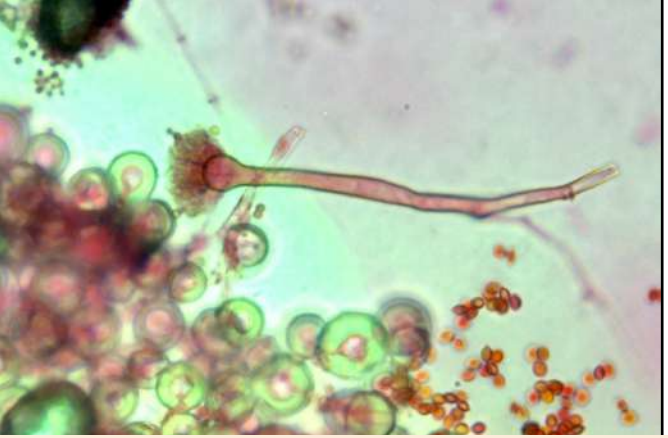


KLİMİK MİÇG-ADÇG Simpozyumu
9-10 Haziran 2023 Ankara
Oturum 4: İnvaziv Fungal Enfeksiyonlarda Antifungal Direnç ve Getirileri

Küf Mantarlarında Direnç Durumu ve Getirileri

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

SUNUM AKIŞI

- Temel Bilgiler ve Doğal Direnç (Tedavi Altında Gelişen Enfeksiyonlar)
- Kazanılmış Direnç: Önem Kazanan/Yeni Sorunlar, Yeni Gelişmeler, Getirileri
  - *Aspergillus*
- Sonuçlar

Fungal Nomenclature: Managing Change is the Name of the Game

Open Forum Infectious Diseases, Volume 10, Issue 1, January 2023

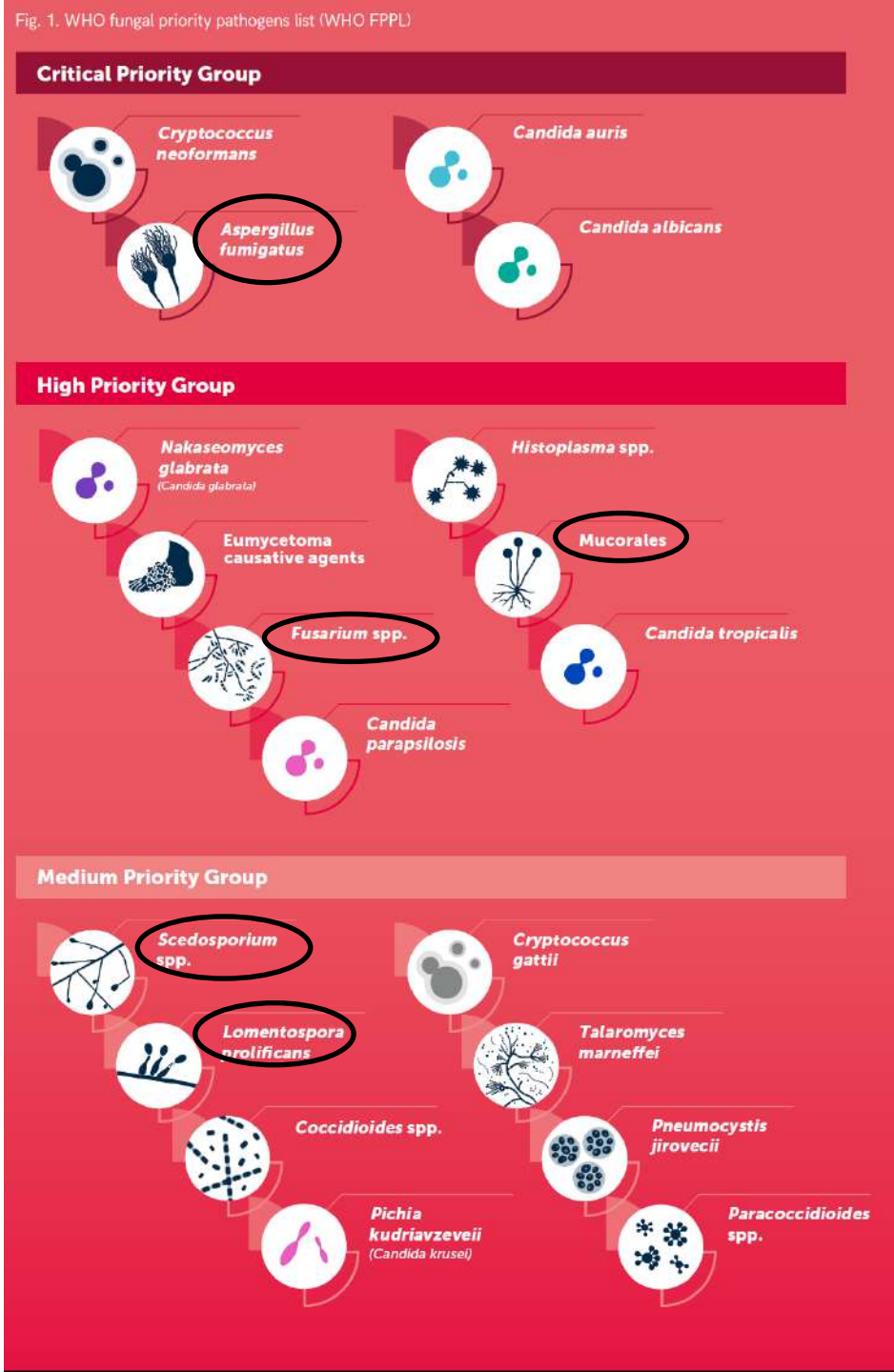
Sarah E. Kidd,[1,2] Alireza Abdolrasouli,[3,4] and Ferry Hagen[5,6,7]

Previous Name(s)	Current Name	Commonly Associated Infections	Reference
Acremonium kiliense	*Sarocladium kiliense*	Fungemia, subcutaneous infections	[58]
Acremonium roseogriseum	*Gliomastix roseogrisea*	Not associated with infection	[58]
Acremonium strictum	*Sarocladium strictum*	Cutaneous, invasive infections	[58]
Arthroderma benhamiae	*Trichophyton benhamiae*	Cutaneous infections	[59]
Cerinosterus cyanescens, *Sporothrix cyanescens*	*Quambalaria cyanescens*	Peritonitis, pneumonia, postsurgical complications	[60]
Fusarium dimerum	*Bisifusarium dimerum*	Keratitis, invasive infections	[61]
Fusarium falciforme, *Acremonium falciforme*	*Neocosmospora falciformis*	Keratitis, invasive infections	[61]
Fusarium keratoplasticum	*Neocosmospora keratoplastica*	Keratitis, invasive infections	[61]
Fusarium lichenicola	*Neocosmospora lichenicola*	Keratitis, invasive infections	[61]
Fusarium petroliphilum	*Neocosmospora petroliphila*	Keratitis, invasive infections	[61]
Fusarium solani	*Neocosmospora solani*	Keratitis, invasive infections	[61]
Geosmithia argillacea, *Penicillium argillaceum*	*Rasamsonia argillacea*	Respiratory infections, especially in cystic fibrosis	[62]
Gibberella fujikuroi	*Fusarium fujikuroi*	Keratitis, invasive infections	[63]
Lecythophora hoffmannii, *Phialophora hoffmannii*	*Coniochaeta hoffmannii*	Subcutaneous infections	[64]
Microsporum cookei	*Paraphyton cookei*	Cutaneous infections	[59]
Microsporum fulvum	*Nannizzia fulva*	Cutaneous infections	[59]
Microsporum gallinae	*Lophophyton gallinae*	Cutaneous infections	[59]
Microsporum gypseum	*Nannizzia gypsea*	Cutaneous infections	[59]
Microsporum nanum	*Nannizzia nana*	Cutaneous infections	[59]
Microsporum persicolor	*Nannizzia persicolor*	Cutaneous infections	[59]
Neosartorya fischeri, *Neosartorya pseudofischeri*, *Aspergillus thermomutatus*	*Aspergillus fischeri*	Respiratory, invasive infections, allergic conditions	[50]
Neosartorya udagawae	*Aspergillus udagawae*	Respiratory, invasive infections, allergic conditions	[50]
Paecilomyces lilacinus	*Purpureocillium lilacinum*	Keratitis, cutaneous infections	[65]
Paecilomyces marquandii	*Marquandomyces marquandii*	Cutaneous infections (rare)	[66]
Penicillium marneffei	*Talaromyces marneffei*	Systemic infections	[67]
Penicillium purpureogenum	*Talaromyces purpureogenus*	Pulmonary infections (rare)	[67]
Trichophyton terrestre	*Arthroderma terrestre*	Doubtful pathogenicity	[59]
Trichophyton ajelloi	*Arthroderma uncinatum*	Cutaneous infections	[59]
Trichophyton mentagrophytes			
var *interdigitale*	*Trichophyton interdigitale*	Cutaneous infections	[68]
var *mentagrophytes*	*Trichophyton mentagrophytes*	Cutaneous infections	[68]
genotype VIII	*Trichophyton indotineae*	Cutaneous infections	[69]

SAA 06/2023

WHO fungal priority pathogens list to guide research, development and public health action

25/Oct/2022



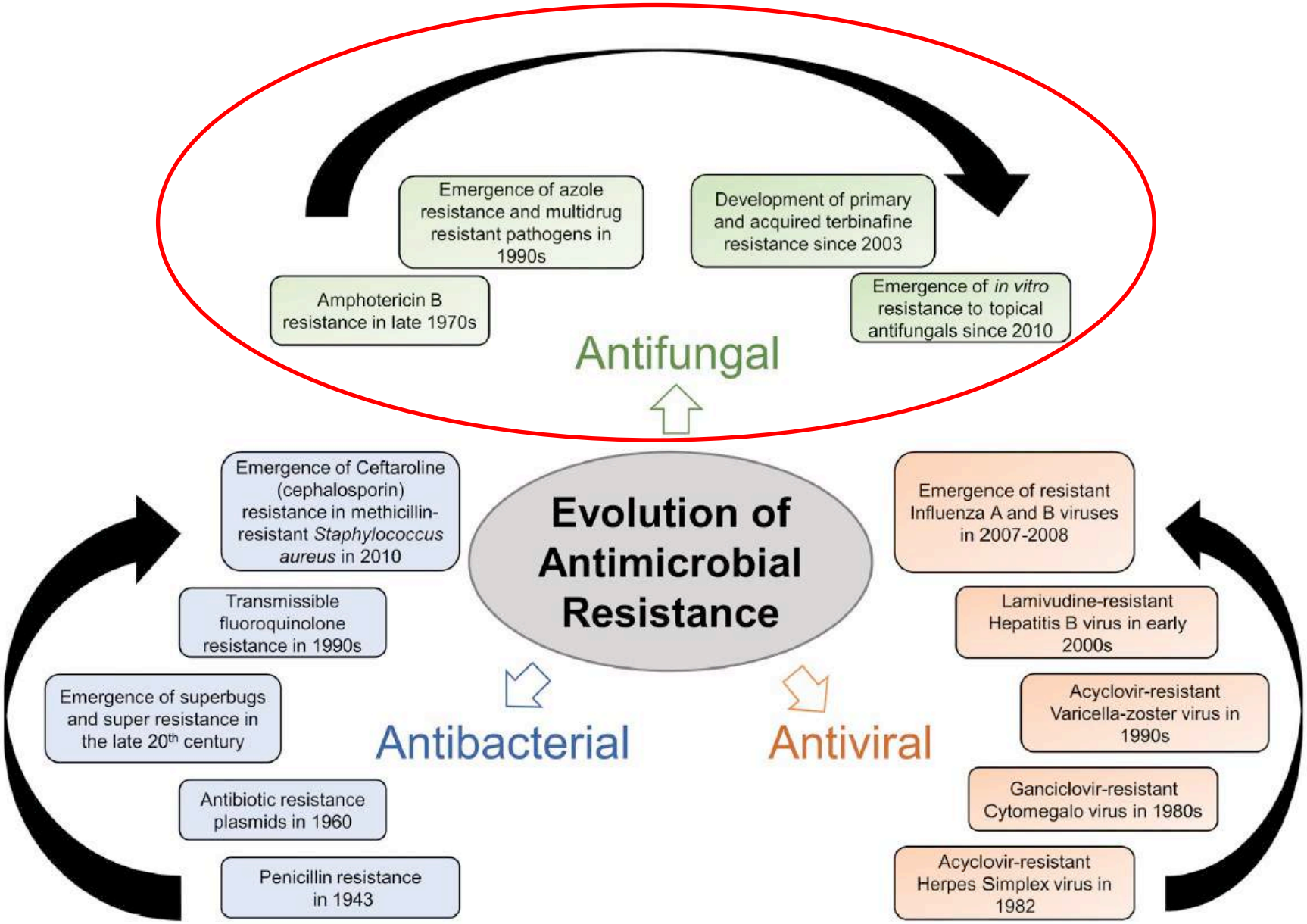


Figure 1. Evolution of antimicrobial resistance.

JOURNAL OF DERMATOLOGICAL TREATMENT
2022, VOL. 33, NO. 4, 1888–1895
https://doi.org/10.1080/09546634.2021.1942421

İklim değişikliği ve dirençli mantarların ortaya çıkışı…

Climate change and the emergence of fungal pathogens

Nnaemeka Emmanuel Nnadi[1], Dee A. Carter[2]*

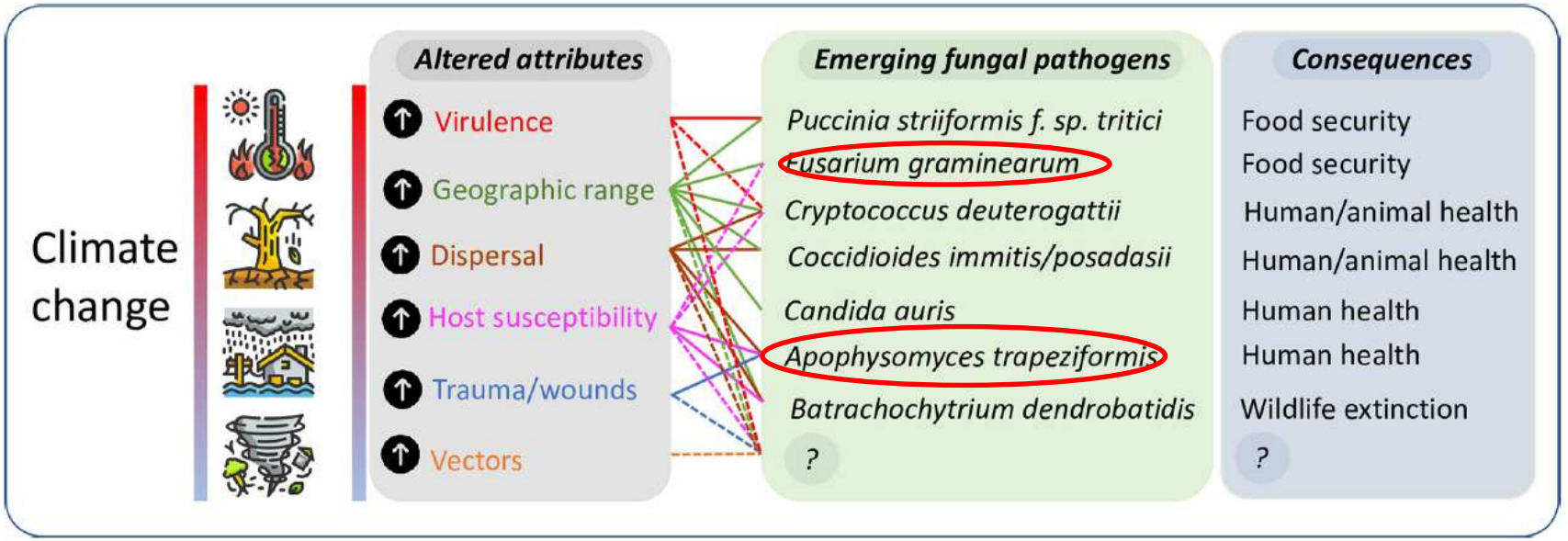


Fig 1. The effect of climate change on the emergence of fungal pathogens. Climate change alters attributes of the fungus, the environment, and the host, which can then drive the emergence of novel, uncommon, or adapted fungal species, with consequences for health, biodiversity, and food security. On this figure, solid lines between attributes and fungal species show links supported by published evidence; dashed lines show probable but unproven links. "?" represents the emergence of as-yet unknown fungal species and unknown consequences.

PLoS Pathog 17(4): e1009503 2021

In vitro direnç, klinik yanıtı belirleyen faktörlerden sadece birisidir

FUNGUS

- In vitro resistance

Primary (Intrinsic)
Secondary (Acquired)

ANTIFUNGAL

- PK/PD - -
  Ineffective dose
  Fungistatic effect
  Suboptimal bioavailability
- Potential drug-drug interactions

- Immune status
- Foreign body
- Abscess formation
- Noncompliance

HOST

DİRENÇ ve TOLERANS
Tanımlar

BOTH are defined as «ability of growth at high concentrations of antifungal drugs above the defined (breakpoint) MIC» BUT:

an inhibitory drug. Resistance is due to genetic changes that directly affect either the drug target and/or intracellular drug concentrations and cause a heritable effect on the entire population of cells in a given isolate. By contrast, tolerance is a feature of susceptible (non-resistant) isolates that relies upon several central stress response pathways; it is a consequence of phenotypic heterogeneity, in which some cells in the population grow, albeit slowly, in drug. Differences in tolerance levels between isolates is assumed to have a genetic basis, and to affect the proportion of cells able to grow in drug. The mechanisms that drive cell-to-cell differences in drug responses within a single isolate remain to be determined; but, at least for azoles, they seem to be connected to differences in intracellular drug concentration between different cells.

Nat Rev Microbiol. 2020 February 11; 18(6): 319–331

Tanımlar

Heteroresistance	Heteroresistance is a clinical term for isolates that contain small subpopulations of cells (generally <1%) that have the ability grow at drug concentrations that are at least 8-times above the minimum inhibitory concentration (MIC) for the vast majority of susceptible cells in the population.

Trailing growth	Trailing growth is generally defined as reduced but persistent visible growth of *Candida* spp. at fluconazole concentrations above the minimum inhibitory concentration (MIC). Trailing has also been described as an increase in the MIC during growth beyond 24h (the standard endpoint for MIC measurements for *Candida* species). It can be measured as the residual growth in the presence of fluconazole concentrations above the MIC. Trailing was quantified in a recent study as the percentage of residual yeast growth at fluconazole concentrations above the MIC in each well and mean trailing as the geometric mean of trailing observed in all the wells above the MIC.

Nat Rev Microbiol. 2020 February 11; 18(6): 319–331

Antifungal İlaçlar

Table 1 Essential antifungal agents as assessed by the WHO. Access and antifungal price by country is visible here: https://wwwgaffiorg/antifungal-drug-maps/.

Antifungal	Route(s)	Primary indications	Resistance concerns
Griseofulvin	Oral	Tinea corporis and capitis	Some clinical resistance described
Fluconazole	Oral, IV	Mucosal candidiasis, prophylaxis in leukaemia, HSCT and intensive care, treatment and maintenance therapy for cryptococosis	All moulds, including *Aspergillus* resistant. Lower response rates for endemic mycoses such as histoplasmosis. All *Candida auris* and *Candida krusei* strains resistant—some other species less susceptible or resistant
Amphotericin B	IV and topical	Invasive candidiasis and cryptococcal meningitis, endemic fungal infections. Empiric therapy in febrile neutropenia. Lower response rate for invasive aspergillosis than azoles	*Aspergillus terreus* and *nidulans* resistant. Some strains of *Candida auris* resistant. Several intrinsically resistant fungi
Flucytosine	Oral, IV*	Cryptococcal meningitis, neonatal candidiasis and *Candida* endocarditis and endophthalmitis, other rare fungal infections	Low levels of resistance in *Candida* and *Cryptococcus*. Aspergilli and most moulds and endemic fungi resistant
Itraconazole	Oral, IV*	All skin infections, all forms of aspergillosis, endemic fungal infections, mucosal candidiasis, prophylaxis in leukaemia	Rising problems with resistance in *Aspergillus fumigatus*, *flavus* and *niger*. Some cross resistance with fluconazole in *Candida*
Voriconazole	Oral, IV	Invasive and chronic aspergillosis, some rare moulds	Some azole cross resistance in *Aspergillus*. Mucorales intrinsically resistant
Natamycin 5%	Topical, eye	Fungal keratitis	Most effective agent, but some rarer fungi resistant, probably
Echinocandins (micafungin, caspofungin, anidulafungin)	IV	Candidaemia, invasive candiasis, invasive and chronic pulmonary aspergillosis, prophylaxis	Most effective agent for most *Candida* infections, notably the majority of *Candida auris* strains. Less effective than azoles for aspergillosis.

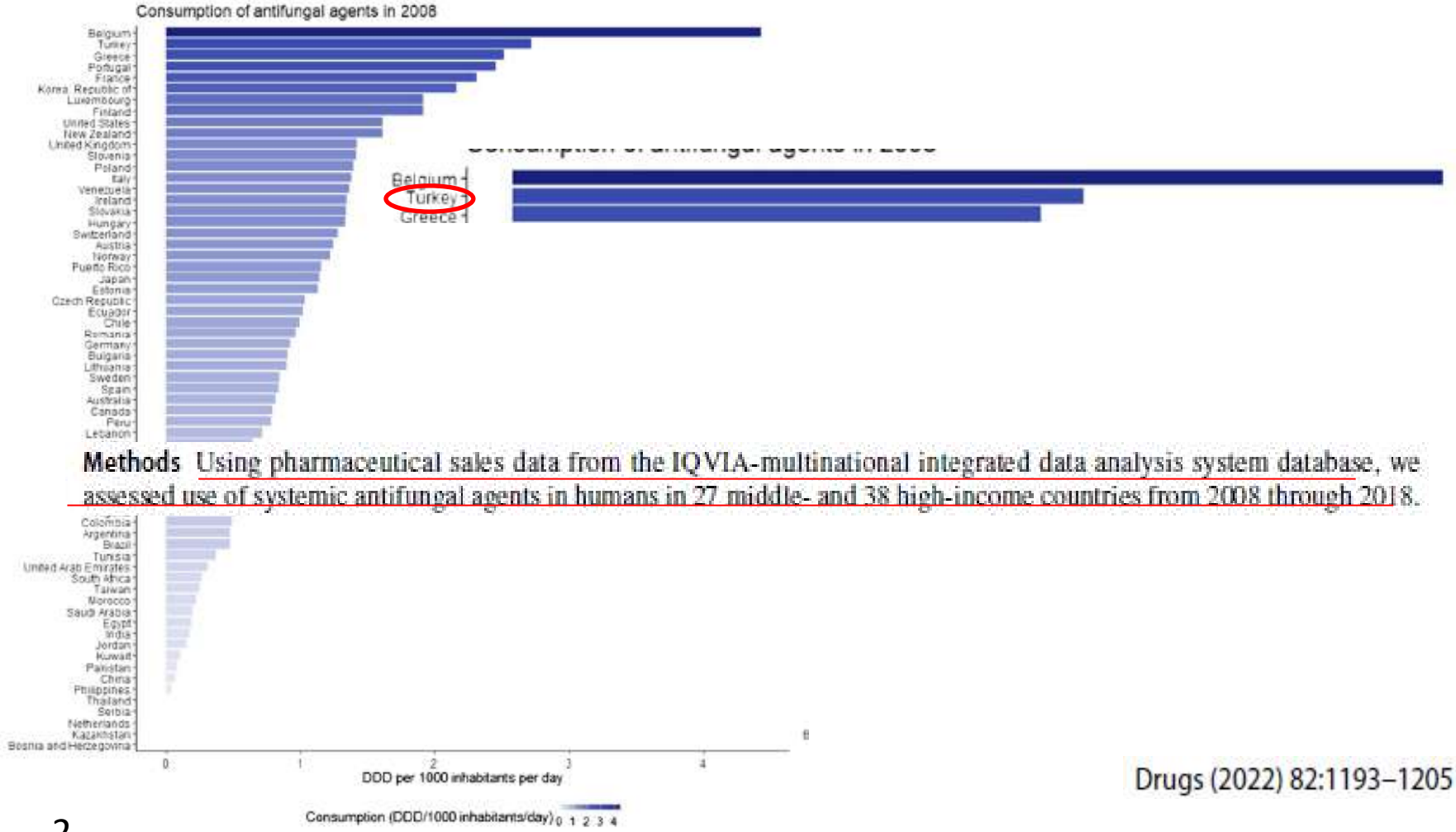
*Many countries only have oral
HSCT, haematopoetic stem cell transplant; ; IV, intravenous.

Denning DW. *Eur J Hosp Pharm* 2022;**29**:109–112

2008 yılı

Global Consumption Trend of Antifungal Agents in Humans From 2008 to 2018: Data From 65 Middle- and High-Income Countries

Swathi Pathadka[1,2] · Vincent K. C. Yan[1] · Chin Fen Neoh[3,4,5,6] · Daoud Al-Badriyeh[7] · David C. M. Kong[8,9,10] · Monica A. Slavin[3,4,11] · Benjamin J. Cowling[12] · Ivan F. N. Hung[13] · Ian C. K. Wong[1,14,15,16] · Esther W. Chan[1,16,17,18]



Methods Using pharmaceutical sales data from the IQVIA-multinational integrated data analysis system database, we assessed use of systemic antifungal agents in humans in 27 middle- and 38 high-income countries from 2008 through 2018.

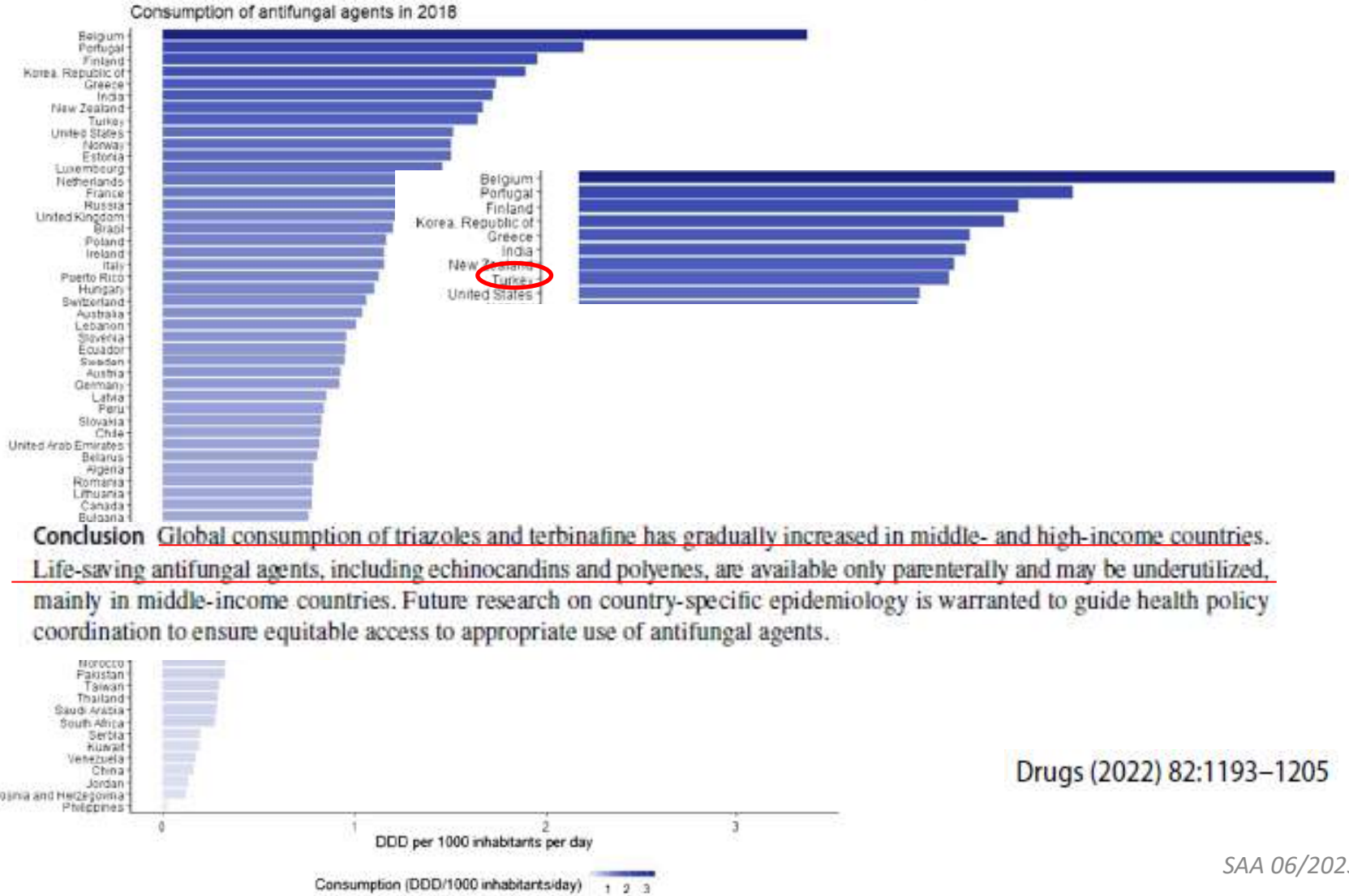
Drugs (2022) 82:1193–1205

2.

2018 yılı

Global Consumption Trend of Antifungal Agents in Humans From 2008 to 2018: Data From 65 Middle- and High-Income Countries

Swathi Pathadka[1,2] · Vincent K. C. Yan[1] · Chin Fen Neoh[3,4,5,6] · Daoud Al-Badriyeh[7] · David C. M. Kong[8,9,10] · Monica A. Slavin[3,4,11] · Benjamin J. Cowling[12] · Ivan F. N. Hung[13] · Ian C. K. Wong[1,14,15,16] · Esther W. Chan[1,16,17,18]

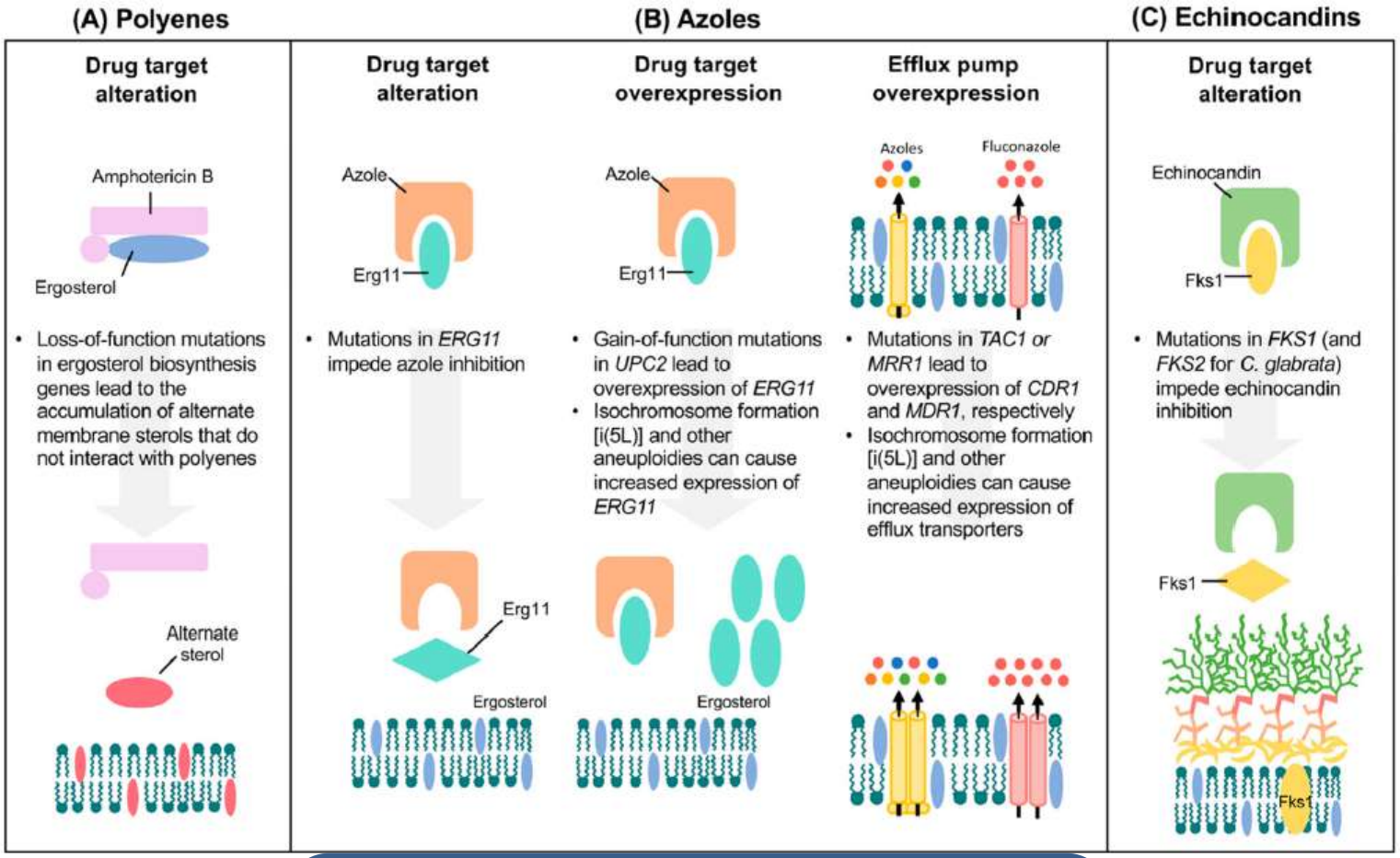


Conclusion Global consumption of triazoles and terbinafine has gradually increased in middle- and high-income countries. Life-saving antifungal agents, including echinocandins and polyenes, are available only parenterally and may be underutilized, mainly in middle-income countries. Future research on country-specific epidemiology is warranted to guide health policy coordination to ensure equitable access to appropriate use of antifungal agents.

Drugs (2022) 82:1193–1205

8.

Antifungal Dirençte Rol Oynayan Moleküler Mekanizmalar



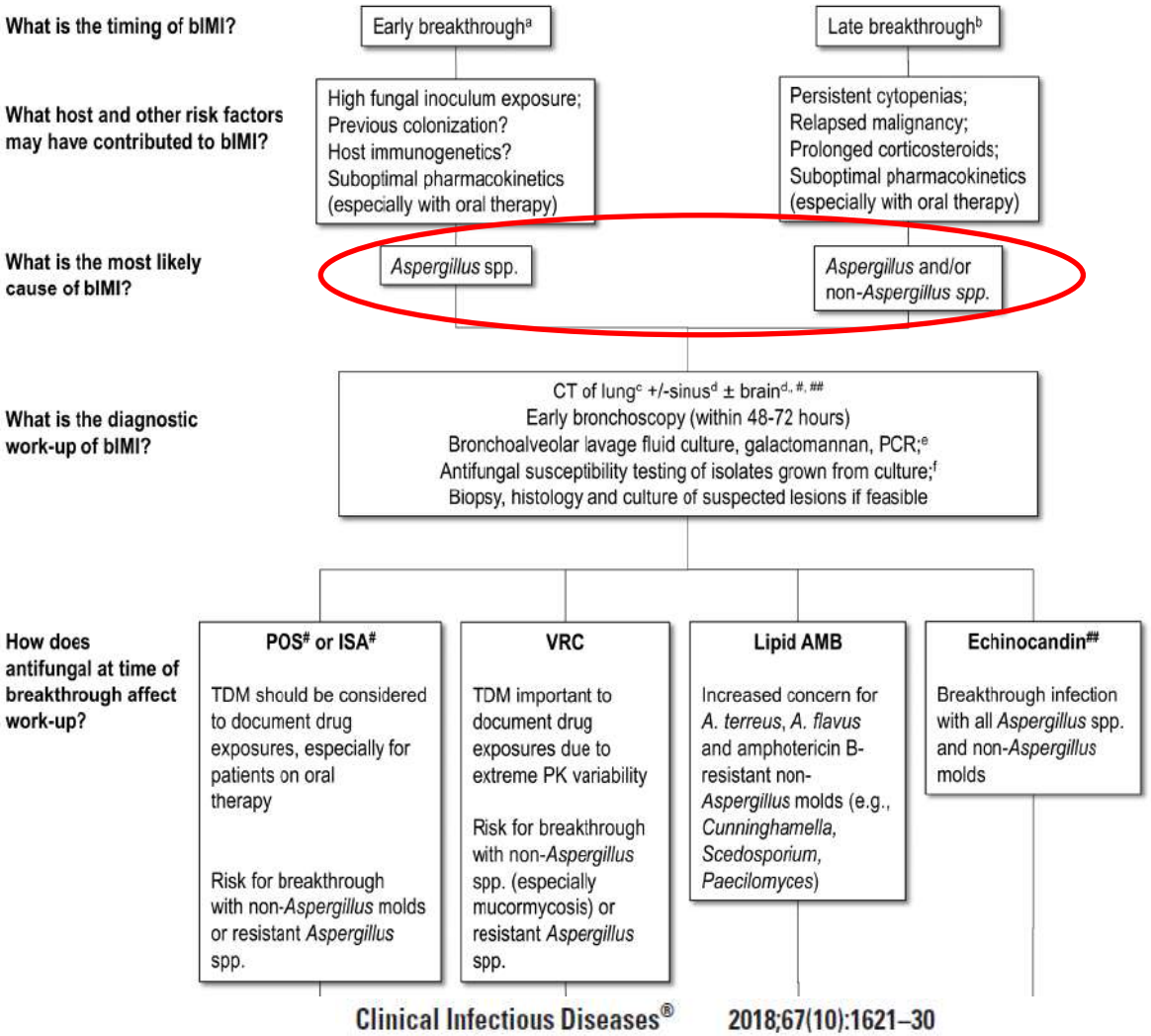
Mechanisms of *Intrinsic* Resistance:
Absence of target
Low affinity target
Low permeability
Efflux mechanisms

Chem Rev. 2021 March 24; 121(6): 3390–3411

Küfler ve Doğal Direnç

Breakthrough Invasive Mold Infections in the Hematology Patient: Current Concepts and Future Directions

Michail S. Lionakis,[1] Russell E. Lewis,[2] and Dimitrios P. Kontoyiannis[3]



Clinical Infectious Diseases® 2018;67(10):1621–30

SAA 06/2023

«Kriptik» ASPERGILLUS türleri: Antifungal İlaçlara Direnç/Azalmış Duyarlılık Düşündüren Yüksek MİK Değerleri

Species	Section	Antifungal drug(s)	**References**
A. alabamensis	Terrei	AMB	(Balajee et al., 2009a)
A. alliaceus	Flavi	AMB, CAS*	(Alastruey-Izquierdo et al., 2013; Balajee et al., 2007)
A. calidoustus	Usti	AMB, Azoles (ITC, POS, VRC), CAS*	(Baddley et al., 2009; Balajee et al., 2009b; Negri et al., 2014; Varga et al., 2008; Won et al., 2018)
A. flavus	Flavi	AMB	(Gomez-Lopez et al., 2003; Goncalves et al., 2013; Khodavaisy et al., 2016; Koss et al., 2002; Lionakis et al., 2005; Taghizadeh-Armaki et al., 2017)
A.foetidus (A.acidus)	Nigri	Azoles (ITC)	(Alcazar-Fuoli et al., 2009; Howard et al., 2011)
A. fumigatiaffinis	Fumigati	AMB, Azoles (ITC, VRC)	(Alastruey-Izquierdo et al., 2013; Alcazar-Fuoli et al., 2008)
A. lentulus	Fumigati	AMB, Azoles (ITC, VRC), CAS*	(Alcazar-Fuoli et al., 2008; Alhambra et al., 2008; Balajee et al., 2009b; Montenegro et al., 2009; Won et al., 2018)
A. niger	Nigri	Azoles* (ITC, VRC)	(Hashimoto et al., 2017; Howard et al., 2011; Howard et al., 2013; Iatta et al., 2016)
A. tubingensis	Nigri	Azoles* (ITC, VRC)	(Alcazar-Fuoli et al., 2009; Gomez-Lopez et al., 2003; Hashimoto et al., 2017; Howard et al., 2011; Iatta et al., 2016; Pfaller et al., 2008)
A. sydowii	Versicolores	AMB, Azoles* (ITC)	(Pfaller et al., 2008; Siqueira et al., 2016; Takahata et al., 2008; Won et al., 2018)
A. terreus	Terrei	AMB, Azoles* (POS, VRC)	(Baddley et al., 2009; Baddley et al., 2003; Caston et al., 2007; Hachem et al., 2004; Lass-Flörl et al., 2005; Risslegger et al., 2017; Steinbach et al., 2004; Sutton et al., 1999; Zoran et al., 2018)
A. udagawae	Fumigati	AMB, Azoles (ITC, VRC)	(Balajee et al., 2009b; Lyskova et al., 2018; Tamiya et al., 2015; Vinh et al., 2009)
A.versicolor	Versicolores	AMB*, Azoles* (ITC)	(Pfaller et al., 2008; Torres-Rodriguez et al., 1998)
A. welwitschiae	Nigri	Azoles* (ITC, VRC)	(Hashimoto et al., 2017)

*Variable susceptibility AMB: Amphotericin B CAS: Caspofungin ISA: Isavuconazole ITC: Itraconazole POS: Posaconazole VRC: Voriconazole

Doğal Direnç-*Aspergillus* Tedavi Önerileri

Table 18
Antifungal regimens in intrinsic resistance

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Amphotericin B MIC ≥1 mg/L	To cure IA	Replace AmB with azole, if azole tested susceptible	B	II		[17,170,515–520]
IA due to *A. terreus*	To cure IA	Voriconazole	A	II	Avoid AmB	[162,521,522]
		Isavuconazole	A	II		
		Posaconazole	B	III		
		Itraconazole	B	III		
IA due to *A. calidoustus*	To cure IA	Lipid formulation of AmB	A	II	Avoid azoles	[103,523]
IA due to *A. tubingensis* (*A. niger* complex)	To cure IA	Other than azole monotherapy	C	III	Higher azole MIC common, but no data on clinical impact	[496,524,525]
IA due to *A. lentulus* (*A. fumigatus* complex)	To cure IA	Other than azole monotherapy				
IA due to *A. alliaceus* (*A. flavus* complex)	To cure IA	Other than AmB monotherapy	C	III	Avoid AmB	[526]
IA due to *A. niger* complex	To cure IA	Other than itraconazole and isavuconazole	B	III	Isavuconazole, posaconazole, and voriconazole MIC in general one dilution higher compared with *A. fumigatus*; itraconazole MIC in general two steps higher; limited clinical data	[496,507]
IA due to *A. nidulans*	To cure IA	Voriconazole	C	III	AmB MIC elevated, poor clinical responses in chronic granulomatous disease	[527,528]

Abbreviations: AmB, amphotericin B; IA, invasive aspergillosis; MIC, minimum inhibitory concentration; QoE, Quality of evidence; SoR, Strength of recommendation.

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

Clinical Microbiology and Infection 24 (2018) e1–e38

Nadir Küfler ve Doğal Direnç
(Ekinokandin tedavisi Altında Gelişen Enfeksiyonlar)

Echinocandin-associated bIMIs			
Primary prophylaxis, empirical or directed treatment for IFIs in hematological malignancy or HSCT; retrospective, multicenter observational study	IA most common, mucormycosis, fusariosis, *Hormographiella aspergillata* infection	7.3% (7/96)	[32]
Primary prophylaxis during neutropenia in HSCT recipients; prospective, double-blind, randomized, multicenter clinical trial	IA, mucormycosis and fusariosis	0.7% (3/425)	[33]
Primary prophylaxis in HSCT recipients; prospective, randomized, single-center clinical trial	Probable bIMIs most common, IA	7.3% (12/165)	[34]
Twice/thrice-weekly high-dose micafungin primary prophylaxis in HSCT recipients; retrospective, single-center observational study	IA most common, mucormycosis	4.8% (4/83)	[35]
Primary prophylaxis in HSCT recipients; retrospective, single-center observational study	IA most common, mucormycosis, *Exserohilum* infection, unspeciated mold infection	4.9% (6/123)	[36]
Primary prophylaxis in HSCT recipients with GvHD; retrospective, single-center observational study	Mucormycosis	4.8% (1/21)	[37]
Secondary prophylaxis in hematology patients with neutropenia; prospective, multinational registry observational study	Probable bIMI, IA	28.6% (8/28)	[31]
Parenteral AMB[c]-associated bIMIs			
Twice-weekly L-AMB primary prophylaxis in ALL patients during remission-induction chemotherapy; prospective, double-blind, randomized, multicenter clinical trial	Probable pulmonary bIMIs	7.5% (17/228)	[38]
Once-weekly L-AMB secondary prophylaxis in leukemia patients; retrospective, single-center observational study	IA	7.1% (1/14)	[39]
AMB-deoxycholate primary prophylaxis in autologous HSCT recipients with neutropenia; prospective, blinded, randomized, single-center clinical trial	IA	1.1% (1/91)	[40]

Nadir Küfler ve Doğal Direnç

Table 1. Inherited and acquired resistance reported among pathogenic fungi infecting patients with hematological malignancies.

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

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

Maria N. Gamaletsou[1], Thomas J. Walsh[2], Nikolaos V. Sipsas[3]

Turk J Hematol 2018;35:1-11

Yeni Ortaya Çıkan/Yeni Fark Edilen Mantarlar ve Doğal Direnç

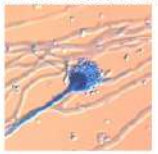
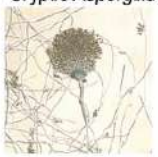
Pathogen	Potential Underlying Causes of Emergence
Candida auris 	• Climate change • Environmental exposure to antifungals • Infection control in healthcare settings with patients with chronic medical conditions
Azole-resistant *Aspergillus fumigatus* 	• Environmental exposure to azole-like antifungals antifungals • Increased use of azoles in clinical settings • Increased awareness & antifungal susceptibility testing/surveillance
Cryptic *Aspergillus* spp. (e.g., *Aspergillus lentulus*) 	• Improved methods of fungal species identification • Increased awareness/surveillance
Mucorales (e.g , *Rhizopus arrhizus*) 	• COVID-19 associated mucormycosis • Corticosteroid use • Poorly control diabetes mellitus
Rasamsonia argillacea 	• Taxonomic changes • Improved methods of fungal species identification • Antifungal resistance
Antifungal resistant dermatophytes (e.g., *Trichophyton indotinae*) 	• Topical use of products containing corticosteroids & antifungals

Fig. 1. Representative examples of emerging fungal pathogens and potential underlying causes for their emergence.

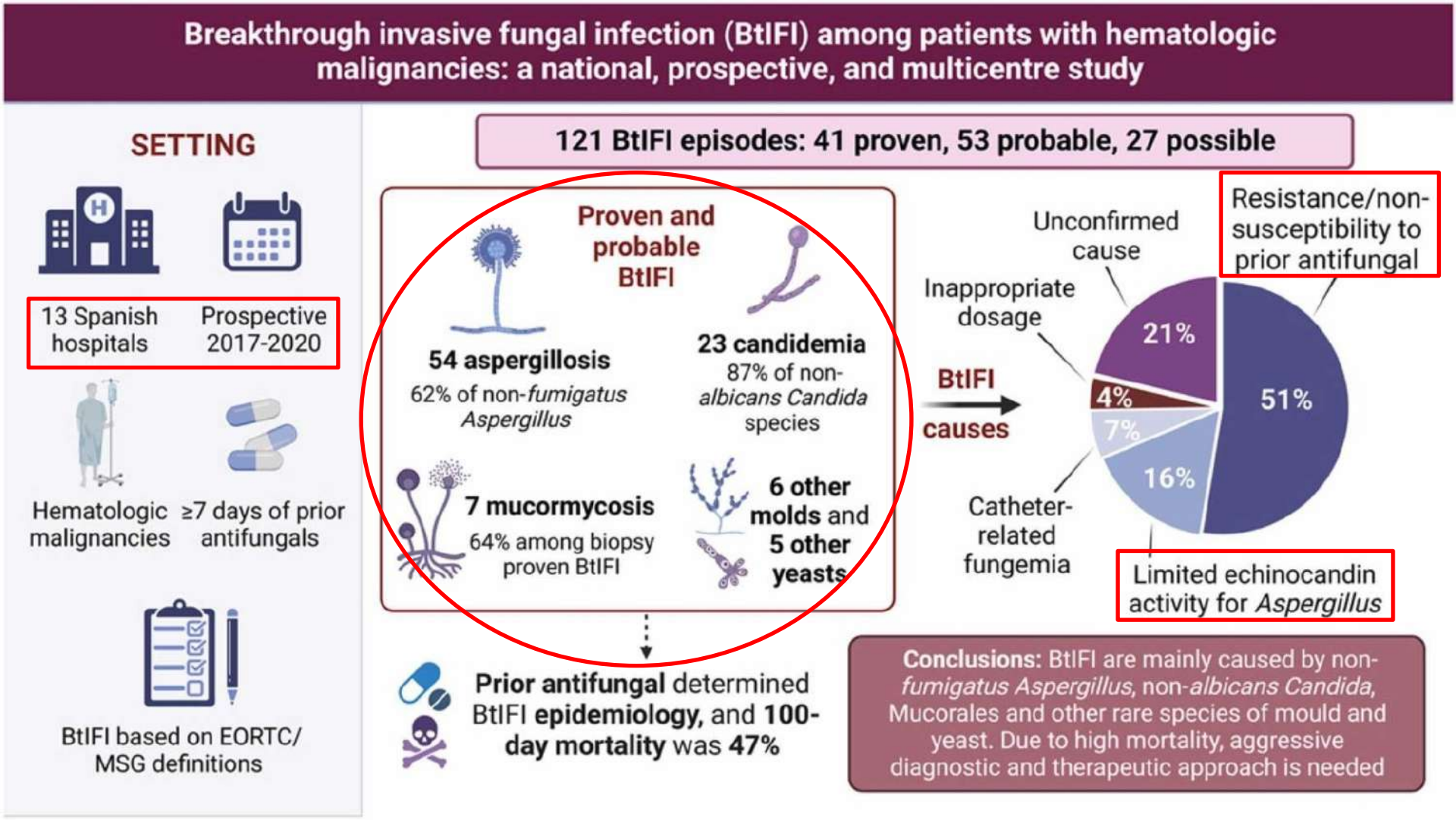
Table 1. Examples of other newly recognized or reclassified fungal species of clinical significance, including some with resistance to antifungals.

Current name/classification	Previous name/classification	Clinical relevance
Blastomyces helicus	*Emmonsia helica*	• Atypical and disseminated blastomycosis in immunocompromised humans and companion animals [Schwartz et al. (57)]. • Cases reported in western states and provinces of US and Canada.
• *Emergomyces* species • *Emergomyces africanus* • *E. canadensis* • *E. europaeus* • *E. orientalis* • *E. pasteurianus*	*Emmonsia*-like species	• Disseminated infections in patients with advanced-HIV/AIDS [Kenyon et al. (58)]. • Systemic infections in other immunocompromised patients [Schwartz et al. (59) and Spallone et al. (60)].
Rasamsonia argillacea species complex	*Geosmithia* species	• Invasive disease in those with chronic granulomatous disease and hematologic malignancies, and colonization in cystic fibrosis patients [Houbraken et al. (61)]. • Intrinsic resistance to voriconazole and isavuconazole [Houbraken et al. (61) and Steinmann et al. (62)]. • Often misidentified as *Penicillium* or *Paecilomyces*.
Sporothrix brasiliensis	*Sporothrix schenckii*	Zoonotic transmission can occur with outbreaks in humans reported due to infected cats [Barros et al. (63) and Brandolt et al. (64)].
Trichophyton indotineae	*Trichophyton mentagrophytes* species complex (*T. interdigitale*)	Outbreaks of dermatophytosis with emerging resistance to terbinafine, fluconazole, and griseofulvin in patients in Northern India, leading to clinical failures in the treatment of tinea corporis/cruris infections [Singh et al., Tang et al., and Kano et al. (65–67)].

Nathan P. Wiederhold **Clinical Chemistry** 68:1 83–90 (2022)

SAA 06/2023

Tedavi altında gelişen invaziv fungal enfeksiyonlarda sebep büyük oranda in vitro direnç…



Doğal Direnç Görülen İnvaziv Nadir Küf Enf.larında Tedavi

GLOBAL
ECMM
ISHAM
ASM
RARE
MOULD
GUIDELINE

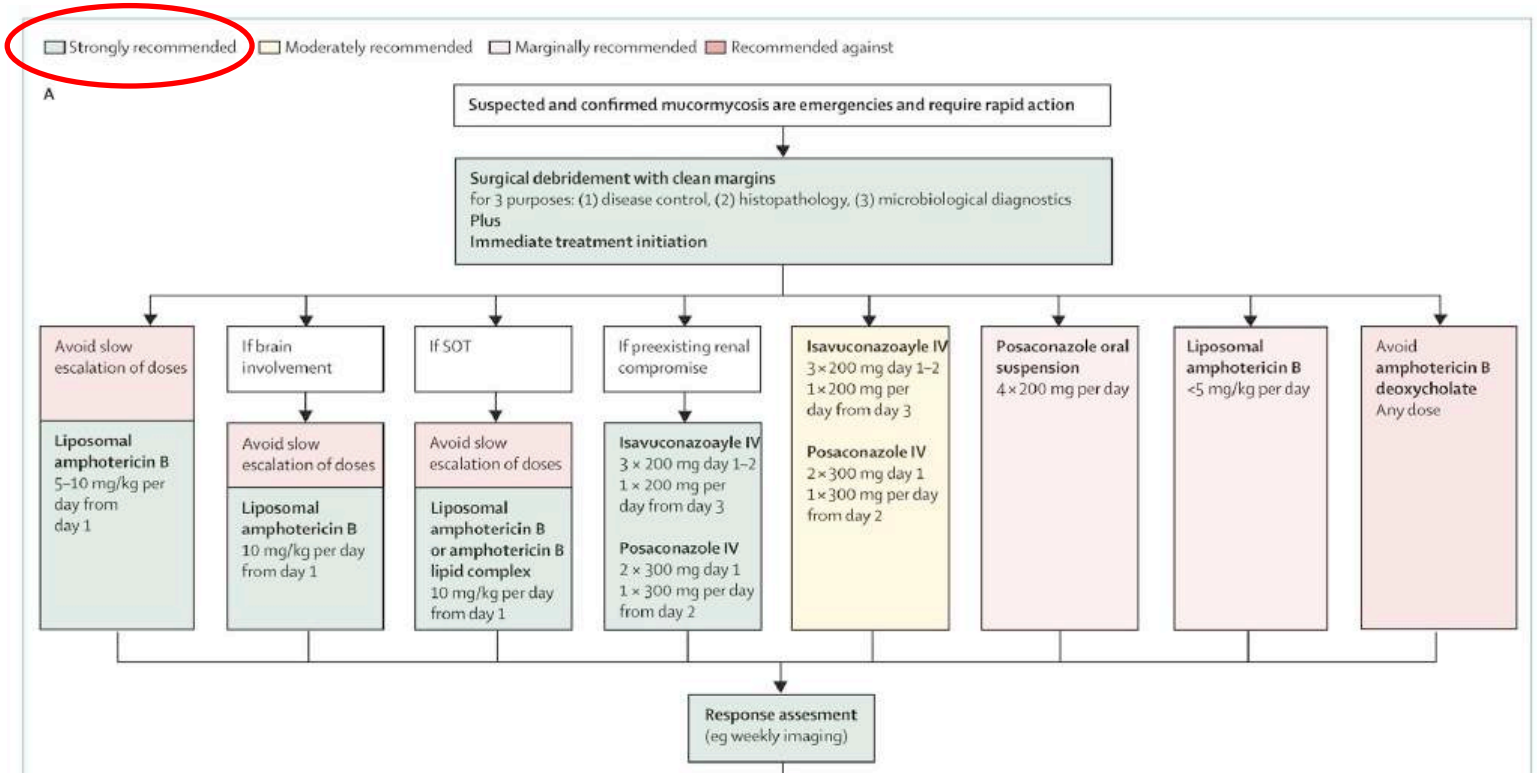
Strongly recommended | Moderately recommended | Marginally recommended | Recommended against

	First-line	First-line alternative	Second-line	Treatments to avoid	Salvage treatments
Fusariosis	Voriconazole, or voriconazole plus L-AmB, or voriconazole plus ABLC	L-AmB, or ABLC	Isavuconazole, or posaconazole	D-AmB	Posaconazole
Lomentosporosis	Voriconazole plus terbinafine	Voriconazole	Isavuconazole, or posaconazole	L-AmB	Voriconazole
Scedosporiosis	Voriconazole	Voriconazole in combination with L-AmB, ABLC, echinocandins, or terbinafine	Isavuconazole, or posaconazole, or itraconazole	L-AmB	Voriconazole echinocandins, or posaconazole
Phaeohyphomycosis: localised infection	Voriconazole	L-AmB with or without echinocandins, or triazole	Isavuconazole	D-AmB	Isavuconazole, or posaconazole, or voriconazole
Phaeohyphomycosis: cutaneous or subcutaneous infection	Itraconazole or voriconazole	L-AmB with or without echinocandins, or triazole	Isavuconazole	D-AmB	Isavuconazole, or posaconazole, or voriconazole
Phaeohyphomycosis: disseminated infection	Posaconazole, or voriconazole plus echinocandins, or voriconazole plus terbinafine	L-AmB with or without echinocandins, or triazole	Isavuconazole	D-AmB	Isavuconazole, or posaconazole, or voriconazole
Phaeohyphomycosis: *Exserohilium rostratum*	Voriconazole with or without L-AmB	..	L-AmB plus triazoles other than voriconazole	D-AmB	..
Rasamsonia spp	Caspofungin, or micafungin	Caspofungin plus L-AmB or posaconazole, or micafungin plus L-AmB or posaconazole	..	Azole monotherapy	..
Schizophyllum commune	L-AmB; stepdown to posaconazole	..	Voriconazole	..	..
Schizophyllum spp other than *S commune* and other basidiomycetes (eg, *Coprinopsi cinereal*, *Hormographiella aspergillata*)	L-AmB with or without inhaled L-AmB, or L-AmB with or without voriconazole	..	Voriconazole	Echinocandins	L-AmB, or voriconazole
Scopulariopsis spp	Isavuconazole, or voriconazole	L-AmB with or without voriconazole	..	..	Posaconazole with or without micafungin with or without terbinafine
Penicillium spp: disseminated infection	L-AmB with or without other antifungals	..	..	..	Voriconazole
Penicillium spp: lung infection	Posaconazole	..	..	..	Voriconazole
Non-*marneffei Talaromyces* spp	L-AmB	..	..	..	Voriconazole, or echinacondine plus terbinafine
Paecilomyces spp	L-AmB	..	..	..	Itraconazole, or posaconazole
Purpureocillium spp	Voriconazole	..	Itraconazole or L-AmB or posaconazole	..	Itraconazole, or L-AmB, or posaconazole
Purpureocillium spp: cutaneous or subcutaneous infection	Voriconazole plus terbinafine	..	Itraconazole or L-AmB or posaconazole	..	Itraconazole, or L-AmB, or posaconazole

www.thelancet.com/infection Published online February 16, 2021 https://doi.org/10.1016/S1473-3099(20)30784-2

Doğal Direnç Görülen İnvaziv Nadir Küf Enf.larında Tedavi: Mukormikoz

GLOBAL ECMM MSG ERC MUCORMYCOSIS GUIDELINE



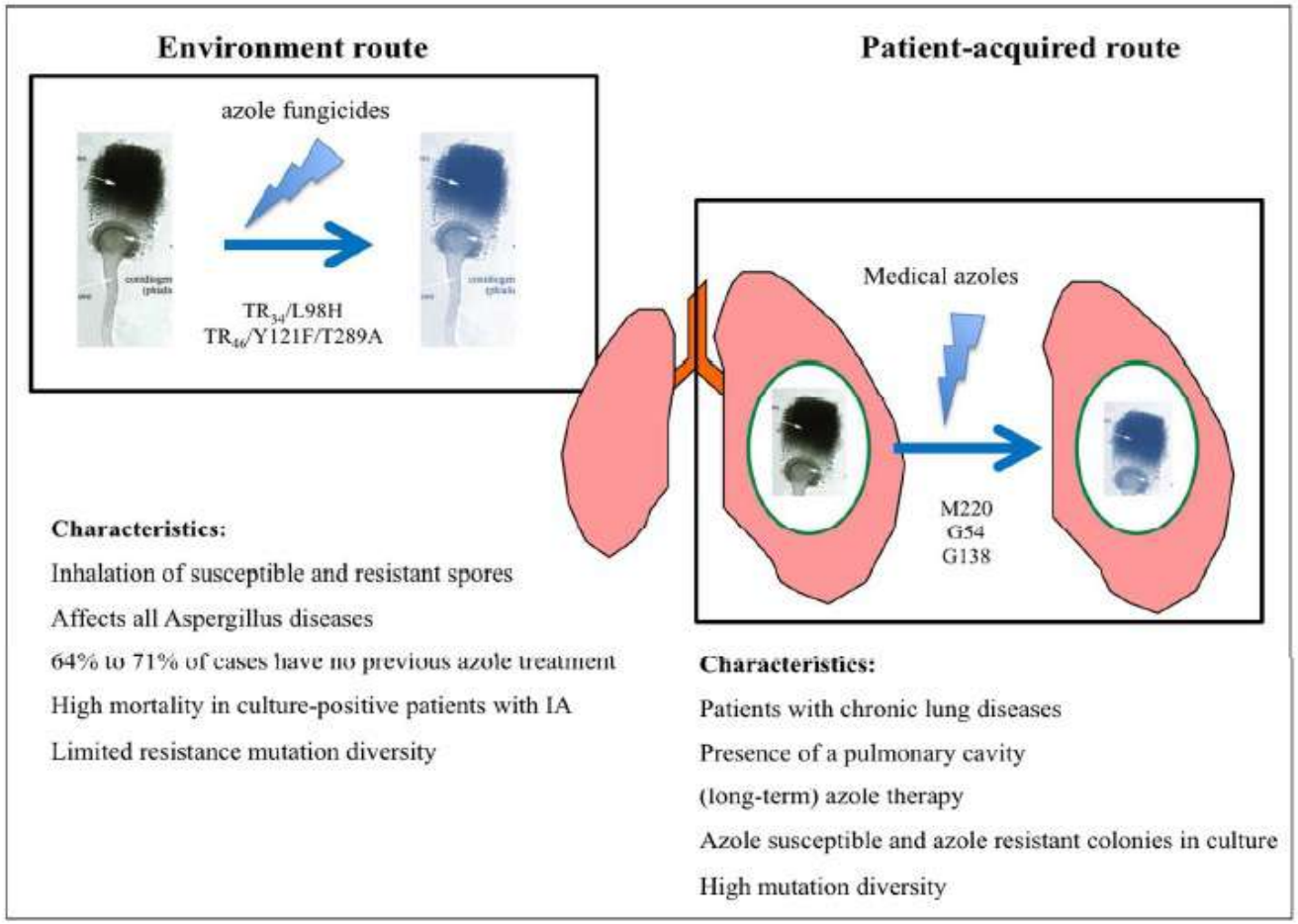
Lancet Infect Dis. 2019 December ; 19(12): e405–e421. doi:10.1016/S1473-3099(19)30312-3

SUNUM AKIŞI

- Temel Bilgiler ve Doğal Direnç (Tedavi Altında Gelişen Enfeksiyonlar)
- Kazanılmış Direnç: Önem Kazanan/Yeni Sorunlar, Yeni Gelişmeler, Getirileri

  Aspergillus
- Sonuçlar

Kazanılmış Direnç: *A. fumigatus*-Azoller
Çevresel Faktörler ve Tedavi Kaynaklı Direnç Gelişimi



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

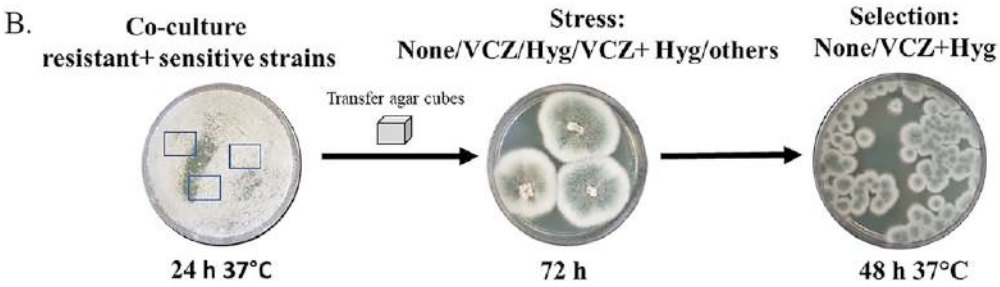
Meis et al. Philos Trans R Soc Lond B Biol Sci. Clinical implications of globally emerging azole resistance in A. fumigatus

Kazanılmış Direnç: *A. fumigatus*-Azoller
Olası Diğer Mekanizmalar…

Horizontal Gene Transfer of Triazole Resistance in *Aspergillus fumigatus*

Alma Morogovsky,[a] Mariana Handelman,[a] Ammar Abou Kandil,[a] Yona Shadkchan,[a] Nir Osherov[a]

are alterations in the *cyp51A* gene or promoter. We tested the hypothesis that *A. fumigatus* can acquire triazole resistance by horizontal gene transfer (HGT) of resistance-conferring gene *cyp51A*. HGT has not been experimentally analyzed in filamentous fungi. Therefore, we developed an HGT assay containing donor *A. fumigatus* strains carrying resistance-conferring mutated *cyp51A*, either in its chromosomal locus or in a self-replicating plasmid, and recipient strains that were hygromycin resistant and triazole sensitive. Donor and recipient *A. fumigatus* strains were cocultured and transferred to selective conditions, and the recipient strain tested for transferred triazole resistance. We found that chromosomal transfer of triazole resistance required selection under both voriconazole and hygromycin, resulting in diploid formation. Notably, plasmid-mediated transfer was also activated by voriconazole or hypoxic stress alone, suggesting a possible route to HGT of antifungal resistance in *A. fumigatus*, both in the environment and during host infection. This study provides, for the first time, preliminary experimental evidence for HGT mediating antifungal resistance in a pathogenic fungus.



Microbiology Spectrum
May/June 2022 Volume 10 Issue 3

Mekanizmalar

Azole resistance mechanisms in *Aspergillus*: update and recent advances

Alba Pérez-Cantero, Loida López-Fernández, Josep Guarro, Javier Capilla*

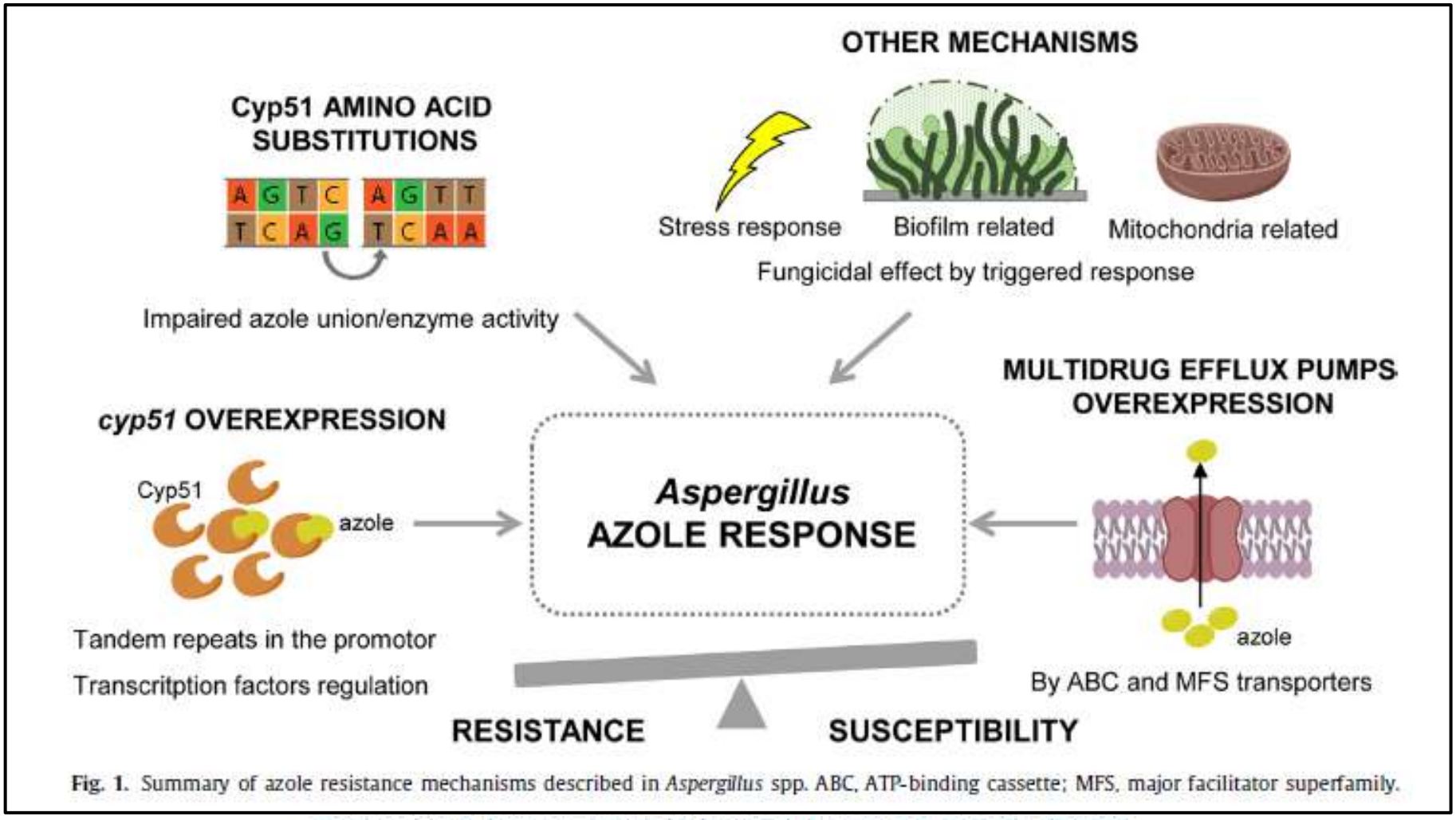


Fig. 1. Summary of azole resistance mechanisms described in *Aspergillus* spp. ABC, ATP-binding cassette; MFS, major facilitator superfamily.

International Journal of Antimicrobial Agents 55 (2020) 105807

Kazanılmış Direnç: A. *fumigatus*-Azoller

TABLE 1 Representative mutations and substitutions associated with azole resistance in *Aspergillus fumigatus*

De novo (patient) route			
Gene	**Tandem repeats**	**Amino acid substitution**	**Ref.**
cyp51A	–	G54E, V, or R	19,28
	–	G138C	29
	–	H147Y	23
	–	P216L	23
	–	M220K, or T	23
	–	H285Y	7
	–	Y431C	23
	–	G432S	8
	–	G434C	23
	–	G448S	23
	TR_{120}		30
hapE	–	P88L	31
hmg1	–	S269F	32
mdr1	–	–[a]	33
mdr2	–	–[a]	33
mdr3	–	–[a]	34
mdr4	–	–[a]	34
Environmental route			
Gene	**Tandem repeats**	**Amino acid substitution**	**Ref.**
cyp51A	–	G54E, A, or R	35–38
	TR_{34}	L98H	39
	TR_{34}	L98H/S297T/F495I	40
	TR_{46}	Y121F/T289A	41
	TR_{46}	Y121F/M172I/T289A/G448S	42
	TR_{53}	–	43

Note:
[a]These genes were overexpressed.

Sofia Marisel Rivelli Zea[1] | **Takahito Toyotome**[1,2,3] *Microbiol Immunol.* 2022;66:135–144

Mutasyonlar &

Table 1. Common *cyp51A*-mediated mechanisms of azole resistance in *Aspergillus fumigatus* [11,42]

Codon Position	Resistance Phenotype
G54	Itraconazole and posaconazole resistance, variable voriconazole susceptibility
G138	Pan-azole resistance
G448	Itraconazole, voriconazole, and isavuconazole resistance, variable posaconazole susceptibility
M220	Itraconazole and posaconazole resistance, variable voriconazole and isavuconazole susceptibility
TR_{34}/L98H	Itraconazole and posaconazole resistance, variable voriconazole and isavuconazole susceptibility
TR_{46}/Y121F/T289A	Voriconazole and isavuconazole, variable itraconazole and posaconazole susceptibility

Curr Opin Infect Dis

Volume 33 • Number 4 • August 2020

Nathan P. Wiederhold[a] *and Paul E. Verweij*[b]

Direnç Fenotipleri

Kazanılmış Direnç: *A. fumigatus*-Azoller Global Direnç Epidemiyolojisi

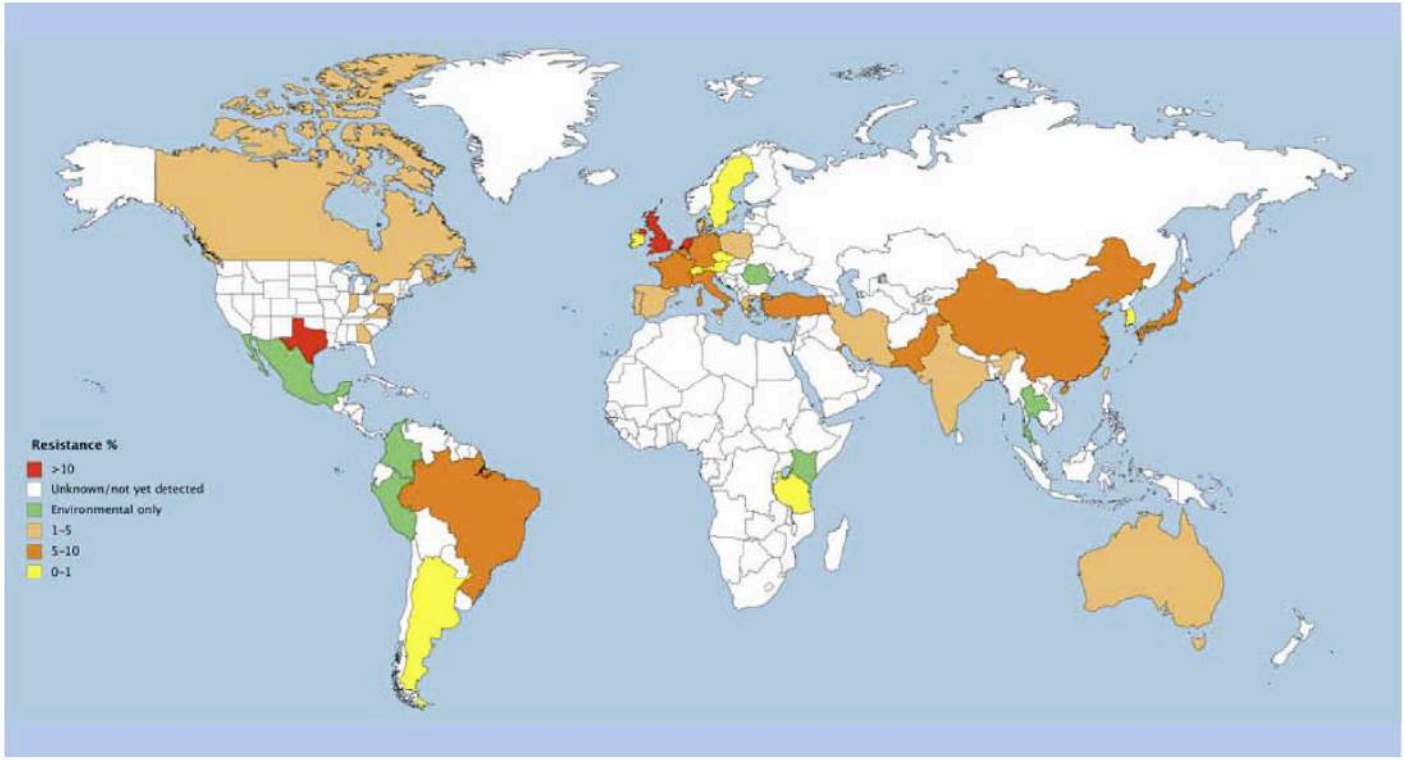


Fig. 1. Global epidemiology of azole resistance frequencies in clinical and environmental *A. fumigatus* isolates. Resistance prevalence was classified for clinical isolates. If only cases were reported they were classified as 0–1%. Average frequencies were calculated when multiple studies on resistance frequencies were available. The number of screened isolates varied as well as the number of studies that were performed in certain countries. Resistance rates may vary between regions within one country or vary for different patient groups. Many countries that have reported resistance in clinical isolates have also found triazole-resistant *A. fumigatus* in the environment, IE: Australia, Belgium, Brazil, China, Denmark, France, Germany, India, Iran, Ireland, Italy, Japan, Kuwait, the Netherlands, Switzerland, Taiwan, Tanzania, the United Kingdom and the United States of America. For references see text. Peru and Mexico were added based on personal communication with Agustin Reséndiz Sharpe.

P.P.A. Lestrade [1, *], J.F. Meis [2, 3], W.J.G. Melchers [3, 4], P.E. Verweij

Clinical Microbiology and Infection 25 (2019) 799–806

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

cyp51A gene and its promoter region was determined for all in vitro azole-resistant isolates. Itraconazole resistance was found in 10.2% of the *A. fumigatus* isolates. From 2000 onwards, patients were observed annually with an itraconazole-resistant isolate. According to in vitro susceptibility tests, amphotericin B 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.

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.

Klinik ve Çevresel Örneklerden Elde Edilen *Aspergillus fumigatus* İzolatlarında Azol Direncinin Fenotipik ve Genotipik Olarak Değerlendirilmesi

Özlem DOĞAN[1,2](ID), Dolunay GÜLMEZ[1](ID), Sevtap ARIKAN AKDAĞLI[1]

rıca seçili izolatlarda *cyp51A* geni dizisi incelenerek mutasyon analizi yapılmıştır. Çalışmaya klinik örneklerden 483, çevre örneklerinden 65 toprak *A.fumigatus* sensu stricto izolatı dahil edilmiştir. Klinik izolatların birinci grubu 1997-2015 yıllarına ait 215 izolattan oluşmuş ve retrospektif olarak test edilmiştir. İkinci grup ise *A.fumigatus* kompleksi için rutin azol agar tarama testinin yapıldığı 2016-2018 yıllarına ait 268 izolattan oluşmuştur. Tüm klinik izolatlar (n= 483) birlikte değerlendirildiğinde izolatlardan biri 2015 yılından önce, 10'u 2016-2018 yılları arasında olmak üzere 11 (%2.3)'i itrakonazole dirençli, 5 (%1)'i artmış maruziyette duyarlı (Intermediate-I) *A.fumigatus* izolatı saptanmıştır. Azole dirençli izolatlarda incelenen cyp51A geninde, *Aspergillus* izolatlarında azol direnci ile ilişkilendirilmiş mutasyonların hiçbiri saptanmamış ve bu dirençli izolatlarda, direnç ile ilişkisi henüz tam olarak aydınlatılamamış bazı polimorfizmler (Y46F, G89G, V172M, T248N, E255D, L358L, K427E, C454C, Y431D ve bir izolatta bu polimorfizme ek olarak Q141H) gösterilmiştir. Çalışmamızda *A.fumigatus* izolatlarında azol direnci düşük oranda (%2.3) saptanmıştır. Saptanan polimorfizmlerin azol direncine olası etkisinin gösterilmesi ve yüksek azol MİK değerleri ile ilişkili diğer mekanizmaların aydınlatılması için ileri çalışmalara gereksinim olduğu düşünülmüştür. Ayrıca ülkemizde bir bölgeden yüksek azol direnci bildirilmiş olması nedeniyle, farklı bölgelerde azol direnç durumunun ve azol direnci oranı için aralığın belirlenmesi ve ülkemize özgü olabilecek direnç mutasyonlarının açığa çıkarılması amacıyla çok merkezli çalışmaların gerekli olduğu sonucuna varılmıştır.

Mikrobiyol Bul 2020;54(2):291-305,

J Antimicrob Chemother 2022; **77**: 1894–1898

TÜRKİYE-ÇOK MERKEZLİ

Frequency of azole resistance in clinical and environmental strains of *Aspergillus fumigatus* in Turkey: a multicentre study

Beyza Ener[1]*, Çağrı Ergin[2], Dolunay Gülmez[3], Harun Ağca[1], Melek Tikveşli[4], Seçil Ak Aksoy[5], Müşerref Otkun[6], Ali Korhan Sığ[3], Dilara Öğünç[7], Betil Özhak[7], Tuncay Topaç[8], Aslı Özdemir[6], Dilek Yeşim Metin[9], Süleyha Hilmioğlu Polat[9], Yasemin Öz[10], Nedret Koç[11], Mustafa Altay Atalay[11], Zayre Erturan[12], Asuman Birinci[13], Nilgün Çerikçioğlu[14], Demet Timur[1], Fahriye Ekşi[15], Gonca Erköse Genç[12], Duygu Findik[16], Şaban Gürcan[4], Ayşe Kalkanci[17] and Sevtap Arikan-Akdagli[3]

Toplam 21 merkez
Prospektif 2018-2019

9 Merkez: Klinik izolat ve Çevre izolatı
9 Merkez: Sadece Çevre izolatı
3 Merkez: Sadece Klinik izolat

-2288 çevre örneğinden 458 *A.fumigatus* suşu
-12 merkezden 392 klinik *A. fumigatus* izolatı

-EUCAST E.DEF 10.1 Agar tarama
-EUCAST E.DEF 9.3 Mikrodilüsyon - - Doğrulama

J Antimicrob Chemother 2022; **77**: 1894–1898

TÜRKİYE-ÇOK MERKEZLİ

Figure 1. Distribution of participating centres. The grey circles show where the environmental samples were collected; the green section of each circle indicates the growth percentage of that sample, while the red indicates the resistance rate. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Results: In total, resistance was found in 1.3% of the strains that were isolated from environmental samples and 3.3% of the strains that were isolated from clinical samples. Mutations in the *cyp51A* gene were detected in 9 (47.4%) of the 19 azole-resistant isolates, all of which were found to be TR34/L98H mutations. Microsatellite genotyping clearly differentiated the strains with the TR34/L98H mutation in the *cyp51A* gene from the strains with no mutation in this gene.

Düşük direnç oranları

J Antimicrob Chemother 2022; **77**: 1894–1898

TÜRKİYE-ÇOK MERKEZLİ

Table 1. MICs determined using the EUCAST microdilution method (E.DEF 9.3) and mutations in the *cyp51A* gene for the strains that were resistant by the agar screening method

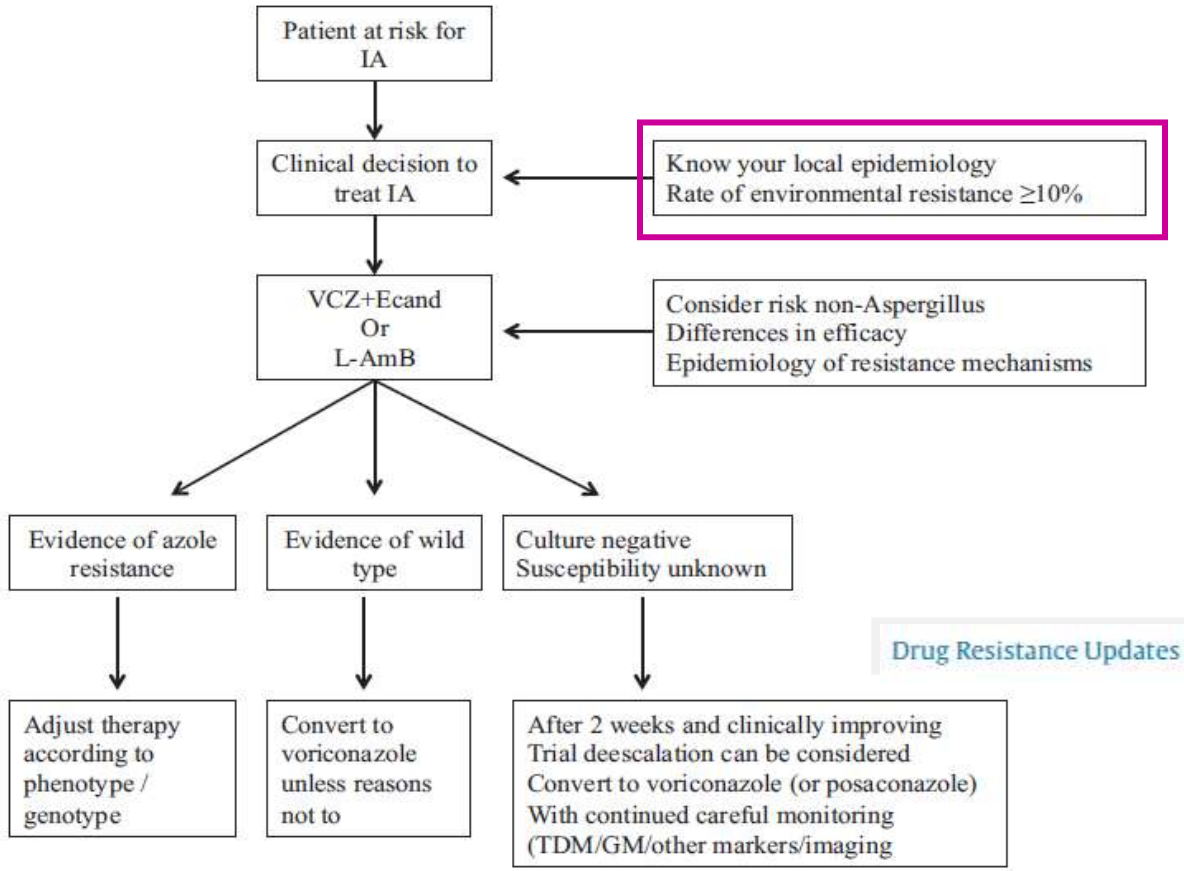
				MIC (mg/L) - EUCAST E.DEF 9.3			
Isolate	City code	Sample type	Age (years)	itraconazole	voriconazole	posaconazole	*cyp51A* mutation
ÇK1	34	hospital environment	-	4	4	2	none
CRK1	34	hospital environment	-	4	4	2	none
CRK2	34	hospital environment	-	4	4	2	none
011KS06SN-B1	06	agricultural soil	-	>8	4	0.5	none
011KS06SN-B2	06	agricultural soil	-	>8	4	0.5	none
267MT22MR/B	22	agricultural soil	-	4	4	2	none
60986	16	sputum	45	>8	>8	2	TR34/L98H
61568	16	sputum	63	>8	>8	2	TR34/L98H
62946	16	bronchoalveolar lavage fluid	81	>8	>8	2	TR34/L98H
63413	16	sputum	74	>8	>8	2	TR34/L98H
63653	16	tracheal aspirate	67	>8	>8	2	TR34/L98H
64955	16	bronchoalveolar lavage fluid	80	>8	>8	2	TR34/L98H
2455	06	pleural fluid		>8	>8	2	TR34/L98H
457	06	pus		>8	>8	2	TR34/L98H
MY	27	bronchoalveolar lavage fluid		2	2	0.5	TR34/L98H
RT1	34	sputum	75	4	4	0.5	none
RT2	34	sputum	75	4	4	0.5	none
11b	07	sputum	18	4	4	2	none
13b	07	sputum	54	>8	4	2	none

cyp51A mutasyonlarının saptanmadığı suşlar

SAA 06/2023

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.

Azol Dirençli Aspergilloz
Tedavi Önerileri

Table 20
Optimal therapy in documented azole-resistance

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Isolate with voriconazole MIC = 2 mg/mL	To cure IA	Voriconazole + echinocandin combination therapy or L-AmB monotherapy for IA (as well as for CPA)	A	III	The probability of voriconazole treatment failure may be higher than in voriconazole MIC <2	[529–532]
Isolate with voriconazole MIC >2 mg/mL	To cure IA	L-AmB	A	II_u		[113,114,533]
		AmB lipid complex	C	III		No reference found.
		Voriconazole & anidulafungin	B	III		[529]
		Posaconazole & caspofungin	C	III	Posaconazole not licensed for primary treatment	[534]
		Caspofungin or micafungin	C	III	Patients with contra-indications to AmB and other azoles	No reference found.

Abbreviations: AmB, Amphotericin B; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; L-AmB, liposomal amphotericin B; QoE, Quality of evidence; SoR, Strength of recommendation.

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

Clinical Microbiology and Infection 24 (2018) e1–e38

Azole-Resistant COVID-19-Associated Pulmonary Aspergillosis in an Immunocompetent Host: A Case Report

Eelco F. J. Meijer [1,2,3], Anton S. M. Dofferhoff [3,4], Oscar Hoiting [5], Jochem B. Buil [1,2] and Jacques F. Meis [1,2,3,6,*]

We report the first case of azole-resistant CAPA, which occurred in an immunocompetent host during ICU support without a previous history of azole therapy. The *A. fumigatus cyp51A* gene TR_{34}/L98H mutation found in this patient has been well described as an environmentally acquired mutation [16], which is in line with data from clinical studies where two-thirds of patients with azole-resistant infections had no history of azole pretreatment [10]. This case underscores the importance of early diagnosis and the need for resistance surveillance, comparable to what has been described in influenza patients [9,17], given the emergence of triazole resistance [18,19].

J. Fungi **2020**, *6*, 79

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]

CID 2017:65 (15 July)

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.

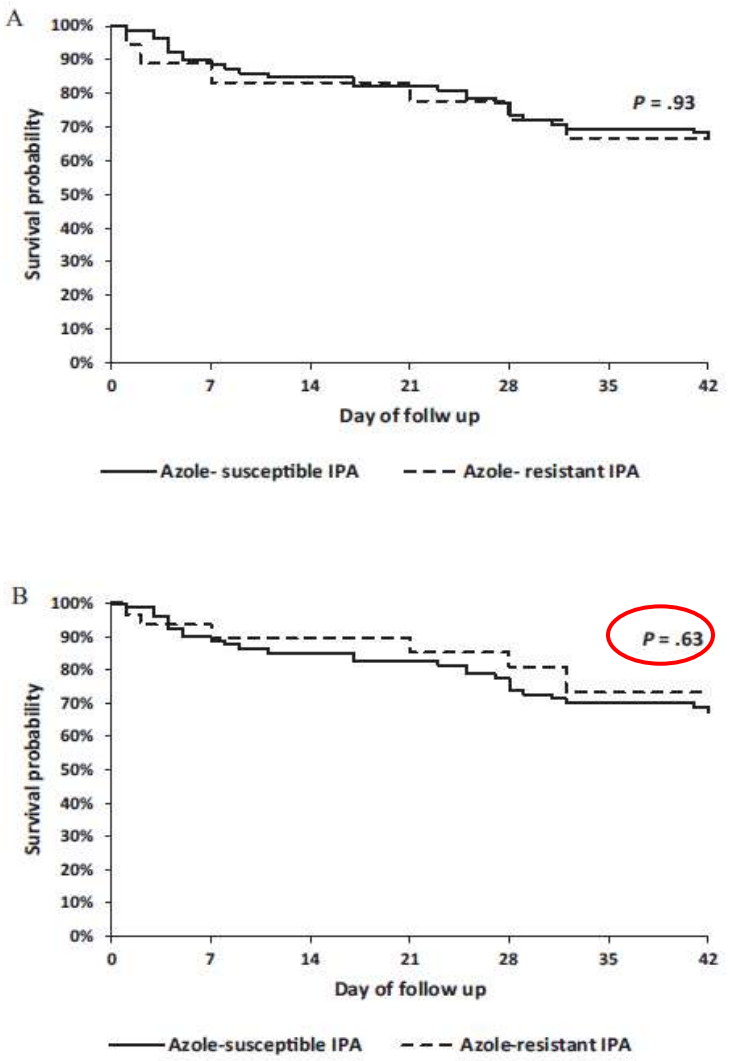


Figure 2. Survival curves for patients who had either azole wild-type or azole non–wild-type invasive pulmonary aspergillosis (IPA). *A*, Kaplan-Meier survival curve. *B*, Adjusted Kaplan-Meier survival curve (adjusted for history of neutropenia, lymphopenia, intensive care unit admission, and time period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

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

J Antimicrob Chemother 2016; **71**: 3528–3535

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.

Voriconazole Resistance and Mortality in Invasive Aspergillosis: A Multicenter Retrospective Cohort Study

Pieter P. Lestrade,[1,2,a,b] Robbert G. Bentvelsen,[3,a] Alexander F. A. D. Schauwvlieghe,[4,a] Steven Schalekamp,[5] Walter J. F. M. van der Velden,[2,6] Ed J. Kuiper,[3] Judith van Paassen,[7] Ben van der Hoven,[8] Henrich A. van der Lee,[1,2] Willem J. G. Melchers,[1,2] Anton F. de Haan,[9] Hans L. van der Hoeven,[2,10] Bart J. A. Rijnders,[4] Martha T. van der Beek,[3] and Paul E. Verweij[1,2]

CID 2019:68 (1 May)

Background. Triazole resistance is an increasing problem in invasive aspergillosis (IA). Small case series show mortality rates of 50%–100% in patients infected with a triazole-resistant *Aspergillus fumigatus*, but a direct comparison with triazole-susceptible IA is lacking.

Methods. A 5-year retrospective cohort study (2011–2015) was conducted to compare mortality in patients with voriconazole-susceptible and voriconazole-resistant IA. *Aspergillus fumigatus* culture-positive patients were investigated to identify patients with proven, probable, and putative IA. Clinical characteristics, day 42 and day 90 mortality, triazole-resistance profiles, and antifungal treatments were investigated.

Results. Of 196 patients with IA, 37 (19%) harbored a voriconazole-resistant infection. Hematological malignancy was the underlying disease in 103 (53%) patients, and 154 (79%) patients were started on voriconazole. Compared with voriconazole-susceptible cases, voriconazole resistance was associated with an increase in overall mortality of 21% on day 42 (49% vs 28%; $P = .017$) and 25% on day 90 (62% vs 37%; $P = .0038$). In non-intensive care unit patients, a 19% lower survival rate was observed in voriconazole-resistant cases at day 42 ($P = .045$). The mortality in patients who received appropriate initial voriconazole therapy was 24% compared with 47% in those who received inappropriate therapy ($P = .016$), despite switching to appropriate antifungal therapy after a median of 10 days.

Conclusions. Voriconazole resistance was associated with an excess overall mortality of 21% at day 42 and 25% at day 90 in patients with IA. A delay in the initiation of appropriate antifungal therapy was associated with increased overall mortality.

Keywords. invasive aspergillosis; *Aspergillus fumigatus*; voriconazole resistance; mortality.

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

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.

				MIC/MEC (mg/L)										
#	Lab no.	Date received	ID	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

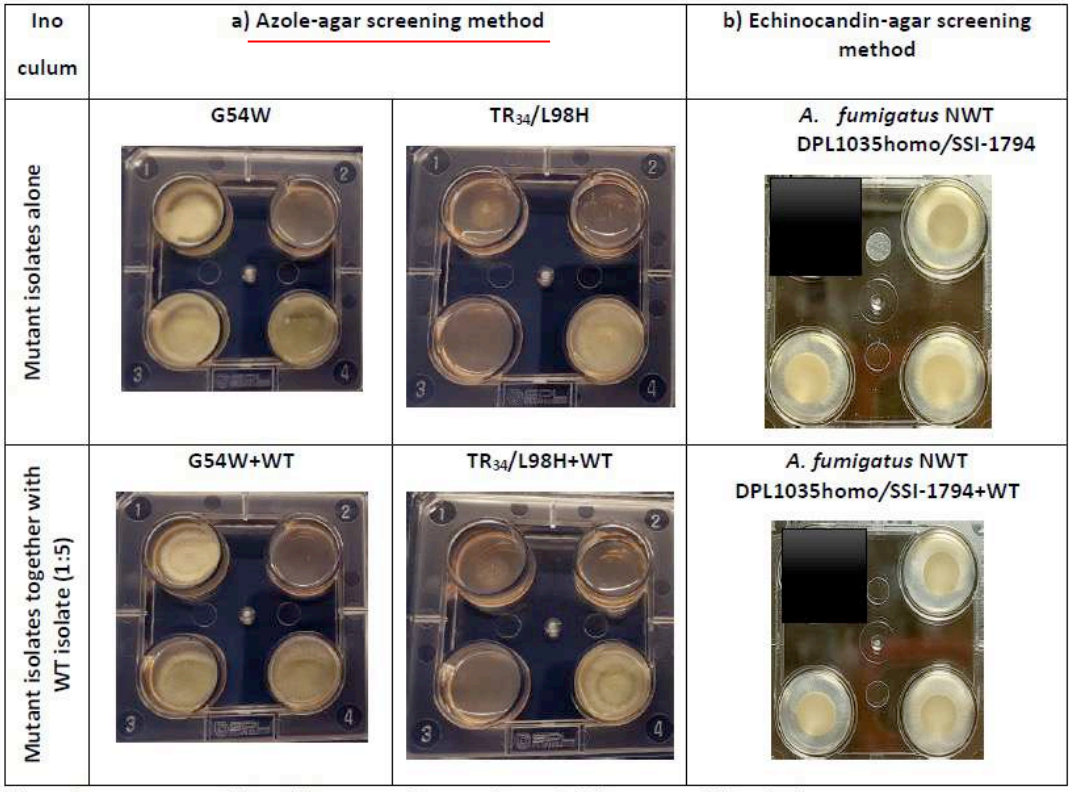
*Ref strain used Af293 §ND = not determined #Ref strain used *A. flavus* NRRL3357

EUCAST DEFINITIVE DOCUMENT E.Def 10.2

Screening method for the detection of azole and echinocandin resistance in *Aspergillus* using antifungal-containing agar plates, exemplified by *A. fumigatus*

J. Meletiadis[1,2], J Guinea[3,4,5], S. Arikan-Akdagli[6], N. Friberg[7], G. Kahlmeter[8], MC Arendrup[9,10,11] and the Subcommittee on Antifungal Susceptibility Testing (AFST) of the ESCMID European Committee for Antimicrobial Susceptibility Testing (EUCAST)*

Figure 1. Detection of mixed inocula using azole resistant/susceptible isolates (Pictures a) and echinocandin NWT/WT isolates (Pictures b)*. Expected growth patterns for two azole-resistant *A. fumigatus* QC strains harbouring G54W (SSI-5586) and TR_{34}/L98H (SSI-4524) *cyp51A* substitutions, respe echinocandin-NWT *A. fumigatus* (DPL1035homo/SSI-1794) alone and in mix with the WT *A* 204305 isolate. Pictures (a and b) show the growth pattern of the mutant isolates alone (top i 1 to 5 with a WT isolate (bottom images). Azole susceptible strains, including the QC strain *A* 204305, show no growth on the azole agars (not shown). Wells of the plate contain itracona 1 [upper left]), voriconazole (2 mg/L; well 2 [upper right]), posaconazole (0.5 mg/L; well 3 azole-free agar (growth control; well 4 [lower right]). Echinocandin-WT *A. fumigatus* isolate compact appearance in drug containing wells (well 2 [upper right], anidulafungin 0.25 mg/L; micafungin 0.125 mg/L) (Figure 4). The QC strains are available from the CCUG strain collecti



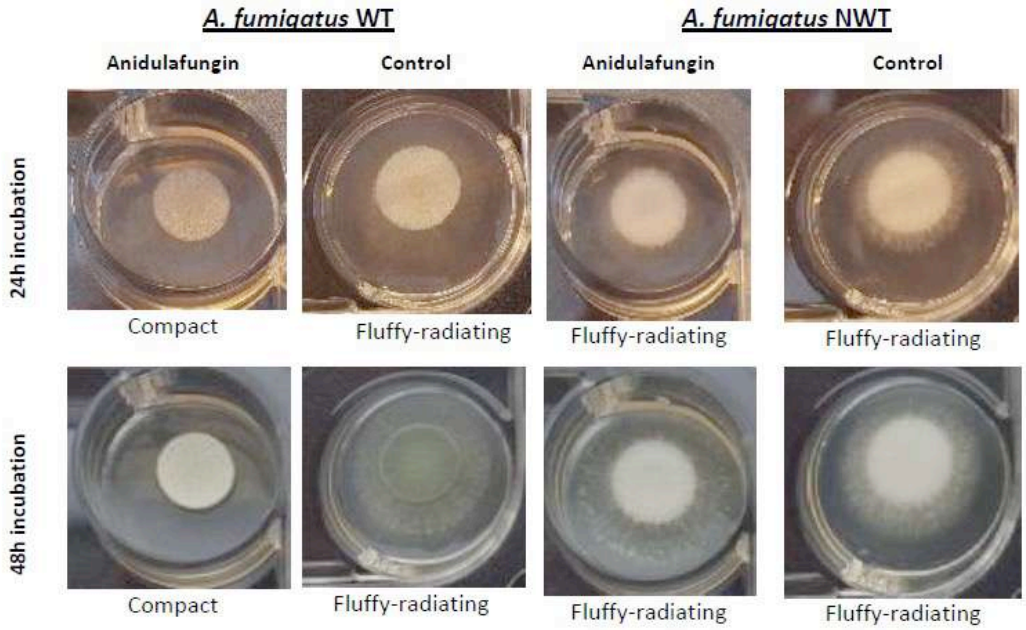
*Inocula were prepared by mixing one resistant colony with five susceptible colonies.

EUCAST DEFINITIVE DOCUMENT E.Def 10.2

Screening method for the detection of azole and echinocandin resistance in *Aspergillus* using antifungal-containing agar plates, exemplified by *A. fumigatus*

J. Meletiadis[1,2], J Guinea[3,4,5], S. Arikan-Akdagli[6], N. Friberg[7], G. Kahlmeter[8], MC Arendrup[9,10,11] and the Subcommittee on Antifungal Susceptibility Testing (AFST) of the ESCMID European Committee for Antimicrobial Susceptibility Testing (EUCAST)*

Figure 2. Echinocandin screening. Characteristic colony morphology of an *A. fumigatus* NWT (DPL1035homo/SSI-1794) and an *A. fumigatus* WT strains on anidulafungin-containing agar (0.25 mg/L) and drug-free agar after 24h and 48h of incubation. Note the fluffy (colony diameter ≥15 mm) versus compact appearance. Ignore production of irregular or small halos usually observed after incubation for 48h.



Pandemi Döneminde Antifungal Direnç Oranları Arttı mı?

Impact of COVID-19 on the antifungal susceptibility profiles of isolates collected in a global surveillance program that monitors invasive fungal infections

Michael A. Pfaller[1,2], Cecilia G. Carvalhaes[1], Sean DeVries[1], Paul R. Rhomberg[1] and Mariana Castanheira[1,*]

SENTRY

2018- 2019 / 2020 suşları

cantly decreased ($P < .05$). Fluconazole resistance in *C. glabrata* decreased from 5.8% in 2018–2019 to 2.0% in 2020, mainly due to fewer hospitals in the US having these isolates (5 vs. 1 hospital). Conversely, higher fluconazole-resistance rates were noted for *C. parapsilosis* (13.9 vs. 9.8%) and *C. tropicalis* (3.5 vs. 0.7%; $P < .05$) during 2020. Voriconazole resistance also increased for these species. Echinocandin resistance was unchanged among *Candida* spp. Voriconazole susceptibility rates in *A. fumigatus* were similar in these two periods (91.7% in 2018 and 2019 vs. 93.0% in 2020). Changes were also noticed in the organisms with smaller numbers of collected isolates. We observed variations in the occurrence of organisms submitted to a global surveillance and the susceptibility patterns for some organism-antifungal combinations. As the COVID-19 pandemic is still ongoing, the impact of this event must continue to be monitored to guide treatment of patients affected by bacterial and fungal infections.

C. parapsilosis ve C. tropicalis - FLUKONAZOL ve VORİKONAZOL

Candida türleri – EKİNOKANDİNLER: Değişiklik yok

A. fumigatus – VORİKONAZOL: Değişiklik yok

İZLENMELİ!

Medical Mycology, 2022, 60, myac028

SUNUM AKIŞI

- Temel Bilgiler ve Doğal Direnç (Tedavi Altında Gelişen Enfeksiyonlar)
- Kazanılmış Direnç: Önem Kazanan/Yeni Sorunlar, Yeni Gelişmeler ve Getirileri
  - Aspergillus
- Sonuçlar

SONUÇLAR

- ✓ İn vitro direnç, tedaviye yanıtı belirleyen faktörlerden sadece birisidir.
- ✓ Doğal direnç ile ilgili bilgiler, kriptik türlerin moleküler yöntemlerle ortaya çıkarılması ile birlikte her geçen gün artmaktadır. Doğal direnç küf mantarlarında özellikle tedavi altında gelişen enfeksiyonların nedeni olarak önem taşımaktadır.
- ✓ Kazanılmış direnç ise bazı türler-ilaçlar için artan sıklıkta görülmekte / daha çok dikkat çekmektedir:

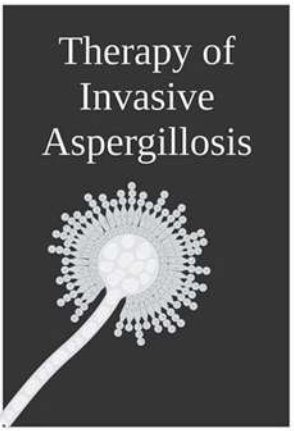
  (*A.fumigatus*-triazoller, Aspergillus-Ekinokandinler)
- ✓ Antifungal direnç oranlarında bölgeler/merkezler arasında önemli farklılıklar gözlenmektedir. Bu nedenle, farkındalık ve klinik etki yönünden direnç oranlarının saptanmasına yönelik sürveyans çalışmalarının yapılması büyük önem taşımaktadır.

Treatment of Invasive Aspergillosis: How It's Going, Where It's Heading

Johannes Boyer · Simon Feys · Isabella Zsifkovits · Martin Hoenigl · Matthias Egger

Mycopathologia
https://doi.org/10.1007/s11046-023-00727-z

Published online: 26 April 2023



Present	Future drug options	Immunotherapy - *potential approaches*
#1 ***First Line*** Voriconazole/ Isavuconazole	***Monotherapy*** Fosmanogepix Olorofim	***Cellular*** Ex vivo stimulation of CD4+ T-cells
Alternative LAmB	***Combination approaches*** Fosmanogepix/ Ibrexafungerp + LAmB	CAR CD8+ cells with artifical *Aspergillus* specific receptor
Posaconazole	Rezafungin/ Ibrexafungerp/ Opelconazole + m.a. antifungal	***Humoral*** (anti-)cytokines: rIFN-γ, anakinra…
Salvage° LAmB ± Echinocandin	Opelconazole + LAmB/ fosmanogepix/ olorofim/ echinocandin/ ibrexafungerp	Checkpoint inhibitors - anti-PD1
Azole ± Echinocandin	***Oral step-down options*** Fosmanogepix Olorofim	natural anti-*Aspergillus* antibodies*
	Salvage Azole + opelconazole LAmB + opelconazole	***Vaccination*** Encouraging results in immunocompromised mice
	Fosmanogepix/ olorofim/ ibrexafungerp + opelconazole	

SAA 06/2023