

OLGU TARTIŖMALARI: AteŖli nötropenik hastayı nasıl izliyoruz? İkinci basamak tedavisi - geç dönem tanı ve salvage

Dr. Oğuz ReŖat Sipahi
Ege Üniversitesi Tıp Fakóltesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD
Bornova-İzmir
www.sipahi.tk



Hangi takımı tutuyorsunuz?

- A)Ankaragücü
- B)Beşiktaş
- B)Bursaspor
- C)Eskişehirspor
- D)Fenerbahçe
- E)Galatasaray
- F)Göztepe
- G)Trabzonspor
- H)Diğer



Süperfinal'i kim alır?

- A)Bjk
- B)Gs
- C)Fb
- D)Ts



0213 Cremona Italy

Edition Eulenburg *100 513*

No. 405

BEETHOVEN

Op. 55

Symphony No. 3

E♭ major—Mib majeur—Es dur

(Eroica)

Presented to Indiana University
School of Music
from the family of
Robert L. Cowart Sr.
English Horn
Los Angeles Philharmonic



Ernst Eulenburg, Ltd.
London - Zurich - Stuttgart - New York

Symphony N°3

1

Allegro con brio $\text{♩} = 60$

L. van Beethoven, Op. 55
1770-1827

2 Flauti

2 Oboi

2 Clarinetti in B

2 Fagotti

3 Corni in Es

2 Trombe in Es

Timpani in Es-B

Violino I

Violino II

Viola

Violoncello

Contrabasso

No. 405

E. E. 3605 Ernst Eulenburg Ltd., London Zürich



Tchaikovsky
Symphony No.6
Pathétique
in B Minor
Op. 74

1. in A
Klar.
2. in A
Flg. 1.2
1.2 in F
Hrn.
3.4 in F
Viol. 1
Viol. 2
Vla.
Vln.
Vc.
Kb.
Png. 1.2
Vln. div.
Vln. 1
Vln. 2
Vln. 3
Vln. 4
Png. 1.2
Png. 2
Png. 3

N
N
ritenuto
pppp
ritenuto



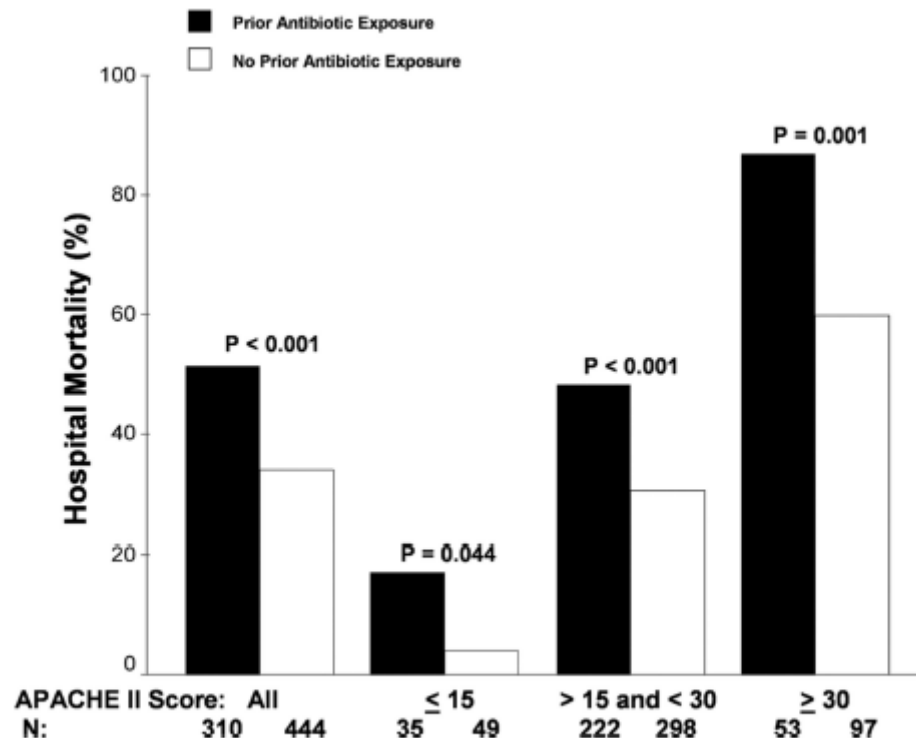


Figure 1. Hospital mortality stratified by Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Johnson MT, Reichley R, Hoppe-Bauer J, Dunne WM, Micek S, Kollef M. Impact of previous antibiotic therapy on outcome of Gram-negative severe sepsis. Crit Care Med. 2011 Aug;39(8):1859-65.

Table 2. Patients infected with Gram-negative organism(s) susceptible to commonly prescribed antimicrobials for Gram-negative infections^a

Antimicrobial Agent	Prior Antibiotic Exposure (n = 310)	No Prior Antibiotic Exposure (n = 444)	p
Cefepime	71.0%	93.0%	<.001
Piperacillin-tazobactam	68.1%	88.5%	<.001
Imipenem/meropenem	80.0%	97.5%	<.001
Ciprofloxacin	60.3%	82.4%	<.001
Gentamicin	73.9%	92.1%	<.001
Multidrug-resistant ^b	37.4%	11.3%	<.001

^aPatients with polymicrobial bacteremia had to have all isolated bacteria susceptible to the antibiotic to be considered susceptible; ^brefers to the number of patients in each group having bacteremia with multidrug-resistant Gram-negative bacteria. Multidrug-resistant isolates were defined as a bacterial isolate with *in vitro* resistance to at least two antipseudomonal antibiotics, which included cefepime, piperacillin-tazobactam, imipenem or meropenem, gentamicin or tobramycin, or amikacin.



OLGU

- 53 yaşında kadın hasta
- Multiple myelom
- VAD 5 kür
- Kemoterapiye yanıt yok
 - (%70 plazma hücreleri)
- Velcade+Dekort
- OKİT (Alkeran)



MM-OKİT

- 6. gün
 - Lökosit $152/\text{mm}^3$ nötrofil $105/\text{mm}^3$
 - Ateş 38,7

Fizik bakıda enfeksiyon odağı yok
Kan/kateter kültürleri alındı
Sefoperazon/sulbaktam 3X2 g iv



Tedavinin 3. günü

- Genel durumu bozuldu
- TA: 80/60 mmHg
- Vankomisin alerji
- Teikoplanin
- Kan kültürleri + kateter kültürü (port)



Tedavinin 4. günü

- Genel durumu kötü
- Öksürük, balgam çıkarma
- Solunum muayenesinde bilateral raller
- Hipoksi
- YBÜ
- Balgam kültürü gönderildi
- GM antijeni





Hastanenizde bu tip olguların
%kaçına bronkoskopi
yapabiliyorsunuz?

- A) <%10
- B) %11-33
- C) %34-66
- D) >%66



Hastanenizde düzenli galaktomannan testi çalışılıyor mu?

- A)Evet
- B)Hayır



Tedavi yaklaşımınız

- A) Karbapeneme geçirim
- B) Antifungal eklerim
- C) Trimetoprim sulfometaksazol eklerim
- D) Karbapenem + TMP/SMX
- E) Karbapenem + TMP/SMX + Antifungal

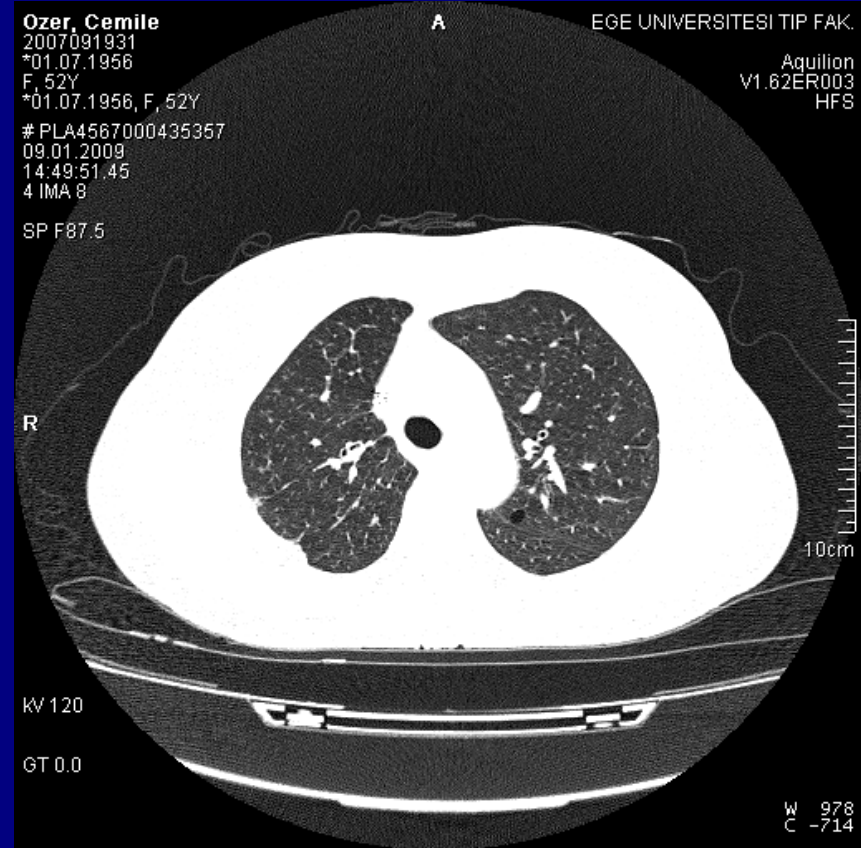
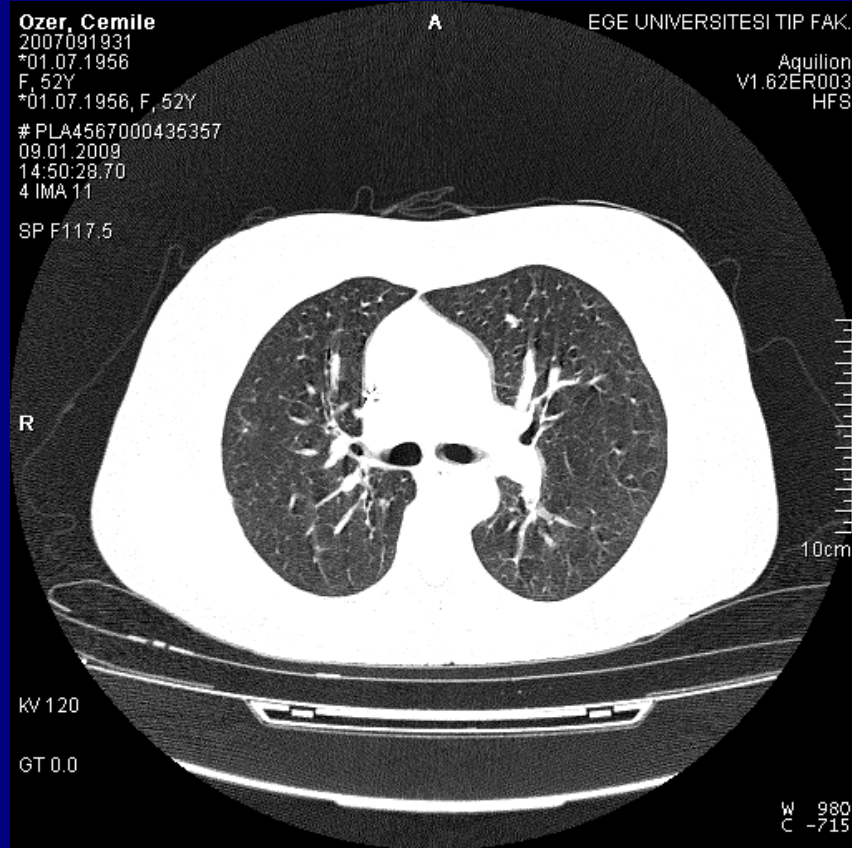


Karbapenem + TMP/SMX + Antifungal

- HRCT



Nötropeni öncesi HRCT



Ozer, Cemile

2007091931

*01.07.1956

F, 52Y

*01.07.1956, F, 52Y

#PLA4567000441072

16.01.2009

15:07:12.05

8 IMA 12

SP F345.0

A

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nile

31

Aquilion 6

V1.62ER003

HFS 6, F, 52Y

000461518

1

0

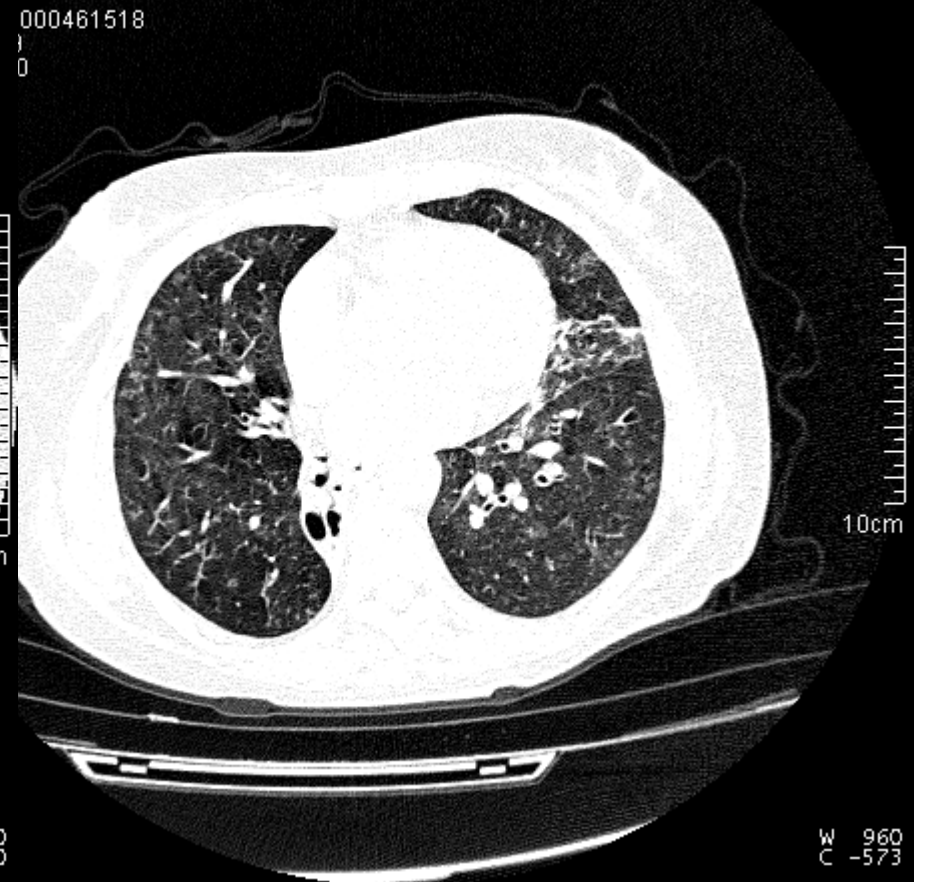
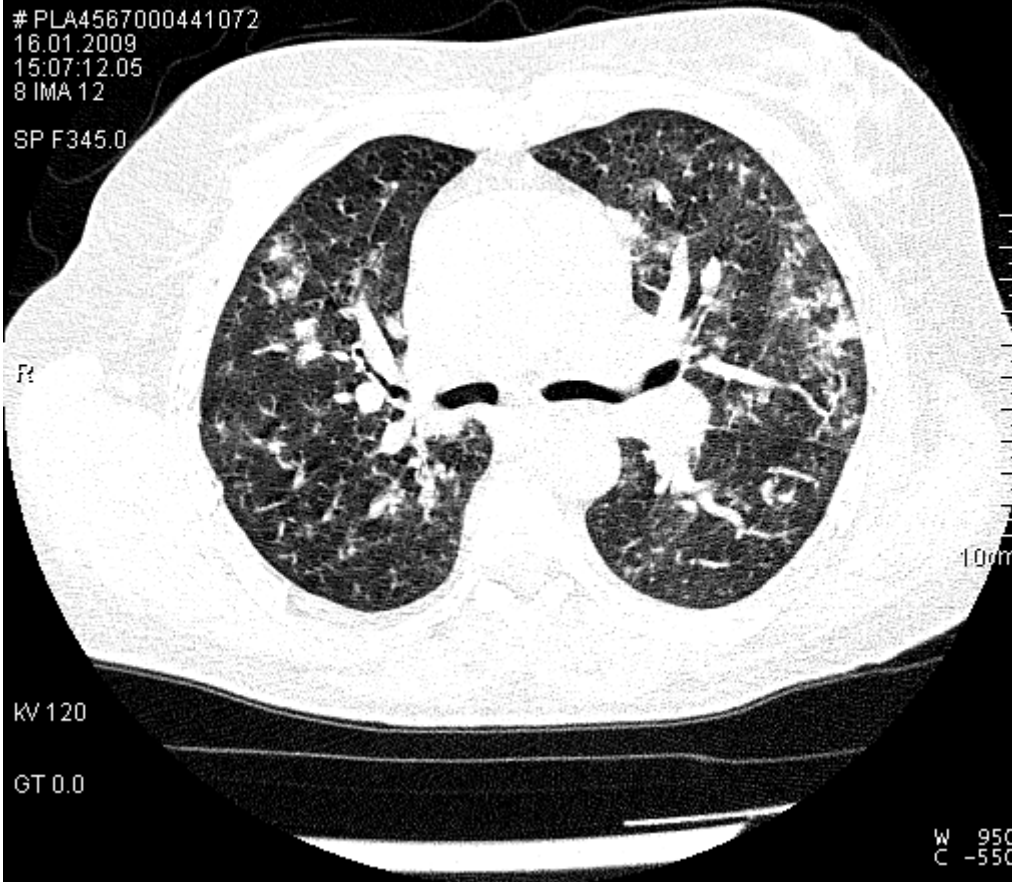
A

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Aquilion

V1.62ER003

HFS



Her iki akciğerde 9 Ocak tarihli BT ile kıyaslamalı değerlendirmede takipte yeni gelişen yaygın dağınık asiner opasiteler fokal konsolidasyon alanları izlenmektedir. Görünüm fungal enfeksiyona sekonder olabilir.



Kateter kan kültürü MRKNS
Kan kültürlerinde üreme yok

GM antijeni 0,77

Klasik Amfo B
Kreatininx2
Vorikonazol



Tedavinin 6. günü

- Ateş yanıtı yok
- Nötropeni devam 148/
mm³
- Balgam kültürü (2):
Acinetobacter baumannii

AMİKASİN	S
SEFTAZİDİM	R
DOKSİSİKLİN	R
SEFEPİM	R
İMİPENEM	R
MEROPENEM	R
NETİLMİSİN	I
SEFOPER/SULB	I
KOTRİMOKSAZOL	R
TİGESİKLİN	S
PİP/TAZO	R



Tedavi yaklaşımınız?

Karbapenemi kesip

- A) Sefo/sulb.+Amikasin
- B) Tigesiklin
- C) Kolistin iv/inh
- D) Sefo/sulb.+ Amikasin + Tigesiklin



Sefo/sulb.+ Amikasin +
Tigesiklin (3 gün sonra)

Laboratuvardan kolistin
ve rifampisin çalışması
istendi

ENDİKASYON DIŞI İLAÇ KULLANIM TALEP FORMU

("Bireysel Reçete" Bazında "Endikasyon Dışı" İlaç Reçete Etme İçin Eksiksiz Doldurulması
Gereken Başvuru Formu)

HASTA KİMLİK BİLGİLERİ

Hasta Adı:

T.C. Kimlik No:

Yaş:

Cinsiyet:

Dosya Numarası:

KLİNİK BİLGİLER:

Tamı

Tam Tarihi:

Kısa Klinik Özet:

Kısa Laboratuvar Özeti:



9. gün

- Ateşleri devam ediyor, genel durumu orta
- Nötrofil: $710/\text{mm}^3$
- Trombositopeni



11. gün

- Balgam kültürü:
C. albicans
- AMB-0.75
- FLU-3
- İTR-0.016
- VOR-32[^]
- CASP-0.047



Candida etken mi?

- A) Etken olma olasılığı yüksek tedavi değişikliği yaparım
- B) Etken olma olasılığı düşük tekrar solunum yolu örneği gönderirim



Kandida pnömonisi

- Solunum yollarından Candida ?
Çoğunlukla kolonizasyon

(Rello et al Chest 1998)

Postmortem örnekleme ile % 40 solunum yollarında Candida kolonizasyonu ancak % 8 Candida pnömonisi saptanmış.

Am J Respir Crit Care Med 1997



- Oral sürüntü örneđi aynı antifungal duyarlılıđa sahip *C. albicans*
- Uygun ağız temizliđi yapıldıktan sonra alınan balgam örneđinde üreme yok



13. gün

- Öksürük, balgam, ateşleri devam ediyor
- Solunum muayenesinde raller mevcut
- BRONKOSKOPİ



15. GÜN

- BAL ve bronkoskoik aspirasyon örnekleri
- *Acinetobacter baumannii*
 - Kolistin S
 - Rifampisin R
- Mantar elemanı görülmedi, üreme olmadı
- *Pneomocystis jirovecii* -



- Sefo/sulb. 10. gün
- Amikasin 10. gün
- Tigesiklin 7. gün
- Tedavi altında kültür pozitifliği devam ediyor



- Colistin inhaler + iv tedavisi eklendi



25. gün

- Ateş yok
- Solunum bulguları geriledi
- Kontrol balgam kültürlerinde üreme yok



Ozer, Cemile

2007091931

*01.07.1956

F, 52Y

*01.07.1956, F, 52Y

#PLA4567000461518

10.02.2009

14:29:24.30

4 IMA 14

SP H30.5

A

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Cemile

91931

Aquilion .1956

V1.62ER003

HFS .1956, F, 52Y

1567000461518

2009

43.45

17

.5

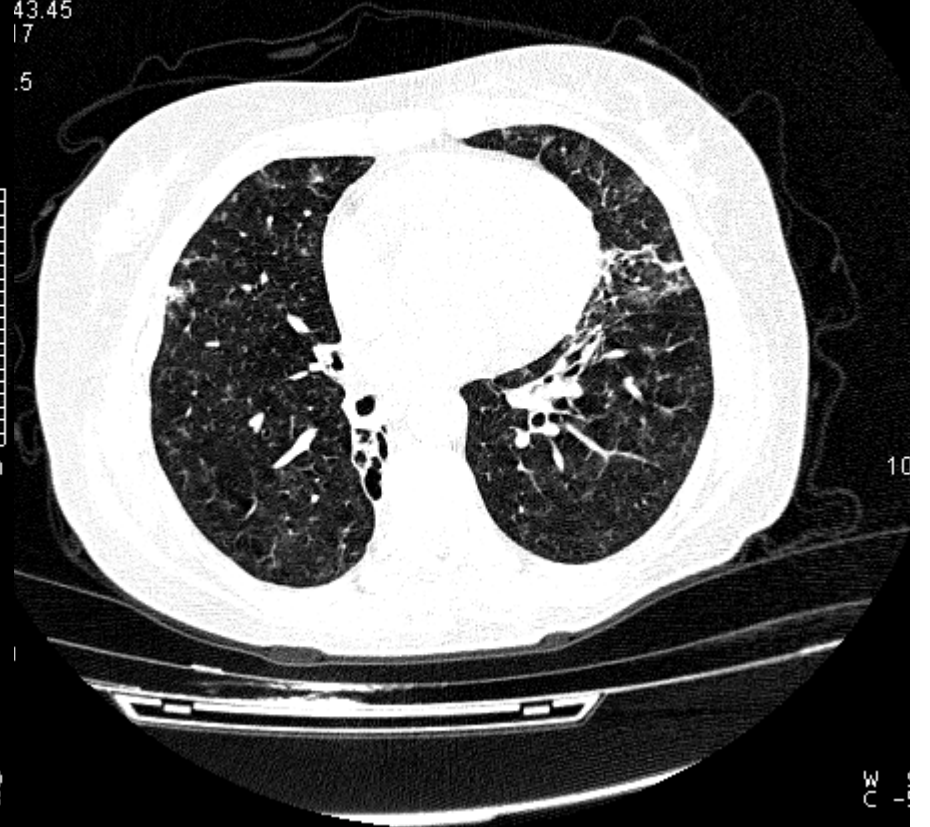
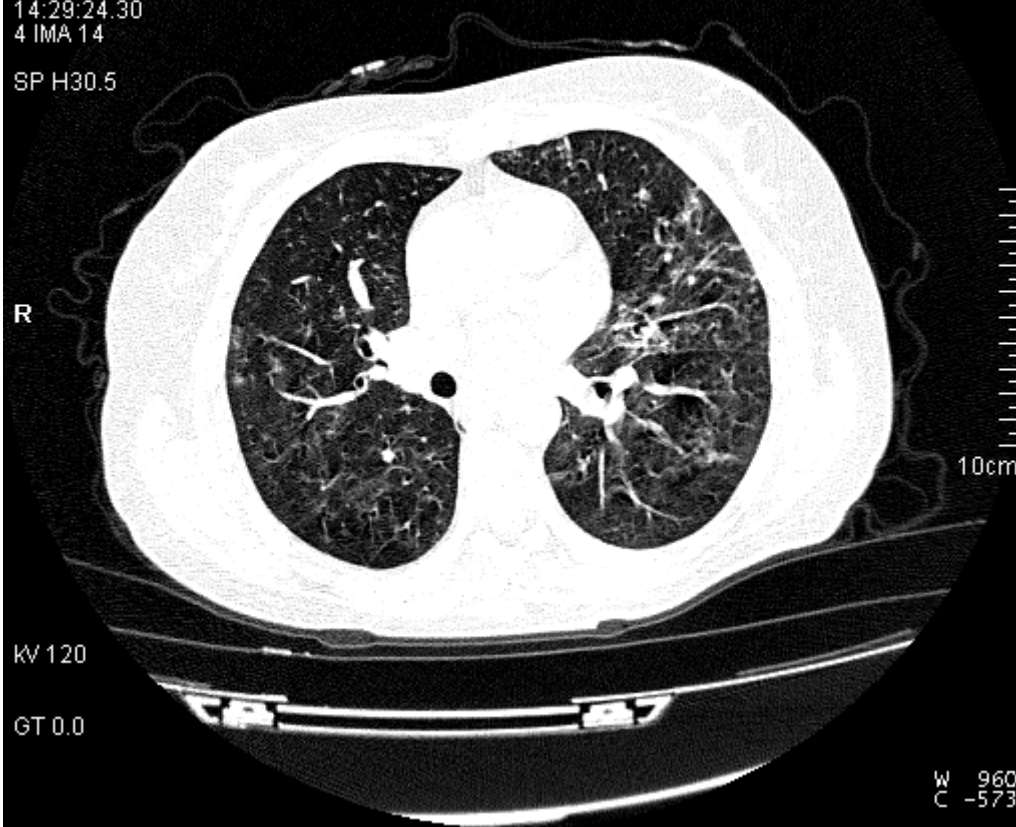
A

EGE UNIVERSITESI TIP FAK.

Aquilion

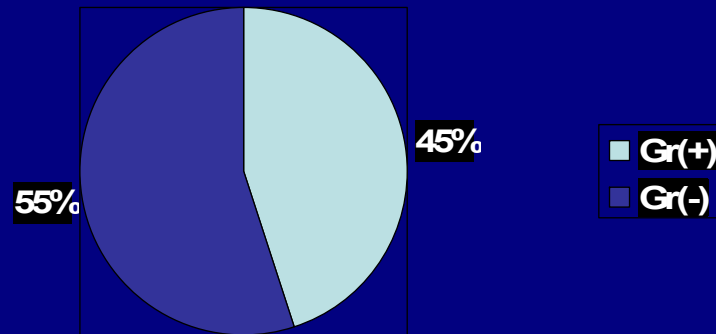
V1.62ER003

H



Ege Hematoloji Sürveyans

- FEN atak :231
 - NBA :111
 - MDE :120



E.coli :%43
Acinetobacter spp. :%26
Klebsiella spp. :%21
Pseudomonas spp. :%10

KNS :%65

Enterococcus spp :%20

S. aureus : %15



ESBL

E.coli %33

Klebsiella spp. %28

Acinetobacter spp.

Karbapenem R:%82

Sefo/sulb R:%23 I:%41

Netilmisin R:%12

Pseudomonas spp.

Karbapenem R:%33

Kinolon R:%50

Amikasin R:%16

• MR

– KNS %86

– *S. aureus* %50

• *Enterococcus* spp.

– VRE (3/11) %27

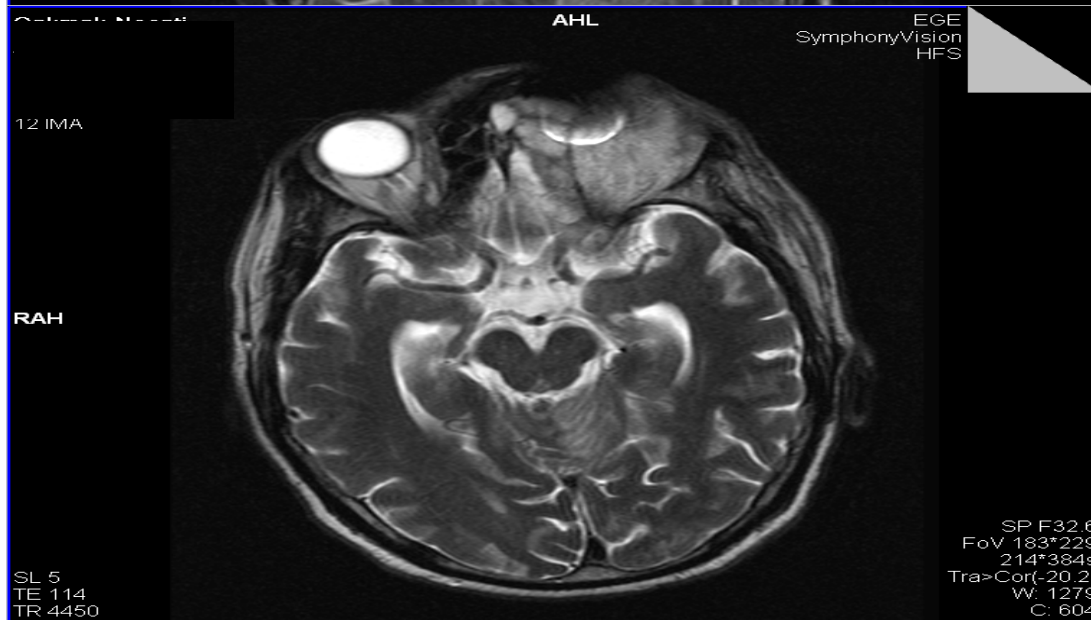




Olgu

- 38 y, E, NHL(3yıl)
- 2 kez OKİT engrafman –
- Febril nötropeni: ampirik pip/tazo,
– ateş yanıtı yok
- HRCT: Fungal pnömoni
- Vorikonazol iv/po
- Tedavinin 45. günü sol orbita üzerinde
selülit



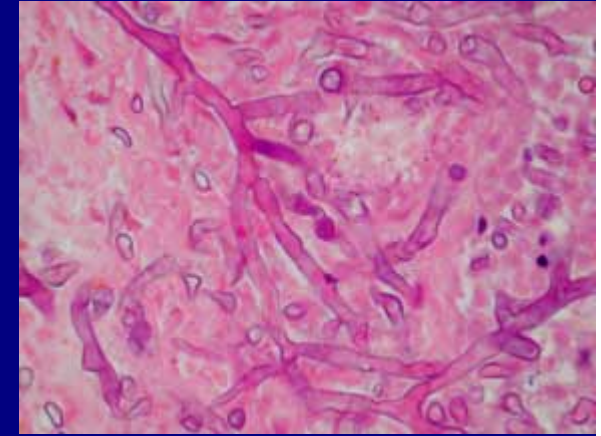


- Mukormikoz düşünülerek LAMB (4 hafta)
- Biyopsi: Mukormikoz
- Kültürde üreme olmadı
- Posokonazol (6 hafta)
- Klinik iyileşme
- Kontrol MR belirgin gerileme,



Zigomikoz

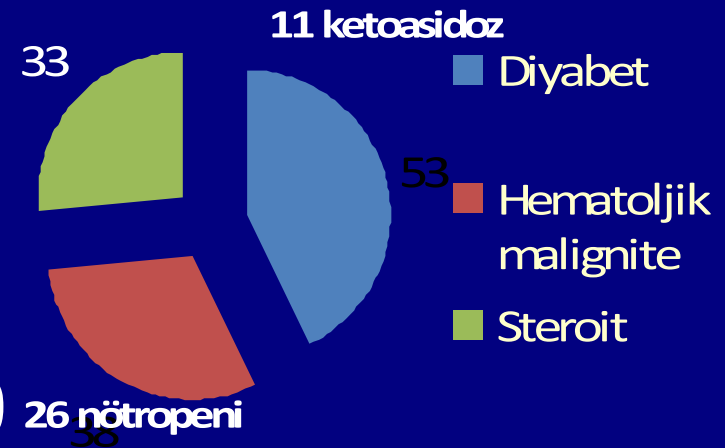
- Geniş, septasız, kalın duvarlı, dik açı ile dallanan hifler
- Kolay ürer (Sikloheksimitli SDA)
- *Rhizopus*, *Rhizomucor*, *Mucor*, *Absidia*
- *Rhizopus arrhizus*
 - İnsan olgularının %60
 - Rinoserebral %90
- Toprak, su, hava
- Giriş yolu: inhalasyon
- Damar ve doku invazyonu
- Kültür duyarlılığı %30



**TÜRKİYE'DEN 1995-2009 YILLARI ARASINDA YAYINLANMIŞ 100
MUKORMİKOZ OLGUSUNUN HAVUZ ANALİZ YÖNTEMİ İLE
DEĞERLENDİRİLMESİ**

Arzu Nazlı, Meltem Işıkgöz Taşbakan, Hüsnü Pullukçu, Oğuz Reşat Sipahi, Tansu Yamazhan, Bilgin Arda

- 22 uluslararası, 26 ulusal yayın
- 53 erkek, 47 kadın olgu
- Yaş ortalaması 46
- Patolojik tanı: 83
- Radyolojik tanı: 76
- Mikolojik tanı: 21/40



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Arzu Nazlı, Meltem Işıkgöz Taşbakan, Hüsnü Pullukçu, Oğuz Reşat Sipahi, Tansu Yamazhan, Bilgin Arda

- Cerrahi + Antifungal : 85 olgu
- Cerrahi : 5 olgu
- Antifungal : 7 olgu (7 ex)
- Toplam mortalite: 57
- Diyabetli olgularda mortalite daha yüksek



Zigomikoz

Klinik

- Rinoserebral
- Serebral
- Pulmoner
- Gastrointestinal
- Deri
- Dissemine



Zigomikoz

- Diyabetik ketoasidoz
- Hematolojik malinite
- Steroit kullanımı
- Desferroksamin enjeksiyonu
- Travma
- Kontamine bant
- Kontamine dil basacağı



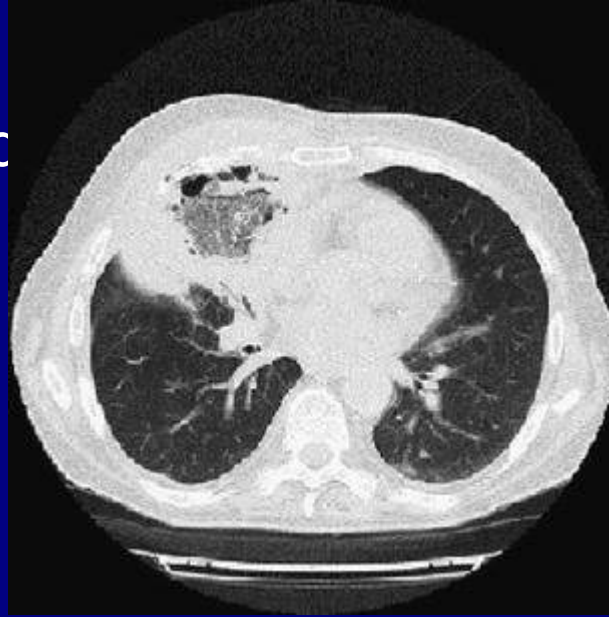
Rinoserebral Zigomikoz

- Nazal veya yumuşak damak nekrozu %50
 - 3 gün içinde
- Nekroz yokluğu tanıyı dışlamaz
- Agresif tedavi yapılmazsa serebral ve orbital komplikasyon
- BT, MRG
- Biyopsi-kültür



Akciğer Zigomikozu

- Aspergilloza benzer
- Ateş
- Öksürük (nonprod)
- Göğüs ağrısı
- İlerleyici dispne
- Kavite
- Hemoptizi



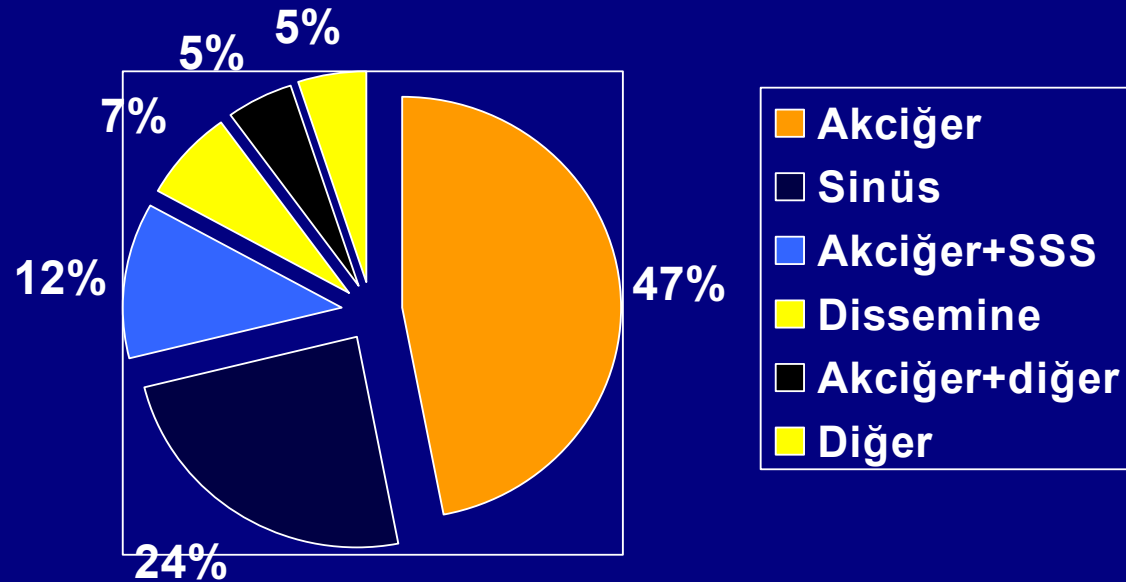
- Antifungal profilaksi (vorikanazol, ekinokandin)
- Galaktomannan ag(-)

Mortalite %50-70

Dissemine %95



Zigomikoz'lu hematolojik hastada enfeksiyon bölgesi



Pagano et al. Haematologica 2004



Zigomikoz

Risk faktörü	Sağkalım (%)
Diyabet	61
Nötropeni	28
Desferoksamin	14
İV uyuturucu	33
Prematürite	22
KİT	20

Am J Health Syst Pham 2005 Medscape



Vorikonazol tedavisi altında zigomikoz

- AKİT
 - 13/139 “breakthrough” infeksiyon
 - 6/13 zigomikoz

Imhof A CID 2004;39

- KİT (2003-6) Vori profilaksi
 - 4/45 (%8,9) “breakthrough” zigomikoz

Siwek GT. CID 2004;39:584-587



Kaspofungin “breakthrough” Zigomikoz

Zigomikoz, 2 olgu

Fusarium, 1 olgu

Tricosporon, 1 olgu

Walsh TJ N Engl J Med 2004;35:14



Antifungal duyarlılık

- Amfo B ++
- L-Amfo B +++++
- 5-Flusitozin +
- Posakonazol +++++
- İtrakonazol ---
- Kaspofungin ---
- Vorikonazol ---



Zigomikoz tedavi

- Altta yatan hastalığın kontrolü
- Erken ve geniş cerrahi debritleme
- Antifungal tedavi
 - Amfo B 1-1,5 mg/kg/gün
 - Lipit bileşenli Amfo B
 - Posakonazol
- Tedavi süresi ?
 - Radyolojik düzelme
 - Biyopsi ve kültür (-)
 - İmmünsüpresyonun durumu



Zigomikoz tedavisinde Posakonazol

- Standart tedavilere yanıtsız olası veya yüksek olası zikomikoz olguları
 - 24 olgu (14 HM)
 - Posakonazol (800mg/gün)
 - Tedavi başarısı %70

Greenberg RN, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother 2006;50(1):126–33.



Posaconazole Is Effective as Salvage Therapy in Zygomycosis: A Retrospective Summary of 91 Cases

Jo-Anne H. van Burik,¹ Roberta S. Hare,² Howard F. Solomon,³
Michael L. Corrado,³ and Dimitrios P. Kontoyiannis⁴

91 olgu

- 69 kesin
- 22 yüksek olası
- 81 olgu refrakter
- 10 olgu intoleran
- %62 tek odak
- %85 L-AMB

– Posa 4x200mg 2x400mg

12. Hafta tedavi başarısı



Posaconazole Is Effective as Salvage Therapy in Zygomycosis: A Retrospective Summary of 91 Cases

Jo-Anne H. van Burik,¹ Roberta S. Hare,² Howard F. Solomon,³
Michael L. Corrado,³ and Dimitrios P. Kontoyiannis⁴

64 olguda cerrahi girişim

38 ted öncesi

9 ted sırasında

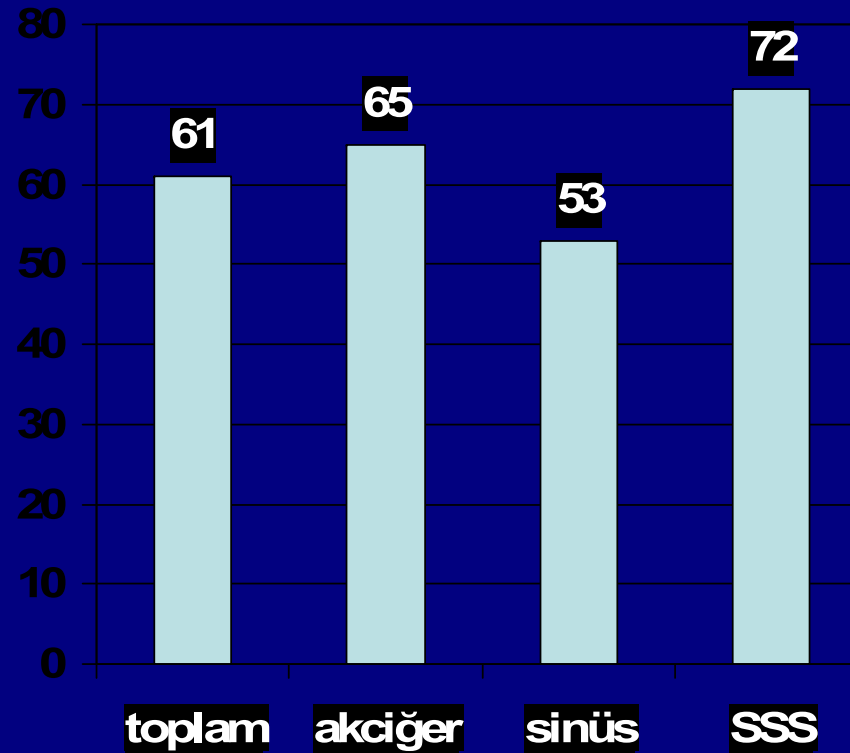
17 önce+sonra

Cerrahi girişim uygulanıp

uygulanmaması tedavi

başarısını etkilememiş

%61-62



[Mucormycosis: retrospective evaluation of 12 cases].

[Article in Turkish]

Arda B, Erdem A, Sipahi OR, Işıkgöz Taşbakan M, Pullukçu H, Taşbakan MS, Ceylan N, Metin DY, Midilli R, Yamazhan T, Ulusoy S.

Ege University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, İzmir, Turkey.

Tablo II. Olguların Demografik ve Klinik Özellikleri

Yaş/ No Cinsiyet	Altta yatan hastalık	Klinik tanı	Mikolojik tanı	Patolojik tanı	Radyolojik tanı	VCZ prx	Tedavi (gün)	Cerrahi tedavi	Tedavi süresi	Sonuç
1 74/K	Aplastik anemi	RO	-	+	+	+	L-AMP (30) + ITC (50)	-	80	Y
2 56/E	Diş absesi	RO	-	+	+	-	L-AMP (90) + PCZ (90)	Sinüs cerrahi	180	Y
3 38/E	NHL (OKIT)	RS	-	+	+	+	L-AMP (30) + PCZ (45)	-	75	Ex
4 55/E	DM + siroz	RS	<i>Rhizopus</i>	+	+	-	L-AMP (10)	+	10	Ex
5 74/K	MDS	RO	-	-	+	+	L-AMP (14) + PCZ (20)	-	34	Ex
6 55/K	DM	RS	Mikolojik muayene +++	+	+	-	L-AMP (52)	+	52	Ex
7 65/E	DM + diş absesi	RS	<i>Mucor</i> + <i>Aspergillus</i>	+	+	-	L-AMP (38) + PCZ (40)	+	78	Y
8 22/K	Aplastik anemi + Steroid kullanımı	RO	Mikolojik muayene +++	+	+	-	ABLC (56)	-	56	Y
9 63/E	Akciğer kanseri	Pulmoner	<i>Rhizopus</i>	+	+	-	L-AMP (10) + PCZ (60)	Lobektomi	70	Y
10 40/K	Adrenal yetmezlik + Steroid kullanımı	RO	<i>Rhizopus</i>	+	+	-	L-AMP (6)	-	6	Ex
11 50/K	MDS	RSI + pulmoner	<i>Rhizopus</i> + <i>Aspergillus</i>	+	+	-	L-AMP (8)	-	8	Ex
12 18/K	Aplastik anemi	RO	-	-	+	-	L-AMP (30) + PCZ (50)	-	80	Y

VCZ: Vorikonazol, L-AMP: Lipozomal amfoterisin B, ITC: İtrakonazol, PCZ: Posakonazol, ABLC: Amfoterisin B lipid kompleksi, RS: Rinoserebral, RO: Rinoorbital, Prx: Profilaksi, NHL (OKIT): Non-Hodgkin lenfoma (otolog kemik iliği transplantasyonu), DM: Diabetes mellitus, MDS: Miyelodisplastik sendrom, Y: Yaşayıcı, Ex: Eksitus.





- AML-M3
- 1. kür konsolidasyon
- 13. gün nötropenik ateş
- Sefepim+isepamisin
- 4. gün teikoplanin
- 6. gün amfoterisin b



- 8. gün nötropeniden çıkıyor.
 - Ateş devam
- Sağ hipokopndriyumda ağrı ve hassasiyet
- USG ve MR hepatosplenik kandidoz
 - Kan ve kemik iliği kültürü olumsuz
 - Bx
 - Gönül ister aradığını...
 - Olası hepatosplenik kandidoz



- L-amb üç hafta yanıt yok
- Üç hafta +kaspofungin
- 2 hafta tek kaspofungin
- Radyolojik regreesyon
- 2 ay flukonazol oral idame



- Amfo B
- Lipozomal amfo B
- Kaspofungin
- Vori
- Kombinasyon tedavisi



Kaspofungin monoterapi???

Clin Infect Dis. 2002 Nov 1;35(9):1135-6.

Successful treatment with caspofungin of hepatosplenic candidiasis resistant to liposomal amphotericin B.

Sorà F, Chiusolo P, Piccirillo N, Pagano L, Laurenti L, Farina G, Sica S, Leone G.



Vorikonazol+kaspofungin

Ann Biol Clin (Paris), 2005 Jul-Aug;63(4):423-7.

[Hepatosplenic and kidneys candidasis complicating an acute myeloblastic leukemia. A case treated with voriconazole and caspofungin].

[Article in French]

Elouennass M, Doghmi K, Fagot I, Soler C, Mac Nab C, Foissaud V, De Revel I, Hervé V.

Service de biologie médicale, hôpital d'instruction des armées Percy, Clamart. elouennassm@yahoo.fr



Hepatosplenic candidiasis in the era of new antifungal drugs: a study in Paris 2000-2007.

De Castro N, Mazover E, Porcher R, Raffoux E, Suarez F, Ribaud P, Lortholary O, Molina JM.

Departments of Infectious Diseases Biostatistics and Medical Informatics Haematology, AP-HP Hôpital Saint-Louis, Denis Diderot -Paris 7 University, France and René Descartes-Paris 5 University Department of Haematology, AP-HP Hôpital Necker Enfants-Malades, Centre d'Infectiologie Necker Pasteur Haematology-Stem Cell Transplantation, AP-HP Hôpital Saint-Louis, Denis Diderot -Paris 7 University, France and René Descartes-Paris 5 University Department of Infectious and Tropical Diseases, AP-HP Hôpital Necker Enfants-Malades, Centre d'Infectiologie Necker Pasteur Institut Pasteur, Centre National de Référence Mycologie et Antifongiques, CNRS, Paris, France.

- 24 olgu
 - 6 kesin
 - 3 yüksek olasılıklı
 - 15 olası
- 15 hasta bx yapılabilmiş

HSC localization, n (%)	
Liver + spleen	16 (67)
Spleen	3 (13)
Liver	5 (21)
Kidney	3 (13)
Lungs	10 (42)



Tedavi

%54 başarı/2 net başarısızlık diğerleri ölüm

First-line antifungal therapy for HSC ($n = 24$)^a

None, n (%) ^b	1 (4)
Azoles, n (%)	13 (54)
Polyenes, n (%)	3 (13)
Caspofungin, n (%)	4 (17)
Combination, n (%)**	3 (13)

Maintenance antifungal therapy for HSC ($n = 24$)^a

None, n (%) ^b	1 (4)
Azoles, n (%)	15 (62)
Polyenes, n (%)	3 (13)
Caspofungin, n (%)	3 (12)
Others, n (%)***	2 (8)



Sağkalım analizi

Table 2. Univariate and multivariate models for survival analysis

Variable	Univariable model		Multivariable model	
	HR (95% CI)	p	HR (95% CI)	p
Female gender	2.52 (0.72–8.85)	0.15	–	–
Age (per 10 years)	1.29 (0.96–1.73)	0.091	–	–
>45 year	1.57 (0.46–5.39)	0.47	–	–
No haematological remission at HSC	5.12 (1.34–19.6)	0.017	5.60 (1.39–22.5)	0.015
Duration of neutropenia (per week)	1.46 (1.08–1.96)	0.013	–	–
>1 month	3.96 (1.20–13.1)	0.024	4.33 (1.24–15.2)	0.022
<i>Candida</i> colonization	0.50 (0.11–2.39)	0.39	–	–
Time to empiric therapy (per week)	0.40 (0.13–1.28)	0.12	–	–
Steroid therapy for HSC	0.61 (0.19–2.00)	0.41	–	–
Delayed chemotherapy because of HSC	1.16 (0.24–5.52)	0.85	–	–

HSC, hepatosplenic candidiasis; HR, hazard ratio; 95% CI, 95% confidence interval.





- 56 yaşında erkek hasta
- NHL
- 4 senedir kemoterapi ve radyoterapi
- 89C41A
 - Endoksan, siklofosfomit, doksorubisin, vinkristin, sitozin arabinozit, mtx
- 5. gün nötrofil: 90/mm³
- Meropenem+amikasin



- 3. gün teikoplanin
- 6. gün L-amb
- 9. gün
 - Nötropenik ve ateşli
- ???



- 8. gün iki kan kültürü
 - *B. melitensis*
- Dox+rif+sipro
- 4. gün ateş N
- 45 gün tedavi
- Bruselloz tedavisinden 15 gün sonra eksitus



- Bruselloz toplumda sık...
- Febril nötropenide nadir.



10 olgu sunumu var.

[Med Oncol](#). 2011 Mar;28(1):255-7. Epub 2010 Feb 19.

Brucellosis: a rare cause of febrile neutropenia in acute myeloblastic leukemia.

[Ozbalci D](#), [Ergene U](#), [Cetin CB](#).

Hematology Department, School of Medicine, Celal Bayar University, Manisa, Turkey. drdemircan@hotmail.com

[Leuk Lymphoma](#). 2006 May;47(5):954-6.

Brucellosis in all patients with febrile neutropenia.

[Metan G](#), [Sardan YC](#), [Hascelik G](#).

[Pediatr Hematol Oncol](#). 2011 Feb;28(1):83-5. Epub 2010 Sep 23.

Brucella melitensis: a rare cause of febrile neutropenia.

[Citak EC](#), [Arman D](#).

Department of Pediatric Oncology, Gaziantep Children Hospital, Sehitkamil, Gaziantep, Turkey. caglarcitak@yahoo.com

Abstract

Although brucellosis is endemic in Middle Eastern and Mediterranean countries, febrile neutropenia caused by Brucella species has rarely been reported in childhood. In this report the authors described an unusual case of febrile neutropenia due to Brucella melitensis.

PMID: 20863159 [PubMed - indexed for MEDLINE]

[Int J Clin Pract](#). 2007 Jul;61(7):1237-8. Epub 2007 Mar 2.

Brucella melitensis in the aetiology of febrile neutropenia: report of two cases brucellosis and febrile neutropenia.

[Arda B](#), [Tasbakan MI](#), [Pullukcu H](#), [Sipahi OR](#), [Aydemir S](#), [Buyukkececi F](#), [Ulusoy S](#).



Türkiye dışı tek olgu sunumu...

Cases J. 2009 Jan 27;2(1):91.

Brucella bacteremia in a recipient of an allogeneic hematopoietic stem cell transplant: a case report.

Al-Anazi KA, Jafar SA, Al-Jasser AM, Al-Omar H, Al-Mohareb FI.

Section of Adult Hematology and Hematopoietic Stem Cell Transplant, King Faisal Cancer Centre, King Faisal Specialist Hospital and Research Centre, P.O. Box: 3346, Riyadh 11211, Saudi Arabia. kaa_alanazi@yahoo.com.

Abstract



- Pastörize olmayan süt ve süt ürünleri kullanımı
- Hayvan besleme
- Veteriner meslek kazası
- Risk faktörü yok
- Türkiye
 - STW: $\geq 1/40 = \%0.3-3.3\%$
- İzmir-Ödemiş n=257
 - $\%7$ STW: $\geq 1/160$



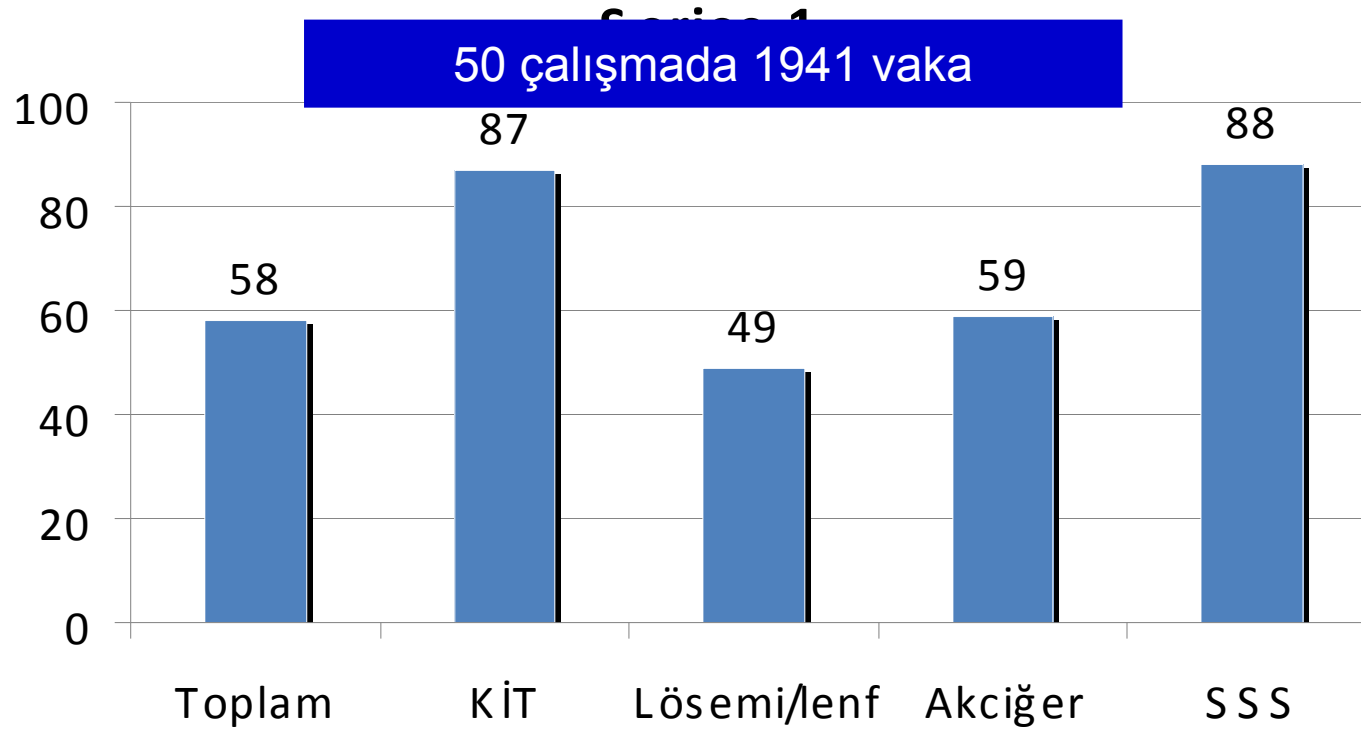


Kurtarma (“Salvage”)



İnvazif aspergillos-Mortalite

mortalite



Linn et al. CID 2001;32:358



“Kurtarma” Tedavisi Çalışmalarında Sorunlar

- Endikasyon:
 - Refrakter / intoleran
 - Refrakter tanımı
- Başlangıç ilacının etkisinin devam etmesi (AmB yarı ömrü uzun), sonuçta kombinasyonun etkinliği?



Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy.

Maertens J, Raad I, Petrikos G, Boogaerts M, Selleslag D, Petersen FB, Sable CA, Kartsonis NA, Ngai A, Taylor A, Patterson TF, Denning DW, Walsh TJ; Caspofungin Salvage Aspergillosis Study Group.

University Hospital, Gasthuisberg, Leuven, Belgium.

Abstract

BACKGROUND: Invasive aspergillosis (IA) is an important cause of morbidity and mortality among immunocompromised patients. Echinocandins are novel antifungal molecules with in vitro and in vivo activity against *Aspergillus* species.

METHODS: We investigated the efficacy and safety of caspofungin in the treatment of IA. Ninety patients with IA who were refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B, or triazoles were enrolled to receive caspofungin.

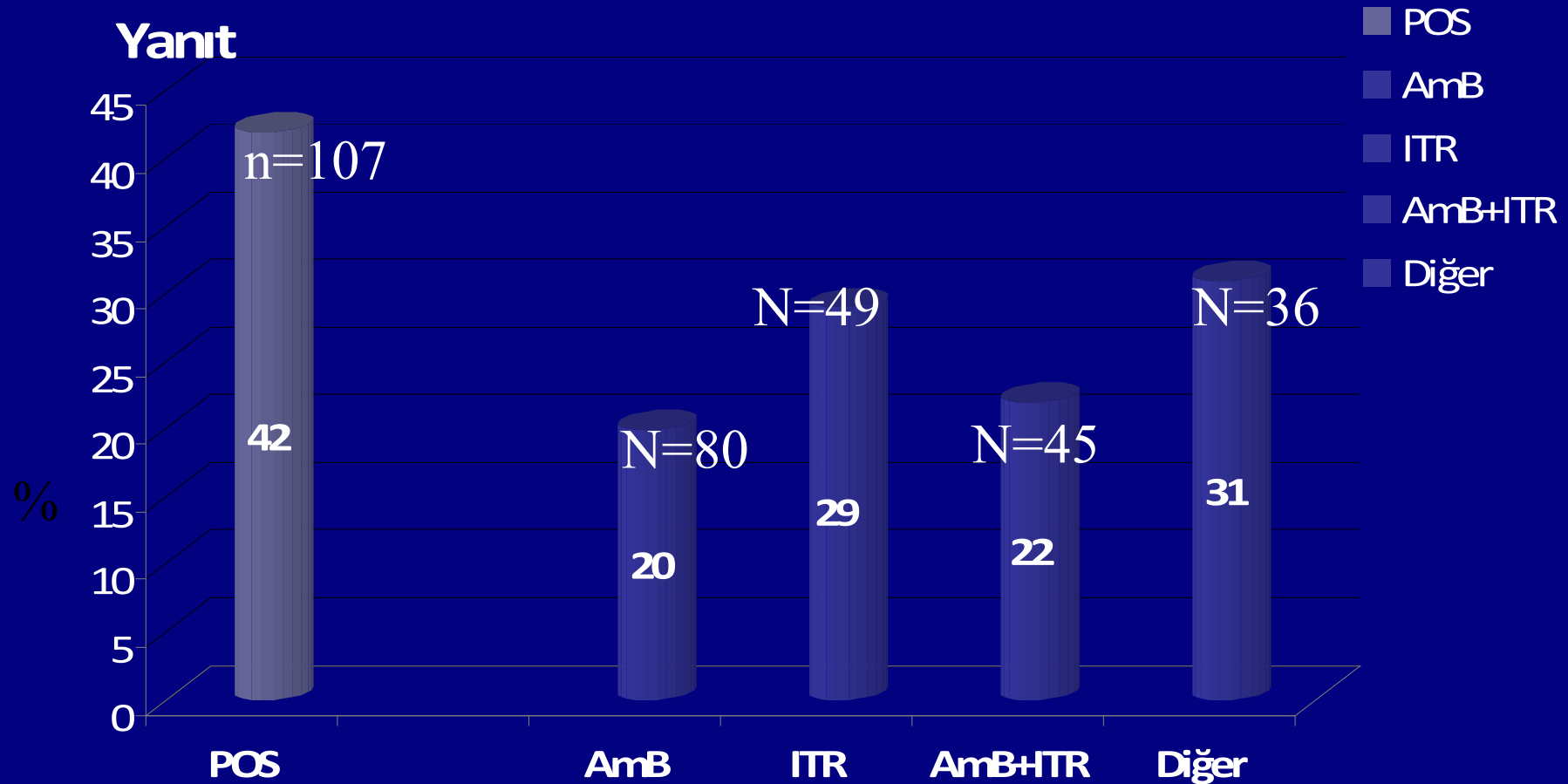
RESULTS: Efficacy was assessed for 83 patients who had infection consistent with definitions of IA and who received ≥ 1 dose of study drug. Common underlying conditions included hematologic malignancy (48% of patients), allogeneic blood and marrow transplantation (25% of patients), and solid-organ transplantation (11% of patients). Seventy-one patients (86%) were refractory to and 12 patients (14%) were intolerant of previous therapy. A favorable response to caspofungin therapy was observed in 37 (45%) of 83 patients, including 32 (50%) of 64 with pulmonary aspergillosis and 3 (23%) of 13 with disseminated aspergillosis. Two patients discontinued caspofungin therapy because of drug-related adverse events. Drug-related nephrotoxicity and hepatotoxicity occurred infrequently.

CONCLUSION: Caspofungin demonstrated usefulness in the salvage treatment of IA.



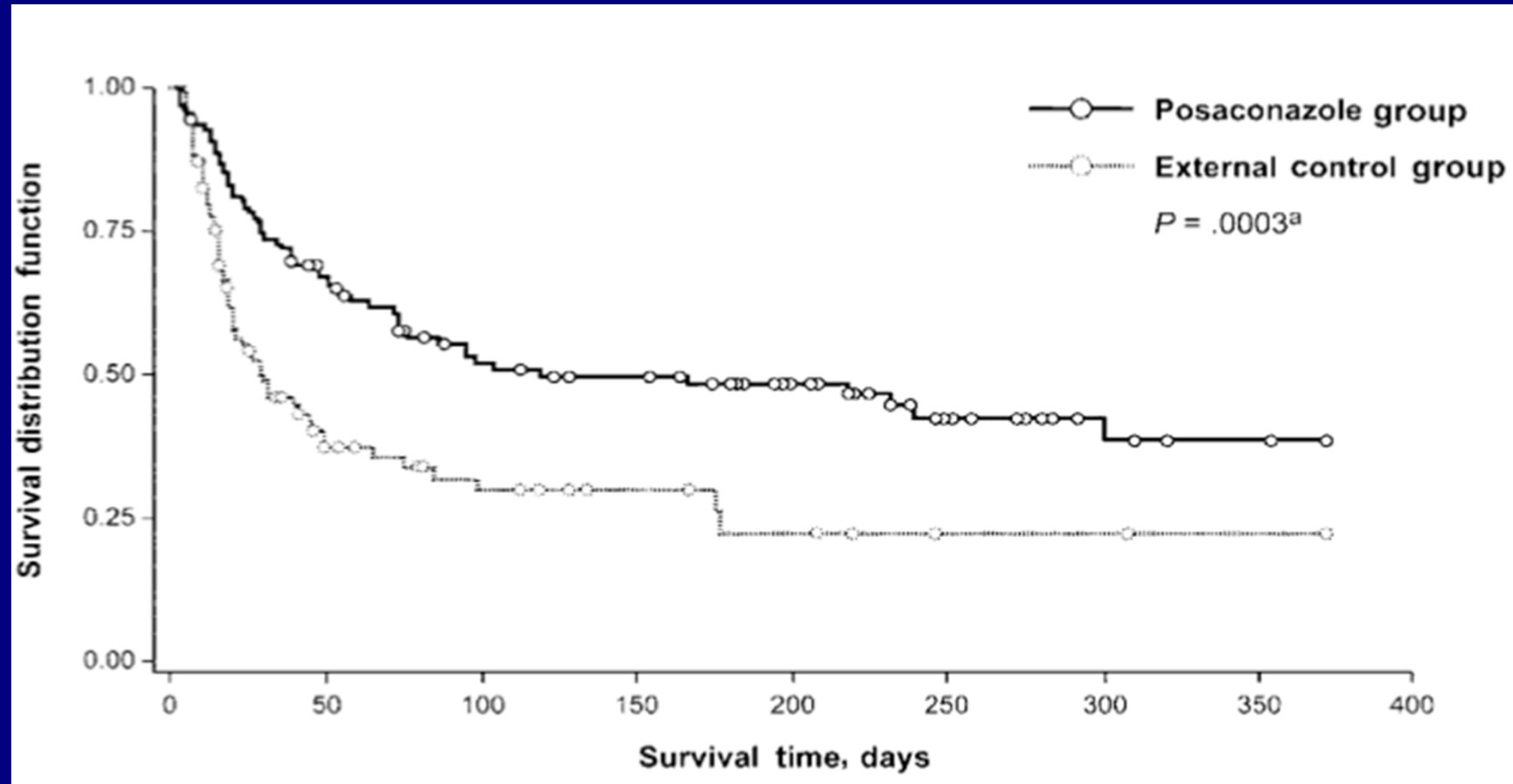
Tedaviye Yanıt

Walsh J et al. CID 2007;44:2



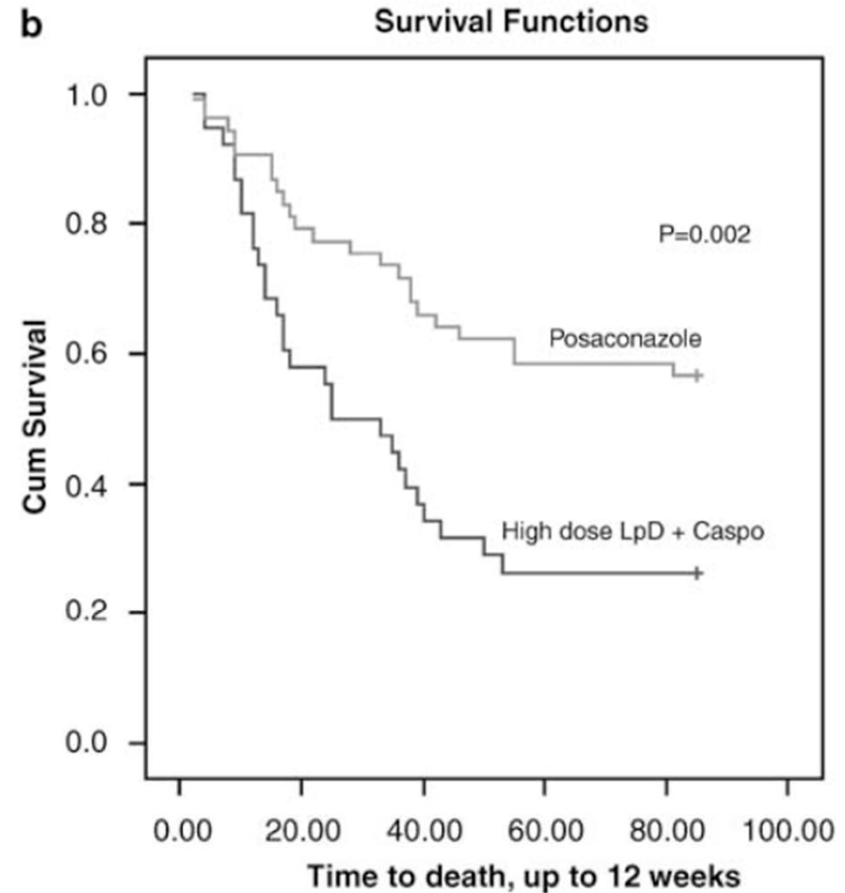
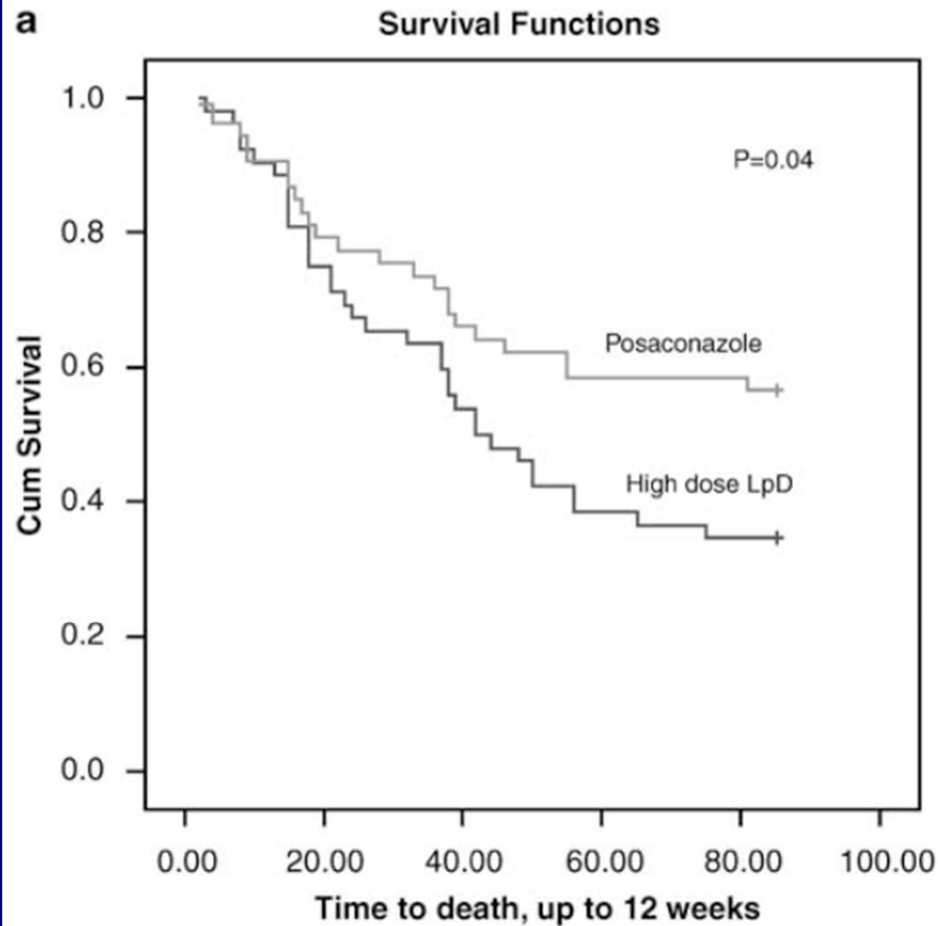
Sağkalım

Walsh J et al. CID 2007;44:2



IA "Kurtarma" Tedavisinde POS

Raad II, et al. Leukemia 2008;22:496.



Invasive aspergillosis: salvage

Agent	Grade	Comments
Ambisome	B III	no data in voriconazole failure
ABLC	B III	no data in voriconazole failure
Caspofungin	B II	no data in voriconazole failure
Posaconazole	B II	no data in voriconazole failure
Voriconazole	B II	if not used in 1st line
Itraconazole	C III	Insufficient data

Hiç hasta yakınlarından sözlü şiddete maruz kaldınız mı?

- A)Evet
- B)Hayır



Hiç hasta yakınlarından fiziksel şiddete maruz kaldınız mı?

- A)Evet
- B)Hayır





MJIMA

Mediterranean Journal of Infection, Microbes & Antimicrobials
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KONGRE ÖNCESİ KURSLAR

PATENT NASIL ALINIR?

Tarih : 8 Mayıs 2012, Salı
Kurs Koordinatörü : Dr. Oğuz Reşat SİPAHİ

13:00 - 14:30

OTURUM 1

Kursun tanıtımı

Dr. Oğuz Reşat SİPAHİ

Patent nedir? Patent tipleri nedir? Patent neyi korur neyi korumaz?

Dr. Tanıl KOCAGÖZ

Patent almanın önemi ve olası faydaları nelerdir?

Dr. Oğuz KARABAY

14:30 - 15:00

Kahve Arası

15:00 - 16:30

OTURUM 2

Ulusal ve uluslararası perspektiften patent alma süreci

Dr. Şaban GÜRCAN

16:30 - 17:00

Kahve Arası

17:00 - 18:40

OTURUM 3

Patent alma sürecinde olası teknik zorluklar.

Dr. Tanıl KOCAGÖZ

Patent alma sürecinde olası hukuki zorluklar.

Av. Adem UMUR

Enfeksiyon hastalıkları ve klinik mikrobiyoloji alanından patent örnekleri

Dr. Oğuz KARABAY

Patent almanın maliyeti nedir? Nereleden maddi destek sağlanabilir?

Cem TUNA





Sercan Ulusoy

Bilgin Arda

Tansu Yamazhan

Meltem Tasbakan

Husnu Pullukcu

Oguz Resat Sipahi





Altı bıçak darbesi
Her yıla bir tane

Kanayan
Et değil, tırnak değil.
Kaburgamın orta yeri
Şah damarım
Kaçamak uykularım
Korkularım
Umutlarım

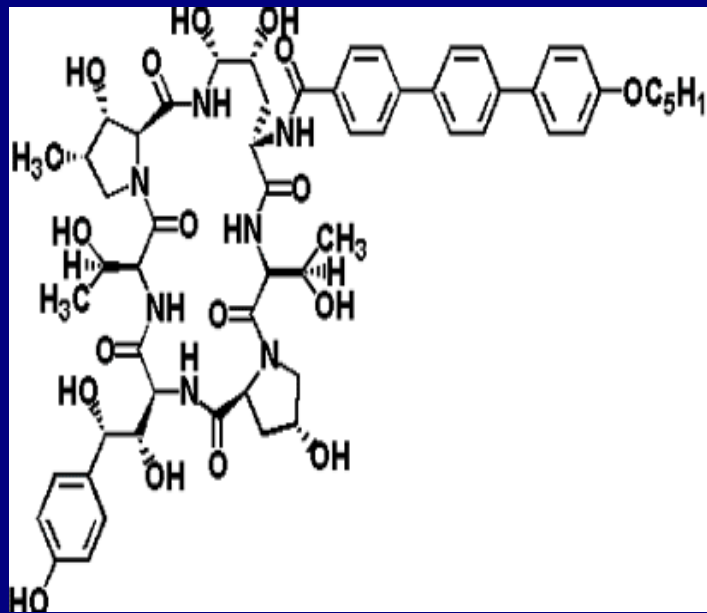
Alın ödedim işte
Kışkırtılmış öfkeye
Verilen son kurbanım
Biz orta yer mahyız
Peşkeş çekin herkese

Bir çocuğun öfkesi öldürür mü insanı
Ölüm suskunluğumuzda saklı
Ölüm çaresizliğimizde.
G.A.



ANİDULAFUNGİN

LY303366



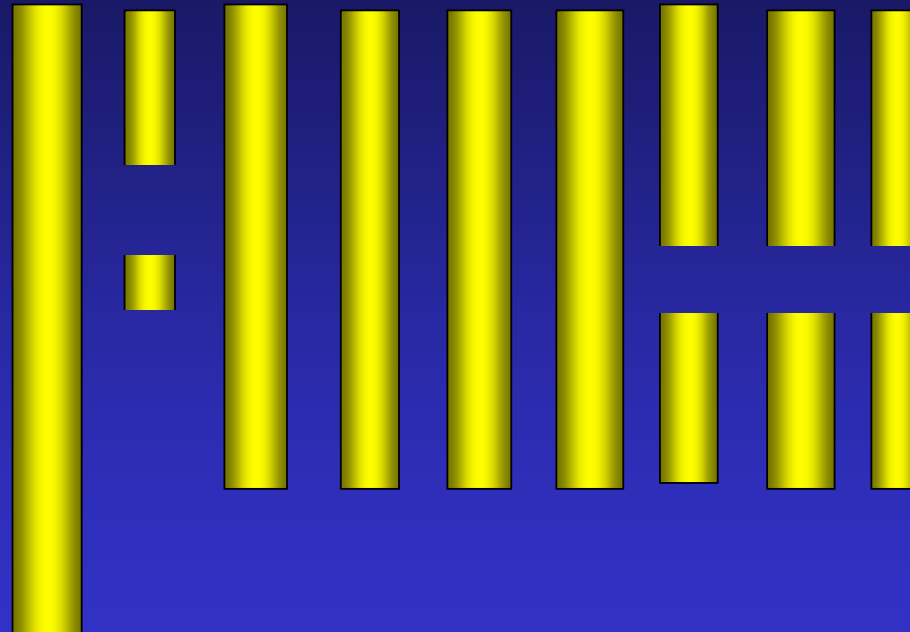
- Glukan sentetaz inhibitörü
- Di

Antifungal aktivite

Fungus

AMB FKZ ITZ VZ PKZ RKZ KF MF AF

Candida albicans
Candida tropicalis
Candida parapsilosis
Candida krusei
Candida glabrata
Cryptococcus neoformans
Histoplasma capsulatum
Blastomyces dermatitidis
Coccidioides immitis
Paracocci brasiliensis
Aspergillus fumigatus
Mucor spp
Rhizopus spp
Fusarium spp



Slide: Malcolm Richardson, 2002 Adapted from JP Donnelly



Candida spp'nin Antifungal Duyarlılığı

Tür	Flu	Itra	Vori	AmB	Kandinler
<i>C. albicans</i>	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S (I)
<i>C. glabrata</i>	SDD - R	SDD - R	S - I	S- I	S
<i>C. krusei</i>	R	SDD - R	S - I	S- I	S
<i>C. lusitaniae</i>	S	S	S	R	S



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

Table 2. Summary of recommendations for the treatment of candidiasis.

Condition or treatment group	Therapy		Comments
	Primary	Alternative	
Candidemia			
Nonneutropenic adults	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily or an echinocandin ^a (A-I). For species-specific recommendations, see text.	LFAmB 3–5 mg/kg daily; or AmB-d 0.5–1 mg/kg daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid (A-I)	Choose an echinocandin for moderately severe to severe illness and for patients with recent azole exposure. Transition to fluconazole after initial echinocandin is appropriate in many cases. Remove all intravascular catheters, if possible. Treat 14 days after first negative blood culture result and resolution of signs and symptoms associated with candidemia. Ophthalmological examination recommended for all patients.



Kandidemi tedavi – Nötropenik olmayan hasta

Flukonazol (AI)
Caspofungin (AI)
Anidulafungin (AI)
Vorikonazol (AI)

Kritik hasta
Azol öyküsü

(-) Flukonazol (AI)

(+) Azol öyküsü (Caspofungin (Caspofungin), Anidulafungin (Anidulafungin)) (AIII)

İzolasyon duyarlıysa ve hasta klinik olarak stabilse flukonazole geç (AI)

C. glabrata → Ekinokandin (BII)
C. parapsilosis → Flukonazol (AI)

Klinik düzelme var, kontrol kültürlerde üreme yoksa başlangıç tedavisine devam (BIII)

Amfoterisin B → Doksorubisin (BII)
bulunamadığında Amfoterisin B varsa (AI)

İzolasyon duyarlıysa ve hasta klinik olarak stabilse flukonazole geç (AI)

Seçilmiş derin sistemik tedavi → Vorikonazol (BIII)

Tedavi süresi: Son negatif kan kültüründen sonra 2 hafta

Kateter çekilmesi kuvvetle önerilir (AII)



IDSA 2009 Kandidiyaz Tedavi Kılavuzu



ORIGINAL ARTICLE

Anidulafungin versus Fluconazole for Invasive Candidiasis

Annette C. Reboli, M.D., Coleman Rotstein, M.D., Peter G. Pappas, M.D.,
Stanley W. Chapman, M.D., Daniel H. Kett, M.D., Deepali Kumar, M.D.,
Robert Betts, M.D., Michele Wible, M.S., Beth P. Goldstein, Ph.D.,
Jennifer Schranz, M.D., David S. Krause, M.D., and Thomas J. Walsh, M.D.,
for the Anidulafungin Study Group

- At the end of intravenous therapy, treatment was successful in 75.6% of patients treated with anidulafungin, as compared with 60.2% of those treated with fluconazole (difference, 15.4 percentage points; 95% confidence interval [CI], 3.9 to 27.0).
- The frequency and types of adverse events were similar in the two groups.
- The rate of death from all causes was 31% in the fluconazole group and 23% in the anidulafungin group ($P = 0.13$).



ORIGINAL ARTICLE

Anidulafungin versus Fluconazole for Invasive Candidiasis

Annette C. Reboli, M.D., Coleman Rotstein, M.D., Peter G. Pappas, M.D., Stanley W. Chapman, M.D., Daniel H. Kett, M.D., Deepali Kumar, M.D., Robert Betts, M.D., Michele Wible, M.S., Beth P. Goldstein, Ph.D., Jennifer Schranz, M.D., David S. Krause, M.D., and Thomas J. Walsh, M.D., for the Anidulafungin Study Group

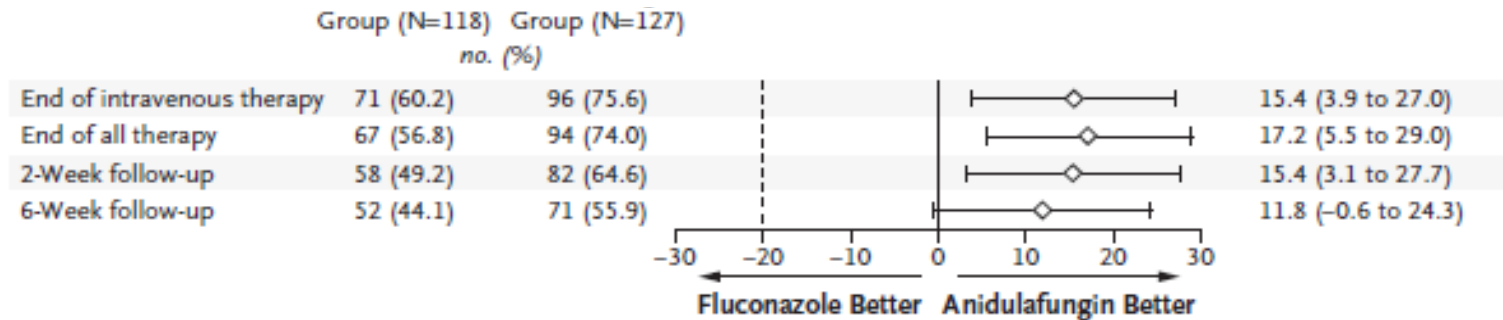


Figure 1. Global Response to Treatment for Prespecified Time Points in the Modified Intention-to-Treat Population.

A successful global response required both clinical success (defined as the resolution of signs and symptoms of invasive candidiasis and no additional systemic antifungal therapy) and microbiologic success (defined as the eradication of candida species present at baseline as determined on follow-up culture, or the presumed eradication if culture data were not available for a patient with a successful clinical response). $P < 0.02$ for the comparison between the anidulafungin group and the fluconazole group at the end of intravenous therapy. $P < 0.02$ for the comparison between the two groups at the end of all therapy and at the 2-week follow-up. At the end of intravenous therapy, 33 patients in each of the two groups (26% in the anidulafungin group and 28% in the fluconazole group) switched to oral fluconazole. For multiple comparisons of the secondary end points, 98.3% confidence intervals (CI) adjusted post hoc were 2.9 to 31.6 at the end of all therapy, 0.4 to 30.4 at the 2-week follow-up, and -3.4 to 27.0 at the 6-week follow-up. The dashed vertical line represents the prespecified margin for noninferiority.



Candidemia in hematologic patients before species identification

	Overall population	Hematological pts
Micafungin	A I	B II
Anidulafungin	A I	B II
Caspofungin	A I	B II
Ambisome	A I	B II
Other lipid-AmB	A II	B II
AmB deoxycholate		A I *
		C III *
Fluconazole	A I **	C III
Voriconazole	A I ***	B II

* DIII if concomitant nephrotoxic drug and EIII if renal impairment

** Not in severely ill patients or in patients with previous azole prophylaxis

*** Not in patients with previous azole prophylaxis



Candidemia after species identification (1/2)

		Overall population	Hematological pts
Micafungin	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II
Anidulafungin	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II
Caspofungin	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II

Clin Infect Dis. 2004 Sep 15;39(6):770-5. Epub 2004 Aug 27.

A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis.

Krause DS, Simjee AE, van Rensburg C, Viljoen J, Walsh TJ, Goldstein BP, Wible M, Henkel T.

Vicuron Pharmaceuticals, King of Prussia, Pennsylvania 19406, USA. dkrause@vicuron.com

Abstract

Anidulafungin is a novel antifungal agent of the echinocandin class. This randomized, double-blind, double-dummy study compared the efficacy and safety of intravenous anidulafungin to that of oral fluconazole in 601 patients with endoscopically and microbiologically documented esophageal candidiasis. Patients received intravenous anidulafungin (100 mg on day 1, followed by 50 mg per day) or oral fluconazole (200 mg on day 1, followed by 100 mg per day) for 7 days beyond resolution of symptoms (range, 14-21 days). At the end of therapy, the rate of endoscopic success for anidulafungin (242 [97.2%] of 249 treated patients) was found to be statistically noninferior to that for fluconazole (252 [98.8%] of 255 treated patients; treatment difference, -1.6%; 95% confidence interval, -4.1 to 0.8). The safety profile of anidulafungin was similar to that of fluconazole; treatment-related adverse events occurred in 9.3% and 12.0% of patients, respectively. Laboratory parameters were similar between treatment arms. Anidulafungin is as safe and effective as oral fluconazole for the treatment of esophageal candidiasis, when assessed at the completion of therapy.



Farmakokinetik profil

- Fungal infeksiyonlu hastalarda ve sağlıklı gönüllülerde benzerdir.
- Farklı hasta popülasyonlarında yapılan çalışmalarda benzer farmakokinetik profiller elde edilmiştir; doz ayarı gerektirmez:
 - Yaş (65 yaş altı ve üstü hastalarda benzer farmakokinetik profil)
 - Vücut ağırlığı
 - Cinsiyet, ırk
 - HIV (+) olmak, eşzamanlı antiretroviral tedavi görmek



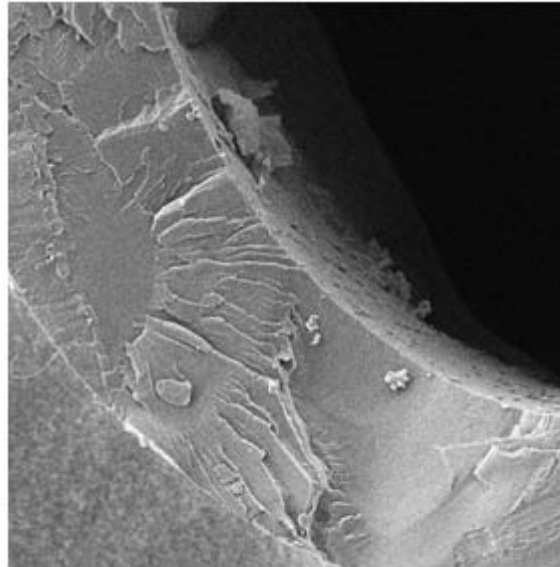
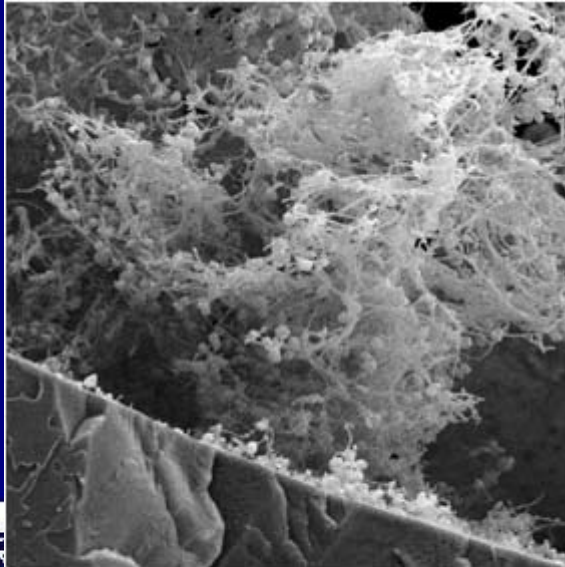
Farmakokinetik profil- Eliminasyon

- $T_{1/2} \sim 24$ saat
- Kimyasal degradasyona uğrayarak inaktif bir peptide dönüşür ve sonrasında fekal yoldan elimine olur
 - Enzim aracılığı yok
 - Hepatik yolla metabolize olmaz
 - Sitokrom P450 enzimlerini indüklemeyebilir veya inhibe etmez
 - Renal klirensi ihmal edilebilir düzeyde
- Böbrek yetmezliği ya da hafif – ciddi karaciğer yetmezliği olan hastalarda doz ayarlaması gerekmez



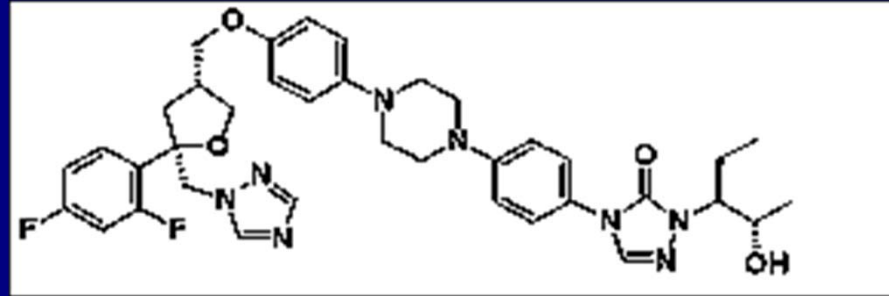
Anidulafunginin biyofilm üzerine etkisi

- Anidulafungin de, diğer ekinokandinler gibi, in vitro olarak biyofilmler üzerinde etkinliğe sahiptir.  Klinik yansıması ?



Jacobson MJ et al AAC 2008;52(6):2242-2243

POSAKONAZOL



- Itrakonazalün hidroksillenmiş analoğu, triazol
- Oral süspansiyonp450 14 α -demetilaz inhibisyonu itrakonazole göre 10 kat↑

Antifungal aktivite

Fungus	AMB	FKZ	ITZ	VZ	PKZ	RKZ	KF	MF	AF
<i>Candida albicans</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Candida tropicalis</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Candida parapsilosis</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Candida krusei</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Candida glabrata</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Cryptococcus neoformans</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Histoplasma capsulatum</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Blastomyces dermatitidis</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Coccidioides immitis</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Paracocci brasiliensis</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Aspergillus fumigatus</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Mucor spp</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Rhizopus spp</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full
<i>Fusarium spp</i>	Full	Short	Full	Full	Full	Full	Full	Full	Full

Slide: Malcolm Richardson, 2002 Adapted from JP Donnelly



Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

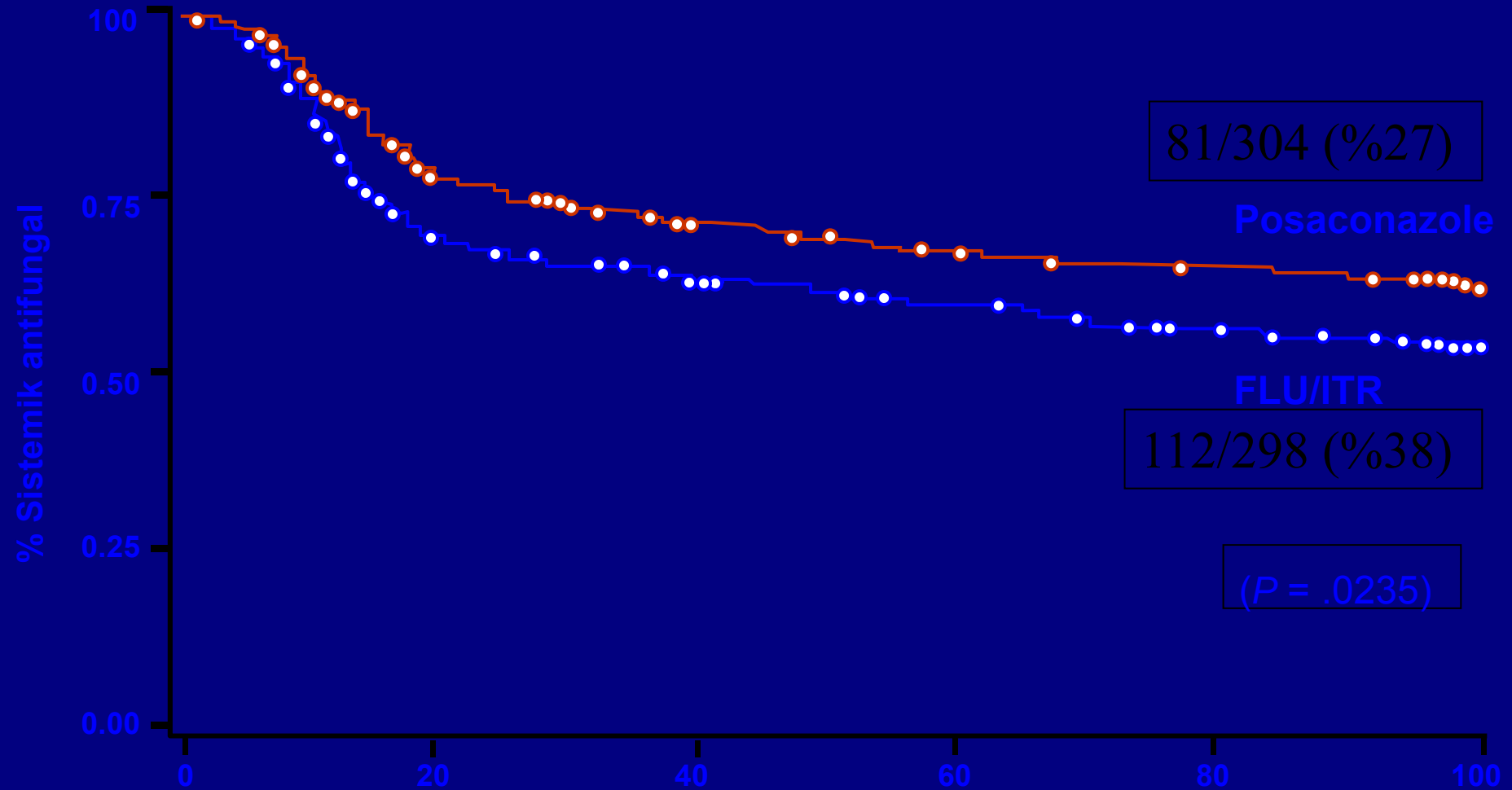
Oliver A. Cornely, M.D., Johan Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Helfgott, M.D., Jerzy Holowiecki, M.D., Dick Stockelberg, M.D., Yeow-Tee Goh, M.D., Mario Petrini, M.D., Cathy Hardalo, M.D., Ramachandran Suresh, Ph.D., and David Angulo-Gonzalez, M.D.*

Posaconazole
3x 200 mg

Fluconazole
1x 400 mg
or
Itraconazole
2x 200 mg



Profilaksi altında ampirik antifungal kullanımı

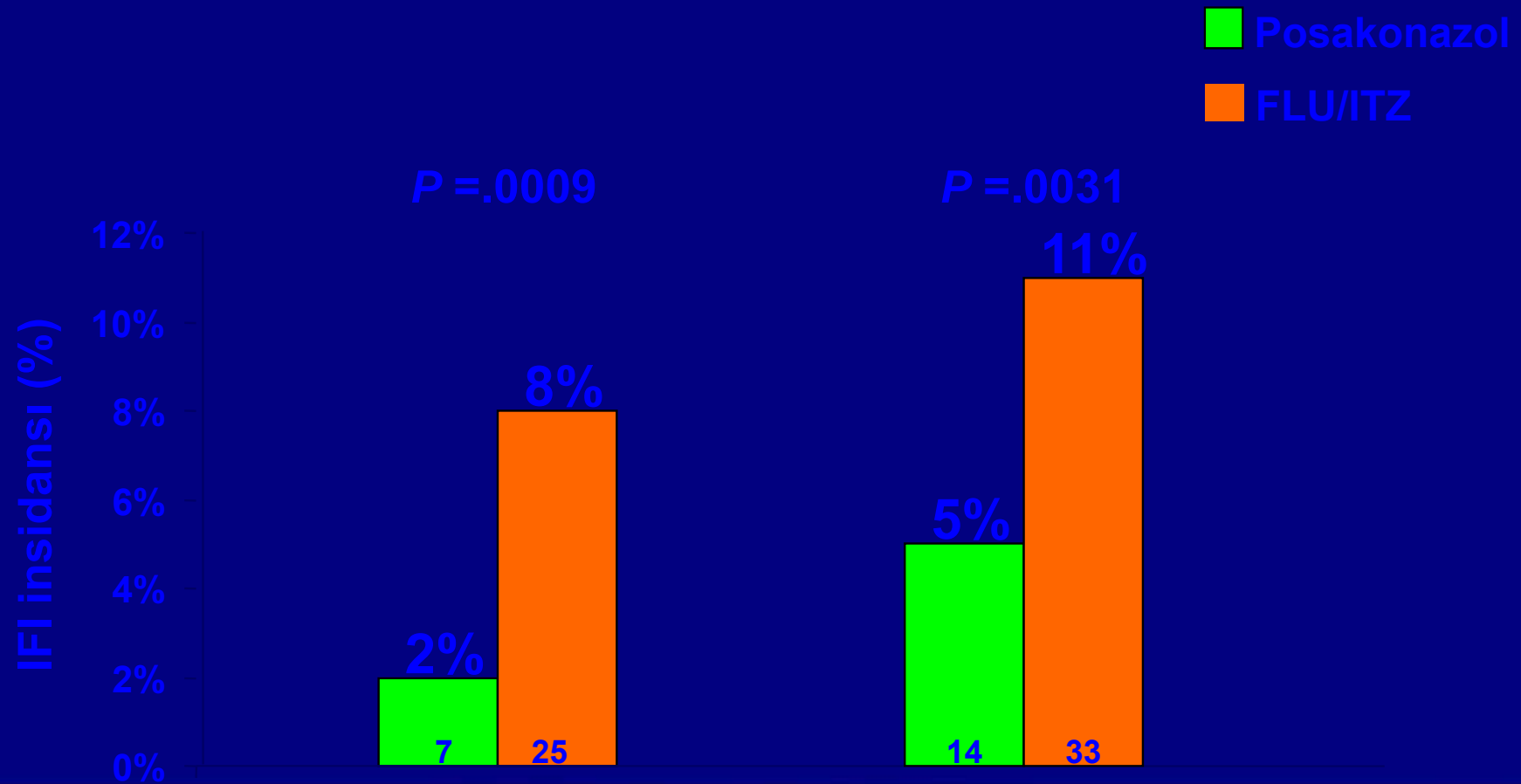


Randomizasyon sonrası günlerde sistemik antifungal kullanımı



Posakonazol vs. Flukonazol/Itrakonazol

Breakthrough İFİ insidansı



Profilaksi süresince İFİ



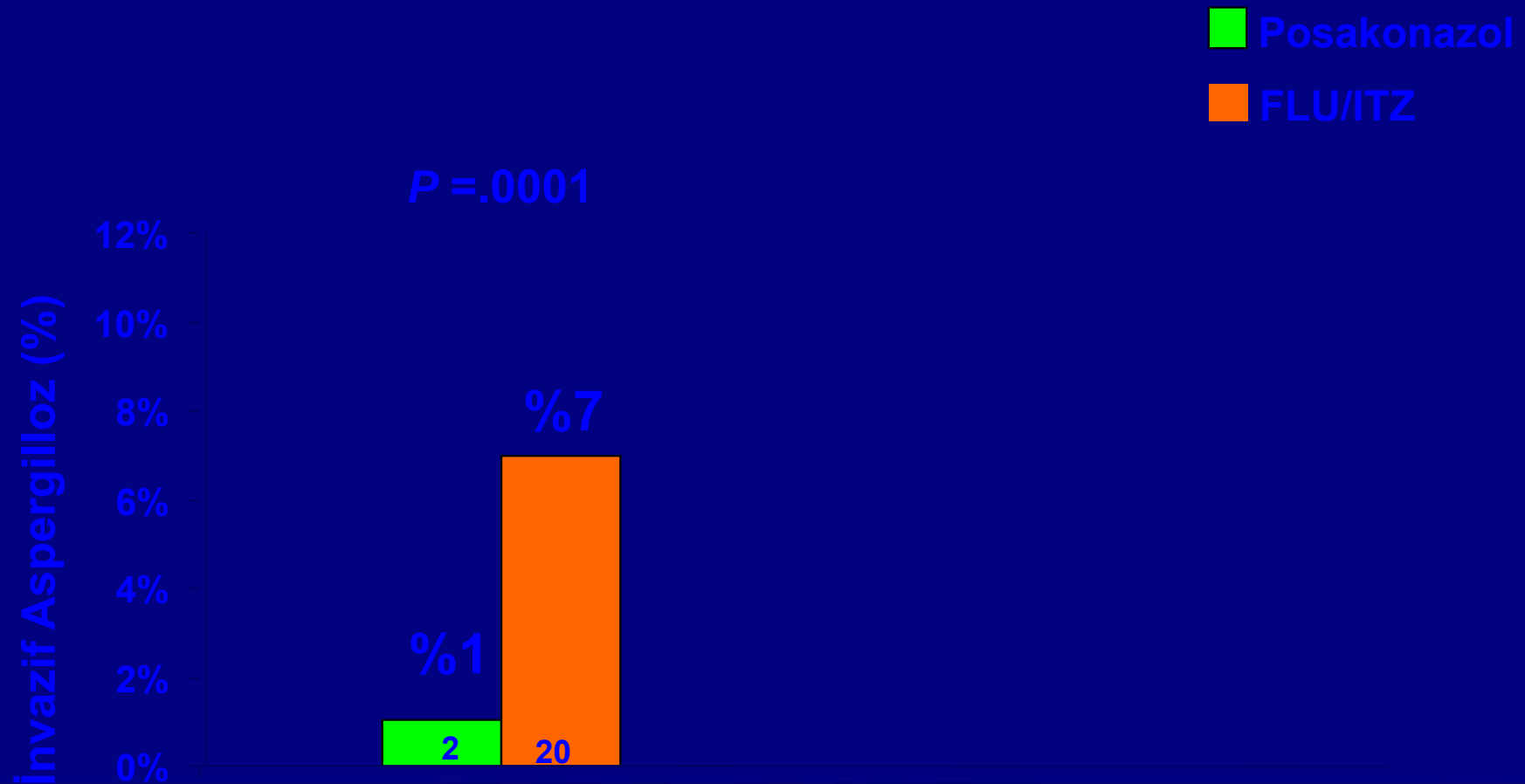
100 gün içinde İFİ



Cornely OA et al. NEJM 2007.

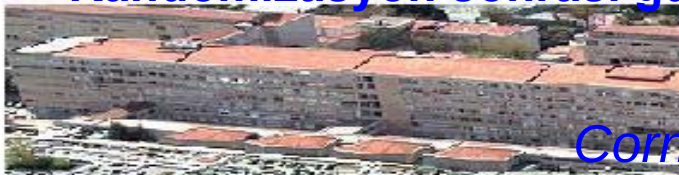
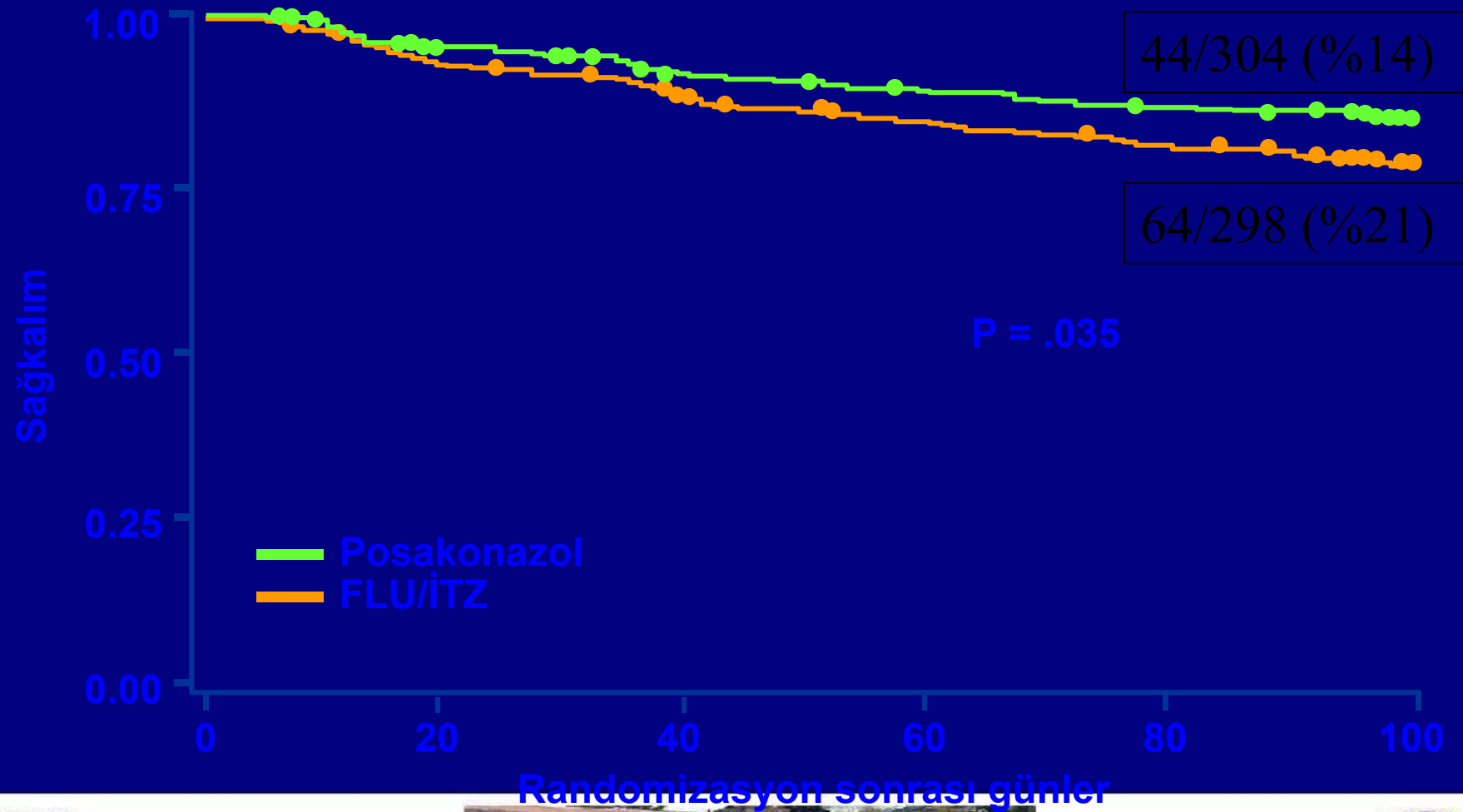
Posakonazol vs. Flukonazol/Itrakonazol

İnvazif aspergilloz



Cornely OA et al. NEJM 2007.

Posakonazol vs. Flukonazol/İtrakonazol Sağkalım



Cornely OA et al. NEJM 2007.

Primary antifungal prophylaxis in leukemia patients

- Induction chemotherapy of acute leukemia
 - Fluconazole 50-400 mg qd iv/oral: CI^{2,5}
 - Itraconazole oral solution 2.5 mg/kg bid: CI^{1,2,3}
 - Posaconazole 200 mg tid oral: AI^{2,3}
 - Candins iv: insufficient data
 - Polyene⁴ iv: CI
 - Aerosolized liposomal amphotericin B in combination with oral fluconazole: BI

1. may be limited by drug interactions and/or patient tolerability
2. azoles should not be used empirically in case of prior azole prophylaxis
3. it is recommended to monitor serum drug concentrations
4. includes low doses of conventional amphotericin B and lipid formulations.
5. combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections

The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI



Primary antifungal prophylaxis in leukemia patients

- **Allogeneic hematopoietic stem cell transplantation: neutropenic phase**
 - Fluconazole 400 mg qd iv/oral: AI^{2,5}
 - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI^{1,2,3}
 - Posaconazole 200 mg tid oral: no data
 - Micafungin 50 mg qd iv: CI
 - Polyene⁴ iv: CI
 - Voriconazole 200 mg bid oral: provisional AI
 - Aerosolized liposomal amphotericin B plus fluconazole: BII
- **Allogeneic hematopoietic stem cell transplantation: GvHD phase**
 - Fluconazole 400 mg qd iv/oral: CI²
 - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI^{1,2,3}
 - Posaconazole 200 mg tid oral: AI^{2,3}
 - Candins iv: insufficient data
 - Polyene iv: CI
 - Voriconazole 200 mg bid oral: provisional AI
 - Aerosolized liposomal amphotericin B plus fluconazole: insufficient data



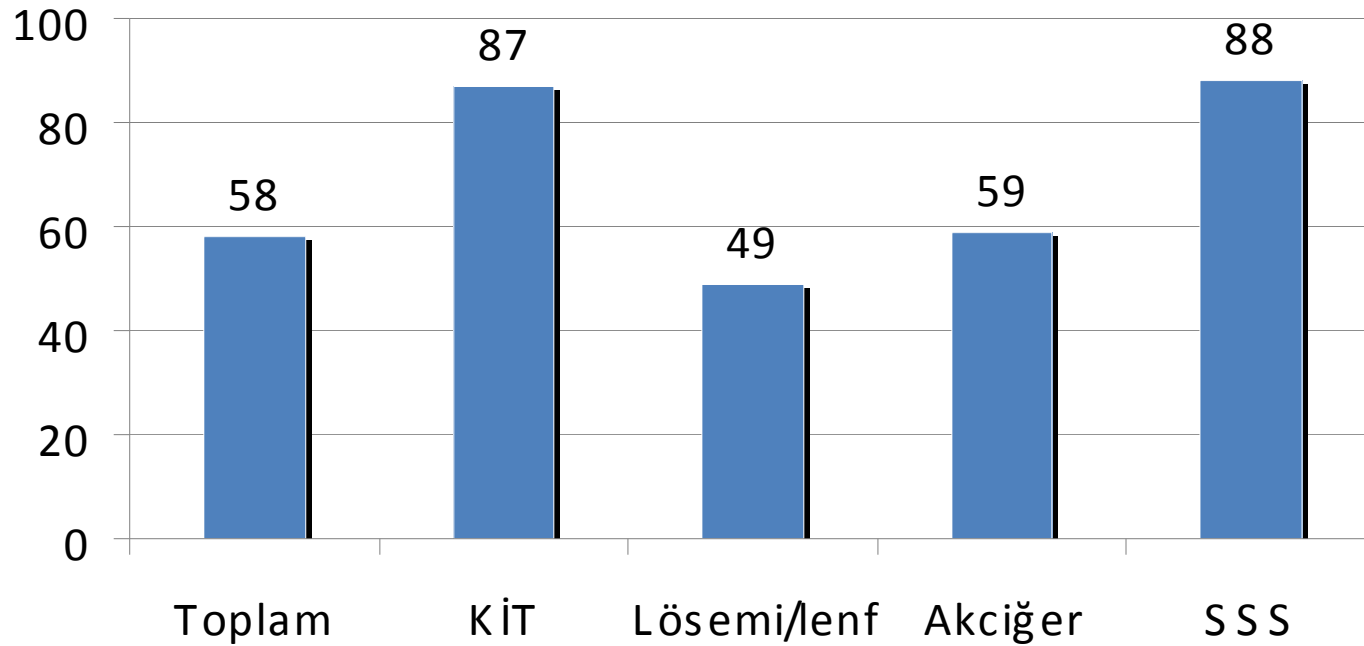
Kurtarma (“Salvage”)



İnvazif aspergillos-Mortalite

mortalite

50 çalışmada 1941 vaka



Linn et al. CID 2001;32:358



“Kurtarma” Tedavisi Çalışmalarında Sorunlar

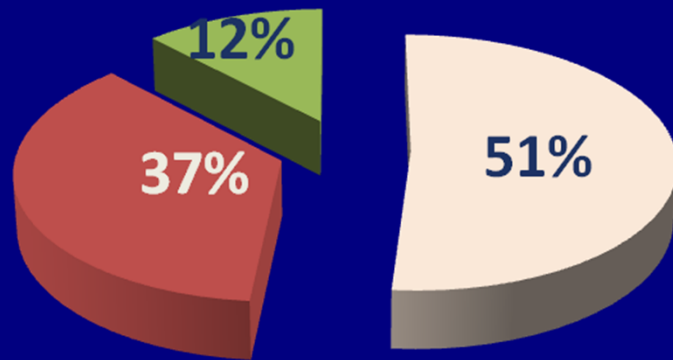
- Endikasyon:
 - Refrakter / intoleran
 - Refrakter tanımı
- Başlangıç ilacının etkisinin devam etmesi (AmB yarı ömrü uzun), sonuçta kombinasyonun etkinliği?



IA'de "Kurtarma": POS

Walsh TJ et al. CID 2007;44:2

N=107



- refrakter
- intoleran
- intoleran+refrakter



CR+PR*

%42 (45/107)

Hematolojik malignite	%79
HSCT	%45
Nötropeni	%20



Tedaviye Yanıt

Walsh J et al. CID 2007;44:2

Table 3. Responses at end of therapy: overall response, site of infection, and reason for enrollment.

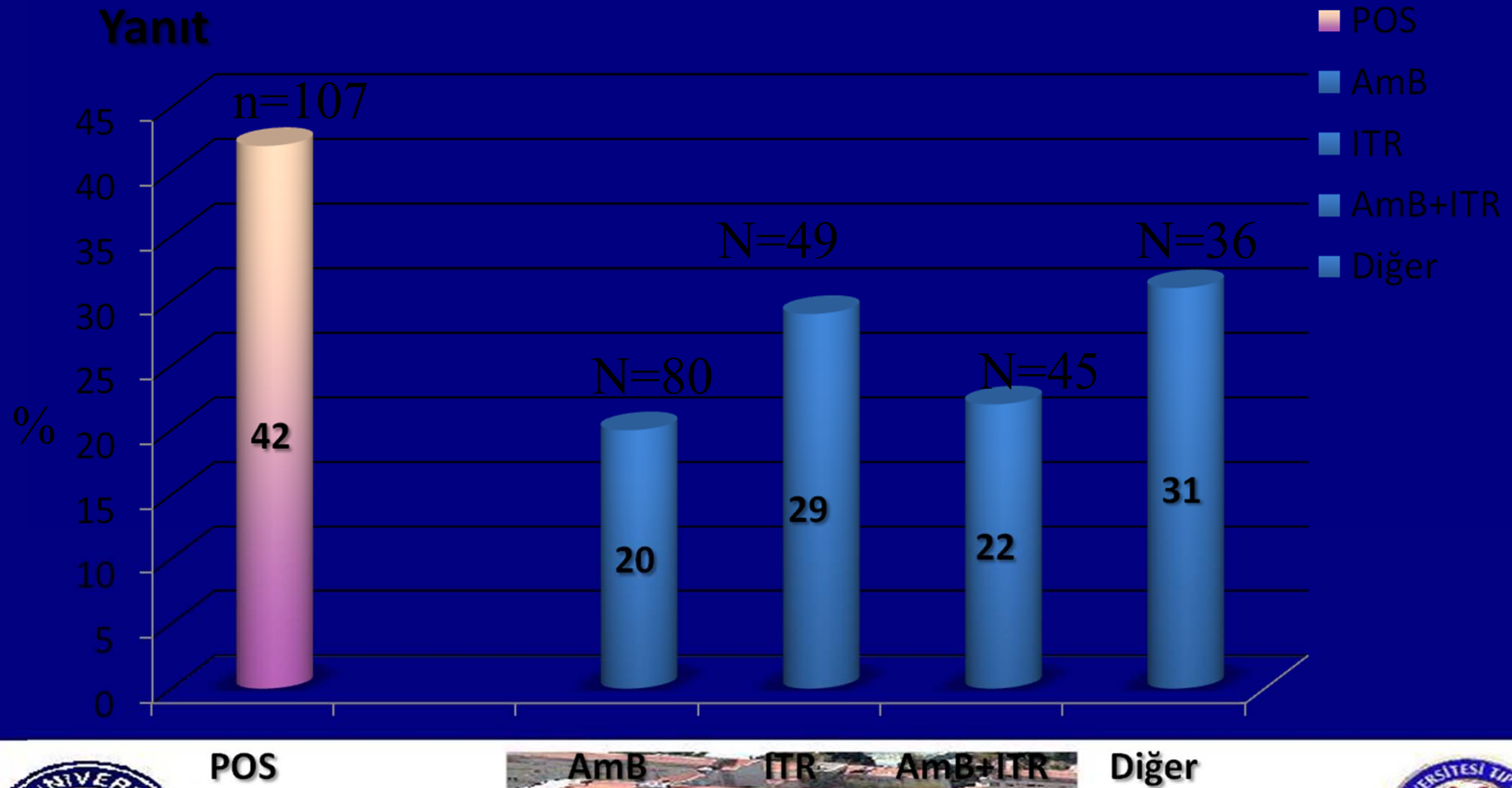
Variable	Posaconazole group (n = 107)	Control group (n = 86)
Overall response		
Complete and partial	45 (42)	22 (26)
Complete	7 (7)	8 (9)
Partial	38 (36)	14 (16)
Stable	10 (9)	7 (8)
Failure	39 (36)	52 (60)
Unable to be determined	13 (12)	5 (6)
Complete and partial responses according to site of infection		
Pulmonary	31/79 (39)	17/67 (25)
Extrapulmonary ^a	10/19 (53)	5/11 (45)
Disseminated ^b	4/9 (44)	0/8 (0)
CNS ^c	2/4 (50)	0/2 (0)



Dış kontrol: Retrospektif kontroller

Tedaviye Yanıt

Walsh J et al. CID 2007;44:2

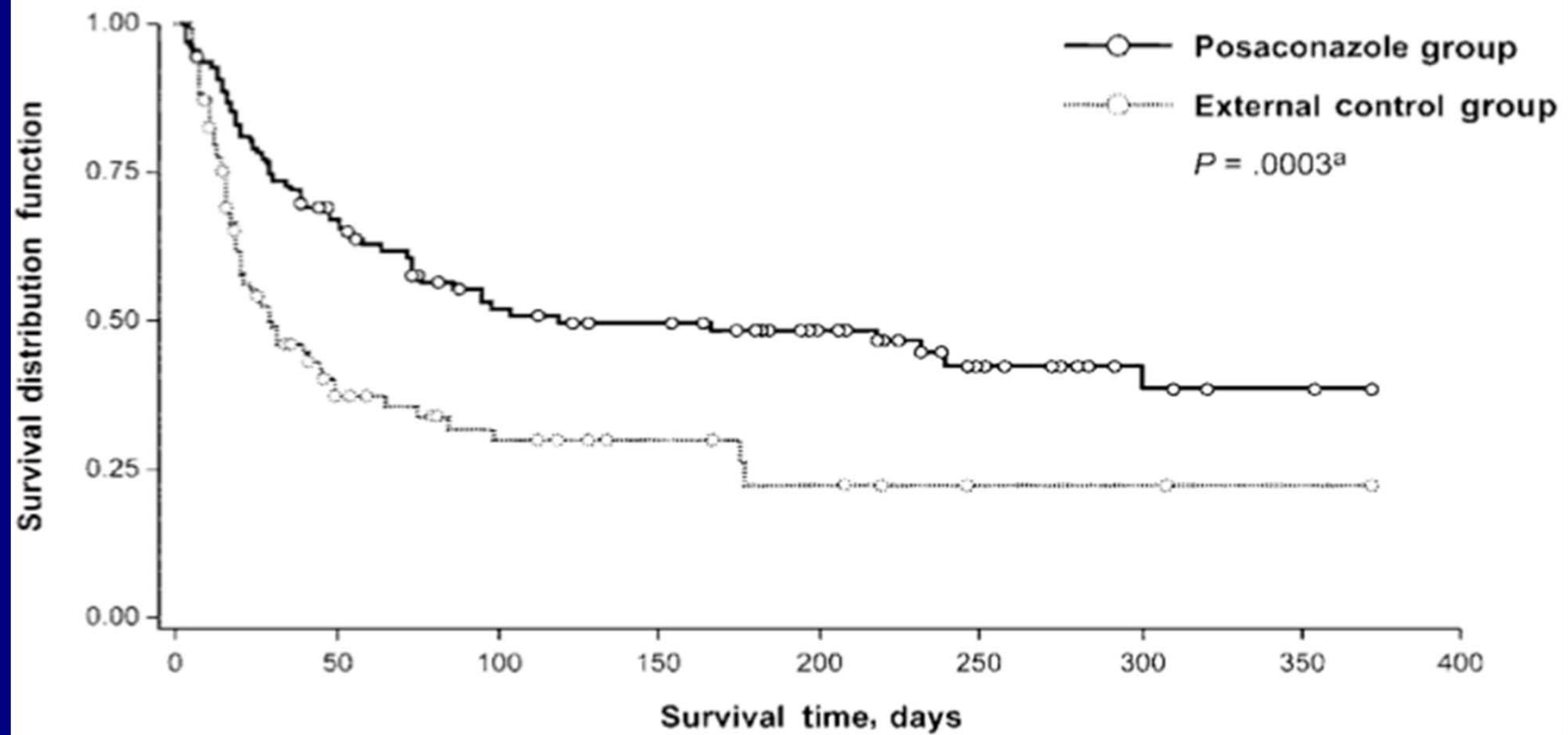


*Diğer tedavileri alan hastaların 2'si hariç hepsi birlikte AmB veya ITR



Sağkalım

Walsh J et al. CID 2007;44:2



IA “Kurtarma” Tedavisinde POS

Raad II, et al. Leukemia 2008;22:496.

PRİMER TEDAVİ	POS	YD L-AMB* (≥7.5mg/kg/gün)	YD L-AMB* + CAS
L-AMB	35 (66)	32 (62)	24 (63)
L-AMB + ITR	6 (11)	6 (12)	1 (3)
L-AMB + CAS	4 (8)	2 (4)	5 (13)
CAS	3 (6)	0	5 (13)
ITR	4 (8)	9 (17)	0
AMB	1	2	0



VRC içeren şema

**retrospektif*



0

53

1

52

3

38



IA “Kurtarma” Tedavisinde POS

Raad II, et al. Leukemia 2008;22:496.

Table 5 Factors associated with favorable response in multiple logistic regression analysis

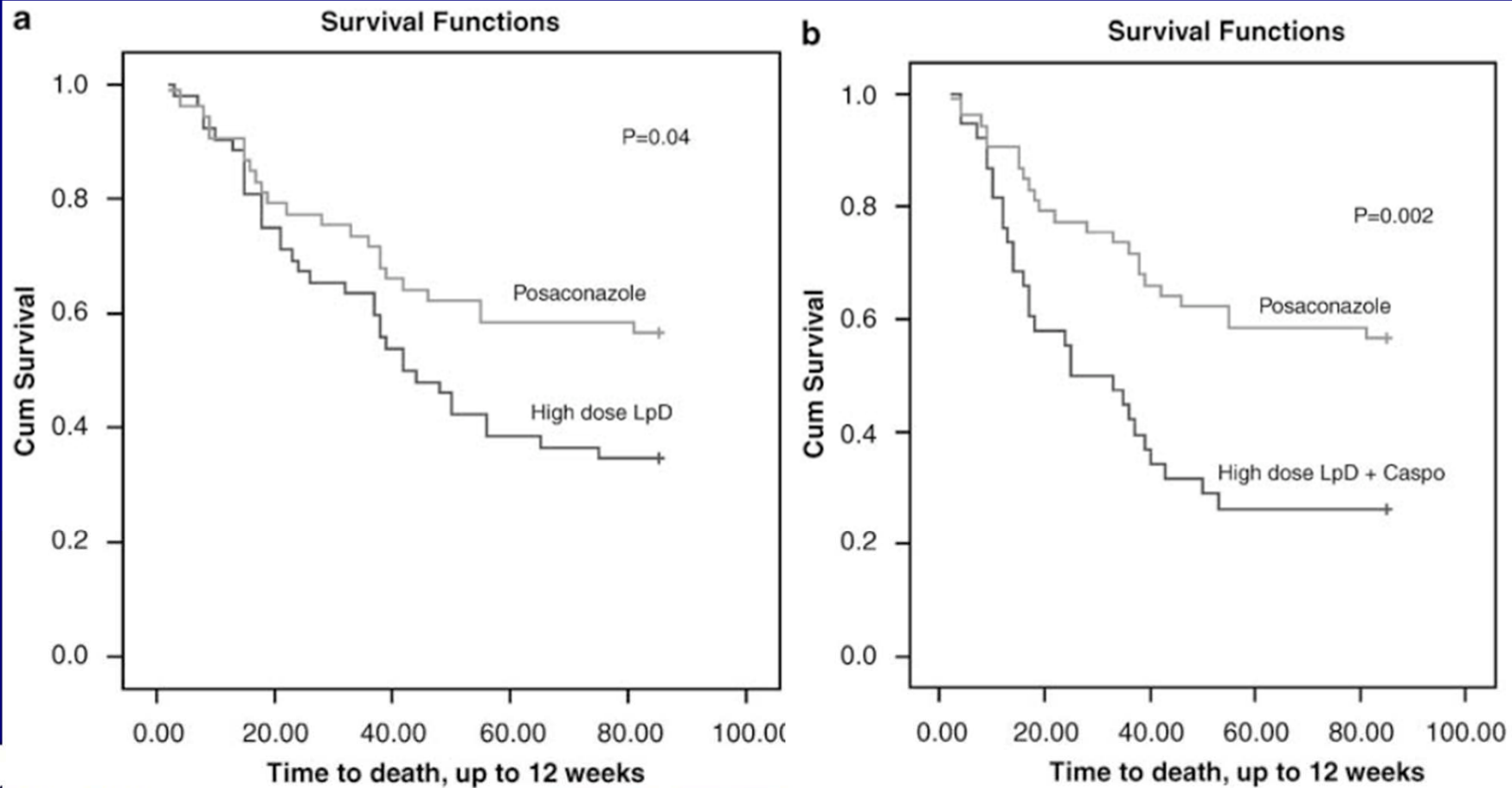
Factor	No. of patients (no. of responses)	Odds ratio	95% CI	P-value
Posaconazole versus high-dose LPD/AMB				
Posaconazole	53 (21)	9.5	(2.8–32.5)	<0.001
HD-LPD/AMB	52 (4)	1.0		
WBC transfusion				
No	79 (24)	1.0	(0.009–0.62)	0.017
Yes	26 (1)	0.07		
Posaconazole versus high-dose LPD/AMB+casprofungin				
Posaconazole	53 (21)	4.0	(1.1–14.5)	0.031
HD-LPD/AMB+casprofungin	38 (4)	1.0		
ICU				
No	56 (21)	1.0	(0.07–0.85)	0.027
Yes	35 (4)	0.2		
Persistent neutropenia				
No	68 (23)	1.0	(0.03–0.77)	0.023
Yes	63 (2)	0.2		

HD-LPD/AMB ≥ 7.5 mg/kg/gün



IA “Kurtarma” Tedavisinde POS

Raad II, et al. Leukemia 2008;22:496.



IA “Kurtarma” Tedavisinde POS

Raad Il, et al. Leukemia 2008;22:496.

- Retrospektif kontroller
- Olguların %75’i standard doz AMB’ye yanıtızsız.
- Mekanik ventilasyondaki hastalarda POS kullanımı daha az.



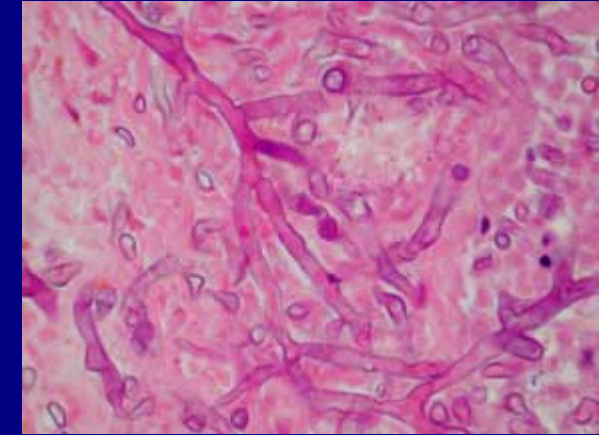
Invasive aspergillosis: salvage

Agent	Grade	Comments
Ambisome	B III	no data in voriconazole failure
ABLC	B III	no data in voriconazole failure
Caspofungin	B II	no data in voriconazole failure
Posaconazole	B II	no data in voriconazole failure
Voriconazole	B II	if not used in 1st line
Itraconazole	C III	Insufficient data



Zigomikoz

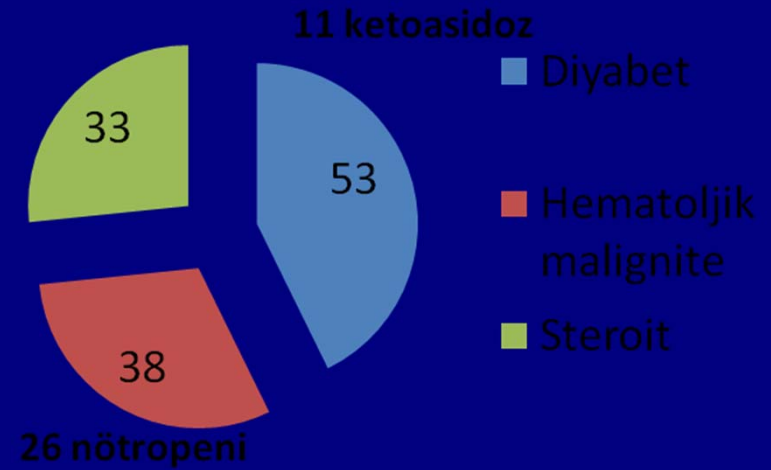
- Geniş, septasız, kalın duvarlı, dik açı ile dallanan hifler
- Kolay ürer (Sikloheksimitli SDA)
- *Rhizopus*, *Rhizomucor*, *Mucor*, *Absidia*
- *Rhizopus arrhizus*
 - İnsan olgularının %60
 - Rinoserebral %90
- Toprak, su, hava
- Giriş yolu: inhalasyon
- Damar ve doku invazyonu
- Kültür duyarlılığı %30



**TÜRKİYE'DEN 1995-2009 YILLARI ARASINDA YAYINLANMIŞ 100
MUKORMİKOZ OLGUSUNUN HAVUZ ANALİZ YÖNTEMİ İLE
DEĞERLENDİRİLMESİ**

Arzu Nazlı, Meltem Işıkgöz Taşbakan, Hüsnü Pullukçu, Oğuz Reşat Sipahi, Tansu Yamazhan, Bilgin Arda

- 22 uluslararası, 26 ulusal yayın
- 53 erkek, 47 kadın olgu
- Yaş ortalaması 46
- Patolojik tanı: 83
- Radyolojik tanı: 76
- Mikolojik tanı: 21/40



**TÜRKİYE'DEN 1995-2009 YILLARI ARASINDA YAYINLANMIŞ 100
MUKORMİKOZ OLGUSUNUN HAVUZ ANALİZ YÖNTEMİ İLE
DEĞERLENDİRİLMESİ**

Arzu Nazlı, Meltem Işıkgöz Taşbakan, Hüsnü Pullukçu, Oğuz Reşat Sipahi, Tansu Yamazhan, Bilgin Arda

- Cerrahi + Antifungal : 85 olgu
- Cerrahi : 5 olgu
- Antifungal : 7 olgu (7 ex)
- Toplam mortalite: 57
- Diyabetli olgularda mortalite daha yüksek



Zigomikoz

Klinik

- Rinoserebral
- Serebral
- Pulmoner
- Gastrointestinal
- Deri
- Dissemine



Rinoserebral Zigomikoz

- Nazal veya yumuşak damak nekrozu %50
 - 3 gün içinde
- Nekroz yokluğu tanıyı dışlamaz
- Agresif tedavi yapılmazsa serebral ve orbital komplikasyon
- BT, MRG
- Biyopsi-kültür



Antifungal duyarlılık

- Amfo B ++
- L-Amfo B +++++
- 5-Flusitozin +
- Posakonazol +++++
- İtrakonazol ---
- Kaspofungin ---
- Vorikonazol ---



Zigomikoz tedavi

- Altta yatan hastalığın kontrolü
- Erken ve geniş cerrahi debritleme
- Antifungal tedavi
 - Amfo B 1-1,5 mg/kg/gün
 - Lipit bileşenli Amfo B
 - Posakonazol
- Tedavi süresi ?
 - Radyolojik düzelme
 - Biyopsi ve kültür (-)
 - İmmünsüpresyonun durumu



Zigomikoz tedavisinde Posakonazol

- Standart tedavilere yanıtızsız olası veya yüksek olası zikomikoz olguları
 - 24 olgu (14 HM)
 - Posakonazol (800mg/gün)
 - Tedavi başarıısı %70

Greenberg RN, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother 2006;50(1):126–33.



Posaconazole Is Effective as Salvage Therapy in Zygomycosis: A Retrospective Summary of 91 Cases

Jo-Anne H. van Burik,¹ Roberta S. Hare,² Howard F. Solomon,³
Michael L. Corrado,³ and Dimitrios P. Kontoyiannis⁴

91 olgu

- 69 kesin
- 22 yüksek olası
- 81 olgu refrakter
- 10 olgu intoleran
- %62 tek odak
- %85 L-AMB

– Posa 4x200mg 2x400mg



12. Hafta tedavi başarısı



Posaconazole Is Effective as Salvage Therapy in Zygomycosis: A Retrospective Summary of 91 Cases

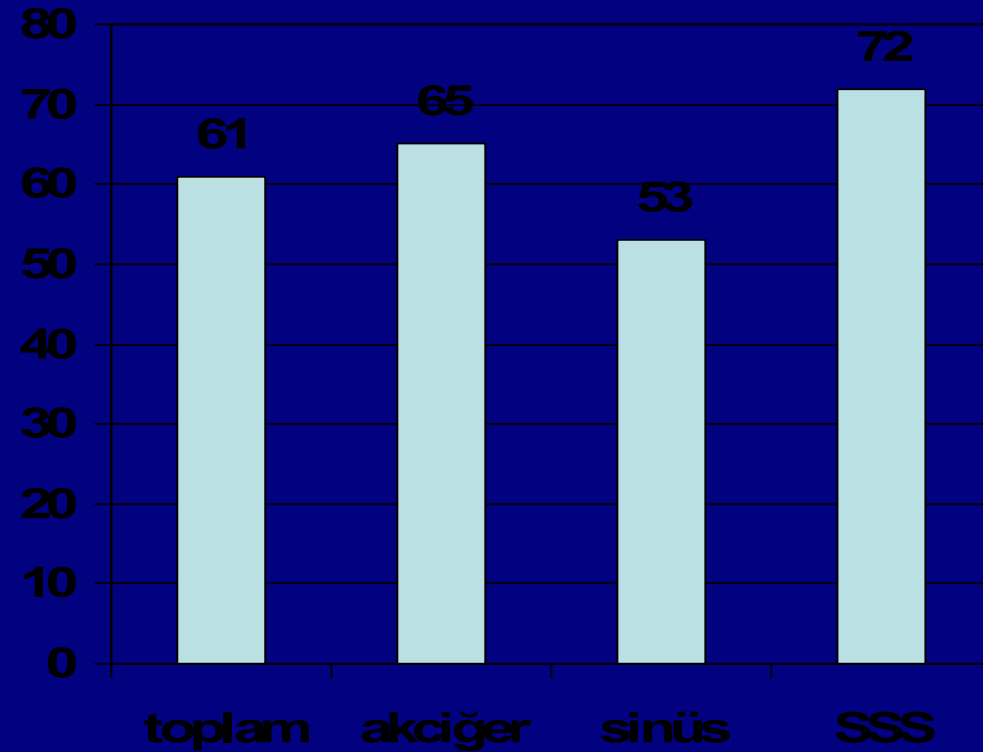
Jo-Anne H. van Burik,¹ Roberta S. Hare,² Howard F. Solomon,³
Michael L. Corrado,³ and Dimitrios P. Kontoyiannis⁴

64 olguda cerrahi girişim

38 ted öncesi

9 ted sırasında

17 önce+sonra



Cerrahi girişim uygulanıp uygulanmaması tedavi başarısını etkilememiş %61-62



[Mucormycosis: retrospective evaluation of 12 cases].

[Article in Turkish]

Arda B, Erdem A, Sipahi OR, Işıkgöz Taşbakan M, Pullukçu H, Taşbakan MS, Ceylan N, Metin DY, Midilli R, Yamazhan T, Ulusoy S.

Ege University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, İzmir, Turkey.

Tablo II. Olguların Demografik ve Klinik Özellikleri

No	Yaş/ Cinsiyet	Altta yatan hastalık	Klinik tanı	Mikolojik tanı	Patolojik tanı	Radyolojik tanı	VCZ prx	Tedavi (gün)	Cerrahi tedavi	Tedavi süresi	Sonuç
1	74/K	Aplastik anemi	RO	-	+	+	+	L-AMP (30) + ITC (50)	-	80	Y
2	56/E	Diş absesi	RO	-	+	+	-	L-AMP (90) + PCZ (90)	Sinüs cerrahi	180	Y
3	38/E	NHL (OKİT)	RS	-	+	+	+	L-AMP (30) + PCZ (45)	-	75	Ex
4	55/E	DM + siroz	RS	<i>Rhizopus</i>	+	+	-	LAMP (10)	+	10	Ex
5	74/K	MDS	RO	-	-	+	+	L-AMP (14) + PCZ (20)	-	34	Ex
6	55/K	DM	RS	Mikolojik muayene +++	+	+	-	LAMP (52)	+	52	Ex
7	65/E	DM + diş absesi	RS	<i>Mucor</i> + <i>Aspergillus</i>	+	+	-	L-AMP (38) + PCZ (40)	+	78	Y
8	22/K	Aplastik anemi + Steroid kullanımı	RO	Mikolojik muayene +++	+	+	-	ABLC (56)	-	56	Y
9	63/E	Akciğer kanseri	Pulmoner	<i>Rhizopus</i>	+	+	-	L-AMP (10) + PCZ (60)	Lobektomi	70	Y
10	40/K	Adrenal yetmezlik + Steroid kullanımı	RO	<i>Rhizopus</i>	+	+	-	L-AMP (6)	-	6	Ex
11	50/K	MDS	RSI + pulmoner	<i>Rhizopus</i> + <i>Aspergillus</i>	+	+	-	L-AMP (8)	-	8	Ex
12	18/K	Aplastik anemi	RO	-	-	+	-	L-AMP (30) + PCZ (50)	-	80	Y

VCZ: Vorikonazol, L-AMP: Lipozomal amfoterisin B, ITC: İtrakonazol, PCZ: Posakonazol, ABLC: Amfoterisin B lipid kompleksi, RS: Rinoserebral, RO: Rino-orbital, Prx: Profilaksi, NHL (OKİT): Non-Hodgkin lenfoma (otolog kemik iliği transplantasyonu), DM: Diabetes mellitus, MDS: Miyelodisplastik sendrom, Y: Yaşayıcı, Ex: Eksitus.





Mikafungin

- Kandida özefajiti
- Kandidemi nötroopenik ve nötroopenik olmayan hastada kandidemi.
 - 100 mg/gün
- Profilaksi???



Lancet. 2007 May 5;369(9572):1519-27.

Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial.

Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, Sekhon JS, Freire A, Ramasubramanian V, Demeyer I, Nucci M, Leelarasamee A, Jacobs F, Decruyenaere J, Pittet D, Ullmann AJ, Ostrosky-Zeichner L, Lortholary O, Koblinger S, Diekmann-Berndt H, Cornely OA; Micafungin Invasive Candidiasis Working Group.

Klinik für Viszeral und Transplantationschirurgie, Hannover, Germany.

Abstract

BACKGROUND: Invasive candidosis is increasingly prevalent in seriously ill patients. Our aim was to compare micafungin with liposomal amphotericin B for the treatment of adult patients with candidaemia or invasive candidosis.

METHODS: We did a double-blind, randomised, multinational non-inferiority study to compare micafungin (100 mg/day) with liposomal amphotericin B (3 mg/kg per day) as first-line treatment of candidaemia and invasive candidosis. The primary endpoint was treatment success, defined as both a clinical and a mycological response at the end of treatment. Primary analyses were done on a per-protocol basis. This trial is registered with ClinicalTrials.gov, number NCT00106288.

FINDINGS: 264 individuals were randomly assigned to treatment with micafungin; 267 were randomly assigned to receive liposomal amphotericin B. 202 individuals in the micafungin group and 190 in the liposomal amphotericin B group were included in the per-protocol analyses. Treatment success was observed for 181 (89.6%) patients treated with micafungin and 170 (89.5%) patients treated with liposomal amphotericin B. The difference in proportions, after stratification by neutropenic status at baseline, was 0.7% (95% CI -5.3 to 6.7). Efficacy was independent of the *Candida* spp and primary site of infection, as well as neutropenic status, APACHE II score, and whether a catheter was removed or replaced during the study. There were fewer treatment-related adverse events--including those that were serious or led to treatment discontinuation--with micafungin than there were with liposomal amphotericin B.

INTERPRETATION: Micafungin was as effective as--and caused fewer adverse events than--liposomal amphotericin B as first-line treatment of candidaemia and invasive candidosis.



Candidemia in hematologic patients before species identification

	Overall population	Hematological pts
Micafungin	A I	B II
Anidulafungin	A I	B II
Caspofungin	A I	B II
Ambisome	A I	B II
Other lipid-AmB	A II	B II
AmB deoxycholate		A I *
		C III *
Fluconazole	A I **	C III
Voriconazole	A I ***	B II

* DIII if concomitant nephrotoxic drug and EIII if renal impairment

** Not in severely ill patients or in patients with previous azole prophylaxis

*** Not in patients with previous azole prophylaxis



Candidemia after species identification (1/2)

		Overall population	Hematological pts
Micafungin	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II
Anidulafungin	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II
Caspofungin	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II

Özet

- Anidulofungin
 - Non-nötropenik hastada kandidemi
 - Candida özefajiti
- Posakonazol
 - Profilaksi
 - AML, MDS indüksiyon kemoterapisi
 - AKİT GVHD
 - İnvaziv aspergilloz kurtarma tedavisi
 - Mukormikoz







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