

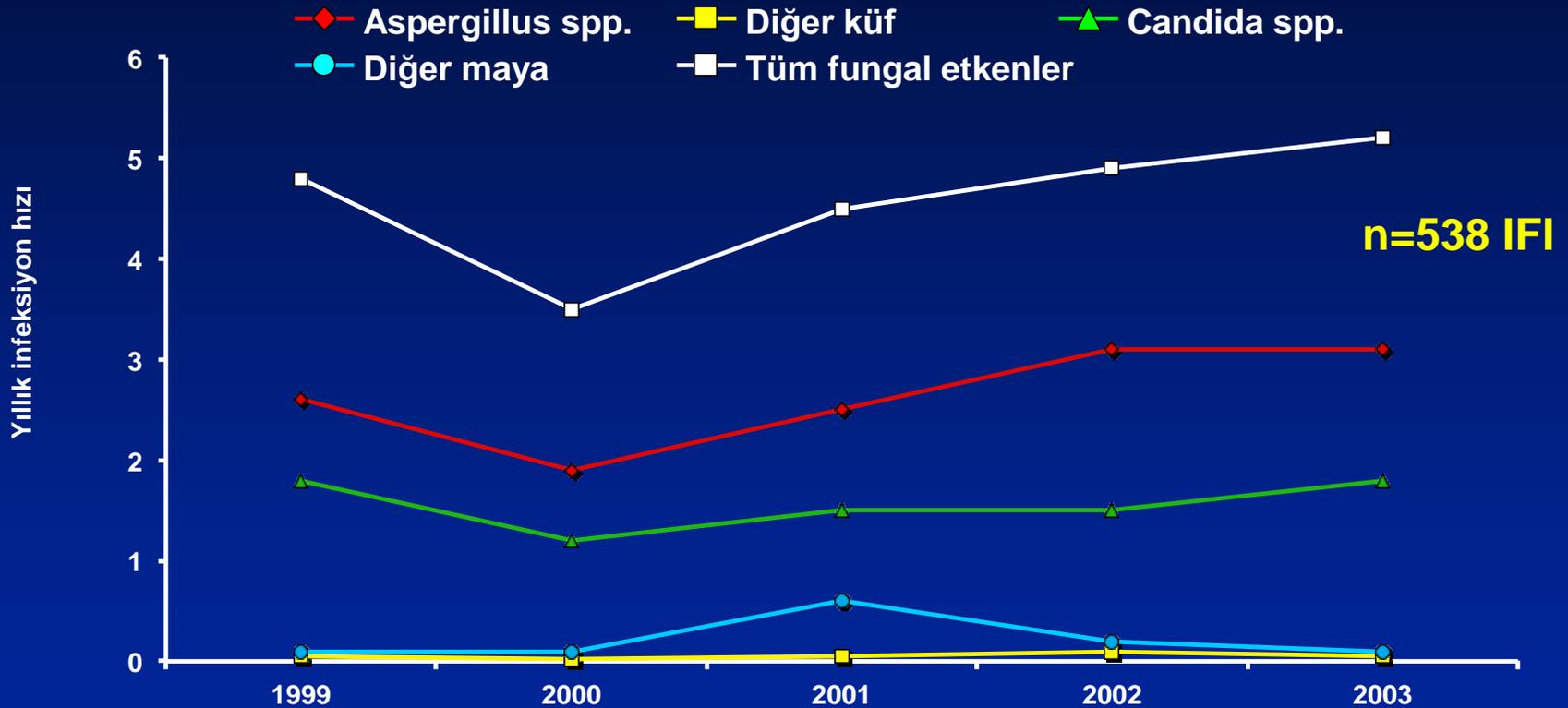
Candida İnfeksiyonları

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**Hacettepe Üniversitesi Tıp Fakültesi
İç Hastalıkları Anabilim Dalı,
İnfeksiyon Hastalıkları Ünitesi,
Ankara**

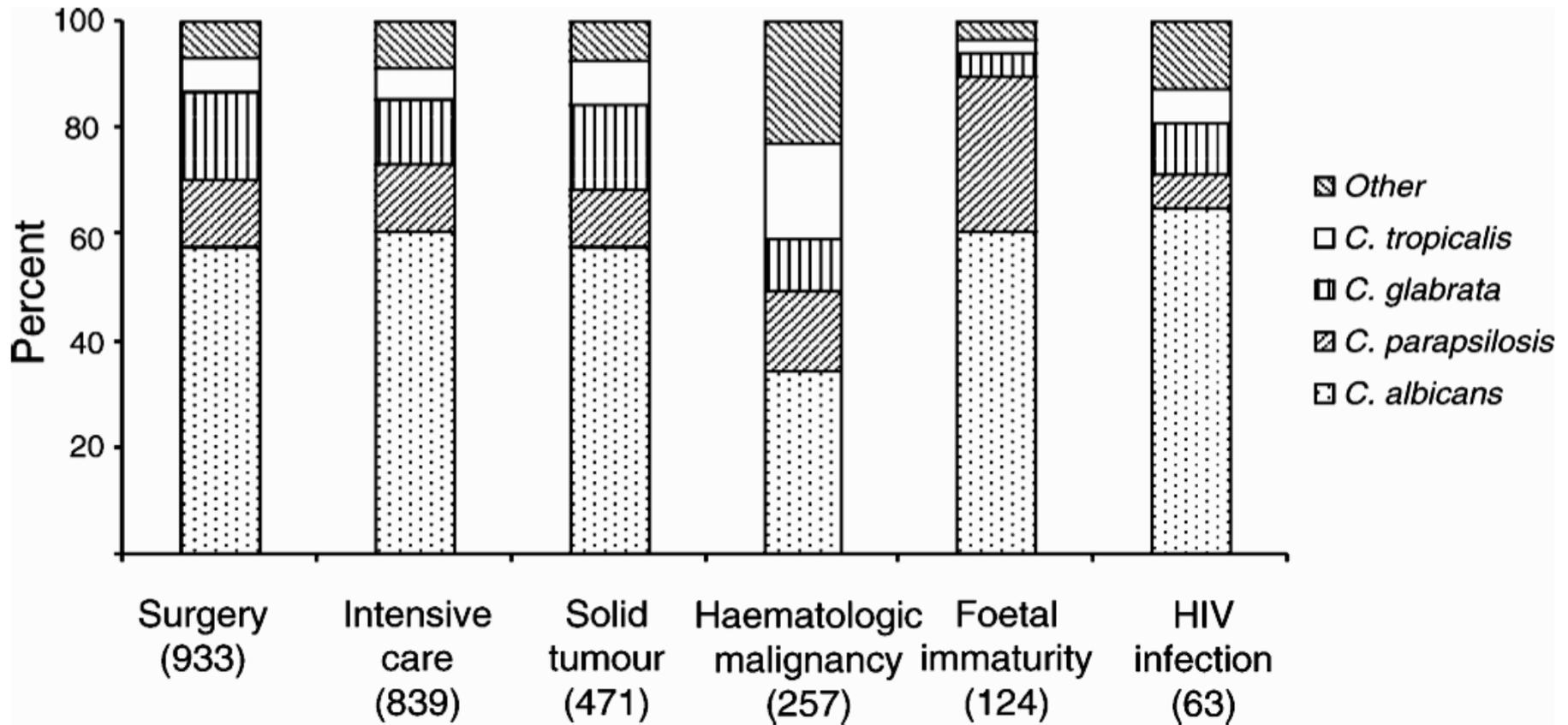


Hematolojik Kanserli Hastalarda İnvaziv Fungal İnfeksiyon Sıklığı



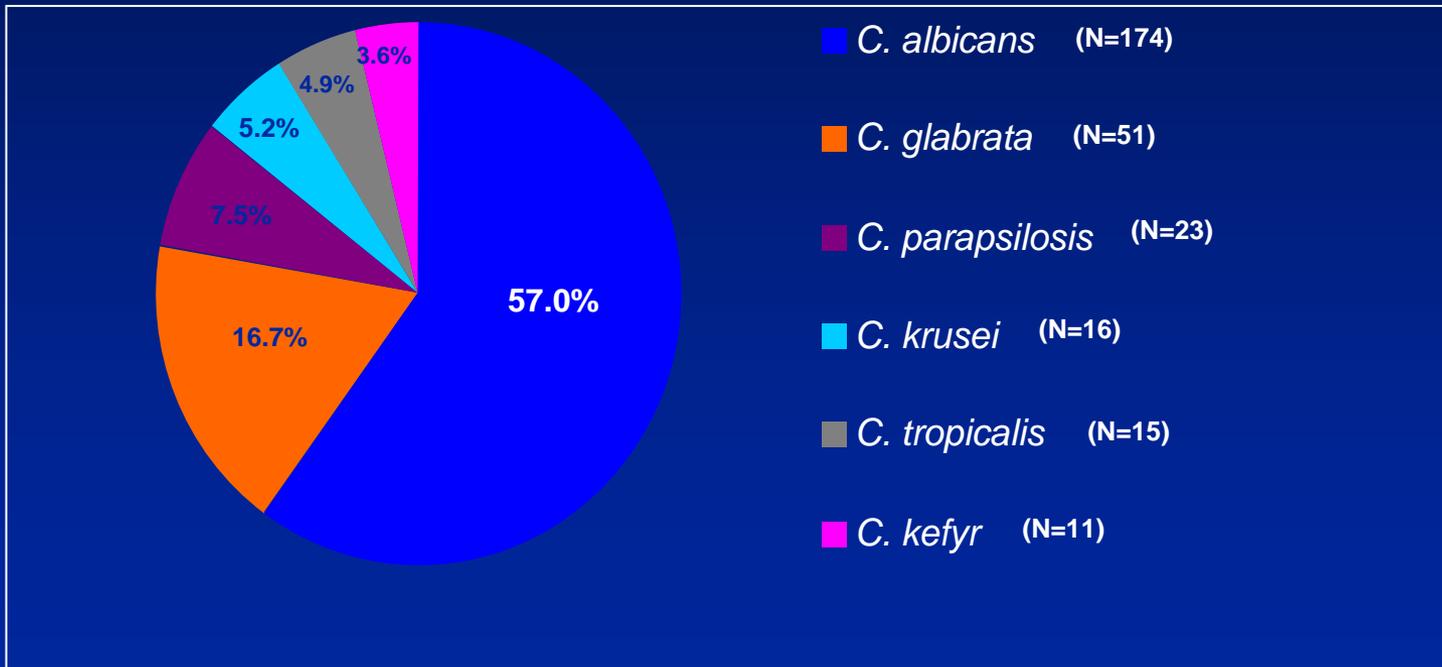
Avrupa'da Kandidemi

Kandida Türlerinin Dağılımı



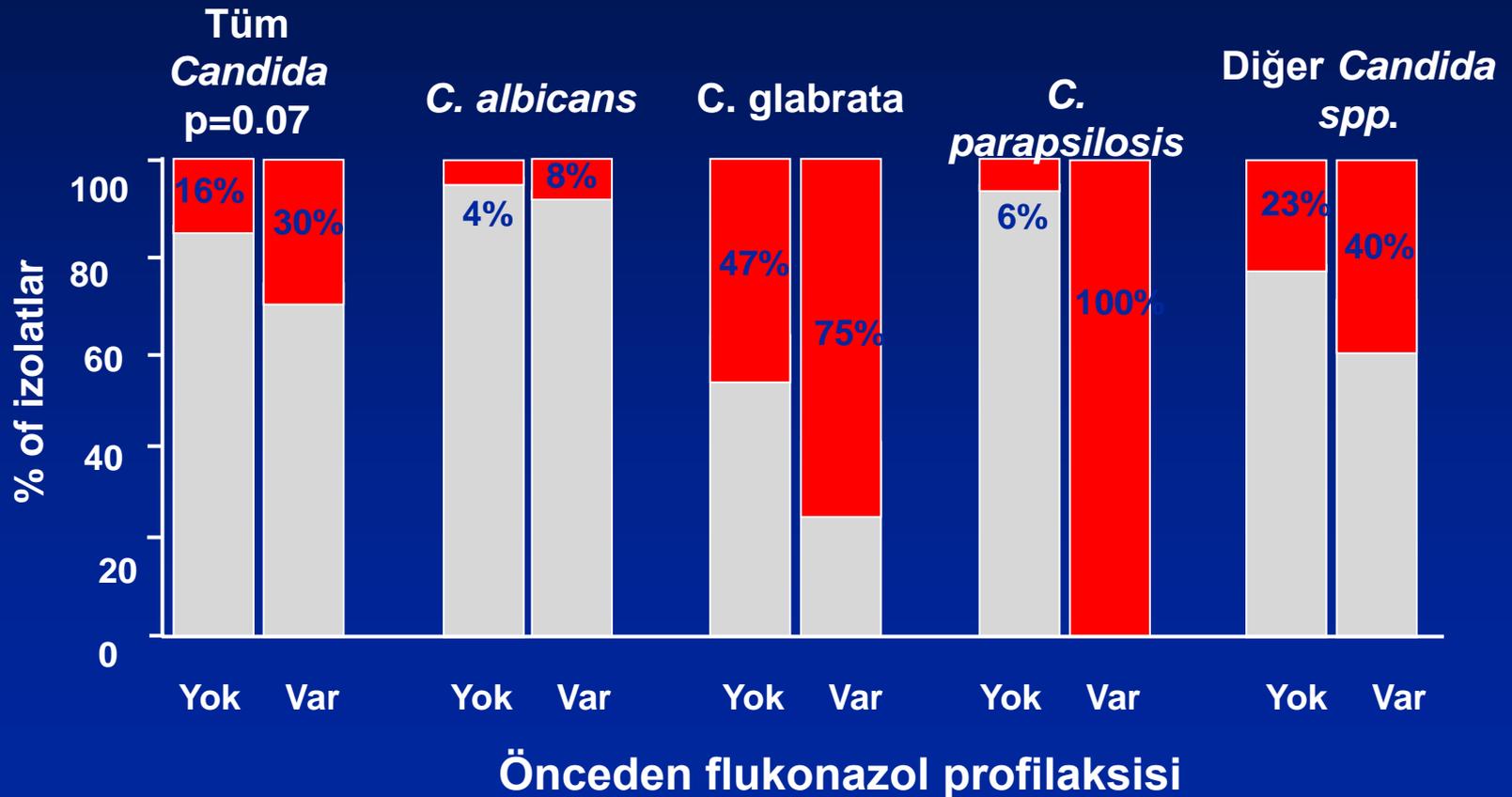
İnvaziv kandida İnfeksiyonlarının YBÜ'deki Epidemiyolojisi

- Prospektif, çok merkezli çalışma
- Candida infeksiyonu olan 271 erişkin hasta, Ekim 2005 - Mayıs 2006 arası
 - 305 *Candida spp.* izole edilmiş



YBÜ'de İnvaziv Kandida İnfeksiyonları

- 210 kandida izolatında *in vitro* flukonazol duyarlılığı

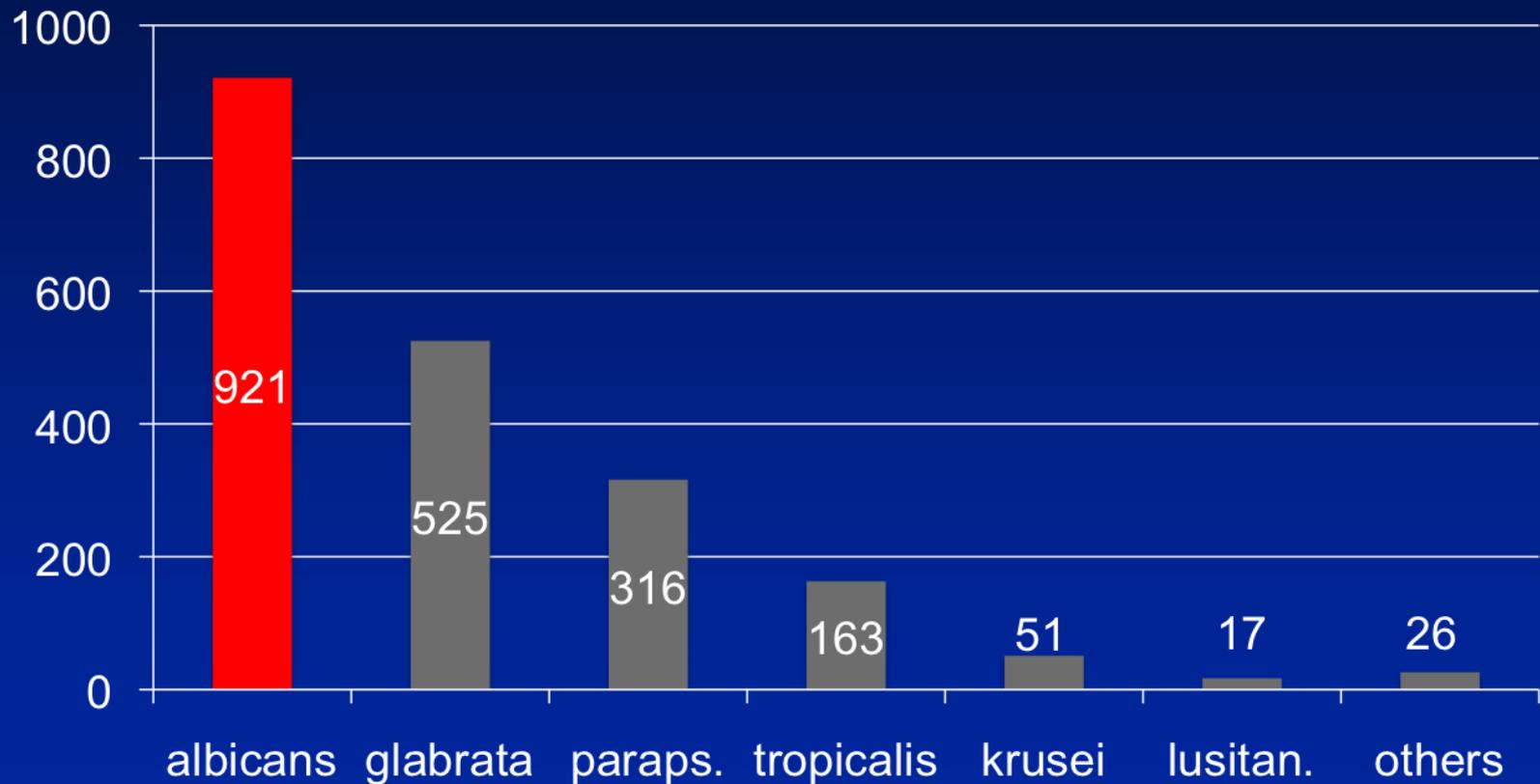


“Prospective Antifungal Therapy (PATH) Alliance” Çalışmasında Kandidemi

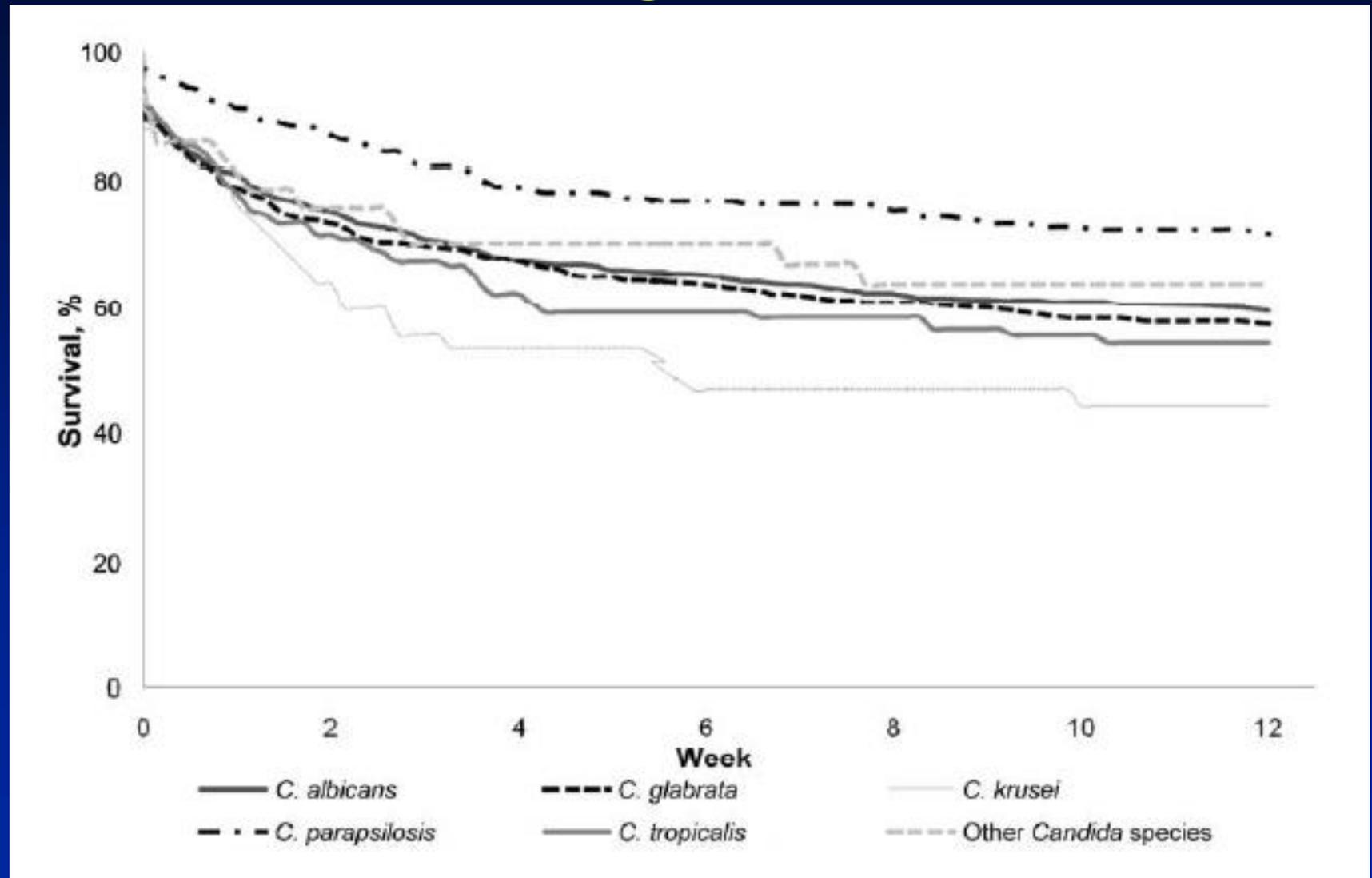
- **2019 hasta**
 - **1 Temmuz 2004-5 Mart 2008**
- ***C. albicans* (%45.6)**
- **12. haftada kaba mortalite %35.2**
 - ***C. parapsilosis* %23.7**
 - ***C. krusei* %52.9**

Kandida Türlerinin Dağılımı

“*PATH Registry*”



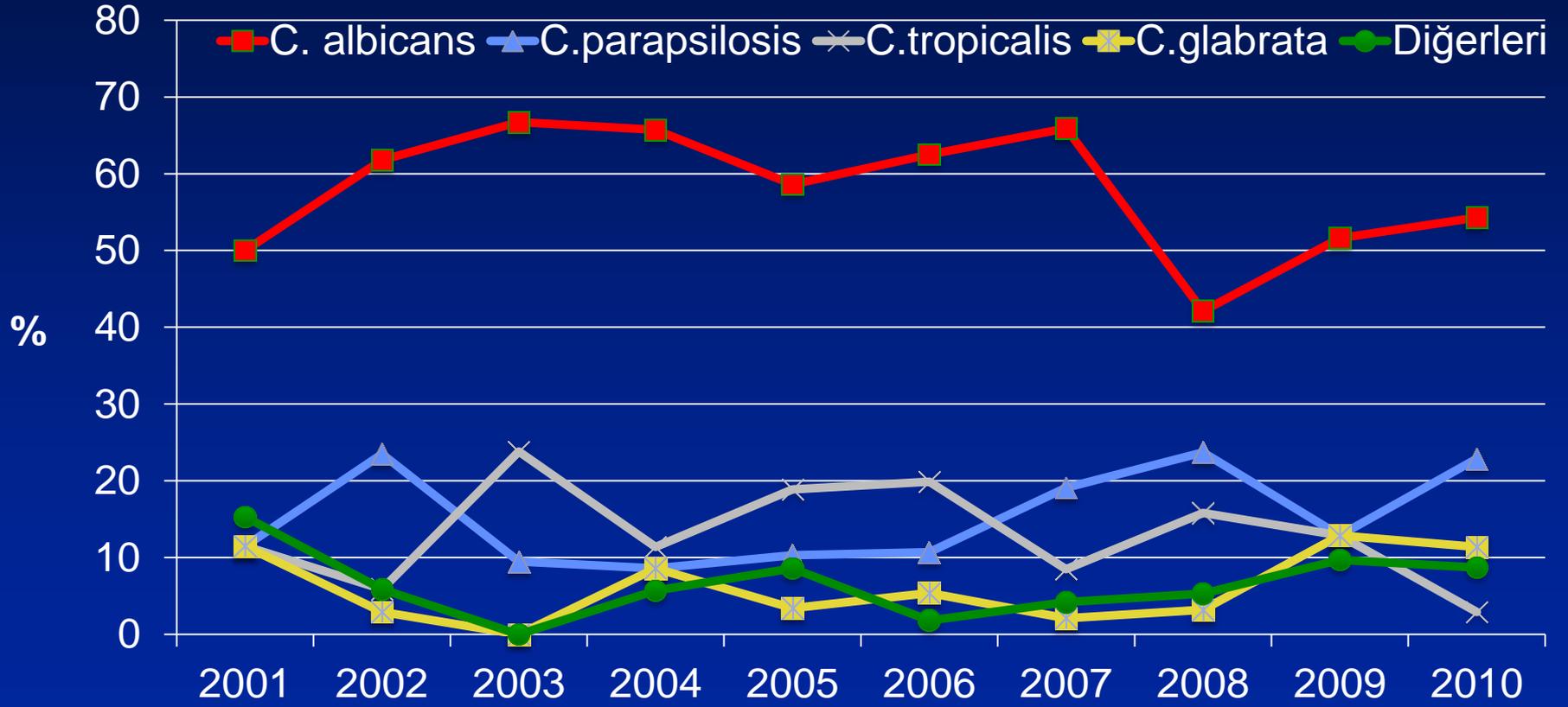
Kandidemili Hastalarda 12. Haftada Sağkalım-PATH



Hacettepe'de Kandidemi

- 2001-2011, retrospektif analiz
- 18.426 pozitif kan kültürü
 - 858 kandida-pozitif kan kültürü
 - 381 izolat, tek hasta, ilk atak
 - Kanıda en sık üretilen 5. patojen

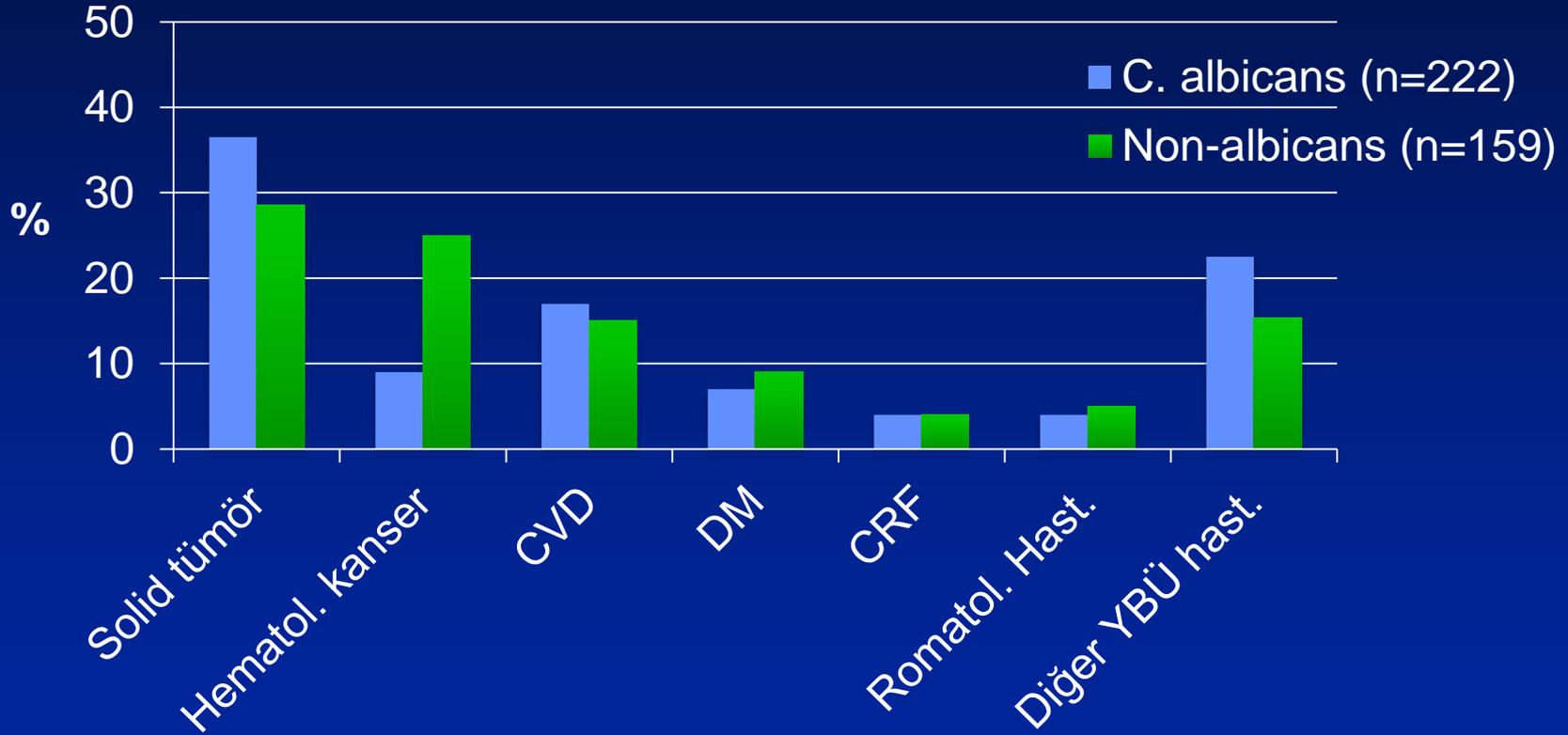
Hacettepe'de Kandidemi İzolatları n=381



Alp S, Arıkan-Akdağlı S & Akova M. 2012

Alta Yatan Hastalıklar

Hacettepe 2001-2010

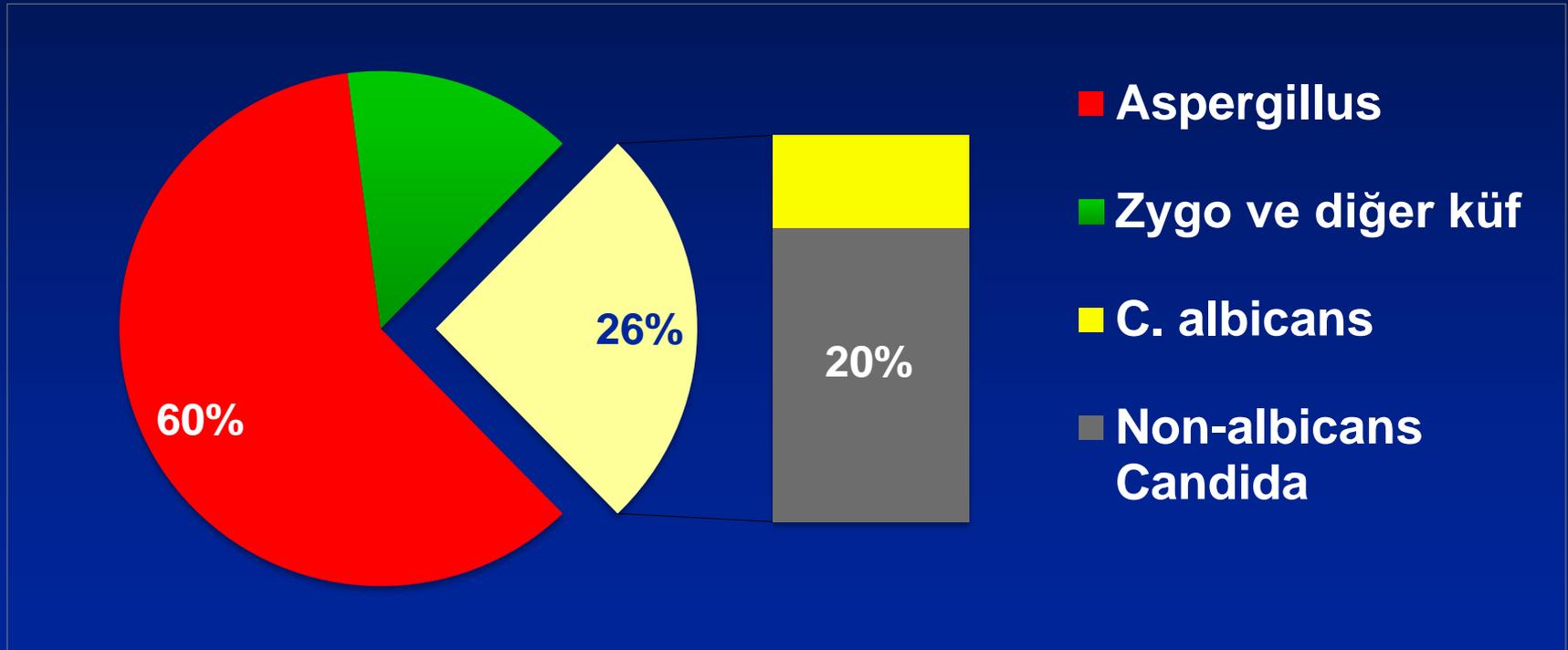


Erişikin Kök Hücre Nakli Yapılan Hastalarda İnvaziv Fungal İnfeksiyonlar

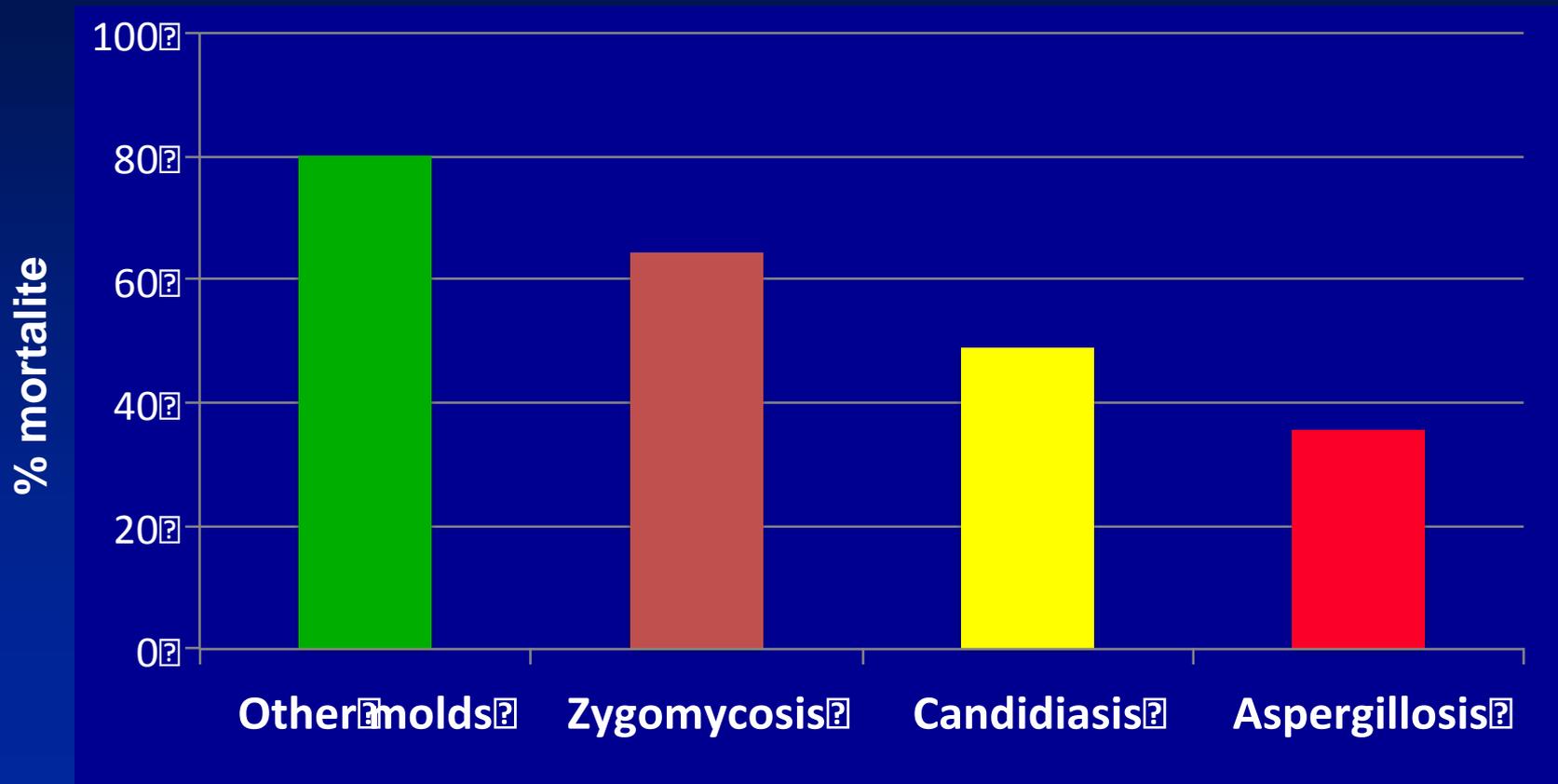
‘PATH Alliance Registry’

- **Kuzey Amerika’da 16 merkezde 234 hastada 250 IFI**
 - **%69 allojeneik**
 - **%31 otolog**
 - **IFI dağılımı**
 - **6 ve 12. haftalarda sağkalım**

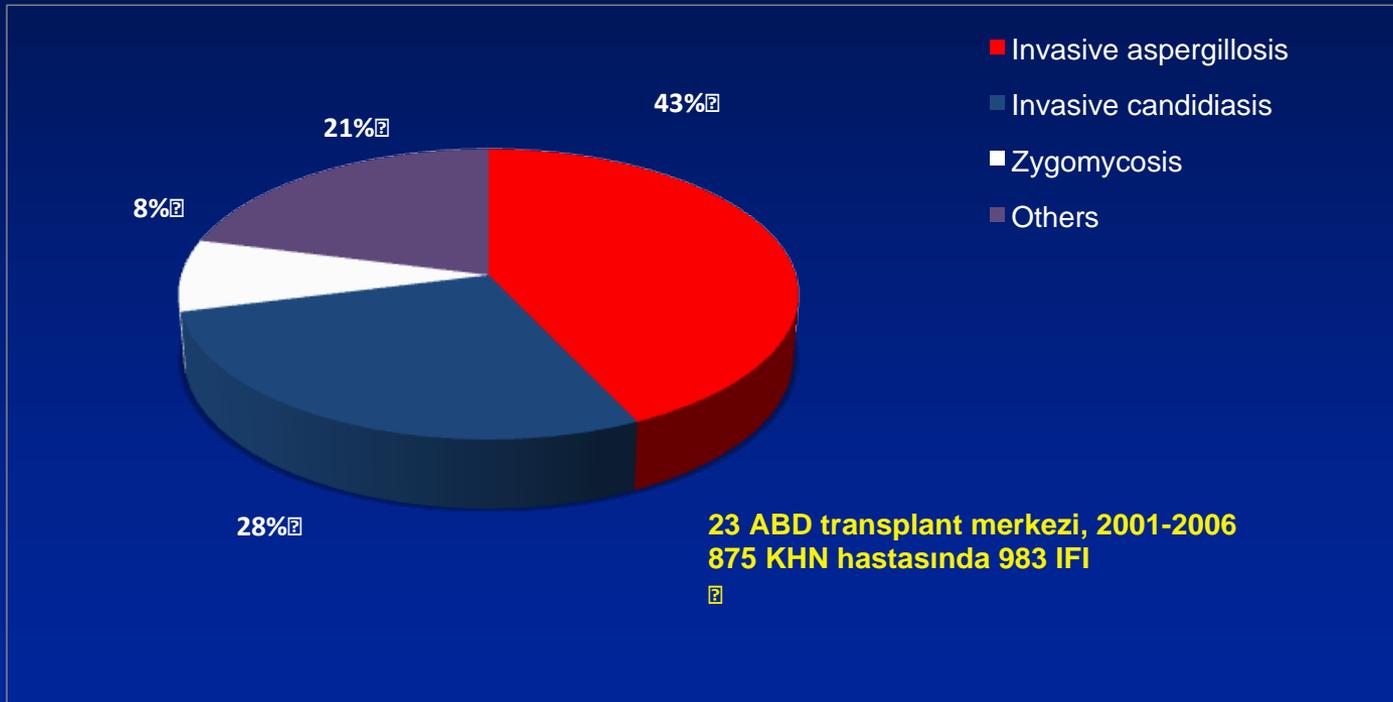
İnvaziv Fungal İnfeksiyon Dağılımı



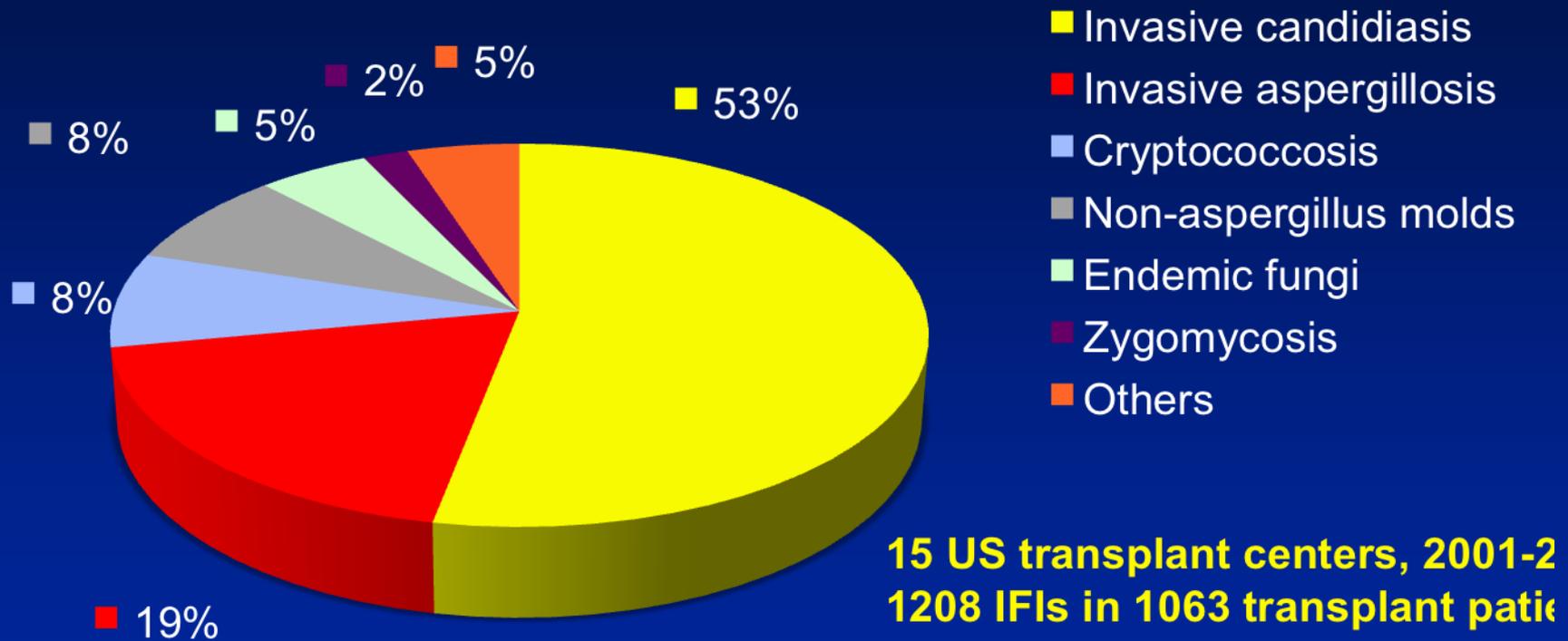
12. Haftada Mortalite



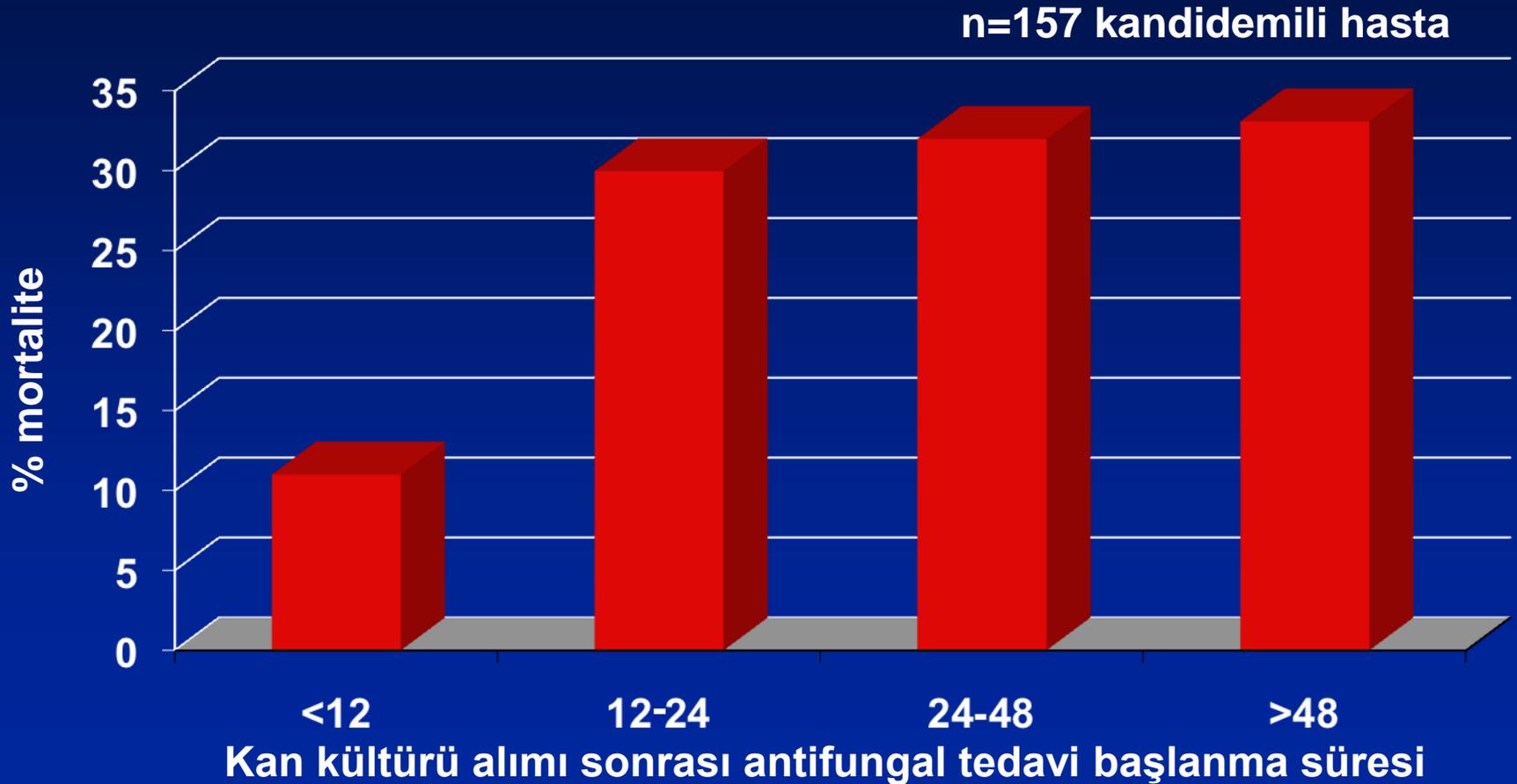
Kök Hücre Alıcılarında IFI TRANSNET Veritabanı



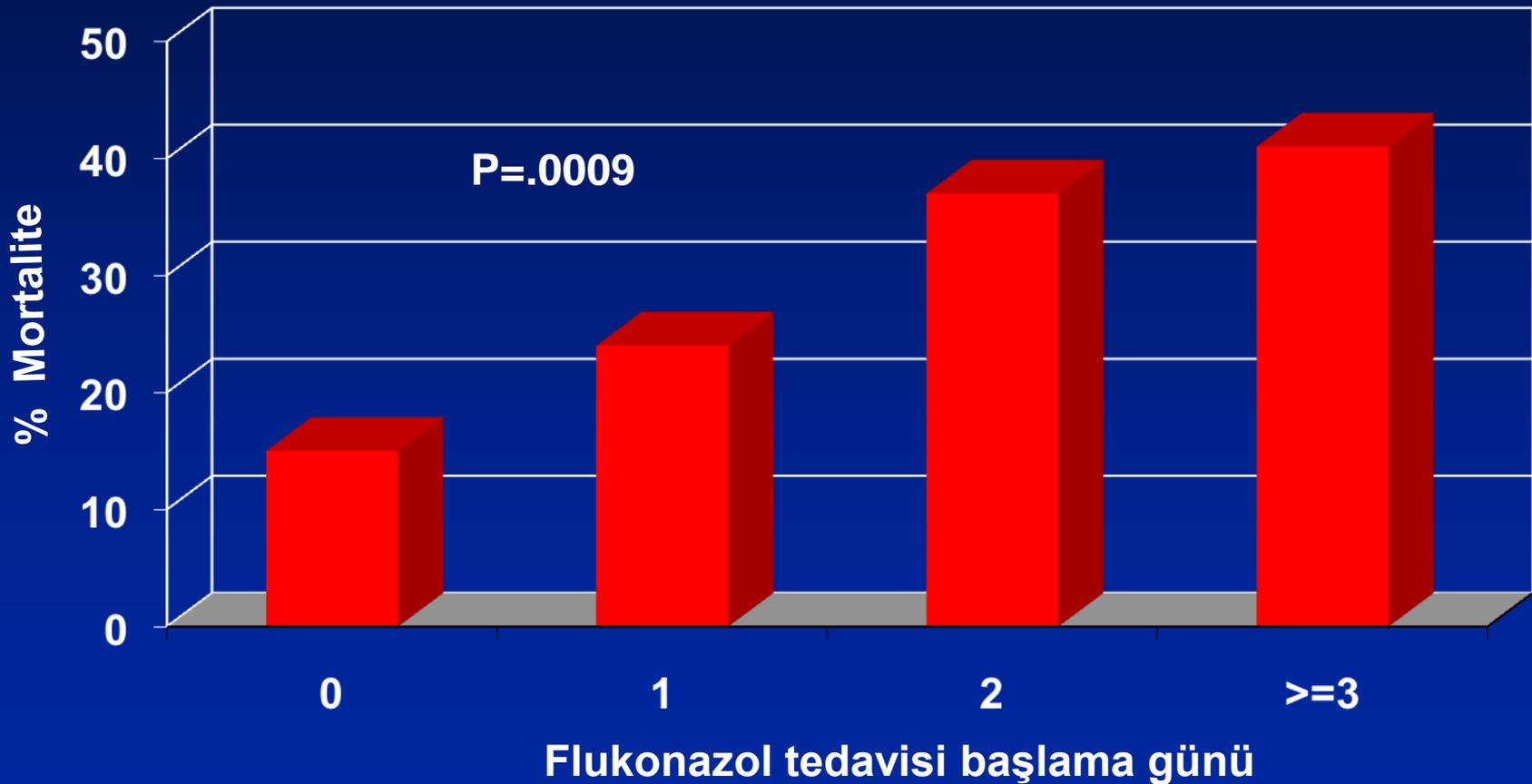
Solid Organ Alıcılarında IFI- TRANSNET



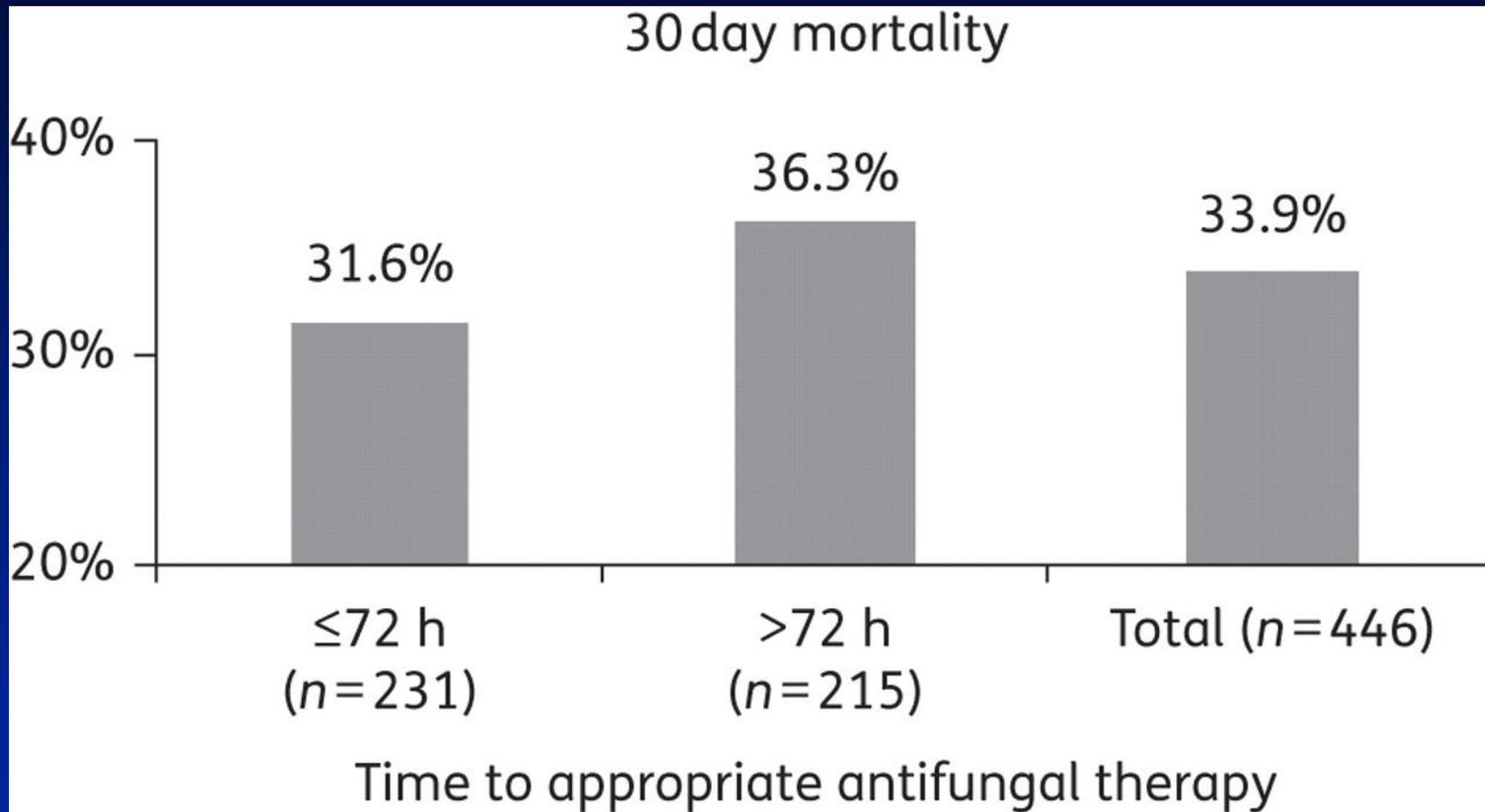
Kandidemide Empirik Tedavi Gecikmesi



Kandidemi Mortalitesi ve Flukonazol Tedavisinde Gecikme



Uygun Antifungal Tedavi Başlangıç Zamanına Göre Mortalite

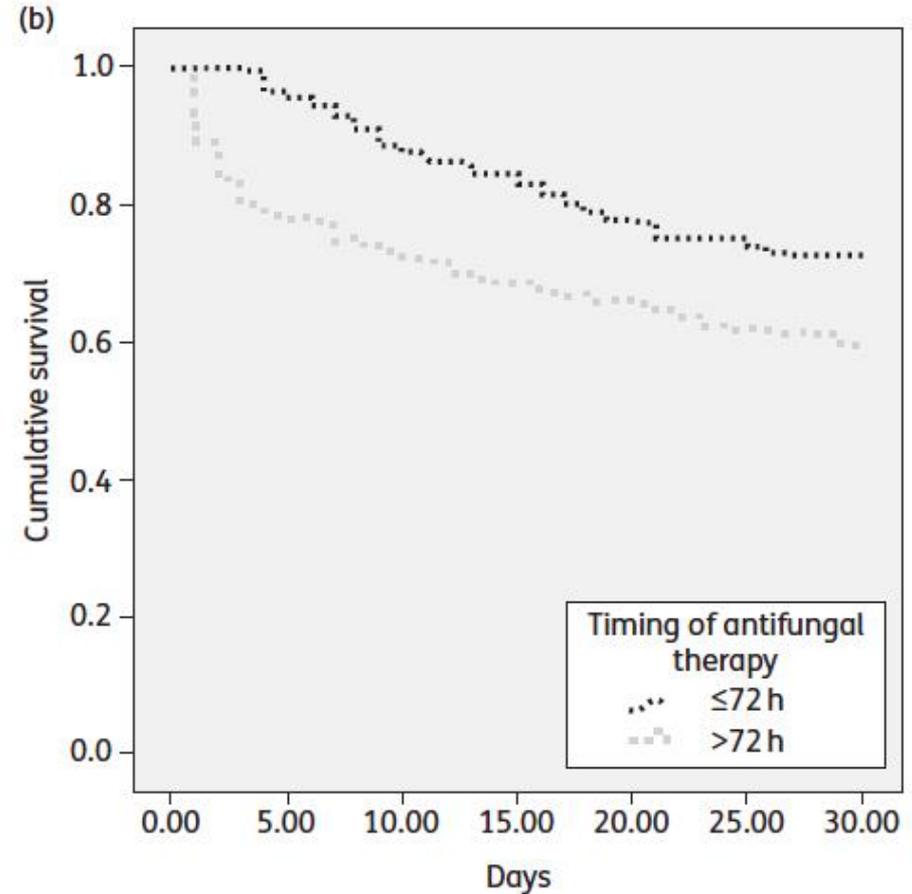
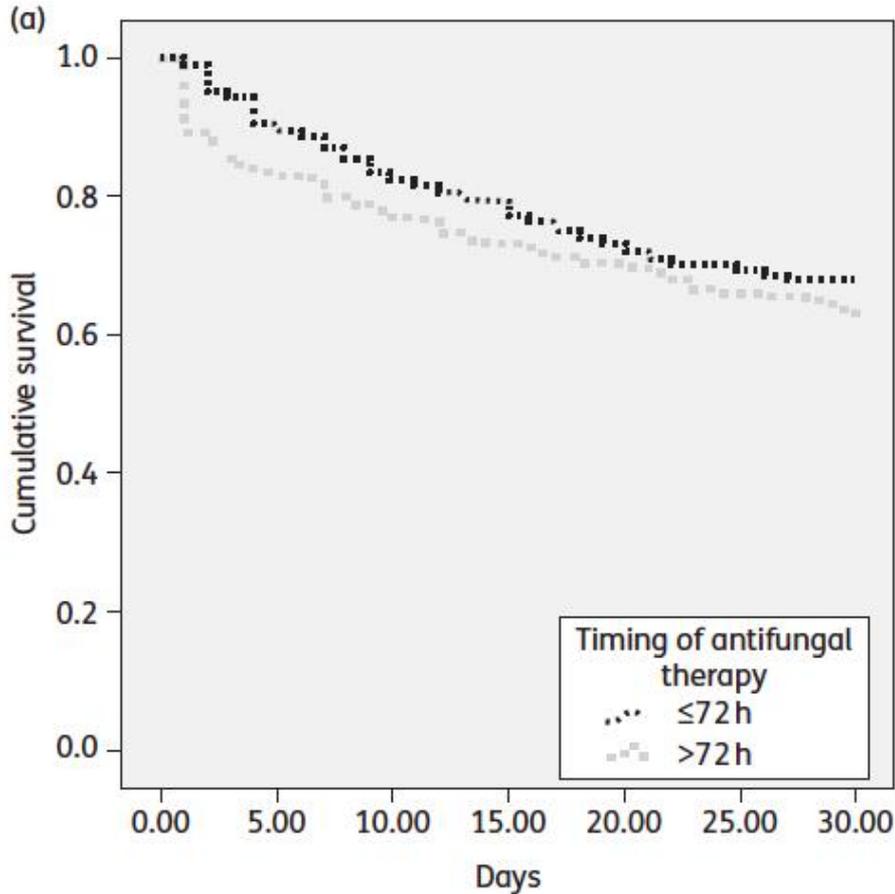


Bağımsız Mortalite Faktörleri

Çok Değişkenli Analiz

Characteristic	HR	95% CI	P value
APACHE II Score	1.11	1.09-1.13	<0.001
Cirrhosis	2.15	1.48-3.13	<0.001
HIV infection	2.03	1.11-3.72	0.02
Age (years)	1.01	1.00-1.02	0.06
Serum crea. >2 mg/dL	0.84	0.58-1.20	0.34
Antifungal timing >72 h	1.10	0.80-1.52	0.57

Tedavi Süresi ve Mortalite



Tüm antifungal tedavi alanlar

>24 s tedavi alanlar

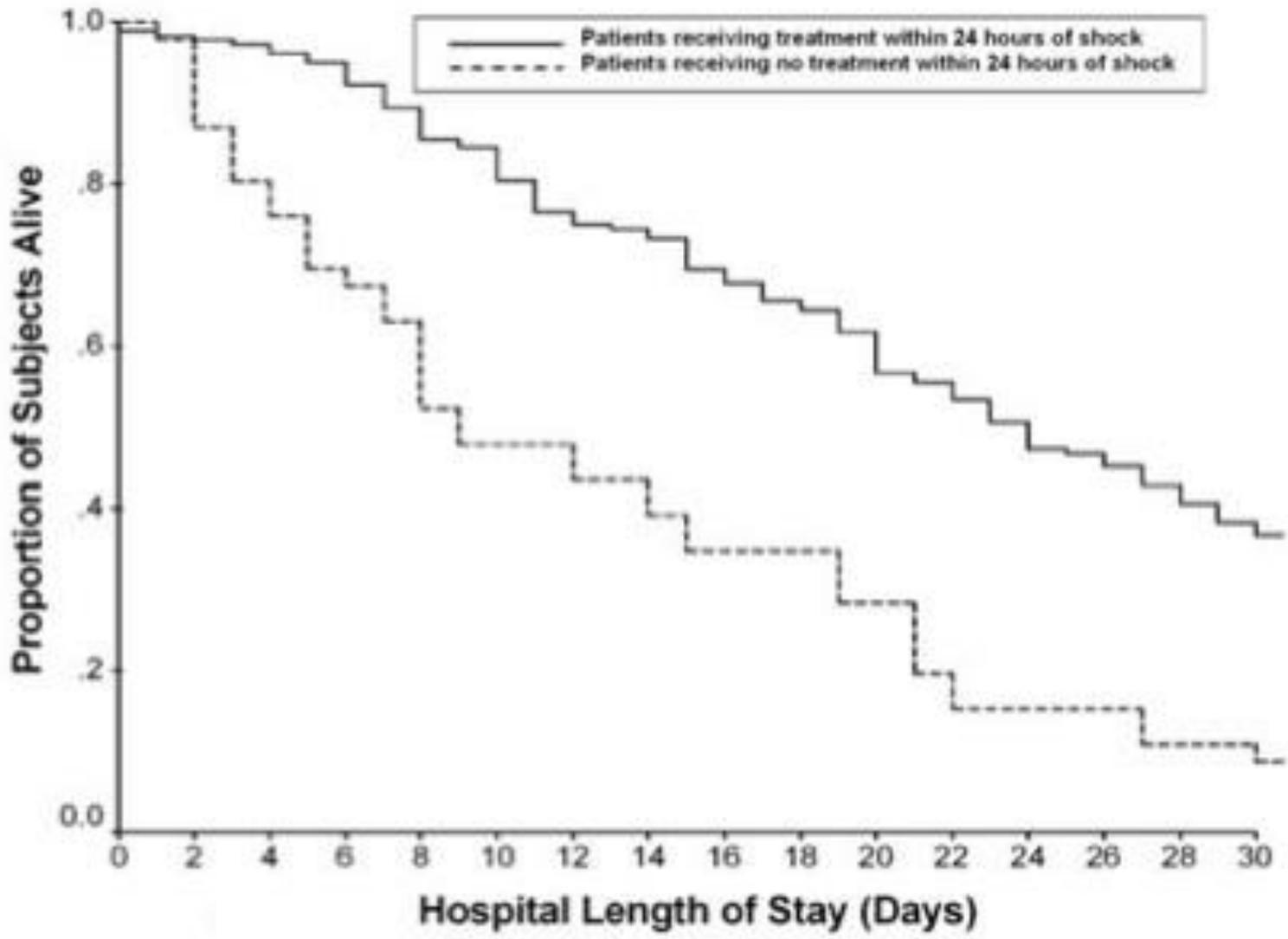
Grim SA, et al. J. Antimicrob. Chemother. 2012;67:707

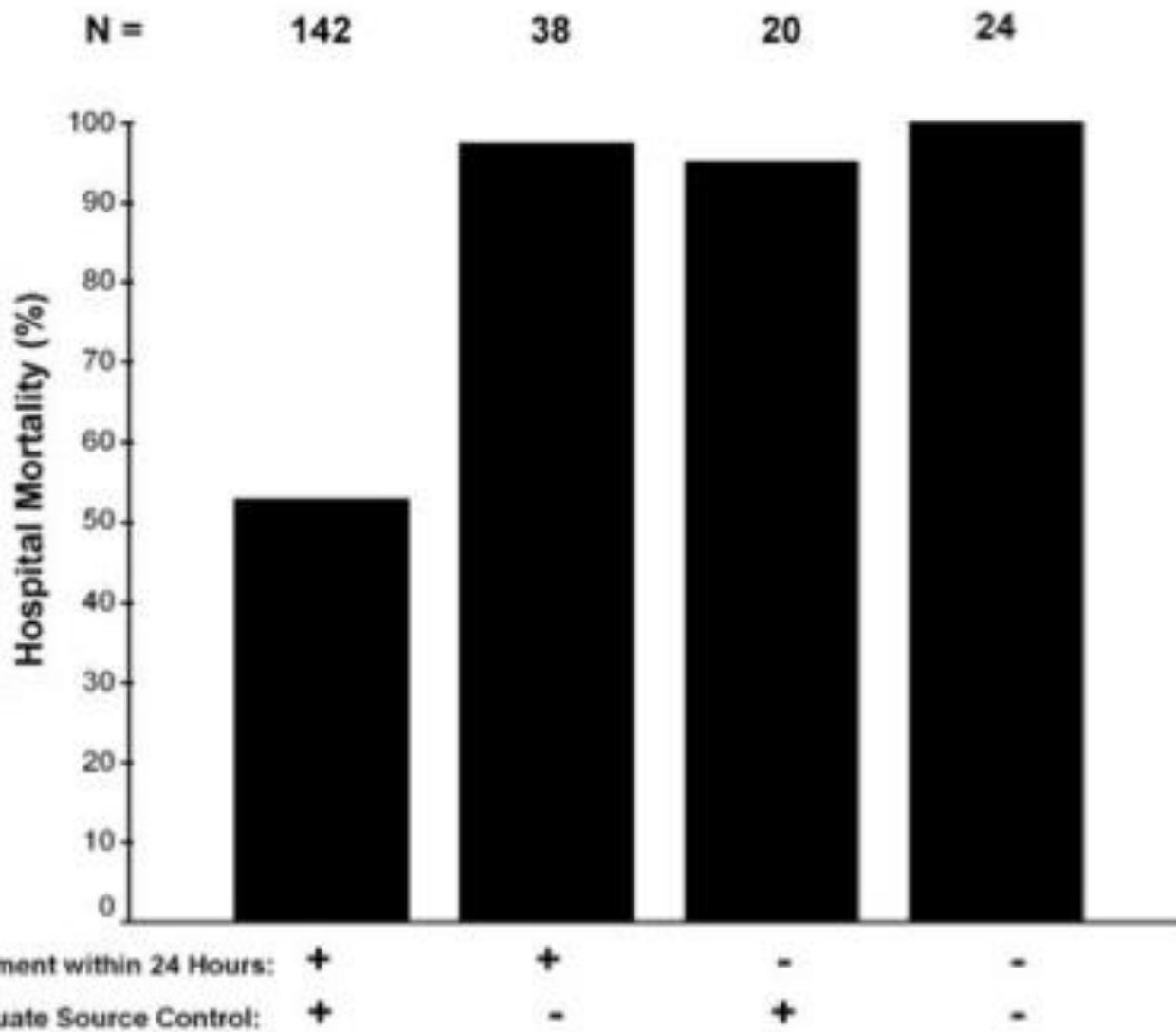
Uygun Antifungal Tedavi ve Erken SVK Çekilmesinin Mortalite Üzerine Etkisi

	Total cohort, <i>n</i> (%)	Survival, <i>n</i> (%)	Death, <i>n</i> (%)	<i>P</i>
Total cohort	188	121	67	
adequate antifungal treatment (<48 h)	66 (35.1)	43 (35.5)	23 (34.4)	0.298
CVC removal in first 48 h	71 (37.8)	58 (47.9)	13 (19.4)	<0.001
antifungal+CVC removal	37 (19.7)	30 (24.8)	7 (10.4)	0.018
Primary candidaemia	148	100	48	
adequate antifungal treatment (<48 h)	50 (33.8)	36 (36)	14 (18.9)	0.411
CVC removal in first 48 h	64 (43.2)	53 (53)	11 (22.9)	0.001
antifungal+CVC removal	34 (23)	28 (28)	6 (12.5)	0.036
Secondary non-catheter-related candidaemia	40	21	19	
adequate antifungal treatment (<48 h)	16 (40)	7 (33)	9 (47.4)	0.366
CVC removal in first 48 h	7 (17.5)	5 (23.8)	2 (10.5)	0.412
antifungal+CVC removal	3 (7.5)	2 (9.5)	1 (5.3)	0.999

Cerrahi Yoğun Bakım'da Kandidemiye Bağlı Septik Şok

- 2002-2010, retrospektif çalışma
- 224 hasta, kandidemi ve septik şok
- Toplam mortalite % 63.5
 - % 52.8: şok başlangıcından sonra 24 saat içinde antifungal alan ve kaynak kontrolü sağlanan hastalar
 - % 97.6: diğer hastalar





YBÜ Hastaları İçin Kandida Skoru

- 73 tıbbi-cerrahi YBÜ, İspanya
- 1699 hasta, ≥ 7 gün YBÜ'de kalış
 - Multifokal kolonizasyon (+1)
 - Parenteral beslenme (+1)
 - Cerrahi (+1)
 - Ağır sepsis (+2)

YBÜ Hastaları İçin Kandida Skoru

- ≥ 3 erken antifungal tedavi için başlama kriteri
 - % 61 duyarlılık
 - % 86 özgüllük
 - Risk oranı >7.75 (%95 güvenlik aralığı 4.74 to 12.66)

Kandida Skoru Değerlerine Göre İnvaziv Fungal İnfeksiyon Sıklığı

Cutoff value	Incidence rate (%) (95% CI)	Relative risk (95% CI)
<3	2.3 (1.1-3.5)	1
3	8.5 (4.2-12.7)	3.7 (1.8-7.7)
4	16.8 (9.7-23.9)	7.3 (3.7-14.5)
5	23.6 (12.4-34.9)	10.3 (5.0-21.0)

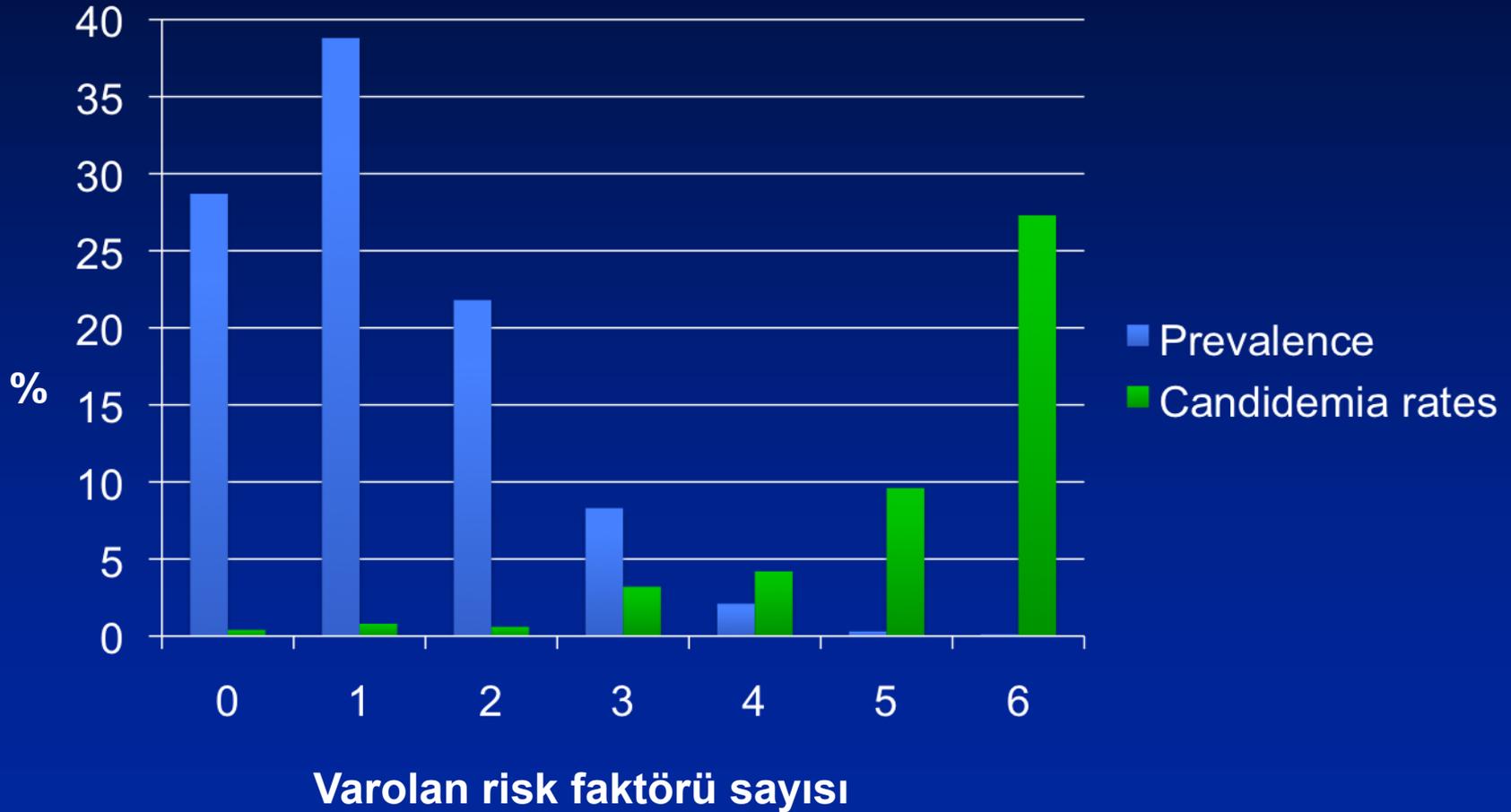
Kandidemi Risk Skoru

- ABD'de 176 hastane
- 64.019 kan dolaşımı infeksiyonu olan hasta (*derivation cohort*)
 - 2000-2005
- 24.685 hasta (*validation cohort*)
 - 2006-2007

Kandidemi Risk Skoru

- Yaş <65
- Vücut ısı <36,6 °C
- Ciddi bozuk mental durum
- Kaşeksi
- Son 30 gün içinde hastaneye yatma
- Başka bir sağlık kurumundan transfer
- Mekanik ventilasyon gereksinimi

Prevalans ve Kandidemi Oranları



İnvaziv Kandidiyazis Tedavisi IDSA 2009

Flukonazol-S suş olası
Hasta stabil



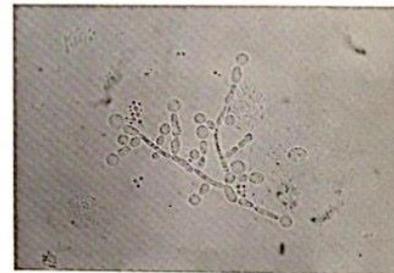
IMPACT FACTOR: 4.540

CMI CLINICAL MICROBIOLOGY AND INFECTION

Volume 18

Supplement 7

December 2012



ESCMID Guideline for the Diagnosis and Management of *Candida* Diseases

ESCMID Guideline for the Diagnosis & Management of Candida Diseases 2012

Authors: Murat Akova, Maiken Arendrup, Sevtap Arikan-Akdagli, Matteo Bassetti, Jacque Bille, Thierry Calandra, Elio Castagnola, Oliver A. Cornely, Manuel Cuenca-Estrella, Peter Donnelly, Jorge Garbino, Andreas Groll, Raoul Herbrecht, William Hope, Henrik Elvang Jensen, Bart-Jan Kullberg, Cornelia Lass-Flörl, Olivier Lortholary, Wouter Meersseman, Georgios Petrikos, Malcolm Richardson, Emmanuel Roilides, Andrew J. Ullmann, Paul Verweij, Claudio Viscoli

Main Coordinator: Andrew J. Ullmann



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Çalışma Grupları

Diagnostic procedure

Maiken Arendrup, Sevtap Arikan-Akdagli, Jacques Bille, **Manuel Cuenca-Estrella**, Peter Donnelly, Henrik Elvang Jensen, Cornelia Lass-Flörl, Malcolm Richardson, Paul Verweij

ICU (medical & surgical)

Other non-immunocompromised (medical & surgical), other immunocompromised situations

Matteo Bassetti, Thierry Calandra, **Oliver Cornely**, Jorge Garbino, Bart-Jan Kullberg, Wouter Meersseman

Paediatrics

PICU

Elio Castagnola, Andreas Groll, **William Hope**, Emmanuel Roilides

Haematology/Oncology

Murat Akova, Raoul Herbrecht, **Andrew Ullmann**, Claudio Viscoli

HIV/AIDS

Olivier Lortholary, Georgios Petrikkos

TABLE 2. Strength of the ESCMID recommendation and quality of evidence

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of evidence	
Level I	Evidence from at least 1 properly designed randomized controlled trial
Level II*	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

*Added index:

r_r : meta-analysis (or systematic review of randomized controlled trials).

t_t : transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.

h_h : comparator group: historical control.

u_u : uncontrolled trials.

a_a : published abstract (presented at an international symposium or meeting).

Allojeneik KHN Kandida Profilaksisi

	Intention: Morbidity reduction		Intention: Survival improvement	
	SoR	QoE	SoR	QoE
Intervention (anti-Candidal prophylaxis) during the neutropenic phase				
Fluconazole 400 mg qd if no prophylaxis is considered	A	I	A	I
Itraconazole* 2.5 mg/kg oral solution tid	B	I	C	I
Posaconazole* 200 mg tid	A	II _t	B	II _t
Voriconazole* 200 mg bid	A	I	C	I
Caspofungin* 70/50 mg qd	C	II _u	C	III
Micafungin* 50 mg qd	A	I	C	I
Anidulafungin	NR	ND	NR	ND
Liposomal amphotericin B 50 mg every other day iv, 100 mg/weekly	B	II	C	III
Intervention (anti-Candidal prophylaxis) during the first 100 days without GVHD and neutrophil recovery				
Fluconazole 400 mg qd	A	I	A	I
Itraconazole* 2.5 mg/kg oral solution tid	B	I	C	I
Posaconazole* 200 mg tid	C	III	C	III
Voriconazole* 200 mg bid	A	I	C	I
Caspofungin* 70/50 mg qd	C	II _u	C	II _u
Micafungin* 50 mg	C	III	C	III
Anidulafungin	NR	ND	NR	ND
Liposomal amphotericin B 50 mg every other day iv, 100 mg/weekly	C	III	C	III
Intervention (anti-Candidal prophylaxis) in GVHD				
Fluconazole 400 mg qd	A	I	C	I
Itraconazole* 2.5 mg/kg oral solution tid	C	I	C	I
Posaconazole* 200 mg tid	A	I	B	I
Voriconazole* 200 mg bid	B	I	C	I
others	NR	ND	NR	ND

Ullmann AJ, Akova M, Herbrecht R, et al.
Clin Microbiol Infect 2012;18 (suppl.7):53-67

Otolog KHN ve Kemoterapiye Bağlı Nötropenik Hastada Kandida Profilaksisi

Intention	Situation	Autologous HCT		Severe and prolonged neutropenia	
		Intervention	SoR/QoE	Intervention	SoR/QoE
Reduce morbidity and mortality (during and after high dose chemotherapy) Additional antibody treatment (e.g. rituximab)		Any prophylaxis	DIII	Any prophylaxis	DIII
		Any prophylaxis	DIII	Any prophylaxis	DIII
Morbidity reduction or survival advantage*	Neutropenia*	Fluconazole	ND	Fluconazole	CI
		Itraconazole	CII	Itraconazole	CI
		Posaconazole	CIII	Posaconazole	CIII
		Voriconazole	ND	Voriconazole	ND
		Anidulafungin	ND	Anidulafungin	ND
		Caspofungin	ND	Caspofungin	CI
		Micafungin	ND	Micafungin	ND
		Nystatin	DIII	Nystatin	DII
Any amphotericin B formulation	ND	Any amphotericin B formulation	DI		

*If an institution wishes prophylaxis, weak recommendations for selected antifungal agents are provided.

ND, no data.

Olası Kandidemi İçin Empirik Tedavi

Intention	Intervention	Allogeneic HCT included	SoR	QoE
Morbidity reduction	Liposomal amphotericin B (3 mg/kg/day)	Yes	A	I
	Caspofungin (70 mg on day 1 then 50 mg)	Yes	A	I
	Amphotericin B colloidal dispersion (4 mg/kg/day)	Yes	C	I
	Amphotericin B lipid complex (5 mg/kg/day)	Yes	B	I
	Itraconazole (200 mg iv q12h on day 1 & 2 then 200 mg iv/day)	ND	B	I
	Voriconazole (2 × 6 mg/kg on day 1 then 2 × 3 mg/kg/day) [§]	Yes	B	I
	Fluconazole (400 mg/day)	ND	C*	I*
	Amphotericin B deoxycholate (0.5–1.0 mg/kg/day)	Yes	D	II _t
	Micafungin (100 mg)	Yes	B	II
	Anidulafungin	ND	NR	

*Limited use since fluconazole has no mould activity. Application requires appropriate work-up to rule out mould disease.
NR, no recommendation; ND, no data available, [§], dosis according to trial [48].

İnvaziv Kandidiyazis'te Hedeflenmiş Tedavi

Intention	Intervention	SoR	QoE	Comment
Morbidity reduction and survival improvement	Fluconazole	C	II _t	Caution regarding resistance. Fluconazole should rather be considered as a step-down treatment option
	Itraconazole	D	III	Only abstract in non-neutropenics
	Posaconazole	D	III	One case report in a non-neutropenic
	Voriconazole	C	II _t	Alternative agent due to better susceptibility data in comparison with fluconazole but limited clinical data
	Amphotericin B colloid dispersion	C	III	Considerable nephrotoxicity
	Amphotericin B deoxycholate	D	II _t	Unacceptable toxicity
	Amphotericin B lipid complex	C	II _a	Considerable nephrotoxicity
	Anidulafungin	B	II _t	<3% of the participants were neutropenic
	Caspofungin	A	II _t	~10% of the participants were neutropenic
	Liposomal amphotericin B	B	II _t	
	Micafungin	A	II _t	~10% of the participants were neutropenic consider EMA warning

Kronik Dissemine Kandidiyazis Tedavisi

Intention	Intervention	Duration	SoR/QoE	Comments
Eradication	Fluconazole	Reported duration minimum 3 months	BIII	[125,126]
	Other azoles (if susceptibility is expected)		BIII	Lacking data
	Amphotericin B deoxycholate		DIII	Toxicity issues
	Lipid formulations of amphotericin B		AIII	Better exposure
Defervesce	Steroid therapy	Until defervesce	CIII	

Ullmann AJ, Akova M, Herbrecht R, et al. Clin Microbiol Infect 2012;18 (suppl.7):53-67

Kateterle İlişkili Kandidemi Tedavisi

Intention	Intervention	SoR/QoE	Comment
Survival advantage	Early catheter removal	All _u	Retention and high APACHE II and thrombocytopenia also associated with higher mortality.
Morbidity reduction	Catheter retention	CII _t	Patients in trials treated with echinocandins and CVC retention had equal outcome (low numbers)
	If catheter retention use echinocandins or liposomal amphotericin B, not azoles or amphotericin B deoxycholate	CII _t	Worse outcome in non echinocandins trials
	Other implanted hardware (pace-maker, port-a-cath)	CIII	Keep unless proven associated with candidaemia. No published data available

Ullmann AJ, Akova M, Herbrecht R, et al. Clin Microbiol Infect 2012;18 (suppl.7):53-67

ESCMID Kandida Kılavuzu 2012

‘Nötropenik Olmayan Hastalar’

- **Solunum sekresyonlarından kandida üremesi tedavi gerektirmez**
- **Organ tutulumunu belirlemek için fundoskopi ve TEE**
- **Hedeflenmiş tedavide öncelikle ekinokandinler, daha düşük düzeyde L-Amp B ve vorikonazol, daha sonra flukonazol**
 - **Deoksikolat Amp B önerilmez**

ESCMID Kandida Kılavuzu 2012

‘Nötropenik Olmayan Hastalar’

- **Tedavi süresi son pozitif kan kültüründen sonra minimum 14 gün**
- **Genel durumu iyi olan hastalarda 10 günlük iv tedavi sonrası oral tedaviye geçilebilir**
- **Kandidemik hastalarda kateterler mutlaka çekilmelidir**
 - **Eğer çekilemiyorsa tedavi lipid AmpB veya ekinokandinler ile sağlanmalı**

Teşekkürler...