

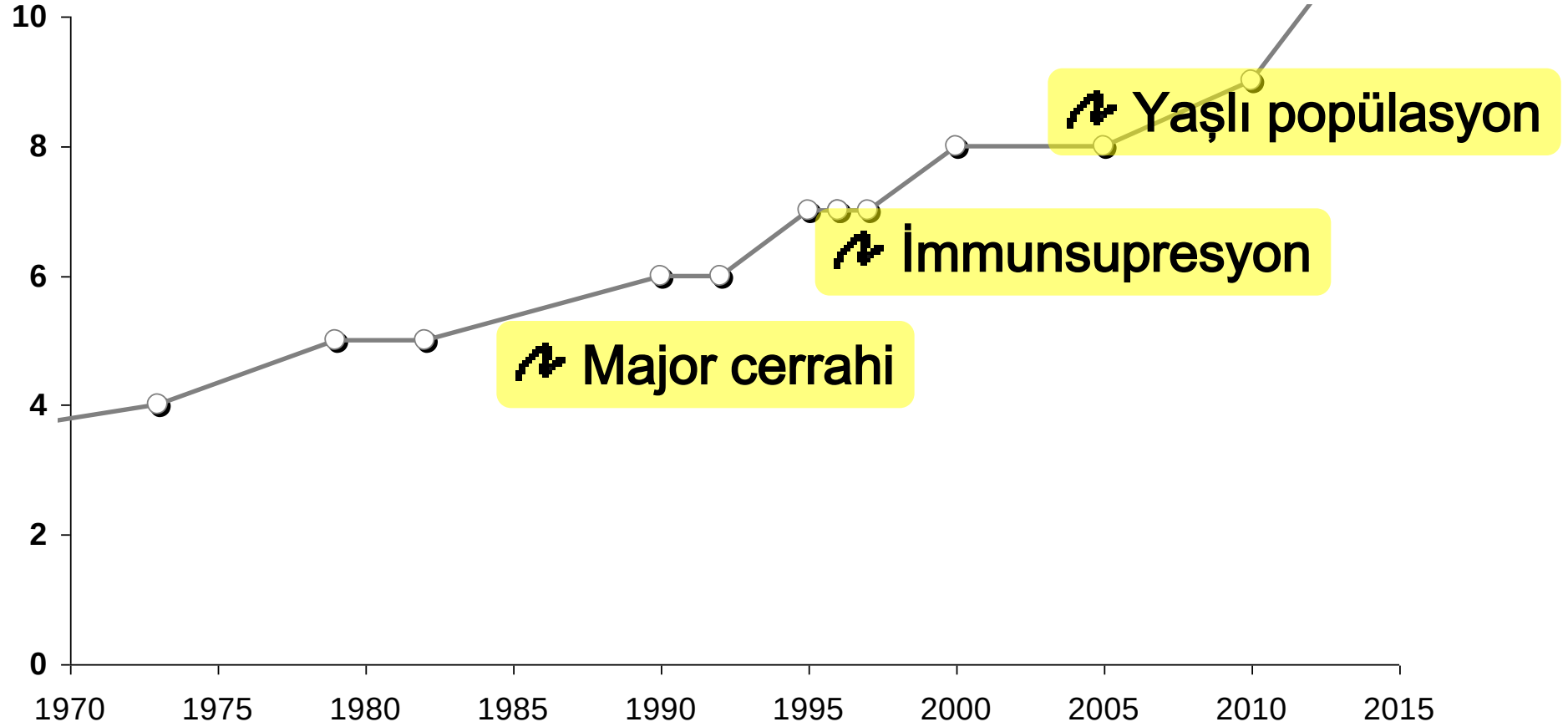
A microscopic image showing Candida albicans hyphae and spores. The hyphae are long, thin, and branching, with spores (small, round cells) attached to them. The background is a light greenish-blue.

Antifungallerin Doğru Kullanımı

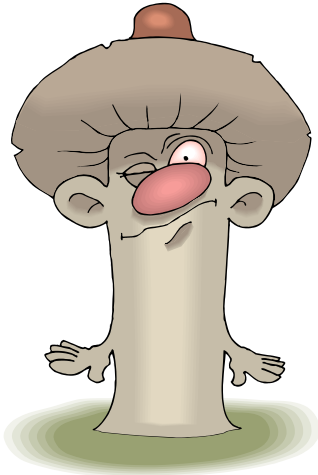
Prof. Dr. Özlem TÜNGER

**MCBÜ Enfeksiyon Hastalıkları ve Klinik
Mikrobiyoloji AD**

İFi son 20 yılda çok arttı



Epidemiyolojik Değişiklikler



Candida albicans

Aspergillus fumigatus

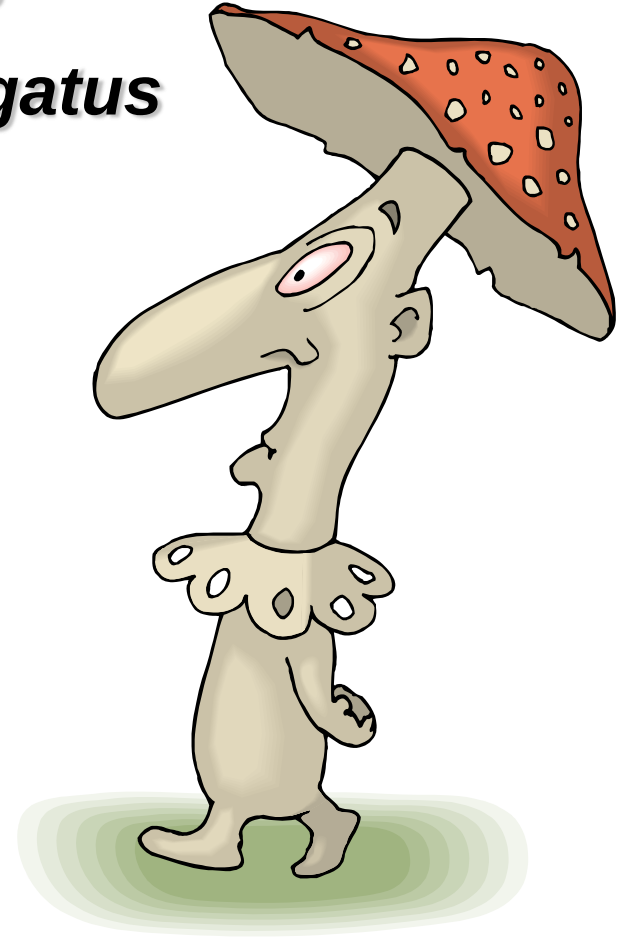
Non *albicans* *Candida* türleri

Aspergillus flavus

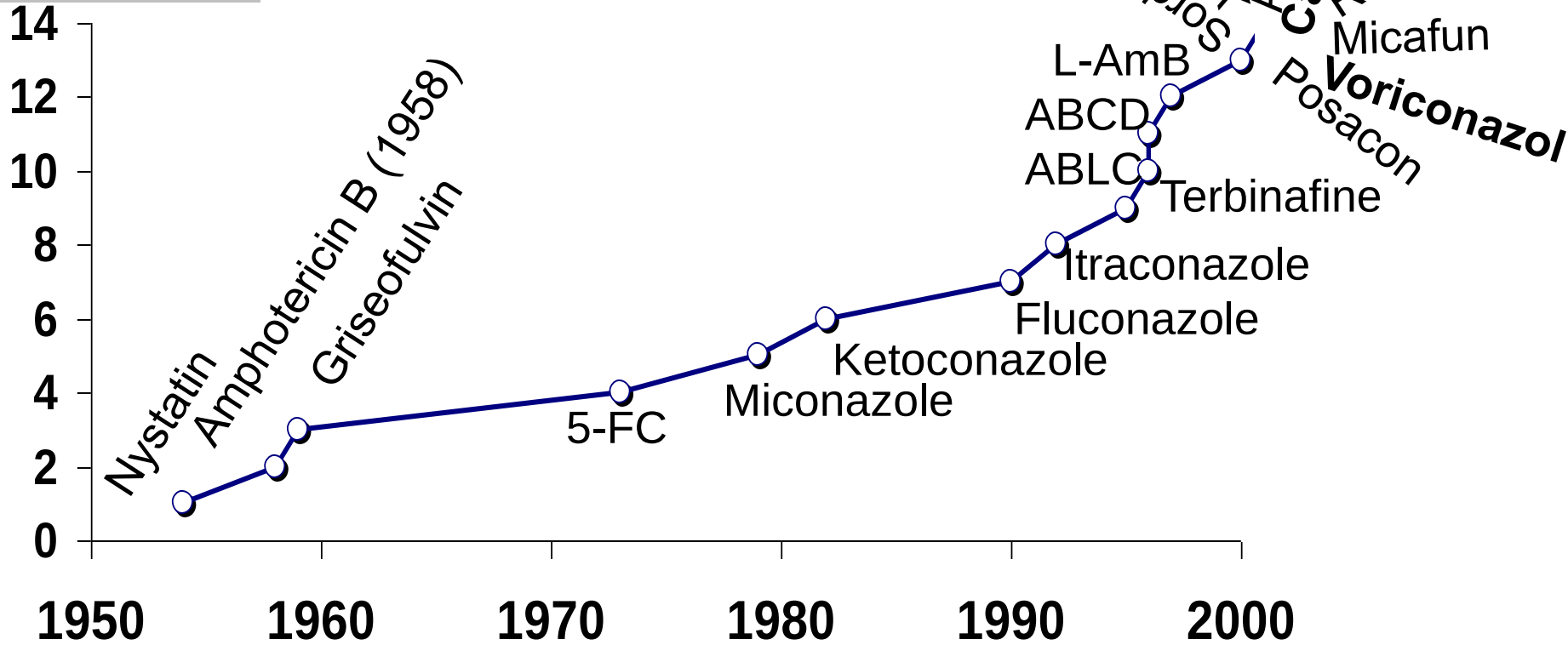
Aspergillus terreus

Scedosporium spp

Zygomycetes



ilaçlar



Transplant-Associated Infection Surveillance Network (TRANSNET)

23 merkez, 2001-2006

HKHT en yüksek (allojenik %8.1)

Sıklık

1 yıllık yaşam

Azol profilaksisi !!!

%25.4

%33.6

%28

3. Mukormikozis %8

Transplant-Associated Infection Surveillance Network (TRANSNET)

SOT, 15 merkez, 2001-2006

İFi %3.1 (%1.2-6.1)

	<u>Sıklık</u>	<u>1 yıllık yaşam</u>
1. Kandidiyazis	%53	%66
2. Aspergilloz	%19	%59
3. Kriptokokkoz	%8	



Livio Pagano
Morena Caira
Anna Candoni
Massimo Offidani
Luana Fianchi
Bruno Martino
Domenico Pastore
Marco Picardi
Alessandro Bonini
Anna Chierichini
Rosa Fanci
Cecilia Caramatti
Rosangela Invernizzi
Daniele Mattei
Maria Enza Mitra
Lorella Melillo
Franco Aversa
Maria Teresa Van Lint
Paolo Falcucci
Caterina Giovanna Valentini
Corrado Girmenia
Annamaria Nosari

Correspondence:
Livio Pagano, Istituto di Ematologia
Università Cattolica del Sacro Cuore
Largo Francesco Vito, 1, I-00168
Rome, Italy.
E-mail: lpagano@rm.unicatt.it

Hematolojik malignite (11.832)

İFi %4.6

AML %12

ALL %6.5

KML %2.5

KLL %0.5

Lenfoma %0.7-1.6

Mortalite

invaziv kandidyazis %33

invaziv aspergillozis %42

mukormikozis %64



Maliyet !!!

Olgu-kontrol çalışması (akut lösemi ve HKHT)

Uygun tedavi alan invaziv kandidiyazis hastalarında

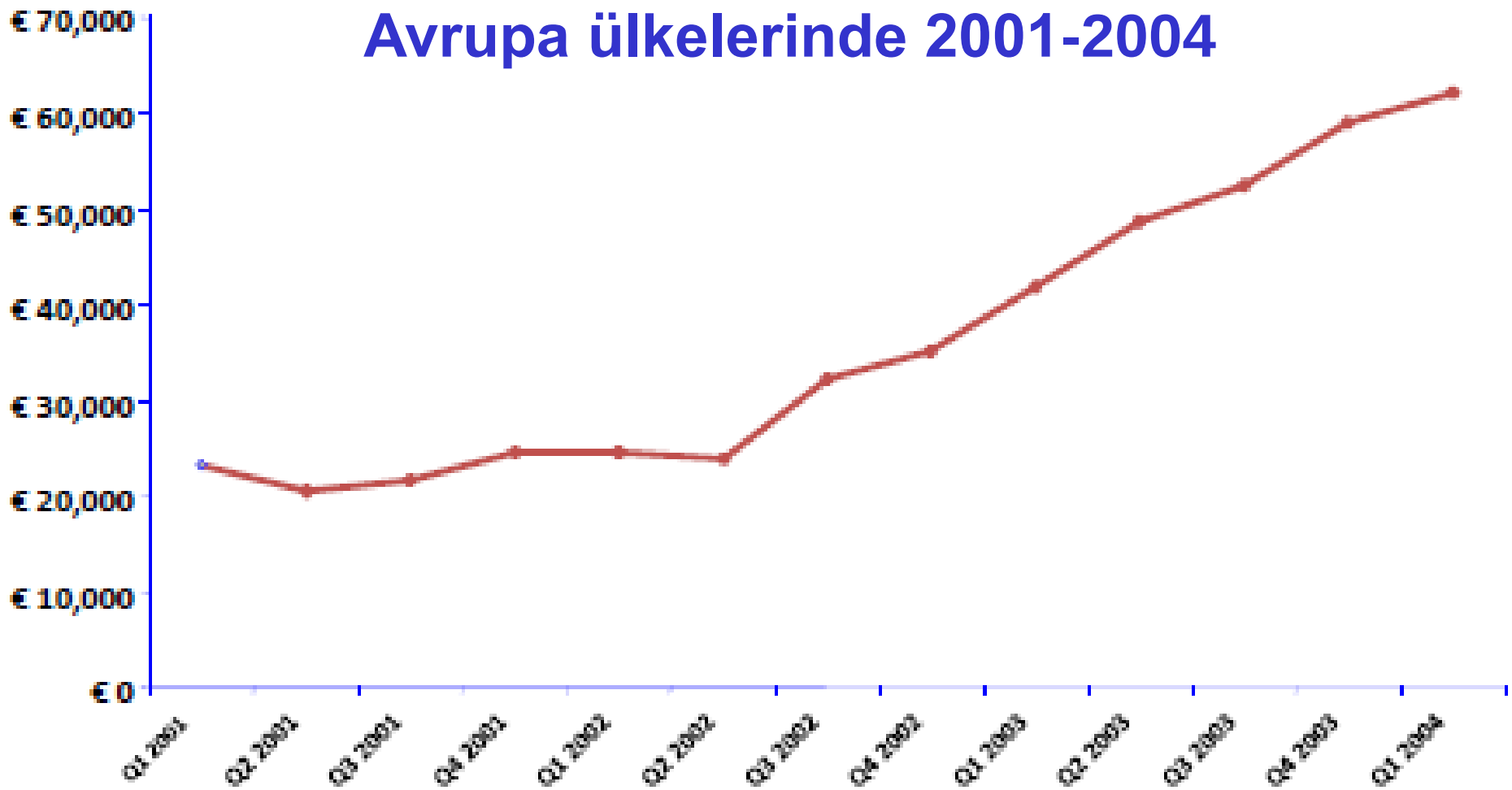
Hastanede yatış süresi: 3 gün → 13 gün

Maliyet: 3.000\$ → 22.000\$

Morgan J, Infect Control Hosp Epidemiol 2005; 26:540-7

(x1000) €

Avrupa ülkelerinde 2001-2004

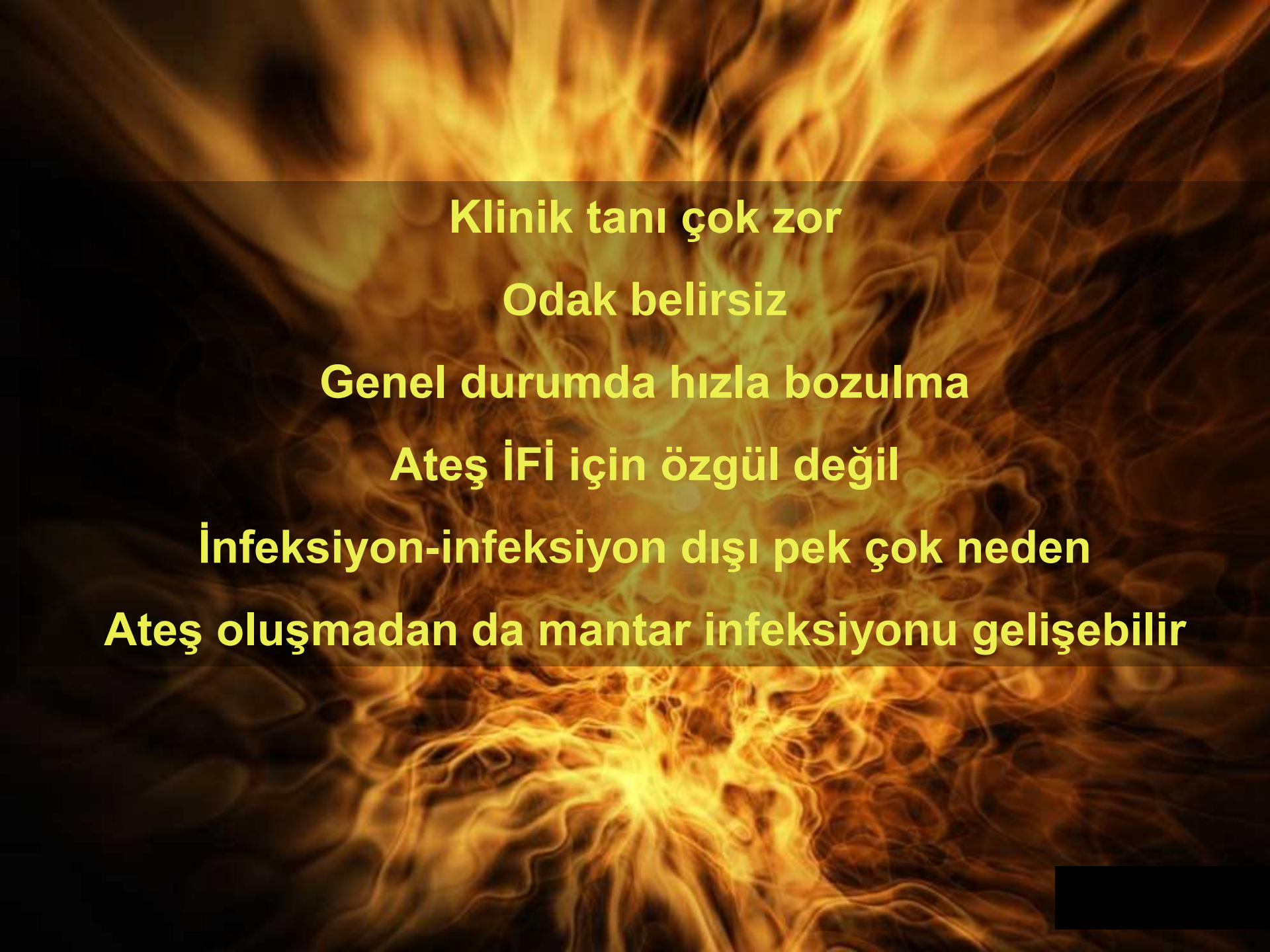


Febril nötropeni hastaların 2/3'ü antifungal almakta

Fungal infeksiyonların insidansı ~%10

Hastaların %90'ında gerçekte mantar infeksiyonu yok





Klinik tanı çok zor

Odak belirsiz

Genel durumda hızla bozulma

Ateş İFİ için özgül değil

İnfeksiyon-infeksiyon dışı pek çok neden

Ateş oluşmadan da mantar infeksiyonu gelişebilir



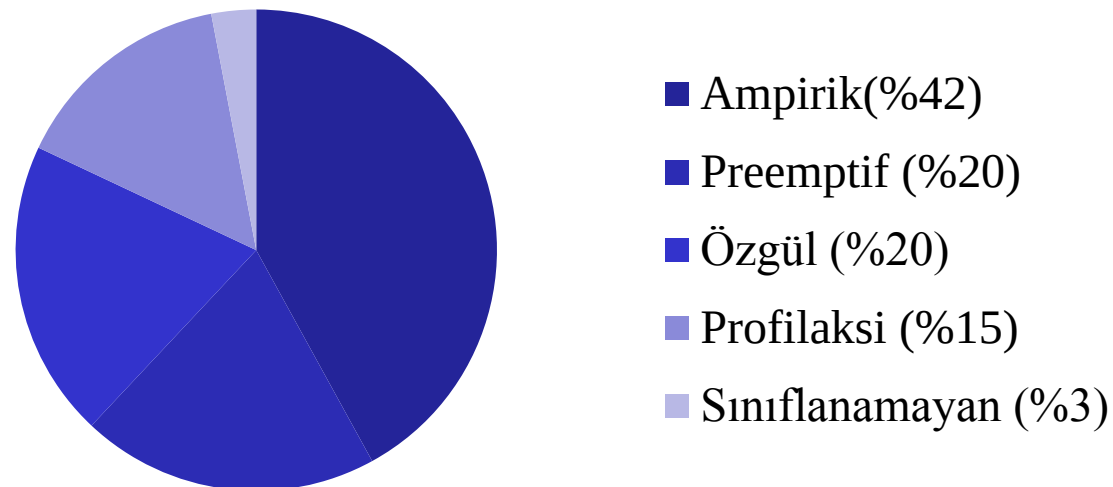
Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed

Maricela Valerio^{1,2}, Carmen Guadalupe Rodriguez-Gonzalez^{2,3}, Patricia Muñoz^{1,2,4*}, Betsabe Caliz^{2,3}, Maria Sanjurjo^{2,3} and Emilio Bouza^{1,2,4} on behalf of the COMIC Study Group (Collaborative Group on Mycoses)†

¹Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain; ²Instituto de Investigación Sanitaria del Hospital Gregorio Marañón, Madrid, Spain; ³Pharmacy Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain; ⁴Medicine Department, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

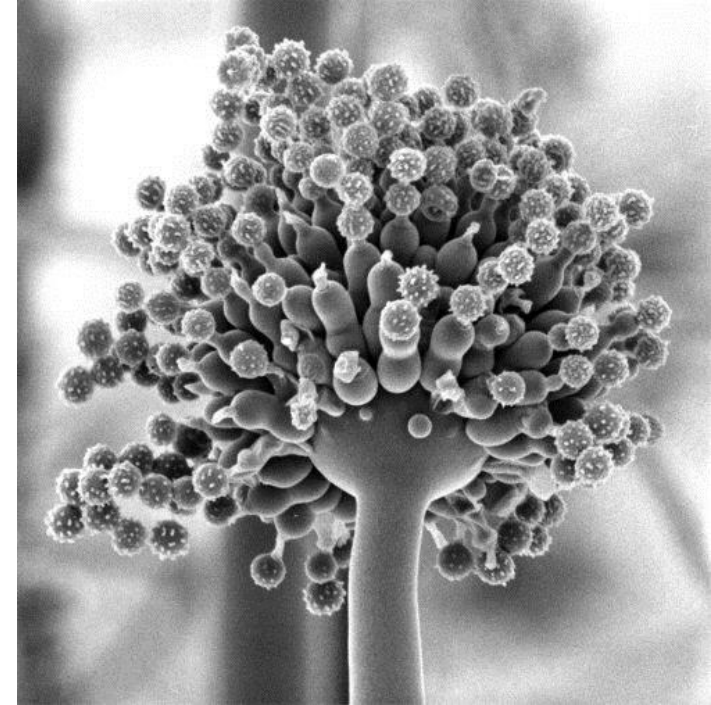
*Corresponding author. Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, Doctor Esquerdo 46, 28007 Madrid, Spain. Tel: +34-91-5868453; Fax: +34-91-5044906; E-mail: pmunoz@micro.hggm.es

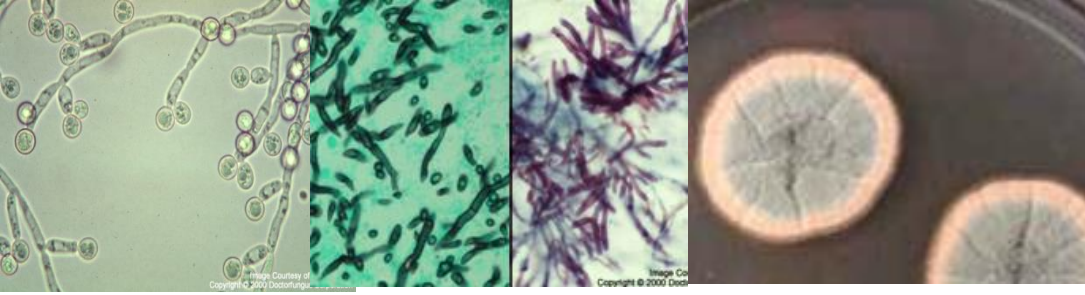
†Members are listed in the Acknowledgements section.



Mantar infeksiyonunun tanısını koymak zor
Erken tedavi prognozla direkt ilişkili ama tanı
için zaman yetersiz

Ampirik tedavi





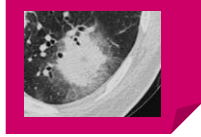
Kanıtlanmış

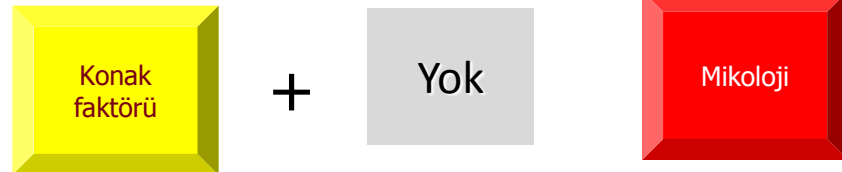


= Yüksek olasılı

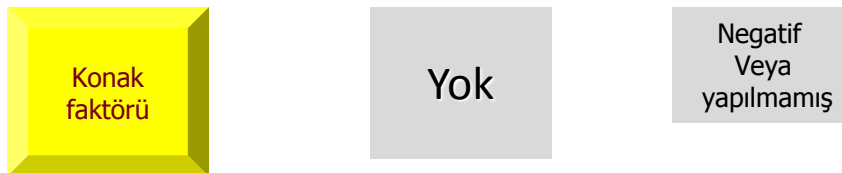
Preemptif tedavi



=  } Olasılı
GM, BDG



= Olasılı
Sınıflandırılmamış



= Sınıflandırılmamış

Kültür Dışı Mikrobiyolojik Yöntemler

	GM	BDG	PCR
<i>A. fumigatus</i>			
Diğer Aspergilluslar			
<i>Fusarium</i>			
Zygomycetes			
<i>Candida</i>			
<i>Cryptococcus</i>			
<i>Penicillium</i>			
<i>Paecilomyces</i>			

- ✓ **Test ile fungal yük arasındaki korelasyon?**
- ✓ **Profilaksi veya tedavinin testin performansına etkisi?**
- ✓ **Optimal eşik değeri?**
- ✓ **Ne sıklıkta yapılması gerektiği?**
- ✓ **Yalancı pozitif / negatifliklerin nasıl değerlendirileceği?**
- ✓ **Ekinokandinlerle tedavi sırasında kullanımı?**

İnvaziv Kandidiyazisde Hızlı Tanı Testleri

- ✓ **Multiplex polimeraz zincir reaksiyonu: Multiplex PCR**
- ✓ **T2 kandida paneli (T2 manyetik rezonans)**

Bauer KA, Clin Infect Dis 2014; 59(Suppl 3):S134-45

	MALDI-TOF	Multipleks PCR	PNA FISH	T2MR
Kan kültür temelli	Evet	Hayır	Evet	Hayır
Tanımlama	>200 bakteri veya maya	24 bakteri ve maya (5 kandida türü, 3 antibiyotik direnç geni)	5 kandida türü	5 kanıda türü
Manuel süre	1 dk	2 dk	5 dk	<5 dk
Tüm işlem süresi	5 dk	60 dk	90 dk	180-300 dk
FDA onayı	Var	Var	Var	Yok
Antifungal yönetimde kullanımına ilişkin çalışma	Var	Var	Var	Yok

EORTC-MSG

**European Organization for Research and Treatment of
Cancer Mycoses Study Group**

BT'de aşağıdaki bulgulardan 1 veya daha fazlası:

- ✓ **Hiperdens lezyonlar ($\pm$ halo belirtisi)**
- ✓ **Hava hilal belirtisi**
- ✓ **Kavitasyon**



BT pulmoner anjiyografi

Duyarlılık %83, özgüllük %93

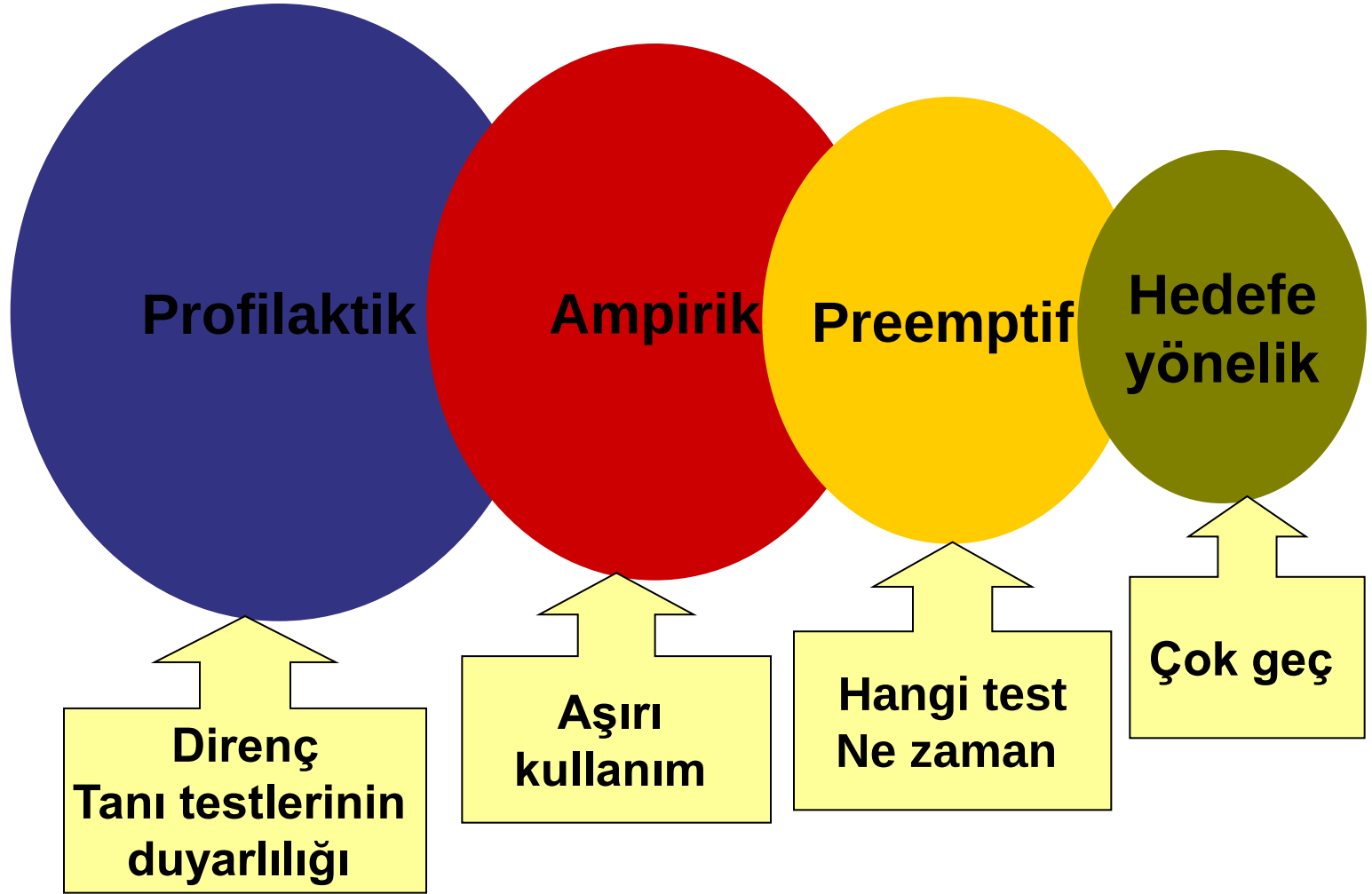
Stanzani M, Curr Fungal Infect Rep 2016; 10:78-86

	Hebart ve ark.	Cordonnier ve ark.	Morrissey ve ark.
Yöntem	Çok merkezli, randomize kontrollü	Çok merkezli, randomize kontrollü açık uçlu, eş-değerlik	Çok merkezli, randomize kontrollü açık uçlu, paralel-grup
Hasta grubu	Allojenik HKHT	Kemoterapi alan hematolojik maligniteler, otolog HKHT	Akut lösemi, allojenik HKHT
Hasta sayısı	211 ampirik, 198 preemtif	150 ampirik 143 preemtif	122 ampirik 118 preemtif
Profilaksi	Flukonazol 200 mg/gün, Amp B susp 4x5 ml/gün	Lokal rehberler	Lokal rehberler
İzlem	Haftada 2 Candida- Aspergillus PCR (30 gün), Preemptiflerde bu süreye ek haftada 1 PCR (90 gün)	Haftada 2 GM (nötropeni düzelinceye kadar)	Yatan hastalarda haftada 2 GM ve PCR, ayaktan hastalarda haftada 1 GM ve PCR
Primer sonuç	Olası ve kanıtlanmış İFİ oranları aynı	Sağkalım iki grupta aynı	Ampirik kullanımda belirgin azalma
Sekonder sonuç	- 30 günde ampirik grupta mortalite daha yüksek - 100 günde sağkalım ve İFİ aynı	- Preemtif grupta olası ve ve kanıtlanmış İFİ daha fazla - Ateş süresi aynı - Tedavi süresi ampirik grupta daha fazla - Maliyet ampirik grupta daha fazla	- Mortalite açısından fark yok - Preemtif grupta olası İA daha fazla - Toksisite açısından fark yok

*Hebart H, Bone Marrow Transplant 2009; 43:553-61
Cordonnier C, Clin Infect Dis 2009; 48:1042-51
Morrissey CO, Lancet Infect Dis 2013; 13:519-28*

**Acaba yüksek riskli hastalarda
antifungal profilaksi İFi'yi
önleyebilir mi?**







Centers for Disease Control and Prevention

SEARCH

	Percentage of <i>Candida</i> bloodstream isolates testing resistant	Estimated number of infections per year	Estimated number of deaths
Fluconazole-resistant <i>Candida</i> species	7%	3,400	220

Resistance

About Antimicrobial Resistance

Biggest Threats

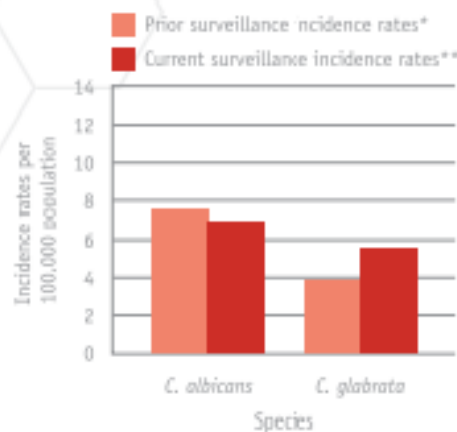
Protecting Yourself and Your Family

Protecting Patients and Stopping Outbreaks

Protecting the Food Supply

Antibiotic Resistance Threats in the United States, 2013

There is increasing incidence of *Candida* infections due to azole- and echinocandin-resistant strains.

Changes Over Time in Incidence of Resistant Species of *Candida*

*This accounts for data collected from Atlanta, GA from 1992–1993 and from Baltimore, MD from 1998–2000.

**This accounts for data collected from 2008–present.



TR

16:04
18.03.2017



Epidemiology and molecular mechanisms of antifungal resistance in *Candida* and *Aspergillus*

Sarah Santos Gonçalves,¹ Ana Carolina Remondi Souza,¹ Anuradha Chowdhary,² Jacques F. Meis^{3,4} and Arnaldo Lopes Colombo¹

¹Laboratório Especial de Micologia, Disciplina de Infectologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil,

Countries	Author [Reference]	Number of centres	Number of isolates	Species distribution ¹ (%)					DDS/Resistance to FCZ ² (%)				
				Ca	Ct	Cp	Cgla	Ck	Ca	Ct	Cp	Cgla	Ck
Latin America	Nucci et al. [290]	21	672	37.6	17.6	26.5	6.3	2.7	0.4	0	1.1	100	100
Argentina													ND
Chile													100
Venezuela													96
Colombia													100
Mexico													ND
Brazil													100
Brazil													37.5
Brazil													ND
Brazil	et al. [298]												
Brazil	Colombo et al. [29]	9	300	34	24	26	7	3	0	3	0	64	100
Brazil	Santos et al. [299]	1	422	35.7	9.71	46.6	3.5	0.9	9.9	26.8	7.1	100	100
Brazil	da Costa et al. [300]	1	93	28.7	30.5	24.1	8.3	1.8	3.7	3.2	26.9	0	ND

***C. parapsilosis* ABD %3.4-7.5, Avrupa'da %0-6**

***C. tropicalis* ABD %2.4-9.0, Avrupa'da %1.7-22.0**

En yüksek direnç oranı onkoloji hastalarında

MD Anderson Kanser Merkezi

Flukonazol direnci %20.5

Ekinokandin direnci %10.3

Çoklu ilaca direnç %6.8

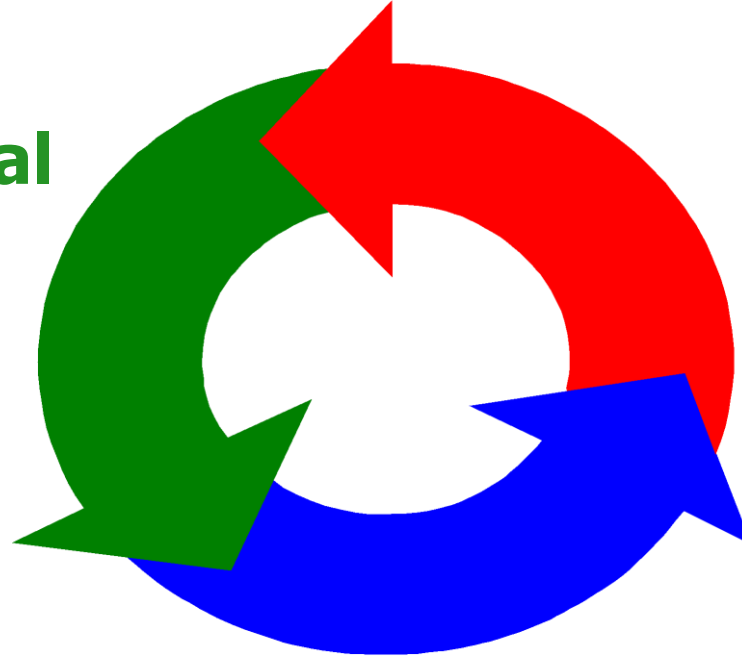


***C. glabrata* kandidemisi**

Farmakiotis D, Emerg Infect Dis 2014; 20:1833-40

Yeni antifungal

Direnç



Kullanım

Aşırı kullanım

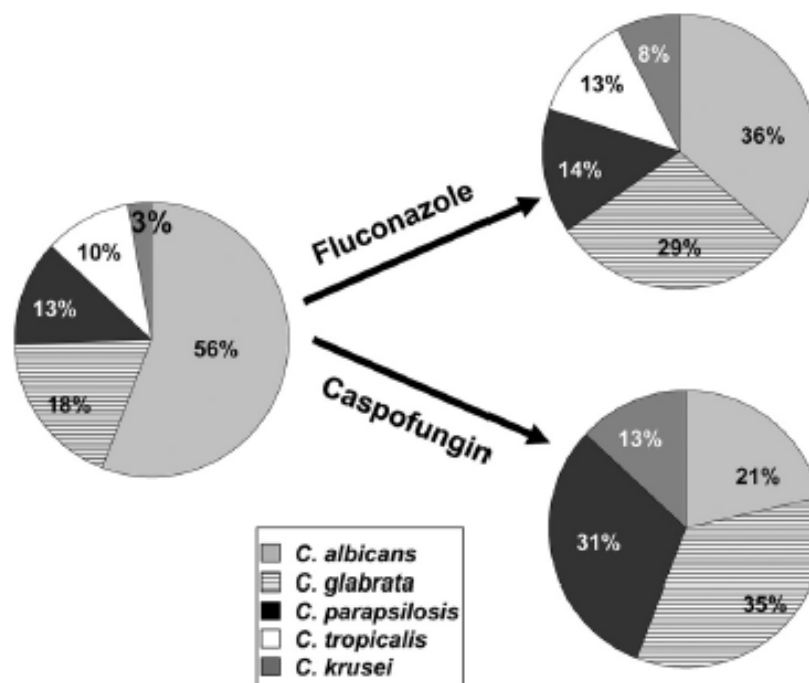
Recent Exposure to Caspofungin or Fluconazole Influences the Epidemiology of Candidemia: a Prospective Multicenter Study Involving 2,441 Patients[▽]

Olivier Lortholary,^{1,2,3} Marie Desnos-Ollivier,^{1,2} Karine Sitbon,^{1,2} Arnaud Fontanet,⁴ Stéphane Bretagne,^{1,2,5} Françoise Dromer,^{1,2*} and the French Mycosis Study Group†

Institut Pasteur, Unité de Mycologie Moléculaire, Centre National de Référence Mycologie et Antifongiques, Paris,¹ CNRS URA3012, Paris,² Université Paris Descartes, Service des Maladies Infectieuses et Tropicales, Centre d'Infectiologie Necker-Pasteur, Hôpital Necker-Enfants Malades, APHP, Paris,³ Institut Pasteur, Unité d'Epidémiologie des Maladies Emergentes, Paris,⁴ and Laboratoire de Parasitologie-Mycologie, Université Paris-Est, and

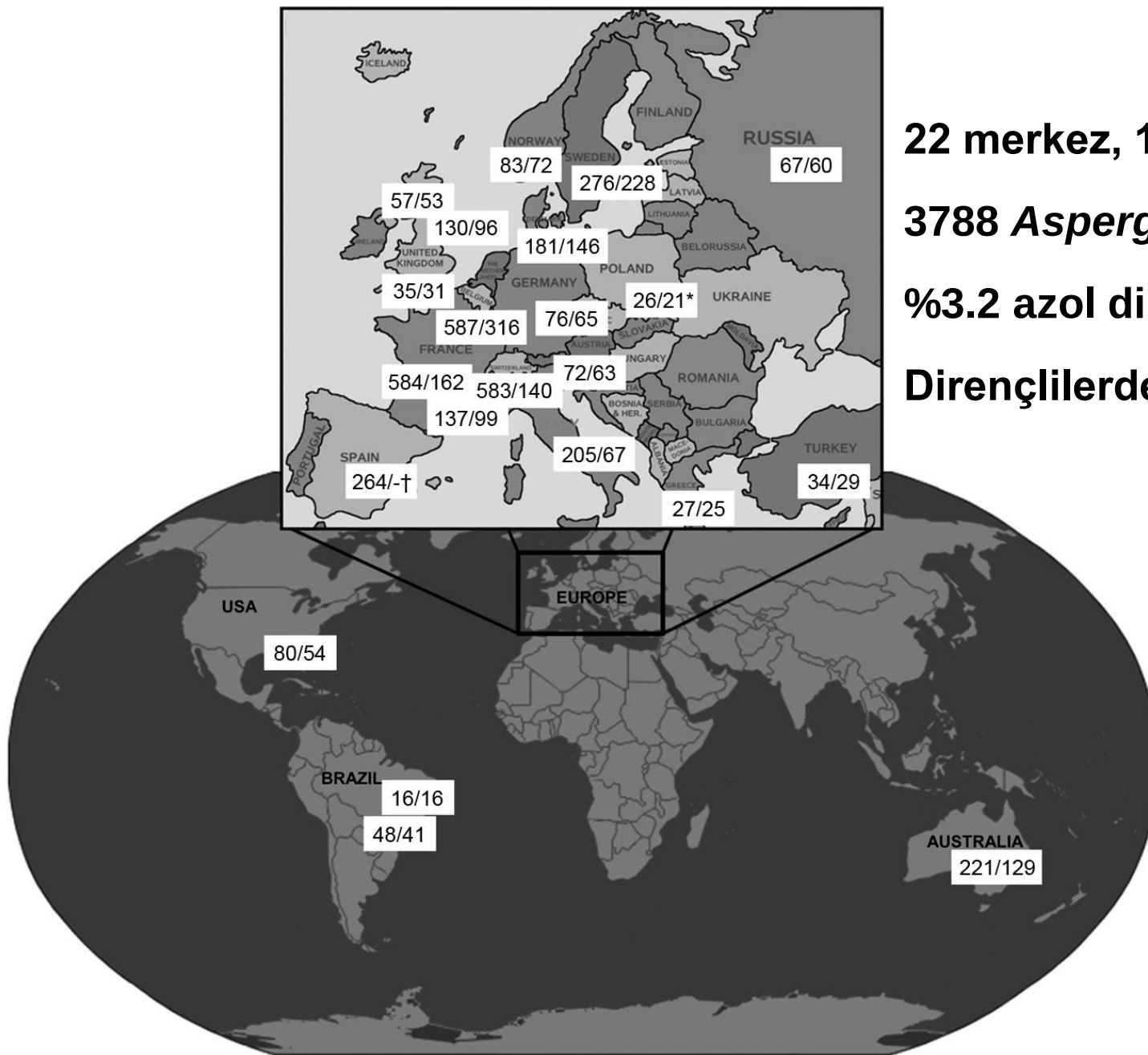
Received 1

A prospective study in Paris, France, area surgery) or age (ad 2,441 patients. Certain methodology were p antifungal drugs. We on the proportions decreased prevalence the former and *C. p* multivariate analysis independently asso 1.39 to 4.31; $P = 0.0$ while the risk of bei associated with an : caspofungin (OR = recommendations for the



ber 2010

implemented in the hematology, and over 7 years from ing the EUCAST been treated with ofungin ($n = 61$) associated with a α and *C. krusei* for $P = 0.001$). In the to fluconazole was e interval [CI] = 0.3, 13; $P < 0.001$), was independently recent exposure to nce future recom-

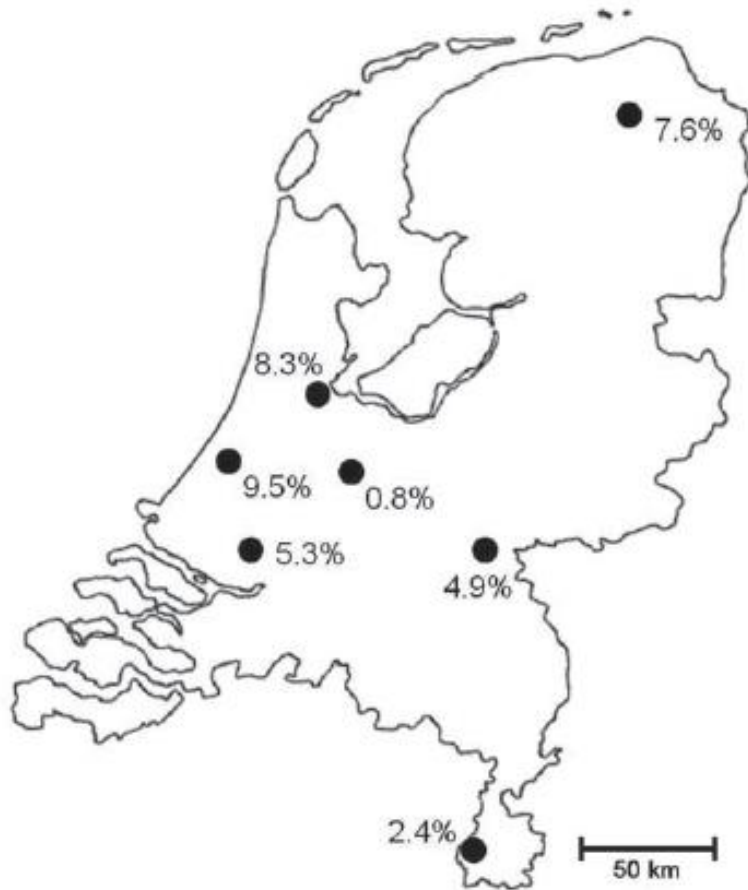


22 merkez, 19 ülke

3788 *Aspergillus* suşu

%3.2 azol direnci

Dirençlilerde fatalite %70



Azol direnci %5.3

TR/L98H mutasyonu

Hastaların çoğu azol naiv

Sürveyans !!!

Triazole Fungicides Can Induce Cross-Resistance to Medical Triazoles in *Aspergillus fumigatus*

Eveline Snelders^{1,3,9}, Simone M. T. Camps^{1,3,9}, Anna Karawajczyk^{2,10}, Gijs Schaftenaar², Gert H. J. Kema⁵, Henrich A. van der Lee^{1,3}, Corné H. Klaassen⁴, Willem J. G. Melchers^{1,3}, Paul E. Verweij^{1,3*}

1 Department of Medical Microbiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, **2** Center for Molecular and Biomolecular Informatics, Nijmegen Center for Molecular Life Sciences, Nijmegen, The Netherlands, **3** Nijmegen Institute for Infection, Inflammation, and Immunity (N4i), Radboud University Nijmegen, Nijmegen, The Netherlands, **4** Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands, **5** Plant Research International, Wageningen University, Wageningen, The Netherlands

Abstract

Background: Azoles play an important role in the management of *Aspergillus* diseases. Azole resistance is an emerging global problem in *Aspergillus fumigatus*, and may develop through patient therapy. In addition, an environmental route of resistance development has been suggested through exposure to 14 α -demethylase inhibitors (DMIs). The main resistance mechanism associated with this putative fungicide-driven route is a combination of alterations in the *Cyp51A*-gene (TR₃₄/L98H). We investigated if TR₃₄/L98H could have developed through exposure to DMIs.

Methods and Findings: Thirty-one compounds that have been authorized for use as fungicides, herbicides, herbicide safeners and plant growth regulators in the Netherlands between 1970 and 2005, were investigated for cross-resistance to medical triazoles. Furthermore, CYP51 protein homology modeling and molecule alignment studies were performed to

CONCISE COMMUNICATION

Inappropriate Use of Antifungal Medications in a Tertiary Care Center in Thailand: A Prospective Study

Apisada Suteupvarnon, MD;
Anucha Apisarnthanarak, MD; Bernard Camins, MD;
Kristin Mondy, MD; Victoria J. Fraser, MD

The incidence and factors associated with inappropriate use of antifungal medications were studied in a Thai tertiary care center. The incidence of inappropriate antifungal use was 74% (in 42 of 57 patients). Isolation of *Candida* species from urine ($P = .004$) was a risk factor, whereas receipt of an infectious diseases consultation ($P = .004$) was protective.

Infect Control Hosp Epidemiol 2008; 29:370-373

(APACHE-II) score, and the antifungal agent prescribed, indication for antifungal prescription, request for infectious diseases consultation, appropriateness of antifungal use, and reasons for any inappropriate antifungal use. Through a review of the medical records, antifungal therapy was classified as empirical treatment for a suspected infection, prophylaxis for fungal opportunistic infection, or treatment for a documented fungal infection. All data were collected by one investigator (A.S.) and recorded into a data collection tool. The prescribing physicians were unaware that the study was being performed at the time of medical chart review. The hospital's institutional review board approved the study.

The criteria used to define the appropriateness of antifungal prescription were adopted from the current edition of *Principles and Practices of Infectious Diseases*.³ Specific use categories were modeled after those of Kunin et al.⁴ and were modified to fit local practices by an expert panel consisting of 3 infectious diseases physicians who were not directly in-



Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Mortalite ve morbiditeyi azaltmak

Maliyeti düşürmek

Yan etki gelişimini önlemek

Direnç gelişimini önlemek

- ✓ **Reçetelerin denetlenmesi**
- ✓ **Lokal rehberlerin oluşturulması**
- ✓ **Riskli gruplarda hızlı tanı testlerinin kullanılması**
- ✓ **İlaç düzeylerinin izlenmesi**
- ✓ **De-eskalasyon, ardışık tedavi**

Reçetelemenin denetlenmesi



Volume 31, Issue 7 July 2010, pp. 722-727

Cited by 20

[Get access](#)

Impact of Education and an Antifungal Stewardship Program for Candidiasis at a Thai Tertiary Care Center

Anucha Apisarntharak^(a1), Apiwat Yatraserit^(a1) and Linda M. Mundy^(a2) 

DOI: <https://doi.org/10.1086/653616> Published online: 01 January 2015

Abstract

Uygunsuz antifungal kullanım azalmış (%71-- %24)
Flukonazol kullanımı azalmış
Dirençli türler (*C. glabrata*, *C. krusei*) azalmış
Maliyet azalmış

Reduction in broad-spectrum antimicrobial use associated with no improvement in hospital antibiogram

Paul P. Cook^{1*}, Paul G. Catrou², John D. Christie^{1,2}, Pamela D. Young^{3†} and Ronald E. Polk⁴

¹*Division of Infectious Diseases, Department of Medicine, Brody School of Medicine at East Carolina University, Brody 3E-113, Greenville, NC 27858;* ²*Department of Pathology, Brody School of Medicine at East Carolina University, Greenville, NC 27858;* ³*University Health Systems of Eastern Carolina,*

Farmakolog ve infeksiyon hastalıkları uzmanı

Tüm antifungaller (flukonazol hariç)

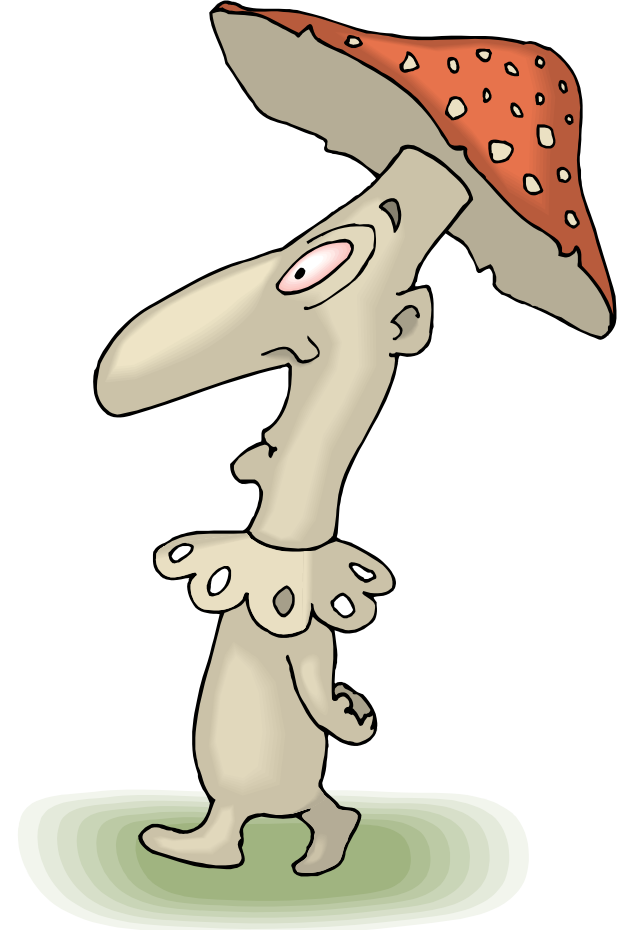
Uyum %90'ın üzerinde

Antifungal kullanımında %28 azalma

Hastane yatış süresi ve maliyette belirgin azalma



Tür tayini
Antifungal direnç
Sürveyans



İlaç Düzeylerinin İzlenmesi

- ✓ Özellikle çocuklarda, vorikonazol düzeyi (1-5.5 mg/L)
- ✓ 110 erişkin İFİ, karşılaştırmalı klinik çalışma
- ✓ İlaç düzeyi izlenen grupta;
 - yan etkiye bağlı ilaç kesme oranında azalma
 - klinik yanıt oranlarında belirgin artma

İlaç Düzeylerinin İzlenmesi

- ✓ Posakonazol düzeyi (1 mg/L) ??
- ✓ Serumdan alveoler hücrelere ve monositlere geçiş çok
- ✓ Oral biyoyararlanım, veriliş yolu, tedavi değişikliği gibi değişkenlerin doğru tanımlanmasında

Eđitim řart

İlaç özellikleri (FK, FD)

İlaç toksisiteleri

İlaç etkileřimleri

De-eskalasyon

Ardışık tedavi



İlaç etkileşimleri

- ✓ **Azoller ve immünsüpresif ilaçlar**
- ✓ **Azoller sitokrom P450 veya taşıyıcı P- glikoproteinlerin inhibisyonu**
- ✓ **Farmakolojik özellikler hakkında bilgi düzeyinin artırılması**
- ✓ **Organ fonksiyon takibi**
- ✓ **İlaç reçeteleyenlerin ve kullanıcıların eğitimi**
- ✓ **İlaç düzeylerinin takibi**



Rehberler

- ✓ **Pratik değil**
- ✓ **Uyum zor**
- ✓ **Hastalar kitap gibi olmuyor**
- ✓ **Kanıt düzeyleri ??**

Tarımda fungisid kullanımı kontrol altına alınmalı



A close-up photograph of a green leaf with a single water droplet about to fall from its tip. The droplet is captured mid-fall, creating a series of concentric ripples in a pool of water below. The background is a bright blue sky with soft, white clouds. The overall scene is clean and fresh, symbolizing nature and purity.

Antifungallere dođada ne oluyor?

Kurumlararası İşbirliđi ve Ulusal Politikalar



Antifungal tüketim oranları

Riskli gruplarda İFİ sıklığı

İFİ tedavi oranları

Direnç oranları

Maliyet analizleri

Yakın
izlem

Hızlı tanı testleri

Eczane uyarı sistemleri

Lokal rehberler ve akış şemaları

Eğitim programlarının düzenlenmesi

Antifungal reçetelerin denetlenmesi

Multidisipliner komitelerin oluşturulması



