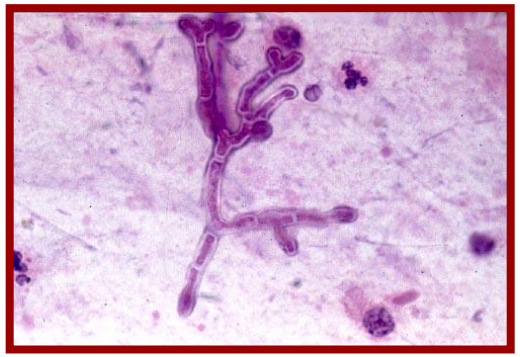
Fungal İnfeksiyon Yönetimi ve Tedavi Yaklaşımı

Ne Zaman Ekinokandin?
Ne Zaman Flukonazol?

Dr. Süda TEKİN

Koç Üniversitesi Hastanesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Bölümü



Neler konuşulacak?

- Fungal infeksiyonlar Epidemiyoloji
- Risk faktörleri
- Tan& tedavi
- Rehberler

İnvazif Fungal İnfeksiyon

- İFİ'lara bağlı mortaliye artmaktadır
- ABD verilerine göre İFİ ölümcül infeksiyonlar arasında;

- Kandidemi yoğun bakım ünitelerinde **5. ölüm** nedeni
- 1–8 olgu 100,000/ülkede yaşayanlar

Atfedilen mortalite

❖Erişkinlerde %15–35

❖Yenidoğanlarda %10–15

Bouza E, et al. Int J Antimicrob Agents 2008;32:S87-1.
Diagn Microbiol Infect Dis. 2012;73(1):45–8.

Kandidaya bağlı kan dolaşım infeksiyonları

- ✓Tüm kan dolaşımı infeksiyonların %8-15'i kandidalar
- ✓ Nozokomiyal kan dolaşım infeksiyonları arasında **4. sırada**
- ✓Yoğun bakım ünitelerinde kan dolaşımı infeksiyonları arasında **3. sırada**
- ✓Yoğun bakımda kandidemi insidansı diğer yatan hastalara göre 5-10 kat daha fazla görülmektedir.
- ✓Kandidemi vakalarının yarısı YBÜ'de oluşmaktadır.

Vincent J, et al. J*AMA* 2009;302: 2323-2329.
Leroy O, et al. *Crit Care Med* 2009;37:1612-18
Kullberg BJ, et al. *Clin Microbiol Infect* 2011; 17 : 1–12

İnvazif fungal infeksiyonlar önemlidir!

Olumsuz konak koşulları

- **Düşük klinik yanıt oranları**
- **Yüksek mortalite**

Dirençli cins ve suşlar

Erken tanıda zorluklar

Antifungal tedaviye suboptimal yanıt

Richardson. *JAC* 2005; 56(S1): i5, Bille et al. *Curr Opin Infect Dis* 2005; 18: 314

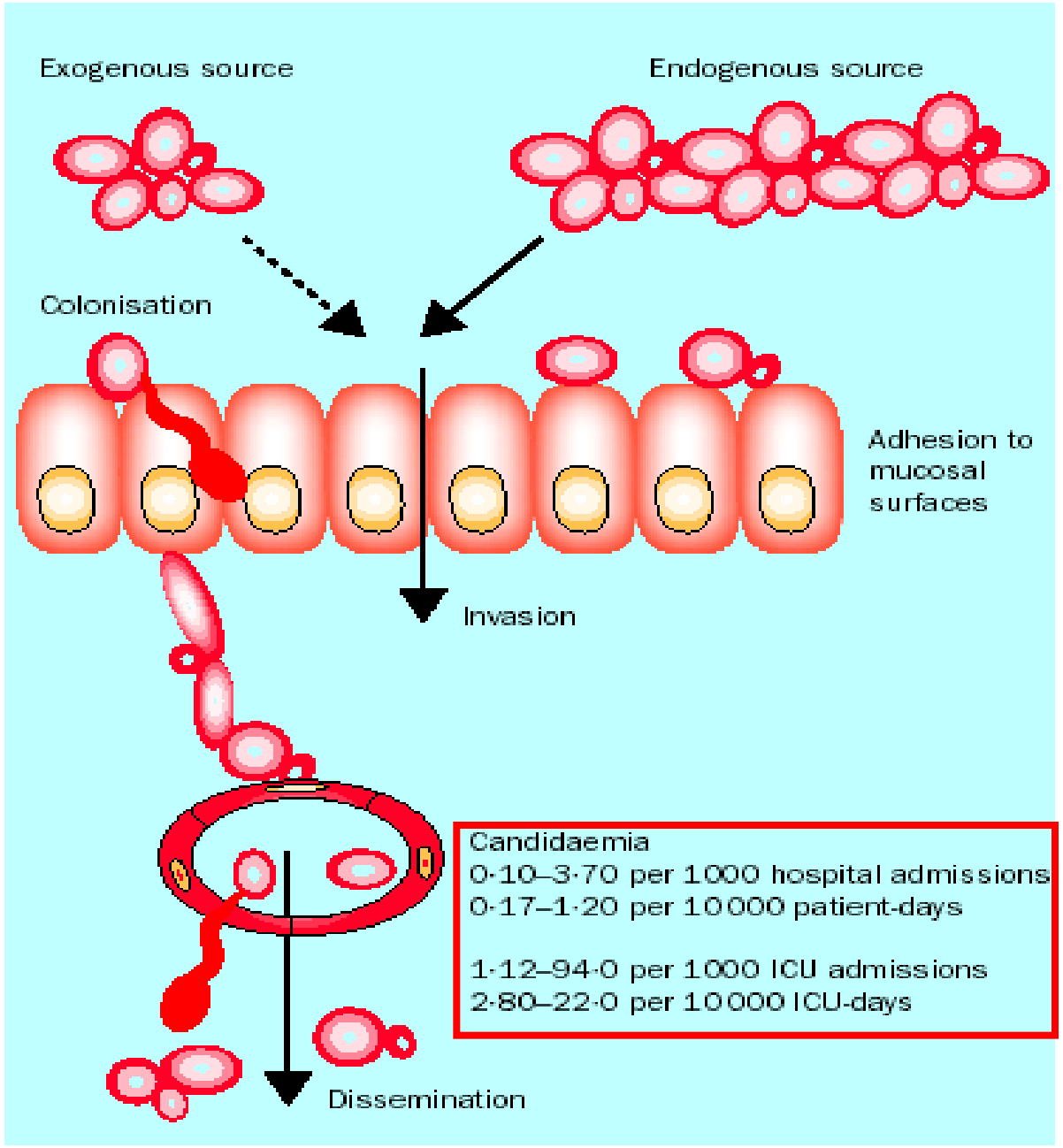
Kolonizasyon

Endojen (en sık)

1. GİS
2. Cilt
3. Mukoza

Eksojen (nozokomiyal)

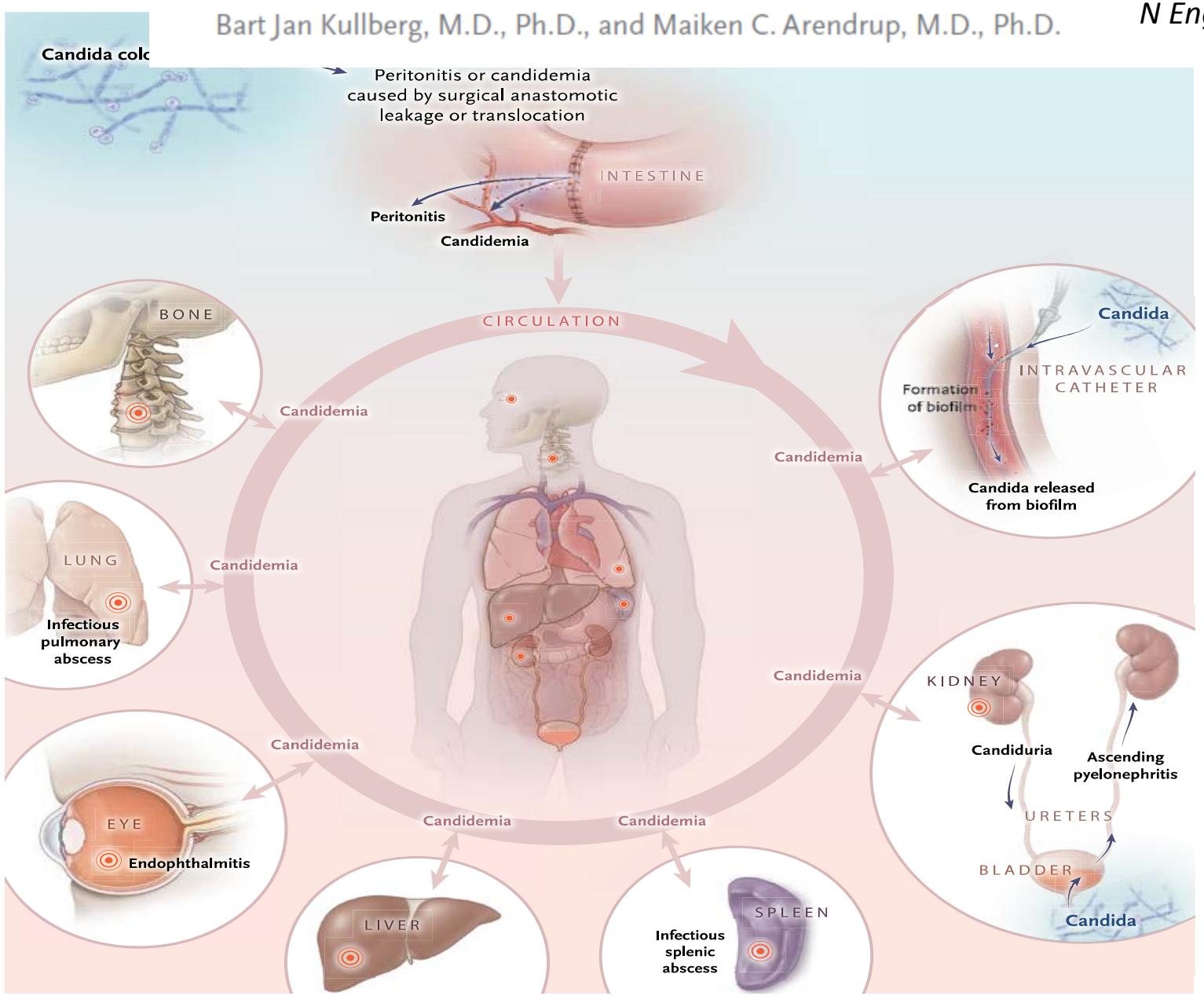
1. Sağlık çalışanı
2. Kolonize aletler



Invasive Candidiasis

Bart Jan Kullberg, M.D., Ph.D., and Maiken C. Arendrup, M.D., Ph.D.

N Engl J Med. 2015;373:1445-56



Invazif Kandidiyaz:

Kandidemi ve «deep-seated» doku kandidiyazı

Fatalite %40

Open Forum Infectious Diseases

MAJOR ARTICLE

Epidemiology and Clinical Features of Invasive Fungal Infection in a US Health Care Network

IFI in a US Health Network. 2018

Brandon J. Webb,[1,2] Jeffrey P. Ferraro,[3,4] Susan Rea,[3] Stephanie Kaufusi,[3,5] Bruce E. Goodman,[3,5] and James Spalding[6]

- 3154 hastada 3374 IFI epizotu
- Ortalama insidans **27.2/100 000** olgu/hasta yılı
- Artış **0.24 olgu/100 000** (*P* = .21).
- **Kandidiyaz** en sık, **%55**.

Candida spp.: Genel bakış

	Features	Antifungal direnç
C. albicans	Responsible for about **50%** of Candidemia	Fluconazole **1-2%**
C. parapsilosis	Biofilm Skin contamination Fatality is < than *C.albicans* Southern Europe	MIC of echinocandins are **high**
C. glabrata	Elderly, HIV+ Northern Europe	Dose related resistance for azoles
C. tropicalis	More common among cancer pts	Less R to Fluconazole
C. krusei	Less common Fatality is > *C.albicans*	R to fluconazole **Echinocandins** considered

Azap O, Ergonul O, AFS, 2017

Mycopathologia
https://doi.org/10.1007/s11046-018-0293-2

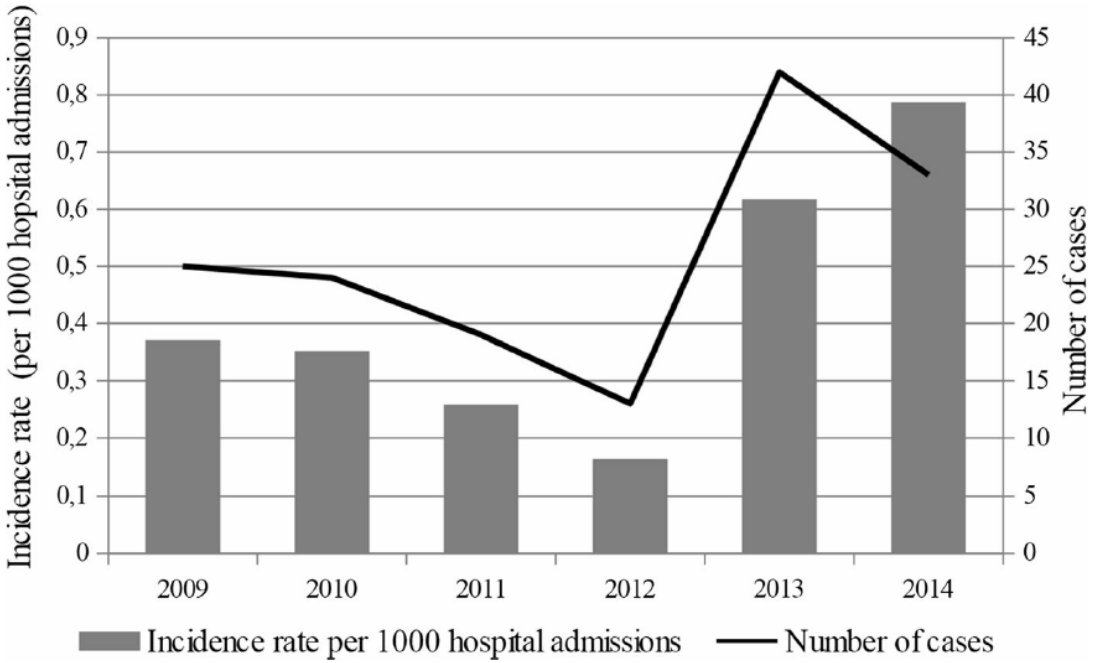
ORIGINAL PAPER

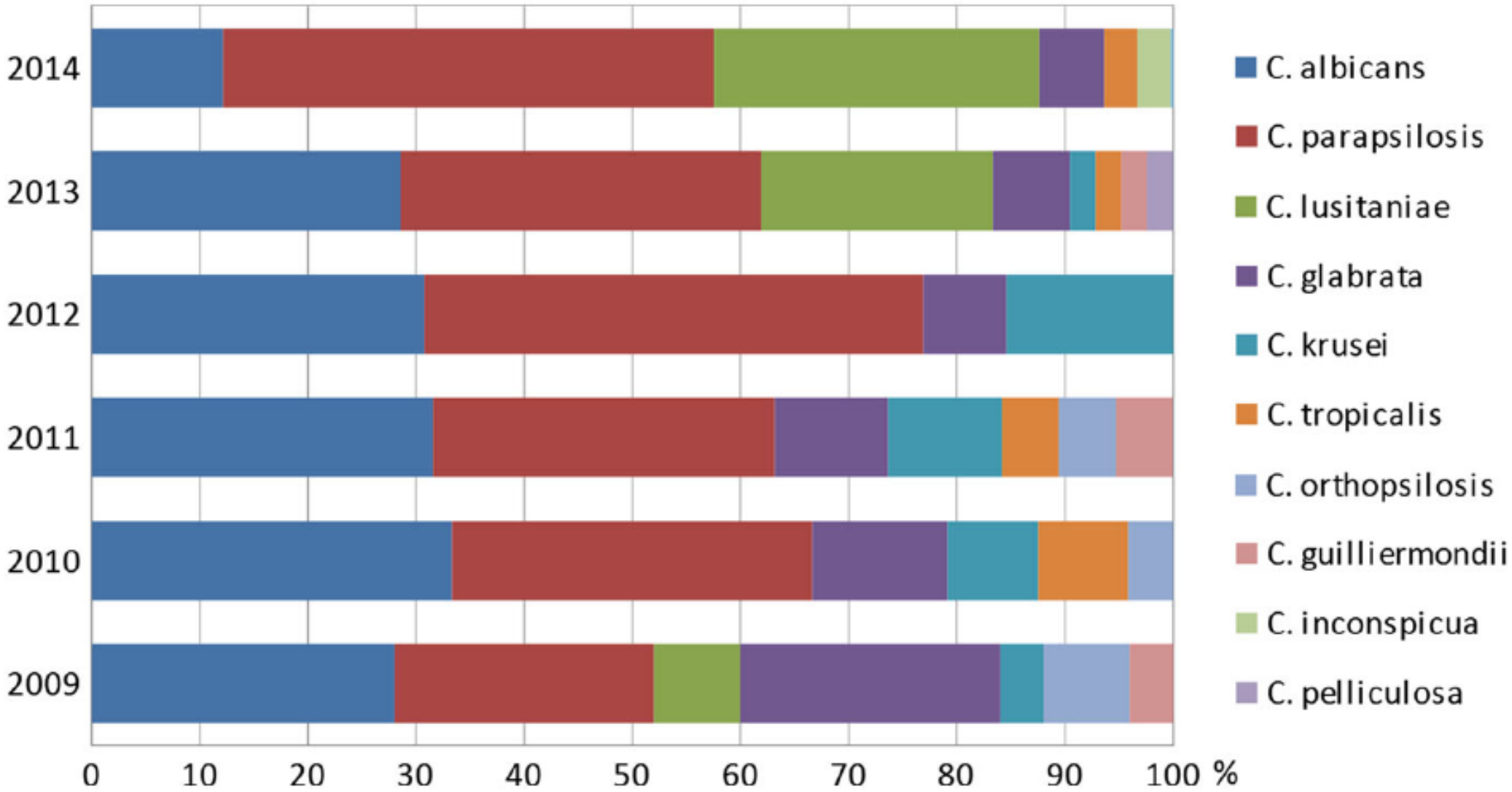
Invasive Fungal Infection in Romania: Changing Incidence and Epidemiology During Six Years of Surveillance in a Tertiary Hospital

Floredana-Laura Şular · Edit Szekely · Violeta Corina Cristea · Minodora Dobreanu

- ✓ Romanya, çok merkezli çalışma 2009-2014
- ✓ Kandidemili hastalar, 175 *Candida* spp.
- ✓ Antifungal duyarlılık; MALDI-TOF MS

Fig. 1 Patients with Candida IFI and incidence rate observed during a 6-year period





Mycopathologia. 2018.

Table 1 *Candida* spp. isolates presenting both resistant and non-wild-type phenotypes according to applied CLSI BPs and ECVs

Strain code	Year	Species identification	FL MIC (mg/L)	VOR MIC (mg/L)	PZ MIC (mg/L)	IZ MIC (mg/L)	CAS MIC (mg/L)	MCF MIC (mg/L)
1835	2009	*Candida orthopsilosis*	32	0.25				
1729	2009	*Candida glabrata*	128	1	2			
1719	2009	*C*						
2362	2009	*C*						
2419	2009	*C*					0.25	
591	2010	*C*						
1064	2014	*Candida glabrata*	16	0.5				0.25

BP break point; *ECV* epidemiological cut-off value; *CLSI* Clinical and Laboratory Standards Institute; *FL* fluconazole; *MF* micafungin; *VOR* voriconazole; *PZ* posaconazole; *IZ* itraconazole; *CAS* caspofungin; *MCF* micafungin

Kendi ünitenizin lokal verilerini bilin ve tedavi yönetimini buna göre karar verin.

Sonuç:

C. glabrata %23.5'i flukonazole dirençli,

C. parapsilosis %5.08 flukonazole dirençli

C. albicans, C. tropicalis and *C.lusitaniae* isolatlarında flukonazole direnci saptanmamış

C. glabrata 1(%5.8) isolatı ekinokandin dirençli

Mycopathologia. 2018.

American Journal of Infection Control 45 (2017) e61-e63

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Brief Report

Risk factors, characteristics, and outcomes of candidemia in an adult intensive care unit in Turkey

Elif Tukenmez Tigen MD [a,*], Huseyin Bilgin MD [a], Hande Perk Gurun MD [b], Arzu Dogru MD [c], Beste Ozben MD [d], Nilgun Cerikcioglu MD [e], Volkan Korten MD [a]

- 2011-2013 arası YBÜ yatan hastalar
- Kandidemi gelişen hastalar değerlendirilmiş
- Kan kültüründe üreme
- MIC, EUCAST

Table 1
Characteristics of the candidemia and noncandidemia groups

		Candidemia group (n = 36)	Noncandidemia group (n = 37)	*P* value
Age, y		65 (52-73)	62 (48-72)	**.046**
Male sex		19 (52.8)	18 (48.6)	.724
Abdominal surgery		8 (22.2)	3 (8.1)	.112
Central venous catheter		32 (88.9)	9 (24.3)	**<.001**
Mechanical ventilation		32 (88.9)	26 (70.3)	.081
Total parenteral nutrition		27 (75)	13 (35.1)	**.001**
Concomitant bacteremia		22 (61.1)	4 (10.8)	**<.001**
Trauma		1 (2.8)	5 (13.5)	.199
Previous hospitalization		28 (77.)	14 (37.8)	**.001**
Steroid therapy		17 (47.2)	11 (29.7)	.124
Intensive care unit (internal medicine)		23 (63.9)	8 (21.6)	**<.001**
Solid organ malignancy		8 (22.2)	12 (32.4)	.328
Chronic renal failure with replacement therapy		14 (38.9)	4 (10.8)	**.007**
Diabetes		10 (27.8)	13 (35.1)	.499
Chronic obstructive pulmonary disease		8 (22.2)	10 (27)	.634
Acute Physiology and Chronic Health Evaluation II score > 20		11 (30.6)	18 (48.6)	.114
Use of broad antibiotic		36 (100)	22 (59.5)	**<.001**
Course	Discharge	6 (16.7)	20 (54.1)	**.001**
	Exitus	30 (83.3)	17 (45.9)	
Sequential Organ Failure Assessment score		9 (7-15)	6 (3.5-10)	**.009**
Total length of intensive care unit stay (days)		22 (18-30)	5.5 (2.25-15.75)	**.004**

MIC values according to EUCAST breakpoints among isolates of *Candida spp.* considered in this study

	Antifungals	Range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	No (%)
C albicans	Caspofungin	0.006-0.25	0.06	0.12	27 (75)
	Posaconazole	0.008-2	0.015	0.12	
	Voriconazole	0.003-0.25	0.008	0.06	
	Itraconazole	0.012-1	0.03	0.12	
	Fluconazole	0.25-16	0.5	8	
	Amphotericin B	0.5-1	0.5	0.5	
C glabrata	Caspofungin	0.12-4	0.12	–	4 (11)
	Posaconazole	1-2	2	–	
	Fluconazole	16-32	1.6	–	
	Amphotericin B	0.5-1	0.5	–	
	Itrocanozole	1			
C tropicalis	Caspofungin	0.06-0.25	0.155	–	3 (0.08)
	Posaconazole	0.06-0.5	0.28	–	
	Voriconazole	0.03-0.12	0.075	–	
	Itraconazole	0.12-1	0.56	–	
	Fluconazole	0.5-2	1.25	–	
C parapsilosis	Caspofungin	0.12-0.5	0.31	–	2 (0.05)
	Voriconazole	0.08-0.12	0.064	–	
	Itraconazole	0.06-0.5	0.28	–	
	Fluconazole	1-8	4.5	–	

E. Tukenmez Tigen et al. / AJIC: 2017; 45: e61-e63

Received: 10 October 2016 | Revised: 23 February 2017 | Accepted: 23 February 2017

DOI: 10.1111/myc.12618

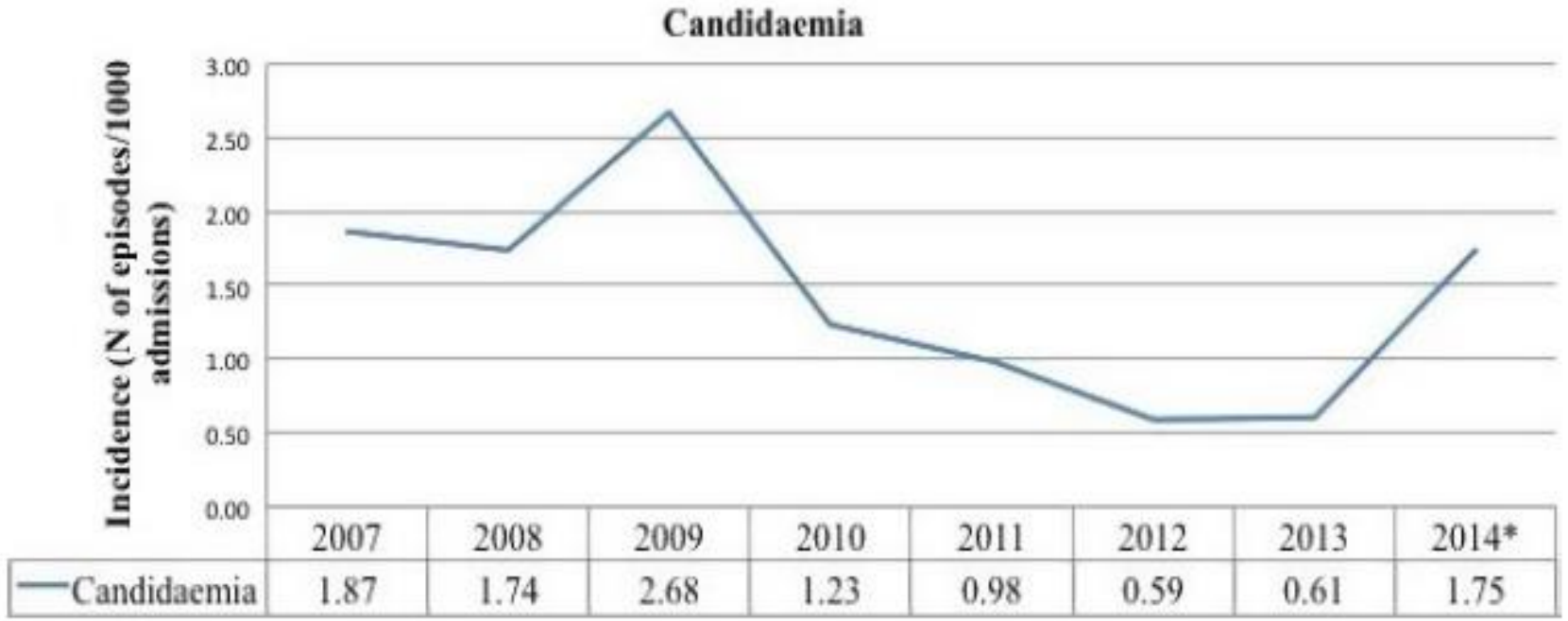
ORIGINAL ARTICLE

WILEY mycoses

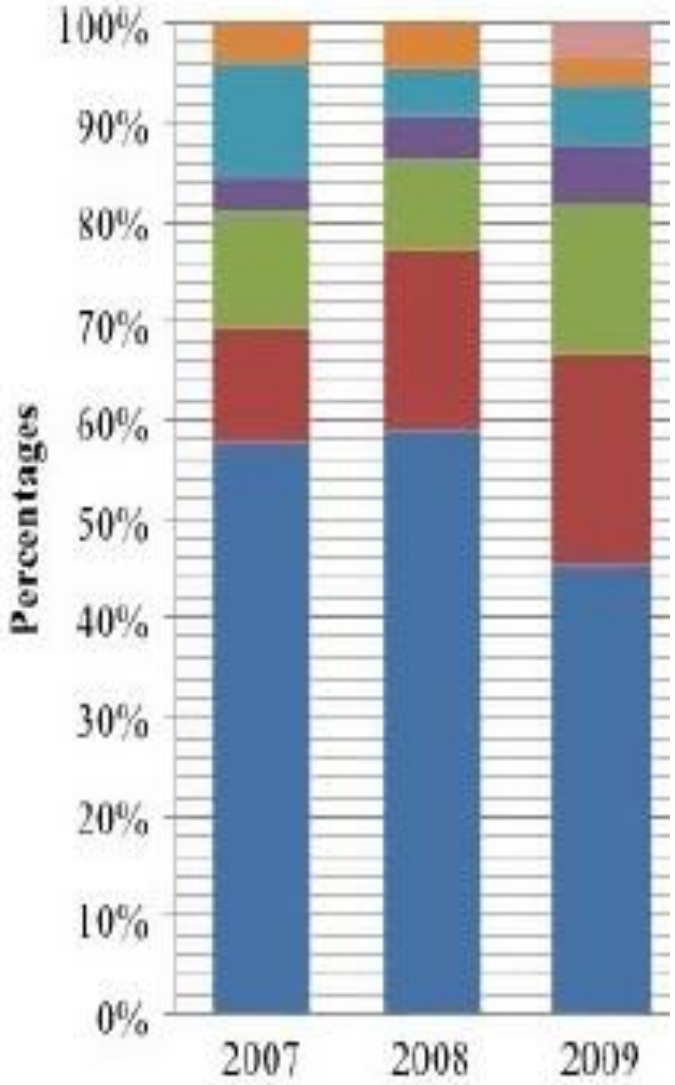
Epidemiology, species distribution, clinical characteristics and mortality of candidaemia in a tertiary care university hospital in Turkey, 2007-2014

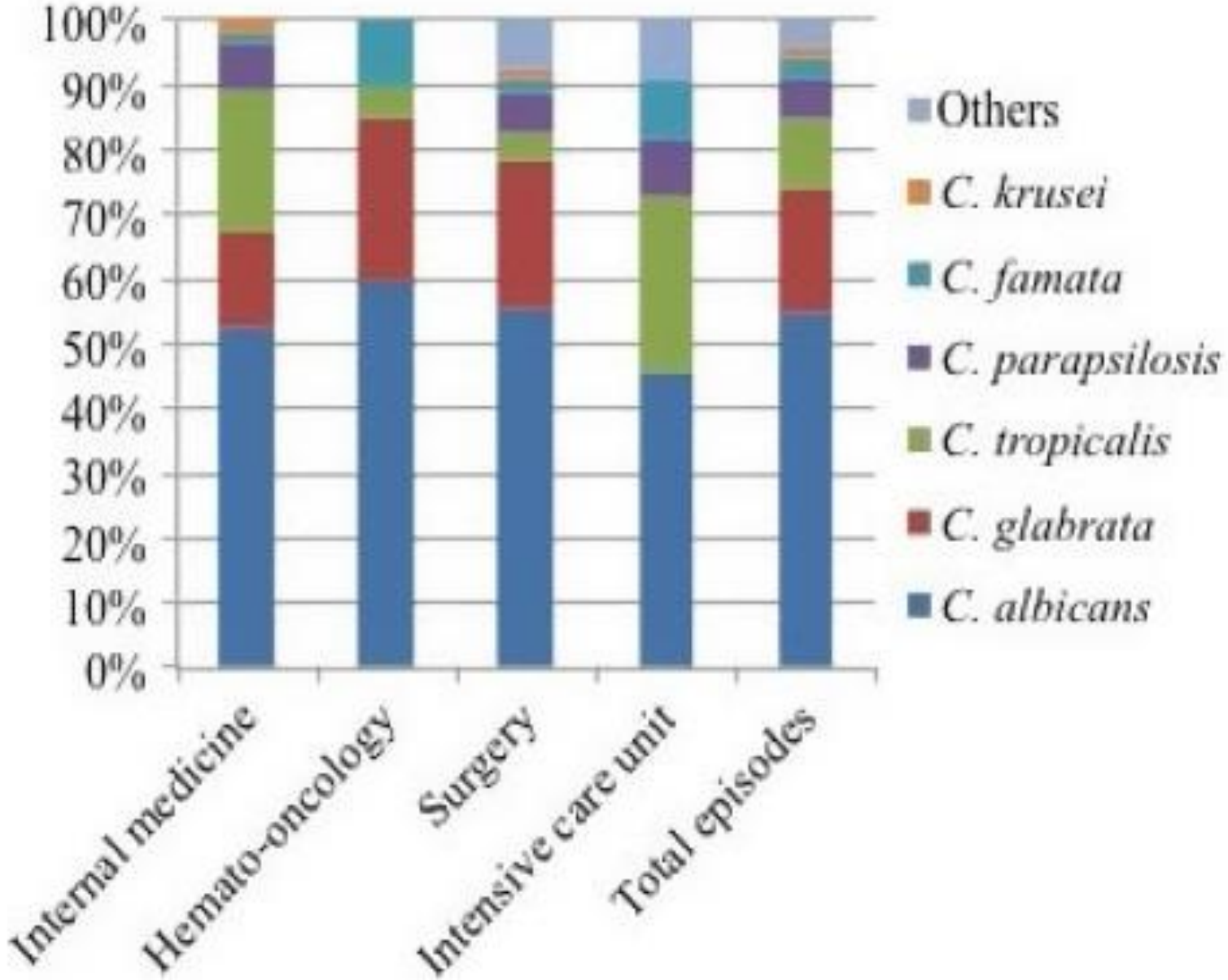
Ayşegül Yeşilkaya[1] | Özlem Azap[1] | Mehtap Aydın[1] | Mehtap Akçil Ok[2]

- 235 yetişkin hastada
- 243 kandidemi atağı



	2007	2008	2009	2010	2011	2012	2013	2014*
Candidaemia	1.87	1.74	2.68	1.23	0.98	0.59	0.61	1.75


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentages
2007
2008
2009


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Others
C. krusei
C. famata
C. parapsilosis
C. tropicalis
C. glabrata
C. albicans
Internal medicine
Hemato-oncology
Surgery
Intensive care unit
Total episodes

Received: 10 October 2016 | Revised: 23 February 2017 | Accepted: 23 February 2017

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ORIGINAL ARTICLE

WILEY mycoses

Epidemiology, species distribution, clinical characteristics and mortality of candidaemia in a tertiary care university hospital in Turkey, 2007-2014

Ayşegül Yeşilkaya[1] | Özlem Azap[1] | Mehtap Aydın[1] | Mehtap Akçil Ok[2]

Sonuçlar;

- ✓ Kandidemi insidansı: **1.23 /1000** başvuru epizotu
- ✓ non-*albicans Candida* üreyen hastaların hastanede kalma süresi daha uzun
- ✓ Kandidemilerin **%52.5**'ünde kaynak bilinmiyor
- ✓ SVK non-*albicans Candida* kandidemisinde
- ✓ Üriner kateter olanlarda *Candida albicans* kandidemisi yüksek
- ✓ **Lokal epidemiyoloji bilinmeli**

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

Matthew Morrell,[1] Victoria J. Fraser,[2] and Marin H. Kollef[1]*

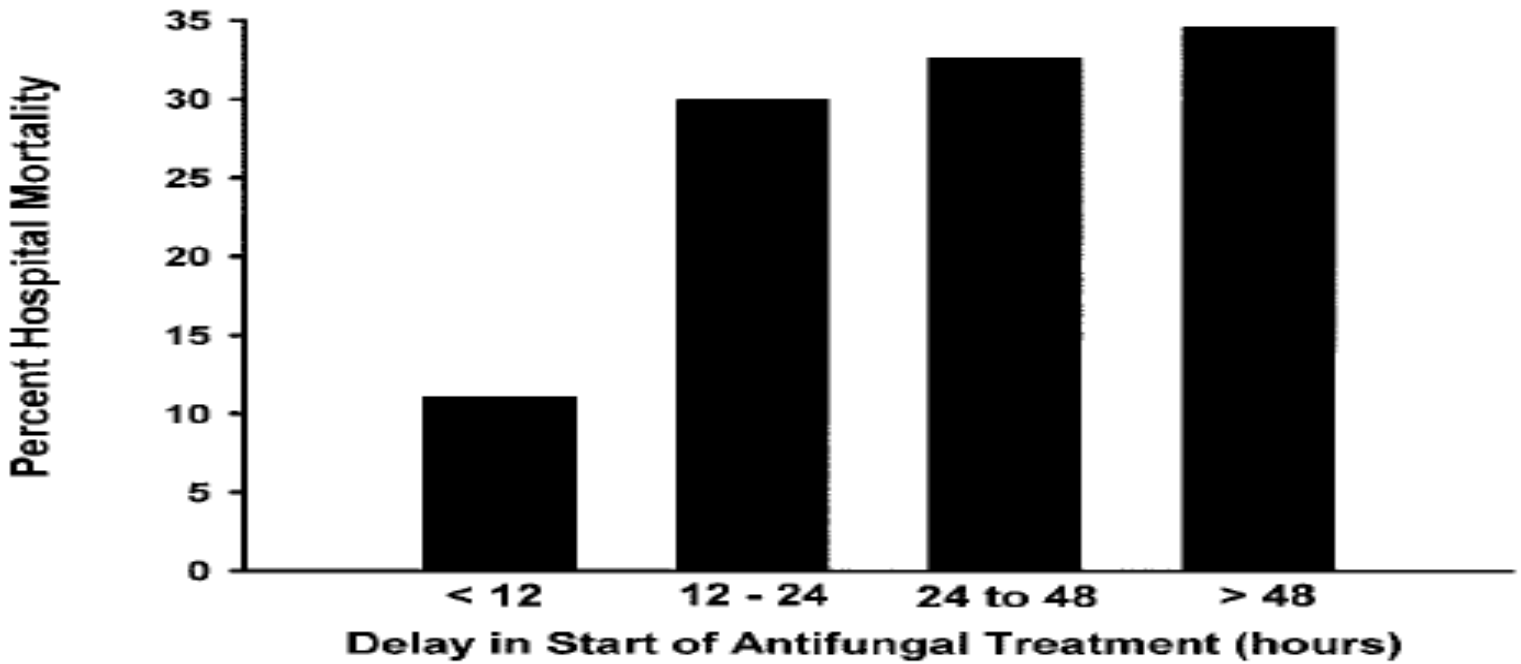
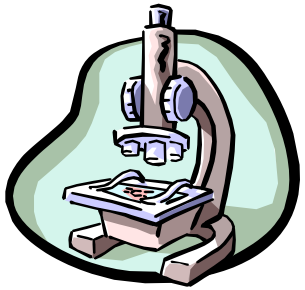
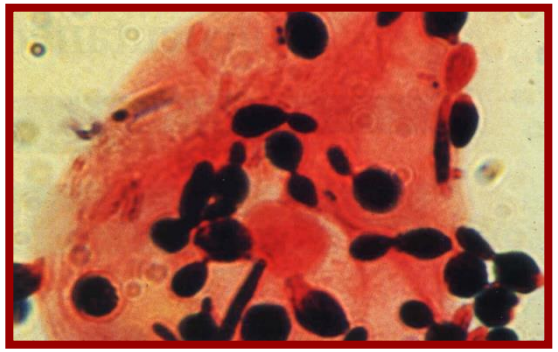


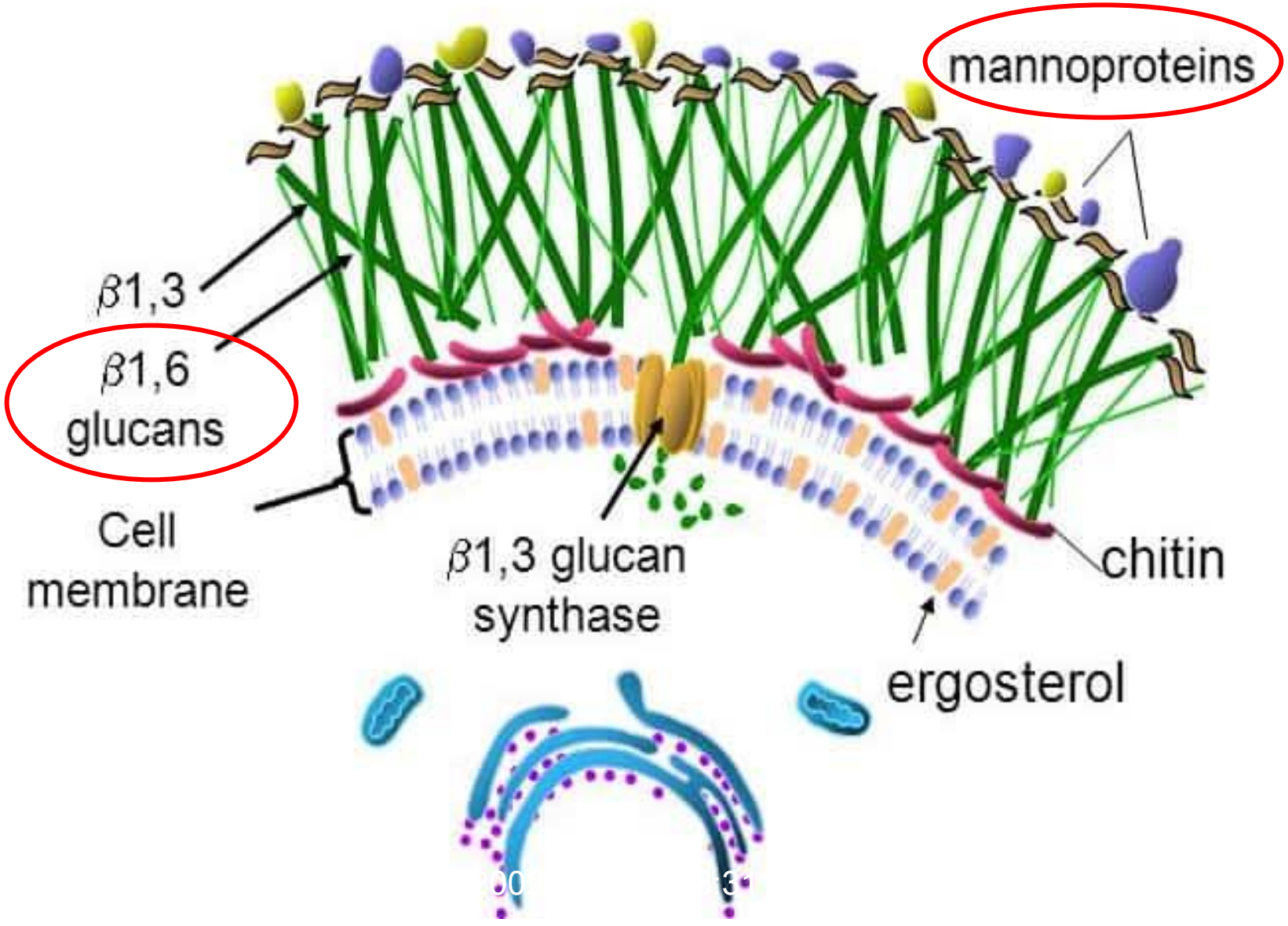
FIG. 1. Relationship between hospital mortality and the timing of antifungal treatment. The timing of antifungal therapy was determined to be from the time when the first blood sample for culture positive for fungi was drawn to the time when antifungal treatment was first administered to the patient.

TANI





Candida yapısı: Antijenleri



European Journal of Internal Medicine 34 (2016) 21–28

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Narrative Review

Candidemia and invasive candidiasis in adults: A narrative review

Spinello Antinori [a,b,*], Laura Milazzo [b], Salvatore Sollima [b], Massimo Galli [a,b], Mario Corbellino [b]

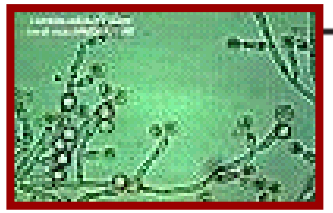
Derleme

- 1997 ile Mart 2016 arasında
- Anahtar kelimeler;

Kandidemi, invasif kandidiyaz, kandida endocarditi, intra-abdominal kandidiyaz, epidemioloji, tanı, ilaç direnci, tedavi, rehber

Diagnostic tests available and their efficiency in diagnosing candidemia and invasive candidiasis.

Diagnostic test	Candidemia	Invasive candidiasis	Comment
Blood culture	Positive in 70–80% of patients	Rarely positive	Considered the gold standard
1,3-β-D-Glucan	Sensitivity 68%	Sensitivity 56%; specificity 73% [29]; sensitivity 65%, specificity 78%; PPV 68%, NPV 77%[a] [58]	A pan-fungal marker (except for cryptococcosis and zygomicosis) Recommended cut-off level ≥80 pg/mL in 2 determinations May anticipate a diagnosis of intra-abdominal candidiasis by 5 days
Mannan Ag/anti-mannan antibodies	Sensitivity 59%; specificity 97%	Sensitivity 83%, specificity 86%	Sensitivity of mannan Ag higher for *C. glabrata* and *C. tropicalis* Recommended cut-off for Ag ≥125 pg/mL; antibody cut-off ≥10 AU/mL
T2 MR *Candida*	Sensitivity 91.1%; specificity 99.4% [64] Sensitivity 92.3% *C. albicans*/*C. tropicalis*; 94.2% *C. parapsilosis*; 88.1% *C. glabrata*/*C. krusei*	Very few data; it seems to detect 100% of cases	Very rapid (mean time for *Candida* detection and species identification 4.4 ± 1 h)
Polymerase chain reaction	Sensitivity 59% [29]	Sensitivity 80%; specificity 70%[b] Sensitivity 89%[c] [29]	Precedes a diagnosis of candidemia by a median of 3 days. Persistently positive results associated with death.



European J Int Med 34 (2016) 21–28

Skorlama

A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization*

Leon, et al. *Crit Care Med*. 2006.

Cristóbal León, MD; Sergio Ruiz-Santana, MD, PhD; Pedro Saavedra, PhD; Benito Almirante, MD, PhD; Juan Nolla-Salas, MD, PhD; Francisco Álvarez-Lerma, MD, PhD; José Garnacho-Montero, MD; María Ángeles León, MD, PhD; EPCAN Study Group

Cut-off 2.5: duyarlılık 81% ve özgüllük 74%

*__sepsis & 3__ risk faktöründen biri varsa

hastaya **ampirik antifungal** başlanmalı

kolonizasyonu		
YBÜ yatışta cerrahi öykü	**0.997**	**1**
Sepsis	**2.038**	**2**
TPN	**0.908**	**1**

Rehberler

Endüstrinin etkisi

Tedavi

Liderler

Yerel veriler

Antifungal kullanım nedenleri

Etken spesifik

"Kültürü pozitif" olanlara

Pre-emptive

"Testi pozitif" olanlara

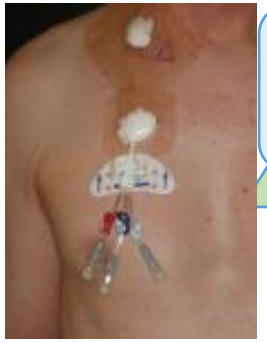
Belirteçler

Empirik

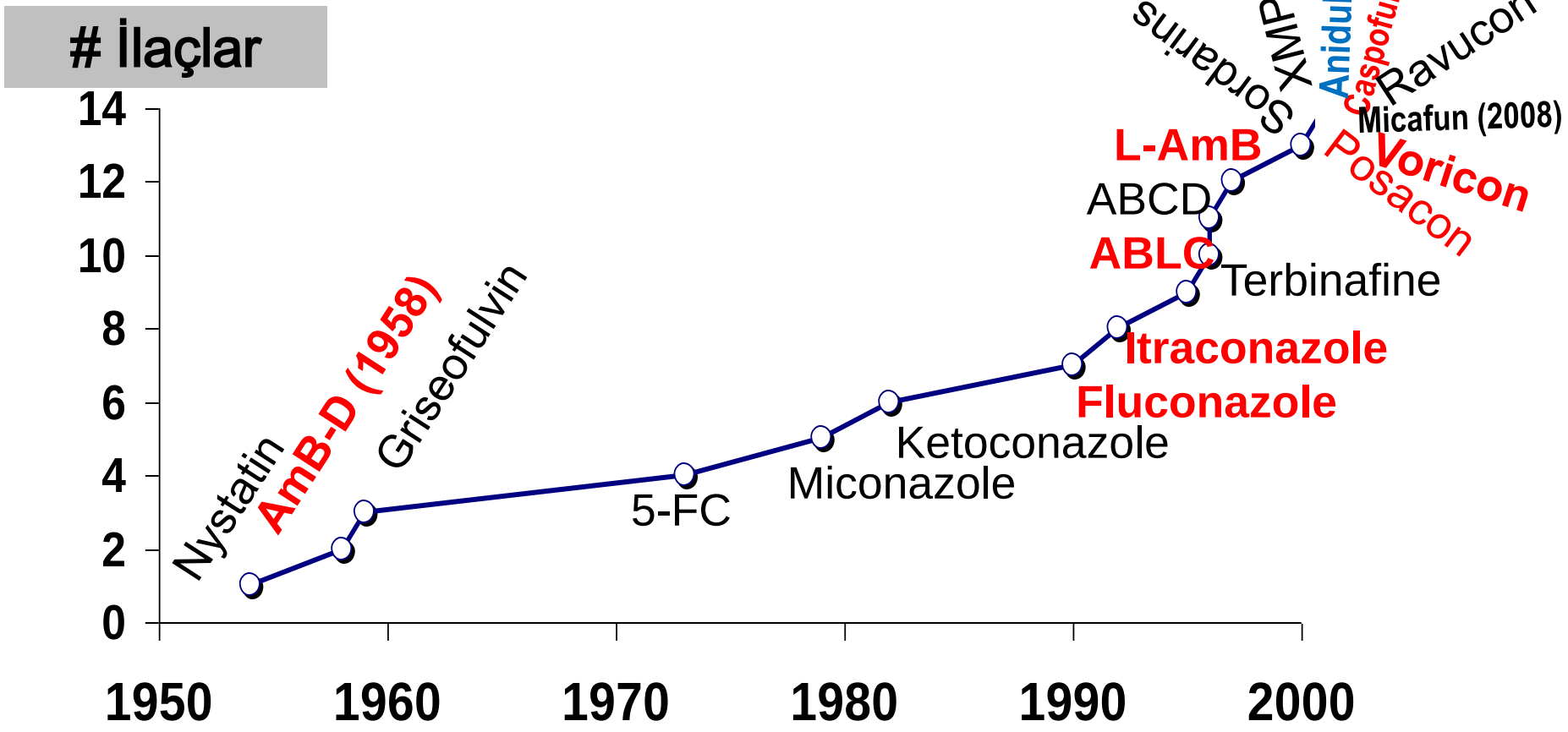
Risk altında olup "ateşi" olanlara

Profilaksi

"Risk" altındaki herkese

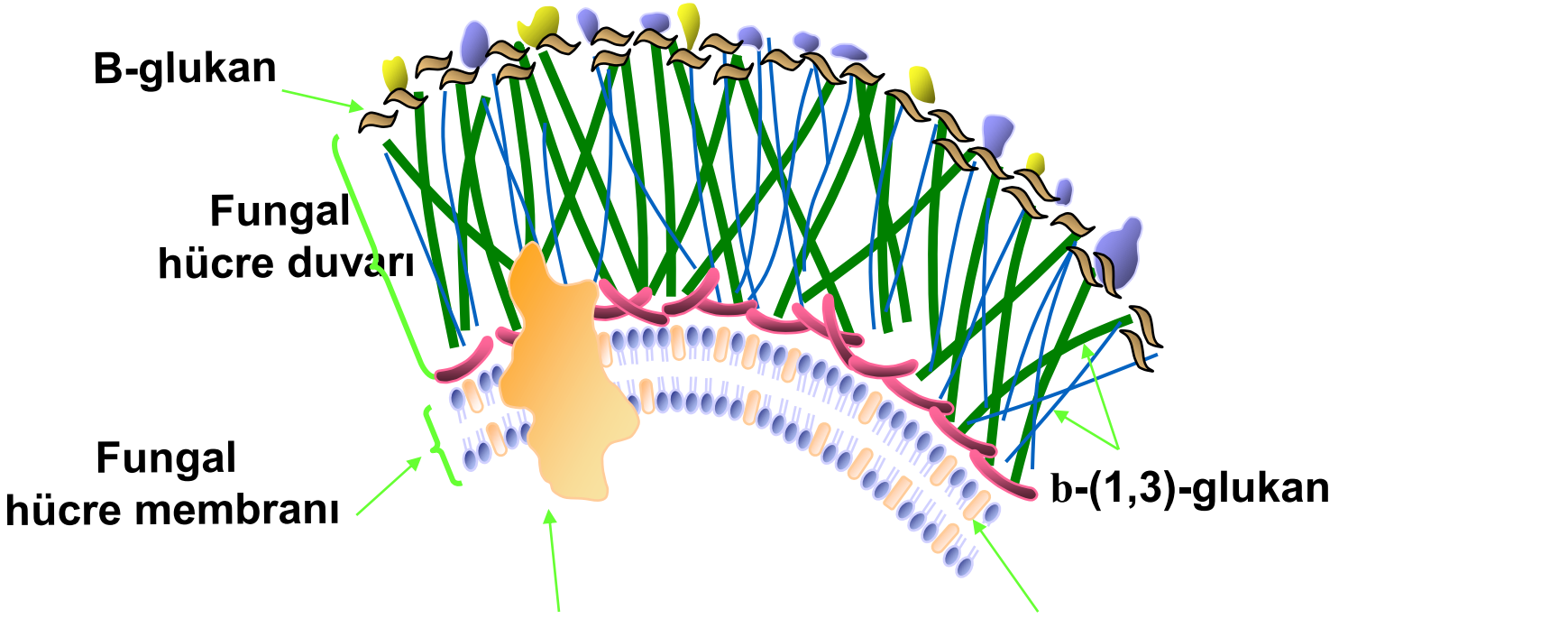


Tıbbi mikoloji: Son 60 yılı



Antifungallerin mantarda etki yerlerine göre sınıflaması

1. Mantar duvar sentezini bozanlar→ **Ekinokandinler**
2. Mantar sitoplazmik membranını bozanlar→ **Polienler / Triazoller**
3. Mantar DNA sentezini bozanlar→ **Pirimidin analoğu**



Ekinokandinlerle azoller arasında çapraz direnç oluşmaz

Antifungal tedavi seçiminde önemli noktalar

- Son dönemde azol, ekinokandin kullanımı
- Lokal epidemiyoloji – Baskın olan *Candida* türü, duyarlılık verileri
- Antifungal dirençli *Candida* türleri ile kolonizasyon
- Antifungal ilaca intolerans öyküsü
- İlaç etkileşimleri

Antifungal tedavi seçiminde önemli noktalar

- Hastalığın şiddeti

Antifungal ilaç;

✓Etken mikroorganizmaya duyarlı

✓İnfeksiyon dokusunda yeterli konsantrasyona ulaşmalı

RESEARCH ARTICLE

The Effect on Mortality of Fluconazole or Echinocandins Treatment in Candidemia in Internal Medicine Wards

Francesco G. De Rosa[1☯*], Silvia Corcione[1☯], Claudia Filippini[2], Stefania Raviolo[1],

670 Kandidemi atağı, **mortalite %39**

Ekinokandin & flukonazol; %11.7 Vs %39 **p=0.02**

Table 3. Multivariate subgroup analysis in patients treated.

Variable	OR	IC 95%	
Early treatment	0.462	0.216	0.988
Removal of CVC ≤ 48h	0.129	0.061	0.274
Age	1.024	1.002	1.047
Sepsis [a]	3.629	1.768	7.450
Cirrhosis	7.913	2.471	25.340
Neurologic diseases	2.618	1.311	5.226
Definitive therapy with echinocandins	0.473	0.222	1.000

[a]Sepsis include 32 patients with severe sepsis and 8 with septic shock.

J Antimicrob Chemother 2017; **72**: 2368–2377
doi:10.1093/jac/dkx116 Advance Access publication 28 April 2017

Journal of Antimicrobial Chemotherapy

Efficacy of anidulafungin in 539 patients with invasive candidiasis: a patient-level pooled analysis of six clinical trials

Bart Jan Kullberg[1]*, José Vasquez[2], Piroon Mootsikapun[3], Marcio Nucci[4], José-Artur Paiva[5], Jorge Garbino[6],

Toplam 636 hasta, invazif kandida infeksiyonu

- Anidulafungin only: *n* = 378 (200 mg yükleme, 100 mg idame)
- Anidulafungin → oral flukonazol (*n* = 157)
- Anidulafungin → oral vorikonazol (*n* = 101)

Table 3. Distribution of patients with infections caused by a single or multiple *Candida* isolates, at baseline, global response at end of intravenous therapy (EOivT) and all-cause mortality (days 14 and 28) in the modified ITT (mITT) population ($N = 539$)

			All-cause mortality, *n* (%)	
Patients with *Candida* infection at baseline		Global response at EOivT, *n* (%); 95% CI	day 14	day 28
Patients with single *Candida* isolate, *n* (%)	496 (92.0)			
C. albicans, *n* (%)	227 (45.8)	177 (78.0); 72.6%–83.4%	32 (14.1)	44 (19.4)
C. non-*albicans*, *n* (%)	269 (54.2)	204 (75.8); 70.7%–81.0%	33 (12.3)	51 (19.0)
Patients with multiple *Candida* isolates	43 (8.0)			
C. albicans and ≥1 *C.* non-*albicans*	31 (72.1)	23 (74.2); 58.8%–89.6%	3 (9.7)	6 (19.4)
>1 *C.* non-*albicans*	12 (27.9)	8 (66.7); 40.0%–93.3%	2 (16.7)	2 (16.7)

Sonuçta;

- Tedavi başarısı anidulafungin ile %76.4
- 14 günlük mortalite %13.0
- 28 günlük mortalite %19.1
- **Anidulafungin** etkili, yan etki açısından güvenilir antifungal

J Antimicrob Chemother 2017; 72: 2368–2377

Ekinokandinler

- Kandidemi ve invazif kandidozda tercih edilmektedir.

- Santral sinir sistemi
- Göz tutulumu
- Üriner sistem infeksiyonu

!

- Vorikonazol → ~~ÜSİ~~
- Flukonazol

ÜSİ'de AmB deoksikolat tercih edilir

- Lipozomal Amfoterisin B ± flusitozin

Asemptomatik kandidüri-üriner kateter

- Üriner kateteri çıkar.
- Çıkarmak mümkün değilse değiştir.
- Asemptomatik kandidürisi olan hastalarda üriner kateterin çıkartılması **%41**, üriner kateterin değişimi %20 oranında kandidürinin kaybolması ile sonuçlanır.

Clinical Infectious Diseases
IDSA GUIDELINE

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- Kandida türleri İK sonrası önemli mortalite ve morbidite nedeni
- >%90 invazif hastalıktan;
- *C. albicans, C. glabrata C. tropicalis, C. parapsilosis, C. krusei* sorumlu

IDSA Management of Candidiasis CID 2016:62

Comparison of ESCMID and IDSA guidelines for the treatment of invasive candidiasis.

Clinical syndrome	IDSA 2016 [82]	ESCMID 2012 [83]
Candidemia, non-neutropenic patient	Echinocandin (Caspofungin 70/50 mg, Micafungin 100 mg, Anidulafungin 200/100 mg): *strongly recommended*; *high-quality evidence* Fluconazole 800 mg (12 mg/kg) then 400 mg/d: *strongly recommended*; *high-quality evidence*[a] Lipid formulation AMB (3–5 mg/kg/d): *strongly recommended*; *high-quality of evidence*[b]	Echinocandin (Caspofungin 70/50 mg, Micafungin 100 mg, Anidulafungin 200/100 mg): SoR: A; QoE:I Liposomal amphotericin B 3 mg/kg/d: SoR: B; Qoe:I Voriconazole 6/3 mg/kg/d: SoR: B; Qoe:I Fluconazole 400–800 mg/d: SoR: C; Qoe:I
Candidemia, neutropenic patient	Echinocandin (Caspofungin 70/50 mg, Micafungin 100 mg, Anidulafungin 200/100 mg): *strongly recommended*; *moderate-quality evidence* Fluconazole 800 mg (12 mg/kg) then 400 mg/d: *weakly recommended; low-quality evidence*	Echinocandin (Caspofungin 70/50 mg, Micafungin 100 mg): SoR: A; Qoe: II Anidulafungin 200/100 mg/d: SoR: B; Qoe: II Liposomal amphotericin B 3 mg/kg/d: SoR: B; Qoe: II
Chronic disseminated candidiasis (hepatosplenic)	Lipid formulation AMB (3–5 mg/kg/d) or an echinocandin for several weeks followed by oral fluconazole 400 mg/d: *strongly recommended*; *low-quality evidence*	Lipid formulation AMB for 8 weeks: SoR: A; Qoe: III Fluconazole for 3 months; *SoR: B; Qoe: III*
Candida endocarditis: native valve	Lipid formulation AMB (3–5 mg/kg/d) ± flucytosine 25 mg/kg 4 times/d or high dose echinocandin (Caspofungin 150 mg/d; Micafungin 150 mg/d; Anidulafungin 200 mg/d): *strongly recommended*; *low-quality evidence*	Liposomal amphotericin B ± flucytosine for 6–8 weeks followed by fluconazole: SoR: B; Qoe: II Surgery within 1 week: *SoR: A*; *Qoe: II*
Candida endocarditis: prosthetic valve	Same anti-fungal regimens: *strongly recommended*; *low-quality evidence* Chronic suppressive anti-fungal therapy with fluconazole (400–800 mg daily): *strongly recommended*; *low-quality evidence*	Liposomal amphotericin B 5 mg/kg/d: SoR: B; Qoe: III Surgery
Candida osteomyelitis	Fluconazole 400 mg/d for 6–12 months or an echinocandin for at least 2 weeks followed by fluconazole 400 mg/d for 6–12 months: *strongly recommended*; *low-quality evidence*	Fluconazole 400 mg/d for 6–12 months: SoR: A; Qoe: II Liposomal amphotericin B 3 mg/kg/d or lipid formulation 5 mg/kg/d for 2–6 weeks followed by fluconazole 400 mg/d for 5–11 months: SoR: A; Qoe: II
Candida chorioretinitis without vitritis	Fluconazolo 800 mg/d then 400–800 mg/d or voriconazole 400 mg × 2/d then 300 mg × 2/d for 4–6 weeks: *strongly recommended*; *low-quality evidence*	Liposomal amphotericin B 5 mg/kg/d: SoR: B; Qoe: III
Candida chorioretinitis with vitritis	Same as above plus intravitreal injection (AMB deoxycholate 5–10 μg/0.1 mL sterile water or voriconazole 100 μg/0.1 mL sterile water): *strongly recommended*; *low-quality evidence*	Same as above plus intravitreal injection (AMB deoxycholate 5–10 μg/0.1 mL sterile water): SoR: B; Qoe: II Same as above plus intravitreal injection (voriconazole 100 μg/0.1 mL sterile water): SoR: B; Qoe: III
Central nervous system candidiasis	Liposomal AMB 5 mg/kg) ± flucytosine 25 mg/kg 4 times/d followed by fluconazole 400–800 mg/kg/d: *strongly recommended*; *low-quality evidence*	Liposomal AMB 3 mg/kg + flucytosine 150 mg/d for 10 weeks followed by fluconazole 3 mg/kg/d for 5 weeks: SoR: B; Qoe: III Liposomal AMB 3 mg/kg/d + fluconazole 6 mg/kg/d for 4 weeks: SoR: B; Qoe: III

Nötropenik olmayan hastada kandidemi

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[1]University of Alabama at Birmingham; [2]Veterans Affairs Ann Arbor Healthcare System and University of Michigan Medical School, Ann Arbor; [3]University of Wisconsin, Madison; [4]University of Pittsburgh, Pennsylvania; [5]Johns Hopkins University School of Medicine, Baltimore, Maryland; [6]University of Texas Health Science Center, Houston; [7]Cooper Medical School of Rowan University, Camden, New Jersey; [8]University of Pennsylvania, Philadelphia; [9]Georgia Regents University, Augusta; [10]Weill Cornell Medical Center and Cornell University, New York, New York; [11]Children's Hospital of Pennsylvania, Philadelphia; and [12]Harper University Hospital and Wayne State University, Detroit, Michigan

Keywords. candidemia; invasive candidiasis; fungal diagnostics; azoles; echinocandins.

EXECUTIVE SUMMARY

Background

Invasive infection due to *Candida* species is largely a condition associated with medical progress, and is widely recognized as a major cause of morbidity and mortality in the healthcare environment. There are at least 15 distinct *Candida* species that cause human disease, but >90% of invasive disease is caused by the 5 most common pathogens, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. Each of these organisms has unique virulence potential, antifungal susceptibility, and epidemiology, but taken as a whole, significant infections due to these organisms are generally referred to as invasive candidiasis. Mucosal *Candida* infections—especially those involving the oropharynx, esophagus, and vagina—are not considered to be classically invasive disease, but they are included in these guidelines. Since the last iteration of these guidelines in 2009 [1], there have been new data pertaining to diagnosis, prevention, and treatment for proven or suspected invasive candidiasis, leading to significant modifications in our treatment recommendations.

Summarized below are the 2016 revised recommendations for the management of candidiasis. Due to the guideline's relevance to pediatrics, the guideline has been reviewed and endorsed by the American Academy of Pediatrics (AAP) and the Pediatric Infectious Diseases Society (PIDS). The Mycoses Study Group (MSG) has also endorsed these guidelines. The panel followed a guideline development process that has been adopted by the Infectious Diseases Society of America (IDSA), which includes a systematic method of grading both the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong) [2] (Figure 1). [3] The guidelines are not intended to replace clinical judgment in the management of individual patients. A detailed description of the methods, background, and evidence summaries that support each recommendation can be found in the full text of the guideline.

I. What Is the Treatment for Candidemia in Nonneutropenic Patients?

Recommendations

1. An echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) is recommended as initial therapy *(strong recommendation; high-quality evidence)*.
2. Fluconazole, intravenous or oral, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species *(strong recommendation; high-quality evidence)*.
3. Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant *Candida* isolates. Testing for echinocandin susceptibility should be considered in patients who have had prior treatment with an echinocandin and among those who have infection with *C. glabrata* or *C. parapsilosis (strong recommendation; low-quality evidence)*.

Received 28 October 2015; accepted 2 November 2015.
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Clinical Infectious Diseases®

DOI: 10.1093/cid/civ933

1. Başlangıç tedavisi olarak bir ekinokandin önerilir. (Güçlü öneri; yüksek nitelikli kanıt)

Nötropenik olmayan hastada kandidemi

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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2. Fluconazole, intravenous or oral, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species *(strong recommendation; high-quality evidence)*.
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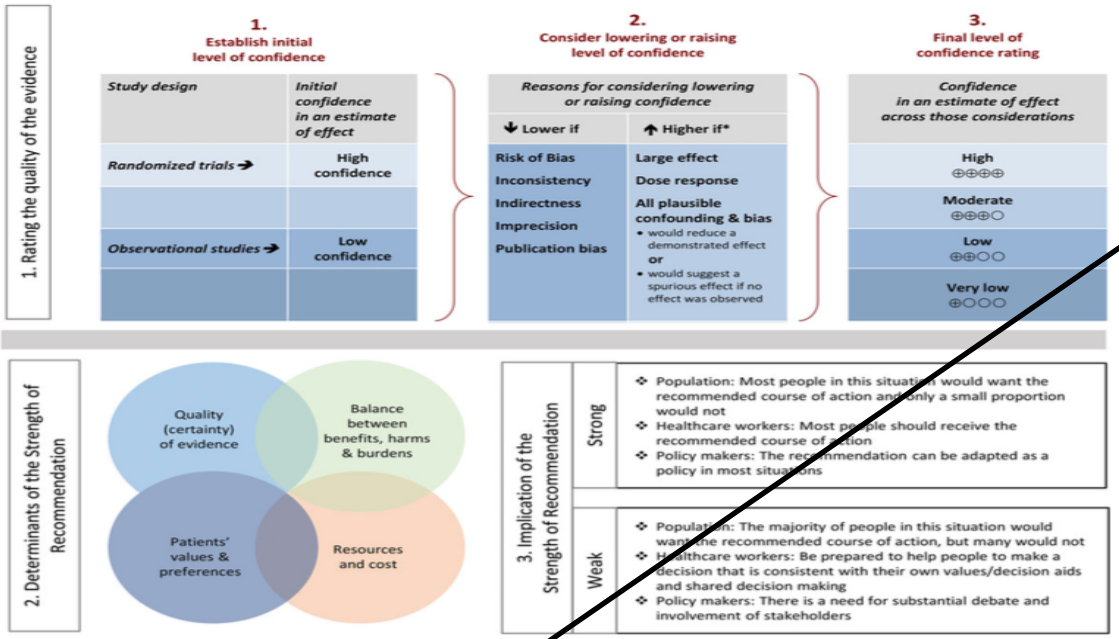
2. Flukonazol (i.v ya da oral) ancak kritik düzeyde hasta olmayan ve flukonazole dirençli olmadığı düşünülen Candida türlerinden kaynaklanan kandidemi gibi bazı hasta gruplarında başlangıç tedavisi için kabul edilebilir bir alternatif olabilir. (Güçlü öneri; yüksek nitelikli kanıt)

Nötropenik olmayan hastada kandidemi



igure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development nd Evaluation (GRADE) methodology (unrestricted use of the figure granted by the US GRADE Network) [3].

4. Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (eg, *C. albicans*), and have negative repeat blood cultures following initiation of antifungal therapy *(strong recommendation; moderate-quality evidence)*.
5. For infection due to *C. glabrata*, transition to higher-dose fluconazole 800 mg (12 mg/kg) daily or voriconazole 200–300 (3–4 mg/kg) twice daily should only be considered among patients with fluconazole-susceptible or voriconazole-susceptible isolates *(strong recommendation; low-quality evidence)*.
6. Lipid formulation amphotericin B (AmB) (3–5 mg/kg daily) is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents *(strong recommendation; high-quality evidence)*.
7. Transition from AmB to fluconazole is recommended after 5–7 days among patients who have isolates that are susceptible to fluconazole, who are clinically stable, and in whom repeat cultures on antifungal therapy are negative *(strong recommendation; high-quality evidence)*.
8. Among patients with suspected azole- and echinocandin-resistant *Candida* infections, lipid formulation AmB (3–5 mg/kg daily) is recommended *(strong recommendation; low-quality evidence)*.
9. Voriconazole 400 mg (6 mg/kg) twice daily for 2 doses, then 200 mg (3 mg/kg) twice daily is effective for candidemia, but offers little advantage over fluconazole as initial therapy *(strong recommendation; moderate-quality evidence)*. Voriconazole is recommended as step-down oral therapy for selected cases of candidemia due to *C. krusei (strong recommendation; low-quality evidence)*.
10. All nonneutropenic patients with candidemia should have a dilated ophthalmological examination, preferably performed by an ophthalmologist, within the first week after diagnosis *(strong recommendation; low-quality evidence)*.
11. Follow-up blood cultures should be performed every day or every other day to establish the time point at which

3. Başlangıç antifungal tedavisi sonrası ekinokandinden flukonazole geçiş (genellikle **5-7** gün sonra), klinik olarak stabil, tekrarlanan kan kültürü negatif olan hastalarda ve flukonazole duyarlı izolatlarda ve önerilir. (Güçlü öneri, orta nitelikte kanıt)

IDSA 2016: Nötropenik olmayan hastalar

- Başlangıç tedavisi **ekinokandin**
  - Durumu kritik olmayan hastalarda, direnç düşünülmüyorsa flukonazol

- Azol ve ekinokandin duyarlılık testi:
  - Daha önce ekinokandin tedavisi alanlar
  - *C. glabrata* veya *C. parapsilosis* infeksiyonları

- Klinik durum stabilleşirse ve flukonazole duyarlıysa ekinokandinden

flukonazole geçiş 5-7 gün

- *C. glabrata* infeksiyonunda, yüksek doz flukonazol 800

mg (12 mg/kg) veya vorikonazol 200 - 300 (3-4 mg/kg)

günde 2 kez düşünülebilir.

IDSA 2016: Nötropenik hastalar

- Başlangıç tedavisi **ekinokandin**
  - Daha düşük alternatif: amfoterisin B (lipid)
  - Durumu kritik olmayanlarda flukonazol: daha önce flukonazol maruziyeti yoksa.

- ***C krusei:*** **ekinokandin**, amfoterisin B (lipid), veya voriconazole

- Metastatik komplikasyonlarda: minimum tedavi süresi eradikasyonu dökümente ettikten sonra 2 hafta
- Funduskopik muayene: nötropeniden çıktıktan 1 hafta sonra
- Kateter çıkarımı olguya özgü değerlendirilmelidir.

Antifungaller ve immünosüpresiflerin klinik etkileşimleri

	Siklosporin A	Takrolimus	Mikofenolat mofetil	Sirolimus
Lipozomal AmB[1]	Potansiyel nefrotoksisite	Potansiyel nefrotoksisite	NR	NR
Flukonazol[2]	Siklo AUC ↑ (1.8 kat)	Oral takro kons ↑ (5 katta kadar)	NR	Sirol kons ↑
İtrakonazol[3]	Siklo ↑	Takro ↑	NR	Sirol kons ↑
Vorikonazol[4]	Siklo C_{max} & AUC ↑ (%13, %70)	Takro C_{max} & AUC ↑ (%117, % 221)	NR	Sirol C_{max} & AUC ↑ (6.6 kat, 11 kat)
Posakonazol[5]	Siklo kons↑	Takro C_{max} & AUC ↑ (%121, % 358)	NR	Sirol C_{max} & AUC ↑ (6.7-kat, 8.9-kat)
Kaspofungin[6]	Kaspofungin AUC ↑ (%35)	Takrolimus C_{min} ↓ (% 26)	–	NR
Mikafungin[7]	–	–	–	Sirol AUC ↑ (%21)
Anidulafungin[8]	–	–	NR	NR

NR — KUB'de spesifik öneri yok

Doz ayarlaması gerekmez

Eş zamanlı kullanılabilir , ancak monitorizasyon/doz ayarlaması gerekir

Kontra-indikedir

1. AmBisome® (amfoterisin B) Kısa Ürün Bilgisi. Gilead Sciences. August 2012; **2.** TRIFLUCAN® (flukonazol) Kısa Ürün Bilgisi. Pfizer Ltd. Ekim 2009
3. Sporanox® (itrakonazol) Kısa Ürün Bilgisi .Janssen.Haziran 2014; **4.** Vfend® (vorikonazol) Kısa Ürün Bilgisi. Pfizer Ltd. Ocak 2014
5. Noxafil® (posakonazol) Kısa Ürün Bilgisi. Merck Sharp & Dohme. Şubat 2014; **6.** Cancidas® (kaspofungin) Kısa Ürün Bilgisi. Merck Sharp & Dohme. Ağustos 2014
7. MYCAMINE™ (mikafungin sodyum) Flakon Kısa Ürün Bilgisi. Astellas Pharma İlaç Tiç.A.Ş. Ocak –Şubat 2014 **8.** Eraxis® (anidulafungin) Kısa Ürün Bilgisi. Pfizer Ltd. Temmuz 2014

Tedavi başarısızlığı

- Klinik bulguların kötüleştiği veya klinik iyileşmenin olmadığı hastalarda **tedavi başlangıcından üç günden sonra** kan kültürlerinde üremenin devam etmesi

Ne yapalım?

- Öncelikle mikrobiyolojiyi zorlayalım.
  - ✓Kandida türü?
  - ✓Antifungal duyarlılık testleri?
- Kontrol kan kültürü alalım
- Tedaviyi değiştirelim mi?

IDSA & ESCMID Rehberleri;

❖Ampirik olarak başka bir antifungal başlanmışsa bile hasta

- Nötropenik değilse,
- Stabilse
- Kan kültüründe üreme olmamış
- Üreyen kandida suşu flukonazole duyarlıysa
- 10 gün içinde **flukonazole** geçilebilir (‘’step down strateji’’)
- Dökümante edilmiş kandidemide toplam tedavi süresi ilk alınan negatif kan kültüründen sonra **14 gün**

European J Int Med 34 (2016) 21–28

Sağlıklı günler...