Hematolojik Onkoloji Hastalarında Invaziv Fungal İnfeksiyonların Yönetimi

Prof. Dr. Filiz VURAL
Ege Üniversitesi Tıp Fakültesi
İç Hastalıkları Hematoloji Bilim Dalı

HOD 2015 KKTC

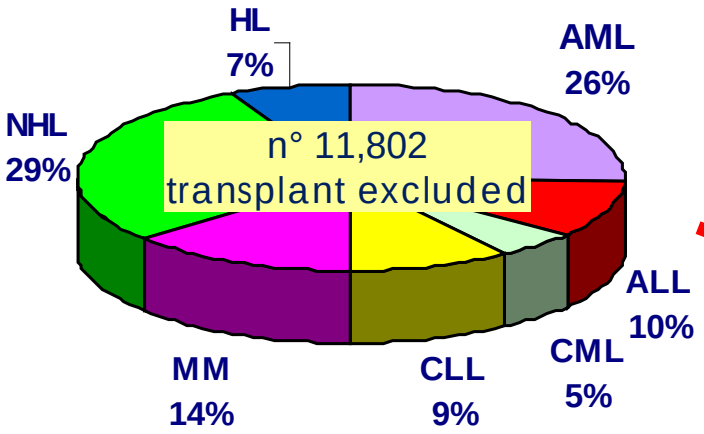
IFI riski

ÇOK YÜKSEK RISK	YÜKSEK RISK	ORTA RISK	DÜŞÜK RISK
AML	AML (relaps)	ALL	Oto-HSCT
Allo-HSCT	OLT	Kalp Tx	Böbrek Tx
MDS	Allo-HSCT (no GVHD)	KLL	Solid tumor
AC Tx		KOAH	Immun Yetmezlik
		AIDS	
		NHL	

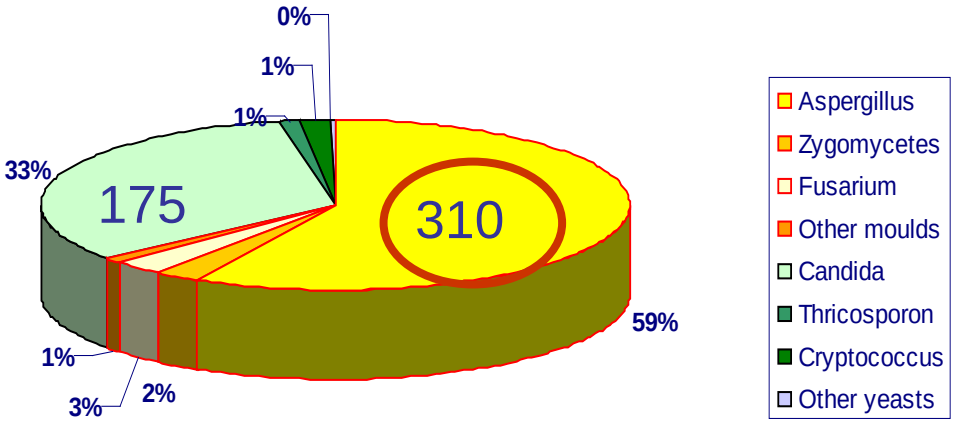
Pagano et al, JAC 2011

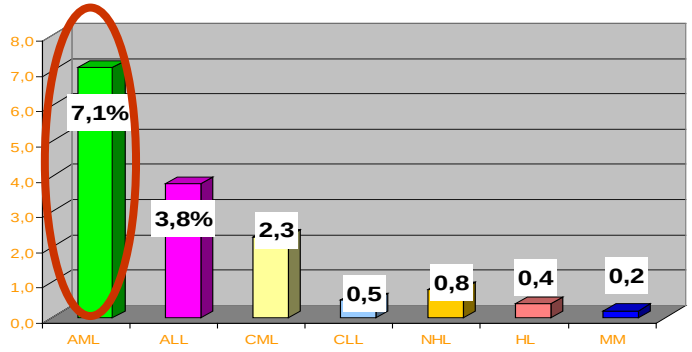
The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study

Haematologica 2006



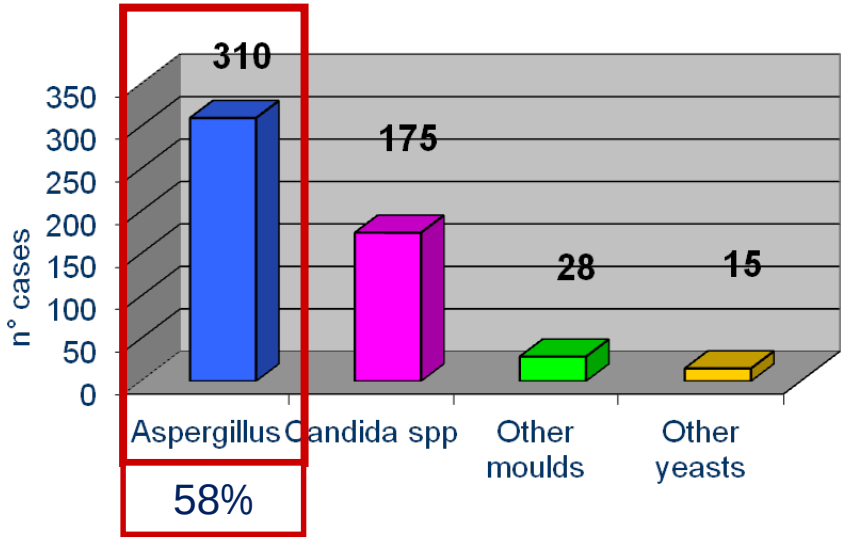
Overall Incidence: 4.6%
Yeasts/Moulds 1:3





AML:

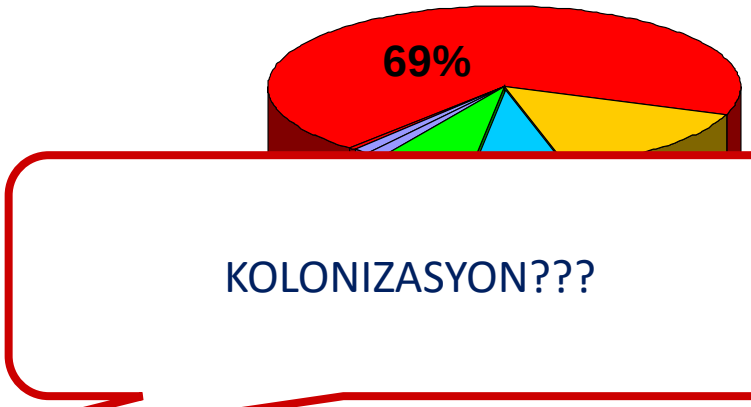
EPISODES 213/310 INCIDENCE 7,1%



AML Tedavi Fazları

AML tedavisinin tüm fazlarında IA riski sabit değil

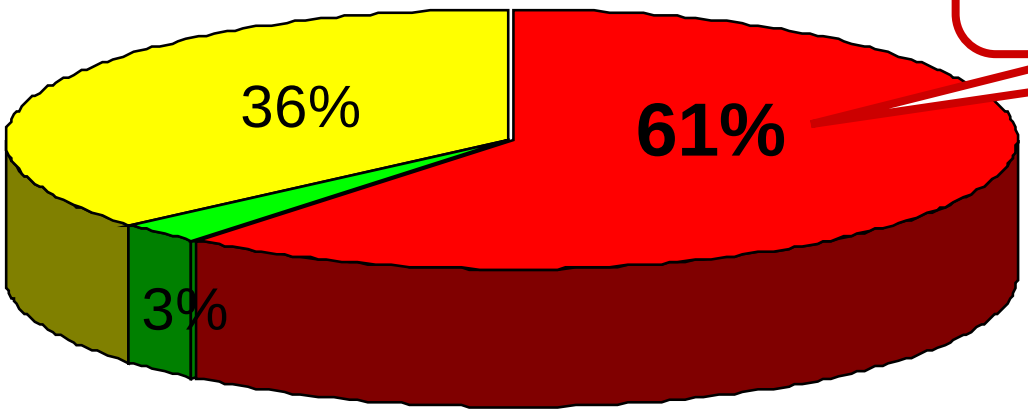
391 hasta



KOLONIZASYON???

001

140 AML hastası

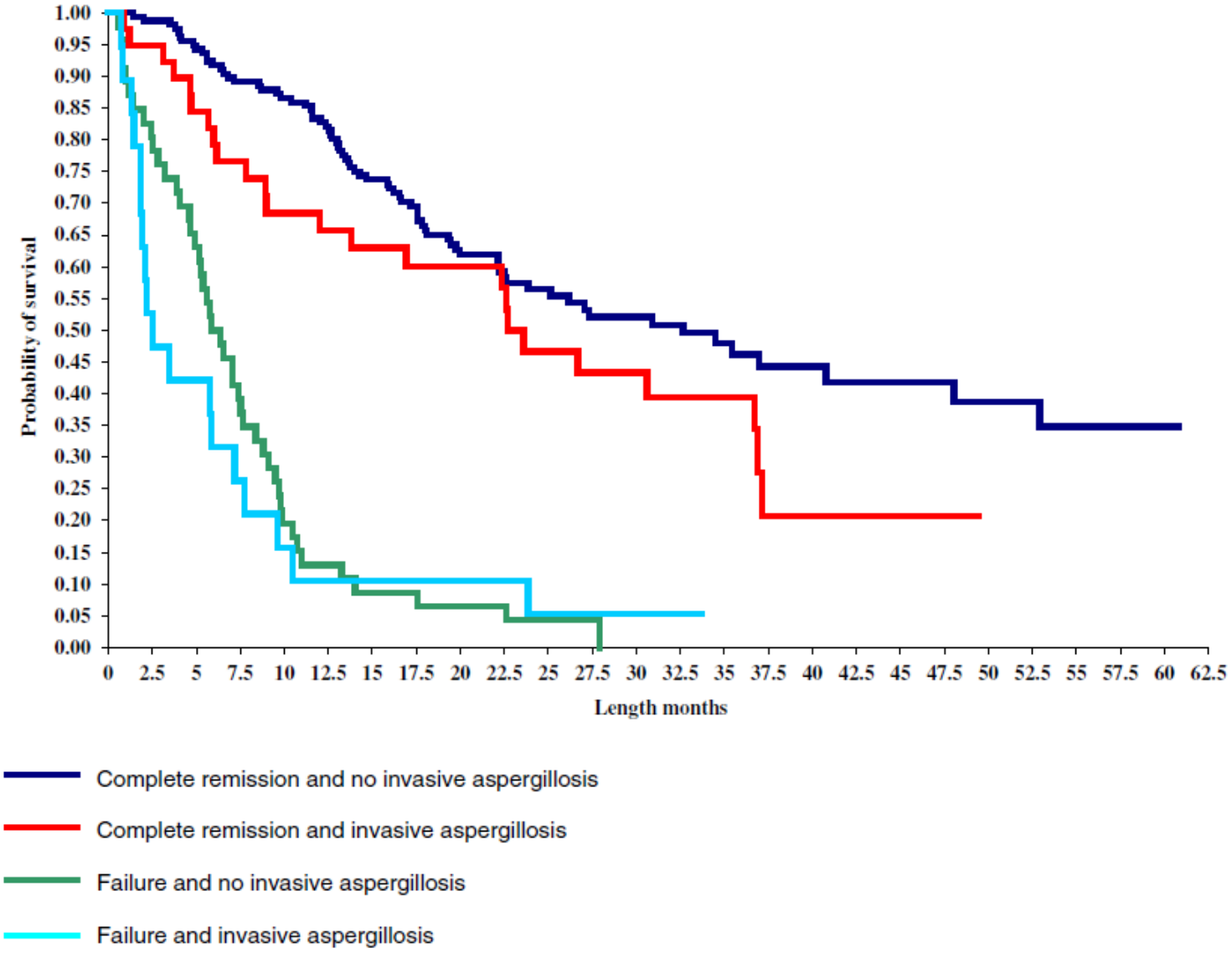


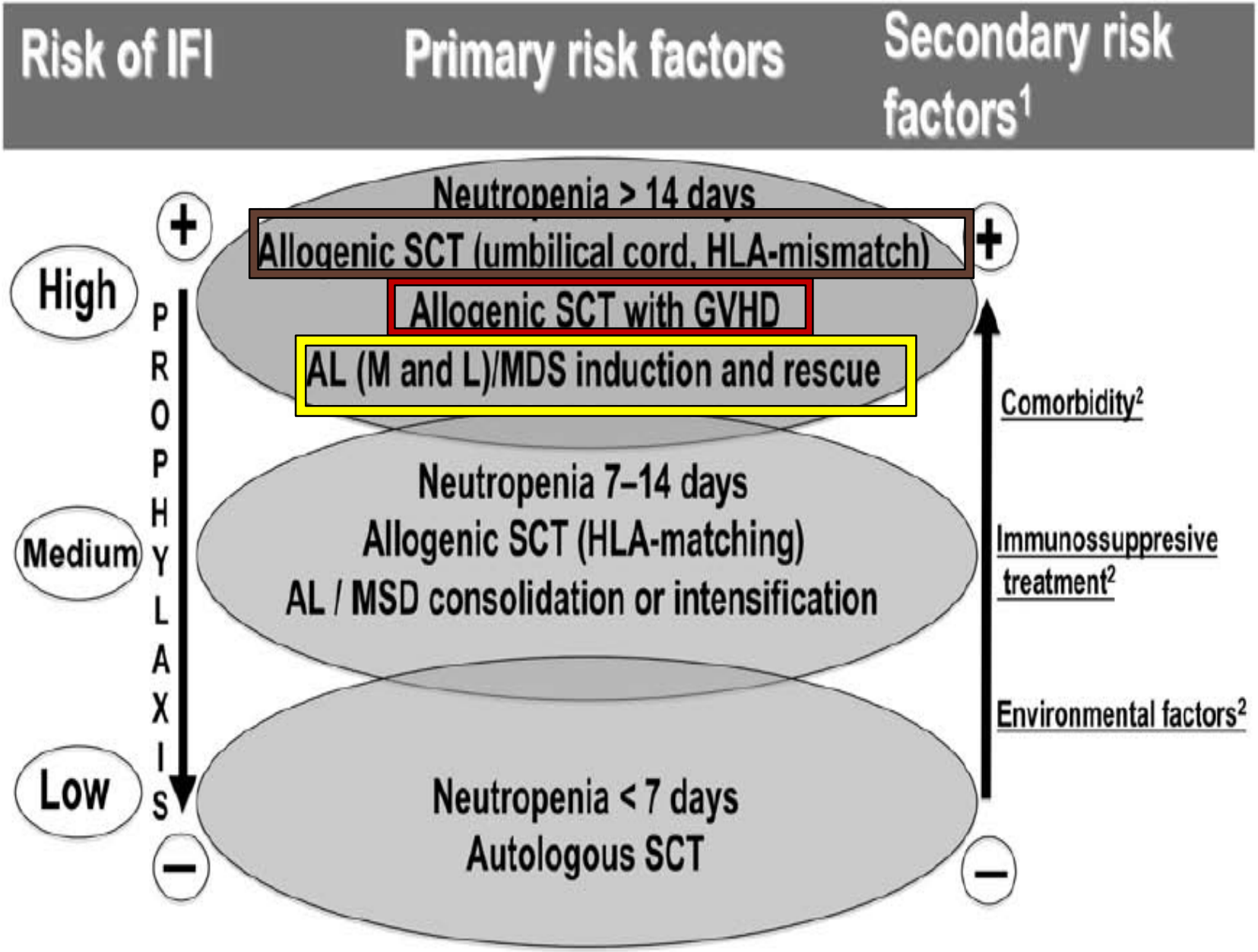
1st induction therapy
complete remission
relapse/progression

Pagano et al, Haematologica 2009

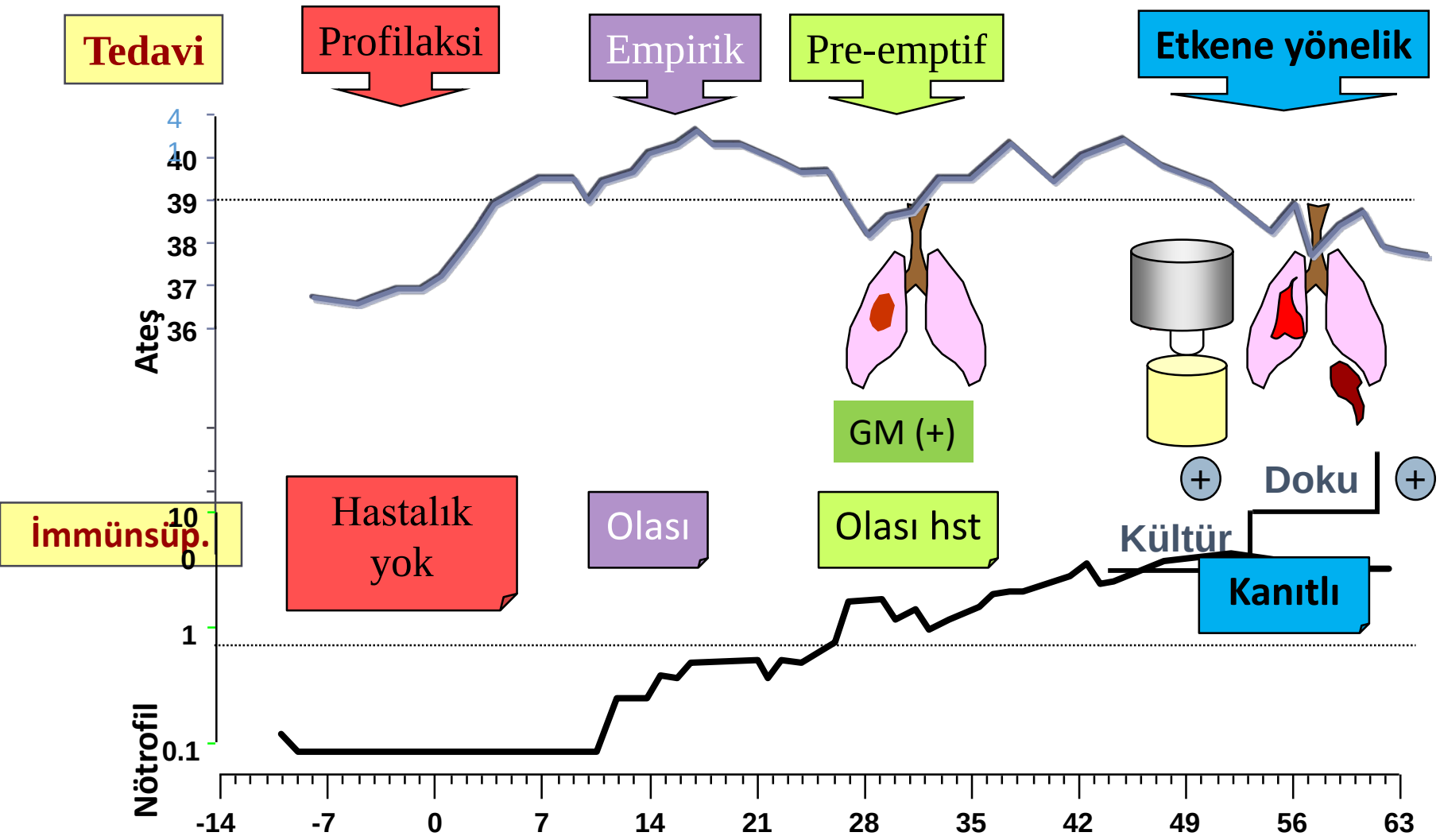
Invaziv aspergillöz: AML hastalarının uzun ve kısa dönem sağkalım üzerine etkili risk faktörleri

Michallet et al, Eur J Clin Micr Infect Dis 2011




Risk of IFI
Primary risk factors
Secondary risk factors[1]
Neutropenia > 14 days
Allogenic SCT (umbilical cord, HLA-mismatch)
Allogenic SCT with GVHD
AL (M and L)/MDS induction and rescue
Neutropenia 7–14 days
Allogenic SCT (HLA-matching)
AL / MSD consolidation or intensification
Neutropenia < 7 days
Autologous SCT
High
Medium
Low
+
–
PROPHYLAXIS
Comorbidity[2]
Immunossuppresive treatment[2]
Environmental factors[2]

Tedavi Stratejileri



Antifungal TEDAVİLER

EMPİRİK TEDAVİ:

Sadece host faktörler ve ateş

PRE-EMPTİF TEDAVİ:

Mikrobiyolojik ve klinik faktörler (pozitif candida kültürleri hariç) eşliğinde IFI tanısı

HEDEFE YÖNELİK TEDAVİ:

İnvaziv yöntemlerle (biyopsi vb) steril vücut sıvıları ve kan kültürlerinde pozitif *Candida* ile IFI tanısı

Antifungal TEDAVİLER

EMPİRİK TEDAVİ:

Sadece host faktörler ve ateş

P

N **da**

k

Hematolojik malinitelerde kaç hastada kanıtlanmış IFI?

< 2%

HEDEFE YÖNELİK TEDAVİ:

İnvaziv yöntemlerle (biyopsi vb) steril vücut sıvıları ve kan kültürlerinde pozitif *Candida* ile IFI tanısı

EMPİRİK TEDAVİ

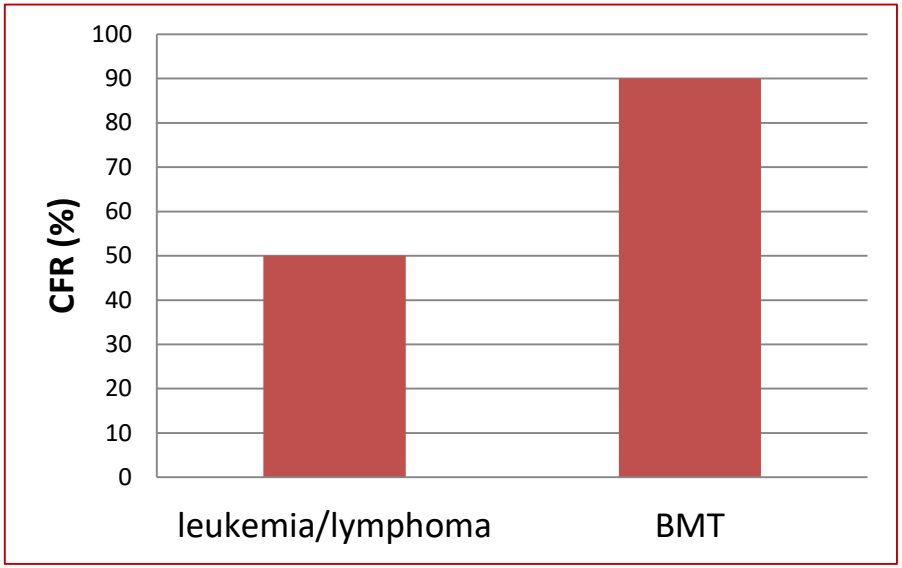
Empirik tedavi

düşünmenin

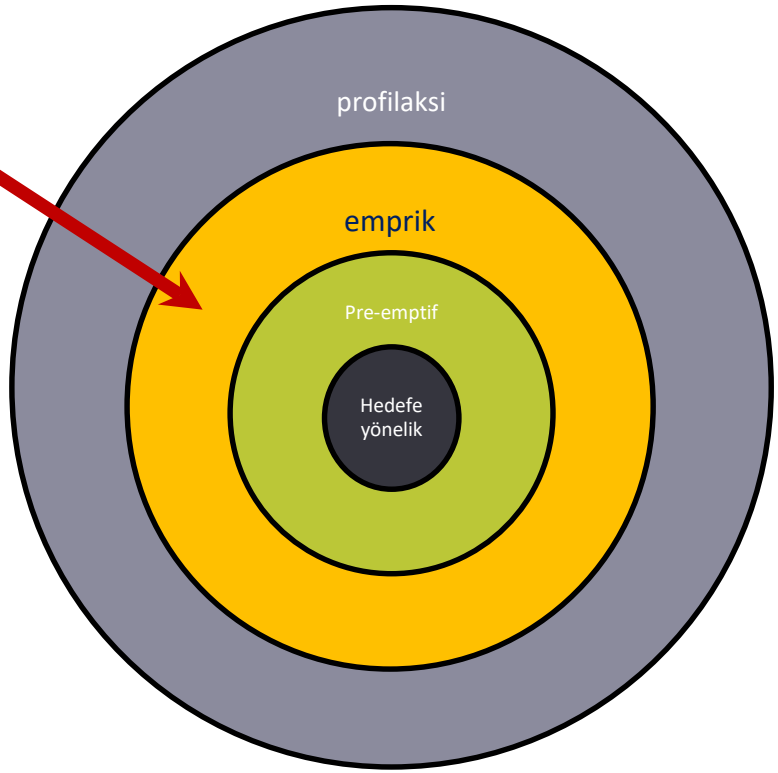
yerine geçer.

Empirik Antifungal Tedavi

Patojen saptanmadan İnfeksiyona ait klinik semptom ve bulgular



Lin et al, CID 2001



	Sayı	Tasarım	Tedavi	Primer sonlanım
Prentice, 1997	338	Açık	Lipo AmB 1 or 3 vs AmB-d 1	Severe toxicity
White, 1998	196	Çift kör	ABCD 4 vs AmB-d 0.8	Nephrotoxicity
Walsh, 1999	687	Çift kör	Lipo AmB 0.6 vs AmB-d 0.6	Equivalent efficacy (± 10%)
Wingard, 2000	244	Çift kör	Lipo AmB 3 or 5 vs ABLC 5	Infusion-related toxicity
Winston, 2000	317	Açık	Fluco 400 vs AmB-d 0.5	Equivalent efficacy (± 15%)
Boogaerts, 2001	360	Açık	Itra 200, then 400 vs AmB-d 0.7-1	Equivalent efficacy (± 15%)
Ehninger, 2002	162	Açık	Itra 200, then 400 vs AmB-d 0.7-1	Severe toxicity
Walsh, 2002	837	Açık	Vori 6, then 400 vs Lipo AmB 3	Non-inferior efficacy (± 10%)
Walsh, 2004	1095	Çift kör	Caspo 50 vs Lipo AmB 3	Non-inferior efficacy (± 10%)

Neden Empirik Antifungal Tedavi?

Possible Causes of Fever	Approximate Frequency in High-Risk Patients (%)
Fungal infections susceptible to empirical therapy	40
Fungal infections resistant to empirical antifungal therapy	5
Bacterial infections (with cryptic foci and resistant organisms)	10
Toxoplasma gondii, mycobacteria, or fastidious pathogens (legionella, mycoplasma, *Chlamydia pneumoniae*, bartonella)	5
Viral infections (herpesviruses, cytomegalovirus, Epstein–Barr virus, human herpesvirus 6, varicella–zoster virus, herpes simplex virus) and respiratory pathogens such as parainfluenza virus, respiratory syncytial virus, influenzaviruses	5
Graft-versus-host disease after hematopoietic stem-cell transplantation	10
Undefined (e.g., drug fever, toxic effects of chemotherapy, antitumor responses, undefined pathogens)	25

1. Nötropenk hastada persistan ateş

ATEŞ genellikle hematolojik onkoloji hastalarında ilk ve tek uyarıcı bulgu olabilir

FUO 45%'i Fungal Infeksiyon

Corey & Boeckh. N Engl J Med 2002

Neden Empirik Antifungal Tedavi?

- 19 Itayan Hematoloji Merkezi (2007-09)
- 3197 teni tanı hasta

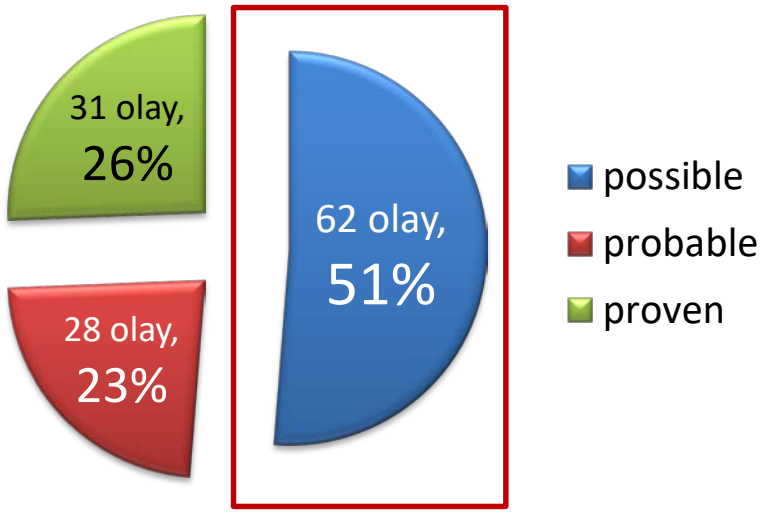
869 FEBRIL OLAY

2. Tanıda güçlük

44% FUO

51% olası FI

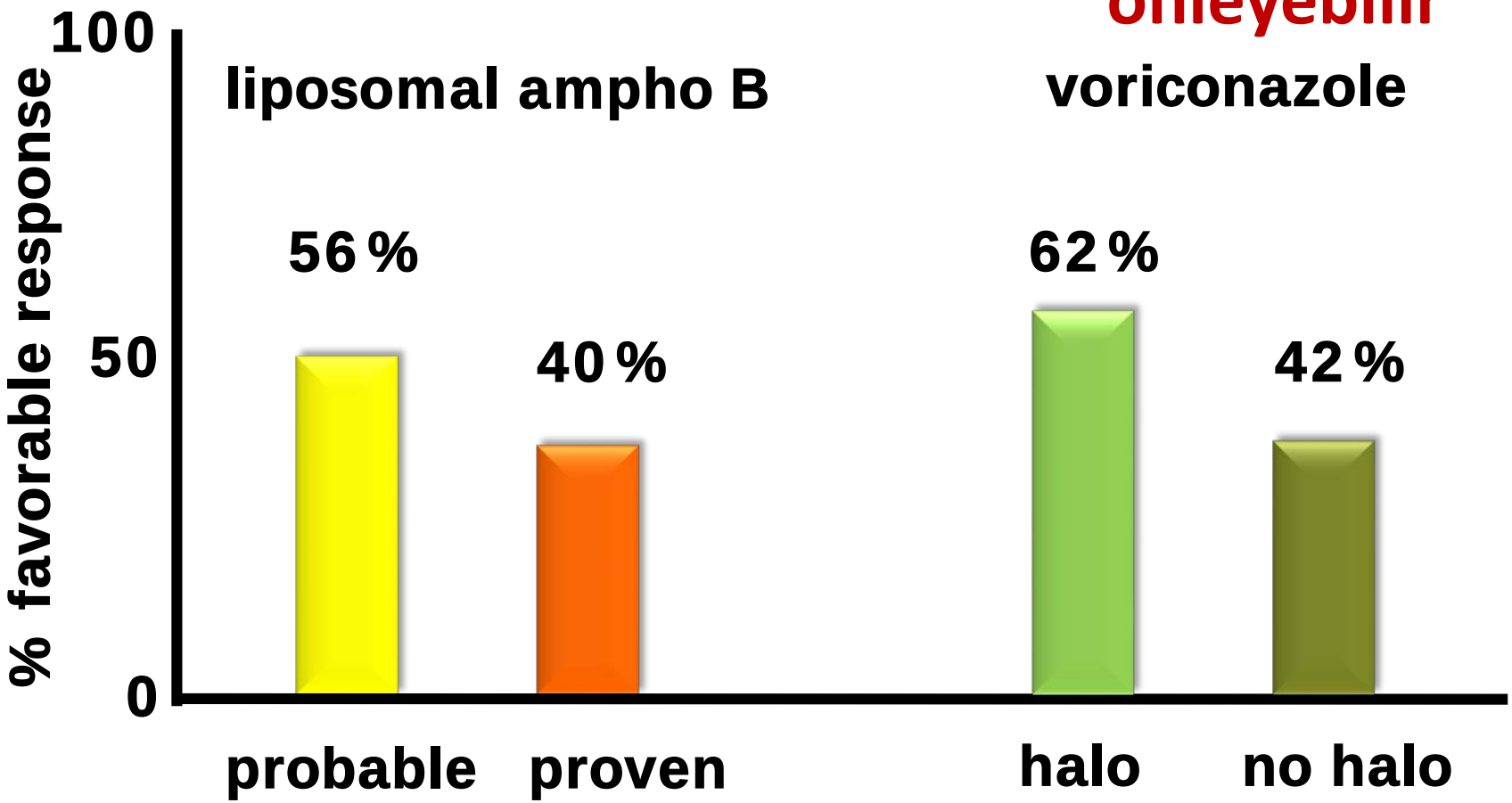
	EVT	%
Bakteriyel	301	34.6
Fungal	95	10.9
Viral	7	0.8
DTRF	48	5.5
FUO	386	44.4
Mix infeksiyon	32	3.6
TOTAL	869	



Pagano et al, Ann Hematol 2012

Neden Empirik Antifungal Tedavi?

3. Tedavide gecikmeyi önleyebilir



Greene et al. Clin Infect Dis 2007; 44:373-379

Cornely et al. J Antimicrob Chemother 2010; 65:114-117

Empirik antifungal tedavi: ECIL-4

Antifungal agent	Daily dose	Level of recommendation	CDC grading level of evidence for Efficacy	Safety
Ampho B deoxy	0.5-1 mg/kg iv	B/D	I	I
Liposomal AmB	3 mg/kg iv	A	I	I
ABLC	5 mg/kg iv	B	I	I
ABCD	4 mg/kg iv	B	I	I
Fluconazole	400 mg iv	C	I	I
Itraconazole	200 mg iv	B	I	I
Voriconazole	2 x 3 mg/kg iv	B	I	I
Caspofungin	50 mg	A	I	I
Micafungin	100 mg	B	II	II

Maertens J et al. Bone Marrow Transpl. 2011

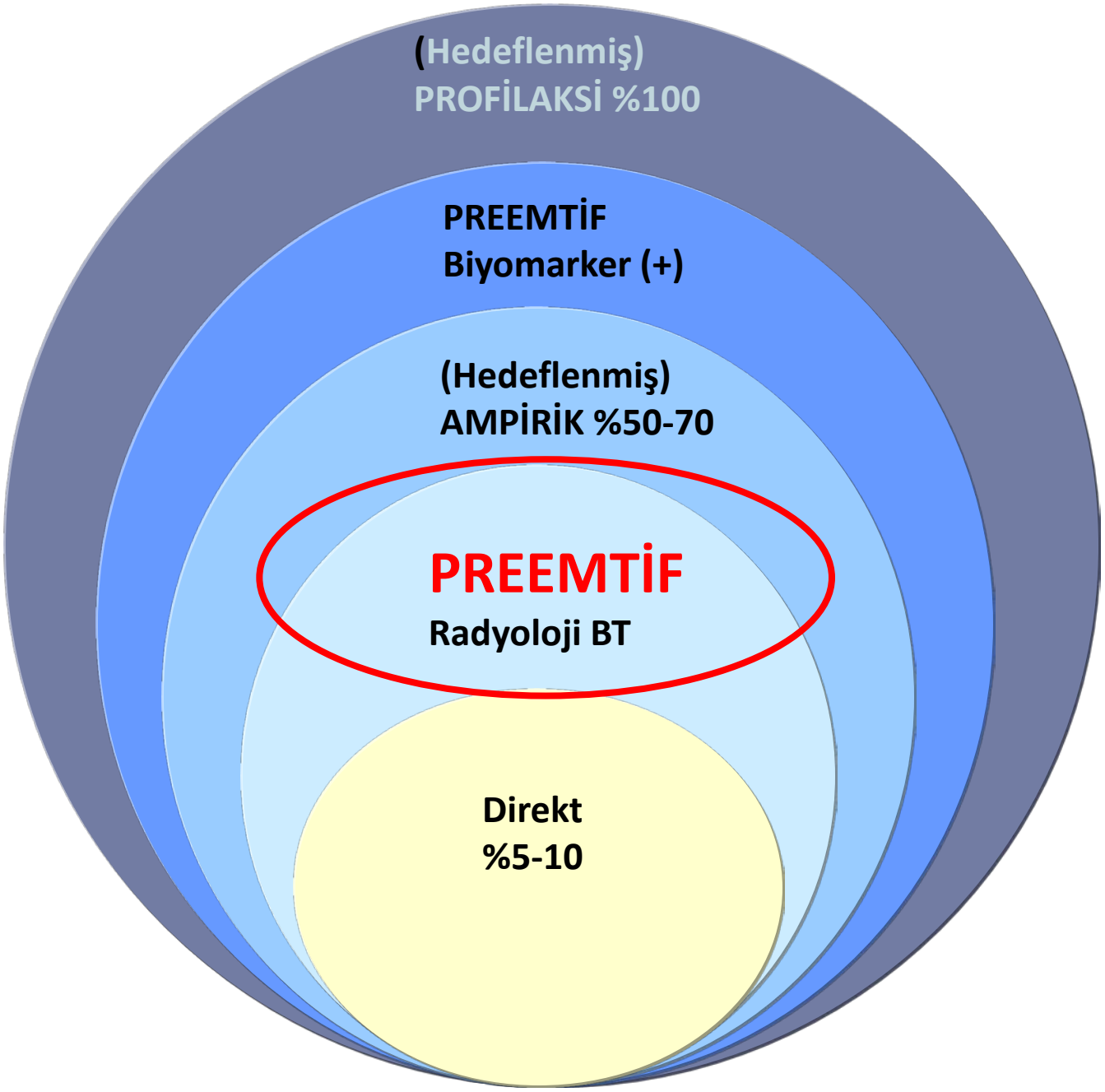
Empirik antifungal tedavi

Avantajları

- Erken tedavi
  - **Sağkalıma etkisi?**
- IFI atlama olasılığını düşürür

Dezavantajları

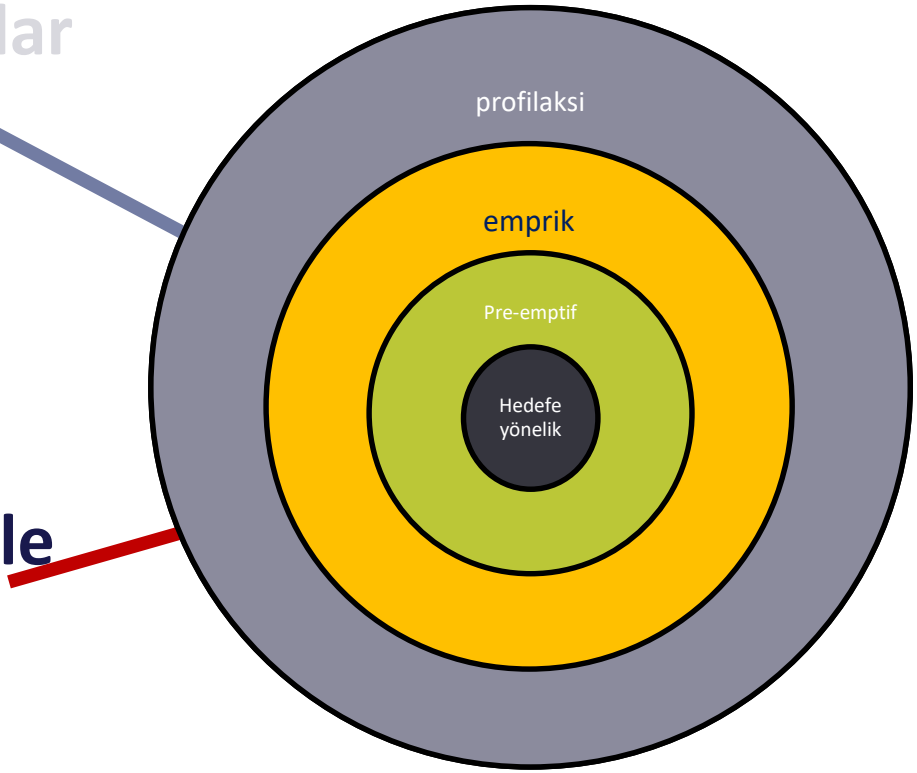
- Gereksiz tedavi
- Toksisite
- İlaç etkileşimi
- Direnç ?
- Maliyet


(Hedeflenmiş)
PROFİLAKSİ %100
PREEMTİF
Biyomarker (+)
(Hedeflenmiş)
AMPİRİK %50-70
PREEMTİF
Radyoloji BT
Direkt
%5-10

PRE-EMPTİF TEDAVİ

EMPIRIK TEDAVİ:
Patojen saptanmadan İnfeksiyona ait klinik semptom ve bulgular

PRE-EMPTİF TEDAVİ:
Laboratuvar testleri ve radyolojik bulgular (histopatolojik veya kültür ile kesin kanıt yok)



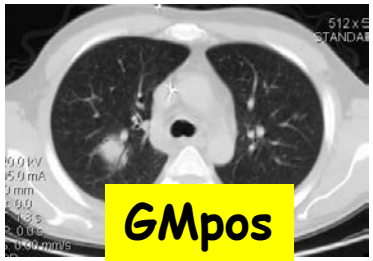
TANISAL YÖNTEMLERE DAYALI YAKLAŞIM

PRE-EMPTİF

SURVEY

TC

TC



TC

Risk Period

GM GM GM GM GM GM GM GM GM GM GM

Maertens et al. Clin Infect Dis 2005

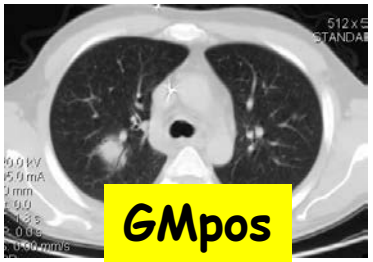
Girmenia et al. JCO 2009

4gg

GM GM GM

Fever

TC



TANISAL YÖNTEMLERE DAYALI

SEMPTOMATİK YAKLAŞIM

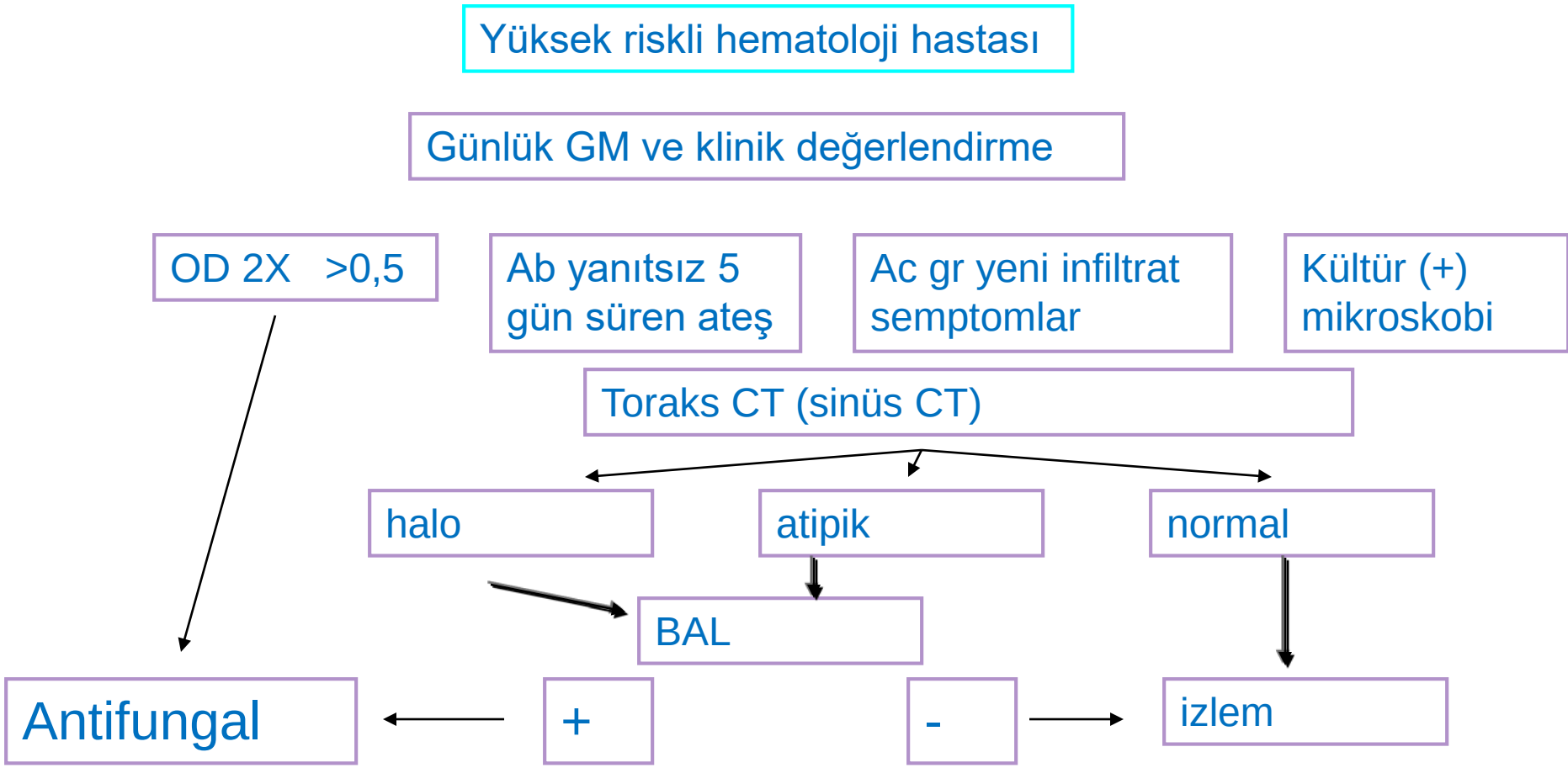
Courtesy of C. Girmenia

Pre-emptif strateji kriterleri

Reference	Intensive work-up	Criteria to start pre-emptive
Maertens *et al*, 2005	- Cultures of blood, sputum and infected sites - Chest CT - Bronchoscopy with BAL	- GM ≥ 0.5 x 2; or - Pos for both TAC and BAL
Oshima *et al*, 2007	Not specified	- Fever ≥ 7 days + GM ≥ 0.6 x 2; or - Pos Rx +/- TAC
Cordonnier *et al*, 2009	- Blood cultures x 2, urine culture - X-ray	- Fever ≥ 4 days + GM ≥ 1.5 x 1; or - Clinical suspicion of IFD
Dignan *et al*, 2009	- Blood cultures x 2, X-ray - Chest CT	- Fever ≥ 3 days + pos TAC; or - Clinical suspicion of IFD
Aguilar-Guisado *et al*, 2010	- Blood cultures, X-ray - Chest CT	- Fever ≥ 5 days + sever sepsis, septic shock, infection of lung, skin CNS, sinus, abdomen
Girmenia *et al*, 2010	- Blood cultures x 3, GM x 3, CT	Fever ≥ 4 days + proven/probable/possible IFD
Tan *et al*, 2011	- GM x 2	-fever + GM ≥ 0.5 x 2; or -fever + GM ≥ 0.5 + pos CT

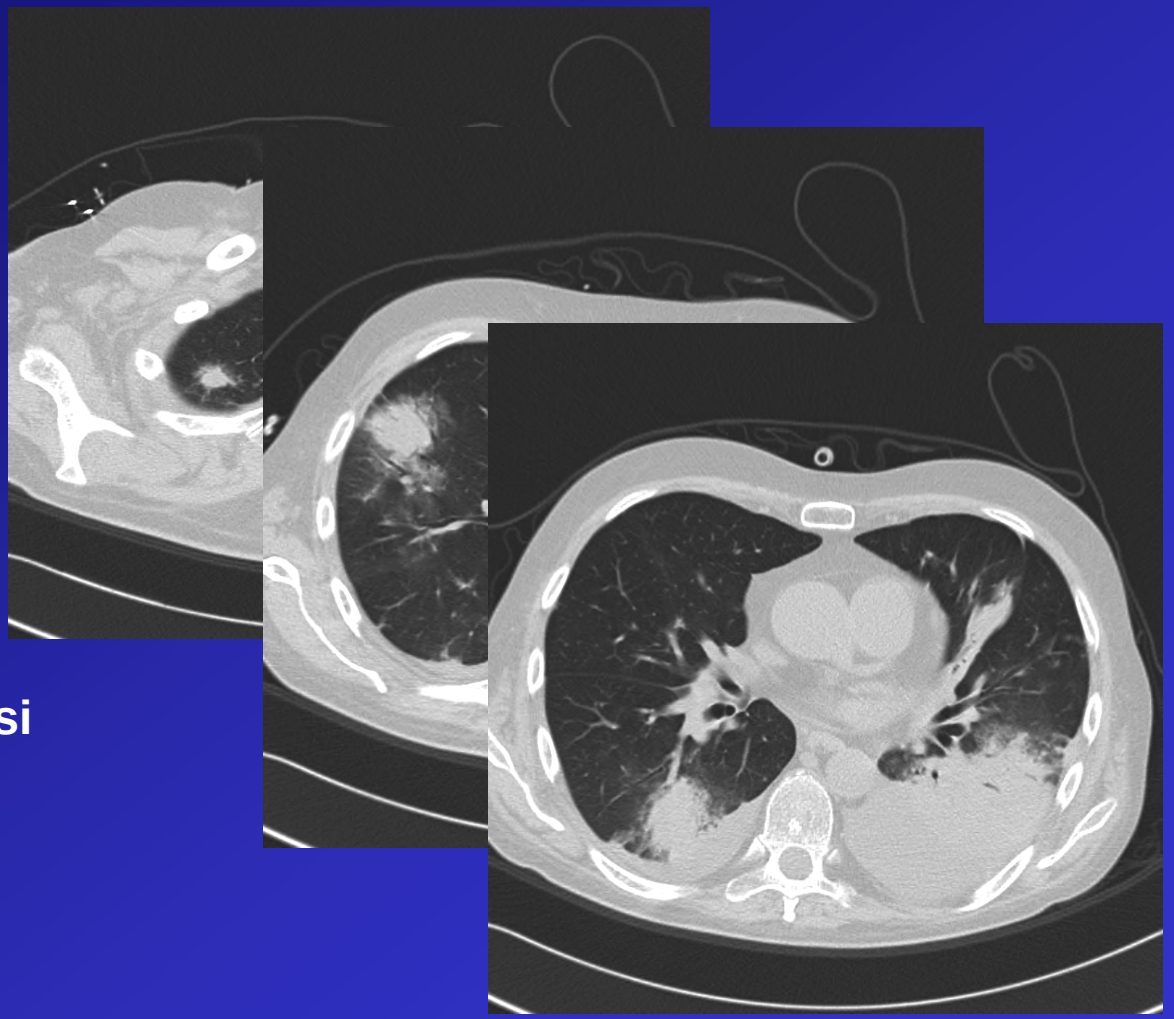
Galactomannan and Computed Tomography–Based Preemptive Antifungal Therapy in Neutropenic Patients at High Risk for Invasive Fungal Infection: A Prospective Feasibility Study

Johan Maertens,[1] Koen Theunissen,[1] Gregor Verhoef,[1] Johnny Verschakelen,[2] Katrien Lagrou,[3] Eric Verbeken,[4] Alexander Wilmer,[5] Jan Verhaegen,[3] Marc Boogaerts,[1] and Johan Van Eldere[5]



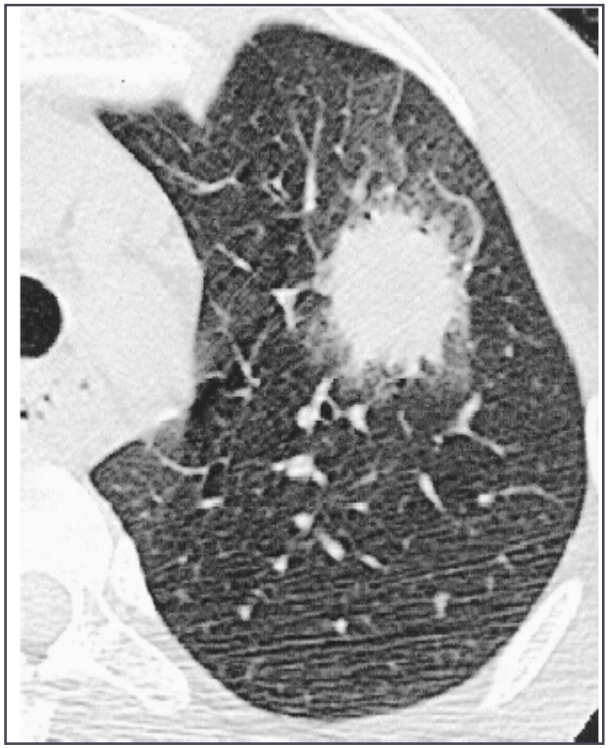
Clinical Infectious Diseases 2005; 41:1242–50

Radyoloji

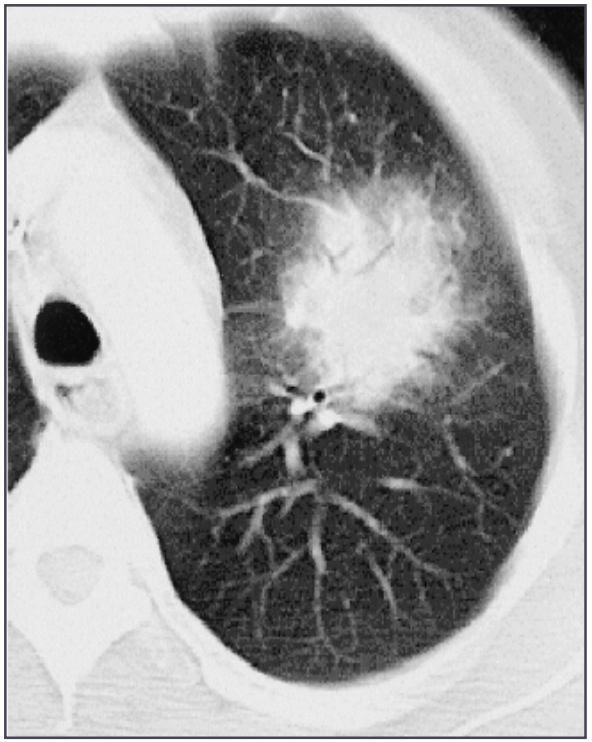


- Dansite, nodül, halo belirtisi
- Hava-hilal belirtisi
- Kavite

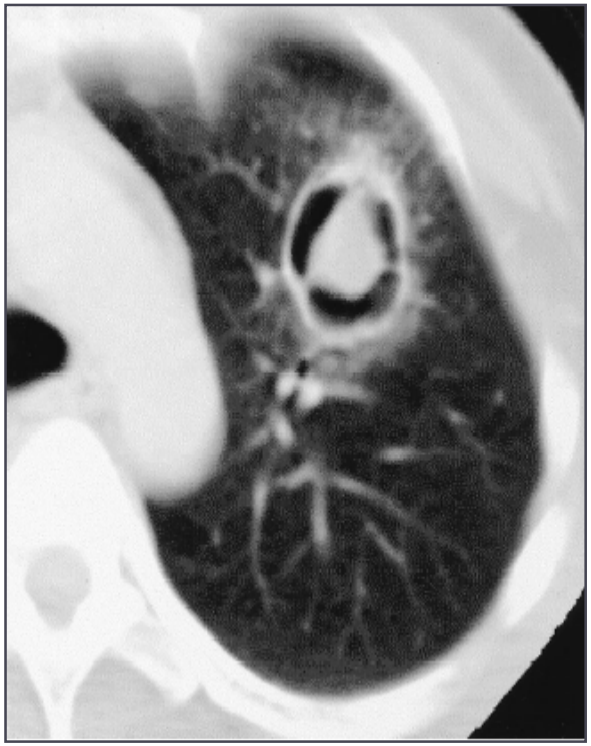
Erken BT
Seri BT



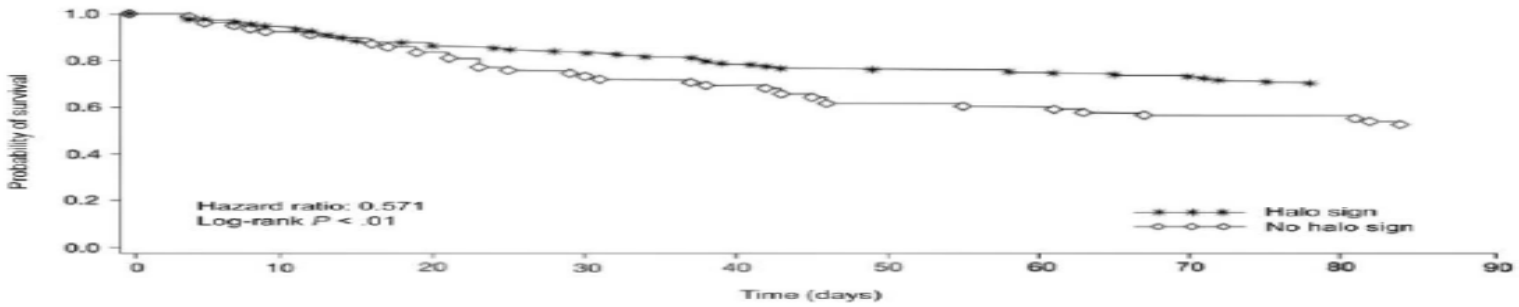
Gün 0
Halo

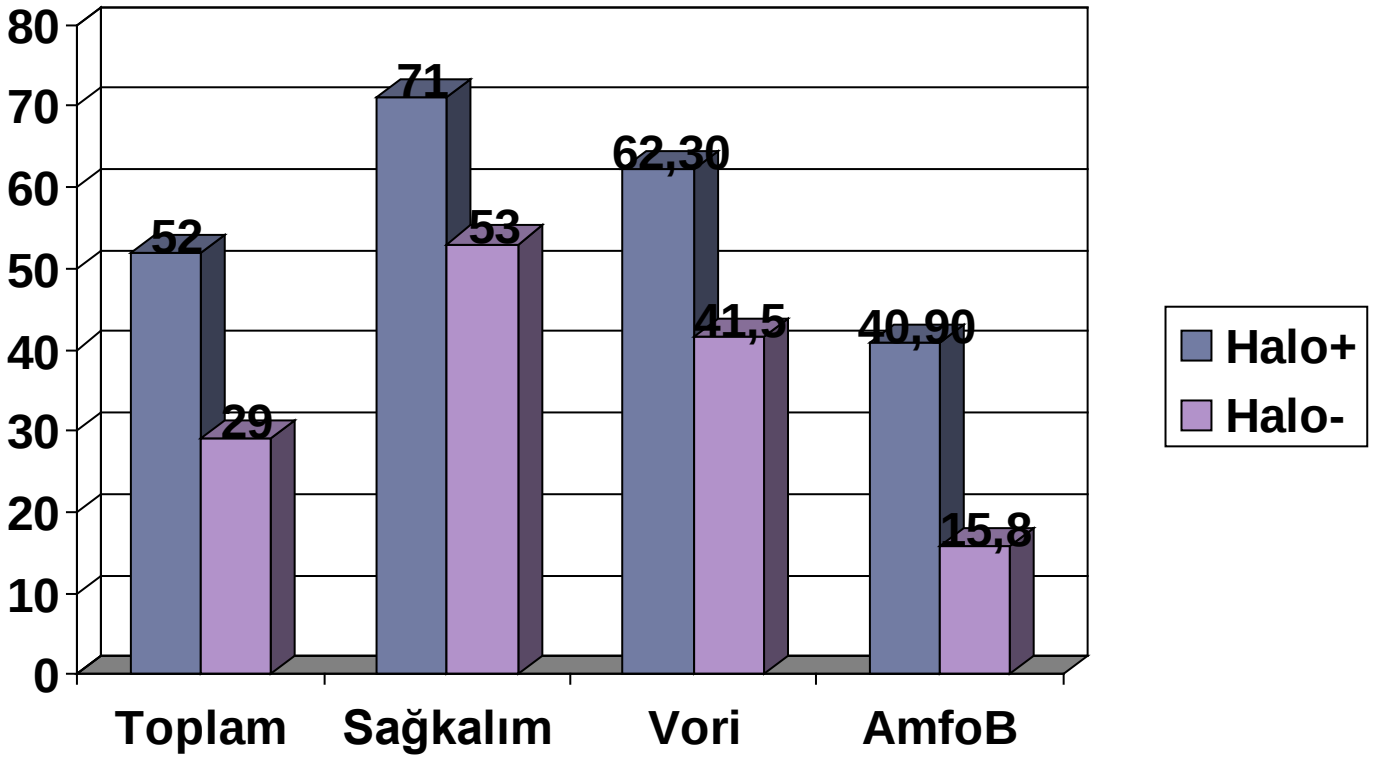


Gün 4
İnfilt
Halo



Gün 10
Hava-hilal


Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
Hazard ratio: 0.571
Log-rank P < .01
Halo sign
No halo sign
0
10
20
30
40
50
60
70
80
90
Time (days)


80
70
60
50
40
30
20
10
0
52
29
71
53
62,30
41,5
40,90
15,8
Toplam
Sağkalım
Vori
AmfoB
Halo+
Halo-

IDSA GUIDELINES

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

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

- Yüksek riskli hastalarda Empirik tedavinin alternatifi olarak kabul edilebilir.
- Geniş sp üren ateş
- Klinik ol
- Sinüs ve akciğer BT normal
- Serolojik testler (-)
- Mantar mikrobiyolojik incelemeleri (-)

Antifungal tedavi başlanmamalı (BII)

Empirical versus Preemptive Antifungal Therapy for High-Risk, Febrile, Neutropenic Patients: A Randomized, Controlled Trial

Catherine Cordonnier,[1] Cécile Pautas,[1] Sébastien Maury,[1] Anne Vekhoff,[4] Hassan Farhat,[11] Felipe Suarez,[5] Nathalie Dhédin,[6] Francoise Isnard,[7] Lionel Ades,[12] Frédérique Kuhnowski,[8] Françoise Foulet,[2] Mathieu Kuentz,[1] Patrick Maison,[3] Stéphane Bretagne,[2] and Michaël Schwarzinger[9,10]

- Yüksek Riskli Hastalar; AML-indüksiyon/konsolidasyon, OTO-KHN
- 2 Tedavi Stratejisi - 2. hf sağkalım (non-inferiorite; %90 sağkalım, <%10 mort. farkı, sınır - %8)AFT; Amfo-B, L-AmB
- Empirik; ATEŞ
- Pre-emptif: 4. gün ateş+ Klinik , Radyolojik , Mikolojik kriter; GM ≥1.5,

Clin Infect Dis 2009;48:1042-51.

Sonuçlar

Table 2. Efficacy end points in the intention-to-treat population (n = 293).

Efficacy end point	Empirical treatment arm (n = 150)	Preemptive treatment arm (n = 143)	Difference (95% CI)	P[a]
Primary				
Alive at study completion	146 (97.3)	136 (95.1)	−2.2 (−5.9 to 1.4)	.31
Secondary				
IFI	4 (2.7)	13 (9.1)	−6.4 (−10.9 to −1.9)	<.02
Duration of temperature ≥38°C,[b] days				
Median (IQR)	13 (5–21)	12 (5–20)	…	NS
Range	1–42	1–59	…	

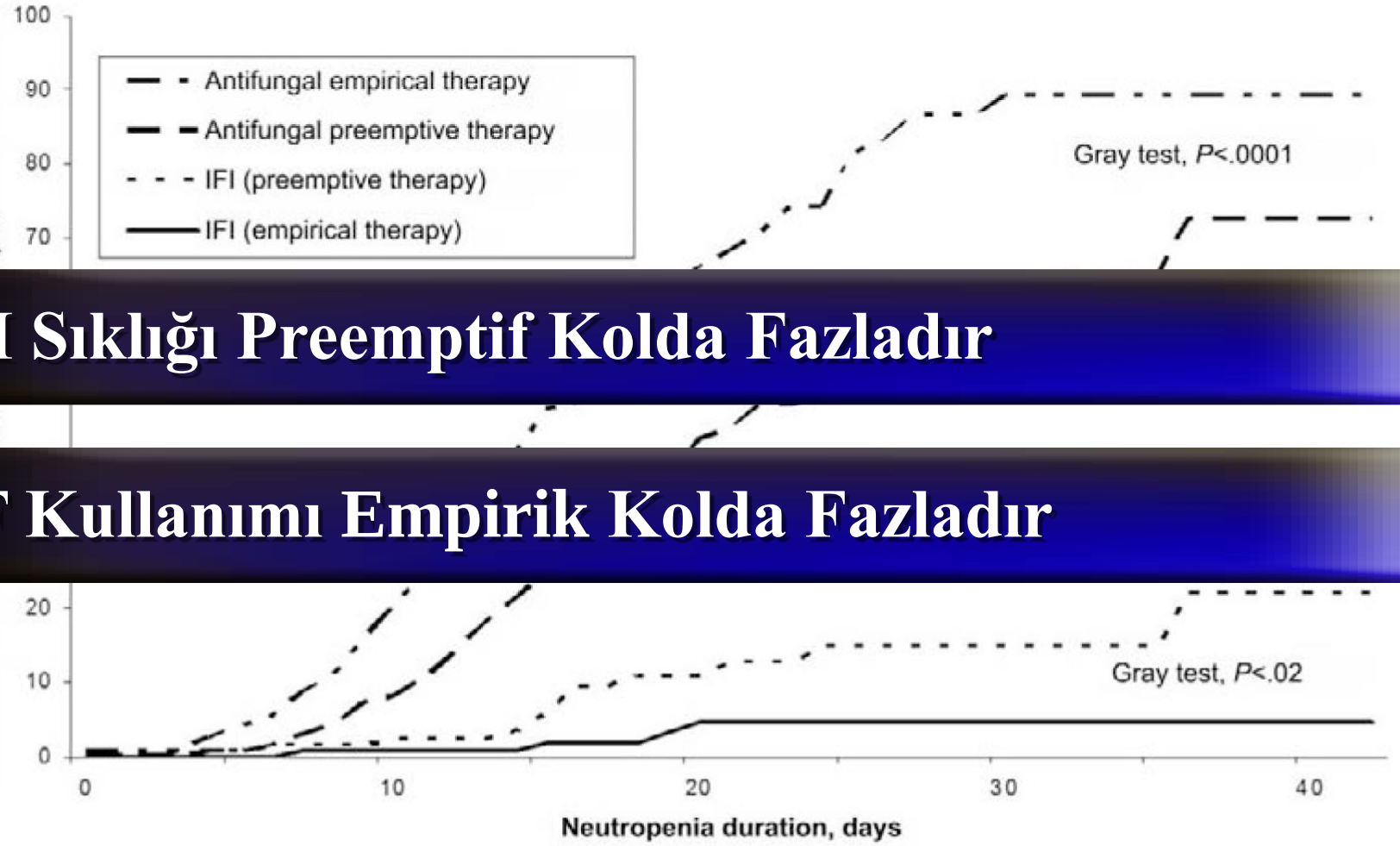
NOTE. Data are no. (%) of patients, unless otherwise indicated. IFI, invasive fungal infection; IQR, interquartile range; NS, not significant.

[a] By Cochran-Mantel-Haenszel test for qualitative variables; by Wilcoxon sum-rank test for skewed quantitative variables.

[b] Excludes 14 patients without fever (8 in the empirical treatment group and 6 in the preemptive treatment group).

Yüksek Riskli Hematolojik Malinitelerde Pre-emptif ve Empirik Tedavi Mortalitesi Farksız

Cordonnier C, et al. Clin Infect Dis 2009;48:1042-51.



IFI Sıklığı Preemptif Kolda Fazladır

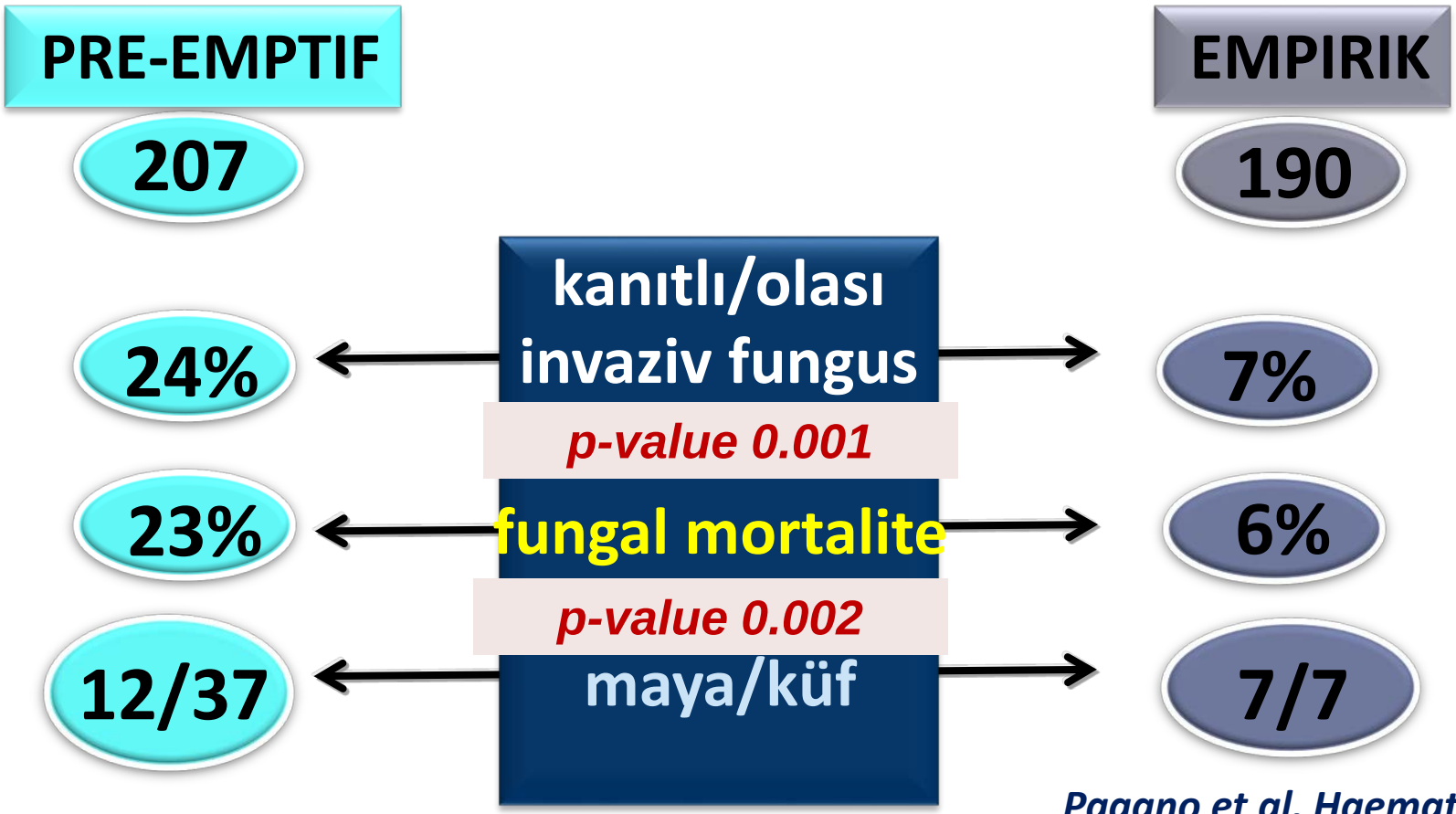
AF Kullanımı Empirik Kolda Fazladır

Figure 2. Cumulative incidence of antifungal therapy and invasive fungal infection (IFI) during neutropenia ($n = 287$)

Cordonnier C, et al. Clin Infect Dis 2009;48:1042-51.

Empirik *vs* pre-emptif yaklaşım: Gözlem çalışması

2007-2009, tanımlayıcı, randomize değil, 19 merkez
379 hematolojik maliniteli hasta



Pagano et al, Haematol 2011

VARIABLES	Dead (n° 45)	Alive (n° 352)	P-value
UNIVARIATE ANALYSIS			
Male sex	29 (64.4)	200 (56.8)	0.32
Age (year [mean SD])	62 ±10	54 ±16	**<0.001**
Underlying HMs			
- AML	34 (75.5)	287 (81.5)	0.33
- NHL	6 (13.3)	24 (6.8)	0.13
- ALL	4 (8.9)	21 (5.9)	0.5
- Other	1 (2.2)	20 (5.7)	
Clinical factors			
- Central venous catheter	21 (46.7)	180 (51.1)	0.57
- Neutropenia	40 (88.9)	326 (92.6)	0.38
- Antifungal prophylaxis	20 (44.4)	194 (55.1)	0.17
- Steroid use	6 (13.3)	27 (7.6)	0.19
Etiology			
- Yeasts	4 (8.9)	15 (4.3)	0.17
- Molds	8 (17.8)	36 (10.2)	0.13
Empirical treatment	12 (26.7)	178 (50.6)	**0.002**
MULTIVARIATE ANALYSIS			
Age (year [mean SD])			**0.006**
Empirical antifungal treatment			**0.01**

Uluslararası Rehberler

	ECIL 2009	IDSA 2010	NCCN 2013
Empirik	B II	A I (yüksek risk IFI)	Önerilir
Pre-emptif	-	B II (sadece yüksek risk hastalar için)	Önerilmez

PROFİLAKSİ

Flukonazol meta analiz

KT sonrası nötropeni gelişen hematolojik maligniteli hastalarda (KHN olmayan) flukonazol profilaksisi

- 16 prospektif, randomize çalışma
- 3734 vaka

- İFİ kökenli mortaliteyi azaltmada etkili değil
- Dirençli kandidalarla kolonizasyon sıklığında artış var

- İFİ insidansının %15 in üzerinde olduğu çalışmalarda etkili
- Yüzeyel kandida infeksiyonlarını engellemede çok etkili
- Flukonazole dirençli kandida infeksiyon sıklığında artma yok

Flukonazol ve vorikonazol

Allo-KHN hastalarında Çok merkezli , randomize , çift kör çalışma
Vorikonazol(305) ve Flukonazol(295) 600 hasta
100 gün boyunca profilaksi
180 gün sonra sağkalım değerlendirmesi

	Flukonazol	Vorikonazol	p
Aspergillus	17	9	0.09
Candida	3	3	
Zygomycetes	3	2	
Diğer	1	1	
Toplam	23	13	0.11

180. gün sağkalım fark yok

Wingard JR etal.Blood. 2010:9;116(24):5111-8

İtraconazol ve vorikonazol

Allo-KHN hastalarında Çok merkezli , randomize , açık etiketli
Vorikonazol (234) ve itrakonazol (255)
100 gün boyunca profilaksi
Tolerabilite

	İtrakonazol	Vorikonazol	p
Tolerabilite	%33.2	%48.7	0.01
Diğer antifungal kullanımı	%41.9	%29.9	0.01
Kesin/Yüksek olası İFİ	%2.1	1.3	NS

180. gün sağkalım fark yok

Marks DI, et al. BJH 2011:155:318-27

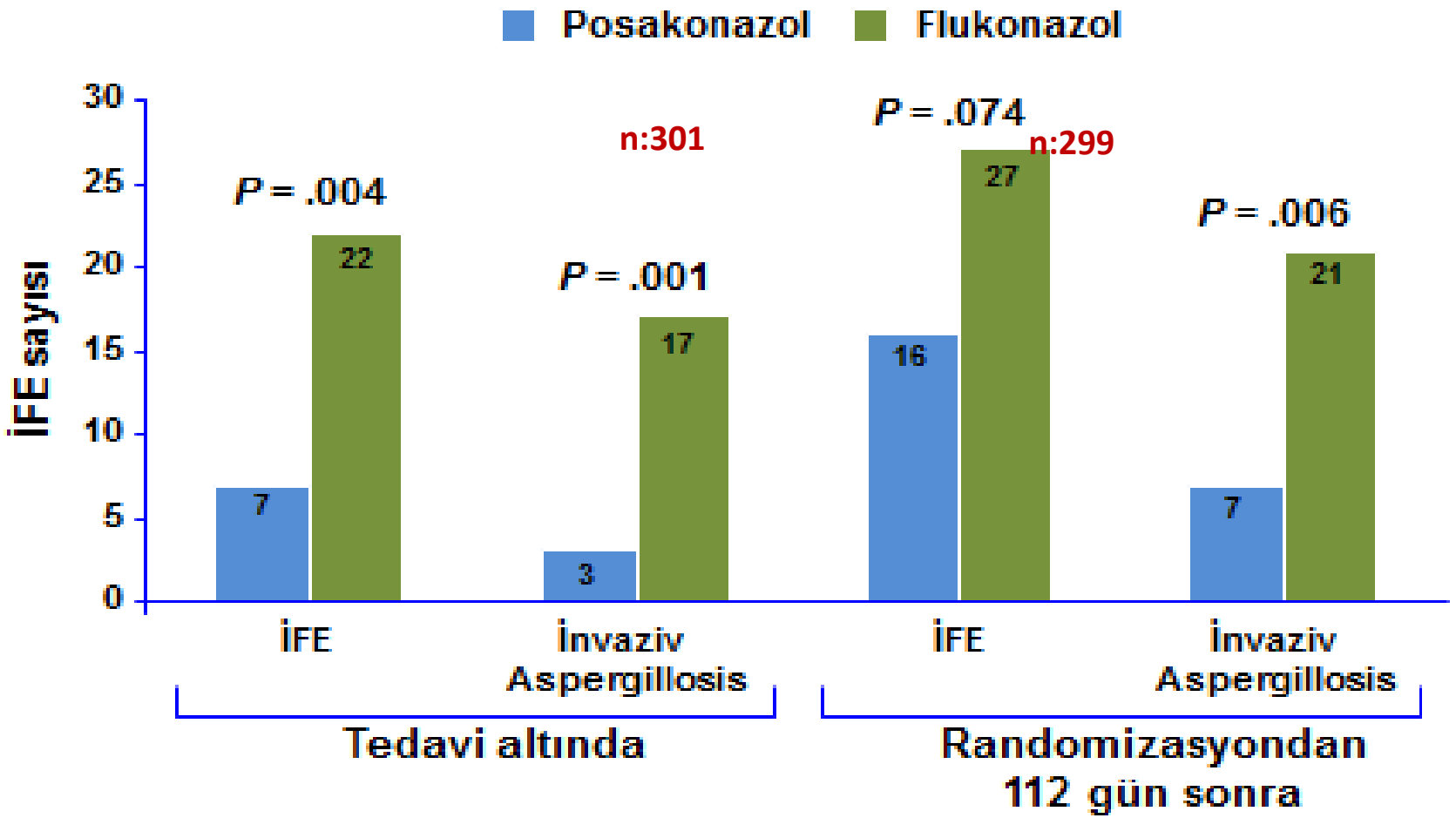
Flukonazol ve Posakonazol

GVHH

- Uluslararası, randomize, çift-kör bir çalışmada
- GVHH gelişen 600 hasta
- Oral flukonazol(299) ile oral posakonazol(301) karşılaştırıldı
- Primer son nokta randomizasyondan sonraki 112. gün

Ullmann AJ et al. N Engl J Med. 2007:25;356(4):335-47

Kanıtlanmış/yüksek olasılıklı İFE insidansı

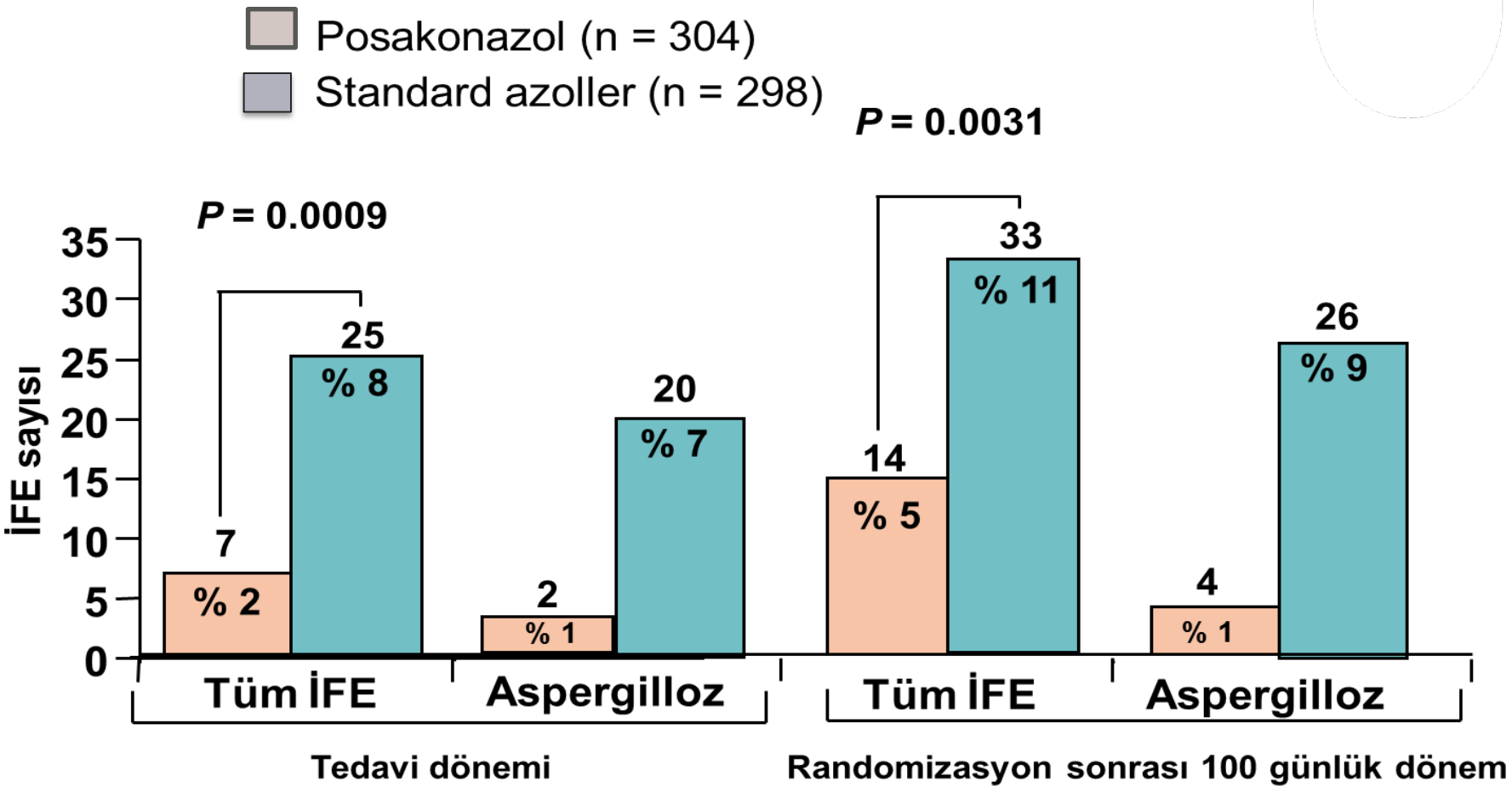


Ullmann AJ et al. N Engl J Med. 2007:25;356(4):335-47

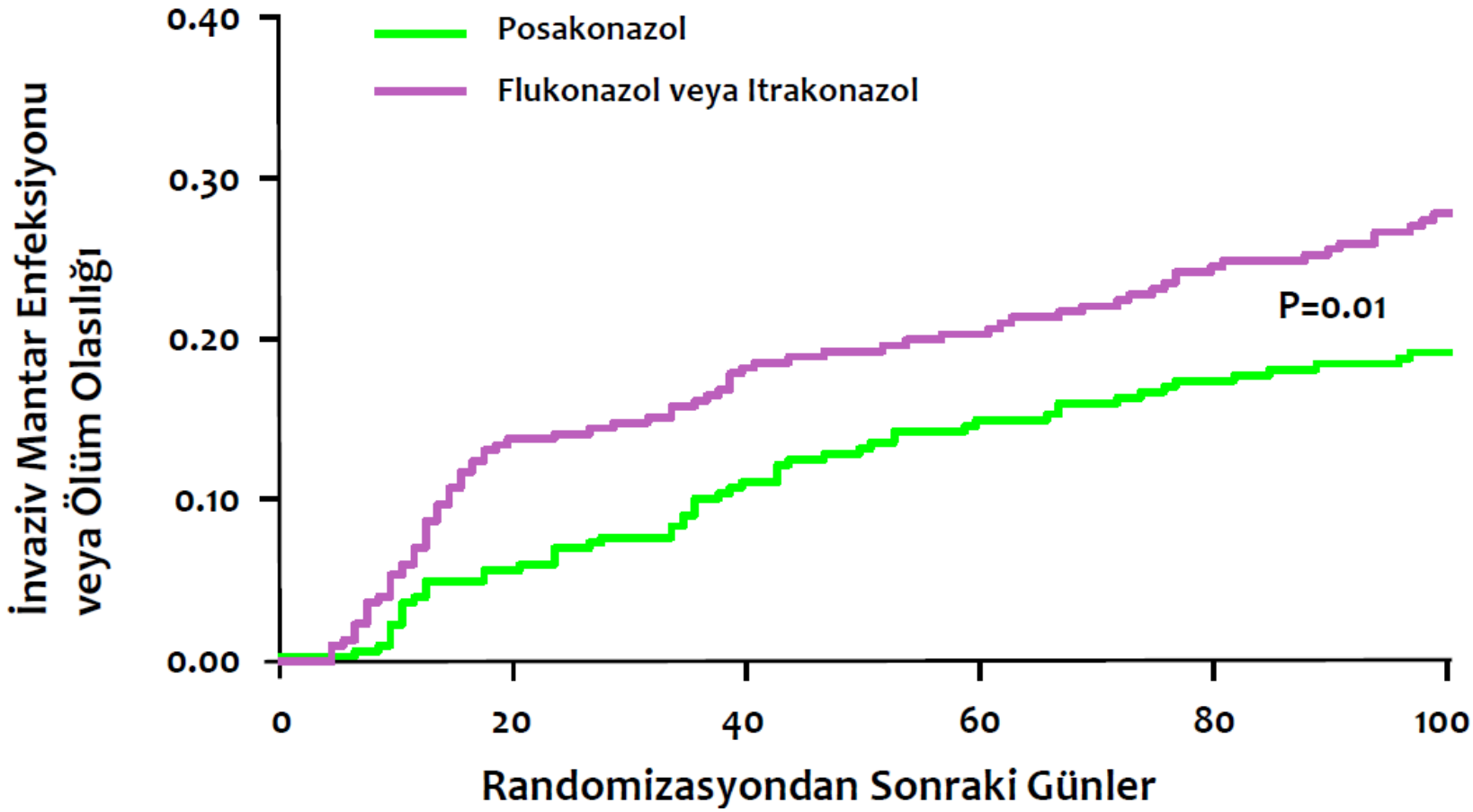
Flukonazol/İtrakonazol ve Posakonazol

AML/MDS

- Uluslararası, çok merkezli, randomize, açık etiketli
- 602 hasta AML/MDS
- Posakonazol (304) ile flukonazol (240)/itrakonazol (58)
- Profilaksi:
  - Tam remisyon ve nötropeni düzelinceye kadar her KT döneminde ya da
  - İFİ oluşuncaya kadar ya da
  - 12. haftaya kadar



Cornely OA et al. N Engl J Med 2007;356:348-59



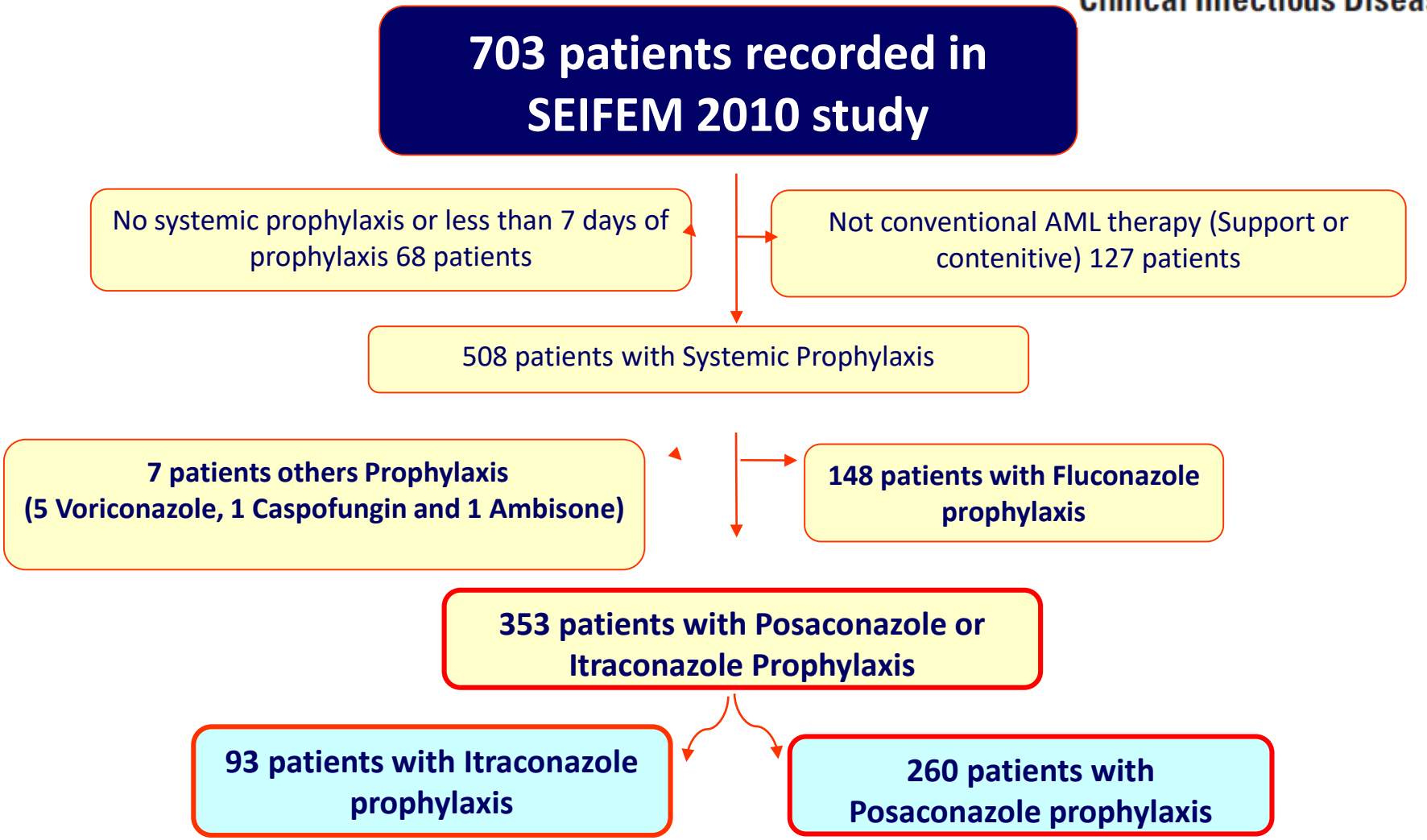
AML hastalarında profilaksi ile genel mortalitede azalma

Cornely OA et al. N Engl J Med 2007;356:348-59

SEIFEM 2010

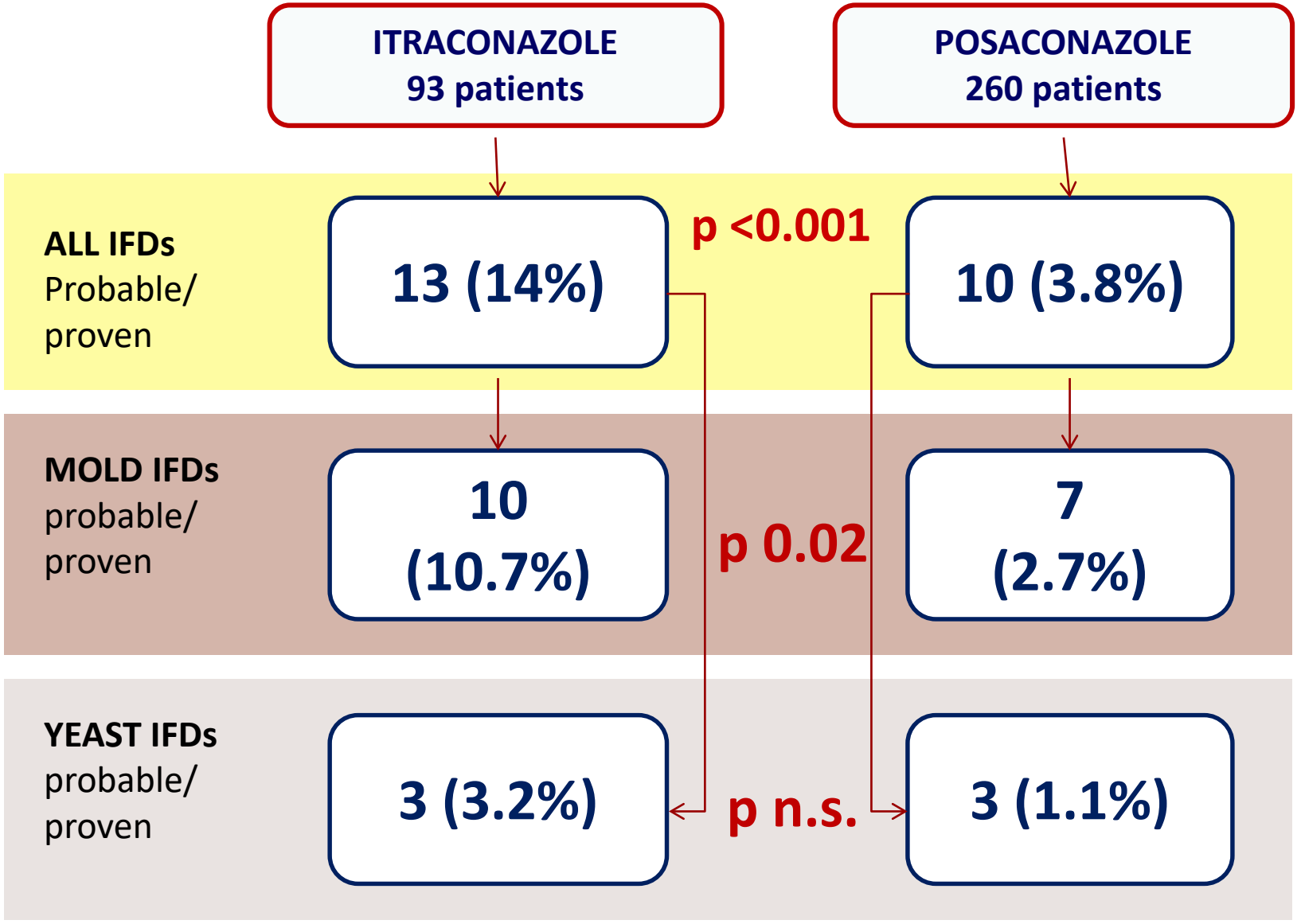
Evaluation of the Practice of Antifungal Prophylaxis Use in Patients With Newly Diagnosed Acute Myeloid Leukemia: Results From the SEIFEM 2010-B Registry

Clinical Infectious Diseases



SEIFEM 2010

Proven/probable IFDs incidence



SEIFEM 2010

SONUÇ

Posaconazole profilaksisi :

- IFI riski

-kısa-dönem mortalite

- antifungal tedavi gereksinimini azaltır

	ITRA N° 93	POSA N° 260	p-value
Frontline antifungal approach	**41 (45.1%)**	**69 (26.6%)**	**0.001**
Empirical	21 (22.6%)	53 (20.3%)	0.49
Pre-emptive	13 (14%)	12 (4.6%)	0.003
Target	7 (7%)	4 (1.5%)	0.004

ECIL-5 2013	POSA	VORİ	İTRA sol	FLU	KASPO	MİKA	L-AmB İV	Aero L-AmB
AML indüksiyon kemoterapisi	AI	BII	BI	BI	CII	CII	CII	+FLU-BI
AKHN yüksek riskli	BII	BI	BI	Öneril mez-AIII	Veri yok	CI	CII	+FLU-BII
AKHN+GVHH	AI	BI	BI	Öneril mez-AII	Veri yok	CII	CII	+FLU-Veri yok

Antifungal Profilaksi için Uluslararası Rehberler

	FLUCO	VORI	ITRA	POSA	CASPO	L-AmB	MICA
ECIL 3-4: CT	C-I	-	C-I	A-I	-	C-I	-
allo HSCT	A-I	A-I	B-I	A-I	-	C-I	C-I
DGHO: nötropenik	C-I	C-II	C-I	A-I	C-I	C-II	-
allo HSCT	A-I	C-II	C-I	A-I	-	-	C-I
IDSA (Candida)							
AL	A-I	-	A-I	A-I	A-I	-	A-I
Allo-HSCT	A-I	-		A-I	-	-	A-I
IDSA (Aspergillus)							
AML-MDS	-			B-I	-	-	-
British guidelines	-	-	A-I	A-I	-	-	-
NCCN: AML-MDS	-	2B	-	1	-	2B	-
allo HSCT	-	2B	-	1	2B	2B	1
ESCMID: AML-MDS	C-I	ND	C-II	C-II	NC	ND	ND
allo HSCT	A-I	A-I	B-I	A-II	C-II	B-II/C-III	A-I/C-III
(SADECE CANDIDA)							

Antifungal profilaksi altında gelişen IFI?

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

Karthaus et al, 2011

Wait and see or rush and switch? New questions for the management of patients with febrile neutropenia receiving antifungal prophylaxis

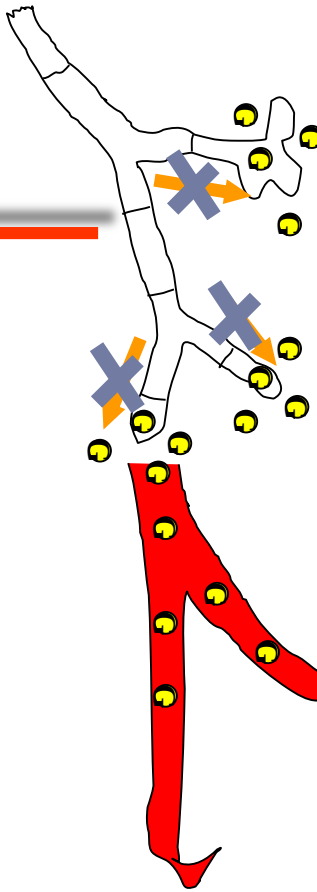
EDITORIALS & PERSPECTIVES

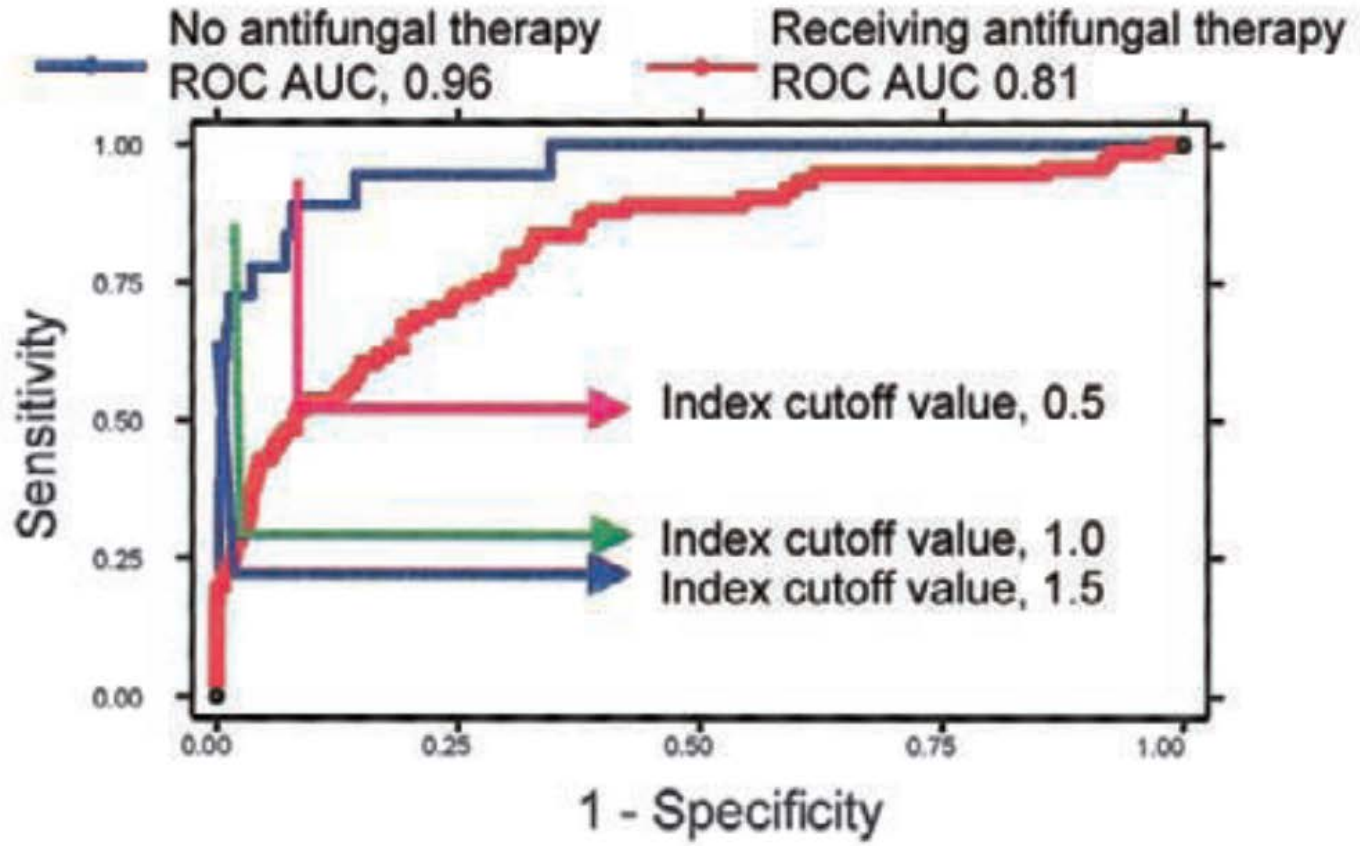
haematologica | 2012; 97(7)

The management of febrile neutropenia in the posaconazole era: a new challenge?

Livio Pagano,[1] Morena Caira[1] and Manuel Cuenca-Estrella[2]

Tanısal testler güvenli mi?
GM



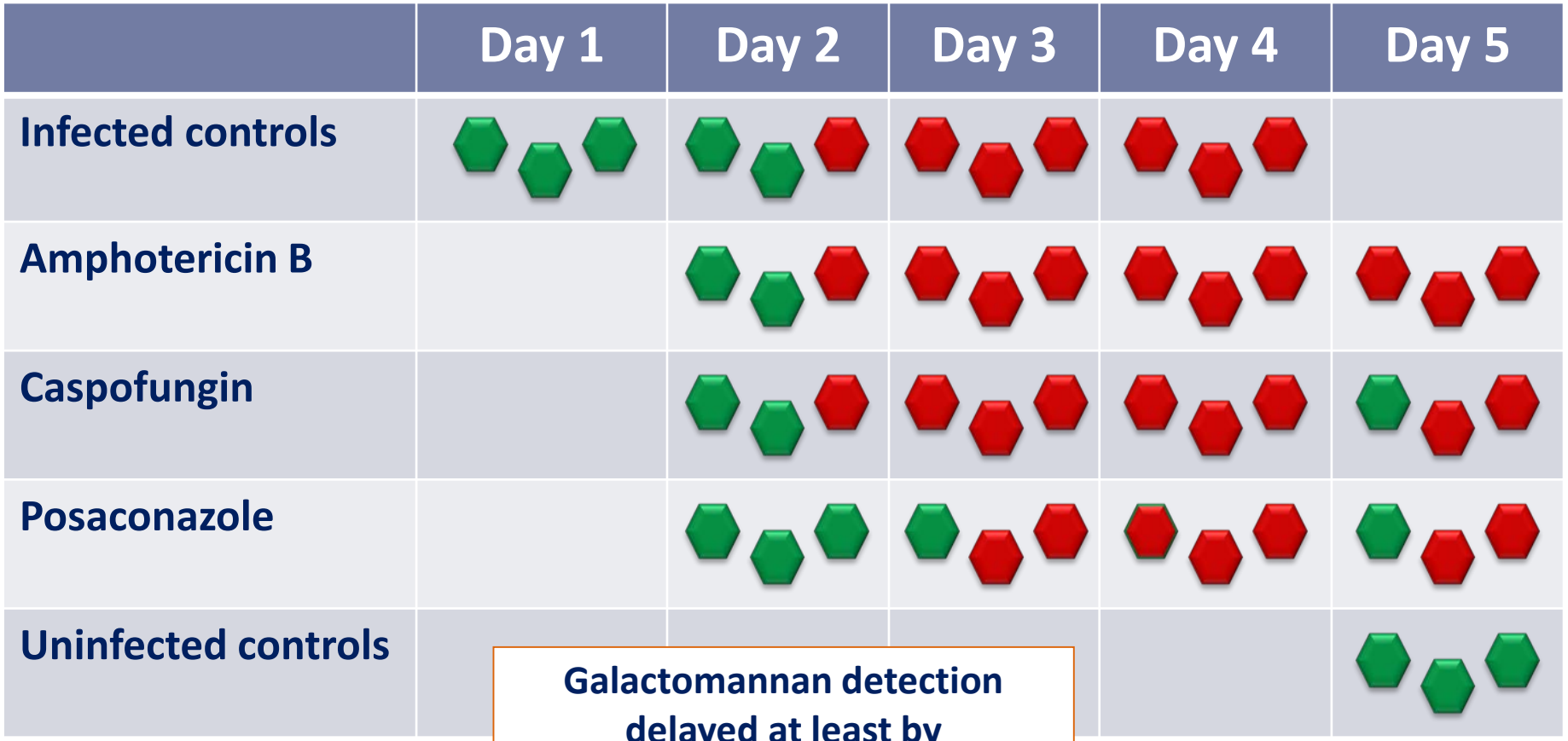


Marr et al, Clin Infect Dis 2005

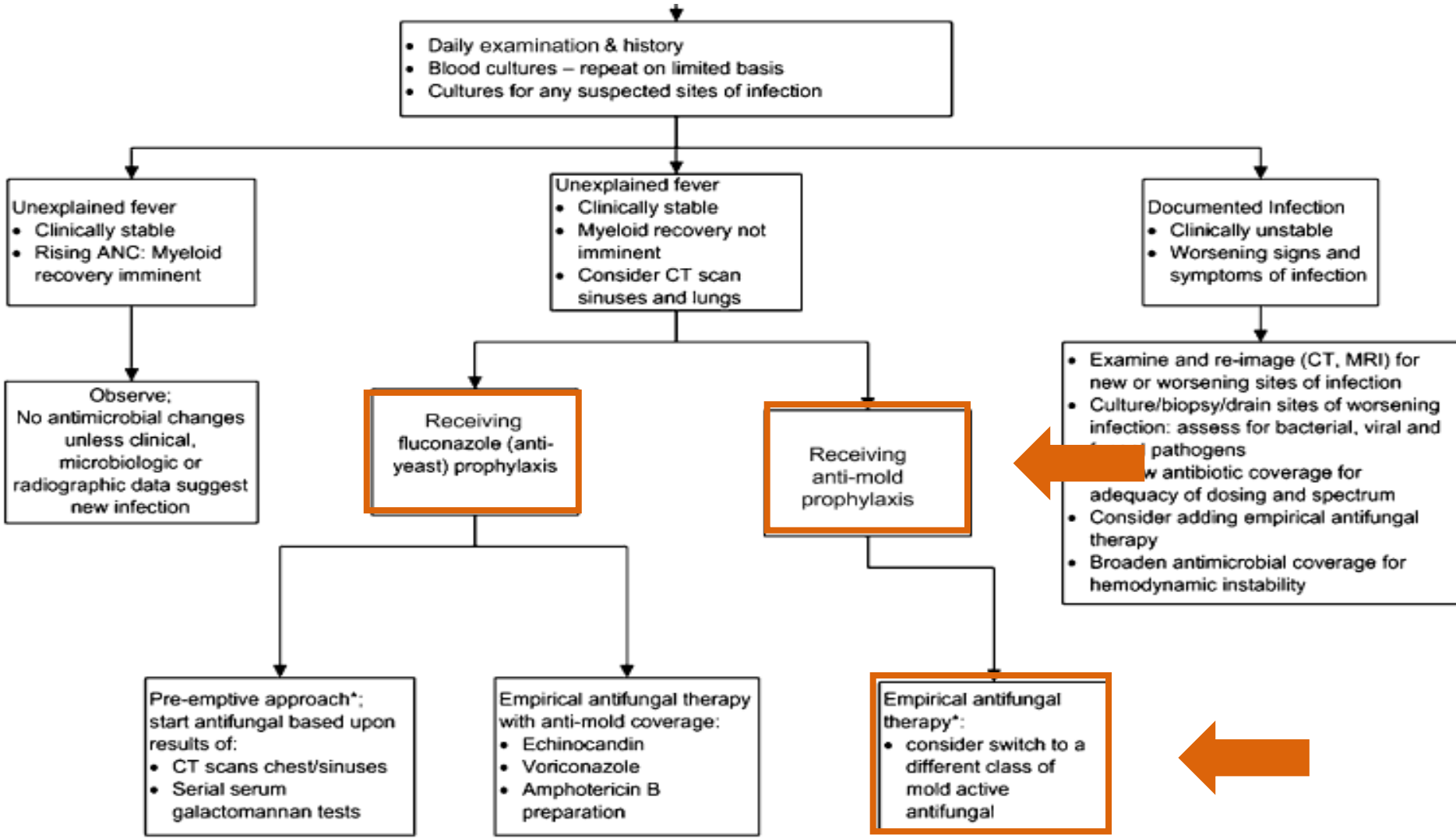
Antifungal treatment affects the laboratory diagnosis of invasive aspergillosis

Elaine McCulloch,[1] Gordon Ramage,[2] Ranjith Rajendran,[2] David F Lappin,[2] Brian Jones,[3] Peter Warn,[4] Raghdaa Shrief,[4] William R Kirkpatrick,[5] Thomas F Patterson,[5] Craig Williams[1]

McCulloch *et al*, J Clin Pathol 2012



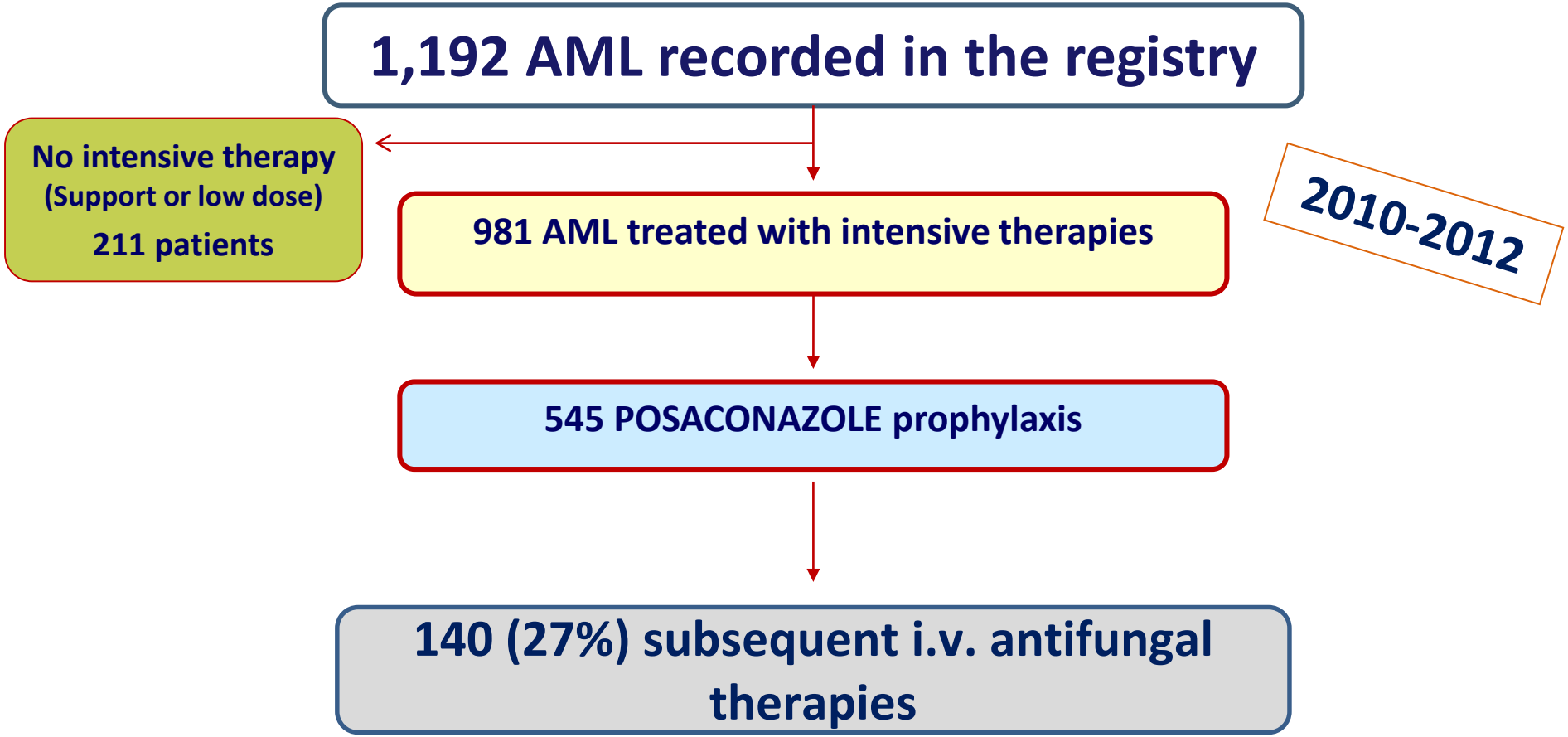
IDSA guidelines: 2010 update



Freifeld et al, Clin Infect dis 2011

Systemic antifungal treatment after posaconazole prophylaxis: results from the SEIFEM 2010-C survey

J Antimicrob Chemother
doi:10.1093/jac/dku227



Pagano et al, JAC 2014

SEIFEM 2010

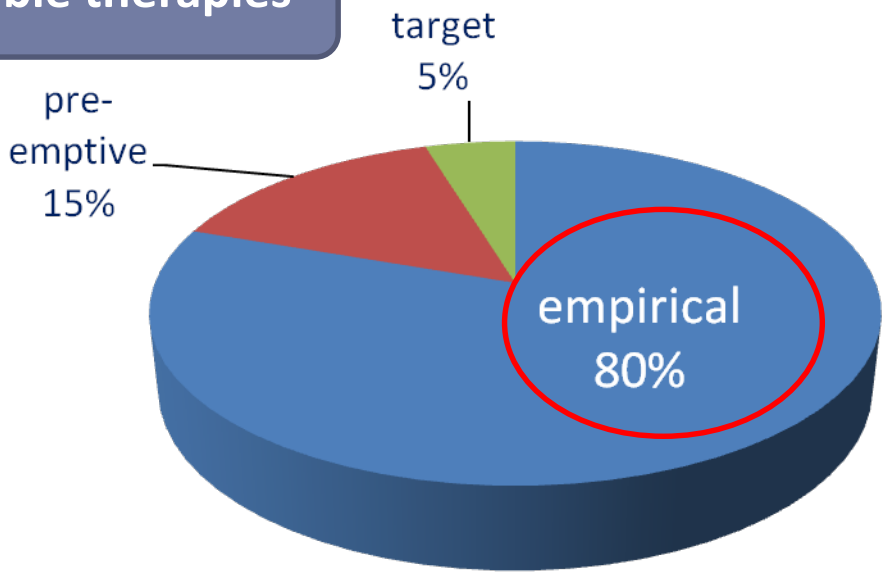
545 POSACONAZOLE prophylaxis

>5 days

140 (26%) subsequent i.v. antifungal therapies

≥7 days

127 evaluable therapies



3 EARLY DEATHS due to IFDs:
- 2 aspergillosis
- 1 PJP

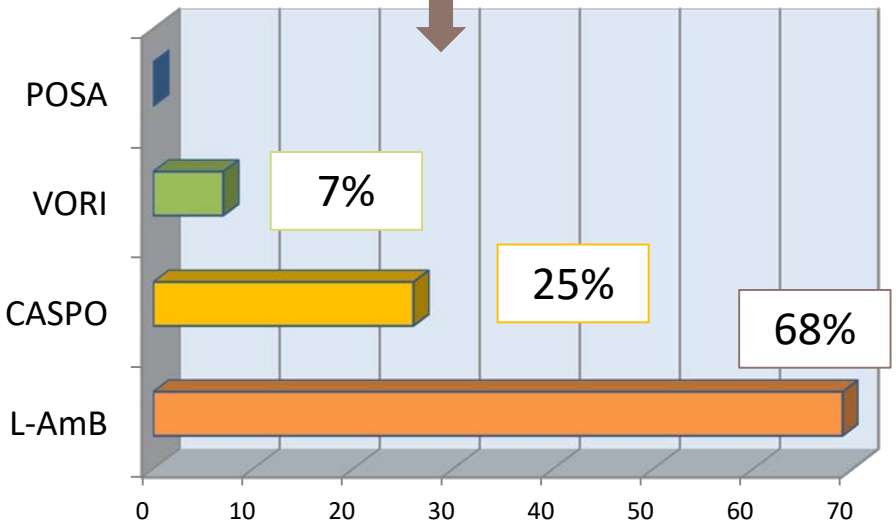
Pagano et al, JAC 2014

SEIFEM 2010

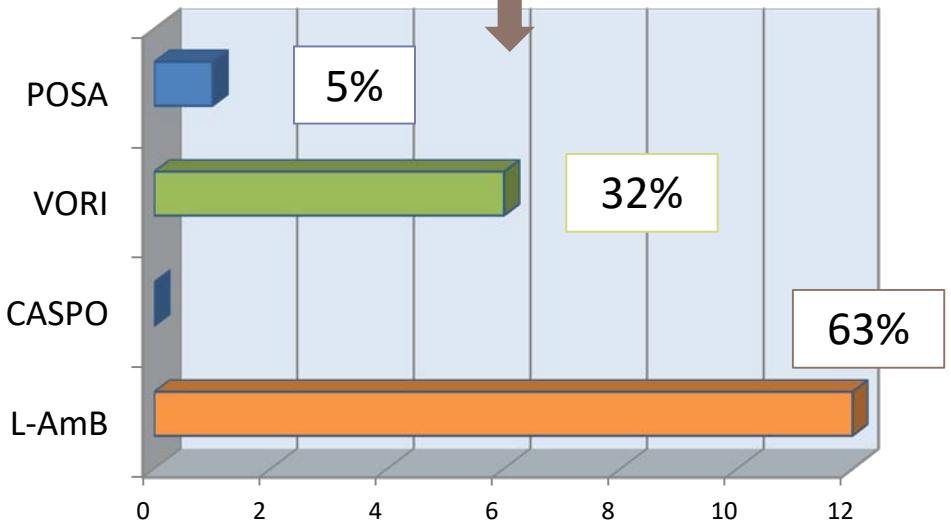
Data from the SEIFEM registry

127 antifungal therapies

102 (80%) empirical



19 (15%) pre-emptive



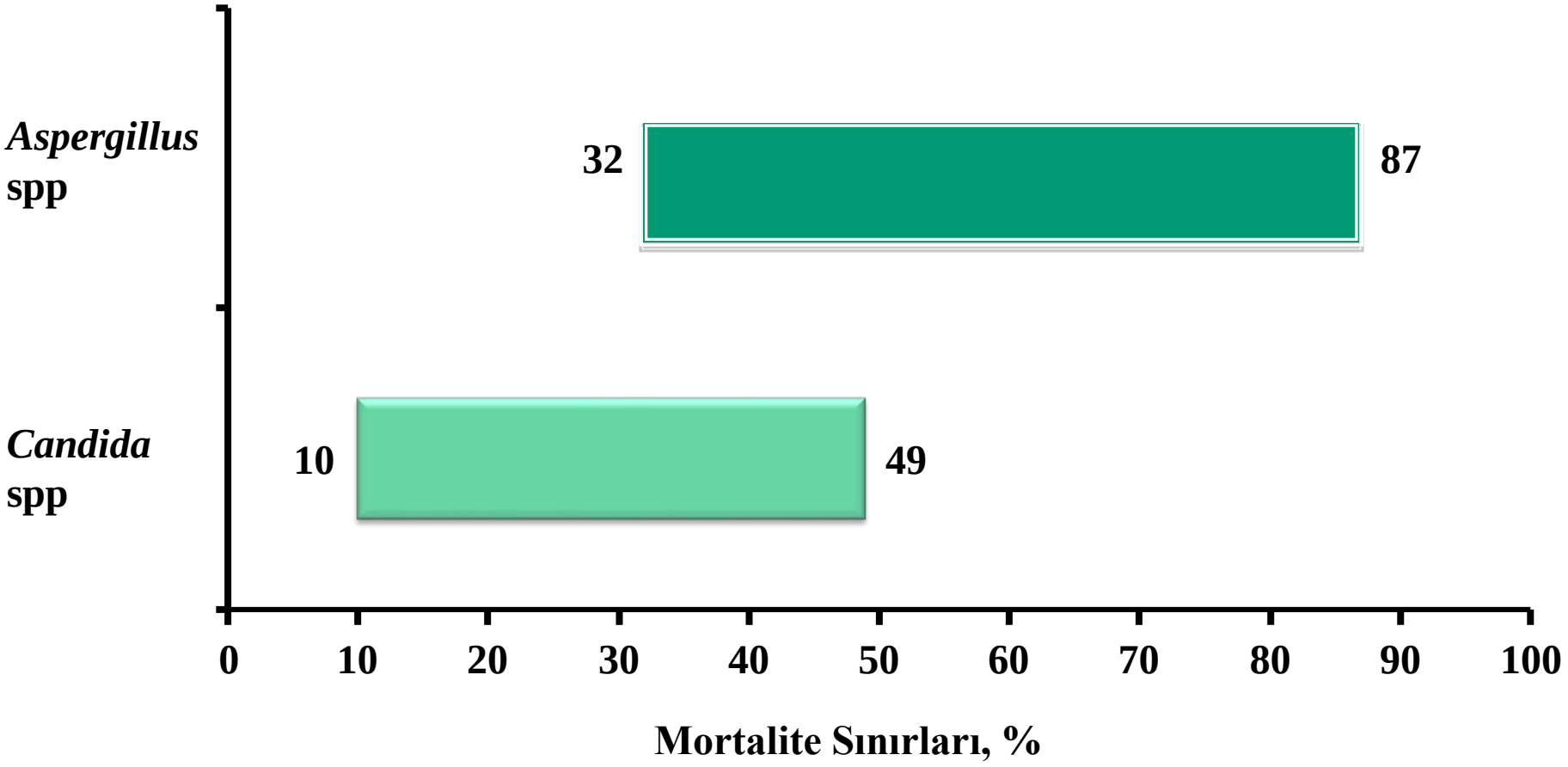
Kind of Evidence	Cases	At 30 days	Duration Mean (range)	AMR	Overall mortality
Empirical	**102**		**14 d (6-90)**	**3 (3%)**	**26 (25%)**
❖ L-AmB	69	FUO 26 Possible 37 Probable 4 Proven 2	13 (6-40)	3	15
❖ Caspofungin	26	FUO 9 Possible 12 Probable 5	11 (14-58)	/	9
❖ Others (4 ABLC, 3 voriconazole)	7	FUO 2 Possible 5	11 (7-19)	/	2
Pre-Emptive	**19**		**18 d (8-42)**	**0**	**4 (21%)**
❖ L-AmB	12	Possible 5 Probable 7 Proven 1	15 (8-30)	/	2
❖ Voriconazole	6	Possible 4 Probable 2 Proven 1			
❖ Posaconazole	1	Possible	22	/	1

No statistical difference between L-AmB and Caspo

No statistical difference between L-AmB and Vori

KANITLANMIŞ İFİ TEDAVİSİ

YÜKSEK RİSKLİ HASTALARDA MORTALİTE



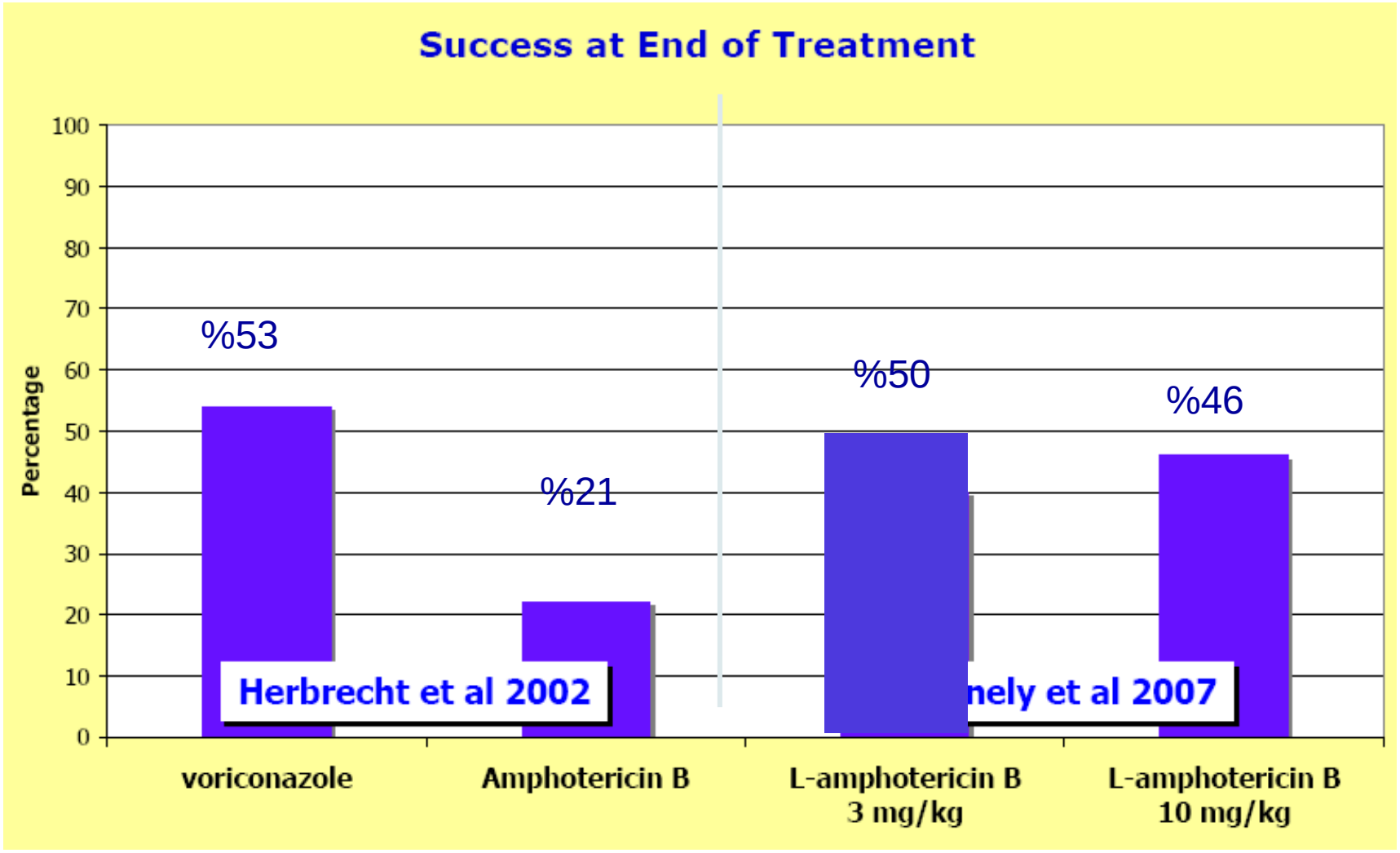
Cornely O, et al. Infection 2008;36:296.

İNVAZİV AKCİĞER ASPERGİLLOZU

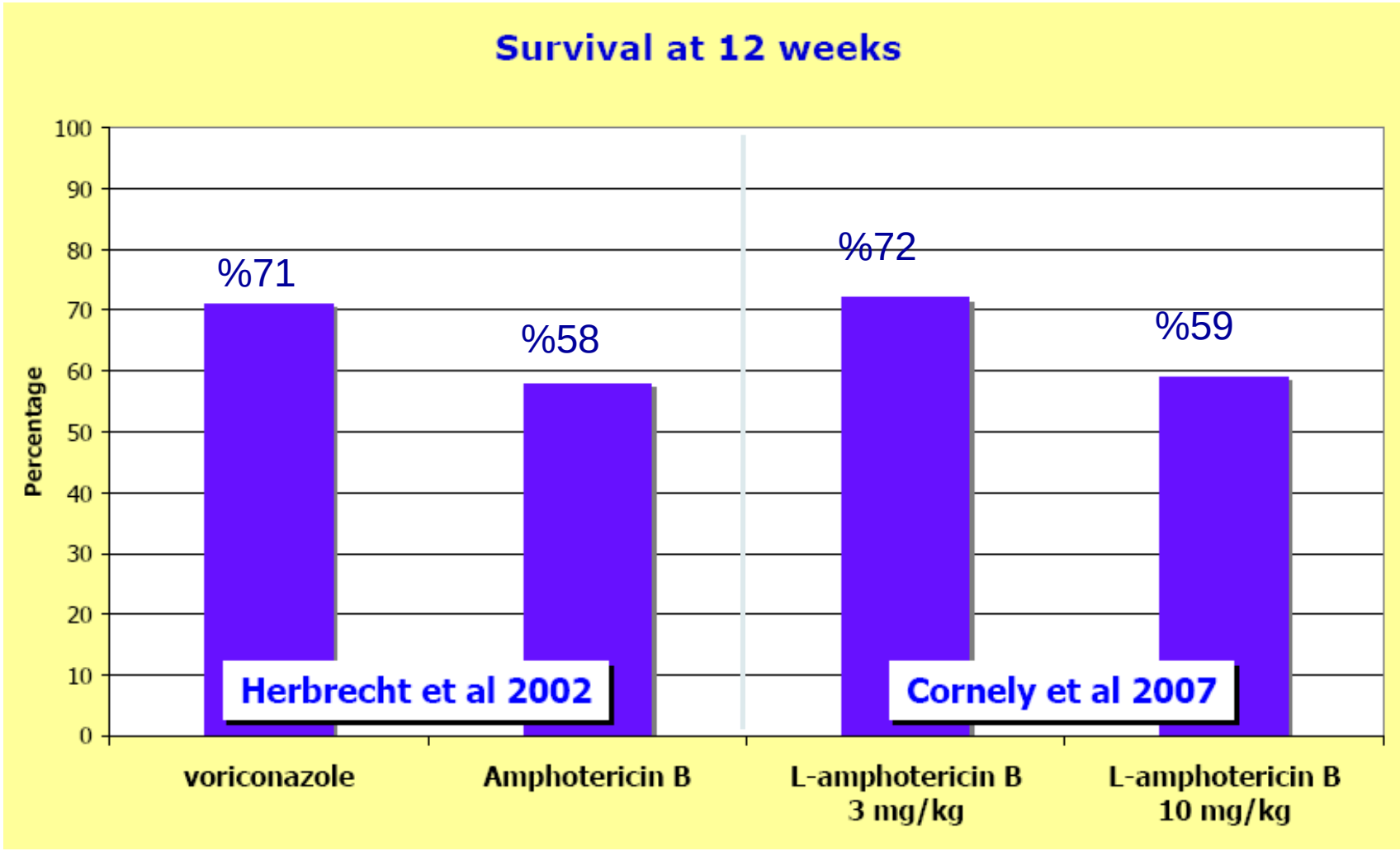
Halo belirtisi

***Candida*, CMV, HSV, tuberkülom, Wegener granülomatozisi**

TEDAVİ SONRASI BAŞARI



SAĞKALIM


Survival at 12 weeks
Percentage
100
90
80
70
60
50
40
30
20
10
0
%71
%58
%72
%59
Herbrecht et al 2002
Cornely et al 2007
voriconazole
Amphotericin B
L-amphotericin B 3 mg/kg
L-amphotericin B 10 mg/kg

İNVAZİF ASPERGİLLOZ

	IDSA2008
L-AMB	**A1**
Vorikonazol	**A1**
ABLC	-
D-AMB	-
Kaspofungin	Alternatif
Mikafungin	Alternatif
Posokonazol	Alternatif
İtrakonazol	Alternatif

Candida spp.


A
L R
1 1
4 5
9 9

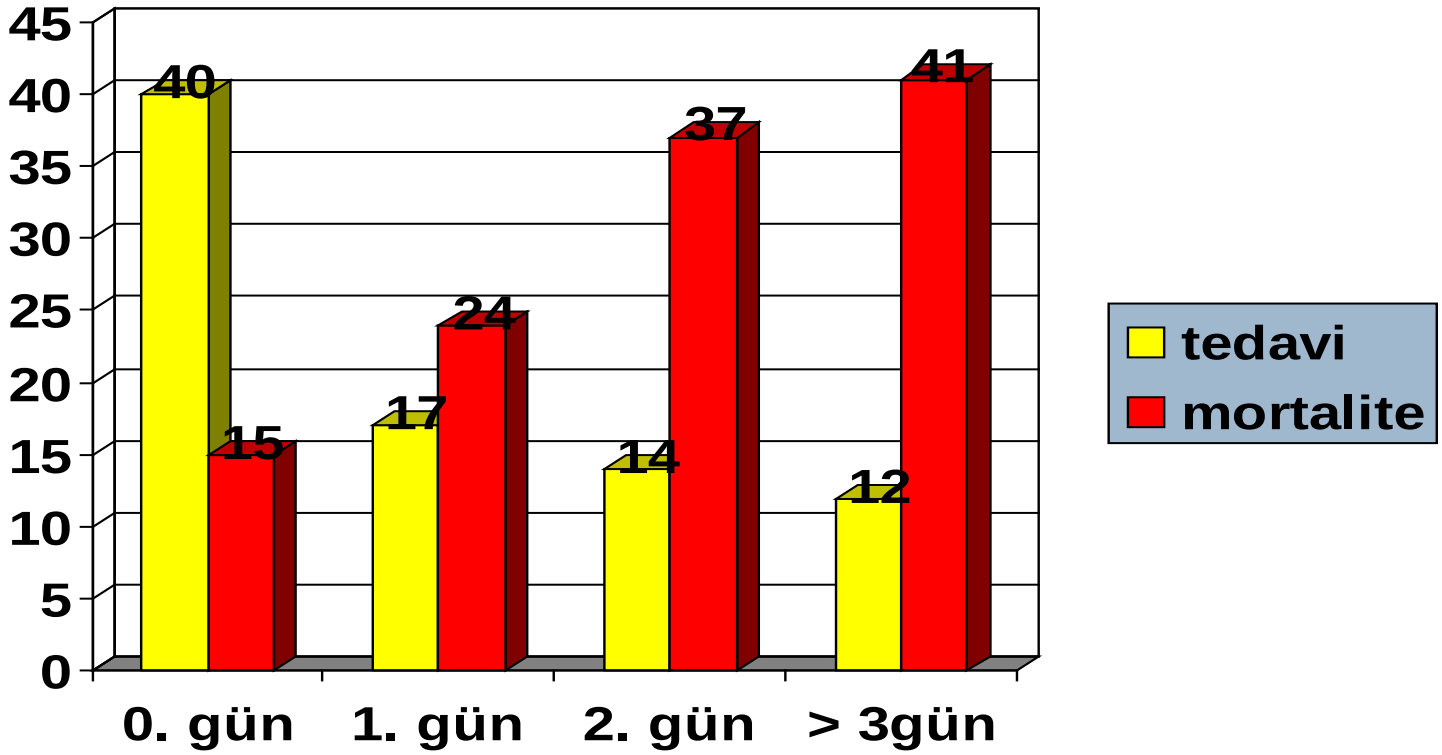

Image Courtesy of M. McGinnis
Copyright © 2000 Doctorfungus Corporation

Mikrobiyoloji
Erken ve Uygun Tedavi İçin

- Candida tür tayini önemli
- MİK tayini önemli
  - MİK ≤ 8 mg/dL başarı %67
  - MİK 16-32 mg/dL başarı %20
  - MİK ≥ 32 mg/dL başarı %0
- Flukonazol / MİK > 50 başarı %74
- ≤ 50 ise % 8

Time to Initiation of Fluconazole Therapy Impacts Mortality in Patients with Candidemia: A Multi-Institutional Study

Kevin W. Garey,[1] Milind Rege,[1] Manjunath P. Pai,[2] Dana E. Mingo,[3] Katie J. Suda,[4] Robin S. Turpin,[5] and David T. Bearden[6]



Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David Andes,[4] Daniel K. Benjamin, Jr.,[5] Thierry F. Calandra,[11] John E. Edwards, Jr.,[6] Scott G. Filler,[6] John F. Fisher,[7] Bart-Jan Kullberg,[12] Luis Ostrosky-Zeichner,[8] Annette C. Reboli,[9] John H. Rex,[13] Thomas J. Walsh,[10] and Jack D. Sobel[3]

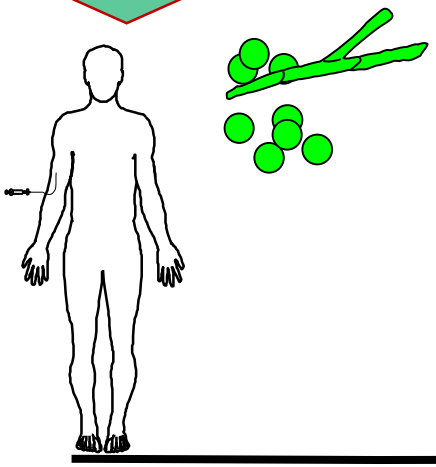
Empirical Treatment for Suspected Invasive Candidiasis in Neutropenic Patients

Kaspofungin yükleme dozu 70 mg, idame 50 mg/gün	(A-I)
LAMB (3–5 mg/kg gün)	(A-I)

IFI Tedavi Stratejileri

- ✓ Yüksek riskli Hasta
- ✓ Yüksek riskli dönem

ATEŞ;
yüksek riskli-
3-5.gün
Orta riskli::5-7
gün



Hastalık yükü

Kaba mortalite
60% to 90%

İNFEKSİYON ODAĞI/YÜKSEK OLASI

Hastalık yok — Sinus/Ac.B — Empirik AFT +CT/ GM POZİTİF KÜLTÜR

Profilaksi — Pre-emp — dite/ rtalite

Perfect et al. Oncology 2004;18:5-14.

TÜRKİYE-UZMAN GÖRÜŞÜ

Türkiye (UZMAN GÖRÜŞLERİ):

"Tanı güdümlü (preemptif) yaklaşım için farklı ünitelerde tanı araçlarına ulaşmada zorluklar söz konusu olduğundan, yüksek riskli hastalarda empirik tedavi başlanıp, tanı testlerinden elde edilecek sonuçlara göre gerekli uyarlamaların yapılması daha doğru olur"

Turk J Hematol 2014;31:111-120


Erken tanı
Erken tedavi
İmmun Fonksiyonların düzelmesi