İFİ TEDAVİSİNde Cevaplanmayan Sorular

Dr. Murat Akova

Dr. Rabin Saba

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Invaziv Fungal Enfeksiyonlarda yeni risk grupları var mı?

İNVAZİV ASPERGİLLOZ
Risk Faktörleri ve Direnç

Prof Dr Zekaver Odabaşı
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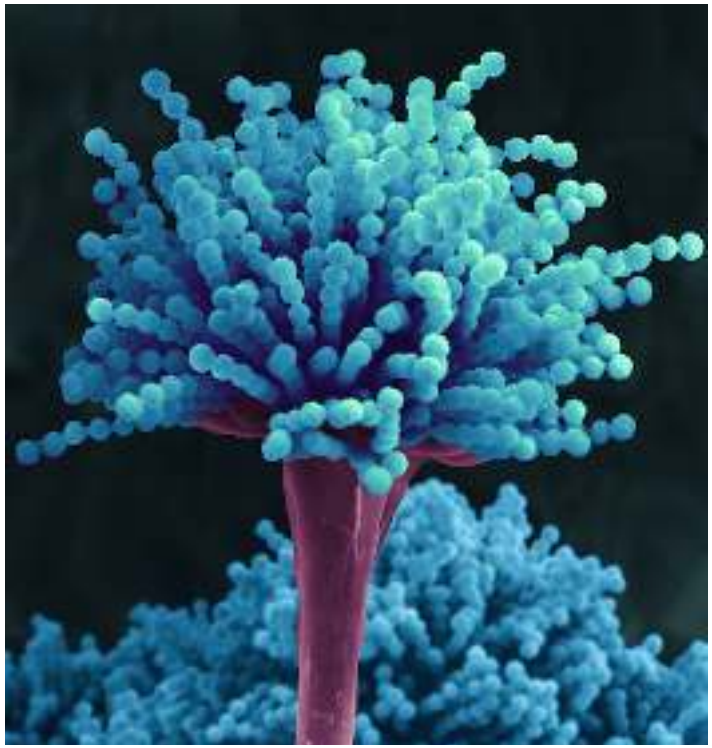


Aspergilloz Açısından Kimler Yüksek Riskli

Cadena et al

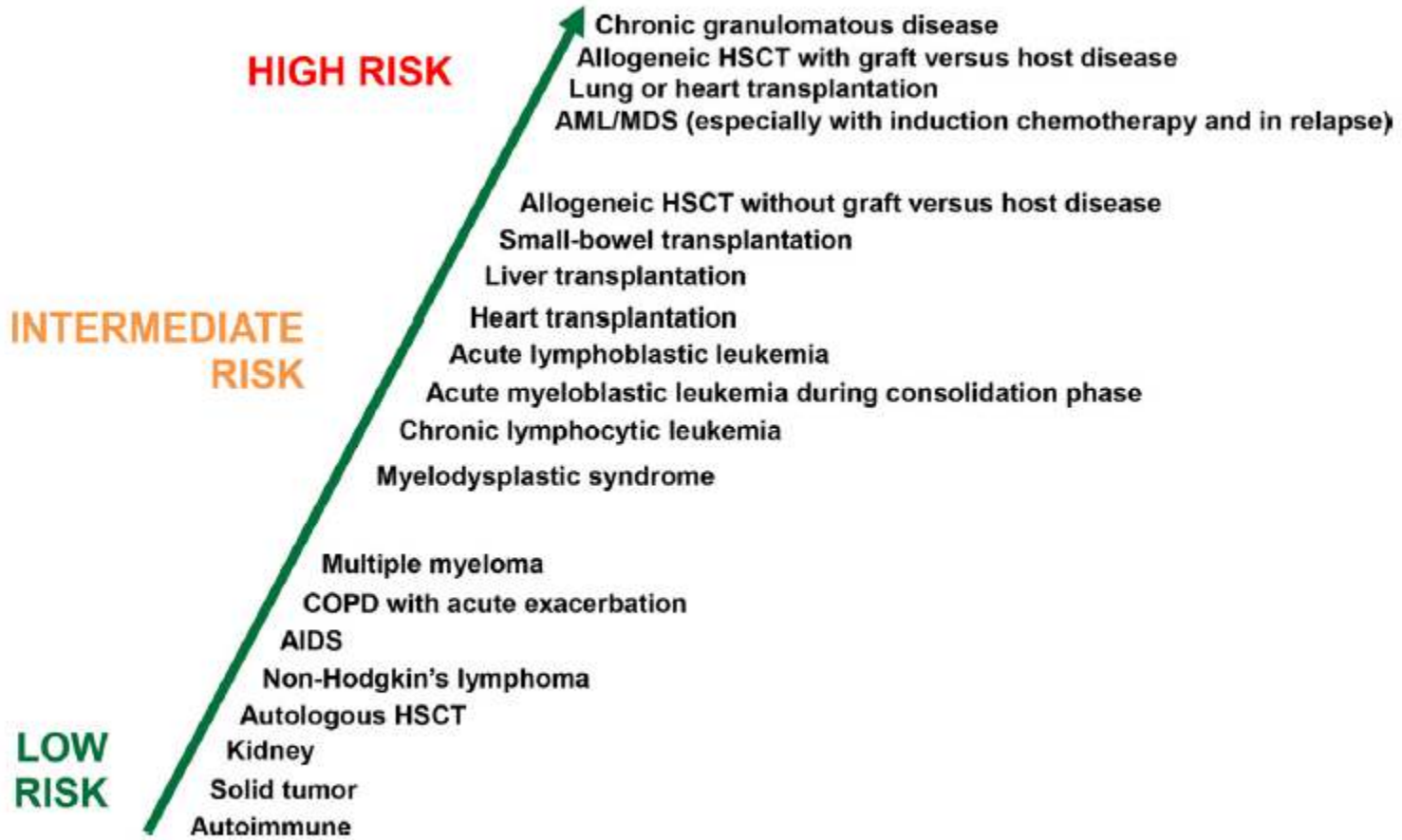


Fig. 1. Spectrum of risk for IA. (*Data from* Pagano L, Akova M, Dimopoulos G, et al. Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. J Antimicrob Chemother 2011;66(Suppl 1):i5–14.)

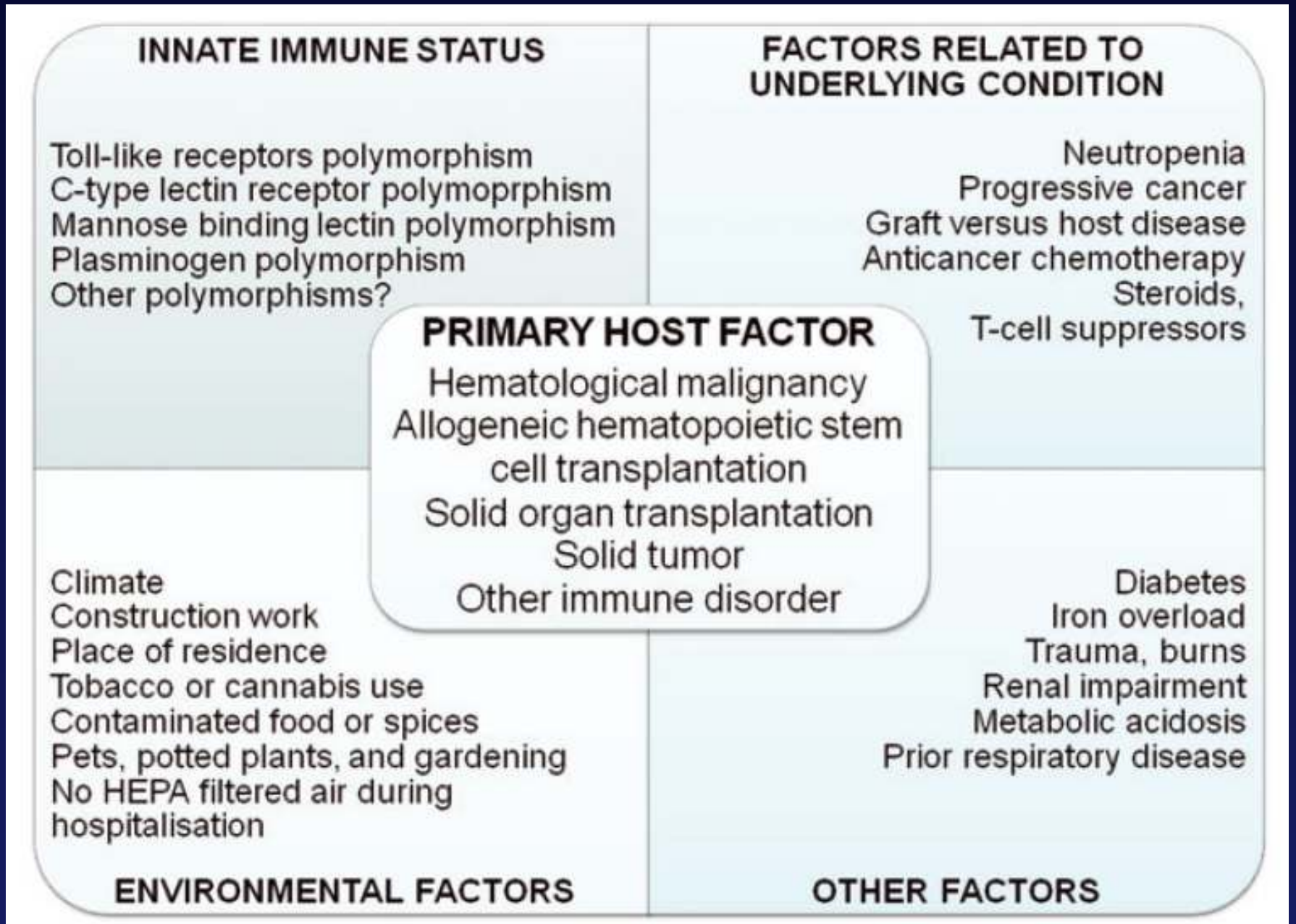
İnvazif Aspergilloz Risk Faktörleri

Kronik granülomatöz hastalık **Allogeneik ilik nakli ve GVHH gelişmesi** Akciğer nakli **AML indüksiyon kemoterapisi veya refrakter** Yüksek doz steroid veya >3 hafta steroid tedavisi	**Yüksek risk**
GVHH olmayan Allogeneik ilik nakli ALL AML (konsolidasyon) MDS KLL Kalp, akciğer, ince barsak nakli	**Orta risk**
Multiple myeloma KOAH alevlenme AIDS Non-Hodgkin lenfoma Otolog ilik nakli Solid tümörler Otoimmün hastalıklar	**Düşük risk**

İnvazif Aspergilloz Risk Faktörleri

Yüksek (15-30%)	Orta (5-15%)	Düşük (1-5%)
Allogeneic HSCT >40 yaş Graft yetmezliği Steroid GVHD Yaz dönemi Laminar hava akımı olmaması **AML** >55 yaş Düşük performans Yüksek doz Ara-C	**Allogeneic HSCT** 19-40 yaş Uyumsuz akraba Uyumlu akraba dışı İnşaat / yapım çalışması **AML**	**Allogeneic HSCT** < 19 yaş Uyumlu akraba **Autologous HSCT**

Camps IR, 2008



Herbrecht et al, 2012 New York Academy of Sciences

Pentraxin 3 (PTX 3) eksikliği / mutasyonu

- Fagositer hücrelerce üretilir
- Aspergillus fumigatusa karşı immün sistem aktivasyonunda rol alır
- Nötrofillerin konidiaları tanımasını sağlar
- **Donöründe** PTX3 eksikliği olan ilik nakli hastalarında belirgin derecede invaziv aspergilloz gelişimi gösterilmiş
  - N Engl J Med 2014 Jan 30;370(5):421)
- **Karaciğer nakli olan ve PTX3 eksikliği** olanlarda belirgin invaziv aspergilloz gelişmiş
  - Clin Infect Dis 2015 Aug 15;61(4):619

- **Dectin-1 allel Y238X** mutasyonu ile belirgin risk artışı
  - J Infect Dis 2011 Mar 1;203(5):736
- Donöründe **toll-like receptor 4 (*TLR4*) gen polimorfizmi** olan ilik nakli vakalarında belirgin risk artışı
  - N Engl J Med 2008 Oct 23;359(17):1766
- C-tip lektin reseptör polimorfizmi
- Mannoz bağlayıcı lektin polimorfizmi
- Plazminojen polimorfizmi
- **$CD8^+$ T-lenfosit sayısı**: hem risk hem de prognostik faktör
  - Na Cui, Crrit care 2013

Hematoloji hastalarında invaziv fungal enfeksiyonların tedavisinde yaklaşım nasıl olmalı?

İFİ Tedavisinde Cevaplanmamış Sorular

Dr. Rabin Saba

Medstar Antalya Hastanesi

EKMUD 12.05.2016

Summary of Recommendations for Haematological Centres

Bacterial Resistance in Haematology-ECIL 4 Study Groups & Participants –Akova M

- NBA tanı, tedavi ve profilaksisi için multidisipliner protokol ve algoritmalar oluşturun
  - *Hematologlar için Enfeksiyon Hastalıkları*
  - *Enfeksiyon Hastalıkları/Klinik Mikrobiyologlar için hematoloji eğitimi planlayın*
  - *Birbirinizi anlamaya çalışın!*

Rabin’cim, bu hasta CMV enfeksiyonu yönünden yüksek riskli, takibini yapalım

İhsan abi; bu hastaya hypercvad değil codox protokolunu verelim

ÖZEL
MEDSTAR
ANTALYA HASTANESİ

Hematoloji ve Kemik İliği Nakil Merkezi

Prof. Dr. İhsan Karadoğan

Prof. Dr. Rabin Saba

Uz. Dr. Hüsnü Altınay

Dr. George Kublasvili

Uz. Dr. Burak Deveci

Dr. Mira Masharipova

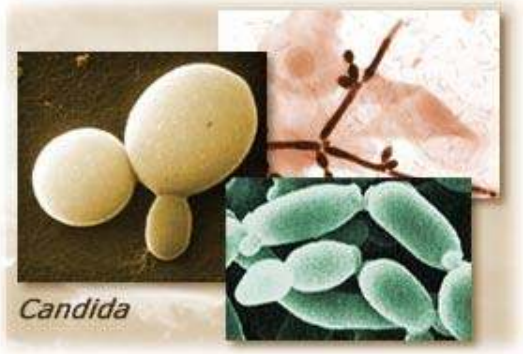
SGK
SOSYAL GÜVENLİK KURUMU
İLE ANLAŞMALIDIR.

444 21 12

EPİDEMİYOLOJİ

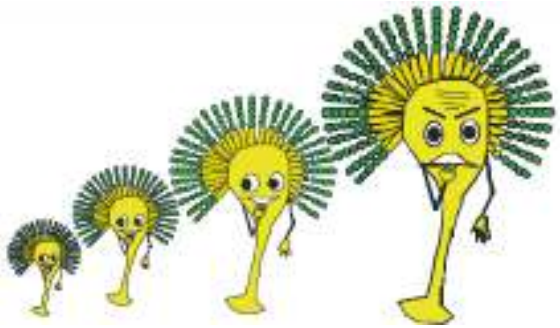
Hematolojik malignite ve KH nakillerinde

en önemli mortalite ve morbidite nedeni



MAYA

- ***Candida***
  - *Albicans*
  - *Non albicans*
- Cryptococcus
- Trichosporon
- M.furfur



KÜF

- ***Aspergillus***
- Zygomycetes
- Fusarium
- Scedosporium
- Sporothrix schenckii

Allojenik KİT	**% 15-25**
AML	**% 10-15**
ALL	**% 5-10**
Otolog KİT	**% 2-6**

1- RİSK DEĞERLENDİRMESİ

2- KORUYUCU STRATEJİNİN SEÇİMİ

3- AMPİRİK /TANI KÖKENLİ TEDAVİ

4- ETKENE YÖNELİK TEDAVİ

5- SEKONDER PROFİLAKSİ

1. Risk Değerlendirme

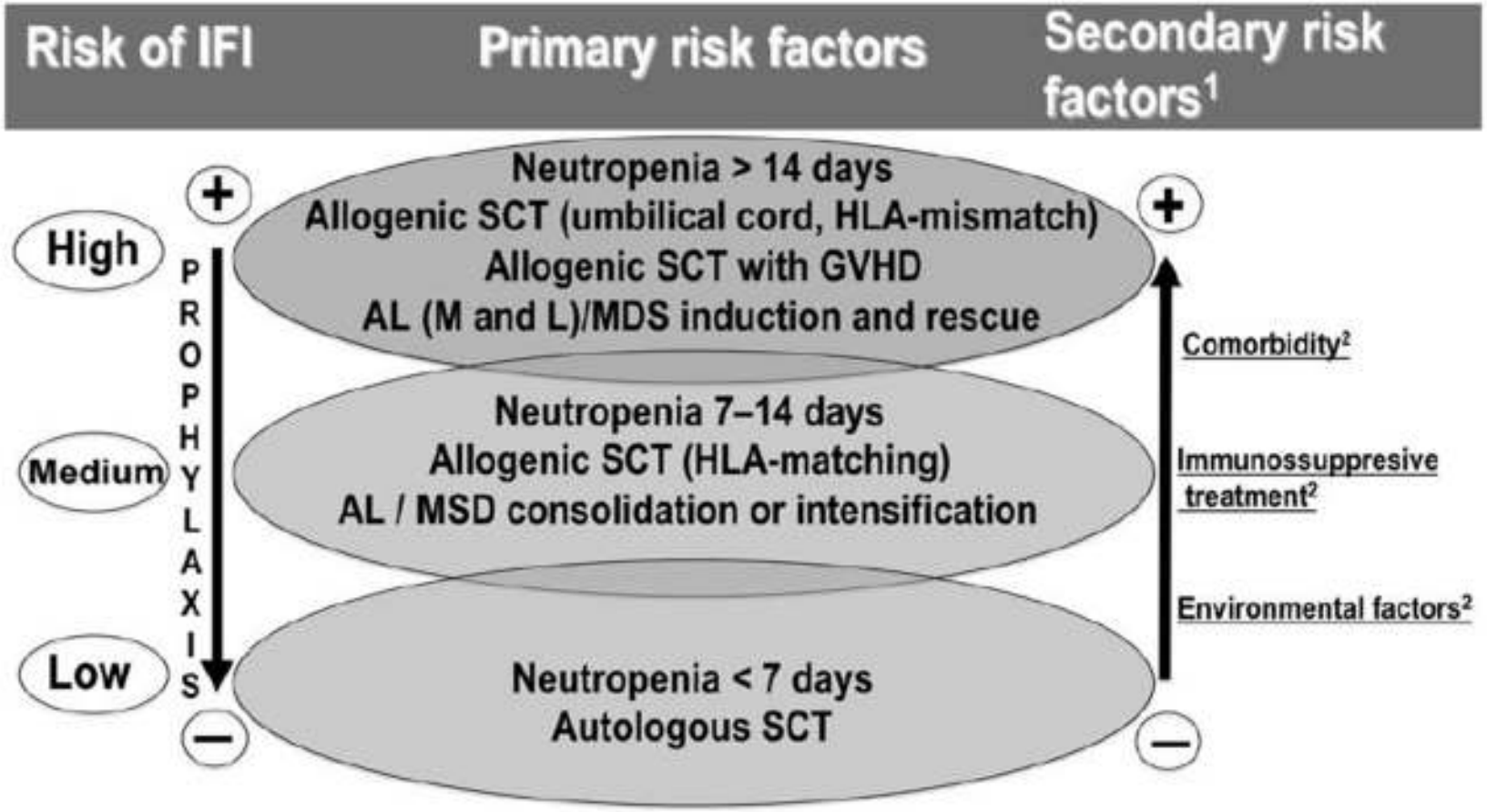
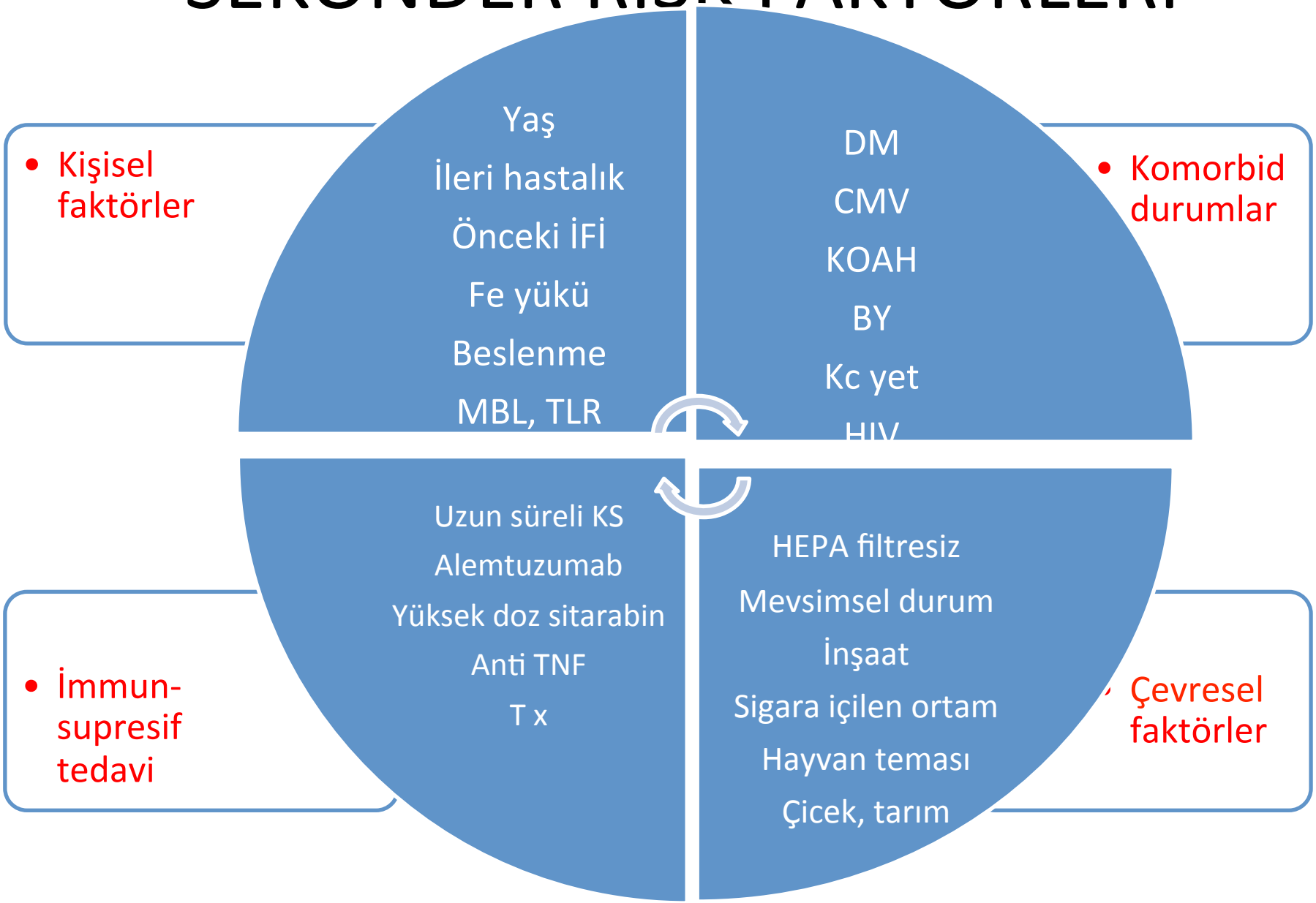


Figure 1 | Classification of the risk groups for IFI.

SEKONDER RİSK FAKTÖRLERİ

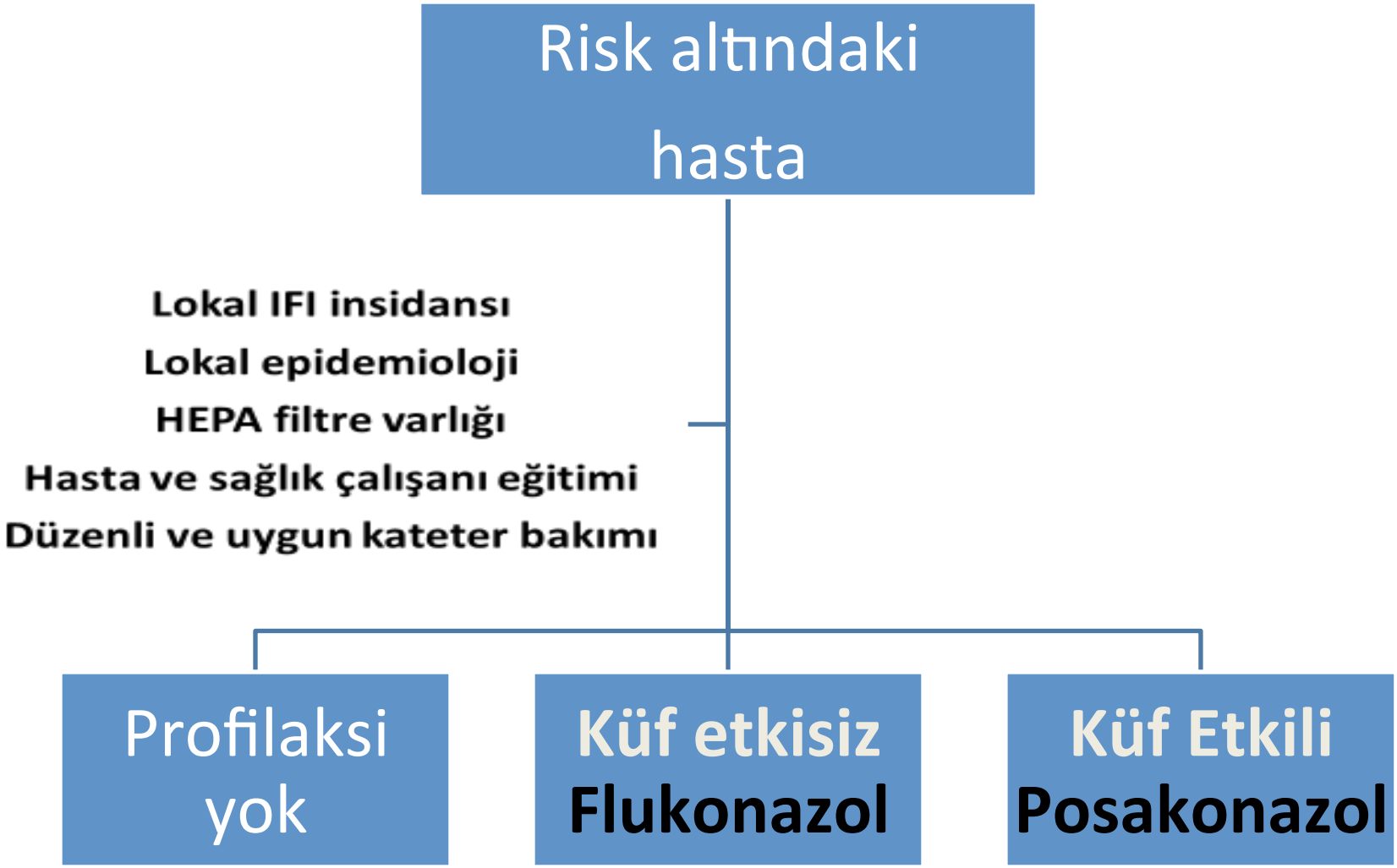


2. Koruyucu Stratejinin Seçimi

NEDEN ANTİFUNGAL PROFİLAKSİ?

- Fungusların neden olduğu invazif infeksiyonlar, bağışıklığı baskılanmış konakta oldukça yüksek mortalite ve morbiditeye neden olmaktadır.
- Hastaların hastanede yatış süreleri uzamakta,
- Tedavide kullanılan ilaçların toksik ve oldukça pahalı olması
- Tanı koymadaki güçlükler

Profilaktik Tedavi Yaklaşımları



Prevention and Treatment of Cancer-Related Infections, Version 1.20

Hastalık	Antifungal profilaksi	Süre
ALL	Flukonazol 2A Amfoterisin B 2B	Nötropeni süresince
AML ve MDS induksiyon Ve reindüksiyon	Posakonazol 1 Flukonazol 2B Vorikonazol 2B Amfoterisin B 2B	
AML konsolidasyon	Öneri yok	
Otolog KHT (mukozit var)	Flukonazol 1 Mikafungin 1	
Otolog KHT (mukozit yok)	Profilaksi yok 2B	
Allogeneik KHT	Flukonazol 1 Mikafungin 1	Nötropeni süresince + 75 gün
Ağır GVHD	Posakonazol 1	GVHD azalana kadar

3. Ampirik / Tanı- kökenli tedavi

Risk taşıyan hasta → **TEDAVİ**

Hastalık belirtisi YOK → **Proflaksi**

Antibiyotik ted. dirençli ATEŞ → **Ampirik** = **Ateş-kökenli *(fever-driven)***

Klinik – Lab. BELİRTEÇ (HRCT-Ag testi) → **Preemptif** = **Tanı-kökenli *(diagnostic-driven)***

Steril alandan Kültür, Histopatoloji → **Kanıtlı**

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[2] Kent A. Sepkowitz,[3] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[6] Issam I. Raad,[7] Kenneth V. Rolston,[8] Jo-Anne H. Young,[9] and John R. Wingard[10]

YÜKSEK RİSKLİ HASTA>4 GÜN ATEŞ

FİZİK MUAYENE VE ANAMNEZ
KAN KÜLTÜRÜ AL
OLASI İNFEKSİYON BÖLGELERİNDEN KÜLTÜR AL

AÇIKLANAMAYAN ATEŞ
- **KLİNİK STABİL**
- **Kİ DÜZELMESİ YAKIN**

İZLE;YENİ İNFEKSİYON KLİNİK VEYA LAB BULGUSU YOKSA AB DEĞİŞİKLİĞİ YAPMA

AÇIKLANAMAYAN ATEŞ
- **KLİNİK STABİL**
- **Kİ DÜZELMESİ YAKIN DEĞİL**
- **AC VE SİNUS CT PLANLA**

ANTİ MAYA PROFİLAKSİSİ (FLUKONAZOL)

ANTİ KÜF PROFİLAKSİSİ

TESPİT EDİLMİŞ İNFEKSİYON
- **KLİNİK ANSTABİL**
- **İNF. BULGULARI**
- **KÖTÜLEŞİYOR**

- **İNFEKSİYON BÖLGESİNİ TEKRAR İNCELE: KÜLTÜR, BİOPSİ VB**
- **AB SPEKTRUMU TEKRAR DEĞERLENDİR**
- **AMPİRİK ANTİFUNGAL EKLEMEYİ DÜŞÜN**
- **AB SPEKTRUMU GENİŞLET**

PRE-EMPTİF
ANTİFUNGAL TEDAVİ
- **CT**
- **SERİ SERUM GALAKTOMANNAN**

AMPİRİK
ANTİFUNGAL TEDAVİ (küf etkili)
- **EKİNOKANDİN**
- **VORİKONAZO**
- **AMP-B**

AMPİRİK ANTİFUNGAL TEDAVİ
- **BAŞKA GRUP ANTİ KÜF AJANA DEĞİŞTİR**

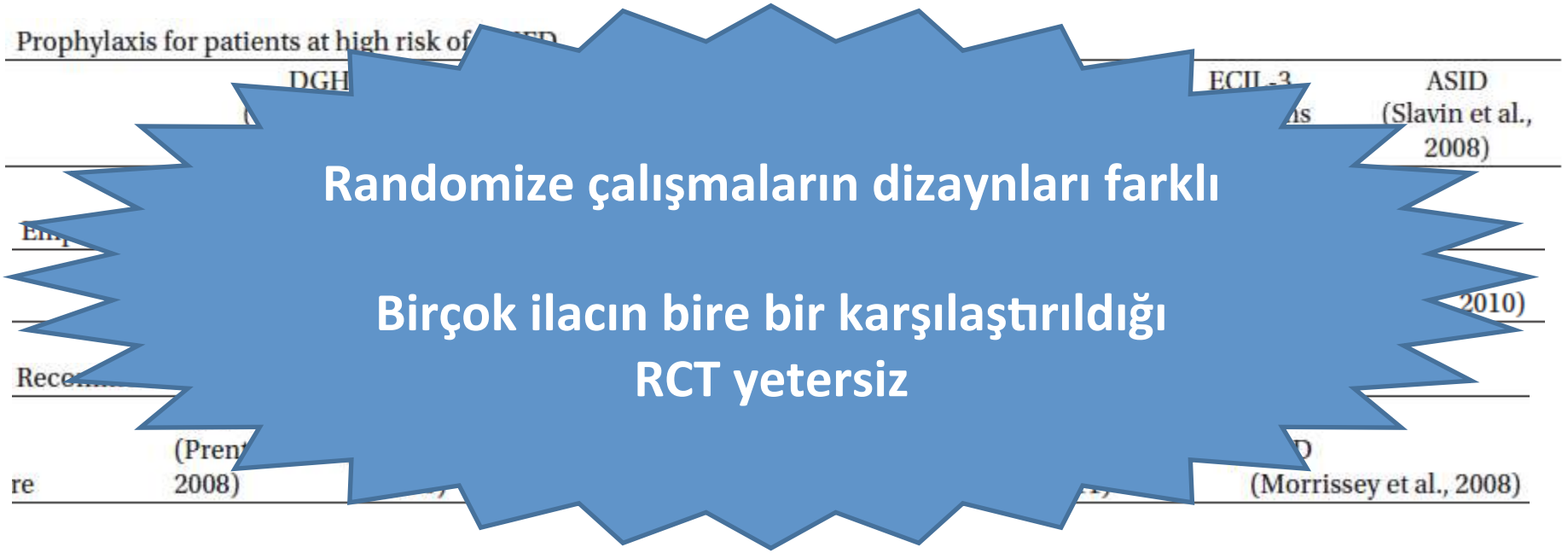
Figure 3. High-risk patient with fever after 4 days of empirical antibiotics. *C. difficile*, *Clostridium difficile*; IV, intravenous.

TEDAVİ

- PROFLAKSİ
- ATEŞ-KÖKENLİ
- TANI-KÖKENLİ
- KANITLI TEDAVİ

HANGİ YAKLAŞIMI TERCİH EDELİM ?

- ✓ ***KİME ?***
- ✓ ***NE ZAMAN ?***
- ✓ ***HANGİ İLAÇLARI ?***



TEDAVİ

- PROFLAKSİ
- ATEŞ-KÖKENLİ
- TANI-KÖKENLİ
- KANITLI TEDAVİ

HANGİ YAKLAŞIMI TERCİH EDELİM ?

- ✓ *KİME ?*
- ✓ ***NE ZAMAN ?***
- ✓ ***HANGİ İLAÇLARI ?***

Critical Reviews in Microbiology, 2012; 38(3): 203–216

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DOI: 10.3109/1040841X.2011.645521

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REVIEW ARTICLE

A practical critique of antifungal treatment guidelines for haemato-oncologists

Samir Agrawal[1], Brian Jones[2], Rosemary Barnes[3], Chris Kibbler[4], Mike Millen[5], Mary Ashcroft[6], Sarjana Jain[7], Anna Last[8], David Lewis[9], Tom Lewis[10], Mitul Patel[11], and Antonio Pagliuca[12]

Ampirik Antifungal Tedavi

DESTEKLEYEN

- ✓ İFH riski yüksek
- ✓ Tanı koymak zor
- ✓ Tedavide geçikme mortaliteyi arttırıyor

KARŞIT

- ✓ Gereksiz, fazla tedavi
- ✓ Potansiyel toksisite
- ✓ Çok pahalı
- ✓ Tanı konmuyor

Preemptif Yaklaşımın Etkin Olması İçin

Gerekenler:

- **Multidisipliner Yaklaşım**
- **Tarafların tam koopere ve uyum içinde çalışması**
- **Tanıda gereken protokollere sıkı uyum**
- **Yeterli lojistik destek**
- **Düzenli moniterizasyon ve bildirim**
- **Aynı çalışma protokolünün haftasonlari da devam etmesi**
- **Tetkiklerde kabul görmüş cihazların kullanılması**
- **Sonuçların yeterince hızlı bildirilmesi gerekir**

Hala…Preemptif yaklaşım önerisi kesin değil. Karar:

  - **Merkezlerin lokal pulmoner küf infeksiyonu prevalanslari**
  - **Diagnostik testlerin yapılabilirliği**
  - **Rutinde anti-küf profilaksi kullanım durumlarına göre verilmelidir**

Maertens J et al.J Antimicrob Chemother 2011; 66 Suppl 1: i37–43

Original Articles

The use and efficacy of empirical *versus* pre-emptive therapy in the management of fungal infections: the HEMA e-Chart Project

Livio Pagano,[1] Morena Caira,[1] Annamaria Nosari,[2] Chiara Cattaneo,[3] Rosa Fanci,[4] Alessandro Bonini,[5] Nicola Vianelli,[6] Maria Grazia Garzia,[7] Mario Mancinelli,[1] Maria Elena Tosti,[8] Mario Tumbarello,[9] Pierluigi Viale,[10] Franco Aversa,[11] and Giuseppe Rossi[3] on behalf of the HEMA e-Chart Group, Italy

Haematologica | 2011; 96(9):1366-70.

397 ateşli hematolojik malignite

190 olgu
Ampirik AF

IFI: 14(%7.4)
IFI ölüm: 1 (%7.1)
Tüm ölüm: 12 (% 6.3)

İFİ:P<0.001
Ölüm:P=0.002

207 olgu
Preemptif AF

IFI: 49 (%23.7)
IFI Ölüm: 11(%22.5)
Tüm ölüm: 33 (%15.9)

Ampirik Antifungal Tedavi

IFI insidansı
IFI ilişkili mortalite
Tüm (90 gün) mortalite

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TEDAVİ

ampirik *vs* pre-emptif

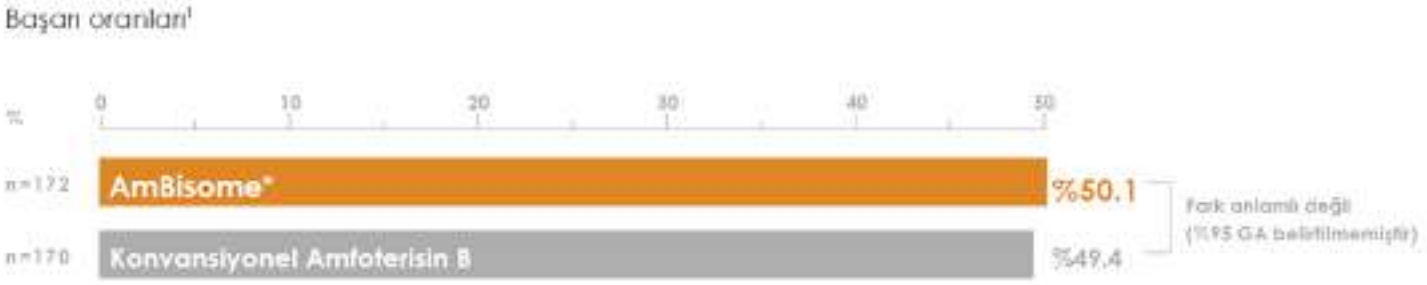
Topic discussed	Consensus	Conflict/unresolved issues
Impact of empirical therapy on patient outcome	Lack of good quality evidence to support impact of empirical antifungal treatment on patient outcome (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010; Prentice et al., 2008; Slavin et al., 2008; Böhme et al., 2009; Cornely et al., 2009)	This lack of evidence has been interpreted in different ways. BSCH discourages empirical therapy, and IDSA recommend it only for high risk patients despite the lack of good quality evidence (Prentice et al., 2008; Walsh et al., 2008; Pappas et al., 2009)
Role of pre-emptive therapy	May be useful, but needs to be studied further. (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010)	Although BCSH recommends routine screening of high-risk patients, it does not make recommendations on choice of antifungal drug for pre-emptive therapy. (Prentice et al., 2008) A new German guideline for managing lung infiltrates in neutropenic patients recommends voriconazole or liposomal amphotericin B for pre-emptive therapy. (Maschmeyer et al., 2009)

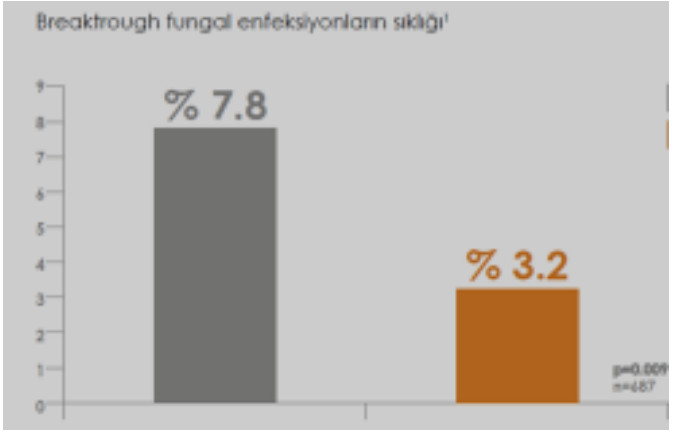
Ampirik tedavi çalışmaları

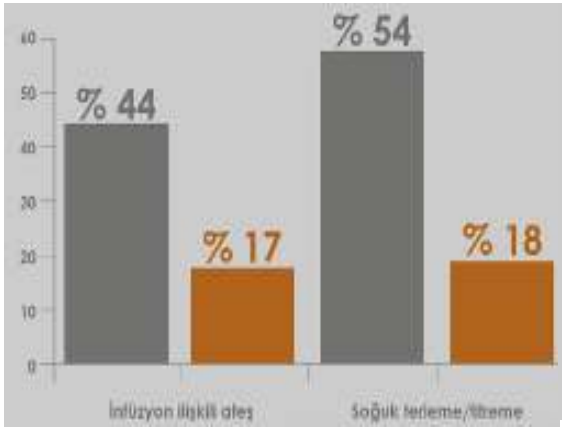
AmB-d vs L AmB: Walsh et al, NEJM, 1999

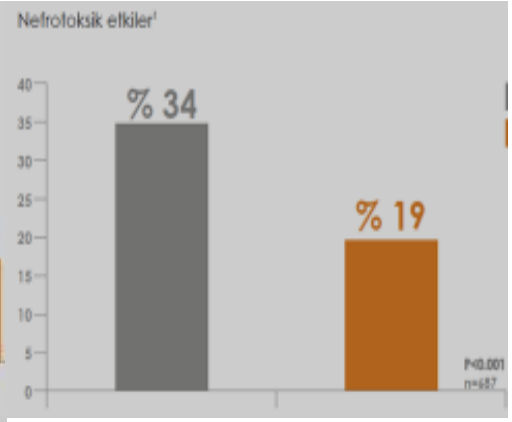
LIPOSOMAL AMPHOTERICIN B FOR EMPIRICAL THERAPY IN PATIENTS WITH PERSISTENT FEVER AND NEUTROPENIA

THOMAS J. WALSH, M.D., ROBERT W. FINBERG, M.D., CAROLA ARNDT, M.D., JOHN HIEMENZ, M.D., CINDY SCHWARTZ, M.D., DAVID BODENSTEINER, M.D., PETER PAPPAS, M.D., NITA SEIBEL, M.D., RICHARD N. GREENBERG, M.D., STEPHEN DUMMER, M.D., MINDY SCHUSTER, M.D., AND JOHN S. HOLCENBERG, M.D., FOR THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES MYCOSES STUDY GROUP*







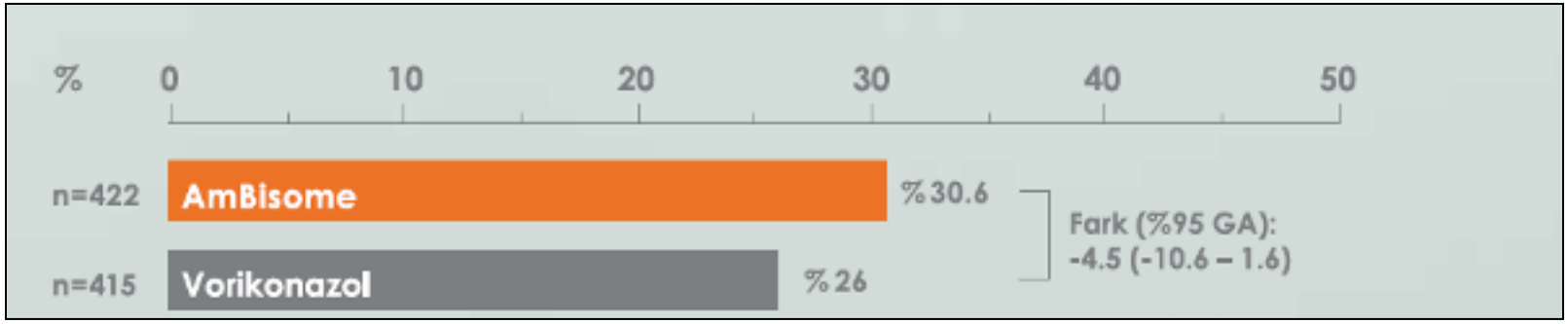


Ampirik tedavi çalışmaları

L AmB vs Vorikonazol: Walsh et al, NEJM, 2002

VORICONAZOLE COMPARED WITH LIPOSOMAL AMPHOTERICIN B FOR EMPIRICAL ANTIFUNGAL THERAPY IN PATIENTS WITH NEUTROPENIA AND PERSISTENT FEVER

THOMAS J. WALSH, M.D., PETER PAPPAS, M.D., DREW J. WINSTON, M.D., HILLARD M. LAZARUS, M.D., FINN PETERSEN, M.D., JOHN RAFFALLI, M.D., SAUL YANOVICH, M.D., PATRICK STIFF, M.D., RICHARD GREENBERG, M.D., GERALD DONOWITZ, M.D., AND JEANETTE LEE, PH.D., FOR THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES MYCOSES STUDY GROUP*



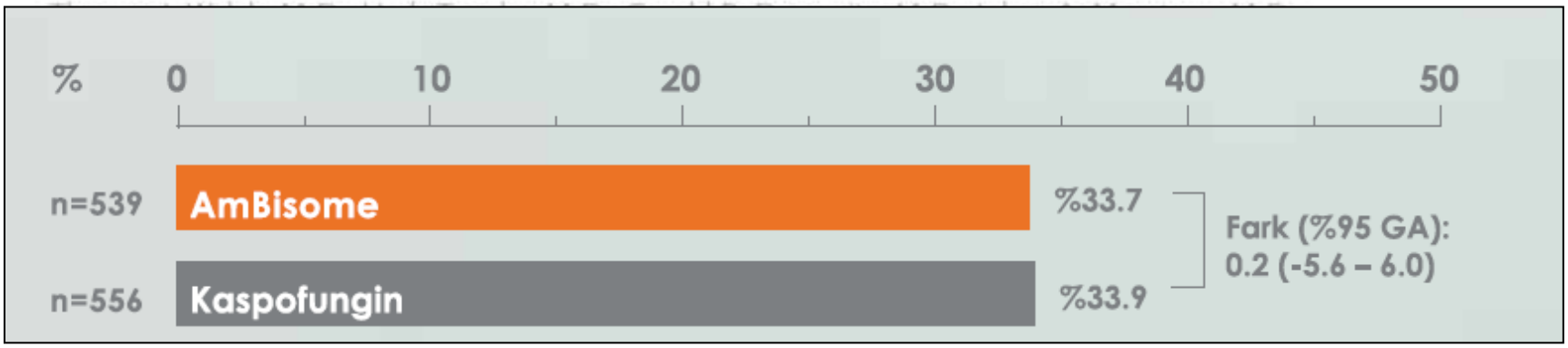
Vorikonazol, non-inferiorite için alt sınıra (-10.0) ulaşamamıştır[1] ve **ampirik tedavi için FDA onayı alamamıştır.[2]**

1.Walsh TJ et al. N Engl J Med 2002;346(4):225-234.
2.Petrikkos G, Skiada A. International Journal of Antimicrobial Agents. 2007; 30:108-117.

Ampirik tedavi çalışmaları

L AmB vs Caspofungin: Walsh et al, NEJM, 2004

Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia



Adverse Olaylar

	Caspofungin (N=564)	Liposomal Amphotericin B (N=547)	Difference (95% CI)*	P Value
	percent of patients		*percentage points*	
Nephrotoxicity†	2.6	11.5	−8.9 (−12.0 to −5.9)	<0.001
Infusion-related event‡	35.1	51.6	−16.4 (−22.2 to −0.7)	<0.001
Discontinuation of study therapy because of a drug-related adverse event	5.0	8.0	−3.1 (−6.0 to −0.02)	0.04
Any drug-related adverse event§	54.4	69.3	−14.9 (−20.5 to −9.2)	<0.001

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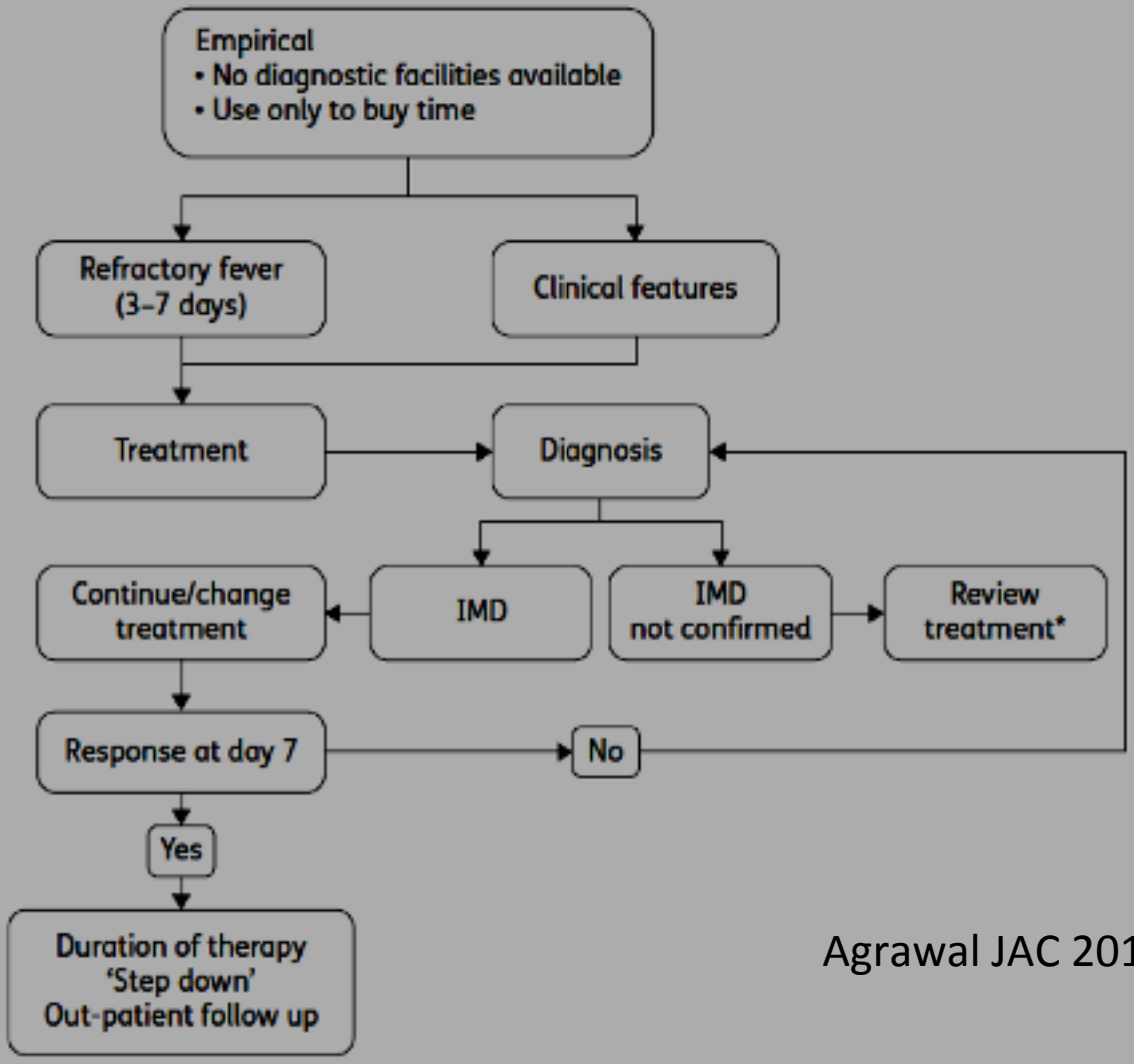
TEDAVİ - ampirik

Topic discussed	Consensus	Conflict/unresolved issues
Criteria for choosing empirical therapy	Efficacy and safety are the main considerations (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010)	Additional factors considered are: activity against *Candida* and *Aspergillus* (the two most common fungal pathogens in this group of patients) by IDSA and ECIL-3; and cost by ECIL-3 (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010)
Choice of empirical agent	Caspofungin and liposomal amphotericin B are common choices with good evidence (A) (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010)	Although voriconazole failed to achieve non-inferiority when compared with liposomal amphotericin B, it is still included in ECIL and IDSA because it is the drug of choice for invasive aspergillosis and it reduces the incidence of breakthrough IFD. ECIL-3 and IDSA also recommend fluconazole for its activity against *Candida*; and itraconazole for its similar efficacy, though acknowledging problems with absorption and toxicity (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010)

Günümüzde ampirik tedavi



Agrawal JAC 2011

TEDAVİ - ampirik

Lipozomal AmB, kaspofungin

vorikonazol, itrakonazol

Antifungal proflaksi almıyor **Enfeksiyon odağı yok** **Pulmoner lezyon yok**	**maya**	Kaspofungin **Lipozomal AmB**
Proflaksi maya (flukonazol) **Pulmoner lezyon var**	**küf**	**Lipozomal AmB** *vorikonazol*
Proflaksi (flukonazol) **Pulmoner lezyon var**	**Küf (mucor)**	**Lipozomal AmB**
Proflaksi küf (posa/vori)		**Lipozomal AmB**

4. Kanıtlı/Etkene yönelik Tedavi

İnvaziv Aspergilloz Tedavisinde
AmB-d vs Vorikonazol

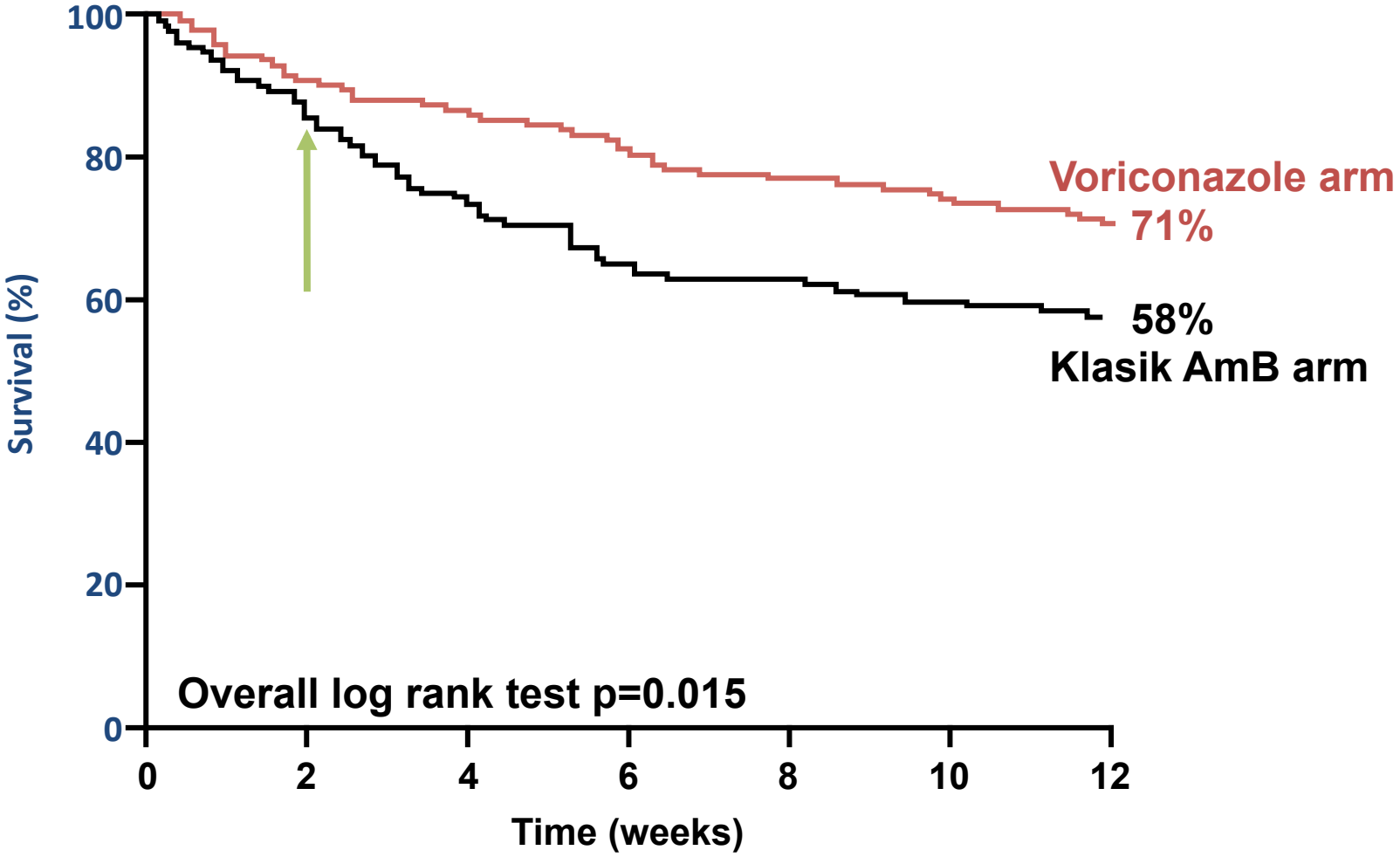
N Engl J Med. 2002 Aug 8;347(6):408-15.

Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis.

Herbrecht R[1], Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, de Pauw B; Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group.

- **Randomize, açık etiketli, 12 haftalık çalışma**
- **Hematolojik malignite veya KHN uygulanmış hastalar**
- **277 IA vakası (kesin veya olası)**
- **IV Vorikonazol ile IV amfoterisin B deoksikolat karşılaştırması**
  - **Voriconazol: 1. gün 2 doz 6 mg/kg, ardından yedi gün günde 2 kez 4 mg/kg, ardından günde 2 kez oral 200 mg**
  - **AmB-d: 1-1,5 mg/kg/gün**
- **SONUÇ:**
  - **Genel başarı oranı: Vorikonazol %52.8, AmB-d %31.6 (%95 GA 10.4-32.9)**
  - **Sağkalım: Vorikonazol %70.8, AmB-d: %57.9 (HR: 0.59, %95 GA, 0.40-0.88)**

Overall survival



Herbrecht et al. N Engl J Med 2002;347:408–415

Voriconazole vs L AmB

birebir karşılaştıran çalışma YOK

Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High–Loading Dose Regimen with Standard Dosing (AmBiLoad Trial)

Oliver A. Cornely, Johan Maertens, Mark Bresnik, Ramin Ebrahimi, Andrew J. Ullmann, Emilio Bouza, Claus Peter Heussel, Olivier Lortholary, Christina Rieger, Angelika Boehme, Mickael Aoun, Heinz-August Horst, Anne Thiebaut, Markus Ruhnke, Dietmar Reichert, Nicola Vianelli, Stefan W. Krause, Eduardo Olavarria, and Raoul Herbrecht, for the AmBiLoad Trial Study Group*

	Herbrecht 2002		AmBiload 2007	
12.haftada Tedavi Başarısı (tam veya kısmi)	Vorikonazol:	% 53	3 mg LAMB	%50
	Amfoterisin B:	% 32	10 mg LAMB	%46
12.Haftada Sağkalım	Vorikonazol:	% 71	3 mg LAMB	%72
	Amfoterisin B:	% 58	10 mg LAMB	%59

Voriconazole vs L AmB

birebir karşılaştıran çalışma YOK

İnvaziv Aspergillosis: Primer Tedavi

İLAÇLAR	IDSA[1]	UK[2]	ECIL-5[5]	DGHO[4]	Avustralya[6]
AmB-d	D	D	D	EI	Alternatif
Lipozomal A	**AI**	**AI**	BI	**AII**	Alternatif
ABLC			BII		
ABCD			D		
Itrakonazol			CIII		
Posakonazol					
Vorikonazol	**AI**	**AI**	**AI**	**AI**	**Önerilir**
Kaspofungin		**AI**	CII	CII	
Mikafungin				CII	
Kombinasyon	Önerilmez	Uygulanmamalı	Uygulanmamalı Vor + anidula CI	CIII	Destekleyici kanıt yok

1. *Walsh TJ, et al. Clin Infect Dis 2008;46:327–60.*
2. *Prentice AG, et al. http://www.bcshguidelines.com/documents/fungal_infection_bcsh_2008.pdf*
3. *Maertens J et al. Bone Marrow Transplantation 2011; 46:709–18*
4. *Bohme A et al. Ann Hematol 2014;99:13–32*
5. *ECIL-5*
6. *Thursky KA, et al. Intern Med J 2008;38:496–520.*

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Vorikonazol	**AI**	**AI**	**AI**	**AI**	**Önerilir**
Kaspofungin		**AI**	CII	CII	
Mikafungin				CII	
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5. *ECIL-5*
6. *Thursky KA, et al. Intern Med J 2008;38:496–520.*

informa

REVIEW ARTICLE

A practical critique of antifungal treatment guidelines for haemato-oncologists

Samir Agrawal[1], Brian Jones[2], Rosemary Barnes[3], Chris Kibbler[4], Mike Millers[5], Mary Ashcroft[6], Sarjana Jain[7], Anna Last[8], David Lewis[9], Tom Lewis[10], Mitul Patel[11], and Antonio Pagliuca[12]

IA primer tedavi

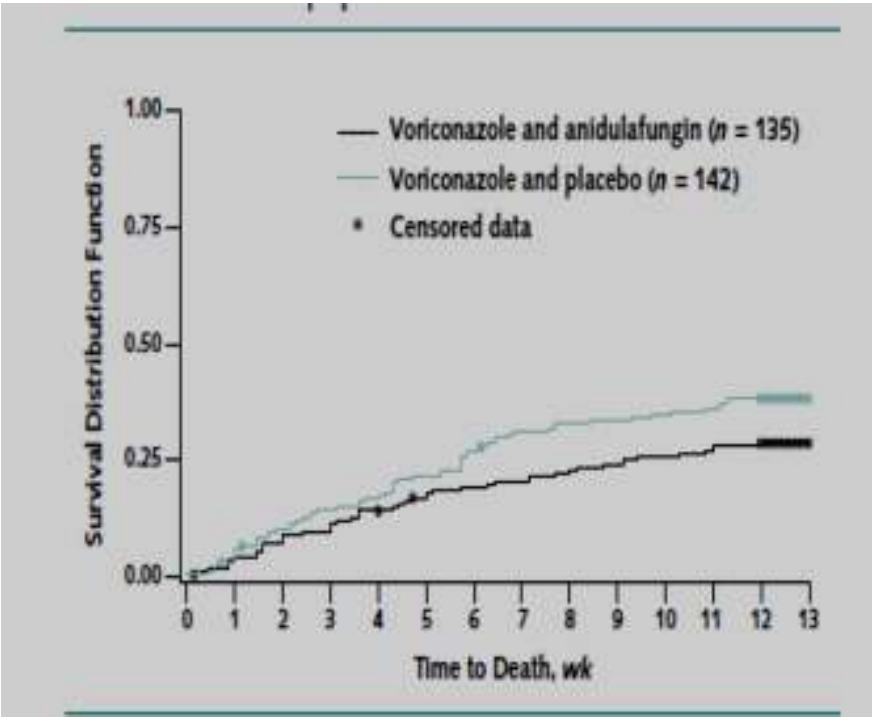
Topic discussed	Consensus	Conflict/unresolved issues
Optimal first-line therapy for invasive aspergillosis	Voriconazole is an appropriate first line agent for proven aspergillosis.	BCSH do not recommend voriconazole in anything less than proven disease. Caspofungin is recommended in BCSH, but not in other guidelines. (Prentice et al., 2008)
	Liposomal amphotericin B is a reasonable alternative in four guidelines and that conventional amphotericin should not generally be considered (Böhme et al., 2009; Thursky et al., 2008; Walsh et al., 2008; Maertens et al., 2010)	Role of other lipid formulations is not clear

IA'de VCZ + ANID veya Plasebo

- Vorikonazol ve anidulafungin kombinasyonu ile 6. hafta tüm nedenlere bağlı mortalite tek başına vorikonazolden daha düşük.
- Bu farklılık, istatistiksel üstünlük için öngörülen değere erişmedi

- MITT hastalarının çoğu GM sonucuna göre yüksek olası IA (218/277, %78.7)
- Yüksek olası grupta post hoc analiz ile üstünlük (+)
- 6. hafta mortalite kombin. grubunda %15.7 (17/108), monoterapi grubunda %27.3 (30/110, p-değeri <0.05 (%95 CI -22.69, -0.4).
- Vorikonazol ve anidulafungin kombinasyonunun güvenilirlik ve tolerabilitesi monoterapi ile eşdeğer.

12. Haftaya dek KM Sağkalım (



Marr et all Ann Intern Med. 2015;162:81-89.

Annals of Internal Medicine

ORIGINAL RESEARCH

Combination Antifungal Therapy for Invasive Aspergillosis

A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc;

Table 3. Data Review Committee-Adjudicated Outcomes in the Modified Intention-to-Treat Population, by Regimen

Outcome	Monotherapy (*n* = 142)*	Combination Therapy (*n* = 135)*	Treatment Difference (95% CI), percentage points†
Deaths attributed to IA at 6 wk	33/39 (84.6)‡	23/26 (88.5)‡	3.9 (−12.9 to 20.6)
Global response at 6 wk			
Success (overall)	61 (43.0)	44 (32.6)	−10.4 (−21.6 to 1.2)
Complete response	17 (12.0)	8 (5.9)	–
Partial response	44 (31.0)	36 (26.7)	–
Failure			
Stable response	19 (13.4)	26 (19.3)	–
Failure of response	7 (4.9)	8 (5.9)	–
Not evaluable	55 (38.8)	57 (42.3)	–
Expired before 6 wk	39 (27.5)	26 (19.3)	–
Missing information	16 (11.3)	31 (23.0)	–

Maya
candida

TEDAVİ

ECIL-5 (2013)

Candidemia in hematologic patients before species identification (Changes in ECIL-5 compared to ECIL-1 to 3)

	Hematological pts	
Micafungin[1]	~~B II~~	A II
Anidulafungin	~~B II~~	A III
Caspofungin	~~B II~~	A II
AmBisome	~~B II~~	A II
ABLC, ABCD	B II	
AmB deoxycholate [2]	~~C III~~	C II
Fluconazole[3,4]	C III	
Voriconazole[4]	B II	

5. Sekonder profilaksi

- Relaps riski
  - KİT hastalarında %19-33
  - AML hastalarında %16
- Sekonder profilaksinin yararı
  - Az sayıda vaka
  - Vorikonazol ile
  - Saptana etkene yönelik olmalı
    - Masomoto et al J Chemother 2011;23:17-23
    - Cordonnier et al Bone Marrow Transplant 2004;33:943

Özellikle hematoloji ve transplant tedavi protokollerinde kullanılan ilaçlar düşünüldüğünde ilaç ilaç etkileşimi sorun mudur?

EVET

ÖZEL MEDSTAR ANTALYA HASTANESİ

MEDSTAR ANTALYA HASTANESİ
KÖK HÜCRE NAKLİ ÜNİTESİ

AKUT LÖSEMİ VE MYELOPROLİFERATİF HASTALIKLARDA ALLOGENEİK KÖK HÜCRE NAKLİ PROTOKOLÜ (Flu5/Bu3)

ADI SOYADI :

BOY: cm, / AĞIRLIK kg. / VÜCUT ALANI: m²

İLAÇ	DOZ	UYGULANACAK DOZ		-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
levofloksasin[1]	1X500 mg/gün	1X500 mg/gün	PO									+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TMP-STZ[2]	1X1 fort 5 kez/hafta	1X1 fort 5 kez/hafta	PO																								
Triflukan[1]	1X400 mg/gün	1X400 mg/gün	PO						+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Asiklovir[1,3]	3X250 mg/m²	3X mg	IV						+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Asiklovir[1,3]	3X400 mg	3X400 mg	PO																				+	+	+	+	+
Busulfan **	3.2 mg/kg/gün	mg/gün	IV				+	+	+																		
Fenitoin	3X100 mg/gün	3X100 mg	PO	+	+	+	+	+	+	+	+	+															
Fludarabin 50mg	30 mg/m² /gün (max 50 mg)	mg/gün	IV				+	+	+	+																	
Siklosporin***	5 mg/kg	mg	IV								+	+	+	+	+	+	+	+	+								
Siklosporin****	2X5 mg/kg	2X mg	PO																	+	+	+	+	+	+	+	+
Metotreksat	10 mg/m²	mg	IV										+		+			+						+			
G-CSF[1]	5 µg/kg	1X34 MIU	SC															+	+	+	+	+	+	+	+	+	+
Lansor	1X1	1X30mg	PO	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Amphotericin b liposomal Drug Interactions

Drug Interactions (174)

A total of **174 drugs** (648 brand and generic names) are known to interact with **amphotericin b liposomal**.

26 major drug interactions (82 brand and generic names)

141 moderate drug interactions (544 brand and generic names)

7 minor drug interactions (22 brand and generic names)

DRUG STATUS

Availability
Prescription only

Pregnancy Category
No proven risk in humans

CSA Schedule
Not a controlled drug

Voriconazole Drug Interactions - Drugs.com - Internet Explorer

http://www.drugs.com/drug-interactions/voriconazole.html

Voriconazole Drug Interactio...

Drugs.com
Know more. Be sure.

Search All

Browse all medications: A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Advanced Search

Sign In

DRUGS A-Z | PILL IDENTIFIER | INTERACTIONS CHECKER | NEWS | Q & A | PRO EDITION | APPS | MORE

Hide

Home › Drugs A to Z › Voriconazole › Interactions

Print Share

Voriconazole Drug Interactions

Overview | Side Effects | Dosage | Interactions | Professional | More

Drug Interactions (710) | Alcohol/Food Interactions (1) | Disease Interactions (2)

A total of **710 drugs** (3341 brand and generic names) are known to interact with **voriconazole**.

- **223 major** drug interactions (1005 brand and generic names)
- **460 moderate** drug interactions (2237 brand and generic names)
- **27 minor** drug interactions (99 brand and generic names)

DRUG STATUS

Availability
Prescription only

Pregnancy Category
Positive evidence of risk

CSA Schedule
Not a controlled drug

Approval History
Drug history at FDA

Başlat | ekmud 2016 gilead | Voriconazole Drug ... | BILMED - bilmed.ande... | THD KIT 2016 IFI Gile...

10:22
06.05.2016

Posaconazole Drug Interactions

A total of **589 drugs** (2830 brand and generic names) are known to interact with **posaconazole**.

186 major drug interactions (889 brand and generic names)

383 moderate drug interactions (1875 brand and generic names)

DRUG STATUS

Availability
Prescription only

Pregnancy Category
Risk cannot be ruled out

CSA Schedule
Not a controlled drug

Approval History
Drug history at FDA

Caspofungin Drug Interactions

Overview | Side Effects | Dosage | Interactions | Professional | More
Drug Interactions (80) Disease Interactions (2)

A total of **80 drugs** (363 brand and generic names) are known to interact with **caspofungin**.

17 major drug interactions (76 brand and generic names)

60 moderate drug interactions (276 brand and generic names)

3 minor drug interactions (11 brand and generic names)

DRUG STATUS

Availability
Prescription only

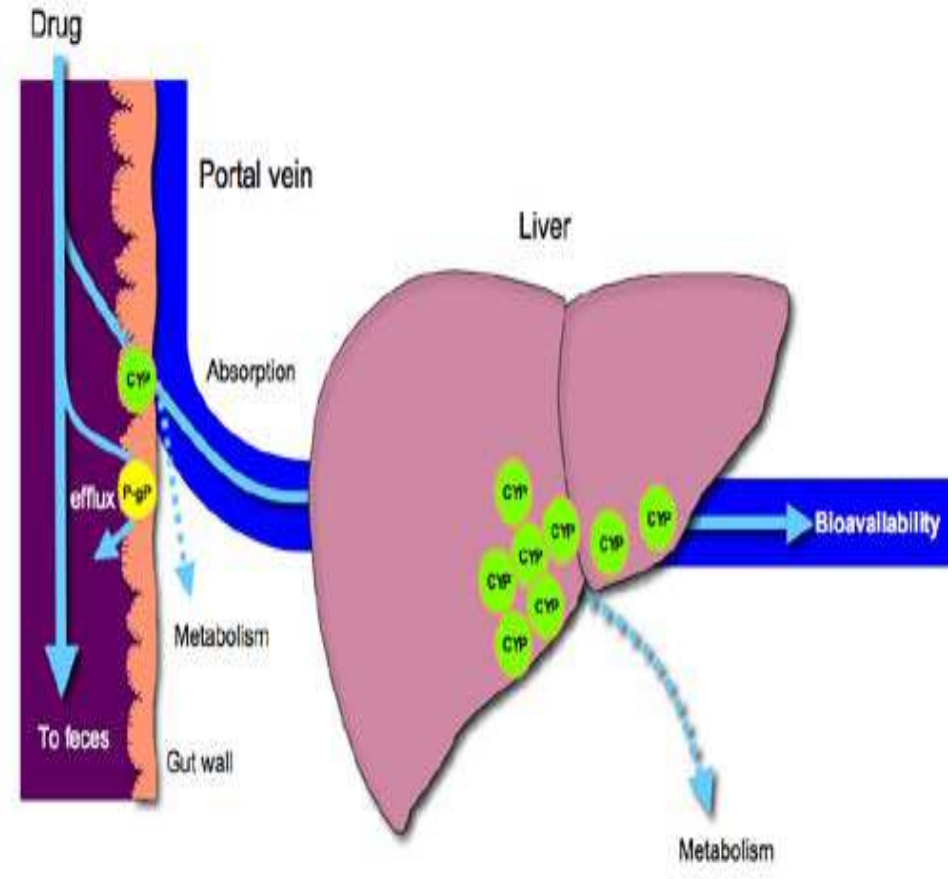
Pregnancy Category
Risk cannot be ruled out

CSA Schedule
Not a controlled drug

Approval History
Drug history at FDA

İLAÇ-İLAÇ ETKİLEŞİMLERİ

- İlaç emilimindeki etkileşimler
- İlaç metabolizmasındaki etkileşimler
  - Sitokrom P450
  - Glomerular filtrasyon
- Toksisite



İlaç emilimindeki etkileşimler

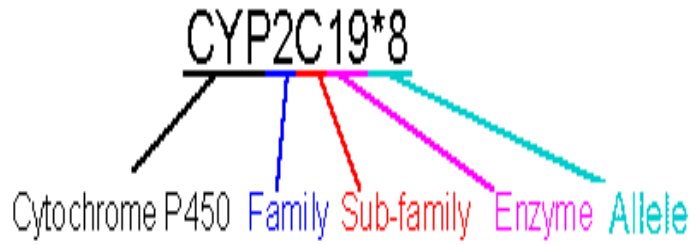
- pH değişikliği
  - Sadece düşük pH'da iyonize olabilen ajanlar
  - Mide asiditesini azaltan ilaçlar
- İyonlarla kompleks oluşturma
  - Antiasidler ve metal iyon içeren bileşikler şelat oluşturarak emilimi azaltabilir
- Transport ve enzimatik metobolizma
  - Presistemik klirens
    - P-glikoprotein (P-gp) lipofilik toksik ilaçların emilimini azaltır
    - CYP 3A4 (kc'dekinden bağımsız)

A ilacı	B ilacı	Sonuç	Öneri
Ketakonazol Itrakonazol (kapsül) Posakonazol	Antiasid H2 reseptor antagonisti Sukralfat	A'nın emlimi ↓	Oral solusyon kullan Diğer ajanlar İlaçları azol tedavisinden İki saat önce veya sonra kullan
Ketakonazol Itrakonazol Posakonazol Vori **	PPİ	A düzeyi ↓ B düzeyi ↑ * Vori emilimi etkilenmez	

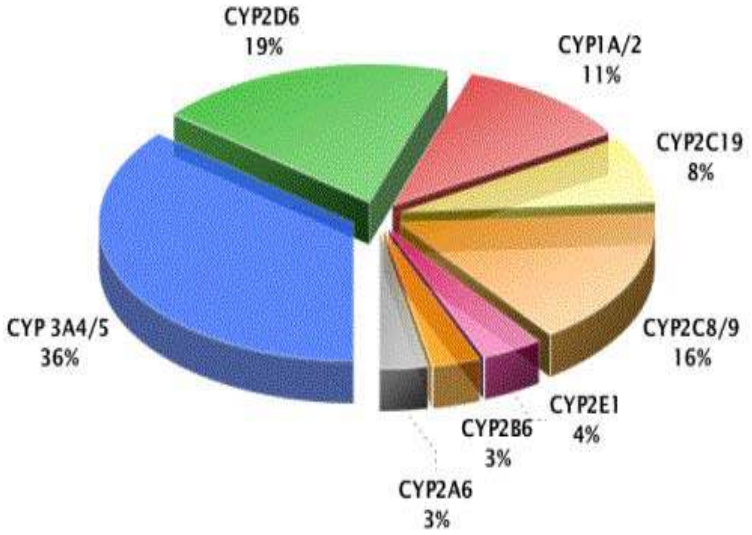
- Presistemik klirens P-gp ve CYP için hem subtrat , hem de inhibitör
- Greyfurt CYP- 3A4 inhibitörü
- Posakonazol yağlı yiyeceklerle
- Vorikonazol aç alınmalı

Sitokrom P450

- İnsan 14 aile mevcut
- %95 6 CYP
- İnsanlar arasında fark var
- CYP 2C19 zayıf metabolize ediciler homozigot ise vorikonazol düzeyi 4 kat artıyor
  - Kafkas ırk %5
  - Asya %15-20



Proportion of Drugs Metabolized by P450 Enzymes



Adapted from: Wrighton SA et al. Crit Review Toxicology 1992;22:1-22.
Kashuba and Bertino. Mechanisms of drug interaction. In Drug Interactions in Infections Diseases. Humana Press. 2001.

	CYP3A4		CYP2C8/9		CYP2C19	
	İnhibitör	Substrat	İnhibitör	Substrat	İnhibitör	Substrat
Flu	++	+	++		+	+
Itra	+++	+++	+			
Vori	+	+	++	+	++	+++
Posa	++					

- Vorikonazol
  - CYP2C19, CYP2C9, CYP3A4
- Posakonazol
  - CYP enzimleri ile metabolize edilmez
  - Glukoronidasyon ile metabolize olur
    - Fenitoin ve rifabutin glukoronidasyonu arttırır
  - CYP3A4 inhibitörü

CYP enzimini indükleyen ilaçlar	Antifungal	Sonuç- Öneri
INH Rifampin Fenitoin Karbamazepin Fenobarbital Ritonavir	Ketokonazol Itrakonazol Flukonazol Vorikonazol Posakonazol	Azoller yıkılır, düzey ↓ Başka bir antifungal Amfo b veya ekinokandin

CYP tarafından metabolize edilen ilaçlar	Antifungal	Öneri
Oral antidiyabetik warfarin Siklosporin Tacrolimus Sirolumis Fenitoin, karbamezepine Triazolam, alprazolam, midazolam, Diltiazem INH ,Rifampin, Rifabutin Kinidin Proteaz inhibitörleri Busulfan, Vinkristin Siklofosfamid Digoxin, Loratidine	Ketokonazol Itrakonazol Flukonazol (yüksek doz) Vorikonazol	İlaçların düzeyi ↑ Vori ve posa ile sirolimus kontrendike Mümkünse beraber kullanımdan kaçın Başka bir grup kullan Serum düzeyi takibi yap Dozu ayarla

A ilacı	B ilacı	Sonuç	Öneri
Ketokonazol Itrakonazol Flukonazol Vorikonazol Posakonazol	Rifampin Hidantoins -Fenitoin - Dilantin	A düzeyi ↓ B düzeyi ↑	Başka bir antifungal Amfo b veya ekinokandin
	Tacrolimus Siklosporin sirolimus	B düzeyi ↑	Vori ve posa ile sirolimus kontrendike

Yaygın CYP-Azol Etkileşimleri Özeti

Azol + Sitokrom P450 indükleyicileri	Karbamazepin Fenobarbital Fenotoin İzoniazid Rifampin Rifabutin Nevirapin Statinler	Azol konsantrasyonunda azalma 
Azol + Sitokrom P450 maddeleri	Siklosporin Takrolimus Sirolimus Proteaz İnhibitörleri (sakinavir, ritonavir) Ca^{2+} kamal blokörleri (diltiazem, verapamil, nifedipin, nisoldipin)	Madde konsantrasyonunda artış 

Lewis R. Medical Mycology 2006;44:S349-S356.

İlaç- ilaç etkileşimleri

A ilacı	B ilacı	Önemi
Amfo B	Antineoplastik	nefrotoksisite ↑
	Digitaller	toksisite B ↑
	Nefrotoksikajanlar -aminoglikozid -sidofovir -siklosporin ……	A'nın nefrotoksisite ↑

- www.drugs.com/drug_interactions.php
- www.medscape.com/druginfo/druginterchecker

Triazole Antifungal Therapeutic Drug Monitoring

ECIL 6 meeting

September 11-12, 2015

Sophia Antipolis, France

Azole affects on metabolism of other drugs

- **Patients should have medication records screened using suitable computerized screening database before starting and stopping antifungals (AIII)**
  - Examples: www.fungalpharmacology.org; www.aspergillus.ork.uk/content/antifungals-drug-interactions, or commerical products such as Lexi-comp Lexi Interact®
- **Patient receiving co-medication metabolized through CYP P450 →esp. CYP3A4:**
  - Consult drug interactions database or clinical pharmacologist **(AIII)**
- **Medications inducing UGT enzymes**
  - Consult drug interactions database or clinical pharmacologist **(AIII)**

Triazole Antifungal Therapeutic Drug Monitoring

ECIL 6 meeting

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Drug interactions affecting azole levels

- **Patient receiving co-medication that induces CYP-P450 enzymes:**
  - Change in therapy to non-interacting antifungal recommended **(AII)**
- **Patient receiving co-medication that induces UGT enzymes:**
  - TDM recommended for posaconazole **(AII)**
- **Patient receiving antacids and PPI with itraconazole capsules or posaconazole suspension**
  - TDM recommended **(AII)**

İLAÇ DÜZEYİ ÖLÇÜMLERİ

Triazole Antifungal Therapeutic Drug Monitoring

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September 11-12, 2015

Sophia Antipolis, France

Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology

H. Ruth Ashbee[1]*, Rosemary A. Barnes[2], Elizabeth M. Johnson[3], Malcolm D. Richardson[4], Rebecca Gorton[5] and William W. Hope[6]

J Antimicrob Chemother 2014; **69**: 1162–1176

İLAÇ DÜZEYİ ÖLÇÜMLERİ

Triazole Antifungal Therapeutic Drug Monitoring

ECIL 6 meeting

September 11-12, 2015

Sophia Antipolis, France

Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology

H. Ruth Ashbee[1]*, Rosemary A. Barnes[2], Elizabeth M. Johnson[3], Malcolm D. Richardson[4], Rebecca Gorton[5] and William W. Hope[6]

J Antimicrob Chemother 2014; **69**: 1162–1176

Therapeutic drug monitoring

- ✓ **No indications** for therapeutic drug monitoring of **amphotericin B** or the **echinocandins**; measurement of fluconazole concentrations is rarely necessary
- ✓ Therapeutic drug monitoring of itraconazole, voriconazole, and posaconazole is usually needed. **Specifically, voriconazole monitoring is needed** in most patients

Recommendation 5: TDM should be performed in the majority of patients receiving voriconazole

Recommendation 6: A minimum lower target concentration for TDM for treatment of established disease is a trough concentration of >1 mg/L or a trough:MIC ratio of 2–5

Recommendation 7: A trough concentration to minimize drug-related toxicity is <4–6 mg/L

Recommendation 8: Voriconazole concentrations should be measured in the first 5 days of therapy and regularly thereafter

Triazole Antifungal Therapeutic Drug Monitoring

ECIL 6 meeting

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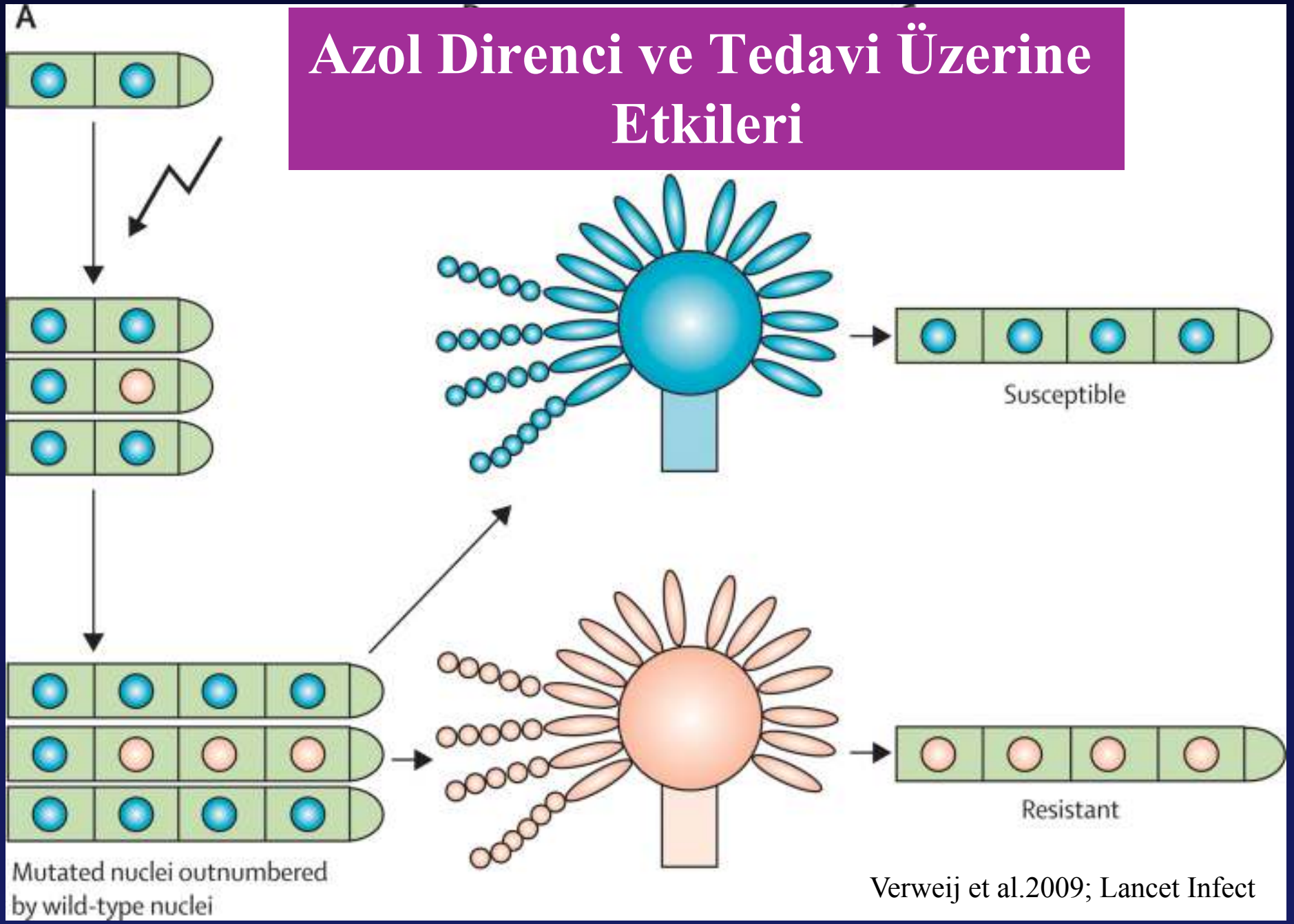
Summary of TDM plasma target level recommendations

Triazole	Recommended plasma range[a]	SOR	Timing of first trough sample
Voriconazole	Prophylaxis and treatment: Acceptable: 1-6 mg/L; Optimal: 2-5 mg/L	AII (efficacy) AII (toxicity)	After 2-5 days; (repeat sampling recommended)
Posaconazole	Prophylaxis: > 0.7 mg/L Treatment: > 1.0 mg/L	BII (efficacy) AII (efficacy)	Tablet/IV: after 3 days: Suspension: 5-7 days.*
Itraconazole	Prophylaxis: 0.5-4 mg/L Treatment: 1-4 mg/L	AII (efficacy) BII (toxicity)	7-15 days;*

Teşekkürler …….

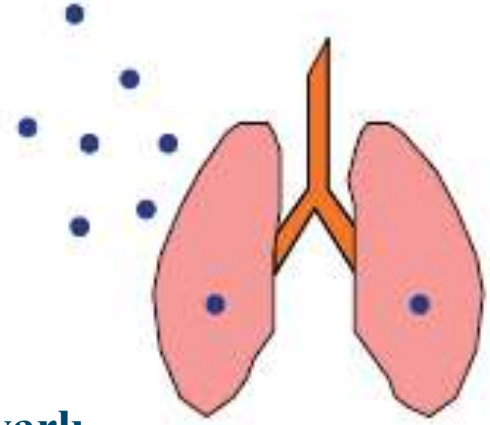
Hematoloji hastalarında en sık fungal enfeksiyon etkenlerinden biri olan Aspergillus spp tedavisinde azol direncinin tedavi başarısı üzerindeki etkileri nelerdir?

Azol Direnci ve Tedavi Üzerine Etkileri

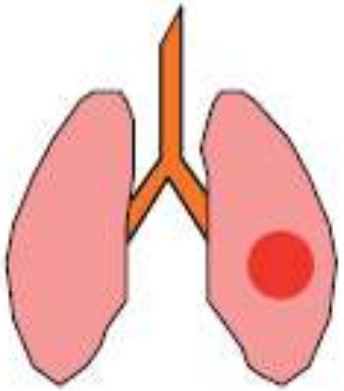


Verweij et al.2009; Lancet Infect

Mavi: azol duyarlı
Kırmızı azol dirençli

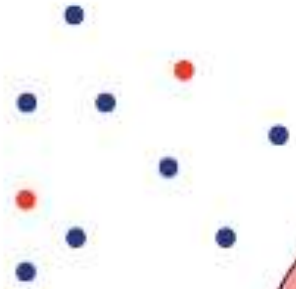


Patient route

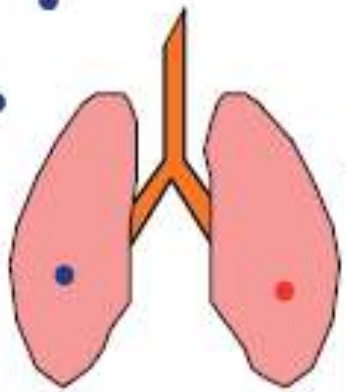


Characteristics
- Long term azole therapy
- Mainly chronic cavitary pulmonary aspergillosis
- Point mutations in the Cyp51A-gene or unknown resistance mechanisms
- Multiple resistance mechanisms may be found in different colonies from a single specimen

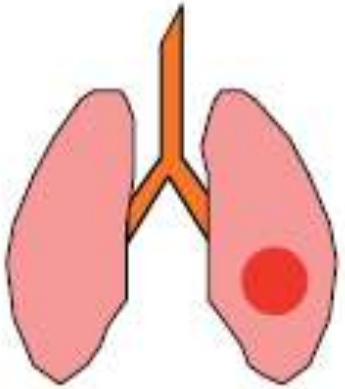
% 80



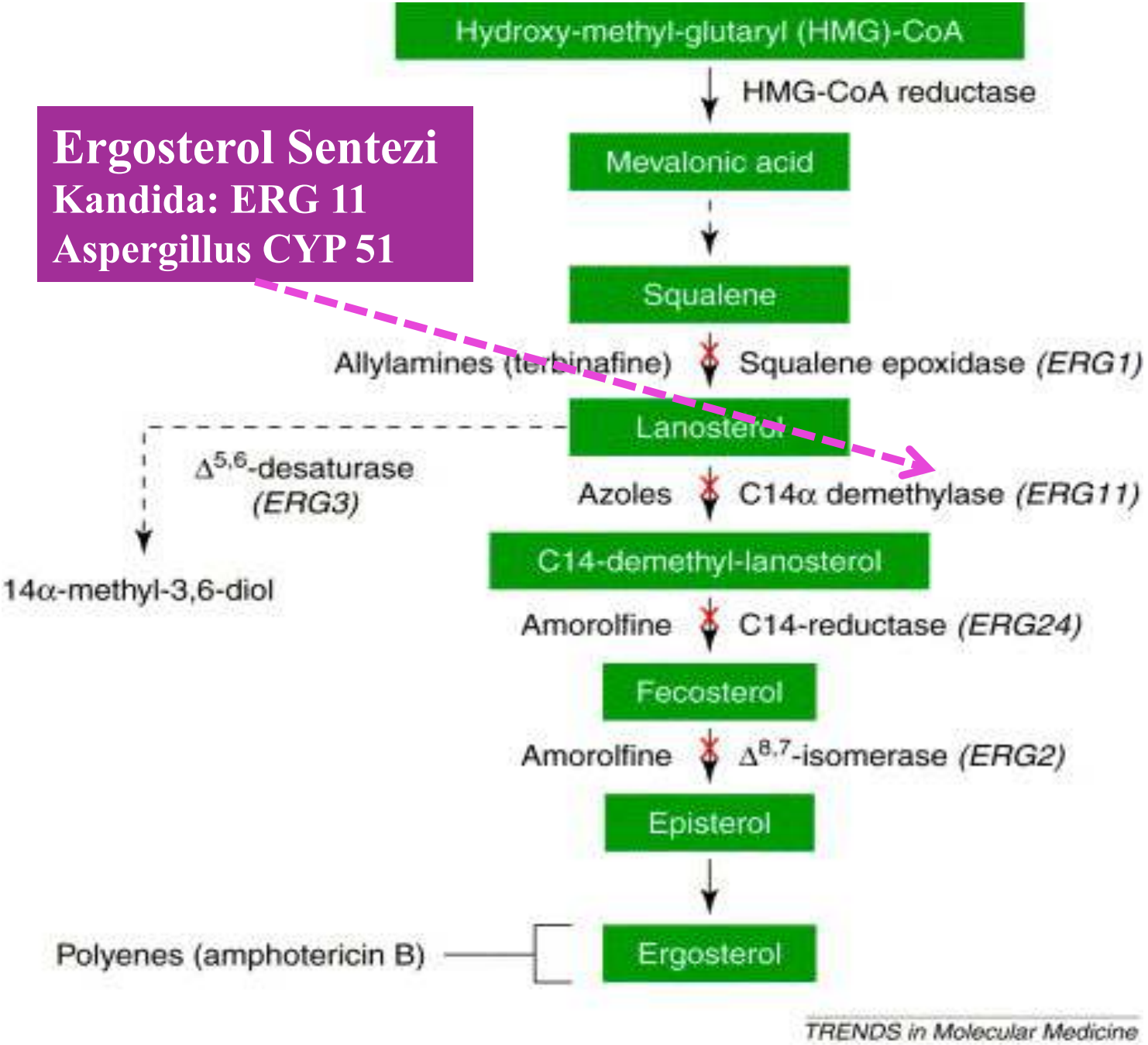
Exposure of *A. fumigatus* in the environment to azole fungicides with activity against aspergilli

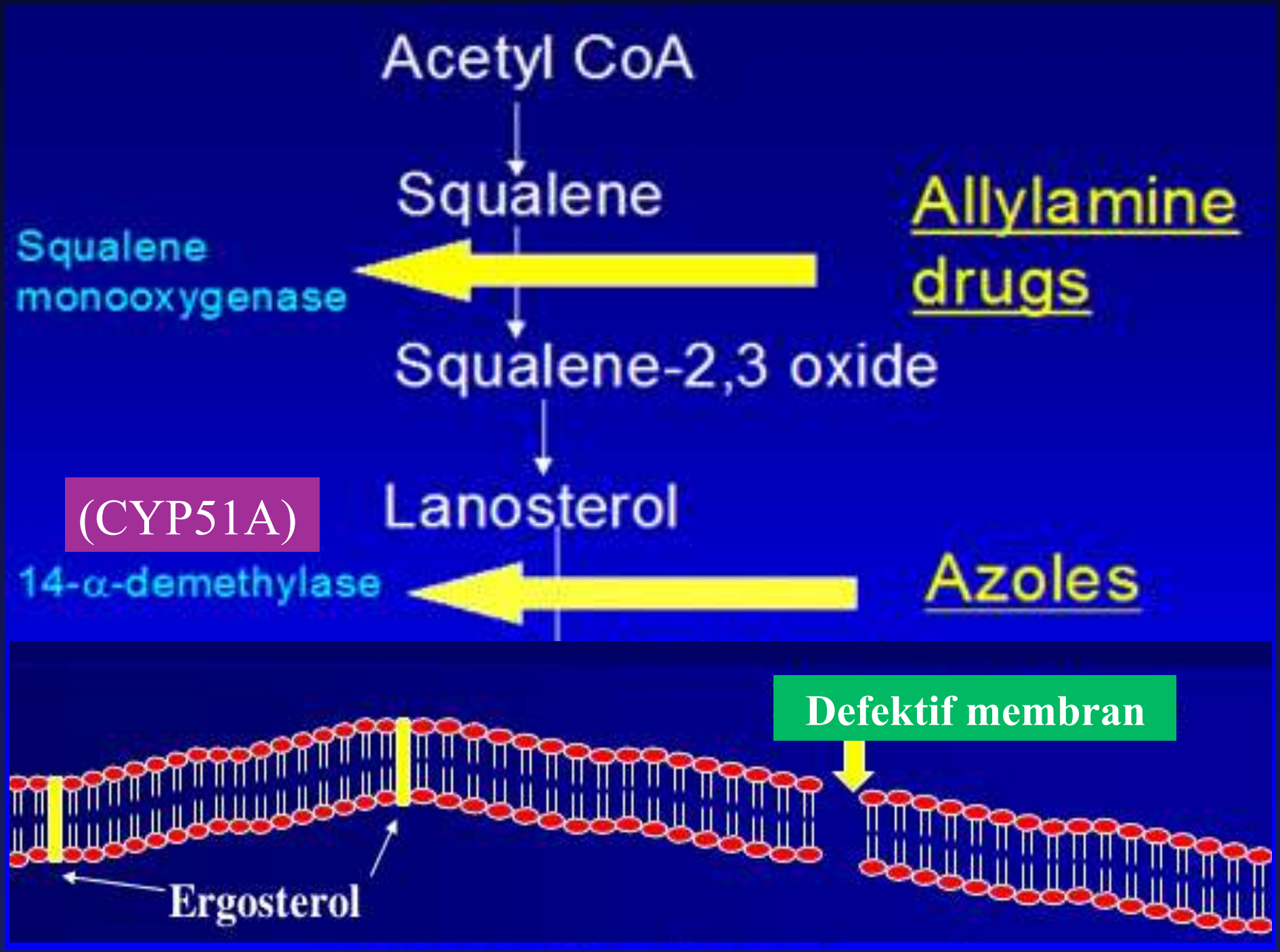


Environmental route

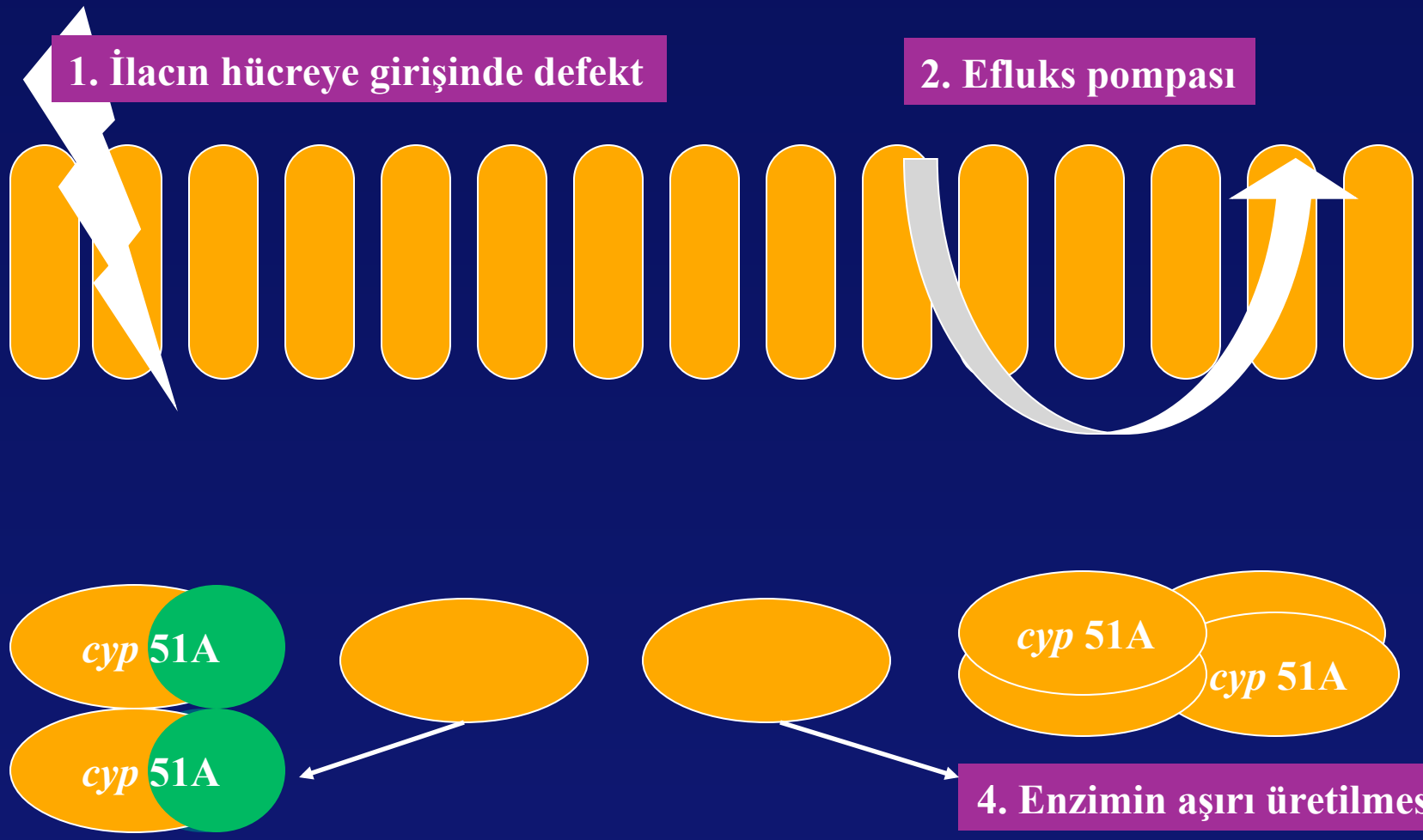


Characteristics
- Majority of patients are azole naïve
- Patients with invasive aspergillosis and chronic aspergillus diseases
- Only a few resistance mechanisms described
- Resistance mechanisms consist of Cyp51A-substitution with transcriptional enhancer


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



CYP 51A Mutasyonları

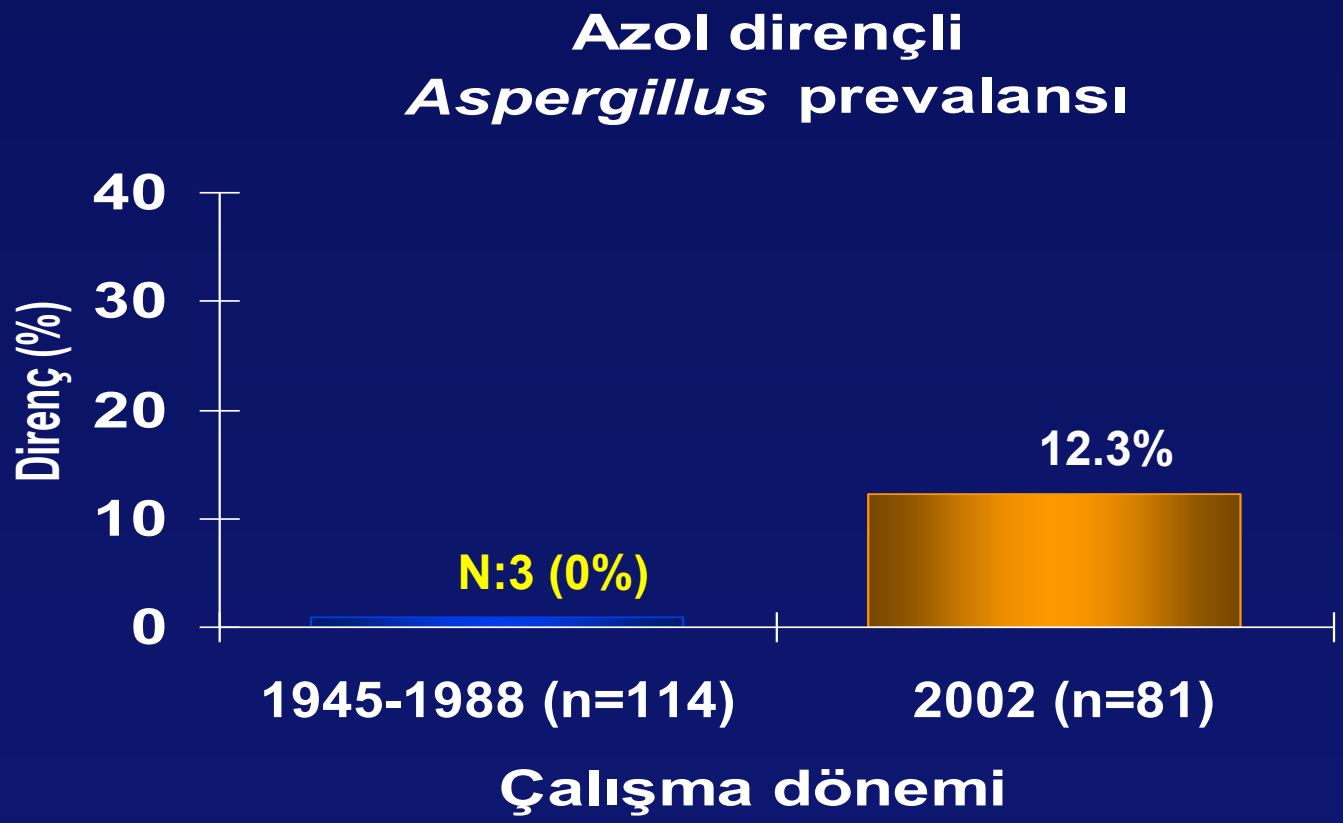
Amino asit mutasyonları	Azol direnci
M220I, M220V, M220K, M220T	**İtrakonazol** direnci ile beraber posakonazol ve vorikonazol duyarlılığında azalma
G54R, G54E, G54W, G54V	İtrakonazol ve pozakonazol direnci
L98H	**Multi azol direnci**
G138C	İtrakonazol, vorikonazol direnci

- **L98H mutasyonu** sonucu promotor gen (tandem repeat) aktivitesi artar
- **CYP 51** üretiminde 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.

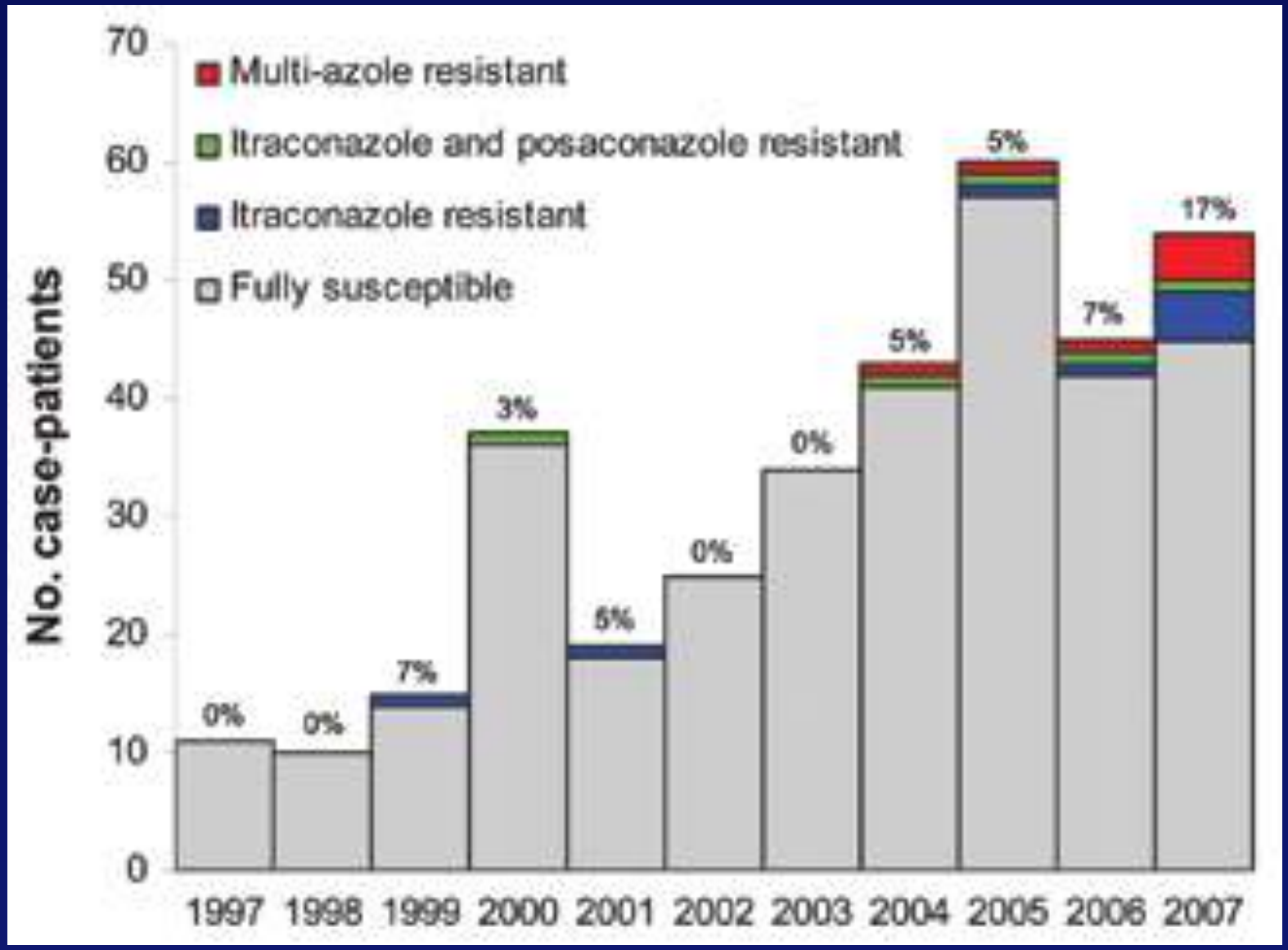
RESEARCH

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

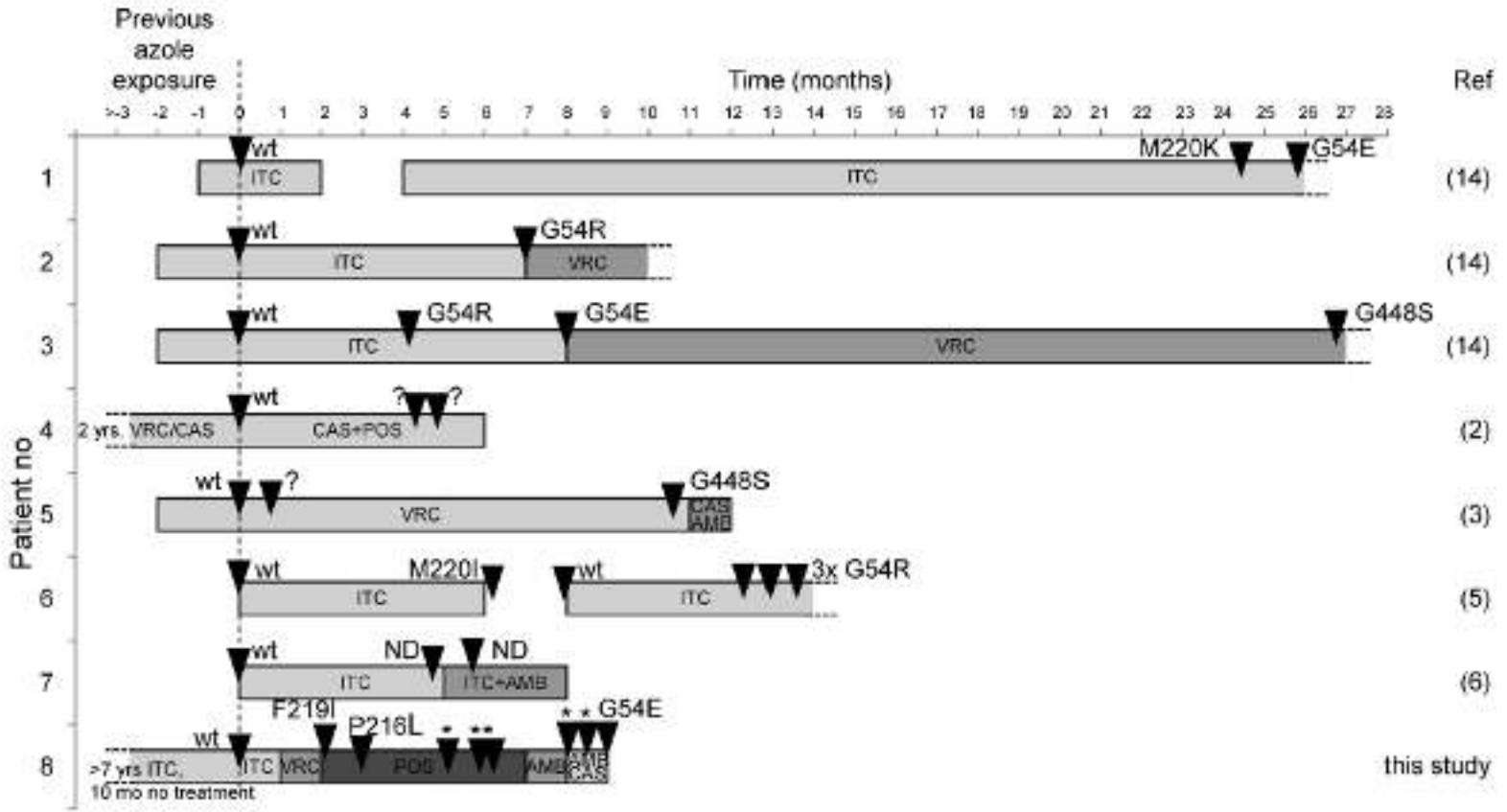


FIG 3 Reported cases of acquired azole resistance in *A. fumigatus* (2, 3, 5, 6, 14). The treatment schedules of all eight patients are indicated with bars, and the *A. fumigatus* isolates obtained from the patients are indicated with triangles. The corresponding resistance mechanisms are also indicated. 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).

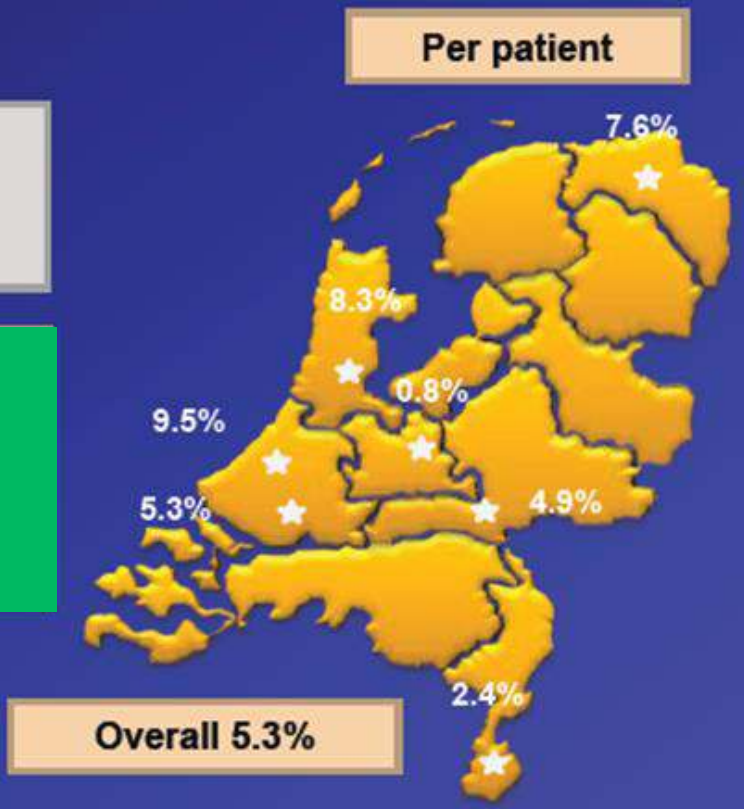
Simone MT, AAC 2012

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



- Proposed resistance mechanism:
  - Point mutations thought to arise in isolates exposed to azoles

Azol dirençli türlerde mortalite: %88

Vakaların %64 ‘ü azol naif

- Has a significant impact on the management of IA

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

FUNGICIDES


HEXAMAX
BLUE DIAMOND
CONTROL
CARBEN
COSAVET DF
MetalMan
TOPGUN-DF
Flo max
Blaster
PEARL


Tebuconazole 25% EW


QUALI-PRO
Tebuconazole
3.6F


Bitkisel Fungisid
Tebuconazole

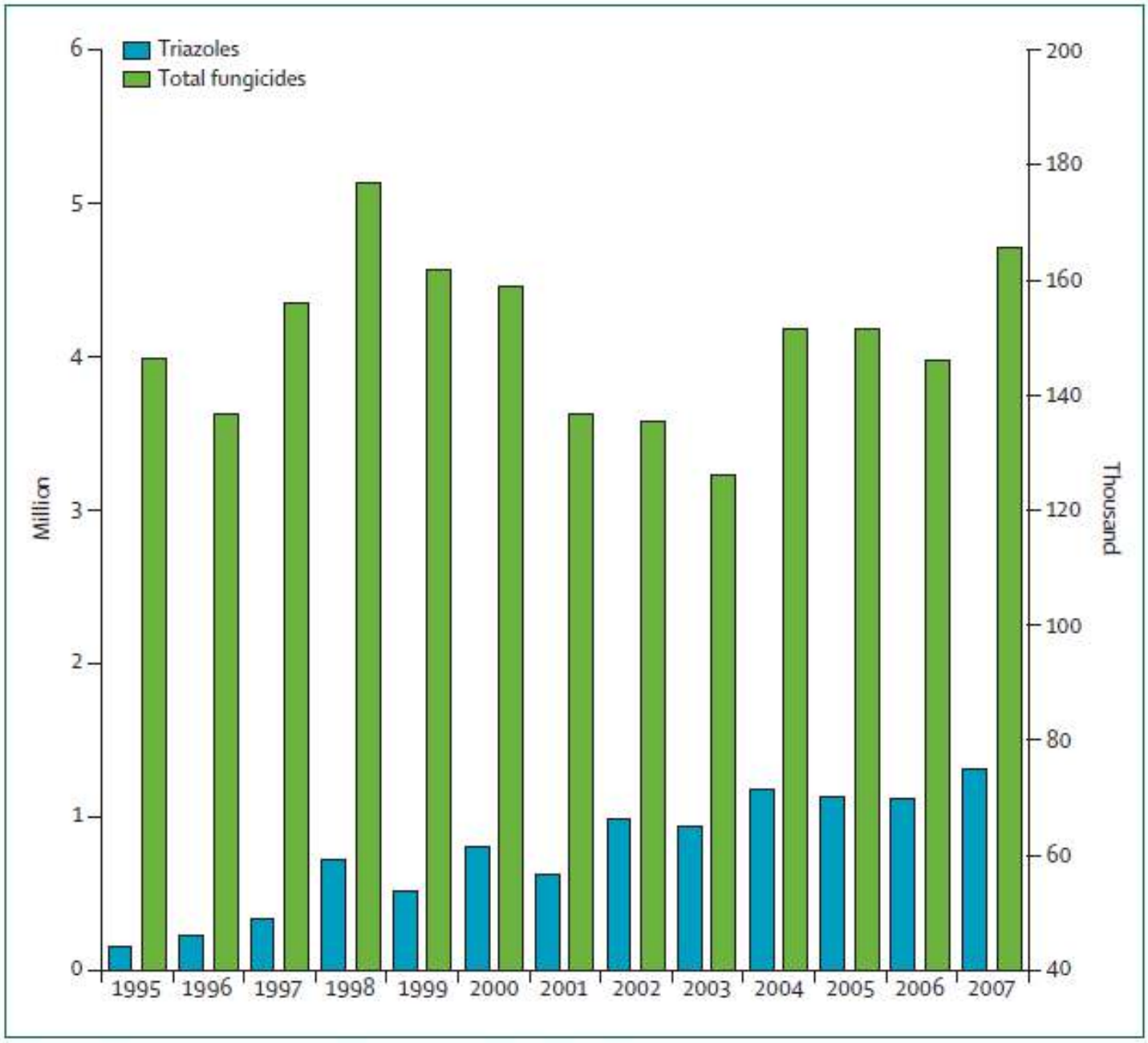


Figure 2: **Total volume of fungicides and triazoles sold in the Netherlands betwee**
Data from the Dutch Foundation for Phytofarmacy (Nefyto, Nederlandse Stichting v

Verweij et al.2009; Lancet Infect

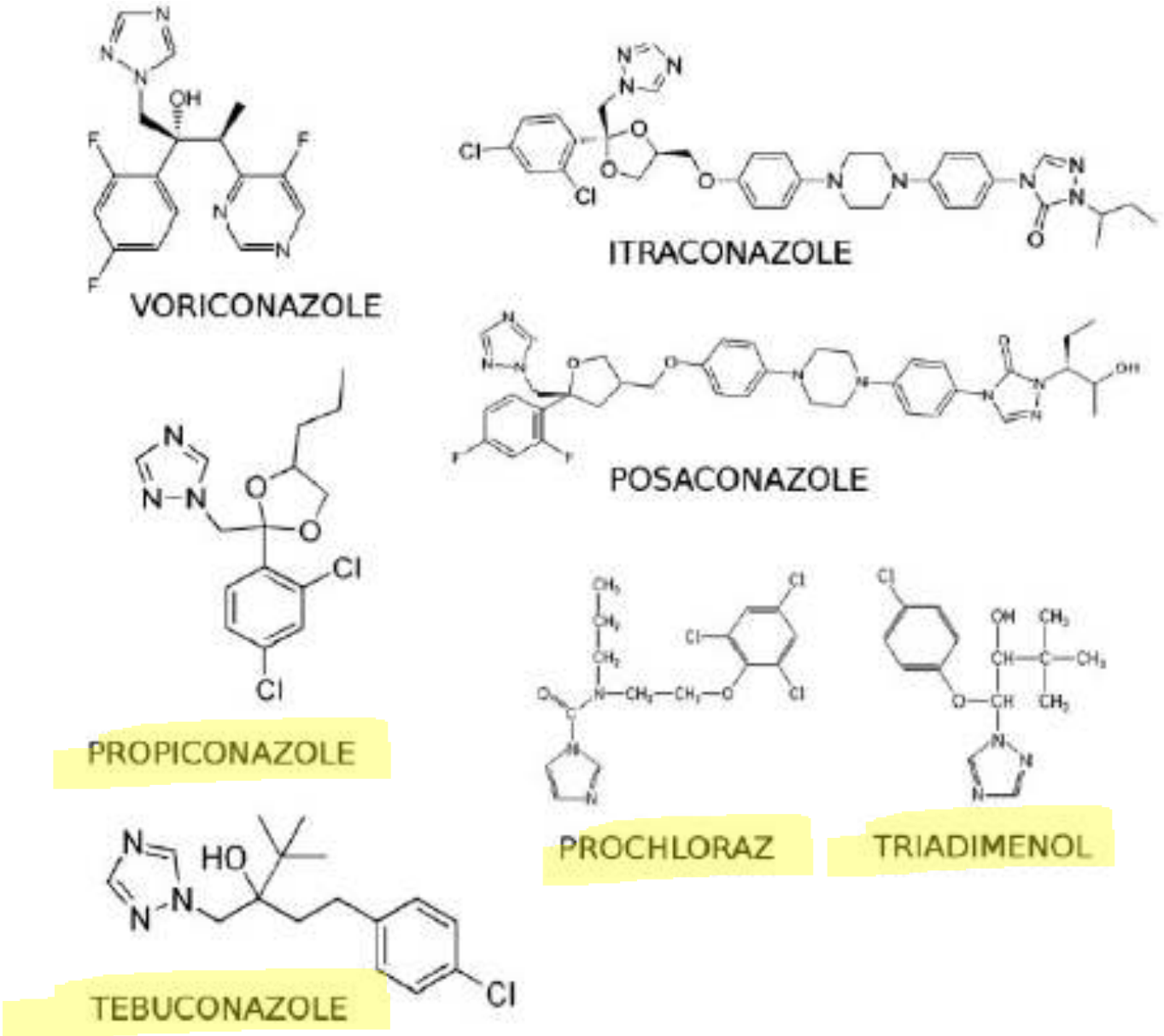


Figure 1. Structures of important triazoles in human (itraconazole, voriconazole and posaconazole) and agricultural use (propiconazole, tebuconazole, prochloraz and triadimenol).

Bowyer P, D Denning, Pest Manag Sci 2014

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

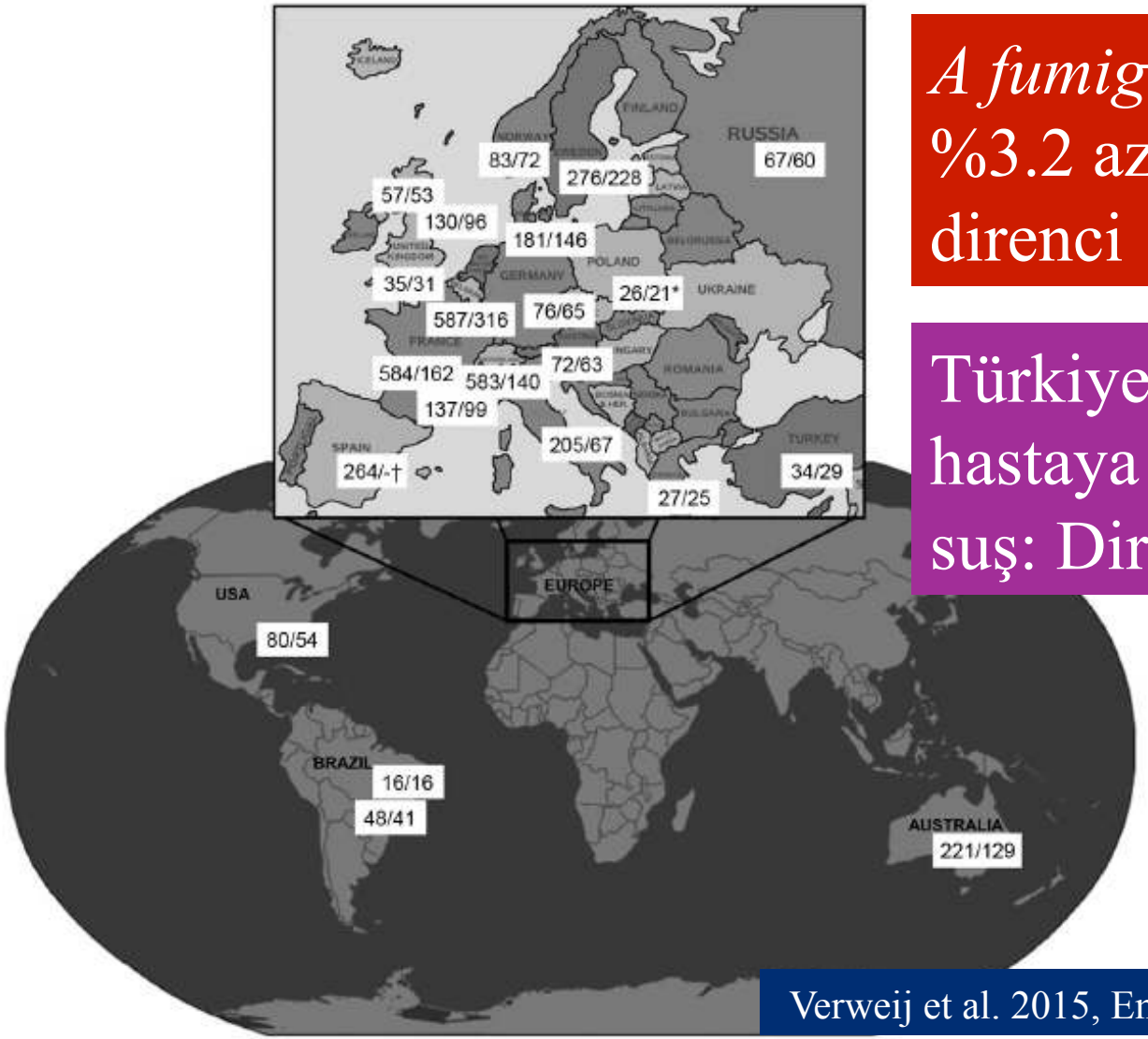
Rui Kano[1,*], Erina Kohata[1], Akira Tateishi[1], Somay Yamagata Murayama[2], Dai Hirose[2], Yasuko Shibata[3,†], Yasuhiro Kosuge[2], Hiroaki Inoue[1], Hiroshi Kamata[1] and Atsuhiko Hasegawa[4]

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

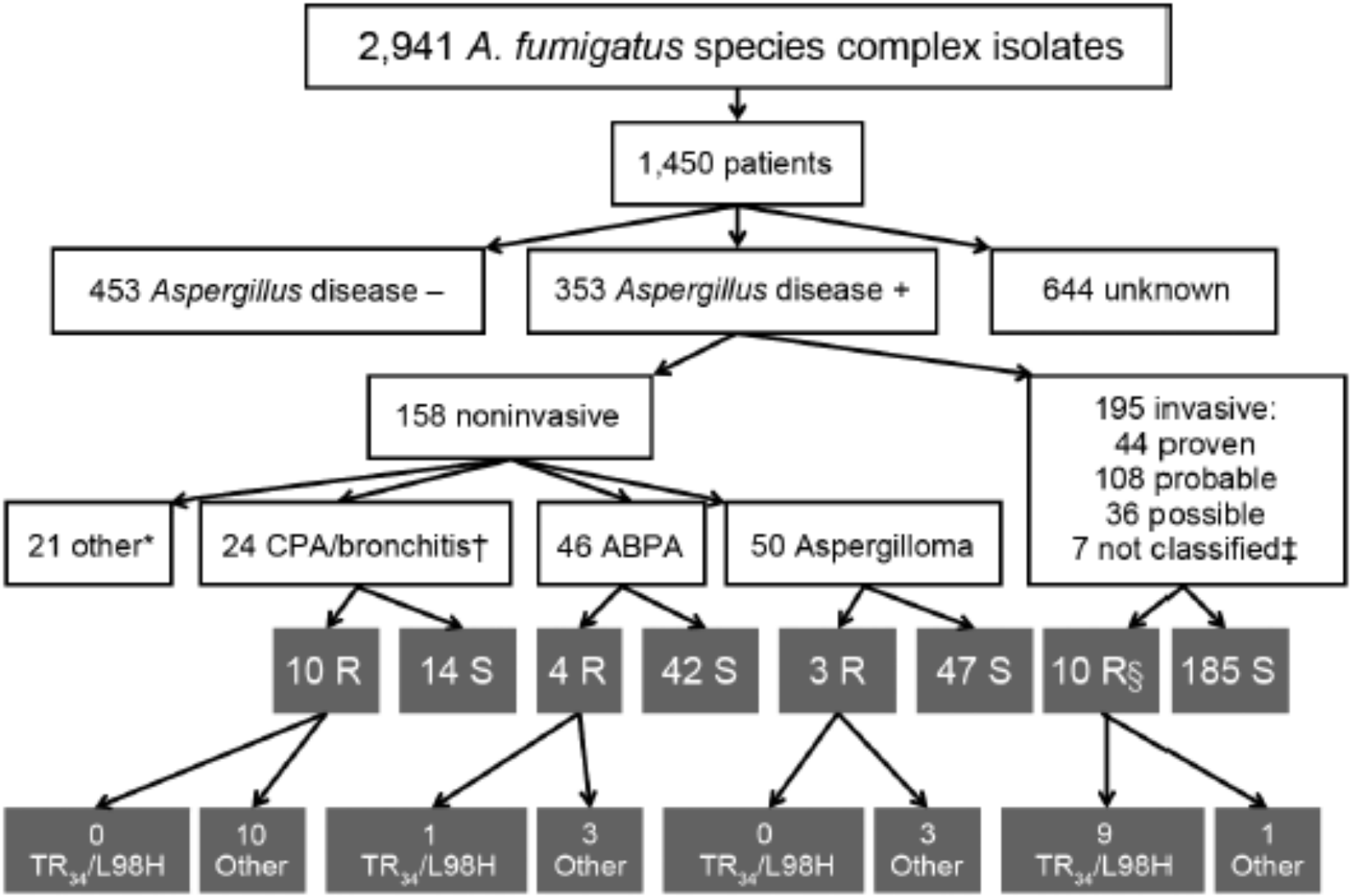
Uluslararası Prospektif Azol direnci taraması
19 Ülkeden 22 merkez



A fumigatus ‘da %3.2 azol direnci

Türkiye ‘den 34 hastaya ait 29 suş: Direnç yok

Verweij et al. 2015, Emerg Infect Dis



Verweij et al. 2015, Emerg Infect Dis

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journal homepage: http://www.elsevier.com/locate/jic

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

Oliver Bader,[a] Jana Tünnermann,[a] Anna Dudakova,[a] Marut Tangwattanachuleeporn,[a,b] Michael Weig,[a] Uwe Groß,[a] MykoLabNet-D

- **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
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]

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.

Aspergillus & Aspergillosis Website

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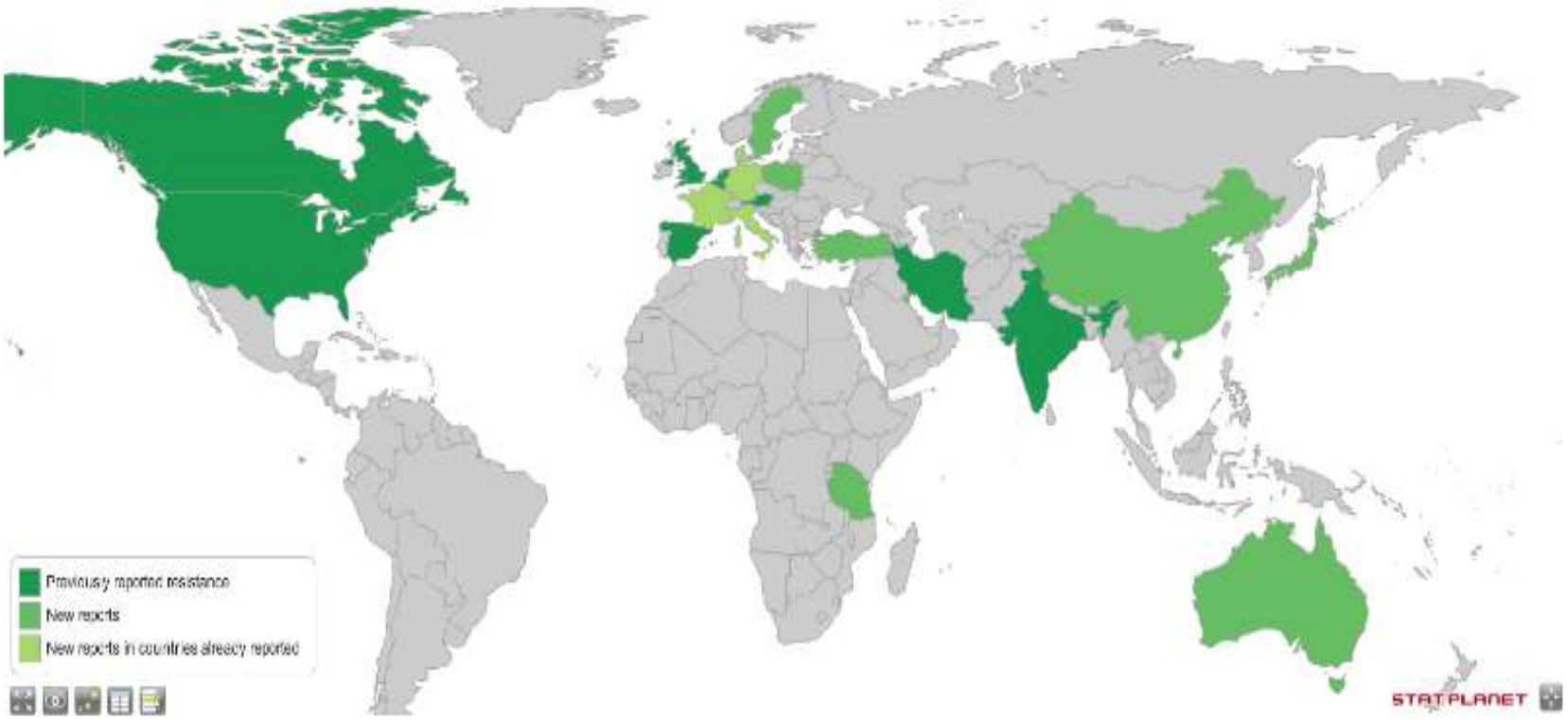
UK calls for agricultural fungicide restraint to reduce azole resistance in Aspergillus



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

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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

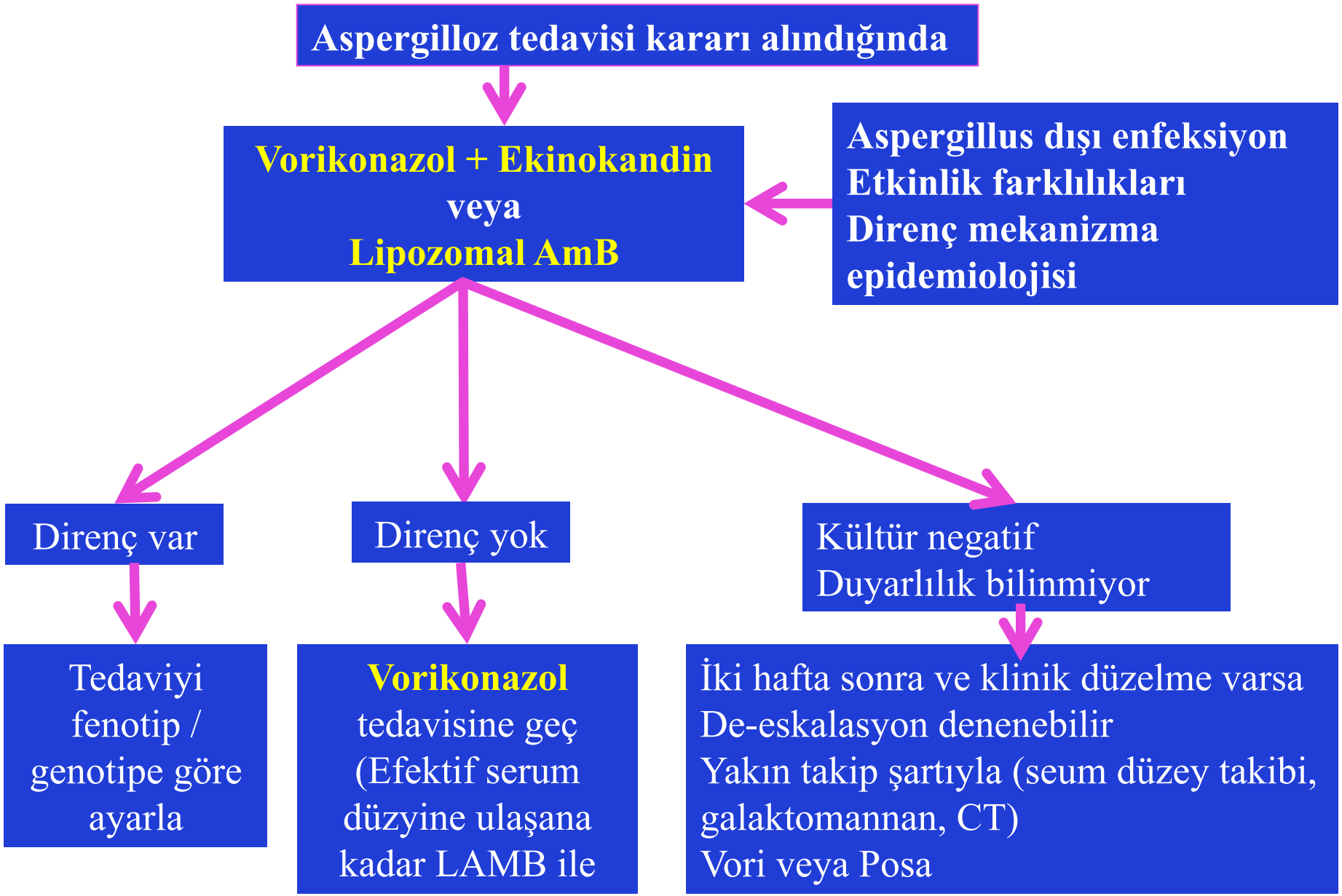
Vorikonazol + Ekinokandin

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**
- 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

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

TEŞEKKÜRLER