Antifungal Yönetim (AFY)

Dr. Özlem Kurt Azap
Başkent Üniversitesi Tıp Fakültesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

Sunum Planı

- Antifungal Yönetim nedir? İhtiyaç var mı?
- Antimikrobiyal (Antibakteriyel) yönetimden farkları
- Antifungal kullanım nedenleri
- Kandida enfeksiyonlarında AFY
- Özet

Antifungal yönetim (AFY) nedir?

- Uygun endikasyon
- Uygun ilaç
- Uygun doz
- Uygun yol
- Uygun süre

- **Tanı yöntemleri**nin uygun kullanılması
- **Kesin tanı**ya ulaşma sıklığının artması
- İlaç kullanımının azalmasına bağlı **yan etkilerin azalması**
- Tedavi modifikasyonu **ile yatış süresinde kısalma**
- Maliyette azalma

MANTARLAR…

- Dünyadaki mantar türü sayısı: **5 milyon**
- Tanımlanmış olan tür sayısı: **120 bin**
- İnsanda hastalık yapan tür sayısı: **300**
- Hastalık etkeni olarak sık görülen tür sayısı: **20-25**

2000'li yılların başında HIV/AIDS hastalarında
yılda 1 milyon dissemine kriptokok enf. görülmekte;
600 bin olgu kaybedilmekte idi

Park, B. J. *et al*. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS* **23**, 525–530 (2009).

Sık görülen invaziv fungal enfeksiyonlar

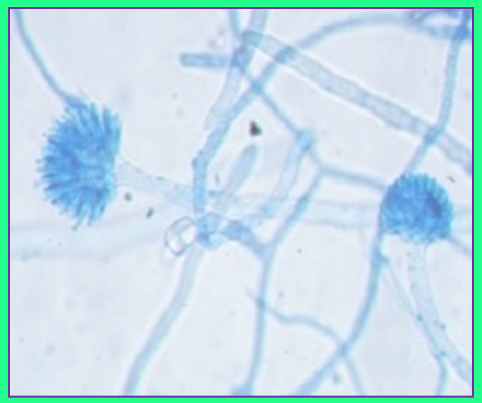
Table 1 | **Common invasive fungal diseases**

Disease	Fungal species	Clinical outlook	Treatment options (in order of preference)	Areas for improvement
Dimorphic mycoses	• *Blastomyces dermatitidis* • *Coccidioides immitis* • *Coccidioides posadasii* • *Histoplasma capsulatum* • *Sporothrix* spp.	• Geographically restricted • Infect both immunocompetent and immunosuppressed individuals	Azoles > polyenes	• A vaccine would be welcomed and is in development • In need of more effective and oral agents, and better diagnostics for earlier identification
Disseminated cryptococcosis	• *Cryptococcus neoformans* • *Cryptococcus gattii*	• Even with ART, there are still many new cases • No new therapies in more than 25 years • Cryptococcal antigen levels are not used to monitor outcome • Differences in outcome correlate with health-care resource availability • IRIS and increased ICP have been associated with this infection and need to be managed	Amphotericin B in combination with 5-flucytosine > monotherapies	Need improved management of IRIS and ICP
Invasive aspergillosis	• *Aspergillus fumigatus* • *Aspergillus flavus* • *Aspergillus terreus* • *Aspergillus calidoutus*	• Increasing resistance to azoles • Early treatment or prevention is essential	Azoles > polyenes > echinocandins	• Genetic susceptibility needs to be defined • A biomarker that can be used for diagnosis and to monitor treatment outcome would be very useful
Invasive candidiasis	• *Candida albicans* • *Candida tropicalis* • *Candida glabrata* • *Candida parapsilosis* • *Candida krusei* • *Candida auris*	• High mortality attributable to infections • Drug resistance develops in pathogens • Requires early-stage treatment	Echinocandins > azoles > polyenes	• Need better integration of new diagnostic tools with specific treatment strategies • An agent with a new mechanism of action would be advantageous for treatment
Mucormycosis	• *Rhizopus* spp. • *Mucor* spp. • *Cunninghamella bertholletiae*	• Control underlying diseases, initiate polyene therapy and consider surgery • Poor prognosis	Polyenes > azoles	• Improved diagnostics to ensure early, accurate diagnosis • Empiric therapy is not often successful

ART, antiretroviral therapy; ICP, intracranial pressure; IRIS, immune reconstitution inflammatory syndrome.

AFY programlarına ihtiyaç var mı?

- Sağlık hizmeti ilişkili enfeksiyonların **%15**'ini fungal enfeksiyonlar oluşturmakta



  - Kandidiyazis: %70-90
  - Aspergillozis: %10-20

- Mortalite yüksek (%40-%70)

AFY programlarına ihtiyaç var mı?

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)†

➢ Uygun OLMAYAN antifungal kullanım oranı çok yüksek

Table 4. Adequacy of antifungal therapy for different indications

	Prophylaxis ($n=15$)	Empirical ($n=42$)	Pre-emptive ($n=20$)	Tailored ($n=20$)	Overall ($n=100$)
Score, mean ± SD	9.1 ± 1.3	6.6 ± 2.7	8.3 ± 2.2	9.5 ± 1.9	7.7 ± 2.6
Inappropriate prescription, *n* (%)	6 (40)	33 (78.6)	10 (50)	5 (25)	57 (57)
Reason for inappropriate prescription, *n* (%)					
no microbiological adjustment	1 (6.7)	21 (50.0)	7 (35.0)	3 (15.0)	35 (35.0)
inappropriate antifungal selection	1 (6.7)	20 (47.6)	3 (15.0)	4 (20.0)	31 (31.0)
inappropriate duration	2 (13.3)	18 (42.9)	4 (20.0)	2 (10.0)	27 (27.0)
inappropriate administration route	1 (6.7)	12 (28.6)	4 (20.0)	3 (15.0)	20 (20.0)
unnecessary prescription (incorrect indication)	1 (6.7)	9 (21.4)	2 (10.0)	1 (5.0)	16 (16.0)
inappropriate dosage	2 (13.3)	9 (21.4)	2 (10.0)	1 (5.0)	16 (16.0)

J Antimicrob Chemother 2014; **69**: 1993–1999

AFY programlarına ihtiyaç var mı?

Antifungal stewardship in a tertiary-care institution: a bedside intervention

M. Valerio[1,2], P. Muñoz[1,2,3], C. G. Rodríguez[2,4], B. Caliz[4], B. Padilla[1], A. Fernández-Cruz[1], M. Sánchez-Somolinos[1], P. Gijón[1], J. Peral[5], J. Gayoso[6], I. Frias[7], M. Salcedo[8], M. Sanjurjo[2,4] and E. Bouza[1,2,3], on behalf of the COMIC Study Group (Collaborative group on Mycosis)

- YBÜ'de antifungal ilaç kullanımı %50 azalmış

TABLE 4. Impact of the antifungal stewardship on clinical and demographical characteristics

	Pre-AFS	During AFS			
	2010	2011	2012	2013	p
Candidaemia incidence/1000 admissions	1.49	1.76	1.44	1.14	0.08
Candidaemia albicans	0.87	0.83	0.67	0.48	**0.01**
Candidaemia parapsilosis	0.27	0.53	0.38	0.35	0.75
Candidaemia tropicalis	0.09	0.13	0.24	0.12	0.35
Candidaemia glabrata	0.16	0.19	0.16	0.08	0.29
Non-albicans *Candida*	0.62	0.93	0.77	0.66	0.97
Non-albicans *Candida* (%)	41.5	52.7	53.5	58.2	**0.05**
Fluconazole resistance in candidaemia (%)	6.1	4.3	4.2	3.6	0.53
Candidaemia-related mortality (%)	28.0	23.7	22.5	16.4	0.12

Significative p values are in bold.

Clin Microbiol Infect 2015; **21**: 492.e1–492.e9

Antifungal Direnç

(*Aspergillus fumigatus*'ta azol direnci)

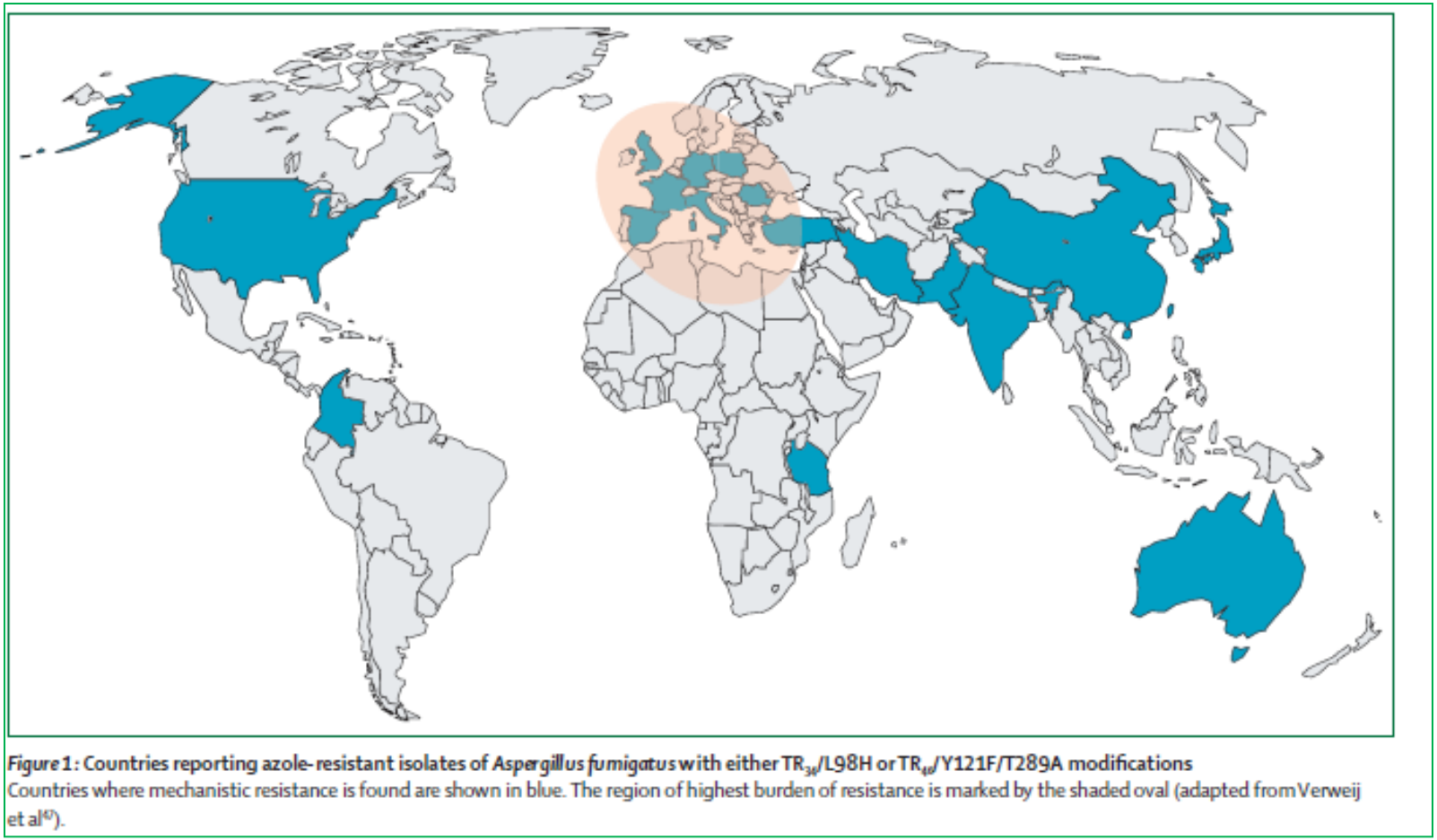


Figure 1: **Countries reporting azole-resistant isolates of *Aspergillus fumigatus* with either TR_{34}/L98H or TR_{46}/Y121F/T289A modifications**
Countries where mechanistic resistance is found are shown in blue. The region of highest burden of resistance is marked by the shaded oval (adapted from Verweij et al[47]).

Lancet Infect Dis 2017; 17: e383–92

Antifungal Direnç

(*Candida glabrata*'da antifungal direnç)

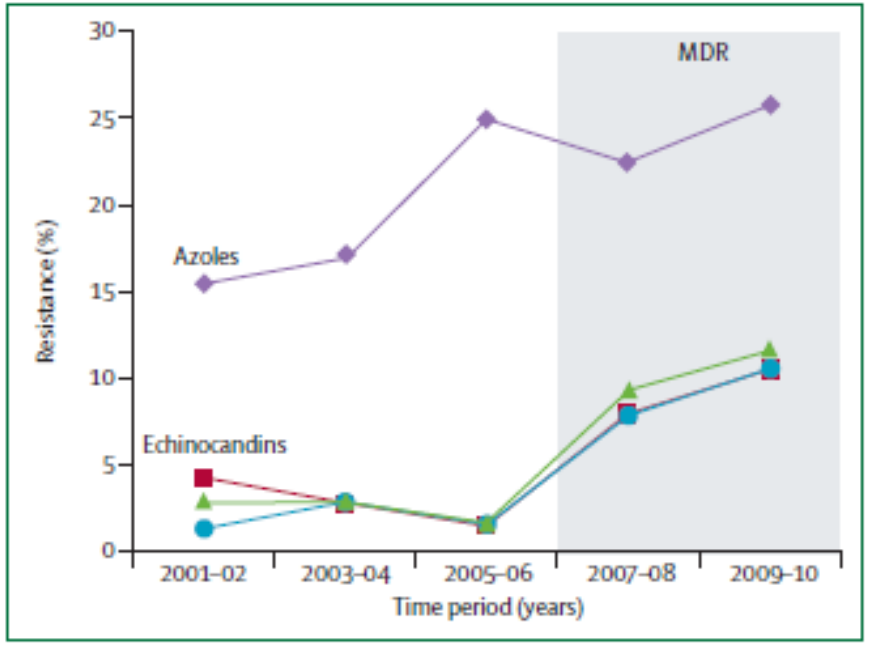
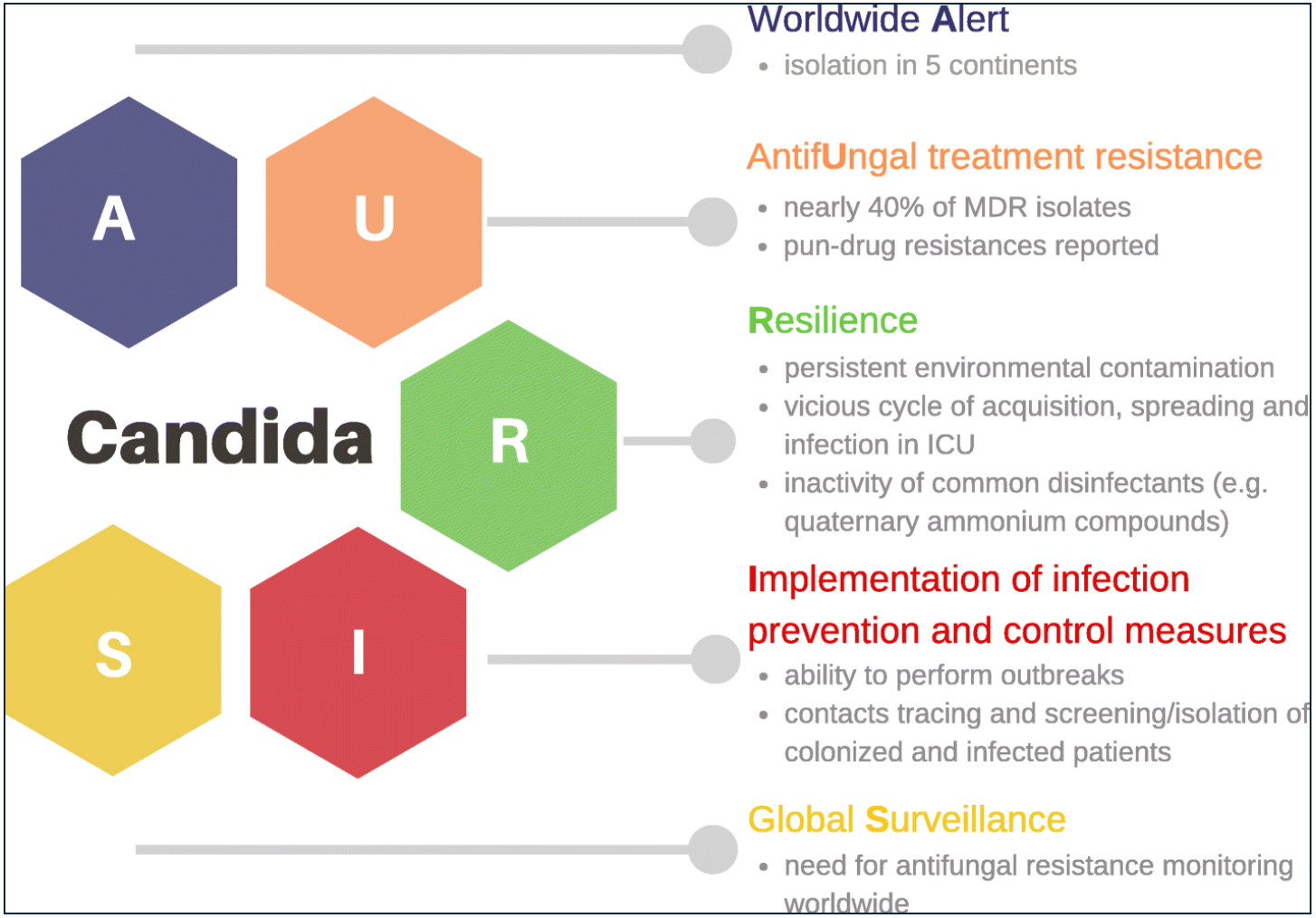


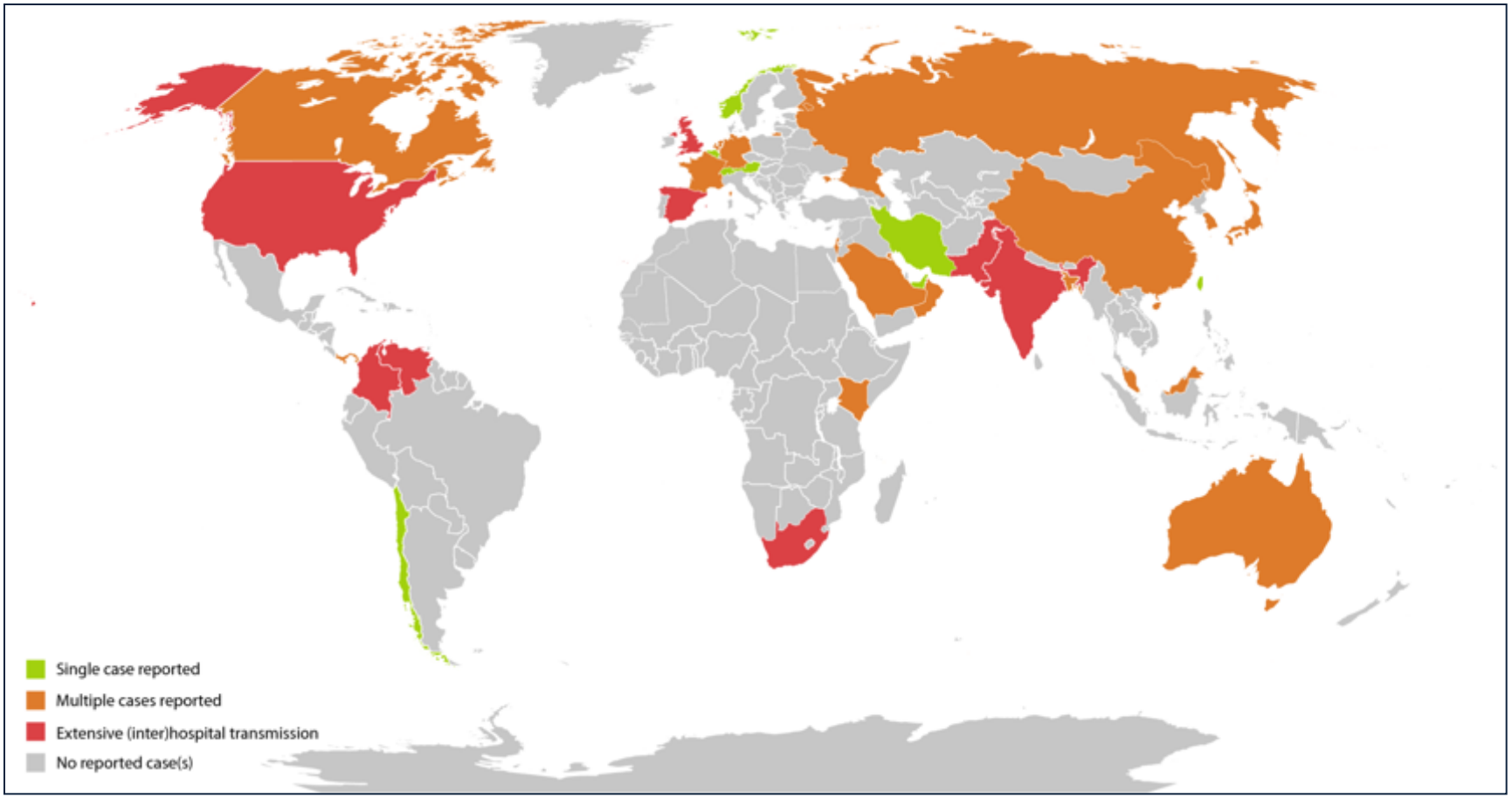
***Figure 3*: Parallel rise in azole and echinocandin resistance in *Candida glabrata* bloodstream isolates over a 10-year period, showing emergence of multidrug-resistant strains**

The grey-shaded box shows the time of emergence of substantial multidrug resistance. The three echinocandin-class drugs are shown: red, anidulafungin; green, caspofungin; blue, micafungin (adapted from Alexander et al[73]). MDR=multidrug resistance.

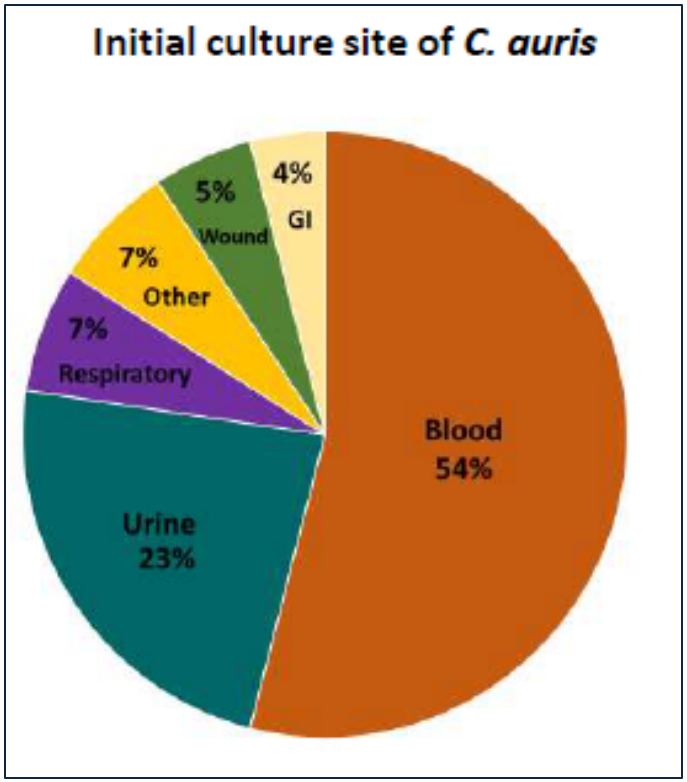
Candida auris

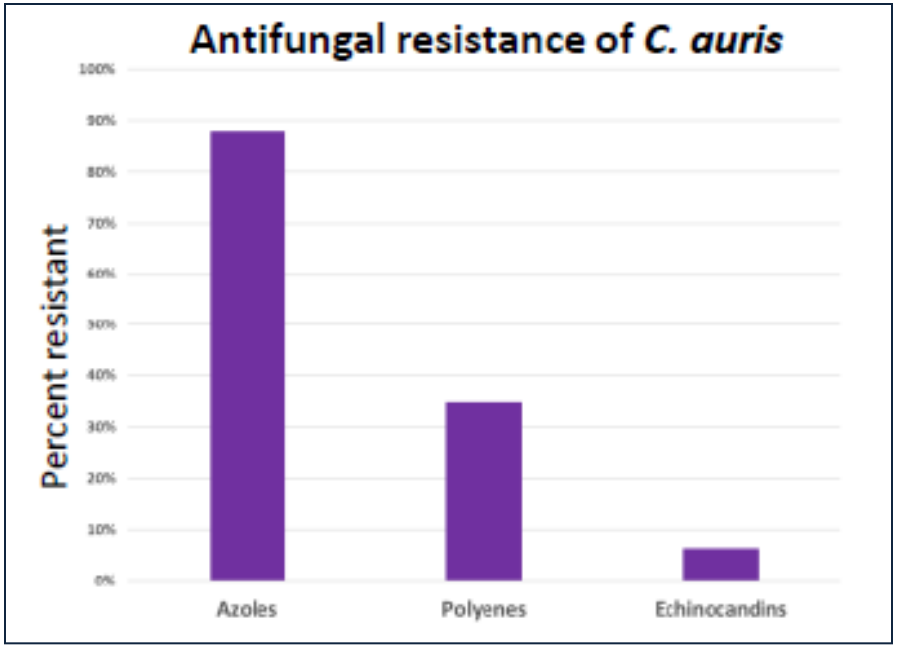


Candida auris



Candida auris-ABD olguları





CDC

Antifungaller

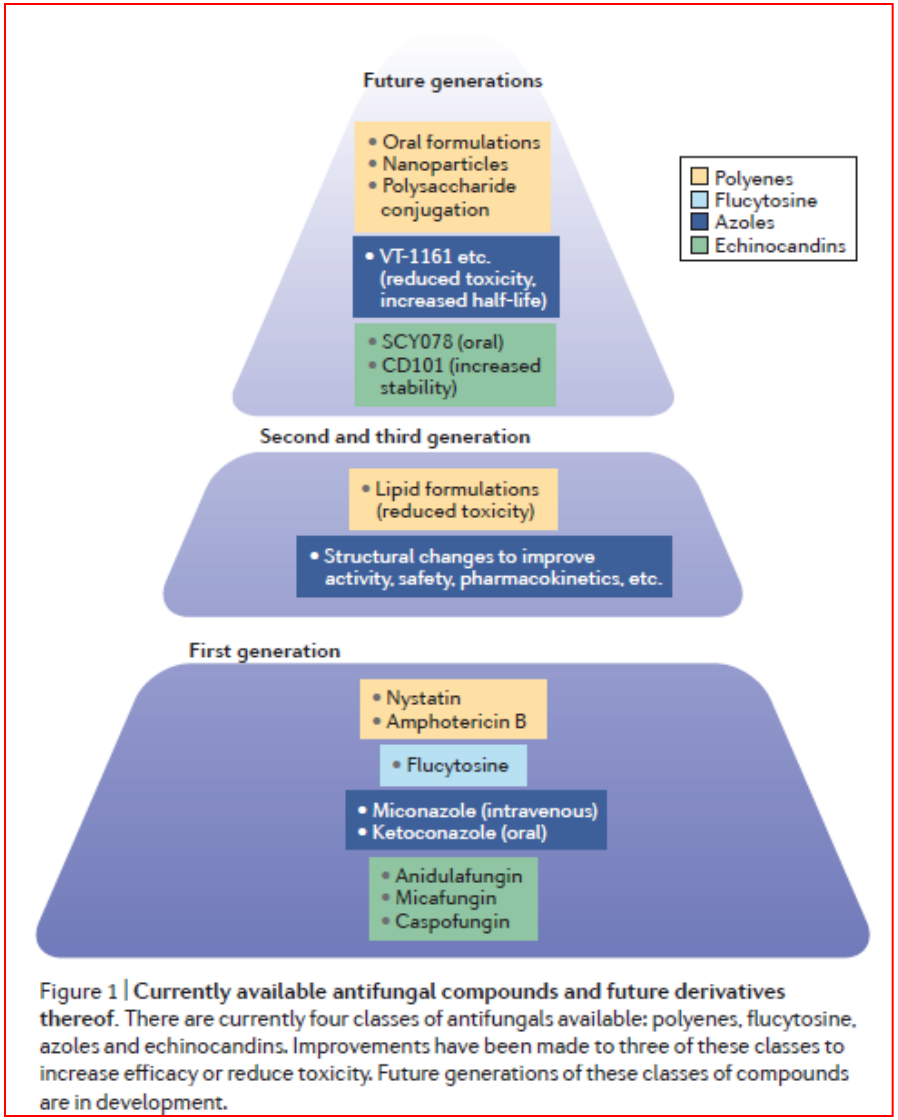


Figure 1 | **Currently available antifungal compounds and future derivatives thereof.** There are currently four classes of antifungals available: polyenes, flucytosine, azoles and echinocandins. Improvements have been made to three of these classes to increase efficacy or reduce toxicity. Future generations of these classes of compounds are in development.

Yeni Antifungaller

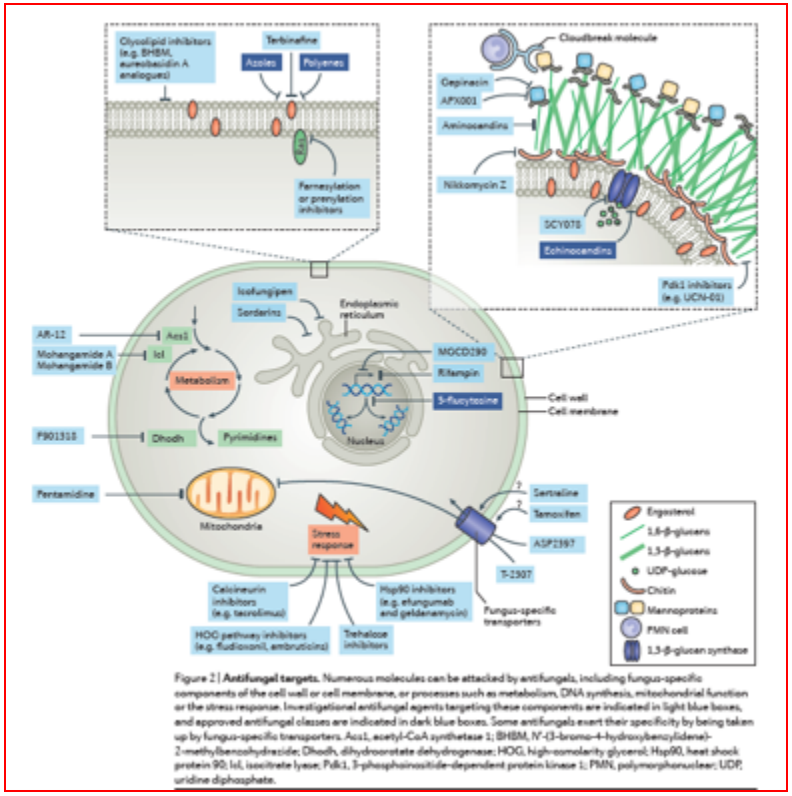


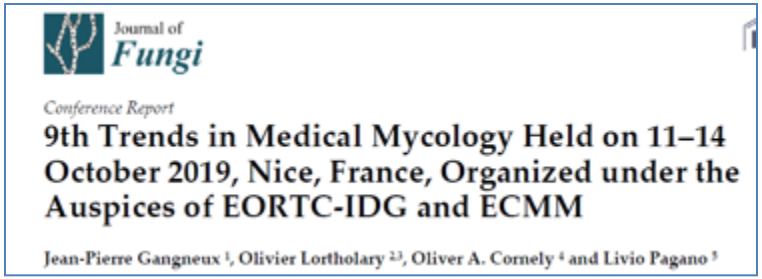
Figure 2 | **Antifungal targets.** Numerous molecules can be attacked by antifungals, including fungus-specific components of the cell wall or cell membrane, or processes such as metabolism, DNA synthesis, mitochondrial function or the stress response. Investigational antifungal agents targeting these components are indicated in light blue boxes, and approved antifungal classes are indicated in dark blue boxes. Some antifungals exert their specificity by being taken up by fungus-specific transporters. Acs1, acetyl-CoA synthetase 1; BHBM, *N*′-(3-bromo-4-hydroxybenzylidene)-2-methylbenzohydrazide; Dhodh, dihydroorotate dehydrogenase; HOG, high-osmolarity glycerol; Hsp90, heat shock protein 90; Icl, isocitrate lyase; Pdk1, 3-phosphoinositide-dependent protein kinase 1; PMN, polymorphonuclear; UDP, uridine diphosphate.

Table 2 | **Antifungal compounds with novel targets in development**

Compound	Molecular target	Target species or relevant disease	Development stage	ClinicalTrials.gov identifier or ref.
Unapproved compounds with novel structures				
APX001	Glycosyl phosphatidylinositol synthesis (prevents attachment of mannose proteins to the outer cell wall)	• Broad-spectrum potency against pathogens, including Mucorales order, *Candida* spp., *Aspergillus* spp., *Fusarium* spp. and *Scedosporium* spp. • Synergizes with approved antifungals	Phase I; phase II planned	NCT02957929 and NCT02956499
AR-12	• Probably blocks fungal acetyl-CoA synthetase 1 • Increases host immune response by downregulating host chaperone proteins	• *Cryptococcus neoformans* • *Candida albicans* • Mucorales order moulds • Hyalohyphomycosis, including those caused by *Fusarium* spp. and *Scedosporium* spp.	Completed phase I for oncology indications	NCT00978523
ASP2397	Unknown, but taken up by Sit1	• *Aspergillus fumigatus* • Some *Candida* spp. • *Fusarium* spp. • *Trichosporon* spp.	Preclinical but potentially approaching clinical studies	–
Aureobasidin A	Inositol phosphorylceramide synthase	Broad spectrum	Preclinical	–
Cloudbreak molecules (bispecific antibodies)	Binds to granulocytes and thereby concentrates the antifungal at the infection	Could have focused or broad-spectrum antifungal activity	Preclinical	–
Efungumab (also known as Mycograb)	Hsp90	*Candida* spp.	Phase II	NCT00324025 and NCT00047658
F901318	Dihydroorotate dehydrogenase	• *Aspergillosis* spp. • *Scedosporidium* spp.	Phase II	NCT02656186
Geldanamycin-like agents	Hsp90	Broad spectrum	Completed phase I for oncology indications	148
MOCD290	Hos2	• Broad spectrum • Synergizes with approved antifungals	Phase II	NCT01497223
Nikkomycin Z	Chitin synthase	• Coccidioidomycosis, histoplasmosis and blastomycosis • Synergizes with approved antifungals	Phase I	NCT00834184
T-2307	Mitochondrial membrane potential	• *Candida* spp. • *Cryptococcus* spp. • *Aspergillus* spp.	Phase I (see Further information for details)	–
Compounds that could be repurposed				
Cyclosporine, tacrolimus or rapamycin	mTOR or calcineurin	• Broad spectrum • To be used alongside existing antifungals	Approved for post-transplant immunosuppression	–
Rifampin	RNA polymerase	• Broad spectrum • To be used alongside existing antifungals	Approved for bacterial infections	–
Sertraline	Serotonin reuptake	• Cryptococcal meningitis • To be used alongside existing antifungals	Approved for depression	–
Tamoxifen	Oestrogen receptor	• Cryptococcosis • To be used alongside existing antifungals	Approved for oestrogen receptor-positive breast cancer	–
Verapamil	Calcium channel	• Broad spectrum • To be used alongside existing antifungals	Approved for cardiac conditions (including hypertension and arrhythmias)	–

Hos2, histone deacetylase 2; Hsp90, heat shock protein 90; mTOR, mechanistic target of rapamycin; Sit1, siderophore iron transporter 1.

Yeni Antifungaller



Journal of *Fungi*

Conference Report

9th Trends in Medical Mycology Held on 11–14 October 2019, Nice, France, Organized under the Auspices of EORTC-IDG and ECMM

Jean-Pierre Gangneux [1], Olivier Lortholary [2,3], Oliver A. Cornely [4] and Livio Pagano [5]

Symposium 11 **The Antifungal Pipeline**

Chairs: David Denning, FECMM, United Kingdom & Oliver Cornely, FECMM, Germany

16:15 S11.1 Olorofim—A Novel Mould-Active Antifungal (F2G)
John Rex, FECMM, UK

16:40 S11.2 Fosmanogepix: A Novel, Broad Spectrum Antifungal Therapy in Clinical Development (Amplyx)
Michael Hodges, USA

17:05 S11.3 Ibrexafungerp (formerly SCY-078) (Scynexis)
David Angulo, USA

J. Fungi **2019**, *5*, 95

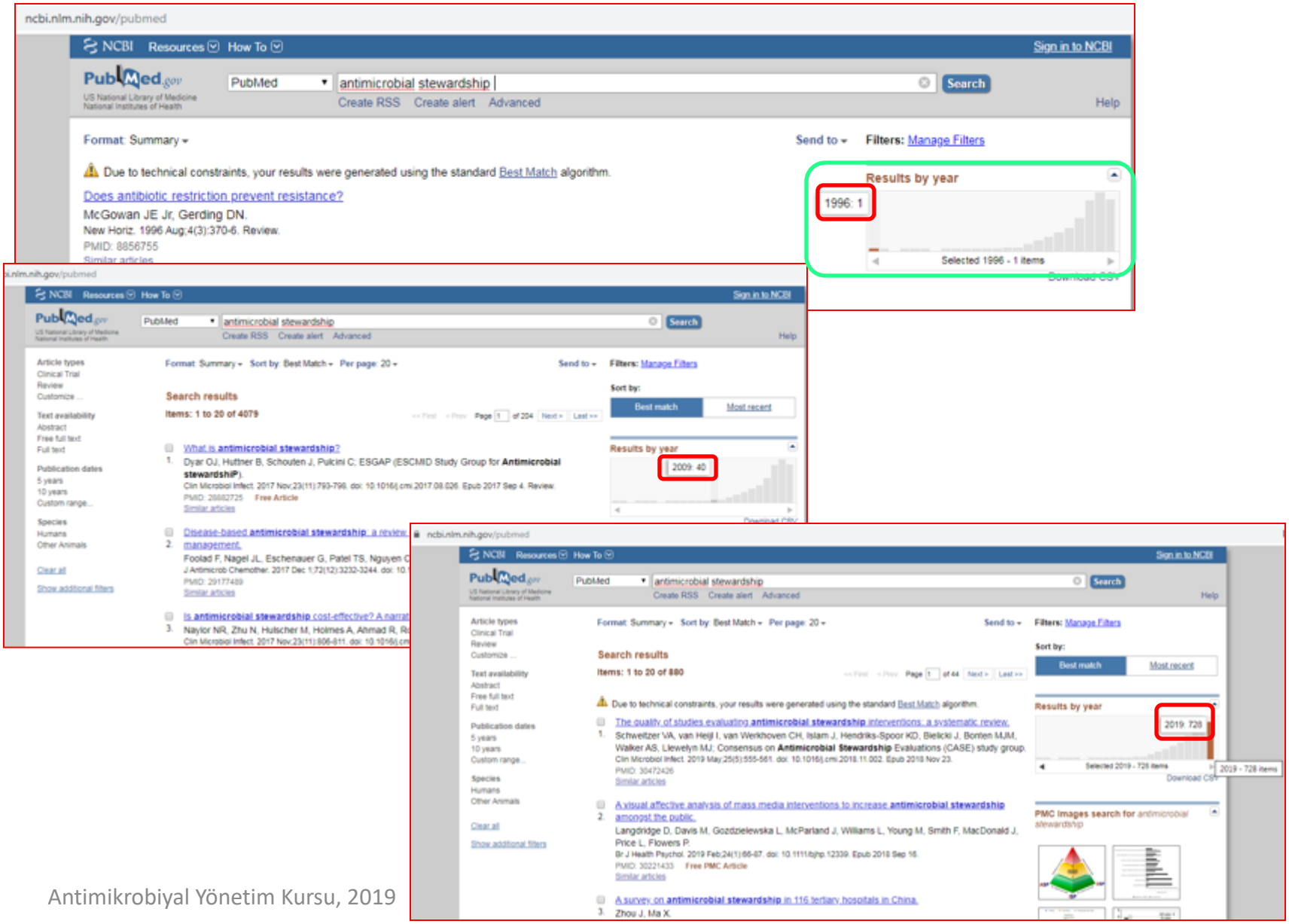
AFY programlarına ihtiyaç var mı?

EVET; çünkü

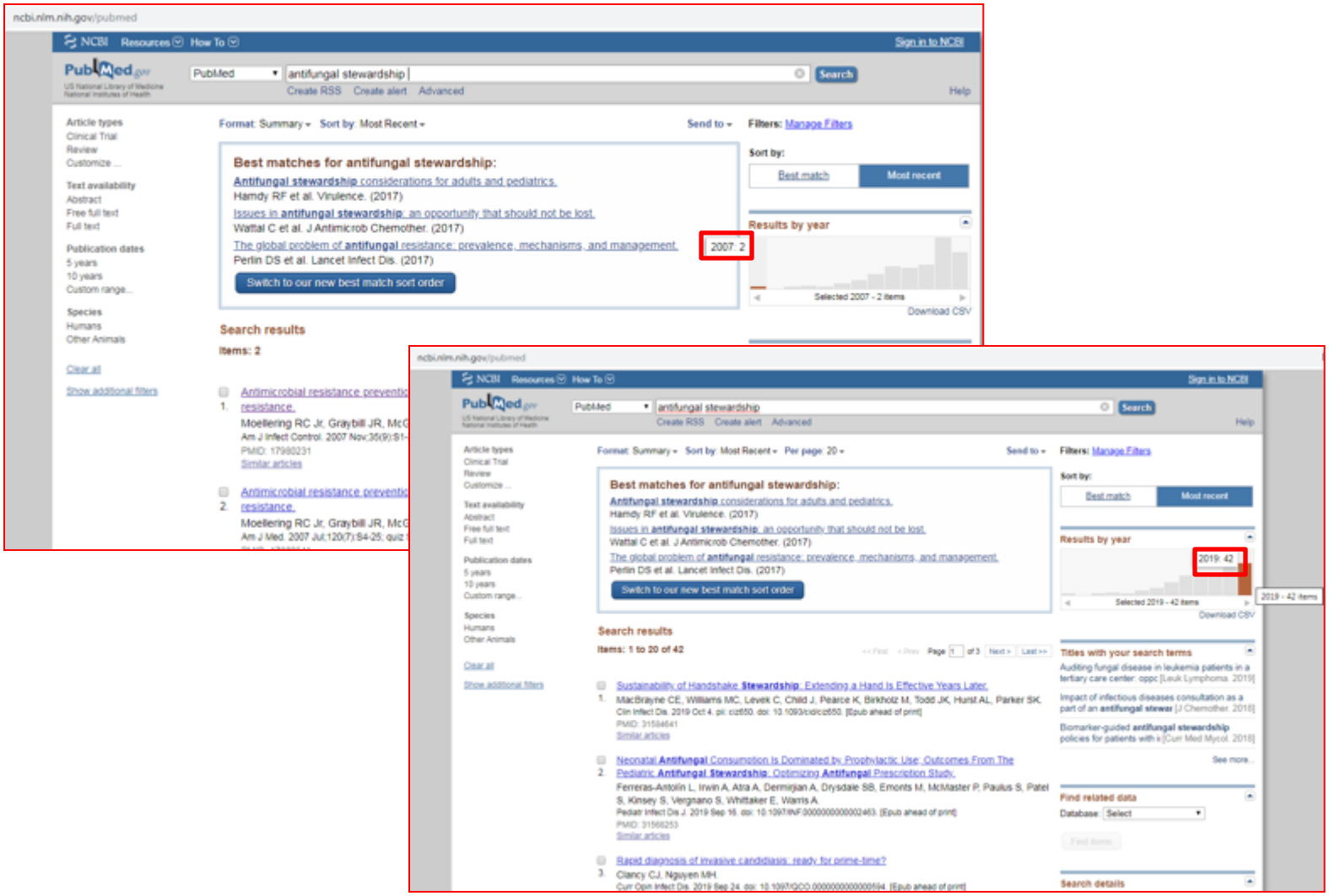
- Tanı olanakları kısıtlı (Mevcut yöntemler pahalı)
- Antifungal ilaç sayısı az
- Genellikle immünsüpresif hastalarda görülüyor, tedavide geç kalmamak gerekiyor
- İlaç seçimi konusunda ve tedavi süresi konusunda net olmayan konular var
- Mortalite yüksek
- Yan etkiler sık görülüyor
- İlaç etkileşimleri sık
- İlaçlar pahalı
- ....

Antimikrobiyal (Antibakteriyel) Yönetimden Farkları

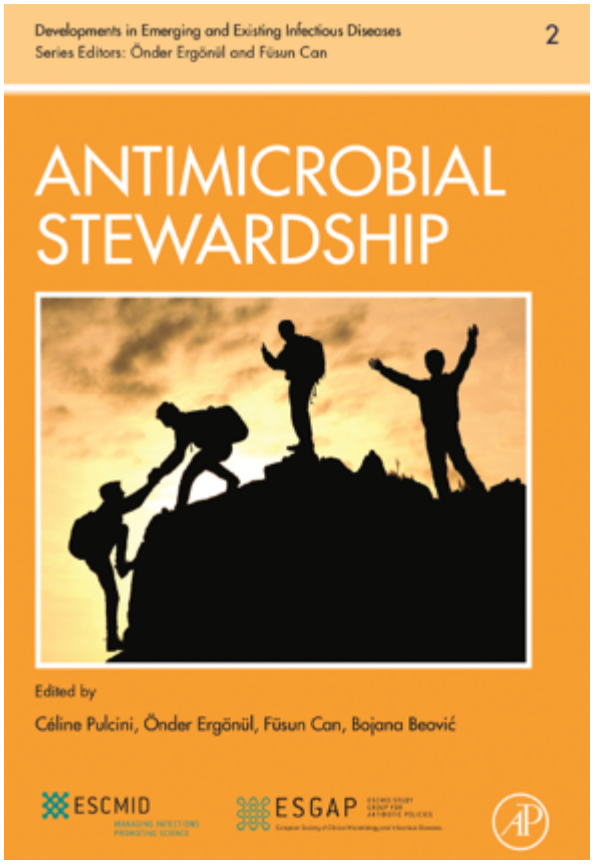
“Antimicrobial Stewardship” makalelerinin sayısı



“Antifungal Stewardship” makalelerinin sayısı



Yıl: 2017



Antibakteriyel İlaçlar

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2011, p. 71–109 Vol. 24, No. 1
0893-8512/11/$12.00 doi:10.1128/CMR.00030-10

Challenges of Antibacterial Discovery

Lynn L. Silver*
LL Silver Consulting, LLC, 955 S. Springfield Ave., Unit C403, Springfield, New Jersey 07081

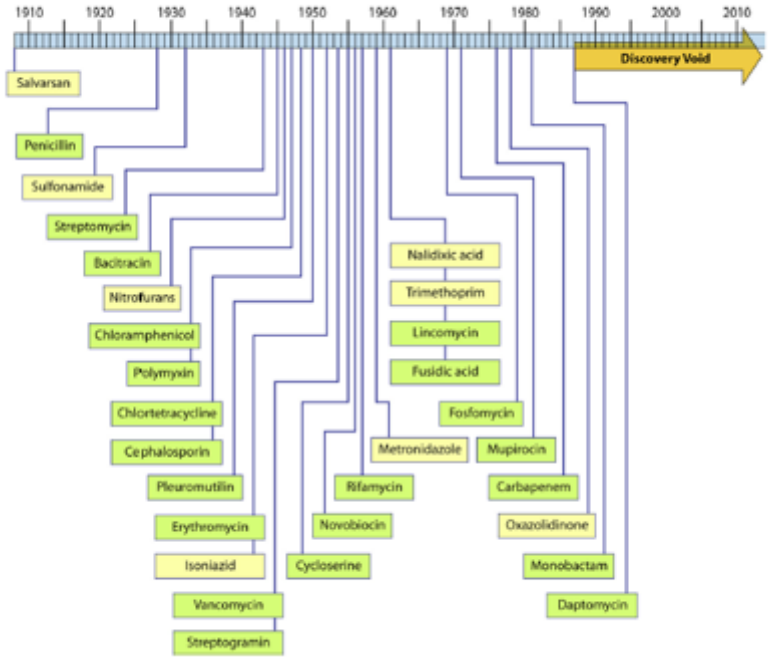
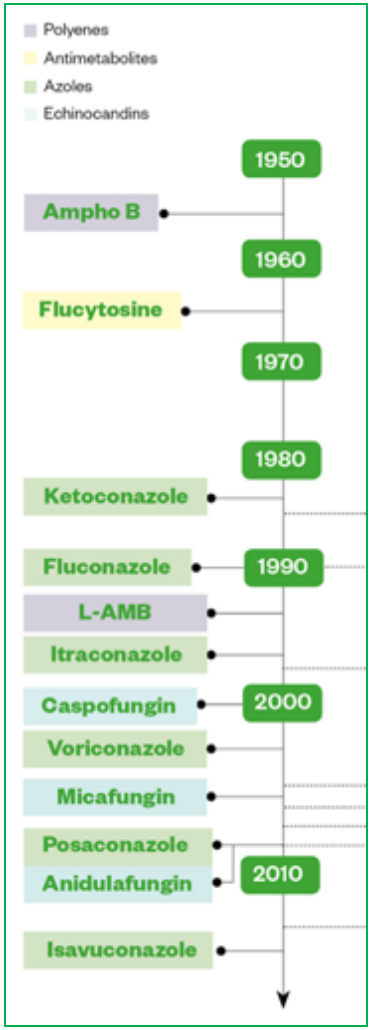


FIG. 1. Illustration of the "discovery void." Dates indicated are those of reported initial discovery or patent.

Antifungal İlaçlar



DSÖ- Öncelikli Patojen Listesi

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

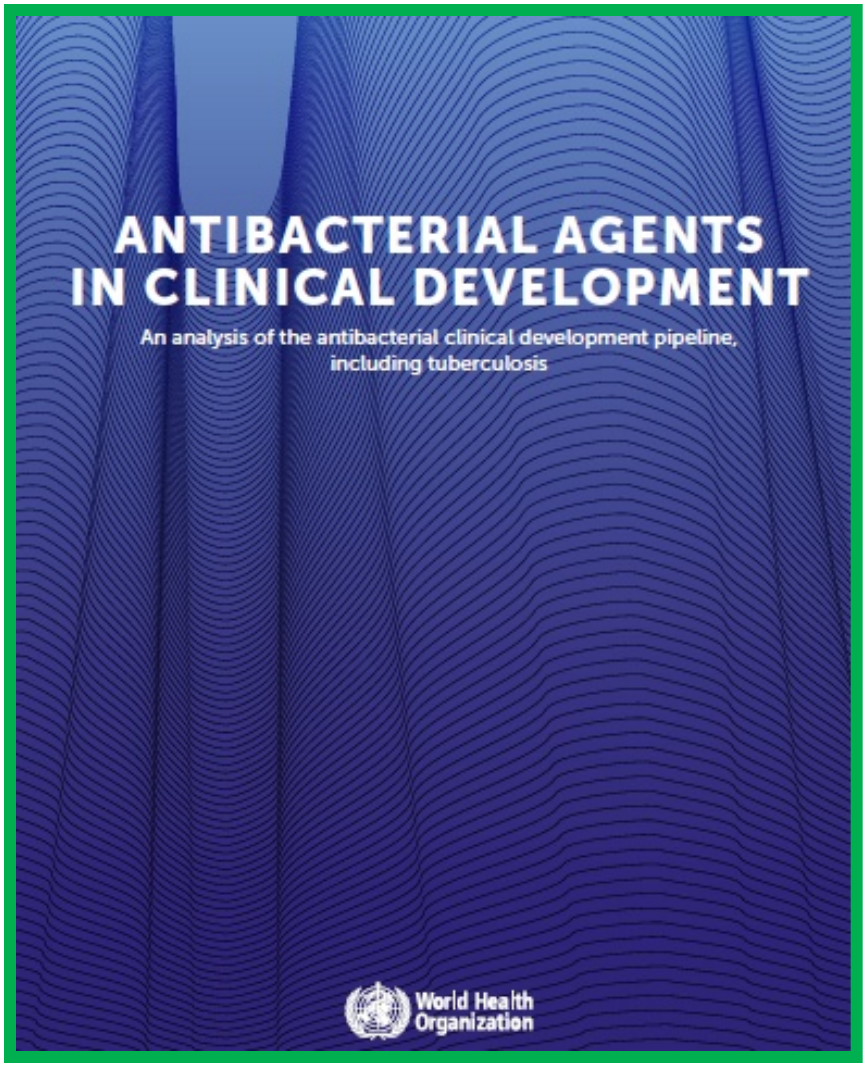
Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant



AMY-AFY Farkları

	AMY	AFY
Hastane uygulamaları	Yaygın	Yaygın değil
Hasta grubu	Ayaktan hastalar, hastanede yatan hastalar	Genellikle hastanede yatan hastalar
Tanıya ilişkin	CRP Prokalsitonin Kültür: Daha erken sonuç elde edilir	Beta D glukan Galaktomannan Bilgisayarlı tomografi Kültür: Erken sonuç elde etmek zor Derin yerleşimli olduğu durumda daha zor
Duyarlılık testleri	Standardize edilmiş durumda	Geliştirilmeye çalışılıyor
Profilaktik yaklaşım	Belirlenmiş	Tam olarak belirlenmiş değil
Tedavi konusunda görüş birliği	Genellikle var	Henüz tam bir görüş birliği yok

Gelir düzeyi düşük olan ülkelerde antimikrobiyal direnç ile mücadele

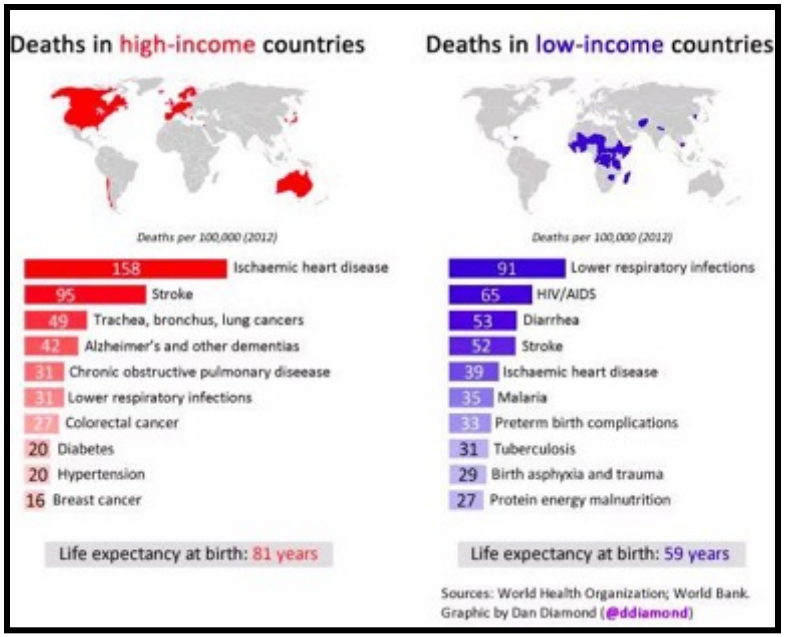
Clinical Infectious Diseases
VIEWPOINTS

Combating Global Antibiotic Resistance: Emerging One Health Concerns in Lower- and Middle-Income Countries

Maya Nadimpalli,[1] Elisabeth Delarocque-Astagneau,[1] David C. Love,[2] Lance B. Price,[3] Bich-Tram Huynh,[1] Jean-Marc Collard,[4] Kruy Sun Lay,[5] Laurence Borand,[6] Awa Ndir,[7] Timothy R. Walsh,[8] and Didier Guillemot[1]; for the Bacterial Infections and antibiotic-Resistant Diseases among Young children in low-income countries (BIRDY) Study Group[9]

[1]Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases Unit (B2PHI), Inserm, Université de Versailles Saint-Quentin-en-Yvelines (UVSQ), Institut Pasteur, Université Paris-Saclay, France; [2]Center for a Livable Future, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [3]Milken Institute School of Public Health, George Washington University, Washington, District of Columbia; [4]Experimental Bacteriology Unit, Institut Pasteur of Madagascar, Antananarivo; [5]Food Microbiology and Water Analysis Laboratory and [6]Epidemiology and Public Health Unit, Institut Pasteur of Cambodia, Phnom Penh; [7]Institut Pasteur of Senegal, Dakar; and [8]Department of Medical Microbiology and Infectious Disease, Institute of Infection and Immunity, Heath Park Hospital, Cardiff, United Kingdom

Antibiotic resistance is a global public health issue. The need for higher-income countries to support lower- and middle-income countries (LMICs) in identifying actionable strategies has been recognized by major global public health institutions, including the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) [1, 2]. Because of unique structural, cultural, and socioeconomic factors contributing to the development of antibiotic resistance, it is widely acknowledged that LMICs require different approaches compared with higher-income countries [3–5]. Specifically, LMICs are challenged to improve antibiotic access for therapeutic uses while minimizing antibiotic misuse that causes population-level resistance [6]. Balancing these issues is critical; more children in LMICs countries die from inadequate access to antibiotics each year than drug-resistant infections [3], yet resistance threatens the long-term viability of these drugs. Most LMIC-specific strategies to date have focused on reducing antibiotic misuse in the human health sector [3, 6]. These include antimicrobial stewardship education, strengthened hospital infection control, and increased surveillance of antibiotic use and resistance, as



Clinical Infectious Diseases® 2018;66(6):963–9

AFY programında önemli başlıklar

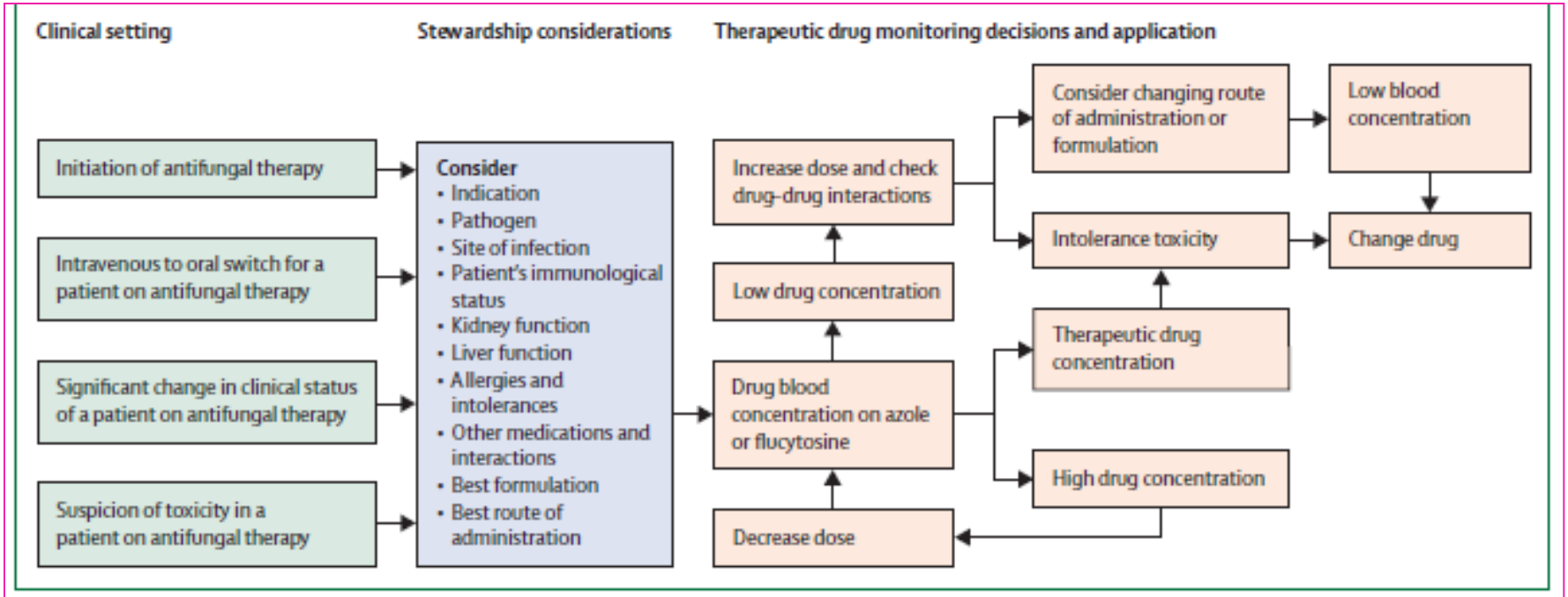


Figure 4: **Antifungal stewardship considerations and the use of therapeutic drug monitoring as a tool in antifungal stewardship programmes**
Therapeutic drug monitoring of itraconazole and voriconazole is required, and of posaconazole or isavuconazole, or both, is recommended.

AFY programında önemli başlıklar

Table 1. Key components of antifungal stewardship programmes

Key components	Considerations
Expert PPRF	Primary AFS intervention recommended Regular bedside reviews focussed on: Key treatment optimization time points (at commencement, key diagnostic results available, clinical response assessment) Application of diagnostic and dosing tools to optimize antifungal use Ideally performed by AFS team members including a clinical pharmacist, ID physician, and/or clinical microbiologist expert in IFD and antifungal management
Antifungal prescribing guidelines and education	Adapt evidence-based guidelines to local patient groups and fungal epidemiology Supported by experts performing PPRF who can individualize advice to patient complexities Targeted education and engagement of key prescribing groups
Fungal diagnostics and antifungal TDM	Consider accessibility, cost, and turnaround time of results Implementation should be supported by AFS team to direct appropriate test application and timely result interpretation to impact on patient outcomes and antifungal use Integrate use into management guidelines adapted to key patient groups (e.g. ICU, haematology, transplantation) to reinforce correct application of tests
Prescribing restrictions and preauthorization requirements	Effective at initially reducing antifungal usage Careful implementation required to avoid excessive delays in initiation of antifungals in high-risk patients Electronic prescribing or approval systems can support restrictions to avoid delays and notify AFS team of new prescriptions for review

AFS, antifungal stewardship; ID, infectious diseases; IFD, invasive fungal disease; PPRF, postprescription review and feedback; TDM, therapeutic drug monitoring.

Reçeteleme sonrası değerlendirme ve geri bildirim

Curr Opin Infect Dis 2018, 31:490–498

Antifungallerin **kantitatif** takibi

Table 2. Key antifungal stewardship metrics reported or proposed in antifungal audit and AFS literature

Antifungal quantitative metrics	Comments and limitations
DDD adjusted for bed occupancy (e.g. 1000-patient days) [2,14,32–34,36,42,43▪▪,44,67,68]	Antifungal drug acquisition costs and consumption are commonly used metrics Limitations: • Monitoring of costs only sensitive to prescribing changes of high-cost agents • Accuracy of consumption data limited outside electronic prescribing • Not indicative of prescribing quality
Prescribed daily doses adjusted for bed occupancy [42,69,70]	
DOT total and adjusted for bed occupancy [14,42,43▪▪]	
Length of therapy (i.e. course duration) [12,37]	
Total cost (antifungal acquisition costs) [2,32,33,35–37,42,43▪▪,68]	
Antifungal costs as a proportion of pharmacy budget [68]	
Potential cost savings (projected) [14,71]	

- İlaç tüketim miktarını takibi
- Yatış süresi
- Maliyet??
- ..

Antifungallerin **kalitatif** takibi

Antifungal quality metrics	
AFS activities: recommendations made ± acceptance rate of recommendations made [32,33,35,36,39]	Antifungal prescribing quality assessment is necessary to complement quantitative metrics Limitations: • Guideline adherence commonly used, however, recommendations are not always appropriate for patient complexities • No consensus method for evaluating antifungal prescribing appropriateness for benchmarking in AFS programmes • Labour-intensive process of evaluation and requires AFS resources often not available
Appropriateness: triazole antifungal quality prescribing indicators (proposed assessment tool) [72]	
Appropriateness: if no changes made by experts [32]	
Appropriateness: concordance with guidelines (proposed assessment tool) [73▪,74▪]	
Appropriateness: concordance with guidelines with expert assessment including indication, dose, DDIs [2,28,75–77]	
Appropriateness: concordance with guidelines with expert assessment including adjustment according to microbiology, IV to oral switch (assessment tool) [14,33]	
Appropriateness: assessment of individual DOT [14]	
Documentation of indication and/or treatment plan [42,78▪]	
Use of TDM for certain triazole AF dose optimization [36,42]	
De-escalation of EAFT [42]	
De-escalation to narrower spectrum [14,33]	
IV to oral switch when appropriate [14,33,71]	
Timeliness and completeness of fungal diagnostic and other investigations [36,38]	
Timeliness of appropriate AF [38]	
Use of first-line agents for IFD [36]	

- Antifungal kullanım uygunluğunun değerlendirilmesi
- Empirik tedavinin de-eskelasyonu
- Rehberlere uyumun izlenmesi
- .....

Ortak noktalar: **Süreç** ölçütleri

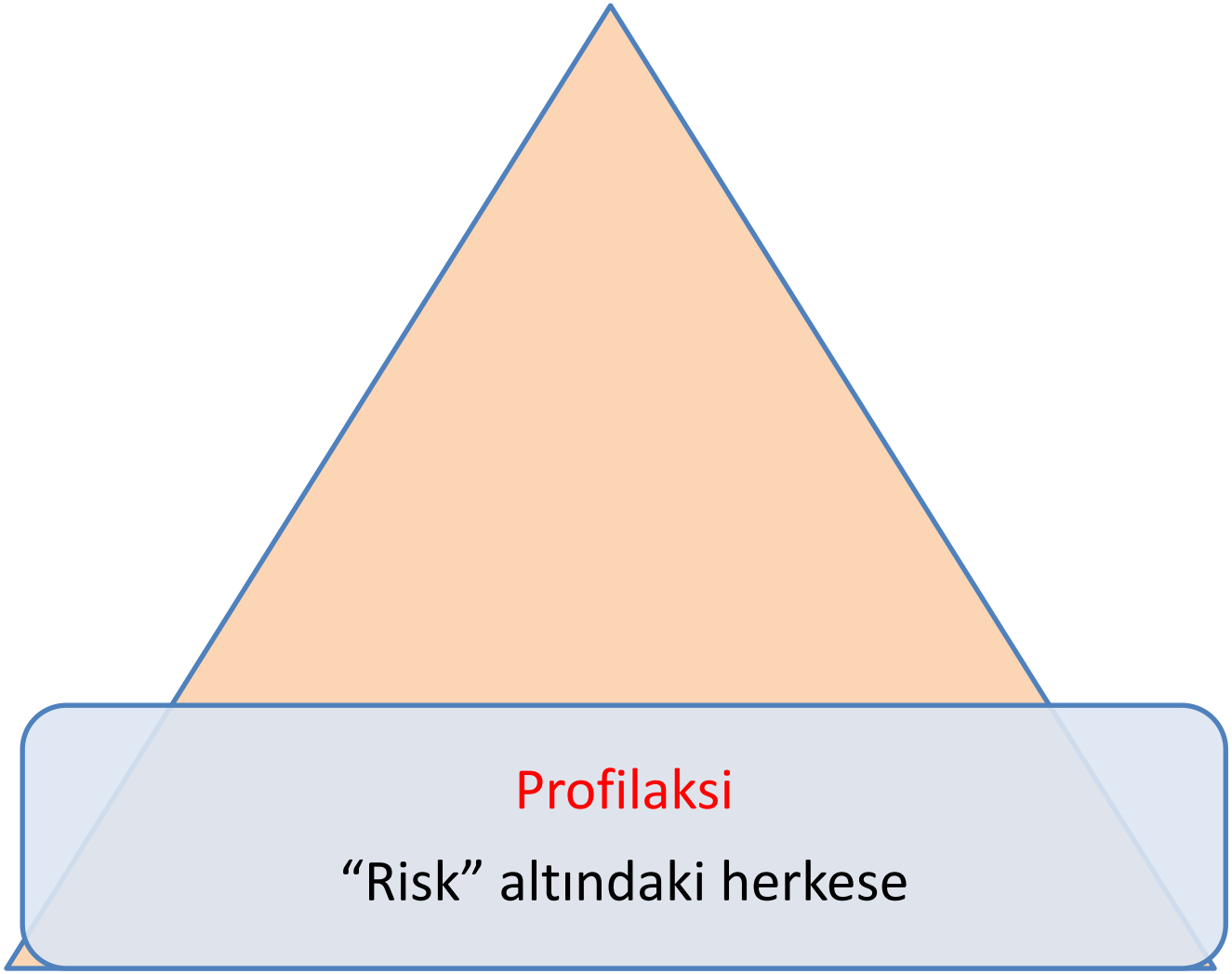
- **Fazladan** tedavi süresi
- Tedavi süresi
- Kurumdaki tedavi algoritmasına uyum oranları
- Laboratuvar sonuçlarına göre ilaç modifikasyon oranları
- Oral tedaviye geçen hasta oranları olarak sıralanabilir
- …..

Ortak noktalar: **Sonuç** ölçütleri

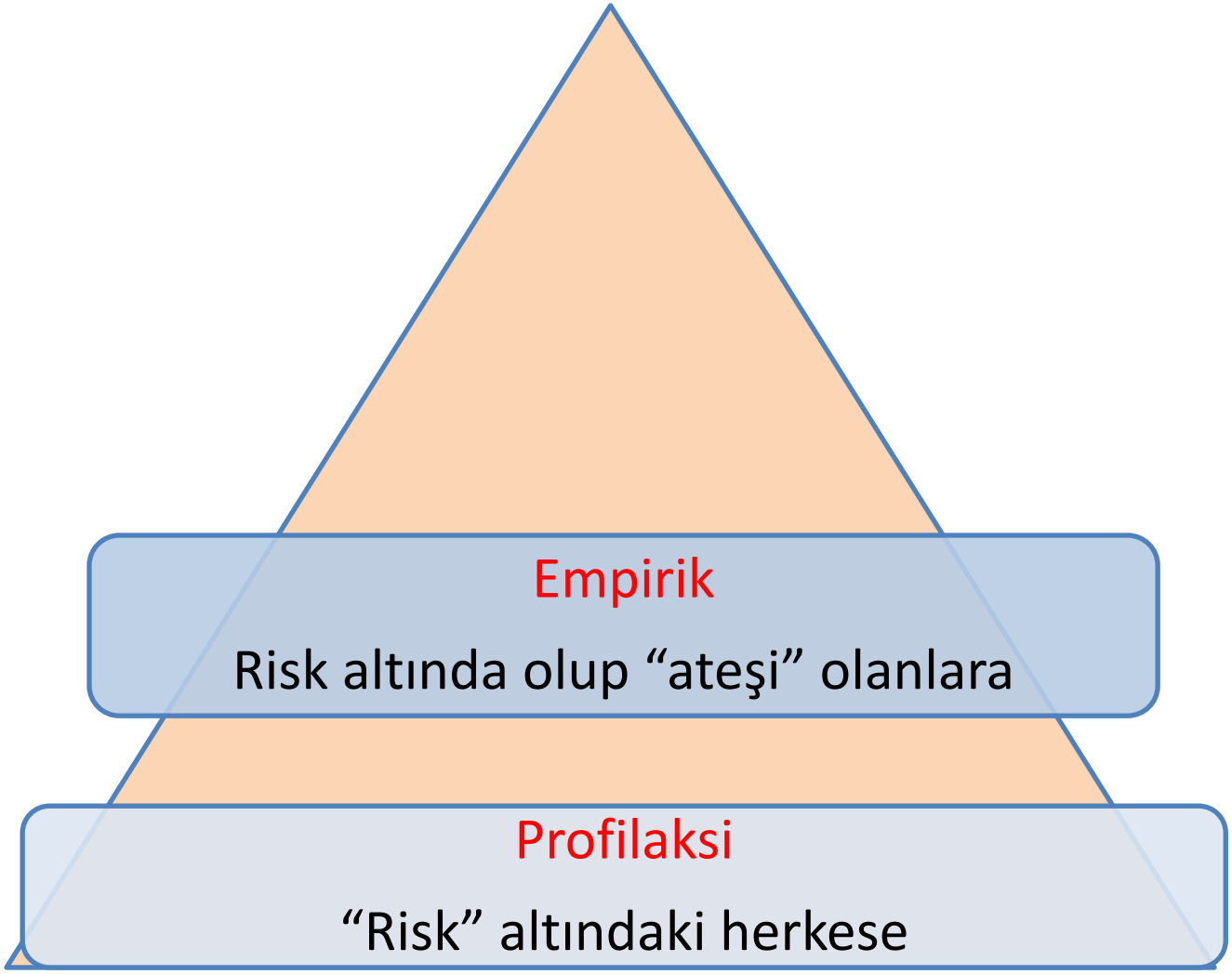
- Hastanede kalış süresi
- 30 günlük mortalite
- Tedavi yetersizliği, rekürrens..vb
- …..

Antifungal Kullanım Nedenleri

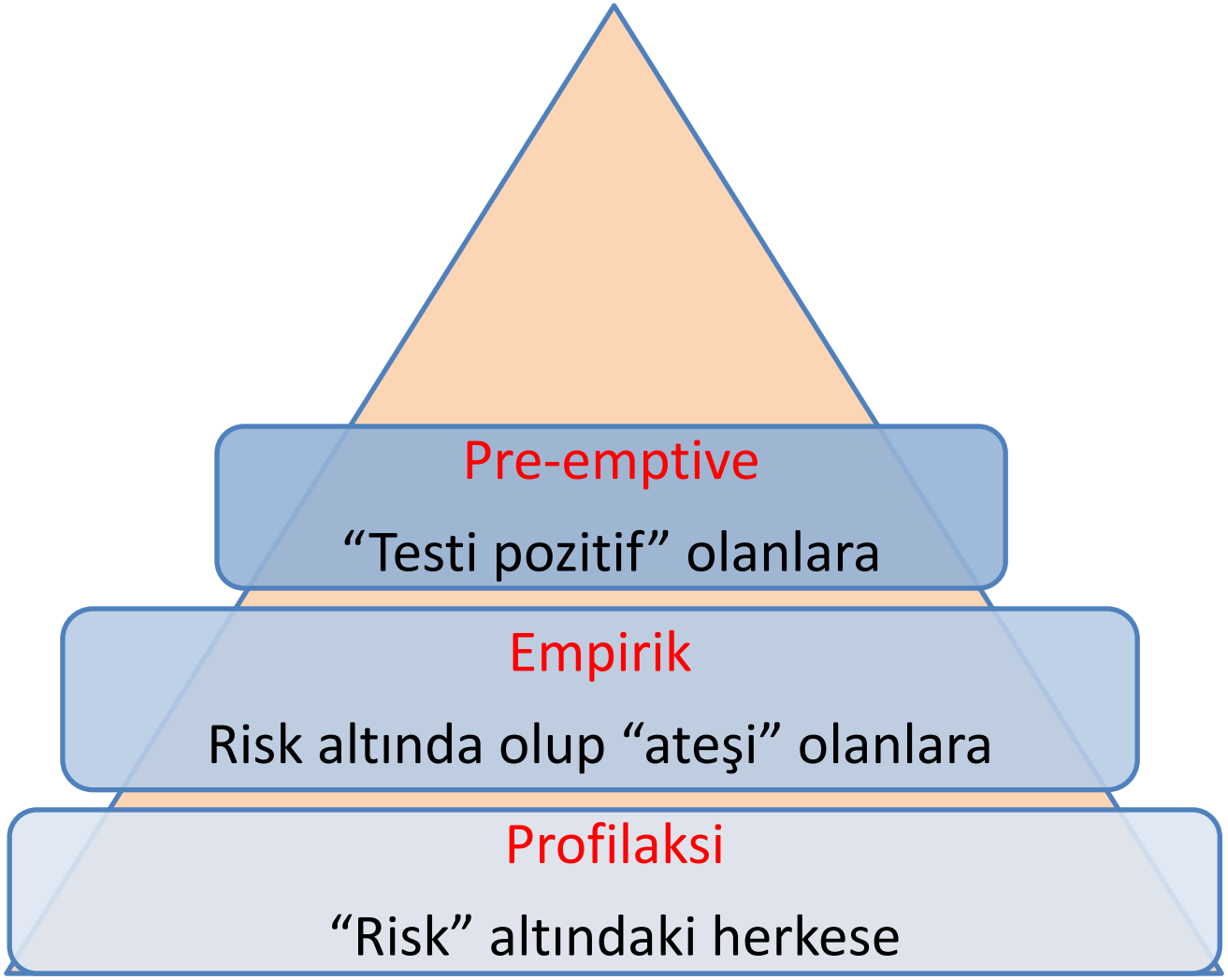
Antifungal kullanım nedenleri



Antifungal kullanım nedenleri



Antifungal kullanım nedenleri



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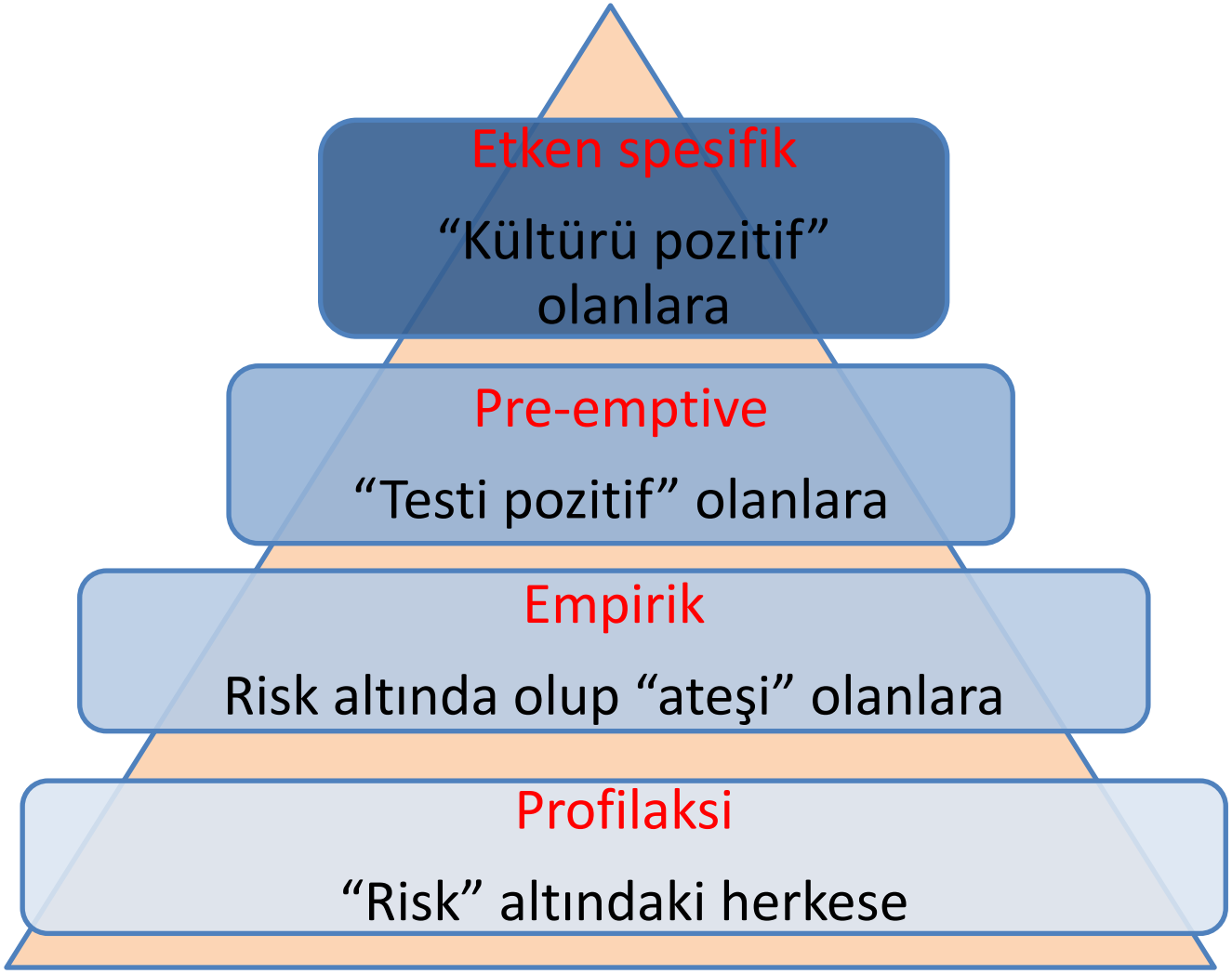


Kandida enfeksiyonlarında AFY

Sorular

- **Ne zaman antifungal başlamak gerekir?**

  Biyobelirteçler: Beta D glukan, mannan, anti-mannan
  Kandida kolonizasyon indeksi
  Kandida skoru
  Diğer ??

- **Hangi antifungali başlamak gerekir?**

  Flukonazol, kaspofungin, vorikonazol, lipozomal amfoterisin B

- **Hangi dozda? Hangi yolla?**

  Flukonazol 200 mg, 400 mg, 800 mg

- **Ne kadar süre kullanmak gerekir?**

- **…**

Clinical Infectious Diseases Advance Access published December 16, 2015

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

ESCMID PUBLICATIONS 10.1111/1469-0691.12039

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients

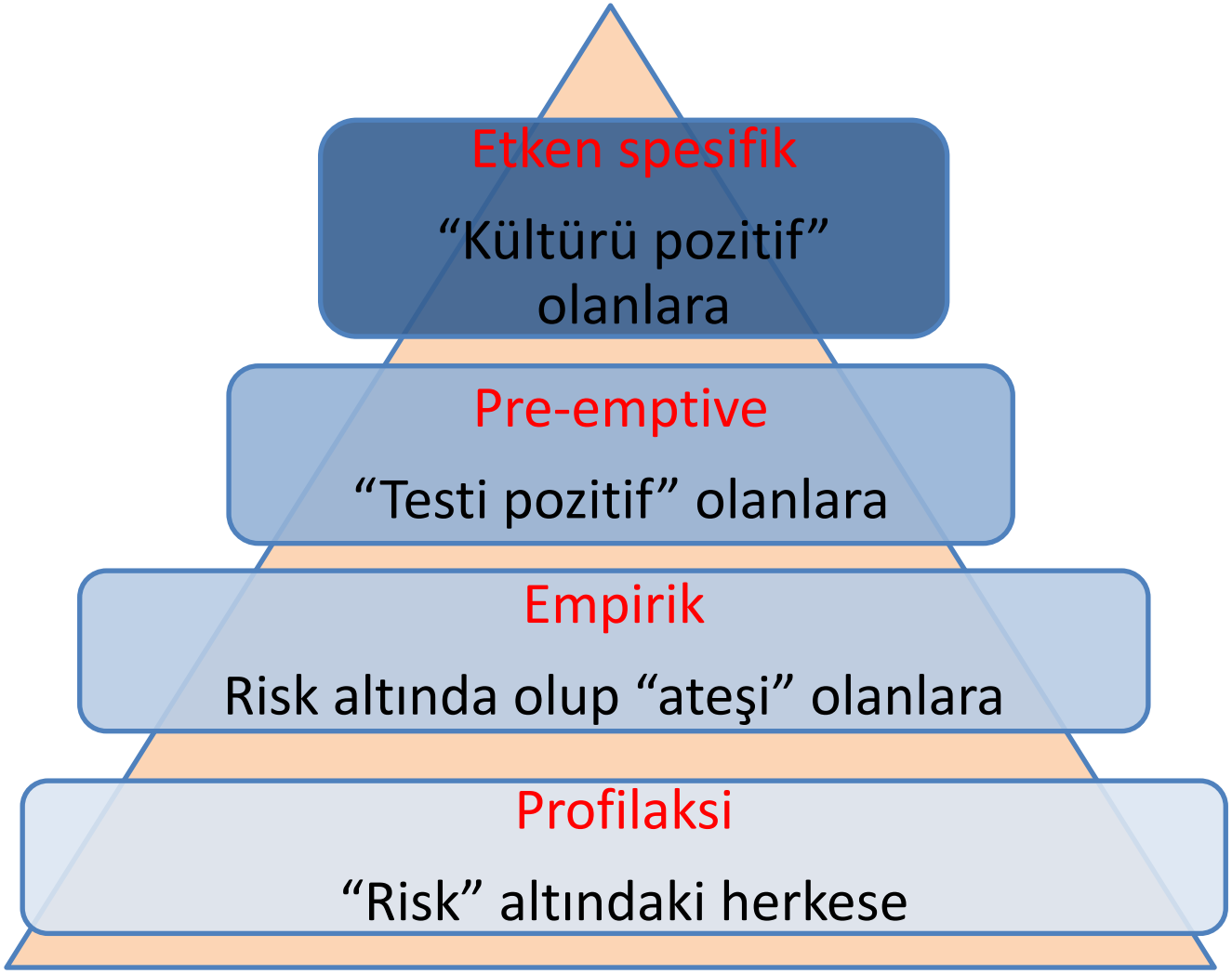
O. A. Cornely[1†], M. Bassetti[2†], T. Calandra[3†], J. Garbino[4†], B. J. Kullberg[5†], O. Lortholary[6,7†], W. Meersseman[8†], M. Akova[9], M. C. Arendrup[10], S. Arikan-Akdagli[11], J. Bille[3], E. Castagnola[12], M. Cuenca-Estrella[13], J. P. Donnelly[5], A. H. Groll[4], R. Herbrecht[15], W. W. Hope[16], H. E. Jensen[17], C. Lass-Flörl[18], G. Petrikkos[19], M. D. Richardson[20], E. Roilides[21], P. E. Verweij[5], C. Viscoli[22] and A. J. Ullmann[23] for the ESCMID Fungal Infection Study Group (EFISG)

INTERNAL MEDICINE JOURNAL

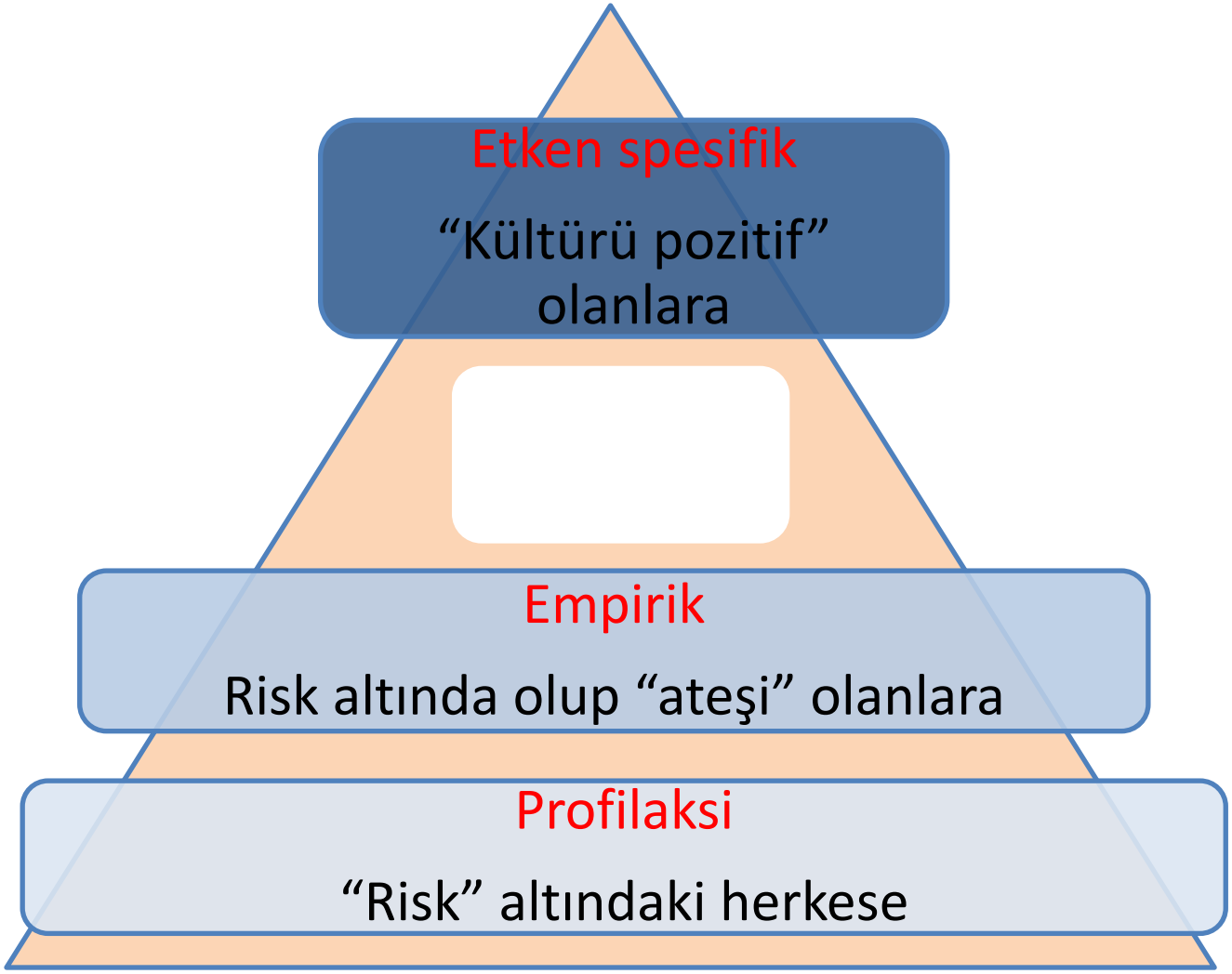
Internal Medicine Journal **44** (2014)

Consensus guidelines for the treatment of yeast infections in the haematology, oncology and intensive care setting, 2014

Antifungal kullanım nedenleri



Antifungal kullanım nedenleri



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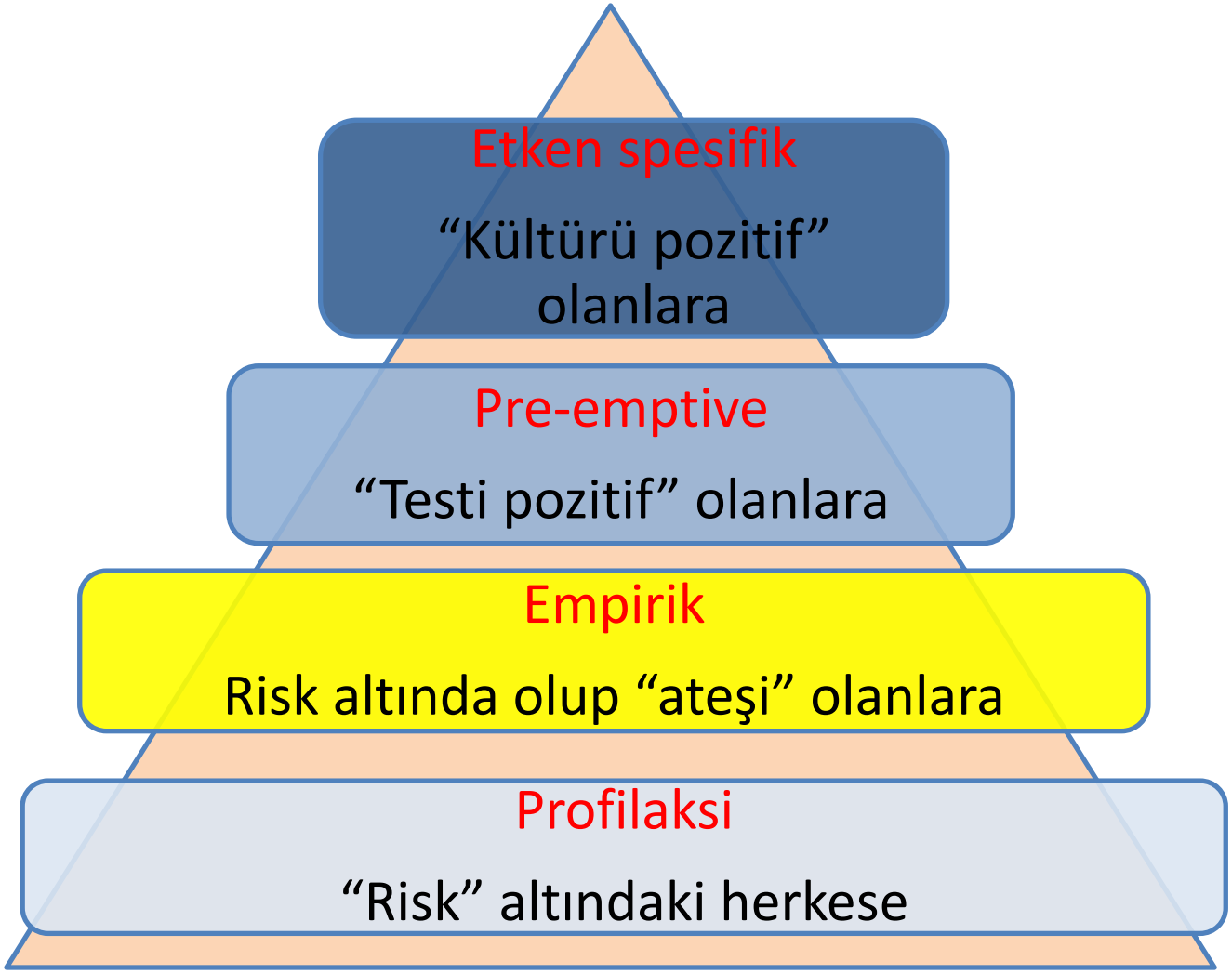
O. A. Cornely[1†], M. Bassetti[2†], T. Calandra[3†], J. Garbino[4†], B. J. Kullberg[5†], O. Lortholary[6,7†], W. Meersseman[8†], M. Akova[9], M. C. Arendrup[10], S. Arikan-Akdagli[11], J. Bille[3], E. Castagnola[12], M. Cuenca-Estrella[13], J. P. Donnelly[5], A. H. Groll[4], R. Herbrecht[15], W. W. Hope[16], H. E. Jensen[17], C. Lass-Flörl[18], G. Petrikkos[19], M. D. Richardson[20], E. Roilides[21], P. E. Verweij[5], C. Viscoli[22] and A. J. Ullmann[23] for the ESCMID Fungal Infection Study Group (EFISG)

Profilaksi önerilenler

- Abdominal cerrahi sonrası tekrarlayan perforasyonu ya da kaçağı olanlar

Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37

Antifungal kullanım nedenleri



İnvaziv kandidiyazis

- **Kandidemi**
  - Primer (kateter ilişkili)
  - Sekonder (İntraabdominal enfeksiyon..vb)
- **Abdominal cerrahi sonrası alınan kültürlerde üreme olması** (Periton sıvısı, dren sıvısı, doku kültürü..vb)
- **Kandidüri**
  - Üriner sistem enfeksiyonu olması/gelişmesi: *Düşük olasılık!*
  - Kandidemi gelişmesi: *Çok düşük olasılık!*

Invasive *Candida* infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006–2008)

- Olguların %10'unda YBÜ'ne **kabul edildiğinde** invaziv kandidiyazis mevcut

- Olguların yarısında kolonizasyon araştırılmış

  % 60'ında Candida spp. saptanmış

  Olguların %95'inde kolonize olan Kandida suşu etken

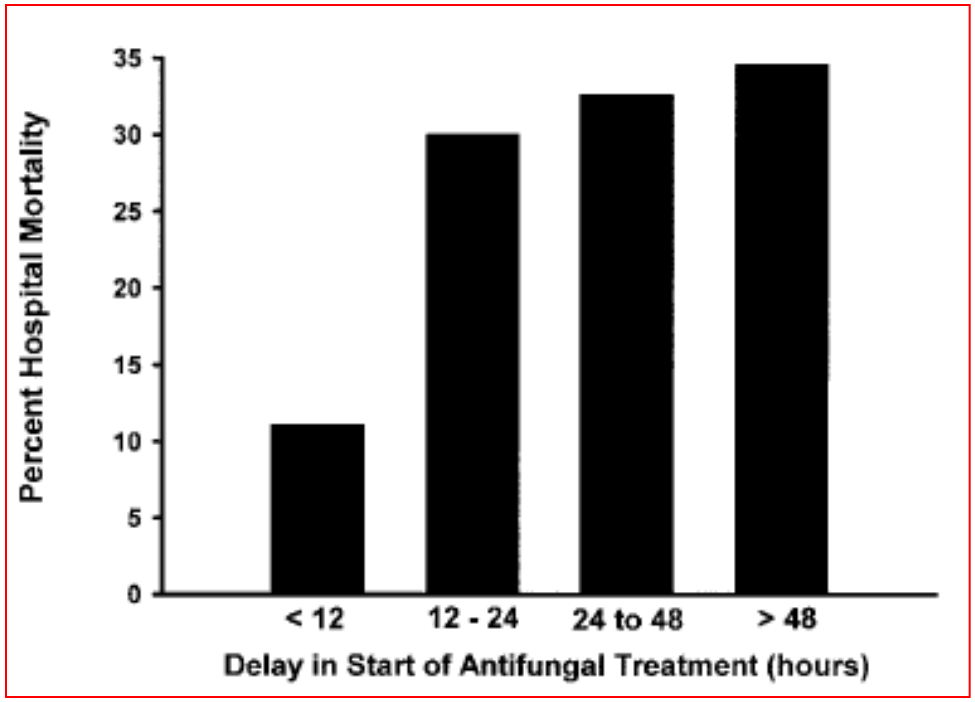
Clin Microbiol Infect 2015; 21: 87.e1–87.e10

Kandidemi

Tedavide gecikme kandidemide mortaliteyi belirgin artırıyor

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2005, p. 3640–3645 Vol. 49, No. 9
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.9.3640–3645.2005

Delaying the Empiric Treatment of *Candida* Bloodstream Infection until Positive Blood Culture Results Are Obtained: a Potential Risk Factor for Hospital Mortality



Tanı- Kültür

- Kan kültürü, kanididemili olguların %50-70'inde pozitif

- Kan, periton sıvısı..vb örneklerin kültüründe üreme olsa bile 2-5 günde sonuçlanıyor

Empirik tedavi önemli!

Tanı- Kültür dışındaki testler

Beta D glukan

- Kriptokok ve zigomiçetler hariç diğer mantarların duvarında bulunuyor;
- Aspergillozda da pozitif
- Pahalı, her laboratuvar çalışmıyor

Mannan, Anti-mannan

- Hepatosplenik kandidiyazis için tanı değeri daha yüksek
- Kandidemideki yeri?
- Her laboratuvar çalışmıyor

PCR: Polimeraz zincir rekasiyonu

- Standardize DEĞİL

Kandida suşları

Kandida suşu	Özellikleri	Antifungal duyarlılık
C. albicans	Kandidemilerin yaklaşık yarısından sorumlu	Flukonazol direnci %1-2'lerde
C. parapsilosis	Cilt kolonizasyonu sık Biyofilm oluşturur Mortalite *C.albicans*'tan daha düşük	Ekinokandin MİK'leri yüksek Flukonazol tercih edilir
C. glabrata	Yaşlılarda ve HIV pozitif hastalarda daha sık	Flukonazol (Azloller) için doza bağımlı duyarlılık/direnç
C. tropicalis	Kanser hastalarında daha sık	Genellikle flukonazole duyarlı
C. krusei	Daha az görülür Mortalite *C.albicans*'tan daha yüksek	Flukonazole direnç var Ekinokandin verilebilir

Az görülen kandida türleri

- ***C. lusitaniae***

  Amfoterisin B'ye dirençli

  Flukonazol ve ekinokandinlere duyarlı

- ***C. guilliermondi***

  Flukonazol ve ekinokandinlere azalmış duyarlılık

  Amfoterisin B'ye duyarlı

- ***C. dubliniensis***

  Fenotipik özellikleri ile *C. albicans*'a benzer

- ***C.auris***

  Çok ilaca dirençli, yüksek mortalite!

Kandida türleri- Duyarlılık

Kandida türü	Flu*	İtra*	Vori*	Posa*	Flusitozin	Amfo B*	Ekinokandin
C. albicans	S**	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S	S - R***
C. glabrata	S-DD***- R	S-DD - R	S-DD - R	S-DD - R	S	S - I	S
C. krusei	R	S-DD - R	S	S	I - R	S - I	S
C. lusitaniae	S	S	S	S	S	S - R	S

Kandidemi saptandığında

Tüm hastalardan

- Gün aşırı (iki günde bir) kan kültürü alınmalı
- Transtorasik EKO yapılmalı; gerekirse transözefageal EKO yapılmalı

Nötropenik olmayan hastalarda

- Santral venöz kateter çekilmeli
- Antifungal başlandıktan sonraki ilk hafta içinde fundoskopik muayene yapılmalı

Nötropenik hastalarda

- Kandidemi kaynağı hastanın endojen florası da olabileceğinden santral venöz kateterin çekilmesi konusu değerlendirilmeli
- Fundoskopik muayene nötropeniden çıktıktan sonraki hafta içinde yapılmalı

Kandidemide Tedavi Süresi

Uzak tutulumu olmayan kandidemi olguları için:

- Son negatif kan kültüründen sonra en az 14 gün

Uzak tutulumu olan kandidemi olguları için:

- Endoftalmit için 6 hafta
- Endokardit için kapak cerrahisinden sonra en az 6 hafta

Kandidemi- Oral tedavi

İlaca duyarlı bir suş olduğunda,

hasta stabil ise

10 günlük iv tedaviden sonra

oral tedaviye geçilebilir

Clin Microbiol Infect 2012; **18** (Suppl. 7): 19–37

Solunum yolu örneğinde kandida…

Intensive Care Med (2009) 35:1526–1531
DOI 10.1007/s00134-009-1482-8

ORIGINAL

W. Meersseman
K. Lagrou
I. Spriet
J. Maertens
E. Verbeken
W. E. Peetermans
E. Van Wijngaerden

Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study

- 1587 YBÜ hastası
  301'i (%19) eX
  232(%77) otopsi

Solunum yolu örneğinde kandida üremesi: **Önemsiz!**

İnvazif Kandidiyazis
Dikkat- 1

- Empirik tedavide **ekinokandin** tercih edilmeli
- Hasta stabilleştiğinde duyarlılık sonucuna göre **tedavi daraltılmalı**
- Flukonazol için ilk gün **yükleme dozu** (800mg, iv) uygulanmalı
- İlaç etkileşimleri göz önünde bulundurulmalı;

  Örneğin; **vorikonazol sirolimus** ile birlikte kullanılamaz veya **kaspofungin ve rifampisinin** birarada kullanılması gerekirse kaspofungin dozu arttırılmalıdır

İnvazif Kandidiyazis
Dikkat- 2

- İlaçların veriliş yollarına dikkat edilmeli;

  Örneğin kreatinin klirensi 50'nin altında olan hastaya **iv** vorikonazol **VERİLMEMELİ**

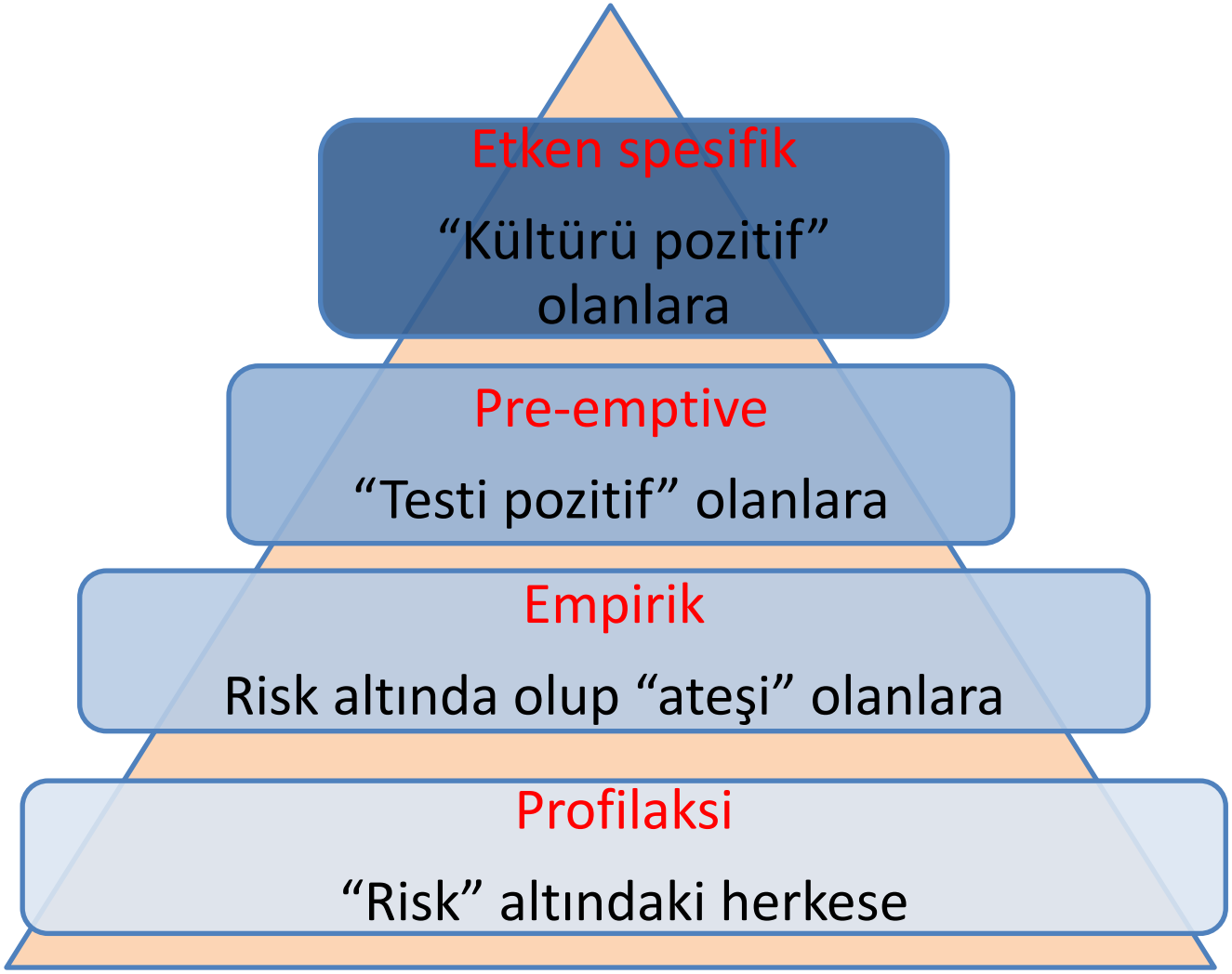
- İlaç dozları böbrek fonksiyon testlerine göre düzenlenmeli;

  Örneğin **KBY'li hastalarda** flukonazol dozu yarıya düşürülmeli

- İlaç dozları karaciğer fonksiyon tetslerine göre düzenlenmeli;

  Örneğin ağır **karaciğer yetmezliğinde** kaspofungin dozu azaltılmalı

Antifungal ilacı ***niçin*** başladığımızı sorgulamalıyız…



ÖZET

- Antifungal yönetime ihtiyaç var; çünkü
  - fungal enfeksiyonların **mortalitesi yüksek**
  - **tanı** olanakları ve antifungal **ilaç** seçenekleri **kısıtlı**
  - antifungal direnç oranları artıyor

- AFY programları, AMY kadar yaygın değil ancak uygulandığında iyi sonuçlar alınıyor

- Fungal enfeksiyonların çeşitliliği ve farklı hasta gruplarında görülme sıklığının değişmesi nedeniyle tek bir AFY programından söz etmek olanaklı değil

- **Gereksinimlere** ve **olanaklara** göre bir AFY programı gerekiyor