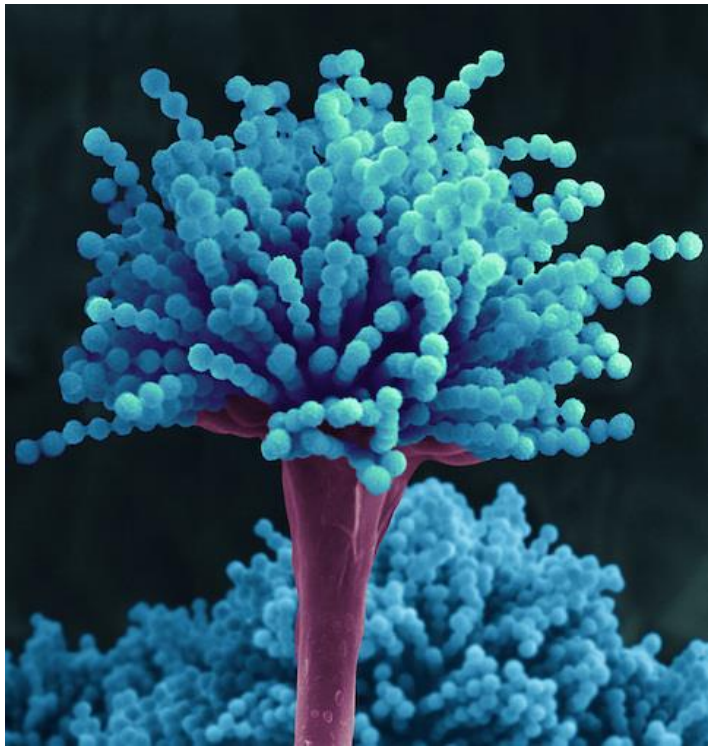
İNVAZİV ASPERGİLLOZ
Direnç

Prof Dr Zekaver Odabaşı
Marmara Üniversitesi



İnvazif Aspergillozis için risk faktörleri

BAĞIŞIKLIK SİSTEMİ

Toll-like reseptörlerin polimorfizmi
C-tipi lektin reseptörü polimorfizmi
Mannoz bağlayan lektin polimorfizmi
Plazminojen polimorfizmi
Diğer polimorfizmler**?**

ALTTA YATAN DURUMA BAĞLI FAKTÖRLER

Nötropeni
Progresif kanser
GvHD

PRİMER KONAĞA BAĞLI FAKTÖRLER

Hematolojik maligniteler
Allojenik HSCT
Solid organ nakli
Solid tümör
Diğer immün bozukluklar

İklim
İnşaatta çalışma
İkamet edilen yer
Tütün veya marihuana kullanımı
Kontamine yemek veya baharat
Evcil hayvan, bitki ve bahçecilik
Hastanede HEPA filtre olmaması

ÇEVRESEL FAKTÖRLER

Travma, yanık
Renal bozukluk
Metabolik asidoz
Önceki respiratuar hastalıklar

DİĞER FAKTÖRLER

Herbrecht R et al. Ann. N.Y. Acad. Sci. 1272 (2012) 23–30

İnvazif Aspergillozis için risk faktörleri

RİSK ARTIŞI

YÜKSEK RİSK

- Kronik granülomatöz hastalık
- Allojenik HKHN ve GvHD
- Remisyon indüksiyon tedavisi ile tedavi edilmiş Myelodisplastik sendrom
- Akciğer veya kalp nakli
- İnce bağırsak nakli
- Karaciğer nakli
- GvHD olmaksızın allojenik HKHN
- Konsolidasyon tedavisi boyunca akut myeloblastik lökemi

ORTA RİSK

- Akut lenfoblastik lösemi
- Kalp nakli
- Kroniklenfositik lösemi
- Myelodispalstik sendrom
- Multipl myelom
- Akut alevlenme ile seyreden KOAH
- AIDS
- Non-Hodgkin lenfoma

DÜŞÜK RİSK

- Otolog HKHN
- Böbrek nakli
- Solid tümör
- Otoimmün hastalıklar

Herbrecht R et al. Ann. N.Y. Acad. Sci. 1272 (2012) 23–30

Invasive aspergillosis: First-line

Agent	Grade	Comments
Voriconazole	A I	2x6 mg/kg D1 then 2x4 mg/kg (initiation with oral: CIII)
Ambisome	B I	dose 3 mg/kg
ABLC	B II	dose 5 mg/kg
Caspofungin	C II	
Itraconazole	C III	
ABCD	C I	
Combination voriconazole + anidulafungin	C I [1]	
Other combinations	C III	
AGAINST THE USE		
Amphotericin B deoxycholate	A I	

[1] *provisional*

In the absence of data in 1st line, posaconazole has not been graded

Invasive aspergillosis: salvage

Agent	Grade	Comments
Ambisome	~~B III~~ B II	no data in voriconazole failure
ABLC	~~B III~~ B II	no data in voriconazole failure
Caspofungin	B II	no data in voriconazole failure
Itraconazole	C III	Insufficient data
Posaconazole	B II	no data in voriconazole failure
Voriconazole	B II	if not used in 1st line
Combination	~~C II~~ B II	different studies, not randomized

IDSA Invazif Aspergilloz Tedavisi 2016

Table 1. Summary of Recommendations for the Treatment of Aspergillosis

Condition	Therapy	
	Primary	Alternative
Invasive syndromes of *Aspergillus*		
IPA	Voriconazole (6 mg/kg IV every 12 h for 1 d, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200–300 mg every 12 h or weight based dosing on a mg/kg basis); see text for pediatric dosing	Primary: Liposomal AmB (3–5 mg/kg/day IV), isavuconazole 200 mg every 8 h for 6 doses, then 200 mg daily Salvage: ABLC (5 mg/kg/day IV), caspofungin (70 mg/day IV × 1, then 50 mg/day IV thereafter), micafungin (100–150 mg/day IV), posaconazole (oral suspension: 200 mg TID; tablet: 300 mg BID on day 1, then 300 mg daily, IV: 300 mg BID on day 1, then 300 mg daily, itraconazole suspension (200 mg PO every 12 h)
Invasive sinus aspergillosis	Similar to IPA	Similar to IPA
Tracheobronchial aspergillosis	Similar to IPA	Adjunctive inhaled AmB may be useful
Aspergillosis of the CNS	Similar to IPA	Similar to IPA Surgical resection may be beneficial in selected cases
Aspergillus infections of the heart (endocarditis, pericarditis, and myocarditis)	Similar to IPA	Similar to IPA
Aspergillus osteomyelitis and septic arthritis	Similar to IPA	Similar to IPA
Aspergillus infections of the eye (endophthalmitis and keratitis)	Systemic IV or oral voriconazole plus intravitreal AmB or voriconazole indicated with partial vitrectomy	Similar to invasive pulmonary aspergillosis; limited data with echinocandins and poor ocular penetration by this class
Cutaneous aspergillosis	Similar to IPA	Similar to IPA
Aspergillus peritonitis	Similar to IPA	Similar to IPA
Empiric and preemptive	For empiric antifungal therapy, Liposomal AmB (3 mg/kg/day IV),	

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann

- İzavukonazol İFİ tedavisinde en az vorikonazol kadar başarılı (non-inferior)
- Primer İFİ tedavisinde kullanılabilir
- Daha az hepatotoksisite, göz ve cilt bulguları
- IV form (siklodekstrin içermez), oral form

Maertens J, Lancet 2016

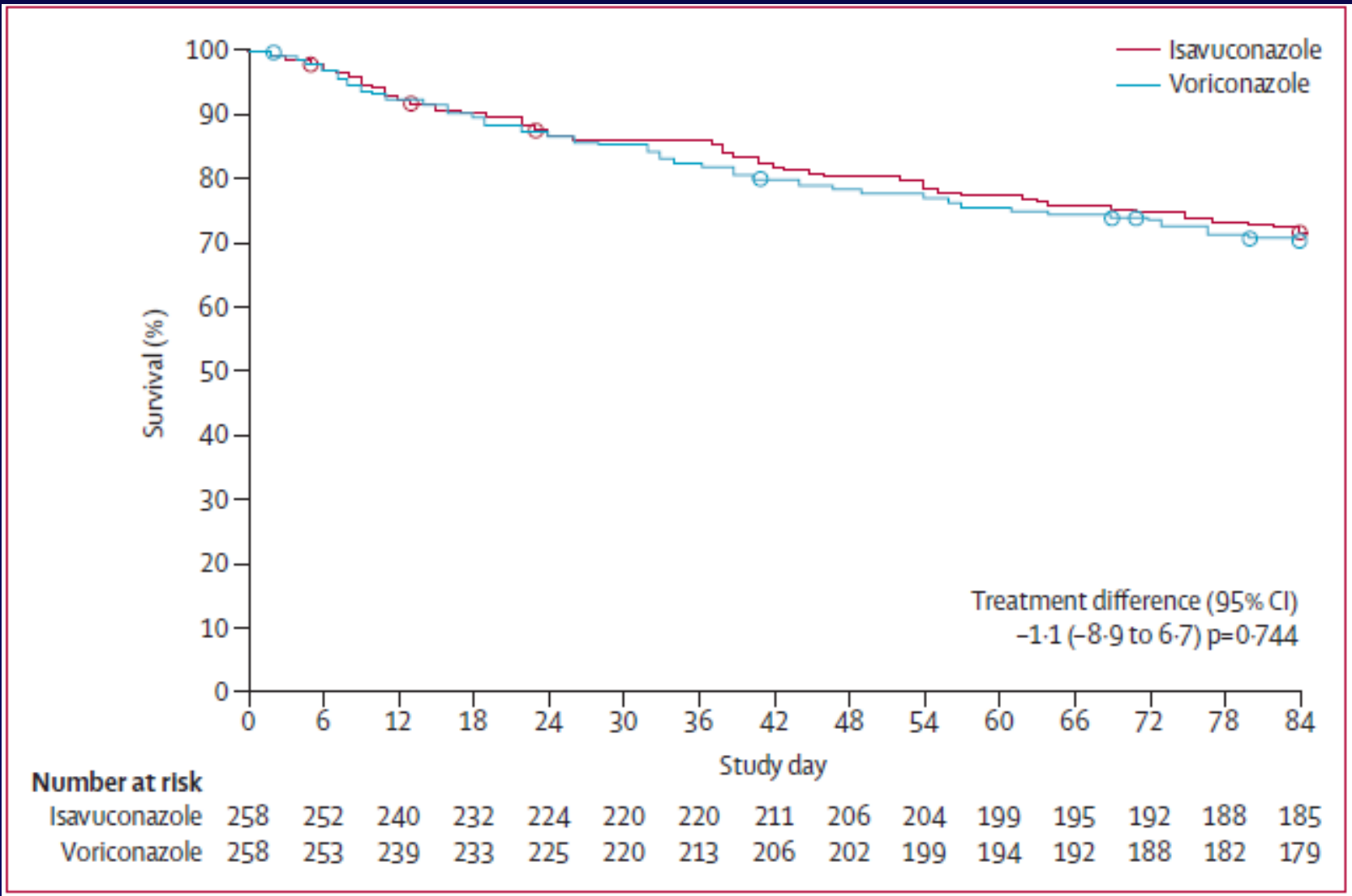
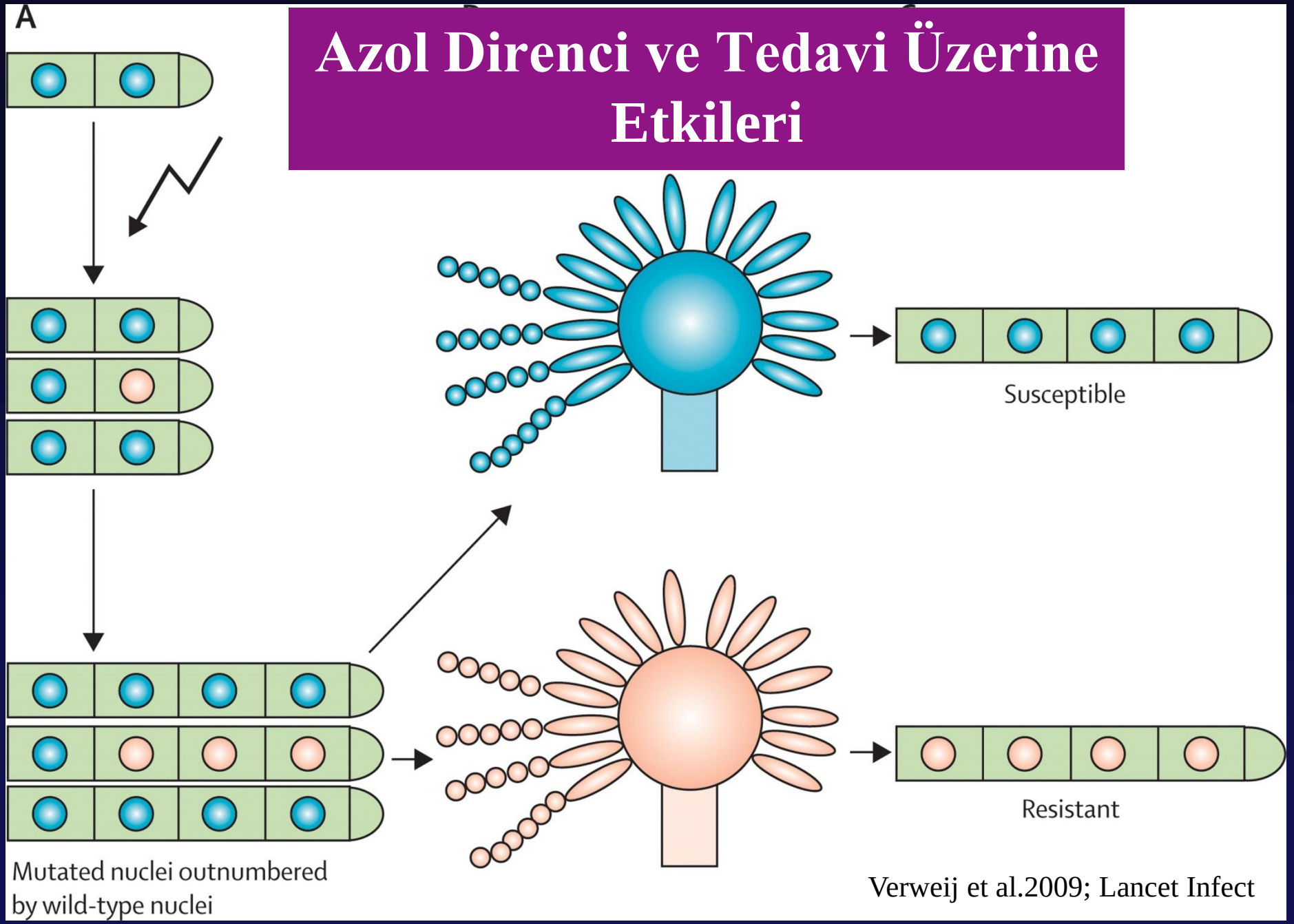


Figure 2: **Survival from first dose of study drug to day 84**

Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

Azol Direnci ve Tedavi Üzerine Etkileri

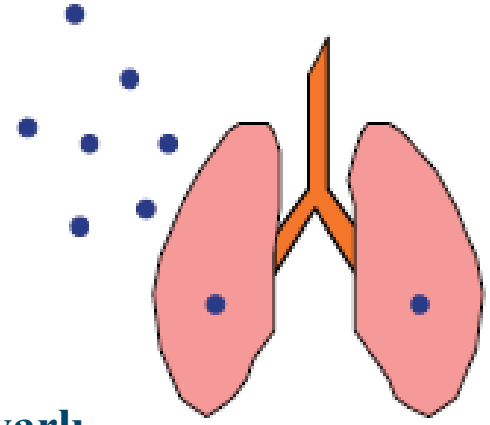


Verweij et al.2009; Lancet Infect

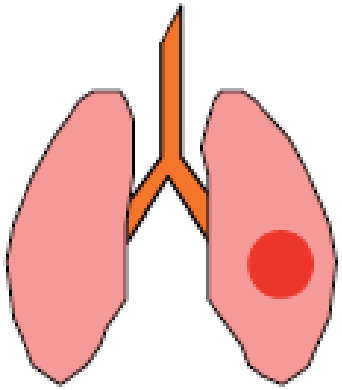
Günümüzde aspergillus türlerinde rastlanan azol direnci en sık hangi mekanizma ile oluşuyor?

A. Hastanın uzun süre küf etkili azol maruziyeti
B. İntrensek direnç
C. Çevresel direnç (doğanın azol maruziyeti)

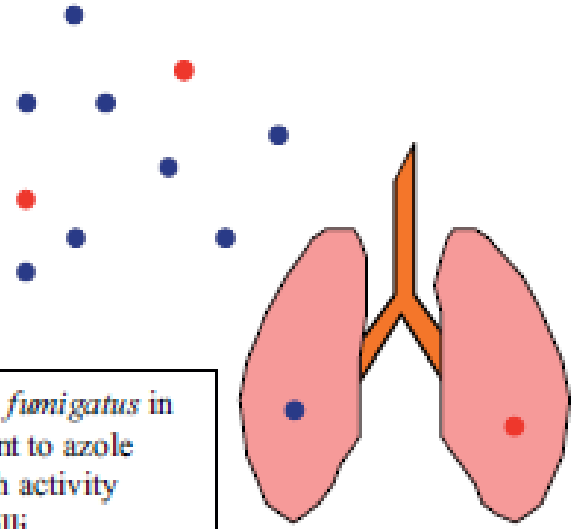
Mavi: azol duyarlı
Kırmızı azol dirençli



Patient route



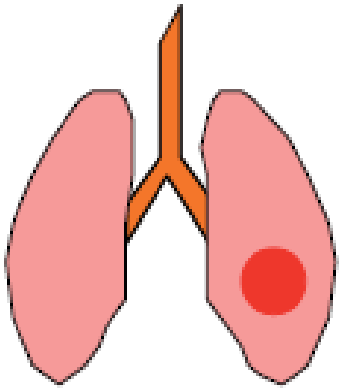
Characteristics
- Long term azole therapy
- Mainly chronic cavitary pulmonary aspergillosis
- Point mutations in the Cyp51A-gene or unknown resistance mechanisms
- Multiple resistance mechanisms may be found in different colonies from a single specimen



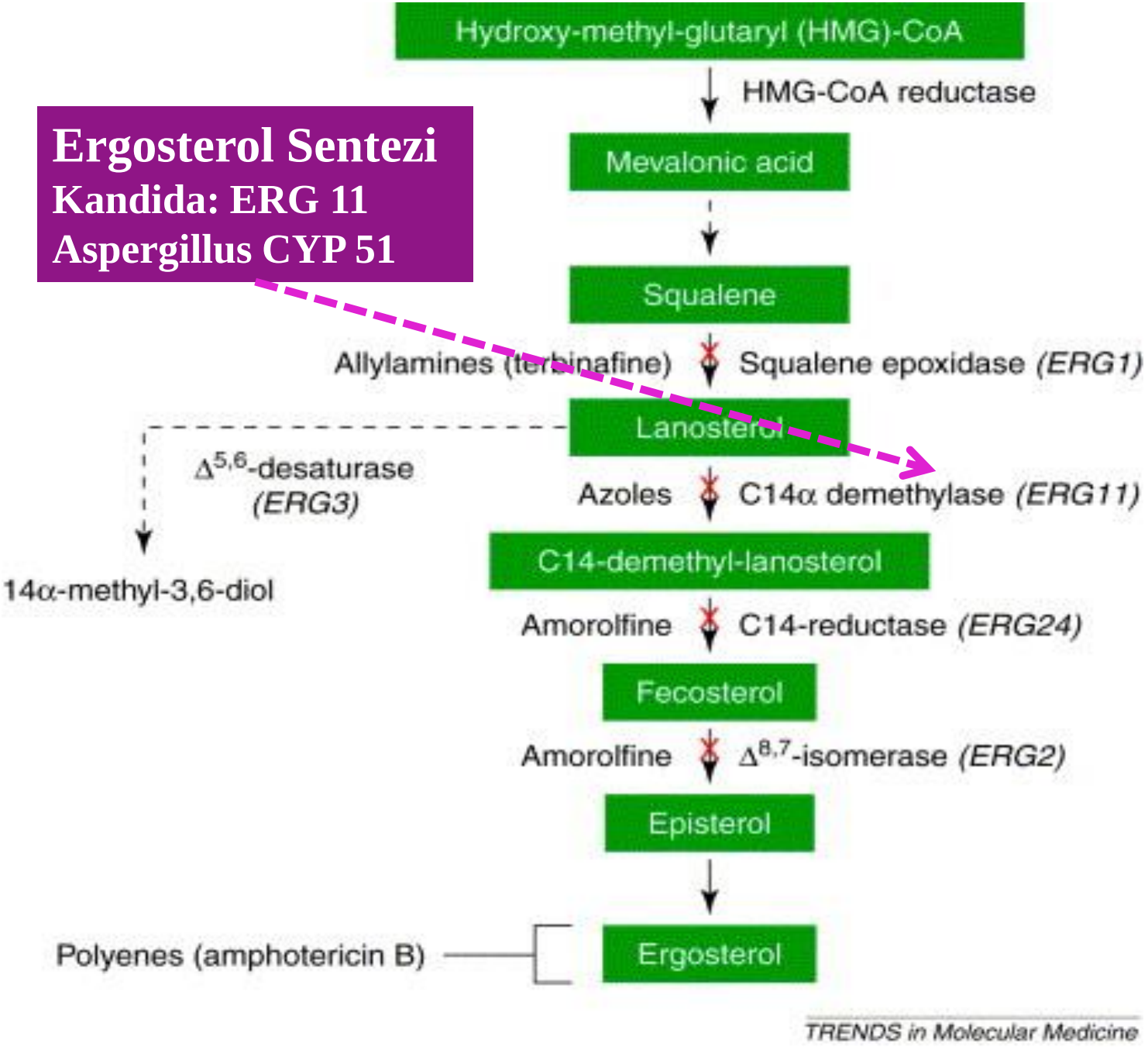
% 80

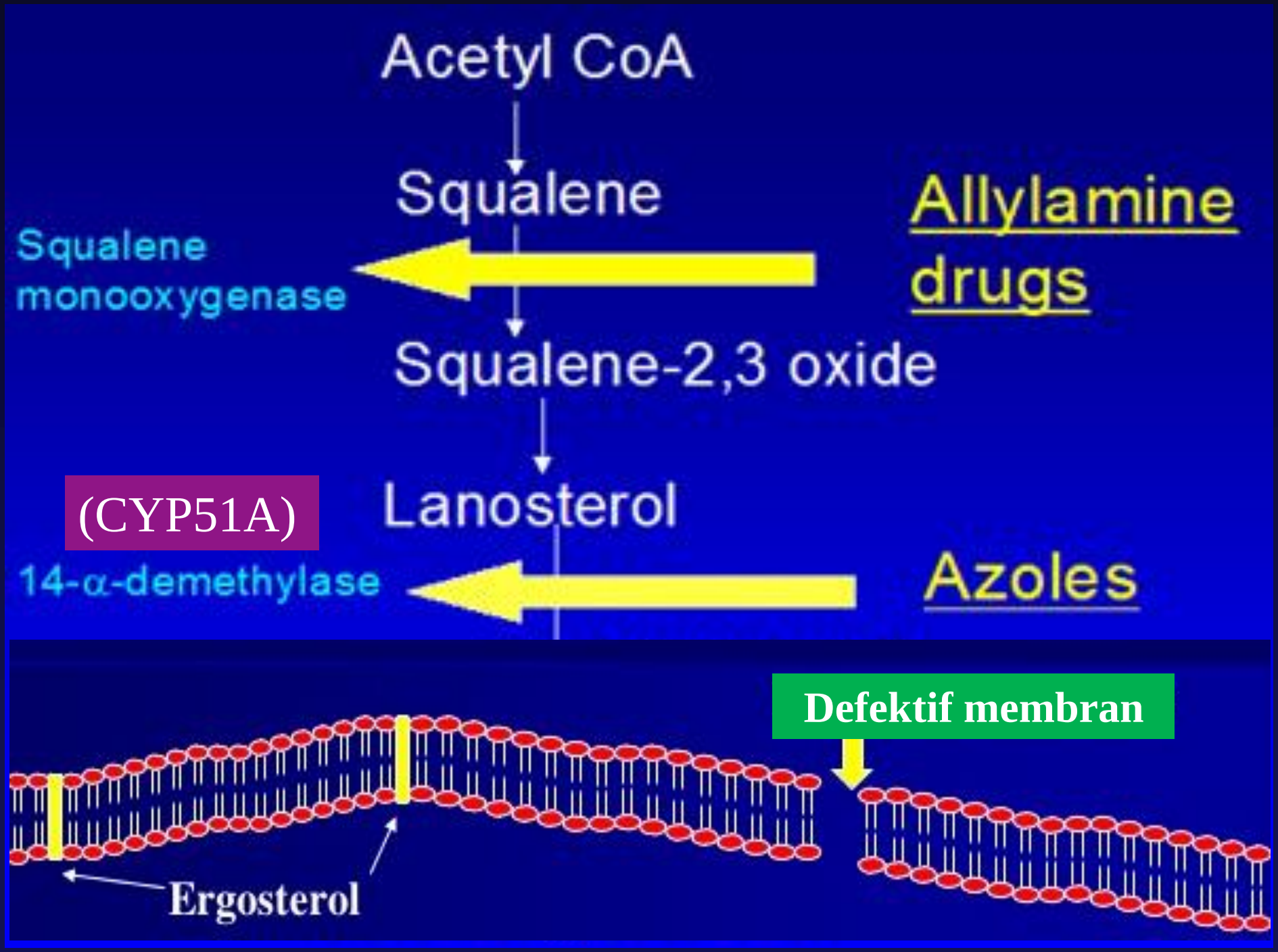
Exposure of *A. fumigatus* in the environment to azole fungicides with activity against aspergilli

Environmental route

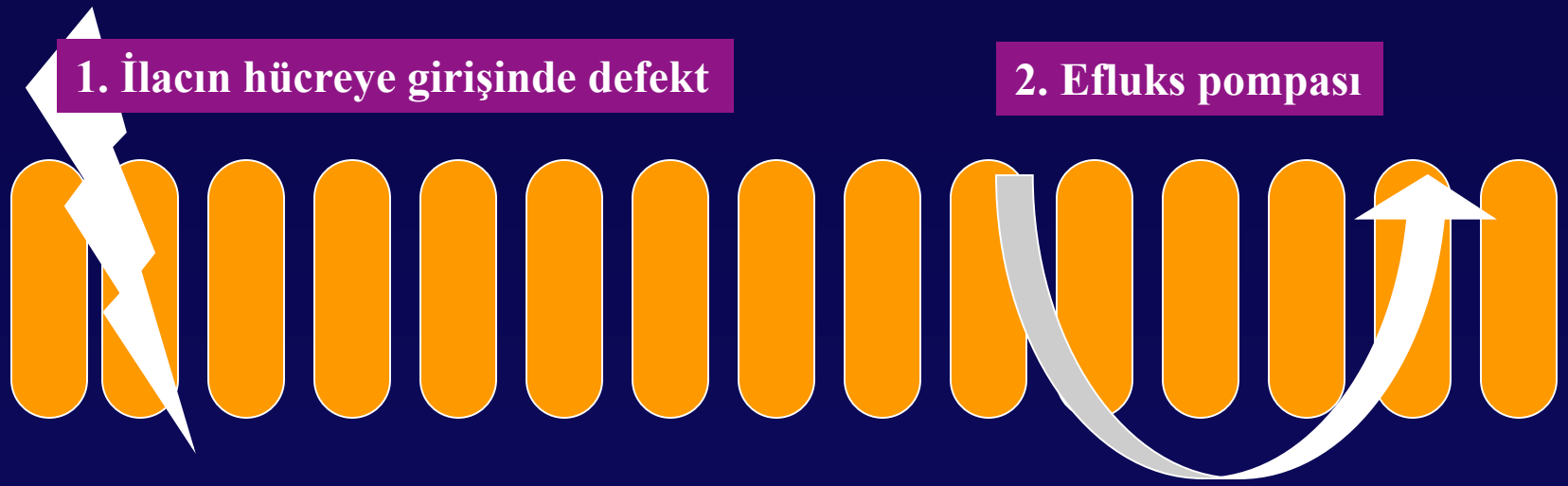


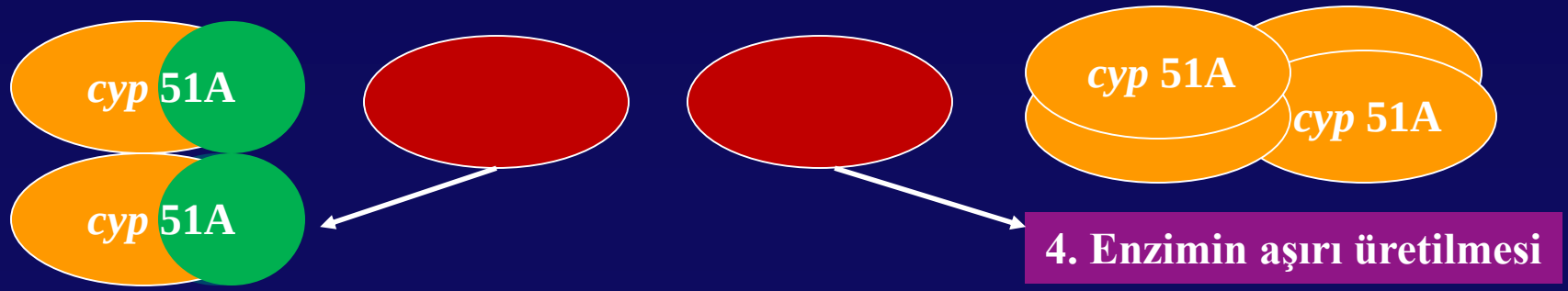
Characteristics
- Majority of patients are azole naïve
- Patients with invasive aspergillosis and chronic aspergillus diseases
- Only a few resistance mechanisms described
- Resistance mechanisms consist of Cyp51A-substitution with transcriptional enhancer


Ergosterol Sentezi
Kandida: ERG 11
Aspergillus CYP 51
Hydroxy-methyl-glutaryl (HMG)-CoA
HMG-CoA reductase
Mevalonic acid
Squalene
Allylamines (terbinafine)
Squalene epoxidase (ERG1)
Lanosterol
Δ5,6-desaturase (ERG3)
14α-methyl-3,6-diol
Azoles
C14α demethylase (ERG11)
C14-demethyl-lanosterol
Amorolfine
C14-reductase (ERG24)
Fecosterol
Amorolfine
Δ8,7-isomerase (ERG2)
Episterol
Polyenes (amphotericin B)
Ergosterol
TRENDS in Molecular Medicine


Acetyl CoA
Squalene
Allylamine drugs
Squalene monooxygenase
Squalene-2,3 oxide
(CYP51A)
Lanosterol
14-α-demethylase
Azoles
Defektif membran
Ergosterol

Azol Direnç Mekanizmaları





3. Enzime bağlandığı bölgede mutasyon

CYP 51A Mutasyonları

Amino asit mutasyonları	Azol direnci
M220I, M220V, M220K, M220T	**İtrakonazol** direnci ile beraber posakonazol ve vorikonazol duyarlılığında azalma
G54R, G54E, G54W, G54V	İtrakonazol ve pozakonazol direnci
L98H	**Multi azol direnci**
G138C	İtrakonazol, vorikonazol direnci

- **L98H mutasyonu** sonucu promotor gen (tandem repeat) aktivitesi artar
- **CYP 51** üretimi ve enzim aktivitesinde 8 kat artma

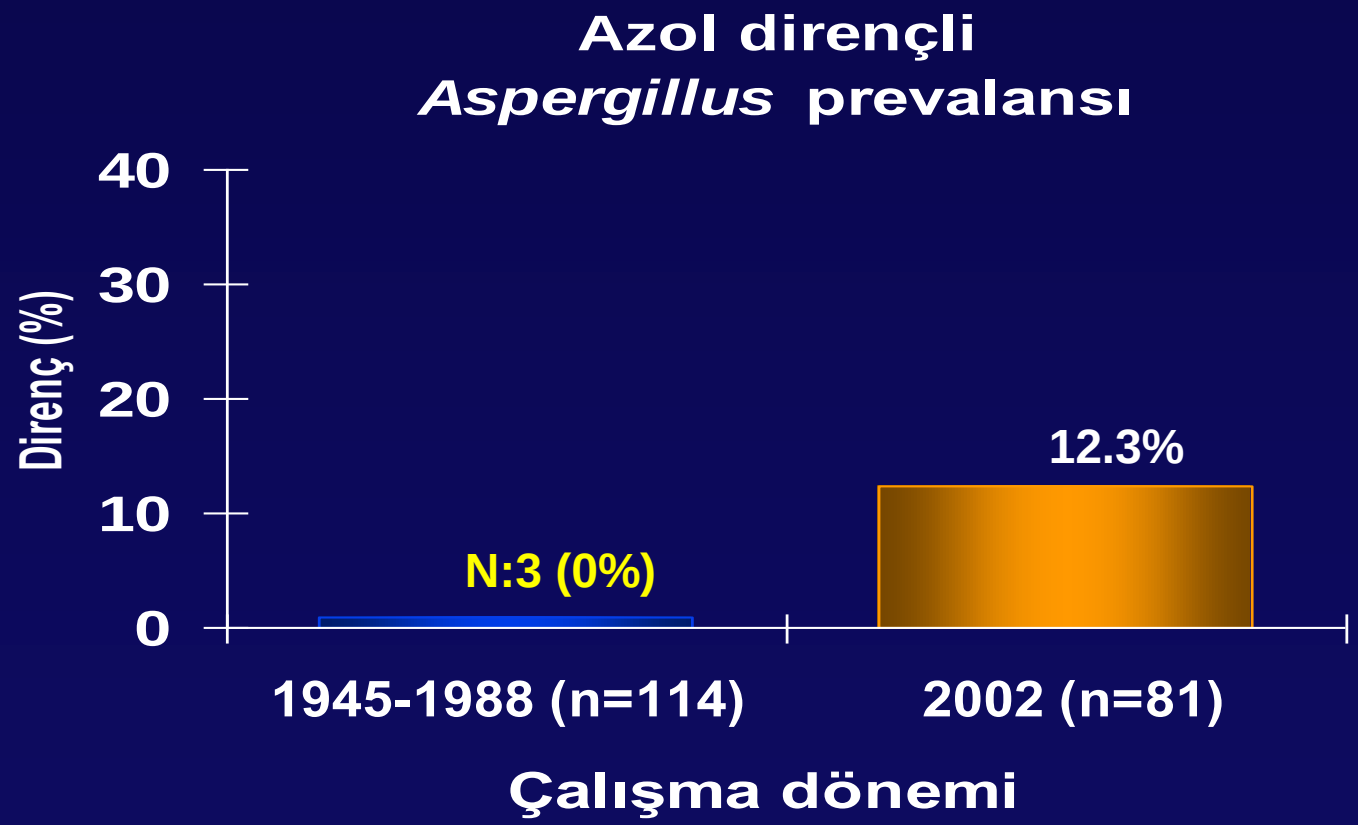
Mellado (2004,2005, 2007), Verweij 2007, Snelders 2009

- **TR34/L98H gen** mutasyonu tarımsal – bahçe bitkileri için kullanılan azollere bağlı gelişir
  - Bir diğeri de **TR46/Y121F/T289A**

- *A terreus* ve *A flavus* ile mutasyonel direnç gelişimi son derece nadirdir

- **Azol direnci tespitinde duyarlılık - MİK tayini şu an için en güvenilir yöntem**
  - EUCAST ve CLSI M38 A2
- Moleküler yöntemler üzerinde çalışılmakta (PCR)
  - Serum ve BAL ‘da azol direnci tayini
    - Chong et al., 2015, White et al., 2015

Aspergillus türlerinde Azol Direnci



Verweij PE, et al. *NEJM* 2007;356:1481-3.

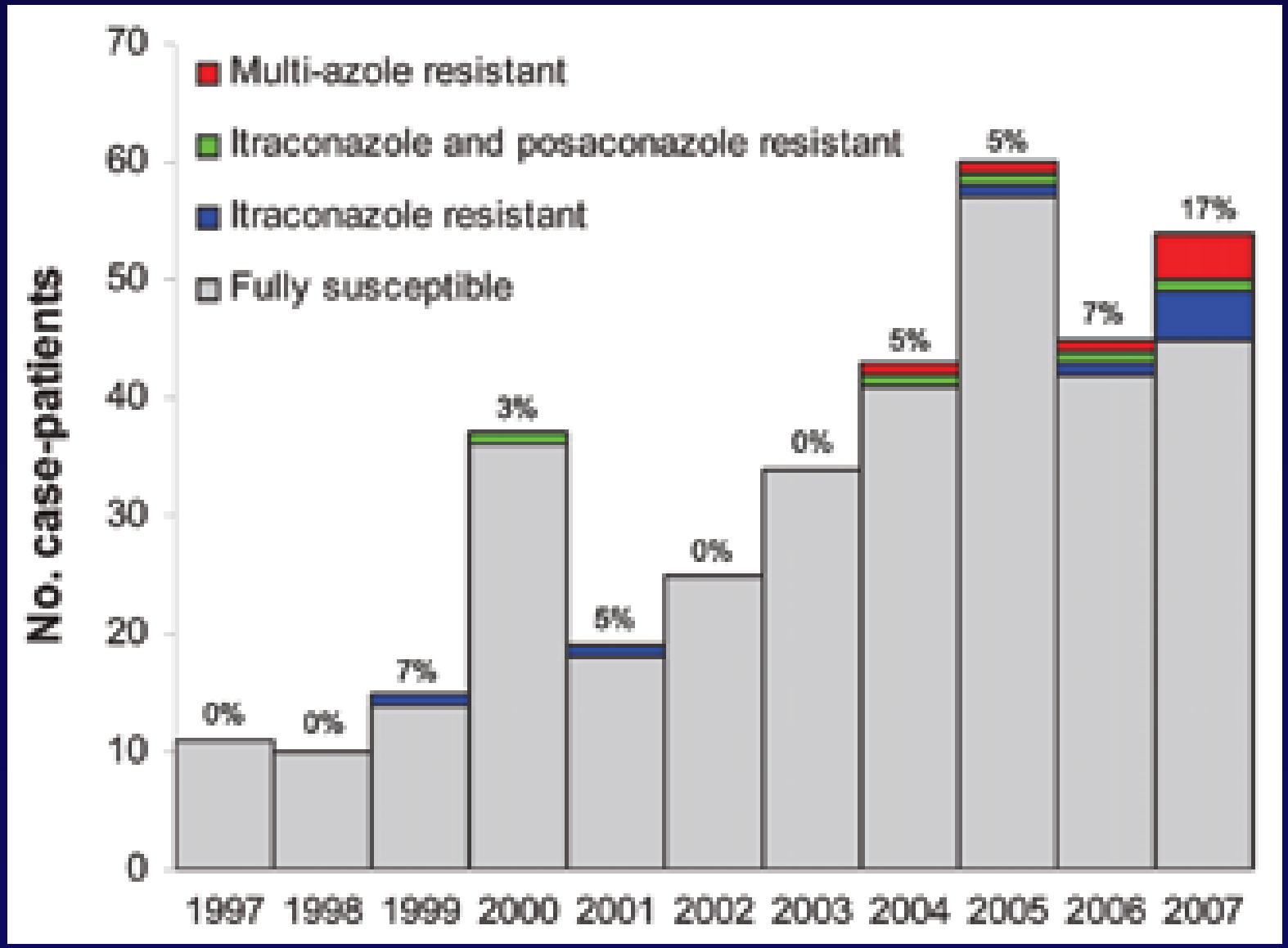
RESEARCH

Frequency and Evolution of Azole Resistance in *Aspergillus fumigatus* Associated with Treatment Failure[1]

Susan J. Howard, Dasa Cerar, Michael J. Anderson, Ahmed Albarrag, Matthew C. Fisher, Alessandro C. Pasqualotto, Michel Laverdiere, Maiken C. Arendrup, David S. Perlin, and David W. Denning

- **519 klinik izolatta itrakonazol direnci %5** (n: 34)
  - **%65 vorikonazol çapraz direnci**
  - **%74 posakonazol direnci**
  - Yıllar içerisinde artış gösteriyor (1997 – 2007)
- Değerlendirilebilen 14 vakanın:
  - **13 'ünde önceden azol kullanımı öyküsü var**
  - 8 'i inde tedaviye rağmen ilerleme
  - 5 'inde stabil yanıt
- **Cyp51A mutasyonu**

Denning D, Emerg Infect Dis ,2009



Denning D, Emerg Infect Dis ,2009

Aspergilloması olan hastadan izole edilen 8 ardışık *A fumigatus* suşunda ortaya çıkan çoğul direnç

AAC
Journals.ASM.org

Rapid Induction of Multiple Resistance Mechanisms in *Aspergillus fumigatus* during Azole Therapy: a Case Study and Review of the Literature

Simone M. T. Camps,[a,b] Jan W. M. van der Linden,[a,b] Yi Li,[a,b] Ed J. Kuijper,[c] Jaap T. van Dissel,[d] Paul E. Verweij,[a,b] and Willem J. G. Melchers[a,b]

Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands[a]; Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Nijmegen, The Netherlands[b]; Department of Medical Microbiology, Leiden University Medical Centre, Leiden, The Netherlands[c]; and Department of Infectious Diseases, Leiden University Medical Centre, Leiden, The Netherlands[d]

Nine consecutive isogenic *Aspergillus fumigatus* isolates cultured from a patient with aspergilloma were investigated for azole resistance. The first cultured isolate showed a wild-type phenotype, but four azole-resistant phenotypes were observed in the subsequent eight isolates. Four mutations were found in the *cyp51A* gene of these isolates, leading to the substitutions A9T, G54E, P216L, and F219I. Only G54 substitutions were previously proved to be associated with azole resistance. Using a Cyp51A homology model and recombination experiments in which the mutations were introduced into a susceptible isolate, we show that the substitutions at codons P216 and F219 were both associated with resistance to itraconazole and posaconazole. A9T was also present in the wild-type isolate and thus considered a Cyp51A polymorphism. Isolates harboring F219I evolved further into a pan-azole-resistant phenotype, indicating an additional acquisition of a non-Cyp51A-mediated resistance mechanism. Review of the literature showed that in patients who develop azole resistance during therapy, multiple resistance mechanisms com-

Simone MT, AAC 2012

TABLE 1 Isolates obtained from the patient suffering from pulmonary aspergilloma

Isolate no.	Date of isolation (day-mo-yr)	Specimen	Cyp51A substitution	MIC (mg/liter)				Microsatellite no. of repeats						Treatment
				ITC	VRC	POS	AMB	3A	3B	3C	4A	4B	4C	
v74-61	29-9-2008	Sputum	A9T	0.5	1	0.063	1	13	9	17	8	9	10	ITC
v76-03	17-11-2008	Sputum	A9T, F219I	>16	1	0.5	1	13	9	17	8	9	10	VRC
v77-41	17-12-2008	Sputum	A9T, P216L	>16	1	1	1	13	9	17	8	9	10	POS
v79-63	25-2-2009	Sputum	A9T, F219I	>16	8	>16	1	13	9	17	8	9	10	POS
v80-28	9-3-2009	Sputum	A9T, F219I	>16	8	>16	1	13	9	17	8	9	10	POS
v80-55	19-3-2009	Sputum	A9T, F219I	>16	8	>16	1	13	9	17	8	9	10	POS
v82-58	16-5-2009	Sputum	A9T, F219I	>16	4	>16	1	13	9	17	8	9	10	POS
v83-11	5-6-2009	Sputum	A9T, F219I	>16	4	>16	1	13	9	17	8	9	10	L-AMB + CAS
v83-14	7-6-2009	BAL	A9T, G54E	>16	0.5	1	1	13	9	17	8	9	10	L-AMB + CAS

Simone MT, AAC 2012

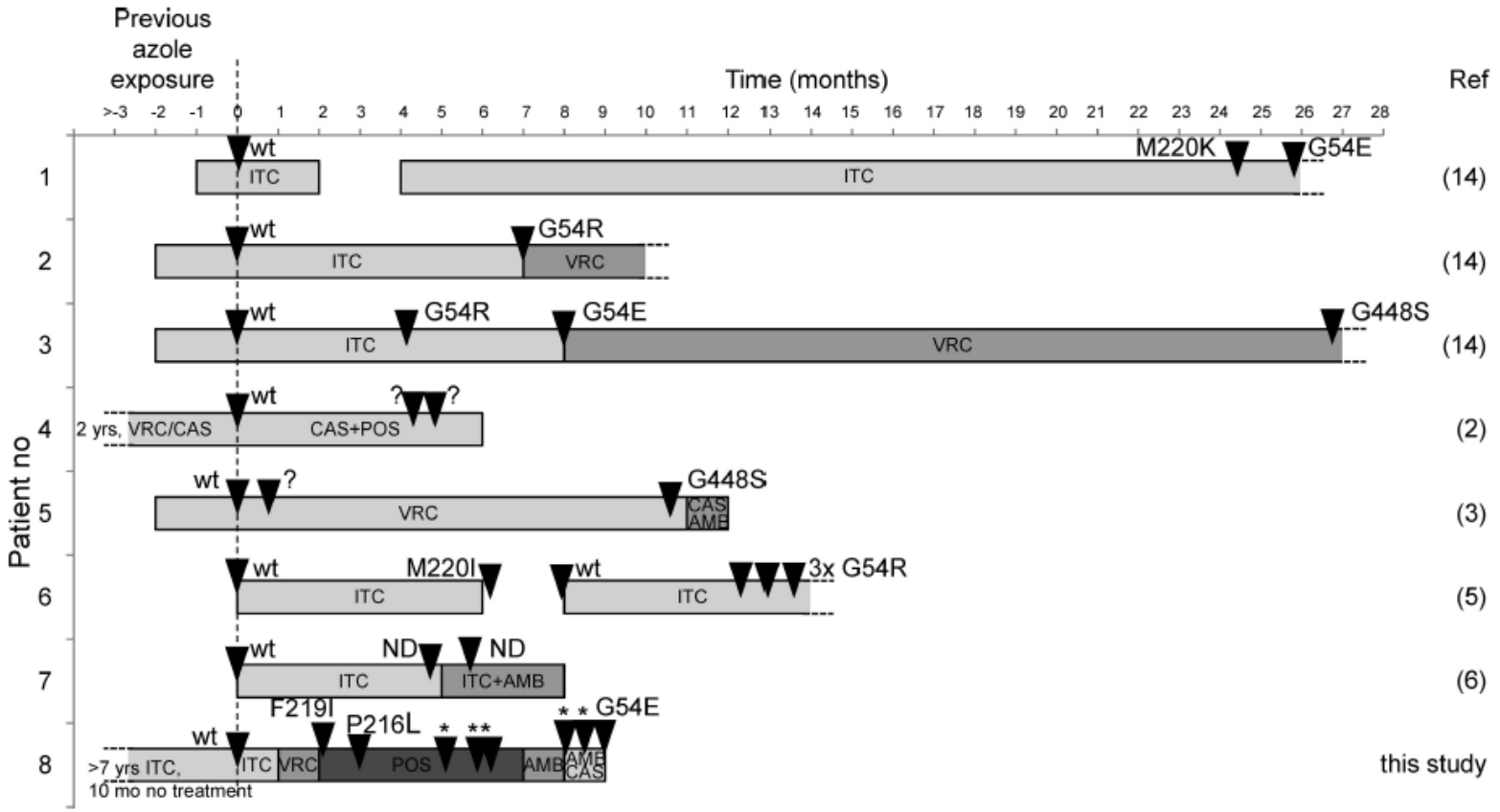


FIG 3 Reported cases of acquired azole resistance in *A. fumigatus* (2, 3, 5, 6, 14). The treatment schedules of all eight patients are indicated with bars, and the *A. fumigatus* isolates obtained from the patients are indicated with triangles. The corresponding resistance mechanisms are also indicated. wt, azole-susceptible wild-type isolate; ?, resistant isolate without any *cyp51A* mutations; ND, *cyp51A* sequence not determined; ITC, itraconazole; VRC, voriconazole; CAS, caspofungin; POS, posaconazole; AMB, amphotericin B (in various formulations). In the isolates marked with an asterisk, the F219I resistance mechanism was found in *cyp51A*. However, this isolate continued to evolve further azole resistance by an additional and yet unknown non-*cyp51A*-related resistance mechanism. Information regarding the treatment of patients 1, 2, and 3 was kindly provided by the author (S. Howard, personal communication).

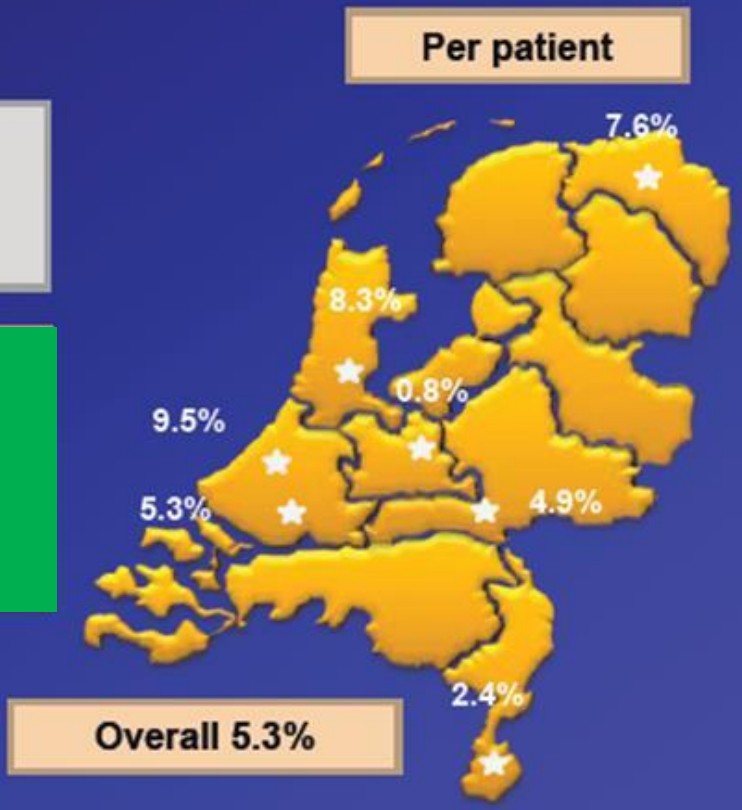
Simone MT, AAC 2012

Mechanism and spread of TR-L98H azole resistance

Prospective surveillance of azole resistance in the Netherlands 2007-2009; 2,062 clinical isolates

Azol direnci olan izolatların

> % 90 ‘ında sebep **TR/L98H** mutasyonu



- Pr[illegible]
  - [illegible] repeat in
    - Point mutations thought to arise in isolates exposed to azoles
- [illegible] exposure to
- Has a significant impact on the management of IA

Azol dirençli türlerde mortalite: %88

Vakaların %64 ‘ü azol naif

Van der Linden *et al.* 2011, Verweij *et al.* 2009

FUNGICIDES


HEXAMAX
HEXACONAZOLE 5% E.C.
BLUE DIAMOND
COPPER OXYCHLORIDE 50% WP
FUNGICIDE
DANGER
CONTROL
THIOPHENATE METHYL 70% W.P.
CARBEN
WETTASUL -80
SULPHUR 80% WP
COSAVET-DF
MetalMan
METALAXYL 8% + MANCOZEB 64%WP
TOPGUN-DF
Flo max
Blaster
PEARL


Tebuconazole 25% EW


QUALI-PRO
Tebuconazole
3.6F
Flowable Fungicide


Bitkisel Fungisid
Tebuconazole

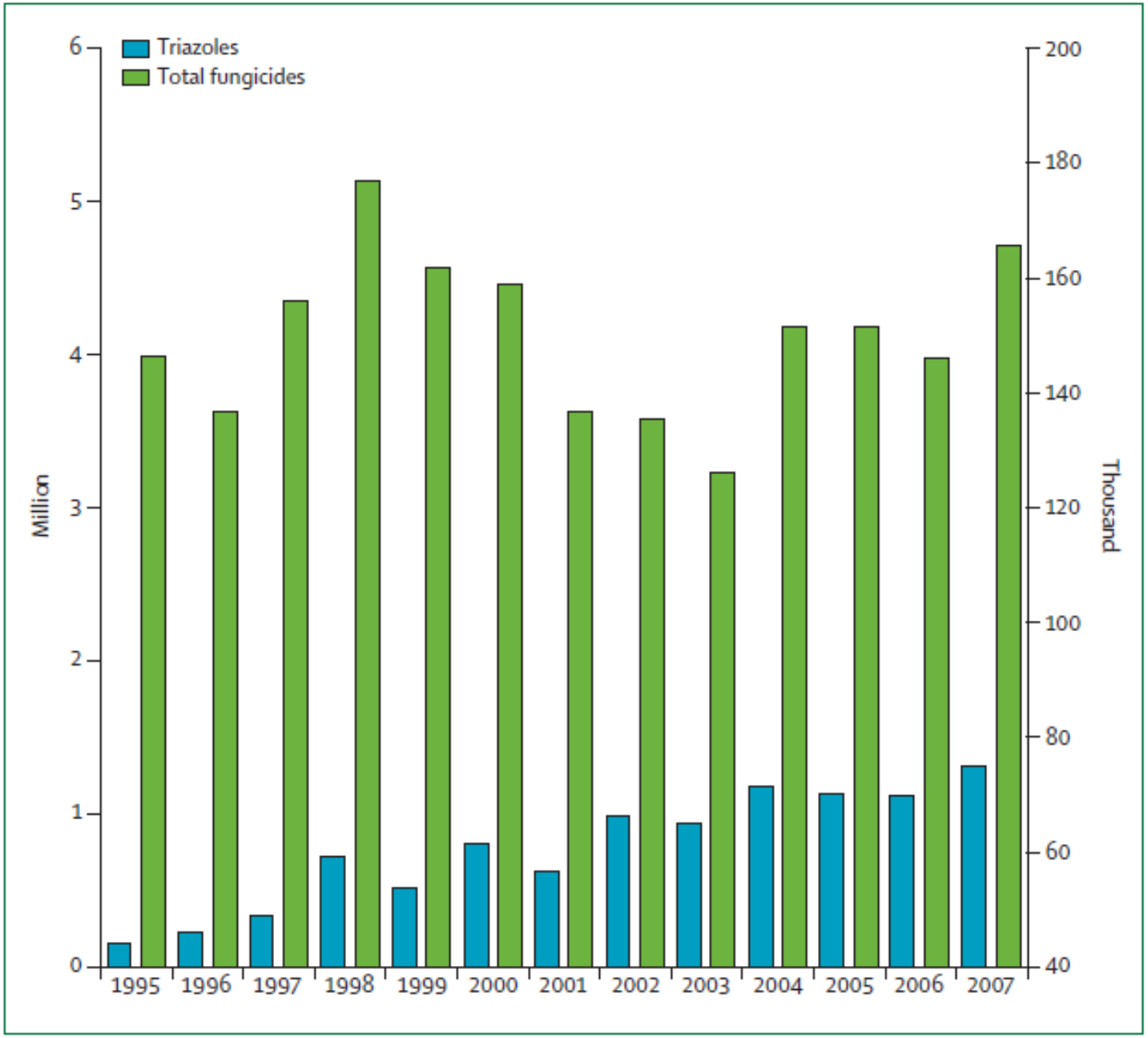


Figure 2: **Total volume of fungicides and triazoles sold in the Netherlands betwee**
Data from the Dutch Foundation for Phytofarmacy (Nefyto, Nederlandse Stichting v

Verweij et al.2009; Lancet Infect

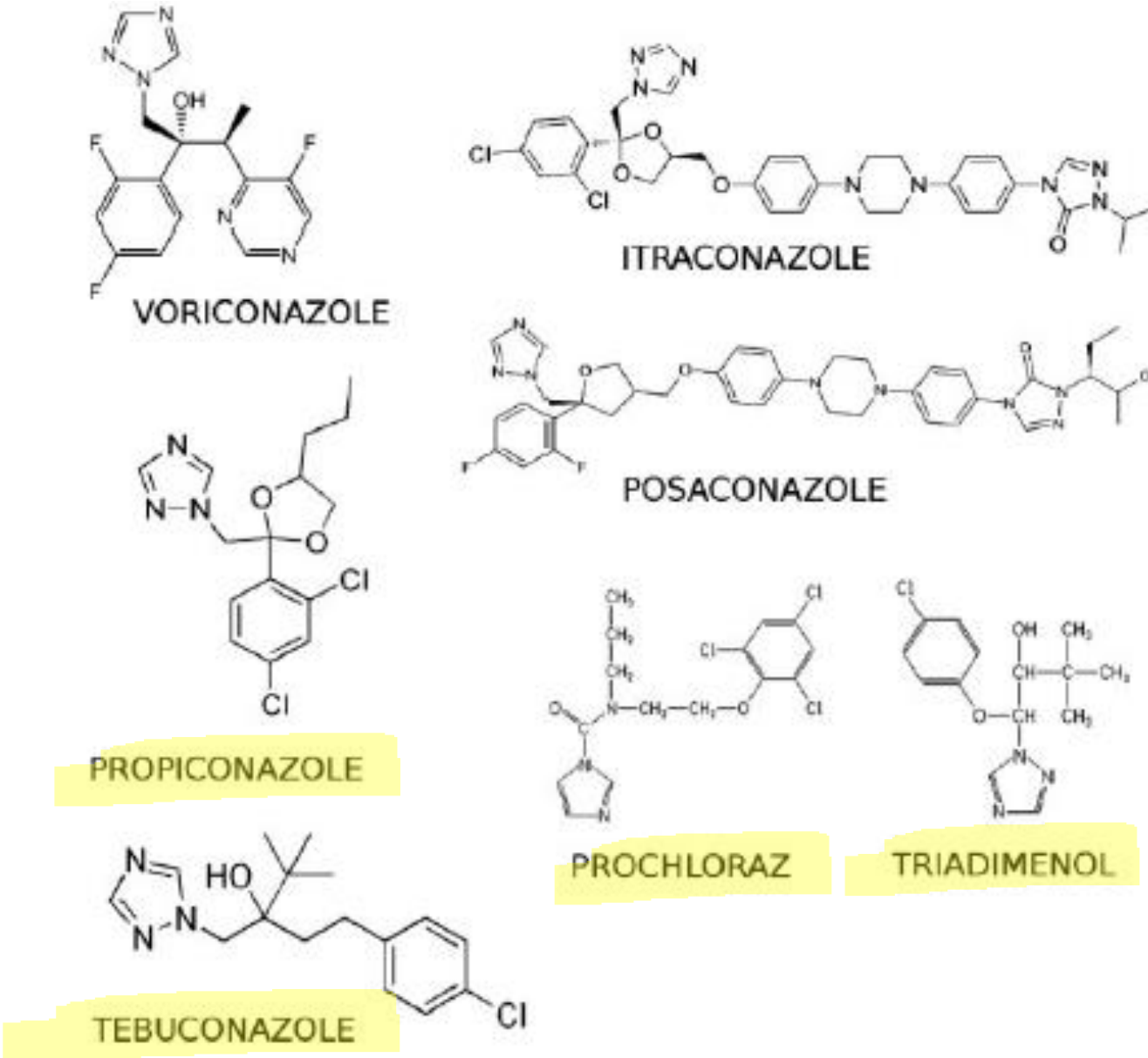


Figure 1. Structures of important triazoles in human (itraconazole, voriconazole and posaconazole) and agricultural use (propiconazole, tebuconazole, prochloraz and triadimenol).

Bowyer P, D Denning, Pest Manag Sci 2014

Does farm fungicide use induce azole resistance in *Aspergillus fumigatus*?

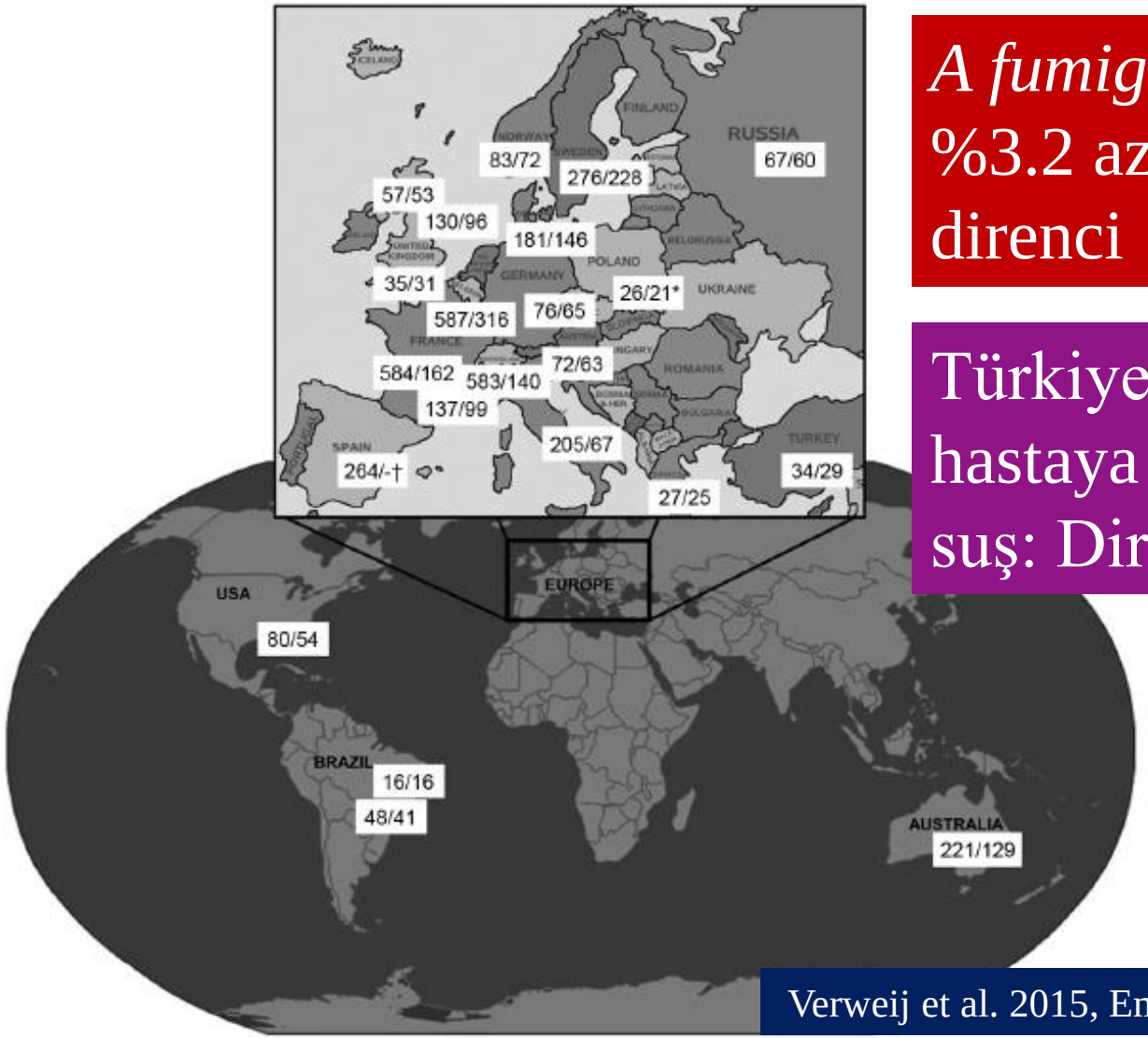
Rui Kano[1,*], Erina Kohata[1], Akira Tateishi[1], Somay Yamagata Murayama[2], Dai Hirose[2], Yasuko Shibata[3,†], Yasuhiro Kosuge[2], Hiroaki Inoue[1], Hiroshi Kamata[1] and Atsuhiko Hasegawa[4]

Abstract

Azole resistance of *Aspergillus fumigatus* isolates has been reported worldwide and it would appear to be mainly due to a point mutation in the 14α-sterol demethylase (*CYP51A*) gene, which is the target enzyme for azoles. The mutation has been confirmed in isolates from patients who received long-term itraconazole (ITZ) therapy and from agricultural fields where high levels of azole fungicides were employed. However, the relationship between farm environments and azole-resistant *A. fumigatus* has not been fully studied. In this investigation, 50 isolates of *A. fumigatus* were obtained from a farm where tetraconazole has been sprayed twice a year for more than 15 years. The mean minimum inhibitory concentration (MIC) of isolates was 0.74 (0.19–1.5) mg/L against ITZ, which was below the medical resistance level of ITZ. The sequence of *CYP51A* from isolates indicated no gene mutations in isolates from the farm. Antifungal susceptibility of isolates to tetraconazole showed that spraying with tetraconazole did not induce resistance to tetraconazole or ITZ in *A. fumigatus*.

Kano R, Medical mycology 2015

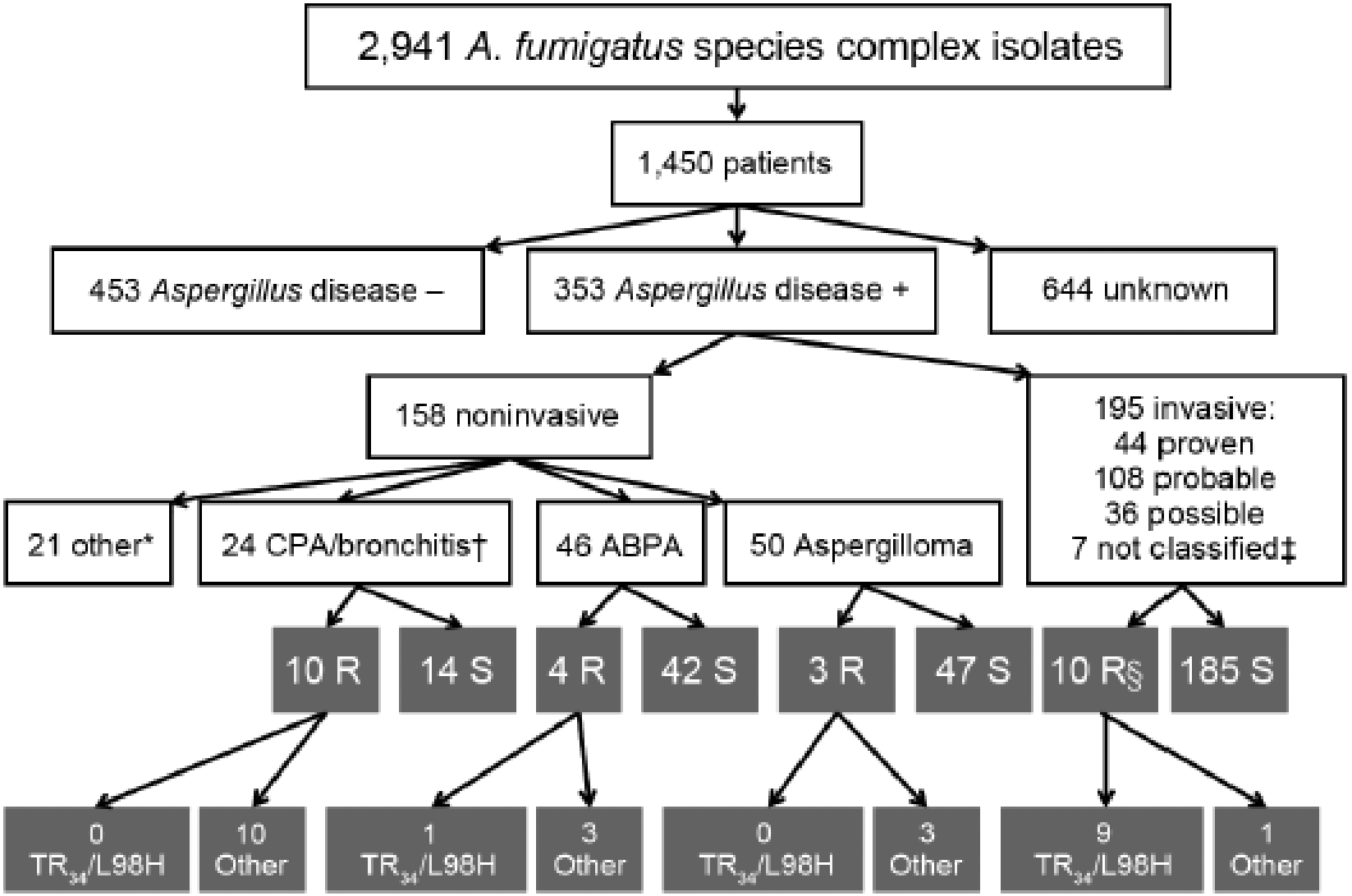
Uluslararası Prospektif Azol direnci taraması
19 Ülkeden 22 merkez



A fumigatus ‘da %3.2 azol direnci

Türkiye ‘den 29 hastaya ait 34 suş: Direnç yok

Verweij et al. 2015, Emerg Infect Dis



Verweij et al. 2015, Emerg Infect Dis

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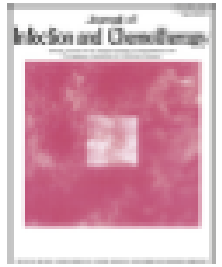

Original artide

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], Bernin Tunca [b], Halis Akalın [c]

- 413 vakadan 746 *A. fumigatus* izolatı (1999-2012)
- **İtrakonazol direnci %10.2**
- **Dirençli izolatlarda TR_{34}/L98H mutasyonu (86.8%)**
- Bursa ve çevresinde yüksek tebukonazol kullanımı

Table 4
In vitro susceptibility results of itraconazole resistant isolates.

	MIC ranges (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Itraconazole	>16	>16	>16
Voriconazole	2–8	8	8
Posaconazole	0.064–4	2	4
Amphotericin B	0.5–2	0.5	1

MIC: Minimal inhibitory concentration.

Özmerdiven GE, J of infection Chemoter2015

Environmental Isolates of Azole-Resistant *Aspergillus fumigatus* in Germany

- **Genel direnç oranı %12, en sık TR/L98H**

TABLE 1 Drug resistance patterns

Cyp51A isoform	*n*	MIC_0 range ($\mu g \cdot ml^{-1}$)		
		Itraconazole	Voriconazole	Posaconazole
TR_{34}/L98H	45	>32	1 to 4 and >32[a]	0.125 to 0.5
TR_{46}/Y121F/T289A	5	1 to 2	4 to >32	1
TR_{46}/Y121F/M172I/T289A	1	1	>32	0.5
G54A	2	>32	0.125	1
M220I	1	>32	1	0.5
Wild type	1	>32	8	1

[a] Forty-four isolates with MIC_0 values within the range of 1 to 4, and one isolate at >32.

Bader O, AAC **2015**

J Antimicrob Chemother 2015; **70**: 1522–1526
doi:10.1093/jac/dku566 Advance Access publication 27 January 2015

Journal of Antimicrobial Chemotherapy

Emergence of azole-resistant invasive aspergillosis in HSCT recipients in Germany

J. Steinmann[1]*†, A. Hamprecht[2]†, M. J. G. T. Vehreschild[3,4], O. A. Cornely[3–5], D. Buchheidt[6], B. Spiess[6], M. Koldehoff[7], J. Buer[1], J. F. Meis[8,9] and P.-M. Rath[1]

- **İki merkezden 762 ilik nakli vakasında**
- **27 vakada *A fumigatus***
- **8 'inde azol direnci** (biri hariç hepsi antifungal profilaksi +)
- **7/8 mortal seyretmiş**
- **5 'inde TR34 / L98H, 2 'sinde TR46 / Y121F**

Bu çalışmada artık nötropenik hastalarda *A fumigatus* izole edildiğinde duyarlılık testi çalışmanın gerekliliği vurgulanıyor

J Antimicrob Chemother 2015; **70**: 1522–1526
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Journal of Antimicrobial Chemotherapy

Emergence of azole-resistant invasive aspergillosis in HSCT recipients in Germany

J. Steinmann[1]*†, A. Hamprecht[2]†, M. J. G. T. Vehreschild[3,4], O. A. Cornely[3–5], D. Buchheidt[6], B. Spiess[6], M. Koldehoff[7], J. Buer[1], J. F. Meis[8,9] and P.-M. Rath[1]

Table 1. Characteristics of HSCT recipients with azole-resistant IA and their corresponding *A. fumigatus* isolates

Patient no.	Sex, age (years)	Underlying disease	aGvHD grade (only if allogeneic Tx)	Date of HSCT	Days after HSCT until ARAF detection (days)	Initial specimen	EORTC/MSG criterion	Antifungal prophylaxis (before detection)	Type of mutation	MIC (mg/L)			Antifungal treatment	Discharge status (100 days after ARAF detection)	Cause of death
										ITC	VRC	POS			
1	M, 46	AML	IV	13.12.2011	140	BAL	probable	CAS	TR_{34}/L98H	>16	2	0.5	CAS	died	sepsis
2	M, 54	AML	II	21.02.2012	112	tracheal secretion	probable	L-AMB	WT	>16	4	0.5	VRC	died	relapse, MOV
3	F, 65	AML	III	22.02.2012	134	sputum	probable	POS	TR_{34}/L98H	>16	4	0.5	POS	died	sepsis, MOV
4	M, 66	Acute biphenotype leukaemia	III	27.06.2012	21	tracheal secretion	probable	POS	TR_{34}/L98H	>16	2	0.5	L-AMB, later VRC	died	sepsis, MOV
5	F, 58	MDS RAEB-II	IV	31.01.2013	137	tracheal secretion	probable	VRC	TR_{34}/L98H	>16	2	0.5	VRC	died	sepsis, MOV
6	F, 38	Plasma cell leukaemia	I	28.03.2013	92	stool	possible	ITC	TR_{34}/L98H	>16	2	0.5	VRC	alive	—
7	M, 43	CLL Binet C	IV	21.12.2012	272	BAL	probable	VRC	TR_{46}/Y121F/T289A	>16	16	0.5	L-AMB, later VRC	died	GvHD, MOV
8	F, 52	Follicular B-NHL grade IIIa	—	26.06.2012	9	BAL	proven	—	TR_{46}/Y121F/T289A	1	>16	0.5	L-AMB, later CAS	died	sepsis

M, male; F, female; MDS, myelodysplastic syndrome; CLL, chronic lymphocytic leukaemia; NHL, non-Hodgkin lymphoma; aGvHD, acute graft-versus-host disease; ITC, itraconazole; VRC, voriconazole; POS, posaconazole; CAS, caspofungin; MOV, multi-organ failure; Tx, transplantation; BAL, bronchoalveolar lavage; RAEB, refractory anaemia with excess blasts.

Steinann J, JAC, 2015

Aspergillus & Aspergillosis Website

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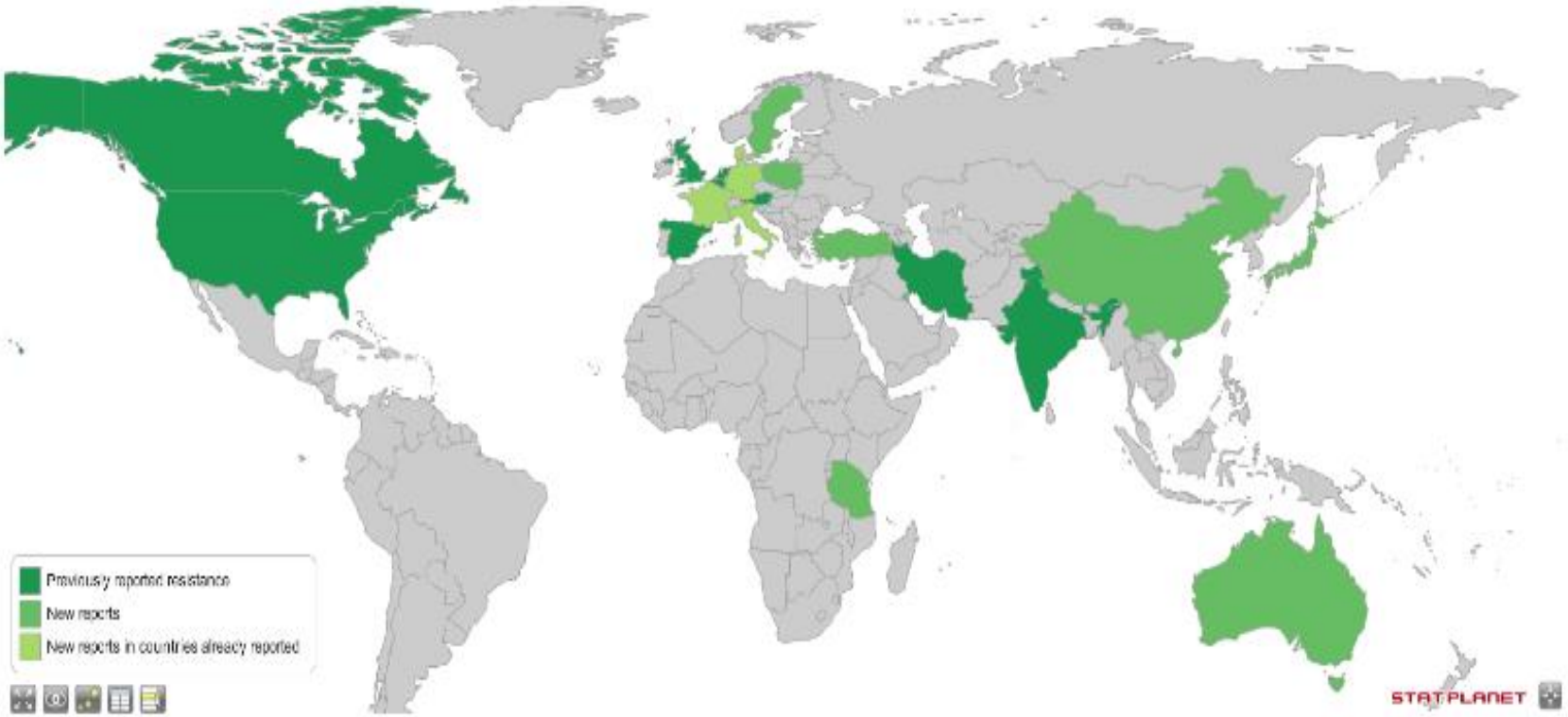
UK calls for agricultural fungicide restraint to reduce azole resistance in Aspergillus



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Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

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]

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Verweij PE, Dru resistance updates 2015

Azol direnci yok veya az görülen (<%5) bölgeler

Tedaviye Vorikonazol ile başlanabilir

Kültürde A fumigatus üretilirse

Şu durumlarda duyarlılık bakılmalı
- **Azol direnci görülen bölge**
- **Hızlı (≤ 72 sonuç alınabiliyorsa**
- **≥ 5 koloni test edilmesi önerilir**

Direnç mekanizması da belirlenmeli

Vahşi tip duyarlılık

Vori ile devam

Azol dirençli

Azol monoterapisinden kaçın

Lipozomal AmB kullan

Veya

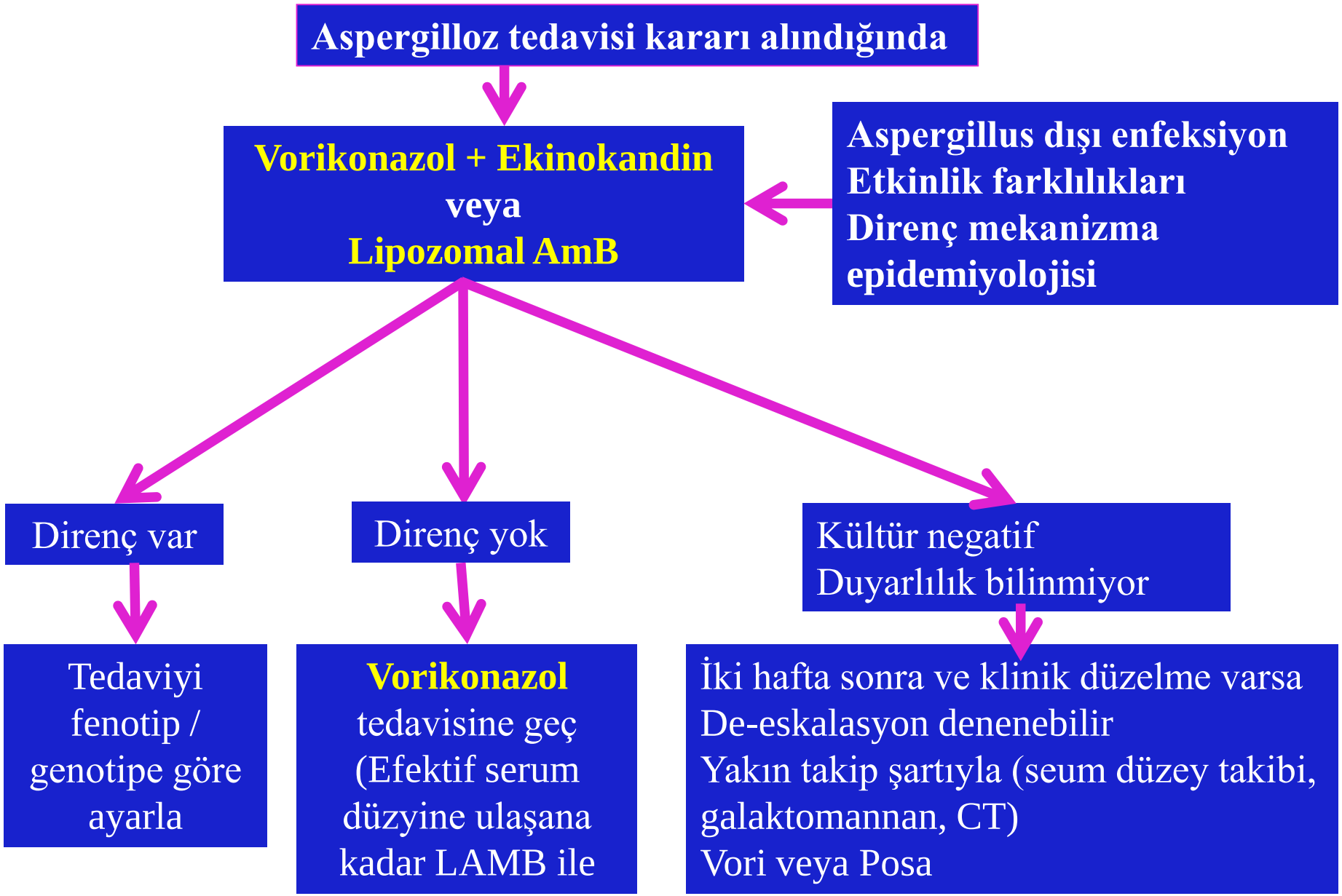
Vorikonazol + Ekinokandin

Veya

Diğer azol dışı tedaviler (ekinokandinler)

Göz önünde bulundur
- Nötropeni süresi
- İlaç etkileşimleri
- İlaç düzeyi takibi
- Organ disfonksiyonu
- Antifungal kullanım öyküsü
- AF duyarlılık sonuçları
- Hastalığın ciddiyeti

Yüksek çevresel Azol Direnci Olan Bölgelerde (>%10)



Panel Önerileri - Genel

- **Özellikle uzun süreli azol alanlarda düzenli kültür yap**
- Balgam kültürü (yüksek volümlü)
- Balgam kültürü üremelerinde **≥5 koloni** test edilmeli

- Uzun süre antifungal alanlarda **sub-optimal serum düzeyi direnç gelişeceğinin kuvvetli göstergesidir**
- Panel bu nedenle **terapötik düzey takibi** önermektedir

IDSA Invazif Aspergilloz Tedavi Rehberi 2016

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)*.

Özet

- Çevresel – zirai kökenli azol direnci artmaktadır
- Azol dirençli funguslarla mortalite yüksektir
- Mümkünse kültür sayımızı arttırmaya çalışmalıyız
- Üreyen izolatlarda duyarlılık çalışmalıyız
- Çevre taraması yapmalıyız
- Uzun süreli azol alanlarda sıkı değerlendirme yapmalı
- Mümkünse serum düzey takibi yapılmalı

TEŞEKKÜRLER