



# Olgu 2

**58 Yaş, erkek hasta, rutin kontrol «Akciğer Ca»**

- **04.12.2025 Sol üst lobektomi ve arterioplasti**
- **22.12.2025 Öksürük, balgam,**

**Akciğer grafisinde: Sol üst lobda infiltrasyon**

**«Sağlık bakımıyla ilişkili pnömoni»**

- **Balgam kültürü, AARB için boyalı preparat, TBC-PCR, mikolojik kültür için örnek**
- **Meropenem 3 x 1 gr/gün IV , siprofloksasin 2 x 400 mg IV**



- 27.12.2025 Toraks bilgisayarlı tomografi:

Plevral efüzyonda artış, ampiyem?

- Balgam örnek direkt preparat : Epitel hücreleri, lökositler, Gram(+) koklar, Gram(+) basiller, mantar hif ve sporları görüldü
- *Balgam kültürü: Normal üst solunum yolu flora elemanları ve Aspergillus fumigatus tür kompleksi (üç farklı balgam örneği)*
- 27.12.2025 Tedavi:
  - Meropenem:3 X 1 g/gün IV
  - Linezolid:2 X 600 mg/gün IV
  - Vorikonazol:2 x 6 mg/kg/g IV yükleme, 2 x 4 mg/kg/ g IV idame



# Aspergilloz

**İnvazif Pulmoner Aspergilloz (İPA)**

**Kronik Rinosinüzit**

**Alerjik  
Bronkopulmoner  
Aspergilloz (ABPA)**

- ✓ **Nötropenik hastada İPA**
- ✓ **Influenza ilişkili İPA (İAPA)  
(Influenza –Associated Pulmonary Aspergillosis)**
- ✓ **COVID 19 ile ilişkili İPA (CAPA)  
(COVID-19 Associated Pulmonary Aspergillosis)**

**Kronik Pulmoner Aspergilloz (CPA)**

**Alerjik Bronşit  
Fungal Astım**



- **29.12.2025 Serum Galaktomannan: Negatif**
- **Tedavi altında plevral effüzyon gerileyince torasentez yapılmamış**
- **05.01.2026 Antibiyotik tedavileri kesilmiş**
- **Vorikonazol devam**
- **14.01.2026 Bronkoskopi yapılıyor**
- **BAL kültür üremesi yok**
- **BAL GM (+) Cut-off 5.05**
- **27.12.2025-03.02.2026 IV Vorikonazol**
- **Oral vorikonazol tb ile taburcu edildi**
- **Takiplerde kan GM negatif**



30/01/26

(IV vorikonazol altında post op takip)

# Nötropenik olmayan hastada GM

Patients with a haematological malignancy	<u>To diagnose IA</u>	<u>GM in blood<sup>a</sup></u>			<u>Significantly lower sensitivity in non-neutropenic patients</u>
• Neutropenic patients			A	II	
• Non-neutropenic patients			B	II	
ICU patients	To diagnose IA	GM in blood <sup>a</sup>	C	II	Better performance in neutropenic than in non-neutropenic patients
Solid organ recipients	To diagnose IA	GM in blood <sup>a</sup>	C	II	Low sensitivity, good specificity Most data for lung SOT
Any other patient	To diagnose IA	GM in blood <sup>a</sup>	C	II	Piperacillin/tazobactam may no longer be responsible for false-positive results according to recent studies Cross-reactivity in case of histoplasmosis, fusariosis, talaromycosis (formerly: penicilliosis) False-positive results reported due to ingestion of ice-pops, transfusions, antibiotics, Plasmalyt® infusion

Ullmann A.J., et al. Clin Microbiol Infect 2018; 24 Suppl 1:e1-e38.

# BAL Galaktomannan Meta Analiz

D'Haeze J et al. JAC 2012; 50:1258-63

Hematoloji ve diđer hastalar (Karışık popölasyon)

$OI \geq 3$  PPD %100;  $OI \leq 0,5$  NPD %98

- 02.04.2026 Hemoptizi

PA AC grafisinde akciğer sol üst lobda kaviter lezyon, aspergilloma?

- Embolizasyon
- 08.04.2026 Fungus topu ile akciğer sol lobu total rezeksiyon

Fungus topu operasyon materyali *Aspergillus fumigatus* tür kompleksi

Plevral biyopsi kültür *Aspergillus terreus* tür kompleksi



02.04.2026

# Antifungal duyarlılık testi yapalım mı?

All clinically relevant <i>Aspergillus</i> isolates (in patient groups or regions with known azole resistance)	Identify azole resistance	Reference MIC testing	A II
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Any	Confirm or reject azole resistance in clinical <i>A. fumigatus</i> isolates when antifungal treatment is considered	Azole agar screening test followed by reference MIC test where needed	A III	MIC testing as soon as the strain is isolated and without waiting for species ID
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# First determination of azole resistance in *Aspergillus fumigatus* strains carrying the TR34/L98H mutations in Turkey

Gülşah Ece Özmerdiven<sup>a</sup>, Seçil Ak<sup>b</sup>, Beyza Ener<sup>a,\*</sup>, Harun Ağca<sup>a</sup>, Burcu Dalyan Cilo<sup>a</sup>, Berrin Tunca<sup>b</sup>, Halis Akalın<sup>c</sup>

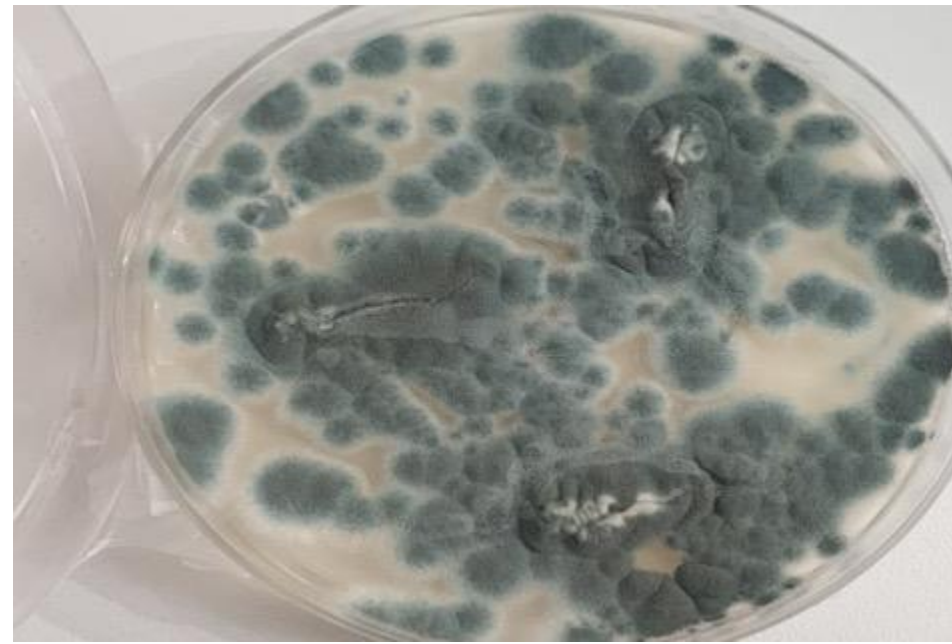
<sup>a</sup> Uludağ University, Faculty of Medicine, Department of Medical Microbiology, Görükle, 16059 Bursa, Turkey

<sup>b</sup> Uludağ University, Faculty of Medicine, Department of Medical Biology, Görükle, 16059 Bursa, Turkey

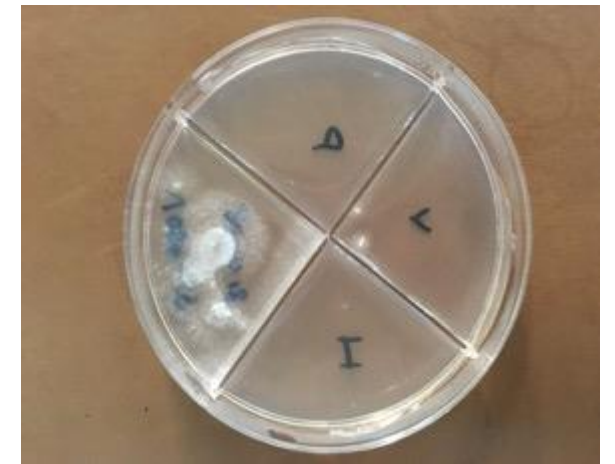
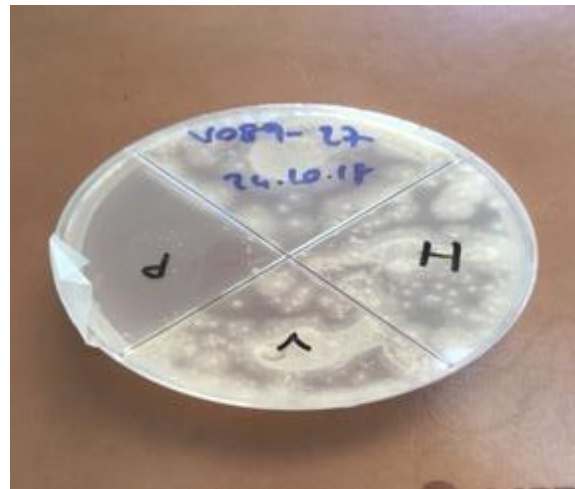
<sup>c</sup> Uludağ University, Faculty of Medicine, Department of Clinical Microbiology and Infectious Diseases, Görükle, 16059 Bursa, Turkey

J Infect Chemother 21 (2015) 581–586

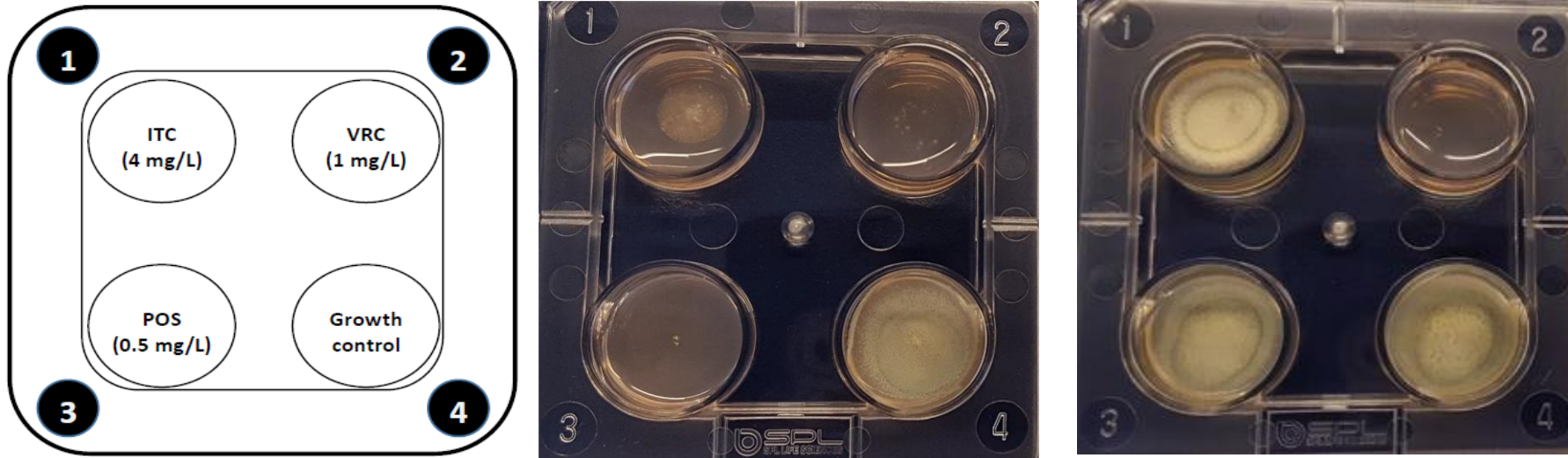
*Aspergillus fumigatus* is the most important etiological agent of invasive aspergillosis. Recently, an increasing number of azole-resistant *A. fumigatus* isolates have been described in various countries. The prevalence of azole resistance was investigated in this study using our culture collection of *A. fumigatus* isolates collected between 1999 and 2012 from clinical specimens. Seven hundred and forty-six *A. fumigatus* isolates, collected from 419 patients, were investigated. First, all isolates were screened for resistance to itraconazole by subculturing on Sabouraud dextrose agar that contained 4 mg/L itraconazole. For isolates that grew on the itraconazole containing agar, the in vitro activities of amphotericin B, itraconazole, voriconazole and posaconazole were determined using the Clinical and Laboratory Standards Institute (CLSI) M38-A reference method. After PCR amplification, the full sequence of the *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.



*Aspergillus fumigatus* tür kompleksi



# VIPcheck™78 , Nijmegen, the Netherlands

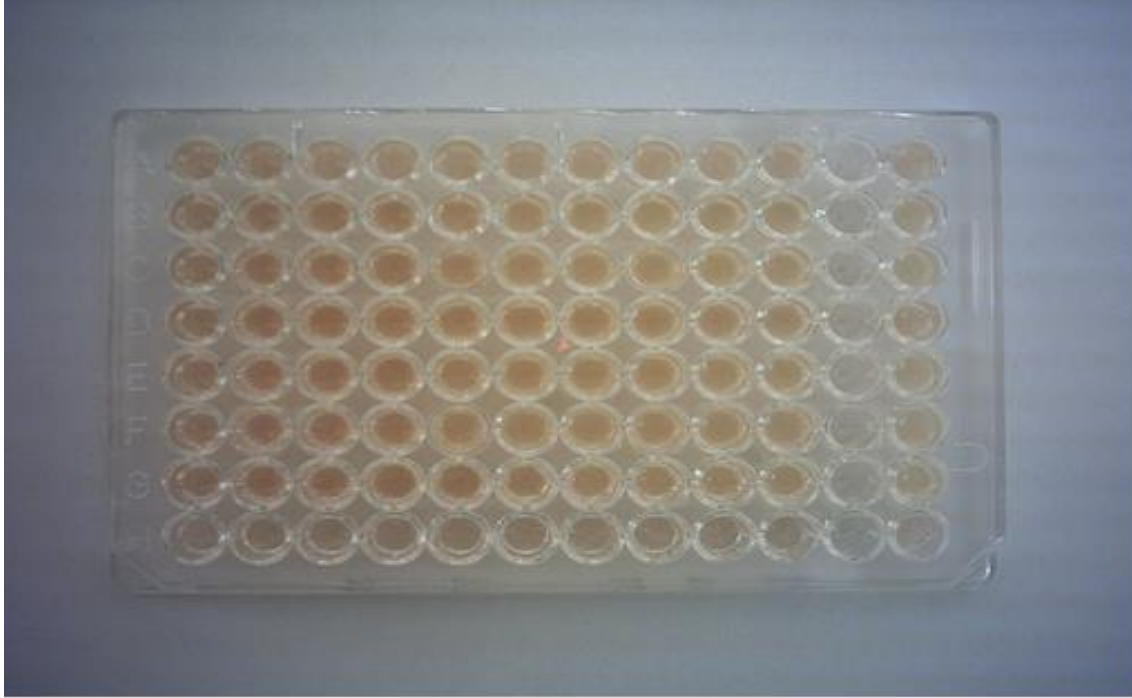


Guinea J, et al How to: EUCAST recommendations on the screening procedure E.Def 10.1

for the detection of azole resistance in *Aspergillus fumigatus* isolates using four well azole-containing agar plates, *Clinical Microbiology and Infection* (2018), doi: <https://doi.org/10.1016/j.cmi.2018.09.008>.

# Referans antifungal duyarlılık testi (CLSI M38)

## *Aspergillus fumigatus* tür kompleksi



- *A. fumigatus* tür kompleksi
  - Itr > 16 µg/ml **non-WT**
  - Vor = 16 µg/ml **dirençli** ( $2 \geq \mu\text{g/ml R}$ )
  - Pos = 0,5 µg/ml **WT**
  - Anf  $\leq 0,015$  µg/ml **WT**
  - Micf = 0,03 µg/ml **WT**
  - AmB = 1 µg/ml **WT**

CLSI *Aspergillus fumigatus* tür kompleksi epidemiyolojik eşik değerleri

Itr = 1 µg/ml

Vor = 1 µg/ml

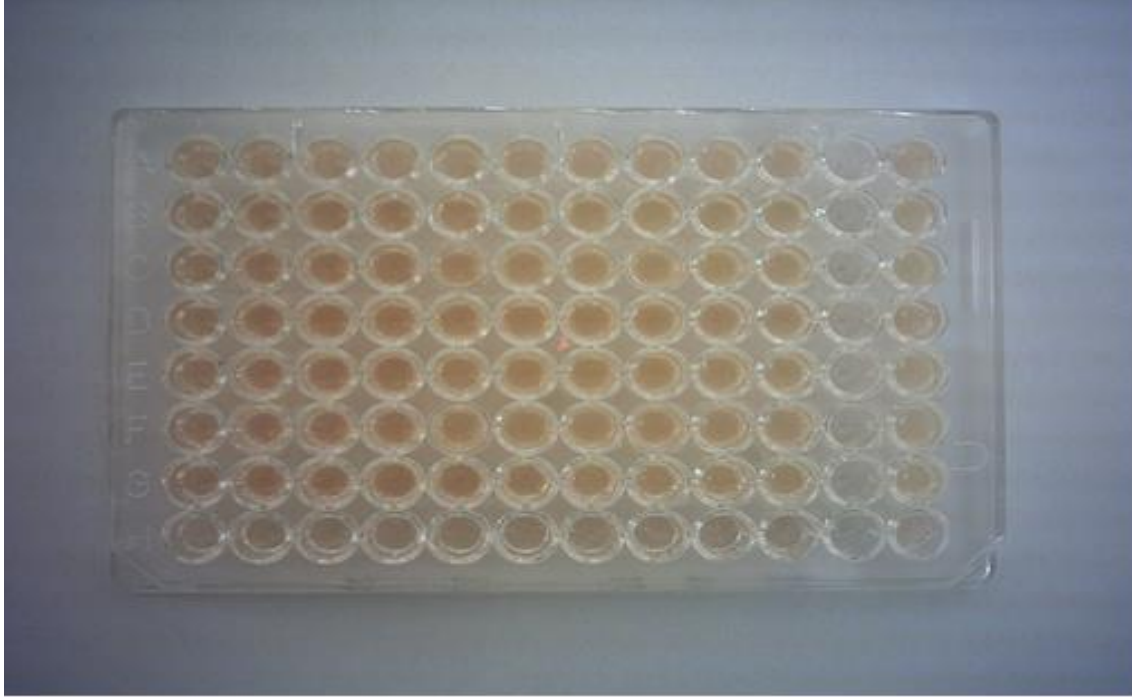
Pos = 0,5 µg/ml

AmB = 2 µg/ml

Cas = 0,5 µg/ml

# Referans antifungal duyarlılık testi (CLSI M38)

## *Aspergillus terreus* tür kompleksi



- *A. terreus* tür kompleksi
  - Itr 0,5 µg/ml **WT**
  - Vor = 0,5 µg/ml **WT**
  - Pos = 0,25 µg/ml **WT**
  - Anf = 0,03 µg/ml **WT**
  - Micf = 0,64 µg/ml **WT**
  - AmB = 8 µg/ml **NWT**

CLSI *Aspergillus terreus* tür kompleksi epidemiyolojik eşik değerleri

Itr = 2 µg/ml

Vor = 2 µg/ml

Pos = 1 µg/ml

AmB = 4 µg/ml

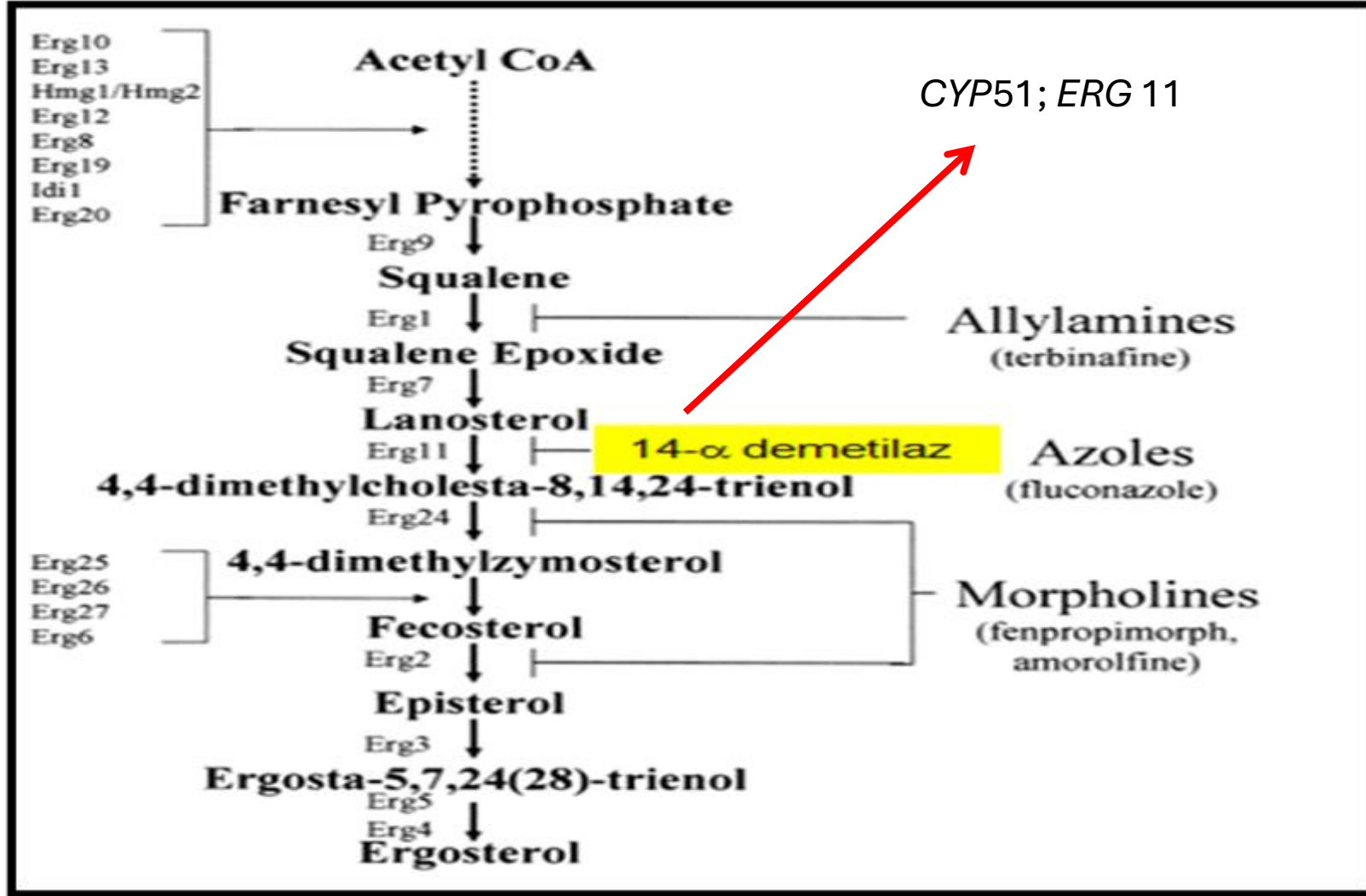
Cas = 0,125 µg/ml

# Hastanın tedavisi

## Kombine tedavi

- 15.04.2026 Lipozomal amfoterisin B 3 mg/kg/ IV
- Vorikonazol 2 X 4 mg/kg IV devam
- 19.04.2026 sol retorakotomi ve bronkoplevral fistül onarımı

# Azollerin Etki Mekanizması

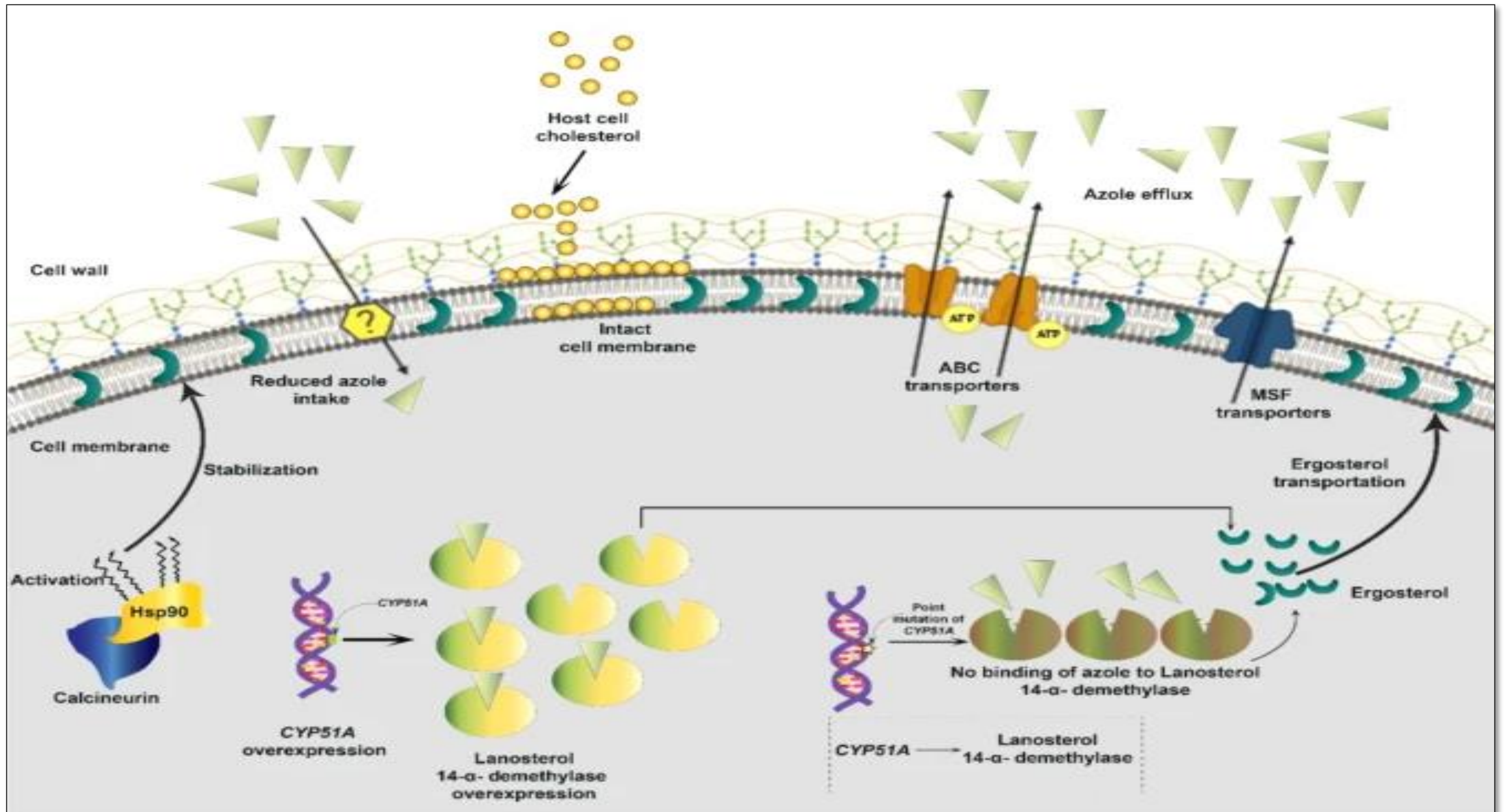


Mantar hücre zarında bulunan ergosterol sentezini inhibe ederek

# *Aspergillus fumigatus* tür kompleksinde azol direnci

*Aspergillus fumigatus* tür kompleksinde azol direncine değişik mekanizmalar

1. Hedef enzim değişikliği: *CYP51A* geni küf mantarlarında hedef enzimin (14 alfa demetilaz) sentezini kodlar. *CYP51A* genindeki mutasyonlar 14 alfa demetilaz yapısını bozarak azol bağlanmasını azaltır, azole dirençli suşlar ortaya çıkar
2. Hedef genin aşırı ekspresyonu (genin promotör bölgesinde rastgele tekrarlar)
3. Dışa atım pompalarının aşırı çalışması
4. Biyofilm yapımı



# CYP51A gen ve promotor bölgesinde mutasyon olması için suşun azol grubu ilaçlara uzun süre maruz kalması gerekir

- Kronik pulmoner aspergilloz, aspergilloma
- Önceden azol kullanımı
- Aynı hastada hem dirençli hem de duyarlı suşlar bulunması
- Tek azol veya multi, pan azol direnç olabilmesi
- Azol dirençli suşlar arasında büyük genotipik varyasyonlar

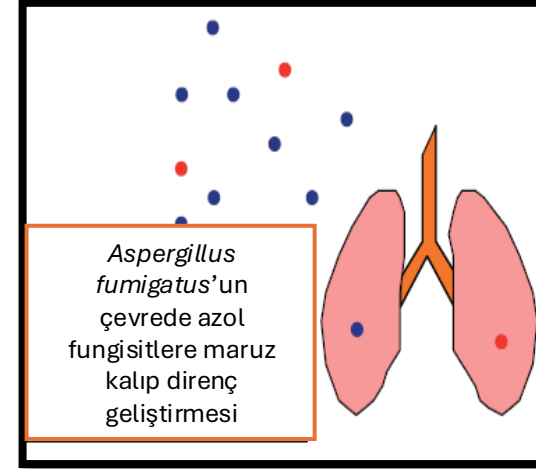


Hasta ile ilişkili direnç

Değişen kodonlar	Minimal İnhibitör Konsantrasyon (µg/ml)		
	İtrakonazol	Vorikonazol	Pasokonazol
G54E	>8	0,25-0,5	0,25-1
G54R	>8	0,12-0,5	1
G54V	>8	0,25-1	Belirlenmedi
G54W	>8	0,12-0,5	>8
G138C	>8	4->8	1->8
P216L	>8	1	1
M220I	>8	1	0,5
M220K	>8	1-2	1->8
M220R	>8	2	2
M220T	>8	0,5-1	0,25-0,5
M220V	>8	1-2	0,5-1
Y431C	>8	4	1
G432S	>8	0,5	0,25
G434C	>8	4	1
G448S	>8	>8	0,5-1

# CYP51A gen ve promotor bölgesinde mutasyon olması için suşun azol grubu ilaçlara uzun süre maruz kalması gerekir

- Tüm aspergillus hastalıkları
- Hastaların 2/3'ünde önceden azol kullanımı yok
- Direnç mekanizmaları benzer
- TR34/L98H ve TR46/Y121F/T289A
- Multi ya da pan azol direnç olabilmesi
- Dirençli suşlar arasında genetik farklılık az
- Aynı hastada hem dirençli hem de duyarlı suşların bulunması



Çevre ile ilişkili direnç

W	CAGAGTTGTCTAGAAATCACGCGGTCCGGATGTGTGCTGAGCCGAATGAAAGTGCCTAATTA
T	
TR	CAGAGTTGTCTAGAAATCACGCGGTCCGGATGTGTGCTGAGCCGAAT
34	<b>GAATCACGCGGTCCGGATGTGTGCTGAGCCGAAT</b> GAAAGTGCCTAATTA
TR	CAGAGTTGTCTAGAAATCACGCGGTCCGGATGTGTGCTGAGCCGAATGAAAGTTG
46	<b>TCTAGAAATCACGCGGTCCGGATGTGTGCTGAGCCGAATGAAAGTTG</b> CCTAATTA
TR	CAGAGTTGTCTAGAAATCACGCGGTCCGGATGTGTGCTGAGCCGAATGAA
46	<b>AGTTGTCTAGAAATCACGCGGTCCGGATGTGTGCTGAGCCGAATGAA</b> AGTTGCCTAATTA
TR	CAGAGTTGTCTAGAAATCACGCGGTCCGGATGTGTGCTGAGCCGAATGAAAGTTGCCTAA
53	<b>TGTCTAGAAATCACGCGGTCCGGATGTGTGCTGAGCCGAATGAAAGTTGCCTAA</b> TTA

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

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

- 2018-2019, 12 merkezden 392 klinik ve 18 merkezden alınan çevresel *Aspergillus fumigatus* izolatlarında azol direnci araştırılmış
- Dirençli izolatlarda *CYP51A* geni araştırılmış
- Çevresel izolatlarda azol direnci %1.3
- Klinik örneklerde azol direnci %3.3
- 9/19 azol dirençli suşta *CYP51A* (TR34/L98H) mutasyonu

- Türkiyede *A.fumigatus*'ta azol direnci düşük
  - *CYP51A* gen mutasyonlarından farklı mekanizma?

Isolate	City code	Sample type	Age (years)	MIC (mg/L) - EUCAST E.DEF 9.3			cyp51A mutation
				itraconazole	voriconazole	posaconazole	
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



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

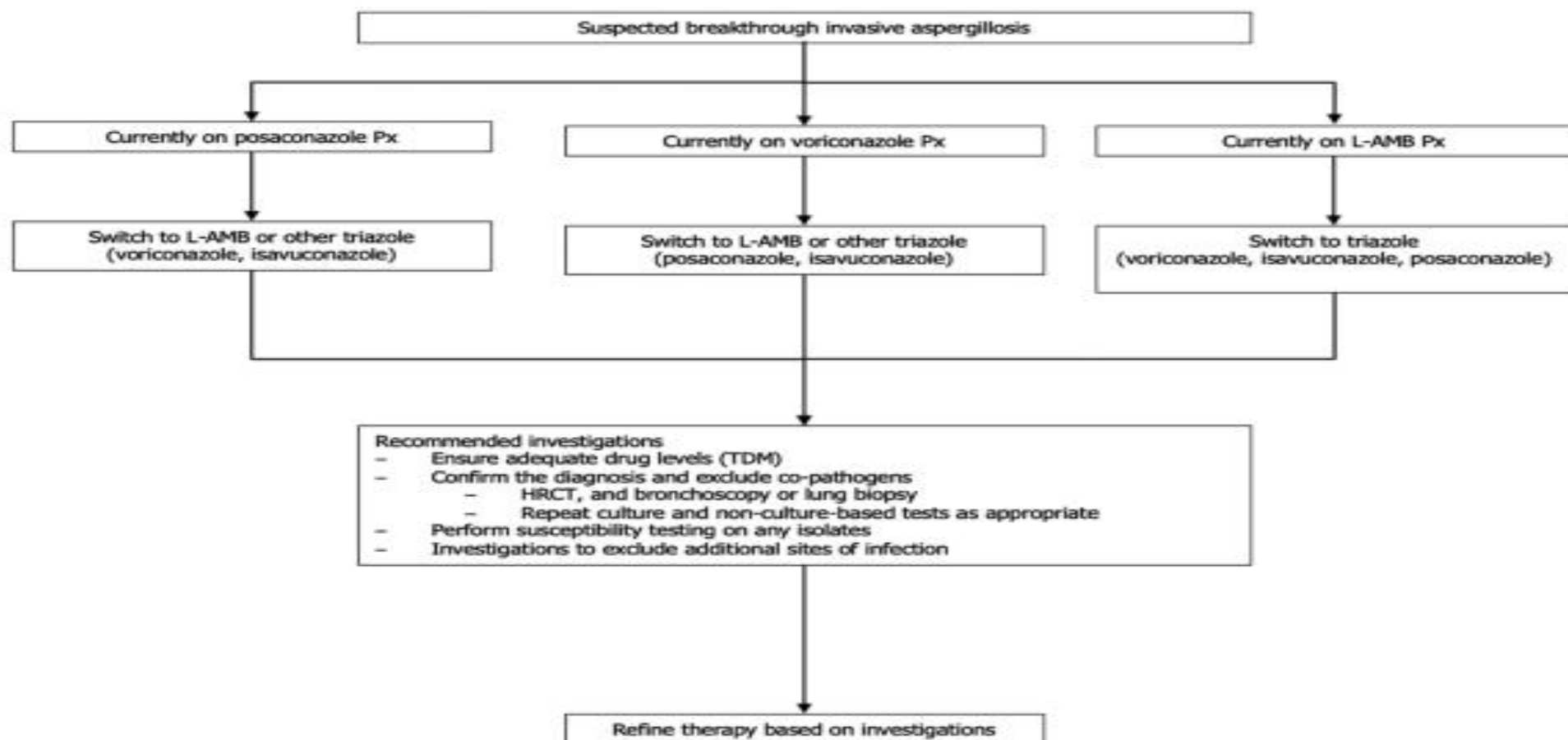
Paul E. Verweij<sup>a,\*</sup>, Michelle Ananda-Rajah<sup>b</sup>, David Andes<sup>c</sup>, Maiken C. Arendrup<sup>d</sup>,

- Kültür pozitif ise antifungal tedavi öncesi in vitro duyarlılık testi önerilmektedir
- Tek azol direncinden ziyade çoklu azol direnci daha yaygındır
- ✓ İFA azole dirençli *Aspergillus*'a bağlı ise vorikonazolden lipozomal amfoterisin B'ye değişim önerilmektedir
- ✓ Eğer çevresel direnç %10'dan fazla ise vorikonazol-ekinokandin kombinasyonu veya L-AmB başlangıç tedavisinde önerilmektedir
- ✓ SSS Aspergillozunda L-AmB ana tedavi olarak belirlenmiştir, ikincil ajan olarak flusitozin eklenmesi önerilir
- ✓ Kronik pulmoner aspergillozda ise mikafungin veya L-AmB intermitant veya sürekli tedavi için önerilir

## SUPPLEMENT ARTICLE

**Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021**

Abby P. Douglas,<sup>1,2,3,4</sup> Olivia C. Smibert,<sup>1,2,3,4</sup> Ashish Bajel,<sup>2,5</sup> Catriona L. Halliday,<sup>6,7</sup> Orly Lavee,<sup>8</sup> Brendan McMullan,<sup>3,9,10</sup> Michelle K. Yong,<sup>1,2,3,11</sup> Sebastiaan J. van Hal<sup>12,13</sup> and Sharon C.-A. Chen,<sup>6,7,12</sup> the Australasian Antifungal Guidelines Steering Committee



# SONUÇ

- Mikrobiyolojik testler direnci belirlemedeki tek yol
- Mutlaka laboratuvara örnek göndermeye çalışalım
- Rutin direnç testleri yapılmalı
- Hasta bazında laboratuvarca saptanmış bir azol direnci varsa

Population	Intention	Intervention	SoR	QoE	Comment
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
Isolate with voriconazole MIC >2 mg/mL	To cure IA	L-AmB	A	II <sub>u</sub>	
		AmB lipid complex	C	III	
		Voriconazole & anidulafungin	B	III	
		Posaconazole & caspofungin	C	III	Posaconazole not licensed for primary treatment
		Caspofungin or micafungin	C	III	Patients with contra-indications to AmB and other azoles

Ullmann A J, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. CMI 2018; 24 (suppl 1): E1-E38. (10.1016/j.cmi.2018.01.002)