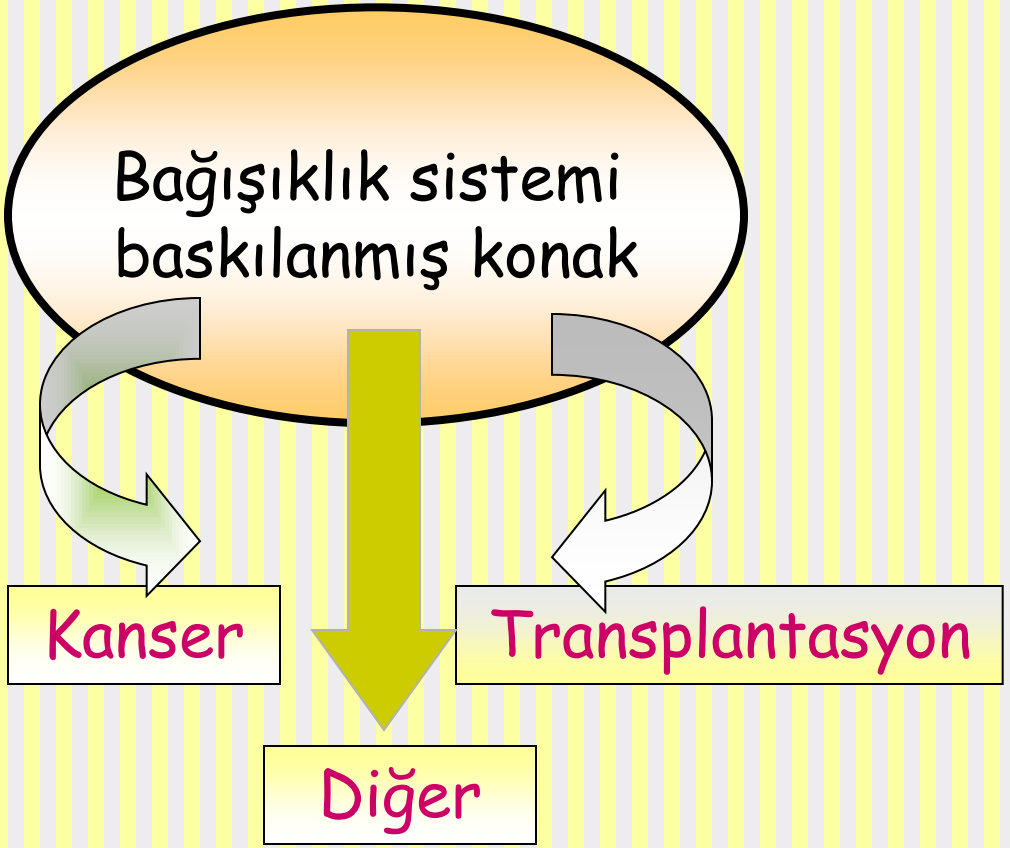
Temel bilgiler

YÖNTEM ve DEĞERLENDİRME

DİRENÇ VARLIĞI / ORANI

ÖNERİLER

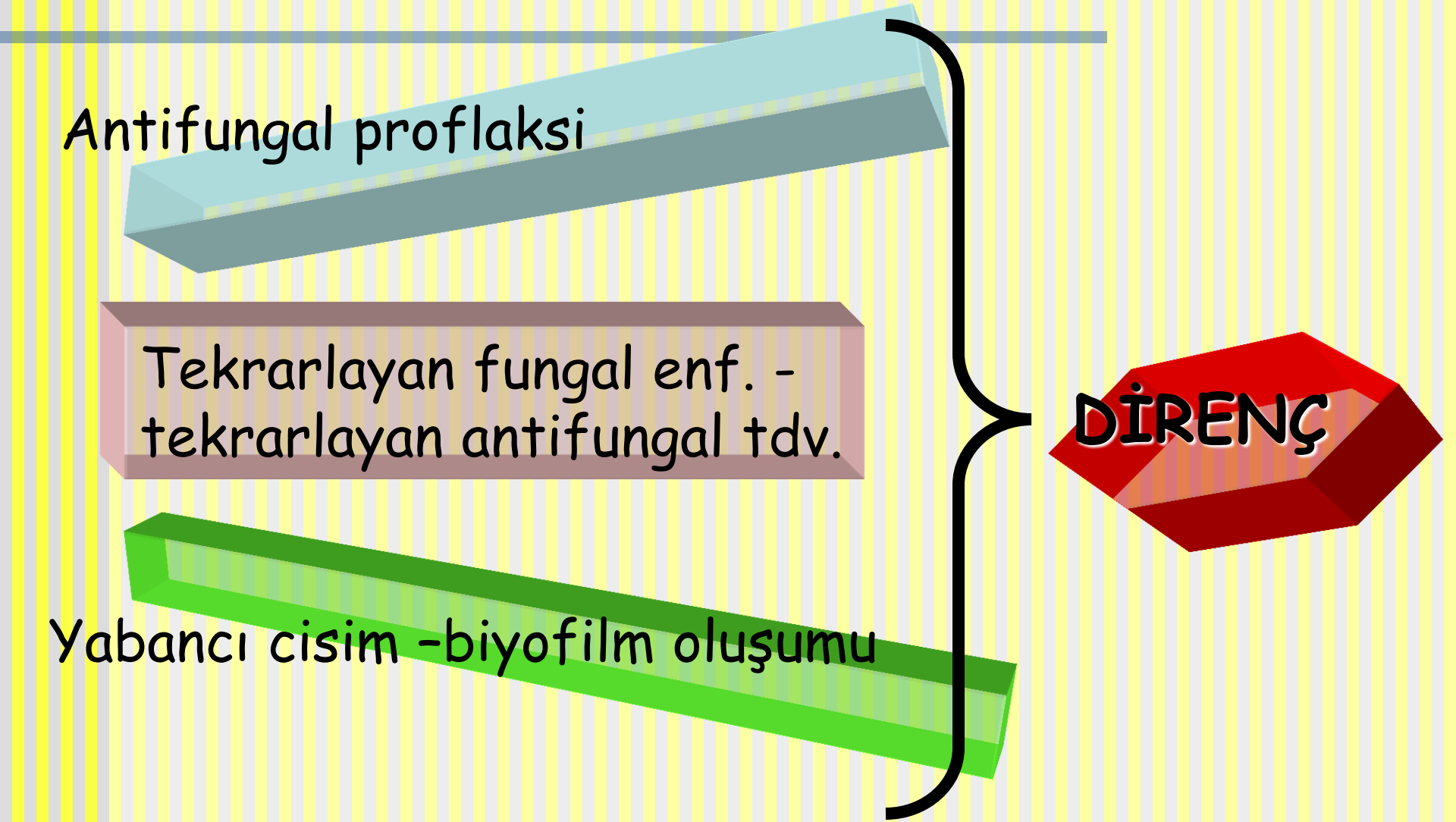
# Fırsatçı mantar enfeksiyonları: KONAK




- 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

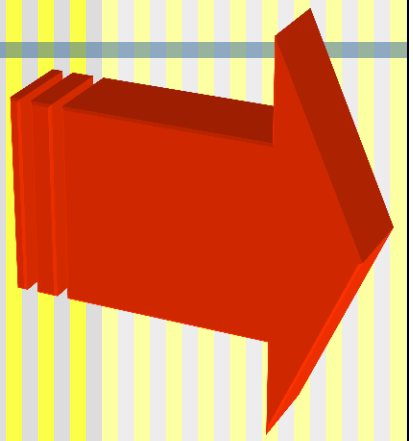
1970'ler
Ekonazol
Mikonazol (IV)

1980'ler
Ketokonazol
(po)

1990'lar
Flukonazol
Itrakonazol
Terbinafin
Lipid Amfo
bileşikleri

2000'ler
Kaspofungin
Vorikonazol

Mikafungin
Anidulafungin
Posakonazol
.....



**Candida ve Aspergillus**

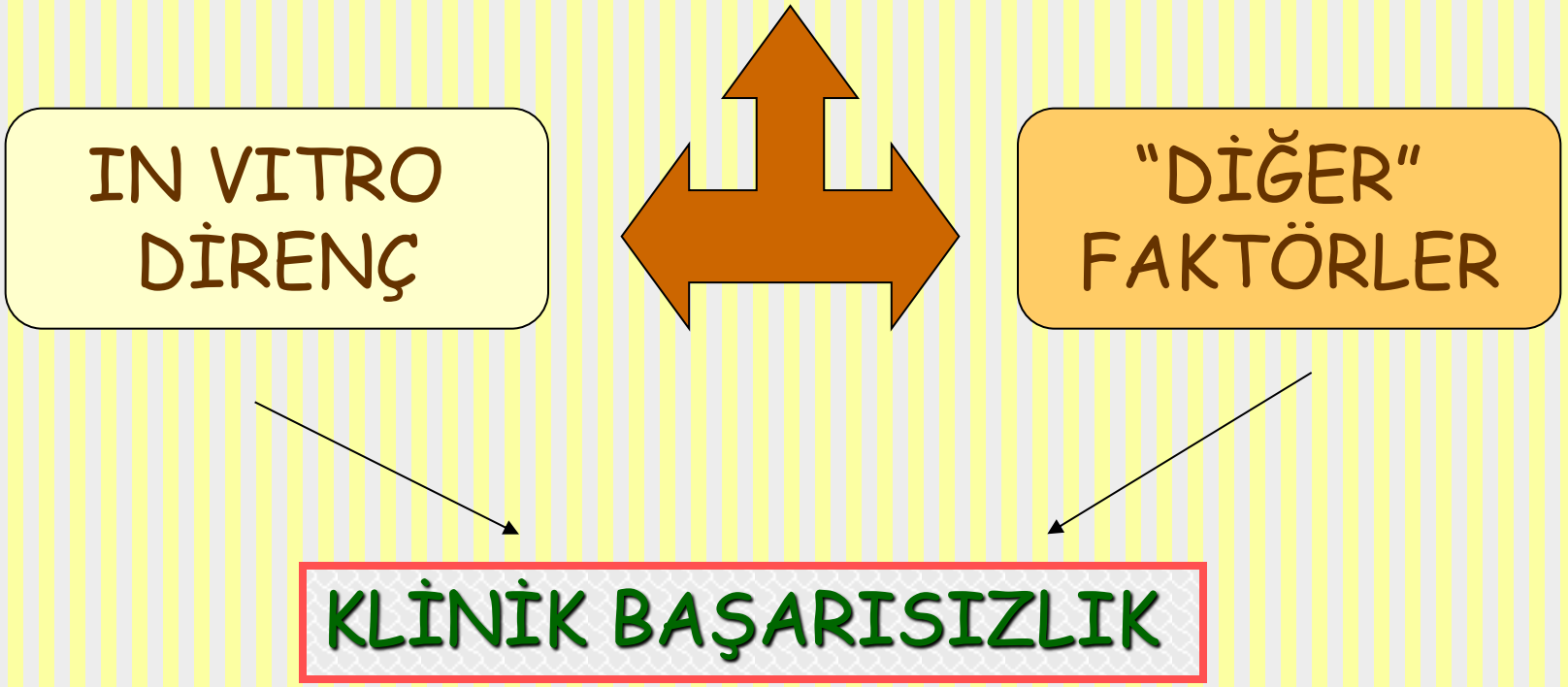
SUŞLARINDA

ANTİFUNGAL DİRENÇ

**Candida**
Ekinokandin
Multipl ilaç direnci

**Aspergillus**
Azol
Ekinokandin

# 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

# Antifungal direncin getirdiği sorunlar

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

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

# Primer ve Sekonder direnç

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


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

**TABLE 3.** Intrinsic susceptibility pattern for *Candida* species

**EUCAST breakpoints have been established for the common *Candida* species allowing classification if wild-type isolates into S, I and R categories. For the uncommon *Candida* species, breakpoints have not been established. For these species, an 'X' denotes that the MICs for the antifungal compound are elevated compared with those for *Candida albicans***

| | AMB | ECS | FCO | Comments |
|---|---|---|---|---|
| Common *Candida* species | | | | |
| *C. albicans* | S | S | S | |
| *C. dubliniensis* | S | S | S | Closely related to *C. albicans*; fluconazole resistance acquired more easily |
| *C. glabrata* | S | S | I | Efflux pumps often induced during azole therapy |
| *C. krusei* | S | S | R | |
| *C. parapsilosis* | S | I | S | |
| *C. tropicalis* | S | S | S | |
| Uncommon *Candida* species | | | | |
| *C. lusitaniae* | X | | | |
| *C. fermentati* | | X | | |
| *C. guilliermondii* | | X | X | |
| *C. metapsilosis* | | X | | Closely related to *C. parapsilosis* |
| *C. orthopsilosis* | | X | | Closely related to *C. parapsilosis* |
| *C. cifferrii* | | | X | |
| *C. inconspicua* | | | X | |
| *C. humicula* | | | X | |
| *C. lambica* | | | X | |
| *C. lipolytica* | | | X | |
| *C. norvegensis* | | | X | |
| *C. palmioleophila* | | | X | |
| *C. rugosa* | | | X | |
| *C. valida* | | | X | |
| *S. cerevisiae*[a] | | | X | Closely related to *C. glabrata* |

ECS: echinocandins; FCO: fluconazole.
[a]Anamorphic state is *C. robusta*.

**TABLE 2.** Intrinsic resistance (R) and variable (V) susceptibility in *Aspergillus*

| | AMB | Azoles | Echinocandins |
|---|---|---|---|
| *Aspergillus* section *fumigati* | | | |
| *A. fumigatiaffinis* | R | R | |
| *A. lentulus* | R | R | V |
| *N. pseudofischeri* | V | R | |
| *A. viridinutans* | R | R | |
| *N. udagawae* | R | R (vor) | |
| *A. terreus* (and *A. alabamensis*) | R | | |
| *A. flavus* | R | R | |
| *A. versicolor* (and *A. sydowi*) | R | V | |
| *A. calidoustus* | | R | V |
| *A. allilaceus* | V | | V |

Data compiled from [12–15].
Vor, Voriconazole.

# Sunum Planı

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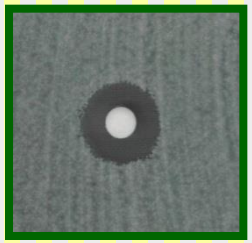
DİRENÇ VARLIĞI / ORANI

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 M60 | M27 ve M44; Kalite kontrol değerleri |
| CLSI M51-A | Dermatofit dışı küfler |



# Direncin in vitro saptanması: Antifungal duyarlılık testleri-II

EUCAST E.Dis 7.3.1 — Candida

15 Ocak 2017

EUCAST E.Dis 9.3.1 — Konidyum oluşturan küfler

15 Ocak 2017

DIN-58940-84

# Duyarlılık testlerinin rutin amaçlı uygulanma endikasyonları

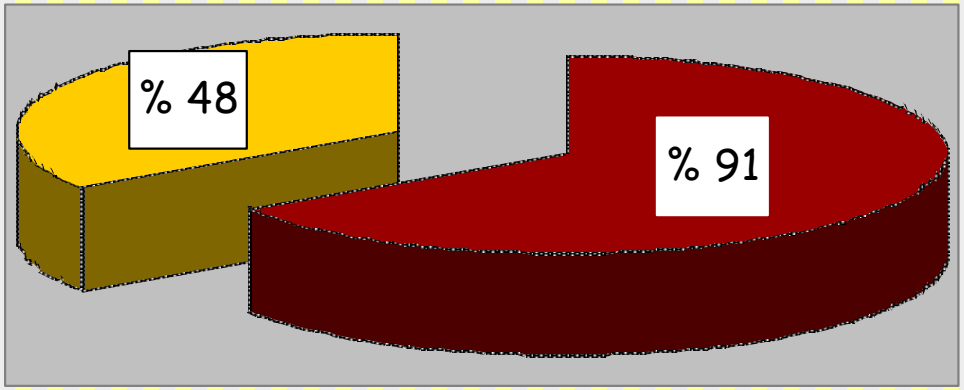
(Candida)

- 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

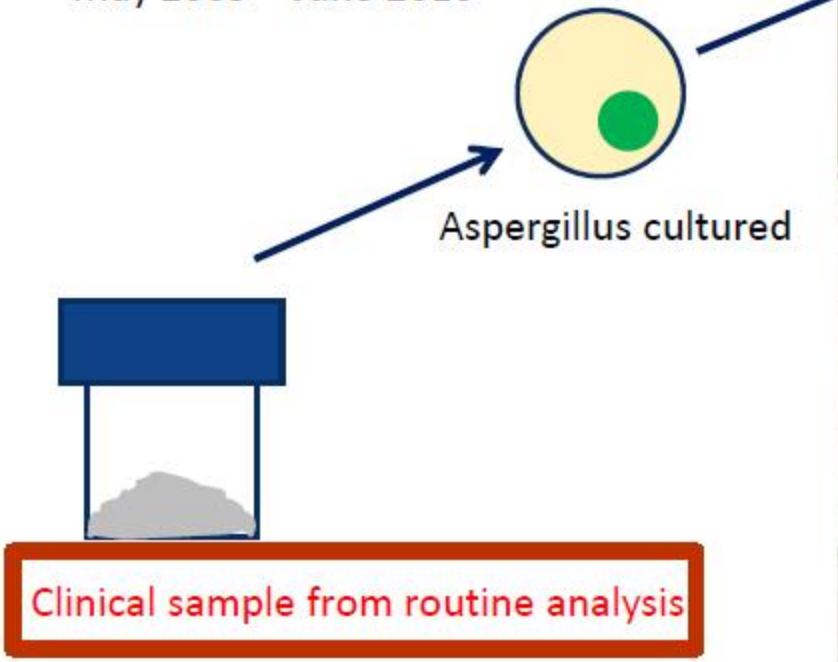
- EUCAST E.Dis 9.3.1

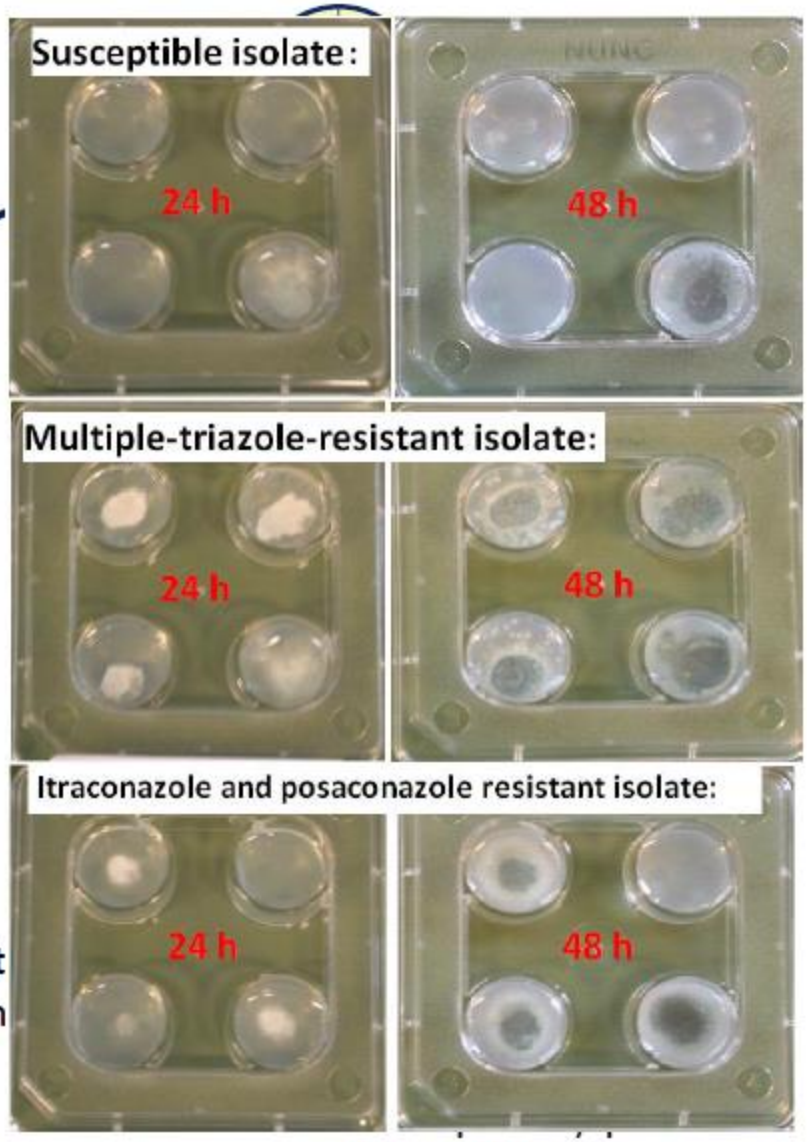
15 Ocak 2017

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

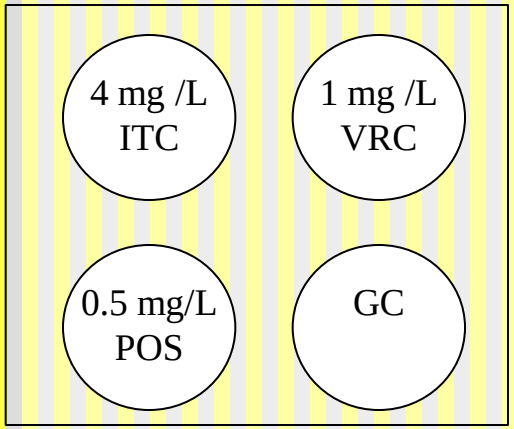
## Prospective Multicenter International Surveillance of Azole Resistance in *Aspergillus fumigatus*

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

# Multicenter validation of the 4-well plates: Agar screening method for azole R in A.fumigatus [1]

- 40 WT
- 39 *cyp51A* mutant
- Simulated mixed samples




Inter-plate agreement
Inter-observer agreement
EA
CA
Sens
Spec

In-house vs. commercial plates, three lab.s, two observers, scoring (0-3)

Arendrup et al. JAC 2017 Oct 4. doi: 10.1093/jac/dkx319

# Multicenter validation of the 4-well plates: Agar screening method for azole R in A.fumigatus [2]

| | % Range |
|---|---|
| Inter-observer agreement | 80-100 |
| Qualitative agreement (NG vs. G) | 87-100 |
| Sensitivity - overall | 97-100 |
| Sensitivity - simulated WT-mutant | 83-100 |
| Specificity - overall | 95-100 |

High inter-plate agreement

*Rutin Lab. kullanımı için pratik ve güvenilir*

Arendrup et al. JAC 2017 Oct 4. doi: 10.1093/jac/dkx319

# Aspergillus- AFDT

# 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

Clinical Microbiology and Infection xxx (2018) e1–e38

# Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

A.J. Ullmann [1, 62, 63], J.M. Aguado [2, 62, 63], S. Arikan-Akdagli [3, 62, 63], D.W. Denning [4, 5, 6, 63], A.H. Groll [7, 62, 63], K. Lagrou [8, 62, 63], C. Lass-Flörl [9, 62, 63], R.E. Lewis [10, 62], P. Munoz [11, 12, 13, 62, 63], P.E. Verweij [14, 62, 63], A. Warris [15, 62, 63], F. Ader [16, 17, 65], M. Akova [18, 62, 63], M.C. Arendrup [19, 62, 63], R.A. Barnes [20, 63], C. Beigelman-Aubry [21, 65], S. Blot [22, 23, 65], E. Bouza [11, 12, 13, 62, 63], R.J.M. Brüggemann [24, 62], D. Buchheidt [25, 62, 63], J. Cadranel [26, 65], E. Castagnola [27, 62], A. Chakrabarti [28, 63], M. Cuenca-Estrella [29, 62, 63], G. Dimopoulos [30, 65], J. Fortun [31, 62, 63], J.-P. Gangneux [32, 62, 63], J. Garbino [33, 62, 63], W.J. Heinz [1, 62, 63], R. Herbrecht [34, 62], C.P. Heussel [35, 63], C.C. Kibbler [36, 63], N. Klimko [37, 63], B.J. Kullberg [24, 62, 63], C. Lange [38, 39, 40, 65], T. Lehrnbecher [41, 63], J. Löffler [1, 62, 63], O. Lortholary [42, 62, 63], J. Maertens [43, 62, 63], O. Marchetti [44, 45, 62, 63], J.F. Meis [46, 62, 63], L. Pagano [47, 63], P. Ribaud [48], M. Richardson [4, 5, 6, 62, 63], E. Roilides [49, 50, 62, 63], M. Ruhnke [51, 62, 63], M. Sanguinetti [52, 62, 63], D.C. Sheppard [53, 62, 63], J. Sinkó [54, 62], A. Skiada [55, 62, 63], M.J.G.T. Vehreschild [56, 57, 58, 63], C. Viscoli [59, 62, 63], O.A. Cornely [56, 58, 60, 61, 62, 63, 64, *]

**Table 15**
Indications for testing for azole resistance in clinical *Aspergillus* isolates

| Population | Intention | Intervention | SoR | QoE | Comment | Ref. |
|---|---|---|---|---|---|---|
| All clinically relevant *Aspergillus* isolates (in patient groups or regions with known azole resistance) | Identify azole resistance | Reference MIC testing | A | II | In situations where rapid testing is available | [105,111,114,116,300,474–484] |
| Clinically relevant *Aspergillus* isolates in patient groups with high prevalence of azole resistance or patients unresponsive to treatment | Identify isolates with intrinsic resistance | Species identification to complex level | A | III | Some species are intrinsically resistant—e.g. *A. calidoustus* (azole resistant) *and A. terreus* (AmB resistant) | [103,485] |
| Clinically relevant *A. fumigatus* isolates | Identify azole-resistant *A. fumigatus* | Routine azole agar screening | B | III | Identifies resistant colonies that require MIC-testing | [118,486] |
| All isolates –resistance surveillance | Determine the local epidemiology of azole resistance | Periodical reference MIC testing of *A. fumigatus* complex | A | II | Test at least 100 isolates | [105,111,114,300,477–480,482–484] |
| Azole-resistant isolates | Determine nature and trends in Cyp51A mutation distribution | Cyp51A-gene mutation analysis | A | II | Test resistant isolates from surveillance survey | [107] |

Abbreviations: AmB, Amphotericin B; MIC, minimum inhibitory concentration; QoE, Quality of evidence; SoR, Strength of recommendation.

# 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<br>*n* = 36<br>*n* = 217<br>*n* = 45<br>*n* = 77<br>*n* = 18, *Apophysomyces elegans*<br>*n* = 21<br>*n* = 66<br>Review | 86<br>88<br>87<br>21<br>92<br>83<br>91<br>90<br>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<br>Easily recovered on routine mycological media without cycloheximide<br>Accurate species assignment is important for guiding clinical management | [2,190] |
| | Histopathology | A | IIu | Essential investigation<br>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<br>High negative predictive values | [36–38] |
| | Multiplex PCRs[a] | C | III | Not yet validated<br>Cover limited number of species/genera | [30,37,39] |
| | *In situ* hybridization | C | III | Not yet evaluated<br>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<br>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

CLSI M59

Epidemiological Cutoff Values for Antifungal Susceptibility Testing, 2nd ed.

This document includes epidemiological cutoff values and quality control tables developed according to criteria provided in the Clinical and Laboratory Standards Institute guideline M57.

# AMB, Azoller, Kandin- Candida

## EUCAST

*Candida* spp.

**EUCAST Antifungal Clinical Breakpoint Table v. 9.0 valid from 2018-02-12**

**MIC method (EUCAST standardised broth microdilution method)**
**Medium:** RPMI1640-2% glucose, MOPS buffer
**Inoculum:** Final $0.5x10^5 - 2.5x10^5$ 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) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *C. albicans* | | *C. dubliniensis* | | *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 > | S ≤ | R > |
| Amphotericin B | 1 | 1 | IE | IE | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | IE | IE | IE | IE |
| Anidulafungin | 0.032 | 0.032 | IE | IE | 0.064 | 0.064 | 0.064 | 0.064 | 0.002 | 4 | 0.064 | 0.064 | IE[2] | IE[2] | IE | IE |
| Caspofungin | Note[3] | Note[3] | IE | IE | Note[3] | Note[3] | Note[3] | Note[3] | Note[3] | Note[3] | Note[3] | Note[3] | IE[2] | IE[2] | IE | IE |
| Fluconazole | 2 | 4 | IE | IE | 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 | IE | IE |
| Itraconazole | 0.064 | 0.064 | 0.064 | 0.064 | IE[2] | IE[2] | IE[2] | IE[2] | 0.125 | 0.125 | 0.125 | 0.125 | IE[2] | IE[2] | IE | IE |
| Micafungin | 0.016 | 0.016 | IE | IE | 0.032 | 0.032 | IE[4] | IE[4] | 0.002 | 2 | IE[4] | IE[4] | IE[4] | IE[4] | IE | IE |
| Posaconazole | 0.064 | 0.064 | 0.064 | 0.064 | IE[2] | IE[2] | IE[2] | IE[2] | 0.064 | 0.064 | 0.064 | 0.064 | IE[2] | IE[2] | IE | IE |
| Voriconazole[6] | 0.064[5] | 0.25[5] | 0.064 | 0.25 | IE | IE | IE | IE | 0.125[5] | 0.25[5] | 0.125[5] | 0.25[5] | IE[2] | IE[2] | IE | IE |

# AMB & Azoles -Asp

## EUCAST

*Aspergillus* spp.

**EUCAST Antifungal Clinical Breakpoint Table v. 9.0 valid from 2018-02-12**

**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) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *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 |
| 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] | 0.125[5] | 0.25[5] | IE[2] | IE[2] | IE[2] | IE[2] | 0.125[5] | 0.25[5] | IE | IE |
| Voriconazole[4] | IE[2] | IE[2] | 1 | 2 | IE | IE | IE[2] | IE[2] | IE[2] | IE[2] | IE | IE |

# Sunum Planı

Temel bilgiler

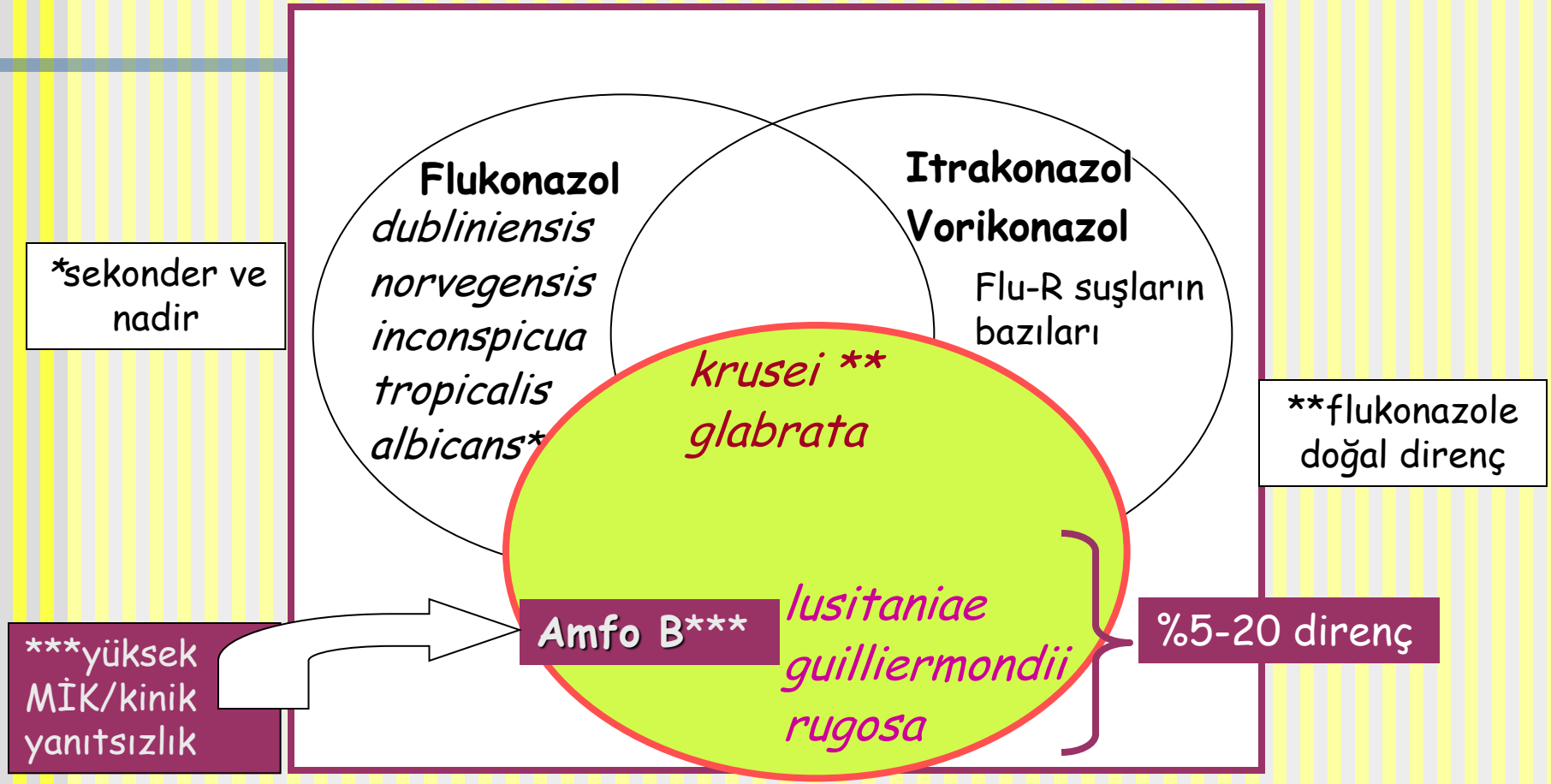
YÖNTEM ve DEĞERLENDİRME

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

# CD101, a long-acting echinocandin, and comparator antifungal agents tested against a global collection of invasive fungal isolates in the SENTRY 2015 Antifungal Surveillance Program

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

International Journal of Antimicrobial Agents 50 (2017) 352–358

589 Candida suşu
C. glabrata, Flukonazol direnci: %6.6
C.parapsilosis, Flukonazol direnci: % 3.6
C. glabrata, Kandin direnci: %0.8

**Table 3**
FKS alterations detected in *Candida spp.* isolates displaying non-wild-type echinocandin MIC values.

| State, Country | Organism | MIC according to CLSI method (μg/mL): | | | | 1,3-β-D-glucan synthase mutations: | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | CD101 | Anidulafungin | Caspofungin | Micafungin | *fks1* HS1 | *fks1* HS2 | *fks2* HS1 | *fks2* HS2 |
| NY, USA | *Candida albicans* | 0.25 | 0.25 | 1 | 1 | S645P | WT | NT | NT |
| TX, USA | *Candida glabrata* | 0.25 | 0.25 | 0.06 | 0.03 | WT | WT | WT | WT |
| CA, USA | *Candida glabrata* | 1 | 1 | 1 | 0.25 | F625S | NT | WT | WT |
| VA, USA | *Candida glabrata* | 0.12 | 0.12 | 0.06 | 0.12 | WT | WT | WT | WT |

HS=hot spot; NT=not tested; WT=wild type.

C.albicans n=304
C. glabrata n=121
C. parapsilosis n=83
C. tropicalis n=55

# C. glabrata: Ekinokandin direnci Oranlar; *Coğrafi Farklılıklar*

A.B.D.

Son 10 yılda %2 den > %13'e (A.B.D.)

Alexander B et al. CID 2013; 56: 1724

%3.1-%3.6 (CDC ... A.B.D.-4 şehir

58: 4690

Avrupa

< %1 (

16; 59:312

Ekinoka

Ekinokandin direnç ... suşlarının %36' sında

Pham et al. AAC 2014; 58: 4690

MSH2 DNA «mismatch repair» (MMR) gen delesyonları sonucu ortaya çıkan "mutator fenotip" ⇨ Flu, Ekino, AMB direnci

# 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*

# FLU, VOR, Kandin, Candida

## Kan k. izolatları (n=328; 2011-2016)

**Hacettepe Üniv.**

**Table.** The number of *Candida* isolates with available AST results interpreted according to CBPs[3,4] or ECVs[4].
In presence of established CBPs, the isolates were categorized as susceptible (S), dose-dependent susceptible (S-DD) or resistant (R). For the species with no established CBPs and available ECVs for the drugs under study, the categories were determined as wild-type (WT) or non-wild-type (non-WT). The number of isolates determined by using ECVs are shaded in blue.

| No. of *Candida* isolates tested | No. of isolates in each interpretative category (Fluconazole) | | | No. of *Candida* isolates tested | No. of isolates in each interpretative category (Voriconazole) | | | No. of *Candida* isolates tested | No. of isolates in each interpretative category (Echinocandin) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | S / WT | S-DD | R / Non-WT | | S / WT | S-DD | R / Non-WT | | S / WT | I | R / Non-WT |
| *C.albicans* (130) | 130 | - | - | *C.albicans* (129) | 129 | - | - | *C.albicans* (109) | 108 | - | 1 |
| *C.parapsilosis* (46) | 32 | 1 | 13 | *C.parapsilosis* (45) | 42 | 3 | - | *C.parapsilosis* (39) | 39 | - | - |
| *C.glabrata* (33) | - | 32 | 1 | *C.glabrata* (33) | 32 | - | 1 | *C.glabrata* (29) | 29 | - | - |
| *C.tropicalis* (23) | 23 | - | - | *C.tropicalis* (24) | 24 | - | - | *C.tropicalis* (21) | 21 | - | - |
| *C.kefyr* (7) | 7 | - | - | *C.kefyr* (7) | 7 | - | - | *C.kefyr* (6) | 5 | - | 1 |
| *C.krusei* (4) | - | - | 4 | *C.krusei* (2) | 2 | - | - | *C.krusei* (2) | 2 | - | - |
| *C.lusitaniae* (4) | 4 | - | - | *C.lusitaniae* (4) | 4 | - | - | *C.lusitaniae* (4) | 4 | - | - |
| *C.dubliniensis* (3) | 3 | - | - | *C.dubliniensis* (3) | 3 | - | - | *C.dubliniensis* (2) | 2 | - | - |
| *C.guilliermondii* (2) | 2 | - | - | *C.guilliermondii* (2) | 2 | - | - | *C.guilliermondii* (1) | 1 | - | - |
| *C.pelliculosa* (1) | - | - | 1 | *C.pelliculosa* (1) | 1 | - | - | *C.pelliculosa* (1) | 1 | - | - |
| *C.rugosa** (1) | - | - | - | *C.rugosa** (1) | - | - | - | *C.rugosa** (1) | - | - | - |

Alp et al. ECCMID 2017 Vienna P 0959 The changing epidemiology of candidemia in a tertiary care university center

# 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*

# Kandidemi - Çok Merkezli Antifungal Direnç

**12 merkez**
**n= 1992** **1996-2017**
**Hacettepe Üniv. - Mikoloji Laboratuvarı**
**CLSI referans mikrodilüsyon**

Hacettepe Üniv, Dokuz Eylül Üniv, Ege Üniv, Erciyes Üniv., Gazi Üniv., İstanbul Üniv. İstanbul Tıp Fak., Marmara Üniv., Ondokuz Mayıs Üniv., Osmangazi Üniv., Sağlık Bilimleri Üniv. Gülhane Tıp Fak., Selçuk Üniv, Uludağ Üniv.

| | n |
|---|---|
| C.albicans | 852 |
| C.parapsilosis | 575 |
| C.glabrata | 216 |
| C.tropicalis | 203 |
| C.krusei | 52 |
| C.kefyr | 33 |
| C.lusitaniae | 23 |
| C.guilliermondii | 16 |
| C.inconspicua/norvegensis | 7 |
| C.dubliniensis | 6 |
| C.pelliculosa | 3 |
| C.rugosa | 2 |
| C.utilis | 2 |
| C.lipolytica | 1 |
| C.sake | 1 |
| | 1992 |

*Arıkan Akdağlı S*
*Yayınlanmamış Veri*

# Kandidemi - Çok Merkezli Antifungal Direnç

**12 merkez**
**n= 1992** **1996-2017**
**Hacettepe Üniv. - Mikoloji Laboratuvarı**
**CLSI referans mikrodilüsyon**

**Resistance %, n**

| CLSI M27-S4 | Pfaller 2012 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fluconazole | % | | | | | n | | | | | |
| | S | SDD | R | WT | non-WT | n | S | SDD | R | WT | non-WT |
| C.albicans | 99.8 | 0.2 | 0.0 | 96.6 | 3.4 | 852 | 850 | 2 | 0 | 823 | 29 |
| C.parapsilosis | 89.0 | 3.3 | 7.7 | 89.0 | 11.0 | 575 | 512 | 19 | 44 | 512 | 63 |
| C.glabrata | 0.0 | 99.1 | 0.9 | 99.1 | 0.9 | 216 | 0 | 214 | 2 | 214 | 2 |
| C.tropicalis | 100.0 | 0.0 | 0.0 | 100.0 | 0.0 | 203 | 203 | 0 | 0 | 203 | 0 |
| C.krusei | 0.0 | 0.0 | 100.0 | 94.2 | 5.8 | 52 | 0 | 0 | 52 | 49 | 3 |
| C.kefyr | - | - | - | 100.0 | 0.0 | 33 | - | - | - | 33 | 0 |
| C.lusitaniae | - | - | - | 95.7 | 4.3 | 23 | - | - | - | 22 | 1 |
| C.guilliermondii | - | - | - | 100.0 | 0.0 | 16 | - | - | - | 16 | 0 |
| C.inconspicua/norvegensis | - | - | - | - | - | 7 | - | - | - | - | - |
| C.dubliniensis | - | - | - | 100.0 | 0.0 | 6 | - | - | - | 6 | 0 |
| C.pelliculosa | - | - | - | 100.0 | 0.0 | 3 | - | - | - | 3 | 0 |
| C.rugosa | - | - | - | - | - | 2 | - | - | - | - | - |
| C.utilis | - | - | - | - | - | 2 | - | - | - | - | - |
| C.lipolytica | - | - | - | - | - | 1 | - | - | - | - | - |
| C.sake | - | - | - | - | - | 1 | - | - | - | - | - |
| | | | | | | 1992 | | | | | |

*Arıkan Akdağlı S. Yayınlanmamış Veri*

# Kandidemi - Çok Merkezli Antifungal Direnç

**12 merkez**
**n= 1992** **1996-2017**
**Hacettepe Üniv. - Mikoloji Laboratuvarı**
**CLSI referans mikrodilüsyon**

**Resistance %, n**

| Voriconazole | % | | | | | n | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | SDD | R | WT | non-WT | n | S | SDD | R | WT | non-WT |
| C.albicans | 100.0 | 0.0 | 0.0 | 99.9 | 0.1 | 852 | 852 | 0 | 0 | 851 | 1 |
| C.parapsilosis | 97.9 | 2.1 | 0.0 | 97.9 | 2.1 | 575 | 563 | 12 | 0 | 563 | 12 |
| C.glabrata | - | - | - | 99.5 | 0.5 | 216 | - | - | - | 215 | 1 |
| C.tropicalis | 100.0 | 0.0 | 0.0 | 100.0 | 0.0 | 203 | 203 | 0 | 0 | 203 | 0 |
| C.krusei | 100.0 | 0.0 | 0.0 | 100.0 | 0.0 | 52 | 52 | 0 | 0 | 52 | 0 |
| C.kefyr | - | - | - | 100.0 | 0.0 | 33 | - | - | - | 33 | 0 |
| C.lusitaniae | - | - | - | 100.0 | 0.0 | 23 | - | - | - | 23 | 0 |
| C.guilliermondii | - | - | - | 100.0 | 0.0 | 16 | - | - | - | 16 | 0 |
| C.inconspicua/norvegensis | - | - | - | - | - | 7 | - | - | - | - | - |
| C.dubliniensis | - | - | - | 100.0 | 0.0 | 6 | - | - | - | 6 | 0 |
| C.pelliculosa | - | - | - | 100.0 | 0.0 | 3 | - | - | - | 3 | 0 |
| C.rugosa | - | - | - | - | - | 2 | - | - | - | - | - |
| C.utilis | - | - | - | - | - | 2 | - | - | - | - | - |
| C.lipolytica | - | - | - | - | - | 1 | - | - | - | - | - |
| C.sake | - | - | - | - | - | 1 | - | - | - | - | - |

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# Kandidemi - Çok Merkezli Antifungal Direnç

**Resistance %, n**

| Itraconazole | % | | | | | n | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | S | SDD | R | WT | non-WT | n | S | SDD | R | WT | non-WT |
| C.albicans | 99.4 | 0.6 | 0.0 | 99.4 | 0.6 | 852 | 847 | 5 | 0 | 847 | 5 |
| C.parapsilosis | - | - | - | 99.8 | 0.2 | 575 | - | - | - | 574 | 1 |
| C.glabrata | - | - | - | 100.0 | 0.0 | 216 | - | - | - | 216 | 0 |
| C.tropicalis | - | - | - | 100.0 | 0.0 | 203 | - | - | - | 203 | 0 |
| C.krusei | - | - | - | 100.0 | 0.0 | 52 | - | - | - | 52 | 0 |
| C.kefyr | - | - | - | - | - | 33 | - | - | - | - | - |
| C.lusitaniae | - | - | - | 100.0 | 0.0 | 23 | - | - | - | 23 | 0 |
| C.guilliermondii | - | - | - | 100.0 | 0.0 | 16 | - | - | - | 16 | 0 |
| C.inconspicua/norvegensis | - | - | - | - | - | 7 | - | - | - | - | - |
| C.dubliniensis | - | - | - | 100.0 | 0.0 | 6 | - | - | - | 6 | 0 |
| C.pelliculosa | - | - | - | - | - | 3 | - | - | - | - | - |
| C.rugosa | - | - | - | - | - | 2 | - | - | - | - | - |
| C.utilis | - | - | - | - | - | 2 | - | - | - | - | - |
| C.lipolytica | - | - | - | - | - | 1 | - | - | - | - | - |
| C.sake | - | - | - | - | - | 1 | - | - | - | - | - |
| | | | | | | 1992 | | | | | |

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# Kandidemi - Çok Merkezli Antifungal Direnç

**12 merkez**
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**Hacettepe Üniv. - Mikoloji Laboratuvarı**
**CLSI referans mikrodilüsyon**

**Resistance %, n**

| Posaconazole | % | | | | | n | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | SDD | R | WT | non-WT | n | S | SDD | R | WT | non-WT |
| C.albicans | - | - | - | 100.0 | 0.0 | 852 | - | - | - | 852 | 0 |
| C.parapsilosis | - | - | - | 96.5 | 3.5 | 575 | - | - | - | 555 | 20 |
| C.glabrata | - | - | - | 100.0 | 0.0 | 216 | - | - | - | 216 | 0 |
| C.tropicalis | - | - | - | 100.0 | 0.0 | 203 | - | - | - | 203 | 0 |
| C.krusei | - | - | - | 98.1 | 1.9 | 52 | - | - | - | 51 | 1 |
| C.kefyr | - | - | - | 100.0 | 0.0 | 33 | - | - | - | 33 | 0 |
| C.lusitaniae | - | - | - | 100.0 | 0.0 | 23 | - | - | - | 23 | 0 |
| C.guilliermondii | - | - | - | 100.0 | 0.0 | 16 | - | - | - | 16 | 0 |
| C.inconspicua/norvegensis | - | - | - | - | - | 7 | - | - | - | - | - |
| C.dubliniensis | - | - | - | 100.0 | 0.0 | 6 | - | - | - | 6 | 0 |
| C.pelliculosa | - | - | - | 100.0 | 0.0 | 3 | - | - | - | 3 | 0 |
| C.rugosa | - | - | - | - | - | 2 | - | - | - | - | - |
| C.utilis | - | - | - | - | - | 2 | - | - | - | - | - |
| C.lipolytica | - | - | - | - | - | 1 | - | - | - | - | - |
| C.sake | - | - | - | - | - | 1 | - | - | - | - | - |
| | | | | | | 1992 | | | | | |

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# Kandidemi - Çok Merkezli Antifungal Direnç

**12 merkez**
**n= 1992** **1996-2017**
**Hacettepe Üniv. - Mikoloji Laboratuvarı**
**CLSI referans mikrodilüsyon**

**Resistance %, n**

| Micafungin | % | | | | | n | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | SDD | R | WT | non-WT | n | S | I | R | WT | non-WT |
| C.albicans | 100.0 | 0.0 | 0.0 | 99.6 | 0.4 | 852 | 852 | 0 | 0 | 849 | 3 |
| C.parapsilosis | 99.8 | 0.2 | 0.0 | 100.0 | 0.0 | 575 | 574 | 1 | 0 | 575 | 0 |
| C.glabrata | 100.0 | 0.0 | 0.0 | 99.1 | 0.9 | 216 | 216 | 0 | 0 | 214 | 2 |
| C.tropicalis | 100.0 | 0.0 | 0.0 | 100.0 | 0.0 | 203 | 203 | 0 | 0 | 203 | 0 |
| C.krusei | 100.0 | 0.0 | 0.0 | 76.9 | 23.1 | 52 | 52 | 0 | 0 | 40 | 12 |
| C.kefyr | - | - | - | 100.0 | 0.0 | 33 | - | - | - | 33 | 0 |
| C.lusitaniae | - | - | - | 100.0 | 0.0 | 23 | - | - | - | 23 | 0 |
| C.guilliermondii | 100.0 | 0.0 | 0.0 | 100.0 | 0.0 | 16 | 16 | 0 | 0 | 16 | 0 |
| C.inconspicua/norvegensis | - | - | - | - | - | 7 | - | - | - | - | - |
| C.dubliniensis | - | - | - | 100.0 | 0.0 | 6 | - | - | - | 6 | 0 |
| C.pelliculosa | - | - | - | - | - | 3 | - | - | - | - | - |
| C.rugosa | - | - | - | - | - | 2 | - | - | - | - | - |
| C.utilis | - | - | - | - | - | 2 | - | - | - | - | - |
| C.lipolytica | - | - | - | - | - | 1 | - | - | - | - | - |
| C.sake | - | - | - | - | - | 1 | - | - | - | - | - |
| | | | | | | 1992 | | | | | |

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**12 merkez**
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**Hacettepe Üniv. - Mikoloji Laboratuvarı**
**CLSI referans mikrodilüsyon**

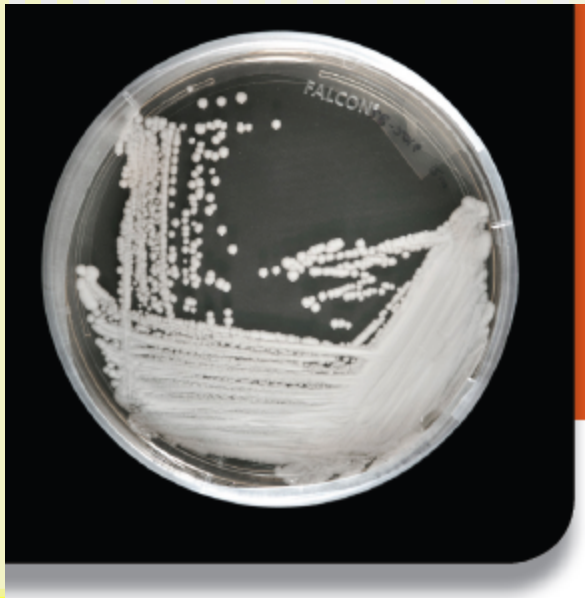
# Kandidemi - Çok Merkezli Antifungal Direnç

**Resistance %, n**

| Amphotericin B | % | | | | | n | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | SDD | R | WT | non-WT | n | S | SDD | R | WT | non-WT |
| C.albicans | - | - | - | 100.0 | 0.0 | 852 | - | - | - | 852 | 0 |
| C.parapsilosis | - | - | - | 100.0 | 0.0 | 575 | - | - | - | 575 | 0 |
| C.glabrata | - | - | - | 100.0 | 0.0 | 216 | - | - | - | 216 | 0 |
| C.tropicalis | - | - | - | 100.0 | 0.0 | 203 | - | - | - | 203 | 0 |
| C.krusei | - | - | - | 100.0 | 0.0 | 52 | - | - | - | 52 | 0 |
| C.kefyr | - | - | - | - | - | 33 | - | - | - | - | - |
| C.lusitaniae | - | - | - | 100.0 | 0.0 | 23 | - | - | - | 23 | 0 |
| C.guilliermondii | - | - | - | 100.0 | 0.0 | 16 | - | - | - | 16 | 0 |
| C.inconspicua/norvegensis | - | - | - | - | - | 7 | - | - | - | - | - |
| C.dubliniensis | - | - | - | 100.0 | 0.0 | 6 | - | - | - | 6 | 0 |
| C.pelliculosa | - | - | - | - | - | 3 | - | - | - | - | - |
| C.rugosa | - | - | - | - | - | 2 | - | - | - | - | - |
| C.utilis | - | - | - | - | - | 2 | - | - | - | - | - |
| C.lipolytica | - | - | - | - | - | 1 | - | - | - | - | - |
| C.sake | - | - | - | - | - | 1 | - | - | - | - | - |
| | | | | | | 1992 | | | | | |

*Arıkan Akdağlı S. Yayınlanmamış Veri*

Tsay et al. CID 2017; Aug 17




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

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

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

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

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

CID 2017:64 (15 January)

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

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

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

# Why is *Candida auris* a problem?

**It causes serious infections.** *C. auris* can cause bloodstream infections and even death, particularly in hospital and nursing home patients with serious medical problems. More than 1 in 3 patients with invasive *C. auris* infection (for example, an infection that affects the blood, heart, or brain) die.

**It's often resistant to medicines.** Antifungal medicines commonly used to treat *Candida* infections often don't work for *Candida auris*. Some *C. auris* infections have been resistant to all three types of antifungal medicines.

**It's becoming more common.** Although *C. auris* was just discovered in 2009, it has spread quickly and caused infections in more than a dozen countries.

**It's difficult to identify.** *C. auris* can be misidentified as other types of fungi unless specialized laboratory technology is used. This misidentification might lead to a patient getting the wrong treatment.

**It can spread in hospitals and nursing homes.** *C. auris* has caused outbreaks in healthcare facilities and can spread through contact with affected patients and contaminated surfaces or equipment. Good hand hygiene and cleaning in healthcare facilities is important because *C. auris* can live on surfaces for several weeks.

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

## Scientists are still learning about *Candida auris*

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

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


## What is CDC doing?

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

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

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

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

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

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

# Candida auris

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

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

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

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

Lockhart et al.

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

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

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

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

**Antifungal Susceptibility Testing**

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

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

Antimicrobial Agents and Chemotherapy®

June 2017 Volume 61 Issue 6 e00485-17

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

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

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

| Drug and AFST method | MIC (mg/liter)[a] | | | | | | | | | | | | | | | | MIC range (no. of dilutions[b]) | GM | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.002 | 0.004 | 0.008 | 0.016 | 0.032 | 0.064 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | ≥64 | | | | |
| FLU | | | | | | | | | | | | | | | | | | | | |
| CLSI | | | | | | | | | | | - | 10 | | 7 | 15 | (91) | 4 to ≥64 (5) | 43.38 | ≥64 | ≥64 |
| EUCAST | NT[c] | NT | NT | NT | | | | | 1 | | 2 | | | 2 | 10 | (108) | 0.5 to ≥64 (8) | 53.74 | ≥64 | ≥64 |
| ITC | | | | | | | | | | | | | | | | | | | | |
| CLSI | | | | | 25 | 12 | 57 | 20 | 7 | 1 | 1 | | | | | | 0.032 to 2 (7) | 0.11 | 0.125 | 0.25 |
| EUCAST | NT | NT | (4) | 9 | 4 | 14 | 36 | 35 | 20 | 1 | | | | | | | ≤0.008 to 1 (8) | 0.13 | 0.125 | 0.5 |
| VRC | | | | | | | | | | | | | | | | | | | | |
| CLSI | | | | | 1 | 11 | 14 | 10 | 27 | 19 | 24 | 13 | 1 | 3 | | | 0.032 to 16 (10) | 0.66 | 0.5 | 4 |
| EUCAST | NT | NT | (1) | | 2 | 1 | 17 | 12 | 35 | 37 | 13 | 5 | | | | | ≤0.008 to 4 (10) | 0.54 | 0.5 | 2 |
| ISA | | | | | | | | | | | | | | | | | | | | |
| CLSI | | | | 26 | 7 | 23 | 20 | 30 | 12 | | 3 | 2 | | | | | 0.015 to 4 (9) | 0.095 | 0.125 | 0.5 |
| EUCAST | NT | NT | (22) | 1 | 19 | 9 | 20 | 20 | 21 | 6 | 5 | | | | | | ≤0.008 to 2 (9) | 0.090 | 0.125 | 0.5 |
| PSC | | | | | | | | | | | | | | | | | | | | |
| CLSI | | | | 73 | 4 | 26 | 9 | 7 | | 1 | 1 | 1 | 1 | | | | 0.015 to 8 (9) | 0.035 | 0.016 | 0.125 |
| EUCAST | NT | NT | (22) | 19 | 33 | 33 | 12 | 3 | 1 | | | | | | | | ≤0.008 to 0.5 (7) | 0.033 | 0.032 | 0.125 |
| AMB | | | | | | | | | | | | | | | | | | | | |
| CLSI | | | | | | | 2 | 16 | 58 | 35 | 4 | 6 | 2 | | | | 0.125 to 8 (7) | 0.66 | 0.5 | 2 |
| EUCAST | NT | NT | | | | | | 1 | 15 | 107 | | | | | | | 0.25 to 1 (3) | 0.91 | 1 | 1 |
| AFG | | | | | | | | | | | | | | | | | | | | |
| CLSI | | | | 1 | | 8 | 61 | 24 | 20 | 2 | | - | 7 | | | | 0.015 to 8 (10) | 0.22 | 0.125 | 0.5 |
| EUCAST | 1 | | | 2 | 11 | 34 | 30 | 12 | 12 | 11 | 2 | 8 | | | | | 0.002 to 2 (12) | 0.17 | 0.125 | 1 |
| MFG | | | | | | | | | | | | | | | | | | | | |
| CLSI | | | | 4 | 4 | 47 | 49 | 9 | 2 | 1 | | | 7 | | | | 0.015 to 8 (10) | 0.12 | 0.125 | 0.25 |
| EUCAST | 1 | | | 1 | 5 | 29 | 69 | 9 | | | | 8 | | | | | 0.002 to 4 (12) | 0.13 | 0.125 | 0.25 |

[a]Modal MICs are indicated with underlined numbers and gray shading, and values in parentheses represent the number of isolates with an MIC equal or less than the MIC indicated due to truncation. Additional peaks are illustrated by underlining.

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

[c]NT, not tested.

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

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

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

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

# 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.

# Azol (sekonder) - Aspergillus

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

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

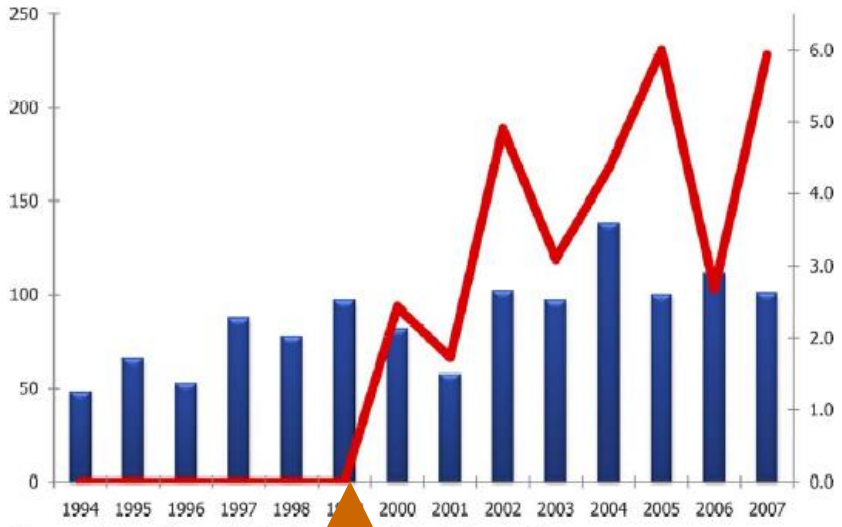



**Figure 1.** Epidemiology of ITZ Resistanc in the *A. fumigatus* Isolates

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*]

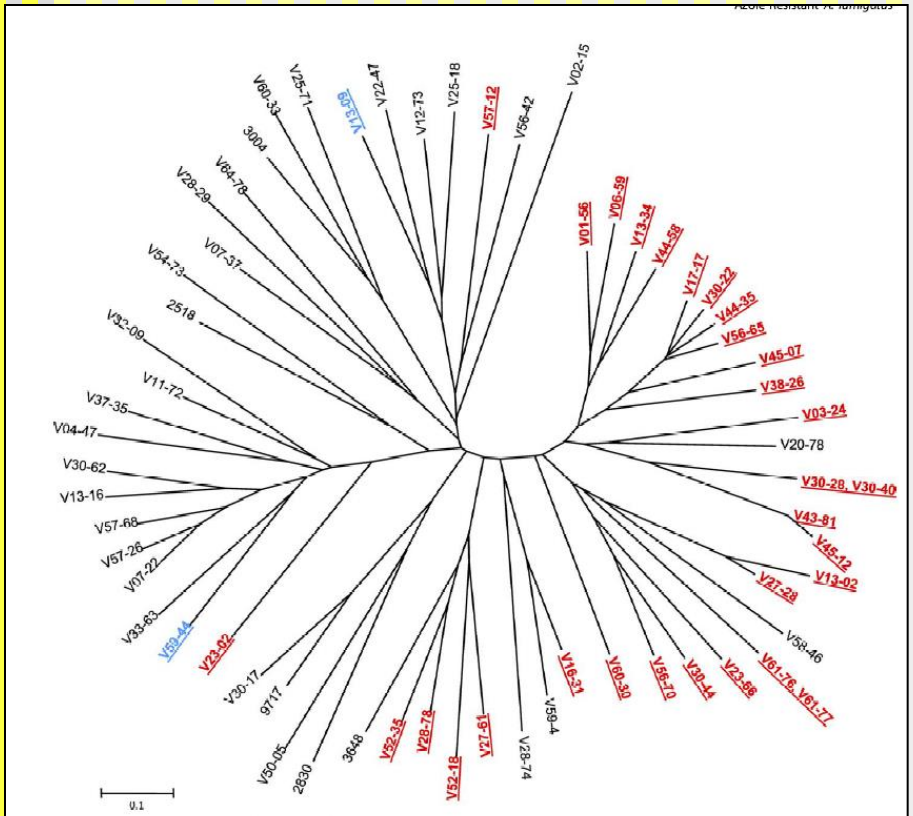



**Figure 3.** Genotypic Relatedness of 32 ITZ+ *A. fumigatus* Isolates and 32 ITZ− Controls

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…

SCARE

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

# 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 |

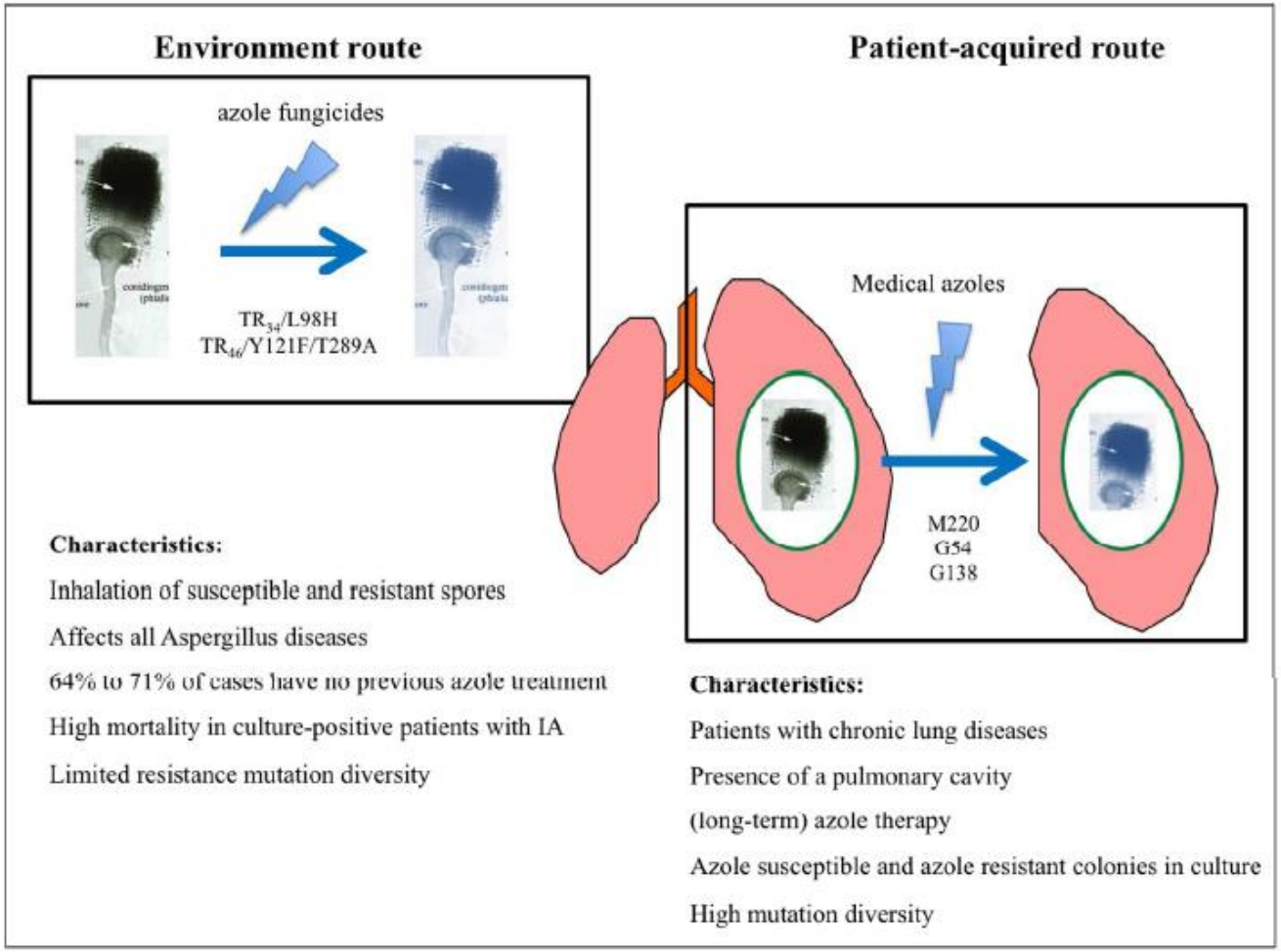
# First determination of azole resistance in *Aspergillus fumigatus* strains carrying the TR34/L98H mutations in Turkey

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?




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

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

# Hangi triazole direnç ?

| | ITR | VOR | POS | ISV |
|---|---|---|---|---|
| TR*34/L98H | R | R | R | R |
| TR46/Y121F/T289A | V | R | R/V | |
| TR53 | R | R | ⇩S | |
| G54 | R | S | R | |
| M220 | R | ⇩S | V | |
| G448 | ⇩S | R | ⇩S | |

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

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

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

# Klinik A. fumigatus izolatları

## Azol direnci

**Retrospektif**
**H.Ü. n=215**
**1997-2015**
**Agar tarama ⇨ EUCAST mikrodilüsyon**
**cyp51A sekans analizi**

# Klinik A. fumigatus izolatları

## Azol direnci

**Retrospektif**
**H.Ü. , n=215 , 1997-2015**
**Agar tarama ⇨ EUCAST mikrodilüsyon**
**cyp51A sekans analizi**

| İzolat no. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **4C** | Y46F | G89G | V172M | T248N | E255D | L358L | K427E | C454C | Y431D | |
| **6C** | Y46F | G89G | V172M | T248N | E255D | L358L | K427E | C454C | Y431D | |
| **7C** | Y46F | G89G | V172M | T248N | E255D | L358L | K427E | C454C | Y431D | |
| **10C** | Y46F | G89G | V172M | T248N | E255D | L358L | K427E | C454C | Y431D | |
| **16C** | Y46F | G89G | V172M | T248N | E255D | L358L | K427E | C454C | Y431D | Q141H |
| **22C** | Y46F | G89G | V172M | T248N | E255D | L358L | K427E | C454C | Y431D | |
| **23C** | Y46F | G89G | V172M | T248N | E255D | L358L | K427E | C454C | Y431D | |

*Arıkan Akdağlı. Yayınlanmamış Veri.*

AAC Accepted Manuscript Posted Online 18 September 2017
Antimicrob. Agents Chemother. doi:10.1128/AAC.01277-17

# Ekinokandin - Aspergillus

## Emergence of Echinocandin Resistance due to a Point Mutation in the *fks1* Gene of *Aspergillus fumigatus* in a Patient with Chronic Pulmonary Aspergillosis

Cristina Jiménez-Ortigosa[1*], Caroline Moore[2], David W. Denning[3] and David S. Perlin[1]

We have identified the first case of a *fks1* hot spot 1 point mutation causing echinocandin resistance in a clinical *Aspergillus fumigatus* isolate recovered from a chronic pulmonary aspergillosis patient with an aspergilloma who first failed azole and polyene therapy, and then subsequently failed micafungin treatment.

**Table 2.** MIC/MEC distributions of the antifungal drugs tested in the study for the *Aspergillus spp.* clinical isolates. Alterations in the Cyp51A and Fks1 together with the sequence type (ST) are also shown. Three wild type (WT) strains have also been included for comparison purposes.

| # | Lab no. | Date received | ID | MIC/MEC (mg/L) ISA | ITR | POS | VOR | CSF | MCF | AMB | TERB | Cyp51A* | Fks1* | ST |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 22432 | 2/9/2010 | *Aspergillus fumigatus* | 0.25 | 0.25 | 0.12 | 0.25 | 0.12 | 0.03 | 2 | 1 | Y46F, V172M, T248N, E255D, K427E | ND[$] | 9 |
| 2 | 23525 | 5/4/2010 | *Aspergillus fumigatus* | 0.25 | 0.25 | 0.12 | 0.12 | 0.12 | 0.03 | 2 | 0.5 | Y46F, V172M, T248N, E255D, K427E | ND | 9 |
| 3 | 24053A | 6/15/2010 | *Aspergillus fumigatus* | 0.25 | 0.25 | 0.25 | 0.25 | 0.12 | 0.03 | 2 | 1 | Y46F, V172M, T248N, E255D, K427E | S53G | 12 |
| 4 | 24053B | 6/15/2010 | *Aspergillus fumigatus* | 0.5 | 0.25 | 0.25 | 1 | 2 | 2 | 2 | 1 | Y46F, V172M, T248N, E255D, K427E | S53G and F675S | 9 |
| 5 | 24555 | 7/28/2010 | *Aspergillus fumigatus* | 0.25 | 0.25 | 0.25 | 0.25 | 0.12 | 0.03 | 2 | 0.5 | Y46F, V172M, T248N, E255D, K427E | ND | 9 |
| 6 | 29576A | 7/27/2011 | *Aspergillus flavus* | 0.25 | 0.5 | 0.25 | 0.25 | 0.12 | 0.03 | 2 | 0.06 | WT[#] | ND | ND |
| 7 | 29576B | 7/27/2011 | *Aspergillus fumigatus* | 0.25 | 0.25 | 0.25 | 0.25 | 0.12 | 0.03 | 2 | 0.5 | Y46F, V172M, T248N, E255D, K427E | ND | 9 |
| 8 | 30906 | 10/25/2011 | *Aspergillus fumigatus* | 0.25 | 0.5 | 0.25 | 0.12 | 0.12 | 0.03 | 2 | 1 | Y46F, V172M, T248N, E255D, K427E | ND | 12 |
| 9 | 33460 | 4/10/2012 | *Aspergillus fumigatus* | 0.25 | 0.5 | 0.25 | 0.12 | 0.12 | 0.03 | 2 | 1 | Y46F, V172M, T248N, E255D, K427E | ND | 9 |
| 10 | 45755 | 12/30/2013 | *Aspergillus fumigatus* | 2 | 1 | 1 | 0.5 | 0.12 | 0.03 | 2 | 1 | Y46F, V172M, T248N, E255D, K427E | ND | 12 |
| 11 | 53619 | 1/28/2015 | *Aspergillus fumigatus* | 0.25 | 0.5 | 0.25 | 0.25 | 0.12 | 0.03 | 2 | 0.5 | Y46F, V172M, T248N, E255D, K427E | ND | 9 |
| 12 | 62194 | 12/24/2015 | *Aspergillus fumigatus* | 0.25 | 0.5 | 0.25 | 0.12 | 0.12 | 0.03 | 2 | 0.5 | Y46F, V172M, T248N, E255D, K427E | ND | 9 |
| | ATCC13073 | | *Aspergillus fumigatus* | 0.25 | 0.25 | 0.25 | 0.25 | 0.12 | 0.03 | 2 | 1 | ND | S53G | ND |
| | R21 | | *Aspergillus fumigatus* | 0.25 | 0.25 | 0.25 | 0.25 | 0.12 | 0.03 | 2 | 2 | ND | WT | ND |
| | Af293 | | *Aspergillus fumigatus* | 0.12 | 0.12 | 0.12 | 0.12 | 0.06 | 0.03 | 1 | 0.5 | ND | WT | ND |

*Ref strain used Af293 [$]ND = not determined [#]Ref strain used *A. flavus* NRRL3357

# 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 2018

## 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<br>A. flavus |

Clinical Microbiology and Infection xxx (2018) e1–e38

# ESCMID-EFISG Aspergillus Guideline 2018

## 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)<br>*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

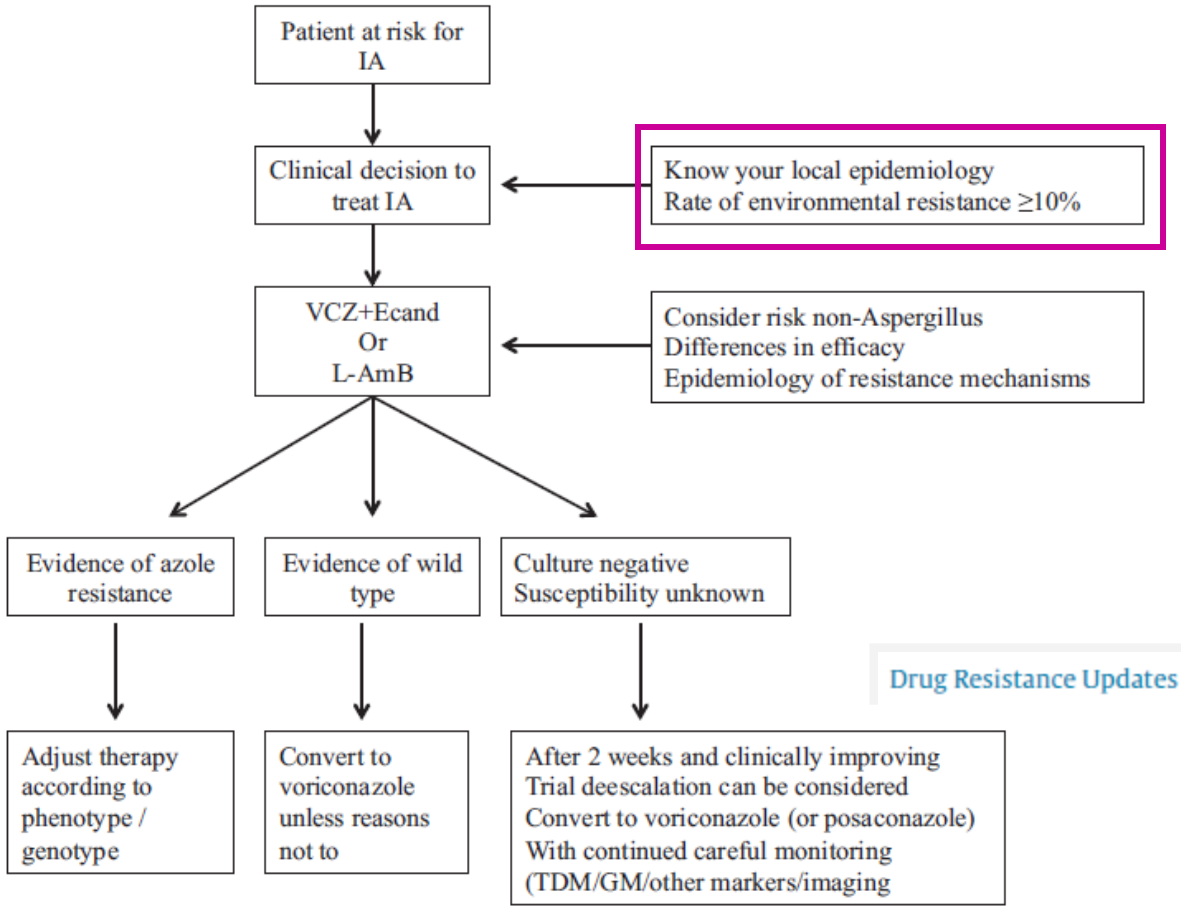
## Direnç nasıl gelişiyor ?

## "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<br>Trends in distribution of resistance mutations<br>Detection of new resistance mutations | A substantial number of isolates may be screened<br>Relatively straightforward to conduct | Includes isolates that are clinically not relevant or from colonized/ untreated patients<br>May not correspond to resistance frequency in specific risk groups | Denominator bias<br>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<br>Variability in underlying diseases<br>Variability in management/ sampling strategy | Case definition, case ascertainment and sampling bias<br>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<br>Relatively uniform management and sampling strategy in single-centre design | Requires a substantial effort to evaluate and classify patients<br>May take a long time to include a meaningful number of cases<br>Variability in management/ sampling strategy in multicentre design | Case definition, case ascertainment and sampling bias<br>Laboratory practice and procedure bias in multicentre design |

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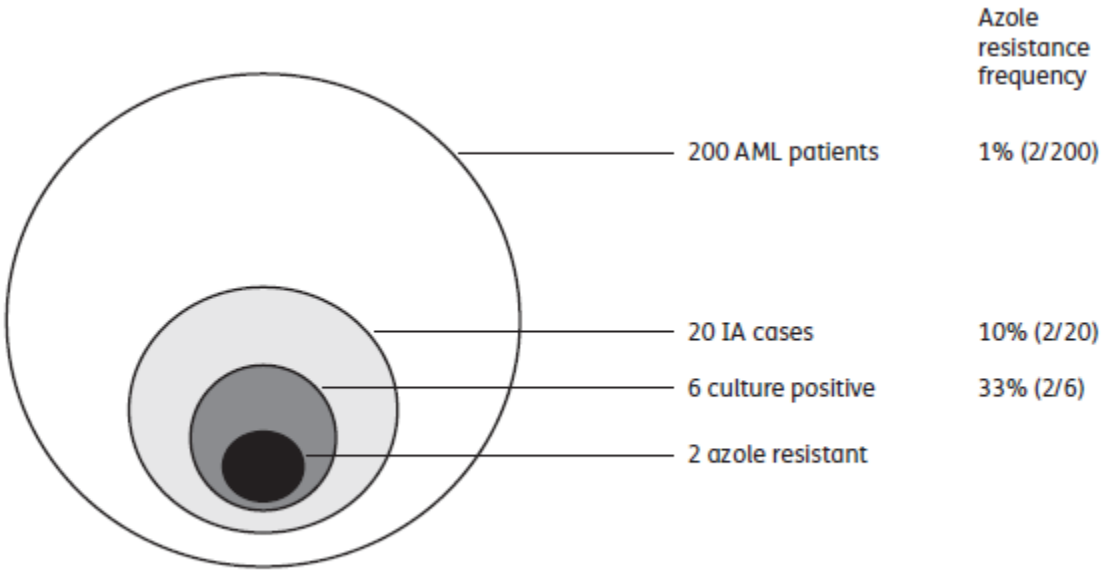


**Figure 1.** Impact of the denominator on the resistance frequency in azole resistance surveillance. Resistance rates are calculated for a theoretical population of 200 AML patients, with a 10% prevalence of IA and 33% culture positivity.

"…….**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……."

CID 2017:65 (15 July)

# Changes in In Vitro Susceptibility Patterns of *Aspergillus* to Triazoles and Correlation With Aspergillosis Outcome in a Tertiary Care Cancer Center, 1999–2015

Sang Taek Heo,[1,2,a] Alexander M. Tatara,[1,3,a,c] Cristina Jiménez-Ortigosa,[4] Ying Jiang,[1] Russell E. Lewis,[1,b] Jeffrey Tarrand,[5] Frank Tverdek,[6] Nathaniel D. Albert,[1] Paul E. Verweij,[7] Jacques F. Meis,[7] Antonios G. Mikos,[3] David S. Perlin,[4] and Dimitrios P. Kontoyiannis[1]

***Methods.*** We examined changes over time in triazole minimum inhibitory concentrations (MICs) of 290 sequential *Aspergillus* isolates recovered from respiratory sources during 1999–2002 (before introduction of the *Aspergillus*-potent triazoles voriconazole and posaconazole) and 2003–2015 at MD Anderson Cancer Center. We also tested for polymorphisms in ergosterol biosynthetic genes (*cyp51A*, *erg3C*, *erg1*) in the 37 *Aspergillus fumigatus* isolates isolated from both periods that had non-wild-type (WT) MICs. For the 107 patients with hematologic cancer and/or HSCT with invasive pulmonary aspergillosis, we correlated in vitro susceptibility with 42-day mortality.

***Results.*** Non-WT MICs were found in 37 (13%) isolates and was only low level (MIC <8 mg/L) in all isolates. Higher-triazole MICs were more frequent in the second period and were *Aspergillus*-species specific, and only encountered in *A. fumigatus*. No polymorphisms in *cyp51A*, *erg3C*, *erg1* genes were identified. There was no correlation between in vitro MICs with 42-day mortality in patients with invasive pulmonary aspergillosis, irrespective of antifungal treatment. Asian race (odds ratio [OR], 20.9; 95% confidence interval [CI], 2.5–173.5; $P = .005$) and azole exposure in the prior 3 months (OR, 9.6; 95% CI, 1.9–48.5; $P = .006$) were associated with azole resistance.

***Conclusions.*** Non-WT azole MICs in *Aspergillus* are increasing and this is associated with prior azole exposure in patients with hematologic cancer or HSCT. However, no correlation of MIC with outcome of aspergillosis was found in our patient cohort.

**Table 4. Crude Mortality Within 42 Days in Patients With Invasive Pulmonary Aspergillosis According to Various Minimum Inhibitory Concentration Cutoffs of the *Aspergillus* Isolates[a]**

| | Rate of Mortality Within 42 Days, no./No. (%) | | |
|---|---|---|---|
| MIC Cutoff, μg/mL | MIC ≤ Cutoff | MIC > Cutoff | *P* Value[c] |
| Itraconazole | | | |
| 1 | 30/83 (36) | 7/19 (37) | .95 |
| 2 | 33/91 (36) | 4/11 (36) | >.99 |
| 3 | 35/95 (37) | 2/7 (29) | >.99 |
| 4 | 37/102[b] (36) | NA | … |
| Voriconazole | | | |
| 1 | 30/86 (35) | 7/16 (44) | .50 |
| 2 | 36/98 (37) | 1/4 (25) | >.99 |
| 3 | 36/100 (36) | 1/2 (50) | >.99 |
| Posaconazole | | | |
| 0.25 | 31/85 (36) | 6/17 (35) | .93 |
| 0.5 | 34/93 (37) | 3/9 (33) | >.99 |
| 1 | 36/97 (37) | 1/5 (20) | .65 |
| 2 | 37/102 (36) | NA | … |
| Isavuconazole | | | |
| 1 | 37/102 (36) | NA | … |

Abbreviations: MIC, minimum inhibitory concentration; NA, not applicable.

[a]Clinical and Laboratory Standards Institute criteria.

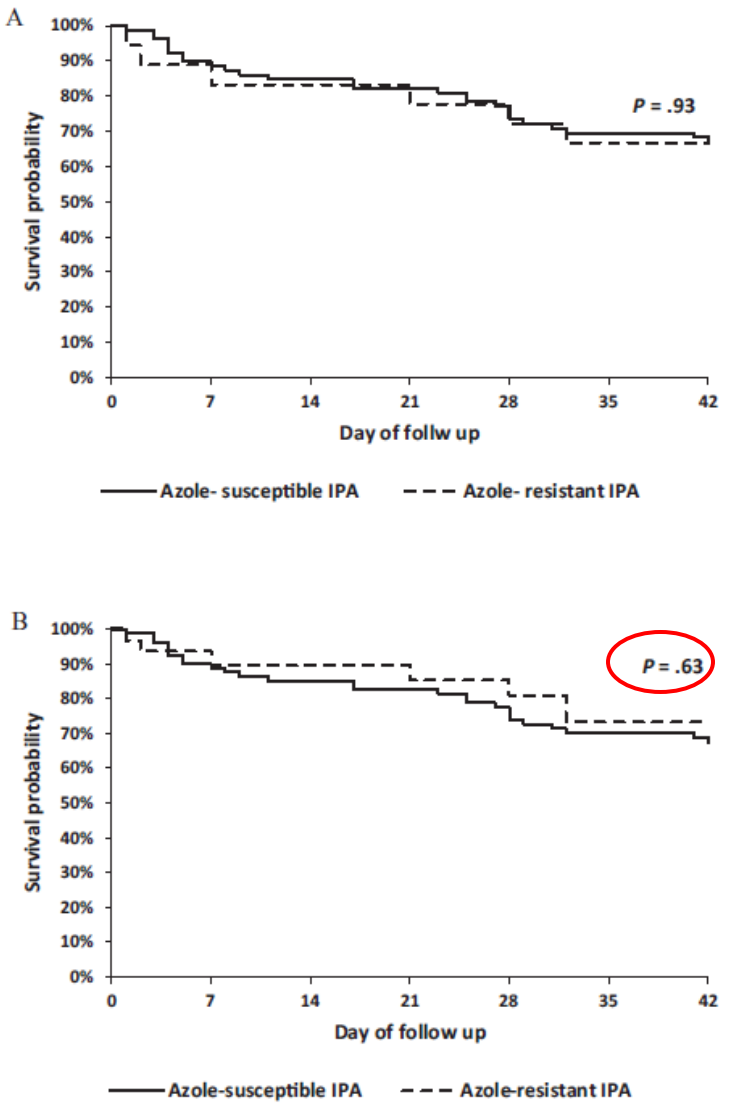


**Figure 2.** Survival curves for patients who had either azole wild-type or azole non–wild-type invasive pulmonary aspergillosis (IPA). *A*, Kaplan-Meier survival curve. *B*, Adjusted Kaplan-Meier survival curve (adjusted for history of neutropenia, lymphopenia, intensive care unit admission, and time period of IPA diagnosis).

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# PCR-based detection of *Aspergillus fumigatus Cyp51A* mutations on bronchoalveolar lavage: a multicentre validation of the AsperGenius assay® in 201 patients with haematological disease suspected for invasive aspergillosis

G. M. Chong[1]*, M. T. van der Beek[2], P. A. von dem Borne[3], J. Boelens[4], E. Steel[5], G. A. Kampinga[6], L. F. R. Span[7], K. Lagrou[8], J. A. Maertens[9], G. J. H. Dingemans[10], G. R. Gaajetaan[10], D. W. E. van Tegelen[10], J. J. Cornelissen[11], A. G. Vonk[12] and B. J. A. Rijnders[1]

**Results:** Two hundred and one patients each contributed one BAL sample, of which 88 were positive controls and 113 were negative controls. The optimal cycle threshold cut-off value for the *Aspergillus* species PCR was <38. With this cut-off, the PCR was positive in 74/88 positive controls. The sensitivity, specificity, positive predictive value and negative predictive value were 84%, 80%, 76% and 87%, respectively. 32/74 BAL samples were culture negative. Azole treatment failure was observed in 6/8 patients with a RAM compared with 12/45 patients without RAMs ($P=0.01$). Six week mortality was 2.7 times higher in patients with RAMs (50.0% versus 18.6%; $P=0.07$).

**Conclusions:** The AsperGenius® assay had a good diagnostic performance on BAL and differentiated WT from *Aspergillus fumigatus* with RAMs, including in culture-negative BAL samples. Most importantly, detection of RAMs was associated with azole treatment failure.

# SONUÇ ve ÖNERİLER

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

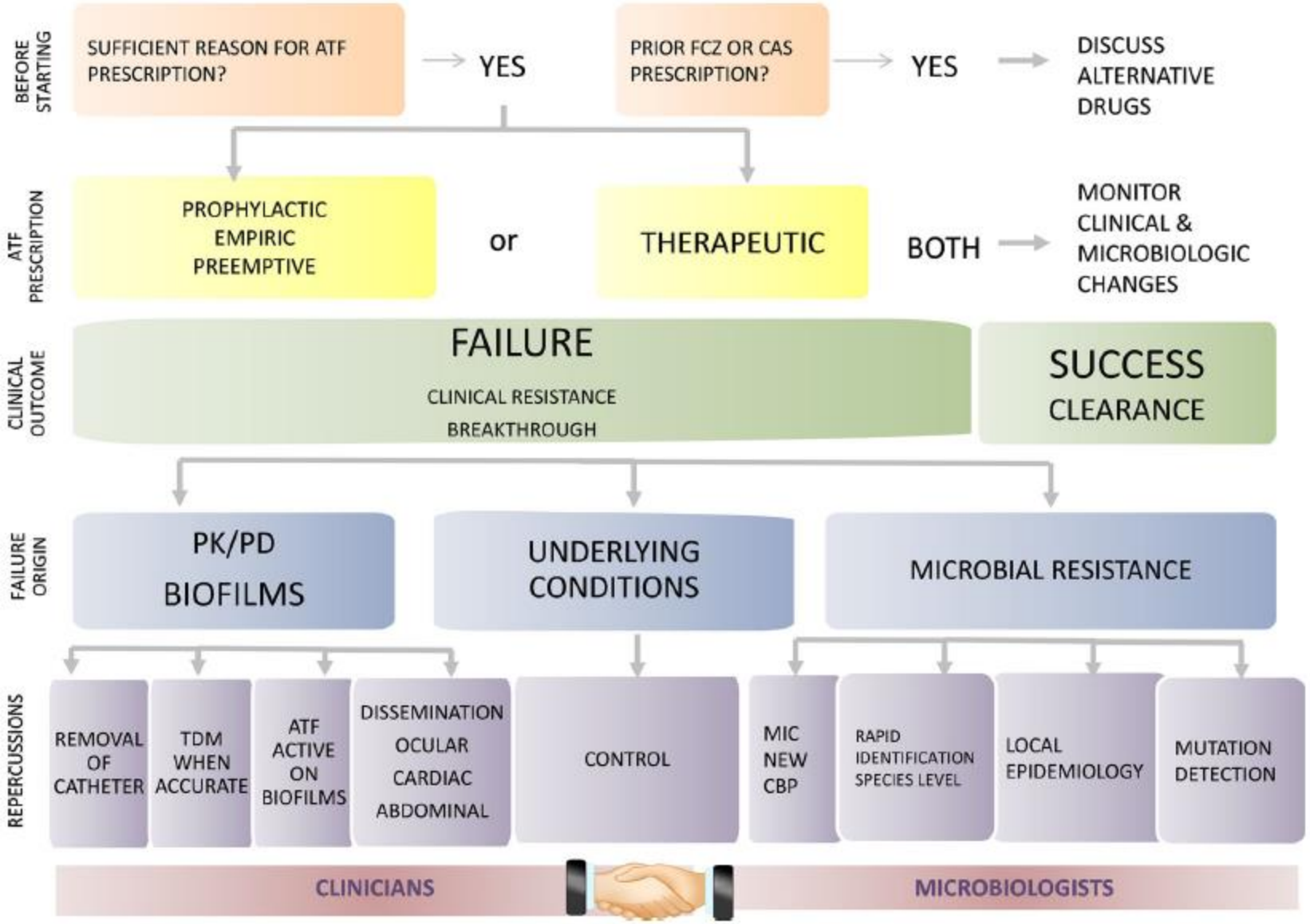


**Fig. 3** Bedside strategy for circumventing antifungal drug resistance in 2014. *ATF* antifungal drug, *FCZ* fluconazole, *CAS* caspofungin, *PK/PD* pharmacokinetics and pharmacodynamics, *TDM* therapeutic drug monitoring, *MIC* minimal inhibitory concentration, *CBP* clinical breakpoint

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